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[Continued on next page]

(54) **Title**: RECONFIGURABLE MODULAR MICROFLUIDIC SYSTEM AND METHOD

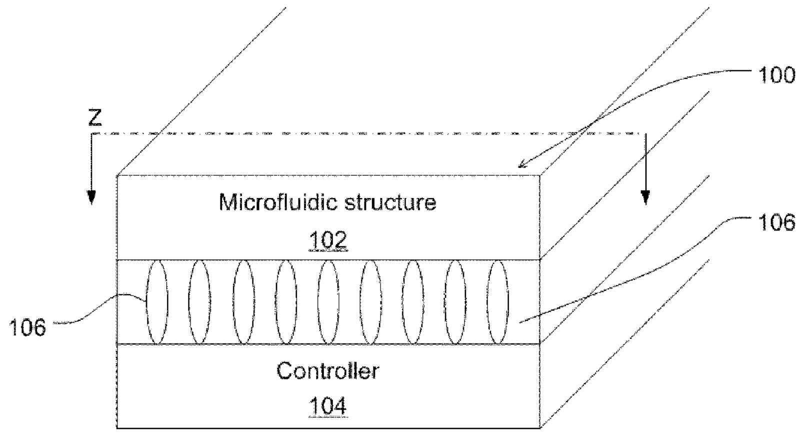

FIG.1

(57) **Abstract**: The present relates to a microfluidic system such as a lab-on-chip (LOC) and a method of producing thereof. The system has an interconnector for connecting a microfluidic structure to a controller. There is a microfluidic structure having at least one electrode that can be connected with an interconnector to an electronic circuit. The interconnector has at least one electrical contact corresponding to the pin-outs of the electronic circuit for replaceably connecting them thereto. Each of the at least one electrical contact is connected to a corresponding one of the at least one electrode. The microfluidic structure and the electronic circuit in a combined configuration form together a re-usable and/or reconfigurable microfluidic system.

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RECONFIGURABLE MODULAR MICROFLUIDIC SYSTEM AND METHOD

Technical Field

This relates to devices, systems and methods for microfluidic manipulation and sensing, such as is applied to lab-on-a-chip (LOC) technology.

Background

A lab-on-a-chip (LOC) is a device that integrates one or more laboratory functions on a single electronic chip that can be as small as a few square micrometers in size. In a LOC device, extremely small volumes (i.e. nanoliters or even picoliters) of sample fluid are handled for performing a chemical or biological analysis. It automates a single or multiple lab processes to perform various chemical or biological analyses such as sampling, sample transport, filtration, dilution, chemical reactions, separation and detection.

The LOC has a microfluidic structure to perform the various laboratory functions. Microfluidic structures have dimensions ranging from millimeters down to micrometers in size and are known to provide various fluid flow control functionalities such as pumping, valve operation and sensing of volumes of a sample fluid. They have a diverse and widespread potential applications, systems and processes that employ this technology include inkjet printers, blood-cell-separation equipment, biochemical assays, chemical synthesis, genetic analysis, drug screening, electrochromatography, and bio-implants.

One of the established techniques used to perform such laboratory functions is dielectrophoresis in which an electrical field is applied on a fluid within the LOC to achieve fluid manipulation.

Conventional microfluidic systems have a hybrid architecture consisting of a microfluidic architecture and an electronic monitoring circuit. The microfluidic architecture has micro-channels for allowing fluid to circulate therein and electrodes that are located within the micro-channels for performing the various fluid flow control functionalities in the micro-channels. The electrodes are controlled by an electronic circuit by applying signals to the electrode.

As microfluidic systems are very small, their method of fabrication and assembly requires a considerable amount of precision. Various techniques have been developed to manufacture such systems. One technique is surface micromachining, two other techniques are laser ablation or etching and mechanical micromilling or hot embossing. However the above described manufacturing techniques do not allow producing a re-usable and reconfigurable microfluidic system.

Summary

It has been discovered that a re-usable and reconfigurable microfluidic system can be produced by providing a microfluidic structure that is independently manufactured and separate from an electronic controller or electronic circuit of the system.

According to one aspect there is a microfluidic structure having at least one microfluidic channel or micro-channel and at least one electrode that can be connected with an interconnector to an electronic circuit. The at least one electrode extends through an electrode support body and is adapted to generate a force field within the microfluidic channel for effecting a microfluidic manipulation. The interconnector has a plurality of electrical contacts, each corresponding to the pin-outs of the electronic cicuit for replaceably connecting them thereto. Each of the plurality of electrical contacts is connected to a corresponding one of the plurality of electrodes. The microfluidic structure and the electronic circuit in a combined configuration form together a re-usable and/or reconfigurable microfluidic system.

According to another aspect, there is a method for producing the modular microfluidic structure. The method comprises forming holes extending through a first plate and providing an electrode within each of the plurality of holes. The method further comprises providing a second plate that is adapted to form with the first plate an interior portion of the microfluidic structure and forming at least one micro-channel that is adapted to extend over the interior portion of the microfluidic structure. The method further comprises securing the first plate to the second plate so as to align at least one of the plurality of holes with the at least one micro-channel.

According to yet another aspect, there is a microfluidic device having an array of electrodes. The device has a micro-channel support body having a micro-channel formed therein, and an electrode support body having an array of electrodes. The electrode support body and the micro-channel support body are aligned to produce with at least one of the array of electrodes a force field within the channel for performing therein a plurality of microfluidic manipulations.

According to yet another aspect, there is a method of manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate. The method comprises defining a plurality of electrode contacts all joined in a single piece and defining in a glass substrate a plurality of through-holes each corresponding to the plurality of electrode contacts. The method further comprises inserting the plurality of electrode contacts into the corresponding plurality of through-holes then depositing a bonding material onto the plurality of electrode contacts so as to adhere to the glass substrate and to immobilise each of the plurality of electrode contacts within the corresponding through-holes. The method further comprises singulating the single piece into a plurality of electrodes, each of the plurality of electrodes corresponding to each of the plurality of electrode contacts.

Brief Description of the Drawings

The invention will be better understood by way of the following detailed description of embodiments of the invention with reference to the appended drawings, in which:

Figure 1 is a perspective view of a partial microfluidic system, according to one embodiment;

Figure 2 is an inside view of a microfluidic structure of the microfluidic system of Figure 1 with a close-up view of an electrode array, according to one embodiment;

Figure 3a is a cross-sectional view of the microfluidic structure, according to one embodiment;

Figure 3b is a plan view of an interconnector of the microfluidic structure of Figure 3a with macro-contacts being connected to individual micro-contacts, according to one embodiment;

Figure 3c is side view of the microfluidic structure of Figure 3a that is connected with the interconnector to a detector, according to one embodiment;

Figure 4a is a cross sectional view of the microfluidic system of Figure 1 where the controller has a matrix of control circuits that are each connected to a signal input array, according to one embodiment;

Figure 4b is a graphical representation of the controller having a matrix of control circuits each having a variety of inputs, according to one embodiment;

Figure 5 is a flow diagram of a method for producing the microfluidic structure, according to one embodiment;

Figure 6a is an exploded cross-sectional view of a microfluidic structure, according to one embodiment;

Figure 6b is an exploded cross-sectional view of a microfluidic structure, according to one embodiment;

Figure 6c is a cross-sectional view of a microfluidic structure, according to one embodiment;

Figure 7a and 7b is a representation of the steps for manufacturing the microfluidic structure, according to one embodiment;

Figure 8a and 8b is a representation of the steps for manufacturing the microfluidic structure, according to one embodiment;

Figure 9a is a cross-sectional view of a microfluidic device having a micro-channel support body and an electrode support body, according to one embodiment;

Figure 9b is a plan view of the electrode support body where the electrodes are positioned on a surface of the support body, according to one embodiment;

Figure 10a is a graphical representation of a dielectrophoresis manipulation using planar electrode configuration principle, according to one embodiment;

Figure 10b is a graph representing a Clausus Mossotti Factor variation, according to one embodiment;

Figure 11 is a graphical representation of a DAC and current to voltage converter circuit, according to one embodiment;

Figure 12 is a graphical representation of a first and second stage amplification circuit with driving circuit, according to one embodiment;

Figure 13 is a diagram of a capacitive sensor array, according to one embodiment;

Figure 14 is a graph representing a magnetic flux density along a line parallel to the surface of the micro-coil and located 10 μm above it and along a line perpendicular to the surface of the micro-coil and cross its center, according to one embodiment;

Figure 15 is an illustration of a magnetic field generated by a coil shaped electrode, according to one embodiment;

Figure 16 is a schematic representation of a principle of circular scanning scheme where (1) beads move into a trapping region of coils array; (2) some beads are captured by front coils and restricted in vicinity of each coil (3) more beads are restricted as coils array is scanned, according to one embodiment;

Figure 17 is a representation of simulation results of magnetic flux density distribution on the plane which is 25 μm above the coils surface, from one single coil to seven coils, according to one embodiment;

Figure 18 is a table representing a comparison of different micro-coils array for the same maximum magnetic (B) field, according to one embodiment;

Figure 19 is a diagram of an electrode support body with an on chip micro-coil electrode array, according to one embodiment;

Figure 20a is a diagram of a plurality of electrode contacts all joined in a single piece, for manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, according to one embodiment;

Figure 20b is a diagram of a glass substrate wherein there is defined through-holes, for manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, according to one embodiment;

Figure 20c is a diagram of the plurality of electrode contacts positioned within a corresponding through-hole of the glass substrate, for manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, according to one embodiment;

Figure 20d, is a diagram of a conductive bonding material deposited onto the electrode contacts for adhering to the glass substrate, for manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, according to one embodiment;

Figure 20e, is a diagram of the conductive bonding material where a portion of the bonding material is removed to electrically singulate the plurality of electrode contacts, for manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, according to one embodiment;

Figure 20f, is a diagram of a non-conductive bonding material deposited onto the electrode contacts for adhering to the glass substrate, for manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, according to one embodiment;

Figure 20g, is a diagram of the single piece of electrode contacts that has been singulated into a plurality of electrodes, for manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, according to one embodiment;

Figure 20h, is a diagram of the non-conductive bonding material where a portion of the bonding material is removed to electrically expose the plurality of electrode contacts and the single piece of electrode contacts that has been singulated into a plurality of electrodes, for manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, according to one embodiment;

Figure 20i, is a diagram of the plurality of singulated electrodes that have been polished to size, for manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, according to one embodiment; and

Figure 20j, is a diagram of the plurality of singulated electrodes that have been polished to size, for manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, according to one embodiment.

Detailed Description

Presented in Figure 1, there is a microfluidic system 100 that is adapted to effect a microfluidic manipulation of a fluid within the microfluidic structure 102 for performing at least one laboratory functionality. The fluid manipulation is controlled by a controller 104 that can be a micro-electronic integrated circuit or an electronic circuit on a printed circuit board and is adapted to electrically connect to the microfluidic structure 102 through electrical connections 106. Various types of fluid manipulations or microfluidic manipulations can be achieved on various types of particles such as cells, proteins, DNA, microspheres, molecules, organisms or any other kind of particles found in the fluid to achieve trapping, transportation, mixing, separation, etc. According to one embodiment, trapping of particles is achieved by generating a force field on a peripheral area surrounding a fluid having particles to be trapped. According to another embodiment, transportation of particles can be achieved by generating a pumping effect, a vertical or horizontal motion effect. According to yet another embodiment, mixing is achieved by generating a rotational effect. Depending on the use, the microfluidic structure 102 may be adapted to implement a single functionality or may be adapted to implement a variety of functionalities sequentially or simultaneously.

The microfluidic structure 102 can have various shapes and forms depending on the functionality or functionalities to implement and how it is to be used. In Figure 2 according to one example, there is an inside view of a microfluidic structure 102. The microfluidic structure 102 has a plurality of micro-channels 202 that each are connected to a liquid access hole 200. A minute amount of fluid, such as a biological fluid may be injected or pumped into the access hole 200 for introducing a liquid or fluid into the micro-channels 202.

The microfluidic structure 102 further has one or more in-channel electrode arrays 204. The electrode array 204 is adapted to create a force field such as an electrical field, an electromagnetic field or any other type of force to generate a fluid manipulation within the micro-channels 202. In Figure 2, the electrode array 204 has a general square shape and has thirty-six square shaped electrodes. Depending on the microfluidic structure 102, it is understood that the general shape of the electrode array 204 can vary from one structure to another. For example, the electrode array 204 can have a general rectangular shape, circular shape or any other suitable shape. Moreover, it is understood that one electrode array 204 can be manufactured with as many electrodes as desired and the shape of each electrode can differ from the one shown in Figure 2. In one embodiment, the electrode array is manufactured with one hundred square shaped electrodes and is used in a 1500μm by 1500μm dimensioned microfluidic structure 102.

A skilled person will understand that for certain fluid manipulations, the electrode array can be replaced by a single electrode without departing from the scope of the present microfluidic structure 102.

In the microfluidic structure 102 of Figure 2, the micro-channels 202 are connected to the liquid access hole 200 at a derivative angle (A) of 45^0. The liquid access hole 200 can have various shapes and sizes that are suitable for injecting a liquid into the micro-channels 202. In this embodiment, the liquid access hole 200 has a circular shape with a diameter (b1) that is smaller than 15mm.

The microfluidic structure 102 of Figure 2 further has an Indium Tin Oxide (ITO) layer contact access hole. The ITO layer contact access hole can have various forms, shapes and sizes that are suitable for providing an electrical ground or an electrical signal to an ITO layer of the microfluidic structure 102. Further details of the ITO layer will be developed in the following description. In this embodiment, the ITO layer contact access hole is a circular hole having a diameter (b2) that is greater than 2mm.

Returning to Figure 1, according to one embodiment, the microfluidic system 100 is a modular system where the microfluidic structure 102 is removably connectable to the controller 104. Maintenance of the modules (102 and 104) may therefore be facilitated since the microfluidic structure 102 and the controller 104 can be cleaned out and re-used in other systems. Just as in a biomedical laboratory, these systems are generally used in areas of application where tolerances to contamination are very low. Before being used or re-used, the microfluidic structure 102 of Figure 2 must be properly cleaned by disinfecting the micro-channels 202 and liquid access holes 200 of the microfluidic structure 102.

In the modular system 100, a defective controller 104 can be separated from the microfluidic structure 102 for being repaired or replaced; the same applies for a defective microfluidic structure 102. During the manufacturing or maintenance of the system 100, each module (102 and 104) may be independently tested prior to system testing for quality assurance purposes. Also troubleshooting may be facilitated as each module can independently be analysed.

According to one embodiment the modules (102 and 104) each have a compatible generic structure for being used in various areas of application and provide various functionalities. Since a same module (102 and 104) can be used in a wide variety of applications, a higher volume of production may be achieved and reduce production costs.

There is presented in Figure 3a a section view of the microfluidic structure 102 with a micro-channel 202 and a plurality of electrodes 204 that form an electrode array. In one embodiment, the electrodes 204 are made from an electrically conductive material that is highly corrosion resistant such as a Tantalum-Gold alloy (Ta-Au) or Tantalum-Platinum alloy (Ta-Pt). When connected to the controller 104, an electrical signal is fed to at least one of the electrodes 204 and the electrode generates an electrical field within the micro-channel 202. The electrical field influences the flow of the fluid within the micro-channel 202 and allows effecting various microfluidic manipulations. By varying a frequency, phase or amplitude of the electrical signal applied to at least one of the electrodes, a non-uniform electrical field is generated and effects a fluid manipulation within the micro-channel. The electrical signal could be applied to only one electrode if there is provided a ground in the micro-channel. Alternatively, electrical signals could be applied to at least two electrodes for generating a stronger electrical field and for generating an electrical field that is easier to control.

A skilled person will understand that by varying a current of the electrical signal applied to at least one of the electrodes, a non-uniform magnetic field is generated and effects a fluid manipulation within the micro-channel.

According to one embodiment, the electrodes 204 are not located directly within the micro-channel 202. The electrodes 204 are in proximity with the micro-channel 202 and are close enough to generate an electrical field therein.

In an alternate embodiment, the electrodes 204 are located within the micro-channel 202 behind an isolation layer for preventing the electrodes 204 from being in direct contact with the liquid therein.

The generic array of electrodes is not functionality specific and can be reconfigured to provide various types of fluid control and sensing functionalities. According to the desired functionality, some electrodes 204 of the array can be intermittently or continuously activated and some electrodes 204 can remain inactive.

In one embodiment, at least a group of electrodes of the array 204 are adapted to generate a specific electrical field and the microfluidic manipulation may result from a combined effect of a plurality of electrical fields generated by the electrodes 204. Depending on the electrodes 204 that are activated, the signals that are applied and the timing of the signal applied to each electrode, a specific manipulation on the fluid is achieved.

Further presented in Figure 3a, there is an interconnector 302 for electrically connecting the microfluidic structure 102 to the controller 104. The interconnector 302 has macro-contacts 304 that are each connected to a corresponding one of the electrodes 204.

Presented in Figure 3b, there is a plan view of the interconnector 302 with the macro-contacts 304 being connected to individual micro-contacts 306 in a fan-out configuration, according to one embodiment. The micro-contacts 306 are each connectable to an electrode of the electrode array 204 and allows signal transmission between the electrodes 204 and the controller 104. The interconnector 302 can have any suitable shape or form. According to one embodiment, the interconnector 302 is a Chrome-Nickel-Gold (Cr-Ni-Au) coated silicon wafer. It shall be understood that various other types of wafer technology could be used without departing from the scope of the present embodiment.

A skilled person will understand that the macro-contacts 304 and the micro-contacts 306 could be replaced by similarly dimensioned and spaced electrical contacts. In this case the interconnector 302 has electrical contacts 304 that are each connected to a corresponding one of the electrodes.

Returning to Figure 2, there is presented a magnified close up view of an electrode array 204 that is located within the micro-channels 202. According to one embodiment, the electrode array 204 is a high density electrode array having an approximate width (W3) of 175μm. Each electrode has an approximate width (e1) of 15μm or less and the electrodes 204 are spaced apart by a distance (d2 and d1) that approximates 25μm. The corresponding micro-contacts 306 are also spaced apart by a comparably similar distance. The macro-contacts 304 are however wider and are distanced further apart for properly aligning with pin-outs of the controller 104 and for connecting to them by wire bonding or flip-chip.

Presented in Figure 3b according to an embodiment, the interconnector 302 has an array of six by six macro-contacts and has an approximate total width (W4) of 700μm. The macro-contacts 304 are at least 50μm wide (e2) and are spaced apart by a distance (d3 and d4) that approximates 50μm.

Further presented in Figure 3b, there is an electrically conductive path that electrically connects the macro-contacts 304 to the micro-contacts 306. According to one embodiment, the conductive path has a width (pw) that is 3μm or lesser and a path thickness (pt) that is greater than 1 μm. The space (ps) between each conductive path is smaller than 1.5μm.

As low voltage values can be applied to the electrodes 204, a skilled person will understand that it is possible for the electrodes to be separated by a distance that is even shorter than 25 μm without creating electrical interference.

A skilled person will also understand that the macro-contacts 304 of the interconnector 302 can be spaced apart by a distance that is greater than 50μm depending on the spacing of the controller 104 pin-outs.

Returning to Figure 3a, according to yet another embodiment, the electrodes 204 of the microfluidic structure are capacitive sensing electrodes. These electrodes 204 are adapted to transmit a signal that is indicative of a property of a fluid within the microfluidic channel 202. In one example, one of the electrodes 204 is a grounded electrode and another one of the electrodes 204 is a capacitive sensing electrode. The capacitive sensing electrode is connected to an electronic detection circuit adapted to measure a variation in the capacitance between the grounded electrode and the capacitive sensing electrode. Depending on the fluid flowing between the two electrodes, a certain variation in the capacitance is measured which indicates a property of the fluid.

It is understood that either one or both of the grounded electrode and the capacitive sensing electrode could be an electrode of the electrode array 204 or could be an electrode that is independent from the electrode array 204.

For analysing a fluid property of the fluid within the micro-channels 202, the microfluidic structure 102 is connected to a detector 308 such as an electronic detection circuit, as presented in Figure 3c. The electrodes 204 are adapted to transmit their signal indicative of the fluid property to the detector 308. Just like the controller 104, the detector 308 is connected to the microfluidic structure 102 with the interconnector 302. The pin-outs of the detector 308 are alignable with the macro-contacts 304 of the interconnector 302.

A skilled reader will understand that the controller 104 and the detector 308 may be integrated in a same module without departing from the scope of the invention.

A skilled reader will further understand that the shape of the electrodes 204 can differ from one embodiment to another. Various shapes and various combinations of shaped electrodes can be present in the microfluidic structure 102. For example, one of the electrodes 204 can have either one of a rectangular shape, a circular shape, an L-shape, a U-shape, a ring shape, a coil shape or any other suitable shape for producing a desired fluid manipulation. Depending on the shape and size of the electrodes 204, the general profile of the generated electrical field changes. A relatively large electrode having a rectangular shape generates electrical fields having a profile that is concentrated around each of its corners. A relatively small electrode having a rectangular shape generates a rather uniform electrical field profile over its whole surface. It is to be noted, that movement of the fluid particles within the micro-channel 202 is influenced by the general profile of the electrical field. Therefore, the shape and size of the electrodes 204 is carefully chosen according to the desired type of fluid manipulation.

Presented in figure 4a according to one embodiment, the controller 104 has a matrix of control circuits 402, each control circuit 404 is connectable to an electrode 204 of the compatible microfluidic structure 102. The controller 104 further has a signal input array 406 that have individual signal inputs that are connectable to a specific signal generator. Each control circuit is connected to the signal input array and each individual signal input is adapted to provide a distinct electrical signal to each control circuit. The control circuit 404 has a multiplexer 412 for multiplexing between the signals and is adapted to provide to the electrode 204 at least one of the signals.

It is understood that the signal generator could be either an analog signal generator or a digital signal generator.

According to one embodiment of the controller 104, there is assigned to each control circuit an address 414 and the control circuit is individually identifiable. When an electrode requires to be configured with at least one signal, the corresponding control circuit is identified and the signal to be applied is selected by the multiplexer 412.

A skilled reader will recognise that various ways of addressing the control circuits can be used without departing from scope of the invention. In one example, the address is a matrix row and column number.

Presented in Figure 4b according to an embodiment, the controller 104 has an analog or digital signals input 416, a digital line decoder input 418 and a digital row decoder input 420. Each control circuit 404 of the array 402 is connected to the signals input 416 for multiplexing at least one of the signals to a corresponding electrode 204. The line decoder input 418 and the row decoder input 420 are connected to a corresponding control circuit 404 for programming a specific electrode. By addressing a specific control circuit 404 with the line decoder input 418 and the row decoder input 420 it is possible to specify the signal for being applied to the corresponding electrode 204.

According to another aspect of the present, there is presented in Figure 5 a method 500 of producing the microfluidic structure 102. The method 500 comprises providing a first plate 502 that is electrically insulating. Concurrently presented in Figure 6a there is a blown up section view of the microfluidic structure 102. According to an embodiment, the first plate 602 has a top surface 604, a bottom surface 606 and an electrode surface 608 that is substantially on the top surface 604.

The method 500 further comprises, forming a plurality of holes 504 within the first plate 602 and providing an electrode 506 within each of the plurality of holes. Presented in Figures 6a and 6b, the plurality of holes 610 extend from the bottom surface 606 to the electrode surface 608. Within each of the plurality of holes, there is provided an electrode 204.

According to one embodiment of the method 500, the providing an electrode 506 consists of depositing a conductive material within the each of the plurality of holes and allowing the conductive material to be dried therein. Various suitable types of conductive materials, such as conductive epoxy, can be used for this. Moreover, various suitable ways of depositing the conductive material can be used, such as spreading a layer of conductive epoxy on the bottom surface 606 or on the electrode surface 608 of the first plate 602 and applying a pressure thereon so as to inject the conductive epoxy into the holes to form the electrode 204 and the electrical contact 704, as concurrently presented in Figure 7b.

According to yet another embodiment of the method 500, the providing an electrode 506 consists of depositing a conductive material by spreading a layer of conductive epoxy on the electrode surface 608 of the first plate 602 to form the shaped electrode 702, as concurrently shown in Figure 7b. In an alternate embodiment, the providing an electrode 506 consists of bonding the electrode with the electrode surface 608 by using techniques such as anodic bonding or any other suitable technique.

The method 500 further comprises, providing a second plate 508 and forming a micro-channel 510 within an interior portion of the microfluidic structure 102. Presented in Figures 6a and 6b, the microfluidic structure 102 has a second plate 612. The second plate 612 has a plate contacting surface 614 that is adapted to contact the top surface 604 of the first plate 602 when secured together. When secured together, the plate contacting surface 614 forms with the top surface 604 an interior portion 616. There is formed within the interior portion 616 a micro-channel 618. The micro-channel 618 extends over at least a section of the interior portion 616.

According to one embodiment, the micro-channel is formed within the second plate 612 on the plate contacting surface 614, as presented in Figure 6a. In an alternate embodiment, the micro-channel is formed within the first plate 602 on the top surface 604, as presented in Figure 6b.

Presented in Figure 6c according to one embodiment, the micro-channel is formed within the second plate 612 with a depth (D) of 25μm. Various techniques can be used for forming the micro-channel such as laser ablation or etching, micromachining or hot embossing or any other suitable technique.

Returning to Figure 5, the method 500 further comprises, securing 512 the top surface 604 of the first plate 602 to the plate contacting surface 614 of the second plate 612, as concurrently presented in Figure 6a. The securing 512 is done so as to align at least one of the plurality of holes 610 with the at least one micro-channel 618. By aligning the plurality of holes 610 with the micro-channel 618, the electrodes 204 provided within the holes 610 can then generate an electric field within the micro-channel 618 or can transmit a signal that is indicative of a fluid property of the micro-channel 618.

A manufacturer may use anodic bonding for securing 512 the first and second plates (602 and 612) together. A skilled person will however recognise that there are other ways of securing the first plate 602 and the second plate 612 together without departing from the scope of the present invention.

Presented in Figure 6c according to one embodiment, the first plate 602 and the second plate 612 can be photoresistive glass plates. The first plate 602 has a thickness (W2) that ranges between 50μm and 100μm and the second plate 612 has a thickness (W1) of 1mm. The plurality of holes within the first plate 602 are formed with a femto laser, the holes have a width of approximately 50 μm and are distanced apart by 75μm or less.

Returning to Figure 5, according to yet another embodiment of the method 500, the method comprises applying 514 an ITO (Indium Tin Oxide) layer within each of the plurality of micro-channels 618. As presented in Figure 6a, an ITO layer 620 is applied within a surface of the micro-channel 618 that is opposite to the first plate 602 to help generating an electrical field when a signal is applied to at least one electrode 204 in the secured first plate 602 and second plate 612 configuration. Presented in Figure 6b, the ITO layer 620 is applied on at least a section of the plate contacting surface 614 which is a surface of the interior portion 616 that is opposite to the holes 610.

According to one embodiment of the method 500, the providing 506 electrodes 204 in the holes 610 further comprises inserting an electrical conductive material within each hole 610. The electrical conductive material can be a conductive epoxy material or any other kind of electrically conductive material such as conductive silicon, gold, platinum, etc.

There are various ways of forming the electrical conductive material before inserting it within the holes 610. In one embodiment, the electrical conductive material is machined by electrical-discharge machining (EDM). The electrical conductive material can be machined to each form a single electrode 204 or a group of electrodes 204. In another embodiment, the electrical conductive material is etched on a silicon wafer such as by Deep Reactive-Ion Etching (DRIE). The electrical conductive material can be etched to form a single electrode 204 or a group of electrodes 204.

Presented in Figures 7a and 7b, there is a chain of steps presented for producing the microfluidic structure 102, according to one embodiment. In step 2, the electrical conductive material is machined to form a plurality of electrodes 204 in a single body or layer. In one example, the single body of electrodes 204 forms a plurality of electrodes 204 in a matrix configuration (ex.: 3x3 electrodes). In another example, the single layer of electrodes 204 forms a plurality of electrodes 204 in a row configuration (ex.: 1x6 electrodes). The body or layer of electrical conductive material is later separated by EDM as presented in step 6 of the method.

Returning to Figure 5, according to another embodiment of the method 500, the providing 506 electrodes 204 in the holes 610 further comprises depositing a shaped electrode 702 on the electrode surface 608. The shaped electrode 702 is deposited on the electrode surface 608 so as to align each shaped electrode 702 with a corresponding one of the holes 610 and to have each shaped electrode 702 electrically connected to a corresponding one of the electrodes 204 (step 4 of Figure 7a).

The shaped electrode 702 can have any suitable shape, form or size that effectively generates an electrical field profile for fluid manipulation or detection within the micro-channel 618. In one embodiment, the shaped electrode 702 is made from an electrically conductive material that is highly corrosion resistant such as a Tantalum-Gold alloy (Ta-Au) or Tantalum-Platinum alloy (Ta-Pt). In this embodiment, the shaped electrode 702 has a square shape with sides of 15 μm long and a thickness (f) that is greater than 200nm, as presented in Figure 6c.

In one embodiment, the shaped electrode 702 is deposited over a corresponding one of the electrodes 204 by electrodeposition. A skilled person will recognise that there are various other ways of depositing the shaped electrode 702 over a corresponding one of the electrodes 204 without departing from the scope of the invention.

According to yet another embodiment of the method 500, the providing 506 electrodes 204 in the holes 610 further comprises setting an electrical contact 704 on the bottom surface. Each electrical contact 704 is set on the bottom surface over a corresponding one of the plurality of holes so as to have electrical contacts 704 that are electrically connected to a corresponding one of the electrodes 204 (step 7 of Figure 7b).

In one embodiment, the electrical contact 704 is an EDM machined piece that is set over a corresponding one of the electrodes 204 by electrodeposition. In another embodiment, the electrical contact 704 is set over a corresponding one of the electrodes by depositing conductive epoxy. A skilled person will recognise that there are various other ways of setting the electrical contact 704 over a corresponding one of the electrodes 204 without departing from the scope of the invention.

There are various ways of forming the electrical contact 704. In one embodiment, the electrical contact 704 is machined by EDM. A conductive material such as conductive epoxy is machined to form a single electrical contact 704 or a group of contacts 704. Presented in Figures 8a and 8b, according to one embodiment, the conductive material is machined to form a plurality of contacts 704 in a single body or layer as presented in steps 2. In one example, a single body of contacts 704 forms a plurality of contacts 704 in a matrix configuration (ex.: 3x3 contacts). In another example, a single layer of contacts 704 forms a plurality of contacts 704 in a row configuration (ex.: 1x6 contacts). The body or layer of conductive material is later separated by EDM as presented in step 6.

Further presented in Figures 8a and 8b, according to another embodiment, the electrodes 204 and the contacts 704 are machined together by EDM. A conductive material such as conductive epoxy is machined to form a group of electrodes 204 and contacts 704, in a single body or layer as presented in step 2. In one example, a single body of electrodes 204 and contacts 704 forms a plurality of electrodes 204 and contacts 704 in a matrix configuration (ex.: 3x3 electrodes and contacts). In another example, a single layer of electrodes 204 and contacts 704 forms a plurality of electrodes 204 and contacts 704 in a row configuration (ex.: 1x6 electrodes and contacts). The body or layer of conductive material is later separated by EDM as presented in step 6 of the figures.

Presented in Figure 9a, according to another aspect of the present, there is a microfluidic device 902. The microfluidic device 902 has a micro-channel support body 904, an electrode support body 906 and a plurality of controller contacts 908. The micro-channel support body 904 has at least one micro-channel 910 formed therein. The shape and size of each micro-channel depends on their area of application.

The electrode support body 906 has an array of electrodes 912. According to one embodiment, the electrodes 912 are 15μm wide and are separated by a distance of 25 μm. A skilled person will understand that the width of electrodes may be less than 15μm and the distance between the electrodes may be less than 25μm. Low voltages (0V-2.5V) are applied to the electrodes 912 and electro-magnetic interference levels are practically undetected even with such closely spaced electrodes 912. It shall be understood that depending on the space between the electrodes, higher voltage can also be applied.

In one embodiment, the electrodes 912 transversally extend through the support body 906 and each of the controller contacts 908 is electrically connected to a corresponding electrode at a bottom portion of the support body. The support body 906 has a plurality of vias that extend therethrough and each via acts as a support for a corresponding electrode.

In another embodiment as presented in Figure 9b, the electrodes 912 are positioned on a surface of the support body 906. The controller contacts 908 are electrically connected to a corresponding electrode at a periphery of the support body. In this embodiment, the electrodes are L-shaped electrodes but a skilled person will understand that various other shaped electrodes could be positioned on the surface of the support body 906.

The electrode support body 906 and the micro-channel support body 904 are aligned to produce with at least one electrode of the array of electrodes 912 an electric field within at least one micro-channel 910.

In one embodiment, the micro-channel support body 904 has a layer of ITO 914 applied within an interior surface of the micro-channels 910. The ITO layer 914 is grounded and a single electrode can generate an electrical field with the ITO layer 914.

In yet another embodiment as presented in Figure 20A, the electrical conductive material is formed using a dicing process. The dicing process makes use of a dicing saw and a laser machine. The dicing saw is used for defining in a conductive material or semi-conductive material such as a silicon wafer 2002 at least one electrode contact 2004. The laser machine is used for defining a through-hole 2006 or an array of through-holes 2006 on a glass substrate 2008 as presented in Figure 29B. Each of the electrode contacts 2904 are carefully aligned and inserted into a respective through-hole 2006 of the glass substrate 2008 as presented in Figure 20C. For preventing the electrode contact 2004 to fall out of the glass substrate 2008, a conductive material 2010 such as silver is deposited onto each of the electrode contacts 2004 so as to adhere to the glass substrate 2008 and to immobilise the electrode contact 2004 within the glass substrate 2008, as presented in Figure 20D. To avoid electrical contact between the electrode contacts 2004, the conductive material 2010 between each electrode contact is removed such as with a dicing saw, as presented in Figure 20E. It is understandable that the conductive material 2010 may further provide an improved electrical contact for the electrode 2004.

Another way of preventing the electrode contact to fall out of the glass substrate 2008 is to apply a non-conductive layer 2012 such as Polydimethylsiloxane (PDMS) over the glass substrate 2008 and over the exposed electrode contacts 2004, such as presented in Figure 20F. To expose the electrode contacts 2004 the non-conductive layer 2012 covering the electrode contacts 2004 is partially removed such as with a dicing saw.

Presented in Figures 20G and 20H, there is formed a set of corresponding electrodes 2014 in the silicon wafer 2002. The silicon wafer material 2002 is partially removed to form a gap reaching the glass substrate 2008, thereby forming the corresponding electrodes 2014. There are various ways of forming the corresponding electrodes 2014, one way is to use a dicing saw to define separations in the silicon wafer 2002. The corresponding set of electrodes 2014 may be further polished for improving the surface quality and obtaining a desired thickness, as presented in Figures 20I and 20J.

According to one embodiment, the micro-channels are defined with a dicing saw, It should however be understood that the micro-channels may instead be defined by a laser machine or any other suitable micro-fabrication technique. The micro-channels may further be instead defined by using the sandwich technique as described above.

It shall further be understood that the glass substrate may be replaced by a flexible material such as a polymer and define a flexible electrode array.

<u>A LOC device using electrical field for particle manipulation and detection</u>

The theory of cells manipulation by dielectrophoresis is mainly based on the attraction or repulsion of these cells, following exposure to a non-uniform electric field. A particle placed between two electrodes, to which AC voltages are applied with different phase shifts, is attracted by the strongest or the weakest electric field region depending on the permittivity of the cells and the environment. Fig. 10a shows this phenomenon in the case of planar electrodes where the applied voltages to four electrodes are dephased by 90 degrees between two consecutive electrodes. This phenomenon is induced by the Clausus-Mossotti factor as shown in eq. (1a).

$$f_{CM} = \frac{K_1 - K_2}{2K_1 + K_2} \qquad (1a)$$

where K_1 and K_2 are the dielectric constants of the particle and the surrounding medium respectively. Fig. 10b shows the Clausus Mossotti factor (f_{CM}) variation which highlights the attractiveness or repulsive effect of cells using dielectrophoresis depending on the frequency. In fact, in low frequency, cells have opposite behaviours as in high frequency which is closely dependant in the f_{CM}.

Furthermore, eq. (1b) shows that the amplitude of the dielectrophoretic force depends also on the electric field which is related to the applied voltage. Then, the dielectrophoretic forces that are applied on the particules depends also on the amplitude of applied voltage, among other parameters as it can be seen in eq. (1b).

$$\vec{F}_{sphere} = 2\pi a^3 Re\left(\frac{\epsilon_0 K_1^*(K_2 - K_1)}{2K_1 + K_2}\right)\nabla|E|^2 \qquad (1b)$$

where K_1^* is the complex conjugate of K_1, E_0 is the permittivity of air, ε is the external electrical field, a the radius of the spherical particle, ▽ the differential vector operator and Re the real part of the complex number.

In addition, the dielectrophoretic force depends on the applied phase as shown in eq. (1c):

$$\langle\vec{F}(t)\rangle = 2\pi\varepsilon r^3\left[Re(f)\nabla\bar{E}_{rms}^2 + I_m(f_{CM})\left(E_{x0}^2\nabla\varphi(x) + E_{y0}^2\nabla\varphi(y) + E_{z0}^2\nabla\varphi(z)\right)\right. \qquad (1c)$$

where $Re(f_{CM})$ and $Im(f_{CM})$ are the real and the imaginary part of the factor f_{CM} respectively. f_{CM} is the Clausisus-Mossotti factor, r is the particle radius and ε is the permittivity of the suspending medium of the particle and φ(x), φ(y) and φ(z) are the phases of each electrical field components (E_x, E_y, E_z) respectively. Thus, cells manipulation is closely related to the frequency, phase and amplitude of electric field.

The proposed detection system is based on LoC capacitive biosensor. This technique has been widely studied and presented in the past few years. Indeed, this technique known as charge-based capacitance measurement consists of a differential measurement of a induced in two circuit branches. Each branch includes a transistor where its drain-source current value depends on the change in the capacitance value connected to its drain. One branch is used for sensing, while the other is a reference. Subsequently, an integration circuit is used to convert the differential current into a voltage. Thus, the output voltage refers to the difference between the two branche capacitances. Hence, the capacitance change of the liquid flowing in the micro channel and passing on the top of the in-channel electrodes is measured. Then, the detection circuit is more sensitive to the variation between the reference and the sensing capacitance, but it is considerably dependant on the integration capacitance. Thus, for better sensitivity, it is suitable to use small size integration capacitance. However, the size of the later is technology dependant and must dominate the parasitic capacitance of transistors, otherwise the sensitivity will be variable as the parasitic capacitance can change depending on the fabrication process and transistors implementation.

According to one embodiment there is an electronic circuit designed for LoC using electric field for cell manipulation and a capacitive sensing system for a wide range of applications. Thus, the proposed circuit can generate four different sinusoidal signals with frequency, phase and amplitude control; in addition it includes a capacitive sensor array for multiple capacitive sensing.

Cell manipulation by dielectrophoresis

The proposed circuit is an integrated part of a LoC microsystem as shown in Fig. 1where microfluidic and microelectronics microsystem are connected together. Furthermore, cell manipulation requires special signals depending on the biological assay characteristics such as signals with defined frequency, amplitude, phase and Clausius-Mossotti factor. Indeed, paramagnetic cells are sensitive to magnetic field, electrically charged cells to electric field and fluorescent cells to light excitation. Thus, depending on the type of cells, the CMOS chip has an architecture and a completely different circuitry. Although the target is manipulation of neurotransmitters which are nanoscale molecules, the microsystem is designed for handling large-scale particles, enabling movement and manipulation of cells whose radius *a* can be in the range of few micrometers. Then, the proposed circuit is dedicated for wide range dielectrophoretic manipulations. The dielectrophoretic force $\vec{F}$ leading to cells manipulation depends on frequency f, phase ϕ and amplitude of applied signals on electrodes and which are generated by the CMOS chip where ε_0 is the vaccum permitivity. Then, by monitoring the frequency f which changes the conductivity and permittivity of the medium, the real part of Clausus Mossotti factor $Re(f_{CM})$ is modified. Consequently, a modification of Clausus Mossotti factor f_{CM} causes a change in force effect going from a repulsive to an attractive manipulation and vice versa in addition to the impact of the imaginary part of f_{CM} which is $Im(f_{CM})$ that is associated with the phase of applied signals on electrodes. Regarding the phase $(\phi(x),\phi(y),\phi(z))$ between applied signals, when the difference between phases is small, the dielectrophoretic forces effect is negligible as it depends on the phase gradient ∇. Finally the amplitude of the applied signals affects the intensity of the generated electric field E and subsequently the intensity of the dielectrophoretic force that depends on the gradient of $|E|^2$. In addition, E depends on the architecture of the in-channel electrodes. Indeed, when applying a small voltage V signal, the electric field E is bigger when the distance λ between the electrodes is smaller. For this reason, the on-chip integration of a cell separation and manipulation system is more suitable. Then, based on f, ϕ and the maximum applied voltage V, a CMOS chip will generate and apply signals on the in-channel electrodes adequately.

In addition to cell manipulation circuit, the capacitive sensing system is mainly based on a sensor network using the CBCM technique. The effectiveness of this technique has already been proven in E. Ghafar-Zadeh, M. Sawan, and D. Therriault, “A 0.18-[mu]m CMOS capacitive sensor lab-on-chip,” Sensors and Actuators A: Physical, vol.141, no. 2, pp. 454 – 462, 2008. The high sensitivity of a CBCM based sensor, which is 1 fF/mV, allows better detection with high accuracy when nanoparticles are injected in micro-channels. However, the system is not designed to detect a single nanoparticle but the change of concentration of the liquid flowing through micro-channels. Then, the CMOS chip controls the variation of the capacitance of the micro-channel resulting from cell separation.

In the next section, the circuit achieving all the functionality previously described is introduced and the architecture of the chip is presented.

Circuit

The CMOS chip is divided into two parts that are completely independent which are the manipulation circuit and the detection circuit.

Signal generation circuit for cells manipulation

The manipulation circuit is based on a control unit (CU) designed on chip that is generating the 4 digital sine waves; each one coded on 8 bits. Among the four signals, one of them is considered as a reference where the three others are generated by delaying the reference sine by the CU.

To proceed the analog conversion, each 8 bits of each sine wave are sent through a data bus D to a digital-to-analog converter DAC. The latter consists of a serie of current mirror as shown in Fig.11. Using such DAC instead of another type like capacitive charge DAC is mainly based on space optimization in addition to an easy integration of transistors on-chip. Thus the current obtained at the output of each DAC is defined by equation 2a.

$$I_{DAC} = \sum_{i=1}^{7} 2^i D i I_0 \qquad (2a)$$

where I_0 is the minimum current that can be generated by the 8-bit DAC which is the equivalent of data value equal to 00000001.

Since dielectrophoresis is sensitive to voltages, the output of the DAC is connected to the reference branch of a current mirror to be converted into voltage. A simple current mirror which can be calibrated by an off-chip resistor R_{CAL} shown in Fig.11 is designed for this purpose. Thus, the voltage offset is reduced to avoid saturation in the following amplifier stages through R_{CAL}. Then the output voltage coming from the current to voltage converter is V_{DAC} as shown in equation 2b.

$$V_{DAC}=\alpha(\beta I_{DAC}) \qquad (2b)$$

while β is the multiplication factor of the current mirror and which is set to 1 in the proposed circuit. P-transistors are biased by V_{BIAS1} and V_{BIAS2} so that the output voltage V_{DAC} to remove the offset in addition to R_{CAL}. Then, the output voltage of the current mirror is connected to a first amplification stage. It consists of a single stage amplifier followed by another independent amplifier circuit. Such architecture enhances the control and the sensitivity of the LoC by having fine and coarse voltage control. The first amplification A_1 allows to adjust the signals to control the intensity of the dielectrophoretic forces through R_{adj}. While A_2 control the dielectrophoretic force effect which are the attractive and the repulsive manipulation through R'_{adj}. Fig.12 shows all previous described steps. Thus the voltage at the end of the second amplifier stage is as follows.

$$V_{Amp}=A_1 A_2 V_{DAC} \qquad (3)$$

Finally, a buffer is connected to the second amplifier to drive high capacitive load and a low resistive load. Therefore, the final Voltage V_{Buff} equation is

$$V_{Buff}=V_{Amp}=A_1 A_2 \alpha\beta I_{DAC} \sum_{i=1}^{7} 2^i D i I_0 \qquad (4)$$

The dielectrophoretic force depends on A_1, A_2 and D. And consequently the new force expression can be written as follows.

$$\vec{F} = 2\pi a^3 \operatorname{Re}(f_{CM}(freq))\nabla|f(A_1, A_2, D)|^2 \qquad (5)$$

where f_{req} corresponds to the operating frequency of the CU and $E \propto \frac{V_{Buff}}{\lambda}$.

Detection circuit

The detection circuit consists of a capacitive sensor array based on CBCM technique. It allows an exhaustive measurement of the capacitance change which corresponds to the variation of cells concentration in the micro-channel. Since the architecture is CBCM-based cell array, the space for each cell of the array should be as low as possible to increase the number of sensor cells. The proposed model can be compared to a SRAM with a precharge and a current sensing circuit for each cell of the array as shown in Fig.13.

The precharge circuit charges the two capacitors on each branch of each cell so that the current in the two branches is similar, i.e. $I_{ref}=I_{sens}$. Once the preload is complete, transistors of each cell discharge the current toward current sensing circuit. Two current mirrors are connected to each branch to amplify the current and to enhance the current detection. Then, the output of each sensor is equal to $I_{ref}-I_{sens}$. Passing by an integration capacity, the current is converted into a voltage then it is connected to a sigma-delta ADC. These steps are done simultaneously for each column of the array. In the proposed architecture, the detection system operates independently from the manipulation circuit to prevent any interference especially for high frequencies applications.

<u>Simulation and experimental results</u>

The CMOS chip was fabricated with TSMC 0.18 technology with the standard process using two different power supplies (3.3V, Ground), (1.8V, Ground), (1.65V, -1.65V) and (0.9V, -0.9V). The use of a large number of power pads is mainly due to the need to reduce the static consumption of the chip. Thus, there is only amplifiers and buffers using negative voltages. ADCs' of the detection circuit are powered with 3.3 V to increase the dynamic range of sensors. Indeed, by using the 3.3V the dynamic range of sensors increases by 50%. As mentioned above, manipulation circuit cannot operate simultaneously with the detection circuit, that is why the chip contains two completely independent power systems. The control unit has been tested to generate low frequencies. The CU is working with 10 MHz frequency and includes a frequency divider to set the dielectrophoretic force frequency.

Once the chip is correctly configured, the phase is controlled digitally and the CU is just adding a programmable delay to generate each signal. The experimental voltage range of the output signal is 2.4V peak-to-peak.

As each signal is generated from a memory where is stored a 100 samples of 8 bits covering one period, then the minimum phase shift is $360^0/100$ which is equivalent to 3.6^0. The buffer is designed to drive resistors lower than 200 *ohm* and a 200 *pf* capacitor. Then, each bloc can sink a minimum current of 9 *mA* for 16 electrodes because the architecture contains 64 electrodes divided into 4 blocs.

Regarding the capacitive sensor, the variation of the output of the converter is a function of capacity. As the variation of capacity is not stable because of the used set-up, the output of sigma-delta converter is unstable also.

An advantage of the proposed circuit and architectures consists of an on-chip fully controllable signal generation based on frequency, phase and amplitude. Consequently, the chip can handle any cell manipulation based on dielectrophoresis for various kind of cell motion. Some parts of the circuit are intentially done offchip for further chip extension. Furthermore, a high sensitivity CBCM based capacitive sensor array is included to realize a complete LoC. The chip is integrated with a microfluidic architecture which leads among the first fully integrated LoC.

<u>A LOC device using electromagnetic field for particle manipulation and detection</u>

Recently, the usage of magnetic beads to manipulate bioparticles (e.g. cells, proteins, DNA) in microfluidics has been attracting noticeable attention due to the high controllability and good biocompatibility, compared to electric field manipulation and optical manipulation. As the solid phase carriers of bioparticles, magnetic beads can be trapped by applying scattering magnetic field in microfluidics, thus different applications can be realized by controlling the scattering of magnetic field, such as separation, mixing, sorting, transport, etc.

For generating the scattering magnetic field in microfluidics, in-channel or on-chip planar coils are more preferable compared with external ferromagnets, because magnetic flux intensity and direction can be changed simply by changing the current passing through the coils, thus resulting in a more flexible control. Many of the previous works are based on single coil manipulation or simple topological coils array manipulation, which applied to single particle or low throughput manipulation. However, for some lab-on-a-chip applications, such as purification, fast detection, etc., high throughput capacity is required. Therefore, the optimization of micro-coils array's topology is necessary. The objective is to achieve the maximum manipulation ability with acceptable power efficiency.

The present aims to explore an efficient topology of planar coils array for manipulating mass magnetic beads in channel. Simulation results show minimizing the dimension of coils to the fabrication limitation results in the best efficiency, reflecting in the enhanced magnetic force and increased total trapping area. Meanwhile, a low power consumption operation scheme based on circular scanning is introduced.

<u>Single coil modeling</u>

From Maxwell tensor equation, the force on a magnetic bead due to the applied magnetic fields is

$$\vec{F}_{mag} = V_{X_m}(\vec{H} \cdot \nabla)\vec{B} \qquad (6a)$$

where *Fmag* is the magnetic force on the bead, *V* is the volume of the bead, X_m is its magnetic susceptibility per unit volume, *H* is the magnetic field intensity, and *B* is the magnetic flux density. In orthogonal coordinate system, extending (6a) in x direction leads to

$$F_X = V_{X_m}\left(B_x \frac{\partial B_x}{\partial x} + B_y \frac{\partial B_y}{\partial y} + B_y \frac{\partial B_z}{\partial z}\right) \qquad (6b)$$

Equation (2) indicates that the magnetic force acting on a bead depends on the magnetic field intensity, as well as magnetic field gradient. Some previous works on the performance of a single planar micro-coil have concluded that circular spiral micro-coils can generate the strongest magnetic field compared to other geometrical configurations (meander, rectangle spiral, etc.), for this reason, in the present, focus is on the planar circular spiral micro-coils.

First, there is investigated the performance of the single coil by FEA (Finite Element Analysis) software Ansys 11.0. For this model, Element Type SOURC36 is selected; wire thickness 1um; inner diameter is 60 μm, outer diameter is 400um.Taking the center of a coil as the origin of coordinator, magnetic flux density versus horizontal direction and vertical direction is shown in Fig.14. Note that the current passing through the coil is 100mA.

Since the model is circular planar coil, magnetic flux density is almost symmetric both in x-direction and z-direction.Fig.14 exhibits the feature that the magnitude of field drops quickly as the distance to the coil's centre increases, which means both the maxima of magnetic flux density and magnetic field gradient locate in the vicinity of the coil's center. This feature leads to a disadvantage in high throughput applications: The magnetic beads tend to concentrate on the center area of coil only, according to some previous researches, one considerable problem of magnetic manipulation in microfluidic channel is that there always exists interaction between the induced beads, these beads are prone to form chain or even cluster in channel, which result in two problems: First, the magnetic poles of concentrated beads are disordered in spatial, so magnetic poles will affect each other, which will weaken the magnetic susceptibility X_m in equation(6a). Thus a stronger magnetic field is required to provide the same attracting force as the case of single bead. In high throughput applications, this influence cannot be ignored. The second problem is that these complex compounds will decrease the separation rate, because some particles which are supposed to be flushed out may be blocked among the beads cluster.

To overcome the first disadvantage, a stronger magnetic field is needed, but a stronger magnetic field is at the cost of bigger current consumption, which conflicts with our low power consumption target for microsystem. On the other hand, even regardless of power consumption, the second problem due to large quantity of beads still exists.

<u>Concept of optimization</u>

There is proposed a new topological micro-coils array to solve these problems altogether.

The principle is as follow: In a given area on the surface of micro-channel, there are seven small coils to replace one big coil. If the smaller coils can generate a magnetic field as strong as the big one, then the advantages will be remarkable. First, the total trapping area is bigger, that means more beads will be trapped on the surface of channel, second, the trapping centers are more dispersed, and for each trapping center generated by smaller coil, the area is smaller than that generated by the original big coil, so fewer beads will gather together, the interaction problem between beads will be eased greatly.

To demonstrate the principle above, consider the magnetic field generated by micro-coils again. Since all the micro-coils are in the same plane and referring to Fig. 14 (a), it's reasonable to draw the conclusion that different micro-coil works independently and doesn't affect each other. The magnetic field within each micro-coil's region can be obtained from the Biot-Savart law:

$$\vec{B} = \int d\vec{B} = \int \frac{\mu_0}{4\pi} \cdot \frac{I d\vec{l} \times \hat{r}}{|r|^2} \qquad (6c)$$

where μ_0 is the magnetic constant; I is the current passing through wire; $d\vec{l}$ is a vector whose magnitude is the length of the differential element of the wire, and whose direction is the direction of current; $\vec{\hat{r}}$ is the displacement unit vector, in the direction pointing from the wire element to the point at which the field is being computed and r is the distance from the wire element to the point at which the field is being computed. The schematic is shown in Fig.15.

Equation (6c) reveals that, approximately, the magnetic flux density generated by coil is directly proportional to the current through it and inversely proportional to its diameter (coil size). As the size of coil shrinks, it need less and less current to generate the required magnetic field. Therefore, there is good reason to believe that in high throughput applications, always following the fabrication limitation to decide the coil's size will bring great benefits. Actually, with the development of fabrication technology, the size of micro-coil would shrink down to a comparable value as the size of micro-beads, then one coil only immobilize one bead, leading to a maximum trapping efficiency.

One may argue that when the wire shrinks to the fabrication limitation, it can not tolerate the huge current passing through it. Actually, from some empirical rules, in the normal CMOS fabrication technology, when the width and thickness of metal wire is 1um, it can sustain a continuous current of up to ~70mA, which far exceeds the minimum current needed. The only remaining issue is when the width of wire is very small, the resistance per unit length will increase, and then Joule heating will increase as the coils' on-time get long, which may heat up the microfluidic, and then damage the bioparticles' activities. To avoid this problem, someone uses on-chip water cycling system or external thermoelectric cooler to keep temperature in channel, which are proved effective in holding temperature, but prior to these passive action, it's better to explore some more economic means to reduce power consumption as well as Joule heating by means of novel design concept or operation principle. Just as presented afore, the miniaturization of coils is a good way to decrease current consumption, because for each smaller coil, lower current is required to generate a same magnetic field as big one does. However, if all the small coils are turned on at the same time to generate a comparable trapping area as the big coil, the total current consumption can not prove any advantage, unless some special operation is exploited.

Circular scanning scheme

For a single magnetic bead in microfluidic, in addition to the magnetic force, it experiences hydrodynamic drag force, gravitational force and buoyancy force, while the latter two forces can be neglected due to bead's small size and the cancellation of each other in some degree. From Stokes' law, there is

$$\vec{F}_{drag} = 6\pi n R_{bead}(\vec{v}_{bead} - \vec{v}_{fluid}) \qquad (6d)$$

where bead $\vec{v}_{bead}, \vec{v}_{fluid}, R_{bead}\ and\ n$ are the bead velocity, microfluidic velocity, bead radius and fluid's viscosity, respectively. Now consider the case when beads are immobilized at the center of micro-coils. If the coil is turned off, magnetic bead will be forced to move along the flow's direction due to equation (6d), at an initial velocity 0 and initial acceleration $6\pi n R_{bead} v_{fluid}/m_{bead}$, where m_{bead} is the mass of micro-bead. Since in most microfluidic applications, $\vec{v}_{fluid}$ is very small, normally tens of micrometers per second, the acceleration is also very small, which means the beads will not escape from the coil's center area for a while even if magnetic force is removed in a short while. As estimation, when the velocity of fluid is 10um/s, it needs more than 3s to move 10um. If the coils are reactivated within the beads' escape time, the beads will be attracted to the center of coils again, from the macroscopic view, the magnetic beads never leave. Note that Brownian motion here is neglected, because the escape time due to Brownian motion is usually bigger than 10s. One advantage of such kind of operation is that threre can be used digital switches to control the on and off of micro-coils, since the high speed of digital switches can be easily achieved, all the coils can share one current source, which is definitely beneficial to power consumption and heating issue. Fig.16 illustrates this principle. During one cycle, the micro-coils are activated one by one from inlet to outlet. When magnetic beads move into the coils' trapping area where there is available room for them, they will be captured, otherwise they move on to other trapping region until they are captured. Once they are captured, they'll move around only in the vicinity of each coil's center.

3D modeling and simulations are performed to demonstrate the advantages of our proposed micro-coils array in trapping area and power consumption. Fig.17 shows directly the magnetic field distribution of different topological micro-coils array. Note that the plane investigated is 10μm above the surface of micro-coils array, and the minimum magnetic flux density to attract micro-beads in our study is 15 Gauss, which means the effective trapping area consists of yellow region and red region. From the previous analysis, as the micro-coil shrinks, it needs less current to generate the same magnetic field as the big one. So our simulation procedure is: First simulate the magnetic field distribution of single coil with current 100mA, then for other coils arrays, increase the current and watch the results until reach the equal maximum magnetic flux density as the single coil.

The parameters in this simulation and the comparison of results are summarized in the table of Figure 18.

Note that the results in the table of Figure 18 are under the condition that different micro-coils array can generate the same maximum magnetic field (28.1Gauss), so the trapping area doesn't increase remarkably, but the power consumption is reduced greatly (from 100mA to 31mA). If the current is kept and shrink the coil, the trapping area will increase highly. It's a tradeoff here and can be adjusted in application, just be aware about that low power consumption and low heating is usually our first consideration.

According to yet another embodiment, there is a magnetic beads based microsystem combining microfluidics and microelectronics structures. Such microsystem is an emerging field, it has a great potential in many application fields, such as real time polymerase chain reaction (PCR), immunoassay and blood sample preparation. Magnetic particle labeling and magnetic manipulation is a very mild technology, since bioparticles are not damaged and retain their biological activity under low frequency magnetic field. Manipulation and detection based on magnetic field have been steadily gaining interest in recent years, due to its low cost and high performance. It can be achieved by modulating a magnetic field over the chip surface via an array of micro-coils. This method allows a very precise control of the magnetic beads and does not require external moving parts. High-sensitivity magnetic sensors can be designed using inductive device which can also be realized by on chip coils.

According to one embodiment, presented in Figure 19 there is an electrode support body 1900 having thereon at least one coil shaped electrode 1902 or at least one micro-coil shaped electrode 1902. In this embodiment, there is a plurality of coil-shaped electrodes that form an array of electrodes, however it is understood that the number and disposition of the electrodes 1902 could differ from one embodiment to another.

Further presented in Figure 19, each coil shaped electrode 1902 is electrically connected to a corresponding controller contact 1904. In this embodiment, the controller contact 1904 is positioned at a periphery of the electrode support body 1900. It is understood that the controller contact 1904 could be located at an opposite side of the electrode support body 1900 and be electrically connected to the coil-shaped electrode 1902 though a conductive material extending through the support body 1900.

A skilled person would understand that the coil-shaped electrode 1902 could be electrically connected to the controller contact 1904 with a combination of the peripheral controller contact 1904 and the controller contact 1904 that is located at an opposite side of the electrode support body 1900.

From Maxwell tensor equation, the force on a magnetic bead due to the applied magnetic fields is

$$\vec{F}_{mag} = V\chi_m(\vec{H}\cdot\nabla)\vec{B} \qquad (1)$$

where $\vec{F}_{mag}$ is the magnetic force on the bead, V is the volume of the bead, χ_m is its magnetic susceptibility per unit volume, $\vec{H}$ is the magnetic field intensity, and $\vec{B}$ is the magnetic flux density. In orthogonal coordinate system, extending (1) in x direction leads to

$$F_x = V\chi_m (B_x \frac{\partial B_x}{\partial x} + B_y \frac{\partial B_x}{\partial y} + B_z \frac{\partial B_x}{\partial z}) \qquad (2)$$

Equation (2) indicates that the magnetic force acting on a bead depends on the magnetic field intensity, as well as magnetic field gradient.

The magnetic field within each micro-coil 1902 region can be obtained from the Biot-Savart law:

$$\vec{B} = \int d\vec{B} = \int \frac{\mu_0}{4\pi} \cdot \frac{Id\vec{l} \times \hat{\vec{r}}}{|r|^2} \qquad (3)$$

where μ_0 is the magnetic constant, I is the current passing through wire, $d\vec{l}$ is a vector whose magnitude is the length of the differential element of the wire, and whose direction is the direction of current, $\hat{\vec{r}}$ is the displacement unit vector, in the direction pointing from the wire element to the point at which the field is being computed and r is the distance from the wire element to the point at which the field is being computed. The schematic is shown in Fig. 15.

Eq. (3) reveals that, approximately, the magnetic field generated by the coil 1902 is directly proportional to the current through it and inversely proportional to its diameter (coil size). As the size of coil shrinks, it need less and less current to generate the required magnetic field.

For a single magnetic bead in microfluidic, in addition to the magnetic force, it experiences hydrodynamic drag force, gravitational force and buoyancy force, while the latter two forces can be neglected due to bead's small size and the cancellation of each other in some degree. From Stokes's law, it is known

$$\vec{F}_{drag} = 6\pi\eta R_{bead}(\vec{v}_{bead} - \vec{v}_{fluid}) \qquad (4)$$

where $\vec{v}_{bead}$, $\vec{v}_{fluid}$, R_{bead} and η are the bead velocity, microfluidic velocity, bead radius and fluid's viscosity, respectively. Considering the case when beads are immobilized at the center of microcoils 1902, when the coil 1902 is turned off, magnetic bead will be forced to move along the flow direction due to Eq. (4), at an initial velocity 0 and initial acceleration $6\pi\eta R_{bead}\vec{v}_{fluid} / m_{bead}$, where m_{bead} is the mass of a microbead. Since in most microfluidic applications, $\vec{v}_{fluid}$ is very small, normally tens of micrometers per second, so the acceleration is also very small, which means the beads will not escape from the coil center area right away even if the magnetic force is removed in a short while.

For the manipulation of magnetic beads, it is always needed to make sure the magnetic force on beads is bigger than hydrodynamic drag force, the bigger the magnetic force, the more sensitive controlling can be achieved.

What is claimed is:

CLAIMS

1. A microfluidic structure adapted to be connected to an electronic circuit, the structure comprising:

   a microfluidic channel;

   at least one electrode extending through an electrode support body and adapted to generate a force field within the microfluidic channel for effecting a microfluidic manipulation; and

   an interconnector having at least one electrical contact, connected to a corresponding one of the at least one electrode for replaceably connecting the microfluidic structure to the electronic circuit.
2. The microfluidic structure of claim 1, wherein the at least one electrode is an electrode array having a plurality of electrodes.
3. The microfluidic structure of claim 2, wherein the electrode array is a high density electrode array, in which the plurality of electrodes are spaced apart by approximately a distance of 25μm or less.
4. The microfluidic structure of any one of claims 1, 2 or 3, wherein the electrical contacts are spaced apart by approximately a distance of 50μm or greater.
5. The microfluidic structure of any one of claims 2, 3 or 4, wherein each of the plurality of electrodes have a width that is approximately 15μm or less.
6. The microfluidic structure of any one of claims 1 to 5, wherein the electrical contacts have a width that is approximately 50μm or greater.
7. The microfluidic structure of any one of claims 1 to 6, wherein the electronic circuit is a controller with contacts corresponding to the plurality of electrical contacts.
8. The microfluidic structure of claim 7, wherein at least some of the electrodes are adapted to receive a signal from the controller and generate a force field within the microfluidic channel according to the signal.

9. The microfluidic structure of any one of claims 1 to 8, wherein the electronic circuit is a detector with contacts corresponding to the plurality of electrical contacts.
10. The microfluidic structure of claim 9, wherein at least some of the electrodes are capacitive sensing electrodes and are adapted to transmit to the detector a signal that is indicative of a sensed property of a fluid that is within the microfluidic channel.
11. The microfluidic structure of any one of claims 1 to 10 wherein the microfluidic structure is a reconfigurable microfluidic structure.
12. The microfluidic structure of any one of claims 1 to 11 wherein the at least one electrode is an L-shaped electrode.
13. The microfluidic structure of any one of claims 1 to 12 wherein the at least one electrode is a coil-shaped electrode.
14. The microfluidic structure of any one of claims 2 to 13 wherein the electrode array is a high density electrode array where the electrodes are spaced apart at a smaller distance than 25μm.
15. The microfluidic structure of any one of claims 1 to 14 wherein the electrical contacts are macro-contacts.
16. A method of producing a microfluidic structure, the method comprising:

    providing a first plate having a top surface and a bottom surface, the first plate being an electrically insulating plate;

    forming a plurality of holes extending from the bottom surface to an electrode surface of the first plate, the electrode surface being substantially in parallel with the top surface;

    providing an electrode within each of the plurality of holes;

    providing a second plate having a plate contacting surface that is adapted to form with the top surface of the first plate an interior portion of the microfluidic structure;

    forming at least one micro-channel adapted to extend over the interior portion of the microfluidic structure; and securing the top surface of the first plate to the plate contacting surface of the second plate so as to align at least one of the plurality of holes with the at least one micro-channel.

17. The method of producing a microfluidic structure of claim 16, wherein the electrode surface and the top surface are a same surface.
18. The method of producing a microfluidic structure of one of claims 16 or 17, wherein forming the at least one micro-channel comprises forming the at least one micro-channel within the plate contacting surface of the second plate.
19. The method of producing a microfluidic structure of one of claims 16 to 18, wherein forming the at least one micro-channel comprises forming the at least one micro-channel within the top surface of the first plate;
20. The method of producing a microfluidic structure of one of claims 16 to 19, wherein a distance between the plurality of holes is 75μm or less.
21. The method of producing a microfluidic structure of one of claims 16 to 20, wherein a width of each of the plurality of holes is 15μm or less.
22. The method of producing a microfluidic structure of one of claims 16 to 20, wherein the first plate is a photoresistive glass plate.
23. The method of producing a microfluidic structure of one of claims 16 to 22, wherein the second plate is a photoresistive glass plate.
24. The method of producing a microfluidic structure of one of claims 16 to 23, wherein the plurality of holes are formed with a femto laser.
25. The method of producing a microfluidic structure of one of claims 16 to 24, further comprising applying a layer of ITO (Indium Tin Oxide) within each of the plurality of micro-channels; and
26. The method of producing a microfluidic structure of one of claims 16 to 25, wherein the providing an electrode comprises inserting an electrical conductive material within each of the plurality of holes;
27. The method of producing a microfluidic structure of one of claims 16 to 26, wherein the providing an electrode further comprises depositing a shaped

electrode on the electrode surface over a corresponding one of the plurality of holes.

28. The method of producing a microfluidic structure of one of claims 16 to 27, wherein the providing an electrode further comprises setting an electrical contact directly on the bottom surface over a corresponding one of the plurality of holes;
29. The method of producing a microfluidic structure of one of claims 26 to 28, further comprising machining (Electric-Discharge Machining (EDM)) the electrically conductive material.
30. The method of producing a microfluidic structure of one of claims 26 to 28, wherein the electrical conductive material is a conductive epoxy.
31. The method of producing a microfluidic structure of one of claims 27 to 30 wherein the depositing comprises an electrodeposition of the shaped electrode.
32. The method of producing a microfluidic structure of one of claims 16 to 31, wherein the electrode is a layer of conductive epoxy that is separated by EDM (Electrical-Discharge Machining).
33. The method of producing a microfluidic structure of one of claims 28 to 32, wherein the electrical contact is a layer of conductive epoxy
34. The method of producing a microfluidic structure of one of claims 28 to 32, wherein the setting comprises an electrodeposition of the electrical contact.
35. The method of producing a microfluidic structure of one of claims 28 to 32, wherein the electrical contact is an EDM (Electrical-Discharge Machining) machined electrical material.
36. The method of producing a microfluidic structure of one of claims 16 to 35, wherein the securing comprises anodic bonding.
37. A microfluidic device adapted to be connected to a controller, the device comprising:

    a micro-channel support body having at least one micro-channel formed therein;

    an electrode support body having an array of electrodes, the electrode support body and the micro-channel support body being aligned to produce with at least one of the array of electrodes a force field within the at least one channel; and

a plurality of controller contacts each being electrically connected to a corresponding electrode of the array of electrodes for performing within the at least one micro-channel a plurality of microfluidic manipulations.

38. The microfluidic device of claim 37, wherein the microfluidic device is further adapted to be connected to a detector and comprises a plurality of detector contacts each being electrically connected to a corresponding electrode for transmitting to the detector a signal that is indicative of a sensed property of a fluid that is within the micro-channel.
39. The microfluidic device of any one of claims 37 or 38 wherein the plurality of microfluidic manipulations is a combination of at least two of the group consisting of trapping, transportation, mixing and separation.
40. The microfluidic device of any one of claims 37 to 39, wherein the array of electrodes has electrodes that are separated by a distance of 25μm or less.
41. The microfluidic device of any one of claims 37 to 40 wherein each electrode of the array of electrodes has a width of 15μm or less.
42. The microfluidic device of any one of claims 37 to 41, wherein the electrode support body comprises a plurality of vias extending therethrough, each of the plurality of vias being for supporting a corresponding electrode of the electrode array therein.
43. The microfluidic device of any one of claims 37 to 42, wherein the electrode array has at least one coil-shaped electrode.
44. The microfluidic device of any one of claims 37 to 43, wherein the force field is an electromagnetic field.
45. The microfluidic device of any one of claims 37 to 43, wherein the force field is an electrical field.
46. The microfluidic device of one of any one of claims 37 to 45, wherein the micro-channel support body comprises a layer of ITO applied within an interior surface of the at least one micro-channel.

47. A method of manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, the method comprising:

    defining a plurality of electrode contacts all joined in a single piece;

    defining in a glass substrate a plurality of through-holes each corresponding to the plurality of electrode contacts;

    inserting the plurality of electrode contacts into the corresponding plurality of through-holes;

    depositing a bonding material onto the plurality of electrode contacts so as to adhere to the glass substrate and to immobilise each of the plurality of electrode contacts within the corresponding through-holes; and

    singulating the single piece into a plurality of electrodes, each of the plurality of electrodes corresponding to each of the plurality of electrode contacts.

48. The method of claim 47, wherein the bonding material is a conductive material, the depositing comprises removing a portion of the bonding material to electrically singulate the plurality of electrode contacts.

49. The method of claim 47, wherein the bonding material is a non-conductive material, the depositing comprises removing a portion of the bonding material to electrically expose the plurality of electrode contacts.

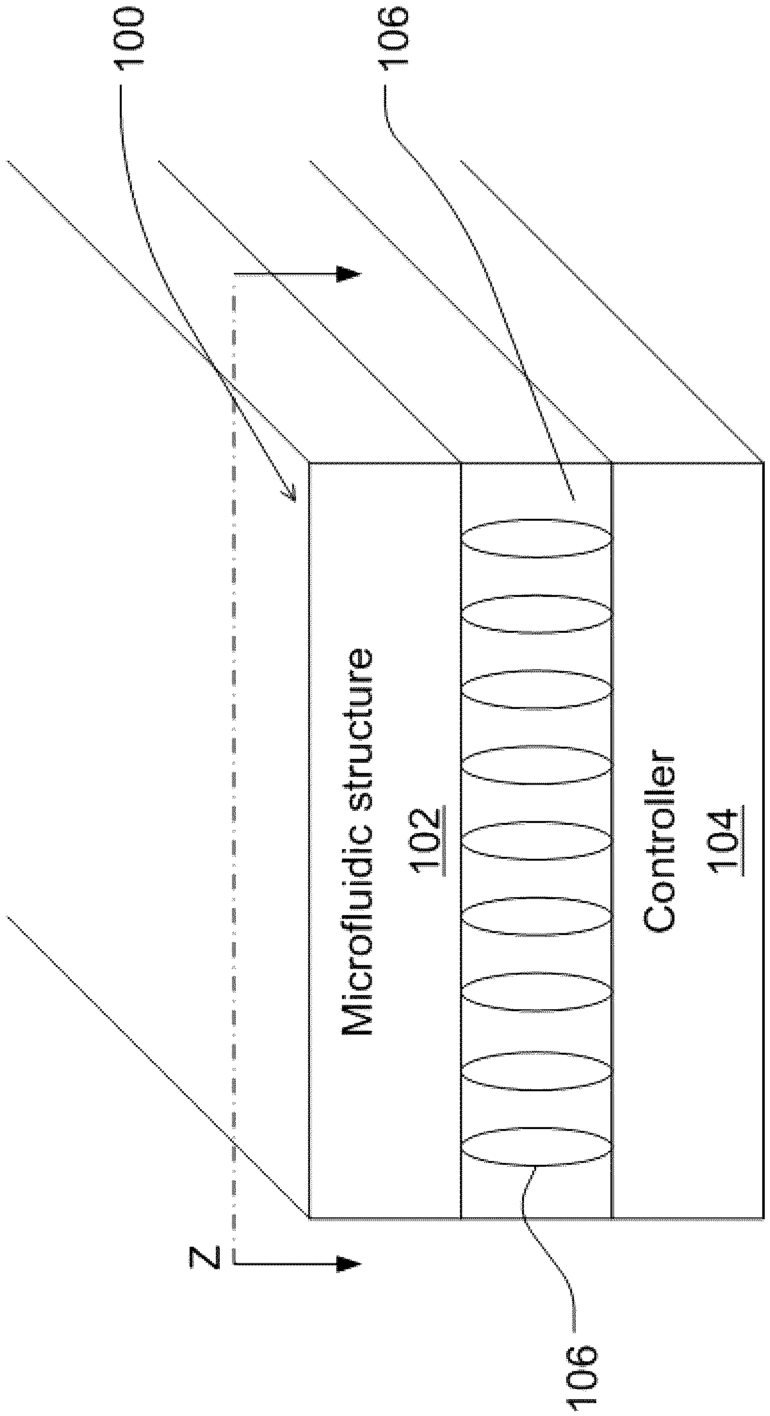


FIG.1

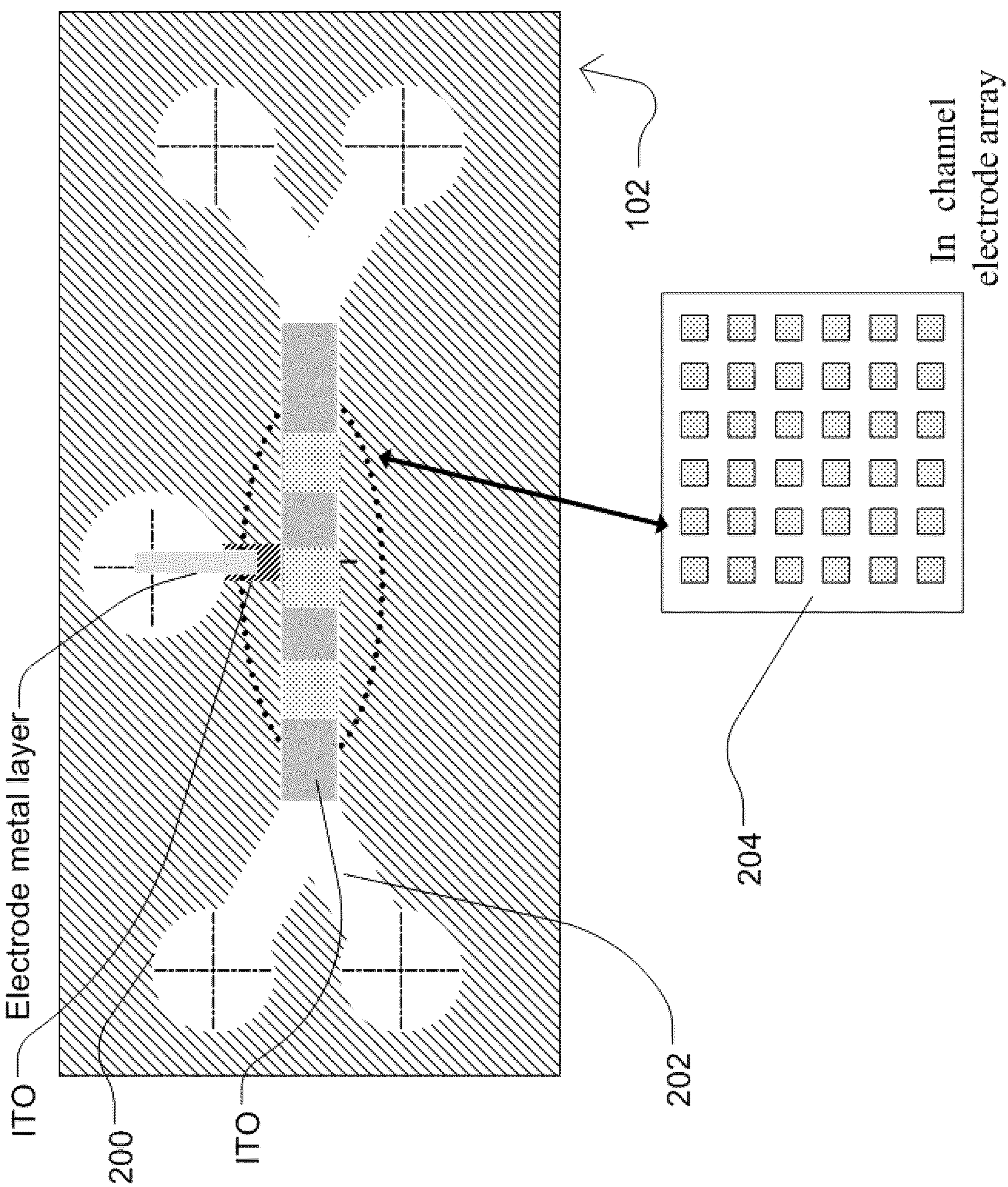

Electrode metal layer
ITO
200
ITO
202
102
204
In channel
electrode array

FIG 2

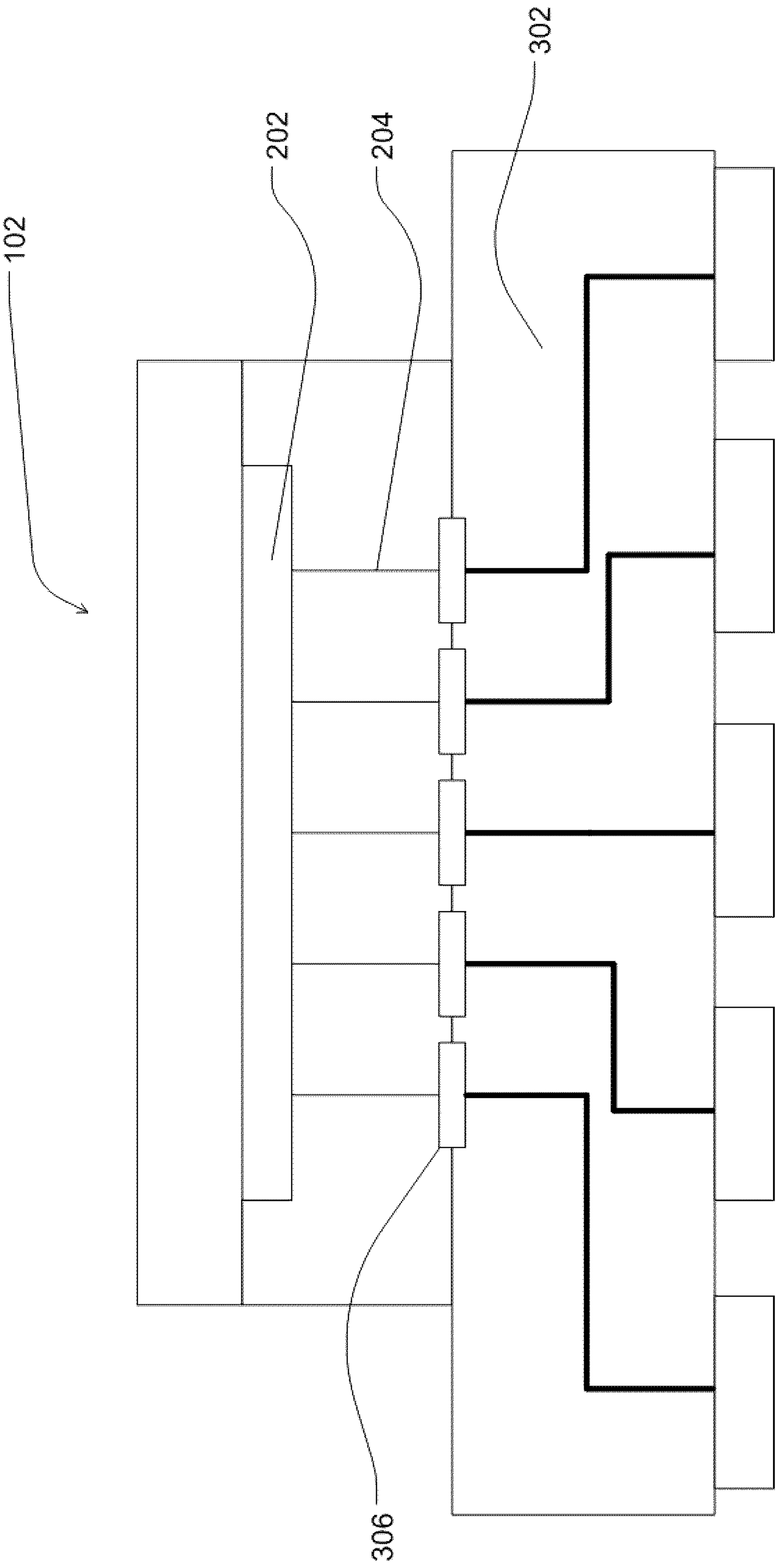


FIG.3A

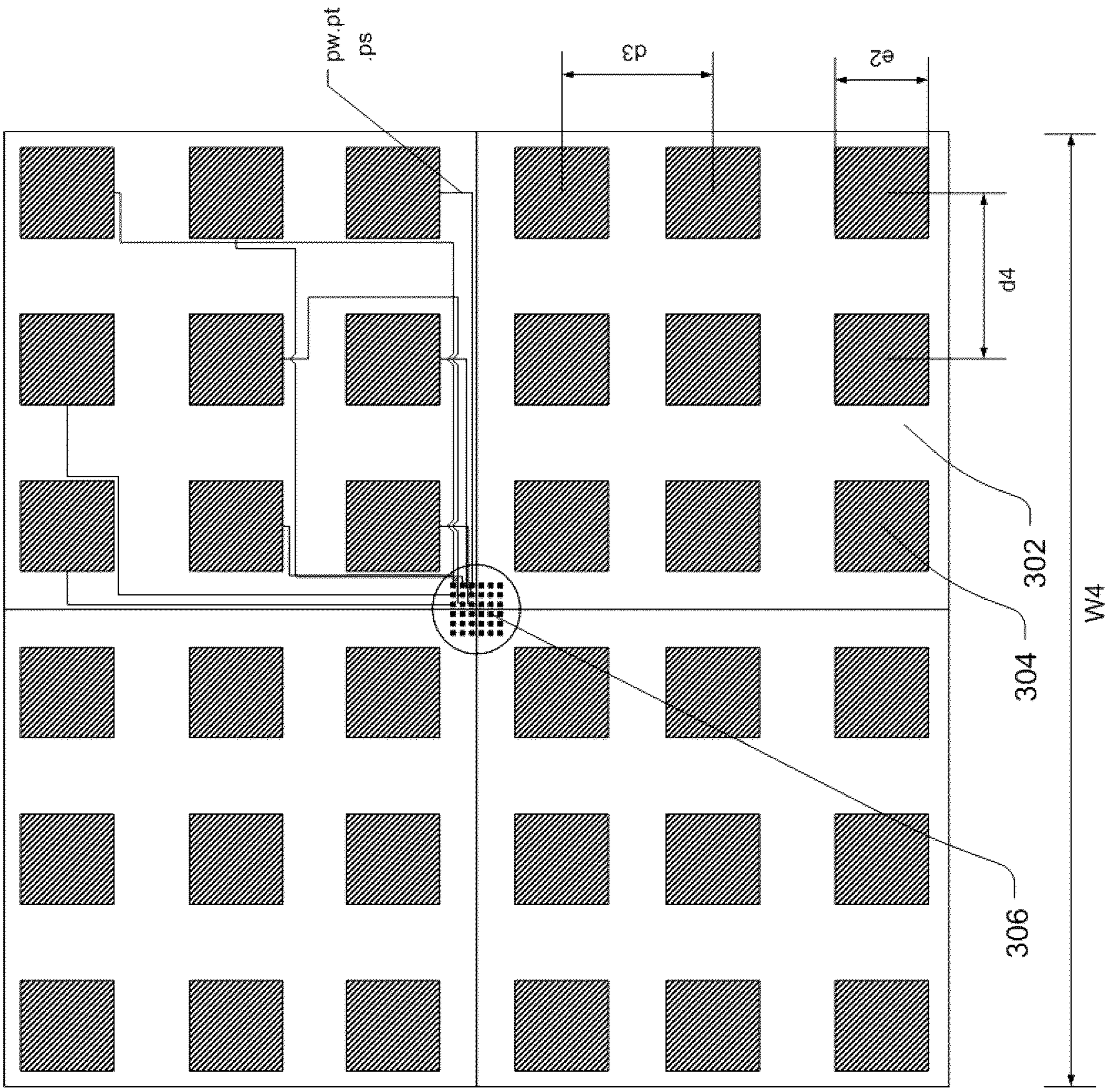


FIG.3B

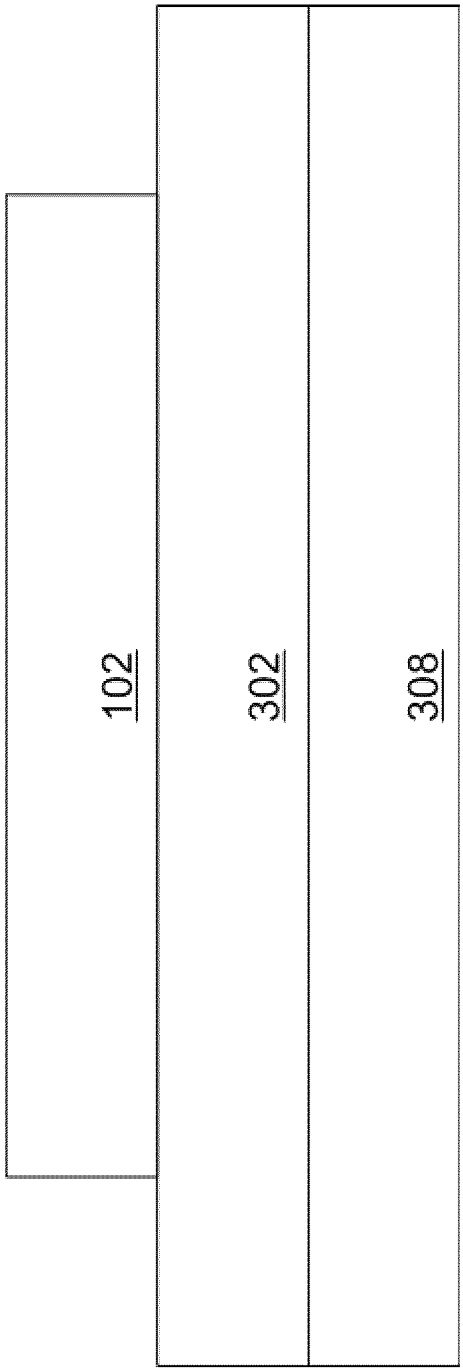
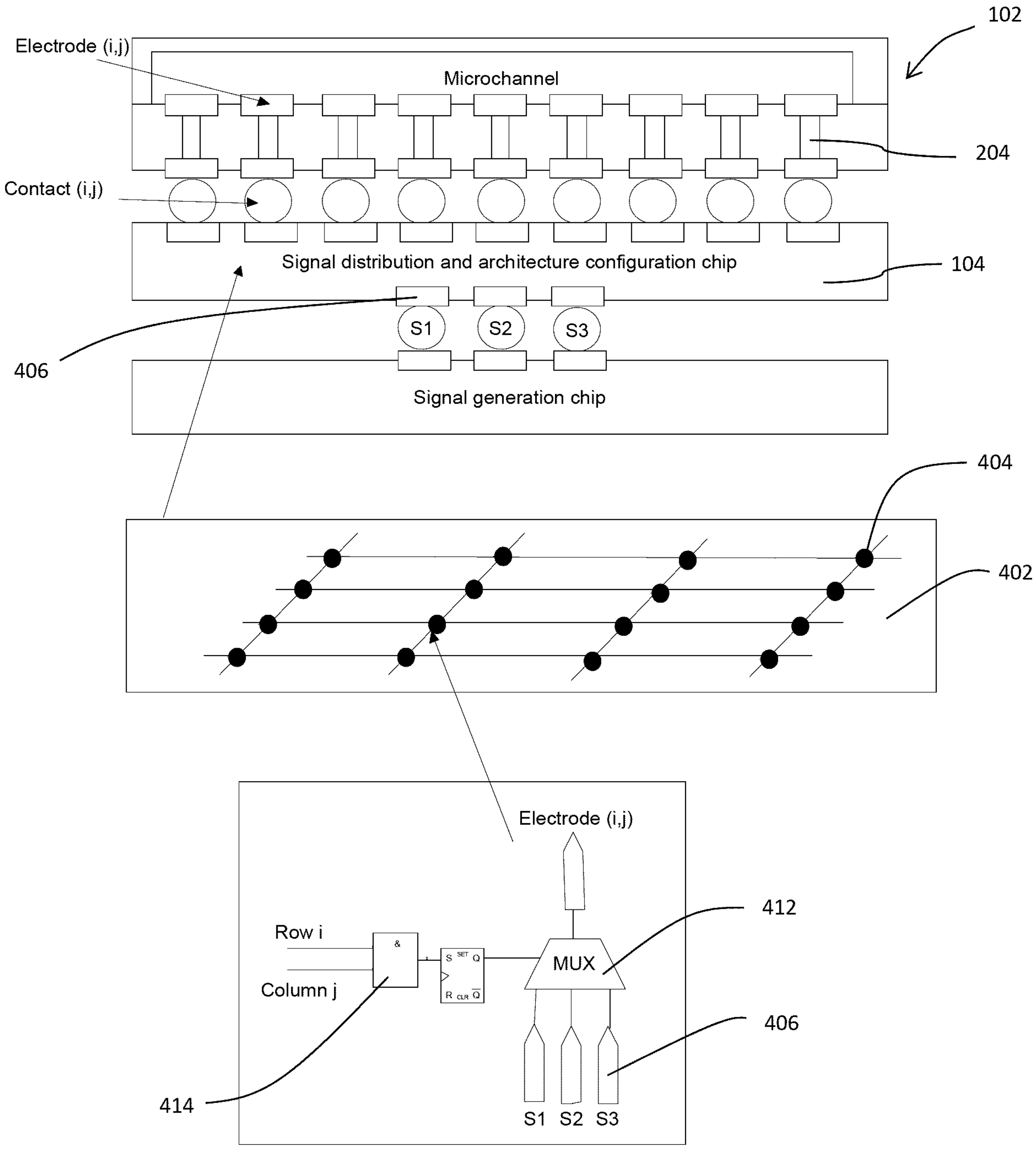


FIG.3C



102
Electrode (i,j)
Microchannel
204
Contact (i,j)
Signal distribution and architecture configuration chip
104
406
S1
S2
S3
Signal generation chip
404
402
Electrode (i,j)
412
Row i
&
S SET Q
R CLR Q
MUX
Column j
406
414
S1 S2 S3

FIG.4A

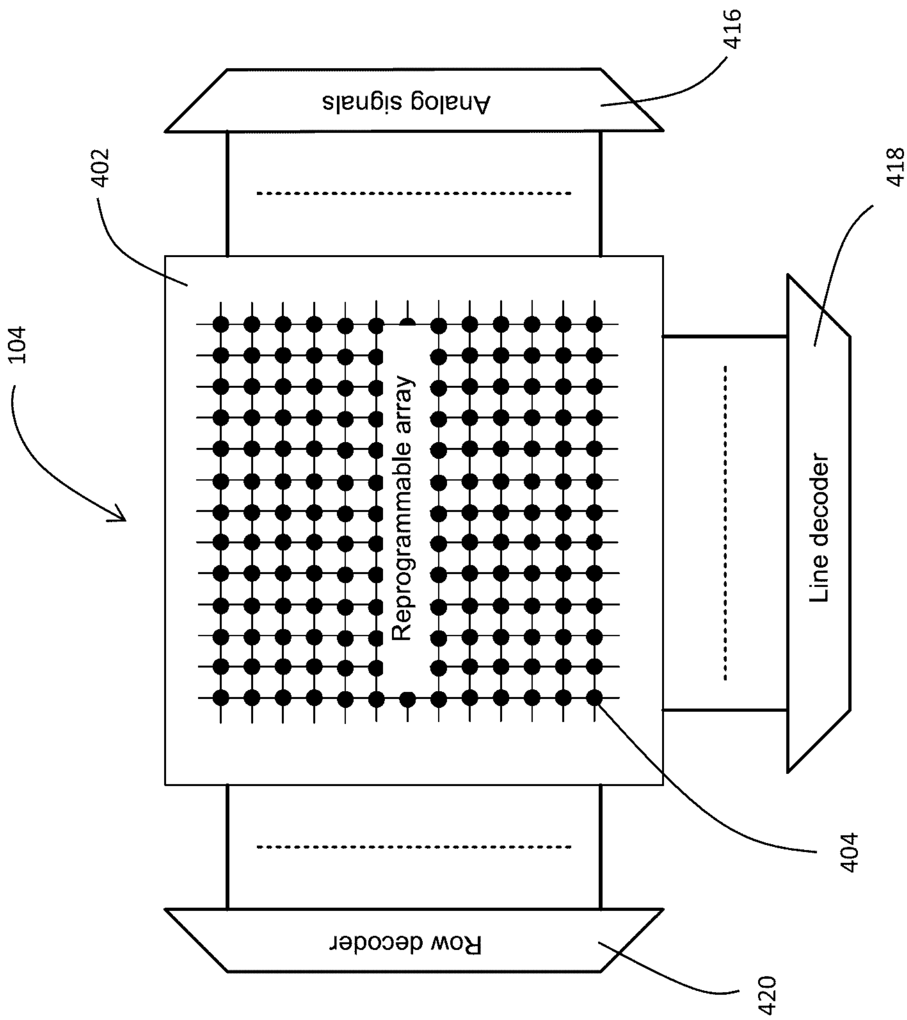

Analog signals
416
402
418
104
Reprogrammable array
Line decoder
404
Row decoder
420

FIG.4B

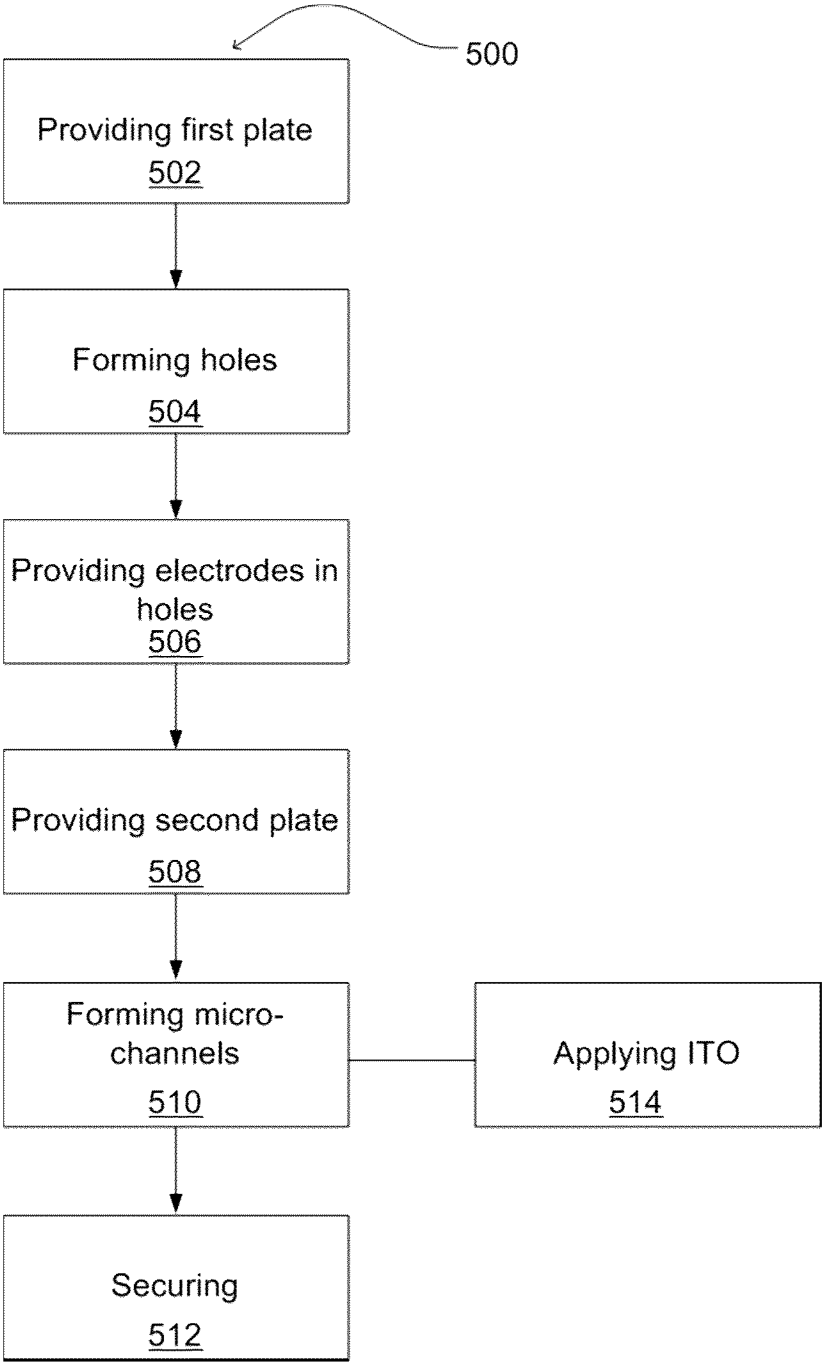

500
Providing first plate
502
Forming holes
504
Providing electrodes in holes
506
Providing second plate
508
Forming micro-channels
510
Applying ITO
514
Securing
512

FIG.5

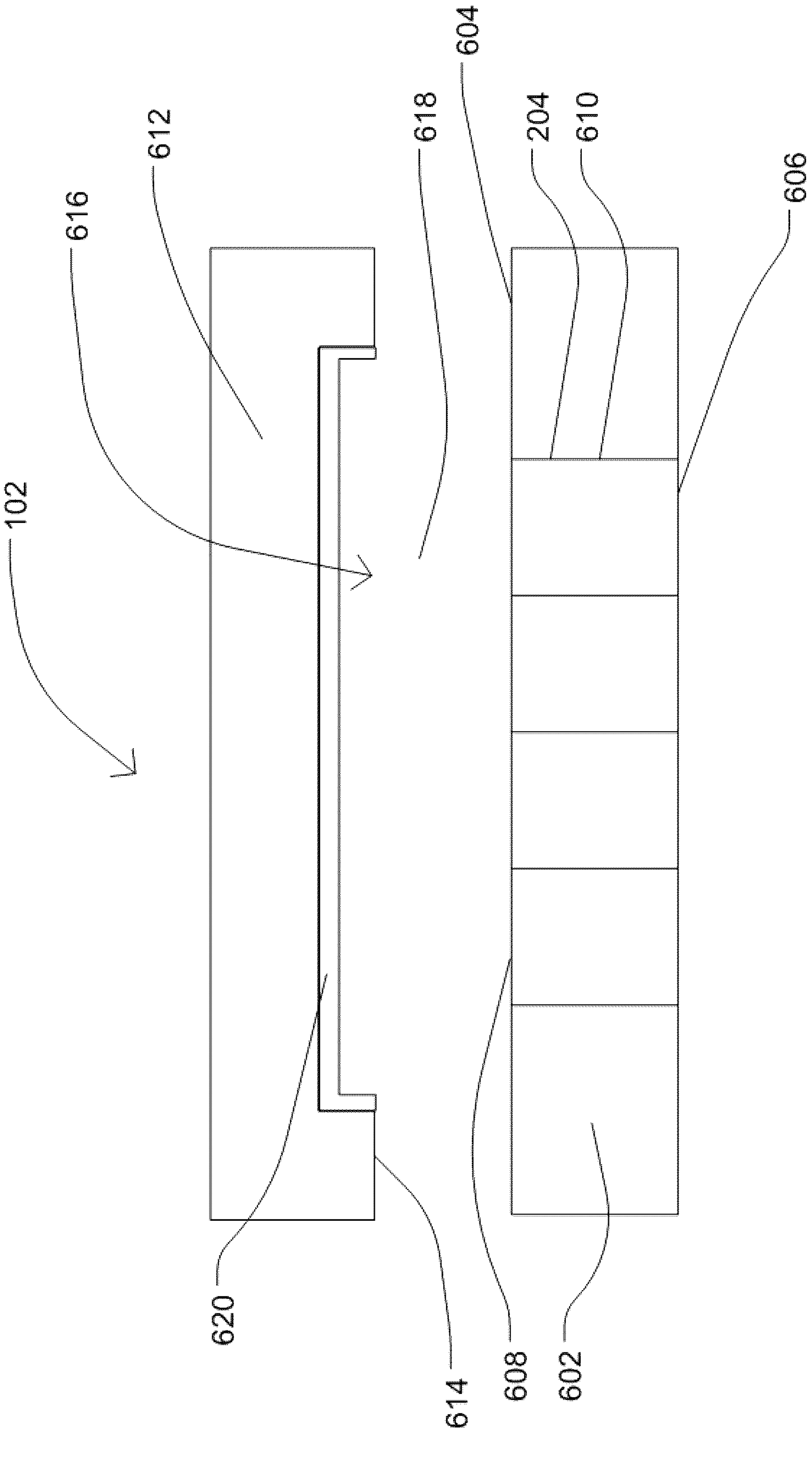


FIG.6A

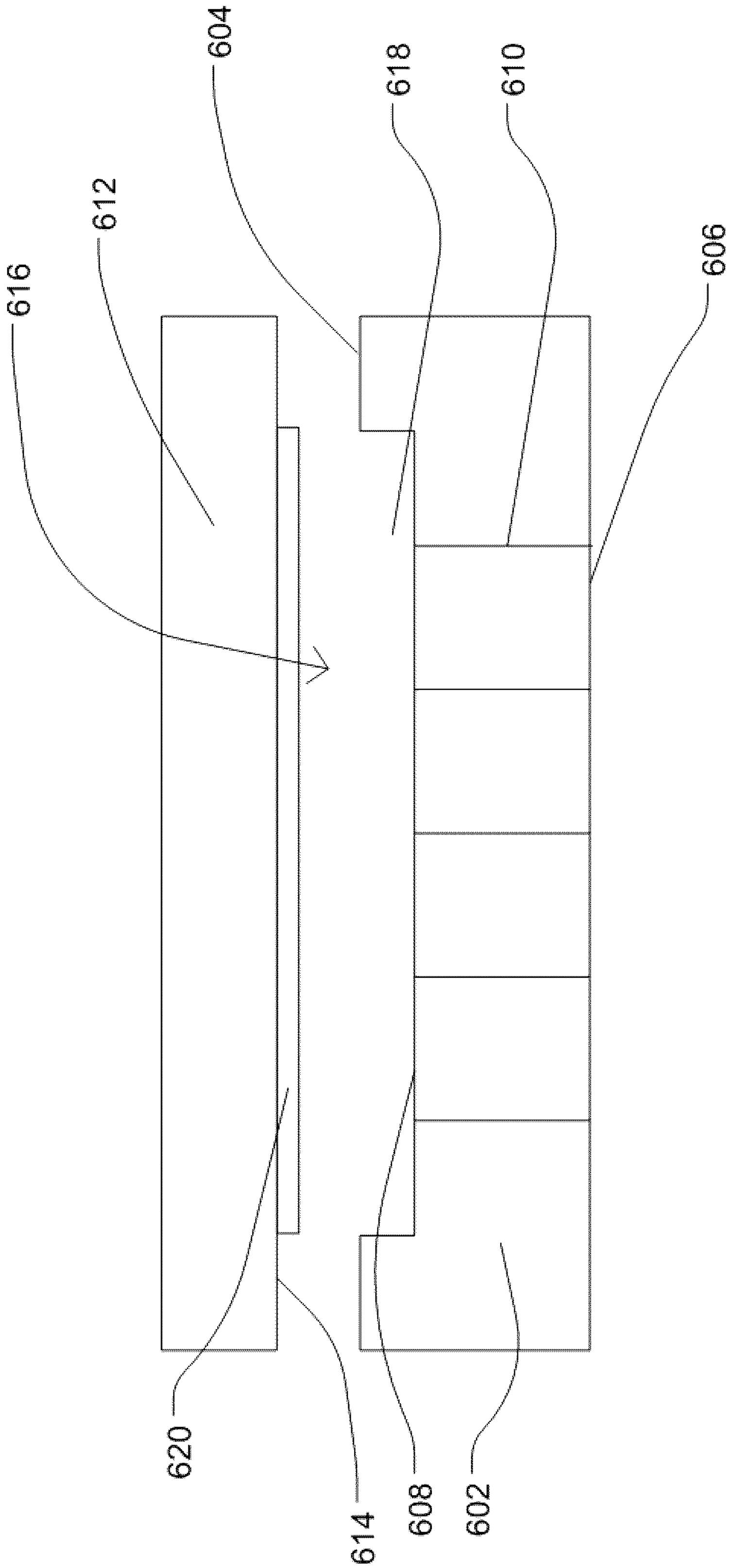


FIG.6B

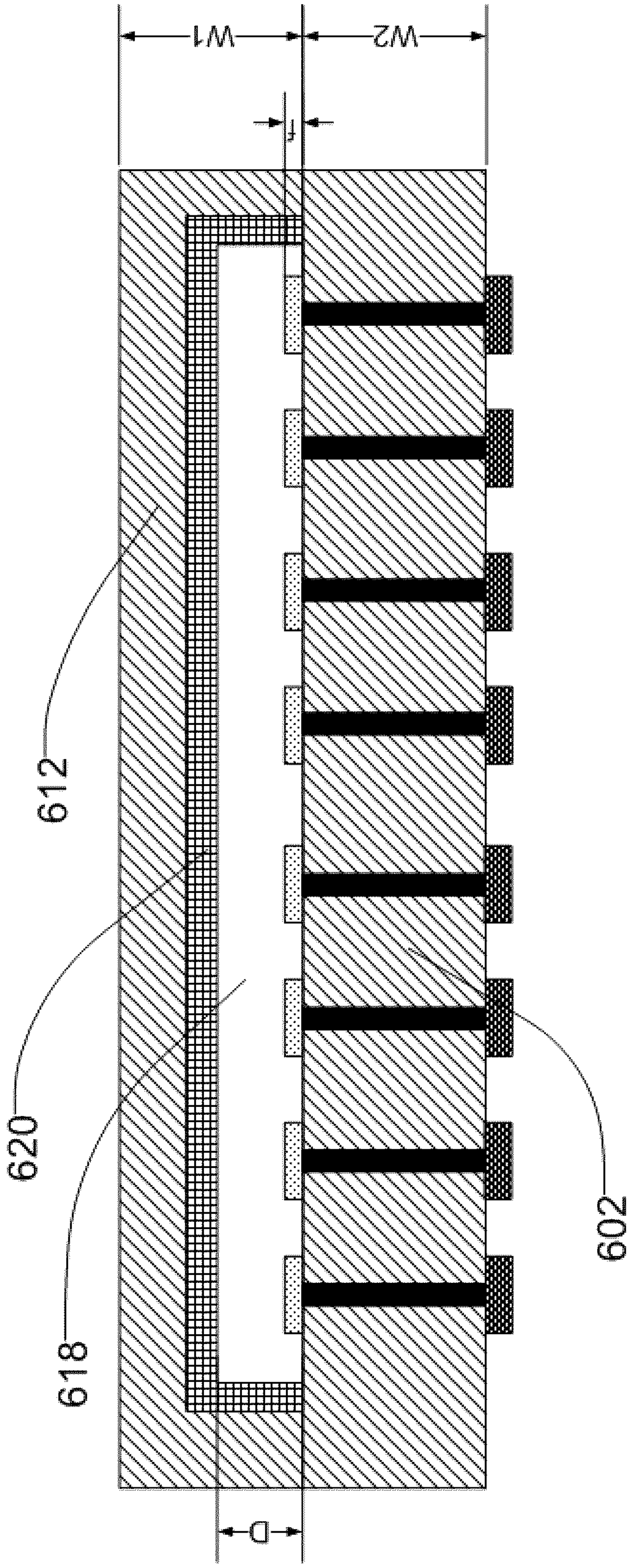


FIG.6C

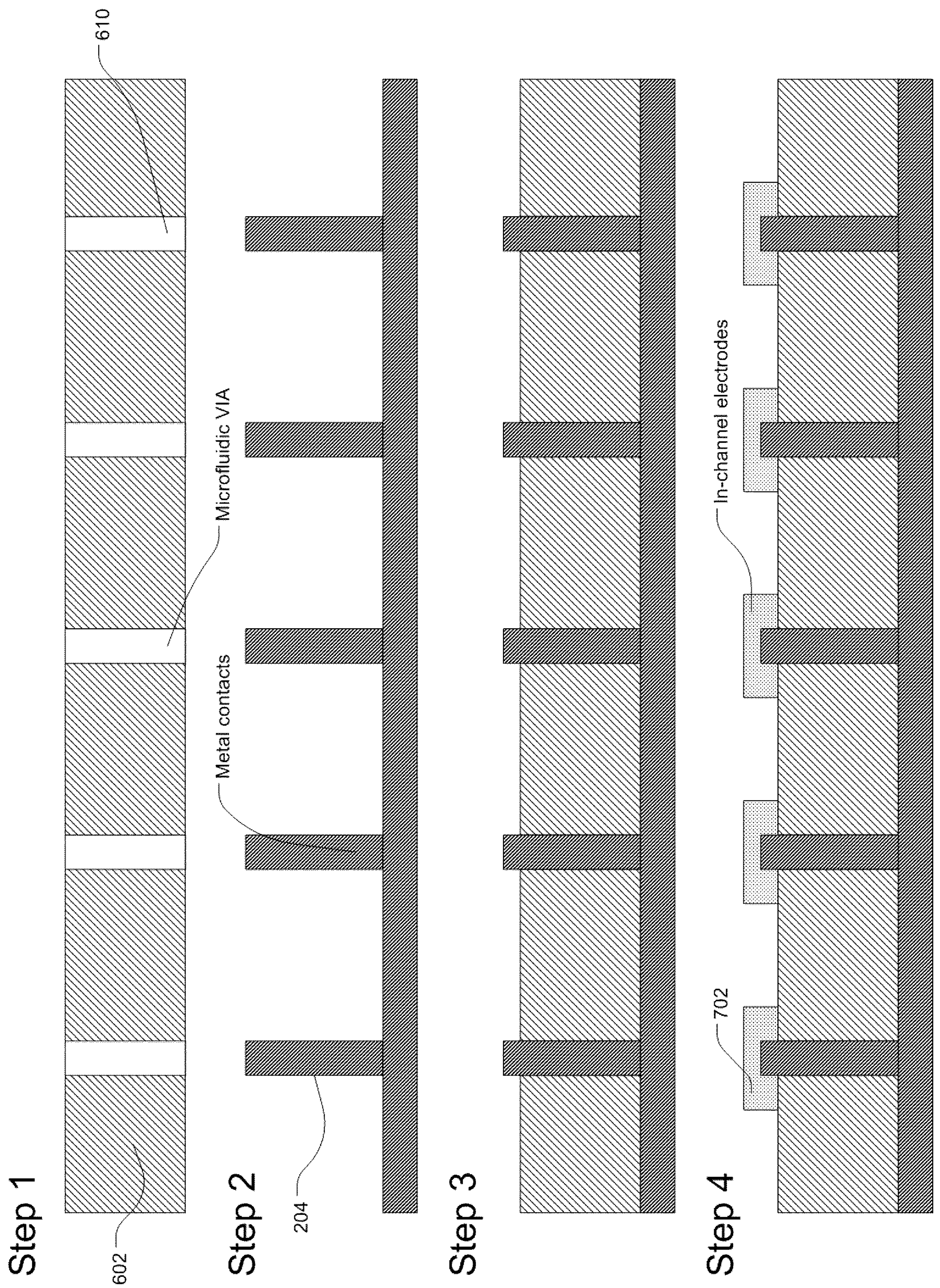

Step 1
610
602
Microfluidic VIA
Step 2
Metal contacts
204
Step 3
Step 4
In-channel electrodes
702

FIG.7A

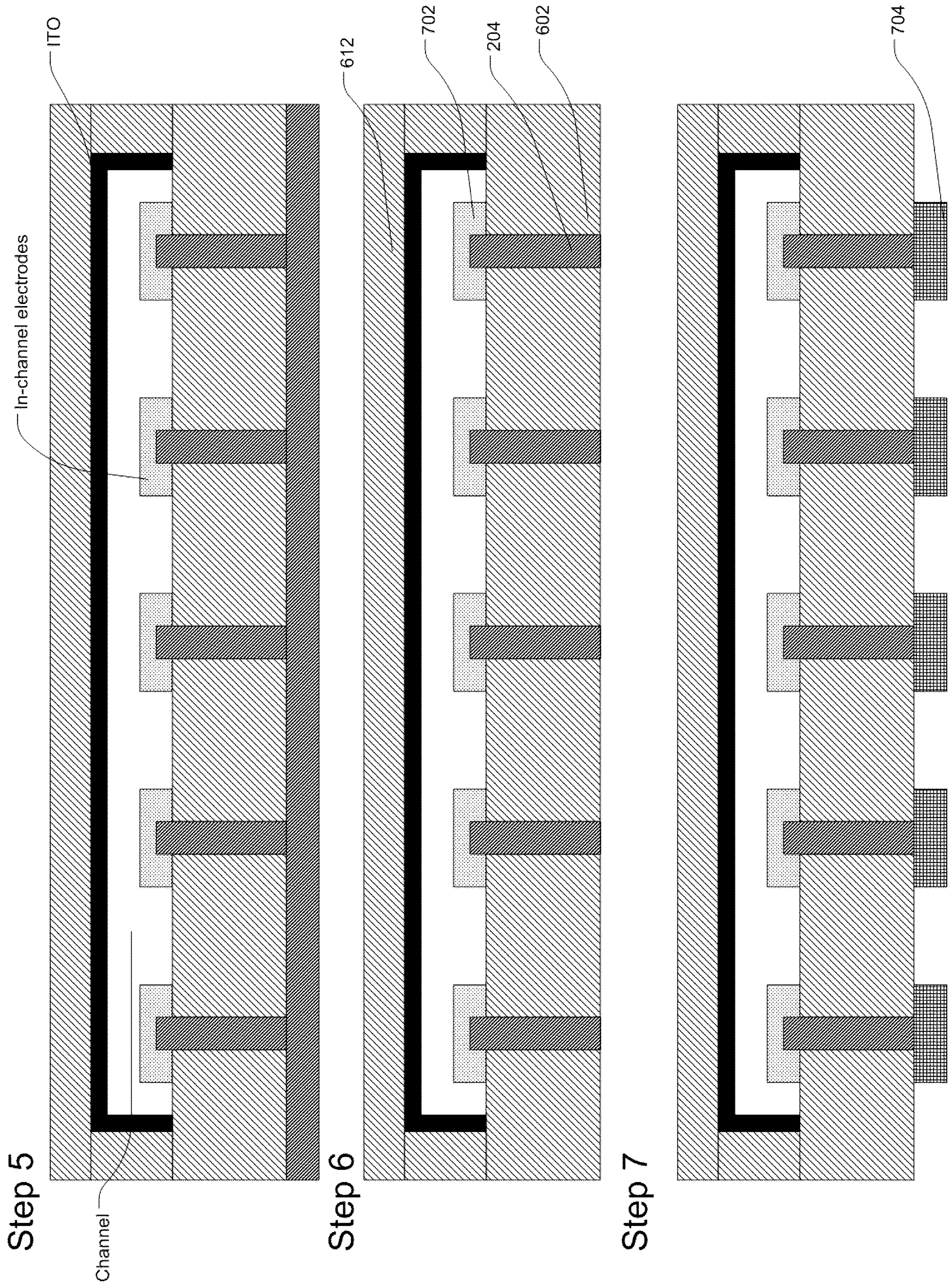

Step 5
ITO
In-channel electrodes
Channel
Step 6
612
702
204
602
Step 7
704

FIG.7B

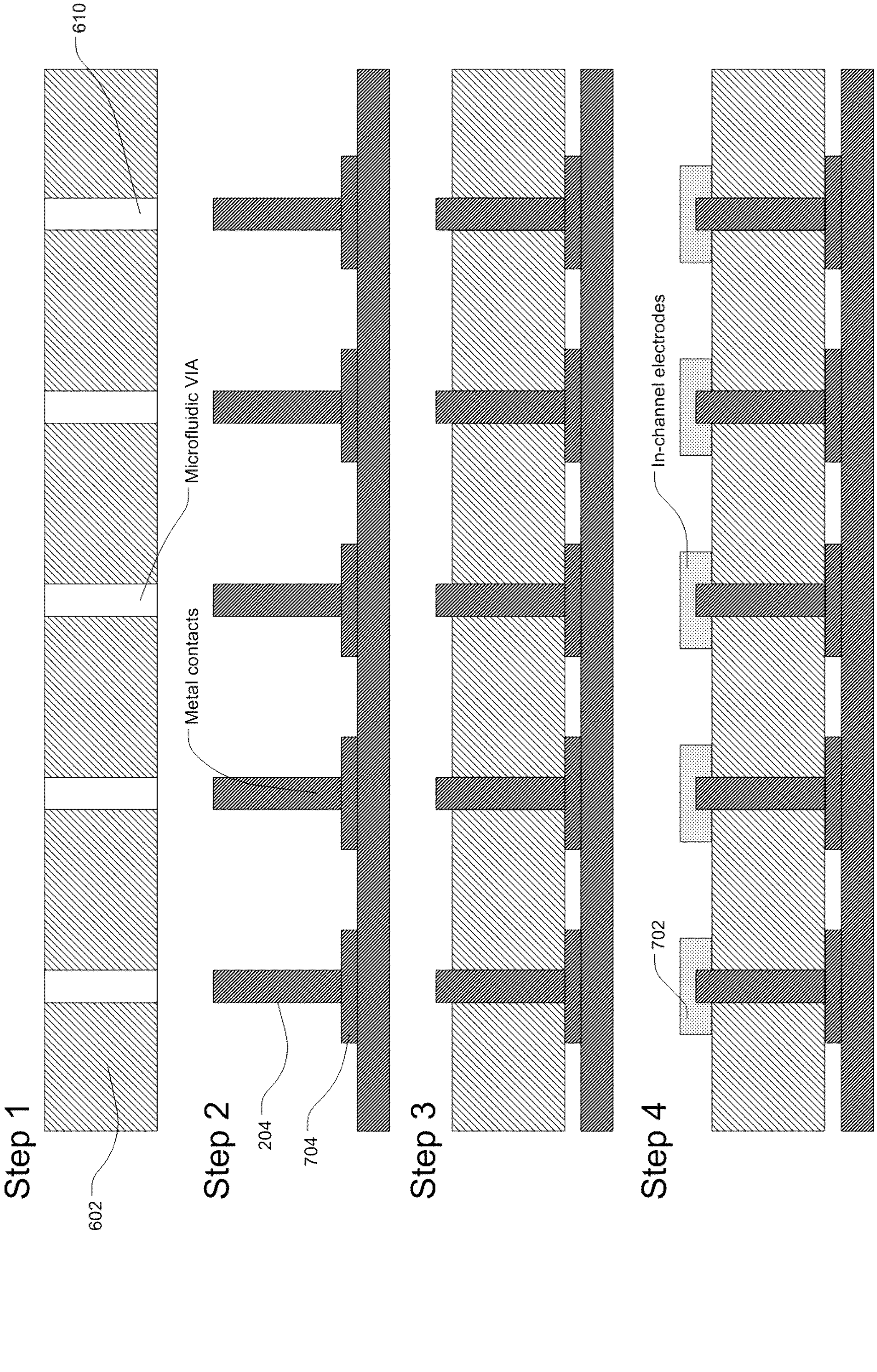

Step 1
Step 2
Step 3
Step 4
610
602
Microfluidic VIA
Metal contacts
204
704
In-channel electrodes
702

FIG.8A

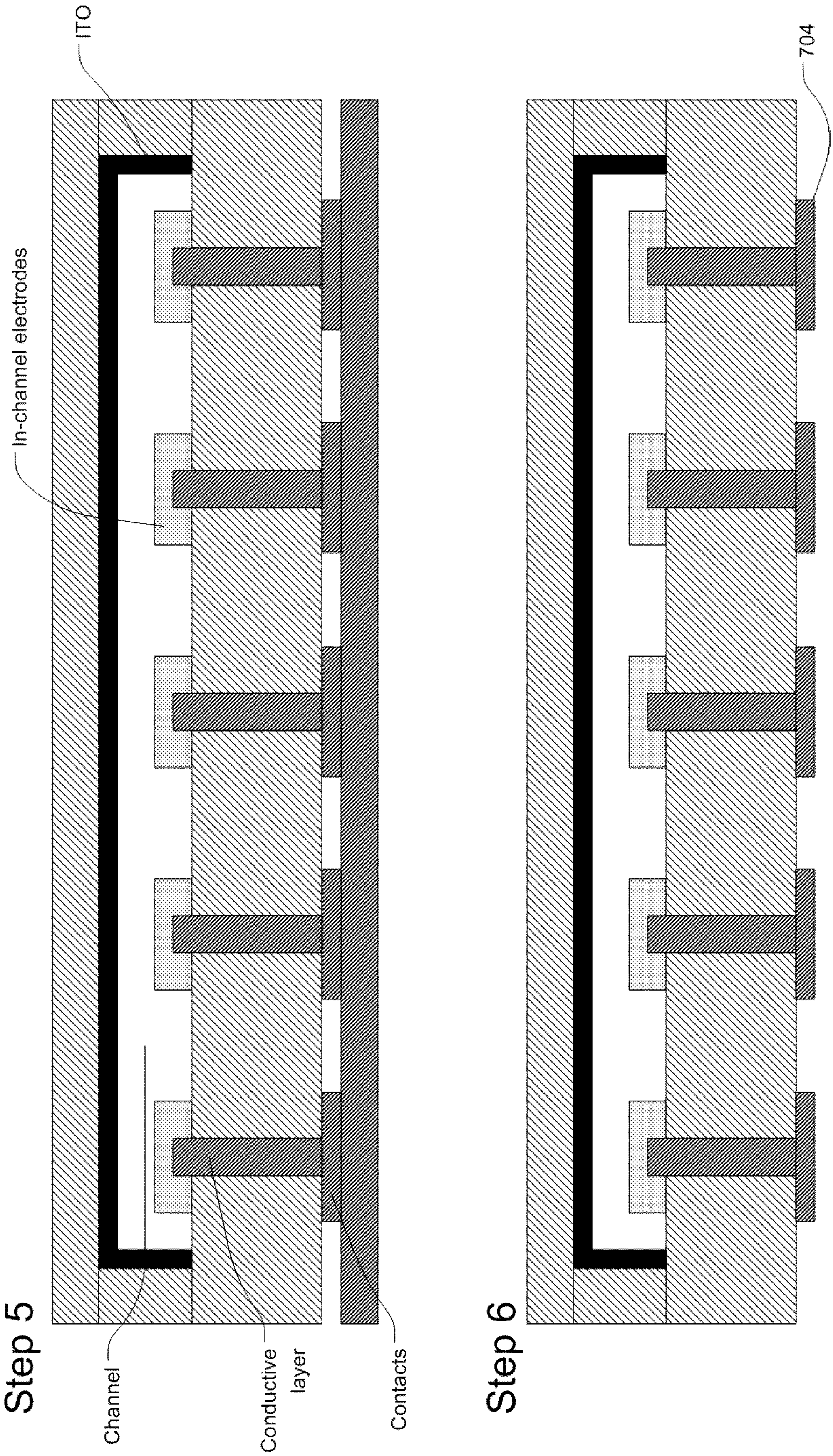

Step 5
ITO
In-channel electrodes
Channel
Conductive layer
Contacts
Step 6
704

FIG.8B

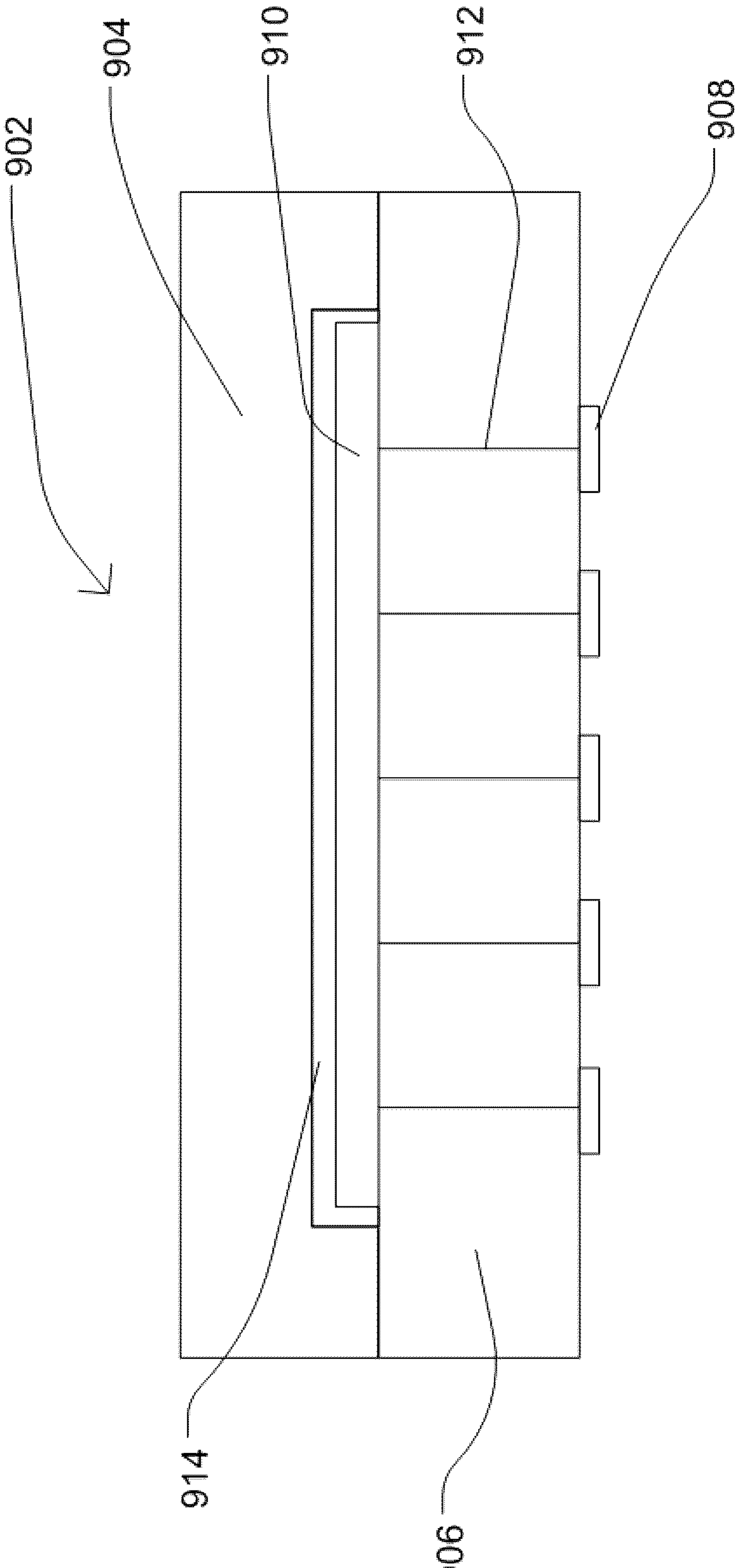


FIG.9A

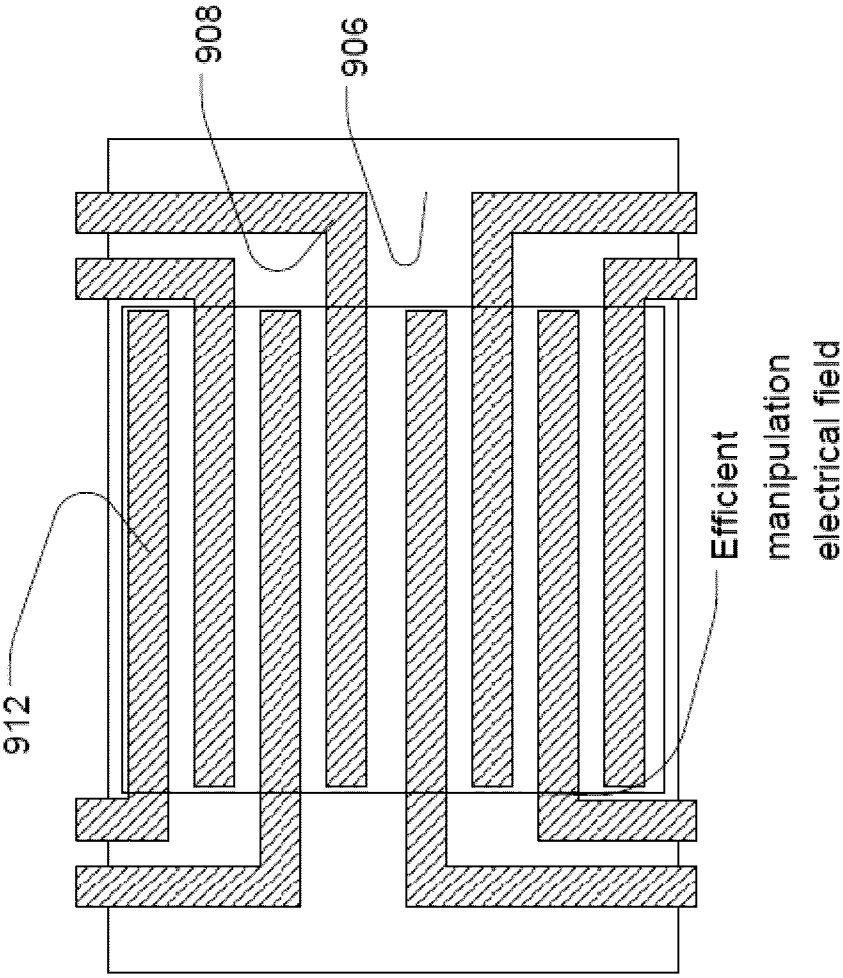


FIG.9B

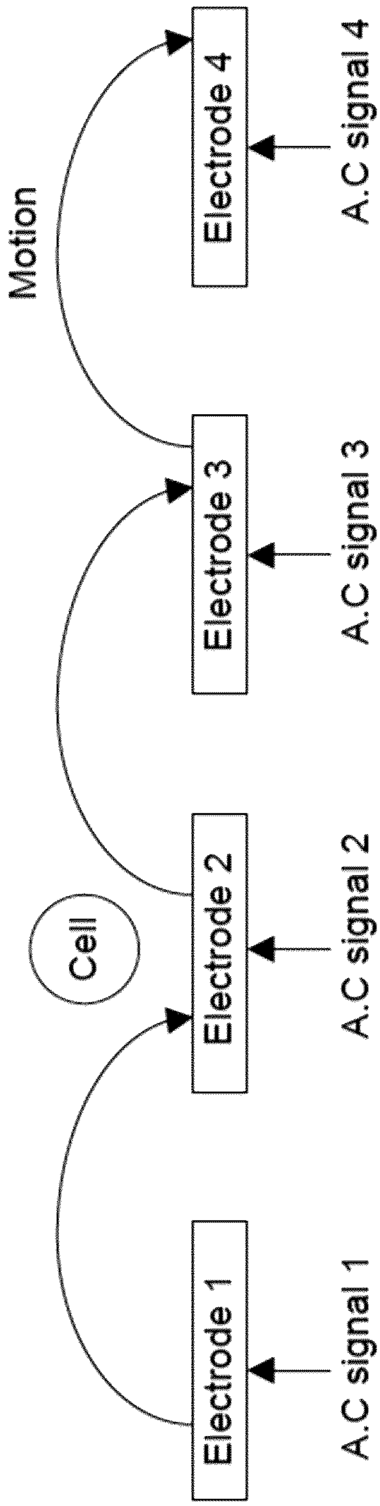

Motion
Electrode 4
Electrode 3
Electrode 2
Electrode 1
Cell
A.C signal 4
A.C signal 3
A.C signal 2
A.C signal 1

FIG.10A

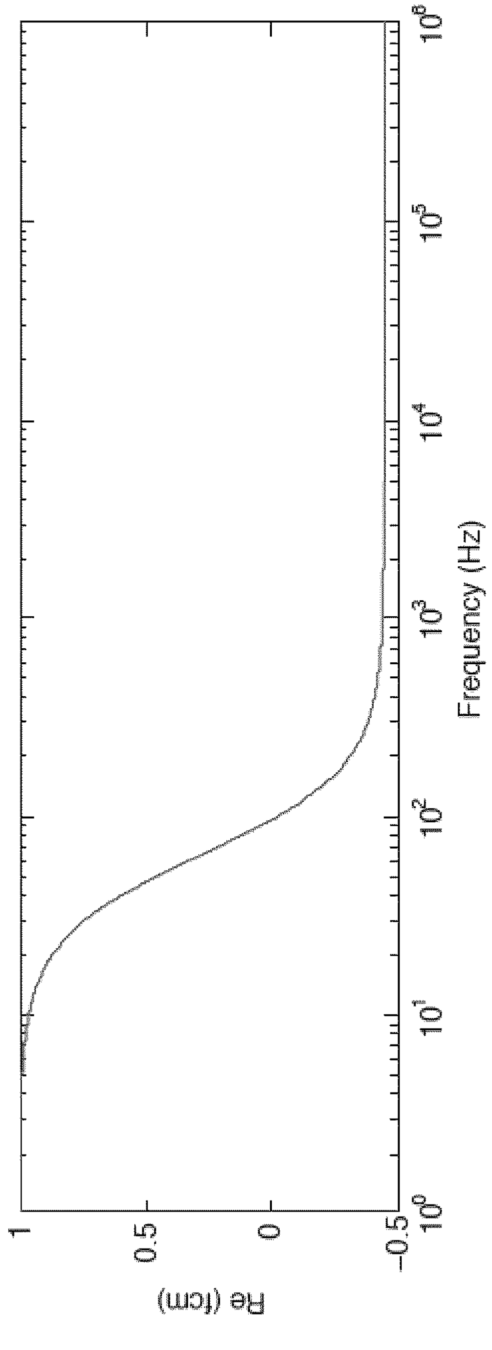


FIG.10B

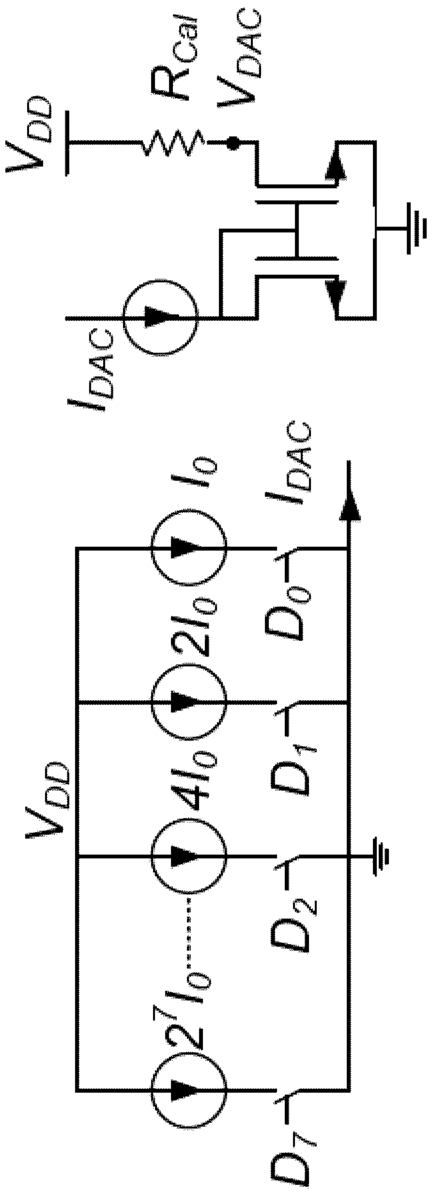


FIG.11

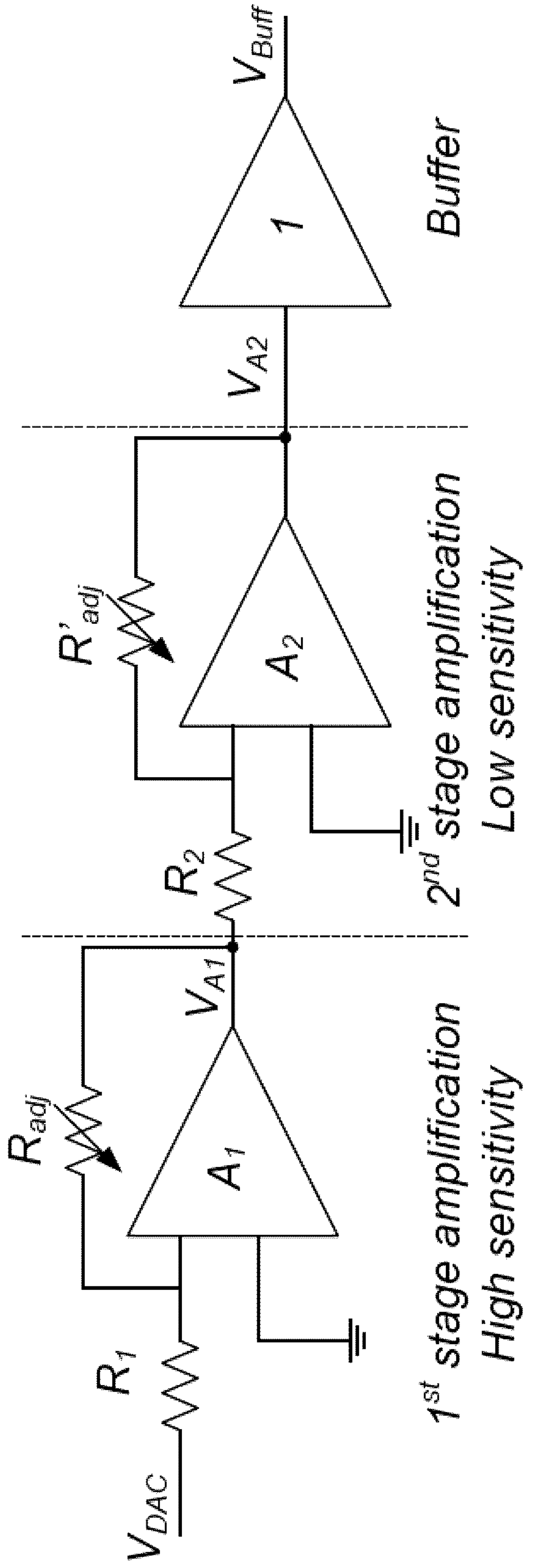

V_{Buff}
1
Buffer
V_{A2}
R'_{adj}
A_2
2^{nd} stage amplification
Low sensitivity
R_2
V_{A1}
R_{adj}
A_1
1^{st} stage amplification
High sensitivity
R_1
V_{DAC}

FIG.12

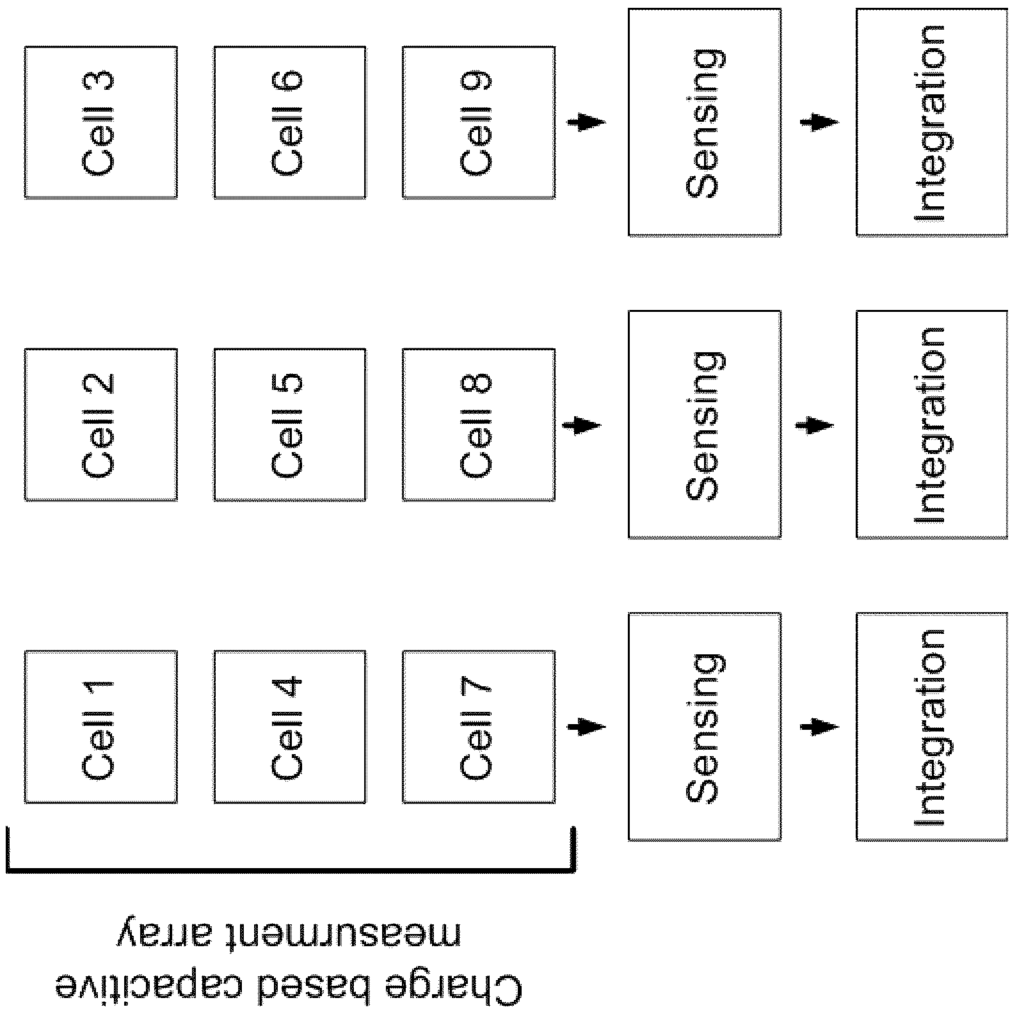

Cell 3
Cell 6
Cell 9
Sensing
Integration
Cell 2
Cell 5
Cell 8
Sensing
Integration
Cell 1
Cell 4
Cell 7
Sensing
Integration
Charge based capacitive measurment array

FIG.13

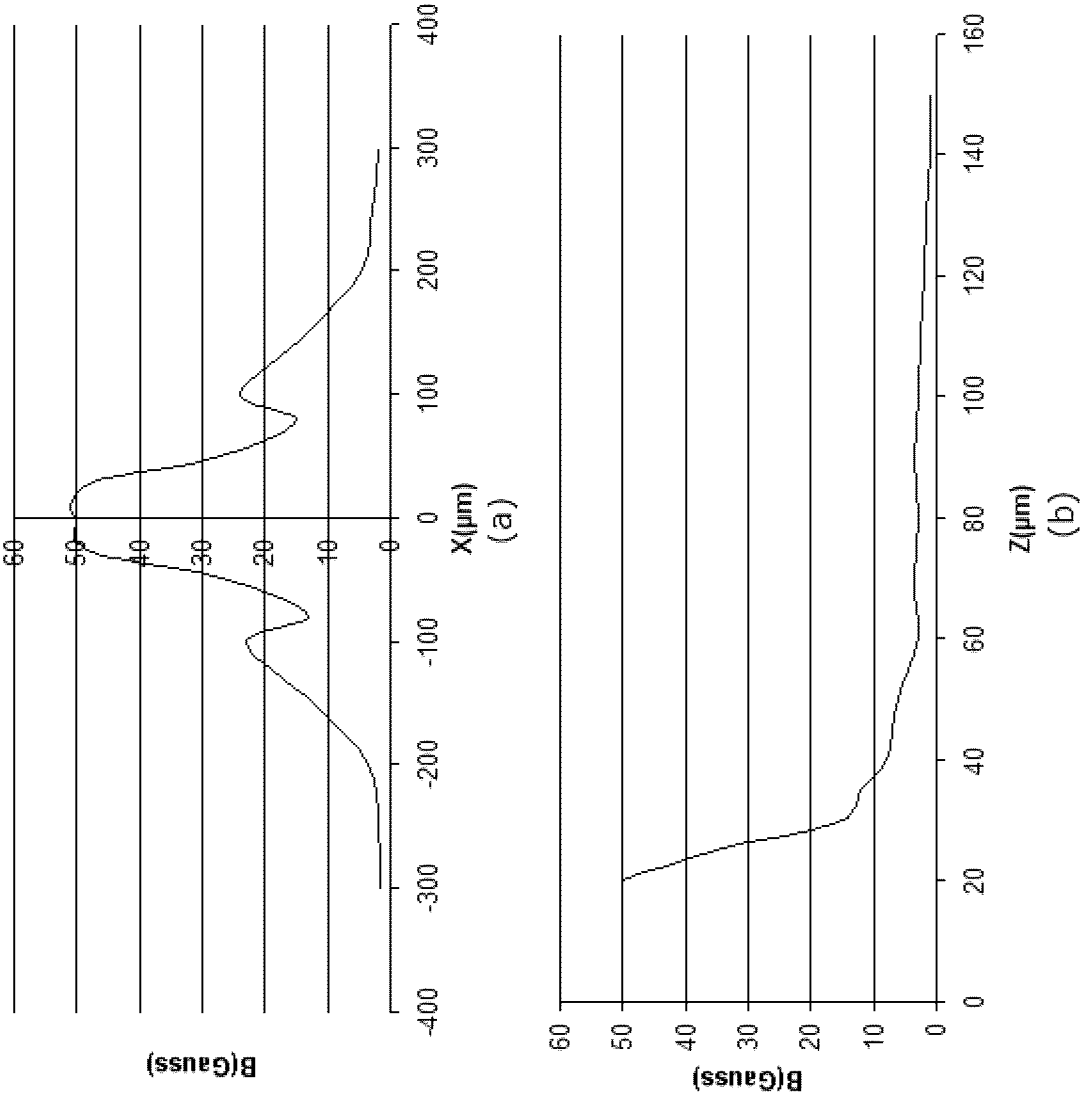

B(Gauss)
60
50
40
30
20
10
0
-400
-300
-200
-100
0
100
200
300
400
X(µm)
(a)
B(Gauss)
60
50
40
30
20
10
0
0
20
40
60
80
100
120
140
160
Z(µm)
(b)

FIG.14

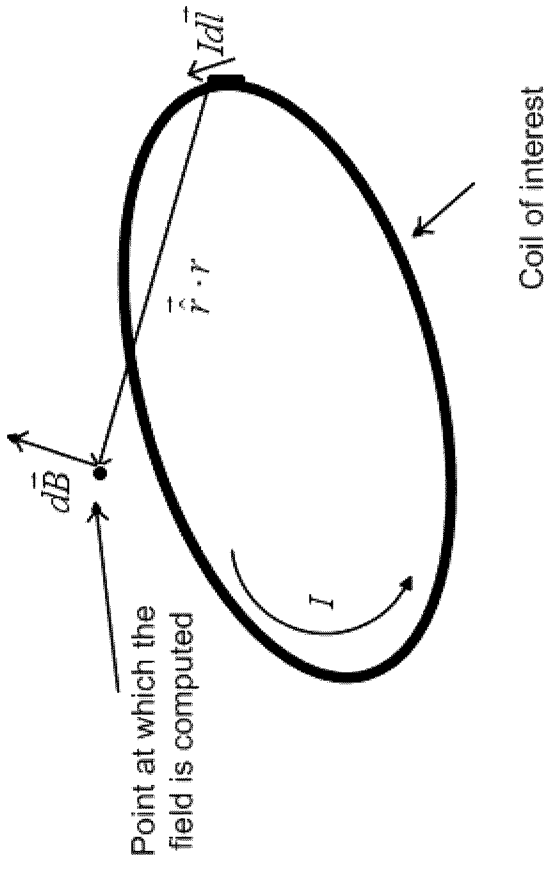

$I\vec{dl}$
$\vec{\hat{r}} \cdot r$
$d\vec{B}$
I
Coil of interest
Point at which the field is computed

FIG.15

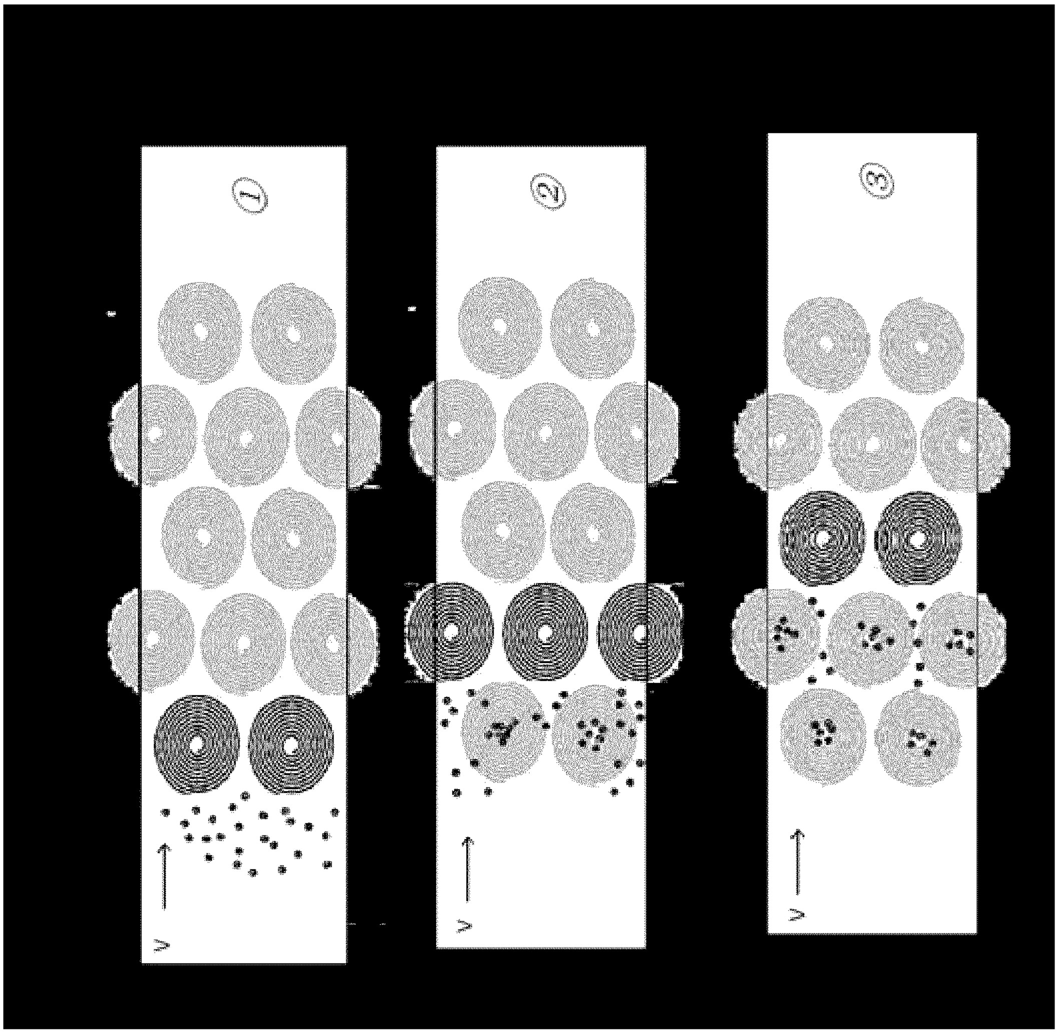


FIG.16

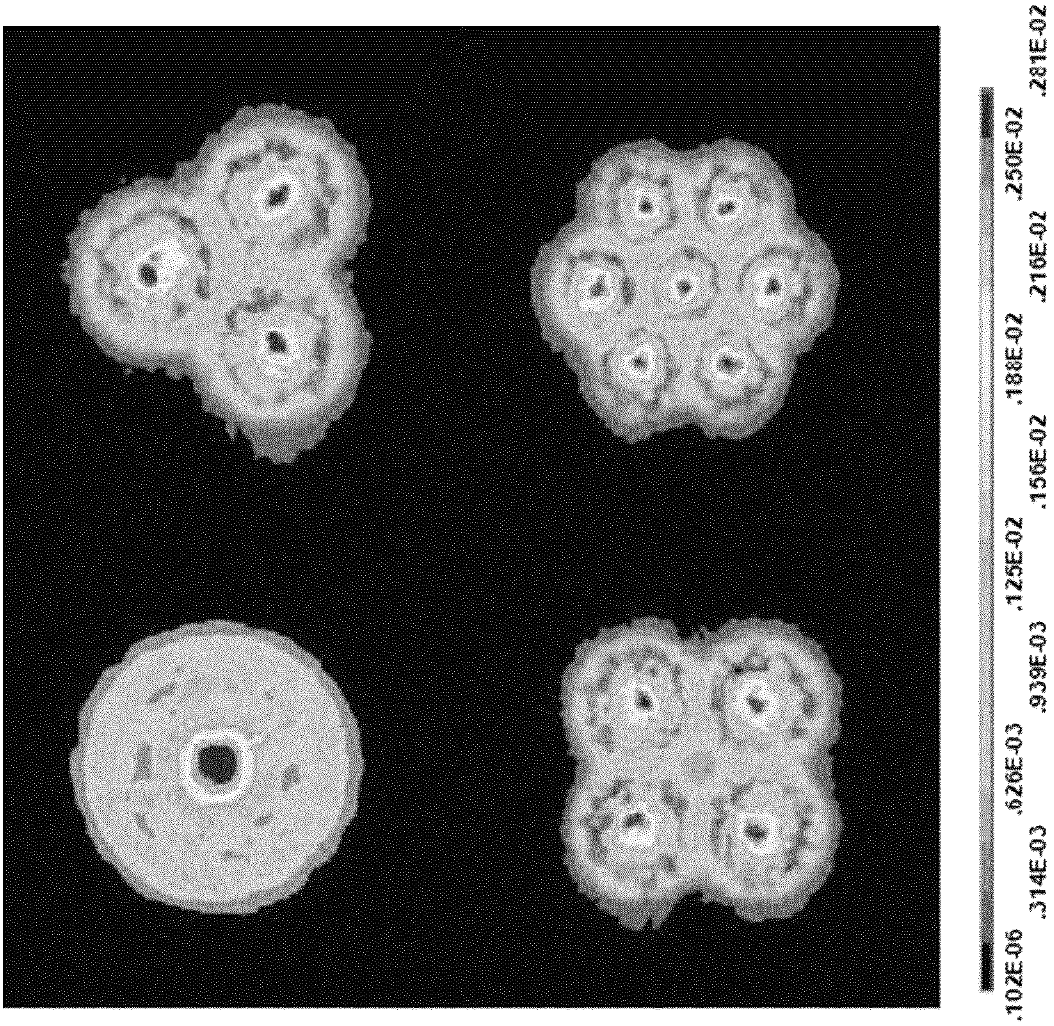

.102E-06
.314E-03
.626E-03
.939E-03
.125E-02
.156E-02
.188E-02
.216E-02
.250E-02
.281E-02

FIG.17

Microcoils array	Maximum **B(**Gauss**)**	Normalized total trapping area	Power consumption(mA)
Single coil	28.1	1	100
Three coils	28.1	1.1	52
Four coils	28.1	1.15	46
Seven coils	28.1	1.21	31

FIG.18

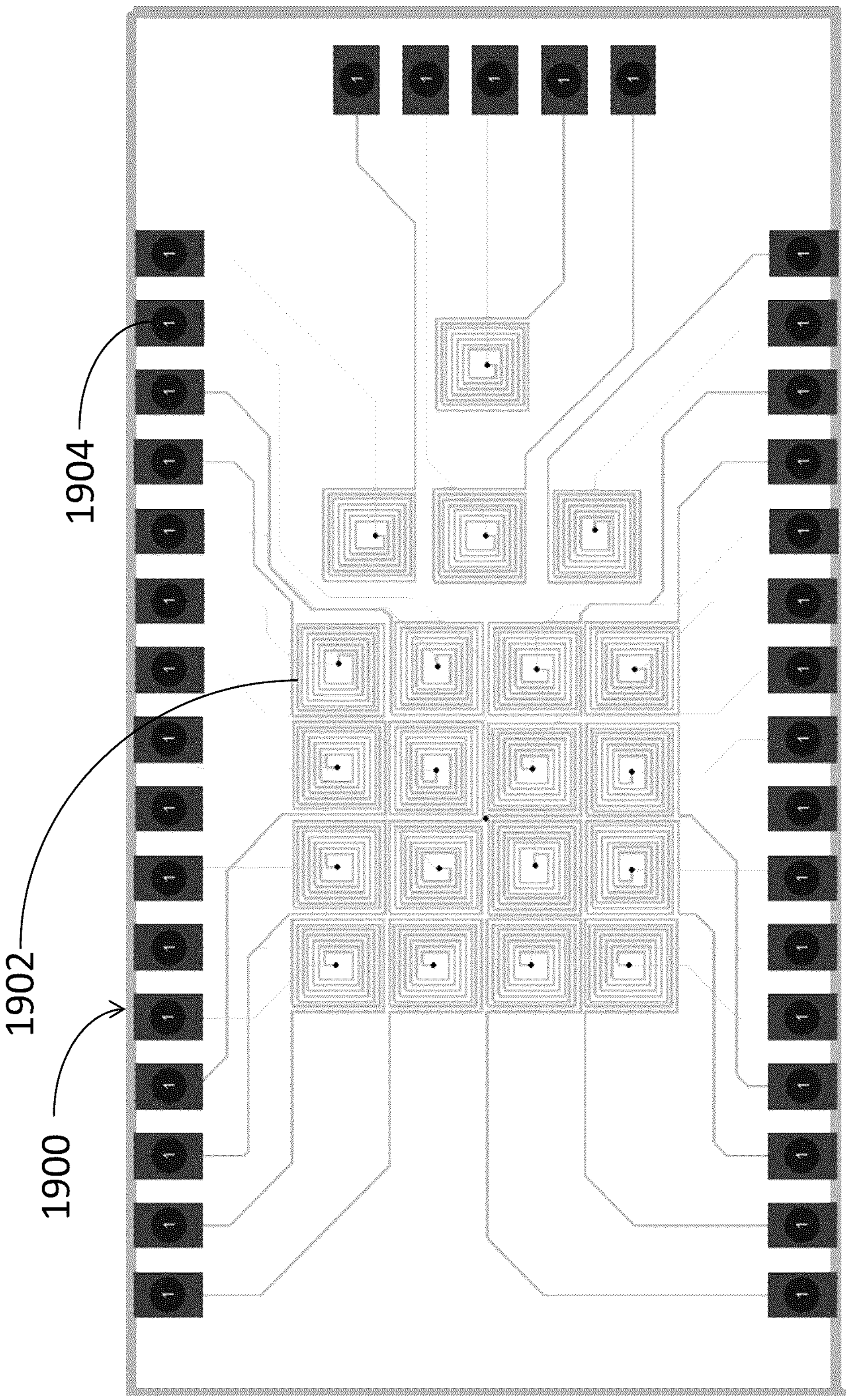


FIG. 19

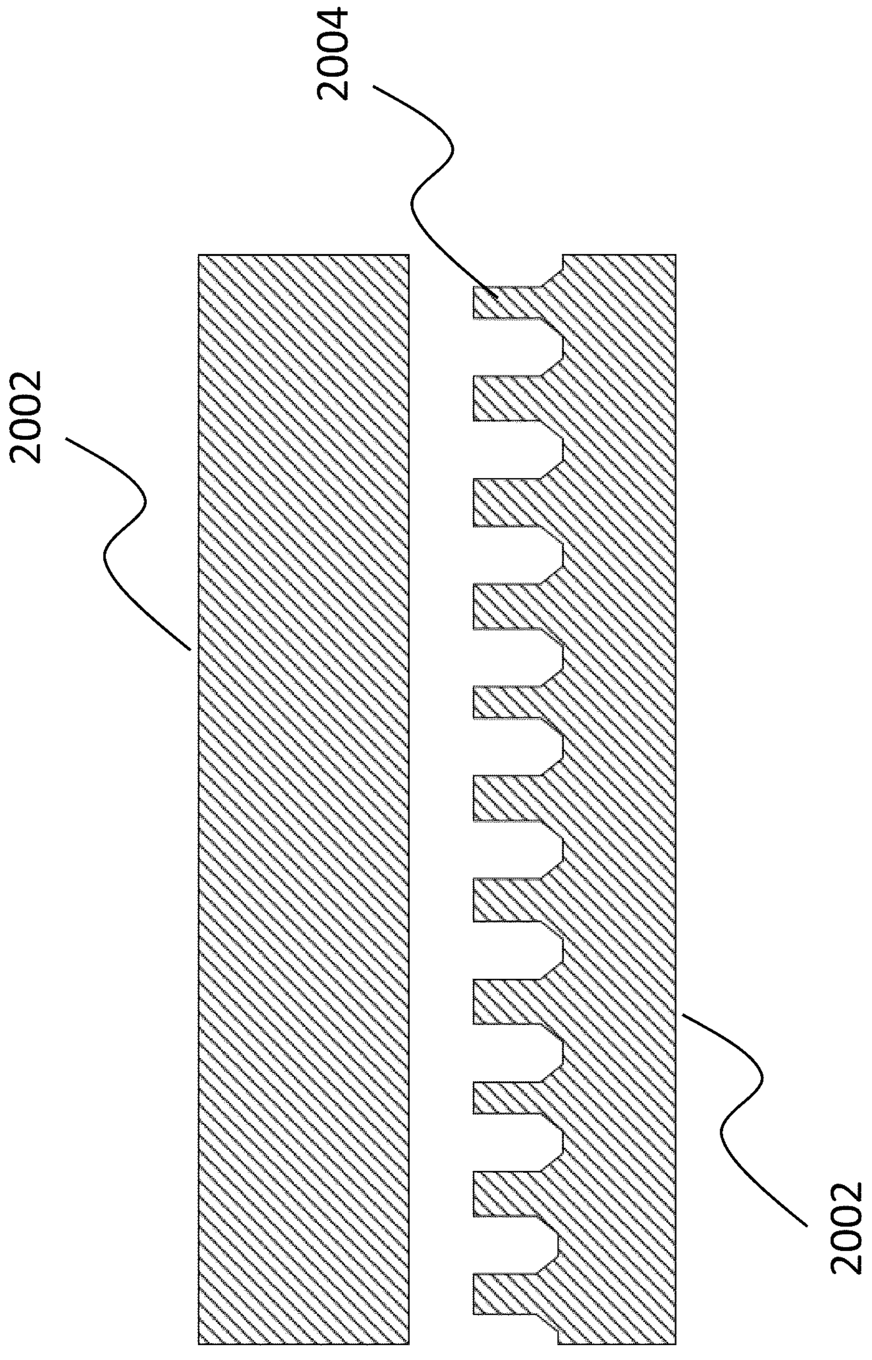


FIG. 20A

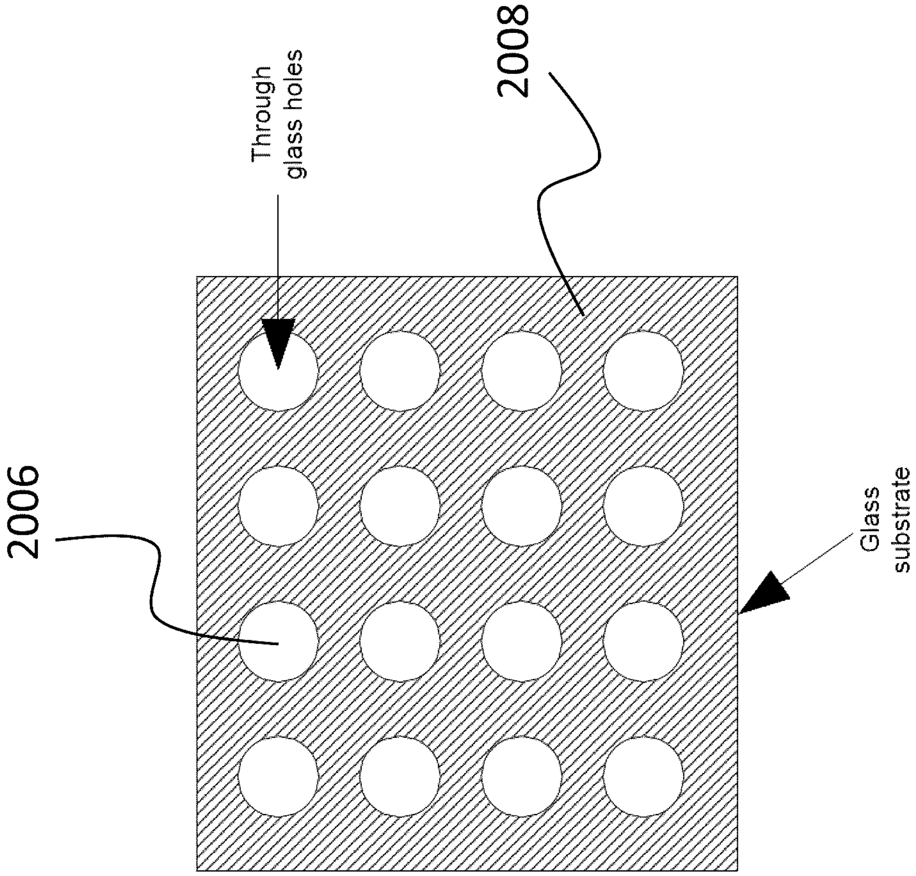


FIG. 20B

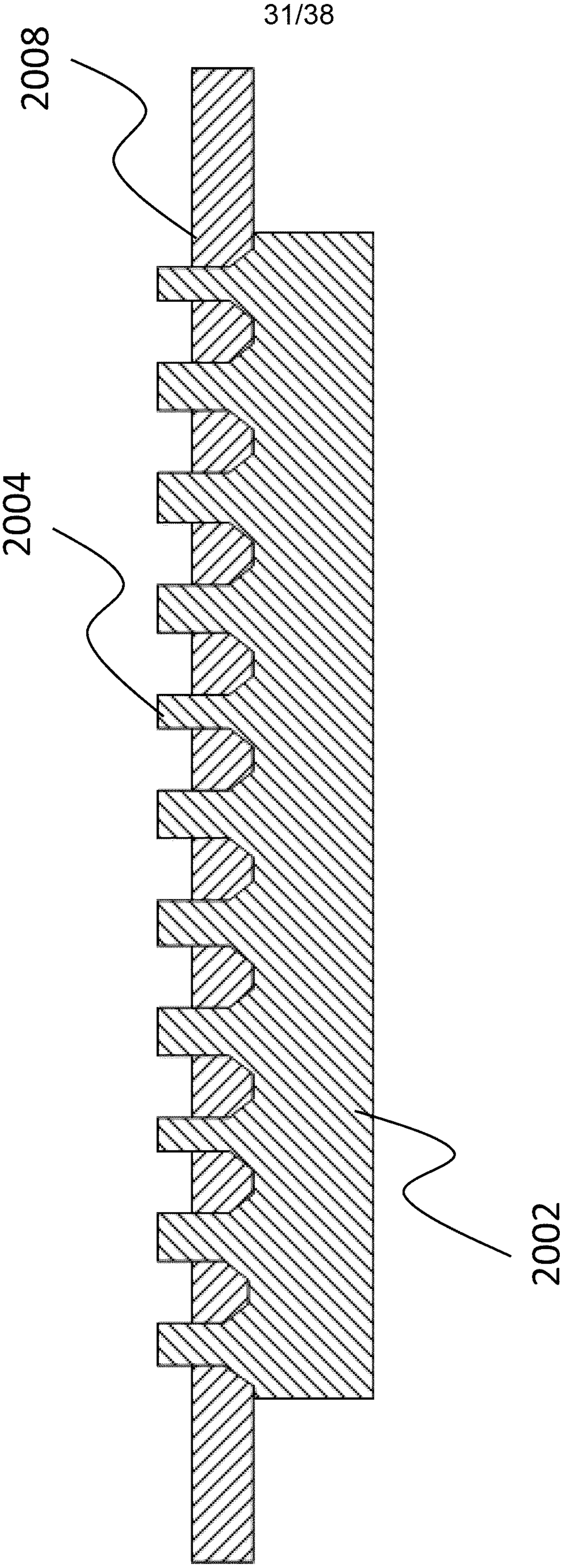


FIG. 20C

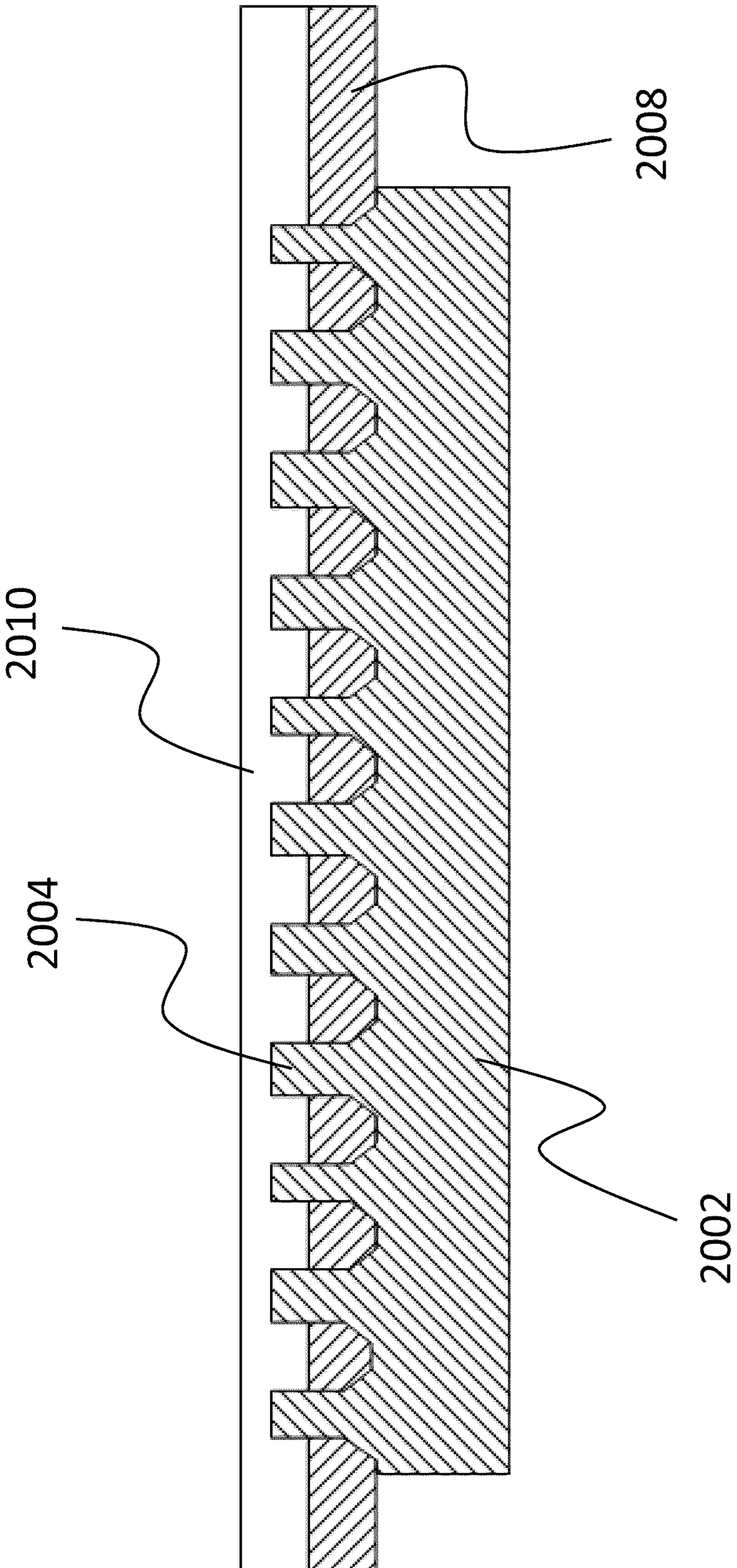


FIG. 20D

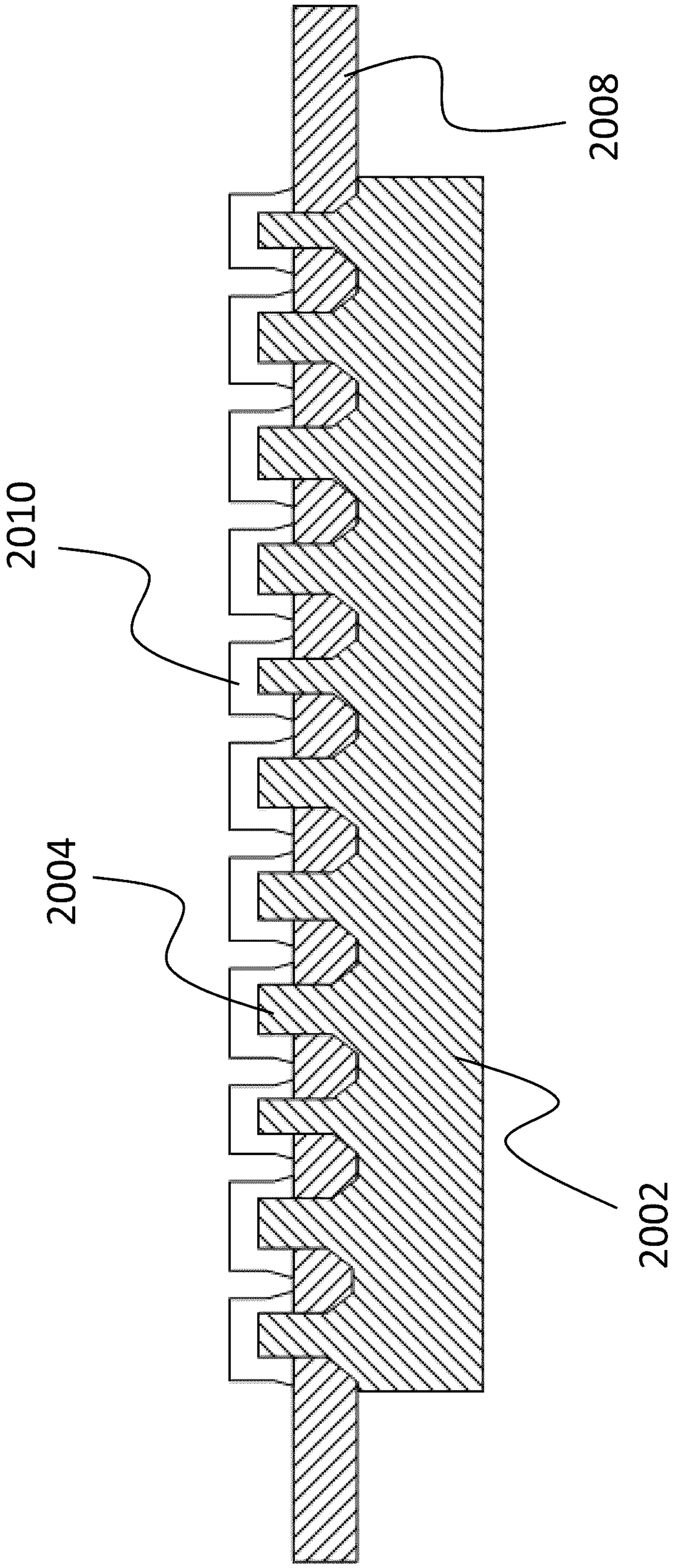


FIG. 20E

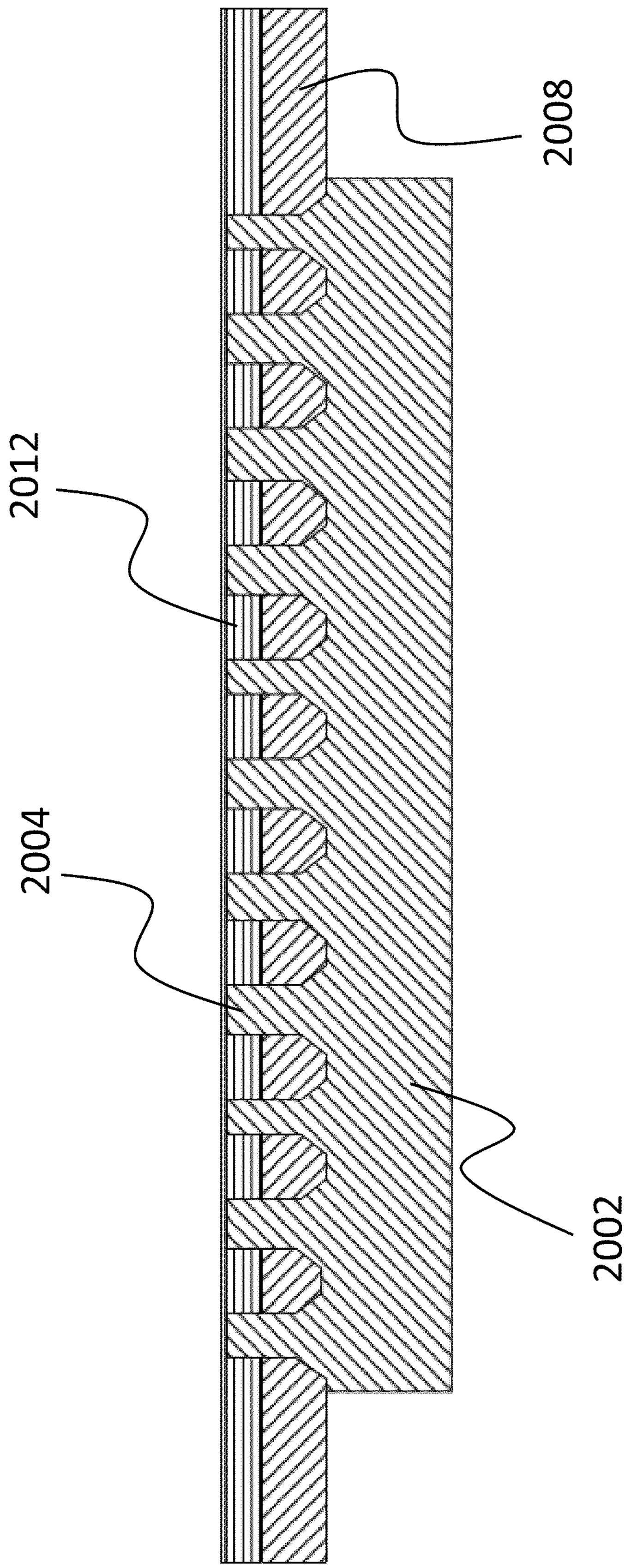


FIG. 20F

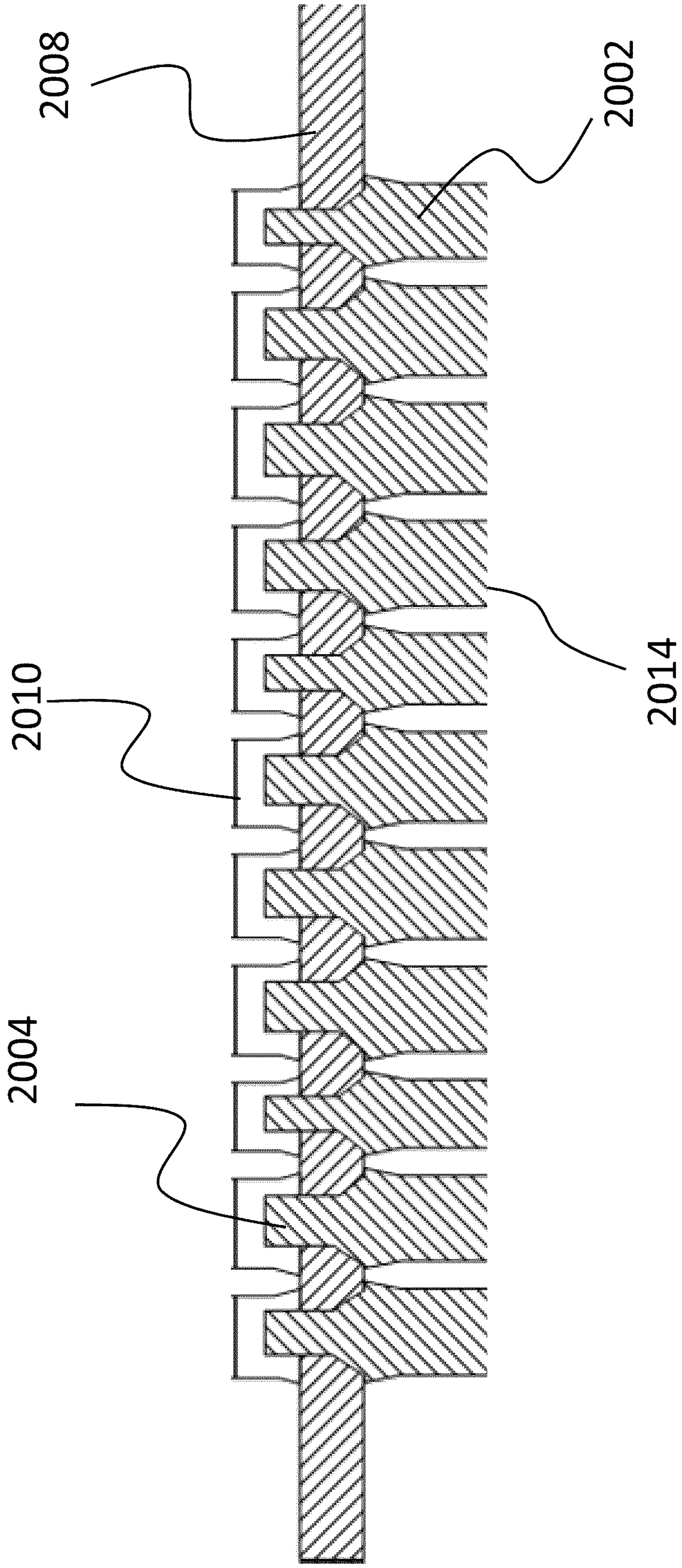


FIG. 20G

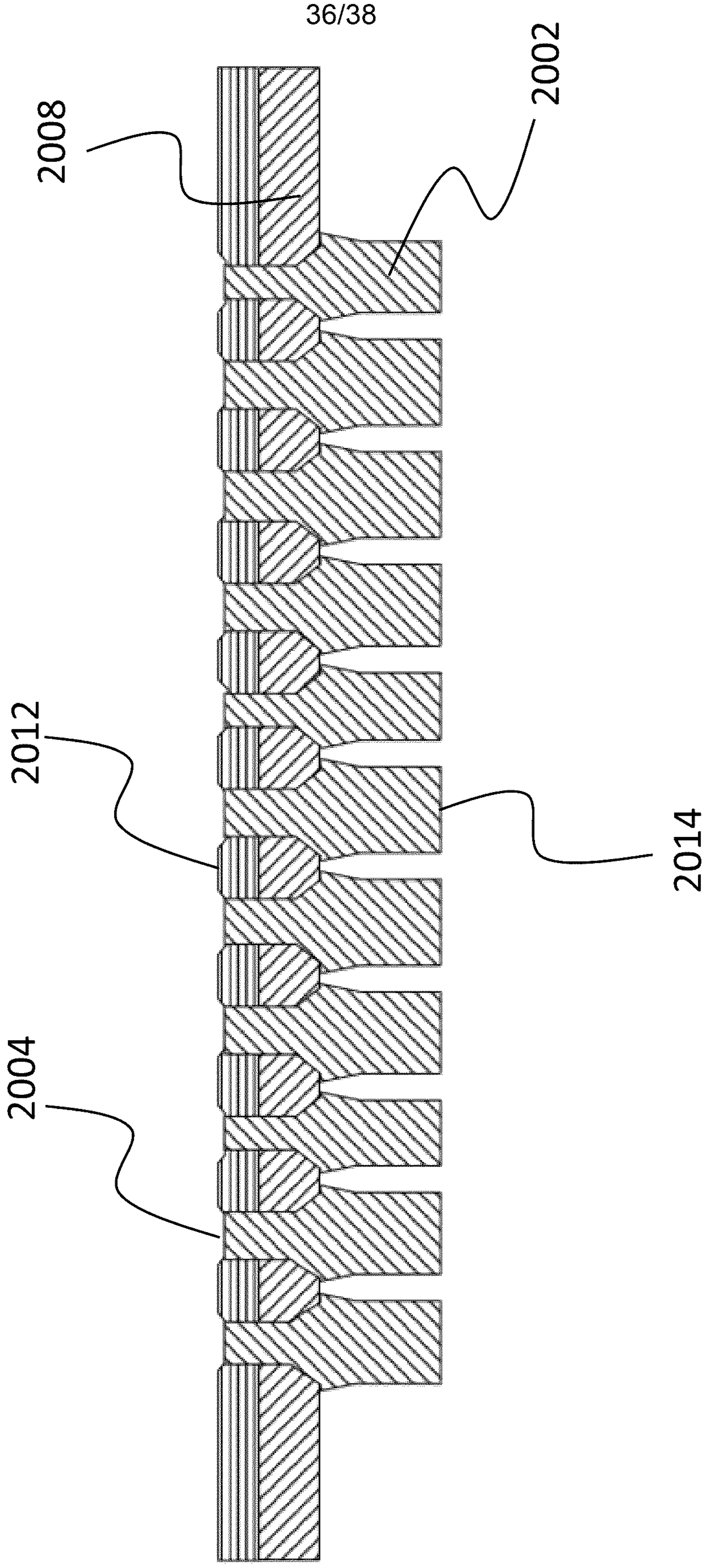


FIG. 20H

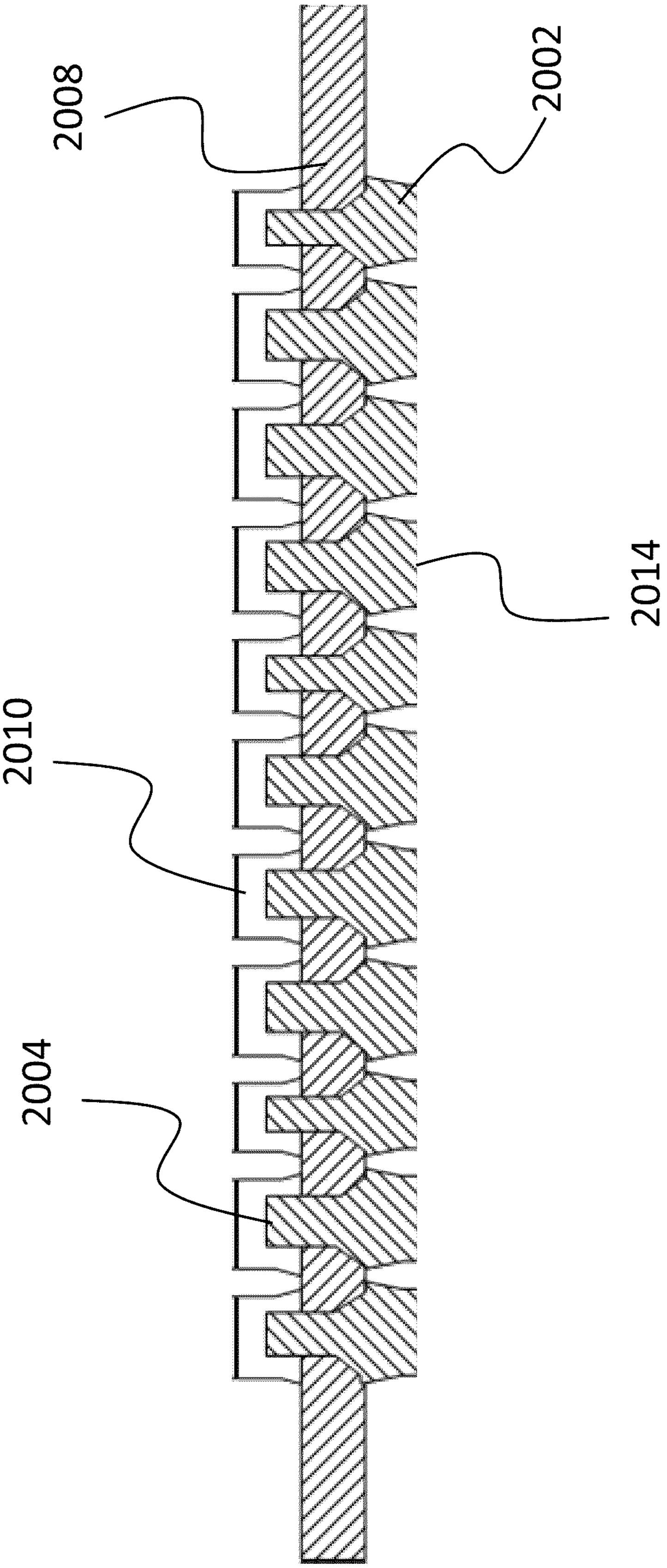


FIG. 20I

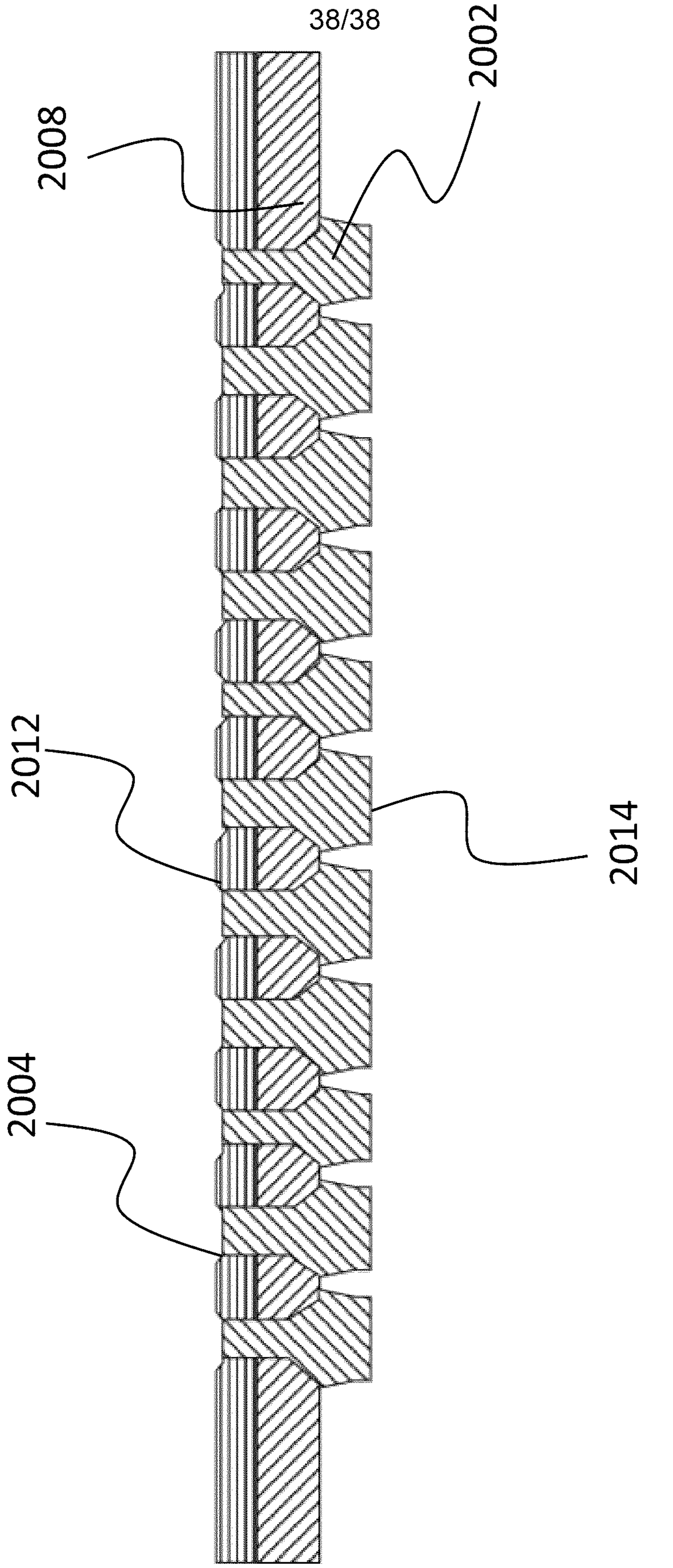


FIG. 20J

INTERNATIONAL SEARCH REPORT	International application No. PCT/CA2012/050314

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***G01N 1/00*** (2006.01) , ***G01N 27/22*** (2006.01) , ***G01N 27/447*** (2006.01)
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)
IPC: ***G01N 1/00*** (2006.01) , ***G01N 27/22*** (2006.01) , ***G01N 27/447*** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
EPOQUE, WEST, Canadian Patent Database: Keywords: fluidic, micro fluidic, flow, manipulation, movement, mixing, trapping, pumping, force field, electric, capacitive, magnetic, controller, connector, interconnector, separable, replaceable, joinable, assemble, disassemble, singulate, singulation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 6942778 Jalali et al (Nanogen Inc) 13 September 2005 (13-09-2005) See col. 4, lines 59 - 67; col. 6, line 45 - col. 7, line 12; col. 7, lines 36 - 50; col. 8, lines 9 - 25; col. 9, line 58 - col. 10, line 45 and col. 11, line 5 - col. 12, line 15. See also the figures particularly 2, 3 and 11.	1, 2, 7-9, 11, 16, 17, 19, 26-28, 37-39, 45 3 - 6, 10, 12 - 15, 18, 20 -25, 29 - 36, 40 - 44, 46 - 49
Y	US 6586707 Boyle et al (Xsil Technology Limited) 1 July 2003 (01-07-2003) See the whole document. Singulation and microfluidic devices are mentioned at various places in the description and claims. See for example claims 15 - 18.	47
Y	"Polymethylsiloxane based Conducting Composites and Their Applications in Microfluidic Chip Fabrication": Gong X. and Wen W.: Biomicrofluidics 3, 012007 (2009). Found at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2717593/ : Accessed 19 June 2012. See the abstract	3 - 6, 10, 12 - 15, 18, 20 -25, 29 - 36, 40 - 44, 46, 48 - 49

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2012 920-06-2012)	08 August 2012 (08-08-2012)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Patrick Norman (819) 997-2156

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 7375404 Park et al (University of Maryland) 20 May 2008 (20-05-2008) See the abstract and col. 2, lines 30 - 32 and 52 - 54; col. 4, lines 40 - 55; col. 5, lines 5 - 8 and 27 - 30; col. 6, line 63 - col. 7, line 33; col. 8, line 3 - col. 9, line 35; col. 18, line 38 - col. 19, line 55.	3 - 6, 10, 12 - 15, 18, 20 -25, 29 - 36, 40 - 44, 46, 48 - 49

Box No. II **Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [ ] Claim Nos. :
because they relate to subject matter not required to be searched by this Authority, namely :

2. [ ] Claim Nos. :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows :

See extra sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. [X] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :
4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest [ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

LACK OF UNITY
The claims are directed to a plurality of inventive concepts as follows:

Group A - Claims 1 - 15 are directed to a microfluidic structure adapted to be connected to an electronic circuit, the structure comprising: a microfluidic channel; at least one electrode extending through an electrode support body and adapted to generate a force field within the microfluidic channel for effecting a microfluidic manipulation; and an interconnector having at least one electrical contact connected to a corresponding one of the at least one electrode for replaceably connecting the microfluidic structure to the electronic circuit.

Group B - Claims 16 - 36 are directed to a method of producing a microfluidic structure, the method comprising: providing a first plate having a top surface and a bottom surface, forming a plurality of holes extending from the bottom surface to an electrode surface of the first plate, providing an electrode within each of the plurality of holes; providing a second plate having a plate contacting surface that is adapted to form with the top surface of the first plate an interior portion of the microfluidic structure; forming at least one micro-channel adapted to extend over the interior portion of the microfluidic structure; and securing the top surface of the first plate to the plate contacting surface of the second plate so as to align at least one of the plurality of holes with the at least one micro-channel.
.
Group C - Claims 37 - 46 are directed to a microfluidic device adapted to be connected to a controller, the device comprising: a micro-channel support body having at least one micro-channel formed therein; an electrode support body having an array of electrodes, the electrode support body and the micro-channel support body being aligned to produce with at least one of the array of electrodes a force field within the at least one channel; and a plurality of controller contacts each being electrically connected to a corresponding electrode of the array of electrodes for performing within the at least one micro-channel a plurality of microfluidic manipulations.
.
Group D - Claims 47 - 49 are directed to a method of manufacturing a plurality of electrodes each positioned within a corresponding through-hole of a glass substrate, the method comprising:
defining a plurality of electrode contacts all joined in a single piece; defining in a glass substrate a plurality of through-holes each corresponding to the plurality of electrode contacts; inserting the plurality of electrode contacts into the corresponding plurality of through-holes; depositing a bonding material onto the plurality of electrode contacts so as to adhere to the glass substrate and to immobilise each of the plurality of electrode contacts within the corresponding through-holes; and singulating the single piece into a plurality of electrodes, each of the plurality of electrodes corresponding to each of the plurality of electrode contacts.

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US6942778B1	13 September 2005 (13-09-2005)	AU3044802A	11 June 2002 (11-06-2002)
		US2005271554A1	08 December 2005 (08-12-2005)
		WO0243827A2	06 June 2002 (06-06-2002)
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US7375404B2	20 May 2008 (20-05-2008)	US2005230767A1	20 October 2005 (20-10-2005)
US6586707B2	01 July 2003 (01-07-2003)	AT346715T	15 December 2006 (15-12-2006)
		AU1085902A	06 May 2002 (06-05-2002)
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		DE60124938T2	20 September 2007 (20-09-2007)
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		EP1328372B1	29 November 2006 (29-11-2006)
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		IE20010600A1	26 June 2002 (26-06-2002)
		IE20010605A2	28 November 2001 (28-11-2001)
		IE20010606A1	01 May 2002 (01-05-2002)
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		IE20010950A1	10 July 2002 (10-07-2002)
		JP2004512690A	22 April 2004 (22-04-2004)
		US2002088780A1	11 July 2002 (11-07-2002)
		WO0234455A1	02 May 2002 (02-05-2002)