



(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
24.09.2008 Bulletin 2008/39

(51) Int Cl.:
B01L 3/00 (2006.01)

(21) Application number: **07104809.4**

(22) Date of filing: **23.03.2007**

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR
Designated Extension States:
AL BA HR MK RS

(72) Inventor: **The designation of the inventor has not yet been filed**

(74) Representative: **Van Velzen, Maaïke Mathilde Philips**
Intellectual Property & Standards
P.O. Box 220
5600 AE Eindhoven (NL)

(71) Applicant: **Koninklijke Philips Electronics N.V.**
5621 BA Eindhoven (NL)

(54) **A micro-fluidic device based upon active matrix principles**

(57) A micro-fluidic device (1) comprising actuation elements controlled by a two-dimensional array of a plurality of first electronic components (2) for processing a fluid and/or for sensing properties of the fluid is suggested.

The active matrix includes a two-dimensional array of second electronic components realized in thin film technology. The active matrix provides a high versatility of the device. The thin film technology ensures a very cost efficient manufacturing also of large devices.

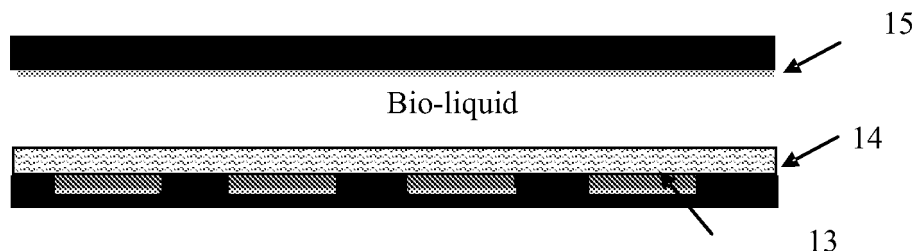


Fig. 2

Description

FIELD OF THE INVENTION

[0001] The present invention is related to a micro-fluidic device including a two-dimensional array of a plurality of components for processing a fluid and/or for sensing properties of the fluid.

BACKGROUND OF THE INVENTION

[0002] Micro-fluidic devices are at the heart of most biochip technologies, being used for both the preparation of fluidic samples and their subsequent analysis. The samples may e.g. be blood based. As will be appreciated by those in the art, the sample solution may comprise any number of things, including, but not limited to, bodily fluids like blood, urine, serum, lymph, saliva, anal and vaginal secretions, perspiration and semen of virtually any organism: Mammalian samples are preferred and human samples are particularly preferred; environmental samples (e.g. air, agricultural, water and soil samples); biological warfare agent samples; research samples (i.e. in the case of nucleic acids, the sample may be the products of an amplification reaction, including both target and signal amplification); purified samples, such as purified genomic DNA, RNA, proteins etc.; unpurified samples and samples containing (parts of) cells, bacteria, viruses, parasites or fungi.

[0003] As it is well known in the art, virtually any experimental manipulation may have been done on the sample. In general, the terms "biochip" or "Lab-on-a-Chip" or alike, refer to systems, comprising at least one micro-fluidic component or biosensor, that regulate, transport, mix and store minute quantities of fluids to rapidly and reliably carry out desired physical, chemical and biochemical reactions in larger numbers. These devices offer the possibility of human health assessment, genetic screening and pathogen detection. In addition, these devices have many other applications for manipulation and/or analysis of non-biological samples. Biochip devices are already being used to carry out a sequence of tasks, e.g. cell lyses, material extraction, washing, sample amplification, analysis etc. They are progressively used to carry out several preparation and analysis tasks in parallel, e.g. detection of several bacterial diseases. As such, micro-fluidic devices and biochips already contain a multiplicity of components, the number of which will only increase as the devices become more effective and more versatile.

[0004] Many of the components are electrical components used to sense or modify a property of the sample or fluid, such as heating elements, pumping elements, valves etc., and are frequently realized by direct fabrication of thin film electronics on the substrate of the device. Suitable properties that can be sensed or modified include, but are not limited to, temperature; flow rate or velocity; pressure, fluid, sample or analyte presence or

absence, concentration, amount, mobility, or distribution; an optical characteristic; a magnetic characteristic; an electrical characteristic; electric field strength, disposition, or polarity.

[0005] One problem of this approach is that every electrical component on the device requires control terminals to independently control the component. Consequently, more space is required to connect the components to the control devices than to realize the devices themselves. Ultimately, the number of control terminals will become so large that it will become impractical to arrange all the terminals at the periphery of the device to make electrical contact. One possibility to realize the electrical contact is the use of an electrical contact foil.

[0006] In numerous biotechnological applications, such as molecular diagnostics, there is a need for biochemical processing modules, comprising an array of temperature controlled reaction compartments that can be processed in parallel and independently to allow high versatility and high throughput. In many of these applications, the analysis system consists of a (disposable) cartridge (e.g. biochip, lab-on-a-chip, microfluidic device or alike system) comprising a biochemical processing module and a bench-top machine. In many of such biochemical systems the components for temperature control as well as analysis (e.g. light source, CCD camera, etc.) are located in the bench-top machine instead of on the, often disposable, cartridge. A major drawback of this approach is that the bench-top machine can only be used for a particular design or a selective number of cartridge designs. Consequently, the performance of various assays requires nowadays a plurality of bench-top machines.

[0007] In order to avoid a large number of control terminals, US patent 6,852,287 proposes embodiments of a method to control a number N of independently controllable components with smaller number of control terminals. In order to achieve this, both the use of multiplexing techniques or passive matrix techniques is proposed. In particular, the matrix technique is extremely attractive, as this allows for the maximum number of components to be controlled with the minimum number of control terminals. Conceptually, if one specific heater element in a passive matrix is activated also a number of other heater elements will be activated unintentionally. As a result, heat will be generated where it is not required, and the heat generated at the intended heater element will be different than required as either some of the applied current has traveled through alternative paths, or the applied voltage is dropped along the rows and columns before reaching the heater element intended to be activated.

[0008] Co-pending application IB2006/053434 discloses a micro-fluidic device, e.g. a biochip, fabricated on a substrate based upon active matrix principles. The device is preferably fabricated from one of the well known large area electronics technologies, such as amorphous silicon (a-Si), LTPS or organic transistor technologies. The active matrix makes it possible to independently con-

trol a larger number of components on the device with a smaller number of control terminals. This device enables accurate and localized control of temperature in an active matrix set up, without the need for a large device periphery to locate the I/O pins.

[0009] Another important aspect of biosensors is the controlled flow of fluid through such devices. Control of fluid flow may be obtained by use of valve, pump and mixing functions. It is an object of the invention to provide a device that provides accurate, local control over valves; pumps and mixing elements to control fluid flow in the device. It is especially an object of the present invention to provide a device that allows to alter the flow of a fluid or at least a component of said flow in a microfluidic device.

SUMMARY OF THE INVENTION

[0010] The present invention relates to a micro-fluidic device comprising actuation elements controlled by a two-dimensional array of a plurality of first electronic components for processing a fluid and/or for sensing properties of the fluid. The first electronic components preferably comprise at least one heater element. Each first component is coupled to at least one control terminal enabling an active matrix to change the state of each component individually. The active matrix includes a two-dimensional array of second electronic components realized in thin film technology. The active matrix provides a high versatility of the device as it allows individual control of a wide variety of functions. The thin film technology ensures a very cost efficient manufacturing also of large devices.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The invention will be better understood and other particular features and advantages will become apparent on reading the following description appended with drawings. In the drawings:

Fig. 1 is a schematic block diagram of a micro-fluidic device according to the invention illustrating the active matrix concept. Preferably at least one of the components (2) is a heater element.

Fig. 2 illustrates a first embodiment of the device according to the invention.

Fig. 3 illustrates a second embodiment of the device according to the invention.

Fig. 4 illustrates a third embodiment of the device according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The invention relates to a micro-fluidic device. The reference to microfluidics implies that the device is meant to be suitable for fluidic transport at small volumes of about picoliters to several hundred milliliters. Preferably the device is suitable for transport of volumes in the

range of nanoliters to about 10 milliliter. The actuation element according to the invention is capable of changing at least one property out of the group comprising swelling, elongation, expansion, porosity, mobility of or affinity to at least one predefined species of molecules, size, permeability, and charge at least of parts of a actuation element (or actuation elements) via a change that is brought about by external stimuli. To illustrate the meaning of "actuation element" it is submitted that in the context of the invention, a change in permeability of a certain polymeric layer for a certain substance is also a form of actuation as the change in permeability often causes a flow of the target compound into or through the layer this providing an actuation mechanism.

[0013] Actuation elements such as pumps, valves and layers with varying permeability are present in a microfluidic device to control fluid and compound displacement. Using fluid displacement, fluid is transported from one compartment of a device to a next compartment via channels, suitably micro fluidic channels. In a preferred embodiment the actuation elements are selected from pumps and valves. The actuation elements are preferably positioned such that they can be controlled by the first electronic components. In the context of the invention it is therefore preferred that the actuation elements are positioned in the proximity of or directly adhered to the first electronic components. In the context of the invention the phrase "in the proximity of" means at such distance that a change in the electronic state of the first electronic component is noticed/sensed/experienced by the actuation element. For example if the change in electronic state of the component leads to a temperature increase, the actuation element is in the proximity of the component in the distance wherein the temperature change is noticeable.

[0014] The actuation elements preferably comprise a material which is responsive to an external stimulus. The external stimulus thus controls for example the opening or closing of a valve. In this exemplary embodiment a temperature responsive hydrogel is positioned in a microchannel in a micro-fluidic device. At storage temperatures of around 15 °C, the hydrogel composition is in a swollen state thereby blocking the channel for fluid passing. Heating the temperature locally to around 40 °C, by using the first and second electronic components of the device, the hydrogel shrinks and soon is much smaller than the channel width, thereby allowing fluid to pass the hydrogel to a next part of the channel. This valve mechanism can also be used in the reversed way thus closing the channel again, provided the shrinking and swelling of the hydrogel composition is a reversible process. By using alternating opening and closing, fluid may be actuated or even transported from one position to another.

[0015] In the context of the present invention, the term "responsive" includes especially that the material is responsive in such a way that it displays a change of shape and total volume upon a change of a specific parameter. An example of a change is melting which may happen if

a wax-like material is heated. In another embodiment polymeric material is used that swells upon a temperature increase such as wax or other low melting point polymers including polyethyleneglycol PEG.

[0016] The change of a specific parameter (stimulus) may be a physical (temperature, pressure) or chemical property (ionic concentration, pH, analyte concentration) or biochemical property (enzymatic activity). In a preferred embodiment, the material is responsive to at least one of a change in temperature, pH, electrical field or a combination thereof. For temperature change, the temperature range for these changes is preferably between 20 and 150°C, more preferably between 30 and 95°C, and most preferably between 40 and 65°C.

[0017] According to an embodiment of the present invention, the device comprises actuation elements which is responsive to at least one external stimulus, upon which the flow of at the least a predefined species of biomolecules is altered.

[0018] The term "external" especially means that the actuation element is triggered by a means and/or stimulus provided and/or arising outside the element, such as a change in pH or temperature, however it will be appreciated that this means and/or stimulus might arise from an actuation element inside the device, such as a heater etc.

[0019] The stimuli preferably include physical stimuli including temperature, pressure, voltage, current, charge; chemical stimuli, including ionic concentration, pH, analyte concentration; or biochemical stimuli including enzymatic activity, presence or absence of analyte.

[0020] The material that is part of the actuation element preferably is a polymeric material, more preferred a hydrogel. In the context of the invention a hydrogel may absorb water to reach a swollen state, and may also expel water to reach a shrunken state. The term "hydrogel material" in the context of the present invention furthermore especially means that at least a part of the hydrogel material comprises polymers that in water form a water-swollen network and/or a network of polymer chains that are water-soluble. Preferably the hydrogel material comprises in swollen state ≥ 50 vol% water and/or solvent, more preferably ≥ 70 vol% and most preferred ≥ 90 vol%, whereby preferred solvents include organic solvents, preferably organic polar solvents and most preferred alkanols such as Ethanol, Methanol and/or (Iso-) Propanol.

[0021] According to an embodiment of the present invention, the actuation element is capable of changing the swelling of at least selected parts of the polymeric layer by at least 5%, preferably by ≥ 10 %, more preferably >30 % and most preferably >50 %.

[0022] According to a preferred embodiment of the present invention, the hydrogel material comprises a material selected out of the group comprising poly(meth) acrylic materials, silicagel materials, substituted vinyl materials or mixture thereof.

[0023] Especially preferred hydrogel materials are substituted vinyl material, most preferably vinylcaprol-

actam and/or substituted vinylcaprolactam.

[0024] According to an embodiment of the present invention, the hydrogel material comprises a poly(meth) acrylic material made out of the polymerization of at least one (meth)acrylic monomer and at least one polyfunctional (meth)acrylic monomer.

[0025] According to an embodiment of the present invention, the (meth)acrylic monomer is chosen out of the group comprising (meth)acrylamide, acrylic esters, hydroxyethyl(meth)acrylate, ethoxyethoxyethyl(meth)acrylate or mixtures thereof.

[0026] According to an embodiment of the present invention, the polyfunctional (meth)acrylic monomer is a bis-(meth)acryl and/or a tri-(meth)acryl and/or a tetra-(meth)acryl and/or a penta-(meth)acryl monomer.

[0027] According to an embodiment of the present invention, the polyfunctional (meth)acrylic monomer is chosen out of the group comprising bis(meth)acrylamide, tetraethylene glycol di(meth)acrylate, triethylene glycol di(meth)acrylate, diethylene glycol di(meth)acrylate, tripropyleneglycol di(meth)acrylates, pentaerythritol tri(meth)acrylate polyethyleneglycoldi(meth)acrylate, ethoxylated bisphenol-A-di(meth)acrylate, hexanedioldi(meth)acrylate or mixtures thereof.

[0028] According to an embodiment of the present invention, the hydrogel material comprises an anionic poly(meth)acrylic material, preferably selected out of the group comprising (meth)acrylic acids, arylsulfonic acids, especially styrenesulfonic acid, itaconic acid, crotonic acid, sulfonamides or mixtures thereof, and/or a cationic poly(meth)acrylic material, preferably selected out of the group comprising vinyl pyridine, vinyl imidazole, aminoethyl (meth)acrylates or mixtures thereof, co-polymerized with at least one monomer selected out of the group neutral monomers, preferably selected out of the group vinyl acetate, hydroxyethyl (meth)acrylate (meth)acrylamide, ethoxyethoxyethyl(meth)acrylate or mixture thereof, or mixtures thereof. These co-polymers change their shape as a function of pH and can respond to an applied electrical field and/or current by as well. Therefore these materials may be of use for a wide range of applications within the present invention.

[0029] According to an embodiment of the present invention, the actuation element comprises a polymeric layer which comprises a hydrogelic material comprising thermosensitive polymers.

[0030] According to an embodiment of the present invention, the actuation element is capable of inducing a LCST (lower critical solution temperature) phase transition in the hydrogel layer.

[0031] According to an embodiment of the present invention, the permeation layer comprises a hydrogelic material comprising monomers selected out of the group comprising poly-N-isopropylamide (PNIPAAm) and copolymers thereof with monomers selected out of the group comprising polyoxyethylene, trimethylol-propane distearate, poly- ϵ -caprolactone or mixtures thereof.

[0032] According to an embodiment of the present in-

vention, the hydrogel material is based on thermo-responsive monomers selected out of the group comprising N-isopropylamide, diethylacrylamide, carboxyisopropylacrylamide, hydroxymethylpropylmethacrylamide, acryloylalkylpiperazine, and copolymers thereof with monomers selected out of the group hydrophilic monomers, comprising hydroxyethyl(meth)acrylate, (meth)acrylic acid, acrylamide, polyethyleneglycol(meth)acrylate or mixtures thereof, and/or co-polymerized with monomers selected out of the group hydrophobic monomers, comprising (iso)butyl(meth)acrylate, methylmethacrylate, isobornyl(meth)acrylate or mixtures thereof. These copolymers are known to be thermo-responsive and therefore may be of use for a wide range of applications within the present invention.

[0033] Optionally the actuation elements comprise an elastic rubber layer.

[0034] The actuation elements may be positioned as pumps or valves. Alternatively a hydrogel layer is applied on top of the first electronic component wherein between the electronic component and the hydrogel, regions are present on the surface of the device where capture probes are present. As long as the hydrogel layer is in the closed state, there is limited permeability for target molecules that are analysed from a sample fluid. The hydrogel layer may be switched to the open state by application of any of the mentioned external stimuli. The open state corresponds to good permeability for the target molecules. Such an embodiment is illustrated in figure 2.

[0035] To enable control over the temperature at specific positions in the device, the first electronic components preferably comprise at least one heater element.

[0036] Optionally the micro-fluidic device comprises further first electronic components for sensing properties of the fluid.

[0037] In a preferred embodiment, the device comprises at least two, even more preferred a multiplicity of heater elements. Such a device is referred to as a thermal processing array. These heater elements are suitable for heating fluid that may be present in cells or compartments of the microfluidic device.

[0038] The thermal processing array can be used to either maintain a constant temperature across the entire compartment area, or alternatively to create a defined time-dependent temperature profile if the reaction compartment is also configured in the form of an array and different portions of the reaction chamber require different temperatures.

[0039] In a most preferred embodiment, the thermal processing array comprises a multiplicity of individually addressable and drivable heating elements, and may preferably comprise additional elements such as temperature sensors and fluid-mixing or fluid-pumping elements or a combination thereof.

[0040] The inclusion of at least one temperature sensor is highly preferred. Even more preferred, the device comprises a multiplicity of temperature sensors to control

a pre-defined temperature profile across an array of components or cells. Preferably, the components for heating, and the other optional components, are all present on a biochemical processing module, which is preferably located in a biochip, lab-on-a-chip, microfluidic device, or alike system. The micro-fluidic device is preferably a disposable unit, which may be a replaceable part of a larger disposable or non-disposable unit (e.g. lab-on-a-chip, genechips, microfluidic device, or alike system). In addition to the components, the device may optionally comprise cells or cavities that can hold a fluid. Such cells are also referred to as array elements.

[0041] In one advantageous embodiment of the invention the second electronic components of the active matrix comprise thin film transistors having gate, source and drain electrodes. In this case the active matrix includes a set of select lines and a set of control lines such that each individual component may be controlled by one select line and one control line and the gate electrode of each thin film transistor is connected to a select line.

[0042] In another advantageous embodiment of the invention a memory device is provided for storing a control signal supplied to the control terminal.

[0043] In an alternative embodiment of the invention the second electronic components are formed by thin film diodes, e.g. metal-insulator-metal (MIM) diodes. It is preferred that a MIM diode connects a first electrode of each first electronic component to a control line, and a second electrode of each first electronic component is connected to a select line.

[0044] In another advantageous embodiment of the invention the thin film diodes are PIN or Schottky diodes, wherein a first diode connects a first electrode of each component to a control line, wherein a second diode connects the first electrode of each component to a common rest line and wherein a second electrode of each component is connected to a select line.

[0045] In an advantageous development of the invention the first diode is replaced by a pair of diodes connected in parallel and the second diode as well is replaced by a pair of diodes connected in parallel.

[0046] In yet another advantageous development the first diode is replaced by a pair of diodes connected in series, and also the second diode is replaced by a pair of diodes connected in series.

[0047] In another advantageous embodiment of the invention the second electronic components comprise circuitry based on transistors or diodes or passive components (such as resistors and capacitors) or combinations thereof.

DESCRIPTION OF PREFERRED EMBODIMENTS

[0048] Fig. 1 illustrates the general concept of a micro-fluidic device based on an active matrix. The micro-fluidic device as a whole is designated with the reference number 1. The device comprises a two-dimensional array of first electrical components 2. Each first electrical com-

ponent 2 is associated with a switching means 3 arranged to selectively activate the component 2. Each switching means is connected to a control line 4 and a select line 6. The control lines 4 are connected to a common control driver 7. The select lines 6 are connected to a common select driver 8. The control lines 4 in conjunction with the select lines 6 form a two-dimensional array. A responsive hydrogel 14 is placed in the vicinity of the first electric components (2) and reacts to a temperature increase by expelling water thus opening a channel which in state (0) is closed due to swelling of the polymer.

[0049] In this way an active matrix is realized to ensure that all components 2 can be driven independently. The component 2 may be any electronic device e.g. a heater element, a pumping element, a valve, a sensing component etc. being driven by either a voltage or a current signal. It is to be understood that the examples for the components 2 are not to be construed in a limiting sense. Activating a component 2 means changing its state e.g. by turning it from on to off, or vice versa or by changing its setting. It is also noted that the individual switching means 3 may comprise a plurality of sub components comprising both active and/or passive electronic components. However, there is no requirement that all sub components are activated together.

[0050] The operation of the micro-fluidic device 1 illustrated in Fig. 1 to independently control a single component 2 is as follows:

- In the non-addressing state, all select lines 6 are set to a voltage where the switching elements 3 are non-conducting. In this case, no component 2 is activated.
- In order to activate a preselected component 2 the select driver 8 applies a select signal to the select line 6 to which the preselected component 2 is coupled. As a consequence all switching means 3 connected to the same select line 6 are switched into a conducting state.
- A control signal generated by the control driver 7, e.g. a voltage or a current is applied to the control line where the preselected component 2 is situated. The control signal is set to its desired level and is passed through the switching means 3 to the component 2, causing the component to be activated.
- The control signals in all other control lines 4 are held at a level, which will not change the state of the remaining components connected to the same select line 6 as the preselected component 2. In this example, they will remain un-activated.
- All other select lines 6 will be held in the non-select state, so that the other components 2 connected to the same control line 4 as the preselected component will not be activated because their associated switching means 3 remain in a non-conducting state.
- After the preselected component is set into the desired state, the respective select line 6 is unselected, returning all switching means 3 into a non-conduct-

ing state, preventing any further change in the state of the preselected component.

[0051] The device will then remain in the non-addressed state until the following control signal requires to change the state of any one of the components 2, at which point the above sequence of operation is repeated.

[0052] The two-dimensional array formed by the control lines 4 and the select lines 6 can also be described in terms of rows and columns, where the select lines 6 define the rows and the control lines 4 the columns.

[0053] It is also possible to control more than one component 2 in a given row simultaneously by applying a control signal to more than one column in the array during the select period. It is possible to sequentially control components in different rows by activating another row by using the select driver and applying a control signal to one or more columns in the array.

[0054] It is also possible to implement feedback control, i.e. linking the actuation element with a local sensor per element, measuring the flow (rate) or other intended activity and providing an actuation signal to the actuation element until the specified sensor readout is reached.

[0055] It is also possible to address the micro-fluidic device 1 such that a component 2 is only activated while the control signal is present. However, in a preferred embodiment, it is advantageous to incorporate a memory device into the component whereby the control signal is remembered after the select period is completed. For the memory device a capacitor or a transistor based memory element is suitable. This makes it possible to have a multiplicity of components at any point across the array activated simultaneously. This option is not available in the passive system known in the prior art. Of course, if a memory device is available, a second control signal will explicitly be required to de-activate the component.

[0056] Preferably the device comprises compartments and channels, most preferred microfluidic channels, that connect one compartment to at least one, or more preferred a plurality of, other compartments. Optionally a valve is located between the compartments. This enables the performance of a reaction with various steps in the device. In such an embodiment, fluids may be moved sequentially from one cell to another or alternatively many cells may be processed in parallel.

[0057] In particular, the invention enables accurate, reproducible, reliable and fast thermal cycling during DNA amplification on a biochip, for instance using (multiplexed) PCR or (multiplexed) real-time quantitative PCR (RQ-PCR), such that the temperature of the array elements may be individually and in parallel controlled, without significant additional costs or issues concerning the number of input and output pins. Moreover, with respect to the situation in which the heating elements are located in the bench-top machine, this invention offers a more optimal and more reliable thermal contact between temperature components and fluid.

[0058] Therefore in a further aspect the invention re-

lates to use of the device according to the invention in a process wherein temperature is controlled.

[0059] In another aspect the invention relates to use of the device according to the invention in a process wherein the temperature is changed according to a pre-defined regime.

[0060] Last but not least, this invention allows an advantageous way of performing RQ-PCR on a biochip by combining a cost-effective high performance thermal processing array (e.g. high resolution, individual and parallel temperature control of compartments, high reproducibility, high reliability and high accuracy) on the disposable, with the high performance (e.g. high resolution, high signal-to-noise ratio) of an optical detection setup (e.g. light source, CCD camera, filters) generally used in a bench-top machine for detection of fluorescent signals in molecular diagnostics.

[0061] Hence in a further aspect the invention relates to a method of performing the PCR process, preferably RQ-PCR process wherein use is made of the micro-fluidic device as described above.

[0062] In another aspect the invention relates to the microfluidic device as described above, in combination with an optical detection set up.

[0063] In a further aspect the invention relates to a method of detecting a product using a diagnostic device comprising a micro-fluidic device according to the invention, wherein the detection is based on optical methods.

[0064] In a further aspect the invention relates to the microfluidic device as described above, in combination with the enclosing and release of chemicals and reagents that are present in fluidic compartments. This covers both drug delivery applications but also release of specific enzymes, PCR primers, antibodies, labels, cytokines, growthfactors etc. needed at a specific time to be released into the fluid.

[0065] After having illustrated the general concept and the advantages of a micro-fluidic device 1 in the following description specific embodiments will be explained.

[0066] Fig. 2 exhibits an active matrix micro-fluidic device 1 using thin film transistors (TFT) to ensure that all first electronic components, for example the heating elements (13), can independently be activated. TFTs are well known switching elements in thin film large area electronics, and have found extensive use e.g. in flat panel display applications. Industrially, the major manufacturing methods for TFTs are based upon either amorphous-silicon (a-Si) or low temperature polycrystalline silicon (LTPS) technologies. But other technologies such as organic semiconductors or other non-Si based semiconductor technologies, such as CdSe, can be used. The device further comprises actuation elements in the form of a hydrogel (14) which covers the first electronic components. The hydrogel responds to a local heating by switching from a closed state to an open state, thus allowing target molecules to penetrate through the hydrogel layer towards a surface having capture probes immobilized thereon. This surface is positioned between

the first electronic components and the hydrogel layer. The operation of the device illustrated in Fig. 2 to independently control a single component 2 is as follows:

[0067] The device of figure 2 is suitable for identification of a specific target molecule in a biological sample, the bio-liquid. Capture sites for target molecules present on the active matrix surface are covered by a homogeneous layer of a responsive hydrogel. This is illustrated in figure 2. In figure 2 use is made of voltage actuation where each capture site has at least one electrode and a counter electrode held (15) at 0V. Initially, the hydrogel layer is in the "closed" state, characterized by minimum permeability to the target molecules. Immediately before the electrophoretic collection of the target molecules, the hydrogel layer covering one or several selected electrodes is switched to the "open" state with maximum permeability. A voltage can then be applied to the selected electrode(s) to attract the target molecules towards the capture sites. Keeping the hydrogel layer "closed" anywhere else in the microelectronic array prevents the adsorption of molecules at other capture sites. After hybridization between target molecules and capture probes at the capture sites, the hydrogel on top of the selected electrodes is switched back to the "closed" state. The procedure may be repeated sequentially to address selectively all electrodes on the microelectronic array. The last step in the procedure (switching to closed state after hybridization) also allows protecting the captured molecules from, e.g., a successive washing step.

[0068] Several alternatives exist for the local actuation mechanism, depending on the type of hydrogel used. As already stated an electrically responsive hydrogel can be used. The advantage of this is that electric field used to attract the particles can also be simultaneously used to trigger the permeability of the hydrogel. Suitable hydrogels are polyelectrolytes as for example crosslinked polyacrylic acid (some other suitable materials are e.g. disclosed in US6,626,417B2).

[0069] In the case of a temperature-sensitive hydrogel (such as polyisopropylacrylamide), resistive (ohmic) heating elements are used to locally heat the hydrogel and change its permeability. We note that the electrodes used to collect the particles could also be made slightly resistive. This would allow them to function also as heaters, thereby eliminating the need for separate heating elements.

[0070] Other possibilities include the use of a pH-responsive (in which case one could exploit pH changes due to hydrolysis at the electrodes) or a photoresponsive hydrogel.

[0071] A further embodiment is illustrated in figure 3. It will be appreciated that the response time of the hydrogel depends on the material and on the actuation principle used. In general, response times in the range of seconds can be easily achieved. A faster response can be achieved by reducing the dimensions of the hydrogel, e.g., by patterning the hydrogel and defining separate compartments for each electrode in the array. Therefore

in a preferred embodiment, the actuation elements are present in the form of a patterned hydrogel. This is illustrated in figure 3. Another advantage of patterning the hydrogel is that it avoids internal stress and possible adhesion stress between the actuated and non-actuated areas of the hydrogel. Figure 3 shows a pattern of hydrogel patches (3A-D) deposited on an active matrix array whereby each of the patches is controlled by a separate first electronic components (2A-2D).

[0072] A further embodiment is illustrated in figure 4. In this example, the actuator takes the form of a valve, which opens (left hand figure) and closes (right hand figure) a channel (21, shown in cross section), in this case a channel formed in a substrate (26). The closing and opening of the valve is realized by swelling of a polymeric material such as a hydrogel (14), which is initiated by e.g. a temperature change realized by a heater element (23). The channel is separated from responsive polymeric material by a thin elastic sheet (24), such as polydimethylsiloxane (PDMS) or other silicon rubbers, siloxanes etc.

[0073] In figure 3 the following reference numbers are used:

21 open channel, 22 closed channel, 14 responsive hydrogel, 23 heater, 24 thin elastic sheet, 25 top substrate, 26 bottom substrate.

[0074] Typically the layer thickness of the elastic sheet is 1-500 μm , preferably 5-300 μm , most preferably 10-150 μm .

[0075] According to a further embodiment, the actuation elements are composed of composite hydrogels.

[0076] According to a further embodiment the actuation element can release molecules stored in or adjacent to said responsive polymeric material into the micro-fluidic device. This release may be into a compartment, a channel or into the flow in the micro-fluidic device.

[0077] According to a preferred embodiment of the present invention, the device comprises a at least one supporting structure. The term "supporting structure" in the context of the present invention includes supporting substrate(s) (either flat or curved, closed for fluid flow or permeable, porous membrane or a mesh like structure) underneath as well as supporting structure(s) as part of the layer, such as rigid or elastic bars, wires, walls etc. or said supporting structure may form compartments, reservoirs, cavities or channels. Said supporting structure preferably comprises rigid or flexible materials selected from group the group comprising glass, silicon, metal, metal oxides, polymeric material (such as PVC, polyimide, PC, but also organic resist material such as SU-8 and the like). Optionally the second electronic components are embedded in the supporting structure.

Claims

1. Micro-fluidic device (1) comprising actuation ele-

ments controlled by a two-dimensional array of a plurality of first electronic components (2) for processing a fluid wherein each component (2) is coupled to an active matrix to change the state of each first electronic component individually, and wherein the active matrix includes a two-dimensional array of second electronic components realized in thin film technology.

2. Micro-fluidic device according to claim 1 wherein the actuation elements are selected from pumps and valves.

3. Micro-fluidic device according to claim 1 wherein the actuation elements comprise a material which is responsive to an external stimulus.

4. Micro-fluidic device according to claim 3 wherein the actuator element comprises a responsive polymeric material.

5. Micro-fluidic device according to claim 1 wherein the actuator element comprises an elastic rubber layer.

6. Micro-fluidic device according to claim 3 wherein the material is responsive to at least one of a change in temperature, pH, electrical field or a combination thereof.

7. Micro-fluidic device according to claim 1 wherein the first electronic components comprise at least one heater element.

8. Micro-fluidic device according to claim 1, which comprises further first electronic components for sensing properties of the fluid.

9. Micro-fluidic device according to claim 1 wherein the actuation element can release molecules stored in or adjacent to said responsive polymeric material into the micro-fluidic device.

10. Micro-fluidic device (1) according to claim 1, wherein the second electronic components of the active matrix are formed by thin film transistors having gate, source and drain electrodes, diodes or MIM diodes.

11. Micro-fluidic device (1) according to claim 1, wherein the active matrix includes a set of select lines (6) and a set of control lines (4) such that each individual first electronic component (2) is controlled by one select line (6) and one control line (4) and in that the gate electrode of each thin film transistor is connected to a select line (6).

12. Micro-fluidic device (1) according to claim 1 comprising at least two heater elements (13).

13. Micro-fluidic device (1) according to claim 1, comprising a multiplicity of individually addressable and drivable heater elements (13).
14. Micro-fluidic device (1) according to claim 1, further comprising a temperature sensor. 5
15. Method of performing a PCR process, wherein use is made of the micro-fluidic device according to any of claims 1-14. 10
16. Use of the device according to any of claims 1-14 in a process wherein temperature is controlled.
17. Method of detecting a product using a diagnostic device comprising a micro-fluidic device according to any of claims 1-14, wherein the detection is based on optical methods. 15

20

25

30

35

40

45

50

55

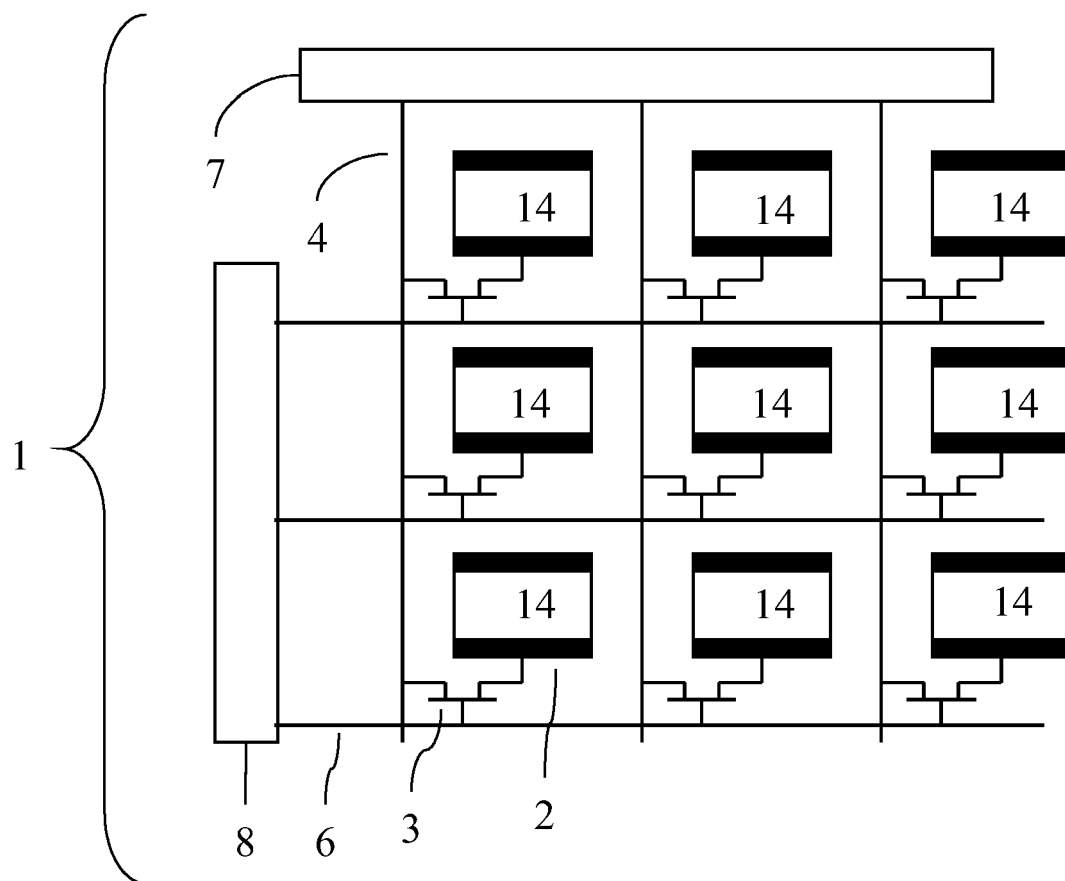


Fig. 1



Fig. 2

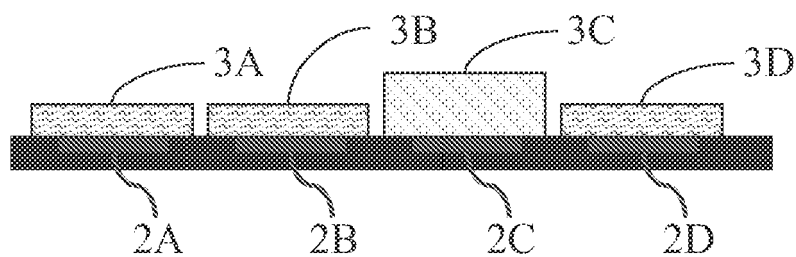


Fig. 3

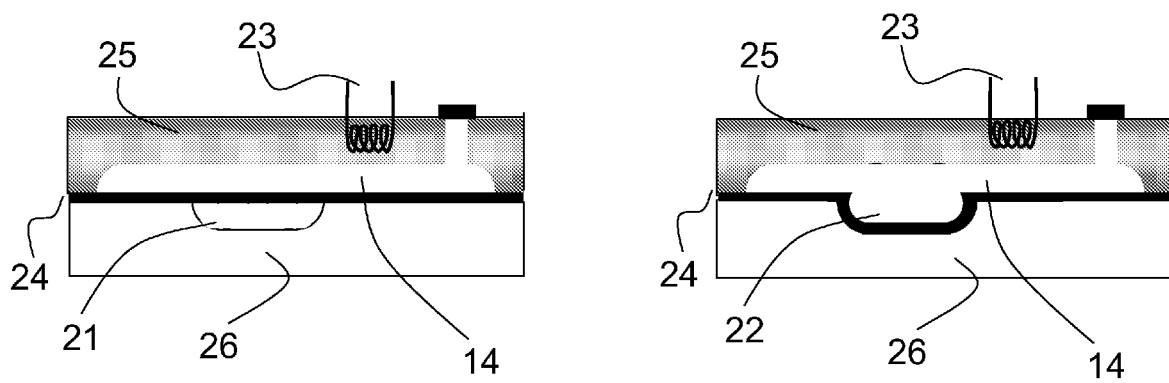


Fig. 4



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 07 10 4809

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 2002/150683 A1 (TROIAN SANDRA M [US] ET AL) 17 October 2002 (2002-10-17) * abstract * * paragraphs [0003], [0010], [0016], [0017], [0054], [0057], [0059], [0062] - [0066], [0077]; figures 1-3,5,8,11 *	1-17	INV. B01L3/00
X	WO 2007/004153 A (KONINKL PHILIPS ELECTRONICS NV [NL]; JOHNSON MARK T [NL]; KURT RALPH []) 11 January 2007 (2007-01-11) * abstract * * page 2, line 19 - page 4, line 33 * * page 6, lines 1-20 * * page 8, line 7 - page 10, line 17 * * page 11, lines 19,20 * * page 12, lines 21-26 * * page 13, lines 12-20 * * figures 1,2 *	1-14,16	
A	US 6 403 367 B1 (CHENG JING [CN] ET AL) 11 June 2002 (2002-06-11) * abstract * * column 5, line 22 - column 6, line 45; claim 1 *	1,12	TECHNICAL FIELDS SEARCHED (IPC) H01L B01L
A	US 2005/084424 A1 (GANESAN KARTHIK [US] ET AL) 21 April 2005 (2005-04-21) * the whole document *	1-14	
A	US 6 382 254 B1 (YANG ZHIHAO [US] ET AL) 7 May 2002 (2002-05-07) * the whole document *	1-7	
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 30 August 2007	Examiner Sinn, Cornelia
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

2

EPO FORM 1503 03.82 (P04C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 07 10 4809

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

30-08-2007

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2002150683	A1	17-10-2002	NONE	

WO 2007004153	A	11-01-2007	NONE	

US 6403367	B1	11-06-2002	NONE	

US 2005084424	A1	21-04-2005	NONE	

US 6382254	B1	07-05-2002	EP 1215399 A2	19-06-2002

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 6852287 B [0007]
- US 6626417 B2 [0068]