

COPY

PTO/SB/80 (11-08)

Approved for use through 11/30/2011, OMB 0651-0035

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☒ Practitioners associated with the Customer Number:

86738

OR

☐ Practitioner(s) named below (If more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☒ The address associated with Customer Number:

86738

OR

<input type="checkbox"/> Firm or Individual Name			
Address			
City	State	Zip	
Country			
Telephone	Email		

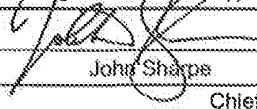
Assignee Name and Address:

Cytonome/ST, LLC
27 Drydock Avenue
Boston, Massachusetts 02210

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	21 AUGUST 2009
Name	John Sharpe	Telephone	617-330-5030
Title	Chief Executive Officer		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 5 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon this individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Cytonome/ST, LLC Exhibit 2011

NanoCollect Biomedical, Inc. v. Cytonome/ST, LLC, IPR2020-00548

Page 1 of 300

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)Applicant/Patent Owner: Cytonome/ST, LLCApplication No./Patent No.: 6,877,528 Filed/Issue Date: April 12, 2005Entitled: MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW
THROUGH A MICROCHANNELCytonome/ST, LLC, a Limited Liability Company
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of less than the entire right, title and interest.
(The extent (by percentage) of its ownership interest is _____ %)

in the patent application/patent identified above by virtue of either:

- A. ☐ An assignment from the inventors of the above-referenced application. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

- B. ☒ A chain of title from the inventors, of the patent application identified above, to the current assignee as follows:

1. From: Coventor, Inc. To: Teragenics, Inc.
The document was recorded in the United States Patent and Trademark Office at Reel 013261, Frame 0145, or for which a copy thereof is attached.

2. From: Coventor, Inc. To: Teragenics, Inc.
The document was recorded in the United States Patent and Trademark Office at Reel 014089, Frame 0475, or for which a copy thereof is attached.

John Richard Gilbert,
Sebastian Bohm and
3. From: Manish Deshpande To: Coventor, Inc.
The document was recorded in the United States Patent and Trademark Office at Reel 014110, Frame 0899, or for which a copy thereof is attached.

☒ Additional documents in the chain of title are listed on a supplemental sheet.

- ☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

<u>/David R. Burns/</u>	<u>July 2, 2013</u>
Signature	Date
<u>David R. Burns</u>	<u>(617) 449-6500</u>
Printed or Typed Name	Telephone Number
<u>Attorney on Record</u>	
Title	

(Attorney Docket No. 118153-01201)

STATEMENT UNDER 37 CFR 3.73(b)

4. From: Teragenics, Inc. To: Cytonome, Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 015289 , Frame 0976 , or for which a copy thereof is attached.

5. From: Cytonome, Inc. To: Cytonome/ST, LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 023525 , Frame 0158 , or for which a copy thereof is attached.

Electronic Acknowledgement Receipt	
EFS ID:	16221767
Application Number:	10179586
International Application Number:	
Confirmation Number:	9722
Title of Invention:	MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW THROUGH A MICROCHANNEL
First Named Inventor/Applicant Name:	John Richard Gilbert
Customer Number:	86738
Filer:	David Burns/Pegah Karimi
Filer Authorized By:	David Burns
Attorney Docket Number:	TGZ-012
Receipt Date:	02-JUL-2013
Filing Date:	24-JUN-2002
Time Stamp:	18:52:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	118153_02101_Copy_of_POA. PDF	261570 1b12ae6c6a1d4fad90d3506d35bf5a0476b2494	no	1
Warnings:					
Information:					

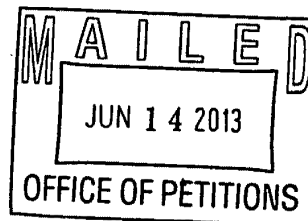
2	Assignee showing of ownership per 37 CFR 3.73.	118153_01201_Statement_under_3_73b.PDF	13894 f34a8af72b77dbe3664c8c5c9c0ae571146ea831	no	2
Warnings:					
Information:					
Total Files Size (in bytes):				275464	
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

MCCARTER & ENGLISH, LLP BOSTON
265 FRANKLIN STREET
BOSTON MA 02110



In re Patent No. 6,877,528
Issued: April 12, 2005
Application No. 10/179,586
Filed: June 24, 2002
Attorney Docket No. TGZ-012

NOTICE

This is a notice regarding your request for acceptance of a fee deficiency submission under 37 CFR 1.28 filed May 15, 2013.

On September 1, 1998, the Court of Appeals for the Federal Circuit held that 37 CFR 1.28(c) is the sole provision governing the time for correction of the erroneous payment of the issue fee as a small entity. See DH Technology v. Synergystex International, Inc. 154 F.3d 1333, 47 USPQ2d 1865 (Fed. Cir. Sept. 1, 1998).

The Office no longer investigates or rejects original or reissue applications under 37 CFR 1.56. **1098 Off. Gaz. Pat. Office 502 (January 3, 1989).** Therefore, nothing in this Notice is intended to imply that an investigation was done.

Your fee deficiency submission under 37 CFR 1.28 is hereby **ACCEPTED**.

This patent is no longer entitled to small entity status. Accordingly, all future fees paid in this patent must be paid at the large entity rate.

Further, it is not apparent whether the person signing the request was ever given a power of attorney or authorization of agent regarding this patent. In accordance with 37 CFR 1.34(a), the signature appearing on the request shall constitute a representation to the United States Patent

and Trademark Office that he/she is authorized to represent the particular party in whose behalf he/she acts.

Telephone inquiries concerning this decision should be directed to the undersigned at (571) 272-7751.

/Joan Olszewski/
Joan Olszewski
Petitions Examiner
Office of Petitions

Docket No.: 118153-01201
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Gilbert, et al.

Patent No.: 6,877,528

Issued: April 12, 2005

For: MICROFLUIDIC SYSTEM INCLUDING A
BUBBLE VALVE FOR REGULATING FLUID
FLOW THROUGH A MICROCHANNEL

**NOTIFICATION OF LOSS OF ENTITLEMENT TO SMALL ENTITY STATUS AND
CORRECTION OF ERROR IN SMALL ENTITY STATUS**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

In accordance with 37 C.F.R. §§ 1.27(g)(2) and 1.28(c), Owner of the above-identified patent hereby notifies the Office of a loss of entitlement to small entity status and respectfully requests excuse of an error in which certain fees were paid as a small entity subsequent to such loss of entitlement to small entity status. Owner asserts that its status as a small entity was established in good faith, and fees paid as a small entity were paid in good faith, and through error and without deceptive intent the Office was not notified of the loss of entitlement to small entity status. Per 37 C.F.R. § 1.28(c)(2), below please find an itemization of the deficiency in fees owed resulting from the previous erroneous payment of fees paid as a small entity.

06/13/2013 CKHLOK 00000006 504876 6877528
01 FC:1559 1205.00 DA
02 FC:1559 2150.00 DA

05/28/2013 MBANGURA 00000050 504876 6877528
01 FC:1599 1205.00 DA

05/28/2013 MBANGURA 00000051 504876 6877528
01 FC:1599 2150.00 DA

MEI 15523189v.1

1

Adjustment date: 06/13/2013 CKHLOK
05/28/2013 MBANGURA 00000051 504876 6877528
01 FC:1599 2150.00 CR

Adjustment date: 06/13/2013 CKHLOK
05/28/2013 MBANGURA 00000050 504876 6877528
01 FC:1599 1205.00 CR

Patent No.: 6,877,528

Docket No.: 118153-01201

Please charge our Deposit Account No. 50-4876, under Order No. 118153-01201 from which the undersigned is authorized to draw, in the amount of \$3,355 for the total deficiency owed.

Fee Type	Current Undiscounted Fee	Small Entity Fee Paid	Deficiency Owed
Maintenance Fee due at 3.5 years	\$1,600	\$490	\$1,110
Maintenance Fee, Surcharge- 3.5 year-Late payment within 6 months	\$160	\$65	\$95
Maintenance Fee due at 7.5 years	\$3,600	\$1,450	\$2,150

Dated: May 15, 2013

Respectfully submitted,

Electronic signature: /Michael L. Mathaisel/
Michael L. Mathaisel
Registration No.: 64,251
MCCARTER & ENGLISH, LLP
265 Franklin Street
Boston, Massachusetts 02110
(617) 449-6500
(617) 607-9200 (Fax)
Attorney/Agent For Applicant

Docket No.: 118153-01201
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Gilbert, et al.

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Dated: May 15, 2013

Respectfully submitted,

Electronic signature: /Michael L. Mathaisel/
Michael L. Mathaisel

Registration No.: 64,251
MCCARTER & ENGLISH, LLP
265 Franklin Street
Boston, Massachusetts 02110
(617) 449-6500
(617) 607-9200 (Fax)
Attorney/Agent For Applicant

Electronic Acknowledgement Receipt	
EFS ID:	15783795
Application Number:	10179586
International Application Number:	
Confirmation Number:	9722
Title of Invention:	MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW THROUGH A MICROCHANNEL
First Named Inventor/Applicant Name:	John Richard Gilbert
Customer Number:	86738
Filer:	Michael L. Mathaisel
Filer Authorized By:	
Attorney Docket Number:	TGZ-012
Receipt Date:	15-MAY-2013
Filing Date:	24-JUN-2002
Time Stamp:	14:37:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no				
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Notification_of_Loss_of_Small Entity_Status_1.pdf	43148 533a85dd83a614634d42719149c692705a daeb71	no	2
Warnings:					
Information:					

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: 118153-01201
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Gilbert, et al.

Patent No.: 6,877,528

Issued: April 12, 2005

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05/28/2013 MBANGURA 00000050 504876 6877528
01 FC:1599 1205.00 DA

05/28/2013 MBANGURA 00000051 504876 6877528
01 FC:1599 2150.00 DA

Patent No.: 6,877,528

Docket No.: 118153-01201

Please charge our Deposit Account No. 50-4876, under Order No. 118153-01201 from which the undersigned is authorized to draw, in the amount of \$3,355 for the total deficiency owed.

Fee Type	Current Undiscounted Fee	Small Entity Fee Paid	Deficiency Owed
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Maintenance Fee due at 7.5 years	\$3,600	\$1,450	\$2,150

Dated: May 15, 2013

Respectfully submitted,

Electronic signature: /Michael L. Mathaisel/

Michael L. Mathaisel

Registration No.: 64,251

MCCARTER & ENGLISH, LLP

265 Franklin Street

Boston, Massachusetts 02110

(617) 449-6500

(617) 607-9200 (Fax)

Attorney/Agent For Applicant



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
10/179,586	6877528	3753	9200



Correspondence Address/Fee Address Change

The following fields have been set to Customer Number 86738 on 09/30/2009

- Correspondence Address
- Maintenance Fee Address
- Power of Attorney Address

The address of record for Customer Number 86738 is:

86738
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

PART 1 - ATTORNEY/APPLICANT COPY

page 1 of 1

Cytonome/ST, LLC Exhibit 2011

NanoCollect Biomedical, Inc. v. Cytonome/ST, LLC, IPR2020-00548

Page 16 of 300



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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
10/179,586	6877528	3753	9200

Correspondence Address / Fee Address Change

The following fields have been set to Customer Number 959 on 09/05/2007

- Correspondence Address
- Maintenance Fee Address

The address of record for Customer Number 959 is:

LAHIVE & COCKFIELD, LLP
ONE POST OFFICE SQUARE
BOSTON,MA 02109-2127



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov



Bib Data Sheet

CONFIRMATION NO. 9722

SERIAL NUMBER 10/179,586	FILING OR 371(c) DATE 06/24/2002 RULE	CLASS 137	GROUP ART UNIT 3753	ATTORNEY DOCKET NO. TGZ-012	
APPLICANTS John Richard Gilbert, Brookline, MA; Sebastian Bohm, Inverness, UNITED KINGDOM; Manish Deshpande, Canton, MA;					
** CONTINUING DATA ***** This appln claims benefit of 60/373,256 04/17/2002					
** FOREIGN APPLICATIONS *****					
IF REQUIRED, FOREIGN FILING LICENSE GRANTED.** SMALL ENTITY ** ** 07/19/2002					
Foreign Priority claimed <input type="checkbox"/> yes <input type="checkbox"/> no 35 USC 119 (a-d) conditions <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> Met after met Allowance Verified and Acknowledged <u>Examiner's Signature</u> <u>Initials</u>		STATE OR COUNTRY MA	SHEETS DRAWING 8	TOTAL CLAIMS 24	INDEPENDENT CLAIMS 9
ADDRESS 000959					
TITLE MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW THROUGH A MICROCHANNEL					
FILING FEE RECEIVED 1764	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit		



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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
10/179,586		3753	37M2

Change of Address/Power of Attorney

The following fields have been set to Customer Number 000959 on

- Correspondence Address
- Maintenance Fee Address

The address of record for Customer Number 000959 is:

LAHIVE & COCKFIELD, LLP.
28 STATE STREET
BOSTON, MA 02109

The Practitioners of record for Customer Number 000959 are:

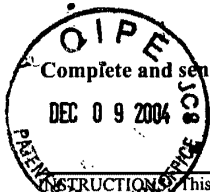
PTO INSTRUCTIONS:

Please take the following action when the correspondence address has been changed to a customer number:

- 1) Add 'ADDRESS CHANGE TO CUSTOMER NUMBER' on the next available content line of the File Jacket.
- 2) Put a line through the old address on the File Jacket and enter the Customer Number as the new address.
- 3) File this Notice in the File Jacket.

Please take the following action when the correspondence address has NOT been changed:

- 1) File this Notice in the File Jacket

12-13-04
PART B - FEE(S) TRANSMITTALExpress Mail
No: EV 465007216 US

Complete and send this form, together with applicable fee(s), to: Mail

Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where applicable. Further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

000959 7590 11/22/2004

LAHIVE & COCKFIELD, LLP.

28 STATE STREET

BOSTON, MA 02109

12/14/2004 WASFAW2 00000021 120080 10179586

01 FC:2501 700.00 DA
02 FC:1504 300.00 DA
03 FC:8001 30.00 DA

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (703) 746-4000, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/179,586	06/24/2002	John Richard Gilbert	TGZ-012	9722

TITLE OF INVENTION: MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW THROUGH A MICROCHANNEL

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO YES	\$1370 700	\$300	\$1670	02/22/2005

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHAMBERS, A MICHAEL	3753	137-827000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list

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- (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

Lahive & Cockfield, LLP
2 Elizabeth A. Hanley
3 Anthony A. Laurentano

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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(A) NAME OF ASSIGNEE

Cytonome, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Watertown, Massachusetts

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:

- ☒ Issue Fee
- ☒ Publication Fee (No small entity discount permitted)
- ☒ Advance Order - # of Copies 10

4b. Payment of Fee(s):

- ☐ A check in the amount of the fee(s) is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 12-0080 (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☒ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above. NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature

Date December 9, 2004

Typed or printed name

Anthony A. Laurentano

Registration No. 38,220

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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TRANSMITTAL FORM (to be used for all correspondence after initial filing)	Application Number	10/179,586-Conf. #9722
	Filing Date	June 24, 2002
	First Named Inventor	John R. GILBERT
	Art Unit	3753
	Examiner Name	A. M. Chambers
Total Number of Pages in This Submission	Attorney Docket Number	TGZ-012

ENCLOSURES (Check all that apply)		
<input checked="" type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment/Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Reply to Missing Parts/Incomplete Application <input type="checkbox"/> Reply to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____ <input type="checkbox"/> Landscape Table on CD	<input type="checkbox"/> After Allowance Communication to TC <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Certificate of Express Mailing Part B copy of Notice Return Receipt Postcard
Remarks		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT			
Firm Name	LAHIVE & COCKFIELD, LLP		
Signature			
Printed name	Anthony A. Laurentano		
Date	December 9, 2004	Reg. No.	38,220

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Dated: December 9, 2004	Signature: (Anthony A. Laurentano)



Application No. (if known): 10/179586

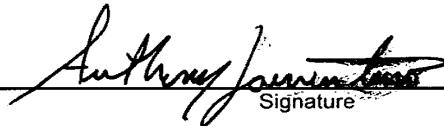
Attorney Docket No.: TGZ-012

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Alexandria, VA 22313-1450

on December 9, 2004
Date


Signature

Anthony A. Laurentano

Typed or printed name of person signing Certificate

38,220
Registration Number, if applicable

(617) 227-7400
Telephone Number

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Transmittal (1 page)
Fee Transmittal (1 page, in duplicate)
Part B copy of Notice (1 page)
Return Receipt Postcard

Charge \$1,030.00 to deposit account 12-0080



FEE TRANSMITTAL for FY 2005 <small>Effective 10/01/2004. Patent fees are subject to annual revision.</small>		Complete if Known																																																																																					
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METHOD OF PAYMENT (check all that apply)		FEE CALCULATION (continued)																																																																																					
<input type="checkbox"/> Check <input type="checkbox"/> Credit Card <input type="checkbox"/> Money Order <input checked="" type="checkbox"/> Deposit Account <input type="checkbox"/> None Deposit Account Number: 12-0080 Deposit Account Name: Lahive & Cockfield, LLP The Director is authorized to: (check all that apply) <input checked="" type="checkbox"/> Charge fee(s) indicated below <input type="checkbox"/> Charge fee(s) indicated below, except for the filing fee <input checked="" type="checkbox"/> Charge any additional fee(s) or any underpayment of fee(s) under 37 CFR 1.16 and 1.17 <input checked="" type="checkbox"/> Credit any overpayments To the above-identified deposit account. <input type="checkbox"/> Other (please identify):		2. EXTRA CLAIM FEES <table border="1"><thead><tr><th>Fee Description</th><th>Fee (\$)</th><th>Small Entity Fee (\$)</th></tr></thead><tbody><tr><td>Each claim over 20</td><td>18</td><td>9</td></tr><tr><td>Each independent claim over 3</td><td>88</td><td>44</td></tr><tr><td>Multiple dependent claims</td><td>300</td><td>150</td></tr><tr><td>For Reissues, each claim over 20 and more than in the original patent</td><td>18</td><td>9</td></tr><tr><td>For Reissues, each independent claim more than in the original patent</td><td>88</td><td>44</td></tr></tbody></table> <table border="1"><thead><tr><th>Total Claims</th><th>Extra Claims</th><th>Fee (\$)</th><th>Fee Paid (\$)</th></tr></thead><tbody><tr><td>- 20 or HP =</td><td>x</td><td>=</td><td></td></tr><tr><td colspan="4">HP= highest number of total claims paid for, if greater than 20</td></tr><tr><th>Indep. Claims</th><th>Extra Claims</th><th>Fee (\$)</th><th>Fee Paid (\$)</th></tr><tr><td>- 3 or HP =</td><td>x</td><td>=</td><td></td></tr><tr><td colspan="4">HP= highest number of independent claims paid for, if greater than 3</td></tr><tr><td colspan="2">Multiple Dependent Claims</td><td>Fee (\$)</td><td>Fee Paid (\$)</td></tr><tr><td colspan="2">Subtotal (2) \$</td><td colspan="2">0.00</td></tr></tbody></table>		Fee Description	Fee (\$)	Small Entity Fee (\$)	Each claim over 20	18	9	Each independent claim over 3	88	44	Multiple dependent claims	300	150	For Reissues, each claim over 20 and more than in the original patent	18	9	For Reissues, each independent claim more than in the original patent	88	44	Total Claims	Extra Claims	Fee (\$)	Fee Paid (\$)	- 20 or HP =	x	=		HP= highest number of total claims paid for, if greater than 20				Indep. Claims	Extra Claims	Fee (\$)	Fee Paid (\$)	- 3 or HP =	x	=		HP= highest number of independent claims paid for, if greater than 3				Multiple Dependent Claims		Fee (\$)	Fee Paid (\$)	Subtotal (2) \$		0.00																																			
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Signature		Registration No. (Attorney/Agent)	38,220																																																																																				
Name (Print/Type)	Anthony A. Laurentano	Telephone	(617) 227-7400																																																																																				
		Date	December 9, 2004																																																																																				

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Dated: December 9, 2004	Signature: (Anthony A. Laurentano)



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000959 7590 11/22/2004

LAHIVE & COCKFIELD, LLP.
28 STATE STREET
BOSTON, MA 02109

EXAMINER

CHAMBERS, A MICHAEL

ART UNIT

PAPER NUMBER

3753

DATE MAILED: 11/22/2004

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/179,586	06/24/2002	John Richard Gilbert	TGZ-012	9722

TITLE OF INVENTION: MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW THROUGH A MICROCHANNEL

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1370	\$300	\$1670	02/22/2005

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. **PROSECUTION ON THE MERITS IS CLOSED.** THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN **THREE MONTHS** FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. **THIS STATUTORY PERIOD CANNOT BE EXTENDED.** SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

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A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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LAHIVE & COCKFIELD, LLP.
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BOSTON, MA 02109

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(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/179,586	06/24/2002	John Richard Gilbert	TGZ-012	9722

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nonprovisional	NO	\$1370	\$300	\$1670	02/22/2005

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHAMBERS, A MICHAEL	3753	137-827000

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- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
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2. For printing on the patent front page, list

- (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, _____ 1
- (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. _____ 2
- _____ 3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
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5. Change in Entity Status (from status indicated above)

- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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UNITED STATES DEPARTMENT OF COMMERCE
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000959	7590	11/22/2004	EXAMINER	
LAHIVE & COCKFIELD, LLP.			CHAMBERS, A MICHAEL	
28 STATE STREET			ART UNIT	PAPER NUMBER
BOSTON, MA 02109			3753	

DATE MAILED: 11/22/2004

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (703) 305-1383. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

Notice of Allowability	Application No.	Applicant(s)	
	10/179,586	GILBERT ET AL.	
	Examiner	Art Unit	
	A. Michael Chambers	3753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS (IS OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to an amendment filed 09/22/04.
2. ☒ The allowed claim(s) is/are 1-16, 19 and 25-33.
3. ☒ The drawings filed on 24 June 2002 are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.


THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
 - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|---|
| <ol style="list-style-type: none"> 1. <input type="checkbox"/> Notice of References Cited (PTO-892) 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) 3. <input checked="" type="checkbox"/> Information Disclosure Statements (PTO-1449 or PTO/SB/08),
Paper No./Mail Date <u>07/02/04</u> 4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit
of Biological Material | <ol style="list-style-type: none"> 5. <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) 6. <input type="checkbox"/> Interview Summary (PTO-413),
Paper No./Mail Date _____. 7. <input type="checkbox"/> Examiner's Amendment/Comment 8. <input type="checkbox"/> Examiner's Statement of Reasons for Allowance 9. <input type="checkbox"/> Other _____. |
|--|---|


 A. Michael Chambers
 Primary Examiner
 Art Unit: 3753

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet

1

of

1

Attorney Docket Number

TGZ-012

U.S. PATENT DOCUMENTS

[illegible]

FOREIGN PATENT DOCUMENTS


[illegible]


***EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 608. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. *Applicant's unique citation designation number (optional). *See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. *Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). *For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. *Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.18 if possible. *Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

NON-PATENT LITERATURE DOCUMENTS		
Examiner Initials	Cite No. 1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
Examiner Signature	Date Considered	
	RM	11/20/04

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Issue Classification 	Application No.	Applicant(s)	
	10/179,586	GILBERT ET AL.	
	Examiner	Art Unit	
	A. Michael Chambers	3753	

ISSUE CLASSIFICATION											
ORIGINAL					CROSS REFERENCE(S)						
CLASS	SUBCLASS				CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					
137	827				137	806	807	830	831		
INTERNATIONAL CLASSIFICATION					204	601					
F	1	5	C	1/04							
				/							
				/							
				/							
				/							
_____ (Assistant Examiner) (Date)					 A. Michael Chambers Primary Examiner (Primary Examiner) (Date)					Total Claims Allowed: 26	
10 year (Legal Instruments Examiner) (Date)										O.G. Print Claim(s) 1	

<input checked="" type="checkbox"/> Claims renumbered in the same order as presented by applicant												<input type="checkbox"/> CPA		<input type="checkbox"/> T.D.		<input type="checkbox"/> R.1.47	
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		31		61		91		121		151		181				
	2		32		62		92		122		152		182				
	3		33		63		93		123		153		183				
	4		34		64		94		124		154		184				
	5		35		65		95		125		155		185				
	6		36		66		96		126		156		186				
	7		37		67		97		127		157		187				
	8		38		68		98		128		158		188				
	9		39		69		99		129		159		189				
	10		40		70		100		130		160		190				
	11		41		71		101		131		161		191				
	12		42		72		102		132		162		192				
	13		43		73		103		133		163		193				
	14		44		74		104		134		164		194				
	15		45		75		105		135		165		195				
	16		46		76		106		136		166		196				
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SEARCH			
Class	Sub.	Date	Exmr.
137	827		
137	833		
137	830		
137	831		
204	601		
137	806		
137	807	09/03	Amc

INTERFERENCE SEARCHED			
Class	Sub.	Date	Exmr.
137	806		
137	807		
137	827		
137	830		
137	831	11/04	Amc
137	833	204/601	11/04

SEARCH NOTES (List databases searched. Attach search strategy inside.)		
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None	11/04	Amc
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BIBDATASHEET

Bib Data Sheet

CONFIRMATION NO. 9722

SERIAL NUMBER 10/179,586	FILING DATE 06/24/2002 RULE	CLASS 137	GROUP ART UNIT 3753	ATTORNEY DOCKET NO. TGZ-012	
APPLICANTS John Richard Gilbert, Brookline, MA; Sebastian Bohm, Inverness, UNITED KINGDOM; Manish Deshpande, Canton, MA; ** CONTINUING DATA ***** <i>yes</i> This appln claims benefit of 60/373,256 04/17/2002 ** FOREIGN APPLICATIONS ***** <i>none</i> IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 07/19/2002					
Foreign Priority claimed <input type="checkbox"/> yes <input checked="" type="checkbox"/> no 35 USC 119 (a-d) conditions met <input type="checkbox"/> yes <input checked="" type="checkbox"/> no <input type="checkbox"/> Met after Allowance Verified and Acknowledged <u>Examiner's Signature</u> <i>amc</i> <u>Initials</u>		STATE OR COUNTRY MA	SHEETS DRAWING 8	TOTAL CLAIMS 24	INDEPENDENT CLAIMS 9
ADDRESS 000959 LAHIVE & COCKFIELD, LLP. 28 STATE STREET BOSTON, MA 02109					
TITLE Microfluidic system including a bubble valve for regulating fluid flow through a microchannel					
FILING FEE RECEIVED 1464	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit		

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number

10/179586
CVZ-012

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	24	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	24 minus 20 =	4
INDEPENDENT CLAIMS	9 minus 3 =	6
MULTIPLE DEPENDENT CLAIM PRESENT <input type="checkbox"/>		

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY
TYPE ☐

OR
OTHER THAN
SMALL ENTITY

RATE	FEE
BASIC FEE	370.00
X\$ 9=	
X42=	
+140=	
TOTAL	

RATE	FEE
BASIC FEE	740.00
X\$18=	72
X84=	504
+280=	
TOTAL	1316

CLAIMS AS AMENDED - PART II

	(Column 1)	(Column 2)	(Column 3)
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	22	24	
Independent	4	9	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

SMALL ENTITY

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OTHER THAN
SMALL ENTITY

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X42=	
+140=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
X\$18=	
X84=	
+280=	
TOTAL ADDIT. FEE	

9-22-04

	(Column 1)	(Column 2)	(Column 3)
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	26	26	
Independent	6	9	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

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TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
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X84=	
+280=	
TOTAL ADDIT. FEE	

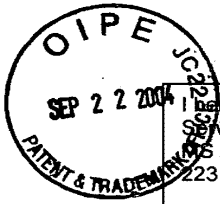
	(Column 1)	(Column 2)	(Column 3)
AMENDMENT C	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total			
Independent			
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

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X42=	
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TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
X\$18=	
X84=	
+280=	
TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
 ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
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 The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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09-24-04

3753

[Handwritten signature]

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV 419929425 US, in an envelope addressed to: U.S. AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: September 22, 2004

Signature:

[Handwritten signature of Anthony A. Laurentano]
(Anthony A. Laurentano)

Docket No.: TGZ-012
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
John R. Gilbert, *et al.*

Application No.: 10/179586

Art Unit: 3753

Filed: June 24, 2002

Examiner: A.M. Chambers

For: MICROFLUIDIC SYSTEM INCLUDING A
BUBBLE VALVE FOR REGULATING FLUID
FLOW THROUGH A MICROCHANNEL

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

MS AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

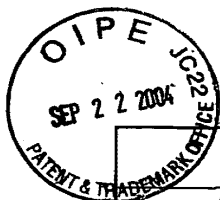
Dear Sir:

INTRODUCTORY COMMENTS

In response to the Office Action dated June 22, 2004 (Paper No. 20040622), please amend the above-identified U.S. patent application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks/Arguments begin on page 7 of this paper.

**AMENDMENT TRANSMITTAL LETTER**Docket No.
TGZ-012Application No.
10/179,586-Conf. #9722Filing Date
June 24, 2002Examiner
A. M. ChambersArt Unit
3753Applicant(s): John R. GILBERT *et al.*

Invention: MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW THROUGH A MICROCHANNEL

TO THE COMMISSIONER FOR PATENTS

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED					
	Claims Remaining After Amendment	Highest Number Previously Paid	Number Extra Claims Present	Rate	
Total Claims	26	- 26 =		x	0.00
Independent Claims	6	- 9 =		x	0.00
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>					
Other fee (please specify):					
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT:					0.00

☐ Large Entity☒ Small Entity☒ No additional fee is required for this amendment.☐ Please charge Deposit Account No. _____ in the amount of \$ _____.
A duplicate copy of this sheet is enclosed.☐ A check in the amount of \$ _____ to cover the filing fee is enclosed.☐ Payment by credit card. Form PTO-2038 is attached.☒ The Director is hereby authorized to charge and credit Deposit Account No. 12-0080
as described below.☒ Credit any overpayment.☒ Charge any additional filing or application processing fees required under 37 CFR 1.16 and 1.17.
Anthony A. Laurentano
Attorney Reg. No. 38,220Dated: September 22, 2004LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV 419929425 US, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: September 22, 2004

Signature: (Anthony A. Laurentano)

AMENDMENTS TO THE CLAIMS

Please amend claims 1 and 19 as set forth in the following listing of claims, which will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A microfluidic device, comprising:
a microchannel having an interior bounded by a side wall;
a valve for regulating the flow of fluid through the microchannel, the valve comprising a gas-filled first reservoir, a fluid meniscus interfacing the reservoir and the interior and an actuator for varying the volume of the first reservoir to increase an internal pressure of the first reservoir to vary the flow of ~~liquid~~ fluid through the ~~channel~~ microchannel; and
a second reservoir for absorbing a pressure variation in the microchannel induced by the actuator.
2. (Original) The microfluidic device of claim 1, wherein the actuator deflects the meniscus into the microchannel interior to regulate the flow of fluid through the microchannel.
3. (Original) The microfluidic device of claim 1, wherein the meniscus comprises a virtual wall formed in an aperture in the side wall of the microchannel when the microchannel is filled with a liquid.
4. (Original) The microfluidic device of claim 1, wherein the actuator generates a gas bubble in the microchannel.
5. (Original) The microfluidic device of claim 4, further comprising a hydrophobic patch attached to an inner wall of the microchannel for anchoring the gas bubble.
6. (Original) The microfluidic device of claim 4, wherein the microchannel defines a cavity for retaining the gas bubble.
7. (Previously Presented) The microfluidic device of claim 1, wherein the gas filled first reservoir comprises a movable membrane.

8. (Original) The microfluidic device of claim 7, wherein the actuator deflects the movable membrane to create a bubble in the microchannel interior.

9. (Previously Presented) A microfluidic device comprising:

a first plate having a groove formed therein defining a microchannel;

a second plate for enclosing the microchannel bonded to the first plate having a first aperture formed on a first side of the groove sized and dimensioned to form a meniscus when the microchannel is filled with a liquid, the first aperture defining a first reservoir adjacent to the microchannel, wherein the meniscus forms an interface between the microchannel and the reservoir and a second reservoir formed on a second side of the groove opposite the first reservoir for absorbing pressure variations in the groove; and

a flexible membrane bonded to the second plate to seal the first reservoir.

10. (Original) The microfluidic device of claim 9, further comprising an actuator for deflecting the flexible membrane, wherein the deflection of the membrane increases the pressure in the reservoir and deflects the meniscus into the microchannel to regulate liquid flow therethrough.

11. (Original) The microfluidic device of claim 10, wherein the actuator comprises one of an electromagnetic element and a piezoelectric element.

12. (Original) The microfluidic device of claim 9, further comprising a hydrophobic patch attached to the groove.

13. (Original) The microfluidic device of claim 9, wherein the meniscus forms a bubble in the microchannel to block liquid flow.

14. (Original) The microfluidic device of claim 13, wherein the groove includes a cavity formed therein for retaining the bubble.

15. (Previously Presented) A microfluidic device, comprising:
a microchannel having an interior bounded by a side wall;
a first bubble valve for creating and injecting a bubble into the microchannel interior to regulate fluid flow through the microchannel;
a buffer in communication with the microchannel for absorbing a pressure variation in the microchannel caused by the bubble; and
a hydrophobic patch for retaining the bubble in a predetermined position in the microchannel interior.
16. (Original) The microfluidic device of claim 15, wherein the bubble valve comprises an aperture in the side wall, wherein a fluid in the microchannel forms a meniscus in the aperture, a sealed chamber formed adjacent to the aperture and an actuator for deflecting the meniscus into the interior by increasing the pressure in the chamber.
17. (Canceled).
18. (Canceled).
19. (Currently Amended) In a particle sorting device a bubble valve for separating particles having a predetermined characteristic from particles not having a predetermined characteristic, the bubble valve comprising:
a first gas-filled reservoir;
a ~~side~~ channel in communication with a channel through which a stream of particles in a carrier fluid passes, wherein the carrier fluid forms a meniscus in the side channel adjacent to the gas-filled reservoir;
an actuator for deflecting the meniscus to create a pressure pulse to selectively deflect a particle having the predetermined characteristic from the stream of particles; and
a second reservoir for absorbing the pressure pulse.
20. (Canceled).
21. (Canceled).

22. (Canceled).

23. (Canceled).

24. (Canceled).

25. (Previously Presented) A microfluidic device, comprising:
a channel for conveying a stream of particles in a carrier fluid;
an actuator for selectively applying a pressure pulse to the stream to deflect a particle in the stream of particles from the stream of particles; and
a buffer for absorbing the pressure pulse.

26. (Previously Presented) The device of claim 25, wherein the channel comprises an inlet, a first outlet and a second outlet, wherein the particles normally flow from the inlet into the first outlet.

27. (Previously Presented) The device of claim 26, wherein the pressure pulse deflects a particle in the stream of particles into the second outlet when a predetermined characteristic of the particle is detected.

28. (Previously Presented) The device of claim 25, further comprising a sensor for sensing a predetermined characteristic in a particle.

29. (Previously Presented) A microfluidic device, comprising:
a primary channel for conveying a stream of particles in a carrier fluid;
a first side channel in communication with the primary channel;
an actuator connected to the first side channel for applying a pressure pulse to the stream of particles to deflect a particle in the stream of particles from the stream of particles;
a second side channel in communication with the side channel; and
a buffer in communication with the second side channel for absorbing the pressure pulse.

30. (Previously Presented) The microfluidic device of claim 29, wherein the actuator comprises a flexible membrane.

31. (Previously Presented) The microfluidic device of claim 29, wherein the buffer comprises a flexible membrane.

32. (Previously Presented) The microfluidic device of claim 29, wherein the actuator comprises air trapped in a sealed reservoir.

33. (Previously Presented) The microfluidic device of claim 29, wherein the buffer comprises air trapped in a sealed reservoir.

REMARKS

The foregoing amendment amends claims 1 and 19. Pending in the application are claims 1-16, 19 and 25-33, of which claims 1, 9, 15, 19, 25 and 29 are independent. The following comments address all stated grounds for rejection and place the presently pending claims, as identified above, in condition for allowance.

Claim 1 is amended in line 6 change the word "liquid" to ---fluid--- and the word "channel" to ---microchannel--- to be consistent with other language in the claim.

Claim 19 amended in line 5 to delete the word "side" preceding "channel". *No new matter is added.*

Amendment of the claims is not to be construed as an acquiescence to any of the objections/rejections set forth in the instant Office Action, and was done solely to clarify the claim language. Applicants reserve the right to pursue the claims as originally filed, or similar claims, in this or one or more subsequent patent applications.

35 U.S.C. 102 Rejections

Applicants thank the Examiner for the close review of the claims and for indicating that claims 9-16 are allowed and that claims 4-6 recite allowable subject matter. In the Office Action, the Examiner rejects claims 1-6, 19, 25-29, 32 and 33, under 35 U.S.C. 102(b) as being anticipated by Dunaway (U.S. Patent Number 3,289,687). Applicants respectfully traverse the rejection and submit that claims 1-6, 19, 25-29, 32 and 33 distinguish patentably over the Dunaway reference. The Dunaway reference does not teach or suggest increasing pressure within a reservoir to influence fluid flow in a microchannel interior, as recited in independent claim 1. The Dunaway reference also does not teach or suggest a reservoir for absorbing a pressure variation or a pressure pulse in a channel generated by an actuator, as recited in independent claim 1, 19, 25 and 29. The Dunaway reference further lacks a teaching or suggestion of an actuator for applying a pressure pulse to a stream of particles in a channel to

deflect a particle in the stream of particles from the stream of particles, as set forth in independent claims 19, 25 and 29.

The Dunaway reference describes an actuator for a fluid amplifier that selectively redirects the flow path of an entire stream of fluid. The fluid amplifier of Dunaway includes a pair of exit ports 24 and 25 in communication with a chamber 27 through which a fluid stream flows. The fluid amplifier further includes a pair of offset orifices 28, 30 in communication with the chamber 27. Each orifice 28, 30 communicates with an aperture 32 or 34, respectively, that is selectively exposed or closed to atmosphere using an actuator. The actuator selectively opens one of the apertures 32 or 34 to create a differential pressure across the chamber 27, which acts across the fluid stream to force the path of the fluid stream towards one of the exit ports 24 or 26. When the actuator closes the first aperture 32 and opens the second aperture 34, the resulting pressure differential forces the fluid stream towards the first exit port 24. When the actuator opens the closes the second aperture 34 and opens the first aperture 32, the resulting pressure differential forces the fluid stream towards the second exit port 26. When both apertures are closed, the fluid stream is split between the two exit ports 24 or 26.

Claim 1 is allowable over the Dunaway reference for at least the following reasons. The chamber 27 of the Dunaway fluid amplifier is not a microchannel, as recited in claim 1. As set forth in the specification, a “microchannel” refers to a channel having cross-sectional dimensions in the range between about 1.0 μm and about 500 μm . Because the dimensions of the chamber 27 of Dunaway are very different from the dimensions of a microchannel, the fluid flowing through the chamber 27 of Dunaway will have vastly different properties. For example, fluid flow through the claimed microchannel will be laminar, while flow through the chamber 27 of Dunaway will not be laminar.

The Dunaway reference also does not teach or suggest *increasing* a pressure of a first gas-filled reservoir to control a flow through a microchannel, as recited in claim 1. Rather, Dunaway teaches selectively sealing one aperture to create a vacuum, i.e., to *decrease* the pressure therein, while maintaining the pressure in the other aperture at ambient pressure (exposed to atmosphere). Therefore, the Dunaway reference in fact teaches *away* from increasing a pressure of a gas-filled reservoir.

Furthermore, the Dunaway reference lacks a teaching or suggestion of a second reservoir or buffer for absorbing a pressure variation in a microchannel induced by an actuator, as set forth in claim 1, or for absorbing a pressure pulse created by an actuator, as set forth in claims 19, 25 and 29. Applicants submit that the actuator of Dunaway does not create a pressure variation or pressure pulse, which are transient increases in pressure, but rather a pressure differential *condition* between two openings. However, even if the pressure differential could be considered a pressure pulse or variation, the pressure differential created by selectively opening one of the apertures in Dunaway is not absorbed by a reservoir or buffer, but rather transferred *to the stream of fluid* to change the flow path of the entire stream. Assuming, *arguendo*, that one of the apertures 32 or 34 *did* generate a pressure pulse or variation, were the other of the apertures 34 or 32 to absorb such a pressure pulse or variation, no pressure differential would be applied to the fluid stream. However, the Dunaway reference *requires* that the pressure differential be applied to the fluid stream, because otherwise, the fluid stream would not be capable of moving between the exit ports. In contrast, the claimed second reservoir *prevents* the pressure variation or pulse from influencing the overall flow of fluid through a channel. Because selectively redirecting the path of a flow stream to one of a plurality of exit ports is an objective of the Dunaway reference, the Dunaway reference therefore teaches *away* from a second reservoir capable of absorbing a pressure variation or pressure pulse.

In addition, Applicants respectfully submit that the Dunaway reference also fails to teach or suggest using a pressure pulse to deflect a particle in a stream of particles flowing through a channel *from* the stream of particles, as recited in claims 19, 25 and 29. Rather, as described above, the Dunaway reference only teaches changing the path of an *entire* stream of fluid between two outlets. The ability to apply a pressure pulse to a stream allows for separation of selected particles from the stream, while a buffer for absorbing the pressure pulse prevents application of the pressure pulse to other particles in the stream, thereby ensuring that only the selected particle is deflected. There is no teaching or suggestion in Dunaway that a selected particle can be separated from the stream of fluid flowing through the fluid amplifier.

For at least these reasons, the Dunaway reference does not teach or suggest all of the features of claims 1-6, 19, 25-29, 32 and 33. As such, Applicants respectfully request that the rejection of these claims under 35 U.S.C. 102(b) be reconsidered and withdrawn.

35 U.S.C. 103 Rejections

Regarding the rejection of claims 7, 8, 19, 30 and 31 under 35 U.S.C. 103(a) as being unpatentable over the Dunaway reference in view of Cho, the claims are patentable over the Dunaway reference for the reasons described above.

In addition, there is no motivation to modify the device of Dunaway to include a “movable membrane.” In fact, the Dunaway reference teaches away from using a movable membrane, because the purpose of the actuator in Dunaway is to selectively expose the apertures 32 and 34 to atmosphere. Were the actuator to comprise a movable membrane, the apertures could not be exposed to atmosphere, and the device of Dunaway would fail to work.

For at least these reasons, pending claims 1-3, 16, 19 and 25-33 are patentable over the cited references. Because the Examiner has indicated claims 9-16 to be allowed, Applicants submit that all pending claims in the application are now in condition for allowance.


CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. If, however, the Examiner considers that obstacles to allowance of these claims persist, we invite a telephone call to Applicant's representative.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. TGZ-012 from which the undersigned is authorized to draw.

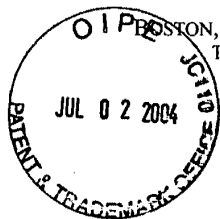
Dated: September 22, 2004

Respectfully submitted,

By 
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* Admitted in TX only
** Admitted in CT only

June 30, 2004

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Re: U.S. Patent Application No.: 10/179586
For: MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR
REGULATING FLUID FLOW THROUGH A MICROCHANNEL
Inventors: Gilbert, John *et al.*
Filed: June 24, 2002
Our Ref. No.: TGZ-012

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

1. Supplemental Information Disclosure Statement;
2. PTO Form SB-08;
3. Copies of references cited in PTO Form SB-08 (4);
4. A copy of the International Search Report; and
5. A Return Postcard.

Please charge \$180.00 due in connection with the enclosed statement to our Deposit
Order Account No. 12-0080. For this purpose, a duplicate of this sheet is attached.

I hereby certify that this correspondence is deposited with the
United States Postal Service as first class mail in an envelope
addressed to: MS Amendment, Commissioner for Patents, P.O.
Box 1450, Alexandria, Virginia 22313-1450:

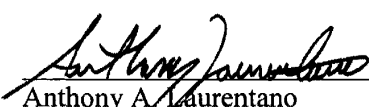
June 30, 2004

Date

Anthony A. Laurentano, Esq.

Reg. No. 38,220

Respectfully submitted,
LAHIVE & COCKFIELD, LLP


Anthony A. Laurentano
Registration No. 38,220
Attorney for Applicants



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Gilbert, John *et al.*

Serial No.: 10/179586

Filed: June 24, 2002

For: MICROFLUIDIC SYSTEM INCLUDING A
BUBBLE VALVE FOR REGULATING FLUID
FLOW THROUGH A MICROCHANNEL

Attorney Docket No.: TGZ-012

Group Art Unit: 3753

Examiner: Chambers, A.M.

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of First Class Mailing (37 CFR §1.8(a))

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 on the date set forth below.

June 30, 2004

Date of Signature and of Mail Deposit

By:



Anthony A. Laurentano

Reg. No. 38,220

Attorney for Applicants

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Applicants and their Attorney have become aware of the following publications and information, cited in an International Search Report mailed October 30, 2003 during the prosecution of PCT/US03/12360 which corresponds to the above-referenced application. In accordance with 37 CFR §1.97, Applicants hereby submit these publications for the Examiner's consideration. These publications are cited on the

07/07/2004 EFLURES 00000157 120080 10179586

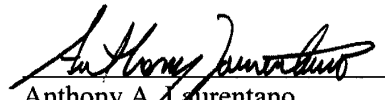
01 FC:1806 180.00 DA

enclosed PTO Form SB-08, and a copy of the Report and each publication cited thereon are enclosed as well.

This statement is not to be interpreted as a representation that the cited publications are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any publication herein be construed *per se* as a representation that such publication is prior art. Moreover, the Applicants understand that the Examiner will make an independent evaluation of the cited publications.

In accordance with 37 CFR §1.97(c)(2) and §1.17(p), please charge the \$180.00 submission fee to our Deposit Order Account No. 12-0080. Please charge any necessary additional fees or credit any overpayments to our Deposit Order Account No. 12-0080.

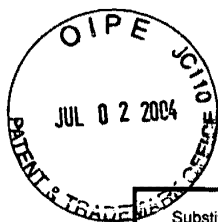
Respectfully submitted,
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Date: June 30, 2004

EAH/AAL/CMB/alf
Enclosures



PTO/SB/08a/b (08-03)
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Substitute for form 1449A/B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	10/179586
				Filing Date	June 24, 2002
				First Named Inventor	Gilbert, John
				Art Unit	3753
				Examiner Name	Chambers, A.M.
Sheet	1	of	1	Attorney Docket Number	TGZ-012

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	B1	4,676,274	06-30-1987	Brown	
	B2	5,065,978	11-19-1991	Albarda <i>et al.</i>	
	B3	5,092,972	03-03-1992	Ghowsi	
	B4	6,561,224 B1	05-13-2003	Cho	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/179,586	06/24/2002	John Richard Gilbert	TGZ-012	9/22
959	7590	06/22/2004		
LAHIVE & COCKFIELD, LLP. 28 STATE STREET BOSTON, MA 02109				
			EXAMINER CHAMBERS, A MICHAEL	
			ART UNIT 3753	PAPER NUMBER

DATE MAILED: 06/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/179,586	GILBERT ET AL.	
	Examiner	Art Unit	
	A. Michael Chambers	3753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16, 19 and 25-33 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 1-16, 19 and 25-33 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 31 March 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

1. This action is in response to an amendment filed April 26, 2004. Claims 1, 7, 9, 15 and 19 have been amended. Claims 17, 18 and 20-24 have been canceled. Claims 25-33 have been added. An informational disclosure document (IDS) filed July 23, 2003, has previously been examined. Claims 1-16, 19, and 25-33 are pending. Figures 16, and 17 A-C in newly submitted drawings filed March 31, 2004, are the best showings of the instant application microfluidic device.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-6, 19, 25-29, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Dunaway. Note Figures 1 in particular in which a “gas-filled reservoirs” 32 and 34 “pressure variation” responsive to fluid pressure valved by solenoid actuated valves shown in Figure 2. See column 48+. Applicants’ remarks, drawn to the teachings of Brown were considered, and in view of amendments to claims 1, 7, 9, 15 and 19 were deemed persuasive. With regard to claims 2 and 3, both a meniscus and bubbles would be a result of actuation of the valves of Figure 2.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

9. Claims 7, 8, 19, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunaway in view of Cho. Brown discloses a "hydrophobic patch" (125', 126', 127') in column 11, lines 43+. Dunaway discloses the claimed invention except for the recitation of a "movable membrane" as taught by Cho. Note the disclosure in Cho of the diaphragm "actuator" in column 7, lines 4+. A number of actuators are disclosed in column 7, lines 35+ including piezoelectric

and magnetic. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the microfluidic device of Dunaway to include a "movable membrane" actuator, as taught by Cho in order to provide more effective control of the passage 16, 19 of Dunaway.

Conclusion

11. Claims 4-6 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 9-16, which include particular microfluidic device first and second fluid reservoir geometric configuration are allowed.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The patents to Barth et al, Kim et al(2) and Field et al are of particular interest.

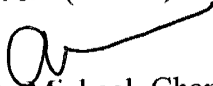
Any inquiry concerning this communication or earlier communications from the examiner should be directed to A. Michael Chambers whose telephone number is 703-308-1016. The examiner can normally be reached on Mon-Thur. 6:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Scherbel can be reached on 703-308-1272. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Application/Control Number: 10/179,586
Art Unit: 3753

Page 5

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


A. Michael Chambers
Primary Examiner
Art Unit 3753

amc
June 21, 2004

Notice of References Cited	Application/Control No. 10/179,586	Applicant(s)/Patent Under Reexamination GILBERT ET AL.	
	Examiner A. Michael Chambers	Art Unit 3753	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-3,289,687	12-1966	DUNAWAY J C	137/831
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 2001

Application or Docket Number

10/179586
CVZ-012

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	24	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	24 minus 20 =	* 4
INDEPENDENT CLAIMS	9 minus 3 =	* 6
MULTIPLE DEPENDENT CLAIM PRESENT <input type="checkbox"/>		

* If the difference in column 1 is less than zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

	(Column 1)	(Column 2)	(Column 3)
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	* 22	Minus ** 24	=
Independent	* 4	Minus *** 9	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

	(Column 1)	(Column 2)	(Column 3)
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus **	=
Independent	*	Minus ***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

	(Column 1)	(Column 2)	(Column 3)
AMENDMENT C	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus **	=
Independent	*	Minus ***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

SMALL ENTITY TYPE ☐

OR OTHER THAN SMALL ENTITY

RATE	FEE	RATE	FEE
BASIC FEE	370.00	BASIC FEE	740.00
X\$ 9=		X\$18=	72
X42=		X84=	504
+140=		+280=	
TOTAL		TOTAL	1316

RATE	ADDITIONAL FEE	RATE	ADDITIONAL FEE
X\$ 9=		X\$18=	
X42=		X84=	
+140=		+280=	
TOTAL ADDIT. FEE		TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE	RATE	ADDITIONAL FEE
X\$ 9=		X\$18=	
X42=		X84=	
+140=		+280=	
TOTAL ADDIT. FEE		TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE	RATE	ADDITIONAL FEE
X\$ 9=		X\$18=	
X42=		X84=	
+140=		+280=	
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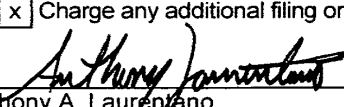
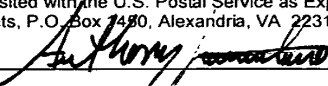
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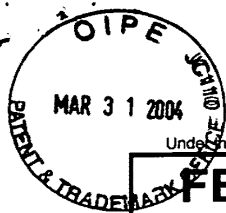


04-02-04

41

3753/\$

AMENDMENT TRANSMITTAL LETTER					Docket No. TGZ-012	
Application No. 10/179586-Conf. #9722		Filing Date June 24, 2002		Examiner A. M. Chambers		
				Art Unit 3753		
Applicant(s): John R. GILBERT <i>et al.</i>						
Invention: MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW THROUGH A MICROCHANNEL						
TO THE COMMISSIONER FOR PATENTS						
Transmitted herewith is an amendment in the above-identified application.						
The fee has been calculated and is transmitted as shown below.						
CLAIMS AS AMENDED						
	Claims Remaining After Amendment	Highest Number Previously Paid	Number Extra Claims Present	Rate		
Total Claims	26	- 24 =	2	x 9.00	18.00	
Independent Claims	6	- 9 =		x	0.00	
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>						
Other fee (please specify): Extension for response within third month					475.00	
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT:					493.00	
<input type="checkbox"/> Large Entity <input checked="" type="checkbox"/> Small Entity						
<input type="checkbox"/> No additional fee is required for this amendment.						
<input checked="" type="checkbox"/> Please charge Deposit Account No. 12-0080 in the amount of \$ 493.00 A duplicate copy of this sheet is enclosed.						
<input type="checkbox"/> A check in the amount of \$ _____ to cover the filing fee is enclosed.						
<input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.						
<input checked="" type="checkbox"/> The Director is hereby authorized to charge and credit Deposit Account No. 12-0080 as described below. A duplicate copy of this sheet is enclosed.						
<input checked="" type="checkbox"/> Credit any overpayment.						
<input checked="" type="checkbox"/> Charge any additional filing or application processing fees required under 37 CFR 1.16 and 1.17.						
 Anthony A. Laurentano Attorney Reg. No. 38,220 LAHIVE & COCKFIELD, LLP 28 State Street Boston, Massachusetts 02109 (617) 227-7400				Dated: March 31, 2004		
RECEIVED APR 08 2004 TECHNOLOGY CENTER R3700						
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Dated: March 31, 2004		Signature:  (Anthony A. Laurentano)				

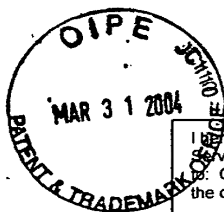


FEE TRANSMITTAL for FY 2004 <small>Effective 10/01/2003, Patent fees are subject to annual revision.</small>				Complete if Known																																	
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27				Application Number	10/179586-Conf. #9722																																
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493.00				First Named Inventor	John R. GILBERT																																
				Examiner Name	A. M. Chambers																																
				Art Unit	3753																																
				Attorney Docket No.	TGZ-012																																
METHOD OF PAYMENT (check all that apply)				FEE CALCULATION (continued)																																	
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** or number previously paid, if greater; For Reissues, see above																																					
SUBMITTED BY				(Complete if applicable)																																	
Name (Print/Type) Anthony A. Laurentano				Registration No. (Attorney/Agent)	38,220																																
Signature				Telephone	(617) 227-7400																																
				Date	March 31, 2004																																

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Dated: March 31, 2004

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Dated: March 31, 2004

Signature: 

(Anthony A. Laurentino)

Docket No.: TGZ-012
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
John R. Gilbert *et al.*

Application No.: 10/179586

Art Unit: 3753

Filed: June 24, 2002

Examiner: A. M. Chambers

For: MICROFLUIDIC SYSTEM INCLUDING A
BUBBLE VALVE FOR REGULATING FLUID
FLOW THROUGH A MICROCHANNEL

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

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APR 08 2004

TECHNOLOGY CENTER R3700

INTRODUCTORY COMMENTS

In response to the Office Action dated October 1, 2003 (Paper No. 9), the response period of which is extended to April 1, 2004 by the accompanying Request for Extension of Time, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims begin on page 2 of this paper.

Amendments to the Drawings begin on page 7 of this paper and include both an attached replacement sheet and an annotated sheet showing changes to Figures 16 and 17A-C.

Remarks/Arguments begin on page 8 of this paper.

04/05/2004 SDENB081 00000060 120080 10179586
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AMENDMENTS TO THE CLAIMS

Please amend claims 1, 7, 9, 15, and 19, cancel claims 17-18 and 20-24 and add new claims 25-33, as set forth in the following listing of claims, which will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently amended) A microfluidic device, comprising:
a microchannel having an interior bounded by a side wall;
a valve for regulating the flow of fluid through the microchannel, the valve comprising a gas-filled first reservoir, a fluid meniscus interfacing the reservoir and the interior and an actuator for varying the volume of the first reservoir to increase an internal pressure of the first reservoir to vary the flow of liquid through the channel; and
a second reservoir for absorbing a pressure variation in the microchannel induced by the actuator.
2. (Original) The microfluidic device of claim 1, wherein the actuator deflects the meniscus into the microchannel interior to regulate the flow of fluid through the microchannel.
3. (Original) The microfluidic device of claim 1, wherein the meniscus comprises a virtual wall formed in an aperture in the side wall of the microchannel when the microchannel is filled with a liquid.
4. (Original) The microfluidic device of claim 1, wherein the actuator generates a gas bubble in the microchannel.
5. (Original) The microfluidic device of claim 4, further comprising a hydrophobic patch attached to an inner wall of the microchannel for anchoring the gas bubble.
6. (Original) The microfluidic device of claim 4, wherein the microchannel defines a cavity for retaining the gas bubble.

7. (Currently amended) The microfluidic device of claim 1, wherein the gas filled first reservoir comprises a movable membrane.

8. (Original) The microfluidic device of claim 7, wherein the actuator deflects the movable membrane to create a bubble in the microchannel interior.

9. (Currently amended) A microfluidic device comprising:
a first plate having a groove formed therein defining a microchannel;
a second plate for enclosing the microchannel bonded to the first plate having ~~an~~ a first aperture ~~adjacent to~~ formed on a first side of the groove sized and dimensioned to form a meniscus when the microchannel is filled with a liquid, the first aperture defining a first reservoir adjacent to the microchannel, wherein the meniscus forms an interface between the microchannel and the reservoir and a second reservoir formed on a second side of the groove opposite the first reservoir for absorbing pressure variations in the groove; and
a flexible membrane bonded to the second plate to seal the first reservoir.

10. (Original) The microfluidic device of claim 9, further comprising an actuator for deflecting the flexible membrane, wherein the deflection of the membrane increases the pressure in the reservoir and deflects the meniscus into the microchannel to regulate liquid flow therethrough.

11. (Original) The microfluidic device of claim 10, wherein the actuator comprises one of an electromagnetic element and a piezoelectric element.

12. (Original) The microfluidic device of claim 9, further comprising a hydrophobic patch attached to the groove.

13. (Original) The microfluidic device of claim 9, wherein the meniscus forms a bubble in the microchannel to block liquid flow.

14. (Original) The microfluidic device of claim 13, wherein the groove includes a cavity formed therein for retaining the bubble.

15. (Currently amended) A microfluidic device, comprising:
a microchannel having an interior bounded by a side wall;
a first bubble valve for creating and injecting a bubble into the microchannel interior to regulate fluid flow through the microchannel;
a buffer in communication with the microchannel for absorbing a pressure variation in the microchannel caused by the bubble; and
a hydrophobic patch for retaining the bubble in a predetermined position in the microchannel interior.

16. (Original) The microfluidic device of claim 15, wherein the bubble valve comprises an aperture in the side wall, wherein a fluid in the microchannel forms a meniscus in the aperture, a sealed chamber formed adjacent to the aperture and an actuator for deflecting the meniscus into the interior by increasing the pressure in the chamber.

17. (Canceled)

18. (Canceled)

19. (Currently amended) In a particle sorting device a bubble valve for separating particles having a predetermined characteristic from particles not having a predetermined characteristic, the bubble valve comprising:
a first gas-filled reservoir;
a side channel in communication with a channel through which a stream of particles in a carrier fluid passes, wherein the carrier fluid forms a meniscus in the side channel adjacent to the gas-filled reservoir;
an actuator for deflecting the meniscus to create a pressure pulse to selectively deflect a particle having the predetermined characteristic from the stream of particles; and
a second reservoir for absorbing the pressure pulse.

20. (Canceled)

21. (Canceled)

22. (Canceled)

23. (Canceled)

24. (Canceled)

25. (NEW) A microfluidic device, comprising:
a channel for conveying a stream of particles in a carrier fluid;
an actuator for selectively applying a pressure pulse to the stream to deflect a particle in the stream of particles from the stream of particles; and
a buffer for absorbing the pressure pulse.

26. (NEW) The device of claim 25, wherein the channel comprises an inlet, a first outlet and a second outlet, wherein the particles normally flow from the inlet into the first outlet.

27. (NEW) The device of claim 26, wherein the pressure pulse deflects a particle in the stream of particles into the second outlet when a predetermined characteristic of the particle is detected.

28. (NEW) The device of claim 25, further comprising a sensor for sensing a predetermined characteristic in a particle.

29. (NEW) A microfluidic device, comprising:
a primary channel for conveying a stream of particles in a carrier fluid;
a first side channel in communication with the primary channel;
an actuator connected to the first side channel for applying a pressure pulse to the stream of particles to deflect a particle in the stream of particles from the stream of particles;
a second side channel in communication with the side channel; and
a buffer in communication with the second side channel for absorbing the pressure pulse.

30. (NEW) The microfluidic device of claim 29, wherein the actuator comprises a flexible membrane.

31. (NEW) The microfluidic device of claim 29, wherein the buffer comprises a flexible membrane.

32. (NEW) The microfluidic device of claim 29, wherein the actuator comprises air trapped in a sealed reservoir.

33. (NEW) The microfluidic device of claim 29, wherein the buffer comprises air trapped in a sealed reservoir

AMENDMENTS TO THE DRAWINGS

Please amend Figures 16-17A-C as set forth in the enclosed sheets of drawings. These sheets, which replace the original sheets including Figures 16 and 17A-C include certain reference numbers previously omitted.

Attachment: Replacement sheet
 Annotated sheet showing changes

REMARKS

The foregoing amendment cancels claims 17-18 and 20-24, amends claims 1, 7, 9, 15 and 19 and adds claims 25-33. The amendment also amends Figures 16 and 17A-C to include certain previously omitted reference numbers. Pending in the application are claims 1-16, 19 and 25-33, of which claims 1, 9, 15, 19, 25 and 29 are independent. The following comments address all stated grounds for rejection and place the presently pending claims, as identified above, in condition for allowance.

Claims 1, 9, 15 and 19 are amended to recite a reservoir (or buffer) for absorbing a pressure variation in a channel. Support for the amendments can be found in page 17, line 21 through page 18, line 23 of the specification and in Figures 16 and 17A-C. *No new matter is added.*

Amendment and/or cancellation of the claims are not to be construed as an acquiescence to any of the objections/rejections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed, or similar claims, in this or one or more subsequent patent applications.

Amendments to the Drawings

The foregoing amendment amends Figures 16 and 17A-17C to include certain reference numerals described in the specification but previously omitted from the drawings.

35 U.S.C. 102 Rejections

In the Office Action, the Examiner rejects claims 1-6 and 19 under 35 U.S.C. 102(b) as being anticipated by Brown, claims 23 and 24 under 35 U.S.C. 102(b) as being anticipated by Ghowsi, and claims 9-11 under 35 U.S.C. 102(e) as being anticipated by Cho. The amendment to the claims traverses the rejection and places the presently pending claims in condition for allowance, as the claimed features of the present invention are not found in the prior art, particularly the prior art cited in the Office Action.

For example, the cited references do not teach or suggest a microfluidic device including a reservoir or other component for absorbing pressure variations in a channel, as recited in independent claims 1, 9, 15, 19 and 25. In addition, the cited references do not teach or suggest a microfluidic device including a valve that varies the *volume* of a reservoir to vary the flow of liquid through an associated channel, as recited in independent claim 1. The cited references also do not teach or suggest a microfluidic including an actuator for deflecting a meniscus to create a pressure pulse to selectively *deflect* a particle having the predetermined characteristic from a stream of particles in an associated channel.

For example, the Brown reference describes a flow control system for controlling the flow of a principal fluid through a capillary. In the embodiments of Figures 14 and 17, cited by the Examiner, a chamber section of the capillary is first filled by closing a downstream control valve 119 and filling the chamber section with the principal fluid. The principal fluid is pumped from the chamber section by opening the control valve 119. The control valve 119 is selectively closed and opened by introducing or stopping gas pressure through a capillary gas passage 127.

The Brown reference does not teach or suggest that the control valve includes an actuator for varying the volume of a reservoir to increase an internal pressure of the reservoir to vary the flow of liquid through a channel. Rather, in Brown, a gas pressure is selectively introduced through a passage to stabilize an interface between the principal fluid and air. However, the volume of the chamber section 117, the capillary gas passage 127, and other components of the flow control system of Brown are constant, and do not vary, as recited in claim 1 of the present application.

Furthermore, the Brown reference does not teach or suggest selectively deflecting a particle having a predetermined characteristic from a stream of particles, as recited in claim 19. The Brown reference only describes a pumping action through a capillary, and includes no component capable of selectively deflecting a particle within the capillary.

In addition, the Brown reference also lacks a teaching or suggestion of a second reservoir for absorbing pressure variations, as recited in amended claims 1 and 19.

Claims 23 and 24 are canceled, thus obviating the rejection of claims 23 and 24 in view of the Ghowsi reference.

Regarding the rejection of claims 9-11 in view of the Cho reference, Applicants respectfully submit that the Cho reference also lacks a teaching or suggestion of a reservoir for absorbing pressure variations in a groove, as recited in claims 9-11. The Cho reference is directed to a valve for controlling fluid flow in a microfluidic system, which includes a diaphragm 131 that moves between a neutral position and a biased position to selectively block fluid flow. The diaphragm 131 divides a channel into a lower section 137 and an upper section 139. The upper section 139 includes a first contact 127 for selectively attracting the diaphragm to increase the volume of the lower section 137 to allow fluid flow therethrough, while blocking fluid flow through the upper section 139. The lower section 137 includes a second contact 129 for selectively attracting the diaphragm to increase the volume of the upper section 139 to allow fluid flow therethrough, while blocking fluid flow through the lower section 137. When the diaphragm is in the neutral position, capillary forces prevent the flow of fluid through the valve, as described in column 7, lines 55-67.

The Cho reference does not teach or suggest a meniscus forming an interface between a microchannel and a reservoir, as recited in claim 9. The Cho reference also does not teach or suggest a reservoir for absorbing pressure variations in a microchannel, as also recited in claim 9.

35 U.S.C. 103 Rejections

Regarding the rejection of claims 7, 8 and 12-18 under 35 U.S.C. 103(a) as being unpatentable over Brown in view of Cho, Applicants traverse the rejection and submit that claims 7, 8 and 12-16 are also patentable over the cited references. Claims 17 and 18 are canceled, obviating the rejection of these claims.

Regarding claims 7, 8, claim 1, from which claims 7 and 8 depend is patentable, therefore claims 7 and 8 are also patentable. Furthermore, the diaphragm of Cho does not create a *bubble* in the channel interior. Rather, as clearly set forth in column 7, line 55 through column

8, line 29, the Figure 5 of Cho depicts the fluid 119 on a microscopic level as bubbles, which adhere to, but are not formed by, the diaphragm.

Regarding claims 12-14, independent claim 9, from which claims 12-14 depend, is patentable over the cited references, as described above. Therefore, claims 12-14, which include the limitations of claim 9, are also patentable.

Regarding claim 15, the cited references do not teach or suggest a buffer in communication with a microchannel for absorbing a pressure variation in the microchannel caused by a bubble formed by a bubble valve.

Claims 20-22 are canceled, thus obviating the rejection of claims 20-22 under 35 U.S.C. 103(a) as being unpatentable over Figure 4 of Ghowsi.

New Claims

New claims 25-32 recite additional features neither taught nor suggested in the cited references. For example, independent claim 25 recites a microfluidic device including a buffer for absorbing a pressure pulse generated by an actuator for deflecting a particle in a stream of particles. As described above, the cited references do not teach or suggest a component capable of absorbing a pressure pulse in a channel.

Independent claim 29 is also patentable over the cited reference, because, as described above, the cited references do not teach or suggest a component capable of absorbing a pressure pulse in a channel.

For at least these reasons, pending claims 1-16, 19 and 25-33 are patentable over the cited references.

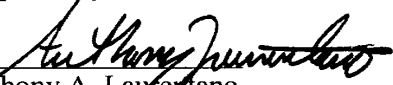
CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. TGZ-012 from which the undersigned is authorized to draw.

Dated: March 31, 2004

Respectfully submitted,

By 
Anthony A. Laurentano
Registration No.: 38,220
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney for Applicants

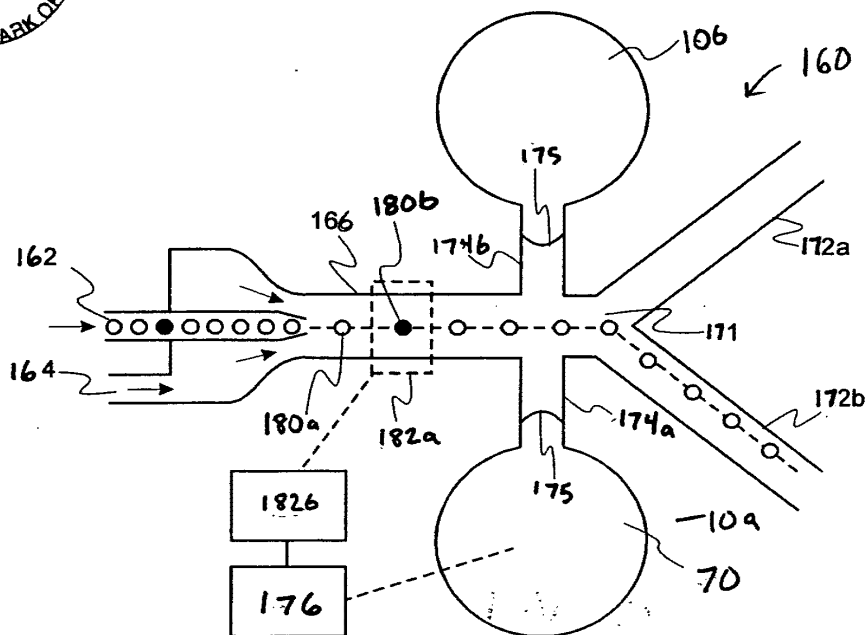
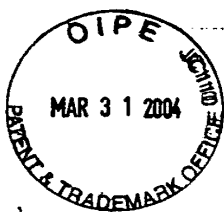


FIG. 16

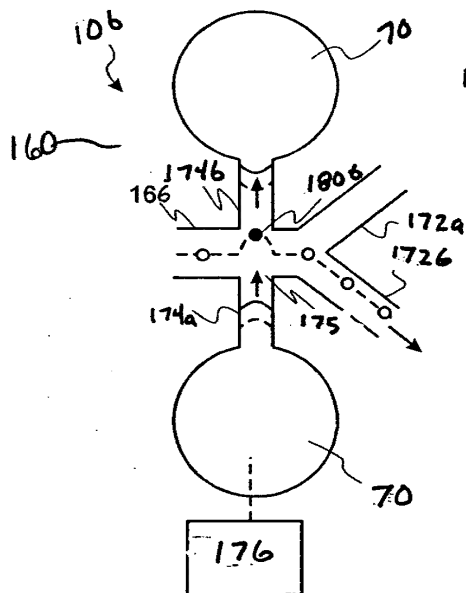


FIG. 17A

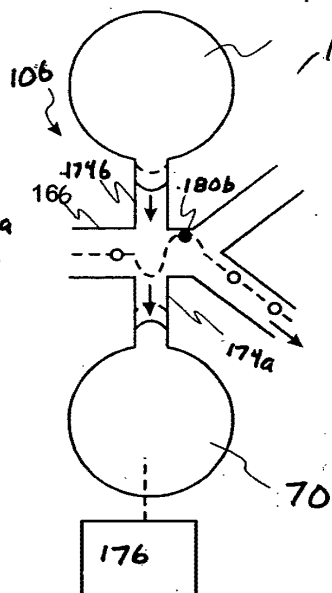


FIG. 17B

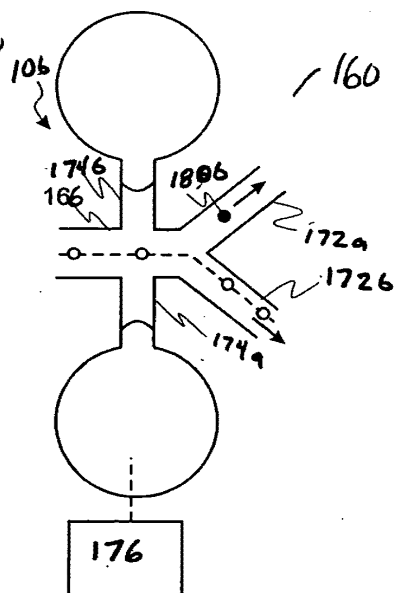


FIG. 17C

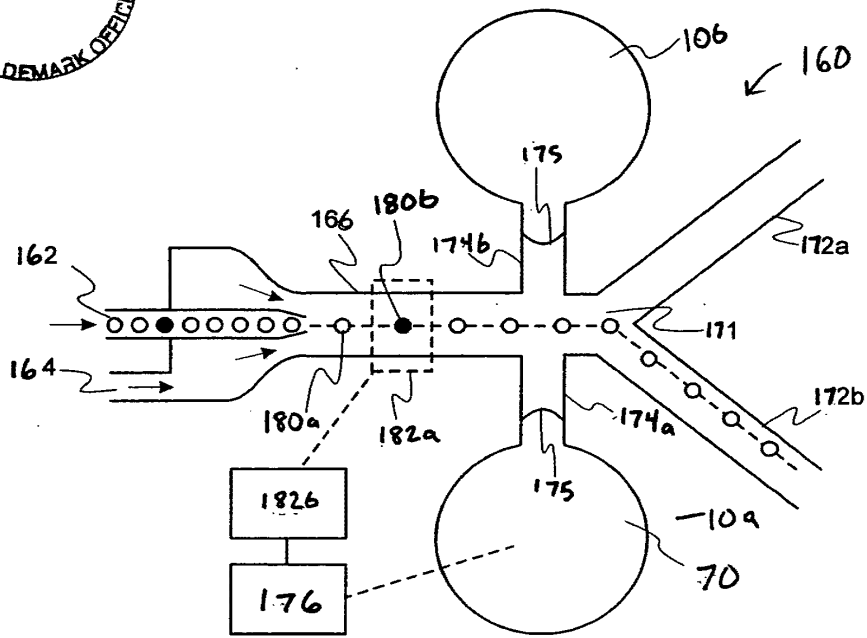


FIG. 16

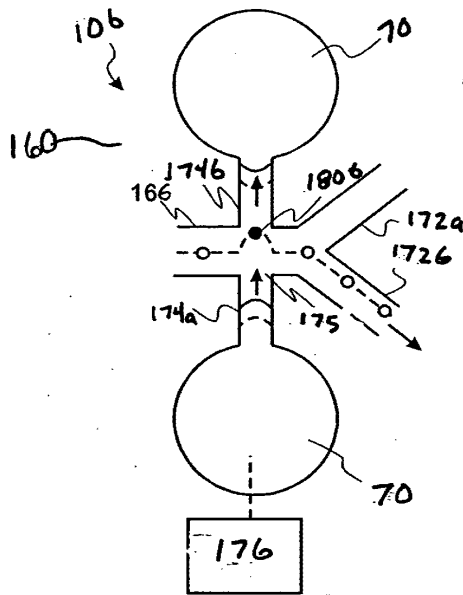


FIG. 17A

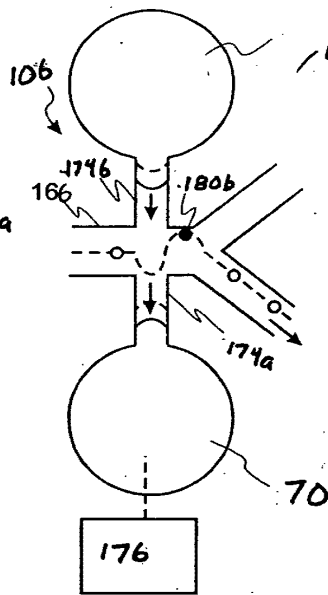


FIG. 17B

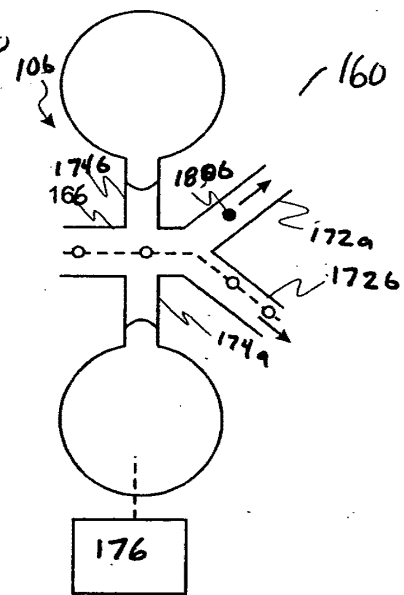


FIG. 17C



PTO/SB/22 (08-03)

Approved for use through 7/31/2006. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket No. (Optional)

TGZ-012

In re Application of John R. GILBERT *et al.*

Application Number

10/179586-Conf. #9722

Filed

June 24, 2002

For:

MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR
REGULATING FLUID FLOW THROUGH A MICROCHANNEL

Art Unit

3753

Examiner

A. M. Chambers

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

☐ One month (37 CFR 1.17(a)(1))☐ Two months (37 CFR 1.17(a)(2))☒ Three months (37 CFR 1.17(a)(3))☐ Four months (37 CFR 1.17(a)(4))☐ Five months (37 CFR 1.17(a)(5))

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TECHNOLOGY CENTER R3700

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\$	
\$	950.00
\$	
\$	

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: \$ 475.00

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 12-0080

I have enclosed a duplicate copy of this sheet.

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.

Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☐ attorney or agent of record. Registration Number

☒ attorney or agent under 37 CFR 1.34(a).

Registration number if acting under 37 CFR 1.34(a)

38,220

March 31, 2004

Date

(617) 227-7400

Telephone Number

Signature

Anthony A. Laurentano

Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below

☐ Total of 1 forms are submitted.

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail; Airbill No. EV378817679US, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: March 31, 2004

Signature:

(Anthony A. Laurentano)



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1/3

Fax Cover Sheet

Date: 18 Mar 2004

To: Catherine Bishop/Anthony Laurentano	From: A. Michael Chambers
Application/Control Number: 10/179,586	Art Unit: 3753
Fax No.: 703-308-7635	Phone No.: 703-308-1016
Voice No.:	Return Fax No.:
Re:	CC:
<input type="checkbox"/> Urgent <input checked="" type="checkbox"/> For Review <input type="checkbox"/> For Comment <input type="checkbox"/> For Reply <input checked="" type="checkbox"/> Per Your Request	

Comments:

Copy of Notice of Non-Compliant FAXED Amendment filed 01/07/04. I called and left a message earlier. Amendment has not been entered. Signature missing from last page. The rejection was mailed 10/01/03. Six months period for response expires 04/01/04..

VIA FAX (617) (742-4214)

Number of pages including this page

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/179,586	06/24/2002	John Richard Gilbert	TGZ-012	9722
959	7590	03/18/2004	EXAMINER	
LAHIVE & COCKFIELD, LLP. 28 STATE STREET BOSTON, MA 02109			CHAMBERS, A MICHAEL	
			ART UNIT	PAPER NUMBER
			3753	#12

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.



UNITED STATES PATENT AND TRADEMARK OFFICE

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Paper No.

Notice of Non-Compliant Amendment (37 CFR 1.121)

The amendment document filed on 11/7/04 is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121, as amended on June 30, 2003 (see 68 Fed. Reg. 38611, Jun. 30, 2003). In order for the amendment document to be compliant, correction of the following item(s) is required. **Only the corrected section of the non-compliant amendment document must be resubmitted (in its entirety), e.g., the entire "Amendments to the claims" section of applicant's amendment document must be re-submitted.** 37 CFR 1.121(h).

THE FOLLOWING CHECKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

- ☐ 1. Amendments to the specification:
- ☐ A. Amended paragraph(s) do not include markings.
 - ☐ B. New paragraph(s) should not be underlined.
 - ☐ C. Other _____
- ☐ 2. Abstract:
- ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
 - ☐ B. Other _____
- ☐ 3. Amendments to the drawings: _____
- ☐ 4. Amendments to the claims:
- ☐ A. A complete listing of all of the claims is not present.
 - ☐ B. The listing of claims does not include the text of all claims (including withdrawn claims)
 - ☐ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified.
 - ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
 - ☒ E. Other: Signature missing from last page.

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP Sec. 714 and the USPTO website at <http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/officeflyer.pdf>.

If the non-compliant amendment is a **PRELIMINARY AMENDMENT**, applicant is given ONE MONTH from the mail date of this letter to supply the corrected section which complies with 37 CFR 1.121. Failure to comply with 37 CFR 1.121 will result in non-entry of the preliminary amendment and examination on the merits will commence without consideration of the proposed changes in the preliminary amendment(s). This notice is not an action under 35 U.S.C. 132, and this ONE MONTH time limit is not extendable.

If the non-compliant amendment is a reply to a **NON-FINAL OFFICE ACTION** (including a submission for an RCE), and since the amendment appears to be a *bona fide* attempt to be a reply (37 CFR 1.135(c)), applicant is given a TIME PERIOD of ONE MONTH from the mailing of this notice within which to re-submit the corrected section which complies with 37 CFR 1.121 in order to avoid abandonment. **EXTENSIONS OF THIS TIME PERIOD ARE AVAILABLE UNDER 37 CFR 1.136(a).**

If the amendment is a reply to a **FINAL REJECTION**, this form may be an attachment to an Advisory Action. The period for response to a final rejection continues to run from the date set in the final rejection, and is not affected by the non-compliant status of the amendment.

X Cooper
Legal Instruments Examiner (LIE)

305/3439
Telephone No.

Rev. 10/03

Jan-07-04 14:10

From-LAHIVE & COCKFIELD, LLP

6177424214

T-352 P.01/13 F-853

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&
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* Admitted in TX only
** admitted in CT only

Facsimile Cover Sheet

To: Examiner A. Michael Chambers
Company: United States Patent and Trademark
Office; Art Unit 3753

Location:
Phone: 703-308-1016
Fax: 703-308-7765

From: Anthony A. Laurentano/Catherine M.
Bishop
Phone: (617) 227-7400
Fax: (617) 742-4214
Case No.: U.S. Appln Serial No. 10/179586
(Attorney Docket No. TGZ-012)

Date: 01/07/04
Sent By: CMB
**Pages including this
cover page:** 13

Message: Dear Examiner Chambers,

Thank you for your phone message regarding the above-referenced U.S. Patent Application. Attached please find a proposed draft response to the Office Action issued in connection with this case, which we would like to discuss with you in a telephone interview at your convenience. Please let us know when you are available.

Regards,
Catherine M. Bishop and Anthony A. Laurentano

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01/07/04 WED 13:10 [TX/RX NO 5394]

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Dated October 22, 2003 Signature _____ DRAFT _____

Docket No.: TG2 012
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Sebastian Böhm, *et al.*

Application No.: 10/179586

Art Unit: 3753

Filed: June 24, 2002

Examiner: A. Michael Chambers

For: MICROFLUIDIC SYSTEM INCLUDING A
BUBBLE VALVE FOR REGULATING FLUID
FLOW THROUGH A MICROCHANNEL

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

MS Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Office Action dated October 1, 2003 (Paper No. 9), please amend the above-identified U.S. patent application as follows:

Amendments to the Claims begin on page 2 of this paper.

Amendments to the Drawings begin on page 7 of this paper and include attached replacement sheets including changes to Figures 16 and 17A-C.

Remarks/Arguments begin on page 8 of this paper.

01/14/2004 TTUT2 00000001 120000 10179586
01 FC:1631 110,00 00

01/07/04 WED 13:10 [TX/RX NO 5394]

Application No.: 10/179586

Docket No.: TGZ-012

AMENDMENTS TO THE CLAIMS**PLEASE AMEND CLAIMS 1, 7, 9, 15, and 17-19 AS FOLLOWS.****PLEASE CANCEL CLAIMS 20-24.****PLEASE ADD CLAIMS 25-30 AS FOLLOWS.**

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently amended) A microfluidic device, comprising:
a microchannel having an interior bounded by a side wall;
a valve for regulating the flow of fluid through the microchannel, the valve comprising a gas-filled first reservoir, a fluid meniscus interfacing the reservoir and the interior and an actuator for varying the volume of the first reservoir to increase an internal pressure of the first reservoir to vary the flow of liquid through the channel; and
a second reservoir for absorbing a pressure variation in the microchannel induced by the actuator.
2. (Original) The microfluidic device of claim 1, wherein the actuator deflects the meniscus into the microchannel interior to regulate the flow of fluid through the microchannel.
3. (Original) The microfluidic device of claim 1, wherein the meniscus comprises a virtual wall formed in an aperture in the side wall of the microchannel when the microchannel is filled with a liquid.
4. (Original) The microfluidic device of claim 1, wherein the actuator generates a gas bubble in the microchannel.
5. (Original) The microfluidic device of claim 4, further comprising a hydrophobic patch attached to an inner wall of the microchannel for anchoring the gas bubble.
6. (Original) The microfluidic device of claim 4, wherein the microchannel defines a cavity for retaining the gas bubble.

Application No.: 10/179586

Docket No.: TGZ 012

7. (Currently amended) The microfluidic device of claim 1, wherein the gas filled first reservoir comprises a movable membrane.
8. (Original) The microfluidic device of claim 7, wherein the actuator deflects the movable membrane to create a bubble in the microchannel interior.
9. (Currently amended) A microfluidic device comprising:
a first plate having a groove formed therein defining a microchannel;
a second plate for enclosing the microchannel bonded to the first plate having ~~an~~ a first aperture ~~adjacent to~~ formed on a first side of the groove sized and dimensioned to form a meniscus when the microchannel is filled with a liquid, the first aperture defining a first reservoir adjacent to the microchannel, wherein the meniscus forms an interface between the microchannel and the reservoir and a second reservoir formed on a second side of the groove opposite the first reservoir for absorbing pressure variations in the groove; and
a flexible membrane bonded to the second plate to seal the first reservoir.
10. (Original) The microfluidic device of claim 9, further comprising an actuator for deflecting the flexible membrane, wherein the deflection of the membrane increases the pressure in the reservoir and deflects the meniscus into the microchannel to regulate liquid flow therethrough.
11. (Original) The microfluidic device of claim 10, wherein the actuator comprises one of an electromagnetic element and a piezoelectric element.
12. (Original) The microfluidic device of claim 9, further comprising a hydrophobic patch attached to the groove.
13. (Original) The microfluidic device of claim 9, wherein the meniscus forms a bubble in the microchannel to block liquid flow.
14. (Original) The microfluidic device of claim 13, wherein the groove includes a cavity formed therein for retaining the bubble.

Application No.: 10/179586

Docket No.: TGZ-012

15. (Currently amended) A microfluidic device, comprising:
a microchannel having an interior bounded by a side wall;
a first bubble valve for creating and injecting a bubble into the microchannel interior to regulate fluid flow through the microchannel;
a buffer in communication with the microchannel for absorbing a pressure variation in the microchannel caused by the bubble; and
a hydrophobic patch for retaining the bubble in a predetermined position in the microchannel interior.
16. (Original) The microfluidic device of claim 15, wherein the bubble valve comprises an aperture in the side wall, wherein a fluid in the microchannel forms a meniscus in the aperture, a sealed chamber formed adjacent to the aperture and an actuator for deflecting the meniscus into the interior by increasing the pressure in the chamber.
17. (Canceled)
18. (Canceled)
19. (Currently amended) In a particle sorting device a bubble valve for separating particles having a predetermined characteristic from particles not having a predetermined characteristic, the bubble valve comprising:
a first gas-filled reservoir;
a side channel in communication with a channel through which a stream of particles in a carrier fluid passes, wherein the carrier fluid forms a meniscus in the side channel adjacent to the gas-filled reservoir;
an actuator for deflecting the meniscus to create a pressure pulse to selectively deflect a particle having the predetermined characteristic from the stream of particles; and
a second reservoir for absorbing the pressure pulse.
20. (Canceled)

Application No.: 10/179586

Docket No.: TGZ 012

21. (Canceled)

22. (Canceled)

23. (Canceled)

24. (Canceled)

25. (NEW) A microfluidic device, comprising:

a channel for conveying a stream of particles in a carrier fluid;

an actuator for selectively applying a pressure pulse to the stream to deflect a particle in the stream of particles from the stream of particles; and

a buffer for absorbing the pressure pulse.

al

26. (NEW) The device of claim 25, wherein the channel comprises an inlet, a first outlet and a second outlet, wherein the particles normally flow from the inlet into the first outlet.

27. (NEW) The device of claim 26, wherein the pressure pulse deflects a particle in the stream of particles into the second outlet when a predetermined characteristic of the particle is detected.

28. (NEW) The device of claim 25, further comprising a sensor for sensing a predetermined characteristic in a particle.

29. (NEW) A microfluidic device, comprising:

a primary channel for conveying a stream of particles in a carrier fluid;

a first side channel in communication with the primary channel;

an actuator connected to the first side channel for applying a pressure pulse to the stream of particles to deflect a particle in the stream of particles from the stream of particles;

a second side channel in communication with the side channel; and

a buffer in communication with the second side channel for absorbing the pressure pulse.

Application No.: 10/179586

Docket No.: TG2 012

30. (NEW) The microfluidic device of claim 29, wherein the actuator comprises a flexible membrane.

31. (NEW) The microfluidic device of claim 29, wherein the buffer comprises a flexible membrane.

32. (NEW) The microfluidic device of claim 29, wherein the actuator comprises air trapped in a sealed reservoir.

33. (NEW) The microfluidic device of claim 29, wherein the buffer comprises air trapped in a sealed reservoir

Application No.: 10/179586

Docket No.: TGZ-012

AMENDMENTS TO THE DRAWINGS

Please amend Figures 16-17A-C as set forth in the enclosed sheets of drawings. These sheets, which replace the original sheets including Figures 16 and 17A-C include certain reference numbers previously omitted.

Application No.: 10/179586

Docket No.: TGZ 012

REMARKS

The foregoing amendment cancels claims 20-24, amends claims 1, 7, 9, 15 and 17-19 and adds claims 25-33. The amendment also amends Figures 16 and 17A-C to include certain previously omitted reference numbers. Pending in the application are claims 1-19 and 25-33 of which claims 1, 9, 15, 17, 18, 19, 25 and 29 are independent. The following comments address all stated grounds for rejection and place the presently pending claims, as identified above, in condition for allowance.

Claims 1, 9, 15 and 19 are amended to recite a reservoir (or buffer) for absorbing a pressure variation in a channel. Support for the amendments can be found in page 17, line 21 through page 18, line 23 of the specification and in Figures 16 and 17A-C. *No new matter is added*

Amendment and/or cancellation of the claims are not to be construed as an acquiescence to any of the objections/rejections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed, or similar claims, in this or one or more subsequent patent applications.

35 U.S.C. 102 Rejections

In the Office Action, the Examiner rejects claims 1-6 and 19 under 35 U.S.C. 102(b) as being anticipated by Brown, claims 23 and 24 under 35 U.S.C. 102(b) as being anticipated by Ghowsi, and claims 9-11 under 35 U.S.C. 102(e) as being anticipated by Cho. The amendment to the claims traverses the rejection and places the presently pending claims in condition for allowance, as the claimed features of the present invention are not found in the prior art, particularly the prior art cited in the Office Action. For example, the cited references do not teach or suggest a microfluidic device including a reservoir or other component for absorbing pressure variations in a channel, as recited in independent claims 1, 9, 15, 19 and 25. In addition, the cited references do not teach or suggest a microfluidic device including a valve that varies the *volume* of a reservoir to vary the flow of liquid through an associated channel, as recited in independent claim 1. The cited references also do not teach or suggest a microfluidic

Application No.: 10/179586

Docket No.: TGZ-012

including an actuator for deflecting a meniscus to create a pressure pulse to selectively *deflect* a particle having the predetermined characteristic from a stream of particles in an associated channel.

For example, the Brown reference describes a flow control system for controlling the flow of a principal fluid through a capillary. In the embodiments of Figures 14 and 17, cited by the Examiner, a chamber section of the capillary is first filled by closing a downstream control valve 119 and filling the chamber section with the principal fluid. The principal fluid is pumped from the chamber section by opening the control valve 119. The control valve 119 is selectively closed and opened by introducing or stopping gas pressure through a capillary gas passage 127.

The Brown reference does not teach or suggest that the control valve includes an actuator for varying the volume of a reservoir to increase an internal pressure of the reservoir to vary the flow of liquid through a channel. Rather, in Brown, a gas pressure is selectively introduced through a passage to stabilize an interface between the principal fluid and air. However, the volume of the chamber section 117, the capillary gas passage 127, and other components of the flow control system of Brown are constant, and do not vary, as recited in claim 1 of the present application.

Furthermore, the Brown reference does not teach or suggest selectively deflecting a particle having a predetermined characteristic from a stream of particles, as recited in claim 19. The Brown reference only describes a pumping action through a capillary, and includes no component capable of selectively deflecting a particle within the capillary.

In addition, the Brown reference also lacks a teaching or suggestion of a second reservoir for absorbing pressure variations, as recited in amended claims 1 and 19.

Claims 23 and 24 are canceled, thus obviating the rejection of claims 23 and 24 in view of the Ghowsi reference.

Regarding the rejection of claims 9-11 in view of the Cho reference, Applicants respectfully submit that the Cho reference also lacks a teaching or suggestion of a reservoir for

Application No.: 10/179586

Docket No.: TGZ 012

absorbing pressure variations in a groove, as recited in claims 9-11. The Cho reference is directed to a valve for controlling fluid flow in a microfluidic system, which includes a diaphragm 131 that moves between a neutral position and a biased position to selectively block fluid flow. The diaphragm 131 divides a channel into a lower section 137 and an upper section 139. The upper section 139 includes a first contact 127 for selectively attracting the diaphragm to increase the volume of the lower section 137 to allow fluid flow therethrough, while blocking fluid flow through the upper section 139. The lower section 137 includes a second contact 129 for selectively attracting the diaphragm to increase the volume of the upper section 139 to allow fluid flow therethrough, while blocking fluid flow through the lower section 137. When the diaphragm is in the neutral position, capillary forces prevent the flow of fluid through the valve, as described in column 7, lines 55-67.

The Cho reference does not teach or suggest a meniscus forming an interface between a microchannel and a reservoir, as recited in claim 9. The Cho reference also does not teach or suggest a reservoir for absorbing pressure variations in a microchannel, as also recited in claim 9.

35 U.S.C. 103 Rejections

Regarding the rejection of claims 7, 8 and 12-18 under 35 U.S.C. 103(a) as being unpatentable over Brown in view of Cho, Applicants traverse the rejection and submit that claims 7, 8 and 12-18 are also patentable over the cited references.

Regarding claims 7, 8, claim 1, from which claims 7 and 8 depend is patentable, therefore claims 7 and 8 are also patentable. Furthermore, the diaphragm of Cho does not create a bubble in the channel interior. Rather, as clearly set forth in column 7, line 55 through column 8, line 29, the Figure 5 of Cho depicts the fluid 119 on a microscopic level as bubbles, which adhere to, but are not formed by, the diaphragm.

Regarding claims 12-14, independent claim 9, from which claims 12-14 depend, is patentable over the cited references, as described above. Therefore, claims 12-14, which include the limitations of claim 9, are also patentable.

Application No.: 10/179586

Docket No.: TGZ-012

Regarding claim 15, the cited references do not teach or suggest a buffer in communication with a microchannel for absorbing a pressure variation in the microchannel caused by a bubble formed by a bubble valve.

The cited references also do not teach or suggest the methods of making a bubble valve recited in claim 17 and claim 18. Specifically, the cited references do not teach or suggest coupling an external actuator to a microfluidic chip. The cited references also do not teach or suggest an external actuator that selectively increases the pressure in a valve chamber to deflect a meniscus into an interior.

Claims 20-22 are canceled, thus obviating the rejection of claims 20-22 under 35 U.S.C. 103(a) as being unpatentable over Figure 4 of Ghowsi.

New Claims

New claims 25-32 recite additional features neither taught nor suggested in the cited references. For example, independent claim 25 recites a microfluidic device including a buffer for absorbing a pressure pulse generated by an actuator for deflecting a particle in a stream of particles. As described above, the cited references do not teach or suggest a component capable of absorbing a pressure pulse in a channel.

Independent claim 29 is also patentable over the cited reference, because, as described above, the cited references do not teach or suggest a component capable of absorbing a pressure pulse in a channel.

For at least these reasons, pending claims 1-19 and 25-33 are patentable over the cited references.

Application No.: 10/179586

Docket No.: TGZ-012

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. TGZ-012 from which the undersigned is authorized to draw.

Dated:

Respectfully submitted,

By **DRAFT**
Anthony A. Laurentano
Registration No.: 38,220
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/179,586	06/24/2002	John Richard Gilbert	TGZ-012	9722
959	7590	10/01/2003		
LAHIVE & COCKFIELD 28 STATE STREET BOSTON, MA 02109				
EXAMINER CHAMBERS, A MICHAEL				
ART UNIT		PAPER NUMBER		
3753				

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/179,586		Applicant(s) GILBERT ET AL.	
	Examiner A. Michael Chambers		Art Unit 3753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on ____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-24 is/are pending in the application.

4a) Of the above claim(s) ____ is/are withdrawn from consideration.

5) ☐ Claim(s) ____ is/are allowed.

6) ☒ Claim(s) 1-24 is/are rejected.

7) ☐ Claim(s) ____ is/are objected to.

8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>3</u> .	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____. 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) 6) <input type="checkbox"/> Other:
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Art Unit: 3753

DETAILED ACTION

1. This application has been examined. An informational disclosure document (IDS) filed July 23, 2003, has been examined. Claims 1-24 are pending.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-6 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown.

Note Figures 14 and 17 in particular in which a “gas-filled reservoir” responsive to fluid pressure in Figure 14. Actuator recitation is readable on the gas pressure source through inlet 125.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Art Unit: 3753

5. Claims 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Figure 2 of Ghowsi. A voltage source is shown.

6. Claims 9-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Cho.

Note the disclosure of the diaphragm “actuator” in column 7, lines 4+. A number of actuators are disclosed in column 7, lines 35+ including piezoelectric and magnetic.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Art Unit: 3753

9. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

10. Claims 7, 8, and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown in view of Cho. Brown discloses a “hydrophobic patch” (125', 126', 127') in column 11, lines 43+. Brown discloses the claimed invention except for the recitation of a “movable membrane” as taught by Cho. Note the disclosure in Cho of the diaphragm “actuator” in column 7, lines 4+. A number of actuators are disclosed in column 7, lines 35+ including piezoelectric and magnetic. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the microfluidic device of Brown to include a “movable membrane” actuator, as taught by Cho in order to provide more effective control of the bubble controlled via passage 125 of Brown. It further would have been obvious to one of ordinary skill in the art to operate the modified “valve” of Brown in view of Cho by the recited method steps (claims 17-19).

11. Claims 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Figure 4 of Ghowsi. Note the resistance measuring apparatus 14. It would have been obvious to one having ordinary skill in the art at the time the invention was made to operate the microchannel of Wapner et al by the recited method steps.

Art Unit: 3753

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The patents to Barth et al, Kim et al(2) and Field et al are of particular interest.

13. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to A. Michael Chambers whose telephone number is 703-308-1016. The examiner can normally be reached on Mon-Thur. 6:30am-5:00pm.

14. If attempts to reach the Examiner by telephone are unsuccessful, the examiner's supervisor, John Rivell can be reached on 703-308-2599. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9302 for regular communications and 703-872-9303 for After Final communications.

15. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0851.



**A. MICHAEL CHAMBERS
PRIMARY EXAMINER
ART UNIT 3753**

amc
September 25, 2003

FORM PTO-892		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		SERIAL NO. 10/179,586	GROUP ART UNIT 3753	ATTACHMENT TO PAPER NO.	9
NOTICE OF REFERENCES CITED				APPLICANT(S) Gilbert et al			
U.S. PATENT DOCUMENTS							
*		DOCUMENT NO.	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	A	4,426,451	1/1984	Columbus	436	518	
	B	4,676,274	6/1987	Brown	137	806	
	C	4,908,112	3/1990	Pace	210	19□2	
	D	5,065,978	11/1991	Albarda et al.	257	419	
	E	5,092,972	3/1992	Ghowi	204	454	
	F	5,789,045	8/1998	Wapner et al	137	807	
	G	6,152,181	11/2000	Wapner et al.	137	807	
	H	6,561,224	5/2003	Cho	137	831	
	I						
	J						
	K						
FOREIGN PATENT DOCUMENTS							
*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB- CLASS
	L						
	M						
	N						
	O						
	P						
	Q						
OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)							
	R						
	S						
	T						
	U						
EXAMINER A. Michael Chambers			DATE September 25, 2003		Form892ccs2106b		
* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05(a).)							

APPLICANT FACSIMILE OF FORM PTO-1449 REV 7-80	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY DOCKET NO CVZ-012	SERIAL NO. 10/179586
LIST OF PUBLICATIONS CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT John Gilbert, et al.	
		FILING DATE June 24, 2002	GROUP 3753

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
<i>Am</i>	A1	5,777,649	07/98	Otsuka et al.	347	94	
<i>Am</i>	A2	6,048,734	04/00	Burns et al.	436	180	
<i>Am</i>	A3	6,062,681	05/00	Field et al.	347	65	
<i>Am</i>	A4	6,102,530	08/00	Kim et al.	347	65	
<i>Am</i>	A5	6,196,525 B1	03/01	Ganan-Calvo	261	76	
<i>Am</i>	A6	6,273,553 B1	08/01	Kim et al.	347	48	
<i>Am</i>	A7	6,360,775 B1	03/02	Barth et al.	137	828	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
<i>Am</i>	A8	WO 98/07069 A1	02/98	PCT				

OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

Examiner	<i>Am</i>	Date Considered	<i>09/03</i>
*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.			

L Number	Hits	Search Text	DB	Time stamp
1	4	137/830.ccls. and bubble	USPAT; US-PGPUB	2003/09/25 14:44
2	4	137/831.ccls. and bubble	USPAT; US-PGPUB	2003/09/25 14:44
3	14	137/827.ccls. and bubble	USPAT; US-PGPUB	2003/09/25 14:57
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7	1	"6561224"	USPAT; US-PGPUB	2003/09/25 15:16
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11	112	137/827.ccls.	USPAT; US-PGPUB	2003/09/25 17:17
12	194	137/833.ccls.	USPAT; US-PGPUB	2003/09/25 17:17
13	2110	electrokinetic	USPAT; US-PGPUB	2003/09/25 17:17
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17	109875	hydrophobic	USPAT; US-PGPUB	2003/09/25 17:17
18	0	(137/827.ccls. and electrokinetic) and hydrophobic	USPAT; US-PGPUB	2003/09/25 17:17
19	56185	piezoelectric	USPAT; US-PGPUB	2003/09/25 17:17
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21	0	(137/827.ccls. and electrokinetic) and piezoelectric	USPAT; US-PGPUB	2003/09/25 17:17
22	15	137/833.ccls. and piezoelectric	USPAT; US-PGPUB	2003/09/25 17:17
31	95	137/806.ccls.	USPAT; US-PGPUB	2003/09/25 17:17
10	28	137/571.ccls. and sensor?	USPAT	2003/09/25 17:17
14	6	137/827.ccls. and electrokinetic	USPAT; US-PGPUB	2003/09/25 17:17
15	3	(137/827.ccls. and electrokinetic) and bubble	USPAT; US-PGPUB	2003/09/25 17:17
23	2	(137/833.ccls. and piezoelectric) and bubble	USPAT; US-PGPUB	2003/09/25 17:17
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25	8	("4859301" "4908112" "5092972" "5126022" "5282942" "5374834" "5429734" "5660703").PN.	USPAT	2003/09/25 17:17

Search History 9/25/03 5:17:23 PM Page 1

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28	14	137/833.ccls. and electrokinetic	USPAT; US-PGPUB	2003/09/25 17:17
29	6	137/827.ccls. and electrokinetic	USPAT; US-PGPUB	2003/09/25 17:17

L Number	Hits	Search Text	DB	Time stamp
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2	112	137/827.ccls.	USPAT; US-PGPUB	2003/09/25 09:53
3	194	137/833.ccls.	USPAT; US-PGPUB	2003/09/25 09:54
4	2110	electrokinetic	USPAT; US-PGPUB	2003/09/25 09:54
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8	109875	hydrophobic	USPAT; US-PGPUB	2003/09/25 09:57
9	0	(137/827.ccls. and electrokinetic) and hydrophobic	USPAT; US-PGPUB	2003/09/25 09:57
10	56185	piezoelectric	USPAT; US-PGPUB	2003/09/25 09:58
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14	2	(137/833.ccls. and piezoelectric) and bubble	USPAT; US-PGPUB	2003/09/25 09:59
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16	12	137/833.ccls. and hydrophobic	USPAT; US-PGPUB	2003/09/25 10:10
17	8	("4859301" "4908112" "5092972" "5126022" "5282942" "5374834" "5429734" "5660703").PN.	USPAT	2003/09/25 10:11
18	50	("3191623" "3327726" "3417770" "3799742" "3993062" "4426451" "4618476" "4676274" "4756884" "4868129" "4946795" "4963498" "5051182" "5077017" "5104813" "5119116" "5223219" "5230866" "5304487" "5378504" "5427946" "5486335" "5498392" "5587128" "5635358" "5637469" "5726026" "5726404" "5730187" "5846396" "5856174" "5866345" "5869004" "5900130" "5910287" "5922591" "5922604" "5928880" "5955029" "5958344" "5976336" "5980719" "5992820" "6004515" "6043080" "6046056" "6048498" "6068752" "6086740" "6086825").PN.	USPAT	2003/09/25 10:14

Search History 9/25/03 10:20:43 AM Page 1

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

7-9-03
#8

In re the application of: John Gilbert *et al.*

Serial No.: 10/179,586

Filed: June 24, 2002

For: *Microfluidic System Including a Bubble Valve for
Regulating Fluid Flow Through a Microchannel*

Attorney Docket No.: TGZ-012

(Formerly CVZ-012)

Group Art Unit: 3753

Examiner: *Not yet assigned*

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MAY 30 2003

TECHNOLOGY CENTER R3700

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

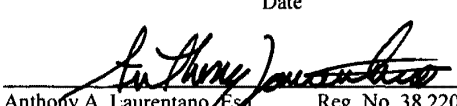
NOTIFICATION OF CHANGE OF ATTORNEY DOCKET NUMBER

Sir:

The Attorney Docket Number of the above-identified patent application has changed.
Please take notice that the correct docket number for this application should now be as follows:

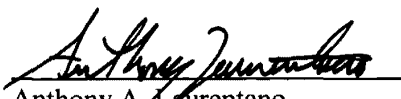
“TGZ-012” instead of “CVZ-012.”

Please reference **TGZ-012** on all future correspondence.

Certificate of First Class Mailing (37 CFR 1.8(a))	
I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on:	
May 27, 2003	_____
Date	_____
	_____
Anthony A. Laurentano, Esq.	Reg. No. 38,220

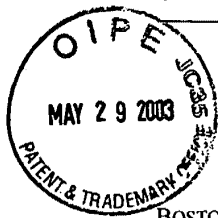
Respectfully submitted,

LAHIVE & COCKFIELD, LLP


Anthony A. Laurentano
Registration No. 38,220
Attorney for Applicants

Dated: May 27, 2003

3753



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* Admitted in TX only
** Admitted in CT only

May 27, 2003

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P.O. Box 1450
Alexandria, VA 22313-1450

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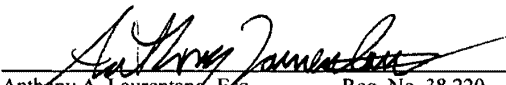
Re: U.S. Patent Application Serial No. 10/179,586
Filed: June 24, 2002
Title: *Microfluidic System Including a Bubble Valve for
Regulating Fluid Flow Through a Microchannel*
Inventor: John Gilbert *et al.*
Our Reference No.: TGZ-012 (formerly CVZ-012)

Dear Sir:

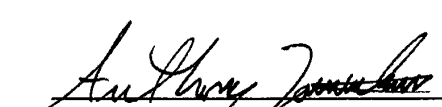
I enclose herewith for filing in the above-identified application the following:

1. Notification of Change of Attorney Docket Number (1 page, *in duplicate*); and
2. Acknowledgment postcard.

Please charge any necessary fees to our Deposit Account No. 12-0080. The undersigned requests any extensions of time necessary to respond. *A duplicate of this sheet is enclosed.*

Certificate of First Class Mailing (37 CFR 1.8(a))	
I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on:	
May 27, 2003	
Date	
	
Anthony A. Laurentano, Esq.	Reg. No. 38,220

Respectfully submitted,
LAHIVE & COCKFIELD, LLP


Anthony A. Laurentano
Reg. No. 38,220
Attorney for Applicants

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: John Gilbert, *et al.*

Serial No.: 10/179586

Filed: June 24, 2002

For: *Microfluidic System Including a Bubble Valve
for Regulating Fluid Flow Through a Microchannel*

Attorney Docket No.: CVZ-012

Group Art Unit: 3753

Examiner: Not yet assigned



Box Missing Parts
Commissioner for Patents
Washington, D.C. 20231

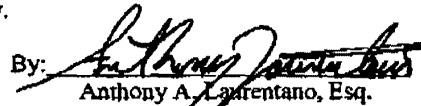
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November 6, 2002

Date of Signature and of Mail Deposit

By:


Anthony A. Laurentano, Esq.
Reg. No. 38,220
Attorney for Applicants

RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION

Dear Sir:

Responsive to the Notice to File Missing Parts of Application dated July 19, 2002, Applicants' attorney submits herewith two executed Declarations, Petitions and Powers of Attorney, and eight (8) sheets of Formal Drawings for the above-identified patent application. A two-month extension of time is being filed concurrently. A copy of the Formalities Letter is also enclosed.

Received from <6177424214> at 12/19/02 4:45:17 PM [Eastern Standard Time]


U.S. Serial No. 10/179,586
Group Art Unit: 3753

Attorney Docket No.: CVZ-012

Please charge the amount of \$130.00 for the surcharge based on large entry to our
Deposit Account No. 12-0080. *A duplicate of this letter is enclosed.*

Respectfully submitted,

LAHIVE & COCKFIELD, LLP


Anthony A. Laurentano, Esq.
Reg. No. 38,220
Attorney for Applicants

Lahive & Cockfield, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400

Dated: November 6, 2002

**LAHIVE
&
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November 6, 2002

Box Missing Parts
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Re: U.S. Patent Application Serial No. 10/179586
Title: *Microfluidic System Including a Bubble Valve for
Regulating Fluid Flow through a Microchannel*
Inventor: John Gilbert, et al.
Filed: June 24, 2002
Group Art Unit: 3753
Attorney Docket No.: CVZ-012

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

1. Response to Notice To File Missing Parts of Non Provisional Application (2 pages, *in duplicate*);
2. Two executed Declarations, Petitions and Powers of Attorney (8 pages total);
3. Eight (8) sheets of Formal Drawings (Figures 1-4, 5A-5C, 6-7, 8A-8C, 9-11, 12A-12C, 13A-13B, 14-16, 17A-17C);
4. Copy of Formalities Letter (2 pages);
5. Request for Two-Month Extension of Time (1 page, *in duplicate*); and
6. Return acknowledgment postcard.

Please charge any necessary fees to our Deposit Account No. 12-0080. The undersigned requests any extensions of time necessary to respond. *A duplicate of this sheet is enclosed.*

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Date: November 6, 2002

Anthony A. Laurentano, Esq. Reg. No. 38,220

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

Anthony A. Laurentano, Esq.
Reg. No. 38,220
Attorney for Applicants

Received from <6177424214> at 12/19/02 4:45:17 PM [Eastern Standard Time]

Dec-19-02 04:34pm

From-LAHIVE & COCKFIELD, LLP

6177424214

T-038 P.02/29 F-831



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
 Washington, D.C. 20231
 www.uspto.gov

Application Number	Filing Date	First Named Applicant	Atty. Docket No.
10/179,586	06/24/2002	Gilbert, John	CVZ-012

959

LAHIVE & COCKFIELD
 28 STATE STREET
 BOSTON MA 02109

*Dec 23, 2002 for Substitute Paper
 no extension*

Title: Microfluidic system including a bubble valve for regulating fluid flow through a microchannel

Date Mailed:12/06/2002

Request for Substitute Papers

The papers filed on 11/13/02 (certificate of mailing dated 11/06/02) are no longer in condition to become part of the permanent records of the United States Patent and Trademark Office (USPTO) for this application (37 CFR 1.52(a)) due to the United States Postal Service sanitization process.

The USPTO requests that applicant provide a copy of the above-identified papers (except for any U.S. or foreign patent documents submitted with the above-identified papers) with a statement that such copy is a complete and accurate copy of the above-identified papers (signing and returning a copy of this notice will provide such a statement). The reply to this letter should be submitted to the USPTO by facsimile at the number indicated 703-746-4060(OIPE).

Alternatively, the reply to this letter may be hand-carried to the Customer Service Window located in Room 1B03 of Crystal Plaza Building 2, Arlington, Virginia, 22202.

The USPTO **strongly** prefers that the reply to this letter be submitted by facsimile. However, if applicant cannot submit the reply to this letter by facsimile (or hand-delivery), the reply may be mailed to: Box Duplicate OIPE, U.S. Patent and Trademark Office, P.O. Box 2327, Arlington, VA 22202-2327.

This letter is not a notice under 37 CFR 1.251. However, failure to timely replay to this notice within two (2) weeks of the date of receipt of this letter may result in the USPTO issuing a notice under 37 CFR 1.251. A copy of this notice should be included with the reply.

The enclosed papers are a complete and accurate copy of the above-identified papers.

Name: Anthony A. Laurentoni, Esq. Registration No.: 38,220

Signature: Anthony A. Laurentoni Date: 12/19/02

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Cytonome/ST, LLC Exhibit 2011

NanoCollect Biomedical, Inc. v. Cytonome/ST, LLC, IPR2020-00548

Page 107 of 300

Dec-19-02 04:42pm From-LAHIVE & COOKFIELD, LLP

6177424214

T-038 P.27/28 F-831

Page 2 of 2

- \$130 Late oath or declaration Surcharge.

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PART 2 - COPY TO BE RETURNED WITH RESPONSE

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Office No. CVZ-012

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IMPRINTED HEREON ACKNOWLEDGES THE FILING OF:**

Description of Paper² and No.: Transmittal Letter (1 page, *in duplicate*); Response to Notice to File Missing Parts of Non-Provisional Application (2 pages, *in duplicate*); Two executed Declarations, Petitions and Powers of Attorney (8 pages in total); Eight (8) sheets of Formal Drawings (Figures 1-4, 5A-5C, 6-7, 8A-8C, 9-11, 12A-12C, 13A-13B, 14-16, 17A-17C); Copy of Formalities Letter (2 pages); Request for Two-Month Extension of Time (1 page, *in duplicate*); and this acknowledgment postcard.

Title: *Microfluidic System Including a Bubble Valve for Regulating Fluid Flow Through a Microchannel*

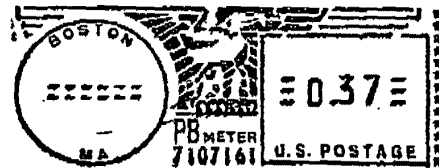
Name of Applicants: John Gilbert, et al.

Intf. or Serial No.: 10/179,586

Attorneys: AAL/CEM

Date: November 6, 2002

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Facsimile Cover Sheet

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Location: Washington, D.C.
Phone:
Fax: (703) 746-4060(OIPE)

From: Anthony A. Laurentano, Esq.
Case No: CVZ-012 (Application No. 10/179,586)
Phone: (617) 227-7400
Fax: (617) 742-4214
Sent by: CEM/dt

Date: December 19, 2002
Pages: 29
(including cover page)

URGENT:

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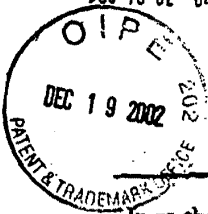
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Dec-19-02 04:43pm

From-LAHIVE & COCKFIELD, LLP

6177424214

T-038 P.28/29 F-831



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: John Gilbert, et al.

Serial No.: 10/179586

Filed: June 24, 2002

For: *Microfluidic System Including a Bubble Valve
for Regulating Fluid Flow Through a Microchannel*

Attorney Docket No.: CVZ-012

Group Art Unit: 3753

Examiner: Not yet assigned

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Washington, D.C. 20231

REQUEST FOR TWO-MONTH EXTENSION OF TIME

Dear Sir:

Applicants request a two-month extension of time pursuant to 37 CFR 1.136(a) in which to respond to the Notice to File Missing Parts mailed from the U.S. Patent and Trademark Office on July 19, 2002.

Please charge the appropriate fee of \$400.00 based on large entity status to our Deposit Account No. 12-0080. *A duplicate of this sheet is enclosed.*

I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: Box Missing Parts, Commissioner for Patents, Washington, DC 20231 on:

November 6, 2002

Date

Anthony A. Laurentano
Anthony A. Laurentano, Esq.

Reg. No. 38,220

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

Anthony A. Laurentano
Anthony A. Laurentano, Esq.

Reg. No. 38,220

Attorney for Applicants

Dated: November 6, 2002

Received from <6177424214> at 12/19/02 4:45:17 PM [Eastern Standard Time]



FIG. 1

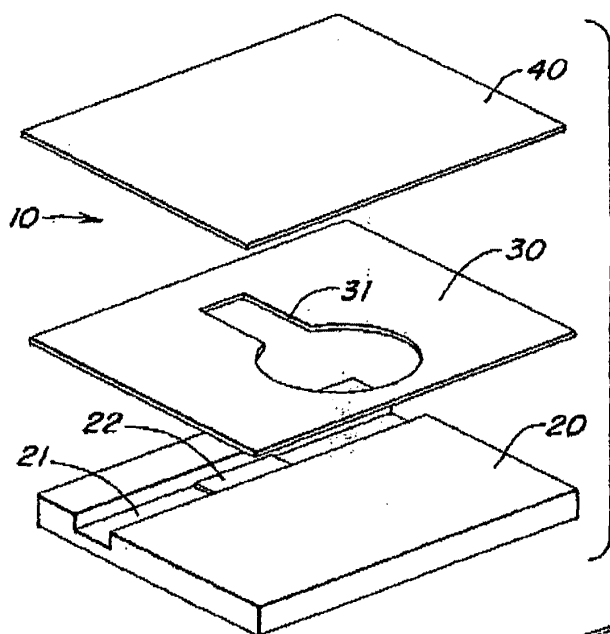
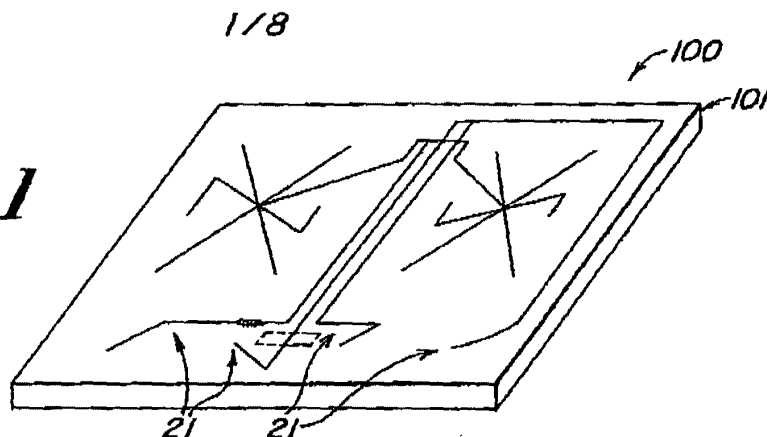


FIG. 2

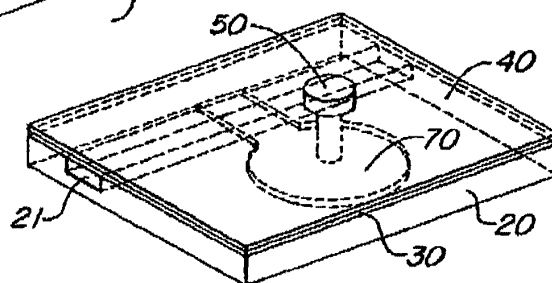
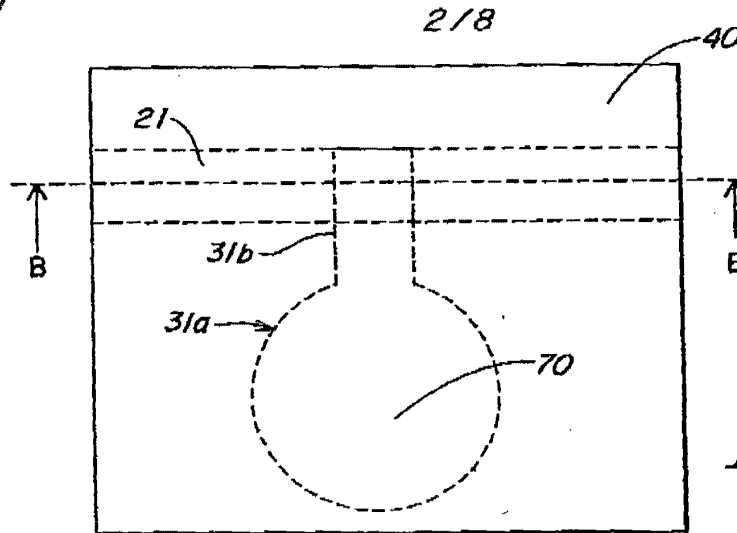
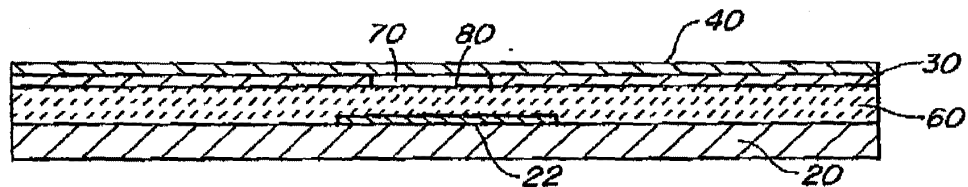
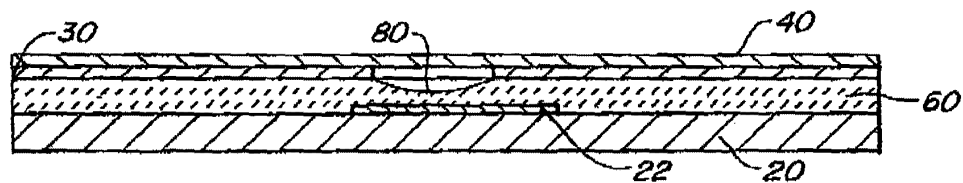
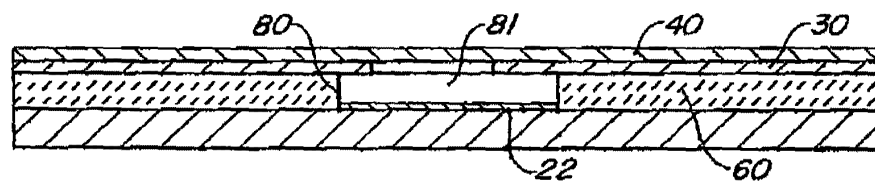


FIG. 3

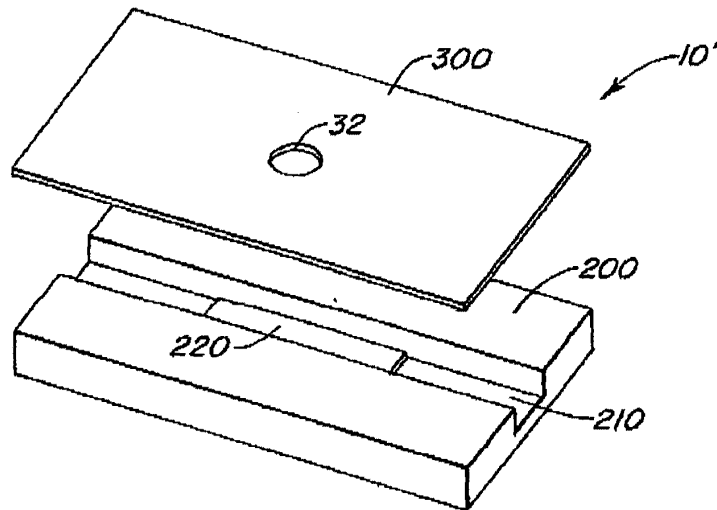
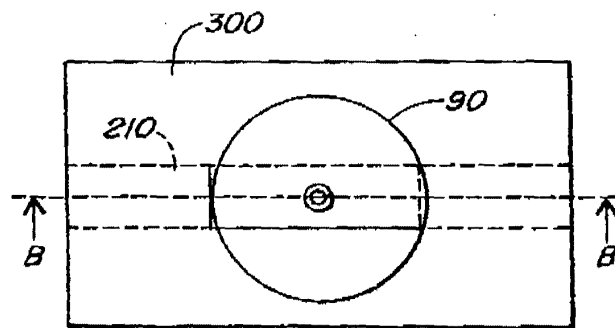
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**FIG. 4****FIG. 5A****FIG. 5B****FIG. 5C**

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3 / 8

**FIG. 6****FIG. 7**

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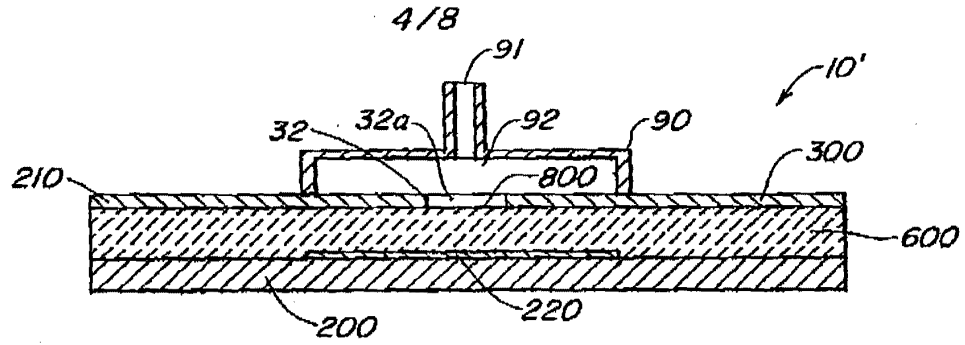


FIG. 8A

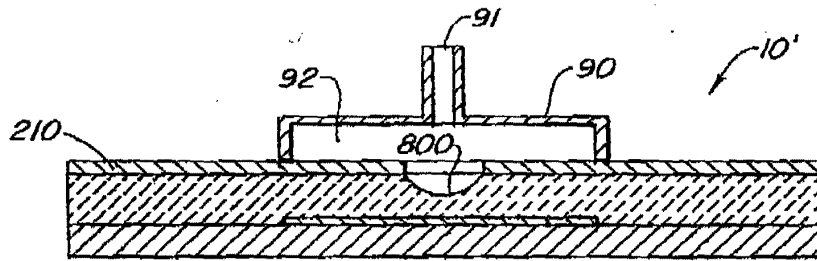


FIG. 8B

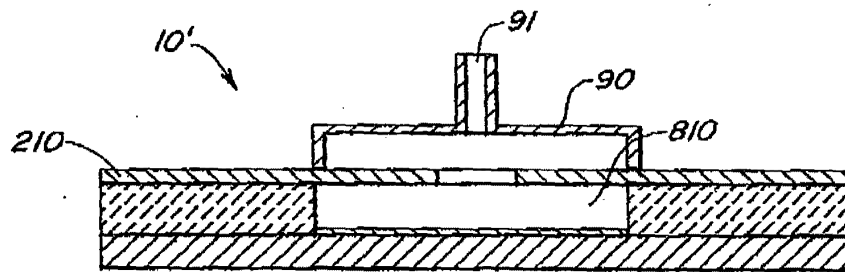


FIG. 8C

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5/8

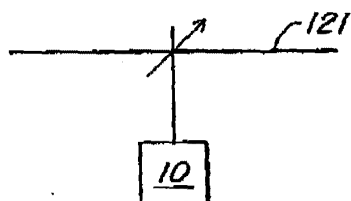


FIG. 9

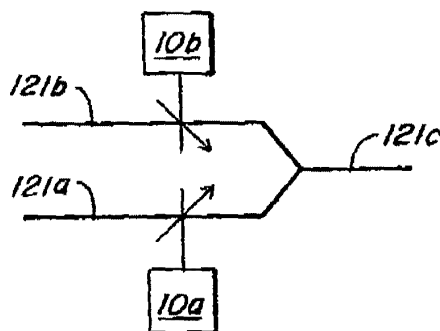


FIG. 10

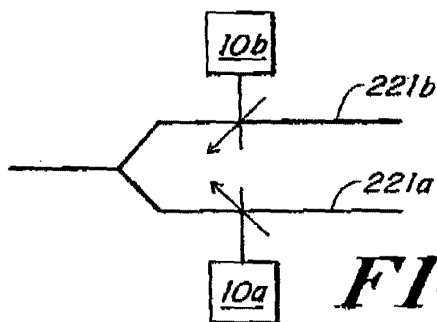


FIG. 11

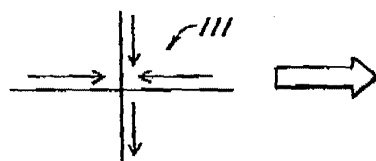


FIG. 12B

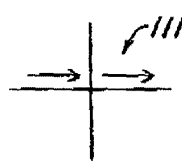


FIG. 12C

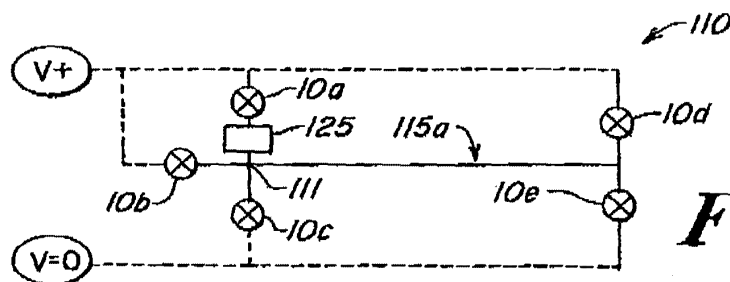


FIG. 12A

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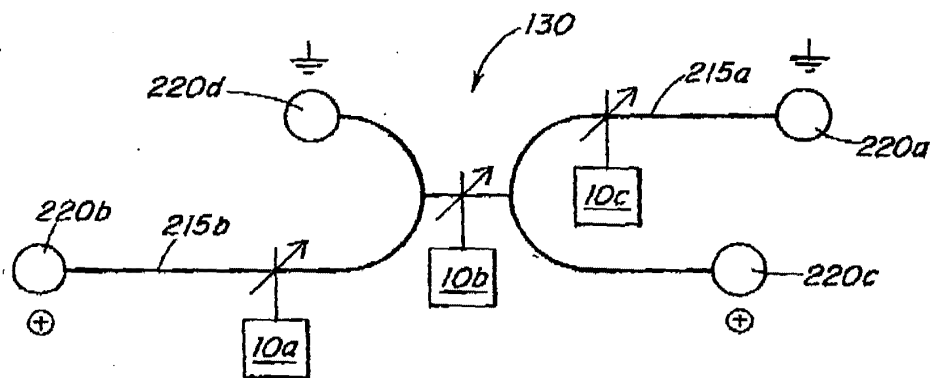


FIG. 13A

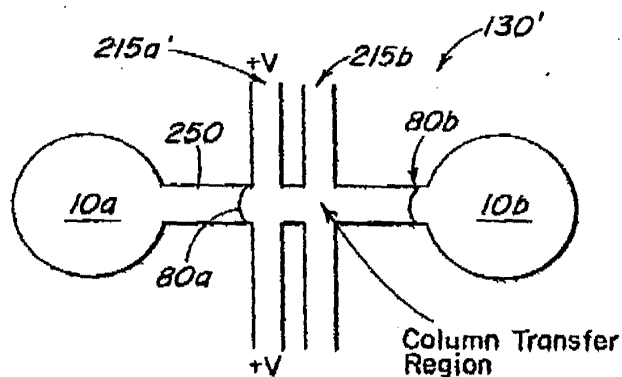
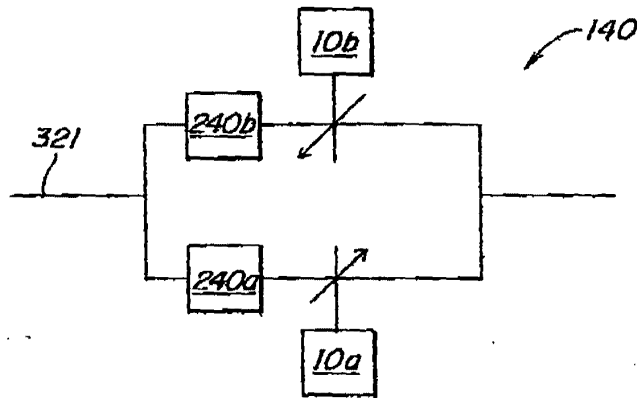
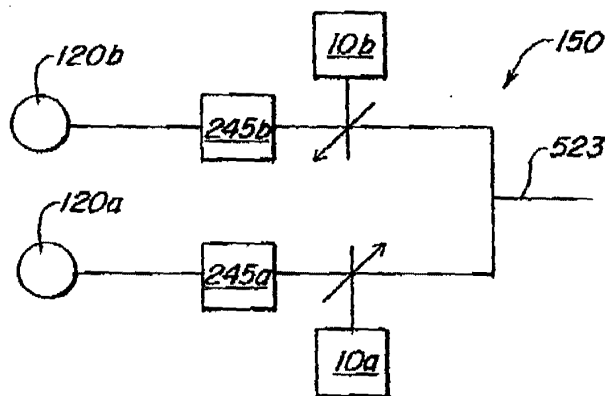


FIG. 13B

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7/8

**FIG. 14****FIG. 15**

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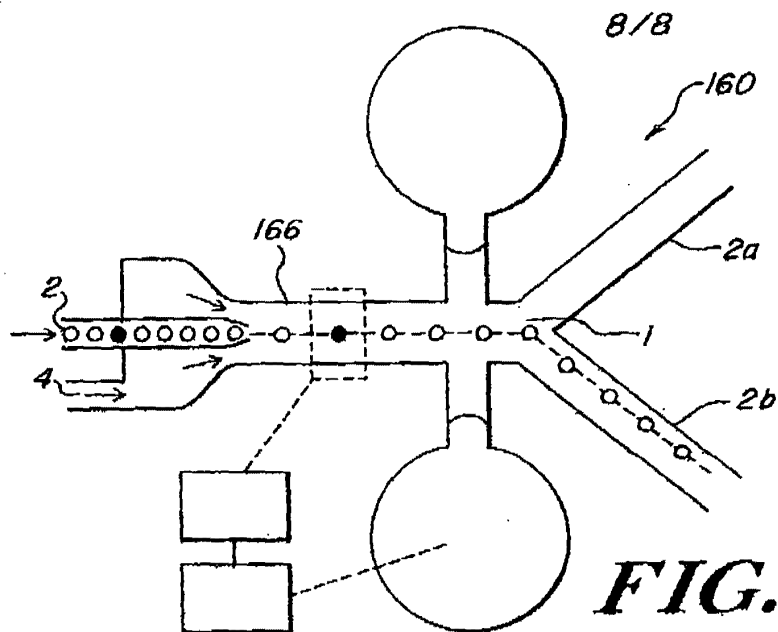


FIG. 16

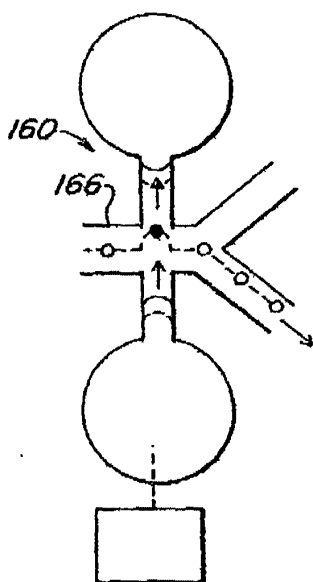


FIG. 17A

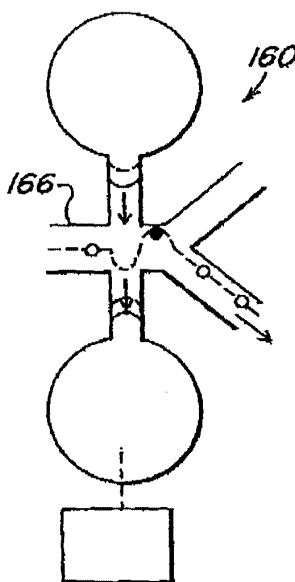


FIG. 17B

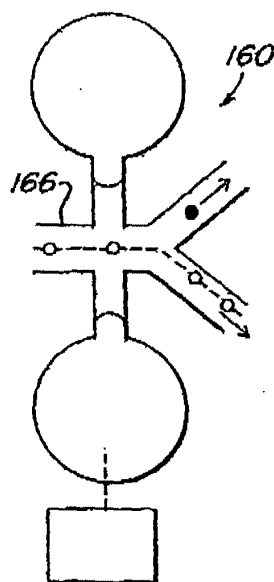


FIG. 17C

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Customer Number: 000959

Attorney's
Docket
Number CVZ-012

Declaration, Petition and Power of Attorney for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW THROUGH A MICROCHANNEL

the specification of which:

is attached hereto.

X was filed on June 24, 2002 as

X Application Serial No. 10/179,586.

and was amended on _____
(if applicable)

I do not know and do not believe that the subject matter of this application was known or used by others in the United States or patented or described in a printed publication in any country before my invention thereof, or patented or described in a printed publication in any country or in public use or on sale in the United States more than one year prior to the date of this application, or first patented or caused to be patented or made the subject of an inventor's certificate by me or my legal representatives or assigns in a country foreign to the United States prior to the date of this application on an application filed more than twelve months (six months if this application is for a design) before the filing of this application; and I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application, that no application for patent or inventor's certificate on the subject matter of this application has been filed by me or my representatives or assigns in any country foreign to the United States, except those identified below, and that I have reviewed and understand the contents of the specification, including the claims as amended by any amendment referred to herein.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

CVZ-012

CLAIM OF BENEFIT OF EARLIER FOREIGN APPLICATION(S)

I hereby claim priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application(s) for patent or inventor's certificate filed by me on the same subject matter having a filing date before that of the application(s) from which priority is claimed.

Check one:

☒ no such applications have been filed.☐ such applications have been filed as follows**EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION**

Country	Application Number	Date of Filing (month,day,year)	Priority Claimed Under 35 USC 119
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

**ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION**

CLAIM FOR BENEFIT OF U.S. PROVISIONAL APPLICATION(S)

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

60/373,256
(Application Serial No.)

April 17, 2002
(Filing Date)

(Application Serial No.)

(Filing Date)

- 2 -

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CVZ-012

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S)

I hereby claim the benefit under Title 35, United States Code, §120 of any earlier United States application(s) or PCT international application(s) designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the earlier application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date(s) of the earlier application(s) and the national or PCT international filing date of this application. As to subject matter of this application which is common to my earlier application(s), if any, described below, I do not know and do not believe that the same was known or used by others in the United States or patented or described in a printed publication in any country before my invention thereof, or patented or described in a printed publication in any country or in public use or on sale in the United States more than one year prior to the date(s) of said earlier application(s), or first patented or caused to be patented or made the subject of an inventor's certificate by me or my legal representatives or assigns in a country foreign to the United States prior to the date(s) of said earlier application(s) on an application filed more than twelve months (six months if this application is for a design) before the filing of said earlier application(s); and I acknowledge that no application for patent or inventor's certificate on said subject matter has been filed by me or my representatives or assigns in any country foreign to the United States except those identified herein.

(Application Serial No.)	(Filing Date)	(Status) (patented,pending,aband.)
--------------------------	---------------	---------------------------------------

(Application Serial No.)	(Filing Date)	(Status) (patented,pending,aband.)
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POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

James E. Cockfield	Reg. No. 19,162	Maria C. Laccorripe	Limited Recognition
Thomas V. Smurzynski	Reg. No. 24,798		Under 37 C.F.R. § 10.9(b)
Ralph A. Loren	Reg. No. 29,325	Debra J. Milasincic	Reg. No. 46,931
Giulio A. DeConti, Jr.	Reg. No. 31,503	David R. Burns	Reg. No. 46,590
Ann Lamport Hammine	Reg. No. 34,858	Sean D. Detweiler	Reg. No. 42,482
Elizabeth A. Hanley	Reg. No. 33,505	Cynthia L. Kanik	Reg. No. 37,320
Amy E. Mandragouras	Reg. No. 36,207	Theodore R. West	Reg. No. 47,202
Anthony A. Laurentano	Reg. No. 38,220	Shayne Y. Huff	Reg. No. 44,784
Kevin J. Canning	Reg. No. 35,470	Hathaway P. Russell	Reg. No. 46,488
Jane E. Remillard	Reg. No. 38,872	Daniel B. Ko	Reg. No. 47,332
DeAnn F. Smith	Reg. No. 36,683	John S. Curran	Reg. No. 50,445
Peter C. Lauro	Reg. No. 32,360	Lisa M. DiRocco	Reg. No. P51,619
Jeanne M. DiGiorgio	Reg. No. 41,710	Richa Nand	Reg. No. P52,059
Megan E. Williams	Reg. No. 43,270		
Jeremiah Lynch	Reg. No. 17,425		
David J. Rikkers	Reg. No. 43,882		

- 3 -

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CVZ-012

Send Correspondence to: Anthony A. Laurentano, Esq. at Customer Number: 000959 whose address is:

LAHIVE & COCKFIELD, LLP, 28 State Street, Boston, MA 02109

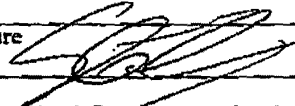
Direct Telephone Calls to:

Anthony A. Laurentano, Esq., (617) 227-7400

Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor John Richard Gilbert	
Inventor's signature	Date
Residence 69 Naples Road, Brookline, MA 02446	
Citizenship United States	
Post Office Address (if different)	

Full name of second inventor, if any Sebastian Böhm	
Inventor's signature 	Date Oct. 31, 2002
Residence 9 Muirfield Court, IV2 4DP, Inverness, Scotland (UK)	
Citizenship Germany	
Post Office Address (if different)	

Full name of third inventor, if any Manish Deshpande	
Inventor's signature	Date
Residence 34 Apple Blossom Way, Canton, MA 02021	
Citizenship United States	
Post Office Address (if different)	

- 4 -

Received from <6177424214> at 12/19/02 4:45:17 PM [Eastern Standard Time]



Customer Number: 000959

Attorney's
Docket
Number CVZ-012**Declaration, Petition and Power of Attorney for Patent Application**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR
REGULATING FLUID FLOW THROUGH A MICROCHANNEL**

the specification of which:

___ is attached hereto.

X was filed on June 24, 2002 as

X Application Serial No. 10/179,586.

___ and was amended on _____
(if applicable)

I do not know and do not believe that the subject matter of this application was known or used by others in the United States or patented or described in a printed publication in any country before my invention thereof, or patented or described in a printed publication in any country or in public use or on sale in the United States more than one year prior to the date of this application, or first patented or caused to be patented or made the subject of an inventor's certificate by me or my legal representatives or assigns in a country foreign to the United States prior to the date of this application on an application filed more than twelve months (six months if this application is for a design) before the filing of this application; and I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application, that no application for patent or inventor's certificate on the subject matter of this application has been filed by me or my representatives or assigns in any country foreign to the United States, except those identified below, and that I have reviewed and understand the contents of the specification, including the claims as amended by any amendment referred to herein.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

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CVZ-012

CLAIM OF BENEFIT OF EARLIER FOREIGN APPLICATION(S)

I hereby claim priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application(s) for patent or inventor's certificate filed by me on the same subject matter having a filing date before that of the application(s) from which priority is claimed.

Check one:

☒ no such applications have been filed.☐ such applications have been filed as follows**EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION**

Country	Application Number	Date of Filing (month,day,year)	Priority Claimed Under 35 USC 119
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

**ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION**

CLAIM FOR BENEFIT OF U.S. PROVISIONAL APPLICATION(S)

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

60/373,256
(Application Serial No.)

April 17, 2002
(Filing Date)

(Application Serial No.)

(Filing Date)

- 2 -

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CVZ-012

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(Application Serial No.)	(Filing Date)	(Status) (patented,pending,aband.)
(Application Serial No.)	(Filing Date)	(Status) (patented,pending,aband.)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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Giulio A. DeConti, Jr.	Reg. No. 31,503	David R. Burns	Reg. No. 46,590
Ann Lamport Hammine	Reg. No. 34,858	Sean D. Derweiler	Reg. No. 42,482
Elizabeth A. Hanley	Reg. No. 33,505	Cynthia L. Kanik	Reg. No. 37,320
Amy E. Mandragouras	Reg. No. 36,207	Theodore R. West	Reg. No. 47,202
Anthony A. Laurentano	Reg. No. 38,220	Shayne Y. Huif	Reg. No. 44,784
Kevin J. Canning	Reg. No. 35,470	Hathaway P. Russell	Reg. No. 46,488
Jane E. Remillard	Reg. No. 38,872	Daniel B. Ko	Reg. No. 47,332
DeAnn F. Smith	Reg. No. 36,683	John S. Curran	Reg. No. 50,445
Peter C. Lauro	Reg. No. 32,360	Lisa M. DiRocco	Reg. No. P51,619
Jeanne M. DiGiorgio	Reg. No. 41,710	Richa Nand	Reg. No. P52,059
Megan E. Williams	Reg. No. 43,270		
Jeremiah Lynch	Reg. No. 17,425		
David J. Rikkers	Reg. No. 43,882		

CVZ-012

Send Correspondence to: Anthony A. Laurentano, Esq. at Customer Number: 000959 whose address is:

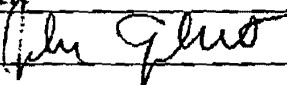
LAHIVE & COCKFIELD, LLP, 28 State Street, Boston, MA 02109

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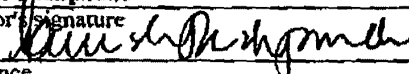
Anthony A. Laurentano, Esq. (617) 227-7400

Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor John Richard Gilbert	
Inventor's signature 	Date 10/28/02
Residence 69 Naples Road, Brookline, MA 02446	
Citizenship United States	
Post Office Address (if different)	

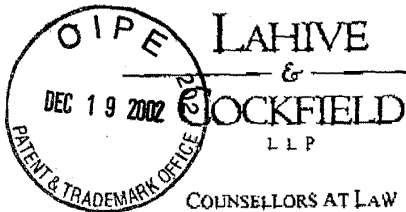
Full name of second inventor, if any Sebastian Böhm	
Inventor's signature	Date
Residence 9 Muirfield Court, IV2 4DP, Inverness, Scotland (UK)	
Citizenship Germany	
Post Office Address (if different)	

Full name of third inventor, if any Manish Deshpande	
Inventor's signature 	Date 10/28/02
Residence 34 Apple Blossom Way, Canton, MA 02021	
Citizenship United States	
Post Office Address (if different)	

- 4 -

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#7



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TELEPHONE (617) 227-7400
FAX (617) 742-4214
lc@lahive.com

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ANN LAMPORT HAMMITTE
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AMY BAKER MANORAGOURAS
ANTHONY A. LAURENTANO
KEVIN J. CANNING
JANÉ E. REMILLARD
DOAN FORAN SMITH
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DANIELLE L. HERRITT
EUNHOON LEE

SENIOR COUNSEL
JAMES E. COCKFIELD

OF COUNSEL
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WILLIAM A. SCOFIELD, JR.
SIBLEY P. REPPERT

PATENT AGENTS
THEODORER WEST
SHAYNE Y. HUFF, Ph.D.

TECHNICAL SPECIALISTS
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CATHERINE E. McPHERSON
JACOB G. WENTHAUS
JONATHAN M. SPARKS, Ph.D.
CRISTIN E. HOWLEY, Ph.D.
JILL ANN MELLO, Ph.D.

*Admitted in TX only
**Admitted in CT only

Facsimile Cover Sheet

To:
Company: U.S. Patent and Trademark Office
Location: Washington, D.C.
Phone:
Fax: (703) 746-4060(OIPE)

From: Anthony A. Laurentano, Esq.
Case No: CVZ-012 (Application No. 10/179,586)
Phone: (617) 227-7400
Fax: (617) 742-4214
Sent by: CEM/dr

Date: December 19, 2002
Pages: 29
(including cover page)

URGENT:

Please Deliver Immediately.

Thank you.

The documents transmitted by this facsimile are intended for the use of the individual or the entity to which it is addressed and may contain information that is privileged, confidential and exempt from disclosure under applicable law. If the reader of the message is not the intended recipient, or the employee or agent responsible for delivering this document to the intended recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by telephone and return the original facsimile to us at the above address via the U.S. Postal Service. Thank you.

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UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
WWW.USPTO.GOV

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/179,586	06/24/2002	John Gilbert	CVZ-012

000959
LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

CONFIRMATION NO. 9722

FORMALITIES LETTER



000000008483837

Date Mailed: 07/19/2002



NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of \$130 for a non-small entity, must be submitted with the missing items identified in this letter.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Substitute drawings in compliance with 37 CFR 1.84 because:
 - drawing sheets do not have the appropriate margin(s) (see 37 CFR 1.84(g)). Each sheet must include a top margin of at least 2.5 cm. (1 inch), a left side margin of at least 2.5 cm. (1 inch), a right side margin of at least 1.5 cm. (5/8 inch), and a bottom margin of at least 1.0 cm. (3/8 inch);

Items Required To Avoid Processing Delays:

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is \$130 for a Large Entity

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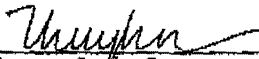
Dec-19-02 04:42pm From-LAHIVE & COCKFIELD, LLP

6177424214

T-038 P.27/28 F-831
Page 4 of 4

- \$130 Late oath or declaration Surcharge.

*A copy of this notice **MUST** be returned with the reply.*



Customer Service Center
Initial Patent Examination Division (703) 308-1202

PART 2 - COPY TO BE RETURNED WITH RESPONSE

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FIG. 1

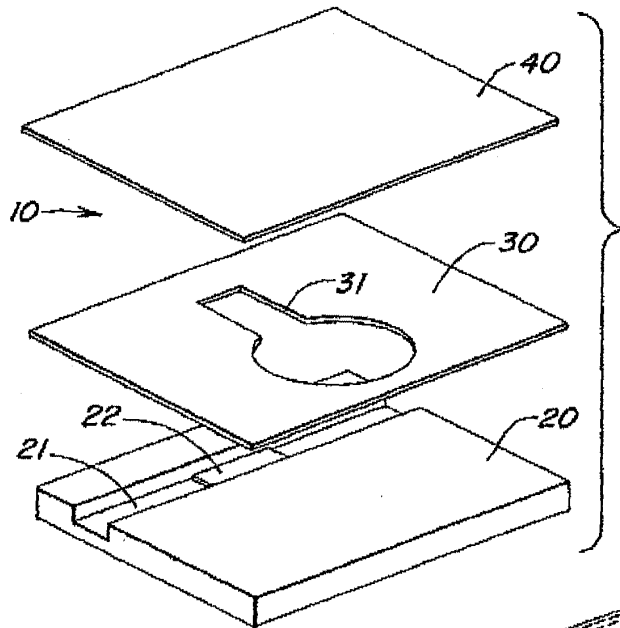
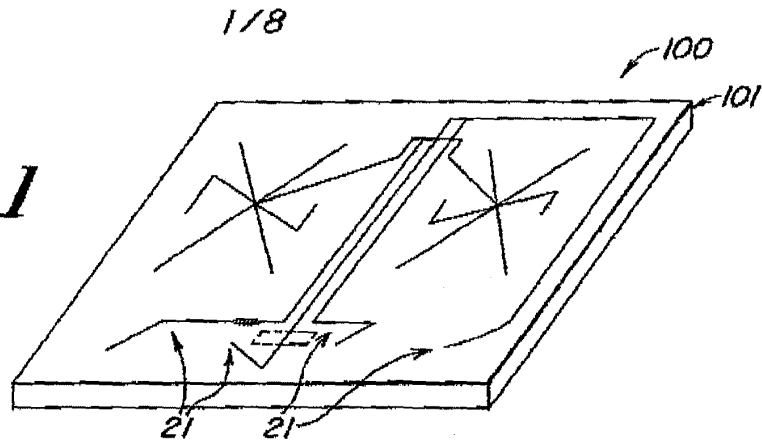


FIG. 2

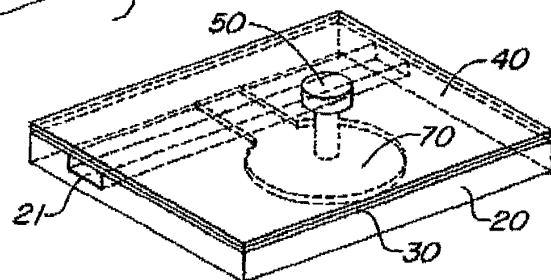


FIG. 3

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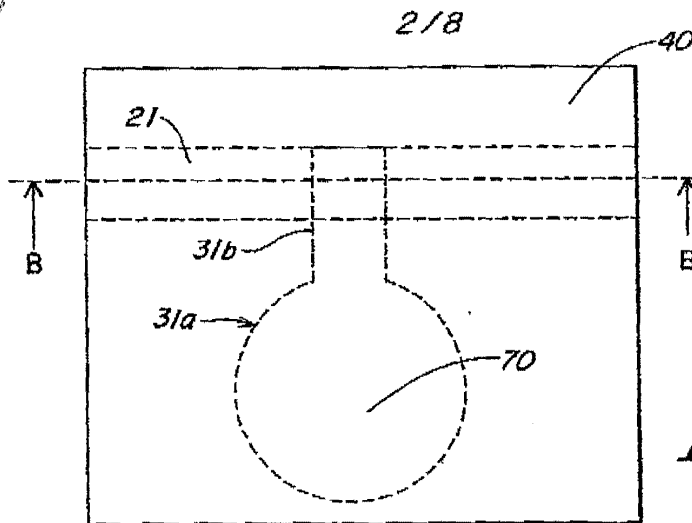


FIG. 4

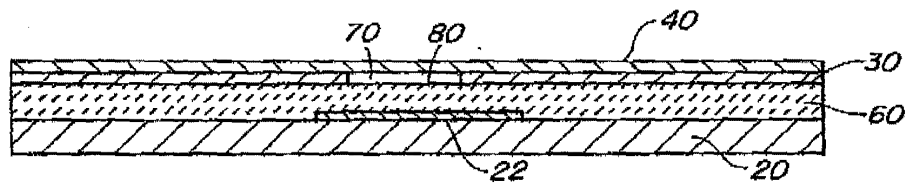


FIG. 5A

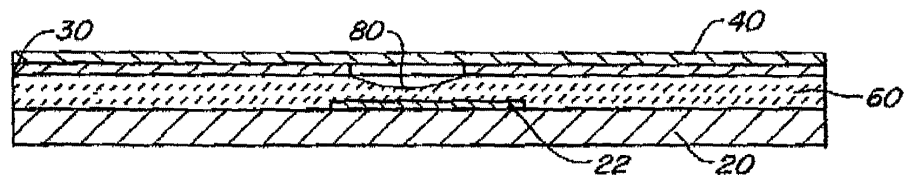


FIG. 5B

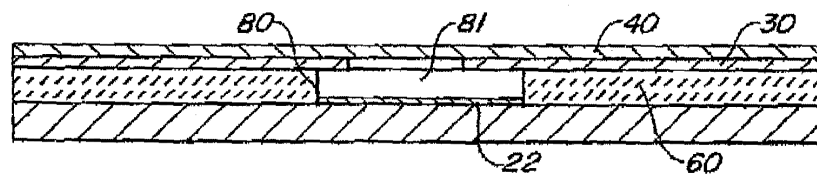


FIG. 5C

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3/8

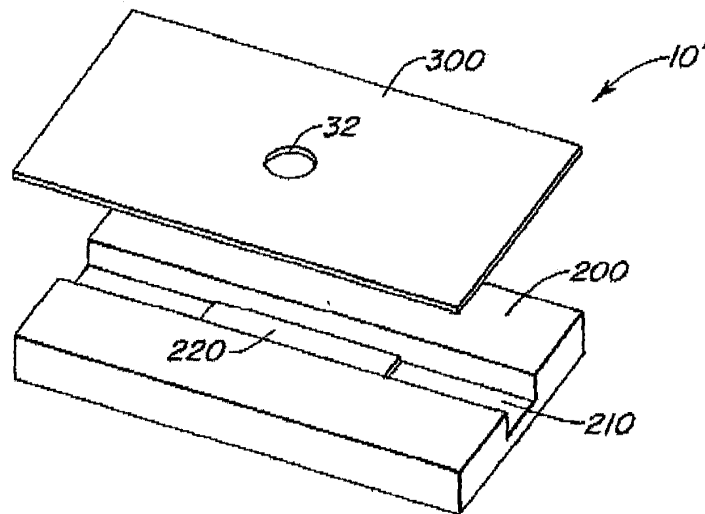


FIG. 6

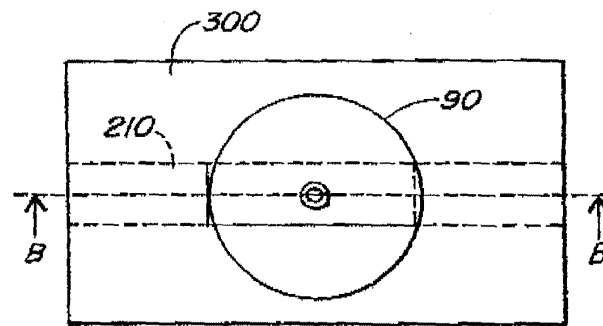
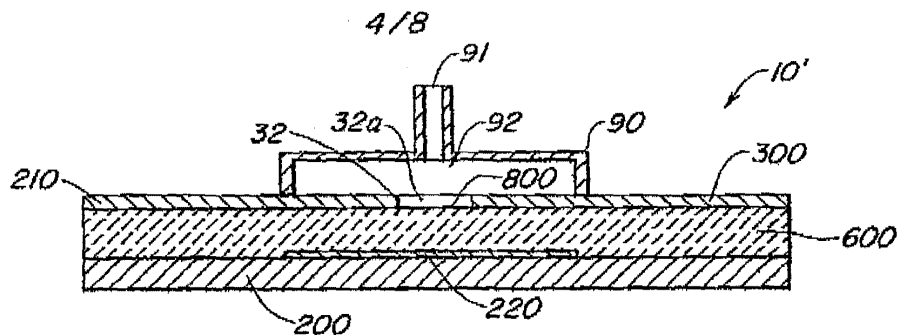
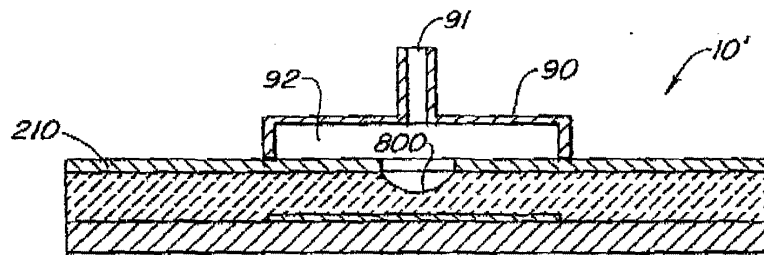
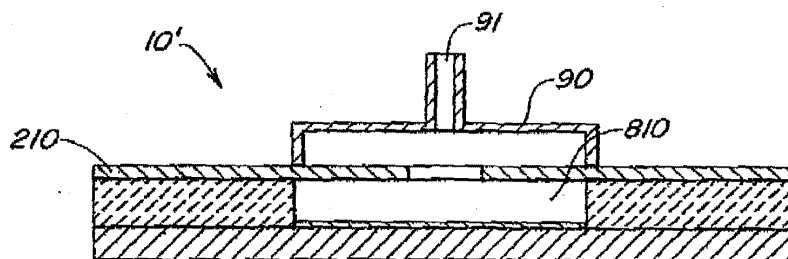


FIG. 7

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**FIG. 8A****FIG. 8B****FIG. 8C**

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5/8

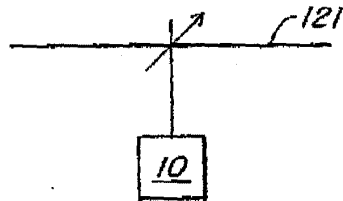


FIG. 9

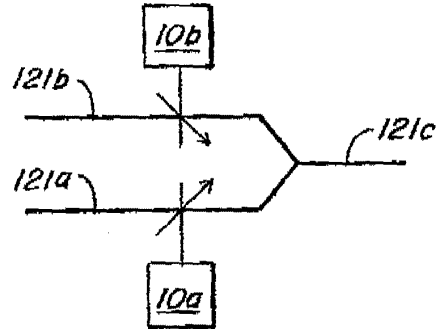


FIG. 10

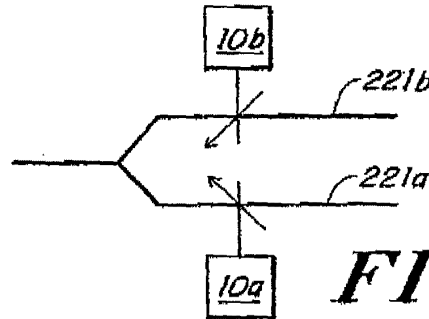


FIG. 11

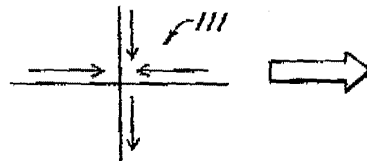


FIG. 12B

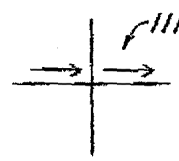


FIG. 12C

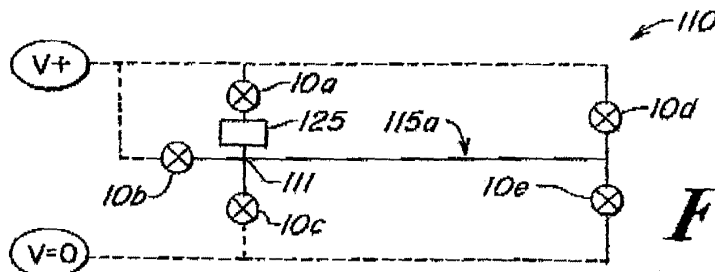


FIG. 12A

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6/8

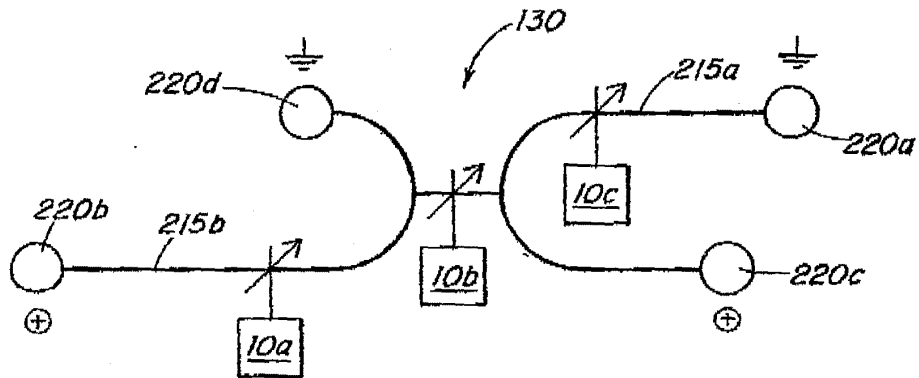


FIG. 13A

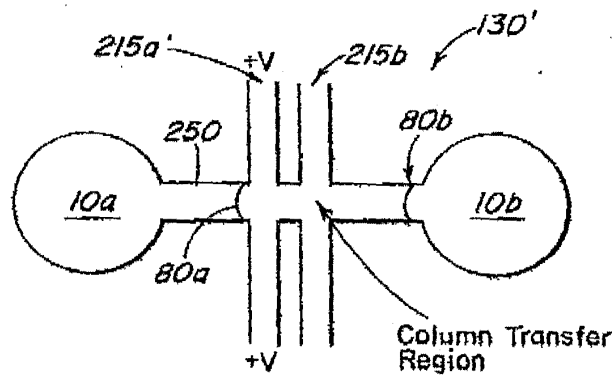


FIG. 13B

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7/8

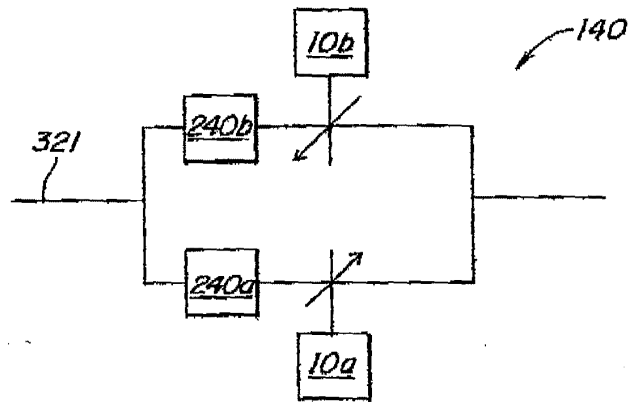


FIG. 14

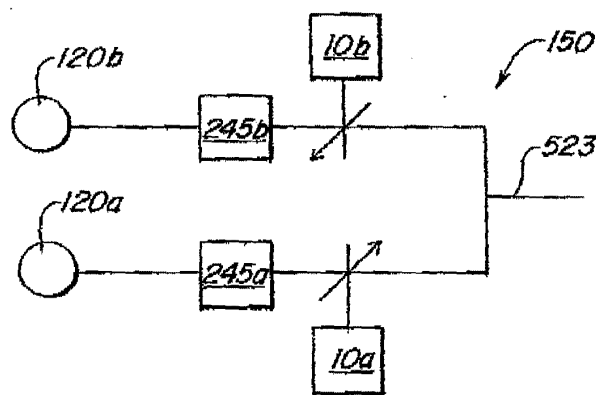
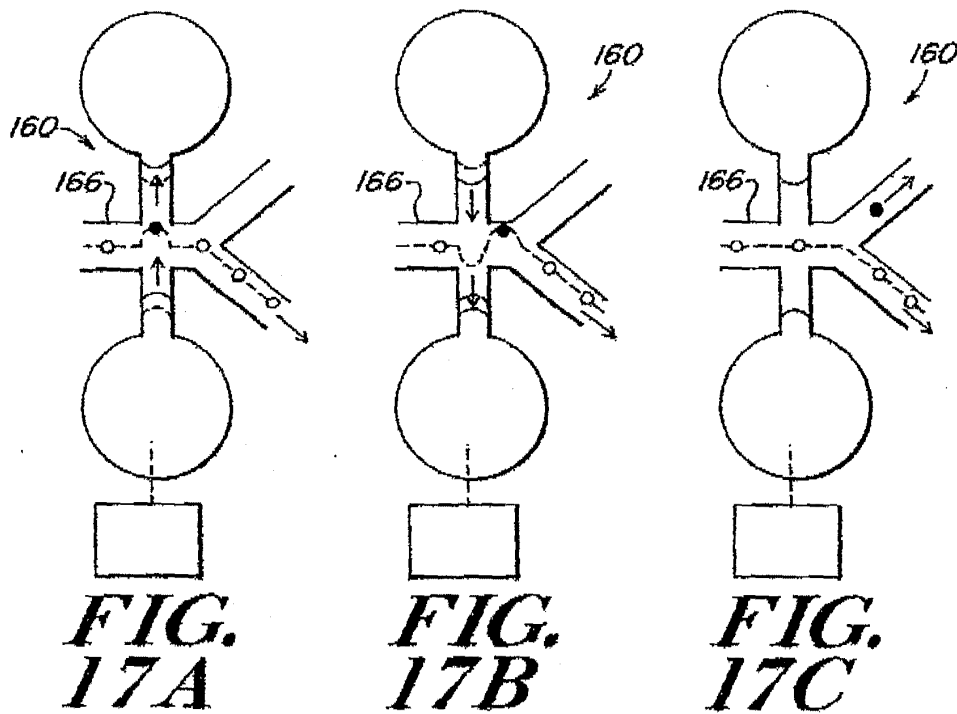
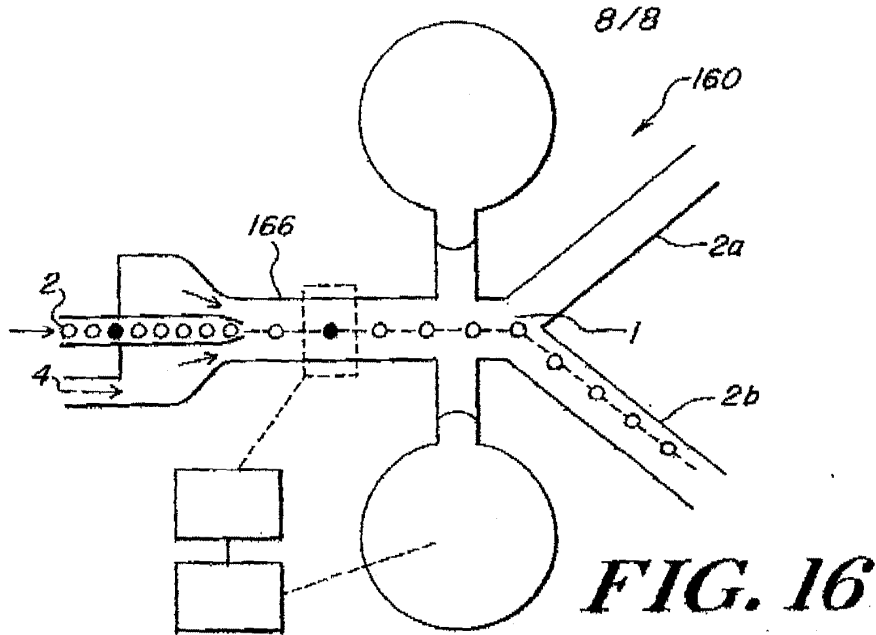


FIG. 15

Received from <6177424214> at 12/19/02 4:45:17 PM [Eastern Standard Time]



Received from <6177424214> at 12/19/02 4:45:17 PM [Eastern Standard Time]



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

Application Number	Filing Date	First Named Applicant	Atty. Docket No.
10/179,586	06/24/2002	Gilbert, John	CVZ-012

959
LAHIVE & COCKFIELD
28 STATE STREET
BOSTON MA 02109

Title: Microfluidic system including a bubble valve for regulating fluid flow through a microchannel

Date Mailed: 12/06/2002

Request for Substitute Papers

The papers filed on 11/13/02 (certificate of mailing dated 11/06/02) are no longer in condition to become part of the permanent records of the United States Patent and Trademark Office (USPTO) for this application (37 CFR 1.52(a)) due to the United States Postal Service sanitization process.

The USPTO requests that applicant provide a copy of the above-identified papers (except for any U.S. or foreign patent documents submitted with the above-identified papers) with a statement that such copy is a complete and accurate copy of the above-identified papers (signing and returning a copy of this notice will provide such a statement). The reply to this letter should be submitted to the USPTO by facsimile at the number indicated **703-746-4060(OIPE)**.

Alternatively, the reply to this letter may be hand-carried to the Customer Service Window located in Room 1B03 of Crystal Plaza Building 2, Arlington, Virginia, 22202.

The USPTO **strongly** prefers that the reply to this letter be submitted by facsimile. However, if applicant cannot submit the reply to this letter by facsimile (or hand-delivery), the reply may be mailed to: Box Duplicate OIPE, U.S. Patent and Trademark Office, P.O. Box 2327, Arlington, VA 22202-2327.

This letter is not a notice under 37 CFR 1.251. However, failure to timely reply to this notice within **two (2) weeks** of the date of receipt of this letter may result in the USPTO issuing a notice under 37 CFR 1.251. **A copy of this notice should be included with the reply.**

The enclosed papers are a complete and accurate copy of the above-identified papers.

Name: _____ Registration No.: _____

Signature: _____ Date: _____



#3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: John Gilbert, *et al.*

Serial No.: 10/179586

Filed: June 24, 2002

For: *Microfluidic System Including a Bubble Valve
for Regulating Fluid Flow Through a Microchannel*

Attorney Docket No.: CVZ-012

Group Art Unit: 3753

Examiner: Not yet assigned

Box Missing Parts
Commissioner for Patents
Washington, D.C. 20231


Certificate of First Class Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Box Missing Parts, Washington, D.C. 20231 on the date set forth below.

November 6, 2002

Date of Signature and of Mail Deposit

By:


Anthony A. Laurentano, Esq.
Reg. No. 38,220
Attorney for Applicants

RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION

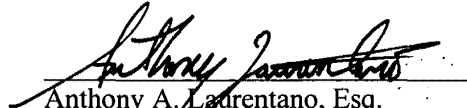
Dear Sir:

Responsive to the Notice to File Missing Parts of Application dated July 19, 2002, Applicants' attorney submits herewith two executed Declarations, Petitions and Powers of Attorney, and eight (8) sheets of Formal Drawings for the above-identified patent application. A two-month extension of time is being filed concurrently. A copy of the Formalities Letter is also enclosed.

Please charge the amount of \$130.00 for the surcharge based on large entity to our
Deposit Account No. 12-0080. *A duplicate of this letter is enclosed.*

Respectfully submitted,

LAHIVE & COCKFIELD, LLP


Anthony A. Laurentano, Esq.
Reg. No. 38,220
Attorney for Applicants

Lahive & Cockfield, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400

Dated: November 6, 2002



LAHIVE
&
COCKFIELD
L L P

COUNSELLORS AT LAW
28 STATE STREET
BOSTON, MASSACHUSETTS 02109-1784
TELEPHONE (617) 227-7400
FAX (617) 742-4214
lc@lahive.com

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ANN LAMPORT HAMMITTE
ELIZABETH A. HANLEY
AMY BAKER MANDRAGOURAS
ANTHONY A. LAURENTANO
KEVIN J. CANNING
JANE E. REMILLARD
DeANN FORAN SMITH
PETER C. LAURO
JEANNE M. DIGIORGIO
DEBRA J. MILASINCIC, Ph.D.
DAVID J. RIKKERS
DAVID R. BURNS
JOHN S. CURRAN
SEAN D. DETWEILER

CYNTHIA L. KANIK, Ph.D.
MEGAN E. WILLIAMS, Ph.D.
RICHANAND
MICHAEL PHILLIPPS *
LISA M. DIROCCO
HATHAWAY P. RUSSELL **
MARIA LACCOTRIPE ZACHARAKIS, Ph.D.
VINCENT P. LOCCISANO
MERIDETH C. ARNOLD
DANIELLE L. HERRITT

SENIOR COUNSEL
JAMES E. COCKFIELD

OF COUNSEL
JEREMIAH LYNCH
WILLIAM A. SCOFIELD, JR.
SIBLEY P. REPPERT

PATENT AGENTS
THEODORE R. WEST
SHAYNE Y. HUFF, Ph.D.
DANIEL B. KO

TECHNICAL SPECIALISTS
CYNTHIA M. SOROOS
PETER W. DINI, Ph.D.
EUIHOON LEE
CATHERINE E. McPHERSON
ERIC F. WAGNER, Ph.D.
JACOB G. WEINTRAUB
JONATHAN M. SPARKS, Ph.D.
CRISTIN E. HOWLEY, Ph.D.

* Admitted in NY only
** Admitted in TX only

November 6, 2002

Box Missing Parts
Commissioner for Patents
Washington, D.C. 20231

Re: U.S. Patent Application Serial No. 10/179586
Title: *Microfluidic System Including a Bubble Valve for
Regulating Fluid Flow through a Microchannel*
Inventor: John Gilbert, et al.
Filed: June 24, 2002
Group Art Unit: 3753
Attorney Docket No.: CVZ-012

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

1. Response to Notice To File Missing Parts of Non Provisional Application (2 pages, *in duplicate*);
2. Two executed Declarations, Petitions and Powers of Attorney (8 pages total);
3. Eight (8) sheets of Formal Drawings (Figures 1-4, 5A-5C, 6-7, 8A-8C, 9-11, 12A-12C, 13A-13B, 14-16, 17A-17C);
4. Copy of Formalities Letter (2 pages);
5. Request for Two-Month Extension of Time (1 page, *in duplicate*); and
6. Return acknowledgment postcard.

Please charge any necessary fees to our Deposit Account No. 12-0080. The undersigned requests any extensions of time necessary to respond. *A duplicate of this sheet is enclosed.*

I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: Box Missing Parts, Commissioner for Patents, Washington, DC 20231 on:

Date November 6, 2002

Anthony A. Laurentano, Esq. Reg. No. 38,220

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

Anthony A. Laurentano, Esq.
Reg. No. 38,220
Attorney for Applicants



UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/179,586	06/24/2002	John Gilbert	CVZ-012

000959
LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109



CONFIRMATION NO. 9722

FORMALITIES LETTER



OC00000008483837

Date Mailed: 07/19/2002

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of \$130 for a non-small entity, must be submitted with the missing items identified in this letter.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Substitute drawings in compliance with 37 CFR 1.84 because:
 - drawing sheets do not have the appropriate margin(s) (see 37 CFR 1.84(g)). Each sheet must include a top margin of at least 2.5 cm. (1 inch), a left side margin of at least 2.5 cm. (1 inch), a right side margin of at least 1.5 cm. (5/8 inch), and a bottom margin of at least 1.0 cm. (3/8 inch);

Items Required To Avoid Processing Delays:

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is \$130 for a Large Entity

11/15/2002 MBIZUNES 00000056 120080 10179586

01 FC:1051 130.00 CH

Cytonome/ST, LLC Exhibit 2011

NanoCollect Biomedical, Inc. v. Cytonome/ST, LLC, IPR2020-00548

Page 144 of 300

- **\$130** Late oath or declaration Surcharge.

*A copy of this notice **MUST** be returned with the reply.*



Customer Service Center

Initial Patent Examination Division (703) 308-1202

PART 2 - COPY TO BE RETURNED WITH RESPONSE



FIG. 1

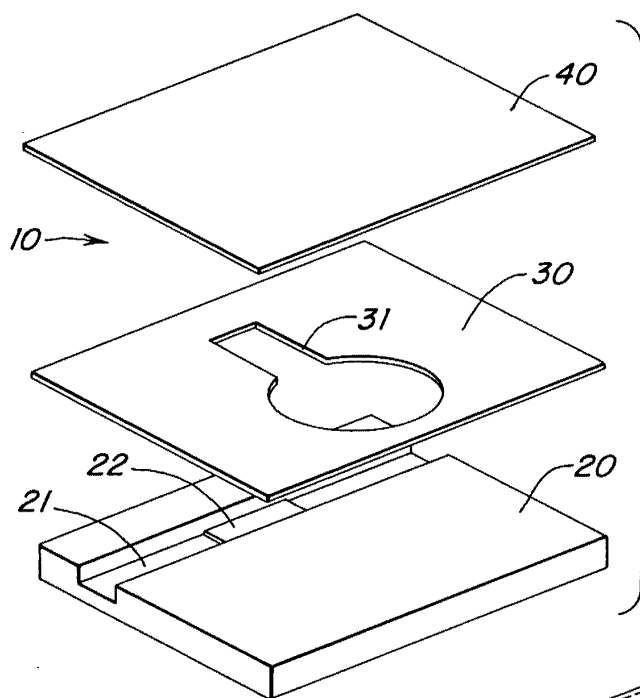
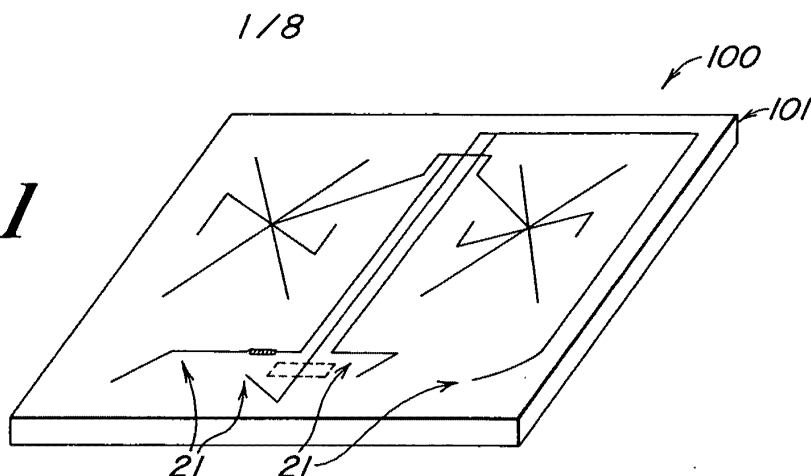


FIG. 2

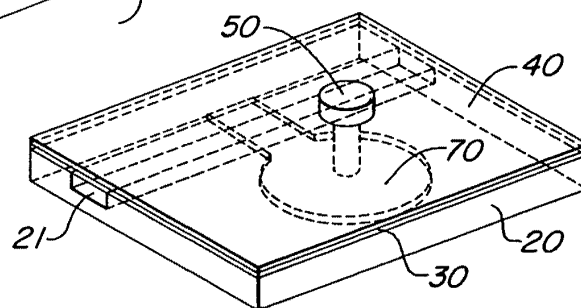


FIG. 3

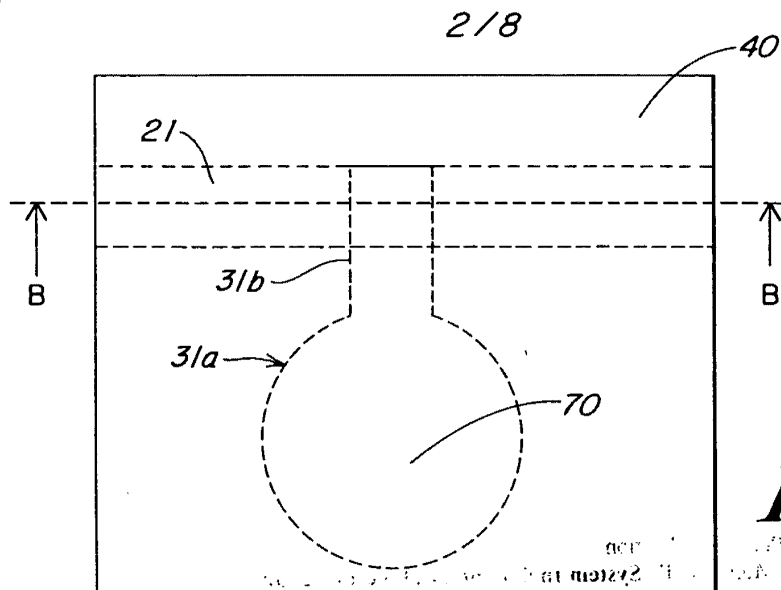


FIG. 4

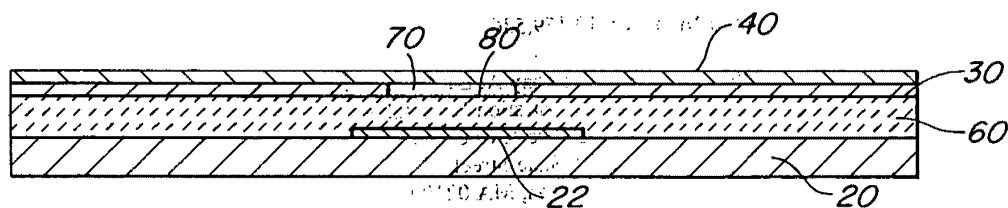


FIG. 5A

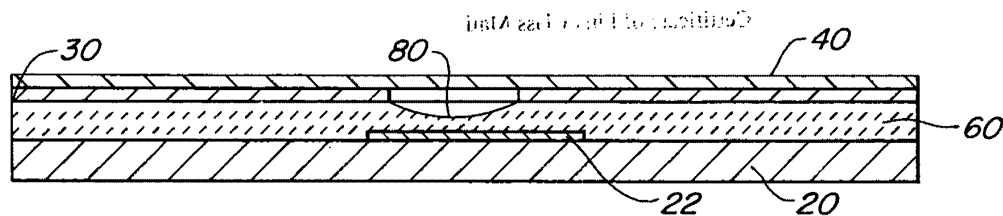


FIG. 5B

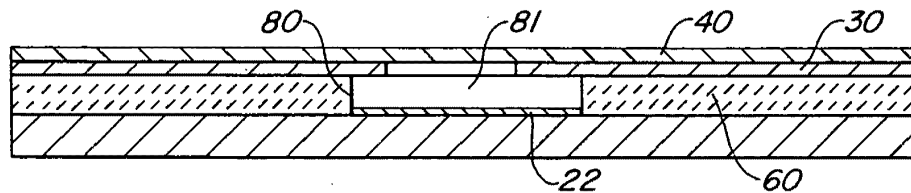


FIG. 5C



3 / 8

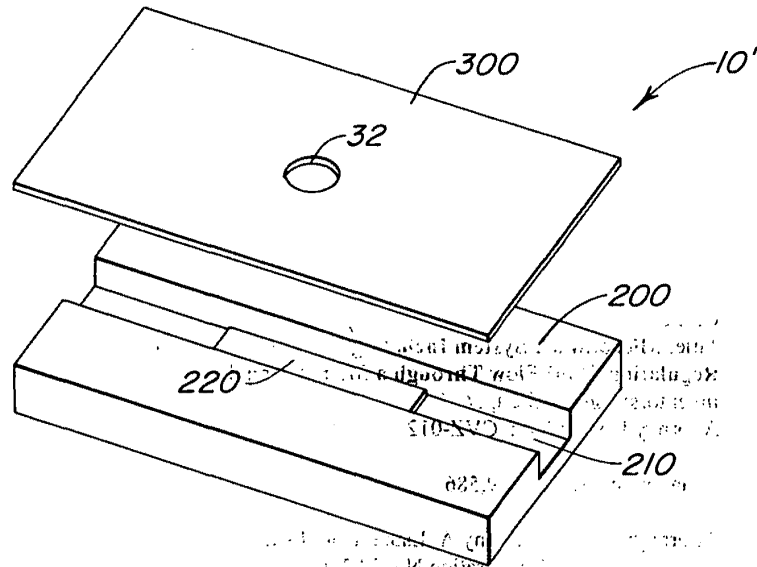


FIG. 6

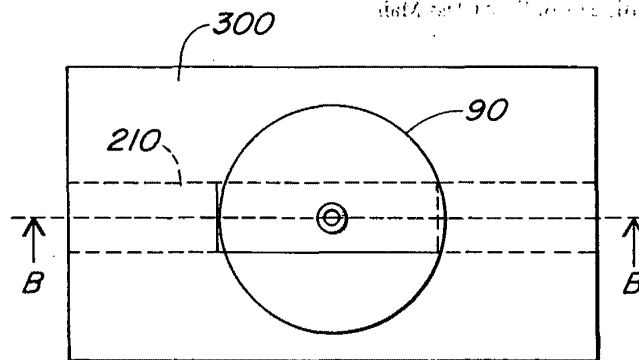


FIG. 7

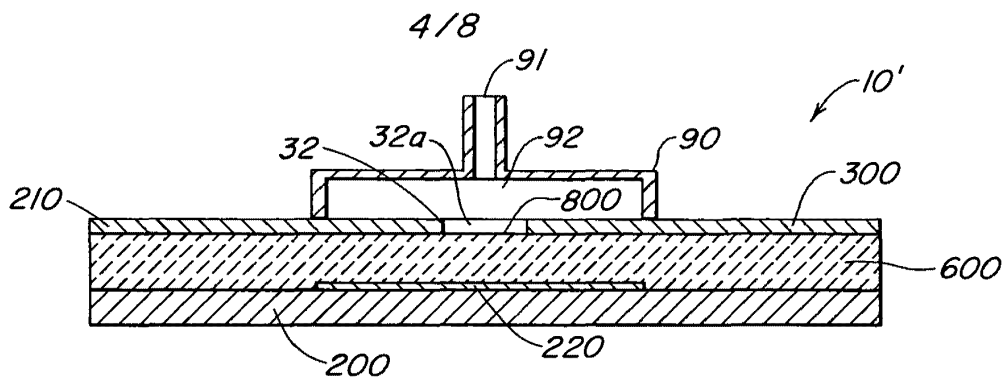


FIG. 8A

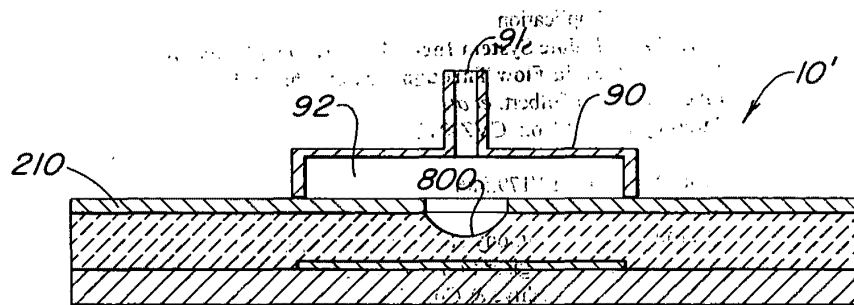


FIG. 8B

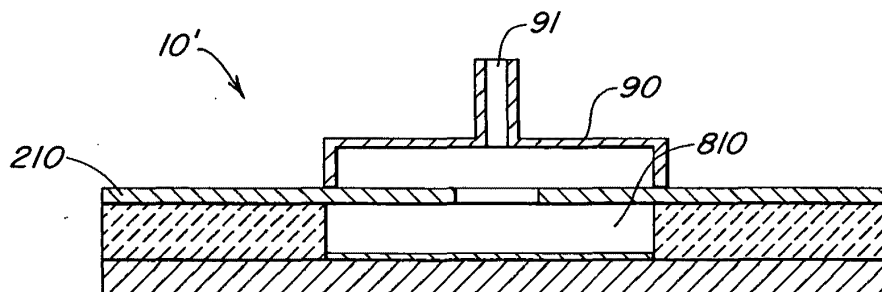


FIG. 8C



5/8

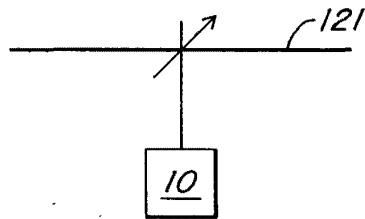


FIG. 9

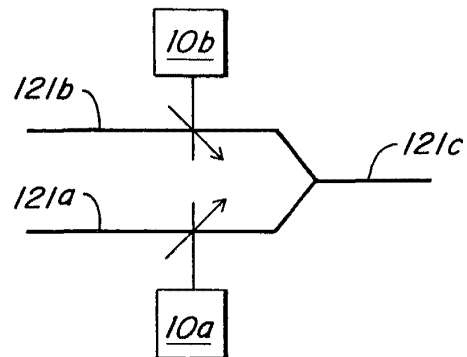


FIG. 10

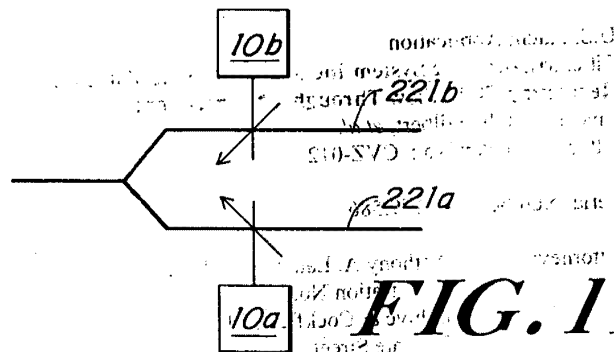


FIG. 11

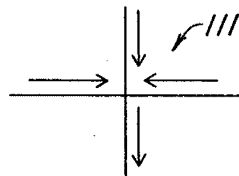


FIG. 12B

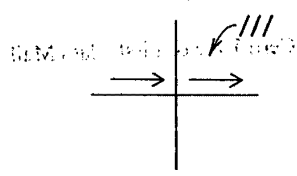
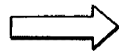


FIG. 12C

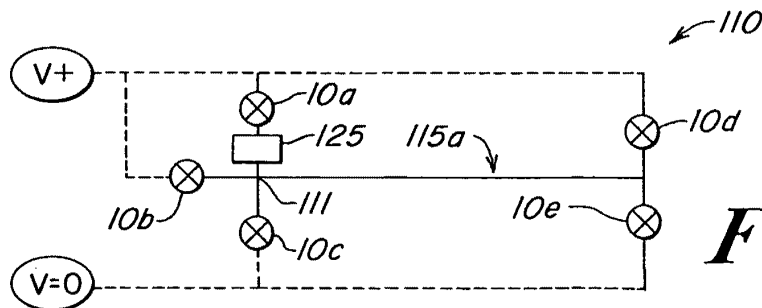


FIG. 12A



6/8

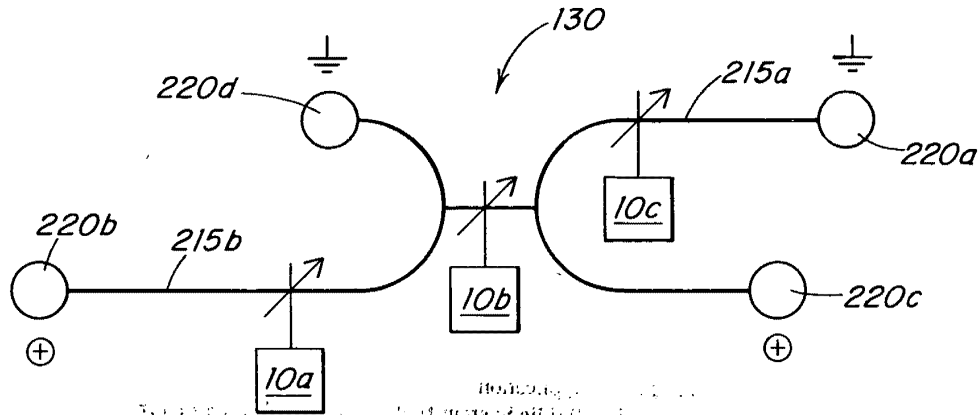


FIG. 13A

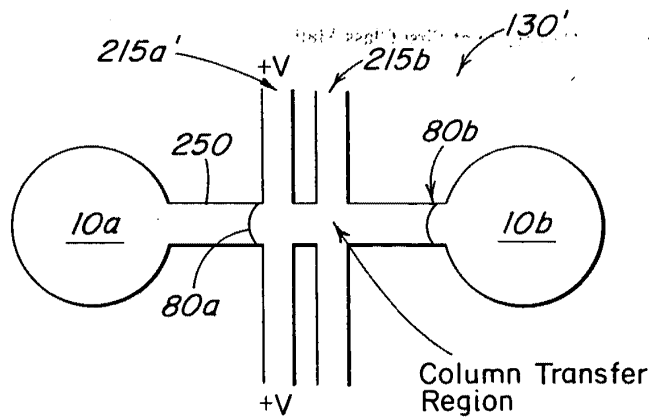


FIG. 13B



7/8

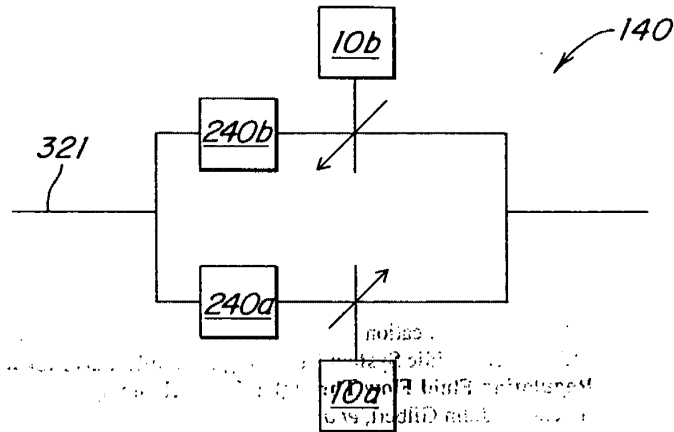


FIG. 14

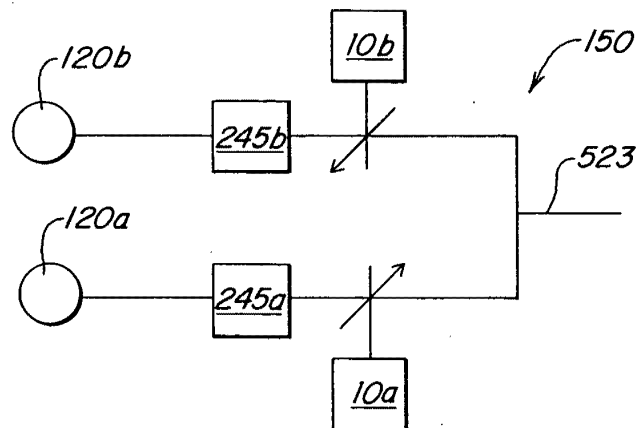
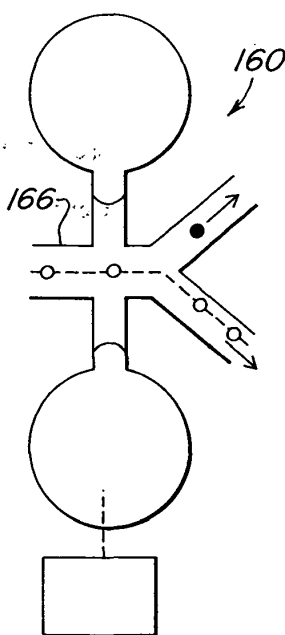
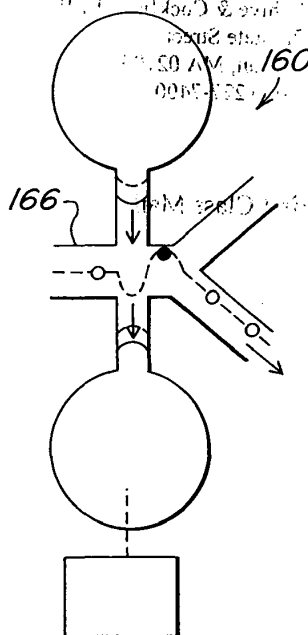
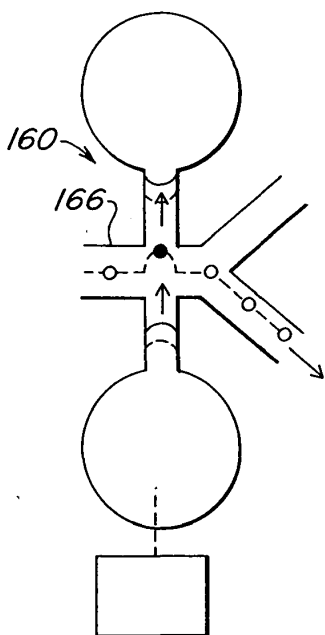
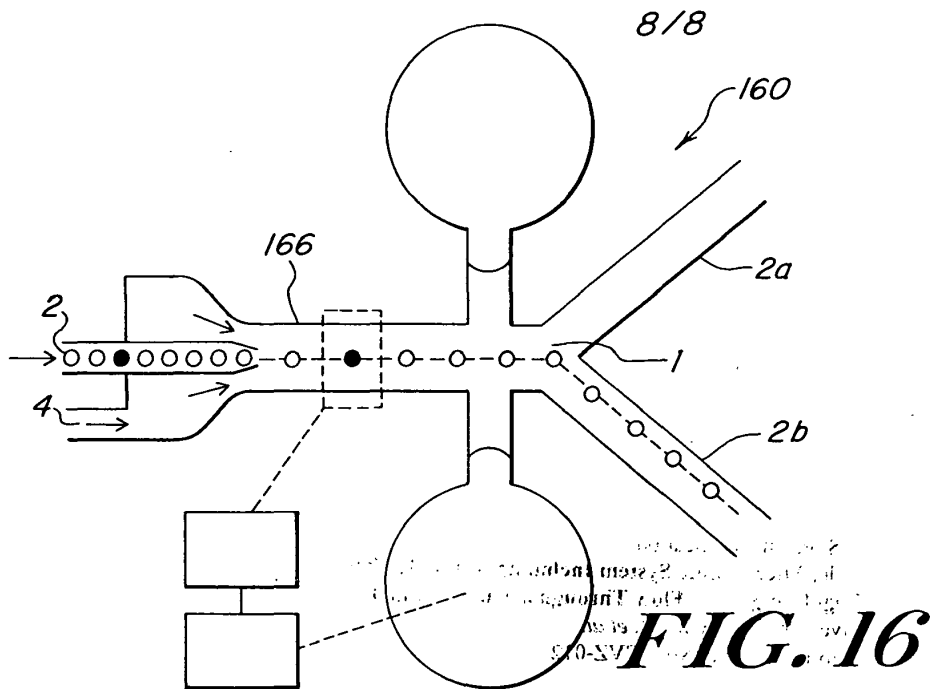


FIG. 15





IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: John Gilbert, *et al.*

Serial No.: 10/179586

Filed: June 24, 2002

For: *Microfluidic System Including a Bubble Valve
for Regulating Fluid Flow Through a Microchannel*

Attorney Docket No.: CVZ-012

Group Art Unit: 3753

Examiner: Not yet assigned

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Commissioner for Patents
Washington, D.C. 20231

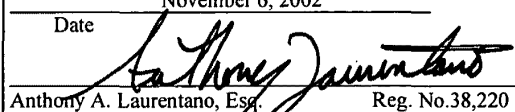
REQUEST FOR TWO-MONTH EXTENSION OF TIME

Dear Sir:

Applicants request a two-month extension of time pursuant to 37 CFR 1.136(a) in which to respond to the Notice to File Missing Parts mailed from the U.S. Patent and Trademark Office on July 19, 2002.

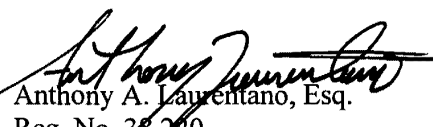
Please charge the appropriate fee of \$400.00 based on large entity status to our Deposit Account No. 12-0080. *A duplicate of this sheet is enclosed.*

I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: Box Missing Parts, Commissioner for Patents, Washington, DC 20231 on:

Date November 6, 2002

Anthony A. Laurentano, Esq. Reg. No. 38,220

Respectfully submitted,

LAHIVE & COCKFIELD, LLP


Anthony A. Laurentano, Esq.
Reg. No. 38,220
Attorney for Applicants

Dated: November 6, 2002

11/15/2002 MBIZUNES 00000058 120080 10179586

01 FC:1252 400.00 CH



Customer Number: 000959

Attorney's
Docket
Number CVZ-012

Declaration, Petition and Power of Attorney for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR
REGULATING FLUID FLOW THROUGH A MICROCHANNEL**

the specification of which:

___ is attached hereto.

X was filed on June 24, 2002 as

X Application Serial No. 10/179,586.

___ and was amended on _____
(if applicable)

I do not know and do not believe that the subject matter of this application was known or used by others in the United States or patented or described in a printed publication in any country before my invention thereof, or patented or described in a printed publication in any country or in public use or on sale in the United States more than one year prior to the date of this application, or first patented or caused to be patented or made the subject of an inventor's certificate by me or my legal representatives or assigns in a country foreign to the United States prior to the date of this application on an application filed more than twelve months (six months if this application is for a design) before the filing of this application; and I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application, that no application for patent or inventor's certificate on the subject matter of this application has been filed by me or my representatives or assigns in any country foreign to the United States, except those identified below, and that I have reviewed and understand the contents of the specification, including the claims as amended by any amendment referred to herein.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S)

I hereby claim the benefit under Title 35, United States Code, §120 of any earlier United States application(s) or PCT international application(s) designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the earlier application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date(s) of the earlier application(s) and the national or PCT international filing date of this application. As to subject matter of this application which is common to my earlier application(s), if any, described below, I do not know and do not believe that the same was known or used by others in the United States or patented or described in a printed publication in any country before my invention thereof, or patented or described in a printed publication in any country or in public use or on sale in the United States more than one year prior to the date(s) of said earlier application(s), or first patented or caused to be patented or made the subject of an inventor's certificate by me or my legal representatives or assigns in a country foreign to the United States prior to the date(s) of said earlier application(s) on an application filed more than twelve months (six months if this application is for a design) before the filing of said earlier application(s); and I acknowledge that no application for patent or inventor's certificate on said subject matter has been filed by me or my representatives or assigns in any country foreign to the United States except those identified herein.

(Application Serial No.)	(Filing Date)	(Status) (patented,pending,aband.)
--------------------------	---------------	---------------------------------------

(Application Serial No.)	(Filing Date)	(Status) (patented,pending,aband.)
--------------------------	---------------	---------------------------------------

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

James E. Cockfield	Reg. No. 19,162	Maria C. Laccotripe	Limited Recognition
Thomas V. Smurzynski	Reg. No. 24,798		Under 37 C.F.R. § 10.9(b)
Ralph A. Loren	Reg. No. 29,325	Debra J. Milasincic	Reg. No. 46,931
Giulio A. DeConti, Jr.	Reg. No. 31,503	David R. Burns	Reg. No. 46,590
Ann Lamport Hammitte	Reg. No. 34,858	Sean D. Detweiler	Reg. No. 42,482
Elizabeth A. Hanley	Reg. No. 33,505	Cynthia L. Kanik	Reg. No. 37,320
Amy E. Mandragouras	Reg. No. 36,207	Theodore R. West	Reg. No. 47,202
Anthony A. Laurentano	Reg. No. 38,220	Shayne Y. Huff	Reg. No. 44,784
Kevin J. Canning	Reg. No. 35,470	Hathaway P. Russell	Reg. No. 46,488
Jane E. Remillard	Reg. No. 38,872	Daniel B. Ko	Reg. No. 47,332
DeAnn F. Smith	Reg. No. 36,683	John S. Curran	Reg. No. 50,445
Peter C. Lauro	Reg. No. 32,360	Lisa M. DiRocco	Reg. No. P51,619
Jeanne M. DiGiorgio	Reg. No. 41,710	Richa Nand	Reg. No. P52,059
Megan E. Williams	Reg. No. 43,270		
Jeremiah Lynch	Reg. No. 17,425		
David J. Rikkers	Reg. No. 43,882		

Send Correspondence to: Anthony A. Laurentano, Esq. at **Customer Number: 000959** whose address is:

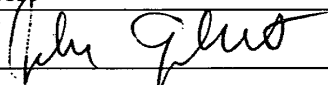
LAHIVE & COCKFIELD, LLP, 28 State Street, Boston, MA 02109

Direct Telephone Calls to:

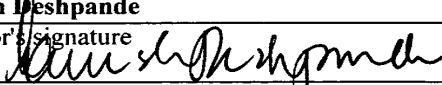
Anthony A. Laurentano, Esq., (617) 227-7400

Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor John Richard Gilbert	
Inventor's signature 	Date 10/28/02
Residence 69 Naples Road, Brookline, MA 02446	
Citizenship United States	
Post Office Address (if different)	

Full name of second inventor, if any Sebastian Böhm	
Inventor's signature	Date
Residence 9 Muirfield Court, IV2 4DP, Inverness, Scotland (UK)	
Citizenship Germany	
Post Office Address (if different)	

Full name of third inventor, if any Manish Deshpande	
Inventor's signature 	Date 10/28/02
Residence 34 Apple Blossom Way, Canton, MA 02021	
Citizenship United States	
Post Office Address (if different)	



#4
Customer Number: 000959

Attorney's
Docket
Number CVZ-012

Declaration, Petition and Power of Attorney for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR
REGULATING FLUID FLOW THROUGH A MICROCHANNEL**

the specification of which:

___ is attached hereto.

X was filed on June 24, 2002 as

X Application Serial No. 10/179,586.

___ and was amended on _____
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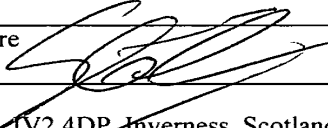
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Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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July 19, 2002

Commissioner for Patents
Washington, D.C. 20231

Re: U.S. Patent Application No.: 10/179586
For: *Microfluidic System Including a Bubble Valve for Regulating Fluid Flow Through a Microchannel*
Inventors: John Gilbert, et al.
Filed: June 24, 2002
Our Ref. No.: CVZ-012

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I enclose herewith for filing in the above-identified application the following:

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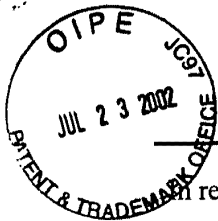
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Respectfully submitted,
LAHIVE & COCKFIELD, LLP

Anthony A. Laurentano
Registration No. 38,220
Attorney for Applicants



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: John Gilbert, *et al.*

Serial No.: 10/179586

Filed: June 24, 2002

For: *Microfluidic System Including a Bubble Valve for
Regulating Fluid Flow Through a Microchannel*

Attorney Docket No.: CVZ-012

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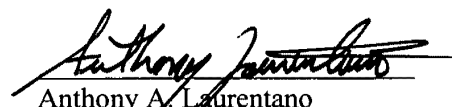
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Respectfully submitted,
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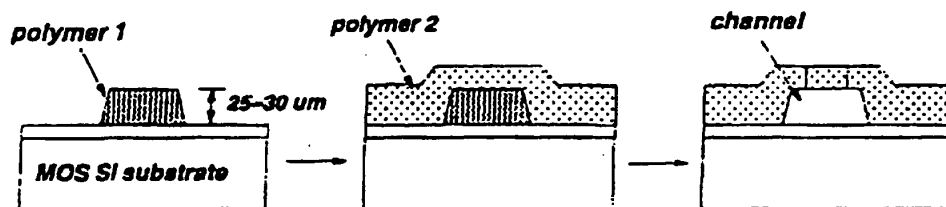
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(71) Applicant (for all designated States except US): THE RE- GENTS OF THE UNIVERSITY OF MICHIGAN [US/US]; Wolverine Tower, Room 2071, 3003 South State Street, Ann Arbor, MI 48109-1280 (US).			
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(54) Title: POLYMER-BASED MICROMACHINING TECHNOLOGY FOR MICROFLUIDIC DEVICES



Simplified fabrication process for plastic channels.

(57) Abstract

The present invention relates to polymer-based micro-electro-mechanical system (MEMS) technology suitable for the fabrication of integrated microfluidic systems, particularly medical and chemical diagnostics system, ink-jet printer head, as well as any devices that requires liquid- or gas-filled cavities for operation. The integrated microfluidic systems may consist of pumps, valves, channels, reservoirs cavities, reaction chambers, mixers, heaters, fluidic interconnects, diffusers, nozzles, and other microfluidic components on top of a regular circuit substrate. This technology is vastly superior than any alternatives available such as glass-based, polysilicon-based MEMS technology as well as hybrid "circuit board" technology because of its simple construction low cost, low temperature processing, and its ability to integrate any electronic circuitry easily along with the fluidic parts.

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**POLYMER-BASED MICROMACHINING
TECHNOLOGY FOR MICROFLUIDIC DEVICES**

This invention was made with U.S. government support under grant NIH-R01-H601044 awarded by the National Institutes of Health. The U.S. government has certain rights in the invention.

FIELD OF THE INVENTION

The present invention relates to compounds and methods for micromachining, and in particular, polymer-based technology for fabricating microfluidic devices.

BACKGROUND

Microfluidic systems are highly useful in medical diagnostics, environmental monitorings, biological food testing, chemical sensing and analysis. Current efforts on the fabrication of microfluidic systems and fluidic technologies have been mainly focused on individual component development. Individual components such as pumps [See M. Esashi *et al.* "Normally Close Microvalve and Micropump Fabricated on a Silicon Wafer," in *International Workshop on Micro Electromechanical Systems (MEMS 89)*, pp. 29-34 (1989); R. Zengerie *et al.*, "A Micro Membrane Pump with Electrostatic Actuation," in *International Workshop on Micro Electromechanical Systems (MEMS 92)*, pp. 19-24 (1992); W. Zang and C.H. Ahn, "A Bi-directional Magnetic Micropump on a Silicon Wafer," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 94-97 (1996)], valves [See T. Ohnstein *et al.*, "Micromachined Silicon Valve," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '90)*, pp. 95-97 (1990); J.G. Smith, "Piezoelectric Micropump with Three Valves Working Peristaltically," *Sensors and Actuators*, Vol. A21-23, pp. 203-206 (1990); Y.-C. Lin *et al.*, "Characteristics of a Polyamide Microvalve," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 113-116 (1996)], fluidic channels [J. Pfahler *et al.*, "Liquid Transport in Micron and Submicron Channels," *Sensors and Actuators*, Vol. A21-23, pp. 431-434 (1990)], reaction chambers [S. Nakagawa *et al.*, "A Micro Chemical Analyzing System Integrated on a Silicon Wafer," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '90)*, pp. 89-94 (1990)], separation stages [D.J. Harrison *et al.*, "Chemical Analysis and Electrophoresis

Systems Integrated on Glass and Silicon Chips," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '92)*, pp. 110-113 (1992); A. Manz *et al.*, "Integrated Electroosmotic Pumps and Flow Manifolds for Total Chemical Analysis Systems," in *Transducers '91*, pp. 939-941 (1991); A. Manz *et al.*, "Planar Chips Technology for Miniaturization and Integration of Separation Techniques into Monitoring Systems: Capillary Electrophoresis on a Chip," *J. Chromatography*, Vol. 593, pp. 253-258 (1992)] and detection techniques [R.C. Anderson, G.J. Bodgdan and R.J. Lipshutz, "Miniaturized Genetic Analysis System," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 258-261 (1996)], have been fabricated using a sundry of technologies. Numerous fluidic propulsional methods have also been developed based on mechanical pumping, pneumatic forces, electroosmosis [D.J. Harrison *et al.*, "Miniaturized Chemical Analysis Systems Based on Electrophoretic Separations and Electroosmotic Pumping," in *Transducers '93*, pp. 403-406 (1993)], dielectrophoresis [H.A. Pohl, *Dielectrophoresis*, Cambridge: Cambridge University Press (1978)], surface tension gradients [M.A. Burns *et al.*, "Microfabricated Structures for Integrated DNA Analysis," *Proc. Natl. Acad. Sci. USA*, 93:5556-5561 (1996); H. Matsumoto and J.E. Colgate, "Preliminary Investigation of Micropumping Based on Electrical Control of Interfacial Tension," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '90)*, pp. 105-110 (1990); G. Beni and M.A. Tenan, "Dynamics of Electrowetting Displays," *J. Appl. Phys.*, Vol. 52, pp. 6011-6015 (1981), bubble generation [L. Lin *et al.*, "Microbubble Powered Actuator," in *Transducers '91*, pp. 1041-1044 (1991)], and evaporation-condensation [T.K. Jun and C.J. Kim, "Microscale Pumping with Traversing Bubbles in Microchannels," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 144-147 (1996)].

However, efforts on system integration of components to date have been limited [S.C. Terry *et al.*, "A Gas Chromatographic Air Analyzer Fabricated on a Silicon Wafer," *IEEE Trans. on Electron Devices*, Vol. ED-26, pp. 1880-1886 (1979); A. van der Berg and P. Bergveld, *Micro Total Analysis Systems*, New York: Kluwer (1994)], which mainly include the use of bulk micromachining and surface micromachining technology. Both of them lack simple construction of components and the capability to integrate all of components with electronic circuitry.

Bulk micromachining technology, which includes the use of glass wafer processing, silicon-to-glass wafer bonding, has been commonly used to fabricate individual microfluidic components. In Europe, this glass-bonding technology has also been used to fabricate

microfluidic systems. In these systems, the control electronics are implemented on a hybrid manner external to the system. This system integration method has several problems. Because these systems rely on bonding of substrates, it is essential that the bonding surfaces create an hermetic seal to prevent the leakage of chemicals and reagents. This poses a great difficulty when interconnection leads are present on the bonding surfaces which prevent the surfaces from being flat. It is well known that it is exceedingly difficult to attain good bonds even using well-characterized techniques such as anodic bonding when steps on the bonding surfaces exceed 0.2 μm . Because of this planarity requirement, these devices require either complex planarization schemes, or the use of diffused leads. Because of these difficulties, only relatively simple fluidic systems can be constructed using this scheme.

Unlike bulk micromachining, surface micromachining technology can be used to fabricate individual fluidic components as well as microfluidic systems with on-chip electronics. In addition, unlike bonded-type devices, hermetic channels can be built in a relatively simple manner using channel walls made of polysilicon [J.R. Webster *et al.*, "Monolithic Capillary Gel Electrophoresis Stage with On-Chip Detector," in *International Conference on Micro Electromechanical Systems (MEMS 96)*, pp. 491-496 (1996)], silicon nitride [C.H. Mastrangelo and R.S. Mullet, "Vacuum-Sealed Silicon Micromachined Incandescent Light Source," in *Int. Electron Devices Meeting (IDEM 89)*, pp. 503-506 (1989)] and silicon dioxide. Surface micromachined channels that are constructed with these thin films have two basic problems. Because the thickness of the films is limited to a few microns, the height of cavities and channels is very small ($< 5 \mu\text{m}$) resulting in sub-pL sample volumes. These exceedingly small sample volumes both strain the requirements for the sensitivity limits of detection schemes and also aggravate the surface adsorption of samples and reagents on the wall which further diminishes the sample concentration. On the fabrication side, due to the strong nature of the silicon based building materials, the formation of long capillaries is difficult to accomplish. This is because the etchants used for the sacrificial etch are relatively slow and in many cases extremely reactive (such as hydrofluoric acid HF). In these structures, it is customary to leave devices in the sacrificial etch solution for many hours. Special passivation layers (primarily silicon nitride SiN) are used to passivate any active electronic devices that must survive the sacrificial etch.

What is needed is micromachining technology that allows for fabrication of channels with a flexibility in cross section and channel length at virtually no loss in system performance. In addition, the technology should be low cost and should not require specialized equipment.

5

SUMMARY OF THE INVENTION

The present invention relates to polymer-based micro-electro-mechanical system (MEMS) technology suitable for the fabrication of integrated microfluidic systems, particularly medical and chemical diagnostics system, ink-jet printer head, as well as any devices that requires liquid- or gas-filled cavities for operation. The integrated microfluidic systems may consist of pumps, valves, channels, reservoirs, cavities, reaction chambers, mixers, heaters, fluidic interconnects, diffusers, nozzles, and other microfluidic components on top of a regular circuit substrate. This technology is vastly superior than any alternatives available such as glass-based, polysilicon-based, MEMS technology as well as hybrid 'circuit board' technology (See e.g. D. VerLee *et al.*, "Fluid Circuit Technology: Integrated Interconnect Technology for Miniature Fluidic Devices," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 9-12 (1996); R.C. Anderson *et al.*, "Miniaturized Genetic Analysis System," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 258-261 (1996); M. Albin *et al.*, "Micromachining and Microgenetics: Where Are They and Where Do They Work Together," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 253-257 (1996), where plastic have been used because of its high versatility to provide transparent surfaces and benign surfaces].

The present invention contemplates both methods and devices. In one embodiment, the present invention contemplates a method for fabricating microchannels, comprising the steps: a) providing a substrate, said substrate having upper and lower surfaces; b) depositing a first polymer layer on said upper surface of said substrate, said first polymer layer having i) a lower surface contacting said upper surface of said substrate and ii) an upper surface; c) depositing a second polymer layer on said upper surface of said first polymer layer, said second polymer layer having i) a lower surface contacting said upper surface of said first polymer layer and ii) an upper surface; and d) sacrificially etching said first polymer layer under conditions such that said second polymer layer comprises walls of a microchannel.

In another embodiment, the present invention contemplates a method for fabricating microchannels, comprising the steps: a) providing a silicon substrate, said silicon substrate having upper and lower surfaces; b) depositing a first polymer layer on said upper surface of said silicon substrate, said first polymer layer having i) a lower surface contacting said upper surface of said silicon substrate and ii) an upper surface; c) photolithographically defining said first polymer layer under conditions such that said first polymer layer has a desired thickness; d) depositing a second polymer layer on said upper surface of said first polymer layer, said second polymer layer having i) a lower surface contacting said upper surface of said first polymer layer and ii) an upper surface; and e) sacrificially etching said first polymer layer under conditions such that said second polymer layer comprises walls of a microchannel.

It is not intended that the microchannels of the present invention be limited to any specific dimensions. In one embodiment, the desired thickness of said first polymer layer is between 0.5 and 200 μ and this thickness defines the height of the channel.

Of course, the present invention contemplates additional fabrication steps. In one embodiment, the present invention contemplates, prior to step (d) the step of photolithographically defining said second polymer layer. In another embodiment, the present invention contemplates after step (d) the step (e) of etching openings in said walls of said microchannel. In yet another embodiment, the present invention contemplates after step (d) and before step (e) the step of depositing a third polymer layer on said upper surface of said second polymer layer.

It is not intended that the present invention be limited by the particular type of polymers. Polymers include, but are not limited to, photoresist, polyamide, benzocyclobutene, polydimethylsiloxane, vapor-deposited p-xylylene, pTFE, PMMA, p-HMDS, polypropylene, starch-based polymers, epoxy, and acrylics. In one embodiment, polymer pairs are selected wherein the first polymer is soluble in a particular solvent, while the second polymer is not soluble in the same solvent. This permits the use of the polymer pair such that sacrificial etching with the solvent (or a mixture of solvents) removes the first polymer but leaves the second polymer intact to serve as the polymer for the microchannel.

It is not intended that the present invention be limited by the particular barrier layer if used. The barrier layers include, but is not limited to, metal, stack of different metals, polymers, silicon-based materials, and other inorganic materials.

The present invention contemplates numerous arrangements of the various polymer layers. For example, in one embodiment, the present invention contemplates a method for

fabricating microchannels, comprising the steps: a) providing a silicon wafer, said silicon wafer having upper and lower surfaces; b) depositing a first layer of a first polymer on said upper surface of said silicon wafer, said first polymer layer having i) a lower surface contacting said upper surface of said silicon wafer and ii) an upper surface; c) depositing a second polymer layer on said upper surface of said first layer, said second polymer layer having i) a lower surface contacting said upper surface of said first layer and ii) an upper surface; d) photolithographically defining said second polymer layer under conditions such that said second polymer layer has a thickness between 0.5 and 200 μ m; e) depositing a second layer of said first polymer on said upper surface of said second polymer layer, said second layer of said first polymer having i) a lower surface contacting said upper surface of said second polymer layer and ii) an upper surface; f) sacrificially etching said second polymer layer under conditions such that said first and second layers of said first polymer comprise walls of a microchannel, said microchannel having a height defined by said thickness of said second polymer layer of step (d); and g) etching one or more openings in said walls of said microchannel.

This latter embodiment can also contain additional polymers. In one embodiment, the method further comprises after step (e) and before step (f) the step of depositing a layer of a third polymer on said upper surface of said second layer of said first polymer.

Again, the present invention is not limited to particular polymers. In the latter embodiment of the method of the present invention, it is preferred that said first and second layers of said first polymer comprise vapor-deposited p-xylylene.

The present invention is not limited to the nature or number of openings. In one embodiment, first and second openings are etched, said first opening serving as an inlet and said second opening serving as an outlet. In one embodiment, said openings are etched from said lower surface of said silicon wafer into said lower surface of said first layer of said first polymer. In another embodiment, said openings are etched from said upper surface of said layer of said third polymer into said upper surface of said second layer of said first polymer.

The polymer-based micromachining technology proposed here encompasses the combined benefits of the plastic fluidic technologies while capable of integration of active microfluidic and electronic devices on a monolithic package. Hermetically sealed channels can be fabricated with a flexibility in cross section and channel length at virtually no loss in system performance. System integration is realized by the ability to fabricate various fluidic components using the same process on top of standard yet complex MOS control circuitry. In

addition, the polymer technology of the present invention is very low cost and does not require specialized equipment.

The devices of the present invention, once fabricated, have a variety of uses. In one embodiment, the present invention contemplates a polymer microchannel fabricated on a silicon substrate, wherein said polymer microchannel is capable of conveying liquids or gases (or both). The present invention is not limited by the nature of the liquid or gas. In one embodiment, the present invention contemplates a polymer microchannel fabricated on a silicon substrate, said microchannel containing one or more microdroplets. In another embodiment, the present invention contemplates a polymer microchannel fabricated on a silicon substrate, said microchannel connected to a reaction chamber, said reaction chamber containing biological reactants.

It is not intended that the present invention be limited by the nature of the flow-directing means used to convey fluids through the polymer channels of the present invention. In one embodiment, the present invention contemplates a device comprising a polymer channel, said polymer channel comprising one or more electrodes positioned such that they will be in contact with a liquid sample placed in said channel. The present invention also contemplates a method of conveying liquid in a microchannel, comprising introducing a liquid into an embodiment of such a device. In one embodiment, two electrodes are employed and a potential is applied between the two electrodes. At both ends of the electrodes, hydrolysis takes place and a bubble is generated. The gas bubble continues to grow as the electrodes continue pumping electrical charges to the fluid. The expanded bubble creates a pressure differential between the two sides of the liquid drop which eventually is large enough to push the liquid forward and move it through the polymer channel.

25 DEFINITIONS

The following definitions are provided for the terms used herein:

The term "biological reactions" is used herein to mean reactions involving biomolecules (and biological reactants) such as enzymes (*e.g.*, polymerases, nucleases, etc.) and nucleic acids (both RNA and DNA). Biological samples are those containing biomolecules, such proteins, lipids, nucleic acids. The sample may be from a microorganism (*e.g.*, bacterial culture) or from an animal, including humans (*e.g.* blood, urine, etc.). Alternatively, the sample may have been subject to purification (*e.g.* extraction) or other treatment. Biological reactions require some degree of biocompatibility with the device. That

is to say, the reactions ideally should not be substantially inhibited by the characteristics or nature of the device components. To this end, in one embodiment, the polymer-based technology of the present invention contemplates polymer-based microchannels comprising biocompatible polymers that do not inhibit biological reactions.

5 "Chemical reactions" means reactions involving chemical reactants, such as inorganic compounds. Again, it is desired that the reactions should not be substantially inhibited by the characteristics or nature of the device components. To this end, in one embodiment, the polymer-based technology of the present invention contemplates polymer-based microchannels comprising polymers that do not inhibit chemical reactions.

10 "Channels" are pathways through a medium (e.g., silicon) that allow for movement of liquids and gasses. Channels thus can connect other components, *i.e.*, keep components "in liquid communication." "Microdroplet transport channels" are channels configured (in microns) so as to accommodate "microdroplets." While it is not intended that the present invention be limited by precise dimensions of the channels or precise volumes for
15 microdroplets, illustrative ranges for channels and microdroplets are as follows: the channels can be between 0.5 and 200 microns in depth (preferably between 10 and 100 μm) and between 50 and 1000 μm in width (preferably 500 μm), and the volume of the microdroplets can range (calculated from their lengths) between approximately one (1) and (100) nanoliters (more typically between ten and fifty).

20 The term "conveying" is used herein to mean "causing to be moved through" as in the case where a microdroplet is conveyed through a transport channel to a particular point, such as a reaction region. Conveying can be accomplished via flow-directing means.

"Flow-directing means" is any means by which movement of liquid (e.g. a microdroplet) in a particular direction is achieved. A variety of flow-directing means are
25 contemplated, including but not limited to pumps such as the "bubble pump" described herein. A preferred directing means employs a surface-tension-gradient mechanism in which discrete droplets are differentially heated and propelled through etched channels. For continuous flow of liquids, pumps are contemplated.

"Initiating a reaction" means causing a reaction to take place. Reactions can be
30 initiated by any means (e.g., heat, wavelengths of light, addition of a catalyst, etc.). The present invention contemplates initiating reactions in the channels and reaction chambers fabricated according to the methods of the present invention.

"Liquid barrier" or "moisture barrier" is any structure or treatment process on existing structures that prevents short circuits and/or damage to electronic elements (e.g., prevents the destruction of the aluminum heating elements). In one embodiment of the present invention, the liquid barrier comprises a first silicon oxide layer, a silicon nitride layer, and/or a second silicon oxide layer.

"Nucleic Acid Amplification" involves increasing the concentration of nucleic acid, and in particular, the concentration of a particular piece of nucleic acid. A preferred technique is known as the "polymerase chain reaction." Mullis, *et al.*, U.S. patents Nos. 4,683,195 and 4,683,202, hereby incorporated by reference, describe a method for increasing the concentration of a segment of target sequence in a mixture of genomic DNA without cloning or purification. This process for amplifying the target sequence consists of introducing a molar excess of two oligonucleotide primers to the DNA mixture containing the desired target sequence. The two primers are complementary to their respective strands of the double-stranded sequence. The mixture is denatured and then allowed to hybridize. Following hybridization, the primers are extended with polymerase so as to form complementary strands. The steps of denaturation, hybridization, and polymerase extension can be repeated as often as needed to obtain a relatively high concentration of a segment of the desired target sequence. The length of the segment of the desired target sequence is determined by the relative positions of the primers with respect to each other, and therefore, this length is a controllable parameter. By virtue of the repeating aspect of the process, the method is referred to by the inventors as the "Polymerase Chain Reaction" (hereinafter PCR). Because the desired segment of the target sequence become the dominant sequences (in terms of concentration) in the mixture, they are said to be "PCR-amplified."

DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic of one embodiment of an integrated microfluidic system using the technology of the present invention.

Figure 2 is a photograph of an electron micrograph of a polymer channel made according to the present invention. Figure 2 (a) is a top view and Figure 2 (b) is a cross-section.

Figure 3 is a schematic showing a simplified fabrication method of the present invention.

Figure 4 (a) shows the top view of a microchannel with toptype inlet fabricated using the methods of the present invention. Figure 4 (b) is a closeup electron-micrograph showing the three polymer construction of a channel made according to the methods of the present invention.

5 Figure 5 (a) shows the top view of a thermal cycling chamber constructed using the methods of the present invention. Figure 5(b) shows the cross-section of a similar PCR thermal cycling chamber showing the large volume of the cavity.

Figure 6 is a series of schematics showing the basic process steps of one embodiment of the fabrication method of the present invention.

10 Figure 7 is a schematic showing the simple suction pump.

Figure 8 is a schematic showing the cross-section of a pass-through valve implemented using the polymer based channel technology of the present invention.

Figure 9 is a schematic showing one embodiment of a bubble pump and capillary valve.

15 Figure 10 is a schematic showing liquid movement via the bubble pump and capillary valve.

Figure 11 shows another embodiment of a reaction chamber constructed using the methods of the present invention.

20 Figure 12 shows another embodiment of a thermocompression suction pump fabricated according to the methods of the present invention.

Figure 13 is a schematic showing one embodiment of the fabrication method for the bubble pump and capillary valve.

DESCRIPTION OF THE INVENTION

25 The present invention relates to polymer-based micro-electro-mechanical system (MEMS) technology suitable for the fabrication of integrated microfluidic systems, particularly medical and chemical diagnostics system, ink-jet printer head, as well as any devices that requires liquid-or gas-filled cavities for operation. The integrated microfluidic systems may consist of pumps, valves, channel, reservoirs, cavities, reaction chambers,
30 mixers, beaters, fluidic interconnects, diffusers, nozzles, and other microfluidic components on top of a regular circuit substrate.

Devices fabricated under this invention consist of two planar levels of functionality (See Figure 1). The top level consists of a polymer-based microfluidic plane, 30-50 μ thick

that is constructed on top of a regular silicon substrate. This plane of functionality contains all the microfluidic components of the diagnostic system such as channels, pumps, valves, thermal cycling reactor chambers, reservoirs, and electrophoresis stages. Beneath the microfluidic plane, the control, detection, drive and communication electronics are constructed in a conventional CMOS substrate chip. A series of holes are etched through the silicon substrate using anisotropic etching thus forming sample and reagent inlets and providing access to the microfluidic plane.

Figure 1(b) shows the proposed packaging assembly. First, access holes are ultrasonically drilled through a PGA ceramic package. The two-plane chip is mounted on the package and wire bonds are connected on the lead side for the electrical interconnects. The "fluidic" interconnects of the system are on the opposite side of the chip and hence do not interfere with the electrical connections. The chip cavity is next closed thus isolating the fragile electronic and microfluidic components from the surrounding environment.

Figure 2 shows SEM photographs of 25 μ -high, 3 mm-long polymer channels with frontside inlet. The details of the fabrication process are discussed in the Experimental section.

The proposed technology is suitable for the construction of a wide range of automated analytical instruments hence serving as a general testbench. When properly constructed, the testbench components can be configured to perform many different functions thus in essence forming a "fluidic microprocessor". The present invention contemplates the use of a common fluidic interconnect (*i.e.*, a fluidic bus) to move samples from any reservoir (or fluidic register) to any other, as well as allowing for controlled mixing. The set of mixing operations performed by the fluidic processor can be controlled by an external logic circuit.

The invention of polymer-based micromachining technology is vastly superior than those based on wafer bonding bulk micromachining, polysilicon surface micromachining, and hybrid plastic 'circuit board' technology in the following six categories. (a) The microfluidic plane fabrication is implemented by deposition of low-temperature layers that do not degrade or change the underlying circuit characteristics or its conventional process flow. (b) The fluidic-plane is fabricated using weak chemicals that do not attack the circuit plane in any way. Therefore, complex microfluidic devices can be fabricated using a regular MOS substrate plane containing the control circuitry, and a polymer-based microfluidic plane constructed on top of it. (c) Leak-tight channels are formed due to the conformality of the polymer deposition (a severe problem present in glass bonded devices): (d) Tall channels and

chambers of different heights can be easily fabricated. Unlike silicon-based films, these polymers can be quite thick with a thickness reported as high as 200 μ . Currently we can fabricate channels that range from 0.5 to 100 μ in height. (e) Very long channels can be fabricated with short etching times (also a problem with poly-Si). (f) Polymer channel walls do not have the severe surface adsorption problems observed in silicon and glass walls. (g) Polymer channels are optically transparent and are therefore are much simpler to test. (h) Its process simplicity and its capability of integrating individual fluidic components together make integrated microfluidic system possible. (i) Its batch-processing ability make microfluidic system inexpensive.

The following sections show several fabrication processes of microfluidic components. These microfluidic components and their process flows are presented to demonstrate the feasibility of polymer-based technology to fabricate the microfluidic systems. It is not intended that the present invention be limited by a particular type of fabrication process.

I. Selection of Polymers and Polymer Pairs

As noted above, it is not intended that the present invention be limited by the particular type of polymers. In one embodiment, polymer pairs are selected wherein the first polymer is soluble in a particular solvent, while the second polymer is not soluble in the same solvent. This permits the use of the polymer pair such that sacrificial etching with the solvent removes the first polymer but leaves the second polymer intact to serve as the polymer for the microchannel.

Selection of polymer pairs and solvents can readily be achieved by making reference to known solubilities of particular polymers with particular solvents. An example of such known solubilities is shown in the Table below (where "+" means soluble, "-" means insoluble, "(+)" means soluble at high temperatures). Specifically, illustrative solvents and polymers are given along with their corresponding δ_1 and δ_2 values.

Illustrative Solubilities and Solubility Parameters of Polymers					
Solvent		Solubility of the Polymer			
	δ_1	Poly(isobutene) $\delta_2 = 7.9$	Poly(methyl methacrylate) $\delta_2 = 9.1$	Poly(vinyl acetate) $\delta_2 = 9.4$	Poly(hexamethylene adipamide) $\delta_2 = 13.6$
Decafluorobutane	5.2	-	-	-	-
Neopentane	6.25	+	-	-	-
Hexane	7.3	+	-	-	-
Diethyl ether	7.4	-	-	-	-
Cyclohexane	8.2	+	-	-	-
Carbon tetrachloride	8.62	+	+	-	-
Benzene	9.2	+	+	+	-
Chloroform	9.3	+	+	+	-
Butanone	9.3	-	+	+	-
Acetone	9.8	-	+	+	-
Carbon disulfide	10.0	-	-	-	-
Dioxane	10.0	-	+	+	-
Dimethyl formamide	12.1	-	+	+	(+)
<i>m</i> -Cresol	13.3	-	+	+	+
Formic acid	13.5	-	+	-	+
Methanol	14.5	-	-	-	-
Water	23.4	-	-	-	-

The utility of the solubility parameter approach is that δ (solubility parameter) can be calculated for both the polymer and solvent. There are three separate forces which together influence the δ 's numerical value. These include: 1) the number of dispersive forces present; 2) the number of dipole-dipole forces present; and 3) the number of hydrogen bonding forces present. As a first approximation and in the absence of strong interactions such as hydrogen bonding, solubility of a polymer in a solvent can be expected if $\delta_1 - \delta_2$ is less than 1.7 - 2.0, but not if appreciably larger.

Thus, as a general rule of thumb, a polymer is expected to be soluble in a solvent where δ_1 is approximately equal to δ_2 . Of course, it is contemplated that these values need

not be equal. The present invention contemplates using polymers and solvents where the values of δ_1 and δ_2 are within approximately 2.0 units (more preferably within approximately 1.0 unit and most preferably within approximately 0.5 units).

It is not intended that the present invention be limited to the solvents and polymers set forth in the above Table. Other solvents and polymers are contemplated. For example, soluble solutions of poly(styrene) ($\delta_2 = 9.3$), are readily obtained with butanone ($\delta_1 = 9.3$) and dimethylformamide ($\delta_1 = 12.1$), but not with acetone ($\delta_1 = 9.8$). In the liquid acetone, the acetone molecules form dimers through dipole-dipole interactions. In these dimers, the keto groups are shielded by the methyl groups, and so are no longer able to solvate the phenyl groups of the poly(styrene). The addition of the cyclohexane ($\delta_1 = 8.2$) decreases the tendency of the acetone molecules toward association, and thus frees keto groups for solvation. For the same reason, it is also possible to have 40% solutions of poly(styrene) in acetone. Butanone, on the other hand, is "internally diluted" by the additional CH_2 group, and is therefore a solvent over the whole concentration range.

Similar reasoning applies to mixtures of solvents. A solvent with a lower solubility parameter (*i.e.* than that of the polymer) can be combined with a solvent with a higher solubility parameter (*i.e.* than that of the polymer). Poly(acrylonitrile) ($\delta_2 = 12.8$), for example dissolves in both dimethylformamide ($\delta_1 = 12.1$) and malodinitrile ($\delta_1 = 15.1$), but not in a mixture of the two. In some embodiments, the present invention contemplates etching with solvent mixtures.

II. Basic Polymer Process: Polymer Channels

The basic fabrication process begins with a conventional silicon CMOS processed substrate, as shown in Figure 3. In this figure, inlet and outlet are etched from the front side. However, backside inlet and outlet can easily be made by etching holes into the substrate from the backside using an anisotropic etchant such as ethylenediamine pyrazine (EDP), tetramethylammonium hydroxide (TMAH) or even XeF_2 , stopping at the passivation oxide or nitride (also see Section III). Other alternatives on passivation layer includes oxide/nitride/oxide and low stress silicon-rich silicon nitride. Next, the microfluidic plane is constructed using the simplified process shown below. First a thick polymer layer is deposited and photolithographically defined onto the substrate with the thickness required for the channel height (0.5-100 μ). Next a second polymer is deposited serving as the walls of the channels. The second polymer is next etched defining the extent of the channel walls. Holes

to polymer 1 can be etched either from the front or through the backside by plasma etching the passivation oxide (see Section III). Polymer 1 is now sacrificially etched leaving a channel behind. In some cases where polymer 2 may react with polymer 1, a third material serves as a barrier layer, is deposited in between polymer 1 and polymer 2. The barrier layer has to be relatively conformal to provide a complete physical contact of polymer 1 from polymer 2.

Figure 4 is an example of a simple polymer channel: Figure 4(a) shows the top view of a 100 μ wide, 25 μ -high channel with toptype inlet fabricated using this process. Channels as long as 3mm are completely sacrificially released in under 20 minutes time. These channels are optically clear. Figure 4(b) shows a closeup SEM showing the three polymer construction of a 15 μ -high channel with 40 μ -thick walls.

In this example, photodefinable polyamide is used a polymer 2, vapor-deposited p-xylylene as the thin intermediate barrier material, and thick photoresist as polymer 1. The details of embodiments of the fabrication process are set forth in the Examples. It is not intended that the present invention be limited by the particular type of polymers. Polymers include, but are not limited to, photoresist, polyamide, benzocyclobutene, polydimethylsiloxane, vapor-deposited p-xylylene, pTEE, PMMA, p-HMDS, polypropylene, starch-based polymers, epoxy, and acrylics. In addition, it is not intended that the present invention be limited by the particular barrier layer. The barrier layers include, but is not limited to, metal, stack of different metals, pTFE, polymers, silicon-based materials, and other inorganic materials. Fluidic Interconnects can also easily be fabricated as shown in Example 2 (below).

III. Fabricating Reservoirs, Mixers, Reaction Chambers, Cavities

Reservoirs, mixers, reaction chambers, and any cavities can be formed by proper enlargement of the channels while heaters, detectors, and active circuits reside on the CMOS plane below. Figure 5 shows an example of a reaction chamber. The details of one embodiment of the fabrication process are set forth in the Examples. Figure 5a shows the top view of 1 mm², 25 μ m-high thermal cycling chamber constructed using this process. The dots on the cavity are posts periodically spaced inside the cavity which enhance mixing and stiffen the cavity to prevent it collapse. The cavity is connected at both ends with short channels leading to top inlets and outlets. Figure 5(b) shows the cross-section of a similar PCR thermal cycling chamber showing the large volume of the cavity. Ink-jet printer head

can be fabricated similar to the PCR reactor except that there are arrays of etch holes (circular or square) on the structural polymer. Instead of forming post in the large cavity, internal walls are built so that each etch hole is isolated and is connected to an internal reservoir, which stores ink. Under each isolate cavities, heaters are placed or suspended on top of the substrate.

IV. Fabricating Actuators

The same process also allows the fabrication of actuators such as valves and pumps. The polymer process must include the following layers: (1) a sacrificial polymer layer for forming cavities and channels; (2) a thick elastic structural polymer layer for forming elastic diaphragms needed in pumps and valves. This thin polymer can also serve as a barrier layer in some cases; (3) a thick structural polymer layer for construction of thick channel walls and bossed diaphragms; and (4) a metal layer that can carry current either embedded between (2) and (3) or on top of layer (3). Figure 6 shows the basic process steps carried out to fabricate the actuator.

The process begins with a conventional CMOS, bipolar, or BiCMOS substrate passivated by a layer of silicon dioxide. Metal lines can be present on the circuit side if desired. The next step in the process consists of the opening of holes on the backside oxide by plasma etching. These holes will provide access to the microfluidic polymer plane. After this step, the circuit substrate is immersed in a silicon rich TMAH solution that anisotropically etches the substrate all the way to the passivation oxide layer. The cavities formed by this etch are bounded by the 111 crystal planes of the substrate. The silicon saturated TMAH solution will not attack any aluminum wires exposed on the surface [U. Schanzenberg *et al.*, "TMAHW Etchants for Silicon Micromachining," in *Transducers '91*, pp. 815-818 (1991)].

After rinsing and drying the substrates, a passivation layer is deposited on top of the circuits and subsequently patterned. The passivation layer is needed if the system being built must handle fluids that contain mobile ions such as sodium ions and potassium ions (many biochemical reactions require weak KCl buffer solutions) which can easily diffuse through the oxide passivation of the circuit plane. Several types of passivation layers can be used (or even none). Conventional materials such as sputtered SiN serve the purpose quite well. Polymers can also be used as a barrier to the contaminant diffusion. The barrier layer is next photolithographically defined and etched on the areas leading to the backside inlet and metal contact areas.

Wafers that have reached this state are ready for the construction of the microfluidic plane. First a thick polymer 1 layer is deposited and etched on top of the substrate. This thick polymer serves as a spacer layer that determines the height of channels and microfluidic components. Multiple thicknesses on the same wafer can be obtained through time etching or multiple depositions. The range of thicknesses for this polymer is between 0.5-200 μ . Next a thin layer of polymer (polymer 2) 0.5-2 μ thick is deposited uniformly onto the wafer. Polymer 2 serves as a thin structural layer that is easily deflected, and as a barrier layer in some cases. Its main purpose is for the fabrication of flexible membranes required by the pumps and valves described earlier. Next, a thin layer 1-2 μ of aluminum is evaporated on top of polymer 2 and it is photolithographically defined to form parallel conductors and interconnects used in the fluidic actuators. The process is followed by the deposition and patterning of a thick polymer (polymer 3) that provides structural support for the channels and microfluidic component walls. Next holes are opened on the thin polymer 2 layer leading to bonding pads on the circuit plane and also providing access to polymer 1 if desired from the front side. At this point the remainder passivation oxide that separates polymer 1 from the backside inlets is etched by plasma etching. In the last step of the process, polymer 1 is sacrificially etched thus releasing the channels and fluidic actuators. The chips are next mounted on a ceramic package and the electrical leads are formed by wire bonding. As an example, polymer 1 can be photoresist, polymer 2 can be p-xylylene, and polymer 3 can be polyamide.

Droplets of the samples must be moved to the various parts of the system in order to perform various tests on the fluidic chip. A thermocompression suction pumps that create a pressure differential between the two sides of the liquid drop can be used. A simple suction pump can be constructed as shown in Figure 7. The pump basically consists of a heater and a valve. This device is constructed with an additional thin polymer layer and an embedded metallization inserted on the microfluidic plane. The construction of this type of pump is thus entirely compatible with the polymer-based technology. This pump basically consists of a heater constructed on a polysilicon heater constructed on the MOS plane placed under the polymer channel, and an exhaust valve. The exhaust valve consists of an enlarged version of the channel with a central outlet. On top of the polymer valve, a series of parallel aluminum wires are patterned. The aluminum wires are placed between a thin polymer and a thick one thus forming a boss region and a diaphragm. This valve is magnetically actuated upon application of a transversal magnetic field B (through an external permanent magnet). The

valve either closes or opens depending on the direction of the current I on the parallel conductors. Magnetic actuation was chosen for the valve because the tall channels generated by the polymer-based process have very high pull-in voltages hence rendering electrostatic actuation impractical.

5 The thermocompression pump operates as follows: first, the exhaust valve is opened and the heater is powered up. Next the valve is closed and the heater is turned off thus forming a partial vacuum on the channels as the trapped air cools down. This partial vacuum propels the drop forward until the pressure difference disappears. The cycle is repeated for continuous pumping. Propulsion of the droplet in the reverse direction can also be achieved
10 by expanding the gas rather than contracting it. This type of simple pump can generate pneumatic pressure differences as high as 0.5μ , well above the threshold needed for the onset of motion of droplets in capillaries. If the pneumatic drop motion mechanism is used, *pass-through valves* are needed into the system. These valves basically constrict the channels at various points in the system thus acting as gates that block the passage of liquids. Pass-
15 through valves are necessary to impede the continuous drawing of liquids onto the capillary. This situation occurs due to the fact that when droplets are moved inside the capillary channels, they form a partial vacuum behind them which can in turn move drops on other parts of the system. Pass through valves impede the entrance of these drops onto places where there exist temporary vacuum pressure differences. It is also important to point out that once a channel
20 is blocked, it is necessary to open an exhaust valve (such as those made for the thermocompression pump) attached to the same end as the blocking valve if additional liquid drop motion is desired. The exhaust valve provides an additional inlet that impedes the formation of a vacuum behind the moving drop that would ultimately stop and additional drop motion.

25 This brings the important point that pumping of discrete drops can only be accomplished when one of channel ends is open to the environment. This problem has been pointed out by Anderson (*supra*) who has proposed the use of permeable membranes to eliminate this problem. Figure 8 shows the cross-section of a pass-through valve implemented using the polymer based channel. The valve basically consists of a flat round segment of an
30 enlarged channel that is constructed in its collapsed form by the deliberate removal of polymer 1. A patch of polymer 3 (Teflon) is placed under the valve such that polymer 2 does not stick to the surface. The valve is opened or closed by applying a current to the

conductors above the pass-through valve which buckle the diaphragm upward thus opening the valve.

V. Bubble Pumps and Capillary Valves

5 As noted above, it is not intended that the present invention be limited by the nature of the flow-directing means used to convey fluids through the polymer channels of the present invention. In one embodiment, the present invention contemplates a polymer channel comprising one or more electrodes in contact with the liquid sample. A schematic of one embodiment of the bubble pump and capillary valve is shown in Figure 9. The bubble pump
10 comprises a polymer channel with several electrodes (e.g. Ti/Pt electrodes) in contact with the liquid sample. When coupled with the capillary valve, the bubble pump can actuate a certain quantity of fluidic samples along the polymer chip. The capillary valve is essentially a narrow section of a polymer channel. In operation, the fluidic sample is first injected in the inlet reservoir. As soon as the fluid is loaded, it moves in the channel by capillary force.
15 The fluid then passes the narrow section of the channel but stops at the edge where the channel widens again (see Figure 10A). After the fluidic sample is loaded, a potential is applied between two electrodes. At both ends of the electrodes, hydrolysis occurs and bubble is generated. The bubble keeps on growing as the electrodes continue pumping electrical charges to the fluid (Figure 10B). The expanding bubble then creates a pressure differential
20 between the two sides of the liquid drop, which eventually large enough to push the liquid forward (Figure 10C).

The combination of bubble pump and capillary valve is an excellent fluid propelling device. This actuating device does not require any moving parts and is easy to fabricate. In addition, the device produces a well-controlled fluid motion, which depends on the bubble
25 pressure. The bubble pressure is controlled by the amount of charges pumped by the electrodes. Furthermore, the power consumption of the device is minimal.

EXPERIMENTAL

The following examples serve to illustrate certain preferred embodiments and aspects
30 of the present invention and are not to be construed as limiting the scope thereof.

EXAMPLE 1

This example describes one embodiment of the fabrication method of the present invention. More specifically, this example describes one embodiment of the process flow for channels and cavities with frontside inlets and outlets.

- 5 The process starts with a 4 inch silicon wafer. Thereafter, the steps are as follows:
0. (Optional) Deposit 2 μ -thick p-xylylene with primer.
 1. HMDS is spread at 200 rpm for 16s, and spun at 4000rpm for 30s.
 2. Photoresist (AZP4620) is spread at 200rpm for 16s, and spun at 750rpm for 50s (about 20 μ -thick). Experiments reveal that this resist does not stick too well with silicon
10 substrate without applying HMDS. For some other resist, HMDS may not be applied.
 3. Remove the resist beads which reside on the edge of the wafer using Q-tip soaked with acetone. This step is necessary because these beads will glue to the mask plate during mask aligning.
 4. Soft baked on a hot plate for 2 mins. at 130°C. Lower temperature with longer
15 bake time should also work.
 5. Patterned and exposed at intensity of 1250 ml/cm².
 6. Developed for 16 mins in AZ312: H2O=1:1.
 7. Hard baked at 130° for 3 mins.
 8. Plasma etching using O₂ at 80W: 250mT for 2 mins. Longer etching time may
20 burn the resist.
 9. Deposit 2 μ m-thick p-xylylene without applying primer. The p-xylylene will crack if it is too thin, and resist will crack if primer is applied. Without primer, the adhesion between p-xylylene and silicon substrate is not too good.
 10. Plasma etching using O₂ at 80W for 2 mins. This dry etching is necessary to
25 improve the adhesion between parylene and polyamide.
 11. Polyamide (Polyamide 7020 from OCG) is spread at 200rpm for 10s, and spun at 2500rpm for 10s (about 40 μ -thick).
 12. Soft bake at 90°C for 2 mins, followed by baking at 110° for 7 mins..
 13. Pattered and exposed at intensity of 350ml/cm².
 - 30 14. Bake at 105° C for 1 mins.
 15. Let it rest for 30 mins.
 16. Develop (QZ2501 from OCG) for 6 mins. Agitate.

17. Rinse (QZ3512 from OCG) for 2 mins. Agitate. If some white residual is observed, put the wafer to the developer.
18. Blow dry.
19. Repeat Step 2 to 6. No HMDS is applied because adhesion between p-xylylene and polyamide is strong enough.
20. Etching p-xylylene: Plasma etching using O_2 at 250W, 250mT for 20 mins.
21. Sacrificial release: Immersed into hot Acetone for 20 mins.
22. Rinse with IPA and water.
23. (Optional) Final Cure 250° for 30 mins. Higher temperature may burn p-xylylene.

EXAMPLE 2

This example describes another embodiment of the fabrication method of the present invention. More specifically, this example describes one embodiment of the process flow for fluidic interconnect. The process starts with a 4 inch silicon wafer. Thereafter the steps are as follows:

1. Repeat Step 11 to 18 from Example 1.
2. Repeat Step 2 to 6 from Example 1.
3. Repeat Step 9 to 22 from Example 1.
4. (Optional) Final Cure 250° for 30 mins. Higher temperature may burn p-xylylene.

EXAMPLE 3

In this example, another embodiment of a reaction chamber is constructed using the methods of the present invention. The fabrication process is same as in Example 1 (above). Figure 11 shows the resulting reaction chamber with one supporting post. The reaction chamber is approximately 1mm long, 1mm wide and 20 μ m high.

EXAMPLE 4

In this example, another embodiment of a thermocompression suction pump is fabricated according to the methods of the present invention. A thermocompression suction pump is fabricated (Figure 12) that is similar to the one described in Figure 7 of the patent. Figure 12 shows a polymer valve of 1mm in diameter with a 30 μ m thick boss of 320 μ m in

diameter. The valve orifice is 80 μm in diameter. A combination of chromium and gold of 50 μm -wide are placed on top of the 4 μm -thick p-xylylene diaphragm. The polymer valve is connected to a stand channel of 100 μm wide.

5

EXAMPLE 5

In this example, one embodiment of the fabrication method for the bubble pump and capillary valve is described. Figure 13 is a schematic showing the embodiment of the fabrication method for the bubble pump and capillary valve.

The process begins with a 100 mm p-type silicon substrate with a 0.7 μm layer of thermally grown silicon dioxide. The hydrolysis electrodes are next formed by evaporating a thin layer of 20 nm of Ti followed by a 30 nm layer of Pt and patterned by liftoff using a 3 μm of Shirley 1827 photoresist and acetone. A uniform thin layer of p-xylylene (Specialty Coating Services, parylene-C) 2 μm -thick is vapor deposited at room temperature on the oxidized substrates. The p-xylylene layer is next roughened with a 100W, 300mT O_2 plasma for 2 minutes to improve the adhesion of the subsequent polymer layer. A 10 μm -thick layer of photosensitive polyamide (OCG Probimide 7020) is next spin-cast at 7000 rpm for 10 sec. serving as a stop. The sample is soft baked at 90°C for 2 min. followed by 110° for 7 min. The soft baked polyamide is next exposed and patterned with a dose of 350mJ/cm² followed by a bath in OCG QZ2501 developer for 5 min and a 1 min. rinse in QZ3512. Next, a second 2 μm layer of p-xylylene is deposited on top of the polyamide and selectively etched on the Pt electrode areas with a 250W, 50mT O_2 plasma for 30 min. After that, the polymer channel is ready to be constructed. First, a 20 μm -thick sacrificial layer of AZP4620 (Hoechst) photoresist is spin cast at 750 rpm for 50 sec. and soft baked at 130° and exposed using a dose of 1750mJ/cm² to define the channel area. A second partial exposure of 250mJ/cm² is performed to define the narrow section of the channel, followed by a 10 min development in AZ 312. After that, the wafer is hard baked at 130°C, followed by a short O_2 plasma descum. A third 2 μm thick layer of p-xylylene is deposited which completely seals the resist layer and prevents the subsequent polyamide solvent from attacking the soft sacrificial resist. The top p-xylylene is next roughened with O_2 plasma and the top structural layer is constructed by spin-casting and patterning a 30 μm thick of photoresist polyamide as described earlier. This is followed by an O_2 plasma descum and a final 1 μm p-xylylene deposition. Access holes to the sacrificial resist are patterned using a 20 μm -thick layer of resist (AZP4620) and etched in a 250 W, 50mT, O_2 plasma for 35 min. that removes the two

p-xylylene layers on top of the sacrificial resist layer and at the same time the three p-xylylene layers on top of the platinum electrodes for electrical contact. The masking resist and the sacrificial resist layer are both removed in a warm bath of acetone for about 50 min, followed by a rinse in isopropyl alcohol and DI water.

5

From the above, it should be clear that the polymer-based technology of the present invention provides a micromachining technology that allows for fabrication of channels with a flexibility in cross section and channel length with virtually no loss in system performance.

10 In addition, the polymer technology of the present invention is low cost and does not require specialized equipment.

CLAIMS

1. A method for fabricating microchannels, comprising the steps:
 - a) providing a substrate, said substrate having upper and lower surfaces;
 - 5 b) depositing a first polymer layer on said upper surface of said substrate, said first polymer layer having i) a lower surface contacting said upper surface of said substrate and ii) an upper surface;
 - c) depositing a second polymer layer on said upper surface of said first polymer layer, said second polymer layer having i) a lower surface contacting said upper surface of said first polymer layer and ii) an upper surface; and
 - 10 d) sacrificially etching said first polymer layer under conditions such that said second polymer layer comprises walls of a microchannel.
2. The method of Claim 1, wherein said substrate is a silicon substrate.
- 15 3. The method of Claim 1, further comprising, prior to step (c) the step of photolithographically defining said first polymer layer under conditions such that said first polymer layer has a desired thickness.
- 20 4. The method of Claim 3, wherein said desired thickness of said first polymer layer is between 0.5 and 200 μ .
5. The method of Claim 1, further comprising, prior to step (d) the step of photolithographically defining said second polymer layer.
- 25 6. The method of Claim 1, further comprising, after step (d) the step (e) of etching openings in said walls of said microchannel.
7. The method of Claim 6, further comprising after step (d) and before step (e) the step of depositing a third polymer layer on said upper surface of said second polymer layer.
- 30 8. The method of Claim 1, wherein said first polymer and said second polymer are selected from the group consisting of photoresist, polyamide, benzocyclobutene,

polydimethylsiloxane, vapor-deposited p-xylylene, pTFE, PMMA, p-HMDS, polypropylene, starch-based polymers, epoxy, and acrylics.

9. A method for fabricating microchannels, comprising the steps:

- 5 a) providing a silicon substrate, said silicon substrate having upper and lower surfaces;
- b) depositing a first polymer layer on said upper surface of said silicon substrate, said first polymer layer having i) a lower surface contacting said upper surface of said silicon substrate and ii) an upper surface;
- 10 c) photolithographically defining said first polymer layer under conditions such that said first polymer layer has a desired thickness;
- d) depositing a second polymer layer on said upper surface of said first polymer layer, said second polymer layer having i) a lower surface contacting said upper surface of said first polymer layer and ii) an upper surface; and
- 15 e) sacrificially etching said first polymer layer under conditions such that said second polymer layer comprises walls of a microchannel.

10. The method of Claim 9, wherein said desired thickness of said first polymer layer of step (c) is between 0.5 and 200 μ .

20

11. The method of Claim 9, further comprising, prior to step (e) the step of photolithographically defining said second polymer layer.

12. The method of Claim 1, further comprising, after step (e) the step (f) of etching openings in said walls of said microchannel.

25

13. The method of Claim 12, further comprising after step (e) and before step (f) the step of depositing a third polymer layer on said upper surface of said second polymer layer.

30 14. The method of Claim 9, wherein said first polymer and said second polymer are selected from the group consisting of photoresist, polyamide, benzocyclobutene, polydimethylsiloxane, vapor-deposited p-xylylene, pTFE, PMMA, p-HMDS, polypropylene, starch-based polymers, epoxy, and acrylics.

15. A method for fabricating microchannels, comprising the steps:
- a) providing a silicon wafer, said silicon wafer having upper and lower surfaces;
 - b) depositing a first layer of a first polymer on said upper surface of said silicon wafer, said first polymer layer having i) a lower surface contacting said upper surface of said silicon wafer and ii) an upper surface;
 - c) depositing a second polymer layer on said upper surface of said first layer, said second polymer layer having i) a lower surface contacting said upper surface of said first layer and ii) an upper surface;
 - d) photolithographically defining said second polymer layer under conditions such that said second polymer layer has a thickness between 0.5 and 200 μ ;
 - e) depositing a second layer of said first polymer on said upper surface of said second polymer layer, said second layer of said first polymer having i) a lower surface contacting said upper surface of said second polymer layer and ii) an upper surface;
 - f) sacrificially etching said second polymer layer under conditions such that said first and second layers of said first polymer comprise walls of a microchannel, said microchannel having a height defined by said thickness of said second polymer layer of step (d); and
 - g) etching one or more openings in said walls of said microchannel.
16. The method of Claim 15, further comprising after step (e) and before step (f) the step of depositing a layer of a third polymer on said upper surface of said second layer of said first polymer.
17. The method of Claim 16, wherein said first and second layers of said first polymer comprise vapor-deposited p-xylylene.
18. The method of Claim 17, wherein, at step (g), first and second openings are etched, said first opening serving as an inlet and said second opening serving as an outlet.
19. The method of Claim 18, wherein said openings are etched from said lower surface of said silicon wafer into said lower surface of said first layer of said first polymer.

20. The method of Claim 18, wherein said openings are etched from said upper surface of said layer of said third polymer into said upper surface of said second layer of said first polymer.
- 5 21. A device, comprising a polymer channel comprising one or more electrodes positioned such that they will be in contact with a liquid sample placed in said channel.
22. The device of Claim 21, wherein said polymer channel comprises two electrodes.
- 10 23. A method of conveying liquid in a microchannel, comprising introducing a liquid into the device of Claim 22.
24. The method of Claim 23, wherein a potential is applied between the two electrodes under conditions such that said potential results in the generation of a gas bubble large enough
- 15 to move at least a portion of said liquid in said polymer channel.

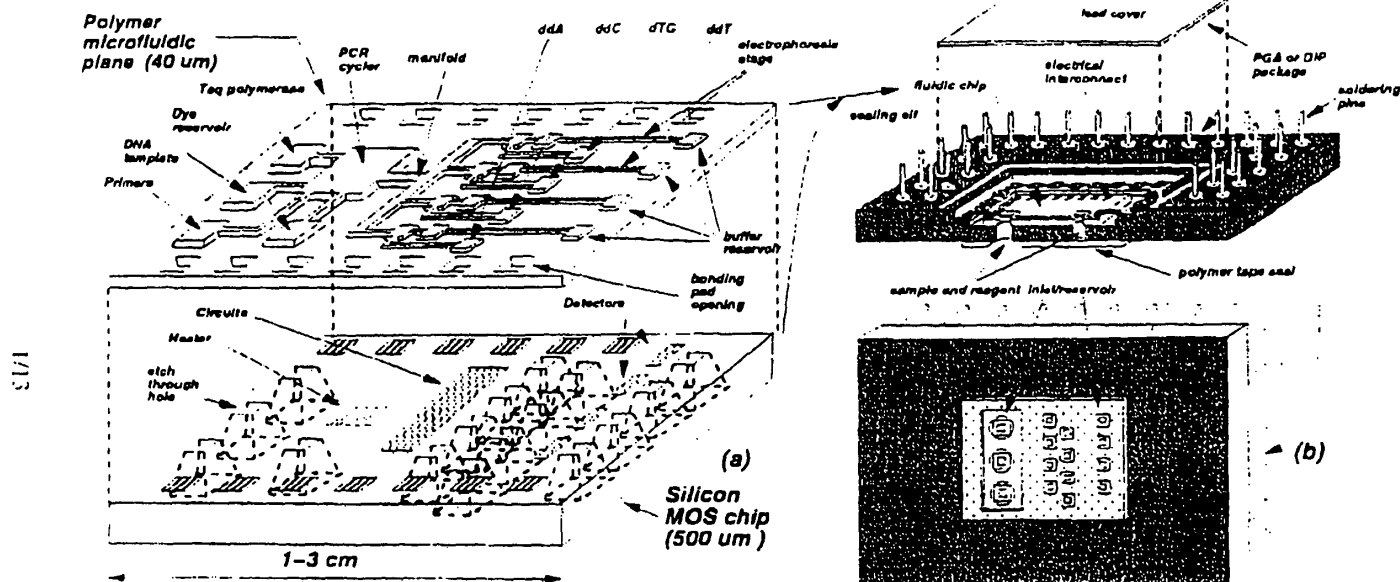


Figure 1: (a) The polymer fluid channels and reservoirs are constructed by deposition of plastics on top of a silicon MOS control chip. Etch-through holes are formed in the silicon substrate to serve as funnel-like inlets and reservoirs for the sample, reagents and buffer solutions. (b) Fluidic chip is mounted on a PGA or MCM package that isolates fluidic and electrical interconnect. Some of the sample inlets are sealed to serve as reagent reservoirs

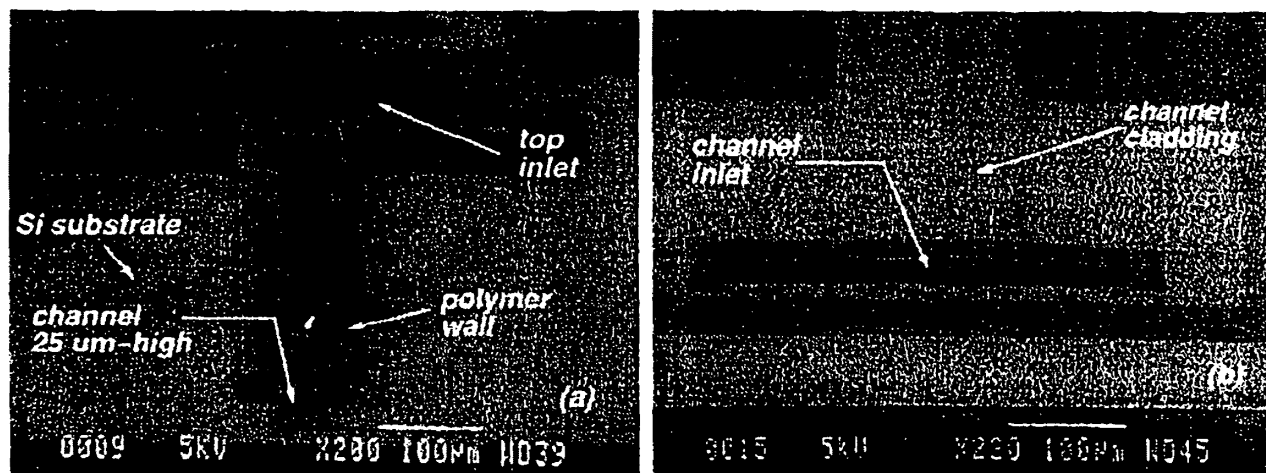


Figure 2: Top view and cross-section (a) of example polymer channel with front side inlet (b) formed on top of a regular Si substrate. Channel heights can be adjusted between 0.5-100 μm .

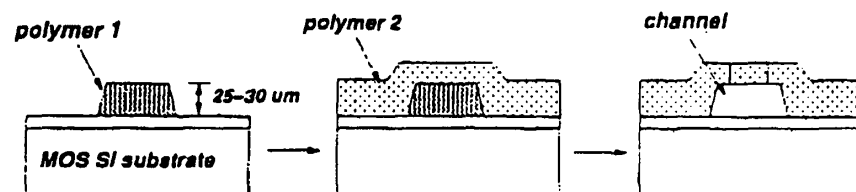


Figure 3: Simplified fabrication process for plastic channels.

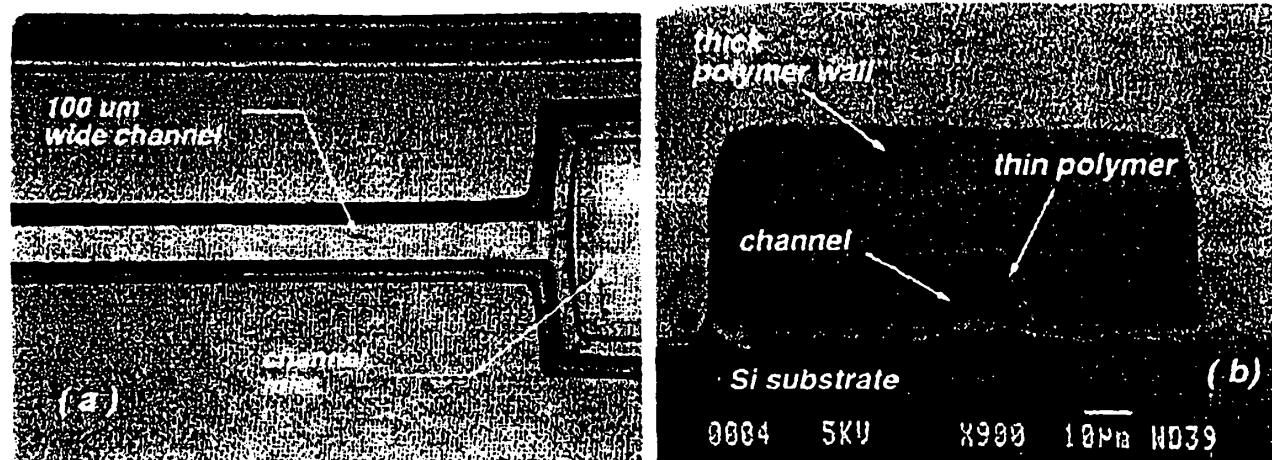


Figure 4: (a) Top view of example three-polymer channel 100 μm wide and 25 μm -thick with front side inlet. (b) closeup cross-section showing the three-polymer construction of the channels.

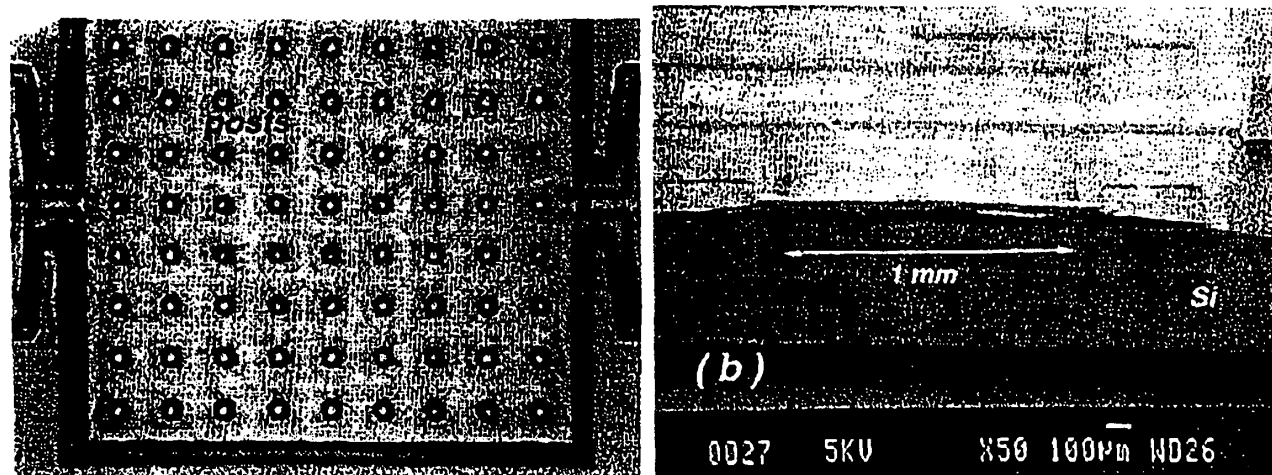


Figure 5: (a) Top view of 1 mm² thermal cycling chamber (b) cross-section of 25 µm-high, 1 mm² polymer PCR chamber fabricated on top of a silicon wafer.

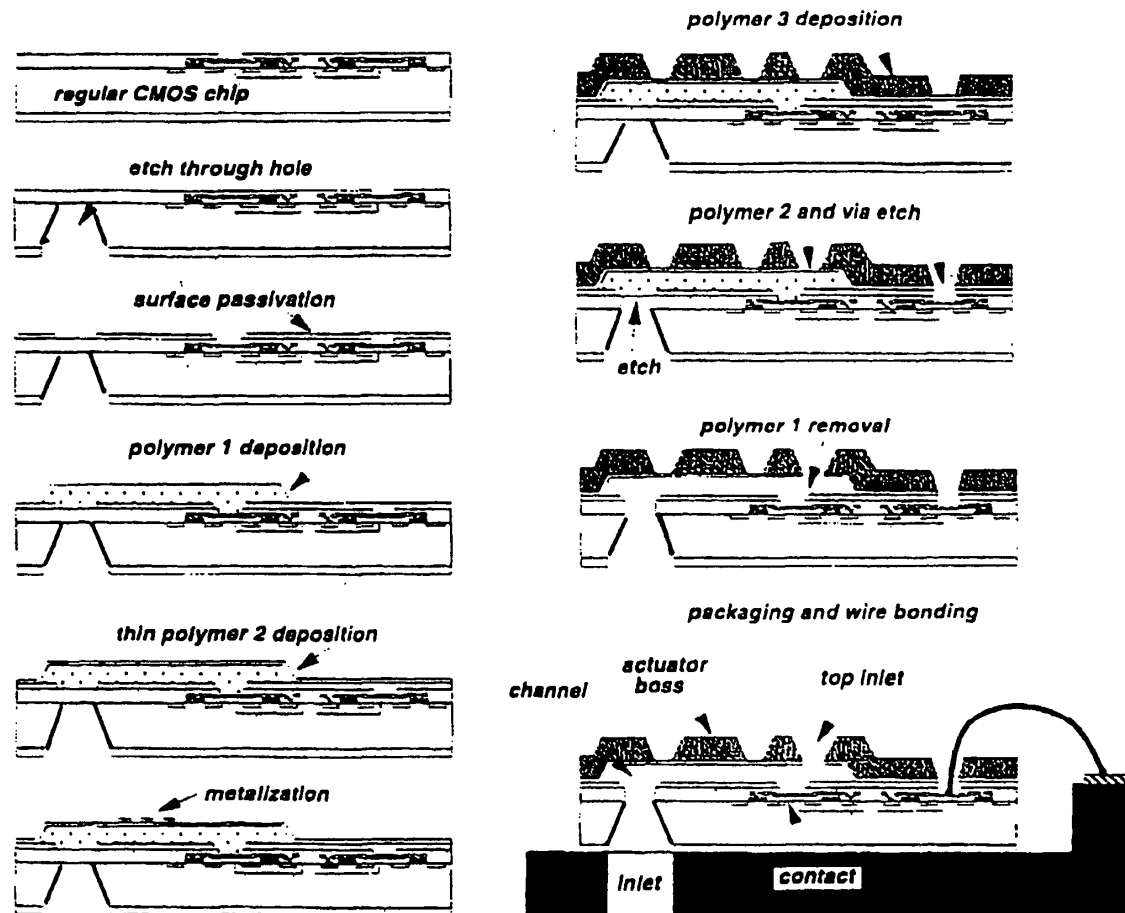


Figure 6: Simplified 3-level polymer process with embedded metalization. This process requires four lithographic masks and is capable of constructing all the microfluidic parts shown in this proposal. The figure shows circuits, backside and front inlets, actuators, channels, and bonding wires.

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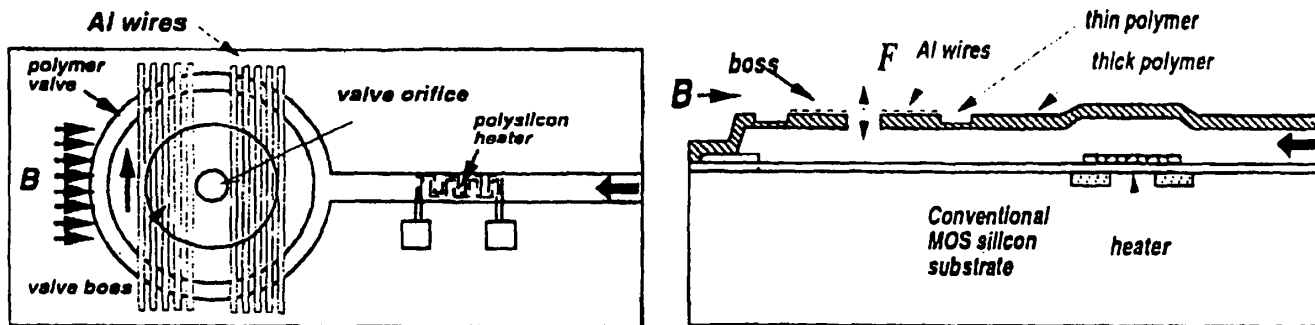


Figure 7: Polymer magnetically activated thermocompression suction pump

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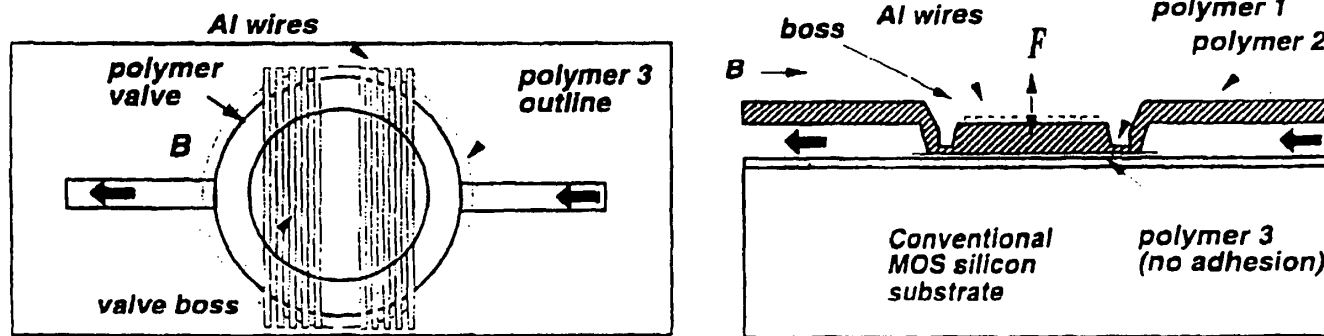


Figure 8: Pass-through valve. The valve is normally closed and opens when the diaphragm is buckled upwards.

FIGURE 9

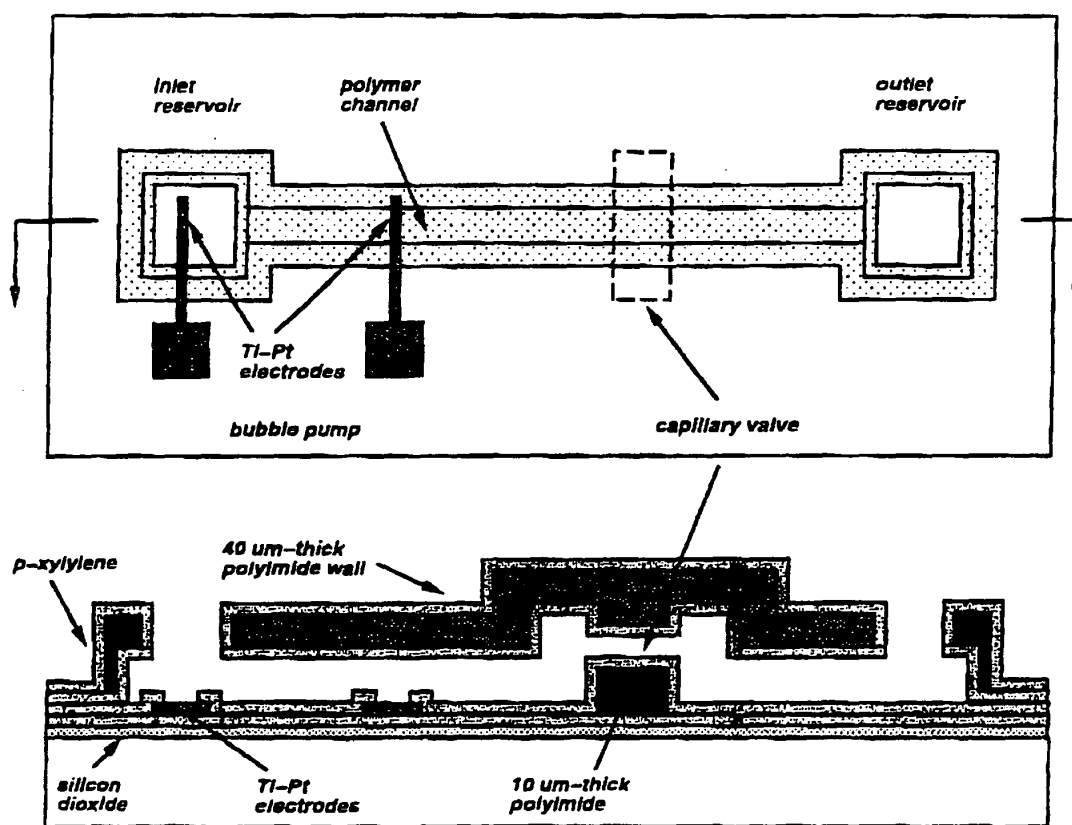


FIGURE 10

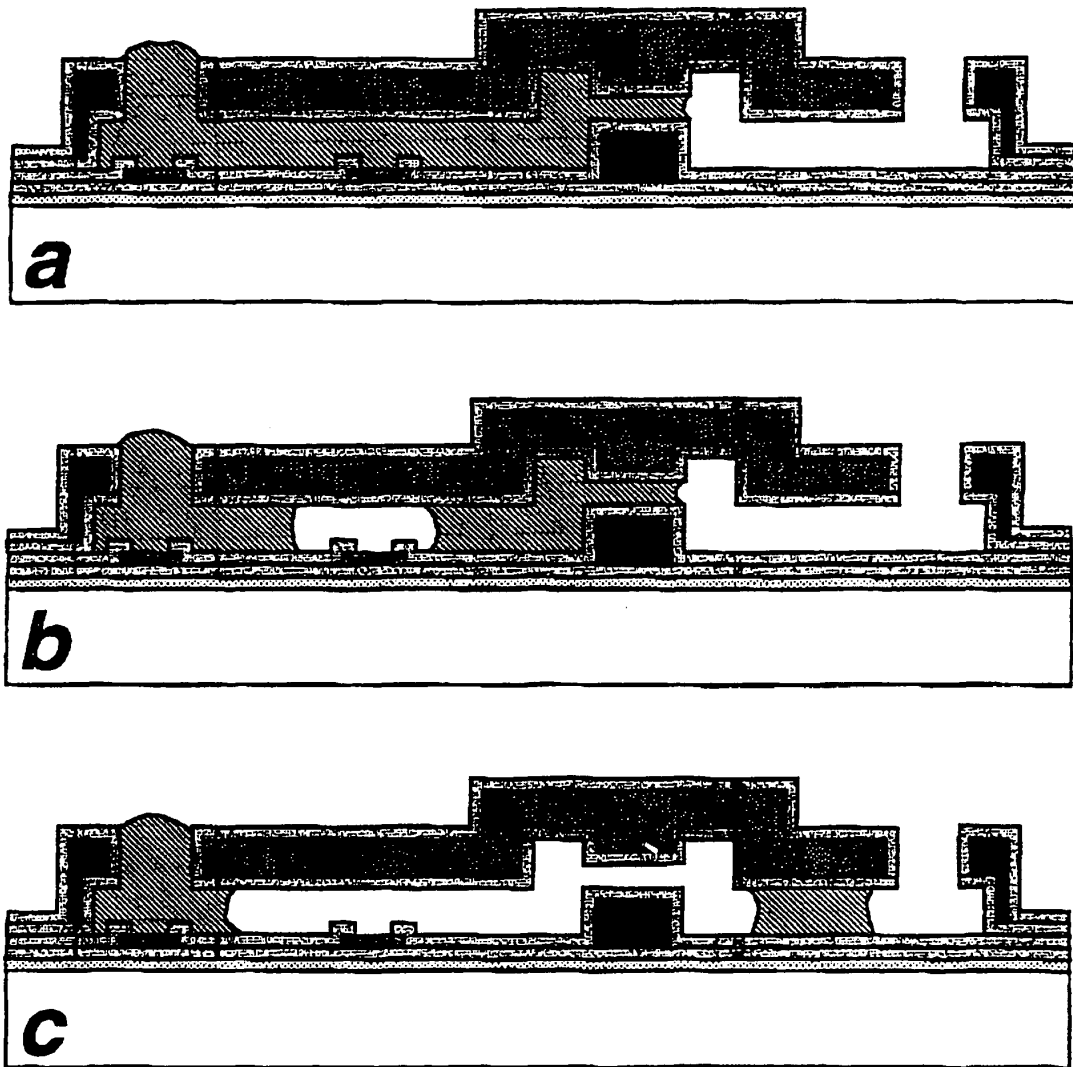
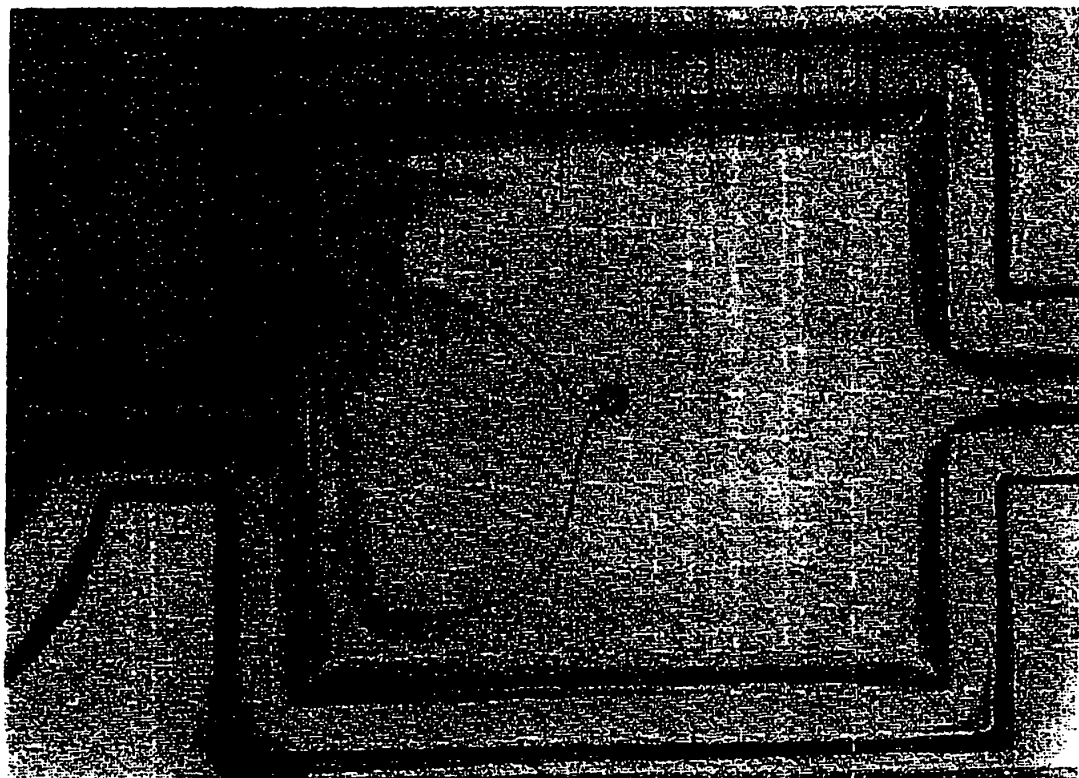


FIGURE 11



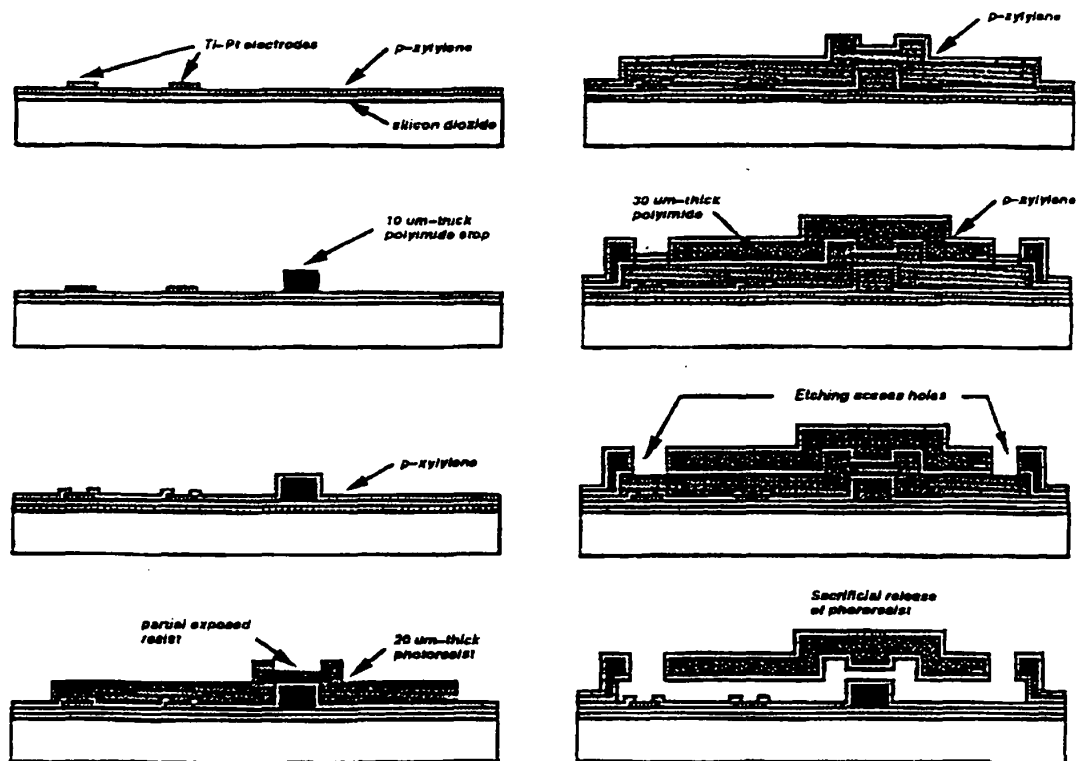
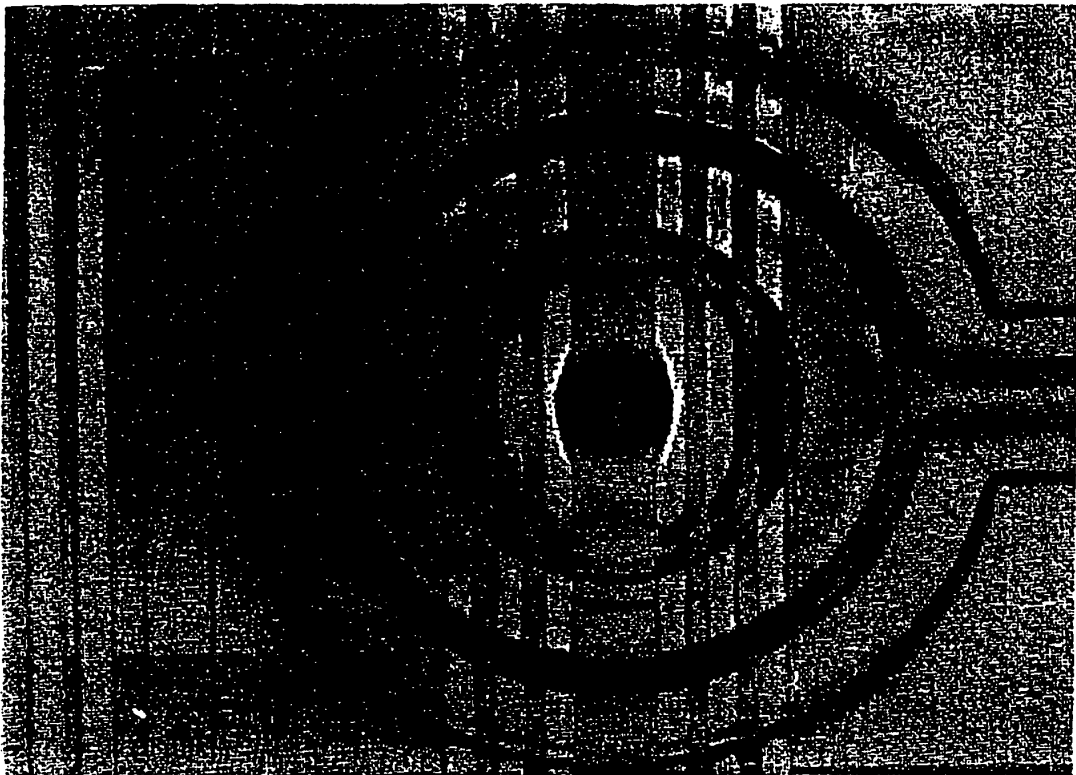


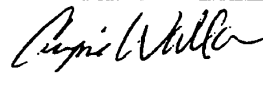
Fig. 13: Process flow of bubble pump and capillary valve

FIGURE 12



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/14054

A. CLASSIFICATION OF SUBJECT MATTER IPC(5) : G03F 7/00 US CL : 430/311, 313, 314, 319, 394 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 430/311, 313, 314, 319, 394 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched NONE Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,153,855 A (FEINGOLD) 08 May 1979, column 2, lines 6-37 and claim 2.	1-24
Y	US 5,265,327 A (FARIS ET AL) 30 November 1993, abstract, column 10, line 53 to column 11, line 12 and claims 3 and 4.	1-24
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
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APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/179,586	06/24/2002	John Gilbert	CVZ-012

000959
LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

CONFIRMATION NO. 9722

FORMALITIES LETTER



OC000000008483837

Date Mailed: 07/19/2002

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

*Filing Date Granted***Items Required To Avoid Abandonment:**

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of \$130 for a non-small entity, must be submitted with the missing items identified in this letter.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Substitute drawings in compliance with 37 CFR 1.84 because:
 - drawing sheets do not have the appropriate margin(s) (see 37 CFR 1.84(g)). Each sheet must include a top margin of at least 2.5 cm. (1 inch), a left side margin of at least 2.5 cm. (1 inch), a right side margin of at least 1.5 cm. (5/8 inch), and a bottom margin of at least 1.0 cm. (3/8 inch);

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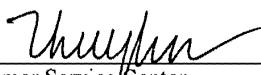
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SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **\$130** for a Large Entity

- \$130 Late oath or declaration Surcharge.

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PATENT NUMBER and
ISSUE DATE

U.S. UTILITY Patent Application

APPL NUM 10179586	FILING DATE 06/24/2002	CLASS 137	SUBCLASS 828	GAU 3753	EXAMINER Chamber
**APPLICANTS: Gilbert John; Bohm Sebastian; Deshpande Manish;					
**CONTINUING DATA VERIFIED: This appln claims benefit of 60/373,256 04/17/2002					
** FOREIGN APPLICATIONS VERIFIED:					
PG-PUB <input type="checkbox"/> DO NOT PUBLISH <input type="checkbox"/>		RESCIND <input type="checkbox"/>			
Foreign priority claimed <input type="checkbox"/> yes <input type="checkbox"/> no		35 USC 119 conditions met <input type="checkbox"/> yes <input type="checkbox"/> no		ATTORNEY DOCKET NO CVZ-012	
Verified and Acknowledged Examiners's initials					
TITLE : Microfluidic system including a bubble valve for regulating fluid flow through a microchannel					

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NOTICE OF ALLOWANCE MAILED		Assistant Examiner	CLAIMS ALLOWED	
			Total Claims	Print Claim for O.G.
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137	806		
137	807	09/03	AMC
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INDEX OF CLAIMS

Claim	Date	Claim	Date	Claim	Date
1		51		101	
2		52		102	
3		53		103	
4		54		104	
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Signature

Larry Taylor

Please Print Name of Person Signing

Sir:

Transmitted herewith for filing is the patent application of

Inventor(s): John Gilbert, *et al.*
 For: MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING
 FLUID FLOW THROUGH A MICROCHANNEL

Enclosed are:

- ☐ This is a request for filing a ☐ continuation ☐ divisional application under 37 CFR 1.53(b), of pending prior application serial no. _____ filed on _____ entitled _____.
- ☒ 19 pages of specification, 4 pages of claims, 1 pages of abstract.
- ☒ 7 sheets of drawings (Figures 1-17C).
- ☒ Unexecuted Declaration, Petition and Power of Attorney (6 pages).
- ☐ An assignment of the invention to _____. A recordation form cover sheet (Form PTO 1595) is also enclosed. (3 pages in total).
- ☐ Applicant claims small entity status. See 37 CFR 1.27.
- ☒ Other Application Data Sheet (3 pages) and return acknowledgment postcard.

The filing fee has been calculated as shown below:

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FOR:	NO. FILED	NO. EXTRA
BASIC FEE	//////////	//////////
TOTAL CLAIMS	24 - 20	= 4
INDEP. CLAIMS	9 - 3	= 6
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIMS PRESENTED		

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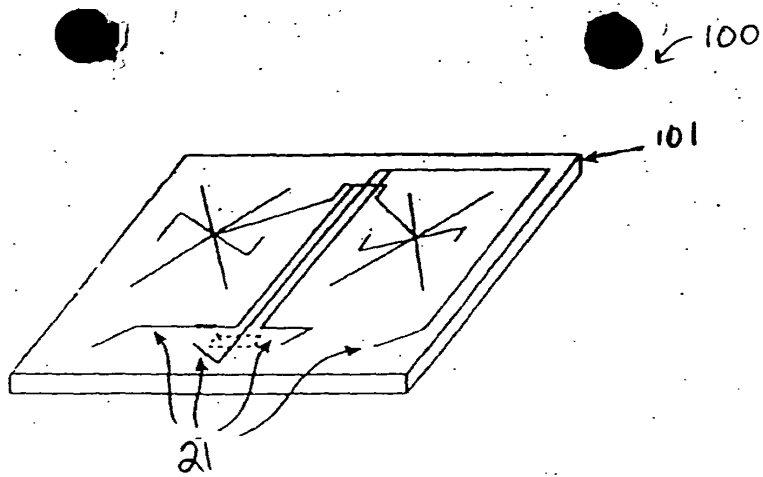
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x 42	\$
+140	\$
TOTAL	0

OTHER THAN SMALL ENTITY	
RATE	FEE
//////////	\$ 740
x 18=	\$ 72
x 84	\$ 504
+280	\$
TOTAL	\$1316.00

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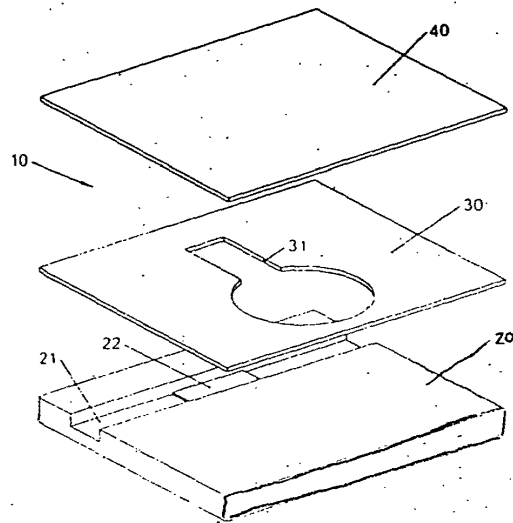


FIG. 2

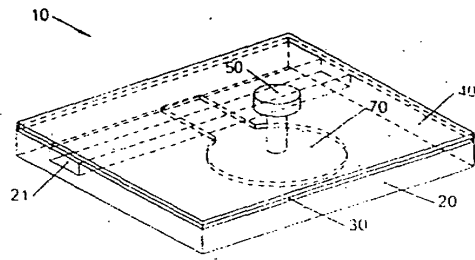


FIG. 3

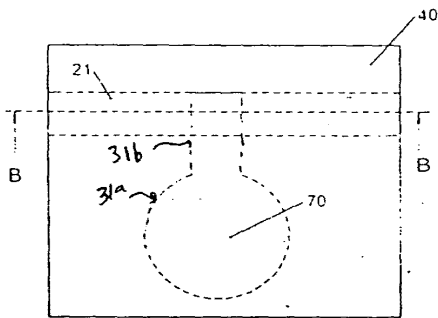


FIG. 4

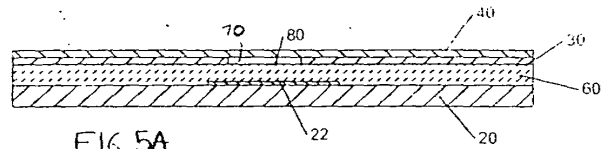


FIG. 5A

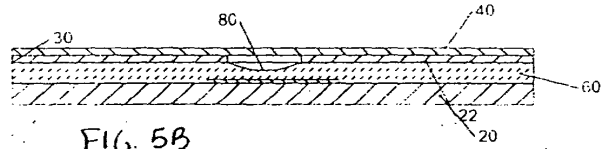


FIG. 5B

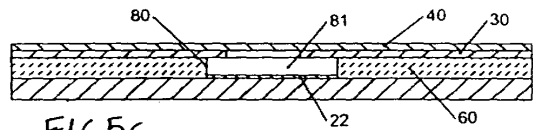


FIG. 5C

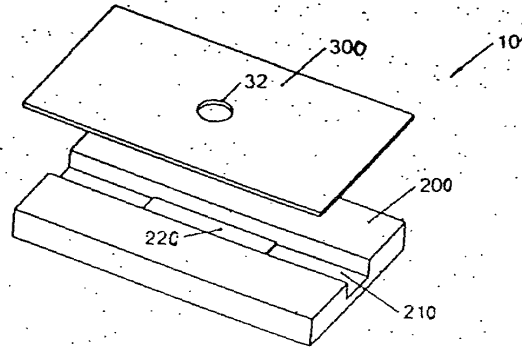


FIG. 6

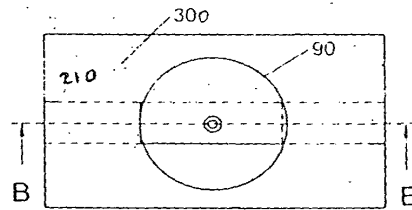


FIG. 7

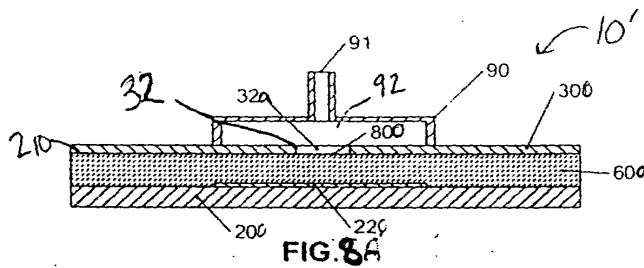


FIG. 8A

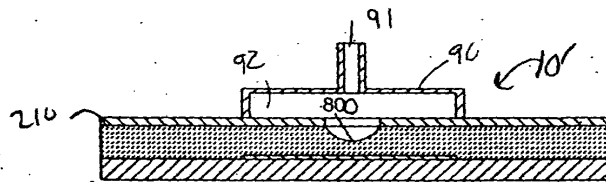


FIG. 8B

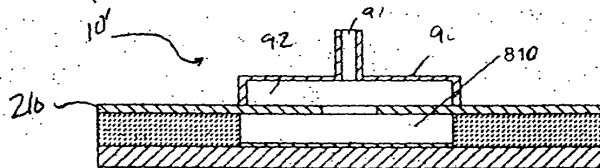


FIG. 8C

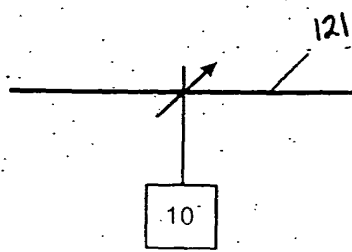


FIG. 9

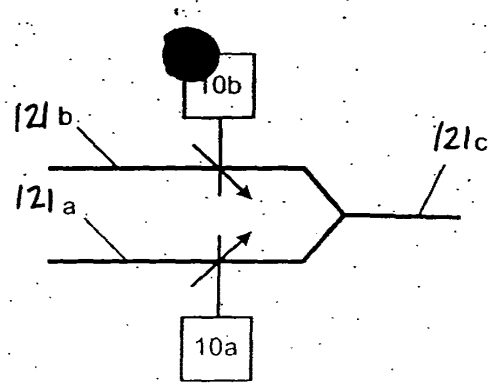


FIG. 10

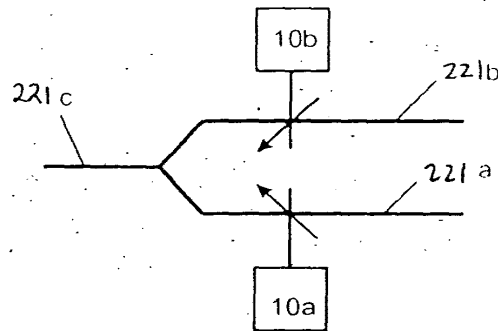


FIG. 11

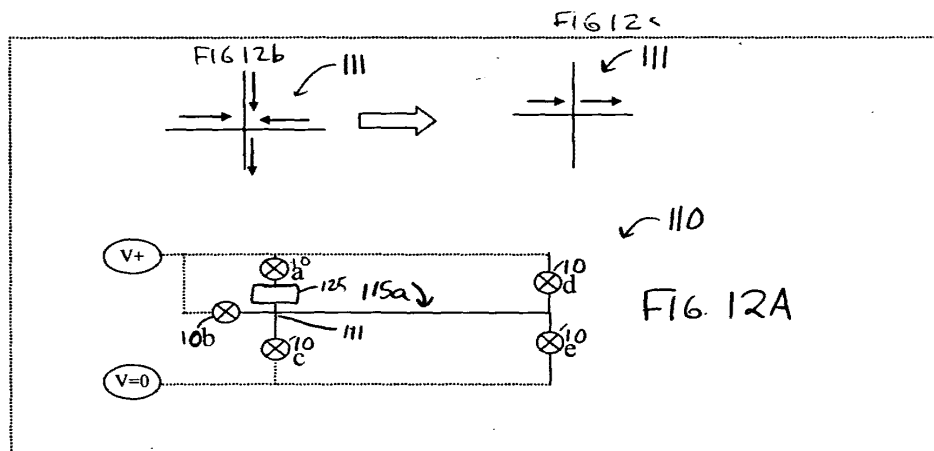


FIG. 12A

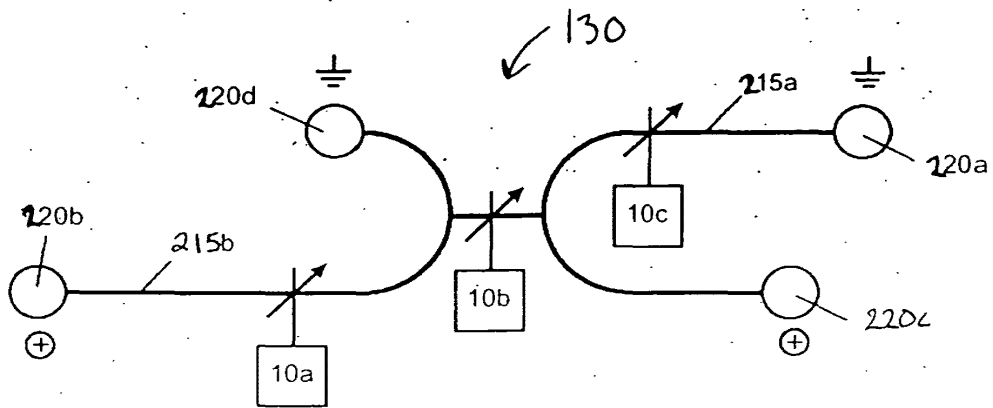


FIG. 13a.

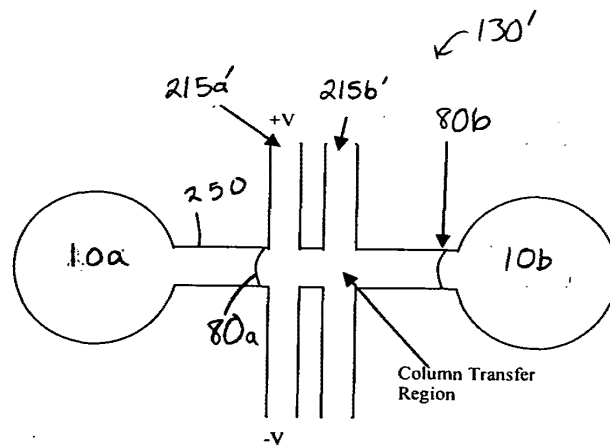


FIG 13b.

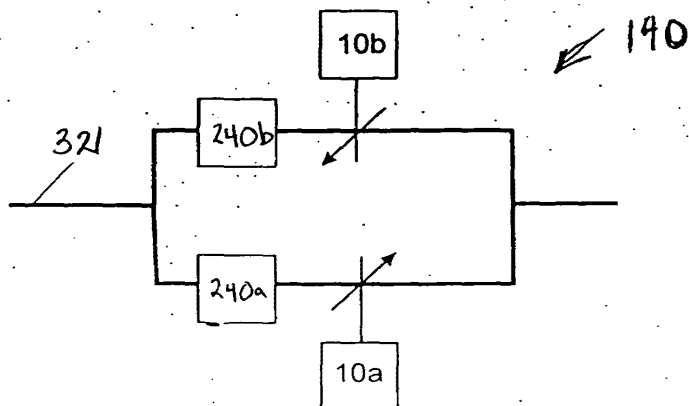


FIG. 14

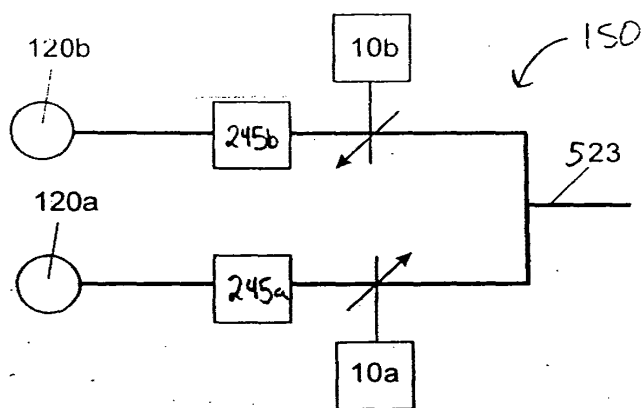


FIG. 15

A schematic diagram of a device with two spherical chambers, 160, connected by a central vertical tube. The upper chamber is connected to a horizontal tube on the right, which then branches into two diagonal tubes. The lower chamber is connected to a rectangular box at the bottom. A central valve assembly is located in the middle of the vertical tube, consisting of a central dot and two upward-pointing arrows. A dashed line with small circles passes through the center of the device, and a dashed arrow points downwards from the right side.

Cytonome/ST, LLC Exhibit 2011
NanoCollect Biomedical, Inc. v. Cytonome/ST, LLC, IPR2020-00548
Page 223 of 300

**Microfluidic System Including a Bubble Valve for Regulating
Fluid Flow Through a Microchannel**

Related Applications

This application claims priority to U.S. Provisional Patent Application No. 60/373,256 entitled "Microfluidic System Including a Bubble Valve for Regulating Fluid Flow Through a Microchannel" filed April 17, 2002; and is related to Attorney Docket No. CVZ-021, entitled "Method and Apparatus for Sorting Particles", filed herewith. The contents of both applications are herein incorporated by reference.

Field of the Invention

The present invention relates to microscale fluid handling devices and systems. More particularly, the present invention relates to a method and system for controlling liquid flow in a microchannel by the introduction of a gas bubble to a microfluidic system.

Background of the Invention

In the chemical, biomedical, bioscience and pharmaceutical industries, it has become increasingly desirable to perform large numbers of chemical operations, such as reactions, separations and subsequent detection steps, in a highly parallel fashion. The high throughput synthesis, screening and analysis of (bio)chemical compounds, enables the economic discovery of new drugs and drug candidates, and the implementation of sophisticated medical diagnostic equipment. Of key importance for the improvement of the chemical operations required in these applications are an increased speed, enhanced reproducibility, decreased consumption of expensive samples and reagents, and the reduction of waste materials.

Microfluidic devices and systems provide improved methods of performing chemical, biochemical and biological analysis and synthesis. Microfluidic devices and systems allow for the performance of multi-step, multi-species chemical operations in chip-based micro chemical analysis systems. Chip-based microfluidic systems generally comprise conventional 'microfluidic' elements, particularly capable of handling and analyzing chemical and biological specimens. Typically, the term microfluidic in the art refers to systems or devices having a network of processing nodes, chambers and reservoirs connected by channels, in which the channels have typical cross-sectional dimensions in the range

between about 1.0 μm and about 500 μm . In the art, channels having these cross-sectional dimensions are referred to as 'microchannels'.

By performing the chemical operations in a microfluidic system, potentially a number of the above-mentioned desirable improvements can be realized. Downscaling dimensions allows for diffusional processes, such as heating, cooling and passive transport of species (diffusional mass-transport), to proceed faster. One example is the thermal processing of liquids, which is typically a required step in chemical synthesis and analysis. In comparison with the heating and cooling of liquids in beakers as performed in a conventional laboratory setting, the thermal processing of liquids is accelerated in a microchannel due to reduced diffusional distances. Another example of the efficiency of microfluidic systems is the mixing of dissolved species in a liquid, a process that is also diffusion limited. Downscaling the typical dimensions of the mixing chamber thereby reduces the typical distance to be overcome by diffusional mass-transport, and consequently results in a reduction of mixing times. Like thermal processing, the mixing of dissolved chemical species, such as reagents, with a sample or precursors for a synthesis step, is an operation that is required in virtually all chemical synthesis and analysis processes. Therefore, the ability to reduce the time involved in mixing provides significant advantages to most chemical synthesis and analysis processes.

Another aspect of the reduction of dimensions is the reduction of required volumes of sample, reagents, precursors and other often very expensive chemical substances. Milliliter-sized systems typically require milliliter volumes of these substances, while microliter sized microfluidic systems only require microliters volumes. The ability to perform these processes using smaller volumes results in significant cost savings, allowing the economic operation of chemical synthesis and analysis operations. As a consequence of the reduced volume requirement, the amount of chemical waste produced during the chemical operations is correspondingly reduced.

In microfluidic systems, regulation of minute fluid flows through a microchannel is of prime importance, as the processes performed in these systems highly depend on the delivery and movement of various liquids such as sample and reagents. A flow control device may be used to regulate the flow of liquid through a microchannel. Regulation includes control of

flow rate, impeding of flow, switching of flows between various input channels and output channels as well as volumetric dosing.

U.S. Patent Number 6,062,681 describes a bubble valve for a liquid flow channel in which the flow of a liquid is controlled by the generation of a gas bubble in the channel using a heater placed in the liquid. As the heater is activated, a bubble is formed which can be enlarged or reduced in size by increasing or decreasing, respectively, the temperature of the heater. The described system presents a number of disadvantages, namely, the required power to operate the valve and the inherent requirement that liquid in the channel be heated upon passing the valve. Even small increases in liquid temperature, by only a couple of degrees, can have disastrous effects on the highly heat sensitive biochemical substances present in the liquids to be controlled in many microfluidic systems. In addition, the required on-chip electric circuitry for the heater increases the complexity of the described valve and consequently results in unacceptably high costs, particularly if the fluidic system employing the bubble valve only used for a single application.

Other valves in the prior art use electrochemical means to produce a bubble in a liquid.

Summary of the Invention

The present invention provides a bubble valve for controlling, regulating or varying fluid flow through a microfluidic system. The bubble valve regulates fluid flow through a channel using an externally operated mechanical or pneumatic actuator. The actuator causes a deflection of a fluid meniscus into the interior of the channel to regulate liquid flow. The actuator may mechanically force a gas bubble into a fluid carrying microchannel to inhibit liquid flow or to cause liquid flow by applying a sufficiently high pressure to the meniscus. The bubble valve effectively controls the flow of liquids in microfluidic systems, without heating the fluid and without complex on-chip circuitry.

The microfluidic system includes a microchannel and a sealed, gas-filled reservoir positioned adjacent to and connected to the microchannel. The gas filled reservoir has a movable wall and a meniscus formed by a liquid in the microchannel that forms an interface between the reservoir and the microchannel interior. The meniscus may form a portion of the side wall of the microchannel. An external mechanical actuator may be used to deflect the

movable wall of the reservoir. As the movable wall is deflected, the volume of the reservoir decreases and the gas pressure inside the reservoir increases, causing the meniscus to deflect into the microchannel, thereby modifying the cross-sectional area of the microchannel and consequently varying the flow of liquid through the channel. The increased pressure in the reservoir pushes gas from the reservoir into the microchannel. The gas may result in a local gas bubble being forced into the microchannel from the gas-filled reservoir. The resulting gas bubble occupies a portion of the cross-section of the channel, allowing liquid flow through the channel to be effectively controlled by controlling the size of the gas bubble via the external actuator.

The meniscus may comprise a virtual wall formed in a side wall of the microchannel. The virtual wall is a meniscus formed by a liquid in the microchannel that fills an aperture formed in the side wall of the microchannel and essentially replaces the removed portion of the side wall without affecting the properties of liquid flow through the channel. A gas bubble can be forced into the channel by applying a gas pressure at the opening using an external pneumatic actuator. The gas pressure forces the meniscus inside the channel, which varies the flow of liquid through the channel interior.

According to one embodiment, the microchannel includes a hydrophobic patch spanning the width of the microchannel at the location where the gas bubble is introduced to enhanced on-off switching of the bubble valve. The hydrophobic patch anchors the bubble in a particular location in the microchannel. If the introduced gas bubble covers the whole area of the patch, the bubble is effectively retained by capillary forces and blocks any liquid flow up to a certain pressure difference, depending on the level of hydrophobicity of the patch.

Alternatively or in combination with a hydrophobic patch, the microchannel can be locally shaped into a cavity for receiving and anchoring the gas bubble. By providing an appropriate cavity, the bubble can be kept in place during operation, reducing the risk that the gas bubble is carried away with the liquid.

According to one aspect of the invention, a microfluidic device is provided. The microfluidic device comprises a microchannel having an interior bounded by a side wall and a valve for regulating the flow of fluid through the microchannel. The valve comprises a gas-filled reservoir, a fluid meniscus interfacing the reservoir and the interior and an actuator for

varying the volume of the reservoir to increase an internal pressure of the reservoir to vary the flow of liquid through the channel.

According to another aspect, a microfluidic device is provided, comprising a first
5 plate having a groove formed therein defining a microchannel, a second plate for enclosing the microchannel and a flexible membrane. The second plate is bonded to the first plate and has an aperture adjacent to the groove sized and dimensioned to form a meniscus when the microchannel is filled with a liquid. The aperture defines a reservoir adjacent to the microchannel, wherein the meniscus forms an interface between the microchannel and the
10 reservoir. The flexible membrane is bonded to the second plate to seal the reservoir.

According to another aspect, a method of making a bubble valve is provided, the method comprises providing a microchannel having an interior bounded by a side wall, an aperture formed in the side wall and a valve chamber adjacent to the aperture in
5 communication with the interior, filling the microchannel with a liquid to form a meniscus of the liquid in the aperture, whereby the step of filling traps a gas in the valve chamber and providing an actuator for increasing the pressure in the valve chamber to deflect the meniscus into the interior.

According to yet another aspect, a method of making a bubble valve is provided. The method comprises providing a microchannel having an interior bounded by a side wall, an aperture formed in the side wall and a valve chamber adjacent to the aperture in
20 communication with the interior, filling the microchannel with a liquid to form a meniscus of the liquid in the aperture and applying and sealing an actuator comprising a chamber to a top surface of the microchannel to form a gas-filled chamber adjacent to the meniscus. The
25 actuator varies the pressure in the gas-filled chamber to deflect the meniscus into the interior, thereby regulating fluid flow.

According to still another aspect, a microfluidic device is provided comprising a
30 microchannel having an interior bounded by a side wall, a bubble valve for creating and injecting a bubble into the microchannel interior to regulate fluid flow through the microchannel and a hydrophobic patch for retaining the bubble in a predetermined position in the microchannel interior.

According to yet another aspect a bubble valve in a particle sorting device for separating particles having a predetermined characteristic from particles not having a predetermined characteristic is provided. The bubble valve comprises a gas-filled reservoir, a side channel in communication with a channel through which a stream of particles in a carrier fluid passes, wherein the carrier fluid forms a meniscus in the side channel adjacent to the gas-filled reservoir and an actuator for deflecting the meniscus to create a pressure pulse to selectively deflect a particle having the predetermined characteristic from the stream of particles.

According to still another aspect, a method of varying an electrical resistance in a microchannel is provided. The method comprises generating a bubble and injecting the bubble into a liquid in the microchannel, whereby the bubble varies the electrical resistance of the microchannel.

According to yet another aspect, an electrophoretic system is provided, comprising an electrokinetically operated microchannel, a sample well for providing an sample to the microchannel, a voltage source and a bubble valve for injecting a bubble into the microchannel to vary the electrical resistance of the microchannel.

According to a final aspect of the invention, an electrokinetic column to column switch is provided, comprising a first electrokinetically operated microchannel, a second electrokinetically operated microchannel in communication with the first electrokinetically operated microchannel and a bubble valve for selectively blocking flow from the first electrokinetically operated microchannel to the second electrokinetically operated microchannel by selectively injecting a bubble into a microchannel.

Brief Description of the Drawings

Figure 1 is a schematic view of a microfluidic system suitable for implementing the illustrative embodiment of the invention.

Figure 2 shows an exploded view of a bubble valve according to an illustrative embodiment of the present invention.

Figure 3 shows an isometric view of the bubble valve of Figure 2.

Figure 4 shows a top view of the bubble valve of Figure 2.

Figures 5a-c are cross-sectional views of the bubble valve of Figure 2 in operation.

Figure 6 shows an exploded view of an alternative embodiment of a bubble valve according to the present invention.

Figure 7 shows a top view of the bubble valve of Figure 6.

5 Figures 8a-c are cross-sectional view of the bubble valve of Figure 6 in operation.

Figure 9 shows an application of the bubble valve of an illustrative embodiment of the present invention in a microchannel.

10 Figure 10 shows a Y-intersection in a microfluidic system of an embodiment of the invention that implements a bubble valve to control liquid flow according to the teachings of the present invention.

Figure 11 shows a Y-intersection in a microfluidic system of another embodiment of the invention that implements a bubble valve to control liquid flow according to the teachings of the present invention.

15 Figures 12a-c shows an electrophoresis system that implements a bubble valve to control electrical current during electrokinetic injection according to the teachings of the present invention.

Figure 13a shows an electrokinetic column-column switch implementing a bubble valve according to the teachings of the present invention.

20 Figure 13b shows an alternate electrokinetic column-column switch implementing a bubble valve according to another embodiment of the present invention.

Figure 14 shows a selective resistance circuit that employs a bubble valve to control electrical current according to the teachings of the present invention.

Figure 15 shows an alternative selective resistance circuit that employs a bubble valve to control electrical current according to the teachings of the present invention.

25 Figure 16 shows a particle sorting system that implements a bubble valve of the present invention to produce fluid impulses to sort particles.

Figures 17a, 17b and 17c illustrate the operation of the particle sorting system of Figure 16.

30 **Detailed Description of the Invention**

The present invention provides an improved bubble valve for controlling fluid flow through a microchannel in a microfluidic system. The invention further provides a method of forming the bubble valve. The bubble valve of the present invention can be applied in numerous microfluidic systems for controlling and switching fluid flows. Examples of

suitable applications include, but are not limited to: flow cytometry, column switching, 2-D separations, cell or particle sorting applications on a chip, regulating pressurized fluid flows including on-off switching, regulating electrokinetic fluid flows and electrokinetically induced processes including on-off switching and electrokinetic sample injection and channel
5 to channel switching.

Figure 1 illustrates a microfluidic system suitable for implementing the illustrative embodiment of the present invention. The illustrative microfluidic system 100 comprises a substrate 101 having one or more microchannels 21 disposed therein. The microchannels
10 transport fluid through the microfluidic system 100 for processing, handling, and/or performing any suitable operation on a liquid sample. As used herein, the term “microfluidic” refers to a system or device for handling, processing, ejecting and/or analyzing a fluid sample including at least one channel having microscale dimensions. The term “channel” as used herein refers to a pathway formed in or through a medium that allows for
15 movement of fluids, such as liquids and gases. The term “microchannel” refers to a channel preferably formed in a microfluidic system or device having cross-sectional dimensions in the range between about 1.0 μm and about 500 μm , preferably between about 25 μm and about 250 μm and most preferably between about 50 μm and about 100 μm . One of ordinary skill in the art will be able to determine an appropriate volume and length of the microchannel.
20 The ranges are intended to include the above-recited values as upper or lower limits. The microchannel can have any selected shape or arrangement, examples of which include a linear or non-linear configuration and a U-shaped configuration. The microfluidic system 100 may comprise any suitable number of microchannels 21 for transporting fluids through the microfluidic system 100.

25 The microfluidic system 100 includes a bubble valve 10, 10' shown in Figures 2-8c for controlling liquid flow through a microchannel of the system. According to the illustrative embodiment, the microchannel is defined by a side wall having any suitable shape enclosing at least a portion of the interior of the channel. The bubble valve may be formed
30 by a gas-filled reservoir positioned adjacent to the microchannel including a meniscus that forms the interface between the reservoir and the microchannel interior. The meniscus may form a portion of the side wall of the microchannel. The bubble valve includes an actuator for modifying the pressure in the reservoir to deflect the meniscus into the channel interior,

thereby modifying the cross-sectional area of the microchannel and consequently varying the flow of liquid through the channel.

According to an alternate embodiment, the bubble valve is formed by a meniscus in a
 5 separate side channel that communicates with and intersects a microchannel through which a liquid to be controlled flows. One skilled in the art will recognize that the meniscus can be located at any location relative to the microchannel through which liquid flows.

The gas-filled reservoir may be formed when filling the microchannel having an
 10 aperture in a side wall and a reservoir formed adjacent to the aperture. An empty microchannel may be filled with liquid, forming the meniscus in the aperture, which traps the gas that forms the gas bubble and forms a gas pocket in the reservoir adjacent to the meniscus. The creation of the gas pocket on filling provides a sterile gas bubble and reduces contaminants in the system. Alternatively, the air pocket may be created by introducing a gas
 15 to the reservoir after filling of the microchannel.

FIG. 2 shows an exploded view of an embodiment of an illustrative bubble valve 10
 of the present invention. The microfluidic system may be formed by a plurality of stacked layers. As shown in Figure 2, the illustrative microfluidic system 100 includes a first plate 20
 20 in which a groove defining the microchannel 21 is provided. A hydrophobic patch 22 may be applied to an inner wall of the microchannel 21. A second plate 30 for enclosing the microchannel is bonded to the first plate 20 and includes an aperture 31. A third plate 40 is bonded on top of second plate 30 to close and seal the stacked structure. The aperture 31 of the intermediate second plate 30 defines a void in the system adjacent to the microchannel 21.

25

FIGS. 3 and 4 illustrates the assembled bubble valve 10. As shown, the stacked first plate 20, second plate 30 and third plate 40 define a closed, gas filled gas reservoir 70, which can be actuated with a displacement actuator 50. According to the illustrative embodiment, the aperture 31 defining the reservoir 70 comprises a main body 31a and a slot 31b extending
 30 from the main body 31a. When the microfluidic system 10 is assembled, the slot 31b of the aperture 31 defines a gap in the side wall of the microchannel 21 that provides access to and communicates with the interior of the microchannel 21.

The bubble valve 10 operates to control the flow of liquid through the microchannel 21. A meniscus is formed in the aperture 31, which interfaces with and separates the microchannel interior from the reservoir 70. According to the embodiment shown in Figures 2-8c, the meniscus is formed by a liquid filling the microchannel in the slot 31b. One skilled in the art will recognize that other suitable devices may be used to form the meniscus. The liquid in the slot 31b is retained in the microchannel by capillary forces. The actuator 50 deflects the upper wall of the reservoir, defined by plate 40, which decreases the volume of the reservoir 70. The actuator 50 may comprise any suitable device for deflecting the wall, such as an electromagnetic actuator or a piezoelectric element. The plate 40 may comprise a flexible membrane. The decreased volume consequently increases the pressure of the reservoir 70 and causes the meniscus 80 to deflect into the channel interior to create a constriction in the channel, thereby impeding fluid flow or pushing fluid away from the meniscus. If a sufficient pressure is applied to the meniscus, the actuator generates and enlarges a bubble in the liquid of the microchannel, which blocks fluid flow. The hydrophobic patch 22 provides an anchor for the bubble and retains the bubble at a selected location in the microchannel.

After the microchannel is filled with a liquid 60, the bubble valve 10 is ready for operation. FIG. 5a-c illustrate the operation of the bubble valve according to the teachings of the invention. FIG. 5a shows the bubble valve in an 'open' state. According to the embodiment of Figures 5a-5c, the meniscus between the reservoir and the interior of the microchannel is defined by the meniscus 80, formed by the liquid 60 in the slot 31b in the second plate 30. In the 'open' state, liquid flows freely through the microchannel 21 and the valve does not impose any additional flow resistance in the channel.

The slot 31b may be sized and dimensioned to form a "virtual wall" in the microchannel. As used herein, "virtual wall" refers to the meniscus 80 formed by the first liquid 60 in the aperture formed in the side wall of the microchannel 20, which essentially replaces the removed portion of the side wall without affecting the properties of the microchannel. The meniscus surface can be, although not required, substantially co-planar with the wall of the microchannel in which the meniscus is formed. The word "virtual" is chosen to express the effect that the overall liquid flow through the microchannel 21 of the microfluidic system 100 is not influenced by the virtual wall, i.e. the flow of liquid in the microfluidic system having a virtual wall is substantially identical to the flow of liquid

through an identical microfluidic system in which no virtual wall is present. One of ordinary skill will recognize that the meniscus may be convex or concave, depending on the appropriate system pressure.

5 When the actuator 50 is actuated, the bubble valve 10 switches to a “pinched” state, as shown in Figure 5b, to inhibit fluid flow through the channel interior. In the ‘pinched’ state, the actuator 50 deflects the top of the gas reservoir 70 for a certain fraction, increasing the pressure in the reservoir 70 and forcing the meniscus 80 down into the channel 21. The deflection of the meniscus locally reduces the cross-section of the channel 21 and introduces
10 an additional flow resistance to the liquid flow. The degree of reduction in the liquid flow through the microchannel corresponds to the amplitude, frequency and duration of the displacement of the meniscus 80, which are controllable by the actuator 50. One skilled in the art will recognize that any suitable means for varying the pressure within the reservoir 70 may be used to deflect the meniscus 80, thereby regulating fluid flow.

15 When the actuator is fully actuated, the bubble valve 10 is switched to a closed state, as illustrated in Figure 5c. As shown, in the closed state, the meniscus 80 deflects fully to form and introduce a gas bubble 81 into the microchannel 21. The gas bubble 81 is retained by the hydrophobic patch 22 formed in the channel wall opposite the slot 31b. As a result,
20 the liquid flow in the channel is substantially blocked. By reducing the pressure on the meniscus 80, the bubble valve 10 can be brought from the ‘closed’ state of Figure 5c via the ‘pinched’ state of Figure 5b back to the ‘open’ state of Figure 5a.

25 According to one embodiment, the bubble valve 10 may be used as a check valve for regulating pressure in the microchannel. When the pressure in the microchannel exceeds a maximum breaking pressure, the bubble collapses, opening the valve and allowing fluid to flow through the channel, thereby reducing the pressure in the microchannel. The breaking pressure depends on the hydrophobicity of the hydrophobic patch 22, as well as the geometry of the microchannel.

30 Alternatively or in combination with the hydrophobic patch 22, the microchannel 21 can be locally shaped into a cavity for receiving and anchoring the gas bubble 81. By providing an appropriate cavity, the bubble can be kept in place during operation, reducing the risk that the gas bubble is carried away with the liquid.

According to the embodiments shown in Figures 2-5c, the actuator 50 is integrated in the microfluidic chip 100. However, one skilled in the art will recognize that an external, reusable actuator may also be used to control formation of a gas bubble in the microchannel.

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FIG. 6 shows an alternative embodiment of a microfluidic system 100' including a bubble valve 10' having an external actuator 90 according to the teachings of the invention. In the embodiment shown in Figure 6, the microfluidic system 100' includes a first plate 200 including a groove defining the microchannel 210 and a second plate 300 bonded to the first plate 200 for enclosing the microchannel 210 and in which a virtual wall opening 32 is formed. The virtual wall opening 32 is sized and dimensioned to form a "virtual wall" when the microchannel 210 is filled with a liquid.

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Upon filling of the microchannel 21 with a liquid, a virtual wall 32a is formed in virtual wall opening 32. As shown in Figures 7, 8a-8c, the microfluidic system further includes an external actuator, illustrated as pressurizer 90, pressed and sealed onto the top of the second plate 300 to form a tight seal. The external pressurizer 90 defines a sealed pressurizing chamber 92 adjacent to the virtual wall 32a. The pressurizer varies the pressure within the pressurizing chamber 92 to control liquid flow through the microchannel 210 by modifying the position of the virtual wall. The pressurizer 90 may include a source of pressurized gas (not shown) and a gas inlet 91 to allow a gas pressure to be applied to the virtual wall 32a in order to move the virtual wall. The pressurizer may alternatively include a flexible wall that deflects to vary the volume of the chamber 92 upon activation of an actuator, such as a piezoelectric element or electromagnetic actuator.

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FIG. 8a shows a cross-section of the bubble valve 10' of Figures 6 and 7 in the 'open' state. As shown, when the microchannel 210 is filled with liquid 600, a virtual wall 32a, defined by a meniscus 800, is formed within the virtual wall opening 32. The meniscus essentially replaces the absent portion of the side wall of the microchannel and allows liquid to flow through the channel interior unimpeded and uninfluenced by the virtual wall.

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FIG. 8b depicts the 'pinched' state of the bubble valve, when the pressurizer 90 is activated. As shown, activation of the pressurizer 90 increases the internal pressure within the pressurizing chamber 92. The increased pressure moves the meniscus 800 down the

channel height and into the microchannel interior, thereby regulating liquid flow. The pressurized controls the level of the internal pressure in order to control the amount of deflection of the meniscus and therefore the rate of fluid flow.

5 To switch the valve to a 'closed' state, as shown in Figure 8c, the pressurizer 90 applies a large pressure that is sufficient to form and introduce a gas bubble 810 into the channel 210. The hydrophobic patch 220 retains the gas bubble 810 in place. As a result, the liquid flow in the channel is blocked up to a 'breaking pressure', which depends on the hydrophobicity of hydrophobic patch 220. A higher hydrophobicity results in a larger
10 breaking pressure. By reducing the pressure on the meniscus 800 the bubble valve 10' can be brought from the 'closed' state of Figure 8c via the 'pinched' state of Figure 8b back to the 'open' state of Figure 8a.

FIG. 9 shows an application of a bubble valve 10 for flow regulation in a
5 microchannel 121 according to one embodiment of the invention. During typical operation of a microfluidic system, a pressure difference is applied over the length of a microchannel 121. A bubble valve 10 can be employed to regulate the flow through the microchannel between zero and a maximum flow rate, depending on the applied pressure difference.

FIG. 10 shows a portion of a microfluidic system according to an embodiment of the invention forming a Y-intersection comprising two inlet microchannels 121a and 121b and an outlet channel 121c that combines the fluids flowing through the two inlet microchannels. The first microchannel 121a carries a first liquid and the second microchannel 121b carries a second liquid. The microchannels 121a and 121b are each controlled by a corresponding
20 bubble valve, 10a and 10b, respectively, for regulating the combined composition and flow rate through the outlet microchannel 121c. One skilled in the art will recognize that that the number of inlet channels is not limited to two, but is presented here merely as an example.

FIG. 11 shows a Y-intersection of a microfluidic system according to another
30 embodiment of the invention. As shown the Y-intersection comprises an inlet microchannel 221c and two outlet microchannels 221a and 221b for splitting the incoming liquid flow from the inlet microchannel 221c. The flow of each outlet channel is regulated by a corresponding bubble valve 200a and 200b, respectively. The incoming liquid flow from the inlet microchannel 221c can be split between microchannel 221a and microchannel 221b in any

required ratio. One skilled in the art will recognize that that the number of inlet channels is not limited to two, but is presented here merely as an example.

FIG. 12a-12c shows the implementation of an electrophoresis system 110 comprising five bubble valves, 10a-e of the present invention, arranged with a crossed microchannel configuration. Regulation of the bubble valve 10a regulates the electric current through the associated electrokinetically operated microchannel 115a. The pinching of the liquid in the electrokinetically operated microchannel 115a by a bubble valve will result in an increased electrical resistance in the microchannel 115a. As a result, the migration of charged species and electro-osmotic flow in the electrokinetically operated microchannel 115a can be regulated. A voltages difference for the injection of sample from a well storing a supply of a sample 125 between the bubble valve 10a and the crossing point 111 of the microchannels and consecutive separation are provided via wells V+ and V0. Electrodes are placed in the V+ and V0 wells and energized with a constant voltage difference during the operation of the electrophoresis system.

In the injection phase, valves 10a, 10b, 10c and 10d are substantially in the open position, allowing passage of electrical current up to a required level for injection (FIG 12b shows direction of current / sample), while bubble valve 10e is closed. The valves are kept in this position long enough for the sample to move from the sample well 125 towards and past the central injection crossing 111. Varying the opening ratio of valves 10a, 10b and 10d can be adjusted to confine the sample to a narrow flow through the injection cross 111, as shown in Figure 12c (i.e. 'pinched injection').

Immediately after the injection phase, a plug of sample is injected and separated in the separation column 115a (microchannel which runs horizontally in figure) by closing bubble valves 10a, 10d and 10c and opening valves 10b and 10e. Now the total voltage difference is applied longitudinally over the separation channel, resulting in the separation of the constituents in the sample (Figure 12c).

FIG. 13a illustrates another application of the bubble valve of the present invention implemented in a column-column switch 130 for electrokinetically transferring a substance from a first electrokinetically operated microchannel 215a to a second electrokinetically operated microchannel 215b. The column-column switch 130 comprises a bubble valve 10b

of the present invention that connects the first electrokinetically operated microchannel 215a to the second electrokinetically operated microchannel 215b. Both electrokinetically operated microchannel 215a and electrokinetically operated microchannel 215b are connected to corresponding wells well 220a-d. In the following example, it is assumed that

5 the substances electrokinetically move from a positive electric potential to ground and that well 120c and well 120b are provided with a positive potential whilst well 120a and well 120d are grounded.

At first, the two electrokinetically operated microchannel 215a and electrokinetically operated microchannel 215b are operated independently and the connecting bubble valve 10b is in the 'closed' state whilst bubble valve 10a and bubble valve 10c are in the 'open' state. To electrokinetically transfer substance from electrokinetically operated microchannel 215a to the electrokinetically operated microchannel 215b, bubble valve 10a and bubble valve 10c are switched to the closed state, and the connecting bubble valve 10b is opened momentarily

5 to allow passage of an amount of substance from the electrokinetically operated microchannel 215a to the electrokinetically operated microchannel 215b. The amount transferred depends directly upon the time bubble valve 10b is opened. After the required amount of substance is transferred, the connecting bubble valve 10b is closed and the bubble valve 10a and bubble valve 10b are opened again.

FIG. 13b illustrates the implementation of another column to column switch 130' to exchange liquid from a first column 215a' selectively into a second column 215b'. The first column and the second column are each crossed by a transfer column 250, operated by a first bubble valve 10a arranged on one end of the transfer column 250 and a second bubble valve

25 10b arranged on the opposite end of the transfer column 250. The first one of the bubble valves is attached to the first column 215a' and is actuated upon transiently by an external actuator for increasing the pressure within the bubble valve reservoir. Increasing the pressure on the bubble valve will deflect the meniscus 80, inducing a transient flow in the transfer column 250 from the pressurized bubble valve 10a towards the second bubble valve 10b,

30 which comprises a compressible volume of gas. This transient flow effectively transfers a liquid volume from the first column 215a' to the second column 215b'. Upon deactivation of the external actuator, the flow in the transfer column 250 reverses as the compressed gas volume in the second bubble valve 10b exerts a pressure on the liquid in the transfer column 250.

FIG. 14 shows a selective resistance circuit employing a bubble valve of the present invention for selectively including a predefined electrical resistance in an electrokinetic circuit. The circuit 140 comprises an inlet microchannel 321, which splits into two paths.

- 5 The first path 322 includes a fluidic resistor 240a and a bubble valve 10a, the second parallel path 323 includes a fluidic resistor 240b and a bubble valve 10b. The fluidic resistors 240a-b comprise a channel of appropriate length to results in a certain electrical resistance. The bubble valve 10a and the bubble valve 10b can be switched each to either on to allow fluid flow through the associated microchannel or off to block fluid flow through the associated
- 10 microchannel. As a result, the overall electrical resistance of the electrokinetic circuit can be switched between four values: infinite (both bubble valves 10a-b are off), the resistance of fluidic resistor 240a (bubble valve 10a on, bubble valve 10b off), the resistance of fluidic resistor 240b (bubble valve 10a off, bubble valve 10b on) and the parallel resistance of fluidic resistor 24a-b (both bubble valves 10a and 10b on).

FIG. 15 shows an alternative resistance circuit 150 according to another application of the invention, now for the selective application of a voltage. By opening either the bubble valve 10a or bubble valve 10b, the voltage imposed on an outgoing channel 523 can be selected. Fluidic resistor 245a and 245b function to limit the electric current in either of the two states to a predetermined value.

- FIG. 16 illustrates another application of the bubble valve 10 of the present invention in a particle sorting application, wherein the bubble valve is positioned in a side channel that communicates with a channel through which particles in suspension flow. According to one
- 25 application of the present invention, a particle sorter 160 comprises a closed channel system of capillary size for sorting particles, such as cells. The channel system comprises a first supply duct 162 for introducing a stream of particles and a second supply duct 164 for supplying a carrier liquid. The first supply duct 162 ends in a nozzle, and a stream of particles is introduced into the flow of carrier liquid. The first supply duct 162 and the
- 30 second supply duct 164 enter a measurement duct 166, which branches into a first branch 172a and a second branch 172b at a branch point 171. A measurement region 182a is defined in the measurement duct 166 and is associated with a detector 182b to sense a predetermined characteristic of particles in the measurement region 182a. Two opposed bubble valves 10a and 10b are positioned in communication with the measurement duct 166 and are spaced

opposite each other. The bubble valves 10a, 10b communicate with the measurement duct 166 through a pair of opposed side passages 174a and 174b, respectively. Liquid is allowed to partly fill these side passages 174a and 174b to form a meniscus 175 therein. An external actuator 176 is also provided for actuating the bubble valves 10a, 10b, which momentarily
5 causes a flow disturbance in the duct to deflect the flow therein when activated by the actuator 176.

In a suspension introduced by the first supply duct 162, two types of particles can be distinguished, normal particles 180a and particles of interest 180b. The flow rates in both
10 branches 172a and 172b are adjusted so that the stream of particles normally flows through the second branch 172b. Upon sensing the predetermined characteristic in the particles in the measurement region 182a, the detector 182b raises a signal. The external actuator 176 activates the bubble valves 10a, 10b when signaled by the detector 182b in response to sensing the predetermined characteristic, to create a flow disturbance in the measurement
15 duct 166 between the sideways passages 174a, 174b, to deflect the particle having the predetermined characteristic so that it flows down the first branch duct 172a rather than the second branch duct 172b. The detector communicates with the actuator 176, so that when the detector 182b senses a predetermined characteristic in a particle, the actuator activates the first bubble valve 10a to cause pressure variations in the reservoir 70 of the first bubble valve.
20 The activation of the first bubble valves causes a transient pressure variation in the first side passage 174a. The second side passage 174b and the second bubble valve 10b absorb the transient pressure variations in the measurement duct 166 induced via the actuator 176. Basically, the reservoir 70b of the second bubble valve 10b is a chamber having a resilient wall or contains a compressible fluid such as a gas. The resilient properties allow the flow of
25 liquid from the measurement duct into the second side passage 174b.

Figures 17a-17c illustrate the operation of the particle sorting system 160 of Figure 16. In Figure 17a, the detector raises a signal to activate the actuator. Upon activation of the actuator, the pressure within the reservoir of the first bubble valve 10a is increased, causing a
30 transient discharge of liquid from the first side passage 174a as indicated by the arrow. The sudden pressure increase caused at this point in the duct causes liquid to flow into the second side passage 174b because of the resilient properties of the reservoir of the second bubble valve 10b. This movement of liquid into the second side passage 174b is indicated with an arrow. Resultingly, as can be seen in the figure, the flow through the duct is deflected causing

the selected particle of interest 178b located between the first side passage 174a and the second side passage 174b to be shifted perpendicular to its flow direction in the normal state. The flow resistances to the measurement duct 166, the first branch 172a and the second branch 172b is chosen so that the preferred direction of the flow to and from the first side passage 174a and the second side passage 174b has an appreciable component perpendicular to the normal flow through the measurement duct 166. This goal can for instance be reached by the first branch 172a and the second branch 172b so that their resistances to flow is large in comparison with the flow resistances of the first side passage 174a and the second side passage 174b.

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Figure 17b shows the particle sorting system 160 during the relief of the first bubble valve reservoir when the particle of interest 178b has left the volume between the first side passage 174a and the second side passage 174b. The actuator 176 is deactivated, causing the pressure inside the reservoir to return to the normal pressure. During this relief phase there is a negative pressure difference between the two reservoirs of the bubble valves, causing a liquid flow through the first side passage 174a and the second side passage 174b opposite to the liquid flow shown in the previous figure and is indicated by the arrows.

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Figure 17c shows the particle sorting system 160 after completion of the switching sequence. The pressures inside the reservoirs of the bubble valves has been equalized so the flow through the measurement duct 166 is normalized. As the particle of interest 178b has been displaced radially, it will flow into the first branch 172a as was the objective of the switching operation.

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According to yet another embodiment, the cross-sectional dimensions of a microchannel including a bubble valve according to the teachings of the present invention may be varied locally to affect the pressure within the microchannel interior. For example, the microchannel may be narrowed or widened at certain locations to increase or decrease the capillary forces acting on a fluid in the microchannel interior. One of ordinary skill in the art will be able to determine a suitable cross-sectional dimension to achieve a desired pressure within the microchannel interior.

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The bubble valve of the present invention may be implemented in a variety of microfluidic devices used for many applications. In a particular application, the bubble valve

is implemented in a flow-cytometer based instrument for sorting or physically separating particles of interest from a sample or for measuring selected physical and chemical characteristics of cells or particles in suspension as they travel past a particular site. The bubble valve may also be employed in devices for sequencing or manipulating DNA, medical
5 diagnostic instruments, devices for drug discovery, chemical analysis and so on.

The present invention provides an improved system and method for regulating fluid flow in a microchannel for a variety of applications. The bubble valve of the present invention is easy to operate and control, simple to manufacture and economical. In addition,
10 the bubble valve does not adversely affect the liquid in the microchannel. The bubble valve effectively controls the flow of liquids in microfluidic systems, without heating the fluid and without complex on-chip circuitry.

The present invention has been described relative to an illustrative embodiment. Since
15 certain changes may be made in the above constructions without departing from the scope of the invention, it is intended that all matter contained in the above description or shown in the accompanying drawings be interpreted as illustrative and not in a limiting sense.

It is also to be understood that the following claims are to cover all generic and
20 specific features of the invention described herein, and all statements of the scope of the invention which, as a matter of language, might be said to fall therebetween.

Having described the invention, what is claimed as new and protected by Letters Patent is:

What is claimed is:

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1. A microfluidic device, comprising:
a microchannel having an interior bounded by a side wall;
a valve for regulating the flow of fluid through the microchannel, the valve comprising a gas-filled reservoir, a fluid meniscus interfacing the reservoir and the interior and an actuator for varying the volume of the reservoir to increase an internal pressure of the reservoir to vary the flow of liquid through the channel.
2. The microfluidic device of claim 1, wherein the actuator deflects the meniscus into the microchannel interior to regulate the flow of fluid through the microchannel.
3. The microfluidic device of claim 1, wherein the meniscus comprises a virtual wall formed in an aperture in the side wall of the microchannel when the microchannel is filled with a liquid.
4. The microfluidic device of claim 1, wherein the actuator generates a gas bubble in the microchannel.
5. The microfluidic device of claim 4, further comprising a hydrophobic patch attached to an inner wall of the microchannel for anchoring the gas bubble.
6. The microfluidic device of claim 4, wherein the microchannel defines a cavity for retaining the gas bubble.
7. The microfluidic device of claim 1, wherein the gas filled reservoir comprises a movable membrane.
8. The microfluidic device of claim 7, wherein the actuator deflects the movable membrane to create a bubble in the microchannel interior.
9. A microfluidic device comprising:
a first plate having a groove formed therein defining a microchannel;

a second plate for enclosing the microchannel bonded to the first plate having an aperture adjacent to the groove sized and dimensioned to form a meniscus when the microchannel is filled with a liquid, the aperture defining a reservoir adjacent to the microchannel, wherein the meniscus forms an interface between the microchannel and the reservoir; and

a flexible membrane bonded to the second plate to seal the reservoir.

10. The microfluidic device of claim 9, further comprising an actuator for deflecting the flexible membrane, wherein the deflection of the membrane increases the pressure in the reservoir and deflects the meniscus into the microchannel to regulate liquid flow therethrough.

11. The microfluidic device of claim 10, wherein the actuator comprises one of an electromagnetic element and a piezoelectric element.

12. The microfluidic device of claim 9, further comprising a hydrophobic patch attached to the groove.

13. The microfluidic device of claim 9, wherein the meniscus forms a bubble in the microchannel to block liquid flow.

14. The microfluidic device of claim 13, wherein the groove includes a cavity formed therein for retaining the bubble.

15. A microfluidic device, comprising:
a microchannel having an interior bounded by a side wall;
a bubble valve for creating and injecting a bubble into the microchannel interior to regulate fluid flow through the microchannel; and
a hydrophobic patch for retaining the bubble in a predetermined position in the microchannel interior.

16. The microfluidic device of claim 15, wherein the bubble valve comprises an aperture in the side wall, wherein a fluid in the microchannel forms a meniscus in the aperture, a

sealed chamber formed adjacent to the aperture and an actuator for deflecting the meniscus into the interior by increasing the pressure in the chamber.

17. A method of making a bubble valve, comprising:

5 providing a microchannel having an interior bounded by a side wall, an aperture formed in the side wall and a valve chamber adjacent to the aperture in communication with the interior;

filling the microchannel with a liquid to form a meniscus of the liquid in the aperture, whereby the step of filling traps a gas in the valve chamber;

10 providing an actuator for increasing the pressure in the valve chamber to deflect the meniscus into the interior.

18. A method of making a bubble valve, comprising:

5 providing a microchannel having an interior bounded by a side wall, an aperture formed in the side wall and a valve chamber adjacent to the aperture in communication with the interior;

filling the microchannel with a liquid to form a meniscus of the liquid in the aperture,

applying and sealing an actuator comprising a chamber to a top surface of the microchannel to form a gas-filled chamber adjacent to the meniscus, wherein the actuator
20 varies the pressure in the gas-filled chamber to deflect the meniscus into the interior, thereby regulating fluid flow.

19. In a particle sorting device a bubble valve for separating particles having a predetermined characteristic from particles not having a predetermined characteristic, the
25 bubble valve comprising:

a gas-filled reservoir;

a side channel in communication with a channel through which a stream of particles in a carrier fluid passes, wherein the carrier fluid forms a meniscus in the side channel adjacent to the gas-filled reservoir;

30 an actuator for deflecting the meniscus to create a pressure pulse to selectively deflect a particle having the predetermined characteristic from the stream of particles.

20. A method of varying an electrical resistance in a microchannel, comprising the steps of:

generating a bubble;
injecting the bubble into a liquid in the microchannel, whereby the bubble varies the
5 electrical resistance of the microchannel.

21. The method of claim 20, wherein the step of generating a bubble comprises applying a pressure to a meniscus formed in a side wall of the microchannel, wherein the meniscus is formed by the liquid in the microchannel filling an aperture in the side wall.

22. The method of claim 21, wherein the step of applying a pressure comprises increasing the pressure within a sealed reservoir formed adjacent to the aperture.

23. An electrophoretic system, comprising
an electrokinetically operated microchannel;
a sample well for providing an sample to the microchannel;
a voltage source;
a bubble valve for injecting a bubble into the microchannel to vary the electrical
resistance of the microchannel.

24. An electrokinetic column to column switch, comprising:
a first electrokinetically operated microchannel;
a second electrokinetically operated microchannel in communication with the first
electrokinetically operated microchannel;

25 a bubble valve for selectively blocking flow from the first electrokinetically operated microchannel to the second electrokinetically operated microchannel by selectively injecting a bubble into a microchannel.

5 interior and an actuator for deflecting the membrane into the microchannel interior to regulate fluid flow. The actuator generates a gas bubble in a liquid in the microchannel when a sufficient pressure is generated on the membrane.

Customer Number: 000959

Attorney's
Docket
Number CVZ-012

Declaration, Petition and Power of Attorney for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW THROUGH A MICROCHANNEL

the specification of which

(check one)

X is attached hereto.

was filed on _____ as

Application Serial No. _____

and was amended on _____
(if applicable)

I do not know and do not believe that the subject matter of this application was known or used by others in the United States or patented or described in a printed publication in any country before my invention thereof, or patented or described in a printed publication in any country or in public use or on sale in the United States more than one year prior to the date of this application, or first patented or caused to be patented or made the subject of an inventor's certificate by me or my legal representatives or assigns in a country foreign to the United States prior to the date of this application on an application filed more than twelve months (six months if this application is for a design) before the filing of this application; and I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application, that no application for patent or inventor's certificate on the subject matter of this application has been filed by me or my representatives or assigns in any country foreign to the United States, except those identified below, and that I have reviewed and understand the contents of the specification, including the claims as amended by any amendment referred to herein.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

CLAIM OF BENEFIT OF EARLIER FOREIGN APPLICATION(S)

I hereby claim priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application(s) for patent or inventor's certificate filed by me on the same subject matter having a filing date before that of the application(s) from which priority is claimed.

Check one:

☒ no such applications have been filed.

☐ such applications have been filed as follows

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

Country	Application Number	Date of Filing (month,day,year)	Priority Claimed Under 35 USC 119
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

CLAIM FOR BENEFIT OF U.S. PROVISIONAL APPLICATION(S)

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

<u>60/373,256</u>	<u>April 17, 2002</u>
(Application Serial No.)	(Filing Date)

(Application Serial No.) (Filing Date)

[illegible]

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S)

I hereby claim the benefit under Title 35, United States Code, §120 of any earlier United States application(s) or PCT international application(s) designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the earlier application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date(s) of the earlier application(s) and the national or PCT international filing date of this application. As to subject matter of this application which is common to my earlier application(s), if any, described below, I do not know and do not believe that the same was known or used by others in the United States or patented or described in a printed publication in any country before my invention thereof, or patented or described in a printed publication in any country or in public use or on sale in the United States more than one year prior to the date(s) of said earlier application(s), or first patented or caused to be patented or made the subject of an inventor's certificate by me or my legal representatives or assigns in a country foreign to the United States prior to the date(s) of said earlier application(s) on an application filed more than twelve months (six months if this application is for a design) before the filing of said earlier application(s); and I acknowledge that no application for patent or inventor's certificate on said subject matter has been filed by me or my representatives or assigns in any country foreign to the United States except those identified herein.

 (Application Serial No.)

 (Filing Date)

 (Status)
 (patented,pending,aband.)

 (Application Serial No.)

 (Filing Date)

 (Status)
 (patented,pending,aband.)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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Megan E. Williams	Reg. No. 43,270	Allan Tameshtit	Limited Recognition
Jeremiah Lynch	Reg. No. 17,425		Under 37 C.F.R. § 10.9(b)
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Anthony A. Laurentano, Esq., (617) 227-7400

Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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10149596-0548

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

07/02/2002 NMOHAMM1 00000015 120080 10179586

01 FC:101	740.00 CH
02 FC:103	72.00 CH
03 FC:102	504.00 CH

PTO-1556
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*U.S. Government Printing Office: 2001 — 481-697/59173

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 2001

Application or Docket Number

CVZ-012

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	24	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	24 minus 20 =	* 4
INDEPENDENT CLAIMS	9 minus 3 =	* 6
MULTIPLE DEPENDENT CLAIM PRESENT <input type="checkbox"/>		

* If the difference in column 1 is less than zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

	(Column 1)	(Column 2)	(Column 3)
CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**
Independent	*	Minus	***
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

	(Column 1)	(Column 2)	(Column 3)
CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**
Independent	*	Minus	***
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

	(Column 1)	(Column 2)	(Column 3)
CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus	**
Independent	*	Minus	***
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."

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SMALL ENTITY TYPE ☐

OR OTHER THAN SMALL ENTITY

RATE	FEE
BASIC FEE	370.00
X\$ 9=	
X42=	
+140=	
TOTAL	

RATE	FEE
BASIC FEE	740.00
X\$18=	72
X84=	504
+280=	
TOTAL	1316

SMALL ENTITY OR

OTHER THAN SMALL ENTITY

RATE	ADDITIONAL FEE
X\$ 9=	
X42=	
+140=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
X\$18=	
X84=	
+280=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
X\$ 9=	
X42=	
+140=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
X\$18=	
X84=	
+280=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
X\$ 9=	
X42=	
+140=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
X\$18=	
X84=	
+280=	
TOTAL ADDIT. FEE	

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APPLICATION DATA SHEET

Application Information

Application Type:: Regular
Subject Matter:: Utility
Title:: MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE
FOR REGULATING FLUID FLOW THROUGH A
MICROCHANNEL

Attorney Docket Number:: CVZ-012

Request for Early Publication:: No

Request for Non-Publication:: No

Total Drawing Sheets:: 7

Small Entity?:: No

Petition Included?:: No

Secrecy Order in Parent Appl.?:: No

Applicant Information

Application Authority Type:: Inventor

Primary Citizenship Country:: US

Status:: Full Capacity

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2067 EH

Application Authority Type::

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State or Province of mailing address::

MA

Country of mailing address::

US

Postal or Zip Code of mailing address::

02021

Correspondence Information

Correspondence Customer Number: 000959

Representative Information

Representative Customer Number::	000959
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Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	Non-Provisional of	60/373,256	04/17/02

Assignee Information

Assignee name:: Coventor, Inc.
Street of mailing address:: 4001 Weston Parkway, Suite 200
City of mailing address:: Cary
State or Province of mailing address:: NC
Country of mailing address:: US
Postal or Zip Code of mailing Address:: 27513



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Page 1 of 2

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Customer No. 000959

Case Docket No. CVZ-012

THE COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231



"Express Mail" Mailing Label Number EL 941615635 US
Date of Deposit June 24, 2002
I hereby certify that this transmittal letter and the papers referred to as being enclosed therein are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, Box Patent Application, Washington, DC 20231.
Larry Taylor
Signature
Larry Taylor
Please Print Name of Person Signing

Sir:

Transmitted herewith for filing is the patent application of

Inventor(s): John Gilbert, *et al.*

For: MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW THROUGH A MICROCHANNEL

Enclosed are:

- ☐ This is a request for filing a ☐ continuation ☐ divisional application under 37 CFR 1.53(b), of pending prior application serial no. _____ filed on _____ entitled _____.
- ☒ 19 pages of specification, 4 pages of claims, 1 pages of abstract.
- ☒ 7 sheets of drawings (Figures 1-17C).
- ☒ Unexecuted Declaration, Petition and Power of Attorney (6 pages).
- ☐ An assignment of the invention to _____. A recordation form cover sheet (Form PTO 1595) is also enclosed. (3 pages in total).
- ☐ Applicant claims small entity status. See 37 CFR 1.27.
- ☒ Other Application Data Sheet (3 pages) and return acknowledgment postcard.

The filing fee has been calculated as shown below:

(Col. 1)		(Col. 2)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR:	NO. FILED	NO. EXTRA	RATE	FEE		RATE	FEE
BASIC FEE	////////////////////		////////	\$	OR	////////	\$ 740
TOTAL CLAIMS	24 - 20	= 4	x 9=	\$	OR	x 18=	\$ 72
INDEP. CLAIMS	9 - 3	= 6	x 42	\$	OR	x 84	\$ 504
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIMS PRESENTED			+140	\$	OR	+280	\$
			TOTAL	0	OR	TOTAL	\$1316.00

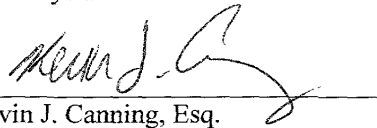
* If the difference in Col. 2 is less than zero, enter "0" in Col. 2.

- ☒ Please charge my Deposit Account No. 12-0080 in the amount of \$ \$1316.00.
A duplicate copy of this sheet is enclosed.
- ☐ A check in the amount of \$ _____ to cover the filing fee is enclosed.
- ☒ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 12-0080.
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- ☒ Any additional filing fees required under 37 C.F.R. 1.16.
- ☒ Any patent application processing fees under 37 C.F.R. 1.17.
- ☐ A check in the amount of \$ _____ to cover the recording of assignment documents is also enclosed.
- ☒ Address all future communications (May only be completed by applicant, or attorney or agent of record)
to Anthony A. Laurentano, Esq. at **Customer Number: 000959** whose address is:

Lahive & Cockfield, LLP
28 State Street
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Date: June 24, 2002

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APPLICATION DATA SHEET

Application Information

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Applicant Authority Type::

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Full Capacity

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Country of mailing address:: US
Postal or Zip Code of mailing Address:: 27513

**Microfluidic System Including a Bubble Valve for Regulating
Fluid Flow Through a Microchannel**

Related Applications

5 This application claims priority to U.S. Provisional Patent Application No. 60/373,256 entitled "Microfluidic System Including a Bubble Valve for Regulating Fluid Flow Through a Microchannel" filed April 17, 2002; and is related to Attorney Docket No. CVZ-021, entitled "Method and Apparatus for Sorting Particles", filed herewith. The contents of both applications are herein incorporated by reference.

Field of the Invention

10 The present invention relates to microscale fluid handling devices and systems. More particularly, the present invention relates to a method and system for controlling liquid flow in a microchannel by the introduction of a gas bubble to a microfluidic system.

Background of the Invention

15 In the chemical, biomedical, bioscience and pharmaceutical industries, it has become increasingly desirable to perform large numbers of chemical operations, such as reactions, separations and subsequent detection steps, in a highly parallel fashion. The high throughput synthesis, screening and analysis of (bio)chemical compounds, enables the economic discovery of new drugs and drug candidates, and the implementation of sophisticated medical diagnostic equipment. Of key importance for the improvement of the chemical operations required in these applications are an increased speed, enhanced reproducibility, decreased consumption of expensive samples and reagents, and the reduction of waste materials.

20 Microfluidic devices and systems provide improved methods of performing chemical, biochemical and biological analysis and synthesis. Microfluidic devices and systems allow for the performance of multi-step, multi-species chemical operations in chip-based micro chemical analysis systems. Chip-based microfluidic systems generally comprise
25 conventional 'microfluidic' elements, particularly capable of handling and analyzing
30 chemical and biological specimens. Typically, the term microfluidic in the art refers to systems or devices having a network of processing nodes, chambers and reservoirs connected by channels, in which the channels have typical cross-sectional dimensions in the range

between about 1.0 μm and about 500 μm . In the art, channels having these cross-sectional dimensions are referred to as 'microchannels'.

By performing the chemical operations in a microfluidic system, potentially a number of the above-mentioned desirable improvements can be realized. Downscaling dimensions allows for diffusional processes, such as heating, cooling and passive transport of species (diffusional mass-transport), to proceed faster. One example is the thermal processing of liquids, which is typically a required step in chemical synthesis and analysis. In comparison with the heating and cooling of liquids in beakers as performed in a conventional laboratory setting, the thermal processing of liquids is accelerated in a microchannel due to reduced diffusional distances. Another example of the efficiency of microfluidic systems is the mixing of dissolved species in a liquid, a process that is also diffusion limited. Downscaling the typical dimensions of the mixing chamber thereby reduces the typical distance to be overcome by diffusional mass-transport, and consequently results in a reduction of mixing times. Like thermal processing, the mixing of dissolved chemical species, such as reagents, with a sample or precursors for a synthesis step, is an operation that is required in virtually all chemical synthesis and analysis processes. Therefore, the ability to reduce the time involved in mixing provides significant advantages to most chemical synthesis and analysis processes.

Another aspect of the reduction of dimensions is the reduction of required volumes of sample, reagents, precursors and other often very expensive chemical substances. Milliliter-sized systems typically require milliliter volumes of these substances, while microliter sized microfluidic systems only require microliters volumes. The ability to perform these processes using smaller volumes results in significant cost savings, allowing the economic operation of chemical synthesis and analysis operations. As a consequence of the reduced volume requirement, the amount of chemical waste produced during the chemical operations is correspondingly reduced.

In microfluidic systems, regulation of minute fluid flows through a microchannel is of prime importance, as the processes performed in these systems highly depend on the delivery and movement of various liquids such as sample and reagents. A flow control device may be used to regulate the flow of liquid through a microchannel. Regulation includes control of

flow rate, impeding of flow, switching of flows between various input channels and output channels as well as volumetric dosing.

U.S. Patent Number 6,062,681 describes a bubble valve for a liquid flow channel in
5 which the flow of a liquid is controlled by the generation of a gas bubble in the channel using
a heater placed in the liquid. As the heater is activated, a bubble is formed which can be
enlarged or reduced in size by increasing or decreasing, respectively, the temperature of the
heater. The described system presents a number of disadvantages, namely, the required
power to operate the valve and the inherent requirement that liquid in the channel be heated
10 upon passing the valve. Even small increases in liquid temperature, by only a couple of
degrees, can have disastrous effects on the highly heat sensitive biochemical substances
present in the liquids to be controlled in many microfluidic systems. In addition, the required
on-chip electric circuitry for the heater increases the complexity of the described valve and
consequently results in unacceptably high costs, particularly if the fluidic system employing
15 the bubble valve only used for a single application.

Other valves in the prior art use electrochemical means to produce a bubble in a
liquid.

20 Summary of the Invention

The present invention provides a bubble valve for controlling, regulating or varying
fluid flow through a microfluidic system. The bubble valve regulates fluid flow through a
channel using an externally operated mechanical or pneumatic actuator. The actuator causes
a deflection of a fluid meniscus into the interior of the channel to regulate liquid flow. The
25 actuator may mechanically force a gas bubble into a fluid carrying microchannel to inhibit
liquid flow or to cause liquid flow by applying a sufficiently high pressure to the meniscus.
The bubble valve effectively controls the flow of liquids in microfluidic systems, without
heating the fluid and without complex on-chip circuitry.

30 The microfluidic system includes a microchannel and a sealed, gas-filled reservoir
positioned adjacent to and connected to the microchannel. The gas filled reservoir has a
movable wall and a meniscus formed by a liquid in the microchannel that forms an interface
between the reservoir and the microchannel interior. The meniscus may form a portion of the
side wall of the microchannel. An external mechanical actuator may be used to deflect the

movable wall of the reservoir. As the movable wall is deflected, the volume of the reservoir decreases and the gas pressure inside the reservoir increases, causing the meniscus to deflect into the microchannel, thereby modifying the cross-sectional area of the microchannel and consequently varying the flow of liquid through the channel. The increased pressure in the reservoir pushes gas from the reservoir into the microchannel. The gas may result in a local gas bubble being forced into the microchannel from the gas-filled reservoir. The resulting gas bubble occupies a portion of the cross-section of the channel, allowing liquid flow through the channel to be effectively controlled by controlling the size of the gas bubble via the external actuator.

The meniscus may comprise a virtual wall formed in a side wall of the microchannel. The virtual wall is a meniscus formed by a liquid in the microchannel that fills an aperture formed in the side wall of the microchannel and essentially replaces the removed portion of the side wall without affecting the properties of liquid flow through the channel. A gas bubble can be forced into the channel by applying a gas pressure at the opening using an external pneumatic actuator. The gas pressure forces the meniscus inside the channel, which varies the flow of liquid through the channel interior.

According to one embodiment, the microchannel includes a hydrophobic patch spanning the width of the microchannel at the location where the gas bubble is introduced to enhanced on-off switching of the bubble valve. The hydrophobic patch anchors the bubble in a particular location in the microchannel. If the introduced gas bubble covers the whole area of the patch, the bubble is effectively retained by capillary forces and blocks any liquid flow up to a certain pressure difference, depending on the level of hydrophobicity of the patch.

Alternatively or in combination with a hydrophobic patch, the microchannel can be locally shaped into a cavity for receiving and anchoring the gas bubble. By providing an appropriate cavity, the bubble can be kept in place during operation, reducing the risk that the gas bubble is carried away with the liquid.

According to one aspect of the invention, a microfluidic device is provided. The microfluidic device comprises a microchannel having an interior bounded by a side wall and a valve for regulating the flow of fluid through the microchannel. The valve comprises a gas-filled reservoir, a fluid meniscus interfacing the reservoir and the interior and an actuator for

varying the volume of the reservoir to increase an internal pressure of the reservoir to vary the flow of liquid through the channel.

According to another aspect, a microfluidic device is provided, comprising a first
5 plate having a groove formed therein defining a microchannel, a second plate for enclosing the microchannel and a flexible membrane. The second plate is bonded to the first plate and has an aperture adjacent to the groove sized and dimensioned to form a meniscus when the microchannel is filled with a liquid. The aperture defines a reservoir adjacent to the
10 microchannel, wherein the meniscus forms an interface between the microchannel and the reservoir. The flexible membrane is bonded to the second plate to seal the reservoir.

According to another aspect, a method of making a bubble valve is provided, the method comprises providing a microchannel having an interior bounded by a side wall, an
15 aperture formed in the side wall and a valve chamber adjacent to the aperture in communication with the interior, filling the microchannel with a liquid to form a meniscus of the liquid in the aperture, whereby the step of filling traps a gas in the valve chamber and providing an actuator for increasing the pressure in the valve chamber to deflect the meniscus into the interior.

According to yet another aspect, a method of making a bubble valve is provided. The method comprises providing a microchannel having an interior bounded by a side wall, an
20 aperture formed in the side wall and a valve chamber adjacent to the aperture in communication with the interior, filling the microchannel with a liquid to form a meniscus of the liquid in the aperture and applying and sealing an actuator comprising a chamber to a top
25 surface of the microchannel to form a gas-filled chamber adjacent to the meniscus. The actuator varies the pressure in the gas-filled chamber to deflect the meniscus into the interior, thereby regulating fluid flow.

According to still another aspect, a microfluidic device is provided comprising a
30 microchannel having an interior bounded by a side wall, a bubble valve for creating and injecting a bubble into the microchannel interior to regulate fluid flow through the microchannel and a hydrophobic patch for retaining the bubble in a predetermined position in the microchannel interior.

According to yet another aspect a bubble valve in a particle sorting device for separating particles having a predetermined characteristic from particles not having a predetermined characteristic is provided. The bubble valve comprises a gas-filled reservoir, a side channel in communication with a channel through which a stream of particles in a carrier fluid passes, wherein the carrier fluid forms a meniscus in the side channel adjacent to the gas-filled reservoir and an actuator for deflecting the meniscus to create a pressure pulse to selectively deflect a particle having the predetermined characteristic from the stream of particles.

According to still another aspect, a method of varying an electrical resistance in a microchannel is provided. The method comprises generating a bubble and injecting the bubble into a liquid in the microchannel, whereby the bubble varies the electrical resistance of the microchannel.

According to yet another aspect, an electrophoretic system is provided, comprising an electrokinetically operated microchannel, a sample well for providing an sample to the microchannel, a voltage source and a bubble valve for injecting a bubble into the microchannel to vary the electrical resistance of the microchannel.

According to a final aspect of the invention, an electrokinetic column to column switch is provided, comprising a first electrokinetically operated microchannel, a second electrokinetically operated microchannel in communication with the first electrokinetically operated microchannel and a bubble valve for selectively blocking flow from the first electrokinetically operated microchannel to the second electrokinetically operated microchannel by selectively injecting a bubble into a microchannel.

Brief Description of the Drawings

Figure 1 is a schematic view of a microfluidic system suitable for implementing the illustrative embodiment of the invention.

Figure 2 shows an exploded view of a bubble valve according to an illustrative embodiment of the present invention.

Figure 3 shows an isometric view of the bubble valve of Figure 2.

Figure 4 shows a top view of the bubble valve of Figure 2.

Figures 5a-c are cross-sectional views of the bubble valve of Figure 2 in operation.

Figure 6 shows an exploded view of an alternative embodiment of a bubble valve according to the present invention.

Figure 7 shows a top view of the bubble valve of Figure 6.

5 Figures 8a-c are cross-sectional view of the bubble valve of Figure 6 in operation.

Figure 9 shows an application of the bubble valve of an illustrative embodiment of the present invention in a microchannel.

10 Figure 10 shows a Y-intersection in a microfluidic system of an embodiment of the invention that implements a bubble valve to control liquid flow according to the teachings of the present invention.

Figure 11 shows a Y-intersection in a microfluidic system of another embodiment of the invention that implements a bubble valve to control liquid flow according to the teachings of the present invention.

15 Figures 12a-c shows an electrophoresis system that implements a bubble valve to control electrical current during electrokinetic injection according to the teachings of the present invention.

Figure 13a shows an electrokinetic column-column switch implementing a bubble valve according to the teachings of the present invention.

20 Figure 13b shows an alternate electrokinetic column-column switch implementing a bubble valve according to another embodiment of the present invention.

Figure 14 shows a selective resistance circuit that employs a bubble valve to control electrical current according to the teachings of the present invention.

Figure 15 shows an alternative selective resistance circuit that employs a bubble valve to control electrical current according to the teachings of the present invention.

25 Figure 16 shows a particle sorting system that implements a bubble valve of the present invention to produce fluid impulses to sort particles.

Figures 17a, 17b and 17c illustrate the operation of the particle sorting system of Figure 16.

30 **Detailed Description of the Invention**

The present invention provides an improved bubble valve for controlling fluid flow through a microchannel in a microfluidic system. The invention further provides a method of forming the bubble valve. The bubble valve of the present invention can be applied in numerous microfluidic systems for controlling and switching fluid flows. Examples of

suitable applications include, but are not limited to: flow cytometry, column switching, 2-D separations, cell or particle sorting applications on a chip, regulating pressurized fluid flows including on-off switching, regulating electrokinetic fluid flows and electrokinetically induced processes including on-off switching and electrokinetic sample injection and channel
5 to channel switching.

Figure 1 illustrates a microfluidic system suitable for implementing the illustrative embodiment of the present invention. The illustrative microfluidic system 100 comprises a substrate 101 having one or more microchannels 21 disposed therein. The microchannels
10 transport fluid through the microfluidic system 100 for processing, handling, and/or performing any suitable operation on a liquid sample. As used herein, the term “microfluidic” refers to a system or device for handling, processing, ejecting and/or analyzing a fluid sample including at least one channel having microscale dimensions. The term “channel” as used herein refers to a pathway formed in or through a medium that allows for
15 movement of fluids, such as liquids and gases. The term “microchannel” refers to a channel preferably formed in a microfluidic system or device having cross-sectional dimensions in the range between about 1.0 μm and about 500 μm , preferably between about 25 μm and about 250 μm and most preferably between about 50 μm and about 100 μm . One of ordinary skill in the art will be able to determine an appropriate volume and length of the microchannel.
20 The ranges are intended to include the above-recited values as upper or lower limits. The microchannel can have any selected shape or arrangement, examples of which include a linear or non-linear configuration and a U-shaped configuration. The microfluidic system 100 may comprise any suitable number of microchannels 21 for transporting fluids through the microfluidic system 100.

25 The microfluidic system 100 includes a bubble valve 10, 10' shown in Figures 2-8c for controlling liquid flow through a microchannel of the system. According to the illustrative embodiment, the microchannel is defined by a side wall having any suitable shape enclosing at least a portion of the interior of the channel. The bubble valve may be formed
30 by a gas-filled reservoir positioned adjacent to the microchannel including a meniscus that forms the interface between the reservoir and the microchannel interior. The meniscus may form a portion of the side wall of the microchannel. The bubble valve includes an actuator for modifying the pressure in the reservoir to deflect the meniscus into the channel interior,

thereby modifying the cross-sectional area of the microchannel and consequently varying the flow of liquid through the channel.

According to an alternate embodiment, the bubble valve is formed by a meniscus in a
 5 separate side channel that communicates with and intersects a microchannel through which a liquid to be controlled flows. One skilled in the art will recognize that the meniscus can be located at any location relative to the microchannel through which liquid flows.

The gas-filled reservoir may be formed when filling the microchannel having an
 10 aperture in a side wall and a reservoir formed adjacent to the aperture. An empty microchannel may be filled with liquid, forming the meniscus in the aperture, which traps the gas that forms the gas bubble and forms a gas pocket in the reservoir adjacent to the meniscus. The creation of the gas pocket on filling provides a sterile gas bubble and reduces contaminants in the system. Alternatively, the air pocket may be created by introducing a gas
 15 to the reservoir after filling of the microchannel.

FIG. 2 shows an exploded view of an embodiment of an illustrative bubble valve 10
 of the present invention. The microfluidic system may be formed by a plurality of stacked layers. As shown in Figure 2, the illustrative microfluidic system 100 includes a first plate 20
 20 in which a groove defining the microchannel 21 is provided. A hydrophobic patch 22 may be applied to an inner wall of the microchannel 21. A second plate 30 for enclosing the microchannel is bonded to the first plate 20 and includes an aperture 31. A third plate 40 is bonded on top of second plate 30 to close and seal the stacked structure. The aperture 31 of the intermediate second plate 30 defines a void in the system adjacent to the microchannel 21.
 25

FIGS. 3 and 4 illustrates the assembled bubble valve 10. As shown, the stacked first plate 20, second plate 30 and third plate 40 define a closed, gas filled gas reservoir 70, which can be actuated with a displacement actuator 50. According to the illustrative embodiment, the aperture 31 defining the reservoir 70 comprises a main body 31a and a slot 31b extending
 30 from the main body 31a. When the microfluidic system 10 is assembled, the slot 31b of the aperture 31 defines a gap in the side wall of the microchannel 21 that provides access to and communicates with the interior of the microchannel 21.

The bubble valve 10 operates to control the flow of liquid through the microchannel 21. A meniscus is formed in the aperture 31, which interfaces with and separates the microchannel interior from the reservoir 70. According to the embodiment shown in Figures 2-8c, the meniscus is formed by a liquid filling the microchannel in the slot 31b. One skilled in the art will recognize that other suitable devices may be used to form the meniscus. The liquid in the slot 31b is retained in the microchannel by capillary forces. The actuator 50 deflects the upper wall of the reservoir, defined by plate 40, which decreases the volume of the reservoir 70. The actuator 50 may comprise any suitable device for deflecting the wall, such as an electromagnetic actuator or a piezoelectric element. The plate 40 may comprises a flexible membrane. The decreased volume consequently increases the pressure of the reservoir 70 and causes the meniscus 80 to deflect into the channel interior to create a constriction in the channel, thereby impeding fluid flow or pushing fluid away from the meniscus. If a sufficient pressure is applied to the meniscus, the actuator generates and enlarges a bubble in the liquid of the microchannel, which blocks fluid flow. The hydrophobic patch 22 provides an anchor for the bubble and retains the bubble at a selected location in the microchannel.

After the microchannel is filled with a liquid 60, the bubble valve 10 is ready for operation. FIG. 5a-c illustrate the operation of the bubble valve according to the teachings of the invention. FIG. 5a shows the bubble valve in an 'open' state. According to the embodiment of Figures 5a-5c, the meniscus between the reservoir and the interior of the microchannel is defined by the meniscus 80, formed by the liquid 60 in the slot 31b in the second plate 30. In the 'open' state, liquid flows freely through the microchannel 21 and the valve does not impose any additional flow resistance in the channel.

The slot 31b may be sized and dimensioned to form a "virtual wall" in the microchannel. As used herein, "virtual wall" refers to the meniscus 80 formed by the first liquid 60 in the aperture formed in the side wall of the microchannel 20, which essentially replaces the removed portion of the side wall without affecting the properties of the microchannel. The meniscus surface can be, although not required, substantially co-planar with the wall of the microchannel in which the meniscus is formed. The word "virtual" is chosen to express the effect that the overall liquid flow through the microchannel 21 of the microfluidic system 100 is not influenced by the virtual wall, i.e. the flow of liquid in the microfluidic system having a virtual wall is substantially identical to the flow of liquid

through an identical microfluidic system in which no virtual wall is present. One of ordinary skill will recognize that the meniscus may be convex or concave, depending on the appropriate system pressure.

5 When the actuator 50 is actuated, the bubble valve 10 switches to a “pinched” state, as shown in Figure 5b, to inhibit fluid flow through the channel interior. In the ‘pinched’ state, the actuator 50 deflects the top of the gas reservoir 70 for a certain fraction, increasing the pressure in the reservoir 70 and forcing the meniscus 80 down into the channel 21. The deflection of the meniscus locally reduces the cross-section of the channel 21 and introduces
10 an additional flow resistance to the liquid flow. The degree of reduction in the liquid flow through the microchannel corresponds to the amplitude, frequency and duration of the displacement of the meniscus 80, which are controllable by the actuator 50. One skilled in the art will recognize that any suitable means for varying the pressure within the reservoir 70 may be used to deflect the meniscus 80, thereby regulating fluid flow.

15 When the actuator is fully actuated, the bubble valve 10 is switched to a closed state, as illustrated in Figure 5c. As shown, in the closed state, the meniscus 80 deflects fully to form and introduce a gas bubble 81 into the microchannel 21. The gas bubble 81 is retained by the hydrophobic patch 22 formed in the channel wall opposite the slot 31b. As a result,
20 the liquid flow in the channel is substantially blocked. By reducing the pressure on the meniscus 80, the bubble valve 10 can be brought from the ‘closed’ state of Figure 5c via the ‘pinched’ state of Figure 5b back to the ‘open’ state of Figure 5a.

25 According to one embodiment, the bubble valve 10 may be used as a check valve for regulating pressure in the microchannel. When the pressure in the microchannel exceeds a maximum breaking pressure, the bubble collapses, opening the valve and allowing fluid to flow through the channel, thereby reducing the pressure in the microchannel. The breaking pressure depends on the hydrophobicity of the hydrophobic patch 22, as well as the geometry of the microchannel.

30 Alternatively or in combination with the hydrophobic patch 22, the microchannel 21 can be locally shaped into a cavity for receiving and anchoring the gas bubble 81. By providing an appropriate cavity, the bubble can be kept in place during operation, reducing the risk that the gas bubble is carried away with the liquid.

According to the embodiments shown in Figures 2-5c, the actuator 50 is integrated in the microfluidic chip 100. However, one skilled in the art will recognize that an external, reusable actuator may also be used to control formation of a gas bubble in the microchannel.

5

FIG. 6 shows an alternative embodiment of a microfluidic system 100' including a bubble valve 10' having an external actuator 90 according to the teachings of the invention. In the embodiment shown in Figure 6, the microfluidic system 100' includes a first plate 200 including a groove defining the microchannel 210 and a second plate 300 bonded to the first plate 200 for enclosing the microchannel 210 and in which a virtual wall opening 32 is formed. The virtual wall opening 32 is sized and dimensioned to form a "virtual wall" when the microchannel 210 is filled with a liquid.

10

Upon filling of the microchannel 21 with a liquid, a virtual wall 32a is formed in virtual wall opening 32. As shown in Figures 7, 8a-8c, the microfluidic system further includes an external actuator, illustrated as pressurizer 90, pressed and sealed onto the top of the second plate 300 to form a tight seal. The external pressurizer 90 defines a sealed pressurizing chamber 92 adjacent to the virtual wall 32a. The pressurizer varies the pressure within the pressurizing chamber 92 to control liquid flow through the microchannel 210 by modifying the position of the virtual wall. The pressurizer 90 may include a source of pressurized gas (not shown) and a gas inlet 91 to allow a gas pressure to be applied to the virtual wall 32a in order to move the virtual wall. The pressurizer may alternatively include a flexible wall that deflects to vary the volume of the chamber 92 upon activation of an actuator, such as a piezoelectric element or electromagnetic actuator.

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FIG. 8a shows a cross-section of the bubble valve 10' of Figures 6 and 7 in the 'open' state. As shown, when the microchannel 210 is filled with liquid 600, a virtual wall 32a, defined by a meniscus 800, is formed within the virtual wall opening 32. The meniscus essentially replaces the absent portion of the side wall of the microchannel and allows liquid to flow through the channel interior unimpeded and uninfluenced by the virtual wall.

30

FIG. 8b depicts the 'pinched' state of the bubble valve, when the pressurizer 90 is activated. As shown, activation of the pressurizer 90 increases the internal pressure within the pressurizing chamber 92. The increased pressure moves the meniscus 800 down the

channel height and into the microchannel interior, thereby regulating liquid flow. The pressurized controls the level of the internal pressure in order to control the amount of deflection of the meniscus and therefore the rate of fluid flow.

5 To switch the valve to a 'closed' state, as shown in Figure 8c, the pressurizer 90 applies a large pressure that is sufficient to form and introduce a gas bubble 810 into the channel 210. The hydrophobic patch 220 retains the gas bubble 810 in place. As a result, the liquid flow in the channel is blocked up to a 'breaking pressure', which depends on the hydrophobicity of hydrophobic patch 220. A higher hydrophobicity results in a larger
10 breaking pressure. By reducing the pressure on the meniscus 800 the bubble valve 10' can be brought from the 'closed' state of Figure 8c via the 'pinched' state of Figure 8b back to the 'open' state of Figure 8a.

FIG. 9 shows an application of a bubble valve 10 for flow regulation in a
15 microchannel 121 according to one embodiment of the invention. During typical operation of a microfluidic system, a pressure difference is applied over the length of a microchannel 121. A bubble valve 10 can be employed to regulate the flow through the microchannel between zero and a maximum flow rate, depending on the applied pressure difference.

20 FIG. 10 shows a portion of a microfluidic system according to an embodiment of the invention forming a Y-intersection comprising two inlet microchannels 121a and 121b and an outlet channel 121c that combines the fluids flowing through the two inlet microchannels. The first microchannel 121a carries a first liquid and the second microchannel 121b carries a second liquid. The microchannels 121a and 121b are each controlled by a corresponding
25 bubble valve, 10a and 10b, respectively, for regulating the combined composition and flow rate through the outlet microchannel 121c. One skilled in the art will recognize that that the number of inlet channels is not limited to two, but is presented here merely as an example.

FIG. 11 shows a Y-intersection of a microfluidic system according to another
30 embodiment of the invention. As shown the Y-intersection comprises an inlet microchannel 221c and two outlet microchannels 221a and 221b for splitting the incoming liquid flow from the inlet microchannel 221c. The flow of each outlet channel is regulated by a corresponding bubble valve 200a and 200b, respectively. The incoming liquid flow from the inlet microchannel 221c can be split between microchannel 221a and microchannel 221b in any

required ratio. One skilled in the art will recognize that that the number of inlet channels is not limited to two, but is presented here merely as an example.

FIG. 12a-12c shows the implementation of an electrophoresis system 110 comprising five bubble valves, 10a-e of the present invention, arranged with a crossed microchannel configuration. Regulation of the bubble valve 10a regulates the electric current through the associated electrokinetically operated microchannel 115a. The pinching of the liquid in the electrokinetically operated microchannel 115a by a bubble valve will result in an increased electrical resistance in the microchannel 115a. As a result, the migration of charged species and electro-osmotic flow in the electrokinetically operated microchannel 115a can be regulated. A voltages difference for the injection of sample from a well storing a supply of a sample 125 between the bubble valve 10a and the crossing point 111 of the microchannels and consecutive separation are provided via wells V+ and V0. Electrodes are placed in the V+ and V0 wells and energized with a constant voltage difference during the operation of the electrophoresis system.

In the injection phase, valves 10a, 10b, 10c and 10d are substantially in the open position, allowing passage of electrical current up to a required level for injection (FIG 12b shows direction of current / sample), while bubble valve 10e is closed. The valves are kept in this position long enough for the sample to move from the sample well 125 towards and past the central injection crossing 111. Varying the opening ratio of valves 10a, 10b and 10d can be adjusted to confine the sample to a narrow flow through the injection cross 111, as shown in Figure 12c (i.e. 'pinched injection').

Immediately after the injection phase, a plug of sample is injected and separated in the separation column 115a (microchannel which runs horizontally in figure) by closing bubble valves 10a, 10d and 10c and opening valves 10b and 10e. Now the total voltage difference is applied longitudinally over the separation channel, resulting in the separation of the constituents in the sample (Figure 12c).

FIG. 13a illustrates another application of the bubble valve of the present invention implemented in a column-column switch 130 for electrokinetically transferring a substance from a first electrokinetically operated microchannel 215a to a second electrokinetically operated microchannel 215b. The column-column switch 130 comprises a bubble valve 10b

of the present invention that connects the first electrokinetically operated microchannel 215a to the second electrokinetically operated microchannel 215b. Both electrokinetically operated microchannel 215a and electrokinetically operated microchannel 215b are connected to corresponding wells well 220a-d. In the following example, it is assumed that

5 the substances electrokinetically move from a positive electric potential to ground and that well 120c and well 120b are provided with a positive potential whilst well 120a and well 120d are grounded.

At first, the two electrokinetically operated microchannel 215a and electrokinetically operated microchannel 215b are operated independently and the connecting bubble valve 10b is in the 'closed' state whilst bubble valve 10a and bubble valve 10c are in the 'open' state. To electrokinetically transfer substance from electrokinetically operated microchannel 215a to the electrokinetically operated microchannel 215b, bubble valve 10a and bubble valve 10c are switched to the closed state, and the connecting bubble valve 10b is opened momentarily

15 to allow passage of an amount of substance from the electrokinetically operated microchannel 215a to the electrokinetically operated microchannel 215b. The amount transferred depends directly upon the time bubble valve 10b is opened. After the required amount of substance is transferred, the connecting bubble valve 10b is closed and the bubble valve 10a and bubble valve 10b are opened again.

FIG. 13b illustrates the implementation of another column to column switch 130' to exchange liquid from a first column 215a' selectively into a second column 215b'. The first column and the second column are each crossed by a transfer column 250, operated by a first bubble valve 10a arranged on one end of the transfer column 250 and a second bubble valve

25 10b arranged on the opposite end of the transfer column 250. The first one of the bubble valves is attached to the first column 215a' and is actuated upon transiently by an external actuator for increasing the pressure within the bubble valve reservoir. Increasing the pressure on the bubble valve will deflect the meniscus 80, inducing a transient flow in the transfer column 250 from the pressurized bubble valve 10a towards the second bubble valve 10b,

30 which comprises a compressible volume of gas. This transient flow effectively transfers a liquid volume from the first column 215a' to the second column 215b'. Upon deactivation of the external actuator, the flow in the transfer column 250 reverses as the compressed gas volume in the second bubble valve 10b exerts a pressure on the liquid in the transfer column 250.

FIG. 14 shows a selective resistance circuit employing a bubble valve of the present invention for selectively including a predefined electrical resistance in an electrokinetic circuit. The circuit 140 comprises an inlet microchannel 321, which splits into two paths.

- 5 The first path 322 includes a fluidic resistor 240a and a bubble valve 10a, the second parallel path 323 includes a fluidic resistor 240b and a bubble valve 10b. The fluidic resistors 240a-b comprise a channel of appropriate length to results in a certain electrical resistance. The bubble valve 10a and the bubble valve 10b can be switched each to either on to allow fluid flow through the associated microchannel or off to block fluid flow through the associated
- 10 microchannel. As a result, the overall electrical resistance of the electrokinetic circuit can be switched between four values: infinite (both bubble valves 10a-b are off), the resistance of fluidic resistor 240a (bubble valve 10a on, bubble valve 10b off), the resistance of fluidic resistor 240b (bubble valve 10a off, bubble valve 10b on) and the parallel resistance of fluidic resistor 24a-b (both bubble valves 10a and 10b on).

FIG. 15 shows an alternative resistance circuit 150 according to another application of the invention, now for the selective application of a voltage. By opening either the bubble valve 10a or bubble valve 10b, the voltage imposed on an outgoing channel 523 can be selected. Fluidic resistor 245a and 245b function to limit the electric current in either of the

15 two states to a predetermined value.

- FIG. 16 illustrates another application of the bubble valve 10 of the present invention in a particle sorting application, wherein the bubble valve is positioned in a side channel that communicates with a channel through which particles in suspension flow. According to one
- 25 application of the present invention, a particle sorter 160 comprises a closed channel system of capillary size for sorting particles, such as cells. The channel system comprises a first supply duct 162 for introducing a stream of particles and a second supply duct 164 for supplying a carrier liquid. The first supply duct 162 ends in a nozzle, and a stream of particles is introduced into the flow of carrier liquid. The first supply duct 162 and the
- 30 second supply duct 164 enter a measurement duct 166, which branches into a first branch 172a and a second branch 172b at a branch point 171. A measurement region 182a is defined in the measurement duct 166 and is associated with a detector 182b to sense a predetermined characteristic of particles in the measurement region 182a. Two opposed bubble valves 10a and 10b are positioned in communication with the measurement duct 166 and are spaced

opposite each other. The bubble valves 10a, 10b communicate with the measurement duct 166 through a pair of opposed side passages 174a and 174b, respectively. Liquid is allowed to partly fill these side passages 174a and 174b to form a meniscus 175 therein. An external actuator 176 is also provided for actuating the bubble valves 10a, 10b, which momentarily
 5 causes a flow disturbance in the duct to deflect the flow therein when activated by the actuator 176.

In a suspension introduced by the first supply duct 162, two types of particles can be distinguished, normal particles 180a and particles of interest 180b. The flow rates in both
 10 branches 172a and 172b are adjusted so that the stream of particles normally flows through the second branch 172b. Upon sensing the predetermined characteristic in the particles in the measurement region 182a, the detector 182b raises a signal. The external actuator 176 activates the bubble valves 10a, 10b when signaled by the detector 182b in response to sensing the predetermined characteristic, to create a flow disturbance in the measurement
 15 duct 166 between the sideways passages 174a, 174b, to deflect the particle having the predetermined characteristic so that it flows down the first branch duct 172a rather than the second branch duct 172b. The detector communicates with the actuator 176, so that when the detector 182b senses a predetermined characteristic in a particle, the actuator activates the first bubble valve 10a to cause pressure variations in the reservoir 70 of the first bubble valve.
 20 The activation of the first bubble valves causes a transient pressure variation in the first side passage 174a. The second side passage 174b and the second bubble valve 10b absorb the transient pressure variations in the measurement duct 166 induced via the actuator 176. Basically, the reservoir 70b of the second bubble valve 10b is a chamber having a resilient wall or contains a compressible fluid such as a gas. The resilient properties allow the flow of
 25 liquid from the measurement duct into the second side passage 174b.

Figures 17a-17c illustrate the operation of the particle sorting system 160 of Figure 16. In Figure 17a, the detector raises a signal to activate the actuator. Upon activation of the actuator, the pressure within the reservoir of the first bubble valve 10a is increased, causing a
 30 transient discharge of liquid from the first side passage 174a as indicated by the arrow. The sudden pressure increase caused at this point in the duct causes liquid to flow into the second side passage 174b because of the resilient properties of the reservoir of the second bubble valve 10b. This movement of liquid into the second side passage 174b is indicated with an arrow. Resultingly, as can be seen in the figure, the flow through the duct is deflected causing

the selected particle of interest 178b located between the first side passage 174a and the second side passage 174b to be shifted perpendicular to its flow direction in the normal state. The flow resistances to the measurement duct 166, the first branch 172a and the second branch 172b is chosen so that the preferred direction of the flow to and from the first side passage 174a and the second side passage 174b has an appreciable component perpendicular to the normal flow through the measurement duct 166. This goal can for instance be reached by the first branch 172a and the second branch 172b so that their resistances to flow is large in comparison with the flow resistances of the first side passage 174a and the second side passage 174b.

Figure 17b shows the particle sorting system 160 during the relief of the first bubble valve reservoir when the particle of interest 178b has left the volume between the first side passage 174a and the second side passage 174b. The actuator 176 is deactivated, causing the pressure inside the reservoir to return to the normal pressure. During this relief phase there is a negative pressure difference between the two reservoirs of the bubble valves, causing a liquid flow through the first side passage 174a and the second side passage 174b opposite to the liquid flow shown in the previous figure and is indicated by the arrows.

Figure 17c shows the particle sorting system 160 after completion of the switching sequence. The pressures inside the reservoirs of the bubble valves has been equalized so the flow through the measurement duct 166 is normalized. As the particle of interest 178b has been displaced radially, it will flow into the first branch 172a as was the objective of the switching operation.

According to yet another embodiment, the cross-sectional dimensions of a microchannel including a bubble valve according to the teachings of the present invention may be varied locally to affect the pressure within the microchannel interior. For example, the microchannel may be narrowed or widened at certain locations to increase or decrease the capillary forces acting on a fluid in the microchannel interior. One of ordinary skill in the art will be able to determine a suitable cross-sectional dimension to achieve a desired pressure within the microchannel interior.

The bubble valve of the present invention may be implemented in a variety of microfluidic devices used for many applications. In a particular application, the bubble valve

is implemented in a flow-cytometer based instrument for sorting or physically separating particles of interest from a sample or for measuring selected physical and chemical characteristics of cells or particles in suspension as they travel past a particular site. The bubble valve may also be employed in devices for sequencing or manipulating DNA, medical
5 diagnostic instruments, devices for drug discovery, chemical analysis and so on.

The present invention provides an improved system and method for regulating fluid flow in a microchannel for a variety of applications. The bubble valve of the present invention is easy to operate and control, simple to manufacture and economical. In addition,
10 the bubble valve does not adversely affect the liquid in the microchannel. The bubble valve effectively controls the flow of liquids in microfluidic systems, without heating the fluid and without complex on-chip circuitry.

The present invention has been described relative to an illustrative embodiment. Since
15 certain changes may be made in the above constructions without departing from the scope of the invention, it is intended that all matter contained in the above description or shown in the accompanying drawings be interpreted as illustrative and not in a limiting sense.

It is also to be understood that the following claims are to cover all generic and
20 specific features of the invention described herein, and all statements of the scope of the invention which, as a matter of language, might be said to fall therebetween.

Having described the invention, what is claimed as new and protected by Letters Patent is:

What is claimed is:

1. A microfluidic device, comprising:
a microchannel having an interior bounded by a side wall;
5 a valve for regulating the flow of fluid through the microchannel, the valve comprising a gas-filled reservoir, a fluid meniscus interfacing the reservoir and the interior and an actuator for varying the volume of the reservoir to increase an internal pressure of the reservoir to vary the flow of liquid through the channel.
- 10 2. The microfluidic device of claim 1, wherein the actuator deflects the meniscus into the microchannel interior to regulate the flow of fluid through the microchannel.
3. The microfluidic device of claim 1, wherein the meniscus comprises a virtual wall formed in an aperture in the side wall of the microchannel when the microchannel is filled
15 with a liquid.
4. The microfluidic device of claim 1, wherein the actuator generates a gas bubble in the microchannel.
- 20 5. The microfluidic device of claim 4, further comprising a hydrophobic patch attached to an inner wall of the microchannel for anchoring the gas bubble.
6. The microfluidic device of claim 4, wherein the microchannel defines a cavity for retaining the gas bubble.
- 25 7. The microfluidic device of claim 1, wherein the gas filled reservoir comprises a movable membrane.
8. The microfluidic device of claim 7, wherein the actuator deflects the movable
30 membrane to create a bubble in the microchannel interior.
9. A microfluidic device comprising:
a first plate having a groove formed therein defining a microchannel;

a second plate for enclosing the microchannel bonded to the first plate having an aperture adjacent to the groove sized and dimensioned to form a meniscus when the microchannel is filled with a liquid, the aperture defining a reservoir adjacent to the microchannel, wherein the meniscus forms an interface between the microchannel and the

5 reservoir; and

a flexible membrane bonded to the second plate to seal the reservoir.

10. The microfluidic device of claim 9, further comprising an actuator for deflecting the flexible membrane, wherein the deflection of the membrane increases the pressure in the
10 reservoir and deflects the meniscus into the microchannel to regulate liquid flow therethrough.

11. The microfluidic device of claim 10, wherein the actuator comprises one of an electromagnetic element and a piezoelectric element.
15

12. The microfluidic device of claim 9, further comprising a hydrophobic patch attached to the groove.

13. The microfluidic device of claim 9, wherein the meniscus forms a bubble in the
20 microchannel to block liquid flow.

14. The microfluidic device of claim 13, wherein the groove includes a cavity formed therein for retaining the bubble.

25 15. A microfluidic device, comprising:
a microchannel having an interior bounded by a side wall;
a bubble valve for creating and injecting a bubble into the microchannel interior to regulate fluid flow through the microchannel; and
a hydrophobic patch for retaining the bubble in a predetermined position in the
30 microchannel interior.

16. The microfluidic device of claim 15, wherein the bubble valve comprises an aperture in the side wall, wherein a fluid in the microchannel forms a meniscus in the aperture, a

sealed chamber formed adjacent to the aperture and an actuator for deflecting the meniscus into the interior by increasing the pressure in the chamber.

17. A method of making a bubble valve, comprising:

5 providing a microchannel having an interior bounded by a side wall, an aperture formed in the side wall and a valve chamber adjacent to the aperture in communication with the interior;

filling the microchannel with a liquid to form a meniscus of the liquid in the aperture, whereby the step of filling traps a gas in the valve chamber;

10 providing an actuator for increasing the pressure in the valve chamber to deflect the meniscus into the interior.

18. A method of making a bubble valve, comprising:

15 providing a microchannel having an interior bounded by a side wall, an aperture formed in the side wall and a valve chamber adjacent to the aperture in communication with the interior;

filling the microchannel with a liquid to form a meniscus of the liquid in the aperture, applying and sealing an actuator comprising a chamber to a top surface of the microchannel to form a gas-filled chamber adjacent to the meniscus, wherein the actuator
20 varies the pressure in the gas-filled chamber to deflect the meniscus into the interior, thereby regulating fluid flow.

19. In a particle sorting device a bubble valve for separating particles having a predetermined characteristic from particles not having a predetermined characteristic, the
25 bubble valve comprising:

a gas-filled reservoir;

a side channel in communication with a channel through which a stream of particles in a carrier fluid passes, wherein the carrier fluid forms a meniscus in the side channel adjacent to the gas-filled reservoir;

30 an actuator for deflecting the meniscus to create a pressure pulse to selectively deflect a particle having the predetermined characteristic from the stream of particles.

20. A method of varying an electrical resistance in a microchannel, comprising the steps of:

generating a bubble;

injecting the bubble into a liquid in the microchannel, whereby the bubble varies the

5 electrical resistance of the microchannel.

21. The method of claim 20, wherein the step of generating a bubble comprises applying a pressure to a meniscus formed in a side wall of the microchannel, wherein the meniscus is formed by the liquid in the microchannel filling an aperture in the side wall.

10

22. The method of claim 21, wherein the step of applying a pressure comprises increasing the pressure within a sealed reservoir formed adjacent to the aperture.

23. An electrophoretic system, comprising

an electrokinetically operated microchannel;

a sample well for providing an sample to the microchannel;

a voltage source;

a bubble valve for injecting a bubble into the microchannel to vary the electrical resistance of the microchannel.

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24. An electrokinetic column to column switch, comprising:

a first electrokinetically operated microchannel;

a second electrokinetically operated microchannel in communication with the first electrokinetically operated microchannel;

25 a bubble valve for selectively blocking flow from the first electrokinetically operated microchannel to the second electrokinetically operated microchannel by selectively injecting a bubble into a microchannel.

Abstract

5 A microfluidic system includes a bubble valve for regulating fluid flow through a microchannel. The bubble valve includes a fluid meniscus interfacing the microchannel interior and an actuator for deflecting the membrane into the microchannel interior to regulate fluid flow. The actuator generates a gas bubble in a liquid in the microchannel when a sufficient pressure is generated on the membrane.

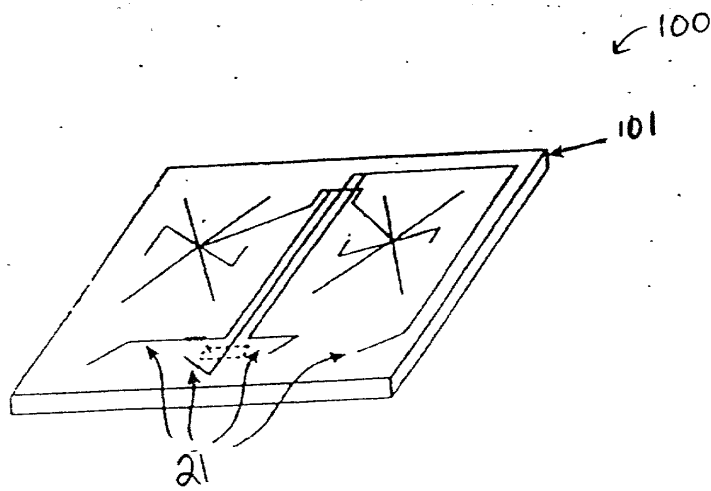


FIG 1

201250 00548

20190909 58562407

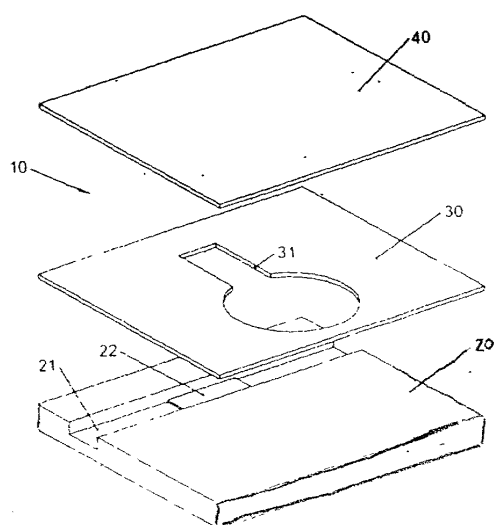


FIG. 2

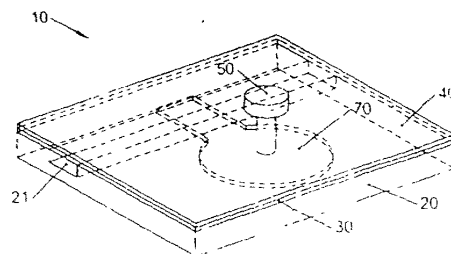


FIG. 3

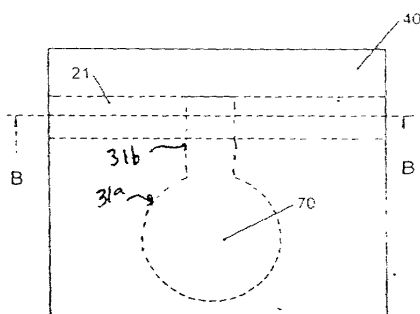


FIG. 4

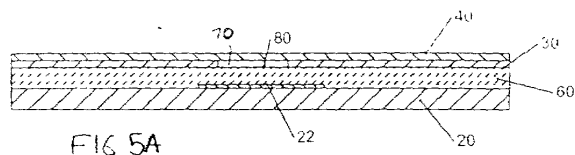


FIG. 5A

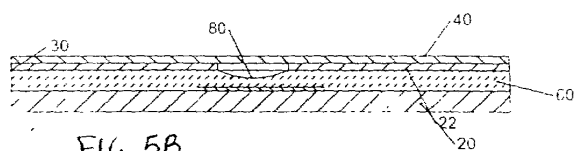


FIG. 5B

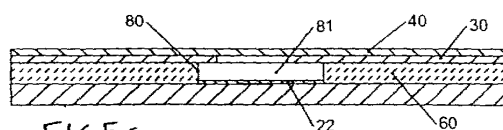


FIG. 5C

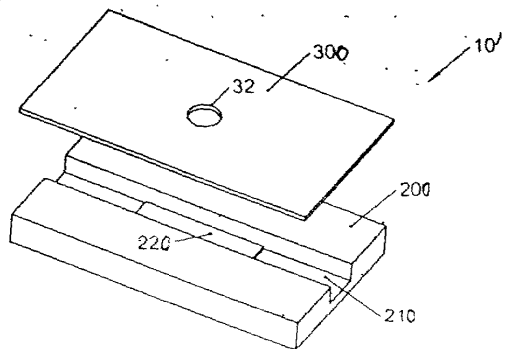


FIG. 6

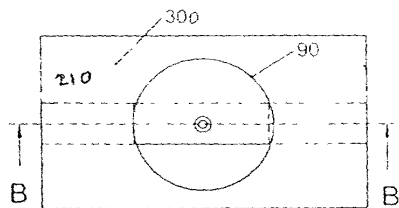


FIG. 7

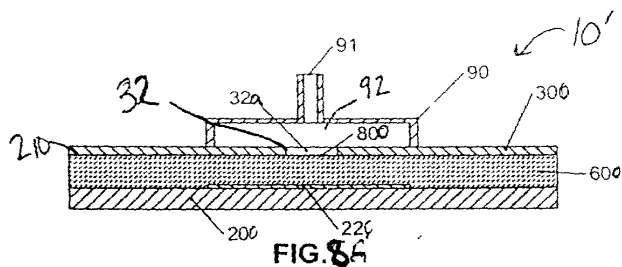


FIG. 8A

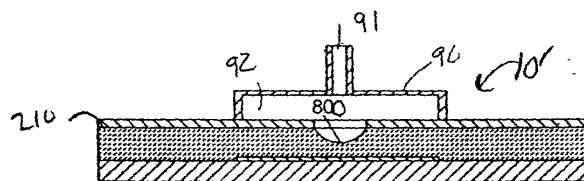


FIG. 8B

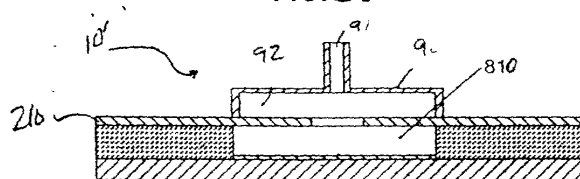


FIG. 8C

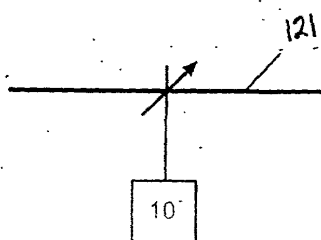


FIG. 9

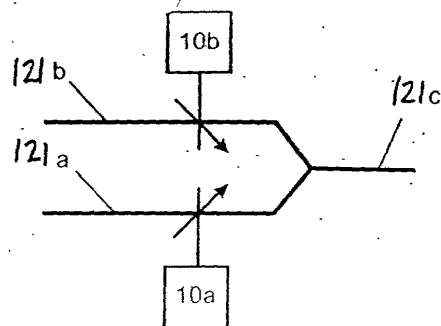


FIG. 10

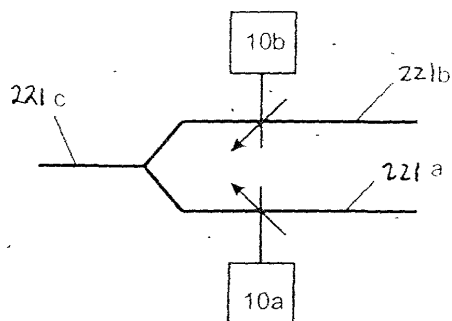
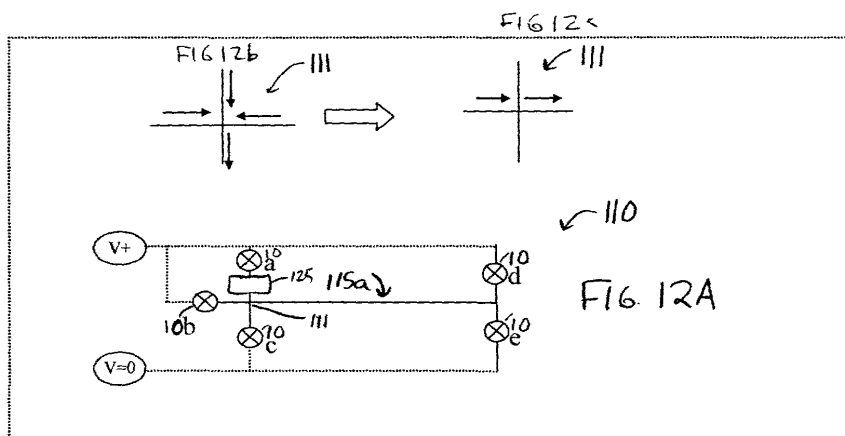


FIG. 11



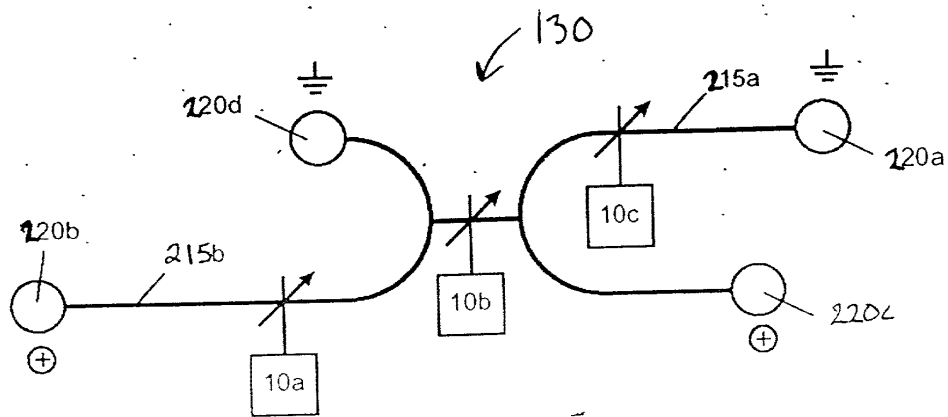


FIG. 13a.

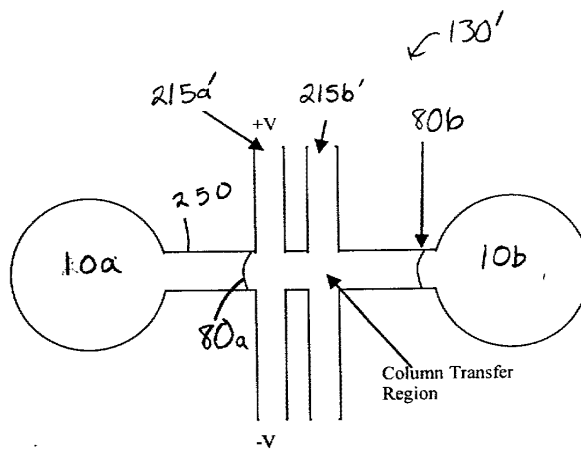


FIG 13b.

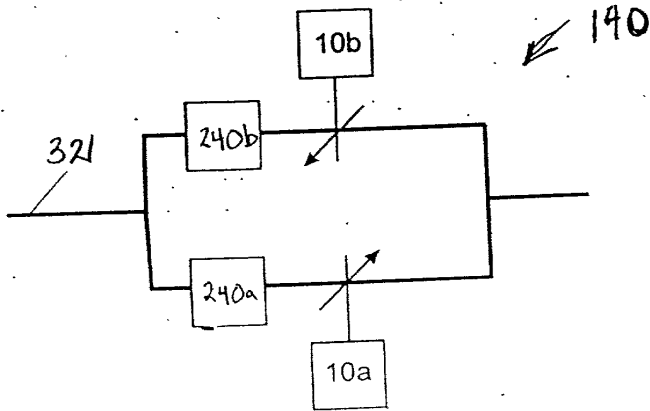


FIG. 14

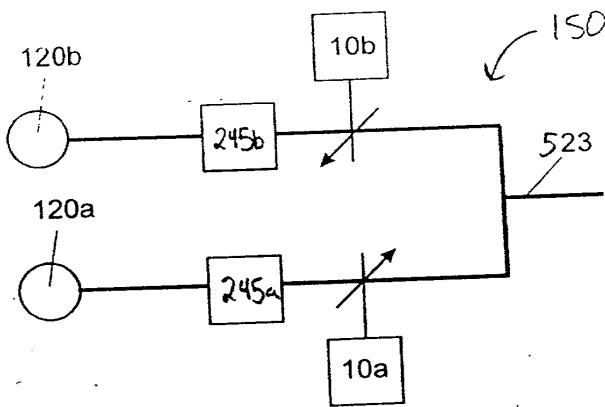


FIG. 15

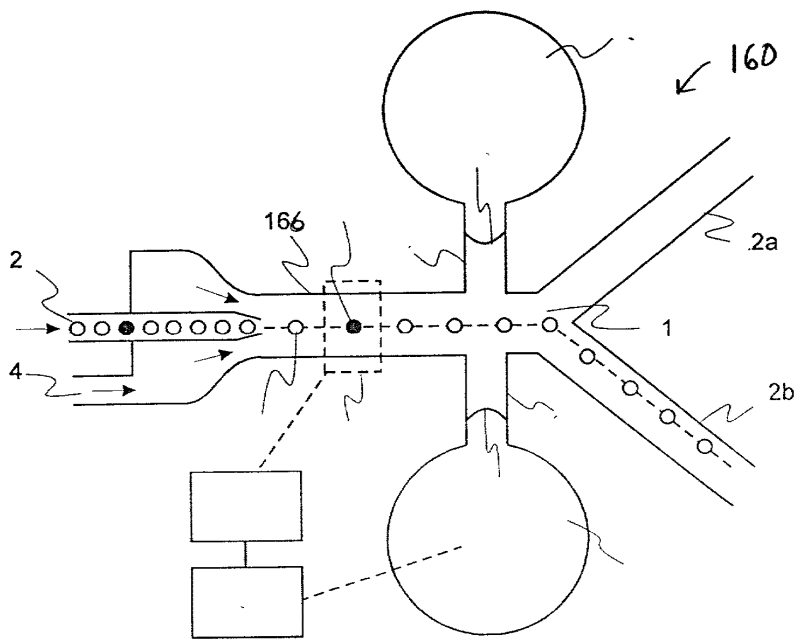


FIG. 16

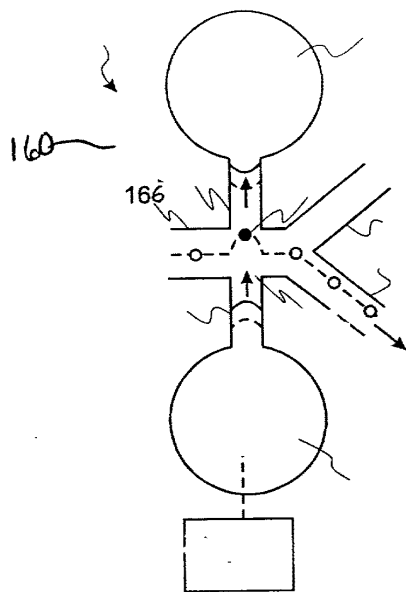


FIG. 17A

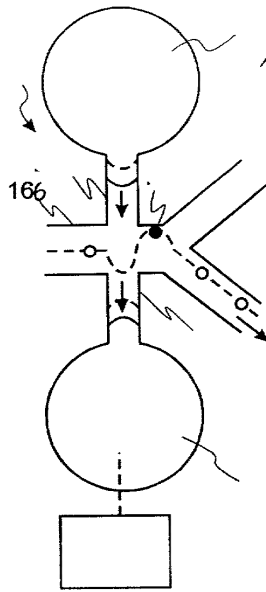


FIG. 17B

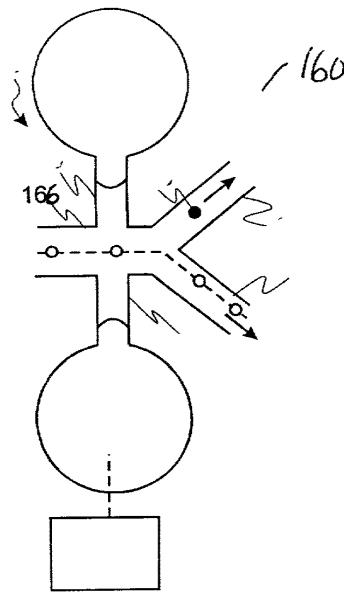


FIG. 17C

Customer Number: 000959

Attorney's
Docket
Number CVZ-012

Declaration, Petition and Power of Attorney for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

MICROFLUIDIC SYSTEM INCLUDING A BUBBLE VALVE FOR REGULATING FLUID FLOW THROUGH A MICROCHANNEL

the specification of which

(check one)

X is attached hereto.

— was filed on _____ as

Application Serial No. _____

and was amended on _____
(if applicable)

I do not know and do not believe that the subject matter of this application was known or used by others in the United States or patented or described in a printed publication in any country before my invention thereof, or patented or described in a printed publication in any country or in public use or on sale in the United States more than one year prior to the date of this application, or first patented or caused to be patented or made the subject of an inventor's certificate by me or my legal representatives or assigns in a country foreign to the United States prior to the date of this application on an application filed more than twelve months (six months if this application is for a design) before the filing of this application; and I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application, that no application for patent or inventor's certificate on the subject matter of this application has been filed by me or my representatives or assigns in any country foreign to the United States, except those identified below, and that I have reviewed and understand the contents of the specification, including the claims as amended by any amendment referred to herein.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

CLAIM OF BENEFIT OF EARLIER FOREIGN APPLICATION(S)

I hereby claim priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application(s) for patent or inventor's certificate filed by me on the same subject matter having a filing date before that of the application(s) from which priority is claimed.

Check one:

☒ no such applications have been filed.

☐ such applications have been filed as follows

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

Country	Application Number	Date of Filing (month,day,year)	Priority Claimed Under 35 USC 119
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

CLAIM FOR BENEFIT OF U.S. PROVISIONAL APPLICATION(S)

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

<u>60/373,256</u>	<u>April 17, 2002</u>
(Application Serial No.)	(Filing Date)

_____	_____
(Application Serial No.)	(Filing Date)

4012950-0240

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S)

I hereby claim the benefit under Title 35, United States Code, §120 of any earlier United States application(s) or PCT international application(s) designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the earlier application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date(s) of the earlier application(s) and the national or PCT international filing date of this application. As to subject matter of this application which is common to my earlier application(s), if any, described below, I do not know and do not believe that the same was known or used by others in the United States or patented or described in a printed publication in any country before my invention thereof, or patented or described in a printed publication in any country or in public use or on sale in the United States more than one year prior to the date(s) of said earlier application(s), or first patented or caused to be patented or made the subject of an inventor's certificate by me or my legal representatives or assigns in a country foreign to the United States prior to the date(s) of said earlier application(s) on an application filed more than twelve months (six months if this application is for a design) before the filing of said earlier application(s); and I acknowledge that no application for patent or inventor's certificate on said subject matter has been filed by me or my representatives or assigns in any country foreign to the United States except those identified herein.

_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status) (patented,pending,aband.)
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_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status) (patented,pending,aband.)
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POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

James E. Cockfield	Reg. No. 19,162	Maria C. Laccotripe	Limited Recognition
Thomas V. Smurzynski	Reg. No. 24,798		Under 37 C.F.R. § 10.9(b)
Ralph A. Loren	Reg. No. 29,325	Debra J. Milasincic	Reg. No. 46,931
Giulio A. DeConti, Jr.	Reg. No. 31,503	David R. Burns	Reg. No. 46,590
Ann Lampion Hammitte	Reg. No. 34,858	Sean D. Detweiler	Reg. No. 42,482
Elizabeth A. Hanley	Reg. No. 33,505	Cynthia L. Kanik	Reg. No. 37,320
Amy E. Mandragouras	Reg. No. 36,207	Theodore R. West	Reg. No. 47,202
Anthony A. Laurentano	Reg. No. 38,220	Shayne Y. Huff	Reg. No. 44,784
Kevin J. Canning	Reg. No. 35,470	Hathaway P. Russell	Reg. No. 46,488
Jane E. Remillard	Reg. No. 38,872	Daniel B. Ko	Reg. No. 47,332
DeAnn F. Smith	Reg. No. 36,683	John S. Curran	Reg. No. 50,445
Peter C. Lauro	Reg. No. 32,360	Lisa M. DiRocco	Reg. No. P51,619
Jeanne M. DiGiorgio	Reg. No. 41,710	Richa Nand	Reg. No. P52,059
Megan E. Williams	Reg. No. 43,270	Allan Tameshtit	Limited Recognition
Jeremiah Lynch	Reg. No. 17,425		Under 37 C.F.R. § 10.9(b)
David J. Rikkers	Reg. No. 43,882		

Send Correspondence to Anthony A. Laurentano, Esq. at **Customer Number: 000959** whose address is:

Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109

Direct Telephone Calls to: (name and telephone number)

Anthony A. Laurentano, Esq. (617) 227-7400

Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor John Gilbert	
Inventor's signature	Date
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Full name of third inventor, if any Manish Deshpande	
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Post Office Address (if different)	