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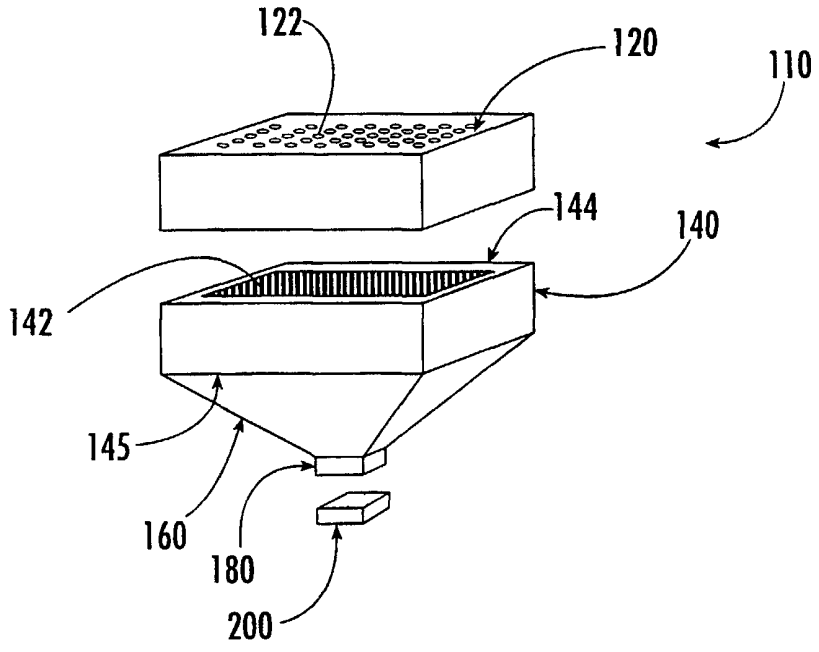

(57) Abstract: A volume-reducing arrayer apparatus is provided, wherein the arrayer apparatus is adapted to deliver a predetermined amount of a liquid solution from a reservoir to a substrate. The arrayer apparatus generally comprises at least one plate disposed between the reservoir and the substrate and a flow control device disposed between the at least one plate and the substrate and in communication with the at least one plate. The at least one plate is in communication with the reservoir and defines at least one plate capillary extending toward the substrate. The at least one plate capillary is configured to have a reduced volume with respect to the reservoir so as to receive a portion of the solution therefrom. The flow control device is in communication with the at least one plate and defines at least one flow control capillary corresponding to the at least one plate capillary and extending toward the substrate. The at least one flow control capillary is configured to have a reduced volume with respect to the at least one plate capillary. The flow control device is further configured to control the flow of a predetermined amount of the solution through the at least one flow control capillary, from the at least one plate capillary to the substrate. Associated methods of fabricating an arrayer apparatus and delivering biosamples to a biochip are also provided.

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VOLUME-REDUCING LIQUID ARRAYER AND ASSOCIATED METHODS

FIELD OF THE INVENTION

The present invention relates to a liquid delivery apparatus and, more particularly, to a volume-reducing liquid arrayer apparatus for delivering a liquid solution from a reservoir to a substrate in the form of an array of portions of the liquid solution and associated methods of use and fabrication.

BACKGROUND OF THE INVENTION

Large scale, multiple sample, parallel biochemistry assays, automated instruments, and system integration (instrument, databases and analytical tools) using the latest bioinformatics technologies are key factors for advancing the field of functional genomics. In recent years, DNA chip technology has been a focal point of genomic scientists and potential customers of genomics technology because of the ability of the DNA chip to assay a large number of genes in parallel. DNA chip technology can be used, for example, in gene expression assaying (parallel Northern blotting) to determine gene functions, in polymorphism detection and molecular marker genotyping (for example, SNP), to provide efficient genetic mapping, and, most importantly, in human disease diagnostics and in phenotype prediction for genetic manipulation of plants and animals. Further, the integration of DNA chip and two-dimensional protein data analyses is an important step in correlating the results of genomic and protemic studies.

Currently, on-chip synthesis and robotic dispensing are two methods used to prepare biosamples on DNA biochips which are used to conduct multiple sample parallel bioassays. On-chip synthesis is disclosed, for example, in U.S. Patent Nos. 5,800,992 and 5,744,305 to Fodor et al. which describe an oligonucleotide-based chip (herein called the "Fodor chip") generally utilizing a flat silicon surface for *in situ* synthesis of the oligonucleotides on the chip surface using combinatory chemistry. The probe arrays are manufactured using a light-directed chemical synthesis process which combines solid-phase chemical synthesis with photolithographic fabrication techniques. A series of photolithographic masks are used to define chip exposure sites before specific chemical synthesis steps are performed to produce the desired

probes. This process constructs high-density arrays of oligonucleotides (probes) with each probe disposed in a predetermined position in the array. Typically, multiple probe arrays are simultaneously synthesized on a large silicon wafer before the wafer is diced and the individual probe arrays are packaged in cartridges for subsequent use in bioassays.

However, the Fodor chip is typically limited to short oligonucleotide lengths, where the oligos have a small number (ie: 25) of nucleotide bases. The Fodor chip, therefore, may also be limited by experimental error associated with on-chip oligonucleotide synthesis and with short oligonucleotide hybridization error, which is generally associated with non-specific hybridization in a relaxed condition. Thus, due to these inherent experimental errors, techniques utilizing the Fodor chip may be prone to poor experimental repeatability. In addition, the Fodor chip may further be limited by slow hybridization rates due to the small effective hybridization area and random probe solution flow on the chip surface. In some instances, RNA amplification may also be required to increase the RNA concentration in the probe solution, which may make the Fodor chip unsuitable for certain applications, for example, monitoring gene expression. Thus, procedures involving the Fodor chip may be cost inefficient due to the complexities and limitations involved in producing the chip (labor intensive and time consuming procedures which add to the cost of the chip), capturing the necessary images, and analyzing the collected data.

Robotic dispensing of biosamples in the preparation of biochips is disclosed, for example, in U.S. Patent No. 5,807,522 to Brown et al. which describes a cDNA-based microarray chip (herein called the "Brown chip") that utilizes cDNA samples disposed in a microarray on the surface of a chip comprising a glass slide. The cDNA segments are typically chosen from cDNA libraries of EST sequencing projects. Each cDNA segment may range in length from several hundred to several thousand nucleotides. The nucleotide sequences in the cDNA segments are generally known, though cDNA segments without nucleotide sequence information and synthetic oligos may also be used in fabricating a Brown chip. The cDNA samples are usually delivered onto the chip using a robot having a three-dimensional motion control system and the ability to concurrently deposit multiple samples on the chip using a plurality of spotting pins. The spotting pins are typically dipped into DNA solutions before being moved to predetermined x-y positions over a glass slide. The pins are

then brought into contact with the surface of the glass slide such that the biosamples are deposited on the slide. The pins must then be washed and dried before being used for further biosample deposition.

However, the Brown chip is limited, for example, in that the robotic system used to deliver the biosamples to the chip can only do so for a portion of a chip (4 to 16 spots) at a time thus contributing to a time-intensive fabrication process. In addition, error in the x-y positioning of the spotting pins by the robot at each successive portion on the chip may contribute to poor accuracy of experimental results. Further, varying amounts of the cDNA samples and other inconsistencies in the biosamples deposited by the spotting pins may contribute to a lack of uniformity in the DNA samples deposited on a single chip and between successive chips. Also, the robotic system necessary to perform the precise and demanding task of biochip fabrication may be very complex and expensive. Robotic systems using spotting pins for delivering the biosamples to the chip further typically require that the DNA solutions be prepared separately before the biosamples are delivered to the chip. Thus, the extra handling necessary for delivering the biosamples from the solution to the chip contributes to inconsistencies in the deposited samples and increases the possibility of sample contamination.

Thus, though the Fodor and Brown DNA chips are useful for some small-scale research in functional genomics, they are not suitable for future practical large-scale applications primarily due to high cost, time intensive fabrication of the DNA chip, and poor accuracy of experimental results. The poor accuracy of a surface-based biosample assay apparatus and method typically results from the low concentration of the complementary strands of DNA (or RNA) in the probe solution and the small effective hybridization area of the spots on surface-based chips. Further, surface-based chips, such as the Brown chip, are often prepared using a robot for transferring biosamples from a mass solution to individual spots on a glass substrate to form the microarray. The biosample transfer may be accomplished, for example, by a robot operating at an overall rate of about four dots per second. Since a microarray may include multiple thousands of individual samples, a surface-based microarray may be prone to lengthy formation times as well as possible sample contamination due to the robotic system.

Thus, there exists a need for a DNA chip preparation apparatus and associated method that is cost-effective and capable of fabricating biochips at a higher rate than current techniques. Preferably, the apparatus and method should be capable of producing more accurate biochips and more repeatable experimental results than is currently available with prior art DNA chips.

SUMMARY OF THE INVENTION

The above and other needs are met by the present invention which, in one embodiment, provides a volume-reducing arrayer apparatus adapted to deliver a predetermined amount of a liquid solution from a reservoir to a substrate. The arrayer apparatus generally comprises at least one plate disposed between the reservoir and the substrate and a flow control device disposed between the at least one plate and the substrate and in communication with the at least one plate. The at least one plate is in communication with the reservoir and defines at least one plate capillary extending toward the substrate. The at least one plate capillary is configured to have a reduced volume with respect to the reservoir so as to receive a portion of the solution therefrom. The flow control device is in communication with the at least one plate and defines at least one flow control capillary corresponding to the at least one plate capillary and extending toward the substrate. The at least one flow control capillary is configured to have a reduced volume with respect to the at least one plate capillary. The flow control device is further configured to control the flow of a predetermined amount of the solution through the at least one flow control capillary, from the at least one plate capillary to the substrate.

Another advantageous embodiment of the present invention provides a volume-reducing arrayer apparatus adapted to deliver a predetermined amount of a liquid solution to a substrate. The arrayer apparatus comprises a reservoir for containing the solution, at least one arrayer block disposed between the reservoir and the substrate, a flow control device disposed between the at least one arrayer block and the substrate, and a stamper head disposed between the flow control device and the substrate. The at least one arrayer block is in communication with the reservoir and defines at least one arrayer capillary extending toward the substrate, wherein the at least one arrayer capillary is configured to have a reduced volume with respect to the reservoir so as to receive a portion of the solution therefrom. The flow control

device is in communication with the at least one arrayer block and defines at least one flow control capillary corresponding to the at least one arrayer capillary and extending toward the substrate. The at least one flow control capillary is also configured to have a reduced volume with respect to the at least one plate capillary. The flow control device is further configured to control the flow of a predetermined amount of the solution through the at least one flow control capillary. The stamper head is in communication with the flow control device and also defines at least one stamper capillary corresponding to the at least one flow control capillary and extending toward the substrate. The at least one stamper capillary is configured to have the predetermined amount of the solution channeled therethrough by the flow control device, from the at least one flow control capillary to the substrate.

A further advantageous aspect of the present invention comprises a method of fabricating a volume-reducing arrayer apparatus adapted to deliver a predetermined amount of a liquid solution from a reservoir to a substrate. First, a first plate defining at least one first plate capillary is operably engaged with a second plate defining at least one second plate capillary so as to form a continuous passage between each first plate capillary and the corresponding second plate capillary. A flow control device is then operably engaged with each of the second plate capillaries, wherein the flow control device is configured to control the flow of the solution through each second plate capillary, from each first plate capillary to the substrate. The at least one first plate capillary is in communication with the reservoir and has a reduced volume with respect thereto so as to receive a portion of the solution therein. The at least one second plate capillary corresponds to the at least one first plate capillary and has a reduced volume with respect thereto.

Still a further advantageous aspect of the present invention comprises a method of delivering a biosample solution to a biochip. First, portions of the biosample solution are delivered from a microtiter plate containing the biosample solution to a plurality of first plate capillaries defined by a first plate, wherein the first plate capillaries are arranged in an array and each of the first plate capillaries has a predetermined diameter. At least a portion of the biosample solution from each of the first plate capillaries is then delivered to a corresponding second plate capillary in a plurality of second plate capillaries defined by a second plate. The second plate capillaries are arranged in an array corresponding to the first plate capillary array.

Further, each of the second plate capillaries has a diameter smaller than the first plate capillary diameter such that the smaller diameter of the second plate capillary provides a reduced volume per unit length of the solution therein with respect to the first plate capillary. At least a portion of the biosample solution from each of the second plate capillaries is then delivered to a substrate to form an array of samples on the substrate.

Thus, embodiments of a volume-reducing arrayer apparatus according to the present invention provide a non-robotic device for delivering biosamples onto biochips. An arrayer apparatus according to the present invention is capable of simultaneously depositing a large number of biosamples onto a number of biochips at a relatively high rate compared to current robotic devices. An arrayer apparatus according to the present invention further provides a relatively low cost and simple apparatus compared to current robotic systems. Since no movement is involved between the arrayer apparatus and the biochip during the delivery of the biosamples to the biochip, the biosamples are deposited on the chip with higher precision and greater uniformity while eliminating handling steps which tend to introduce experimental error. Further, the configuration of an arrayer apparatus according to the present invention facilitates integration of the arrayer apparatus and dispensing system with the DNA solution preparation measures, thus allowing the biosamples to be prepared immediately with the arrayer apparatus and immediately before delivery onto the biochip, thereby further eliminating handling steps in delivering the biosamples from the bulk solution to the biochip. Accordingly, a biochip preparation apparatus and associated method according to the present invention is capable of cost effectively manufacturing biochips at a higher rate than current techniques and results in more accurate biochips with higher repeatability of experimental results than current DNA chips. It will be recognized, therefore, that the present invention facilitates the achievement of these and other distinct advantages over prior art biochip fabrication devices and methods.

BRIEF DESCRIPTION OF THE DRAWINGS

Some of the advantages of the present invention having been stated, others will appear as the description proceeds, when considered in conjunction with the accompanying drawings, which are not necessarily drawn to scale, in which:

FIG. 1 is a perspective view of a volume-reducing arrayer for depositing a predetermined amount of a liquid on a substrate according to one embodiment of the present invention.

FIG. 2 is a side elevation of a volume-reducing arrayer for depositing a predetermined amount of a liquid on a substrate according to an alternate embodiment of the present invention.

FIG. 3A is a schematic of a volume-reducing liquid arrayer for depositing a predetermined amount of a liquid on a substrate according to one embodiment of the present invention.

FIG. 3B shows top and bottom views of each plate comprising a volume-reducing arrayer according to the embodiment of the present invention shown in **FIG. 3A**.

FIG. 4A is a schematic of a volume-reducing arrayer for depositing a predetermined amount of a liquid on a substrate according to an alternate embodiment of the present invention.

FIG. 4B shows top and bottom views of the plates comprising a volume-reducing arrayer according to the embodiment of the present invention shown in **FIG. 4A**.

FIGS. 5A-5C are schematic representations of volume-reducing pathways in an arrayer according to embodiments of the present invention.

FIG. 6 is a schematic representation of a pumping device utilized in a pumping array comprising a portion of a volume-reducing liquid arrayer according to embodiments of the present invention.

FIG. 7 is a flowchart of a method of fabricating a volume-reducing liquid arrayer according to one embodiment of the present invention.

FIG. 8 is a flowchart of a method of delivering an array of biosample solutions to a biochip according to one embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention now will be described more fully hereinafter with reference to the accompanying drawings, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein;

rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. Like numbers refer to like elements throughout.

FIGS. 1 and **2** disclose embodiments of a volume-reducing arrayer apparatus adapted to deliver a predetermined amount of a liquid solution to a substrate, the arrayer apparatus (also referred to herein as an "arrayer") being indicated generally by the numeral **110** and including the features of the present invention. The arrayer **110** generally comprises a reservoir **120**, at least one arrayer block **140**, a flow control device **160**, and a stamper head **180** cooperating to deliver biosamples in the form of a liquid to a biochip **200**.

In one advantageous embodiment of the present invention, the reservoir **120** comprises, for example, a microtiter plate constructed so as to store bulk DNA solutions therein. More particularly, for example, a 20cm x 20cm microtiter plate may contain a plurality of wells **122** arranged in an array, where each well **122** is capable of holding 5 to 200 microliters of a DNA solution. Thus, according to current technology, such a microtiter plate may, for example, hold as many as 10,000 DNA samples therein and may theoretically be used to fabricate approximately 5,000 to 10,000 separate biochips **200**.

Underlying the reservoir **120**, according to one advantageous embodiment, is at least one arrayer block **140**, in the form of a plate, defining at least one and, in some instances, a plurality of arrayer capillaries **142**. The arrayer capillaries **142** may be arranged in an array corresponding to the array of wells **122** in the reservoir **120**. The wells **122** in the reservoir **120** may each have a valve (not shown) for controlling the flow of the liquid solution, and thus the biosamples, from the wells **122** into the corresponding arrayer capillaries **142** in the arrayer block **140**. It is understood, however, that delivery of the solution from the wells **122** to the arrayer capillaries **142** may be accomplished by other delivery methods, wherein the reservoir **120** is in communication with, but not necessarily disposed atop, the arrayer block **140**, consistent with the spirit and scope of the present invention.

A typical biochip **200** is on the order of, for example, about one square centimeter to about four square centimeters and requires microscopically-sized samples to form the necessary oligonucleotide probes on the biochip **200**. Thus, the liquid solution (also referred to herein as the "biosamples') released from the wells

122 must be reduced with respect to both the volume of the individual biosample as well as the area occupied by the well array **122**.

The arrayer block **140** is thus configured to receive and reduce the volume of the biosamples from the reservoir **120** and to reduce the area occupied by the well array **122**. As shown in **FIGS. 3A and 4A**, the arrayer block **140** is typically a flat plate having an upper surface **144** and a lower surface **145** and is sealed and adhered to the reservoir **120** by a thin film of silicon. The arrayer capillaries **142** defined by the arrayer block **140** are arranged in an array corresponding to the well array **122** in the reservoir **120** and each arrayer capillary **142** may extend, in some instances, from the upper surface **144** to the lower surface **145** of the arrayer block **140**. At the lower surface **144** of the arrayer block **140**, an array of indentations **146** is formed, wherein the indentation array **146** corresponds to at least a portion of the arrayer capillary array **142**. In order to reduce the area occupied by the arrayer capillary array **142**, the indentation array **146** is typically formed, for instance, toward the center of the arrayer block **140** and inwardly of at least some of the arrayer capillaries **142**, though a variety of different configuration may be used in accordance with the spirit and scope of the present invention. A plurality of channels **148** are also formed in the lower surface **145** of the arrayer block **140**, with each channel **148** extending between an arrayer capillary **142** and a corresponding indentation in the indentation array **146**. As shown in **FIGS. 3A, 3B,** and **5A**, the reduction in the arrayer capillary array **142** area may be accomplished with a single arrayer block **140**, wherein the entire arrayer capillary array **142** is reduced in area to the size of the indentation array **146** by the single arrayer block **140**.

As shown in **FIGS. 4A, 4B,** and **5B**, reducing the arrayer capillary array **142** area may be alternatively accomplished with multiple arrayer blocks, wherein a first arrayer block **140** and a second arrayer block **150** are shown in this embodiment, and wherein each successive arrayer block reduces the area occupied by a particular subset of the first arrayer capillary array **142**. For example, the second arrayer block **150** may be disposed below the first arrayer block **140** such that the lower surface **145** of the first arrayer block **140** is sealed by the upper surface **154** of the second arrayer block **150**. The upper surface **154** of the second arrayer block **150** seals the first arrayer capillaries **142** in the first arrayer block **140** having channels **148** connected thereto, such that each first arrayer capillary **142** having a connected channel **148**, and

that corresponding channel **148**, are sealed. Accordingly, any portion of the solution flowing through the first arrayer capillary **142** flows through the channel **148** to the corresponding indentation **146**.

The second arrayer block **150** further defines a plurality of second arrayer capillaries **151** therein corresponding to the array of indentations **146** in the first arrayer block **140**. The second arrayer capillaries **151** typically extend through the second arrayer block **150** from the upper surface **154** to the lower surface **155** thereof. In order to reduce the volume of the biosample solution in each capillary, the second arrayer capillaries **151** in the second arrayer block **150** are configured to have a smaller diameter than the first arrayer capillaries **142** in the first arrayer block **140**. For example, in one embodiment of the present invention, the first arrayer capillaries **142** of the first arrayer block **140** have a diameter of between about one millimeter and about two millimeters while the second arrayer capillaries **151** in the second arrayer block **150** have a diameter of between about 50 microns and about 200 microns. The smaller diameter of the second arrayer capillaries **151** in the second arrayer block **150** reduces the volume per unit length of the solution in the capillary and provides more accurate and easier regulated volumetric control over the flow of the biosample solution from the reservoir **120** to the biochip **200**. Thus, it will be understood that, by reducing the dimensions and the spacing of subsequent sets of capillaries, the volume of the individual biosample as well as the area occupied by the corresponding capillary array are accordingly reduced in order to scale the biosamples to the dimensions of the corresponding biochip according to the spirit and scope of the present invention.

In some instances, the first arrayer block **140** may have first arrayer capillaries **142** which are not connected to channels **148** at the lower surface **145** of the first arrayer block **140**. In those instances, the second plate **150** also defines a plurality of continuation capillaries **152** corresponding to the unchanneled first arrayer capillaries **142** of the first arrayer block **140** and being configured to have a substantially similar diameter with respect thereto. Accordingly, when the first arrayer block **140** is engaged with the second arrayer block **150**, some of the first arrayer capillaries **142** continue through the first arrayer block **140** to the corresponding continuation capillaries **152** in the second arrayer block **150**. Where the second arrayer block **150** continues some of the first arrayer capillaries **142** of the first arrayer block **140** with

continuation capillaries **152**, the second arrayer block **150** also includes channels **158** defined in the lower surface **155** thereof, with the channels **158** leading to an array of corresponding indentations **156** also defined by the lower surface **155** of the second arrayer block **150**. In such instances, the second arrayer block **150** completes the reduction of the area of the original capillary array **142**. It is understood, however, that the reduction in the area of the capillary array may be accomplished by various methods consistent with the spirit and scope of the present invention. For example, **FIG. 5C** illustrates the use of two arrayer blocks **140** and **150** to reduce a larger scale capillary array than was illustrated in **FIGS. 3B** and **4B**. In addition, more than two arrayer blocks may be utilized to further expand the scale of the biosample solution volume and the capillary array corresponding thereto so as to accommodate biochips configured for a large array of biosamples. Thus, it will be further understood that the various methods of reducing the area of the capillary array will be applicable herein with respect to the described embodiments in addition to or in the alternative to the specific configuration described.

Once the capillary array **142** has been reduced to the desired area and the individual biosamples have been reduced to the desired volume, a flow control **160** is operably connected to the lower surface **155** of the last arrayer block **150**. The flow control device **160** may include, for example, an array of flow control capillaries **162** corresponding to the previous reduced area capillary array formed by the arrayer blocks. The flow control device **160** is configured to control the flow of the biosamples through the flow control capillaries **162** and may take the form of, for instance, a valve, a pump, or the like. According to one embodiment of the present invention, and as shown in **FIG. 6**, each flow control capillary **162** may be configured with a micropump **165** capable of providing precise control over the flow of the biosamples through the relatively small flow control capillaries **162**. Pumping of a biosample through a capillary **162** may be accomplished using electrostatic pressure generated by a voltage applied along a length of the capillary **162**. Generally, a high voltage of 1 to 20 kV, for example, is required to generate the necessary pressure for pumping the biosample in the capillary **162**. By using electrostatic pressure to pump the biosamples through the capillaries **162**, a precise volume of the biosamples can be pumped through each capillary **162**. Note that, in some instances, the voltage may be controlled and/or adjusted so as to form a microvalve capable of preventing and/or

metering the biosample flow through the capillary **162**. The movement of molecules by the application of a plurality of electrical fields is further described in U.S. Patent No. 5,126,022 to Soane *et al.*, the contents of which are herein incorporated by reference. However, flow control of the biosamples as mentioned herein may also be accomplished, for instance, with an external pump interfaced with the arrayer apparatus **110** for pumping the biosamples through the capillaries, instead of using an electrostatic pump configured as previously described. Alternatively, for example, an external valve may be engaged with the arrayer apparatus **110**, for controlling the flow of the biosamples. Thus, it will be understood that flow control of the biosamples may be achieved in many different manners, in addition to that described, according to spirit and scope of the present invention.

Once the biosamples have been channeled through the flow control device **160**, the biosamples flow through a stamper head **180** operably connected to the flow control device **160** and defining an array of stamper capillaries **182** corresponding to the flow control capillaries **162**. In some instances, the stamper capillaries **182** may have a reduced diameter, and thus a reduced volume per unit length, with respect to the flow control capillaries **162** for further reducing the biosample volume as discussed herein. Generally, the substrate **200** to which the biosamples are delivered is disposed below the stamper head **180**. In order to deliver the biosamples to the substrate **200**, the stamper head may be positioned adjacent to the substrate **200** such that the biosamples released from the flow control capillaries **162** flow through the stamper capillaries **182** and then form droplets at the outlets of the stamper capillaries **182**. The droplets then contact the substrate **200** and are subsequently transferred thereto by surface tension. In the alternative, the stamper head **180** may be brought into contact with the substrate **200** in order to transfer the biosamples to the substrate **200**. A typical sample, for example, may comprise about 100 nanoliters of the original bulk solution. In some instances, the stamper head **180** may also be readily removable and replaceable in order to minimize cross-contamination between subsequent biochips **200**. It will be understood, however, that the volume-reducing arrayer apparatus according to embodiments of the present invention may be utilized for other purposes than herein described such as, for example, in aspects of combinatorial chemistry and integrated circuit packaging, within the spirit and scope of the present invention.

Another advantageous aspect of a volume-reducing arrayer apparatus according to the present invention comprises a method of fabricating a volume-reducing arrayer apparatus adapted to deliver a predetermined amount of a liquid solution from a reservoir to a substrate as shown in **FIG. 7**. First, a first plate defining at least one first plate capillary is operably engaged with a second plate defining at least one second plate capillary so as to form a continuous passage between each first plate capillary and the corresponding second plate capillary (**block 210**). The first and second plate capillaries are typically arranged in corresponding arrays and extend between an upper surface and a lower surface of the corresponding plate. The plates may be comprised of, for example, a material such as silicon, and the capillaries may be formed therein using standard photolithographical techniques commonly employed in the semiconductor industry. According to a photolithographical process, the silicon substrate is coated with a light sensitive photolithographical material, patterned to define shapes corresponding to the capillaries, and the substrate then etched such that the capillaries are formed therein. The second plate capillaries are generally configured to have a diameter smaller than the first plate capillary diameter so as to reduce the volume per unit length of the biosample solution in the capillary. In one embodiment of the present invention, the second plate capillary array extends over an area generally corresponding to the size of the substrate on which the biosamples will be deposited, the area covered by the second plate capillary array being generally smaller than the area covered by the first plate capillary array. A flow control device is then operably engaged with each of the second plate capillaries, wherein the flow control device is configured to control the flow of the solution through each second plate capillary, from each first plate capillary to the substrate (**block 220**).

Still another advantageous aspect of the present invention comprises a method of delivering a biosample solution to a biochip as shown in **FIG. 8**. First, portions of the biosample solution are delivered from a microtiter plate containing the biosample solution to a plurality of first plate capillaries defined by a first plate, wherein the first plate capillaries are arranged in an array and each of the first plate capillaries has a predetermined diameter (**block 230**). At least a portion of the biosample solution from each of the first plate capillaries is then delivered to a corresponding second plate capillary in a plurality of second plate capillaries defined by a second plate (**block 240**). The second plate capillaries are arranged in an array corresponding to

the first plate capillary array. Further, each of the second plate capillaries has a diameter smaller than the first plate capillary diameter such that the smaller diameter of the second plate capillary provides a reduced volume per unit length of the solution therein with respect to the first plate capillary. At least a portion of the biosample solution from each of the second plate capillaries is then delivered to a substrate to form an array of samples on the substrate (**block 250**).

Thus, embodiments of an arrayer apparatus according to the present invention provide distinct advantages in delivering biosamples onto biochips as compared to current methods such as robotic delivery. More particularly, the arrayer apparatus is capable of delivering the biosamples to the biochips at a higher rate since, for example, no washing step is needed between biochips. Further, the arrayer apparatus may be configured to deliver biosamples to a number of biochips simultaneously, wherein the delivery rate would be on the magnitude of, for instance, biochips per second instead of the typical spots per second rate of current robotic systems. In addition, one load of DNA samples in the microtiter plate may potentially generate a large number of biochips. For example, 5,000 biochips may theoretically be generated from a microtiter plate containing 5 microliters of a DNA solution for each sample. Another advantage of the arrayer apparatus is its relatively low cost since, for instance, the multi-tier microchannel array is relatively easy to manufacture compared to a complex robotic system. The ease of manufacture is facilitated in that many of the components may be manufactured using standard photolithography techniques common to the semiconductor industry.

Embodiments of the arrayer apparatus further provide high precision compared to other techniques. For example, the relative x-y positions of biosamples are maintained at a constant between subsequent biochips since there is no moving of each biochip for the application of the biosamples. Further, the concentrations of the biosamples are typically more uniform because all probes on a chip are deposited simultaneously and the DNA samples are maintained integrally with the arrayer apparatus during the sample delivery process. The arrayer apparatus also allows the amount of the biosample deposited onto the biochip to be more precisely controlled by electronic devices. The configuration of the arrayer apparatus further reduces the risk of cross-contamination between biosamples due to reduced handling thereof and the replaceability of the stamper head. In addition, embodiments of the arrayer

apparatus can be integrated with the sample preparation process before delivery of the biosamples onto the biochip such that potential sources of error between sample preparation and biochip formation are eliminated. For example, a bio-reaction cabin may be attached above the arrayer apparatus for DNA amplification using PCR, more particularly lending itself to the application of strand displacement amplification (SDA).

Thus, the arrayer apparatus according to embodiments of the present invention provides expedient fabrication of biochips in a timely and cost-effective manner. The flow control system, comprising a part of the arrayer apparatus, further provides precise flow and delivery of the biosamples to the biochip while the configuration of the arrayer apparatus minimizes or eliminates various deleterious factors present in current biochip fabrication methods, thereby producing more accurate and repeatable process results than current methods of producing biochips.

Many modifications and other embodiments of the invention will come to mind to one skilled in the art to which this invention pertains having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the invention is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

THAT WHICH IS CLAIMED:

1. A volume-reducing arrayer apparatus adapted to deliver a predetermined amount of a liquid solution from a reservoir to a substrate, said arrayer apparatus comprising:

at least one plate disposed between the reservoir and the substrate and in communication with the reservoir, the at least one plate defining at least one plate capillary extending toward the substrate, the at least one plate capillary being configured to have a reduced volume with respect to the reservoir so as to receive a portion of the solution therefrom; and

a flow control device disposed between the at least one plate and the substrate and in communication with the at least one plate, the flow control device defining at least one flow control capillary corresponding to the at least one plate capillary and extending toward the substrate, the at least one flow control capillary being configured to have a reduced volume with respect to the at least one plate capillary, the flow control device being further configured to control the flow of a predetermined amount of the solution through the at least one flow control capillary, from the at least one plate capillary to the substrate.

2. An arrayer apparatus according to Claim 1 wherein the at least one flow control capillary is configured to have a diameter smaller than the diameter of the plate capillary such that the smaller diameter of the flow control capillary provides a reduced volume per unit length with respect to the plate capillary.

3. An arrayer apparatus according to Claim 1 wherein the at least one plate defines a plurality of plate capillaries arranged in an array.

4. An arrayer apparatus according to Claim 3 wherein the flow control device defines a plurality of flow control capillaries arranged in an array corresponding to the plate capillary array.

5. An arrayer apparatus according to Claim 4 wherein at least one of the plate and the flow control device defines a plurality of channels configured such that each channel operably connects one plate capillary in the plate capillary array to one corresponding flow control capillary in the flow control device array.

6. An arrayer apparatus according to Claim 1 wherein the at least one plate comprises a first plate and a second plate, with each plate having a solution entrance surface and a solution exit surface, and wherein the solution exit surface of the first plate is configured to operably engage the solution entrance surface of the second plate.

7. An arrayer apparatus according to Claim 6 wherein the first plate defines a plurality of first plate capillaries arranged in an array, the array further comprising a first portion of first plate capillaries and a second portion of first plate capillaries.

8. An arrayer apparatus according to Claim 7 wherein the solution exit surface of the first plate further defines a plurality of first plate channels, with each first plate channel extending from one capillary in the first portion of first plate capillaries to a corresponding indentation in a plurality of first plate indentations also defined by the solution exit surface of the first plate, the first plate indentations also being arranged in an array.

9. An arrayer apparatus according to Claim 8 wherein the second plate defines a plurality of second plate capillaries arranged in an array, the array further comprising a first part of the second plate capillaries corresponding to the second portion of the first plate capillaries and a second part of second plate capillaries corresponding to the first plate indentations.

10. An arrayer apparatus according to Claim 9 wherein the solution exit surface of the second plate further defines a plurality of second plate channels, with each second plate channel extending from one capillary in the first part of the second plate capillaries to a corresponding indentation in a plurality of second plate

indentations also defined by the solution exit surface of the second plate, the second plate indentations also being arranged in an array.

11. An arrayer apparatus according to Claim 10 wherein the flow control device defines a plurality of flow control capillaries arranged in an array, the flow control capillaries corresponding to the second plate indentations and to the second part of the second plate capillaries corresponding to the first plate indentations.

12. An arrayer apparatus according to Claim 1 further comprising a stamper head disposed between the flow control device and the substrate and in communication with the flow control device, the stamper head defining a plurality of stamper capillaries arranged in an array and corresponding to the flow control capillaries, the stamper head being configured to channel the predetermined amount of the solution from the flow control device to the substrate.

13. An arrayer apparatus according to Claim 12 wherein the stamper capillaries are configured to have a reduced volume with respect to the flow control capillaries.

14. An arrayer apparatus according to Claim 13 wherein the stamper capillaries are each configured to have a diameter smaller than diameter of each flow control capillary such that smaller diameter of the stamper capillary provides a reduced volume per unit length with respect to the flow control capillary.

15. An arrayer apparatus according to Claim 1 wherein the flow control device comprises at least one of a pump and a valve.

16. An arrayer apparatus according to Claim 1 wherein the flow control capillaries are each configured to have a voltage applied between two points along the length thereof so as to form an electrostatic pump capable of causing the solution to flow therealong.

17. An arrayer apparatus according to Claim 16 wherein the voltage is capable of being adjusted so as to form an electrostatic valve capable of selectively preventing flow of the solution through the flow control capillaries.

18. An arrayer apparatus according to Claim 16 wherein the voltage is capable of being controlled such that only a predetermined amount of the solution flows through the flow control capillaries.

19. An arrayer apparatus according to Claim 1 wherein at least one of the flow control device and the at least one plate are comprised of silicon.

20. A volume-reducing arrayer apparatus adapted to deliver a predetermined amount of a liquid solution to a substrate, said arrayer apparatus comprising:

a reservoir for containing the solution;

at least one arrayer block disposed between the reservoir and the substrate and in communication with the reservoir, the at least one arrayer block defining at least one arrayer capillary extending toward the substrate, the at least one arrayer capillary being configured to have a reduced volume with respect to the reservoir so as to receive a portion of the solution therefrom;

a flow control device disposed between the at least one arrayer block and the substrate and in communication with the at least one arrayer block, the flow control device defining at least one flow control capillary corresponding to the at least one arrayer capillary, extending toward the substrate, and being configured to have a reduced volume with respect to the at least one plate capillary, the flow control device being further configured to control the flow of a predetermined amount of the solution through the at least one flow control capillary; and

a stamper head disposed between the flow control device and the substrate and in communication with the flow control device, the stamper head defining at least one stamper capillary corresponding to the at least one flow control capillary and extending toward the substrate, the at least

one stamper capillary being configured to have the predetermined amount of the solution channeled therethrough by the flow control device, from the at least one flow control capillary to the substrate.

21. An arrayer apparatus according to Claim 20 wherein the at least one flow control capillary is configured to have a diameter smaller than the diameter of the at least one arrayer capillary such that smaller diameter of the flow control capillary provides a reduced volume per unit length with respect to the arrayer capillary.

22. An arrayer apparatus according to Claim 20 wherein the at least one stamper capillary is configured to have a diameter smaller than the diameter of the at least one flow control capillary such that smaller diameter of the stamper capillary provides a reduced volume per unit length with respect to the flow control capillary.

23. An arrayer apparatus according to Claim 20 wherein the at least one arrayer block defines a plurality of arrayer capillaries arranged in an array.

24. An arrayer apparatus according to Claim 23 wherein the flow control device defines a plurality of flow control capillaries arranged in an array corresponding to the arrayer capillary array.

25. An arrayer apparatus according to Claim 24 wherein the stamper head defines a plurality of stamper capillaries arranged in an array corresponding to the flow control capillary array.

26. An arrayer apparatus according to Claim 24 wherein at least one of the flow control device and the at least one arrayer block defines a plurality of channels configured such that each channel operably connects one arrayer capillary in the arrayer capillary array to one corresponding flow control capillary in the flow control device array.

27. An arrayer apparatus according to Claim 20 wherein the at least one arrayer block comprises a first arrayer block and a second arrayer block, with each arrayer block having a solution entrance surface and a solution exit surface, and wherein the solution exit surface of the first arrayer block is configured to operably engage the solution entrance surface of the second arrayer block.

28. An arrayer apparatus according to Claim 27 wherein the first arrayer block defines a plurality of first arrayer capillaries arranged in an array, the array further comprising a first portion of first arrayer capillaries and a second portion of first arrayer capillaries.

29. An arrayer apparatus according to Claim 28 wherein the solution exit surface of the first arrayer block further defines a plurality of first arrayer channels, with each first arrayer channel extending from one capillary in the first portion of first arrayer capillaries to a corresponding indentation in a plurality of first arrayer indentations also defined by the solution exit surface of the first arrayer block, the first arrayer indentations also being arranged in an array.

30. An arrayer apparatus according to Claim 29 wherein the second arrayer block defines a plurality of second arrayer capillaries arranged in an array, the array further comprising a first part of the second arrayer capillaries corresponding to the second portion of the first arrayer capillaries and a second part of second arrayer capillaries corresponding to the first arrayer indentations.

31. An arrayer apparatus according to Claim 30 wherein the solution exit surface of the second arrayer block further defines a plurality of second arrayer channels, with each second arrayer channel extending from one capillary in the first part of the second arrayer capillaries to a corresponding indentation in a plurality of second arrayer indentations also defined by the solution exit surface of the second arrayer block, the second arrayer indentations also being arranged in an array.

32. An arrayer apparatus according to Claim 31 wherein the flow control device defines a plurality of flow control capillaries arranged in an array, the flow

control capillaries corresponding to the second arrayer indentations and to the second part of the second arrayer capillaries corresponding to the first arrayer indentations.

33. An arrayer apparatus according to Claim 20 wherein the flow control device comprises at least one of a pump and a valve.

34. An arrayer apparatus according to Claim 20 wherein the flow control capillaries are each configured to have a voltage applied between two points along the length thereof so as to form an electrostatic pump capable of causing the solution to flow therealong.

35. An arrayer apparatus according to Claim 34 wherein the voltage is capable of being adjusted so as to form an electrostatic valve capable of selectively preventing flow of the solution through the flow control capillaries.

36. An arrayer apparatus according to Claim 34 wherein the voltage is capable of being controlled such that only a predetermined amount of the solution flows through the flow control capillaries.

37. An arrayer apparatus according to Claim 20 wherein at least one of the stamper head, the flow control device, and the at least one arrayer block are comprised of silicon.

38. A method of fabricating a volume-reducing arrayer apparatus adapted to deliver a predetermined amount of a liquid solution from a reservoir to a substrate, said method comprising:

operably engaging a first plate defining at least one first plate capillary, the at least one first plate capillary being in communication with the reservoir and having a reduced volume with respect to the reservoir so as to receive a portion of the solution therefrom, with a second plate defining at least one second plate capillary, the at least one second plate capillary corresponding to the at least one first plate capillary and having a reduced volume with respect thereto, so as to form a

continuous passage between each first plate capillary and the corresponding second plate capillary; and

operably engaging a flow control device with each of the second plate capillaries, the flow control device being configured to control the flow of the solution through each second plate capillary, from each first plate capillary to the substrate.

39. A method according to Claim 38 further comprising forming the at least one first plate capillary in the first plate, such that the at least one first plate capillary is configured to extend toward the substrate, prior to engaging the first plate with the second plate.

40. A method according to Claim 38 further comprising forming the at least one second plate capillary in the second plate, such that the at least one second plate capillary is configured to extend toward the substrate, prior to engaging the first plate with the second plate.

41. A method according to Claim 40 wherein forming the at least one second plate capillary further comprises forming the at least one second plate capillary to have a diameter smaller than the diameter of the at least one first plate capillary such that smaller diameter of the second plate capillary provides a reduced volume per unit length with respect to the first plate capillary.

42. A method according to Claim 38 further comprising forming a plurality of first plate capillaries in the first plate, such that the first plate capillaries are arranged in an array, prior to engaging the first plate with the second plate.

43. A method according to Claim 42 further comprising forming a plurality of second plate capillaries in the second plate, such that the second plate capillaries are arranged in an array corresponding to the first plate capillary array, prior to engaging the first plate with the second plate.

44. A method according to Claim 43 further comprising forming a plurality of channels in at least one of the first plate and the second plate such that each channel operably connects one first plate capillary in the first plate capillary array to one corresponding second plate capillary in the second plate capillary array.

45. A method according to Claim 38 wherein the first plate comprises a first arrayer block and a second arrayer block, with each arrayer block having a solution entrance surface and a solution exit surface, and the method further comprises operably engaging the solution exit surface of the first arrayer block with the solution entrance surface of the second arrayer block.

46. A method according to Claim 45 further comprising forming a plurality of first arrayer capillaries in the first arrayer block, the first arrayer capillaries being arranged in an array comprising a first portion of first arrayer capillaries and a second portion of first arrayer capillaries.

47. A method according to Claim 46 further comprising forming a plurality of first arrayer channels in the solution exit surface of the first arrayer block, each first arrayer channel extending from one capillary in the first portion of first arrayer capillaries to a corresponding indentation in a plurality of first arrayer indentations also defined by the solution exit surface of the first arrayer block, the first arrayer indentations also being arranged in an array.

48. A method according to Claim 47 further comprising forming a plurality of second arrayer capillaries in the second arrayer block, the second arrayer capillaries being arranged in an array further comprising a first part of the second arrayer capillaries corresponding to the second portion of the first arrayer capillaries and a second part of second arrayer capillaries corresponding to the first arrayer indentations.

49. A method according to Claim 48 further comprising forming a plurality of second arrayer channels in the solution exit surface of the second arrayer block, each second arrayer channel extending from one capillary in the first part of the

second arrayer capillaries to a corresponding indentation in a plurality of second arrayer indentations also defined by the solution exit surface of the second arrayer block, the second arrayer indentations also being arranged in an array.

50. A method according to Claim 49 further comprising forming a plurality of second plate capillaries in the second plate, the second plate capillaries being arranged in an array and corresponding to the second arrayer indentations and to the second part of the second arrayer capillaries corresponding to the first arrayer indentations.

51. A method according to Claim 38 further comprising applying a voltage between two points along the length of each second plate capillary so as to form an electrostatic pump capable of causing the solution to flow therealong.

52. A method according to Claim 51 further comprising adjusting the voltage so as to form an electrostatic valve capable of selectively preventing flow of the solution through the second plate capillaries.

53. A method according to Claim 51 further comprising controlling the voltage such that only a predetermined amount of the solution flows through the second plate capillaries.

54. A method according to Claim 38 further comprising operably engaging a stamper head with the second plate, the stamper head defining at least one stamper capillary corresponding to the at least one second plate capillary, the at least one stamper capillary being configured to have the predetermined amount of the solution channeled therethrough by the flow control device, from the at least one second plate capillary to the substrate.

55. A method according to Claim 54 wherein forming the at least one stamper capillary further comprises forming the at least one stamper capillary to have a diameter smaller than diameter of the at least one second plate capillary such that

smaller diameter of the stamper capillary provides a reduced volume per unit length with respect to the second plate capillary.

56. A method according to Claim 54 further comprising forming a plurality of stamper capillaries in the stamper head such that the stamper capillaries are arranged in an array.

57. A method of delivering a biosample solution to a biochip, said method comprising:

delivering portions of the biosample solution from a microtiter plate containing the biosample solution to a plurality of first plate capillaries defined by a first plate, the first plate capillaries being arranged in an array, each first plate capillary having a predetermined diameter;

delivering at least a portion of the biosample solution from each of the first plate capillaries to a corresponding second plate capillary in a plurality of second plate capillaries defined by a second plate, the second plate capillaries being arranged in an array corresponding to the first plate capillary array, each of the second plate capillaries having a diameter smaller than the first plate capillary diameter such that the smaller diameter of the second plate capillary provides a reduced volume per unit length of the solution therein with respect to the first plate capillary; and

delivering at least a portion of the biosample solution from each of the second plate capillaries to a substrate to form an array of biosamples on the substrate.

58. A method according to Claim 57 further comprising channeling at least a portion of the biosample solution from each of the first plate capillaries to a corresponding second plate capillary through a channel operably connected therebetween, the channels being defined by at least one of the first plate and the second plate such that each first plate capillary in the first plate capillary array is operably connected to a corresponding second plate capillary in the second plate capillary array.

59. A method according to Claim 57 wherein the first plate comprises a first arrayer block defining a plurality of first arrayer capillaries arranged in an array and a second arrayer block defining a plurality of second arrayer capillaries arranged in an array, with each arrayer block having a solution entrance surface and a solution exit surface and the solution exit surface of the first arrayer block engaging the solution entrance surface of the second arrayer block, such that the method further comprises delivering at least a portion of the biosample solution from each first arrayer capillary in a first part of the first arrayer capillary array to a corresponding second arrayer capillary in a first part of the second arrayer capillary array, each of the second arrayer capillaries in the first part of the second arrayer capillary array having a diameter smaller than the corresponding first arrayer capillary diameter such that the smaller diameter of the second arrayer capillary provides a reduced volume per unit length of the solution therein with respect to the first arrayer capillary.

60. A method according to Claim 59 further comprising channeling at least a portion of the biosample solution from each of the first arrayer capillaries in the first part of the first arrayer capillary array to the corresponding second arrayer capillary in the first part of the second arrayer capillary array through a first arrayer channel operably connected therebetween, the first arrayer channels being defined by at least one of the first arrayer block and the second arrayer block such that each first arrayer capillary in the first part of the first arrayer capillary array is operably connected to a corresponding second arrayer capillary in first part of the second arrayer capillary array.

61. A method according to Claim 60 further comprising delivering at least a portion of the biosample solution from each first arrayer capillary in a second part of the first arrayer capillary array to a corresponding second arrayer capillary in a second part of the second arrayer capillary array, each of the second arrayer capillaries in the second part of the second arrayer capillary array being substantially similar to the corresponding first arrayer capillary in the second part of the first arrayer capillary array and in direct communication therewith.

62. A method according to Claim 61 further comprising channeling at least a portion of the biosample solution from each of the second arrayer capillaries in the second part of the second arrayer capillary array to the corresponding second plate capillary in the second plate capillary array through a second arrayer channel operably connected therebetween, the second arrayer channels being defined by the second arrayer block such that each second arrayer capillary in the second part of the second arrayer capillary array is operably connected to a corresponding second plate capillary in the second plate capillary array.

63. A method according to Claim 62 further comprising delivering at least a portion of the biosample solution from each second arrayer capillary in the first part of the second arrayer capillary array to a corresponding second plate capillary in the second plate capillary array, each of the second arrayer capillaries in the first part of the second arrayer capillary array being substantially similar to the corresponding second plate capillary in the second plate capillary array and in direct communication therewith.

64. A method according to Claim 57 further comprising applying a voltage between two points along the length of each second plate capillary so as to form an electrostatic pump capable of causing the solution to flow therealong.

65. A method according to Claim 64 further comprising adjusting the voltage so as to form an electrostatic valve capable of selectively preventing flow of the solution through the second plate capillaries.

66. A method according to Claim 64 further comprising controlling the voltage such that only a predetermined amount of the solution flows through the second plate capillaries.

67. A method according to Claim 57 wherein delivering at least a portion of the biosample solution from each of the second plate capillaries to a substrate further comprises delivering at least a portion of the biosample solution from each of the second plate capillaries to a substrate through a stamper head operably engaged

with the second plate, the stamper head defining an array of stamper capillaries corresponding to the array of second plate capillaries, the stamper capillary array being configured to have a predetermined amount of the biosample solution channeled therethrough from the second plate capillaries to the substrate.

68. A method according to Claim 67 wherein delivering at least a portion of the biosample solution from each of the second plate capillaries to a substrate further comprises delivering at least a portion of the biosample solution from each of the second plate capillaries to a substrate through a stamper head operably engaged with the second plate and defining an array of stamper capillaries corresponding to the array of second plate capillaries, the stamper capillaries each having a diameter smaller than diameter of the corresponding second plate capillary such that smaller diameter of the stamper capillary provides a reduced volume per unit length with respect to the second plate capillary.

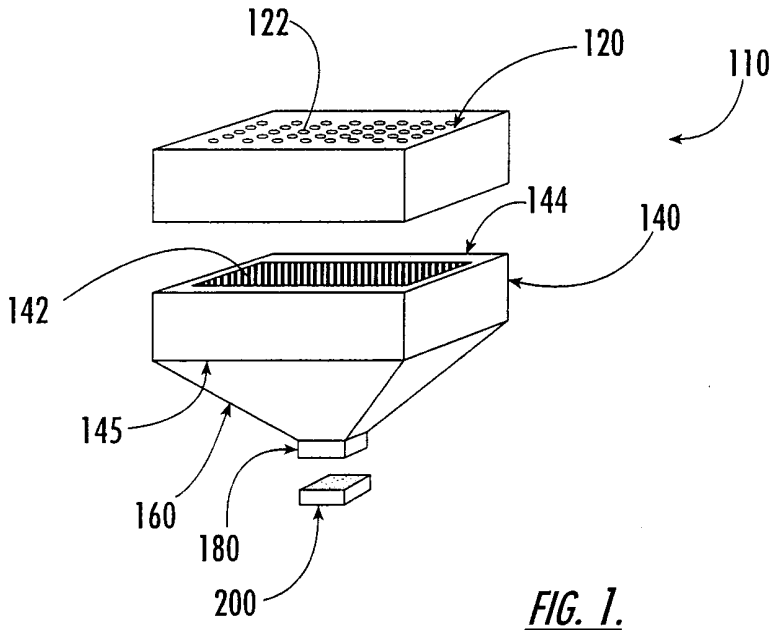

FIG. 1.

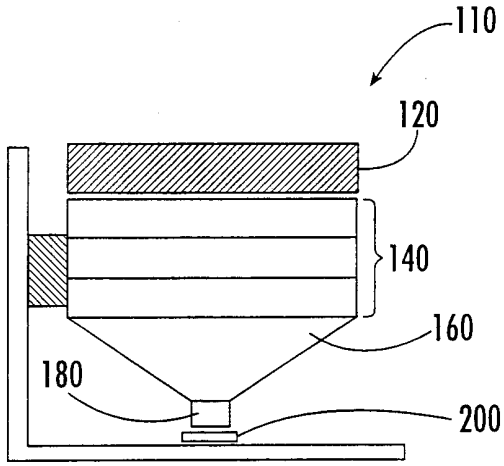

FIG. 2.

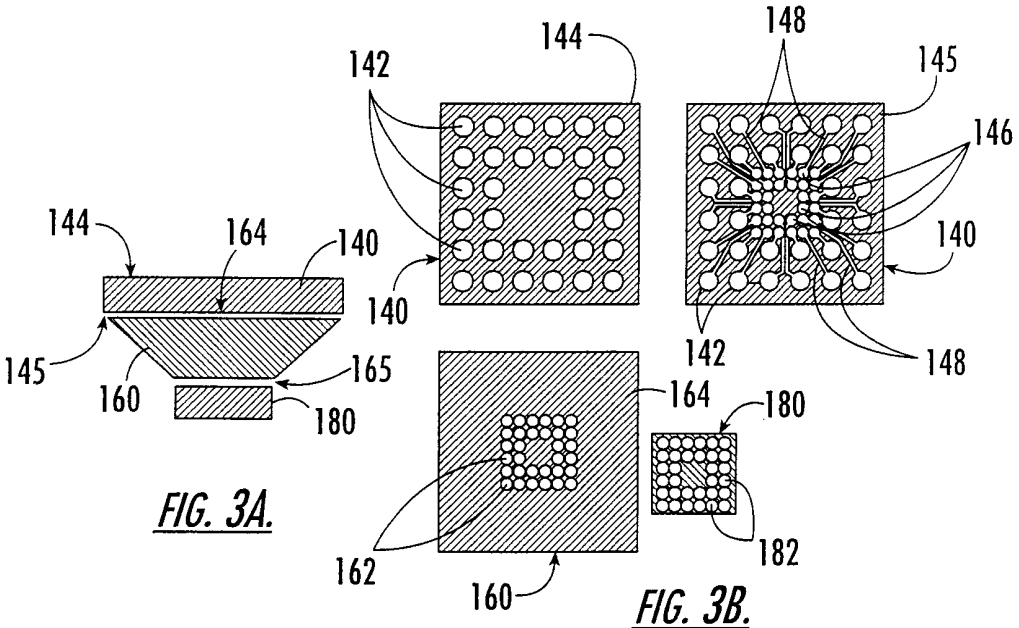

FIG. 3A.

FIG. 3B.

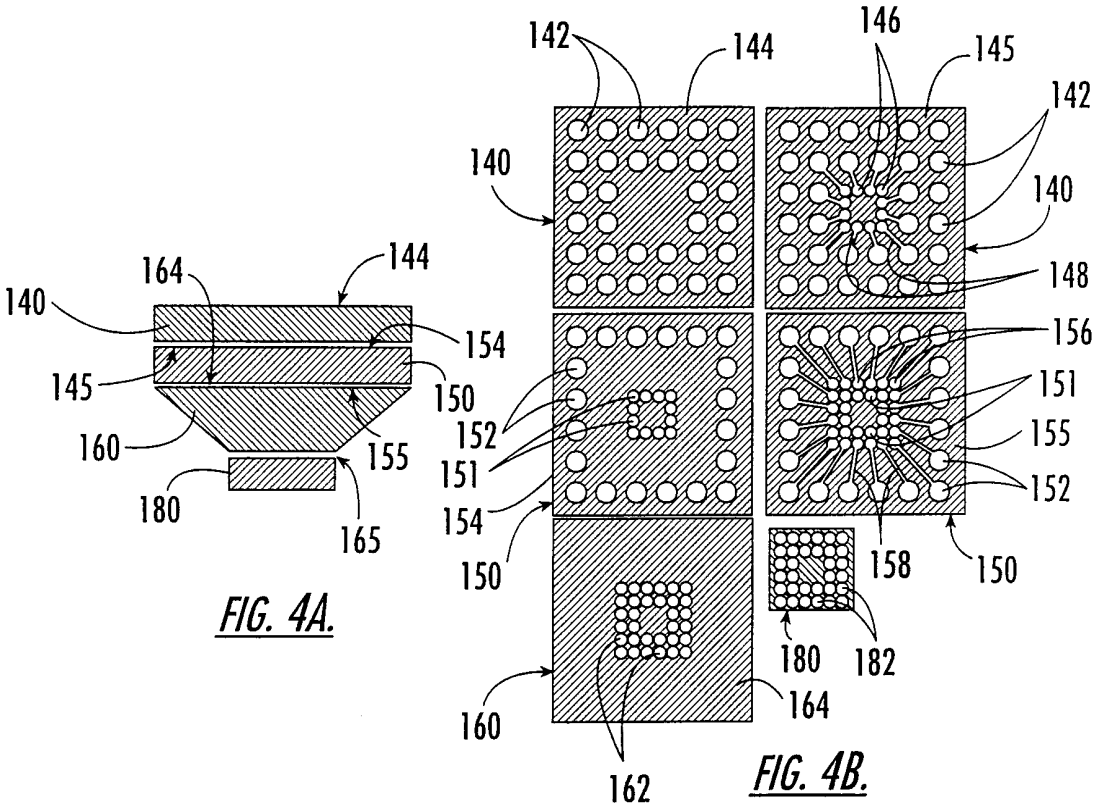

FIG. 4A.

FIG. 4B.

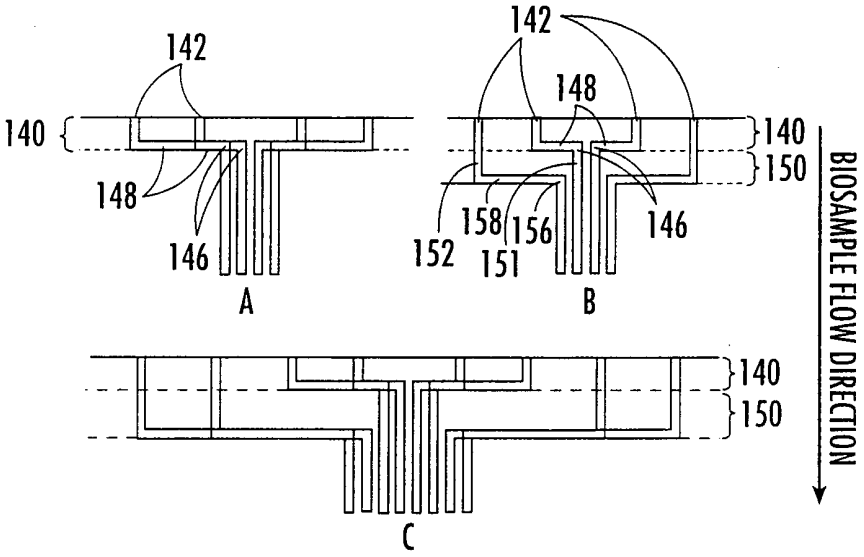
142
140
148
146
A
142
148
140
150
158
156
152
151
146
B
BIOSAMPLE FLOW DIRECTION
140
150
C

FIG. 5.

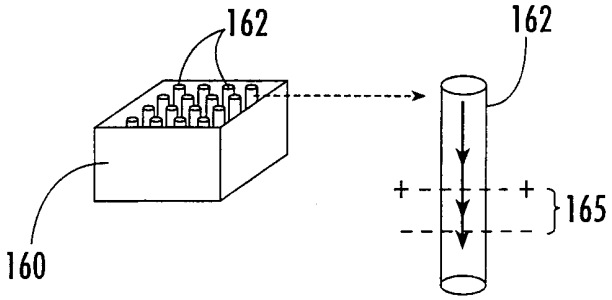
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FIG. 6.

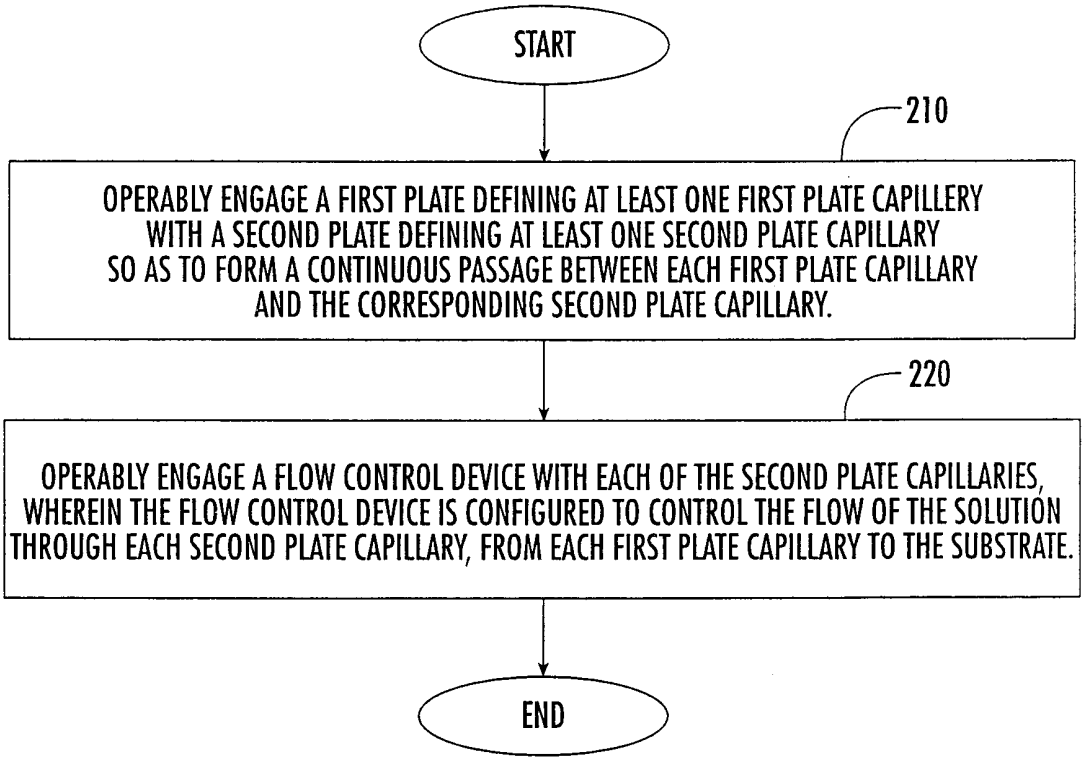
START
210
OPERABLY ENGAGE A FIRST PLATE DEFINING AT LEAST ONE FIRST PLATE CAPILLERY WITH A SECOND PLATE DEFINING AT LEAST ONE SECOND PLATE CAPILLARY SO AS TO FORM A CONTINUOUS PASSAGE BETWEEN EACH FIRST PLATE CAPILLARY AND THE CORRESPONDING SECOND PLATE CAPILLARY.
220
OPERABLY ENGAGE A FLOW CONTROL DEVICE WITH EACH OF THE SECOND PLATE CAPILLARIES, WHEREIN THE FLOW CONTROL DEVICE IS CONFIGURED TO CONTROL THE FLOW OF THE SOLUTION THROUGH EACH SECOND PLATE CAPILLARY, FROM EACH FIRST PLATE CAPILLARY TO THE SUBSTRATE.
END

FIG. 7.

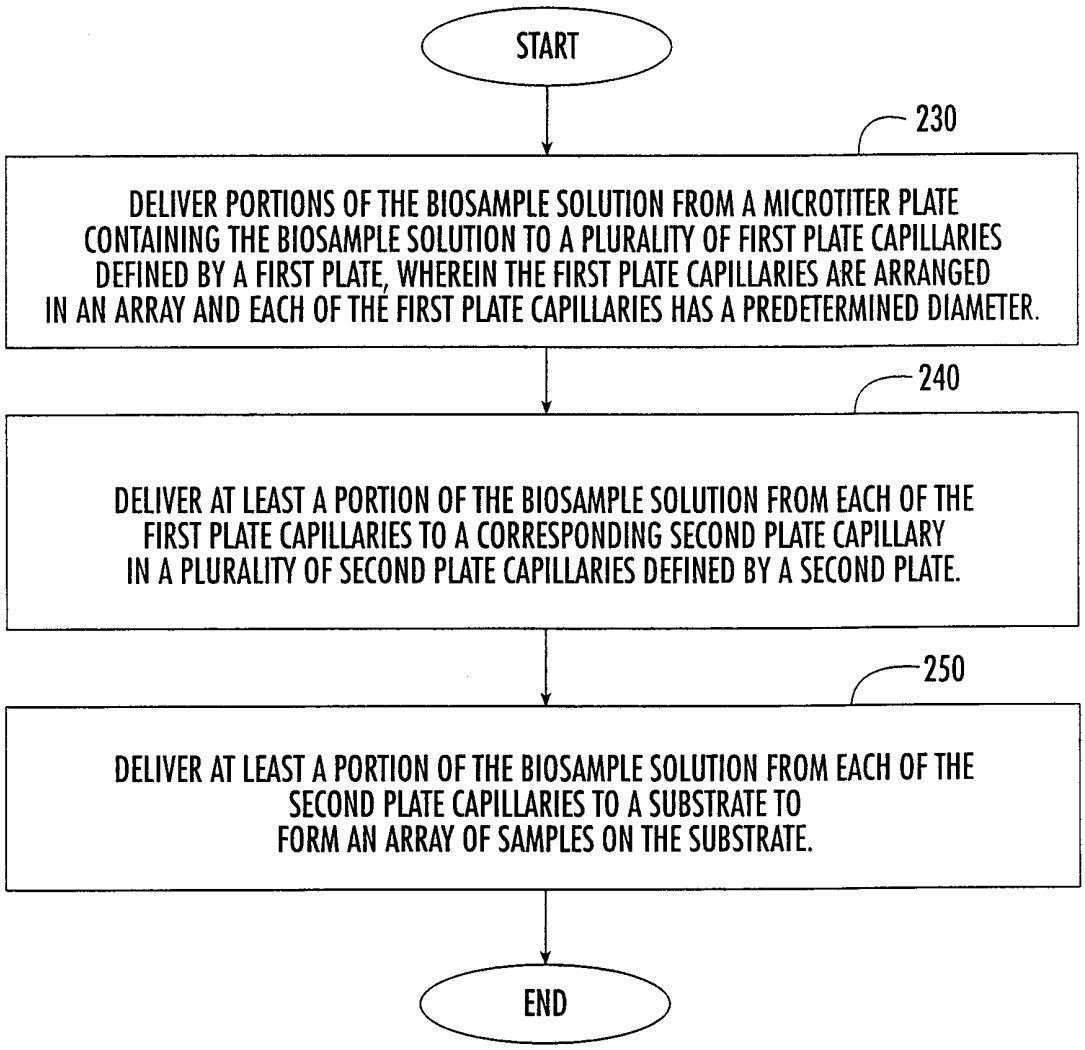
START
230
DELIVER PORTIONS OF THE BIOSAMPLE SOLUTION FROM A MICROTITER PLATE CONTAINING THE BIOSAMPLE SOLUTION TO A PLURALITY OF FIRST PLATE CAPILLARIES DEFINED BY A FIRST PLATE, WHEREIN THE FIRST PLATE CAPILLARIES ARE ARRANGED IN AN ARRAY AND EACH OF THE FIRST PLATE CAPILLARIES HAS A PREDETERMINED DIAMETER.
240
DELIVER AT LEAST A PORTION OF THE BIOSAMPLE SOLUTION FROM EACH OF THE FIRST PLATE CAPILLARIES TO A CORRESPONDING SECOND PLATE CAPILLARY IN A PLURALITY OF SECOND PLATE CAPILLARIES DEFINED BY A SECOND PLATE.
250
DELIVER AT LEAST A PORTION OF THE BIOSAMPLE SOLUTION FROM EACH OF THE SECOND PLATE CAPILLARIES TO A SUBSTRATE TO FORM AN ARRAY OF SAMPLES ON THE SUBSTRATE.
END

FIG. 8.

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/US 00/27690

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01J19/00 B01L3/00 B01L3/02

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 7 B01J B01L

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 197 12 195 A (UNIV SCHILLER JENA) 24 September 1998 (1998-09-24) abstract column 3, line 19 -column 4, line 7 column 4, line 47 - line 53; claims 6-8; figures 1-3 ---	1-14, 20-32, 38-50, 54-63, 67,68
X	PATENT ABSTRACTS OF JAPAN vol. 1995, no. 01, 28 February 1995 (1995-02-28) & JP 06 294771 A (HITACHI LTD), 21 October 1994 (1994-10-21) abstract; figure 1 --- -/--	1-37

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 document but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2001	18/01/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 508 200 A (THAYER PHILLIP ET AL) 16 April 1996 (1996-04-16) abstract column 8, line 11 - line 39; figures 8,9	1,3-15, 20,23-33
A	US 4 085 780 A (HOLLEY JOHN ERNEST FOSTER) 25 April 1978 (1978-04-25) abstract; figure 1	1,20,38, 57
A	US 4 446 104 A (HAEMMERLING GUENTER ET AL) 1 May 1984 (1984-05-01) abstract; claims 1-6; figures 1-3	1-3, 20-23
P,X	WO 99 55460 A (CORNING INC) 4 November 1999 (1999-11-04) abstract page 11, line 13 -page 12, line 8 page 14, line 14 -page 15, line 12 page 26, line 21 -page 28, line 26; claims 1-43; figures 1,11,12	1-37, 57-68
P,X	WO 00 49382 A (PERKIN ELMER CORP) 24 August 2000 (2000-08-24) abstract page 34, line 10 -page 36, line 6; claims 21-31; figures 9-11	1-14, 20-32

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter al Application No
PCT/US 00/27690

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19712195 A	24-09-1998	NONE	
JP 06294771 A	21-10-1994	JP 2974537 B	10-11-1999
US 5508200 A	16-04-1996	NONE	
US 4085780 A	25-04-1978	GB 1520745 A	09-08-1978
		DE 2545777 A	15-04-1976
		FR 2288305 A	14-05-1976
		IT 1043307 B	20-02-1980
		JP 1266269 C	27-05-1985
		JP 51085779 A	27-07-1976
		JP 59044577 B	30-10-1984
US 4446104 A	01-05-1984	DE 3047265 A	15-07-1982
		CH 652829 A	29-11-1985
		FI 814027 A	17-06-1982
		NL 8105125 A	16-07-1982
		SE 8107384 A	17-06-1982
WO 9955460 A	04-11-1999	EP 0955084 A	10-11-1999
		AU 3552499 A	16-11-1999
		AU 3760499 A	16-11-1999
		WO 9955461 A	04-11-1999
WO 0049382 A	24-08-2000	NONE	