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(54) FLUID PROCESSING DEVICE COMPRISING SURFACE TENSION CONTROLLED VALVE

(75) Inventor: **Sergey V. Ermakov**, Hayward, CA (US)

Correspondence Address:
KILYK & BOWERSOX, P.L.L.C.
3603 CHAIN BRIDGE ROAD
SUITE E
FAIRFAX, VA 22030 (US)

(73) Assignee: **Applera Corporation**, Foster City, CA

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(60) Provisional application No. 60/642,828, filed on Jan. 11, 2005.

Publication Classification

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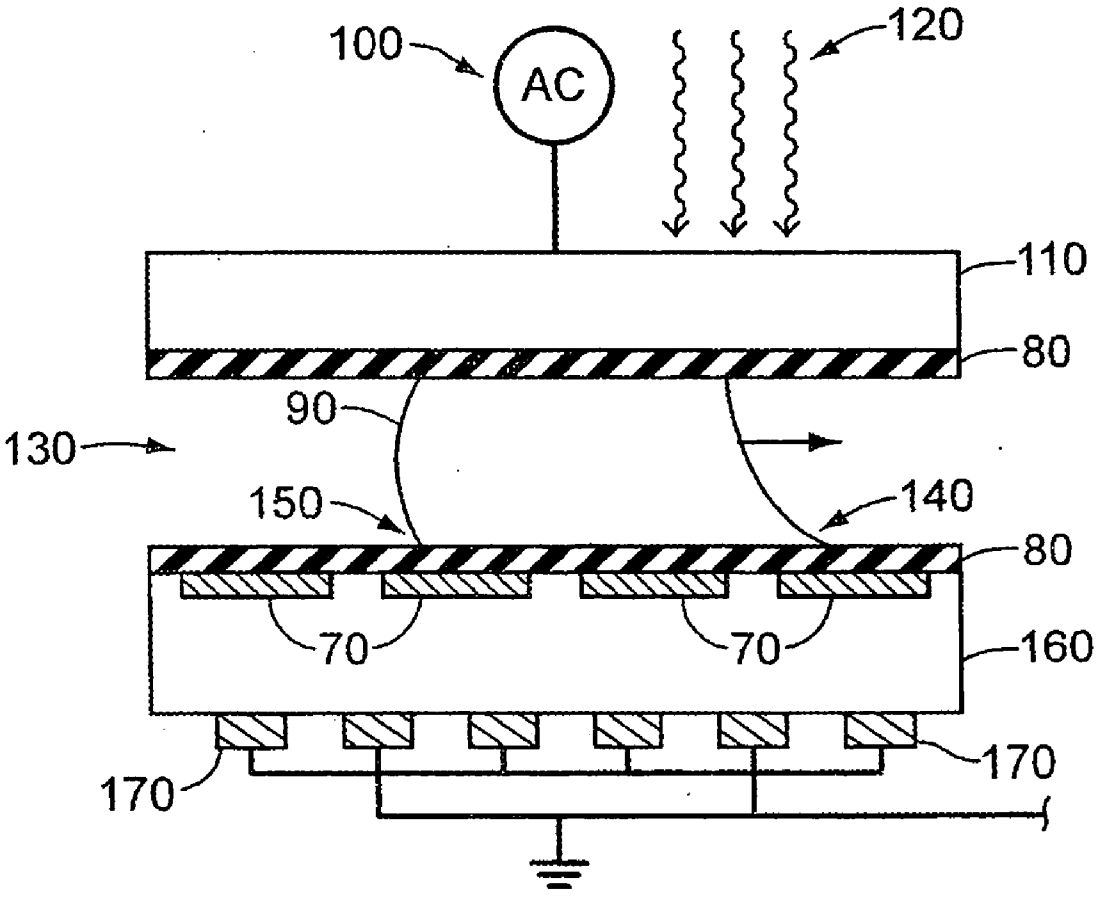
(52) **U.S. Cl.** **422/130**

(57) **ABSTRACT**

A fluid processing device adapted to produce different oligomers in a plurality of respective reaction sites and methods of using the same are provided. The fluid processing device can comprise a first manifold for delivering reactants to the plurality of reaction sites, and a second manifold for removing waste from, and optionally delivering wash fluid to, the plurality of reaction sites. Surface tension controlled valves can be disposed in fluid communication with the first manifold, the second manifold, or both, and can selectively allow reactants and/or fluids into the reaction sites. A method of making oligonucleotides is also provided.



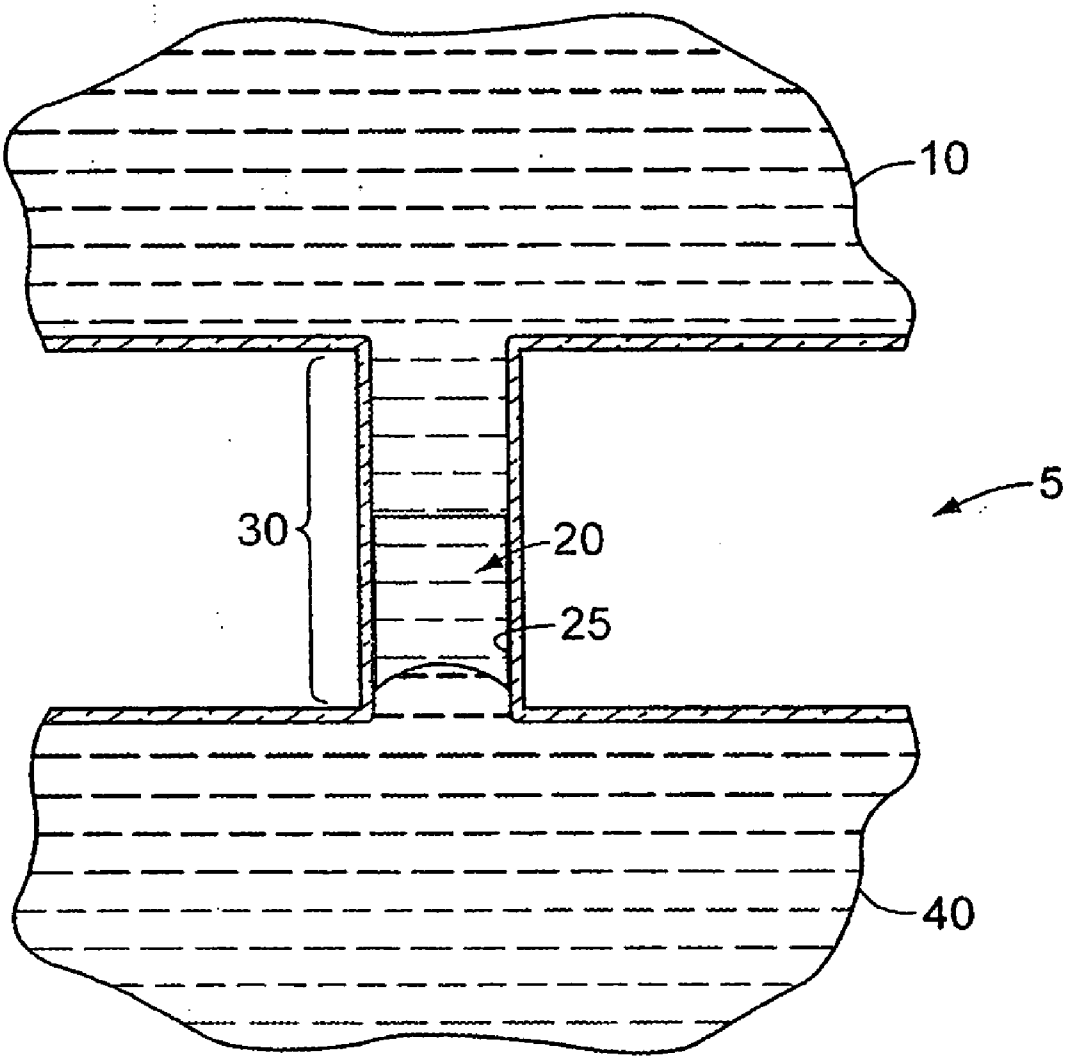


FIG. 1

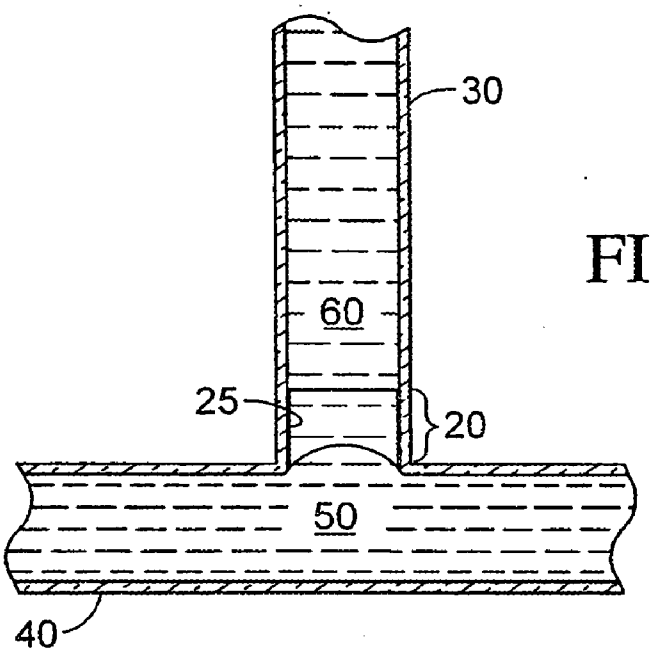


FIG. 2A

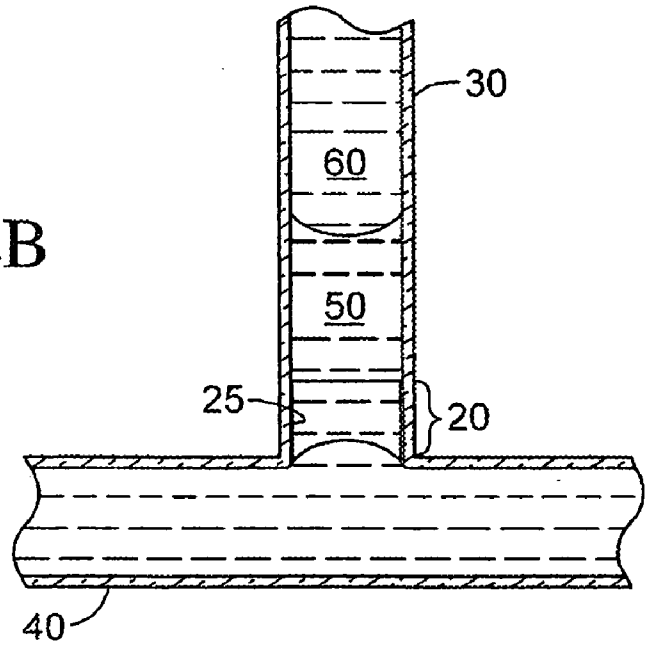


FIG. 2B

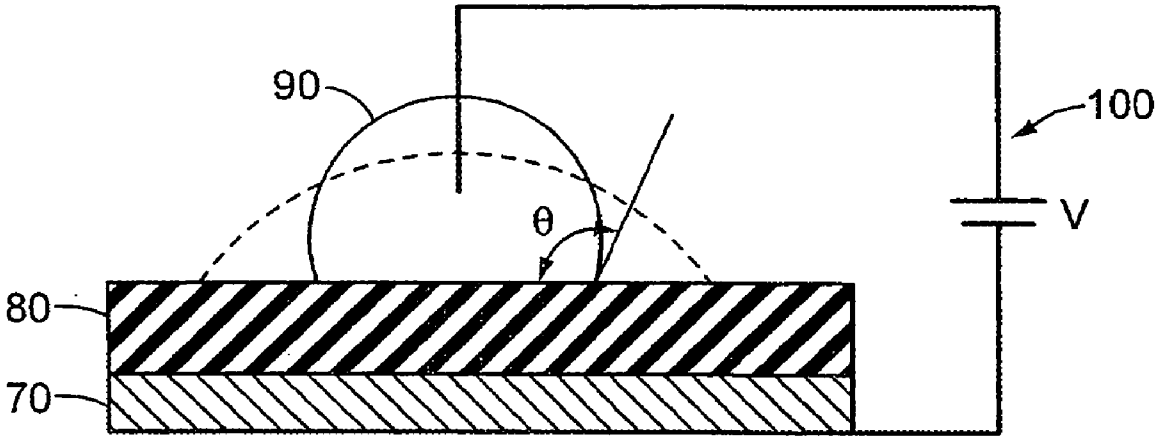


FIG. 3

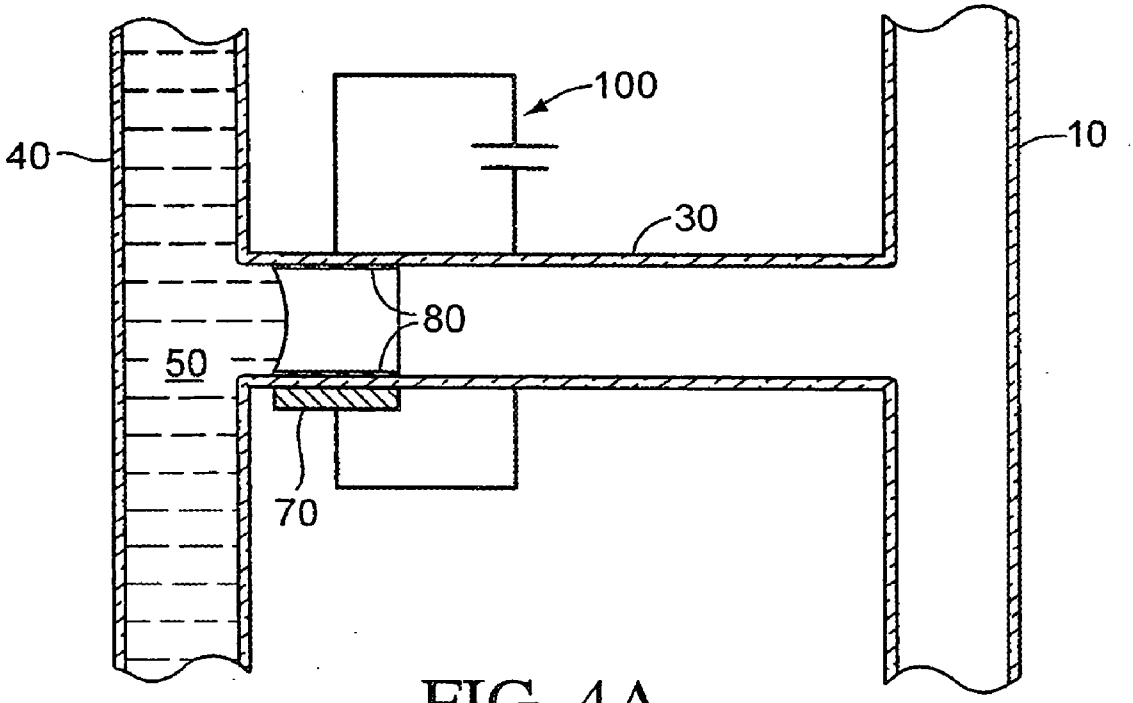


FIG. 4A

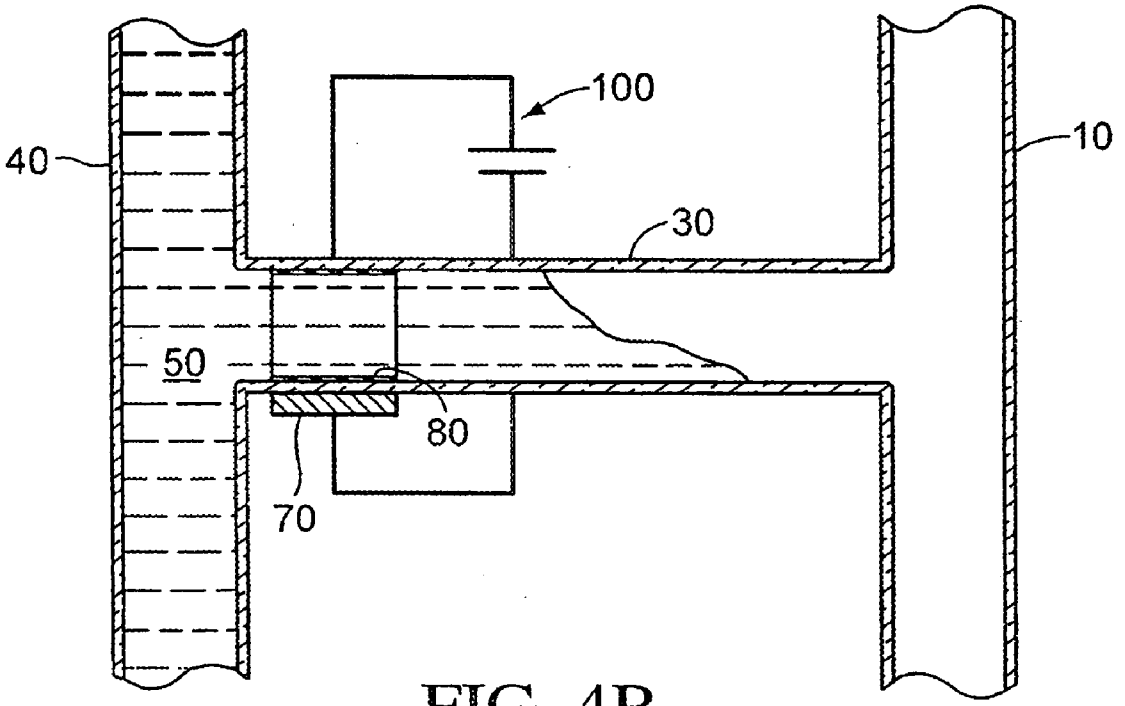


FIG. 4B

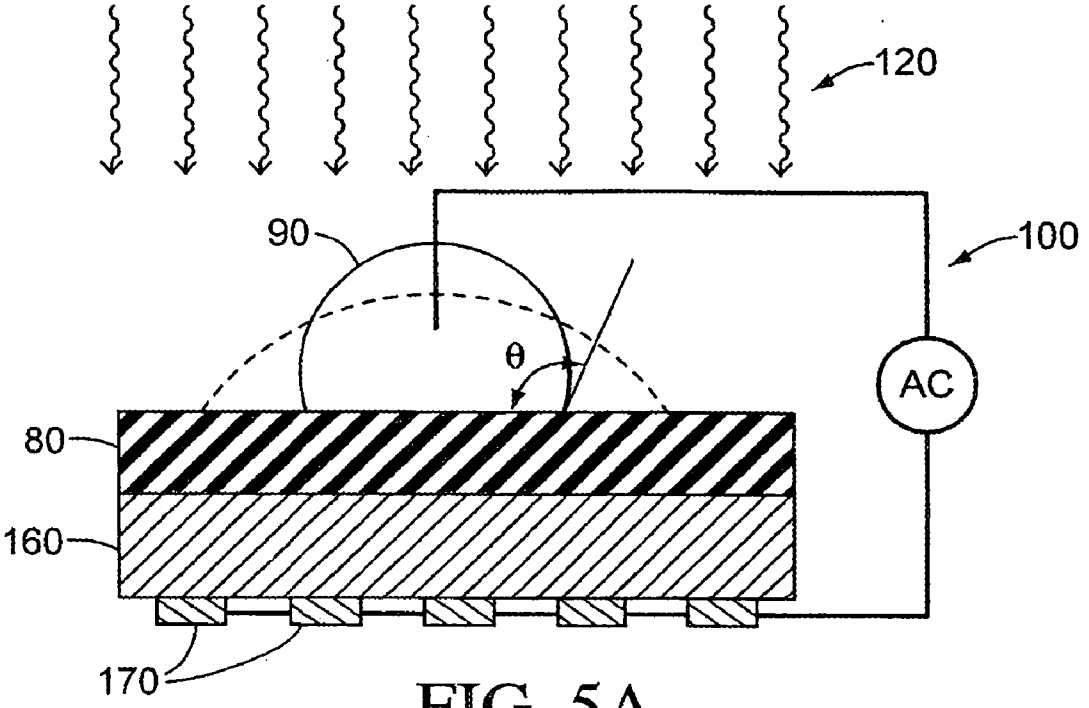


FIG. 5A

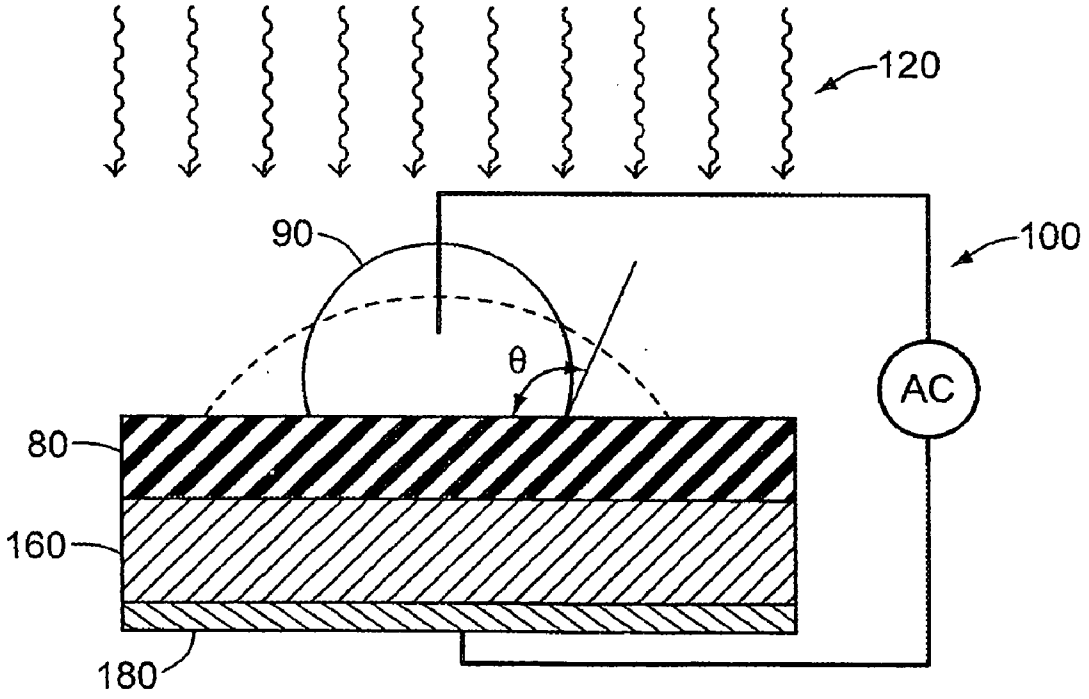


FIG. 5B

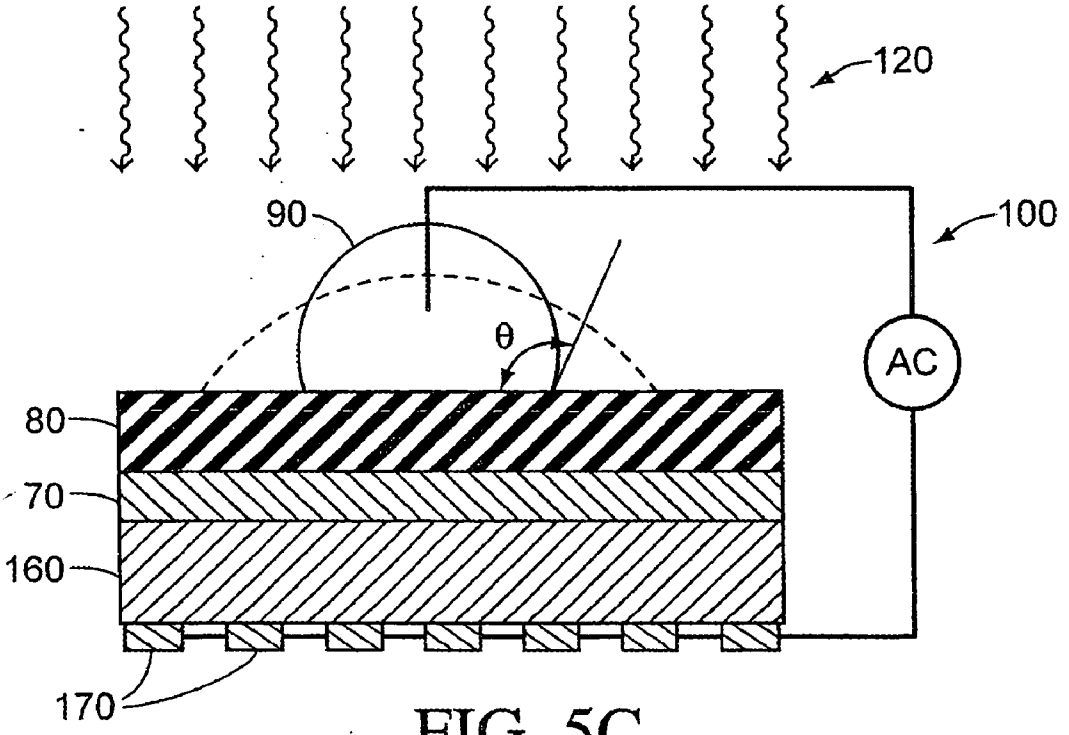

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FIG. 5C

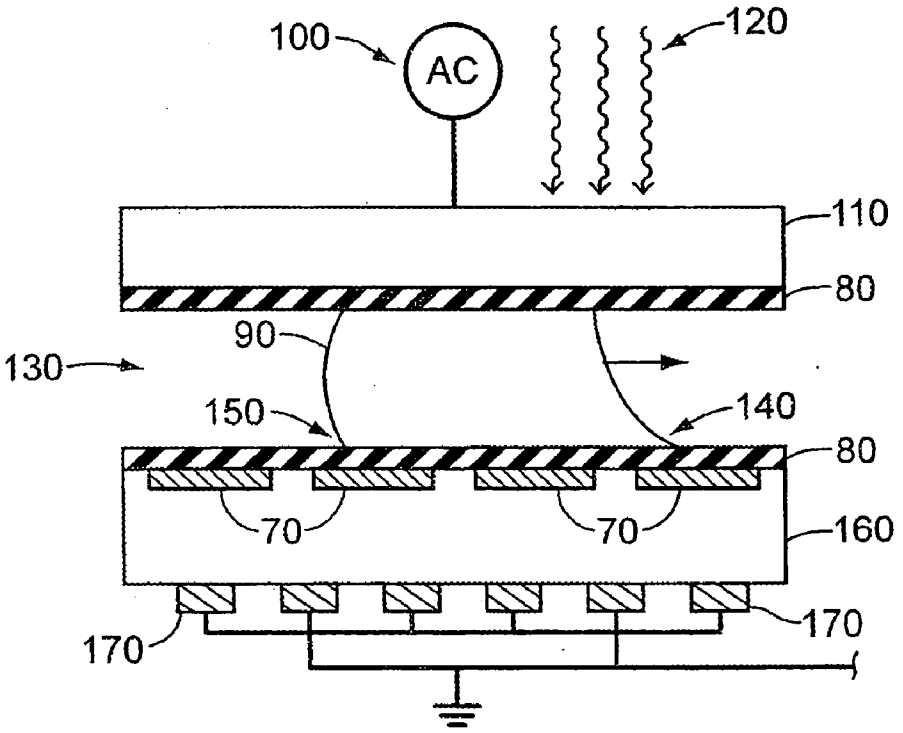
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FIG. 6A

FIG. 6B

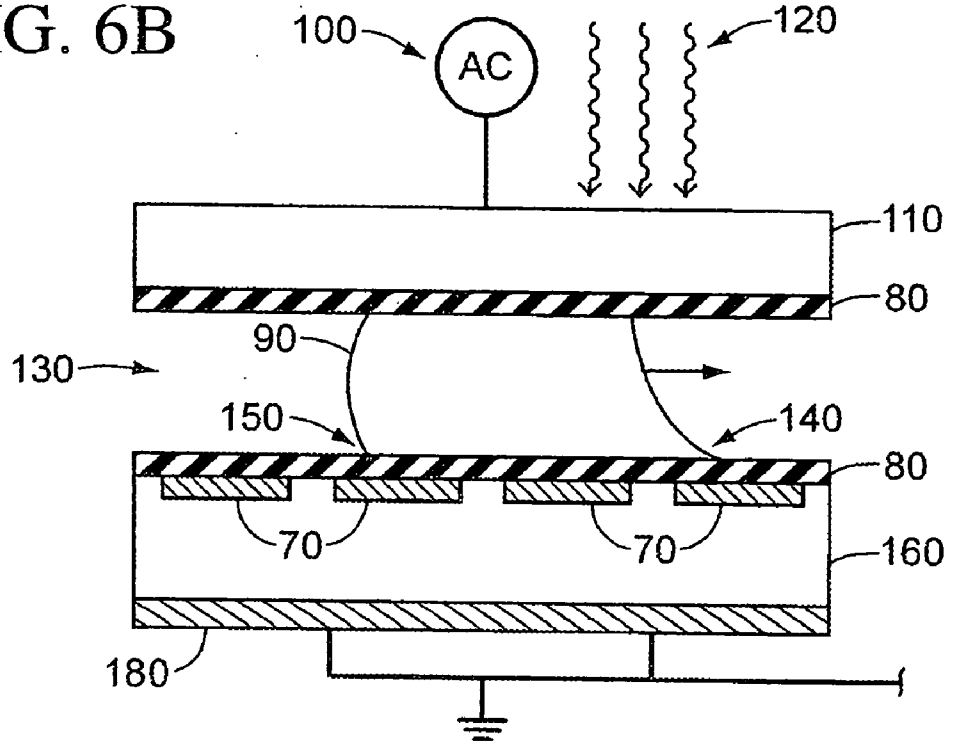
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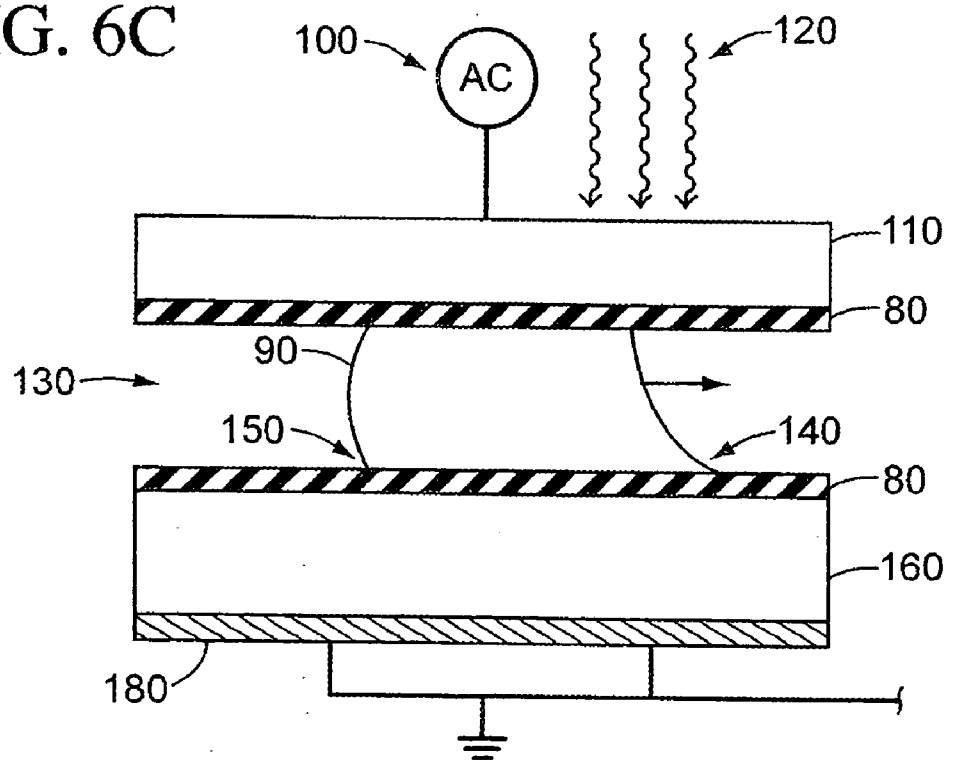
FIG. 6C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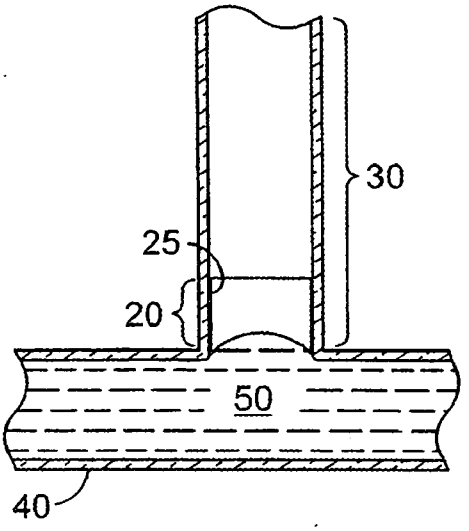

FIG. 7A

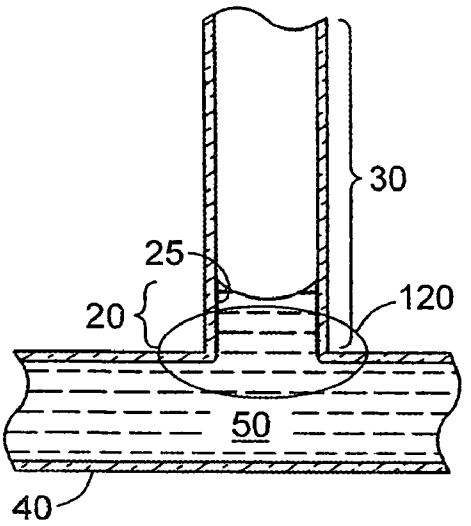

FIG. 7B

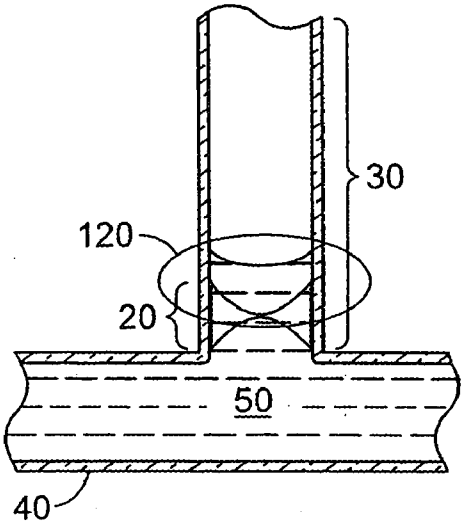

FIG. 7C

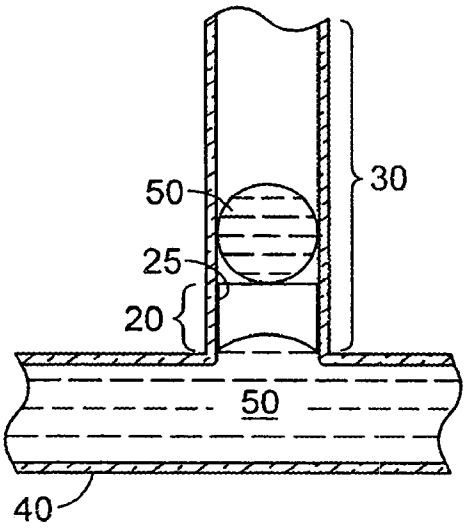

FIG. 7D

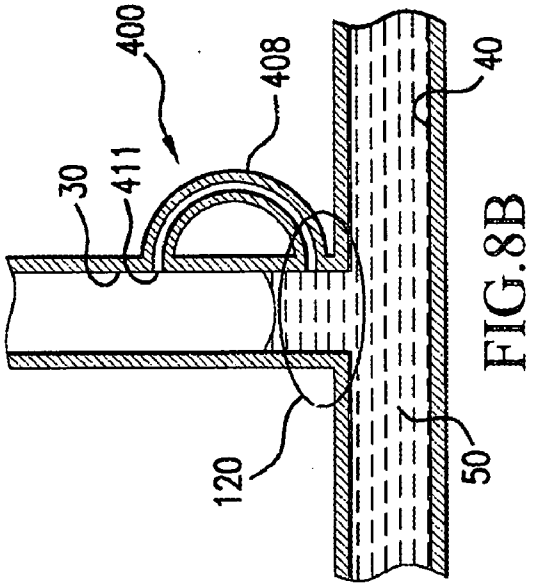

FIG.8B

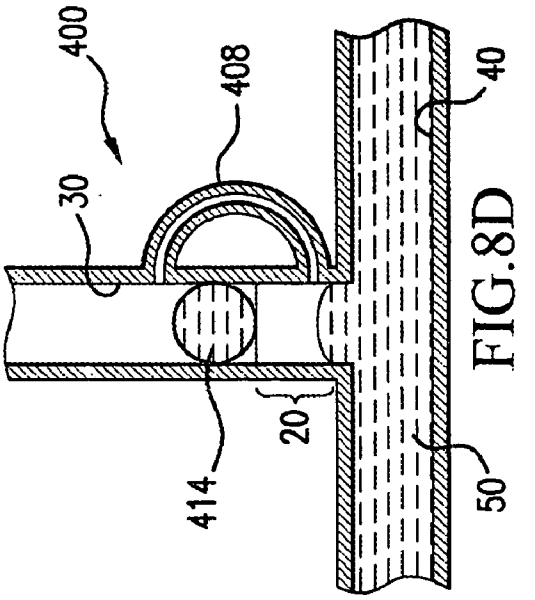

FIG.8D

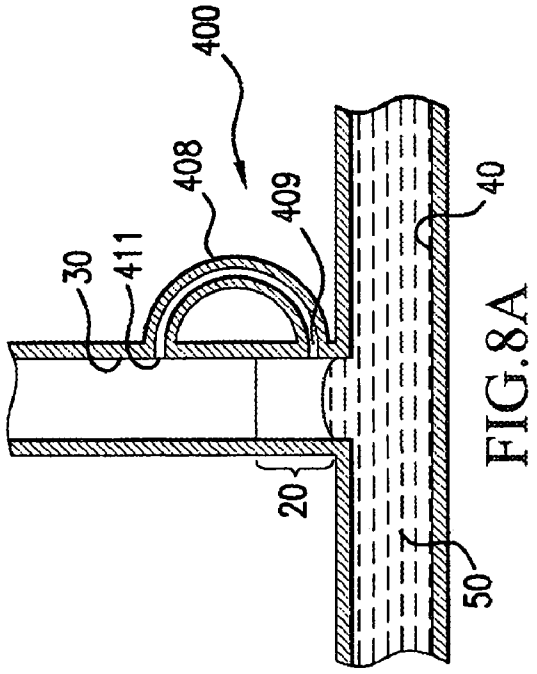

FIG.8A

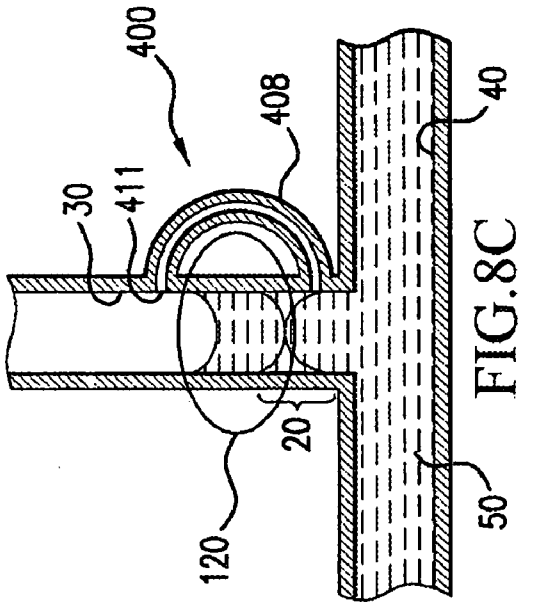

FIG.8C

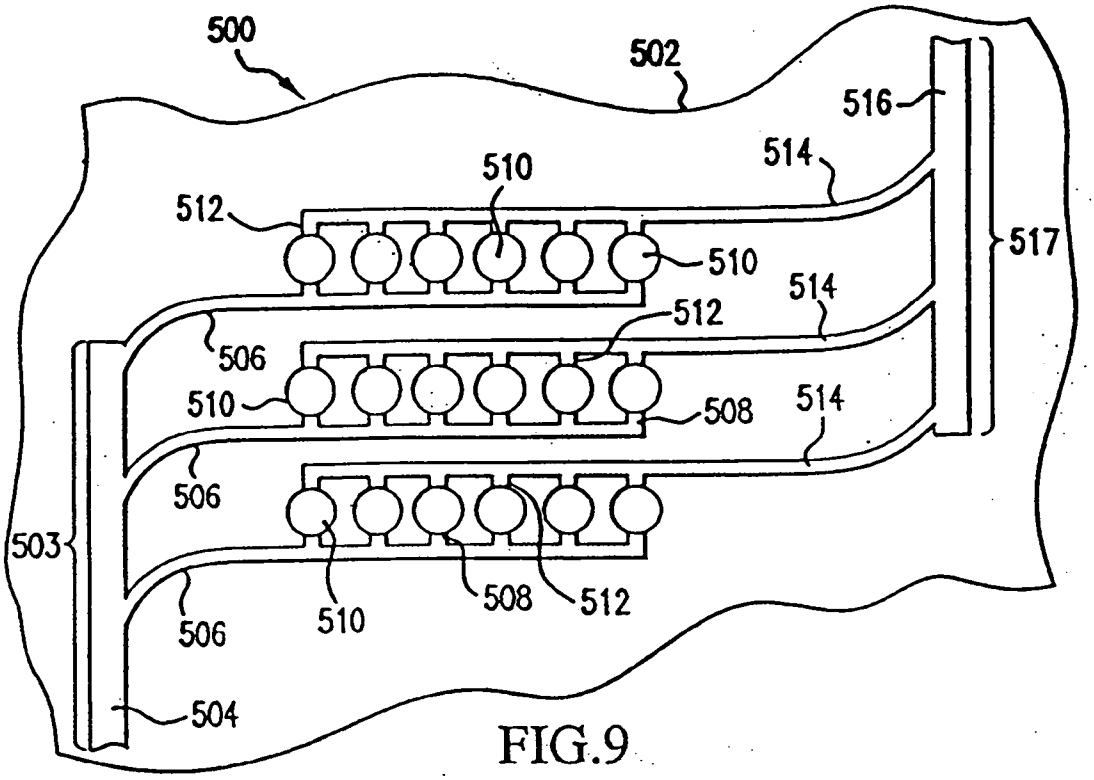
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FIG.9

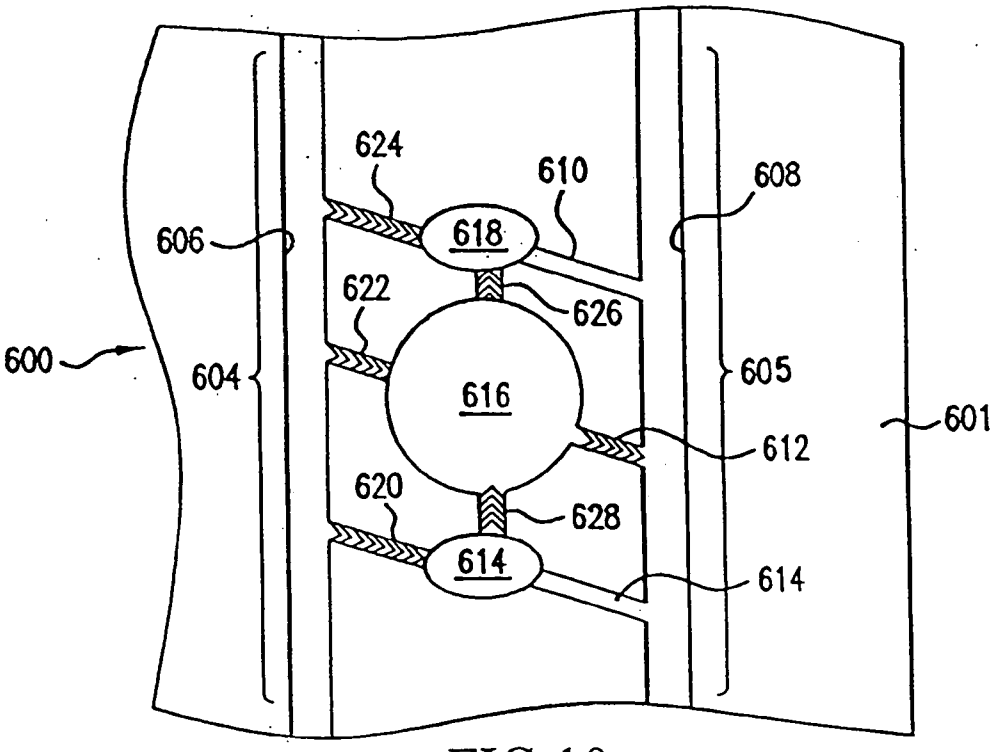
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FIG.10

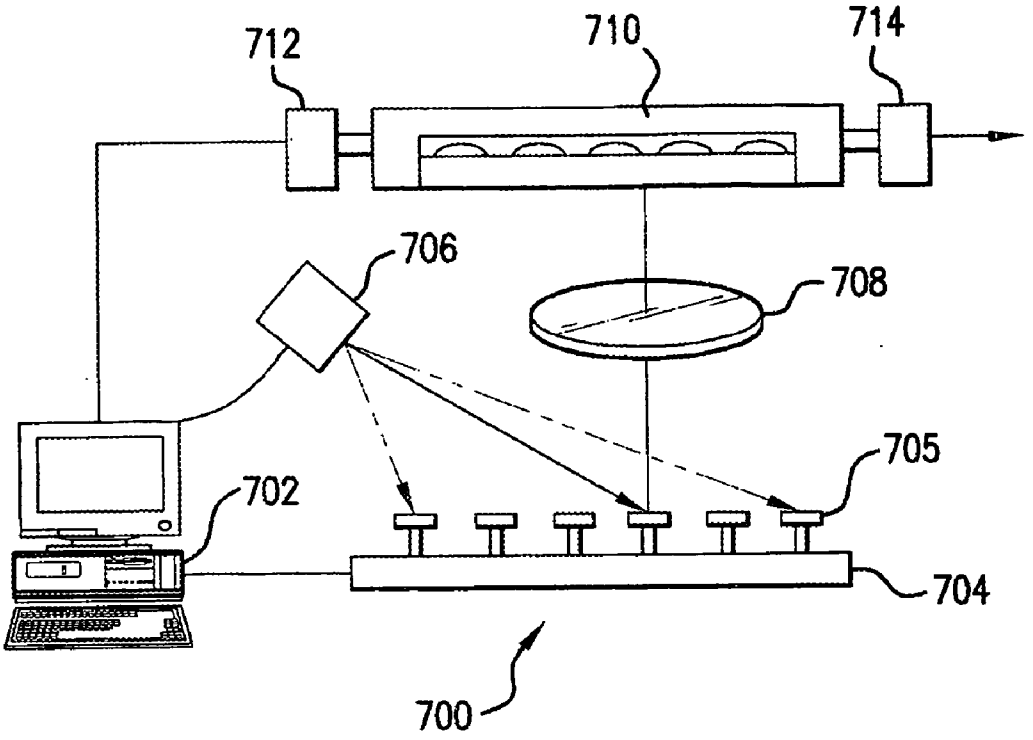


FIG.11

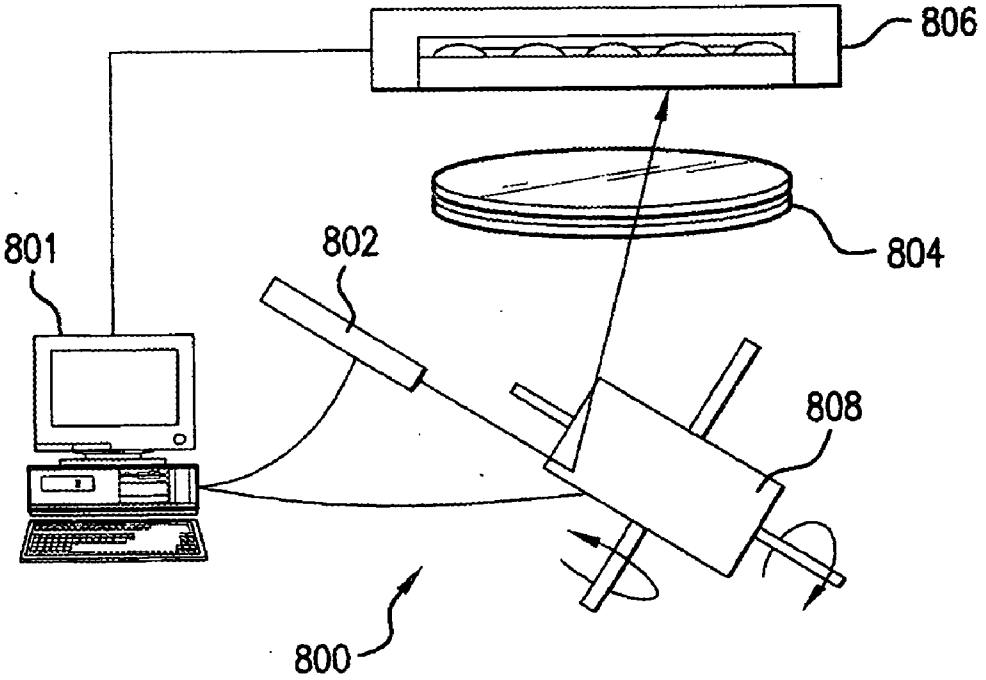


FIG.12

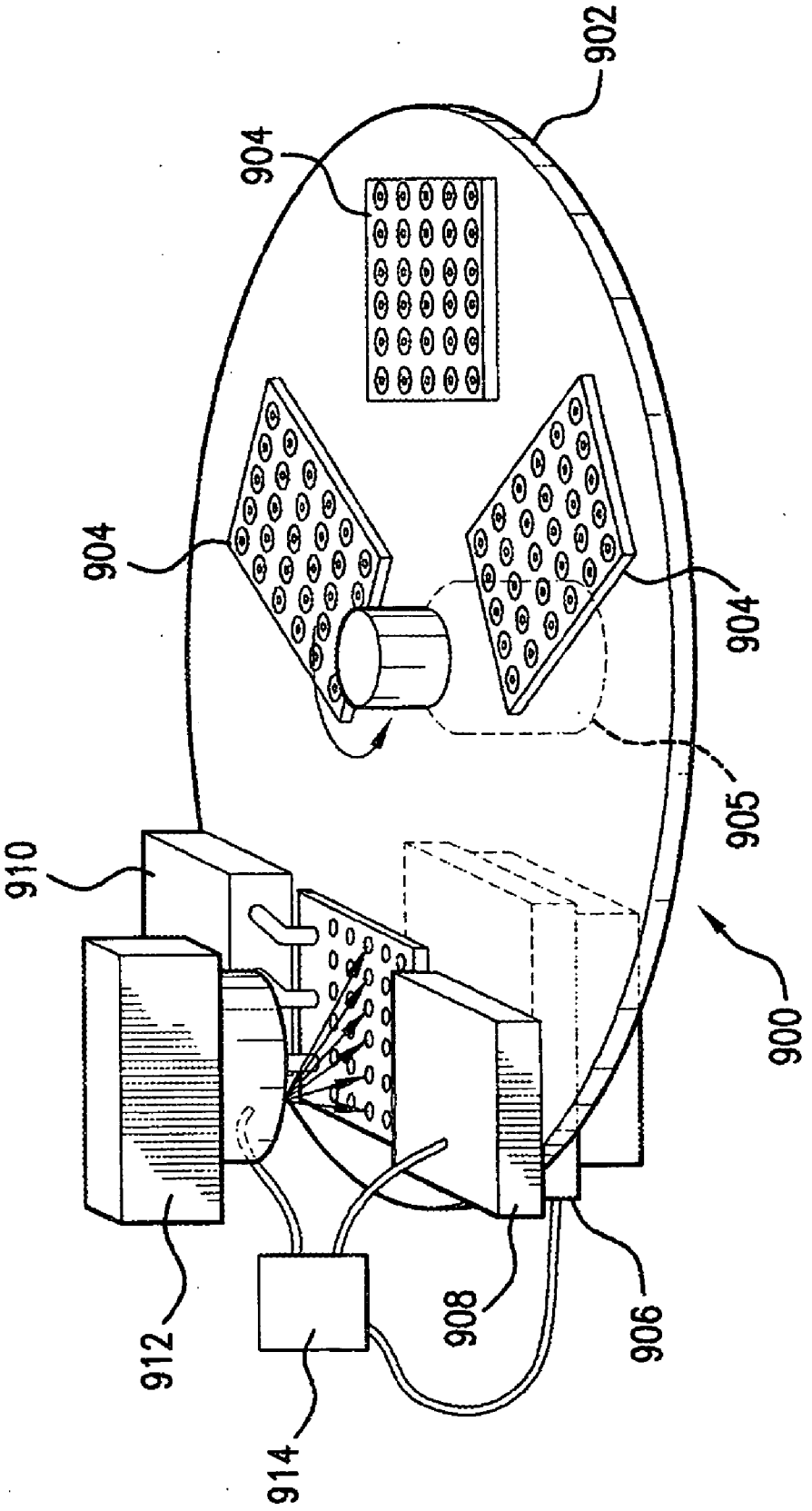


FIG. 13

FLUID PROCESSING DEVICE COMPRISING SURFACE TENSION CONTROLLED VALVE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 11/092,180 filed on Mar. 29, 2005, and claims the benefit under 35 U.S.C. § 119(e) of Provisional Application No. 60/642,828 filed on Jan. 11, 2005, each of which is incorporated herein by reference in its entirety.

FIELD

[0002] The present teachings relate to valves in fluid processing devices, and methods for using the same.

INTRODUCTION

[0003] One of the challenges encountered in fluid processing devices, particularly devices designed for high throughput operations, is how to effectively control fluid flow. A need exists to individually and independently control fluid flow in thousands of micro-channels without resorting to the fabrication of sophisticated valving systems that can make microfluidic devices very expensive.

SUMMARY

[0004] According to various embodiments, a device and method for controlling fluid flow in a microfluidic system is provided. In some embodiments, a surface tension controlled valving system for biological fluid is provided that can comprise a channel connected to an internal volume. The internal volume can be bound by an insulating layer resistant to the flow of the biological liquid, wherein the channel can be non-resistant to the flow of the biological liquid. A photoconductive material can be coupled to the insulating layer. An electrode can be coupled to the photoconductive material and can be configured to electrically couple with the insulating layer through the photoconductive material. A power source can be electrically coupled to the electrode. The power source can be configured to provide an electrical potential difference between the photoconductive material and the biological fluid. The photoconductive material can be activatable by light directed thereat, to provide an electrical potential difference between the insulating layer and the biological fluid. The electrical potential difference can be configured to reduce the resistance, of the insulating layer, to the flow of the biological liquid.

[0005] According to various embodiments, a device for biological fluid handling is provided that can comprise a valve configured for light activation. The device can comprise a channel connected to an internal volume. The internal volume can be bound by an insulating layer resistant to the flow of the biological liquid, wherein the channel can be non-resistant to the flow of the biological liquid. A photoconductive material can be coupled to the insulating layer. An electrode can be coupled to the photoconductive material and configured to electrically couple with the insulating layer through the photoconductive material. A power source can be electrically coupled to the electrode. The power source can be configured to provide an electrical potential difference between the photoconductive material and the biological fluid. A light source can be adapted to activate the photoconductive material thereby providing the electrical potential difference between the insulating layer and the biological fluid. The electrical potential difference can be configured to reduce the resistance of the insulating layer to the flow of the biological liquid.

[0006] According to various embodiments, a device for biological fluid handling is provided that can comprise means for providing the biological fluid to a valving means. The means for providing the biological fluid can be non-resistant to the flow of the biological liquid. The valving means can be resistant to the flow of the biological liquid. The device can comprise a means for electrowetting the valving means to reduce the resistance of the valving means to the flow of the biological liquid. The device can comprise a means for optically activating the means for electrowetting.

[0007] According to various embodiments, a fluid processing device is provided that can comprise a plurality of reaction sites. The fluid processing device can comprise a first fluid transport manifold in fluid communication with each of the plurality of reaction sites. The fluid processing device can comprise a second fluid transport manifold in fluid communication with each of the plurality of reaction sites. The fluid processing device can comprise a plurality of surface tension controlled valves disposed between the first manifold and at least one respective reaction site of the plurality of reaction sites. Each surface tension controlled valve can be in fluid communication with the first manifold and the at least one respective reaction site.

[0008] According to various embodiments, a method is provided for synthesizing oligonucleotides or other chemical structures, from component building blocks, the method can comprise introducing a first monomer into a first fluid distribution manifold of a fluid processing device, opening at least one surface tension control valve in fluid communication with both the first fluid distribution manifold and at least one respective reaction site, to form an open surface tension control valve; moving the first monomer from the first manifold, through the at least one open surface tension control valve, and into the at least one respective reaction site, and attaching the first monomer to a first structure in the at least one respective reaction site to form an extended structure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] Various embodiments of the present teachings are exemplified by the accompanying drawings which are incorporated in and constitute a part of this specification. The teachings are not limited to the embodiments depicted, and can include equivalent structures and methods as set forth in the following description and as would be known or recognized by those of ordinary skill in the art given the present teachings. In the drawings:

[0010] **FIG. 1** is a cross-sectional view of a channel and illustrates connecting two reservoirs;

[0011] **FIGS. 2A and 2B** are cross-sectional views illustrating the functioning of surface tension controlled valves;

[0012] **FIG. 3** is a side view of a surface tension controlled valve and illustrates movement of a liquid by electrowetting and illustrating in phantom the effect that actuation of a surface tension control valve can have on the shape of a drop of water;

[0013] **FIG. 4A** illustrates a surface tension controlled valve closed to the flow of a liquid;

[0014] **FIG. 4B** illustrates a surface tension controlled valve permitting the flow of a liquid;

[0015] **FIG. 5A-5C** illustrates movement of a liquid by opto-electrowetting. The figure illustrates in phantom the effect that actuation of a surface tension control valve can have on the shape of a drop of water;

[0016] **FIG. 6A-6C** illustrates moving a liquid through a channel via opto-electrowetting;

[0017] **FIG. 7A-7D** are cross-sectional views illustrating the operation of a light-activated surface tension controlled valve;

[0018] **FIG. 8A** is a cross-sectional view through a portion of a device according to various embodiments and showing a light-activated surface tension control valve in a closed state;

[0019] **FIG. 8B** is the same cross-sectional view as shown in **FIG. 8A**, but wherein the light-activated surface tension control valve is in an open state;

[0020] **FIG. 8C** is the same cross-sectional view as shown in **FIG. 8A**, but wherein the light-activated surface tension control valve is in an open state and liquid has passed through the valve;

[0021] **FIG. 8D** is the same cross-sectional view as shown in **FIG. 8A**, but wherein the valve is in a closed state after liquid has passed through the valve;

[0022] **FIG. 9** is a top plan view of a portion of a fluid processing device according to various embodiments;

[0023] **FIG. 10** is a top plan close-up view of a portion of a fluid processing device according to various embodiments;

[0024] **FIG. 11** is a perspective view of a system for processing a fluid processing device according to various embodiments;

[0025] **FIG. 12** is a perspective view of a system for processing a fluid processing device according to various embodiments; and

[0026] **FIG. 13** is a perspective view of yet another system for processing a fluid processing device according to various embodiments.

[0027] It is to be understood that both the foregoing general description, figures, and the following detailed description are exemplary and explanatory only.

DESCRIPTION OF VARIOUS EMBODIMENTS

[0028] Reference will now be made to various exemplary embodiments, examples of which are illustrated in the accompanying drawings. Wherever possible, the same reference numbers are used in the drawings and the description to refer to the same or like parts.

[0029] For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing quantities, percentages or proportions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0030] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, can inherently contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Moreover, all ranges disclosed herein are to be understood to encompass any and all subranges subsumed therein. For example, a range of "less than 10" includes any and all subranges between (and including) the minimum value of zero and the maximum value of 10, that is, any and all subranges having a minimum value of equal to or greater than zero and a maximum value of equal to or less than 10, e.g., 1 to 5.

[0031] It is noted that, as used in this specification and the appended claims, the singular forms "a,""an," and "the" can include plural referents unless expressly and unequivocally limited to one referent. Thus, for example, reference to "a channel species" can include two or more different channels. As used herein, the term "include" and its grammatical variants are intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that can be substituted or added to the listed items.

[0032] According to various embodiments, surface tension controlled valves can be operable with any biological liquid that can be manipulated by electrowetting forces. The term "biological liquid" as used herein refers to liquid with biomolecules, for example nucleic acids, peptides, enzymes, cells, etc. Biological liquids that are electrolytic can be used in the surface tension controlled valves according the present teachings. The term "electrolytic" can refer to a liquid containing substances dissolved therein, such as ionic salts, that can enable the liquid to conduct an electric current. By way of non-limiting example, biological liquids that can be used in the surface tension controlled valves according to the present teachings can include aqueous liquids, such as water and buffered saline, as well as non-aqueous fluids such as dimethylsulfoxide and other non-aqueous solvents. The biological liquids can include ionic liquids that can be used in surface tension controlled valves.

[0033] The term "ionic liquids" as used herein refers to salts that are liquid over a wide temperature range, including room temperature. The biological liquid can include various substances, particulate and otherwise. Such substances can include, for example, surfactants, including anionic, non-ionic, cationic, and amphoteric surfactants. The composition of the liquid, including the presence of surfactants, biomolecules, and other substances, can influence the surface wetting, and thus the contact angle, of the liquid.

[0034] The term "reflective material" as used herein refers to any material that can reflect a predetermined wavelength of light. Reflective materials can be a coating, a distinct layer, or a various components described herein can themselves act as a reflective materials. Some exemplary reflective materials comprise, for example, insulators, such as

SiO_2, TiN, SiON; semiconductor materials, such as silicon, germanium, silicon germanium, and compound semiconductors; polymers, such as Teflon®, Teflon® AF; an organic-inorganic hybrid material as disclosed above, or any other reflective material that will be known to one of ordinary skill in the art.

[0035] The term "device" as used herein refers to a device that can be used in any number of biological processes involving microfluidics, e.g. microscale amounts, of fluid or larger scale. Generally, microfluidics can involve handling volumes of one microliter or less. Features contained in microfluidic devices typically have millimeter to submicrometer dimensions, and can be adapted to the specific use of the microfluidic device.

[0036] The term "contact angle" as used herein describes the angle formed as a result of contact between a fluid and a solid surface. It reflects the interfacial affinity between the fluid and the solid surface, i.e., the wettability of the surface with respect to the fluid. The contact angle Θ is inversely correlated with interfacial affinity. When the fluid is in direct contact with the solid surface, the contact angle is at least 0° but less than 180°. A contact angle of 180° or greater indicates that the fluid is not in direct contact with the solid surface. In such a case, the fluid may directly contact the surface through an interposing fluid, or may be levitated from the solid surface. By way of illustration, a highly hydrophilic surface can form a low angle, e.g., 10, with respect to water droplets. Similarly, a highly hydrophobic surface can form a high contact angle, such as 179°, with respect to water.

[0037] According to various embodiments, a surface tension controlled valving system for biological fluid is provided that can comprise a channel connected to an internal volume for the valving system, the internal volume can be bound by an insulating layer resistant to the flow of the biological liquid and the channel cannot be resistant to the flow of the biological liquid. In various embodiments, the biological liquid can be an electrolyte.

[0038] According to various embodiments, a photoconductive material can be coupled to the insulating layer, an electrode can be coupled to the photoconductive material and configured to electrically couple with the insulating layer through the photoconductive material, and a power source can be electrically coupled to the electrode. In various embodiments, the power source can be configured to provide an electrical potential difference between the photoconductive material and the biological fluid, wherein the photoconductive material is activatable by directed light. The photoconductive material can provide an electrical potential difference between the insulating layer and the biological fluid.

[0039] According to various embodiments, the system can comprise a conductive layer between the insulating layer and the photoconductive material. An insulating material can be hydrophobic and can be resistant to the flow of a biological liquid. The resistance of insulating material to the flow of the biological liquid can also be lowered by using an insulating material that is hydrophilic when activated.

[0040] According to various embodiments, the channel can be connected to a first reservoir. A valve can control the flow of the biological liquid from the first reservoir to a second reservoir. The reservoir can comprise wells or channels.

[0041] According to various embodiments, a fluid processing device for biological fluid handling, is provided that can comprise a valve configured for light activation, a channel connected to an internal volume of the valve, wherein the internal volume can be bound by an insulating layer resistant to the flow of the biological liquid. In various embodiments, the device can comprise a channel that may not be resistant to the flow of the biological liquid, a photoconductive material electrically coupled to the insulating layer, an electrode coupled to the photoconductive material and configured to electrically couple with the insulating layer through the photoconductive material, and a power source electrically coupled to the electrode. In various embodiments, the power source can be electrically coupled to the photoconductive material and can be configured to provide an electrical potential difference across the insulating material. In various embodiments, a light source can be configured to activate the photoconductive material thereby providing the electrical potential difference across the insulating layer, wherein the electrical potential difference can be configured to reduce the resistance of the insulating layer to the flow of the biological liquid.

[0042] According to various embodiments, the light source can be a collimated light source. The collimated light source can comprise lasers, lamps, and/or light emitting diodes. In various embodiments, the light source can be directed over a portion of the photoconductive material by an array of microfabricated mirrors. In other embodiments, the light source can be a laser beam, and the laser beam can be directed over a portion of the photoconductive material by a galvo-mirror.

[0043] According to various embodiments, the light source can be configured to direct a beam of light through the insulating layer and through the biological liquid to reach the photoconductive material. The light source can be configured to direct a beam of light to the photoconductive material substantially axially.

[0044] According to various embodiments, the channel of the device can be configured to provide a waveguide for the light. In various embodiments, the walls of the channel can be the waveguide. In other embodiments, the channel can be the waveguide.

[0045] According to various embodiments, a fluid processing device for biological fluid handling is provided that can comprise a means for providing the biological fluid to a valving means. The means for providing the biological fluid can allow the flow of the biological liquid. The fluid processing device can comprise a valving means that can be resistant to the flow of the biological liquid. The fluid processing device can comprise a means for electrowetting the valving means to reduce the resistance of the valving means to the flow of the biological liquid. The fluid processing device and means for optically activating the means for electrowetting. In various embodiments, the means for optically activating can comprise a means for selectively positioning light onto a portion of the valving means.

[0046] According to various embodiments, a fluid processing device is provided that can comprise a plurality of reaction sites, a first fluid transport manifold in fluid communication with each of the plurality of the reaction sites, a second fluid transport manifold in fluid communication with each of the plurality of sites, a plurality of surface tension

controlled valves, or a combination thereof. In various embodiments, at least one of the plurality of surface tension controlled valves can be disposed between the first manifold and at least one respective reaction site of the plurality of reaction sites. Each surface tension controlled valve can be in fluid communication with the first manifold and the at least one respective reaction site. In various other embodiments, at least one of the plurality of surface tension controlled valves can comprise a light-actuated valve. In various embodiments, the system can comprise a plurality of respective different sources of nucleic acid base. The system can comprise a loading device for individually loading the different nucleic acid bases from the plurality of respective different sources into the first manifold.

[0047] According to various embodiments, the first manifold can comprise one or more nucleic acid bases selected from adenine, cytosine, guanine, thymine, and uracil. In various embodiments, the fluid device can comprise a dimethyltrityl-protected phosphoramidite nucleotide monomer disposed in the first manifold.

[0048] According to various embodiments, the fluid processing device can comprise a planar substrate. The first manifold, the second manifold, and the plurality of reaction sites can be formed in the substrate.

[0049] According to various embodiments, at least one of the plurality of surface tension controlled valves can comprise an electrically-actuated or electrically-activated valve. In other embodiments, at least one of the plurality of surface tension controlled valves can comprise a temperature-actuated valve. In various embodiments, the fluid processing device can comprise a fluid communication directly between two adjacent reaction sites of the plurality of reaction sites.

[0050] According to various embodiments, a system is provided that can comprise a fluid processing device that can comprise a plurality of reaction sites. The fluid processing device can comprise a first fluid transport manifold in fluid communication with each of the plurality of the reaction sites. The fluid processing device can comprise a second fluid transport manifold in fluid communication with each of the plurality of sites. The fluid processing device can comprise a plurality of surface tension controlled valves. In various embodiments, at least one of the plurality of surface tension controlled valves can be disposed between the first manifold and at least one respective reaction site of the plurality of reaction sites. Each surface tension controlled valve can be in fluid communication with the first manifold and the at least one respective reaction site.

[0051] According to various embodiments, the system can comprise a pressure differential source in fluid communication with one or more of the first manifold and the second manifold.

[0052] According to various embodiments, the system can comprise an electromagnetic radiation source. The electromagnetic source can be adapted to emit electromagnetic radiation toward one or more of the plurality of surface tension controlled valves. The electromagnetic radiation source can comprise a laser. In various embodiments, the system can comprise a reflective device adapted to reflect electromagnetic radiation emitted from the electromagnetic radiation source toward one or more of the plurality of surface tension controlled valves. The reflective device can comprise a plurality of individually moveable mirrors.

[0053] According to various embodiments, the system can comprise a control unit operatively connected to the electromagnetic radiation source. The control unit can be adapted to control the electromagnetic radiation source. In various embodiments, the system can comprise at least one focusing lens disposed along an emission beam path between the electromagnetic radiation source and at least one of the plurality of surface tension controlled valves.

[0054] According to various embodiments, the fluid processing device can comprise at least one fluid communication between at least two of the plurality of reaction sites, and the at least one fluid communication bypasses the first and second manifolds. In various embodiments, the system can comprise a thermal cycling block adapted to hold the fluid processing device such that at least one of the plurality of reaction sites is in heat-transfer communication with the thermal cycling block. In various other embodiments, the system can comprise a rotatable platen comprising a top surface, and a holder adapted to hold the fluid processing device in or on the top surface.

[0055] According to various embodiments, the system can comprise a pump adapted to connect to the first manifold and force liquid into the first manifold.

[0056] According to various embodiments, the system can comprise a fluid processing device comprising a heater in heat-transfer communication with a temperature-actuated valve. The heater can comprise a control unit operatively connected to it and adapted to control the heater. The fluid processing device can comprise at least one of a plurality of surface tension control valves and an electricity source. The electricity source can be electrically connected to the electrically-actuated valve.

[0057] According to various embodiments, a fluid processing device is provided that can include a plurality of reaction sites, a first manifold in fluid communication with each of the reaction sites, a second manifold in fluid communication with each of the reaction sites, and at least one surface tension controlled valve positioned in at least one channel between the first manifold and at least one of the reaction sites. The reaction sites can each comprise support structures, for example beads, or an inner surface suitable for the attachment of oligomers or oligomer precursors thereto. According to various embodiments, the fluid processing device can comprise a plurality of surface tension controlled valves each in fluid communication with the first manifold and one or more of the reaction sites.

[0058] According to various embodiments, the fluid processing device can comprise reactants and/or reaction components capable of producing an oligomer in at least one of the reaction sites, or a system that includes sources of reactants and/or reaction components.

[0059] According to various embodiments, a system is provided that can comprise a fluid processing device as described herein, and an electromagnetic radiation source capable of emitting electromagnetic radiation and directing the radiation toward one or more surface tension controlled valves in the device. Alternatively or additionally, the system can comprise other valve-actuating devices besides an electromagnetic radiation source. Exemplary actuators can comprise heaters adapted to direct heat toward one or more surface tension controlled valves, or an electrical source

adapted to supply an electrical signal to one or more surface tension controlled valves. By controlling the one or more surface tension controlled valves, the systems described herein can be used in directing the flow of reaction components in an order useful for carrying out an oligonucleotide synthesis reaction within one or more of the plurality of reaction sites.

[0060] According to various embodiments, a system is provided that can comprise an electromagnetic radiation source or other actuating or activating source, a reflective device, a pump, and a thermocycler. The system can be adapted so that the reflective device can direct electromagnetic radiation emitted from the electromagnetic radiation source toward the one or more surface tension controlled valves to selectively open or close the respective one or more surface tension controlled valves. The pump can be adapted to add or remove materials from the channels and reaction sites. The thermocycler can be adapted to control the temperature of the reaction sites, for example, to promote an isothermal or thermally cycled nucleic acid sequence amplification and/or detection assay. The system can comprise one or more control units to control the actuating source, to control the reflective device, to control the pump, and/or to control the thermocycler.

[0061] According to various embodiments, a method is provided that can comprise introducing a first monomer into a first fluid distribution manifold of a fluid processing device, opening at least one surface tension controlled valve in fluid communication with both the first fluid distribution manifold and at least one respective reaction site to form an open surface tension controlled valve, moving the first monomer from the first manifold through the at least one open surface tension controlled valve and into the at least one respective reaction site, and attaching the first monomer to a first structure in the at least one respective reaction site to form an extended structure, or a combination thereof.

[0062] According to various embodiments, the opening of at least one surface tension controlled valve can comprise directing electromagnetic radiation, or reflecting electromagnetic radiation emitted from an electromagnetic radiation source, toward the at least one surface tension controlled valve. The reflecting can comprise individually controlling movement of a plurality of mirrors.

[0063] According to various embodiments, the method can provide a first protected monomer, and a protected extended structure, and the method can comprise washing the at least one respective reaction site subsequent to the attaching, closing the at least one surface tension controlled valve, introducing a deprotecting agent into the first manifold, opening the at least one surface tension controlled valve to form at least one reopened surface tension controlled valve, moving the deprotecting agent from the first manifold, through the at least one reopened surface tension controlled valve and into the at least one respective reaction site, deprotecting the protected extended structure to form a deprotected extended structure, or a combination thereof.

[0064] According to various embodiments, the method can comprise introducing a wash reagent into a second manifold in fluid communication with the at least one respective reaction site, moving the wash reagent from the second manifold into the at least one respective reaction site, and removing the wash reagent from the at least one respective reaction site to form a washed and deprotected extended structure. According to various embodiments, the extended structure can comprise a dimethyltrityl-protected phosphoramidite monomer.

[0065] According to various embodiments, in the method the first structure can be supported by a support. The method can further comprise cleaving the extended structure from the support to form a cleaved structure. In various embodiments, the cleaved structure can be moved from the at least one respective reaction site into a second reaction site that is in fluid communication with the at least one respective reaction site.

[0066] According to various embodiments, a method is provided for synthesizing oligonucleotides or other chemical structures, from component building blocks. The method can comprise, for example, introducing a first monomer into a first fluid distribution manifold of a fluid processing device; opening at least one surface tension controlled valve in fluid communication with both the first fluid distribution manifold and at least one respective reaction site, to form an open surface tension controlled valve; moving the first monomer from the first manifold, through the at least one open surface tension controlled valve, and into the at least one respective reaction site; and attaching the first monomer to a first structure in the at least one respective reaction site to form an extended structure, or a combination thereof. The first monomer can be, for example, a nucleotide, a nucleotide base, a nucleotide analog, a protected chemical building block, or another monomeric building block, unit, or structure that can bond with and extend off of a support or precursor structure. The first monomer can be a protected first monomer, for example, a protected first nucleic acid monomer, and the extended structure can be a protected extended structure. The method can further comprise: washing the at least one respective reaction site subsequent to the attaching; closing the at least one surface tension controlled valve; introducing a deprotecting agent into the first manifold; opening the at least one surface tension controlled valve to form at least one reopened surface tension controlled valve; moving the deprotecting agent from the first manifold, through the at least one reopened surface tension controlled valve, and into the at least one respective reaction site; deprotecting the extended protected structure to form a deprotected extended structure or a combination thereof. An additional monomer can then be added to the deprotected extended structure and the process can be repeated. The at least one surface tension controlled valve can comprise a plurality of surface tension controlled valves, and the at least one respective reaction site comprises a plurality of respective reaction sites.

[0067] According to various embodiments, surface tension controlled valves can comprise channels. Channels can comprise any volume through which a liquid can be transported. The channels can be made of glass, and can optionally be transparent, or at least partially transparent, when employed in light-actuated surface controlled tension valves. The channels can be constructed of any material suitable for containment of a given liquid, for example glass or a polymeric material. The channels can be of any dimension suitable for manipulating fluids in a desired manner. For example, according to various embodiments, the length, width and depth of the channels may range, independently,

from about 0.1 μm to about 10 cm. The channels can range, for example, from about 10 μm to about 1 cm.

[0068] According to various embodiments, surface tension controlled valves can comprise reservoirs. Reservoirs can include any space capable of containing a liquid and communicating with at least one channel. The reservoir can be constructed of any material capable of holding a liquid, for example, a glass or a polymer. The reservoir can be of any shape, for example it can be spherical, semi-spherical, or conical. The reservoir can be of any size sufficient to hold a desired volume of liquid. For example, the reservoir may range in size from about 1 nanoliter to about 1 liter. In various embodiments, the reservoir can be unassociated with an electrode, i.e., the liquid in the reservoir itself can be adapted to not manipulate a liquid by virtue of a significant electrical potential difference being applied to that liquid.

[0069] According to various embodiments, at least one portion of a surface of at least one channel can be coated with a material that it is chemically resistant to the flow of liquid through the channel. Suitable non-limiting examples of such materials that can comprise polymer coatings (e.g., polyamides, polymethylacrylates and their copolymers), BN and SiN, deposited in accordance with any of the thin-film deposition techniques known to those of ordinary skill in the art, and polymer films such as, e.g., Teflon™ (trademark for polytetrafluoroethylene).

[0070] According to various embodiments, at least one layer of insulation material can be formed above the electrode. The surface tension controlled valve can have the insulation layer disposed between the electrode and the internal volume making up the channel. In various embodiments, the insulation layer can include at least one layer of silicon oxide and at least one layer of Teflon™ (trademark for polytetrafluoroethylene). The thicknesses of the two layers can be selected to provide the desired degree of insulation without, in the case of a light-actuated surface tension controlled valve, overly impeding the transmission of light.

[0071] According to various embodiments, electrodes can be made from any conductive material such as, for example, copper, gold, platinum, and conducting polymers, including polymers that are conducting per se, and conducting composites containing a non-conducting polymer and a conducting material such as a metal or a conducting polymer. A single electrode can be used in the surface tension controlled valves disclosed herein, or multiple electrodes, for example, an array of electrodes, can be used. In various embodiments, the electrode can be transparent, for example, can be formed of transparent indium tin oxide. This can permit the passage of light in accordance with certain embodiments of the light actuated valve, and also can permit visual inspection of the operation of the valve. In various embodiments, for example, in the case of a light-actuated surface tension controlled valve, the electrode or array of electrodes can be in electrical contact with a photoconductive material.

[0072] According to various embodiments, the photoconductive material that can be used in the light actuated valves corresponds to a material with a dark conductivity ranging from 10^{-5} to 10^{-12} Ω^{-1}-cm^{-1}. The photoconductive material can exhibit relatively low conductivity when dark, and relatively high conductivity when illuminated by a light source. In various embodiments, an example of a suitable photoconductive material can comprise amorphous silicon, which has a dark conductivity of approximately 10^{-8} Ω^{-1}-cm^{-1}. In various embodiments, light with a wavelength ranging from 400 nm to 1100 nm can be used to illuminate at least portions of the amorphous silicon. The light intensity for activating the light actuated surface tension controlled valve can be low. For example, a light intensity that can be suitable for switching amorphous silicon is 65 mW/cm^2. The layer of photoconductive material can permit optical control of an electrical potential difference across a corresponding portion of the channel.

[0073] According to various embodiments, the power source can be chosen from any source suitable for providing a sufficient electrical potential difference across a liquid in a channel. For example, the power source can be configured to provide an alternating voltage source. The voltage and frequency characteristics can be chosen according to the materials used in the surface tension controlled valve and/or a device in which the valve is situated. The magnitude of the AC voltage source can vary according to the properties, for example, the thickness, of the materials used to construct the surface tension controlled valve. In various embodiments, the AC voltage source can supply an electrical potential difference ranging from 10 volts to several hundred volts, with a frequency ranging from 10 Hz to 500 kHz. In various embodiments, the AC voltage source can be coupled to the surface tension controlled valve with only two leads. In other embodiments, the AC voltage source can be inductively coupled such that no electrical leads are required.

[0074] Exemplary circuits, voltage sources, potential differences, voltages, and materials are described, for example, in U.S. Pat. No. 6,958,132, to Chiou et al., issued Oct. 25, 2005, and U.S. Patent Application Publication No. 2003/0224528 A1, published Dec. 4, 2003, which are incorporated herein in their entireties by reference.

[0075] According to various embodiments, the light actuated surface tension controlled valves can employ a light source to illuminate the photoconductive material associated with the valve. The light source can be chosen based on any light capable of changing the conductive properties of the photoconductive material. Suitable light sources can comprise collimated light sources, and can be chosen from, for example, lamps, for example arc lamps, lasers, and light-emitting diodes (LEDs). In various embodiments, the light source can comprise one or more light sources. For example, a surface tension controlled valve and/or a device containing a surface tension controlled valve can include a first light source and a second light source. In various embodiments comprising more than one light source, the light sources can be chosen from any effective light source. The light source can be directed along at least one axis of the surface tension controlled valve by at least one mirror, for example, a computer-controlled array of microfabricated mirrors. In various embodiments, when the light source is a laser beam, the laser beam may be directed over the surface of the photoconductive material with a computer-controlled galvo-mirror.

[0076] According to various embodiments, the light from the light source can be directed to the photosensitive material by the channel itself. The channel can provide a waveguide to internally reflect and propagate the light so that it reaches the photosensitive material. The waveguide

can direct a beam of light to the photoconductive material substantially axially along the length of the channel. In various embodiments, the channel can be configured to provide a waveguide for the light. In various embodiments, the walls of the channel can provide the waveguide by internally reflecting and propagating the light within the channel wall. The channel walls can be constructed of substantially transparent material with the outer surfaces of the transparent material coated with a reflective material. In various embodiments, the channel itself can be the waveguide by internally reflecting and propagating the light within the channel volume whether filled or empty. The inner walls of the channel can be coated with a reflective material.

[0077] According to various embodiments, the surface tension controlled valves disclosed herein can be used in a variety of applications. For example, the valves can be used to move one or more droplets or combine two or more droplets in a device used for biological synthesis, biological monitoring, or biological screening. In various embodiments, the surface tension controlled valves disclosed herein can be used in microdevices designed for one or more of PCR, ligase chain reactions, antibody binding reaction, oligonucleotide ligations assays, and hybridization assays.

[0078] According to various embodiments, individual fluid control in a fluid processing device **5**, for example a microfluidic device, is provided with a surface tension controlled valve. Referring to **FIG. 1**, a surface tension controlled valve **25** can include channel **30**, and a portion **20** of the channel can initially be resistant to the flow of a liquid (e.g., is hydrophobic in the case of an aqueous liquid) from the internal volume of surface tension controlled valve **25**. As illustrated in **FIG. 1**, a valve **25** can control fluid flow through channel **30** between reservoir **10** and reservoir **40**. The surface tension of the liquid, in combination with the resistance of the surface of at least a portion of channel **30** to the flow of the liquid, can prevent its flow from reservoir **40** to reservoir **10**.

[0079] According to various embodiments, the surface tension controlled valve can comprise a channel or conduit. The channel or conduit can comprise an initially or normally hydrophobic surface. The surface tension controlled valve can be adapted to change the contact angle and wetting of a liquid disposed therein with respect to the inner surface of channel **30**. This change can trigger the movement of a liquid through channel **30**.

[0080] Surface tension controlled valves can exploit the fact that under certain circumstances the surface tension of the liquid can change, and that change in turn can trigger a movement of that liquid. Examples of such circumstances can include applied electric field (electric field), applied electric field and light (opto-electrowetting), local increase in temperature, and the like.

[0081] According to various embodiments, a fluid processing device can comprise a surface tension controlled valve disposed in a valve channel that is in fluid communication with a supply channel and a reaction region. The surface tension controlled valve can comprise a channel with an initially or normally hydrophobic surface. The surface tension controlled valve can be adapted to change the contact angle and wetting of a liquid disposed therein with respect to the inner surface of the valve channel. This change can trigger the movement of a liquid through the valve channel. Examples of the mechanism that can be used to trigger the movement can include the application of an electric field as with electrowetting, the application of an electric field and light as with optoelectrowetting, the application of a local increase in temperature, and the like.

[0082] According to various embodiments, as illustrated in **FIG. 2A**, a portion of a fluid processing device is shown comprising first channel **40** separated from second channel **30** by surface tension controlled valve **25**. The pressure created by the surface tension in the surface tension controlled valve **25** can be sufficient to prevent liquid **50**, for example, an aqueous biological sample, from entering second channel **30**. If the pressure difference across the surface tension controlled valve exceeds a certain threshold pressure, the resistance to the flow due to the hydrophobic properties of the valve can be overcome, and the liquid can flow through the valve. Likewise, if the pressure of the sample liquid is maintained below the threshold pressure, the valve will hold back the liquid sample and prevent flow into channel **30**. According to various embodiments, by changing the surface tension of the valve from having a hydrophobic property to having a hydrophilic property, liquid movement through the valve can be regulated, even at pressure below the threshold pressure described above.

[0083] According to various embodiments, if the surface of a channel is resistant to the flow of a liquid, for example, is hydrophobic, some additional force or pressure can be required to push the liquid through the hydrophobic part of the channel. With reference to **FIG. 2A**, this principle can be used in hydrophobic valves when, for instance, the first liquid **50** under certain pressure P_1 can flow through channel **40** but not channel **30** filled with second liquid **60** (the second liquid can include a gas or be a gas) under pressure P_2 and separated by surface **20** that is resistant to the flow of the first liquid (e.g., the surface is hydrophobic in the case of an aqueous first liquid). If the pressure difference across the valve exceeds a certain threshold pressure, for example, $\delta P_{Treshold}$ (where $P_{Threshold}=P_1-P_2$), the resistance of surface **20** to the flow of first liquid **1** can be overcome and the first liquid can flow into the channel **30** (**FIG. 2B**).

[0084] According to various embodiments, **FIG. 2B** can illustrate the same device as shown in **FIG. 2A**, however, the surface tension of the surface tension controlled valve **25** has been changed to be made hydrophilic, thus enabling liquid **60** to pass through the valve **25** and into the second conduit **30**. Changing the surface tension of the valve can be accomplished by a variety of mechanism as described herein.

[0085] According to various embodiments, a number of techniques are provided that can make the pressure difference across the valve exceed a threshold pressure, thereby allowing the passage of a liquid. One technique can use electric fields to effect fluid movement by relying on the ability of electric fields to change the contact angle of the fluid on a surface that is initially resistant to the flow of a liquid. When an electric field gradient is applied to a droplet on a fluid-transporting surface, different contact angles can be formed between leading and receding surfaces of the droplet with respect to the fluid transporting surface. This imbalance in surface tension forces can produce a net force that moves the droplet. For example, in the case of a polar

liquid droplet, such as a droplet of an aqueous liquid, the application of an electric potential difference across the liquid-solid interface reduces the contact angle, thereby effectively making the surface more hydrophilic. In various embodiments, the electrical potential difference effecting the hydrophilic-hydrophobic conversion can be controlled by closing a circuit to at least one electrode arranged on at least one side of a channel making up the surface tension controlled valve.

[0086] According to various embodiments, the surface tension of a liquid in a surface tension controlled valve can be altered by applying an electric field. An exemplary embodiment is shown in **FIG. 3**.

[0087] According to various embodiments, and as illustrated in **FIG. 3**, the surface tension controlled valve can comprise a layered structure capable of changing the surface tension of a surface. The layered structure can comprise a first electrode **70**, that can comprise an electrode containing layer, positioned adjacent to a second insulating layer **80**. When the structure is connected to a power source **100** through electrical leads, a change in surface tension can be effected by application of an electrical signal to the electrical leads. As a result of such a signal, the valve can change the overall shape of a droplet of liquid **90** from a first shape having a greater contact angle Θ, to a second shape having a lesser contact angle, by creating a difference in electrical potential between the liquid and the electrode. By increasing or decreasing the power of the electrical signal, the shape of the droplet can be changed to take any of a variety of forms.

[0088] According to various embodiments, an electrode **70** can be embedded below a surface of an insulation layer **80**, and a droplet of liquid **90** can be disposed in the channel. The droplet of liquid **90** can be a polar liquid. The droplet of liquid **90** can form a contact angle Θ with the surface of the insulation layer **80**. A power source **100** can be configured to apply an electrical potential difference between the liquid droplet **90** and the electrode **70**. When the circuit including the electrode, power source, and liquid droplet **90** is closed and the electrical potential difference is applied, different contact angles **0**) are formed between leading and receding surfaces of the droplet with respect to the surface **80**. This imbalance in surface tension forces can produce a net force and moves the droplet to the position indicated by the broken line.

[0089] According to various embodiments and as illustrated for example in **FIG. 3**, the top side of the electrode can be insulated from the liquid droplet by an insulation layer **80**. In a microfluidic device, each electrode (and potentially each surface tension controlled valve) can contain an independent electrical addressing/connection, which can be accomplished by, for example, disposing a printed circuit at the bottom of the chip.

[0090] According to various embodiments, one aspect of a surface tension controlled valve is illustrated in **FIG. 4A**. Reservoir **40** can contain liquid **50** that flows into, but not past, a portion of channel **30** that can be resistant to the flow of the liquid. An electrode **70** and insulator **80** can be positioned along one wall of channel **30**, which channel communicates with reservoir **10**. A power source and electro-wetting circuit **100** can be configured to apply an electrical potential difference across at least that portion of the channel **30** that can be resistant to the flow of liquid **50**. Absent the presence of the electrical potential difference, or any other surface tension-breaking source, the liquid will not flow past that portion of channel **30** because the liquid does not exceed a certain threshold pressure necessary to break the surface tension of the liquid.

[0091] According to various embodiments, **FIG. 4B** illustrates the operation of a surface tension controlled valve when circuit **100** is closed and an electrical potential difference exists between electrode **70** and the liquid **50** in channel **30**. The applied electric field can change the contact angle of the edge of the liquid leading into channel **30**, thereby changing surface resistance to the flow. When the power source generates an electrical potential difference, the imbalance in surface tension between the leading and receding edges of the liquid can produce a net force, which can cause movement of the liquid. The liquid is then permitted to flow through channel **30**, past the portion of the channel initially resistant to the flow of the liquid, and into reservoir **10**. In various embodiments, opening the circuit and shutting off the electric field can stop the flow of the liquid through channel **30**.

[0092] As illustrated in **FIGS. 5A-5C**, a layer of photoconductive material **160** can be added between embedded electrode array **170** and electro-wetting circuit **100**. In various other embodiments, a conductive layer (not shown) can be positioned between photoconductive material **160** and insulator **80**. In various other embodiments and as shown in **FIG. 5B**, array **170** can be replaced by a continuous layer of electrically conductive material **180**, which in turn, can be connected to power source **100**. In other embodiments, as shown in **FIG. 5C**, an additional electrode **70** can be positioned between photo conductive material **160** and insulator **80**.

[0093] A droplet **90** of a liquid can form a contact angle Θ with the surface upon which it rests. Although the power source may be providing a current, the electro-wetting circuit will not close unless the photoconductive material is illuminated with light **120**. Only then will the circuit close, enabling an electrical current to flow between electrode array **170**, or conductive layer **70**, and liquid droplet **90**.

[0094] According to various embodiments, the fluid processing device can comprise a surface tension controlled valve that comprises a layered structure. The layered structure can comprise a photoconductive layer, an electrode-containing layer, and an insulating layer. A power supply can be connected through leads to a liquid bead. Applying current can change the shape of the liquid droplet. In other words, when illuminated by light, the photoconductive layer of the surface tension controlled valve can change locally and significantly in conductivity and, as a result, the surface of the insulating layer that contacts the liquid droplet can be made hydrophilic or more hydrophilic. The contact angle or wetting of the liquid with respect to the surface can thus be changed and the liquid can accordingly be propagated in a certain direction.

[0095] **FIGS. 6A-6C** illustrates a channel **130** created by an internal volume between insulating layers **80**. The topside **110** of channel **130** can be sufficiently transparent to allow light beam **120** to pass through to photoconductive layer **160**, that contains electrodes **70**. When illuminated by light beam **120**, the conductivity of the illuminated portion of photoconductive layer **160** can change significantly, thus

allowing circuit **100** to close between electrodes **70** and liquid droplet **90**. More specifically, the portion of the photoconductive material that is illuminated by a beam of light can be capable of transmitting a higher electric field intensity than a portion of the photoconductive layer that is not illuminated. The applied potential difference can make the surface less resistant to the flow of the liquid droplet, for example, more hydrophilic in the case of an aqueous liquid. The contact angle of the liquid can change, and the liquid propagates along the channel.

[**0096**] In an alternative embodiment, and as illustrated in **FIG. 6B**, array **170** is replaced by a continuous layer of electrically conductive material **180**, which in turn is connected to a power source. **FIG. 6C** illustrates yet another embodiment, where a continuous layer of electrically conductive material **180** is connected to a power source, and electrodes **70** are absent.

[**0097**] According to various embodiments, light beams can change the electrical resistance of a photoconductive layer in a light-activated valve, allowing electrical current to flow through one or more electrodes. Electrical current flow changes the contact angle of the liquid in parts of the liquid droplet allowing the liquid droplet to move toward the light beams.

[**0098**] According to various embodiments, biological fluid-handling can be provided based on the above described teachings for a valve configured for light activation. A channel can be connected to section **20** that can form an internal volume of the valve. The internal volume of the valve can be bound by an insulating layer resistant to the flow of the biological liquid. The channel is not resistant to the flow of the biological liquid. The photoconductive material can be coupled to the insulating layer. The electrode that forms the electro-wetting circuit can be coupled to the photoconductive material and configured to electrically couple with the insulating layer through the photoconductive material when the photoconductive material is activated by light. The power source can be electrically coupled to the electrode. The power source can be configured to provide an electrical potential difference across the insulting layer capable of changing the wettability of the insulting material. The light source can be configured to activate the photoconductive material thereby providing the electrical potential difference between the insulating layer and the biological fluid. The amount of electrical potential difference can be configured to reduce the resistance of the insulating layer to the flow of the biological liquid.

[**0099**] According to various embodiments, light beam **120** can be capable of movement, for example, can be directed along the length of the channel **130**. Such movement can be possible by the use of any device capable of moving a beam of light such as, by way of non-limiting example, a galvo-mirror known in the art of laser etching or an array of microfabricated mirrors known in the art of digital light projection. As the light beam is directed along the length of channel **130**, the illuminated portions of the photoconductive material can close the circuit between the respective electrode and liquid droplet **90**. The contact angle of leading edge **140** of the droplet can change to a different contact angle from the receding edge **150**, an imbalance in surface tension can result, and the droplet can thus propagate in the direction of the beam of light.

[**0100**] According to various embodiments, similar approaches can be used to construct light-actuated valve (**FIGS. 7A-7D**). In normal conditions (for example, no light) the valve can be closed, because the liquid in channel **40** has not exceeded a threshold pressure such that it can pass the portion **20** of channel **30** that is resistant to the flow of the liquid **50** (**FIG. 7A**). Portion **20** of channel **30** can be a surface tension controlled valve. Portion **20** can include multi-layers **25** that can include an insulator, an electrode, a photosensitive layer, or a combination thereof, as described above. When light beam **120** illuminates and activates the electro-wetting circuit formed in the area where liquid **50** contacts surface **20**, the surface becomes less resistant to the flow of liquid **50**, and the liquid moves into channel **30** (**FIG. 7B**). The beam of light **120** then shifts toward channel **30** followed by the liquid (**FIG. 7C**). Once light **120** moves across and above surface **20**, and part of surface **20** is not illuminated anymore, some liquid can break apart from the liquid in channel **40**, and after the light is switched off, that liquid can be displaced into channel **30** (**FIG. 7D**).

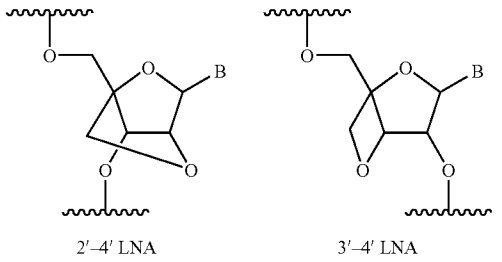
[**0101**] According to various embodiments, a fluid processing device is provided that can be used to manipulate the delivery of reactants or reaction components to a reaction site to enable the production of one or more compounds comprising multiple building blocks, for example, one or more desired oligomers or one or more desired oligonucleotides. Oligomers as defined herein can include polymers of amino acids, polymers of sugars, polymers of nucleotide bases, polymers of nucleotide analogs, and/or polymers of other nucleotide monomeric units herein referred to as nucleotides.

[**0102**] According to various embodiments, the device described herein can be useful in carrying out chemical compound synthesis methods using building blocks, exemplified herein with oligonucleotide synthesis methods. These methods can comprise, for example, various oligonucleotide extension reactions, protecting and/or deprotecting reactions, capping reactions, washing steps, cleaving reactions, and the like. Exemplary oligonucleotide synthesis reactions can include those described, for example, in U.S. patent application Ser. No. 10/891,650, filed Jul. 15, 2004, which is incorporated herein in its entirety by reference.

[**0103**] The term "nucleotide base", as used herein, refers to a substituted or unsubstituted aromatic ring or substituted or unsubstituted aromatic rings. In certain embodiments, the aromatic ring or rings contain at least one nitrogen atom. In certain embodiments, the nucleotide base is capable of forming Watson-Crick and/or Hoogsteen hydrogen bonds with an appropriately complementary nucleotide base. Exemplary nucleotide bases and analogs thereof include, but are not limited to, naturally occurring nucleotide bases, adenine, guanine, cytosine, 6 methyl-cytosine, uracil, thymine, and analogs of the naturally occurring nucleotide bases, e.g., 7-deazaadenine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, N6 -Δ2-isopentenyladenine (6iA), N6 -Δ2-isopentenyl-2-methylthioadenine (2ms6iA), N2-dimethylguanine (dmG), 7-methylguanine (7mG), inosine, nebularine, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, pseudocytosine, pseudoisocytosine, 5-propynylcytosine, isocytosine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O6-methylguanine, N6-methyladenine, O4-methylthymine, **5**,6-dihy-

drothymine, 5,6-dihydrouracil, pyrazolo[3,4-D]pyrimidines (see, e.g., U.S. Pat. Nos. 6,143,877 and 6,127,121 and PCT published application WO 01/38584), ethenoadenine, indoles such as nitroindole and 4-methylindole, and pyrroles such as nitropyrrole. Certain exemplary nucleotide bases can be found, e.g., in Fasman, 1989, Practical Handbook of Biochemistry and Molecular Biology, pp. 385-394, CRC Press, Boca Raton, Fla., and the references cited therein.

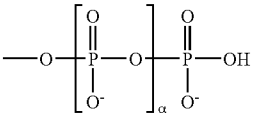
[0104] The term "nucleotide", as used herein, refers to a compound comprising a nucleotide base linked to the C-1' carbon of a sugar, such as ribose, arabinose, xylose, and pyranose, and sugar analogs thereof. The term nucleotide can also encompasses nucleotide analogs. The sugar may be substituted or unsubstituted. Substituted ribose sugars include, but are not limited to, those riboses in which one or more of the carbon atoms, for example the 2'-carbon atom, is substituted with one or more of the same or different Cl, F, —R, —OR, —NR2 or halogen groups, where each R is independently H, C1-C6 alkyl, or C5-C14 aryl. Exemplary riboses include, but are not limited to, 2'-(C1-C6)alkoxyribose, 2'-(C5-C14)aryloxyribose, 2',3'-didehydroribose, 2'-deoxy-3'-haloribose, 2'-deoxy-3'-fluororibose, 2'-deoxy-3'-chlororibose, 2'-deoxy-3'-aminoribose, 2'-deoxy-3'-(C1-C6)alkylribose, 2'-deoxy-3'-(C1-C6)alkoxyribose and 2'-deoxy-3'-(C5-C14)aryloxyribose, ribose, 2'-deoxyribose, 2',3'-dideoxyribose, 2'-haloribose, 2'-fluororibose, 2'-chlororibose, and 2'-alkylribose, e.g., 2'-O-methyl, 4'-anomeric nucleotides, 1'-anomeric nucleotides, 2'-4'- and 3'-4'-linked and other "locked" or "LNA", bicyclic sugar modifications (see, e.g., PCT published application nos. WO 98/22489, WO 98/39352; and WO 99/14226). Exemplary LNA sugar analogs within a polynucleotide include, but are not limited to, the structures:



where B is any nucleotide base.

[0105] Modifications at the 2'- or 3'-position of ribose can comprise hydrogen, hydroxy, methoxy, ethoxy, allyloxy, isopropoxy, butoxy, isobutoxy, methoxyethyl, alkoxy, phenoxy, azido, amino, alkylamino, fluoro, chloro, and bromo. Nucleotides include, but are not limited to, the natural D optical isomer, as well as the L optical isomer forms (see, e.g., Garbesi (1993) Nucl. Acids Res. 21:4159-65; Fujimori (1990) J. Amer. Chem. Soc. 112:7435; Urata, (1993) Nucleic Acids Symposium Ser. No. 29:69-70). When the nucleotide base is purine, e.g. A or G, the ribose sugar is attached to the N9-position of the nucleotide base. When the nucleotide base is pyrimidine, e.g. C, T or U, the pentose sugar is attached to the N1-position of the nucleotide base, except for pseudouridines, in which the pentose sugar is attached to the C5 position of the uracil nucleotide base (see, e.g., Komberg and Baker, (1992) DNA Replication, 2nd Ed., Freeman, San Francisco, Calif.).

[0106] One or more of the pentose carbons of a nucleotide can be substituted with a phosphate ester having the formula:



where α is an integer from 0 to 4. In certain embodiments, a is **2** and the phosphate ester is attached to the 3'- or 5'-carbon of the pentose. In certain embodiments, the nucleotides can be those in which the nucleotide base is a purine, a 7-deazapurine, a pyrimidine, or an analog thereof. "Nucleotide 5'-triphosphate" refers to a nucleotide with a triphosphate ester group at the 5' position, and are sometimes denoted as "NTP", or "dNTP" and "ddNTP" to particularly point out the structural features of the ribose sugar. The triphosphate ester group can comprise sulfur substitutions for the various oxygens, for example, -thio-nucleotide 5'-triphosphates. For a review of nucleotide chemistry, see: Shabarova, Z. and Bogdanov, A. *Advanced Organic Chemistry of Nucleic Acids,* VCH, New York, 1994.

[0107] The term "nucleotide analog", as used herein, refers to embodiments in which the pentose sugar and/or the nucleotide base and/or one or more of the phosphate esters of a nucleotide may be replaced with its respective analog. In certain embodiments, exemplary pentose sugar analogs are those described above. In certain embodiments, the nucleotide analogs can comprise a nucleotide base analog as described above. In certain embodiments, exemplary phosphate ester analogs can comprise, but are not limited to, alkylphosphonates, methylphosphonates, phosphoramidates, phosphotriesters, phosphorothioates, phosphorodithioates, phosphoroselenoates, phosphorodiselenoates, phosphoroanilothioates, phosphoroanilidates, phosphoroamidates, boronophosphates, and the like, and may include associated counterions.

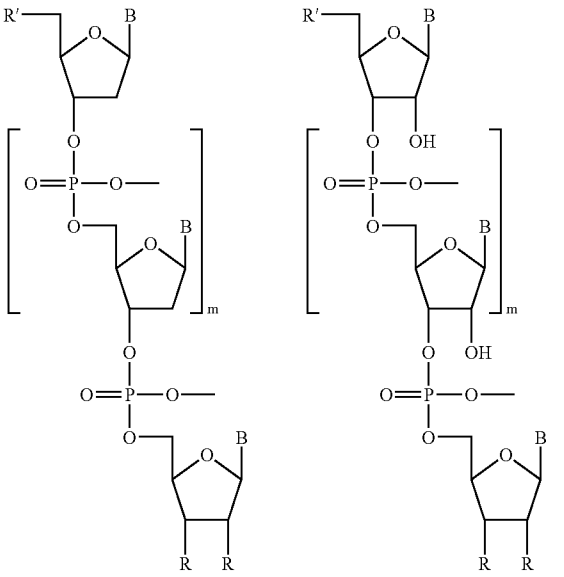
[0108] Also included within the definition of "nucleotide analog" are nucleotide analog monomers that can be polymerized into polynucleotide analogs in which the DNA/RNA phosphate ester and/or sugar phosphate ester backbone is replaced with a different type of intemucleotide linkage. Exemplary polynucleotide analogs can comprise, but are not limited to, peptide nucleic acids, in which the sugar phosphate backbone of the polynucleotide is replaced by a peptide backbone. Also included are intercalating nucleic acids (INAs, as described in Christensen and Pedersen, 2002), and AEGIS bases (Eragen, U.S. Pat. No. 5,432,272).

[0109] As used herein, the terms "polynucleotide", "oligonucleotide", and "nucleic acid" are used interchangeably and mean single-stranded or double-stranded polymers of nucleotide monomers, including 2'-deoxyribonucleotides (DNA) and ribonucleotides (RNA) linked by intemucleotide phosphodiester bond linkages, or intemucleotide analogs, and associated counter ions, e.g., H+, NH4+, trialkylammonium, Mg2+, Na+ and the like. A nucleic acid can be

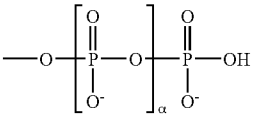
composed entirely of deoxyribonucleotides, entirely of ribonucleotides, or chimeric mixtures thereof. The nucleotide monomer units can comprise any of the nucleotides described herein, including, but not limited to, naturally occurring nucleotides and nucleotide analogs. Nucleic acids typically can range in size from a few monomeric units, e.g. 5-40 when they are sometimes referred to in the art as oligonucleotides, to several thousands of monomeric nucleotide units. Unless denoted otherwise, whenever a nucleic acid sequence is represented, it will be understood that the nucleotides are in 5' to 3' order from left to right and that "A" denotes deoxyadenosine or an analog thereof, "C" denotes deoxycytidine or an analog thereof, "G" denotes deoxyguanosine or an analog thereof, and "T" denotes thymidine or an analog thereof, unless otherwise noted.

[0110] Nucleic acids can comprise genomic DNA, cDNA, hnRNA, mRNA, rRNA, tRNA, fragmented nucleic acid, nucleic acid obtained from subcellular organelles such as mitochondria or chloroplasts, and nucleic acid obtained from microorganisms or DNA or RNA viruses that may be present on or in a biological sample.

[0111] Nucleic acids can be composed of a single type of sugar moiety, e.g., as in the case of RNA and DNA, or mixtures of different sugar moieties, e.g., as in the case of RNA/DNA chimeras. In certain embodiments, nucleic acids can be ribopolynucleotides and 2'-deoxyribopolynucleotides according to the structural formulae below:



wherein each B is independently the base moiety of a nucleotide, e.g., a purine, a 7-deazapurine, a pyrimidine, or an analog nucleotide; each m defines the length of the respective nucleic acid and can range from zero to thousands, tens of thousands, or even more; each R is independently selected from the group comprising hydrogen, halogen, —R", —OR", and —NR"R", where each R" is independently (C1-C6) alkyl or (C5-C14) aryl, or two adjacent Rs are taken together to form a bond such that the ribose sugar is 2',3'-didehydroribose; and each R' is independently hydroxyl or



where α is zero, one or two.

[0112] In certain embodiments of the ribopolynucleotides and 2'-deoxyribopolynucleotides illustrated above, the nucleotide bases B can be covalently attached to the Cl ' carbon of the sugar moiety as previously described.

[0113] The terms "nucleic acid", "polynucleotide", and "oligonucleotide" can comprise nucleic acid analogs, polynucleotide analogs, and oligonucleotide analogs. The terms "nucleic acid analog", "polynucleotide analog" and "oligonucleotide analog" are used interchangeably and, as used herein, refer to a nucleic acid that contains at least one nucleotide analog and/or at least one phosphate ester analog and/or at least one pentose sugar analog. The definition of nucleic acid analogs can also comprise nucleic acids in which the phosphate ester and/or sugar phosphate ester linkages are replaced with other types of linkages, such as N-(2-aminoethyl)-glycine amides and other amides (see, e.g., Nielsen et al., 1991, Science 254: 1497-1500; WO 92/20702; U.S. Pat. No. 5,719,262; U.S. Pat. No. 5,698,685); morpholinos (see, e.g., U.S. Pat. No. 5,698,685; U.S. Pat. No. 5,378,841; U.S. Pat. No. 5,185,144); carbamates (see, e.g., Stirchak & Summerton, 1987, J. Org. Chem. 52: 4202); methylene(methylimino) (see, e.g., Vasseur et al., 1992, J. Am. Chem. Soc. 114: 4006); 3'-thioformacetals (see, e.g., Jones et al., 1993, J. Org. Chem. 58: 2983); sulfamates (see, e.g., U.S. Pat. No. 5,470,967); 2-aminoethylglycine, commonly referred to as PNA (see, e.g., Buchardt, WO 92/20702; Nielsen (1991) Science 254:1497-1500); and others (see, e.g., U.S. Pat. No. 5,817,781; Frier & Altman, 1997, Nucl. Acids Res. 25:4429 and the references cited therein). Phosphate ester analogs include, but are not limited to, (i) C1C4 alkylphosphonate, e.g. methylphosphonate; (ii) phosphoramidate; (iii) C1C6 alkyl-phosphotriester; (iv) phosphorothioate; and (v) phosphorodithioate.

[0114] The surface tension controlled valves that can be used according to various embodiments are herein exemplified by an implementation represented by a channel having an inner surface that is hydrophobic in the absence of illuminating radiation. According to various embodiments, the surface tension controlled valve can exploit the fact that under certain circumstances the contact angle for a liquid of interest, or its surface tension, changes and that change can in-turn trigger a movement of the liquid. Such circumstances can comprise an applied electric field (electrowetting), an applied electric field and light (optoelectrowetting), an applied local increase of temperature (thermo capillary effect), and the like. The liquid can be a liquid sample, for example, a biological sample in water or a biological sample in an aqueous medium. If the liquid is a biological sample, it can comprise, for example, any of the nucleotides, nucleotide bases, and/or nucleotide analogs described herein.

[0115] Exemplary surface tension controlled valves can comprise the microfluidic electrowetting control devices described in U.S. Patent Application Publication No. US

2004/0231987 A1, published Nov. 25, 2004; the electrostatic actuators for microfluidics described in U.S. Patent Application Publication No. US 2002/0043463 A1, published Apr. 18, 2002; the micropump device as described in U.S. Patent Application Publication No. US 2002/0114715 A1, published Aug. 22, 2002; the electrowetting microfluidic control device described in U.S. Patent Application Publication No. US 2003/0164295 A1, published Sep. 4, 2003; the control devices described in U.S. Patent Application Publication No. US 2002/0168671 A1, published Nov. 14, 2002; the optical microfluidic devices described in U.S. Patent Application Publication No. US 2003/0047688 A1; and the injecting devices as described in U.S. Patent Application Publication No. US 2003/0082081 A1; all of which are incorporated herein in their entireties by reference.

[0116] According to various embodiments, and as illustrated in **FIGS. 8A-8D**, fluid processing device **400** can comprise first channel **40** separated from second channel **30** by light-activated surface tension controlled valve **20**. When an area **120** including valve **20** is illuminated by beams of light, the contact angle of liquid in valve **20** changes and enables a liquid droplet **414** (**FIG. 4D**) to be separated from liquid **50** present in first channel **40**. Conduit **408** can function to relieve air pressure differences caused by the movement of drop **414** into second channel **30**. Conduit **408** can include first open end **409** in fluid communication with the interior of the valve **20**, and second open end **411** in fluid communication with second channel **30**.

[0117] According to various embodiments and as depicted in **FIGS. 8A-8D**, a surface tension controlled valve separating a first liquid-containing channel and a second channel can normally or originally be in a closed state in the absence of illuminating radiation. If a light beam illuminates the surface tension controlled valve where the liquid contacts the valve, the valve surface can be made hydrophilic, enabling the liquid to move into the valve. If the beam of light is then moved towards the second conduit, the beam can be followed by the liquid as the localized surface tension of the valve is changed. Once the light beam moves past the valve surface such that part of the valve is no longer illuminated. The localized valve surface will again become hydrophobic and will be closed. A volume of liquid can thus be taken-up from and broken away from the liquid in the first channel. Upon continued movement of the light beam followed by switching off the light, the remaining liquid in the valve can be moved into the second channel.

[0118] According to various embodiments, and as illustrated in **FIG. 9**, a fluid processing device **500** can comprise first manifold **503** in fluid communication with supply conduit **504**. A conduit can be a channel. The first manifold **503** can be in fluid communication with several feeder conduits **506**. A plurality of reaction sites **510** can be in fluid communication with respective feeder channel **506**. Surface tension controlled valves **508** can be disposed in one or more of feeder channels **506** adjacent to each reaction site **510**. A second manifold **517** can be in fluid communication with conduit **516** and a plurality of feeder conduits **514**. Each feeder conduit **514** can be in fluid communication with a respective plurality of reaction sites **510**, for example, on opposite sides of the respective reaction regions relative to the respective feeder channels **506**. In various embodiments, conduits can be channels.

[0119] Fluid processing device **500** can be disposed in or upon a chip or card **502**. The chip or card **502** can comprise glass, silicon, plastic, polycarbonate, polypropylene, polymers of cyclic olefins, copolymers, combinations thereof, or the like. The chip or card **502** can be molded with features and enclosed by one or more cover films or layers. Reaction regions **510** can be any suitable shape, for example, well-shaped.

[0120] The conduits and reaction sites can have any of a variety of dimensions. At least one feature can have at least one dimension of five mm or less, for example, one mm or less, or **500** microns or less. Conduit depths and widths can be equivalent or different from one another. Different channel aspect ratios can be used. According to various embodiments, channels can be dimensioned to permit manipulation of fluids by capillary action, and to promote or induce capillary fluid flow. The conduits can have various cross-sectional shapes, including, for example, a square cross-section, a rectangular cross-section, a circular cross-section, a U-shaped cross-section, a V-shaped cross-section, or a combination thereof.

[0121] If a conduit has an inner surface that contains both hydrophobic and hydrophilic portions, some additional force or pressure can be required to push the liquid through the hydrophobic part of the channel as compared movement through a hydrophilic portion of the same channel.

[0122] According to various embodiments, and as illustrated in **FIG. 10**, a fluid processing device **600** can comprise substrate **601**, and first manifold **604** can comprise main conduit **606** and several feeder conduits **620**, **622**, and **624**, wherein each feeder conduit can comprise a respective surface tension controlled valve. The feeder conduits **620**, **622**, **624** can be in fluid communication with reaction sites **614**, **616**, and **618**, respectively. Reaction sites **616** and **618** can be fluidically connected to one another by a conduit **626** that comprises a surface tension controlled valve. The conduit **626** can be directly between the reaction sites **616** and **618**. Similarly, reaction sites **614** and **616** can be fluidically connected by a conduit **628** having a surface tension controlled valve. Controlling the opening and closing of one or more of the surface tension controlled valves **620**, **622**, **624** can enable the selective production of a different oligomer in each respective reaction site **614**, **616**, **618**. A second manifold **605** comprising a main conduit **608** and several feeder conduits **610**, **612**, **614** can be in fluid communication with the reaction sites **614**, **616**, **618**, respectively. The second manifold **605** can be used to carry away reactants, non-reactive reaction components, and/or wash fluids, from the reaction regions. The second manifold **605** can alternatively, or additionally, be used to supply the reaction sites **614**, **616**, **618** with one or more reactants, non-reactive reaction components, and wash fluids. Through combinations of supply and wash steps and surface tension controlled valve opening and closing steps, different oligonucleotides can simultaneously be synthesized in the different reaction sites of the device, as described in more detail below.

[0123] According to some embodiments, a plurality of sets of different reaction sites can be provided, wherein each set comprises, for example, at least a pair of reaction sites, for example, similar to the reaction site pair **614**, **618** shown in **FIG. 10**. Each set can be configured to carry out a different set of syntheses, for example, to provide a set of reactants

useful to detect a respective target. Each set can comprise a set of oligonucleotides that can be differentially detectable independent from the other sets of reactants. For example, the plurality of sets of reaction sites can comprise four sets of three reaction sites, wherein each set of three reaction sites can carry out the respective synthesis of a particular forward oligonucleotide primer, a corresponding reverse oligonucleotide primer, and a detectable oligonucleotide, for example, labeled with a fluorescent reporter dye. All of the different oligonucleotides from the four sets of three reaction sites can be combined in, for example, a central reaction site, and a multiplexed detection assay can be carried out on a sample. In such an example, the presence, absence, and/or amount, of four different target sequences, can be independently detectable in the central reaction site. The independent detection can be based on different excitation, emission, or both excitation and emission spectra, of the different detectable oligonucleotides. Exemplary of multiplex reactions are those described, for example, in co-pending U.S. Provisional Patent Application No. 60/699,782, filed Jul. 15, 2005, which is incorporated herein in its entirety by reference.

[0124] According to various embodiments, and as illustrated in **FIG. 11**, a fluid processing system **700** can comprise a processing device, for example, computer **702**. The computer can be electrically connected, for example, through wires or through a wireless connection, to a suitable electromagnetic radiation source **706** that is capable of sufficiently illuminating a surface tension controlled valve to cause a change in the hydrophobic/hydrophilic properties of the valve. Electromagnetic radiation source **706** can comprise a laser, an ultraviolet light source, an infrared source, an incandescent bulb, a fluorescent bulb, a light-emitting diode (LED), an array of LEDs, combinations thereof, and the like.

[0125] According to various embodiments, fluid processing system **700** can comprise an apparatus **704** that can direct the electromagnetic radiation toward a plurality of separate surface tension controlled valves incorporated in a fluid processing device **710**, for example, in a card or chip. Apparatus **704** can include an electromagnetic radiation reflective device such as one or more mirrors. Apparatus **704** can comprise a plurality of independently-moveable, computer controllable, micro-mirrors **705**, as shown. The fluid processing system **700** can further comprise one or more lenses **708**, for focusing the electromagnetic radiation reflected by micro-mirrors **705** toward fluid processing device **710**. Pumps **712**, and **714**, can be fluidically connected to fluid processing device **710**, for example, to one or more manifolds in the device, and operatively connected to computer **702**. Operatively connected can be defined as electrically connected, mechanically connected, fluidically connected, combinations thereof, and the like. Pumps **712**, **714**, can be used to control, at least in-part, the flow of fluids to and/or from fluid processing device **710**.

[0126] According to various embodiments, and as illustrated in **FIG. 12**, a fluid processing system **800** is provided that can comprise a mirror **808**, for example, a galvo-mirror, controlled by a computer **801**. Mirror **808** can direct electromagnetic radiation from an electromagnetic radiation source **802** through one or more lenses **804** toward light-activated surface tension controlled valves in a fluid processing device **806**.

[0127] According to various embodiments, and as illustrated in **FIG. 13**, a fluid processing system **900** can comprise a rotatable carousel **902** having a top surface. Disposed upon the top surface of carousel **902** can be a plurality of fluid processing devices **904**. Each device **904** can comprise a first manifold, a second manifold, a plurality of reaction regions, and a plurality of surface tension controlled valves, as described above. Carousel **902** can rotate so as to position each device **904** above a heater **906**, and adjacent two or more pumps or pumping blocks **908**, **910**. Pumping blocks **908** and **910** can be any suitable pumping devices for moving reagents, or can be pumping systems capable of independently addressing and pumping a number of different reagents present inside the block itself, or in fluid communication with the blocks. Reagents that can be pumped into and out of the devices by pumping blocks **908** and **910** can comprise nucleotides, nucleosides, nucleotide analogs, adenine, cytosine, guanine, thymine, uracil, protected versions thereof, deprotecting reagents, acids, capping reagents, wash fluids, or combinations thereof.

[0128] Detection block **912** can comprise an electromagnetic radiation source and an imaging system can be disposed above carousel **902**. Detection block **912** can comprise an electromagnetic radiation source capable of selectively opening one or more surface tension controlled valves of an underlying device **904**. Detection block **912** can also comprise an imaging system capable of recording images of, or viewing, tagged molecules, for example, fluorescently tagged molecules. The imaging system can comprise, for example, an analog camera, a film camera, a digital camera, a CCD, or a combination thereof. Fluid processing system **900** can include drive unit **905** and control unit **914**. Control unit **914** can be operatively connected to optical block **912**, pumping blocks **908**, **910**, heater **906**, carousel **902**, and/or drive unit **905**. Operatively connected can be defined as electrically connected, mechanically connected, fluidically connected, combinations thereof, and the like.

[0129] According to various embodiments, a method of synthesizing oligomers, for example, oligonucleotides, is provided for which traditional phosphoramidite or other appropriate chemistry can be used. The method can be used to create a plurality of identical oligomers in each reaction site or to create a different oligomer in each respective reaction site. The method can comprise providing a fluid processing device as described herein, for example, that can comprise one or more reaction sites each including an inner surface, a first manifold in fluid communication with the one or more reaction sites, a second manifold in fluid communication with the one or more reaction sites, and one or more surface tension controlled valves disposed in the first manifold.

[0130] The method can comprise introducing a first protected monomer into the first manifold, whereby the first protected monomer can be selectively introduced, through the one or more surface tension controlled valves, into the one or more reaction sites, depending upon how many surface tension controlled valves are activated to become open. The first protected monomer can then be attached to a structure or precursor in each reaction site, or can be attached directly to the inner surface of each reaction site. The attachment forms an extended structure. Excess first protected monomer can then be drawn out of the one or more

reaction sites and through the second manifold, for example, by using a pumping block or device to create a negative pressure differential. At the same time, or subsequently, a wash fluid from the first manifold or second manifold can be forced into, or drawn through and away from, the one or more reaction sites that had the first protected monomer loaded therein. The wash fluid can be forced into or drawn through and away from the one or more reaction sites by a pumping block or pump connected to the first manifold, the second manifold, or both manifolds.

[0131] In a subsequent step, according to various embodiments, a deprotecting agent, for example, trichloroacetic acid, or the like, can be introduced into the first manifold and the one or more surface tension controlled valves can be opened, enabling the deprotecting agent to pass through and enter the one or more reaction sites. The deprotecting agent can be moved into the one or more reaction sites by using positive pressure, negative pressure, gravity, centrifuigal force, capillary action, or the like. By contacting the first extended structure with the deprotecting agent in the one or more reaction sites, a deprotected extended structure can be formed in the one or more reaction sites. Excess deprotecting fluid can then be forced out or drawn out of the one or more reaction sites and through the second manifold, for example, by using a pumping block to create a negative pressure differential. At the same time, or subsequently, a wash fluid from the first manifold or second manifold can be forced into or drawn through and away from the one or more reaction sites that had the deprotecting agent loaded therein. The wash fluid can be forced into or drawn through and away from the one or more reaction sites by a pumping block or pump connected to the first manifold, the second manifold, or both manifolds.

[0132] The wash fluid can then be removed from the reaction site by a pumping block, by air pressure, by centrifugal force, or the like. According to various embodiments, the deprotecting agent and the wash fluid can be removed together from one or more of the reaction sites.

[0133] After removing the deprotecting agent, a second protected monomer can then be introduced from the first manifold, through the one or more surface tension controlled valves, and into one or more of the reaction sites. The second monomer can then bond to the deprotected extended structure, if present in the respective reaction site, to thereby form a second extended oligomer structure having at least two monomeric subunits.

[0134] The abovementioned method can be repeated multiple times until a desired oligomer has been formed. Once a completed oligomer has been formed, it can be cleaved from its attachment site in the reaction site and collected, for example, through the first or second manifold.

[0135] According to various embodiments of the method, and with reference to the device shown in **FIG. 9**, first manifold **503** can be used for delivering reagents into the plurality of reaction sites, while second manifold **517** can be used for drawing out or purging excess reagents from the reaction sites. Alternatively or additionally, the second manifold can be used to deliver reagents or wash fluid into one or more of reaction sites **510**. Each surface tension controlled valve can be controlled independently so a user can independently select whether a particular reagent is able to enter a reaction site from first manifold **503**. In this way, a different oligomer can be produced in each reaction site. In oligonucleotide synthesis, this selective synthesis can be accomplished by the selective introduction of monomers, deprotecting agent, washing fluid, or a combination thereof.

[0136] According to various embodiments of the method, the fluid processing device can be used to synthesize at least two different oligonucleotide primers and an oligonucleotide probe (as described above) in three different interconnected reaction regions, for example, in the three different reaction sites of the device shown in **FIG. 10**. In an exemplary embodiment, one primer can be formed in reaction site **614**, a second primer can be formed in reaction site **618**, and a probe can be formed or preloaded into reaction site **616**. After formation of the primers, they can be cleaved from their respective reaction sites and combined into reaction site **616** containing the probe. A nucleic acid sample can then be introduced into the reaction site **616** along with suitable reagents for a PCR reaction. Reaction site **616** can then be sealed with oil, a polymer, or with mechanical valving, to prevent evaporation, and then the contents of the site can be thermally cycled. In such embodiments, the device can be used for reagent synthesis and PCR using the reagent.

[0137] Those skilled in the art can appreciate from the foregoing description that the present teachings can be implemented in a variety of forms. Therefore, while these teachings have been described in connection with embodiments thereof, the teachings should not be so limited. Various changes and modifications can be made without departing from the teachings herein. All references, patents, patent applications, and patent application publications cited herein are incorporated in their entireties by reference for all purposes.

What is claimed:

1. A method comprising:

introducing a first nucleic acid monomer into a first fluid distribution manifold of a fluid processing device;

opening at least one surface tension controlled valve in fluid communication with both the first fluid distribution manifold and at least one respective reaction site, to form an open surface tension controlled valve;

moving the first nucleic acid monomer from the first manifold, through the at least one open surface tension controlled valve, and into the at least one respective reaction site; and

attaching the first nucleic acid monomer to a first structure in the at least one respective reaction site to form an extended structure.

2. The method of claim 1, wherein the first nucleic acid monomer is a first protected nucleic acid monomer, the extended structure is a protected extended structure, and the method further comprises:

washing the at least one respective reaction site subsequent to the attaching;

closing the at least one surface tension controlled valve;

introducing a deprotecting agent into the first manifold then opening the at least one surface tension controlled valve to form at least one reopened surface tension controlled valve;

moving the deprotecting agent from the first manifold, through the at least one reopened surface tension controlled valve, and into the at least one respective reaction site; and

deprotecting the protected extended structure to form a deprotected extended structure.

3. The method of claim 2, further comprising:

introducing a wash reagent into a second manifold in fluid communication with the at least one respective reaction site;

moving the wash reagent from the second manifold into the at least one respective reaction site; and

removing the wash reagent from the at least one respective reaction site to form a washed and deprotected extended structure.

4. The method of claim 1, wherein the first structure is supported by a support and the method further comprises cleaving the extended structure from the support to form a cleaved structure.

5. The method of claim 4, further comprising moving the cleaved structure from the at least one respective reaction site into a second reaction site that is in fluid communication with the at least one respective reaction site.

6. The method of claim 1, wherein the extended structure comprises a dimethyltrityl-protected phosphoramidite monomer.

7. The method of claim 1, wherein opening the at least one surface tension controlled valve comprises directing electromagnetic radiation toward the at least one surface tension controlled valve.

8. The method of claim 1, wherein opening at least one surface tension controlled valve comprises reflecting electromagnetic radiation emitted from an electromagnetic radiation source toward the at least one surface tension controlled valve.

9. The method of claim 8, wherein the reflecting comprises individually controlling movement of a plurality of mirrors.

10. The method of claim 1, wherein the at least one surface tension controlled valve comprises a plurality of surface tension controlled valves, and the at least one respective reaction site comprises a plurality of respective reaction sites.

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