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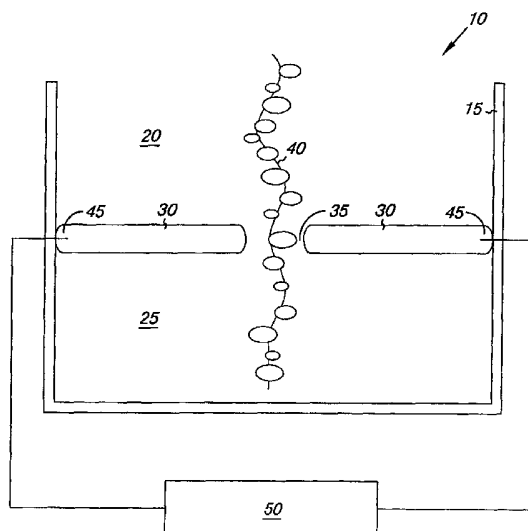
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(54) Title: SOLID STATE MEMBRANE CHANNEL DEVICE FOR THE MEASUREMENT AND CHARACTERIZATION OF
ATOMIC AND MOLECULAR SIZED SAMPLES



(57) Abstract: A solid state device is formed through thin film deposition techniques which results in a self-supporting thin film layer that can have a precisely defined channel bored therethrough. The device is useful in the characterization of polymer molecules by measuring changes in various electrical characteristics as molecules pass through the channel. To form the device, a thin film layer having various patterns of electrically conductive leads are formed on a silicon substrate. Using standard lithography techniques, a relatively large or micro-scale aperture is bored through the silicon substrate which in turn exposes a portion of the thin film layer. This process does not affect the thin film. Subsequently, a high precision material removal process is used (such as a TEM) to bore a precise nano-scale aperture through the thin film layer that coincides with the removed section of the silicon substrate.

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SOLID STATE MEMBRANE CHANNEL DEVICE FOR THE MEASUREMENT AND CHARACTERIZATION OF ATOMIC AND MOLECULAR SIZED SAMPLES

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a device for the characterization of polymer molecules. More specifically, the present invention relates to a solid state device useful for the characterization of polymer molecules as well as a method of making the same.

Description of the Related Art

It has recently been announced that the mapping of the human genome has been completed. This historic development will lead to a myriad of developments ranging from the identification of the genetic basis of various diseases to the formulation and fabrication of new drugs and treatment protocols. All of this will only further serve to increase the already high demand for rapid information processing relating to polymer characterization, particularly that of various nucleic acids (i.e., DNA).

Heretofore, the sequencing of nucleic acids has been performed through chemical or enzymatic reactions. This allows for the nucleic acids to be separated into strains having differing lengths. This is generally tedious and laborious work and requires a significant amount of time and effort to complete. Thus, the results from any desired characterization of a particular polymer sequence are usually quite expensive and take a fair amount of time to obtain.

A significant advancement in the characterization of polymer molecules was introduced by Church et al. in U.S. Patent No. 5,795,782 which issued on August 18, 1998. Church et al. teach a method of causing polymer molecules, and in particular nucleic acids, to pass through an ion channel in an otherwise impermeable organic membrane. The membrane separates two pools of a conductive fluid solution containing a supply of the polymer material in question. By generating a voltage differential across the membrane, the polymer molecules can be ionized or polarized and guided through the ion channel. By measuring the various electrical characteristics

of the membrane, the particular base of the polymer molecule can be identified by identifying the changes in these electrical characteristics as a particular base of the polymer molecule occludes the channel. Thus, each type of base member will exhibit unique characteristics that are identifiable by variations in monitored electrical parameters such as voltage or current.

The drawback of this device is that it is difficult to create an impermeable membrane having a sufficiently small ion channel that will allow the device to function properly. Church, et al. teaches using an organic membrane where an ion channel is created through the membrane via a chemical etching process. This is extremely difficult to do on a cost effective and repetitive scale. Specifically, the formation of an otherwise impermeable organic membrane and chemically etching or otherwise forming the ion channel is a hit or miss operation that may or may not actually produce the appropriately channeled membrane. Thus, while the concept of providing for the rapid determination of the character of polymer molecules is an extremely important one, no device has been provided that can be reliably produced while achieving accurate results.

Therefore, there exists a need to provide a high quality, reliable and easily reproducible polymer characterization device.

SUMMARY OF THE INVENTION

The present invention provides a generally impermeable membrane having a nano-scale aperture. Polymer molecules are caused to travel through the aperture or channel and the electrical characteristics generated by the particular base or monomer occupying the channel at a given time is determined based upon various measurements made by monitoring the membrane.

In one embodiment, the membrane is used to separate two pools of a conductive medium containing quantities of the polymer molecules in question. Unlike membranes used by the previous device which are organic in nature, the membrane of the present invention is inorganic and uses a combination of wafer and thin film technology to accurately and consistently manufacture a membrane having the desired characteristics. The membrane is formed by providing a base preferably using a silicon substrate. A thin film is deposited on at least one side of the silicon substrate. The thin film may include one or more integrated electrical leads that

can ultimately be connected to the testing and monitoring equipment. Using standard lithography techniques and taking advantage of the anisotropic etching characteristics of single crystal silicon wafering, a window or aperture is etched through the silicon substrate. The typical size of the window is from a few microns square to a few hundred microns square. In the selected area, the etching process removes all of the silicon substrate but leaves the thin film entirely intact and unaffected. Thus, a self supporting thin film, such as SiN for example is bridged across a micro-scale aperture in a silicon substrate. Using a focused ion beam or electron beam lithography, a nano-scale aperture is precisely cut through the thin film layer. Thus, the nano-scale aperture provides a channel through which polymer molecules pass and are measured in various ways.

The present invention also provides for differing configurations of the thin film layer. At a minimum, a single electrically conductive layer should be provided. If properly configured, the fabrication of the nano-scale aperture will bisect this conductive layer into two independent and electrically isolated conductive members or leads. Thus, as a molecule passes through the channel, monitoring equipment connected to each of the electrically conductive sections can obtain measurements such as voltage, current, capacitance or the like. This would be a transverse measurement across the channel.

In practice, it may be more practical to provide one or more dielectric layers that effectively protect and insulate the conductive layers. The use of such dielectric layers can simplify the manufacturing process and allows for multi-level conductive layering to be generated. That is, providing a single conductive layer or effectively providing electrical leads in a common plane allows for measurements of the particular polymer base in a transverse direction. However, by stacking conductive layers atop on another (electrically isolated from one another such as by an interposed dielectric layer), measurements of certain electrical characteristics can be taken in the longitudinal direction.

The present invention provides for a variety of lead patterns in both a longitudinal and transverse direction. In one embodiment, a single, shaped electrically conductive layer is provided. The conductive layer is relatively narrow near a medial portion so that a channel formed therethrough by a focused ion beam effectively bisects the electrically conductive layer into two electrically independent sections or leads. The benefit of such a construction is a

minimal number of steps are required to complete the finished product. However, one potential drawback is that the single conductive layer must be applied relatively precisely in that the channel which eventually separates the layer in two will usually have a diameter on the order of ten nanometers.

Since this level of precision may be difficult in some manufacturing processes, another single layer approach is provided. Namely, a single electrically conductive layer is provided. However, the medial portion need not be so narrow as to allow bisection by the formation of a nano-scale aperture. Thus, when a nano-scale aperture is bored through the thin film layer, electrically conductive material remains which effectively connects the two leads. A focused ion beam or other precision material removing apparatus is used to remove a section of the thin film layer so that the two leads are electrically independent.

By providing leads on a single plane, various transverse measurements of electrical characteristics can be performed. Bisecting a single layer results in the formation of two leads. The present invention also provides for fabricating four or more leads in a single plane so that multiple transverse measurements are possible.

By utilizing dielectric layers, electrically conductive leads can be fabricated in multiple planes. This not only allows for transverse measurements to be made, but facilitates longitudinal measurements as well. Any configuration or variation of the single plane lead structures can be repeated with the multi-level thin film layers. Namely, relatively precise conductive layers can be applied relying on the focused ion beam or other precision cutting device to bisect each respective layer. Alternatively, a focused ion beam or other precision cutting device can be utilized for removing a precise amount of the electrically conductive layer in and around the desired channel area, once again resulting in any number of leads being fabricated in any given plane. Thus, multiple transverse and multiple longitudinal measurements can be made between any given pair of leads.

Longitudinal measurements in and of themselves may be sufficient to determine the necessary characteristics in the polymer material in question. That is, it is not necessary to have electrically isolated lead pairs in a single plane. This allows for an embodiment where a relatively imprecise electrically conductive layer is formed in a first plane. A second relatively

imprecise electrically conductive layer is formed in a second plane wherein the second plane is separated from the first by a dielectric layer. By providing a nano-scale aperture through the entirety of the thin film layer (i.e., the dielectric layers and both the conductive layers), a completed structure is fabricated. In this embodiment, electrical measurements are not possible within a single plane. However, by measuring across different planar levels sufficient information may be gathered to characterize the polymer molecule. This configuration provides for relative ease during the manufacturing process and results in a repeatable and highly accurate device.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic illustration of a membrane separating medium bearing pools containing linear molecules wherein the linear molecules pass through a channel in the membrane and are detected by the attached electronic testing equipment.

Figure 2A is an end view of a silicon substrate.

Figure 2B is an end view of a silicon substrate with a thin film layer applied thereto.

Figure 2C is a partially sectional end view of a silicon substrate having a lithography hole bored therethrough with a self supporting thin film layer atop the silicon substrate.

Figure 2D is a schematic view illustrating the orientation of a focused ion beam used to cut a channel through the thin film layer.

Figure 2E is a silicon substrate bearing a self supporting thin film layer having a nano-scale channel bored therethrough.

Figure 3 is a sectional view of a thin film layer having a conductive layer disposed between two dielectric layers.

Figure 4 is a top view of a conductive layer having two leads with a nano-scale channel bored therethrough.

Figure 4A is a top view of a conductive layer having two leads with a nano-scale channel bored therethrough.

Figure 4B is a side elevational view of a silicon substrate with a partially self supporting layer sandwiched between two conductive layers.

Figure 5 is a top view of an electrically conductive layer having two leads and a nano-scale aperture bored therethrough wherein dashed lines are used to indicate excess material that must be removed to electrically isolate the two leads from one another.

Figure 6 is a top view of a shaped, electrically conductive layer.

Figure 7 is a top view of an electrically conductive layer separated into orthogonal lead pairs with a nano-scale aperture bored therethrough.

Figure 8 is a sectional view of a thin film layer having dual electrically conductive layers.

Figure 9 is a top view of the conductive layers forming the dual conductive layer thin film of Figure 8.

Figure 10 is a top view of two electrically conductive layers one atop another with a nano-scale channel board therethrough.

Figure 11 is a schematic illustration of a dual conductive layer thin film and a silicon substrate forming a membrane separating an upper and lower medium bearing liquid.

Figure 12 is a schematic illustration illustrating a thin film having dual conductive layers coupled with a silicon substrate separating an upper and lower medium bearing pool.

Figure 13 shows a 5 nanometer x 25 nanometer straight through pore in a SiN membrane.

Figure 14 shows a 3.5 nanometer x 25 nanometer straight through pore in a SiN membrane.

DETAILED DESCRIPTION OF THE INVENTION

Referring to Figure 1, a channel device is illustrated and generally referred to as 10. Channel device 10 includes container 15 within which resides a volume of fluid. The fluid is separated into an upper pool 20 and lower pool 25 by a membrane 30. The liquid within upper pool 20 and lower pool 25 is preferably a conductive solution and contains a number of linear polymer molecules 40. Polymer molecules 40 are free to travel through the liquid medium contained within container 15. Figure 1 is provided for illustrative purposes only and the components shown are not drawn to scale in general or with respect to each other.

By using various processes, such as introducing a voltage differential across membrane 30, polymer molecules 40 can be directed through channel 35 in membrane 30. Channel 35 is a nano-scale aperture. Typically, channel 35 will have a diameter of up to about 10 nm and

preferably between 2-4 nm. Of course, the actual size will be selected to best serve the desired application. As linear polymer molecule 40 travels through channel 35, the individual monomers will interact with membrane 30 within channel 35. This will result in various electrical and/or physical changes that can be detected by the electronic testing equipment 50 that is interconnected with membrane 30 through leads 45. For example, a given monomer within channel 35 can be determined by changes in measured voltage, conductance, capacitance or various other electrical parameters. In one embodiment, a predetermined amount of current flows across the open channel 35. As the DNA molecule occludes the channel, the amount of current is measurably decreased. The duration of the current drop reflects the size of the molecule. Thus, as polymer molecule 40 passes through channel 35, each individual monomer is characterized. As this data is received and stored, the character of the polymer is accurately identified. In previously known devices utilizing this technique, the membrane consists of a difficult to manufacture and delicate organic membrane hopefully having an appropriately sized channel chemically etched therethrough. Fabricating an otherwise impermeable organic membrane is a difficult and inconsistent process. It is even more difficult to chemically create a single or a controlled number of channels therethrough while of course maintaining the proper dimensions in the fabricated channel. Finally, connecting testing equipment and making electrical measurements from such a membrane is exceedingly difficult. Thus, the present invention provides a reliable, mechanically fabricated inorganic membrane 30.

Figure 2A illustrates the first step in the process of fabricating membrane 30. A supportive substrate 55 is provided. Preferably, substrate 55 is a self supporting member constructed of an etchable material. An ideal material is silicon and, in particular, silicon wafers which are widely available and easy to work with. It should be noted that all of the Figures only illustrate components schematically. Thus, the scale imparted bears no relationship to actual practice. Furthermore, the scale of the components as compared to one another is skewed so as to illustrate concepts.

In Figure 2B, a thin film 60 (e.g., SiN) is deposited on two surfaces of silicon substrate 55. Thin film 60 is shown as a single layer, however its actual construction can be more complicated and will be explained in greater detail below. After thin film 60 has been generated on silicon substrate 55, a hole or window 65 is etched into the silicon substrate 55 and the lower

layer of the thin film using standard lithography techniques, such as wet etching. Such techniques will remove the silicon in the desired area but will have no effect on thin film 60. Thus, over the area defined by lithography hole 65, thin film layer 60 becomes self supporting as illustrated in Figure 2C. Subsequently, a channel 75 (as illustrated in Figure 2E) is cut through thin film 60 with a focused ion beam (FIB) 70 or other suitable precision milling device such as electron beam lithography, neutral particle beam, charged particle beam, x-ray, or other suitable mechanism.

In order to appropriately sequence DNA, the channel size should correspond to the diameter of the molecule under consideration. Thus, channel diameters of 1-5 nm and preferably 2-5 nm would be appropriate. One way to achieve apertures of this scale through a material is with a Transmission Electron Microscope ("TEM"). TEM drilling involves the bombardment of the material by a stream of high energy electrons on the order of 100 KeV. Further, by using the SCRIBE process (Sub-nanometer Cutting and Ruling by an Intense Beam of Electrons), nano-scale apertures on this scale can be fabricated through relatively deep or thick substrates. For example, apertures with a diameter of 1-2 nm can be precisely drilled through depths of 200 nm or more. The SCRIBE process achieves those results when certain materials are chosen that are particularly susceptible to electron bombardment. Such materials include β and β alumina, NaCl, amorphous alumina, CaF₂, MgO, and to some extent Si.

The drilling process produces consistent apertures throughout the drilling depth due to the nature of the interaction of the electron beam with the material. By altering the state of the material via electron stimulated desorption, rows of voids are formed sequentially throughout the depth of material. Material from the surface is sputtered off and the voids formed are "replenished" by the material behind it until the channel is formed. The exact physics of the removal of material by a high density electron beam is likely to be different for different materials. Thus, one technique to form appropriately sized nano scale apertures is to use the TEM to drill the nanopore and then to measure the nanopore, all in one sample presentation to the TEM instrument. Figs. 13 and 14 show nanopores made with a TEM drill and imaged in-situ with the same TEM in a one step process.

When using a FIB, the aspect ratio between the thickness of the thin film and the size of the channel 75 must be considered. That is, a FIB can only mill so deep while maintaining a particular diameter channel. Typical FIB devices have an optimal range of about 1:2, and are functional to about 1:4. Thus, the thickness of this film 60 should be selected to be in accordance with the limitations of the FIB (or the alternative milling device) actually being utilized. Thus, for a channel 75 having an approximate diameter of 10 nm, an optimal thin film 60 thickness would be less than 20 nm (1:2) to less than 40 nm (1:4). The result as illustrated in Figure 2E is a completed membrane 30 having a base or silicon substrate 55 with a relatively large (micro-scale) lithography hole 65 on top of which resides a partially self supporting thin film layer 60 having a nano-scale aperture or channel 75 bored therethrough. As illustrated, channel 75 and lithography hole 65 are aligned so that passage through channel 75 is in no way impeded by any portion of the remaining silicon substrate 55. As explained in greater detail below, thin film layer 60 has electrically conductive portions which may be coupled to testing equipment. This may be accomplished by providing a conductive thin film layer on one or both sides of self supporting membrane 60. Thus, various electrical characteristics of thin film 60 can be monitored by the testing equipment. When membrane 30 as illustrated in Figure 2E is actually used in a polymer molecule characterization device 10, thin film layer 60 effectively acts as the membrane, as silicon substrate 55 is essentially a support member. Depending upon the fluid medium selected, it may be desirable to provide additional material around silicon substrate 55 to protect it. For example, Teflon® or other suitable materials could be utilized.

Another consideration when milling or drilling the channel is that if both sides of the membrane have conductive material, the milling or drilling process may short the two conductive surfaces; thus, it may be desirable in such structures to mill through a single conductive layer, then deposit the second layer and complete fabrication.

Referring to Figure 3, thin film 60 is shown in more detail. Figure 3 is a sectional view of a multi-layer thin film having electrically conductive layer 85 disposed between two non-conductive or dielectric layers 80. Channel 75 effectively serves to isolate the electrically conductive layer 85 into two discrete sections thus forming right lead 90 and left lead 95. Thus, by appropriately monitoring right lead 90 and left lead 95 with the appropriate testing equipment, the characteristic of objects that pass through channel 75 can be determined by their effect on

these electrical characteristics. All of this assumes that a satisfactory signal to noise ratio (SNR) can be achieved for the particular objects in question. Of course, for ease of manufacturer, the configuration could be reversed, that is layers of conductive material could sandwich the dielectric self supporting structure. Or, a single conductive layer (split into two leads) could be formed on either side of the self supporting dielectric layer. Such a configuration is illustrated in Figure 4B. A silicon substrate 91 includes a partially self supporting silicon nitride layer 92. Two conductive layers 93,94 are deposited, one on either side of layer 92. This provides a simple lead structure that allows longitudinal measurements.

Figure 4 is a top view illustrating conductive layer 85 as it is separated into right lead 90 and left lead 95 by channel 75. As illustrated, right lead 90 and left lead 95 are physically separated from one another by the diameter of channel 75. During the fabrication of thin film 60, this lead and channel configuration can be generated in a variety of ways. To begin with, a dielectric layer 80 is applied through a sputtering or other deposition technique. Subsequently, conductive layer 85 is applied in an appropriate pattern. Such a pattern can be that of Figure 5 or Figure 6. Alternatively, as illustrated in Figure 4A, a single conductive layer 85 can be applied and then split into two separate leads 90,95 by cutting or otherwise separating conductive layer 85.

Referring to Figure 5, the initial application of conductive layer 85 results in a pattern that cannot be bisected merely by cutting channel 75 with a focused ion beam. Thus, to produce right lead 90 and left lead 95, the area defined by FIB pattern 100 must be removed by an appropriate technique. A focused ion beam can be used to precisely eliminate those portions of conductive layer 85 designated as removed area 105. While this requires additional milling steps, it is not as time intensive as milling channel 75 since the thickness of the conductive layer is relatively small. Other appropriate material removal techniques could be utilized so long as they can be defined precisely enough to result in the electrical isolation of right lead 90 from left lead 95 as illustrated in Figure 4.

Once right lead 90 and left lead 95 have been so defined, a subsequent layer of dielectric material 80 may be applied completing the fabrication of thin film layer 60. The use of the various dielectric layers 80 provides for some electrical insulation between adjacent electrically

conductive members and also serves to protect the leads from physical contact or abrasion. The specific patterning or arrangement of the various dielectric layers 80 is optional so long as the resulting thin film layer 60 includes electrically conductive leads that can be connected to the appropriate testing equipment and which are capable of detecting the necessary electrical characteristics of the molecules passing through channel 75.

Figure 6 illustrates an alternative pattern for initially forming conductive layer 85 as conductive layer 110. As illustrated, conductive layer 110 provides for an enlarged right lead 90 and an enlarged left lead 95 interconnected by a channel area 115. The precise dimensions of channel area 115 are selected so that it is effectively removed when channel 75 is cut therethrough by a focused ion beam, effectively electrically isolating right lead 90 from left lead 95. Of course, the same effect could be achieved by applying right lead 90 and left lead 95 as separate elements with no interconnection during the deposition process. In either case, sufficient precision must be maintained so that when channel 75 is created, right lead 90 and left lead 95 while electrically isolated from one another are in contact with or relatively close to the outer perimeter of channel 75 so as to be properly effected by molecules passing through channel 75. It may be desirable to have the edge of the leads end prior to channel 75 so that they are not in direct contact with the fluid medium and the polymer molecules during testing. This results in a small section of dielectric material between the edge of the leads and channel 75. Such a modification would simply require additional milling of the conductive layer or that an appropriate initial pattern be applied. Additionally, the electrodes can be chemically treated to help interact with the nucleic acids or other samples.

Figure 7 illustrates a quadrupole arrangement of orthogonal lead pairs 120. Orthogonal lead pairs 120 include right lead 125, left lead 130, upper lead 135, and lower lead 140. All four leads are electrically isolated from one another and abut the perimeter of channel 75. As described above, the leads can instead terminate prior to contacting channel 75. The same techniques used for forming conductive layer 85 of Figure 4 are applicable to forming orthogonal lead pairs 120. The benefit of providing orthogonal lead pairs 120 is that multiple transverse measurements can be made of the molecules passing through channel 75. Thus, measurements are not limited to a single pair of leads. By comparison of the output from any two lead pairs additional data can be obtained about the molecule passing therethrough.

Figure 8 illustrates a dual conductive layer thin film 145. As illustrated, various conductive layers 148 are disposed between various dielectric layers 170 to form this configuration. Once again, it is the orientation of the conductive layers that is important. The particular configuration chosen for the dielectric layers 170 will depend largely upon the selected deposition technique as well as the desired level of resultant protection. In the embodiment shown in Figure 8, a dielectric layer 170 is disposed between the lower conductive layer and the silicon substrate (not shown). Additionally, another dielectric layer 170 is disposed above the top conductive layer. Finally, a third layer of dielectric material 170 is disposed between the two conductive layers which may be necessary to achieve the desired level of electrical isolation. Thus, this series of conductive layers results in a right upper lead 150, a right lower lead 155, a left upper lead 160, and a left lower lead 165 as viewed through a sectional view. The conductive leads abut the outer perimeter of channel 75. Optionally, the leads could terminate prior to contacting channel 75. Thus, as a molecule passes therethrough, the resultant change in various electrical characteristics can be detected by the appropriate testing equipment connected to the various leads. Once again, transverse measurements can be made (i.e., measuring across from right upper lead 150 to left upper lead 160). Additional transverse measurements can be made by measuring across right lower lead 155 to left lower lead 165. However, the dual conductive layer thin film 145 allows for various longitudinal measurements to be made as well. That is, measuring across right upper lead 150 to right lower lead 155 and/or left upper lead 160 to left lower lead 165. The introduction of longitudinal measurements allows for another degree of measurement on the various polymer molecules passing therethrough. Voltage and channel current can be measured in the longitudinal direction. While two conductive layers have been illustrated, more can be introduced as desired.

The distance in the longitudinal direction between consecutive electrodes will affect the resolution of the measurement. That is, if such a distance is greater than the particle size under evaluation, multiple particles may be affecting the electrical characteristics of the channel. Thus, to increase the resolution, the thickness of the membrane, or at least the distance between electrodes should be chosen appropriately. For the measurement of DNA, this distance would be approximately 0.4 nm in order to accurately resolve a base.

Figure 9 illustrates quadrupole orthogonal lead pairs and a dual conductive layer thin film structure. That is, four leads are provided which are electrically independent from one another and abutting channel 75 in a common plane. An additional four leads are provided which are electrically isolated from one another as well as from the first four leads. The second four leads exist in a second plane, separate and spaced apart from the first, and electrically isolated therefrom. More specifically, in a first plane, right upper lead 150, front upper lead 185, left upper lead 160, and back upper lead 175 form a first set of orthogonal lead pairs. Disposed in a parallel plane beneath the first, right lower lead 155, front lower lead 190, left lower lead 165, and back lower lead 180 form a second set of orthogonal lead pairs. This configuration provides a large number of independent measurements that can be made in both the transverse and longitudinal directions. That is, any two lead pairs can be monitored and compared. In addition, multiple measurements can be made by comparing multiple combinations of various lead pairs.

The previously explained embodiments are advantageous in that they allow for a maximum range of measurement possibilities. One potential drawback is the complexity of the lead patterns and the thin film layers. Specifically, the various leads must either be deposited in a very accurate manner, or accurate leads must be defined by a precision material removal process such as using a focused ion beam. In either event, the fabrication of the thin film layer can be complex.

Figure 10 illustrates a configuration where only longitudinal measurements can be made between leads existing in different, electrically isolated planes. Longitudinal measurements alone can provide sufficient information to characterize the molecule. As illustrated, an upper layer 205 of the electrically conductive material is disposed above a lower layer 220 of electrically conducted material. Though not shown, upper layer 205 and lower layer 220 are separated by a sufficient amount of dielectric material to assure electrical isolation. A channel 75 is cut through both upper layer 205 and lower layer 220 as well as any existing dielectric layers. Thus, as before, passage of polymer molecules is allowed through channel 75. Upper layer 205 includes right lead 195 and left lead 200. Likewise, lower layer 220 includes front lead 210 and back lead 215. Channel 75 is cut through these respective layers at an area of intersection 225 where upper layer 205 overlaps lower layer 220. Since only longitudinal measurements are to be made with this configuration, the precision of the previous embodiments is no longer required.

Specifically, channel 75 need not electrically isolate right lead 195 from left lead 200. Similarly, channel 75 need not electrically isolate front lead 210 from back lead 215. The only measurements that can be made are in a longitudinal direction. For example, measuring across front lead 210 to right lead 195. Measurements in the transverse direction are no longer possible in that right lead 195 is not electrically isolated from left lead 200, since a significant amount of electrically conductive material still exists around channel 75. The same configuration occurs in lower layer 220. Thus, it should become readily apparent that longitudinal measurements can be made between either lead of upper layer 205 to either lead of lower layer 220. Thus, it should be further apparent that one lead of each layer is effectively redundant and need not actually be created. The configuration illustrated in Figure 10 takes into account that it may be easier to simply apply certain patterns using thin film deposition techniques even though a portion of that conductive layer may in effect be unnecessary. In any event, all that is required is that an electrically conductive member exists in a first plane electrically isolated from another electrically conductive member located in a second plane. Furthermore, a channel 75 must be bored through each conductive layer (or in close proximity thereto) and any dielectric material existing there between. Thus, the particular configuration or pattern of the selected leads can be selected as desired. What results is a relatively easy thin film configuration to fabricate, thus allowing for a polymer molecule characterization device to be manufactured with a high degree of precision on a cost effective basis.

To allow the embodiment of Figure 10 to make transverse measurements, upper layer 205 and lower layer 220 need only be separated (each into two leads) as indicated by the dotted lines.

Figure 11 schematically illustrates how a completed polymer characterization device, utilizing a dual conductive layer thin film 145, would appear in a sectional view. Dual conductive layer thin film 145 is attached to silicon substrate 55 having a lithography hole 65. Dual conductive layer thin film 145 essentially forms a self supporting member in the area formed by lithography hole 65. Within the area where dual conductive layer thin film 145 forms a self supporting member, channel 75 is bored therethrough. Thin film 145 effectively separates upper pool 20 from lower pool 25. Using various known methods, such as applying a voltage differential across thin film 145, polymer molecules in one pool can be directed into the other. As they pass therethrough, they will effect the electrical characteristics of thin film 145 and these

variations will be detected by taking measurements in a transverse direction. That is, for example, from right upper lead 150 to left upper lead 160 or right lower lead 155 to left lower lead 165. Alternatively measurements in a longitudinal direction could be made, such as by taking measurements across right upper lead 150 to right lower lead 155 or from left upper lead 160 to left lower lead 165. Of course additional measurements could be made from leads on opposite sides of channel 175 which are also located in separate planes. The configuration illustrated in Figure 11 will also be applicable to the dual layer orthogonal lead pairs illustrated in Figure 9.

Figure 12 illustrates the use of a simplified dual conductive thin film 145 which only allows for measurements in a longitudinal direction. That is Figure 12 is illustrative of the pattern illustrated in Figure 10 in a completed application. Measurements can be made from either right lead 195 or left lead 200 to either of front lead 210 or back lead 215 (not illustrated).

Those skilled in the art will further appreciate that the present invention may be embodied in other specific forms without departing from the spirit or central attributes thereof. In that the foregoing description of the present invention discloses only exemplary embodiments thereof, it is to be understood that other variations are contemplated as being within the scope of the present invention. Accordingly, the present invention is not limited in the particular embodiments which have been described in detail therein. Rather, reference should be made to the appended claims as indicative of the scope and content of the present invention.

What is claimed is:

1. A device for the characterization of polymer molecules, comprising:
a substrate forming a base of the device, the substrate including an aperture therethrough;
a thin film disposed on the substrate and extending across the aperture so that the thin film is self supporting over an area defined by the aperture;
a channel formed by a direct electron beam drilling process through the thin film in the area defined by the aperture, wherein the channel is 1-10 nm in diameter so as to allow passage of polymer molecules therethrough so that as a polymer molecule passes therethrough a given monomer will cause a detectable change in the thin film wherein the detectable change will characterize the monomer.
2. The device of claim 1, wherein channel formed by the direct electron beam drilling process is formed by a TEM drilling process.
3. The device of claim 2, wherein the channel is measured using the TEM.
4. The device of claim 3, wherein the formation of the channel and the measurement of the channel are performed in one presentation to the TEM instrument.
5. The device of claim 1, further comprising
a container for holding a fluid medium having a quantity of polymer molecules disposed therein, wherein the substrate including the thin film is disposed within the container and divides the fluid medium into a first pool and a second pool wherein polymer molecules are directed from the first pool through the channel and into the second pool by generating a voltage differential across the thin film.
6. The device of claim 1, further comprising:
a first electrically conductive layer disposed within the thin film so as to form a first set of electrically independent leads, wherein each lead has a first end and a second end and the first end of each lead is proximate the channel.
7. The device of claim 6 wherein the first end of each lead of the first set forms a portion of a perimeter of the channel.
8. The device of claim 6 wherein the first set of electrically independent leads comprises two leads positioned on opposite sides the channel.
9. The device of claim 6 wherein the first set of electrically independent leads comprises four leads positioned evenly around the channel in a quadrapole arrangement.

10. The device of claim 6, further comprising:
a second electrically conductive layer disposed within the thin film so as to form a second set of electrically independent leads, wherein each lead has a first end and a second end and the first end of each lead is proximate the channel.
11. The device of claim 10 wherein the first set of leads is separated from the second set of leads by a dielectric layer.
12. The device of claim 10 wherein the first end of each lead of the second set forms a portion of a perimeter of the channel.
13. The device of claim 10 wherein the second set of electrically independent leads comprises two leads positioned on opposite sides the channel.
14. The device of claim 10 wherein the second set of electrically independent leads comprises four leads positioned evenly around the channel in a quadrapole arrangement.
15. The device of claim 1, further comprising:
a first electrically conductive layer disposed within the thin film so as to form a first electrical lead;
a second electrically conductive layer disposed within the thin film so as to form a second electrical lead, wherein the second electrically conductive layer is separated from the first electrically conductive layer by a dielectric layer, so that the channel is formed to pass through the first electrically conductive layer, the dielectric layer and the second electrically conductive layer.
16. The device of claim 1 where the substrate is silicon.
17. The device of claim 1 wherein the aperture has micro-scale dimensions and the channel has nano-scale dimensions.
18. The device of claim 1 wherein the channel has a diameter of between 2-5 nm.
19. A method of forming a membrane structure for use in a device to characterize polymer molecules, comprising:
providing a support substrate of a predetermined material;
depositing a thin film on the support substrate;
etching a hole through the support substrate that removes all of the material in a predetermined area so that the thin film is self supporting over the predetermined area; and

- drilling a nano-scale channel through a self supporting portion of the thin film.
20. The method of claim 19, wherein the act of drilling comprises using a TEM instrument.
 21. The method of claim 20, wherein the act of drilling further comprises using a SCRIBE process.
 22. The method of claim 20, further comprising measuring the channel using the TEM instrument.
 23. The method of claim 22, wherein the act of drilling and measuring are performed during a single presentation to the TEM instrument.
 24. The method of claim 19 wherein the channel has dimensions that allow passage of polymer molecules therethrough so that as a polymer molecule passes therethrough a given monomer will cause a detectable change in the thin film wherein the detectable change will characterize the monomer.
 25. The method of claim 19 wherein the channel has a diameter of 2-5 nm.
 26. The method of claim 25 wherein the thin film has a thickness of about 30 nm or less.
 27. The method of claim 19 wherein the support substrate is silicon.
 28. The method of claim 19 wherein depositing the thin film further includes:
providing a layer of electrically conductive material having a predetermined pattern such
that boring the channel separates the layer into a plurality of independent
conductive leads.
 29. The method of claim 28 wherein two conductive leads are formed.
 30. The method of claim 28 wherein four conductive leads are formed.
 31. The method of claim 19 wherein depositing the thin film further includes:
providing a layer of electrically conductive material having a predetermined pattern; and
removing a predetermined amount of the layer of electrically conductive material so that
when the channel is drilled, the remainder of the layer of electrically conductive
material is separated into a plurality of conductive leads.
 32. The method of claim 31 wherein two conductive leads are formed.
 33. The method of claim 31 wherein four conductive leads are formed.
 34. The method of claim 19 wherein depositing the thin film further includes:

providing a first layer of electrically conductive material having a predetermined pattern such that drilling the channel separates the layer into a plurality of independent conductive leads;

providing a layer of a dielectric material over the first layer of electrically conductive material;

providing a second layer of electrically conductive material having a predetermined pattern such that drilling the channel separates the layer into a plurality of independent conductive leads, wherein the second layer of electrically conductive material is provided such that the dielectric material separates the second layer of electrically conductive material from the first layer of electrically conductive material.

35. The method of claim 34 wherein two conductive leads are formed in the first layer and two conductive leads are formed in the second layer.

36. The method of claim 34 wherein four conductive leads are formed in the first layer and four conductive leads are formed in the second layer.

37. The method of claim 19 wherein depositing the thin film further includes:

providing a first layer of electrically conductive material having a predetermined pattern; removing a predetermined amount of the first layer of electrically conductive material so that when the channel is bored, the remainder of the first layer of electrically conductive material is separated into a plurality of conductive leads;

providing a layer of dielectric material;

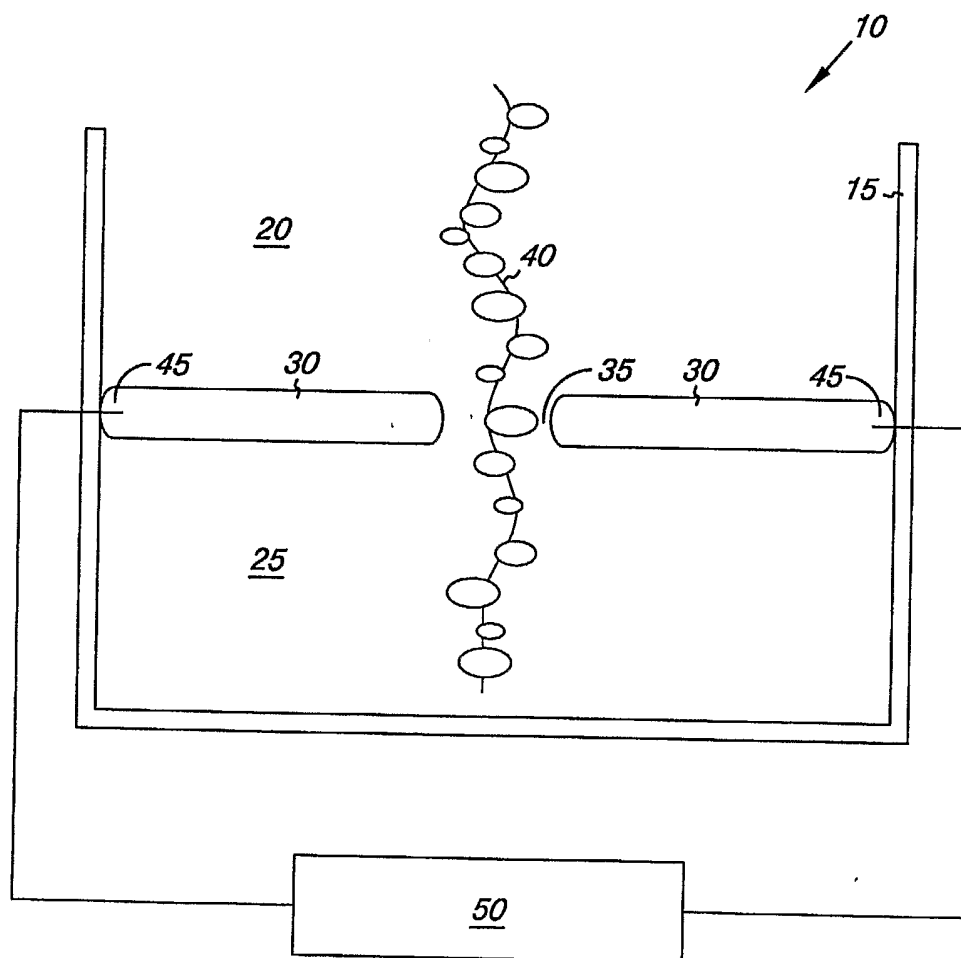
providing a second layer of electrically conductive material having a predetermined pattern, where the dielectric material separates the first layer of electrically conductive material from the second layer of electrically conductive material; and removing a predetermined amount of the second layer of electrically conductive material so that when the channel is bored, the remainder of the second layer of electrically conductive material is separated into a plurality of conductive leads.

38. The method of claim 37 wherein a focused ion beam is used to remove the predetermined amount of the electrically conductive layer from the first layer and from the second layer.

39. The method of claim 37 wherein two conductive leads are formed in the first layer and two conductive leads are formed in the second layer.

40. The method of claim 37 wherein four conductive leads are formed in the first layer and four conductive leads are formed in the second layer.
41. The method of claim 19 wherein depositing the thin film further includes:
providing a first layer of electrically conductive material;
providing a layer of dielectric material;
providing a second layer of electrically conductive material such that the layer of dielectric material separates the first layer of electrically conductive material from the second layer of electrically conductive material and the channel passes through the first layer of electrically conductive material, the dielectric material and the second layer of electrically conductive material.
42. The method of claim 19 wherein etching the hole includes using lithography.
43. Molecular information gathered using the method of claim 22.
44. Molecular information gathered using the device of claim 3.

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*Fig. 1*

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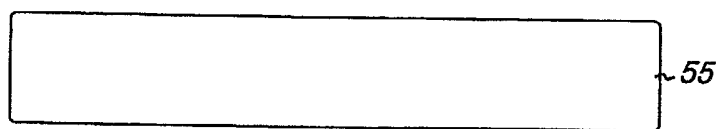


Fig. 2A

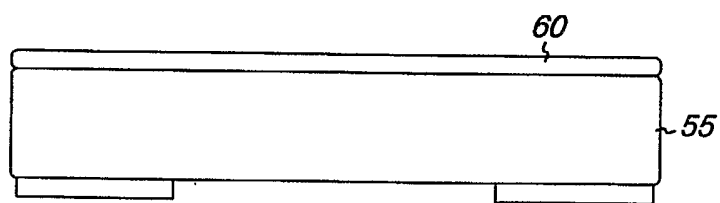


Fig. 2B

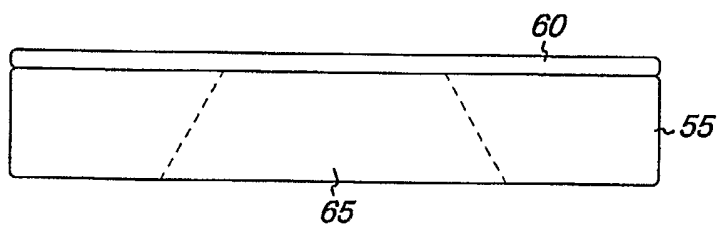


Fig. 2C

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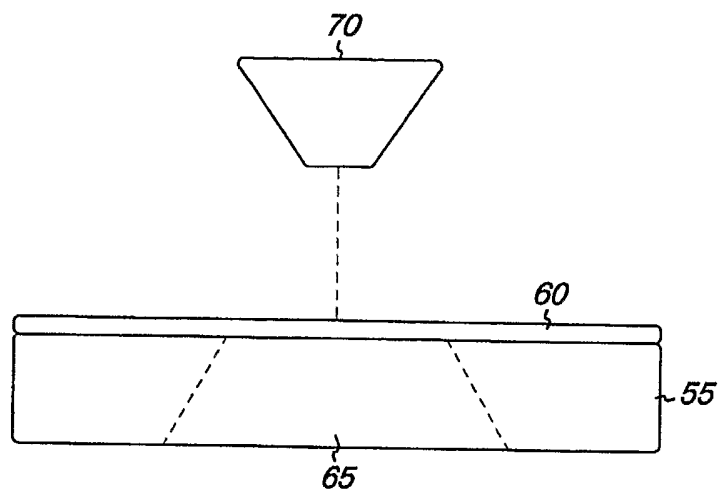


Fig. 2D

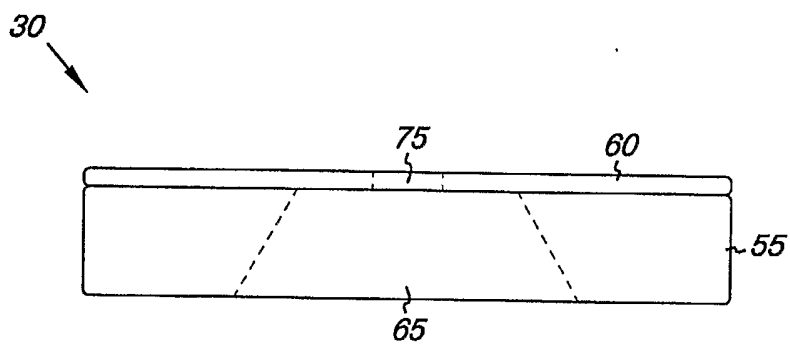


Fig. 2E

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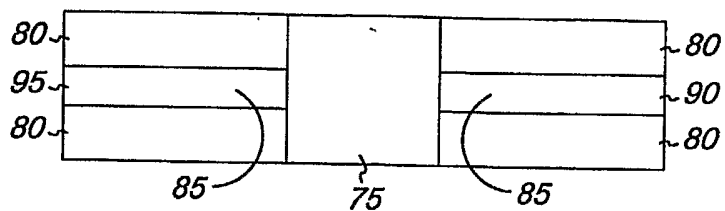


Fig. 3

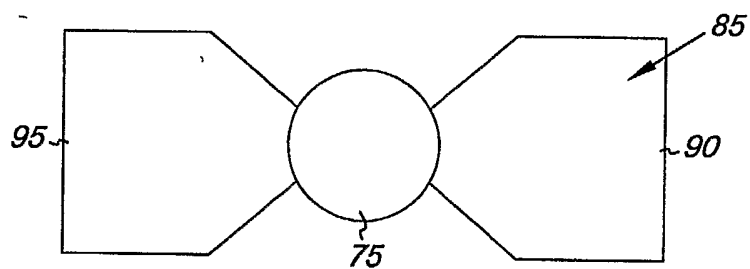


Fig. 4

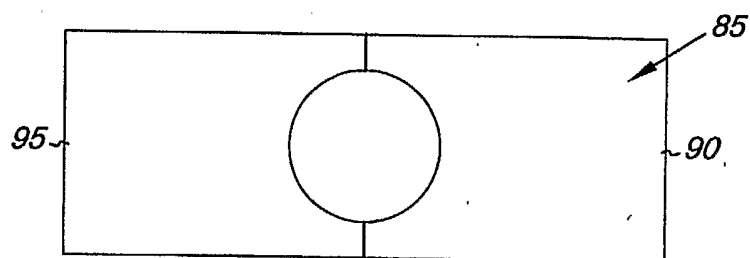
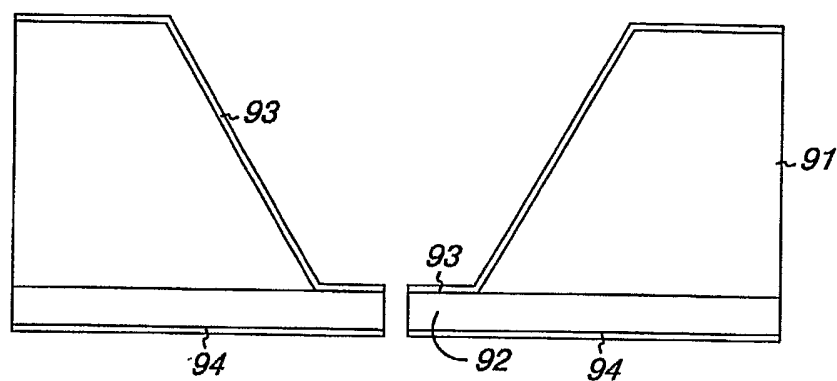
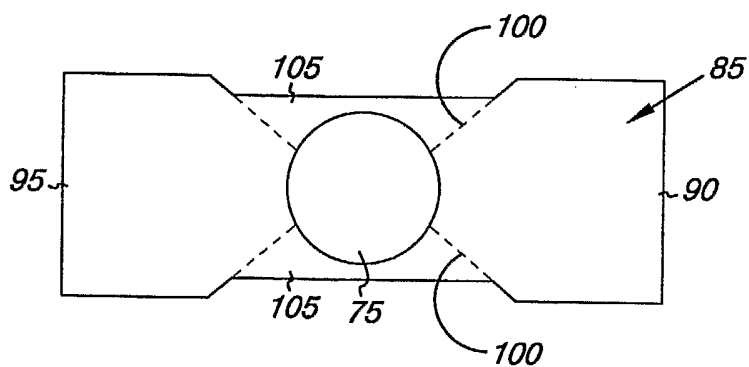


Fig. 4A

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*Fig. 4B**Fig. 5*

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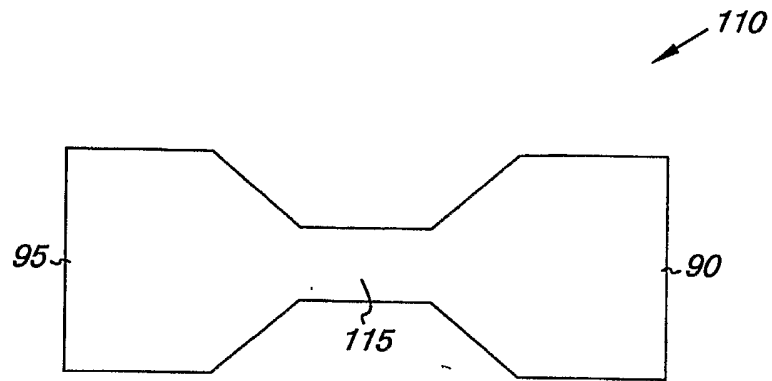


Fig. 6

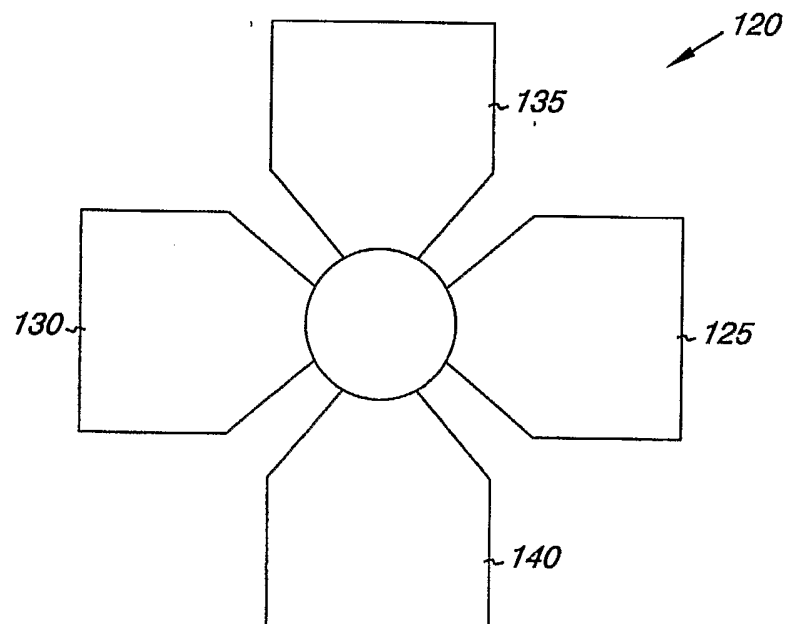
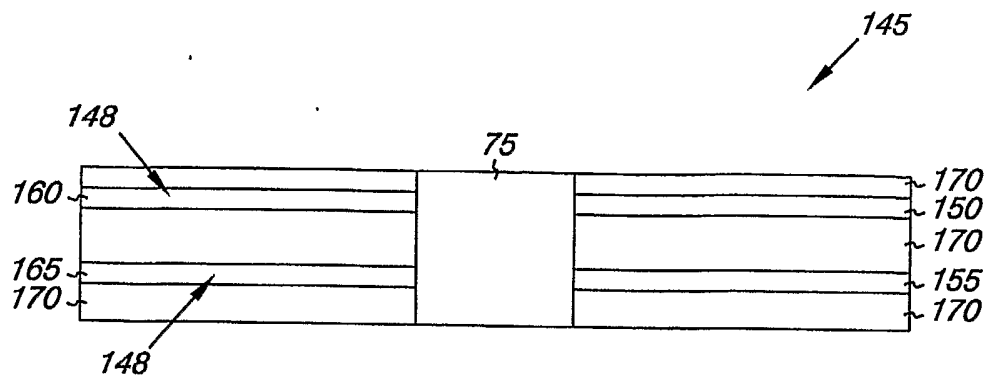
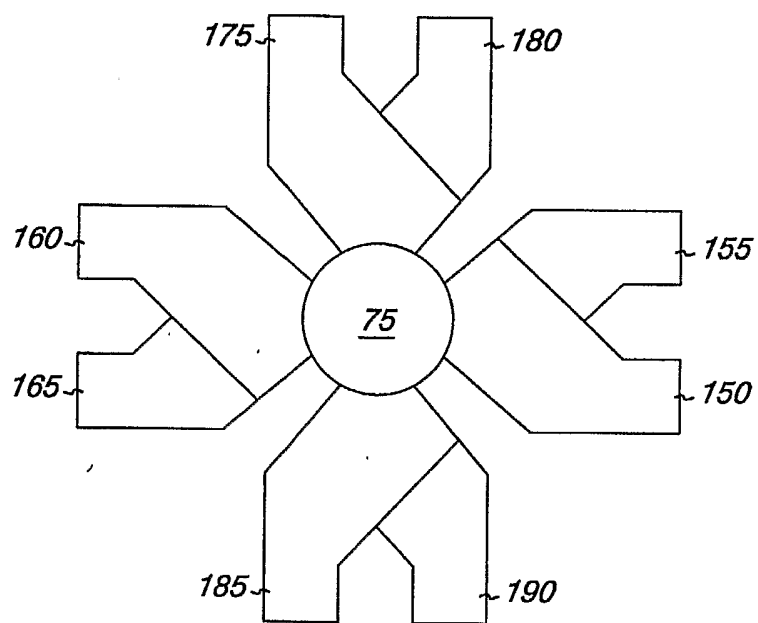


Fig. 7

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*Fig. 8**Fig. 9*

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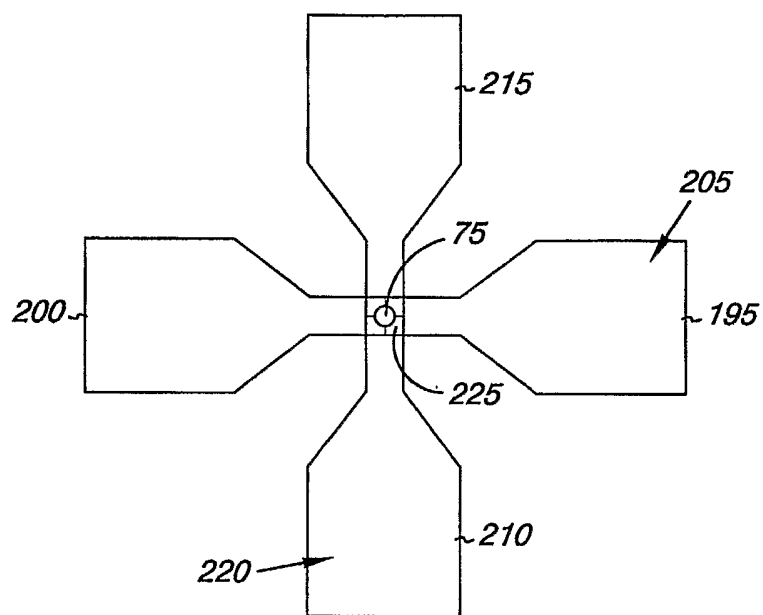
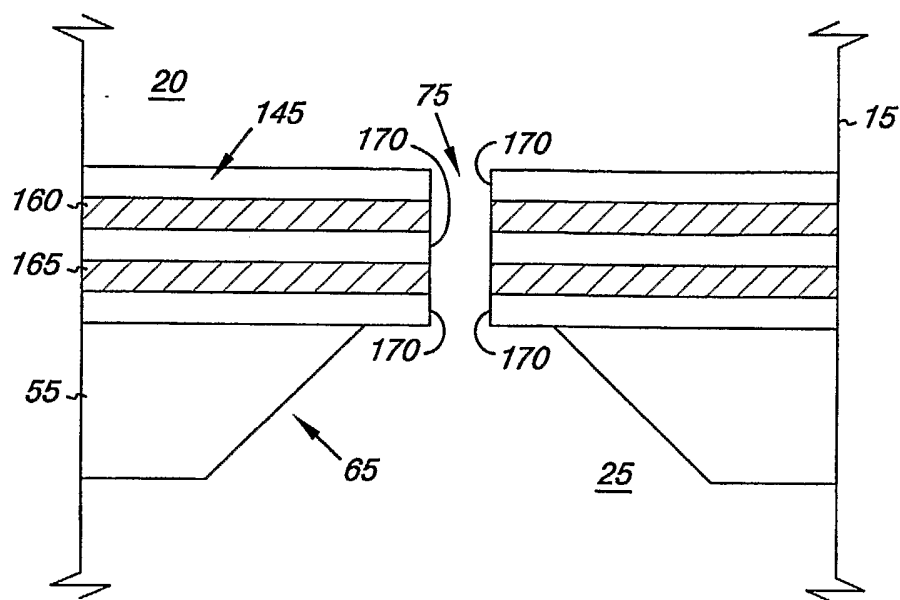
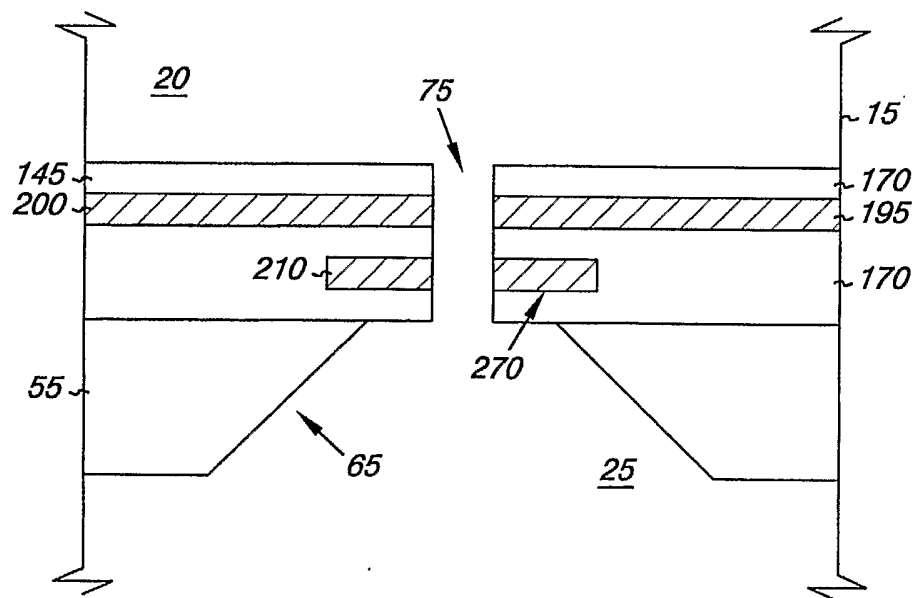


Fig. 10

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*Fig. 11**Fig. 12*

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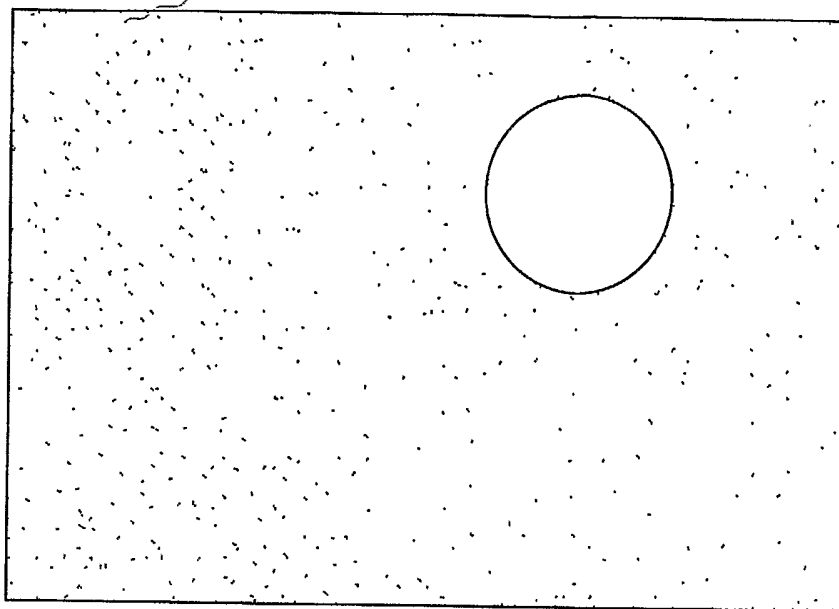


Fig. 13

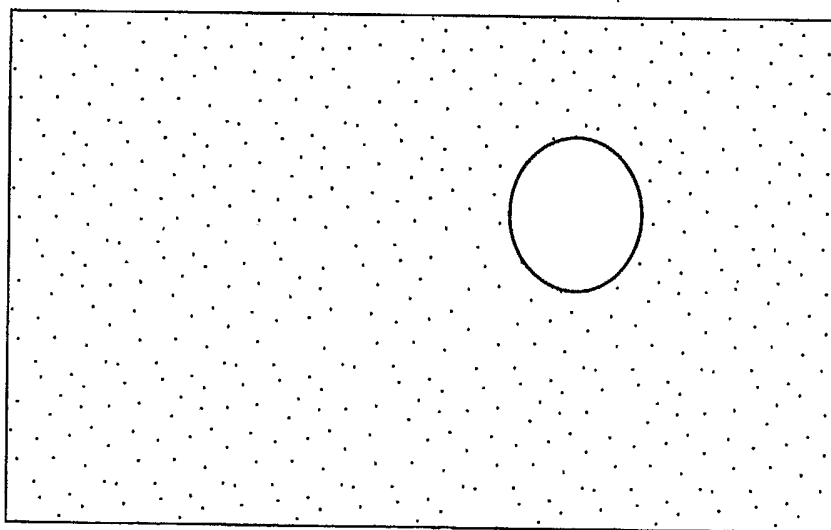


Fig. 14

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/32469

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01L3/00 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 B01L C12Q

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/025277 A1 (DUGAS MATTHEW P ET AL) 28 February 2002 (2002-02-28) figures 1-5 ---	1-42
A	US 6 413 792 B1 (VAN ZEGHBROECK BART JOZEF ET AL) 2 July 2002 (2002-07-02) figures 1,5,7,17,19 ---	1-42
A	US 2002/122873 A1 (HONG SEUNGHUN ET AL) 5 September 2002 (2002-09-05) page 3; figure 2 ---	1-42
A	US 5 838 005 A (LAI JIE ET AL) 17 November 1998 (1998-11-17) figures 8A-B ---	1-42
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

19 February 2004

Date of mailing of the international search report

01/03/2004

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/32469

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 00 78668 A (HARVARD COLLEGE) 28 December 2000 (2000-12-28) figures 1-3 ----	1-42
A	WO 94 25862 A (UNIV WASHINGTON) 10 November 1994 (1994-11-10) figure 4 ----	1-42
A	WO 01 18251 A (DEAMER DAVID W ;UNIV CALIFORNIA (US)) 15 March 2001 (2001-03-15) figures 1,2 -----	1-42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/32469

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 43-44
because they relate to subject matter not required to be searched by this Authority, namely:
Art. 17(2)(a)(i); R. 39.1(v) PCT.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/32469

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