Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2701401 C 2013/05/14

(11)(21) 2 701 401

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2008/10/01
(87) Date publication PCT/PCT Publication Date: 2009/04/09
(45) Date de délivrance/Issue Date: 2013/05/14
(85) Entrée phase nationale/National Entry: 2010/03/31
(86) N° demande PCT/PCT Application No.: US 2008/078491
(87) N° publication PCT/PCT Publication No.: 2009/046136
(30) Priorités/Priorities: 2007/10/01 (US60/976,780);
2007/10/01 (US60/976,774)

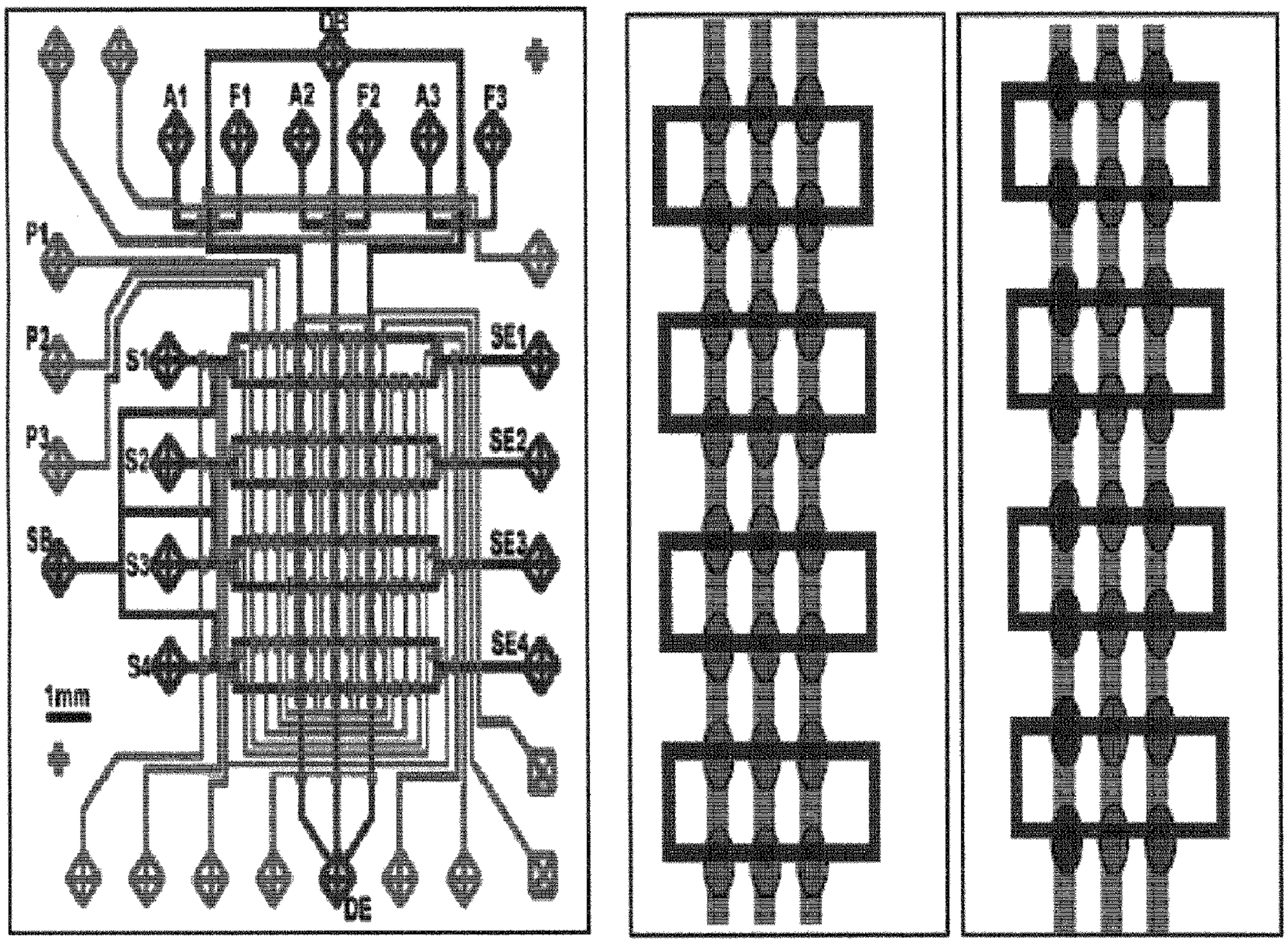
(51) Cl.Int./Int.Cl. *C40B 60/12* (2006.01),
B81B 1/00 (2006.01), *C40B 30/00* (2006.01),
C40B 30/04 (2006.01), *C40B 60/00* (2006.01),
G01N 33/50 (2006.01), *G01N 33/53* (2006.01),
B82Y 15/00 (2011.01)

(72) Inventeurs/Inventors:
ZHOU, CHONGWU, US;
THOMPSON, MARK E., US;
COTE, RICHARD JAMES, US;
KARTALOV, EMIL P., US

(73) Propriétaire/Owner:
UNIVERSITY OF SOUTHERN CALIFORNIA, US

(74) Agent: OYEN WIGGS GREEN & MUTALA LLP

(54) Titre : INTEGRATION MICROFLUIDIQUE AVEC PLATE-FORME A NANA DETECTEURS
(54) Title: MICROFLUIDIC INTEGRATION WITH NANOSENSOR PLATFORM



(57) Abrégé/Abstract:
The present invention describes microfluidics being employed to achieve multiplex surface functionalization of nanosensor chips by selectively delivering probe molecules to individual nanosensors in an array, and microfluidics being employed to achieve delivery of

CA 2701401 C 2013/05/14

(11)(21) 2 701 401

(13) C

(57) Abrégé(suite)/Abstract(continued):
a solution containing multiple analytes over individual nanosensors in an array, where each nanosensor was previously configured with a specific capture molecule.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 April 2009 (09.04.2009)

PCT

(10) International Publication Number
WO 2009/046136 A2

(51) International Patent Classification:
C12M 3/00 (2006.01)

(21) International Application Number:
PCT/US2008/078491

(22) International Filing Date: 1 October 2008 (01.10.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/976,774	1 October 2007 (01.10.2007)	US
60/976,780	1 October 2007 (01.10.2007)	US

(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF SOUTHERN CALIFORNIA** [US/US]; Hughes Center Suite EEB 131, 3740 McClintock Avenue, Los Angeles, CA 90089-2561 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZHOU, Chongwu** [CN/US]; 2411 Briargate Ln, Arcadia, CA 91007 (US). **THOMPSON, Mark, E.** [US/US]; 4447 Pepper Creek Way, Anaheim, CA 92807 (US). **COTE, Richard, James** [US/US]; 911 Hilts Avenue, Los Angeles, CA 90024 (US). **KARTALOV, Emil, P.** [US/US]; 550 N. Catalina Avenue, Apt. 14, Pasadena, CA 91106 (US).

(74) Agents: **SENN, Sean** et al.; Davis Wright Tremaine LLP, 865 S. Figueroa Street, Suite 2400, Los Angeles, CA 90017 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) **Title:** MICROFLUIDIC INTEGRATION WITH NANOSENSOR PLATFORM

Figure 1.

Figure 1(a)

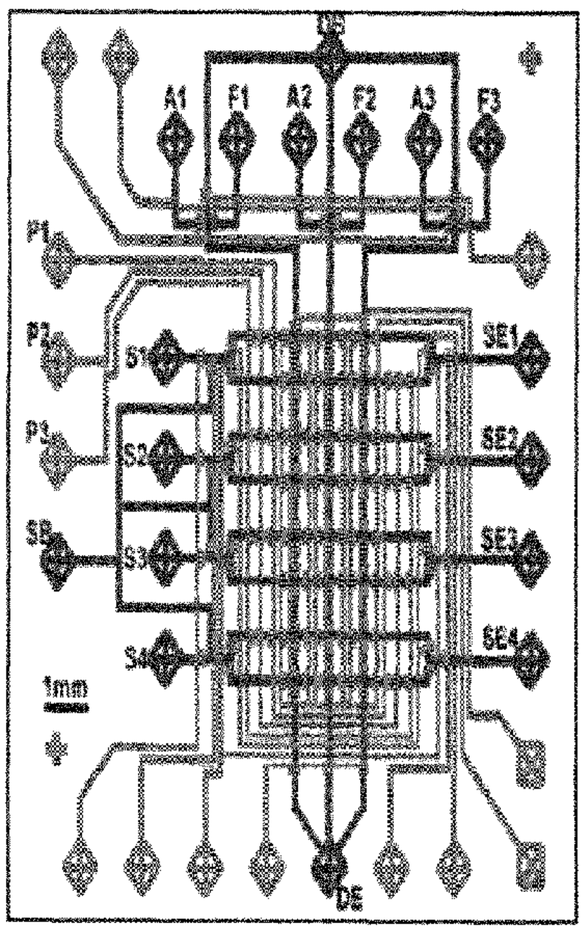


Figure 1(b)

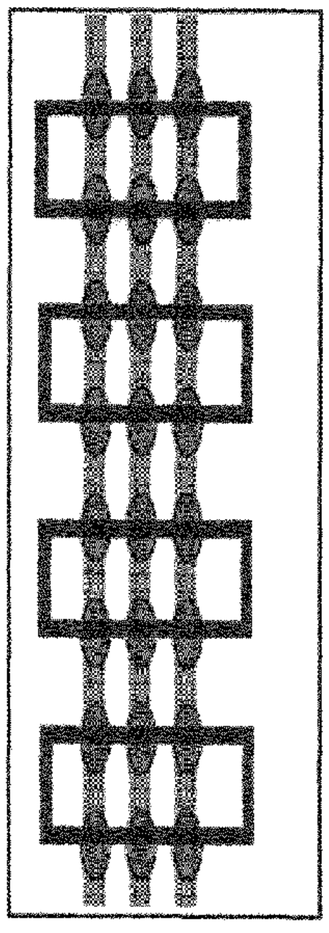
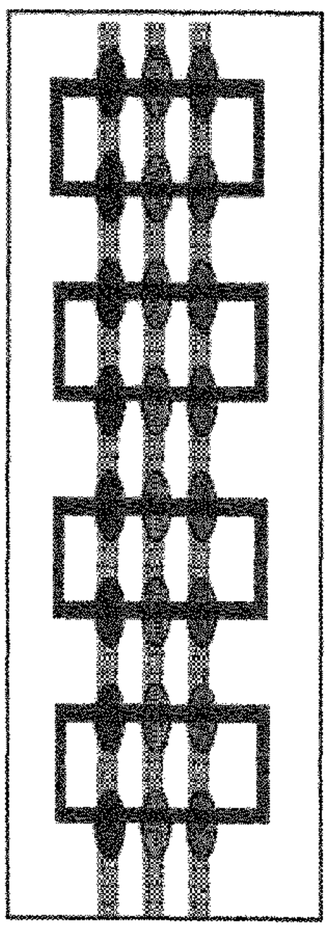


Figure 1(c)



(57) **Abstract:** The present invention describes microfluidics being employed to achieve multiplex surface functionalization of nanosensor chips by selectively delivering probe molecules to individual nanosensors in an array, and microfluidics being employed to achieve delivery of a solution containing multiple analytes over individual nanosensors in an array, where each nanosensor was previously configured with a specific capture molecule.

WO 2009/046136 A2

WO 2009/046136 A2

Published:

— *without international search report and to be republished upon receipt of that report*

MICROFLUIDIC INTEGRATION WITH NANOSENSOR PLATFORM

FIELD OF THE INVENTION

This invention relates to the field of biotechnology in general. More specifically, the invention relates to microfluidics being employed to achieve multiplex surface functionalization of nanosensor chips by selectively delivering probe molecules to individual nanosensors in an array. This invention also relates to microfluidics being employed to achieve delivery of a solution containing multiple analytes over individual nanosensors in an array, where each nanosensor was previously configured with a specific capture molecule.

BACKGROUND

The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

One of the challenges in the field of nanosensors is to have the capability to simultaneously detect multiple targets with an array of sensors on one chip. Although there have been various attempts to develop a device with such a capability, most of these approaches have been problematic. For example, the nanosensor device may be limited to only a small number of sensors with large spacing.

Thus, there is a need in the art to develop novel devices with the capacity to simultaneously detect multiple targets.

SUMMARY OF THE INVENTION

Various embodiments include an apparatus for mulitplex detection of molecules, comprising a microfluidic device, and a plurality of nanosensor arrays integrated therewith, where the plurality of nanosensor arrays are selectively functionalized with one or more capture agents. In another embodiment, the plurality of nanosensor arrays

comprise nanowire/nanotube based field-effect transistors. In another embodiment, the nanowire/nanotube based field-effect transistors are coated with succinimidyl group.

Other embodiments provide a method of preparing a nanosensor chip for multiplex surface functionalization, comprising integrating a microfluidic device with a nanosensor array, and selectively delivering a probe to the nanosensor array. In another embodiment, the probe comprises a polynucleotide and/or a polypeptide. In another embodiment, the nanosensor array comprises a field effect transistor.

Other embodiments provide an apparatus for multiplexed delivery of an analyte, comprising a microfluidic device integrated with a plurality of nanosensor arrays, where the microfluidic device is configured for delivery of a solution containing multiple analytes to the plurality of nanosensor arrays. In another embodiment, each of the plurality of nanosensor arrays are separated from one another by a distance of at least one micron.

Various embodiments provide a device configured for individual addressability of nonsensors for purposes of functionalization, delivery and/or measurement, comprising a microfluidic array integrated with a nanosensor array. In another embodiment, the microfluidic array is configured for flexible selection of a subset of the nanosensor array. In another embodiment, the subset of the nanosensor array contains a plurality of nanosensors.

Other embodiments provide a method for individually functionalizing a nanosensor, comprising integrating a microfluidic array with a nanosensor array, and functionalizing at least one nanosensor in the nanosensor array. In another embodiment, the at least one nanosensor is functionalized by controlling local temperature. In another embodiment, the at least one nanosensor is functionalized by photoexposure. In another embodiment, the at least one nanosensor is functionalized by electrical potential biasing. In another embodiment, the at least one nanosensor is functionalized by chemical specificity.

Other features and advantages of the invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, various embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Exemplary embodiments are illustrated in referenced figures. It is intended that the embodiments and figures disclosed herein are considered illustrative rather than restrictive.

Figure 1A depicts, in accordance with an embodiment described herein, is a flow diagram for the microfluidic system, depicting both control lines and sample/reagent lines.

Figures 1B-1C depicts, in accordance with an embodiment described herein, are schematic diagrams of the core of the system. Sensors are shown as elipses; sample chambers or coliseums are shown as rectangles; the sample is circulated around the rectangular path; and the reagent lines, which can be used to selectively treat FETs to form a multiplexed sensor array, are shown as vertical bars. These reagent lines can be used to selectively treat field effect transistors to form a multiplexed sensor array.

Figure 2 depicts, in accordance with an embodiment described herein, various optical micrographs. (a) depicts optical micrographs of the nanobiosensor chip; (b) depicts optical micrographs of the microfluidics device; (c) depicts optical micrographs of the nanobiosensor chip combined with the microfluidics device; (d) depicts optical micrograph of nanobiosensors inside the microchannels. The inset of figure 2(d) depicts a magnified image of one device.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton *et al.*, *Dictionary of Microbiology and Molecular Biology 3rd ed.*, J. Wiley & Sons (New York, NY 2001); March, *Advanced Organic Chemistry Reactions, Mechanisms and Structure 5th ed.*, J. Wiley & Sons (New York, NY 2001); and Sambrook and Russel, *Molecular Cloning: A Laboratory Manual 3rd ed.*, Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY 2001), provide one skilled in the art with a general guide to many of the terms used in the present application.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described. For purposes of the present invention, the following terms are defined below.

"Therapeutically effective amount" as used herein refers to that amount which is capable of achieving beneficial results in a patient in need of treatment. A therapeutically effective amount can be determined on an individual basis and will be based, at least in part, on consideration of the physiological characteristics of the mammal, the type of delivery system or therapeutic technique used and the time of administration relative to the progression of the disease.

As used herein, "FET" means field effect transistor.

As used herein, "PDMS" means elastomer polydimethylsiloxane.

As disclosed herein, the inventors employed microfluidics to achieve multiplex surface functionalization of a nanosensor chip by selectively delivering probe molecules to individual nanosensors in an array. Examples are disclosed herein as figures 1 and 2. By selectively functionalizing nanosensors with different capturing agents, the inventors are able to achieve multiplex detection. Additionally, as a result, the inventors are able to fabricate a large number of nanosensors with spacing of only several micrometers.

As further disclosed herein, the first step in the fabrication is to prepare arrays of 24 nanowire/nanotube based field-effect transistors (FETs) into a 3 mm x 6 mm space on the substrate, making the interdevice spacing compatible with PDMS based microfluidics. As depicted in figures 1 and 2, each device is independently addressable, electrically and by reagents and samples within the microfluidic block. The FET array, coated with succinimidyl group through a chemical deposition step, is fused to the microfluidic block, and the individual capturing agents are then delivered to the FETs via the reagent delivery channels (see vertical lines in Figure 1). The eight devices along the lines served by A1/F1 will be treated with the same agent, as will those along A2/F2 and along A3/F3. After treatment with the recognition agent, the reagent channel will be filled with aminoethanol to deactivate and remaining succinimidyl groups, preventing

any surface reaction with non-target proteins in the sample. Thus, the six devices in each coliseum will be composed of three sets of different nanosensors (two for each analyte). A sample will be loaded into a given coliseum and the conductance of the six devices monitored over time. The sample will be circulated in the coliseum until a constant reading is observed for each device, indicating that it is at equilibrium with the sample (with respect to analyte binding).

As disclosed herein, the inventors integrated a microfluidic device with nanosensors. As depicted in Figure 1(a), control lines include lines from P1, P2, and P3, and sample/reagent lines include lines from SB, S1, S2, S3, S4, SE1, SE2, SE3, SE4, DE, DB, A1, F1, A2, F2, A3, and F3. The S1 and SE1, S2 and SE2, S3 and SE3, and S4 and SE4, are each directly connected to each other by lines that form a rectangle, each rectangle called a coliseum. The flow lines and sensors have interactions via each of the coliseums depicted, with four coliseums depicted and each coliseum covering six sensors, as also depicted in figure 1(b) and 1(c). All four coliseums are connected to lines from SB. Each of the six sensors are connected to three vertical lines, as also depicted in figure 1(b) and 1(c). These three vertical lines directly connect DE to DB, A1, F1, A2, F2, A3, and F3.

In one embodiment, the present invention provides an apparatus for mulitplex detection of molecules where a microfluidic device is integrated with a plurality of nanosensor arrays selectively functionalized with one or more capture agents.

In one embodiment, the present invention provides a method of multiplex functionalization and/or multiplex delivery of probe molecules to a nanosensor platform. In another embodiment, the present invention provides a microfluidic device integrated with a nanosensor platform, where a nanosensor chip is functionalized by selectively delivering probe molecules to individual nanosensors in an array. In another embodiment, the nanosensors are spaced by only several micrometers. In another embodiment, the microfluidic device integrated with a nanosensor platform is used for multiplex detection of a molecule of interest. In another embodiment, the microfluidic device integrated with a nanosensor platform is used for multiplex detection of a disease and/or condition.

In another embodiment, the present invention provides a method of preparing a microfluidic device with integrated nanosensor platform by the following, or combinations thereof: (1) Prepare arrays of 24 nanowire/nanotube based field-effect transistors (FETs) into a 3 mm x 6 mm space on the substrate, making the interdevice spacing compatible with PDMS based microfluidics; (2) The FET array, coated with succinimidyl group through a chemical deposition step, is fused to the microfluidic block, and the individual capturing agents are then delivered to the FETs via the reagent delivery channels (see vertical lines in Figure 1); (3) The eight devices along the lines served by A1/F1 will be treated with the same agent, as will those along A2/F2 and along A3/F3. (4) After treatment with the recognition agent, the reagent channel will be filled with aminoethanol to deactivate and remaining succinimidyl groups, preventing any surface reaction with non-target proteins in the sample; (5) A sample will be loaded into a given coliseum and the conductance of the six devices monitored over time; (6) The sample will be circulated in the coliseum until a constant reading is observed for each device, indicating that it is at equilibrium with the sample (with respect to analyte binding).

As disclosed herein, the inventors employed a microfluidic device to achieve delivery of a solution containing multiple analytes over individual nanosensors in an array, where each nanosensor was previously configured with a specific capture molecule. The integrated microfluidic device with a nanowire sensor chip allows the delivery of the solution to individual nanosensors in a large array. Moreover, the analyte solution will be delivered to several coliseums (see rectangles in figure 1), each one covering six sensors. The solution will then be circulated in these coliseums until a constant reading is observed for each device. In this way, the chance of capturing analyte molecules from solution can be largely increased and thus a higher sensitivity can be expected.

In one embodiment, the present invention provides a method of multiplex detection of biomarkers and/or multiplexed analyte delivery to a nanosensor device. In one embodiment, the present invention provides a microfluidic device integrated with a nanosensor platform, where microfluidics are employed to achieve delivery of a solution containing multiple analytes over individual nanosensors in an array. In another

embodiment, the present invention provides a method of preparing a microfluidic device with integrated nanosensor platform by the following, or combinations thereof: (1) prepare arrays of 24 nanowire/nanotube based field-effect transistors (FETs) into a 3 mm x 6 mm space on the substrate, making the interdevice spacing compatible with PDMS based microfluidics; (2) each nanowire FET in the array is functionalized with the appropriate probe molecule; and (3) a sample is loaded into a given coliseum and the conductance of the six devices is monitored over time.

In accordance with various embodiments described herein, there are numerous advantages to microfluidic integration with a nanosensor platform. Furthermore, as readily apparent to one of skill in the art, various embodiments described herein may be modified using techniques known in the art to more fully capture these advantages, including: parallelism of functionalization, delivery, and measurement; parsimony of reagents and samples use; parsimony of sample allowing the ability to test pediatric patients (which may have less blood than adults, thus preventing the use of more standard tests); parsimony of sample allowing fingerprick diagnostics (which avoids phlebotomy and related complications); reduction of costs due to inexpensive point-of-care testing.

Other features and advantages of the invention will become apparent from the following detailed description, which illustrate, by way of example, various features of embodiments of the invention.

EXAMPLES

The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art may develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention.

Example 1

Multiplex functionalization/multiplex delivery of probe molecules to nanosensor platforms: Advantages

Microfluidics will be employed to achieve multiplex surface functionalization of nanosensor chips by selectively delivering probe molecules to individual nanosensors in an array. Microfluidic technique has been utilized to define surface chemistry on bulk materials, e.g. printing protein arrays on epoxide substrates for immunoassays. But it has never been used to coat individual nanosensors in an array to achieve selective functionalization. This novel approach will provide several benefits. First of all, microfluidic channels fabricated in micro meters can be integrated with dense arrays of nanosensors with dimensions and spacing in the same scale, and thus enables the construction of large number of selective functionalized sensors on a small chip for the purpose of multiplex detection. It also gives complete isolation of adjacent devices, preventing any change of inadvertent contamination of neighboring devices. Second, the delivery of capturing reagents and analyte solutions is controlled by a nested layer of vials, which can be open and closed by changing the pressure of air in these vials. This method will allow one to selectively target individual devices, without the need for complicated masking strategies, micropipetting manipulation or other methods hat would increase the complication and cost associated with fabricating multiplexed arrays. Third, the microfluidic approach has the added advantage of requiring only small reagent volumes. The microfluidic approach to surface coating devices with the recognition agent will require far less reagent than conventional methods. For some recognition agents, the amount of materials available for surface coating the sensors may be severely limited, making the ability to efficiently coat devices with volumes in the range of tens of nanoliters very important. Last, the flowing of sample solutions in narrow channels accelerate the diffusion of analyte molecules to the surface of nanosensors, and will largely decrease the response time.

Example 2

Multiplex functionalization/multiplex delivery of probe molecules to nanosensor platforms: Methods of making and using

The first step in fabrication is to prepare arrays of 24 nanowire/nanotube based field-effect transistors (FETs) into a 3 mm x 6 mm space on the substrate, making the interdevice spacing compatible with PDMS based microfluidics. Each device is independently addressable, electrically and by reagents and samples within the microfluidic block. The FET array, coated with succinimidyl group through a chemical deposition step, is fused to the microfluidic block, and the individual capturing agents are then delivered to the FETs via the reagent delivery channels (see vertical lines in Figure 1). The eight devices along the lines served by A1/F1 will be treated with the same agent, as will those along A2/F2 and along A3/F3. After treatment with the recognition agent, the reagent channel will be filled with aminoethanol to deactivate and remaining succinimidyl groups, preventing any surface reaction with non-target proteins in the sample. Thus, the six devices in each coliseum will be composed of three sets of different nanosensors (two for each analyte). A sample will be loaded into a given coliseum and the conductance of the six devices monitored over time. The sample will be circulated in the coliseum until a constant reading is observed for each device, indicating that it is at equilibrium with the sample (with respect to analyte binding).

Example 3

Multiplex detection of biomarkers/multiplexed analyte delivery to nanosensor devices: Advantages

Microfluidics will be employed to achieve delivery of a solution containing multiple analytes over individual nanosensors in an array, where each nanosensor was previously configured with a specific capture molecule. The integrated microfluidic device with a nanowire sensor chip allows the delivery of the solution to individual nanosensors in a large array. Moreover, the analyte solution will be delivered to several coliseums (see rectangles in figure 1), each one covering six sensors. The solution will then be circulated in these coliseums until a constant reading is observed for each device. In this way, the chance of capturing analyte molecules from solution can be largely increased and thus a higher sensitivity can be expected.

Example 4

Multiplex detection of biomarkers/multiplexed analyte delivery to nanosensor devices: Methods of making and using

1. The first step in fabrication is to prepare arrays of 24 nanowire/nanotube based field-effect transistors (FETs) into a 3 mm x 6 mm space on the substrate, making the interdevice spacing compatible with PDMS based microfluidics.
2. Each device is independently addressed either electrically and by reagents and samples within the microfluidic block. Each nanowire FET in the array is thus functionalized with the appropriate probe molecule.
3. A sample will be loaded into a given coliseum and the conductance of the six devices monitored over time. The sample will be circulated in the coliseum until a constant reading is observed for each device, indicating that it is at equilibrium with the sample (with respect to analyte binding).

The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

CLAIMS

1. An apparatus for mulitplex detection of molecules, comprising:

a microfluidic device comprising at least two chambers, each individual chamber is configured to address at least one nanosensor of a nanosensor array; and

a plurality of nanosensor arrays integrated therewith,

wherein the plurality of nanosensor arrays are selectively functionalized with one or more capture agents, and wherein the at least two chambers are connected by at least one channel.

2. The apparatus of claim 1, wherein the plurality of nanosensor arrays comprise nanowire/nanotube based field-effect transistors.

3. The apparatus of claim 2, wherein the nanowire/nanotube based field-effect transistors are coated with an agent comprising a succinimidyl group.

4. A method of preparing a nanosensor chip for multiplex surface functionalization, comprising:

integrating a microfluidic device with a nanosensor array, wherein the microfluidic device comprises at least two chambers, each chamber is configured to address at least one nanosensor in the nanosensory array, wherein the at least two chambers are connected by at least one channel; and

selectively delivering a probe to the nanosensor array by loading the probe into the at least one channel.

5. The method of claim 4, wherein the probe comprises a polynucleotide and/or a polypeptide.

6. The method of claim 4, wherein the nanosensor array comprises a field effect transistor.

7. An apparatus for multiplexed delivery of an analyte, comprising:

a microfluidic device integrated with a plurality of nanosensor arrays,

wherein the microfluidic device comprises at least two chambers, each chamber is configured to address at least one nanosensor in the nanosensor array, wherein the at least two chambers are connected by at least one channel for delivery of a reagent, and wherein each individual chamber is connected to an additional channel for loading of a sample solution comprising multiple analytes to the plurality of nanosensor arrays.

8. The apparatus of claim 7, wherein each of the plurality of nanosensor arrays are separated from one another by a distance of at least one micron.

9. A device configured for individual addressability of nanosensors for purposes of functionalization, delivery and/or measurement, comprising:

a microfluidic array integrated with a nanosensor array, wherein the microarray array comprises at least one microfluidic device comprising at least two chambers, each individual chamber configured to individually address at least one nanosensor in the nanosensor array, and wherein the at least two chambers are connected by at least one channel.

10. The device of claim 9, wherein the microfluidic array is configured for flexible selection of a subset of the nanosensor array.

11. The device of claim 10, wherein the subset of the nanosensor array comprises a plurality of nanosensors.

12. A method for individually functionalizing a nanosensor, comprising:

integrating a microfluidic array with a nanosensor array, wherein the microarray array comprises at least one microfluidic device comprising at least two chambers, each individual chamber configured to individually address at least one nanosensor in the nanosensor array, and wherein the at least two chambers are connected by at least one channel; and

functionalizing at least one nanosensor in the nanosensor array.

13. The method of claim 12, wherein the at least one nanosensor is functionalized by controlling local temperature.

14. The method of claim 12, wherein the at least one nanosensor is functionalized by photoexposure.

15. The method of claim 12, wherein the at least one nanosensor is functionalized by electrical potential biasing.

16. The method of claim 12, wherein the at least one nanosensor is functionalized by chemical specificity.

Figures

Figure 1.

Figure 1(a)

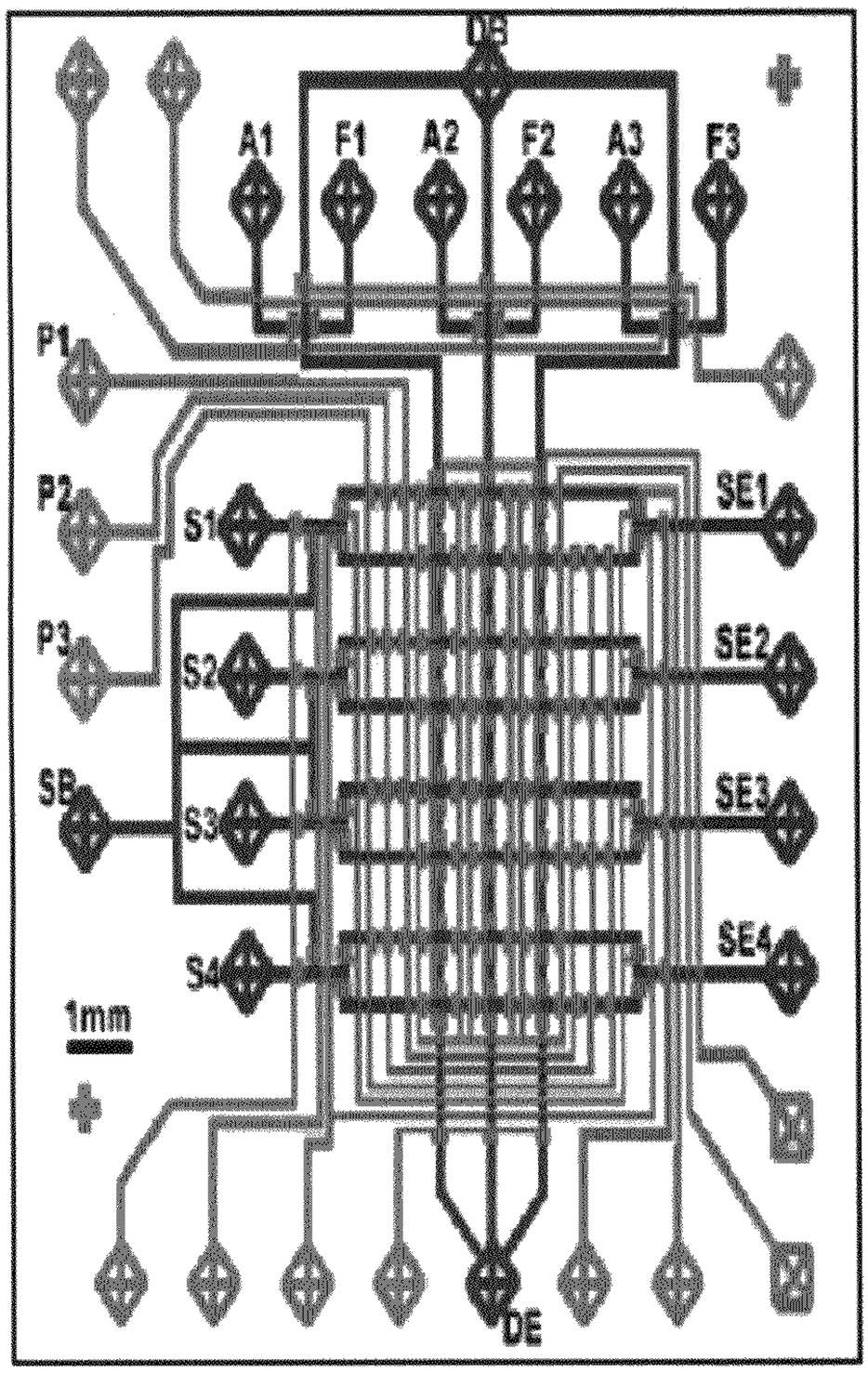


Figure 1(b)

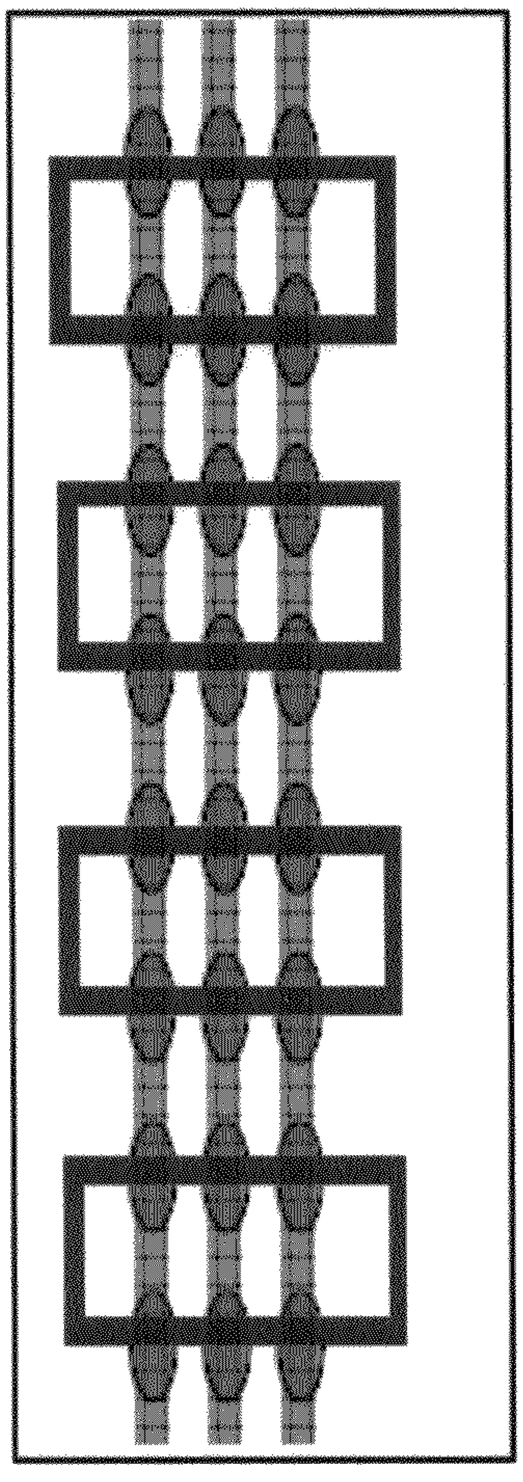


Figure 1(c)

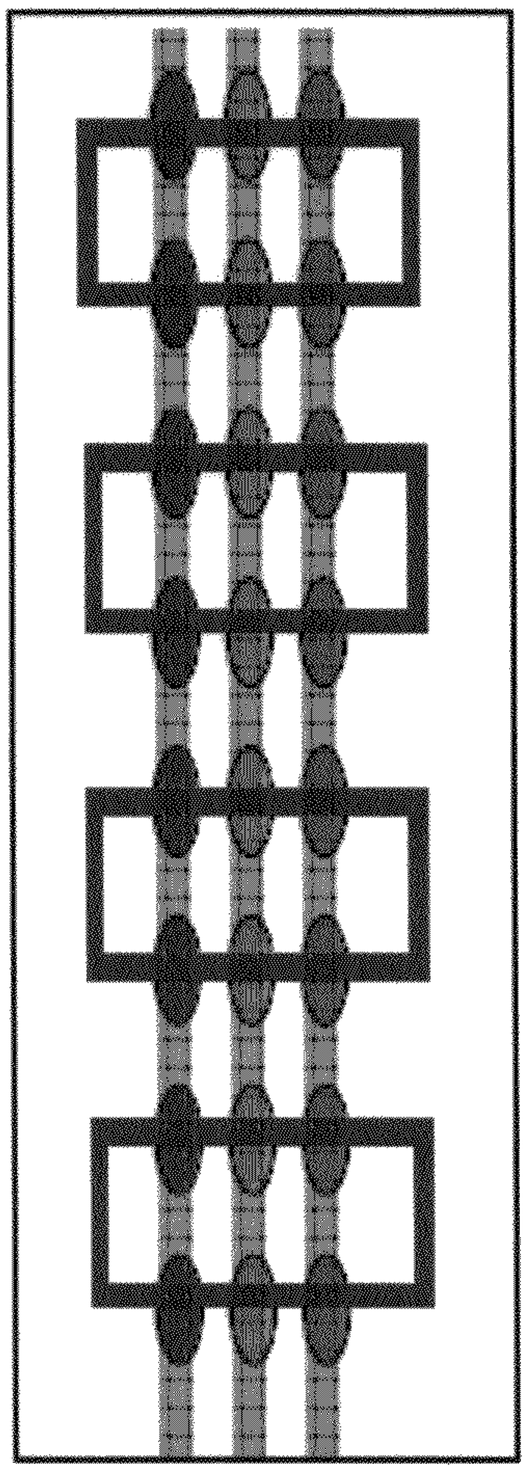


Figure 2.

Figure 2(a)

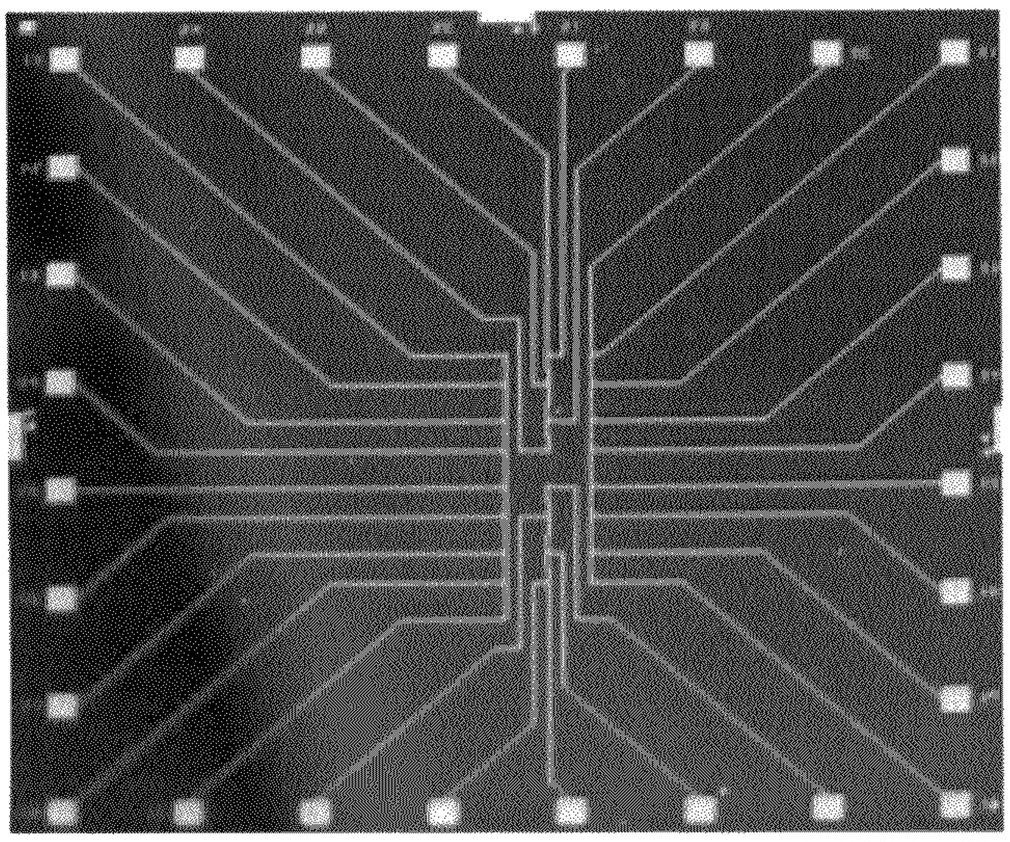
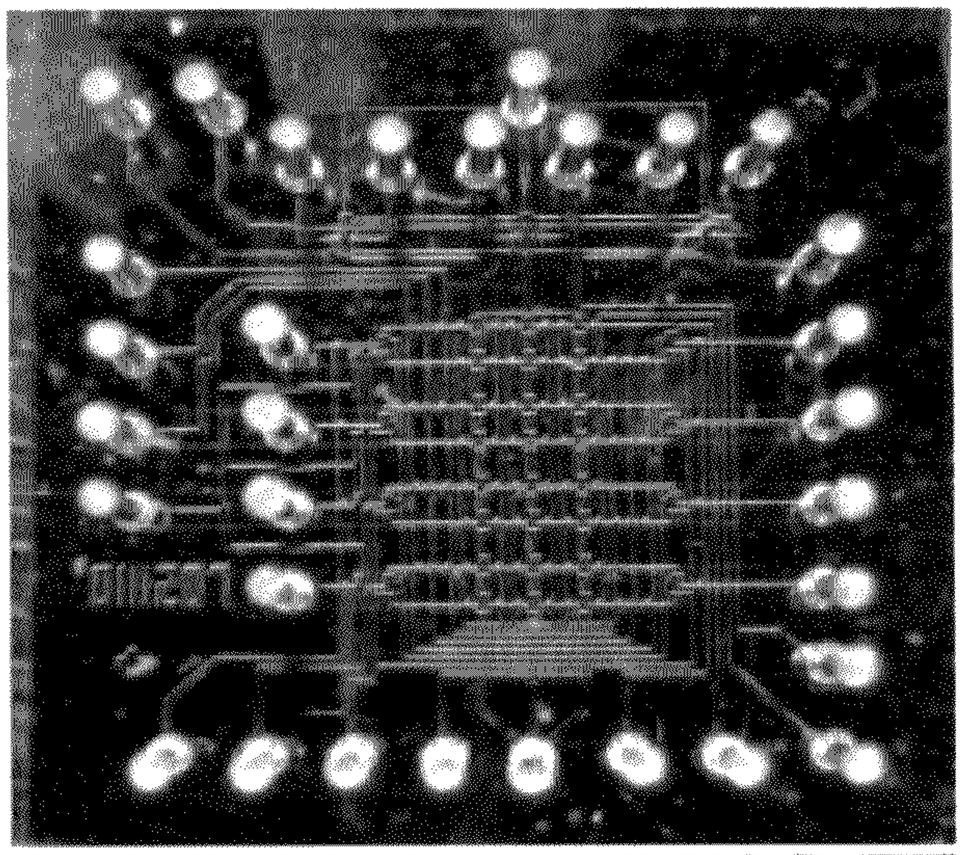


Figure 2(b)



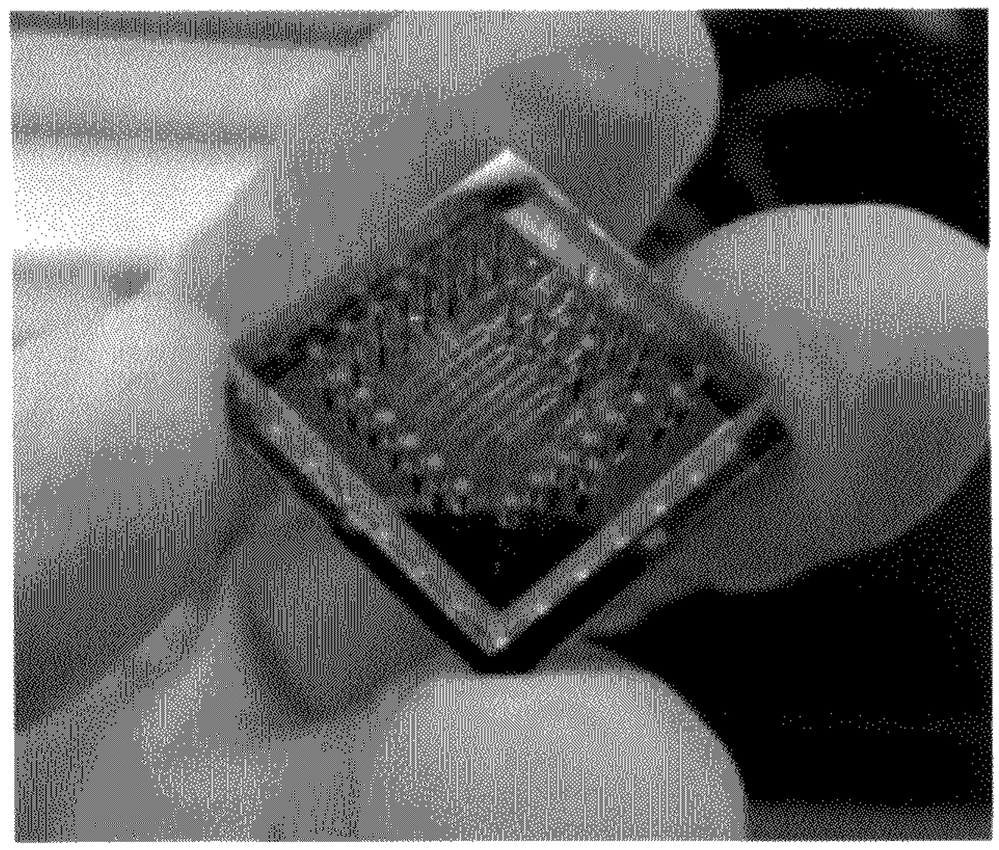


Figure 2(c)

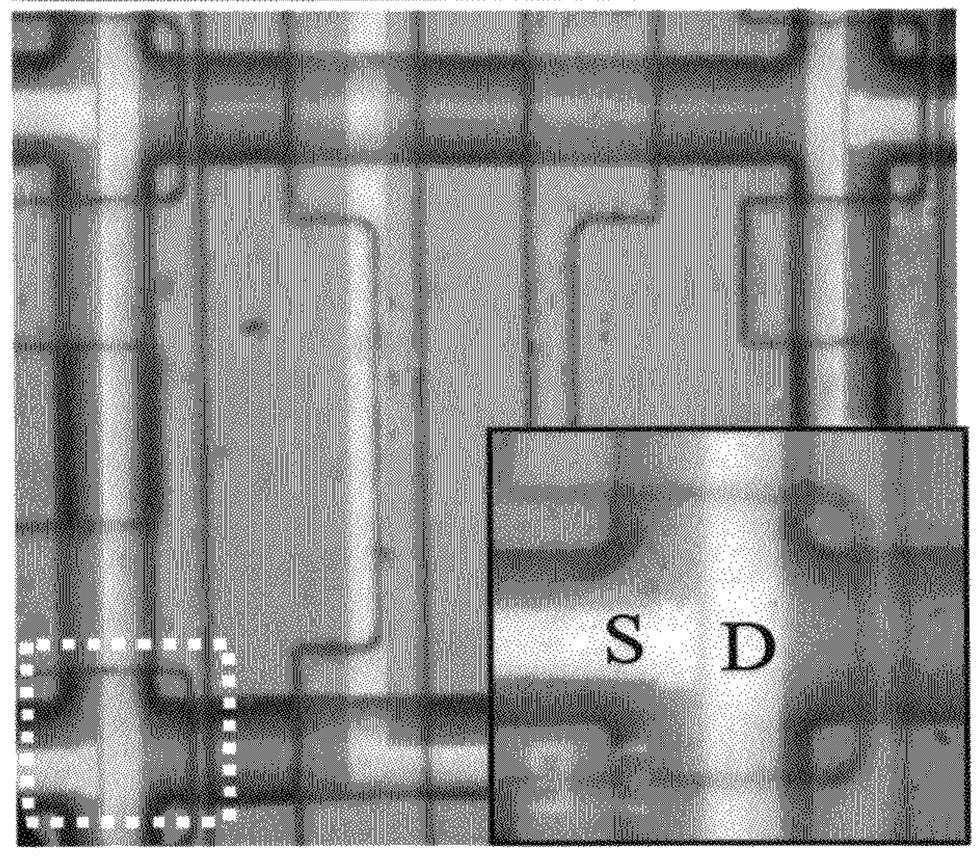


Figure 2(d)

(a)

(b)

(c)