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(54) Manipulation of particles by dielectrophoresis

(57) The present invention provides a dielectrophoretic device for manipulation of at least a first and a second type of particles (1, 2) present in a sample fluid. The device comprises at least one array (3) of electrodes (4), the array (3) comprising at least a plurality of electrodes (4) in a first region (5) and a plurality of electrodes (4) in a second region (6), driving means (32) for driving the electrodes (4) of the first and second region (5, 6) of the array (3) to generate a travelling wave dielectrophoretic force to be exerted on the at least first and second types of particles (1, 2), and a controller (30) for controlling the driving means (32), the controller (30) being adapted for first driving the electrodes (4) of the first and second region (5, 6) with a same driving signal and subsequently changing the driving signal to electrodes (4) of at least one of the first and second region (5, 6) so as to separate at least some particles (1) of the first type from the particles (2) of the second type. The present invention also provides a method for forming such a dielectrophoretic device, a method for manipulation of at least a first and a second type of particles (1, 2) present in a sample fluid and a controller (30) for controlled driving of electrodes (4) of such a dielectrophoretic device.

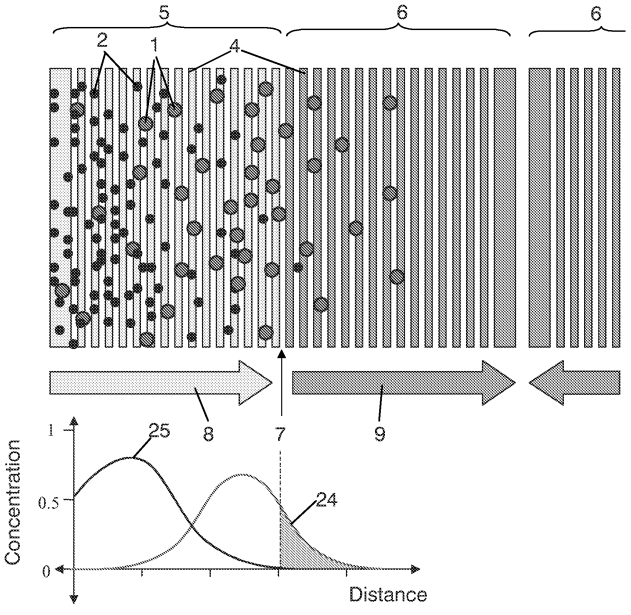

FIG. 5

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Description

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to manipulation of particles in a sample fluid by use of dielectrophoresis. More particularly, the present invention relates to a dielectrophoretic device for manipulation of at least two different types of particles present in a sample fluid, to a method for forming such a dielectrophoretic device, to a method for manipulating at least two different types of particles in a sample fluid by using dielectrophoresis and to a controller for controlling driving of electrodes of a dielectrophoretic device.

BACKGROUND OF THE INVENTION

[0002] Lab-on-a-chip techniques require a combination of electronic and biological expertise to obtain a fully integrated electronic system. Achieving such fully integrated electronic system requires dedicated systems within the chip, such as systems for sample preparation, polymerised chain reaction (PCR) and target detection. Therefore, there is a strong drive to find an accurate method to reliably pass fluids and essay samples around the miniature lab, especially without introducing contaminates.

[0003] One of the methods to achieve this is through electrical manipulation of bio-molecules or particles, which is called dielectrophoresis (DEP), i.e. the movement of dielectric particles in a non-uniform, usually AC, electric field. Unlike electrophoresis, DEP relies on field-induced polarization effects and is independent of the net charge of particles present in the fluids. The DEP force depends on the electrical properties of the particles and of the surrounding medium, on the size and shape of the particles and on the spatial distribution and frequency of the applied field. Depending on these factors, the particles can be attracted to either high-field (positive DEP) or low-field (negative DEP) regions. By using proper electrode configurations and multiphase fields, DEP can be used to levitate particles, trap them in a field cage, rotate them (electro-rotation) or transport them over relatively long distances (traveling wave DEP).

[0004] DEP thus enables, amongst others, transportation, focusing, purification and/or mixing of fluids. This technique also can be applied to locally enhance the performance of biosensors within the lab-on-a-chip. DEP has in the past been applied to manipulate and separate a variety of cells including bacteria, yeast, and mammalian cells in microsystems. In particular, DEP has been used to separate cancer cells from blood, isolate CD34+ stem cells from blood, bacteria from blood and to separate various cell sub-populations of blood.

[0005] It has thus been shown that electrical manipulation of fluids and biomolecules can be achieved by using DEP; however, the differentiation between the contents of mixed samples can be difficult. To make Lab-on-a-Chip techniques into a success, methods to solve this differentiation/filtering problem have to be found.

[0006] Other techniques to sort particles of different types, for example techniques developed by the University of Southampton (Hywel Morgan), require an optical feedback process to adjust electrical fields which are exerted onto the particle or particles of interest. A disadvantage of this technique and of other microfluidic channelling techniques is that they can only operate on a single biomolecule at a time and therefore the throughput of material may be slowed down to a great extent. For example, if a sample comprises 1 million particles and the optical/electrical control system only has a throughput of 10 to 100 particles per second, it may take up to a few hours before the sample has completely been examined. With DEP there is no loss in transport speed. This is because the movement of all particles over the electrodes can occur at once. Therefore the throughput of bio-matter can be orders of magnitudes larger than for other existing techniques. However, the specificity of being able to assess each cell has been lost as all cells will move together and any manipulation of the cells will be applied to all of the cells.

SUMMARY OF THE INVENTION

[0007] It is an object of embodiments of the present invention to provide a good dielectrophoretic device for manipulation of at least two different types of particles present in a sample fluid, and a method for manipulating at least two different types of particles in a sample fluid by using such a dielectrophoretic device.

[0008] The dielectrophoretic device and methods according to embodiments of the invention are able to provide a good selectivity between at least two particles that have similar dielectric properties or Clausius-Mossotti responses by spatially amplifying a subtle difference between the DEP characteristics of the particles of interest, while keeping high throughput capabilities.

[0009] The dielectrophoretic device and methods according to embodiments of the present invention address purification of particles without the loss of transportation efficiency.

[0010] The dielectrophoretic device and methods according to embodiments of the invention may be used in a variety of applications where particle sorting, e.g. cell sorting, particle manipulation, e.g. cell manipulation, filtering, ordering, and/or transportation is important. Such applications may include molecular diagnostics, biological sample analysis or chemical sample analysis.

[0011] The dielectrophoretic device and method according to embodiments of the present invention can be used in Lab-on-a-Chip techniques for manipulation, e.g. moving or sorting, of particles such as cells on a microscopic scale, or cells or molecules which are attached to particles, such as magnetic beads. The dielectrophoretic device and method according to embodiments of the present invention can furthermore be combined with oth-

er sorting and filtering systems.

[0012] The dielectrophoretic device and method according to embodiments of the present invention may be used to improve results of biological experiments. For example, the dielectrophoretic device and method according to embodiments of the present invention may be used to obtain a good efficiency in cell lysing, to improve the obtainable quantity of amplicons for specific polymer chain reaction (PCR) experiments and to improve detection of hybridised DNA.

[0013] The above objective is accomplished by a method and device according to the present invention.

[0014] In a first aspect, the present invention provides a dielectrophoretic device for manipulation of at least a first and a second type of particles present in a sample fluid. The device comprises:

- at least one array of electrodes, the array comprising at least a plurality of electrodes in a first region and a plurality of electrodes in a second region,
- driving means for driving the electrodes of the first and second region of the array to generate a travelling wave dielectrophoretic force to be exerted on the at least first and second types of particles, and
- a controller for controlling the driving means, the controller being adapted for first driving the electrodes of the first and second region with a same driving signal and subsequently changing the driving signal to electrodes of at least one of the first and second region so as to separate at least some particles of the first type from the particles of the second type.

[0015] The device according to embodiments of the invention may be used in a variety of applications including molecular diagnostics, biological sample analysis or chemical sample analysis. The dielectrophoretic device according to embodiments of the present invention may be used to improve results of biological experiments. For example, the dielectrophoretic device according to embodiments of the present invention may be used to obtain a good efficiency in cell lysing, to improve the obtainable quantity of amplicons for specific polymer chain reaction (PCR) experiments and to improve detection of hybridised DNA.

[0016] The device for manipulation of particles according to embodiments of the present invention only relies on electrical field induced effects in order to achieve manipulation of particles, e.g. separation of particles, on a macroscopic level. In a device according to embodiments of the invention, particles, e.g. cells are transported electrically through a stationary fluid. Therefore, in accordance with embodiments of the present invention, the need for liquid flow generation and thus for pumping mechanisms, may be eliminated. This allows, in principle, using very small volumes of suspensions comprising the particles. The dielectrophoretic device according to embodiments of the invention can be used for performing particle manipulation from small, non-flowing volumes of particle suspensions. With small volumes is meant volumes of between 0.5 and 50 μl, for example 10 μl.

[0017] According to embodiments of the invention, the controller may be adapted for changing the driving signal to electrodes of at least one of the first and second region upon reaching of a boundary between the first and second region of the array of electrodes by a predetermined one of the at least first and second type of particles.

[0018] The dielectrophoretic device may furthermore comprise collection means for collecting at least one of the first and second type of particles which have crossed the boundary between the first and second region of the array of electrodes. According to embodiments, the collected particles may then further be used to perform experiments on. According to other embodiments, the collected particles may, for example, be counted.

[0019] The collection means may be formed by a dielectrophoretic trap.

[0020] According to embodiments of the invention, the dielectrophoretic device may furthermore comprise transport means for transporting collected particles towards other regions of the dielectrophoretic device, or optionally away from the device, so as to enable focusing of selected particles. This may allow continued particle movement into further regions of the dielectrophoretic device where they may be used for further reactions or experiments, for example for cell lysing or for detection.

[0021] According to still further embodiments of the invention, the dielectrophoretic device may furthermore comprise detection means for detecting reaching of the boundary between the first and second region of the array of electrodes by the predetermined one of the at least first and second type of particles.

[0022] According to embodiments of the invention, the detection means may be an optical detection means such as e.g. an optical detector, e.g. integrated PIN diodes.

[0023] According to other embodiments of the invention, the detection means may be a time determination means.

[0024] According to still other embodiments of the invention, the detection means may be means for determining a predetermined volume of at least one of the first and second type of particles which have passed the boundary between the first and second region of the array of electrodes.

[0025] According to embodiments of the invention, the dielectrophoretic device may comprise a cascade of arrays of electrodes. This may enhance the efficiency of the manipulation process to a great extent while still maintaining a high throughput of particles. Each array of the cascade may be driven one after the other, and in that way may result in a high degree of separation between the first and second particles present in the sample fluid.

[0026] In a further aspect, the present invention also provides the use of the dielectrophoretic device according to embodiments of the present invention for particle separation or sorting.

[0027] In still a further aspect of the invention, a method

is provided for forming a dielectrophoretic device for manipulation of at least a first and second type of particles in a sample fluid. The method comprises:

- providing at least one array of electrodes, the array comprising at least a plurality of electrodes in a first region and a plurality of electrodes in a second region,
- providing driving means for driving the electrodes of the first and second region of the array to generate a travelling wave dielectrophoretic force to be exerted on the at least first and second types of particles, and
- providing a controller for controlling the driving means, the controller being adapted for first driving the electrodes of the first and second region with a same driving signal and subsequently changing the driving signal to electrodes of at least one of the first and second region so as to separate at least some particles of the first type from the particles of the second type.

[0028] The method may furthermore comprise providing collection means for collecting at least one of the first and second type of particles which have crossed a boundary between the first and second region of the array of electrodes.

[0029] The method may furthermore comprise providing transport means for transporting collected particles towards other regions of the dielectrophoretic device, or optionally away from the device, so as to enable focusing of selected particles.

[0030] The method may furthermore comprise providing detection means for detecting reaching of the boundary between the first and second region by a predetermined one of the at least first and second type of particles. The detection means may be an optical detection means, a time determination means or a means for determining a predetermined volume of at least one of the first and second type of particles which have passed the boundary between the first and second region of the array of electrodes.

[0031] Providing at least one array of electrodes may be performed by providing a cascade of arrays. Each array of the cascade may be provided such that it may be driven one after the other, which may result in a high degree of separation between the first and second particles present in the sample fluid.

[0032] In yet a further aspect, the present invention provides a method for manipulating at least a first and second type of particles in a sample fluid. The method comprises:

a) providing sample fluid comprising the at least first and second type of particles to a microfluidic device comprising at least one array of electrodes, the array comprising at least a plurality of electrodes in a first region and a plurality of electrodes in a second region,

b) applying a same driving signal to electrodes of the first and second regions, the driving signal being such that the first type of particles and the second type of particles move with a different speed, and

c) subsequently changing the driving signal to electrodes of at least one of the first and second regions so as to separate at least some particles of the first type from the particles of the second type.

[0033] The method according to embodiments of the invention may be used in a variety of applications including molecular diagnostics, biological sample analysis or chemical sample analysis. The method according to embodiments of the present invention may be used to improve results of biological experiments. For example, the method according to embodiments of the present invention may be used to obtain a good efficiency in cell lysing, to improve the obtainable quantity of amplicons for specific polymer chain reaction (PCR) experiments or to improve detection of hybridised DNA.

[0034] The method for manipulation of particles according to embodiments of the present invention only relies on electrical field induced effects in order to achieve manipulation of particles, e.g. separation of particles, on a macroscopic level. In a method according to embodiments of the invention, particles, e.g. cells, are transported electrically through a stationary fluid. Therefore, in accordance with embodiments of the present invention, the need for liquid flow generation and thus for pumping mechanisms, may be eliminated. This allows, in principle, using very small volumes of suspensions comprising the particles. With very small volumes is meant volumes of between 0.5 and 50 μl, for example 10 μl.

[0035] The method may furthermore comprise, before changing the driving signal to electrodes of at least one of the first and second region, determining whether a predetermined one of the first and second type of particles has reached a boundary between the first and second region of the array of electrodes.

[0036] According to embodiments of the invention, determining whether a predetermined one of the first and second type of particles has reached the boundary between the first and second region of the array of electrodes may be performed by an optical detection means, for example with an optical detector, e.g. with integrated PIN diodes.

[0037] According to other embodiments of the invention, determining whether a predetermined one of the first and second type of particles has reached the boundary between the first and second region of the array of electrodes may be performed by means of calculating a time period required for the predetermined one of the first and second type of particles to reach the boundary between the first and second region of the array of electrodes.

[0038] According to embodiments of the invention the method may furthermore comprise repeating steps b and

c of applying and changing the driving signal at least once. Repeating steps b and c may be performed as many times as necessary for obtaining good manipulation of the particles, for example for obtaining good separation between a first and second type of particles.

[0039] The method may furthermore comprise collecting at least one of the first and second type of particles which have crossed the boundary between the first and second region of the array of electrodes. According to embodiments, the collected particles may then further be used to perform experiments on.

[0040] The method may furthermore comprise detecting the collected particles. According to other embodiments, the collected particles may, for example, be counted.

[0041] In a further aspect of the invention, a controller is provided for controlled driving of electrodes of an array, the array comprising at least a plurality of electrodes in a first region and a plurality of electrodes in a second region. The controller comprises a control unit for controlling a driving means for first driving the electrodes of the first and second region with a same driving signal and subsequently changing the driving signal to electrodes of at least one of the first and second region so as to separate at least some particles of the first type from the particles of the second type.

[0042] The controller may be adapted for changing the driving signal to electrodes of at least one of the first and second region upon reaching of the boundary between the first and second region of the array of electrodes by a predetermined one of the at least first and second type of particles.

[0043] The present invention also provides a computer program product for performing, when executed on a computing means, a method for manipulating at least a first and second type of particles in a sample fluid according to embodiments of the present invention.

[0044] The present invention also provides a machine readable data storage device for storing the computer program product according to embodiments of the present invention.

[0045] The present invention also provides a transmission of the computer program product according to embodiments of the present invention over a local or wide area telecommunications network.

[0046] Particular and preferred aspects of the invention are set out in the accompanying independent and dependent claims. Features from the dependent claims may be combined with features of the independent claims and with features of other dependent claims as appropriate and not merely as explicitly set out in the claims.

[0047] The above and other characteristics, features and advantages of the present invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, the principles of the invention. This description is given for the sake of example only, without limiting the scope of the invention. The reference figures quoted below refer to the attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0048]

Fig. 1 illustrates Clausius-Mossotti curves (upper graph) and velocity curves (lower graph) for two different types of particles.

Fig. 2 and Fig.3 schematically illustrate the operation principle of a dielectrophoretic device according to embodiments of the present invention.

Fig. 4 illustrates part of a configuration of a dielectrophoretic device according to embodiments of the present invention.

Fig. 5 shows particle distribution curves after applying a same driving signal to electrodes of a first and second region of a dielectrophoretic device according to embodiments of the invention during a predetermined time period for a first and second type of particles with different DEP properties.

Fig. 6 illustrates particle distribution curves for a first and second type of particles with different DEP properties for different periods in time and for different number of changes to the driving signals (different number of resets).

Fig. 7 illustrates concentration of a first type of particles (curve 26) and concentration of a second type of particles 2 (curve 27) that have crossed a boundary between a first and second region of a dielectrophoretic device according to embodiments of the present invention as a function of the number of resets.

Fig. 8 illustrates part of a configuration of a dielectrophoretic device according to embodiments of the present invention.

Fig. 9 illustrates part of a configuration of a dielectrophoretic device according to embodiments of the present invention.

Fig. 10 and Fig. 11 illustrate driving of electrodes of an array of a dielectrophoretic device according to embodiments of the present invention for obtaining travelling wave dielectrophoresis.

Fig. 12 schematically illustrates a system controller for use with a dielectrophoretic device according to embodiments of the present invention.

Fig. 13 is a schematic representation of a processing system as can be used for performing a method according to embodiments of the present invention.

[0049] In the different figures, the same reference signs refer to the same or analogous elements.

DETAILED DESCRIPTION OF THE INVENTION

[0050] The present invention will be described with respect to particular embodiments and with reference to

certain drawings but the invention is not limited thereto but only by the claims. Any reference signs in the claims shall not be construed as limiting the scope. The drawings described are only schematic and are non-limiting. In the drawings, the size of some of the elements may be exaggerated and not drawn on scale for illustrative purposes.

[0051] Where the term "comprising" is used in the present description and claims, it does not exclude other elements or steps. Where an indefinite or definite article is used when referring to a singular noun e.g. "a" or "an", "the", this includes a plural of that noun unless something else is specifically stated.

[0052] Furthermore, the terms first, second and the like in the description and in the claims, are used for distinguishing between similar elements and not necessarily for describing a sequence, either temporally, spatially, in ranking or in any other manner. It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of operation in other sequences than described or illustrated herein.

[0053] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment, but may. Furthermore, the particular features, structures or characteristics may be combined in any suitable manner, as would be apparent to one of ordinary skill in the art from this disclosure, in one or more embodiments.

[0054] Similarly it should be appreciated that in the description of exemplary embodiments of the invention, various features of the invention are sometimes grouped together in a single embodiment, figure, or description thereof for the purpose of streamlining the disclosure and aiding in the understanding of one or more of the various inventive aspects. This method of disclosure, however, is not to be interpreted as reflecting an intention that the claimed invention requires more features than are expressly recited in each claim. Rather, as the following claims reflect, inventive aspects lie in less than all features of a single foregoing disclosed embodiment. Thus, the claims following the detailed description are hereby expressly incorporated into this detailed description, with each claim standing on its own as a separate embodiment of this invention.

[0055] Furthermore, while some embodiments described herein include some but not other features included in other embodiments, combinations of features of different embodiments are meant to be within the scope of the invention, and form different embodiments, as would be understood by those in the art. For example, in the following claims, any of the claimed embodiments can be used in any combination.

[0056] Furthermore, some of the embodiments are described herein as a method or combination of elements of a method that can be implemented by a processor of a computer system or by other means of carrying out the function. Thus, a processor with the necessary instructions for carrying out such a method or element of a method forms a means for carrying out the method or element of a method. Furthermore, an element described herein of an apparatus embodiment is an example of a means for carrying out the function performed by the element for the purpose of carrying out the invention.

[0057] In the description provided herein, numerous specific details are set forth. However, it is understood that embodiments of the invention may be practiced without these specific details. In other instances, well-known methods, structures and techniques have not been shown in detail in order not to obscure an understanding of this description.

[0058] The present invention provides a dielectrophoretic device for manipulation of at least a first and second type of particles present in a sample fluid, a method for forming such a dielectrophoretic device, a method for manipulating at least a first and second type of particles in a sample fluid and a controller for controlling driving of electrodes of a dielectrophoretic device.

[0059] The dielectrophoretic device and methods according to embodiments of the present invention address purification of particles such as e.g. bio-molecules without loss of transportation efficiency as seen in existing systems.

[0060] The dielectrophoretic devices and methods according to embodiments of the invention are able to provide a good selectivity between at least two particles that have similar dielectric properties or Clausius-Mossotti curves by spatially amplifying a subtle difference between the DEP characteristics of the particles of interest, while keeping high throughput capabilities.

[0061] Particles, such as for example B-lymphocytes, T-lymphocytes and erythrocytes, present in a sample fluid can exhibit similar dielectric properties or Clausius-Mossotti responses at key frequencies, resulting in small velocity changes between the populations in negative DEP (-ve DEP in Fig. 1). A Clausius-Mossotti curve gives the difference in velocity for different particle properties. Fig. 1 illustrates Clausius-Mossotti curves of two particles with similar properties (see upper graph, curve 20 for a first particle and curve 21 for a second particle) and their velocities (lower graph, curve 22 for the first particle and curve 23 for the second particle) while levitated above electrodes in -ve DEP.

[0062] The two particles with similar properties in Figure 1 are "similar" in that one can pick a frequency (e.g 10^5 Hz) and there is only a small difference in the velocity's. Normally in DEP, the curves are separated by an order of magnitude in frequency, so that one is held fixed in +DEP while the other levitates and travels in -DEP.

[0063] In this example, the curves in Figure 1 relate to B-lymphocytes and T-lymphocytes.

[0064] They are white cells, which are very hard to distinguish in a blood smear and optical detection, even they are hard to distinguish with impedance spectroscopy.

[0065] Their differences in makeup are very slight, and are derived from the same small lymphocyte parent cell. Their functions differ in that the B cell can develop into a plasma cell for the secretion of antibodies, while the T cells release a range of hormone proteins for communication in the event of an immune response.

[0066] In relation to the curve, the curves show a measure of polarisability of the proteins in the cell and on the cell surface. In the case of a T and B cells, they are coated in antigens, T cells explicitly exhibit an antigen protein called CD3 while B cells do not.

[0067] The dielectrophoretic device and methods according to embodiments of the invention may be used in a variety of applications where particle sorting, e.g. cell sorting, particle manipulation, e.g. cell manipulation, filtering, ordering and/or transportation is important. Such applications may include molecular diagnostics, biological sample analysis or chemical sample analysis.

[0068] The dielectrophoretic device and methods according to embodiments of the present invention can be used in Lab-on-a-Chip techniques for manipulation, e.g. moving or sorting, of particles such as e.g. cells on a microscopic scale, or cells or molecules which are attached to particles such as e.g. magnetic beads, and which can be combined with other sorting and filtering systems.

[0069] The dielectrophoretic devices and methods according to embodiments of the present invention may be used to improve results of biological experiments. For example, the dielectrophoretic devices and methods according to embodiments of the present invention may be used to obtain a good efficiency in cell lysing, to improve the obtainable quantity of amplicons for specific polymer chain reaction (PCR) experiments and improve detection of hybridised DNA.

[0070] The devices and methods according to embodiments of the invention may be used for manipulation of dielectric particles such as microparticles, nanoparticles, cells, or to any other kind of particles having dielectrophoretic properties. Examples of suitable particles which may be used with embodiments of the present invention may be solid dielectric particles such as e.g. polystyrene or latex beads or carrier beads (beads to which molecules or cells can be bound), engineered particles such as e.g. particles with a conductive core and an insulating shell, or vice versa, biological particles such as cells, bacteria, viruses, DNA, RNA, large molecules e.g. large proteins, complexes of molecules.

[0071] With manipulation of particles is, amongst others, meant transporting, sorting or separating particles.

[0072] The sample fluid may be any kind of sample fluid known by a person skilled in the art and may be a gas or a liquid. According to specific embodiments of the invention, the fluid may, for example, be blood or saliva.

[0073] The device and method for manipulation of particles according to embodiments of the present invention only rely on electrical field induced effects in order to achieve manipulation of particles, e.g. separation of particles, on a macroscopic level. In a device according to embodiments of the invention, particles, e.g. cells are transported electrically through a stationary fluid. Therefore, in accordance with embodiments of the present invention, the need for liquid flow generation and thus for pumping mechanisms, may be eliminated. This allows, in principle, using very small volumes of suspensions comprising the particles. The dielectrophoretic device and methods according to embodiments of the invention can be used for performing particle manipulation from small, non-flowing volumes of particle suspensions. With small volumes is meant volumes of between 0.5 and 50 μl, for example 10 μl.

[0074] The devices and methods according to embodiments of the invention may, for example, be used for separating or sorting particles with different dielectric properties. Particle types may differ in size, shape and/or composition, which will lead to different dielectric properties and thus to different dielectrophoretic responses.

[0075] In a first aspect of the present invention, a dielectrophoretic device is provided for manipulation of at least a first and second type of particles present in a sample fluid. The at least first and second type of particles are different from each other. The device comprises:

- an array of electrodes, the array comprising at least a plurality of electrodes in a first region and a plurality of electrodes in a second region,
- driving means for driving the electrodes of the first and second region of the array to generate a travelling wave dielectrophoretic (twDEP) force to be exerted on the at least first and second types of particles, and
- a controller for controlling the driving means, the controller being adapted for first driving the electrodes of the first and second region with a same driving signal and subsequently changing the driving signal to electrodes of at least one of the first and second region so as to separate at least some particles of the first type from the particles of the second type.

[0076] The present invention also provides, in another aspect, a method for manipulating at least a first and second type of particles in a sample fluid. The method comprises:

- providing sample fluid comprising the at least first and second type of particles to a microfluidic device comprising an array of electrodes, the array comprising at least a plurality of electrodes in a first region and a plurality of electrodes in a second region,
- applying a same driving signal to electrodes of the first and second regions, the driving signal being such that the first type of particles and the second type of particles move with a different speed, and

- subsequently changing the driving signal to electrodes of at least one of the first and second region so as to separate at least some particles of the first type from the particles of the second type.

[0077] Hereinafter, the dielectrophoretic device and method for manipulating at least a first and second type of particles in a sample fluid according to embodiments of the invention will be described by means of different embodiments.

[0078] Fig. 2 and Fig. 3 schematically illustrate the principle of a dielectrophoretic device according to embodiments of the invention. This principle is illustrated based on a sample fluid comprising two different types of particles 1, 2, e.g. larger and smaller particles, or particles having a different weight. It has to be understood that this is not intended to limit the invention in any way. The invention may also be applied to manipulate any number of types of particles present in a sample fluid.

[0079] Fig. 2 and Fig. 3 illustrate two steps required to separate a mixture of a first type of particles 1 and a second type of particles 2 present in a sample fluid. The sample fluid may be a liquid or a gas. The dielectrophoretic device comprises an array 3 of electrodes 4. The array 3 comprises at least a plurality of electrodes 4 in a first region 5 and a plurality of electrodes 4 in a second region 6, there being a boundary 7 in between the first and second region 5, 6. The electrodes 4 may have a longitudinal direction and the longitudinal direction of the electrodes 4 may be substantially parallel to each other, both in the first region 5 and in the second region 6. Also the longitudinal direction of the electrodes 4 in the first region 5 and in the second region 6 may be parallel to each other.

[0080] A driving signal is applied to the electrodes 4 in at least the first and second regions 5, 6, for generating a travelling wave dielectrophoretic (twDEP) force to the first and second type of particles 1, 2, so as to cause movement of the first and second type of particles 1, 2. In a first step, which is illustrated in Fig. 2, a same driving signal is applied to all electrodes 4, i.e. to the electrodes 4 of the first and second region 5, 6 of the array 3. In this first step, the driving signal is such that the generated twDEP force results in the first and second type of particles 1, 2 moving with a different speed but in a same direction. For example, the first type of particles 1, e.g. larger particles, may move faster than the second type of particles 2, e.g. smaller particles, or vice versa. In the example illustrated in Fig. 2 and Fig. 3, the driving signal is such that first type of particles 1 moves faster than the second type of particles 2. Hence, upon driving the electrodes 4 of the first and second regions 5, 6 with a same driving signal, the first and second type of particles 1, 2 start to move with a different speed in a direction from a first side of the device to a second side of the device, as indicated with arrows 8 and 9 in Fig. 2. The difference in speed as a result of a same driving signal is caused by the difference in dielectric properties of the first and second type of particles 1, 2. Particle types may differ in size, shape and/or composition, which will lead to different dielectric properties and thus to different dielectrophoretic responses. As, according to the present example, the first type of particles 1 moves faster than the second type of particles 2, the first type of particles 1 will, step by step, be separated from the second type of particles 2. At a certain point in time, the driving signal to the electrodes 4 of at least one of the first and second region 5, 6 may be changed, i.e. it may be changed in magnitude or sign or may be switched off. Changing the signal applied to the electrodes 4 of at least one of the first and second region 5, 6 may also be referred to as resetting of the array 3. This may be done when a predetermined one of the first and second type of particles 1, 2 has reached or is expected to have reached, a boundary 7 between the first and second region 5, 6 (see further). In the example given, according to embodiments of the present invention, the driving signal to the electrodes 4 of at least one of the first and second region 5, 6 may be changed when particles 2 of the second type, e.g. the ones that move slowest under the applied electrical field, have reached or are expected to have reached the boundary 7 between the first and second region 5, 6.

[0081] The point in time when the driving signal to the electrodes 4 of at least one of the first and second region 5, 6 is changed may be determined in different ways. Therefore, the dielectrophoretic device according to embodiments of the present invention can operate in three modes, i.e. a blind mode, a direct detection mode and an integration mode.

[0082] In the blind mode, no detection mechanism is present for determining reaching of one of the first or second type of particles 1, 2, in the example given the second type of particles 2, of the boundary 7 between the first and second region 5, 6 or for determining the relative speed of movement of the first and second type of particles 1, 2. A way to ensure separation of at least some of the particles 1 of the first type from the particles 2 of the second type is by adjusting the time between applying a same driving signal to all electrodes 4 and changing the driving signal applied to electrodes 4 of at least one of the first and second region 5, 6, depending on the required time for the second type of particles 2 to reach the boundary 7 between the first and second region 5, 6. The time required for the second type of particles 2 to reach the boundary 7 between the first and second region 5, 6 may be determined from previous experiments, may be simulated, or may be calculated using knowledge of the DEP response of the first and second type of particles 1, 2, and can then be chosen so as to be a trade-off between speed of separation and percentage of separation.

[0083] In the case of the blind mode as explained above, changing of the driving signal to the electrodes 4 of at least one of the first and second region 5, 6 may be done when at least some of the particles 2 of the second type, e.g. the type of particles which move slowest under the applied electrical field, are expected to have reached

the boundary 7 between the first and second region 5, 6 based on the experiments, simulations or calculations performed.

[0084] The blind mode of operation may be advantageous when the dielectrophoretic device comprises passive arrays and is, for particular reasons, fabricated on a glass substrate, as this mode of operation requires no integration of electronics in the substrate.

[0085] Another kind of operation mode is the direct mode. In the direct mode, a driving scheme may be used for the electrodes 4 that requires a feedback process for detecting crossing of the boundary 7 by a single particle or a group of particles of a particular type 2 as they move under the DEP forces. For example, a detection means may be present in the dielectrophoretic device for determining when, in the example given, at least some of the second type of particles 2 reach the boundary 7 between the first and second region 5, 6. The most suitable means of detection may be via an optical approach, i.e. via an optical detector e.g. with integrated PIN diodes. When a particle or group of particles reduces the level of ambient light falling onto an optical detector, this change can be used to trigger that a particular amount of the particles 1 of the first type which move fastest have reached the boundary 7 between the first and second region 5, 6 and that the signal applied to the electrodes 4 of at least one of the first and second region 5, 6 may be changed. Whether a particle 1 or 2 has passed the optical detector may be determined from the Clausius-Mossotti curve in combination with information obtained from signals detected by the optical detector. Information obtained from such Clausius-Mossotti curves may reveal the speed difference of two types of particles 1, 2, so that after a time x, a finite number of particles 1 of the first type will be expected to have crossed the optical detectors. Hence, from this, it can be approximated how many particles 1 of the first type will have passed the boundary 7 before particles 2 of the second type will pass the boundary 7. In combination with the measured signal, this information can then be used to determine the time for resetting the array 3 of electrodes 4, i.e. for changing the driving signal to electrodes 4 of at least one of the first and second region 5, 6 of the array 3.

[0086] To operate in the direct mode, the dielectrophoretic device may thus comprise at least one position detector, e.g. at least one optical detector 10a, 10b, 10c, present in between two neighbouring electrodes 4 of the second region 6 close to the boundary 7, preferably in a space between the first and second electrode 4 of the second region 6 next to the last electrode 4 of the first region 5 (see Fig. 4). The at least one optical detector 10a, 10b, 10c may, for example, be a photo diode, as used in Low Temperature Poly Silicon (LTPS) technology, or may even be a discrete device mounted on a back of a transparent substrate on which the device is fabricated. According to embodiments of the invention, the at least one optical detector may comprise discrete separate detectors 10a, 10b, 10c or may comprise one large sensor located in between two electrodes 4 of the array 3, preferably located in between two neighbouring electrodes 4 of the second region 6 close to the boundary 7. According to embodiments of the invention a plurality of detectors 10a, 10b, 10c may be provided such that the whole length of the space in between two adjacent electrodes 4 is covered, as is illustrated in Fig. 4.

[0087] In the direct detection mode, changing the driving signal to electrodes 4 of at least the first or second region 5, 6 may be done upon detection of the predetermined type of particles, in the example given the second type of particles 2, reaching the boundary 7.

[0088] Fig. 4 illustrates a possible implementation of detection of the predetermined type of particles, in the example given the second type of particles 2, reaching the boundary 7. Therefore, electronic circuitry may be provided. The electronic circuitry may comprise a multiplexer switch 13, a reference detector 14, a differential amplifier 15, a detection unit 16 and a direction control 17. When particles 1 of the first type are crossing the optical detectors 10a, 10b, 10c, the level of ambient light falling onto these optical detectors 10a, 10b, 10c will be reduced. A signal representative for this reduction may then be applied to the differential amplifier 15 where it is compared with a reference signal, e.g. a signal coming from the reference detector 14. The signal from the reference detector 14 is representative for ambient light falling on the reference detector 14 without being reduced, as there are no particles 1 on this reference detector 14. From this comparison, the level of reduction of the ambient light by the particles 1 can be determined. The output signal of the amplifier 15 is representative for the level of reduction of the ambient light falling onto the optical detectors 10a, 10b, 10c and thus for the amount of particles 1 having crossed the boundary 7. This signal is then sent to the detection unit 16, where, based on this signal, a determination is made of whether a predetermined amount of particles 1 of the first type have crossed the boundary 7. This predetermined amount may be set using the speed difference information obtained from the Clausius-Mossotti curves. The predetermined amount of particles 1 of the fist type may be set to be the amount of particles 1 which has already passed the boundary 7 at the time that particles 2 of the second type reache the boundary 7. When the detection unit 16 determines that the determined amount of particles 1 of the first type equals the predetermined amount, a signal is sent from the detection unit 16 to the direction control 17 which is connected to a system controller (see further) for resetting the direction control 17, i.e. for changing the driving signal to electrodes 4 of at least one of the first and second region 5, 6.

[0089] A direct detection of particles 1, 2 may be a secure approach to prevent undesirable mixing of particles A and B, but detecting a volume of particles which have passed may be a more efficient marker to use before resetting the array. This is called integration mode. By using current integration, the surface of the detector

10 covered by particles will only trigger the reset when a certain volume of first type particles 1 has passed over the detector 10, also shown in Fig. 4.

[0090] In the integration mode, changing the driving signal to electrodes 4 of at least the first or second region 5, 6 may be done upon determining that a predetermined volume of the predetermined type of particles, in the example given the first type of particles 1, has reached the boundary 7, as detected by the at least one detector 10.

[0091] In the embodiment illustrated in Fig. 4, three detectors 10a, 10b, 10c are present in between the first and second electrodes 4 of the second region 6. Crossing of the detectors 10a, 10b, 10c by a particle of the first type 1, is detected by the detectors 10a, 10b, 10c, as discussed hereabove and as illustrated in the right hand side of Fig. 4 for the 3 different cases illustrated in the left hand side of Fig. 4 (graphs of current versus time). When a plurality of particles 1 crosses the detectors 10a, 10b, 10c simultaneously, they will obscure more of the ambient light. From Fig. 4 three different situations are illustrated. These three situations are shown by the current/time plots on the left hand side (first column of graphs) of Fig. 4. In a first case, only one particle 1 crosses the optical detector 10a and a decrease in the detected current is recorded. In a second case, two particles 1 cross the optical detector 10b and there may be a higher decrease in the current. In a third case, two particles 1 cross the third optical detector 10c slightly overlapping, but, when using volume detection (see hereinafter), the reduction in integrated current is the same as in the second optical detector 10b (current x time = charge), this is shown in the charge/time plots (graphs on the right hand side).

[0092] A volume detection of the crossing of the detectors 10 by the particles is also performed, as illustrated in the right hand sided of Fig. 4 for the 3 different cases illustrated in the left hand side of Fig. 4 (graphs of charge versus time). As soon as the volume detection signal shows that a pre-determined volume of particles have passed the at least one sensor 10, and hence have passed the boundary 7, according to embodiments of the present invention, the driving signal to the electrodes 4 of at least one of the first or second region 5, 6 is changed.

[0093] Changing the driving signal to electrodes 4 of at least one of the first or second region 5, 6 may be done either by separately addressed electrodes controlled externally or, if using an Low Temperature Poly Silicon (LTPS) technology, multiplex circuits can be integrated onto a substrate the electrodes 4 are formed on. Changing of the signal applied to the electrodes 4 of at least one of the first or second region 5, 6 may, according to embodiments of the invention, be performed in different ways. For example, the signal applied to the electrodes 4 of the first region 5 may be changed such that first and second types of particles 1, 2 which have not yet reached the boundary 7 and thus are still present above the first region 5 move in the opposite direction as during the first step of the method, i.e. move away from the boundary 7 (indicated by arrow 8 in Fig. 3), while the signal applied to electrodes 4 of the second region 6 is not changed. Hence, particles 1 of the first type which have already reached the second region 6, will keep moving in the direction indicated by arrow 9. However, according to other embodiments of the invention, the signal applied to electrodes 4 of the first region 5 may be switched off while the signal applied to electrodes 4 of the second region 6 is not changed. In that case, the particles 1, 2 which have not yet reached the boundary 7 between the first and second region 5, 6 may substantially stop moving while particles 1 of the first type will keep moving in the direction indicated by arrow 9. According to still other embodiments, the signal applied to electrodes 4 of the second region 6 may also be changed. For example, the signal applied to the electrodes 4 of the second region 6 may be increased so as to speed up the movement of the first type of particles 1 in the direction indicated by reference number 9. Also other driving schemes for driving the electrodes 4 of the first region 5 and second region 6 may be implemented without departing from the teaching of the present invention as defined by the appended claims, the driving scheme being so as to separate at least some particles 1 of the first type from the particles 2 of the second type.

[0094] In the example given in Fig. 2 and Fig. 3, the first type of particles 1 will first arrive at and cross the boundary 7 between the first and second region 5, 6. After a particular time period, depending on the difference in dielectric properties between the first and second type of particles 1, 2, the second type of particles 2 will also reach the boundary 7. According to the present example, reaching the boundary 7 of at least one of the particles 2 of the second type may be optically detected (detector not shown in the figures), as described above. At the moment that at least one of the particles 2 of the second type reaches the boundary 7 (see Fig. 3), the driving signal to the electrodes 4 of the first region 5 is changed such that the direction of movement of the particles 1, 2 which have not yet reached the boundary 7, and which are thus still present above the first region 5 of the array 3 of electrodes 4, is changed to the opposite direction (indicated by arrow 8 in Fig. 3).

[0095] In the example given in Fig. 2 and Fig. 3, the driving signal applied to the electrodes 4 of the second region 6 is not changed. The particles 1 of the first type that crossed the boundary 7 will therefore keep moving (indicated by arrow 9 in Fig. 3) away from the first region 5 of the array 3. It has to be understood that according to other embodiments of the invention the driving signal applied to the electrodes 4 of the second region 6 may also be changed, for example may be increased or enhanced such that the first type of particles 1 moves faster away from the first region 5.

[0096] Thus, in the embodiment illustrated, any particles 1 that have crossed the boundary 7 between the first and second region 5, 6 will continue to travel in the direction they were travelling before. These particles 1 may

then, for example, be collected to be detected or to be used for other purposes. For example, they may move towards a DEP trap 11, where the first type of particles 1 may be held into a confined region, as illustrated in Fig. 3. According to the present example, the DEP trap 11 may mainly comprise particles 1 of the first type (once they have been moved to there). In the example given, the DEP trap 11 may be formed by locating two arrays 3 of electrodes 4 next to each other, such that the second regions 6 of both arrays 3 are adjacent each other. In between the second regions 6 of the arrays 3, any particle having crossed the boundary 7, and thus in particular the first type of particles 1 may then be trapped.

[0097] According to embodiments of the invention, detectors may be located in the DEP trap 11 as well. In that case, detection of the trapped particles 1 may be performed. The detectors may be any type of detectors known by a person skilled in the art.

[0098] Fig. 5 illustrates an example of a distribution of first and second types of particles 1, 2 after a predetermined time of applying a same driving signal to the electrodes 4 of both the first and second region 5, 6 of the array 3. The particles 1, 2 exhibit a small speed difference. Curve 24 shows the particle distribution for the first type of particles 1 and curve 25 shows the particle distribution for the second type of particles 2. The amount of particles 1 of the first type having crossed the boundary 7 between the first and second region 5, 6 is indicated by the dashed area under curve 24.

[0099] According to embodiments of the invention, and as illustrated in Fig. 3, after performing the above-described steps, there may still be particles 1 of the first type present between the particles 2 of the second type, or in other words, separation between the first and second type of particles 1, 2 may not yet be complete. In that case, the steps as described above may be repeated at least once. Upon repeating these steps the result may be a high degree of separation between the first and second type of particles 1, 2 both in location and concentration. The more the steps are repeated, the higher the degree of separation may be, but the longer the separation time is.

[0100] Fig. 6 illustrates particle distribution curves for three different periods in time and after different resets. In Fig. 6 curves 24 show particle distribution curves for the first type of particles 1 and curves 25 show particle distribution curves for the second type of particles 2. The first column shows the particle distribution curves 24, 25 during driving the electrodes 4 by applying a same driving signal to electrodes 4 of both the first and second region 5, 6. In the example given, the first type of particles 1 moves faster than the second type of particles 2 (distribution curve 25 is lagging behind with respect to distribution curve 24). Therefore, the first type of particles 1 will have reached and crossed the boundary 7 between the first and second region 5, 6 first. The amount of the first type of particles 1 that has crossed the boundary 7 after a period of 60 seconds is indicated by the dashed area under curve 24 (lower graph in 1st column of Fig. 6). It can be seen that after these 60 seconds some of the second type of particles 2 have also reached the boundary 7. At that moment, the driving signal may be reset, i.e. the driving signal to electrodes 4 of at least one of the first and second region 5, 6 may be changed. In the example given, the direction of the driving signal applied to the electrodes 4 of the first region 5 is switched such that the particles 1, 2 which have not crossed the boundary 7 go back to their starting position. Then, a second cycle can be started. This is illustrated in the second column of Fig. 6. After the return cycle, time is reset as well. At the starting point of this second cycle, t=0s, the concentration of particles 1 of the first type is lower than when the experiment started because part of these particles 1 have already crossed the boundary 7 during the first cycle. Again, first a same signal is applied to electrodes 4 of both the first and second region 5, 6 of the array 3. After another 60 seconds, another part of the first type of particles 1 have crossed the boundary 7 and some of the second type of particles 2 may have reached the boundary 7 (see lower graph of 2nd column in Fig. 6). At that time, similarly as described above, a reset may be performed by switching the driving signal applied to the electrodes 4 of the first region 5 such that the particles 1, 2 which have not yet crossed the boundary 7 go back to their starting position. A third cycle is illustrated in the third column of Fig. 6. After another 60 seconds, another part of the first type of particles 1 has crossed the boundary 7. It can be seen that in each further cycle, the amount of particles 1 of the first type which have crossed the boundary 7 gets smaller and smaller. This is because the starting concentration (see first figures in each column) gets lower and lower as more particles 1 will have crossed the boundary 7 in each further cycle.

[0101] Fig. 7 illustrates the concentration of a first type of particles 1 (curve 26) and the concentration of a second type of particles 2 (curve 27) that have crossed the boundary 7 between the first and second region 5, 6 of the array 3 of electrodes 4 as a function of the number of resets. Due to the difference in DEP properties, and thus in DEP velocities, the concentration of the first type of particles 1 that has crossed the boundary 7 is higher than the concentration of the second type of particles 2 that has crossed the boundary 7 at a same time. From Fig. 7 it can also be seen, as was already discussed with respect to Fig. 6, that the higher the number of resets, the lower the amount of the first type of particles 1 that crosses the boundary 7. When both types of particles have similar responses, they can still be filtered with the traditional DEP methods, however they will require proportionally more area (longer DEP tracks) to filter them apart and they will end up being spread over a much wider area, both are undesirable as area costs money, and the particle spread then requires re-focusing. This method ultimately saves space by a factor N in return for N resets.

[0102] The dielectrophoretic device and methods ac-

cording to embodiments of the invention may be able to also cope with a mix of different types of particles 1, 2 in a sample fluid, which have similar dielectric properties. The method according to embodiments of the invention may only require a more extensive time period between resets in a blind, direct or integration detection scheme. This may minimise the throughput of particles 2 of the second type but may also reduce the trapping of undesired particles 1 of the first type in a reservoir adapted for being used with a dielectrophoretic device according to embodiments of the invention. Such reservoir may be a reservoir, for example, for collecting particles of the type that moves slowest, this collecting being performed at the start of the array 3 of electrodes 4, i.e. at the starting point as referred to above. Alternatively, the reservoir may be a reservoir for, for example, collecting particles of the type that moves fastest, this collecting then being performed at the end of the array 3 of electrodes 4, i.e. the side opposite to the starting point. The reservoir may have an arbitrary shape, for example defined in a micro fluidic structure with DEP focusing electrodes. The reservoir may be adapted to pull unidentified particles, i.e. particles of no interest in the experiment, out of a stream of buffer fluid or sample fluid, and into another reservoir which holds a similar buffer that may be the same as before, but under no flow conditions or which is chemically modified to be optimised for the DEP process, i.e. to keep the particles of no interest in the reservoir. So the desired or undesired particles can be managed either by moving into a flowing region, or out of a flowing region, or into a different chemical buffer that alters the DEP behaviour, or performs lysis (e.g. cold water, making cells swell and burst).

[0103] In addition the flow might be intermittent, the system might perform:

1. flow in; 2. filter; 3. flow out process.

[0104] According to alternative embodiments of the present invention, the dielectrophoretic device may furthermore comprise transport means for transporting trapped particles, in the example given particles 1 of the first type, towards other regions of the dielectrophoretic device, or optionally away from the device, so as to enable focusing of selected particles. This may allow continued particle movement into further regions of the dielectrophoretic device where they may be used for further reactions or experiments, for example for cell lysing or for detection. The transport means may, for example, comprise additional electrodes 12 in a configuration suitable to transport the trapped or collected particles, in the example given particles 1 of the first type, towards predetermined regions, e.g. collection regions, of the dielectrophoretic device. An example of a suitable electrode configuration is illustrated in Fig. 8. In this configuration, additional electrodes 12 are provided at the end of the second region 6, the additional electrodes 12 being placed in a position perpendicular to the electrodes 4 of the second region 6. The configuration is such that the intersection point of the electrodes 4 of region 6 and the additional electrodes 12 form a diagonal with respect to the configuration illustrated e.g. in Fig. 3. This configuration allows the particles 1 to move in a diagonal direction towards a predetermined region, e.g. collection region, of the dielectrophoretic device, where they can be detected or where experiments or reactions can take place.

[0105] According to further embodiments of the present invention, the dielectrophoretic device may comprise a cascade of arrays 3a-3d, each array 3a-3d comprising first and second regions 5, 6 (see Fig. 9). In the embodiment illustrated in Fig. 9, the cascade is such that a second zone of a preceding array 3a, 3b, 3c is placed adjacent a first zone of a subsequent array 3b, 3c, 3d. This may enhance the efficiency of the manipulation process to a great extent while still maintaining a high throughput of particles 1, 2. Each array 3a-3d of the cascade may be driven one after the other, and in that way may result in a high degree of separation between the first and second particles 1, 2 present in the sample fluid.

[0106] According to embodiments of the invention, electrodes 4 of the first and second region 5, 6 of the array 3 may be driven with power signals, e.g. voltage signals, adapted in order to obtain twDEP. In general, generating twDEP requires a phase shift of 360°/n between neighbouring electrodes 4, with n being higher than 2. For example, n may be chosen to be 3 or 4. The value of n may kept low because in these cases less different signals are required and thus simpler electronics may be provided to the dielectrophoretic device. According to an embodiment of the invention illustrated in Figs. 10 and 11, n may be 4 and neighbouring electrodes 4 in the array 3 may be energized or driven with power signals, e.g. voltage signals, with a mutual phase difference of 90° in order to obtain twDEP, respectively without and with direction control 17.

[0107] The dielectrophoretic device and method according to embodiments of the present invention may be used to improve results of biological experiments. For example, the dielectrophoretic device and method according to embodiments of the present invention may be used to obtain a good efficiency in cell lysing, to improve the obtainable quantity of amplicons for specific polymer chain reaction (PCR) experiments and improve detection of hybridised DNA.

[0108] In a further aspect, the present invention also provides a system controller 30 for use in dielectrophoretic device for controlling driving of the electrodes 4 of an array 3 in a dielectrophoretic device according to embodiments of the present invention. The system controller 30, which is schematically illustrated in Fig. 12, comprises a control unit 31 for controlling a driving means 32 for first driving the electrodes 4 of the first and second region 5, 6 with a same driving signal and subsequently changing the driving signal to electrodes 4 of at least one of the first and second region 5, 6. For example, the control

unit 31 may be adapted for controlling driving means 32 for applying a voltage signal to the electrodes 4 with a mutual phase difference of 360°/n between every two neighbouring electrodes 4, with n being higher than 2. According to embodiments of the invention, n may be 4 and the system controller 30 may be adapted for controlling driving means 32 for applying a voltage signal to the electrodes 4 with a mutual phase difference of 90° between every two neighbouring electrodes 4. The changing of the driving signal may be so as to separate at least some particles 1 of the first type from the particles 2 of the second type. The system controller 30 may be adapted for changing the driving signal to electrodes 4 of at least one of the first and second region 5, 6 upon reaching of the boundary 7 by a predetermined one of the at least first and second type of particles 1, 2. Therefore, the system controller 30 may comprise an input port for receiving a detector signal from a detector 10 detecting reaching of the boundary 7 by a predetermined one of the at least first and second type of particles 1, 2. According to embodiments of the invention, and as illustrated in Fig. 4, electronic circuitry may be present in between the at least one detector 10a, 10b, 10c and the system controller 30.

[0109] The system controller 30 may include a computing device, e.g. microprocessor, for instance it may be a micro-controller. In particular, it may include a programmable controller, for instance a programmable digital logic device such as a Programmable Array Logic (PAL), a Programmable Logic Array, a Programmable Gate Array, especially a Field Programmable Gate Array (FPGA). The use of an FPGA allows subsequent programming of the dielectrophoretic device, e.g. by downloading the required settings of the FPGA. The system controller 30 may be operated in accordance with settable parameters, such as driving parameters, for example temperature and timing parameters, as well as amplitude and frequency of the applied electric fields.

[0110] The method described above according to embodiments of the present invention may be implemented in a processing system 40 such as shown in Fig. 13. Fig. 13 shows one configuration of processing system 40 that includes at least one programmable processor 41 coupled to a memory subsystem 42 that includes at least one form of memory, e.g., RAM, ROM, and so forth. It is to be noted that the processor 41 or processors may be a general purpose, or a special purpose processor, and may be for inclusion in a device, e.g., a chip that has other components that perform other functions. Thus, one or more aspects of the method according to embodiments of the present invention can be implemented in digital electronic circuitry, or in computer hardware, firmware, software, or in combinations of them. The processing system may include a storage subsystem 43 that has at least one disk drive and/or CD-ROM drive and/or DVD drive. In some implementations, a display system, a keyboard, and a pointing device may be included as part of a user interface subsystem 44 to provide for a user to manually input information, such as parameter values. Ports for inputting and outputting data, e.g. desired or obtained flow rate, also may be included. More elements such as network connections, interfaces to various devices, and so forth, may be included, but are not illustrated in Fig. 13. The various elements of the processing system 40 may be coupled in various ways, including via a bus subsystem 45 shown in Fig. 13 for simplicity as a single bus, but will be understood to those in the art to include a system of at least one bus. The memory of the memory subsystem 42 may at some time hold part or all (in either case shown as 46) of a set of instructions that when executed on the processing system 40 implement the steps of the method embodiments described herein.

[0111] The present invention also includes a computer program product which provides the functionality of any of the methods according to the present invention when executed on a computing device. Such computer program product can be tangibly embodied in a carrier medium carrying machine-readable code for execution by a programmable processor. The present invention thus relates to a carrier medium carrying a computer program product that, when executed on computing means, provides instructions for executing any of the methods as described above. The term "carrier medium" refers to any medium that participates in providing instructions to a processor for execution. Such a medium may take many forms, including but not limited to, non-volatile media, and transmission media. Non-volatile media includes, for example, optical or magnetic disks, such as a storage device which is part of mass storage. Common forms of computer readable media include, a CD-ROM, a DVD, a flexible disk or floppy disk, a tape, a memory chip or cartridge or any other medium from which a computer can read. Various forms of computer readable media may be involved in carrying one or more sequences of one or more instructions to a processor for execution. The computer program product can also be transmitted via a carrier wave in a network, such as a LAN, a WAN or the Internet. Transmission media can take the form of acoustic or light waves, such as those generated during radio wave and infrared data communications. Transmission media include coaxial cables, copper wire and fibre optics, including the wires that comprise a bus within a computer.

[0112] It is to be understood that although preferred embodiments, specific constructions and configurations, as well as materials, have been discussed herein for devices according to the present invention, various changes or modifications in form and detail may be made without departing from the scope of this invention as defined by the appended claims.

Claims

1. A dielectrophoretic device for manipulation of at least a first and a second type of particles (1, 2) present

in a sample fluid, the device comprising:

- at least one array (3) of electrodes (4), the array (3) comprising at least a plurality of electrodes (4) in a first region (5) and a plurality of electrodes (4) in a second region (6),
- driving means (32) for driving the electrodes (4) of the first and second region (5, 6) of the array (3) to generate a travelling wave dielectrophoretic force to be exerted on the at least first and second types of particles (1, 2), and
- a controller (30) for controlling the driving means (32), the controller (30) being adapted for first driving the electrodes (4) of the first and second region (5, 6) with a same driving signal and subsequently changing the driving signal to electrodes (4) of at least one of the first and second region (5, 6) so as to separate at least some particles (1) of the first type from the particles (2) of the second type.

2. A dielectrophoretic device according to claim 1, there being a boundary (7) between the first and second region (5, 6), wherein the controller (30) is adapted for changing the driving signal to electrodes (4) of at least one of the first and second region (5, 6) upon reaching of the boundary (7) by a predetermined one of the at least first and second type of particles (1, 2).

3. A dielectrophoretic device according claim 2, furthermore comprising collection means (11) for collecting at least one of the first and second type of particles (1,2) which have crossed the boundary (7).

4. A dielectrophoretic device according to claim 3, wherein the collection means (11) is formed by a dielectrophoretic trap.

5. A dielectrophoretic device according to claim 3 or 4, furthermore comprising transport means (12) for transporting collected particles (1, 2).

6. A dielectrophoretic device according to any of claims 2 to 5, furthermore comprising detection means for detecting reaching of the boundary (7) by the predetermined one of the at least first and second type of particles (1, 2).

7. A dielectrophoretic device according to claim 6, wherein the detection means is an optical detection means (10).

8. A dielectrophoretic device according to claim 6, wherein the detection means is a time determination means.

9. A dielectrophoretic device according to claim 6, wherein the detection means is means for determining a predetermined volume of at least one of the first and second type of particles (1, 2) which have passed the boundary (7).

10. A dielectrophoretic device according to any of the previous claims, wherein the dielectrophoretic device comprises a cascade of arrays (3a-3d) of electrodes (4).

11. Use of the dielectrophoretic device according to any of the previous claims for particle separation or sorting.

12. Method for forming a dielectrophoretic device for manipulation of at least a first and second type of particles (1, 2) in a sample fluid, the method comprising:

- providing at least one array (3) of electrodes (4), the array (3) comprising at least a plurality of electrodes (4) in a first region (5) and a plurality of electrodes (4) in a second region (6),
- providing driving means (32) for driving the electrodes (4) of the first and second region (5, 6) of the array (3) to generate a travelling wave dielectrophoretic force to be exerted on the at least first and second types of particles (1, 2), and
- providing a controller (30) for controlling the driving means (32), the controller (30) being adapted for first driving the electrodes (4) of the first and second region (5, 6) with a same driving signal and subsequently changing the driving signal to electrodes (4) of at least one of the first and second region (4, 5) so as to separate at least some particles (1) of the first type from the particles (2) of the second type.

13. Method according claim 12, there being a boundary (7) between the first and second region (5, 6), wherein the method furthermore comprises providing collection means (11) for collecting at least one of the first and second type of particles (1,2) which have crossed the boundary (7).

14. Method according to claim 12 or 13, furthermore comprising providing transport means (12) for transporting collected particles (1, 2).

15. Method according to any of claims 12 to 14, there being a boundary (7) between the first and second region (5, 6), wherein the method furthermore comprises providing detection means for detecting reaching of the boundary (7) by a predetermined one of the at least first and second type of particles (1, 2).

16. Method according to any of claims 12 to 15, wherein providing at least one array (3) of electrodes (4) is performed by providing a cascade of arrays (3a-3d).

17. Method for manipulating at least a first and second type of particles (1, 2) in a sample fluid, the method comprising:

a) providing sample fluid comprising the at least first and second type of particles (1, 2) to a microfluidic device comprising at least one array (3) of electrodes (4), the array (3) comprising at least a plurality of electrodes (4) in a first region (5) and a plurality of electrodes (4) in a second region (6),
b) applying a same driving signal to electrodes (4) of the first and second regions (5, 6), the driving signal being such that the first type of particles (1) and the second type of particles (2) move with a different speed, and
c) subsequently changing the driving signal to electrodes (4) of at least one of the first and second regions (5, 6) so as to separate at least some particles (1) of the first type from the particles (2) of the second type.

18. Method according to claim 17, there being a boundary (7) between the first and second region (5, 6), wherein the method furthermore comprises, before changing the driving signal to electrodes (4) of at least one of the first and second region (5, 6), determining when a predetermined one of the first and second type of particles (1, 2) has reached the boundary (7).

19. Method according to claim 17 or 18, wherein determining when a predetermined one of the first and second type of particles (1, 2) has reached the boundary (7) is performed by an optical detection means (10).

20. Method according to claim 17 or 18, wherein determining when a predetermined one of the first and second type of particles (1, 2) has reached the boundary (7) is performed by means of calculating a time period required for the predetermined one of the first and second type of particles (1, 2) has reached the boundary (7).

21. Method according to any of claims 17 to 20, furthermore comprising repeating steps b and c at least once.

22. Method according to any of claims 17 to 21, furthermore comprising collecting at least one of the first and second type of particles (1, 2).

23. Method according to claim 22, furthermore comprising detecting the collected particles (1, 2).

24. A controller (30) for controlled driving of electrodes (4) of an array (3), the array (3) comprising at least a plurality of electrodes (4) in a first region (5) and a plurality of electrodes (4) in a second region (6), wherein the controller (30) comprises a control unit (31) for controlling a driving means (32) for first driving the electrodes (4) of the first and second region (5, 6) with a same driving signal and subsequently changing the driving signal to electrodes (4) of at least one of the first and second region (5, 6) so as to separate at least some particles (1) of the first type from the particles (2) of the second type.

25. A controller (30) according to claim 24, there being a boundary (7) between the first and second region (5, 6), wherein the controller (30) is adapted for changing the driving signal to electrodes (4) of at least one of the first and second region (5, 6) upon reaching of the boundary (7) by a predetermined one of the at least first and second type of particles (1, 2).

26. Computer program product for performing, when executed on a computing means, a method as in any of claims 17 to 23.

27. A machine readable data storage device for storing the computer program product of claim 26.

28. Transmission of the computer program product of claim 26 over a local or wide area telecommunications network.

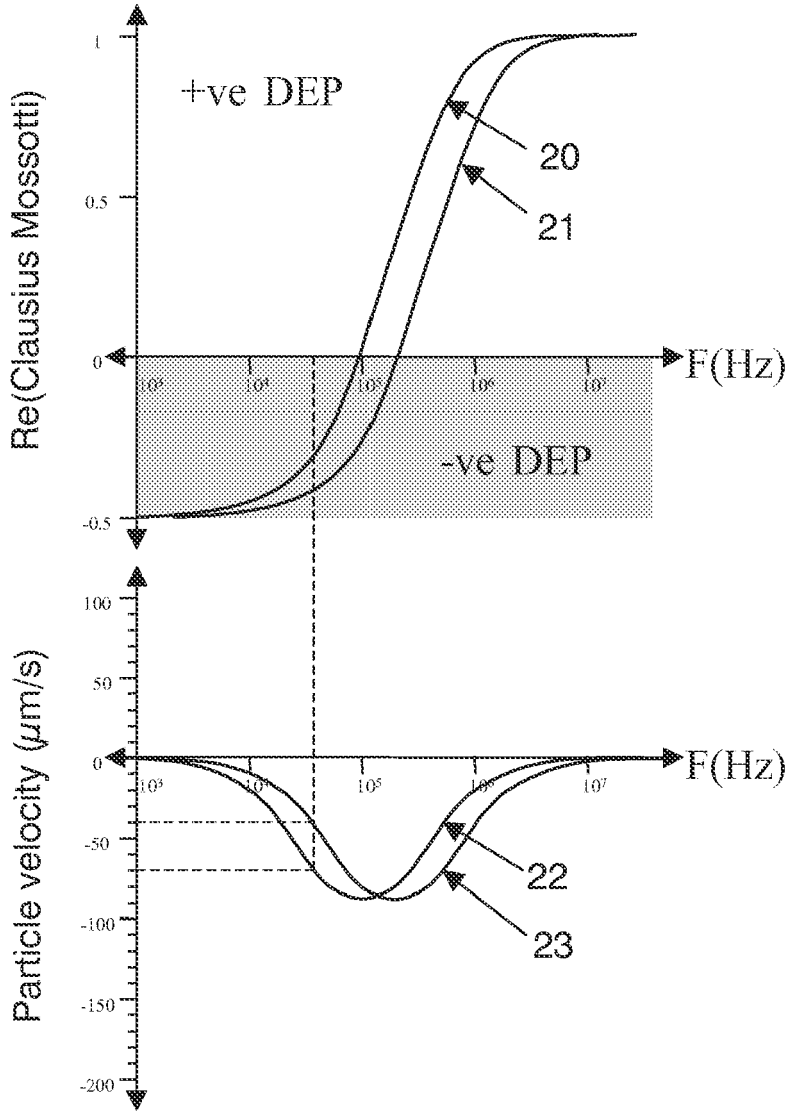
Re(Clausius Mossotti)
1
0.5
0
-0.5
+ve DEP
-ve DEP
20
21
F(Hz)
Particle velocity (μm/s)
100
50
0
-50
-100
-150
-200
22
23
F(Hz)

FIG. 1

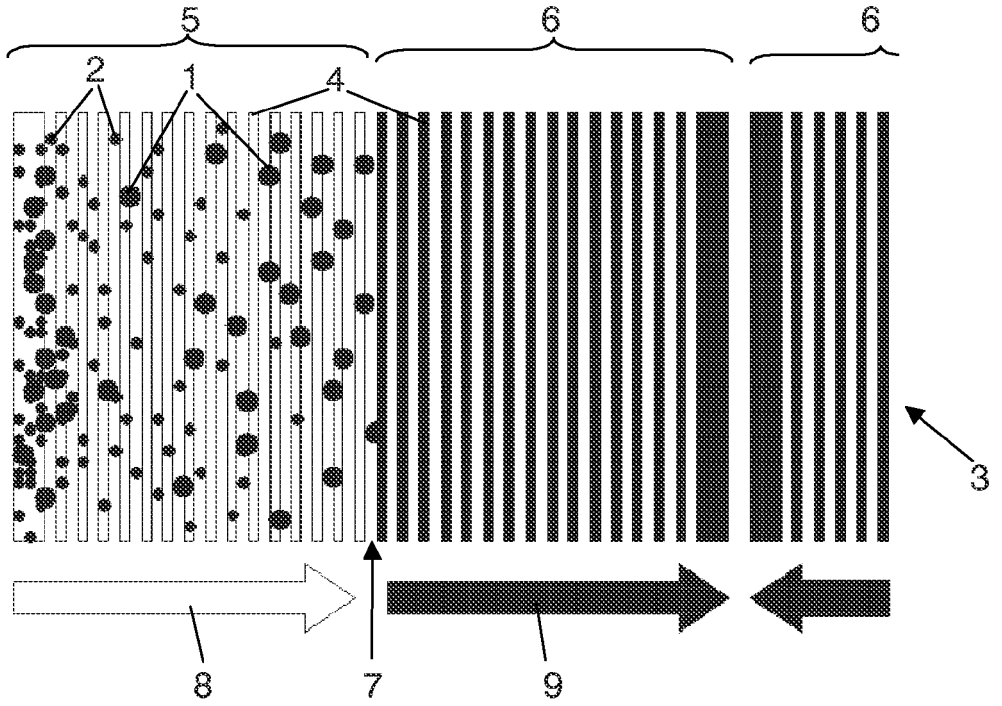

FIG. 2

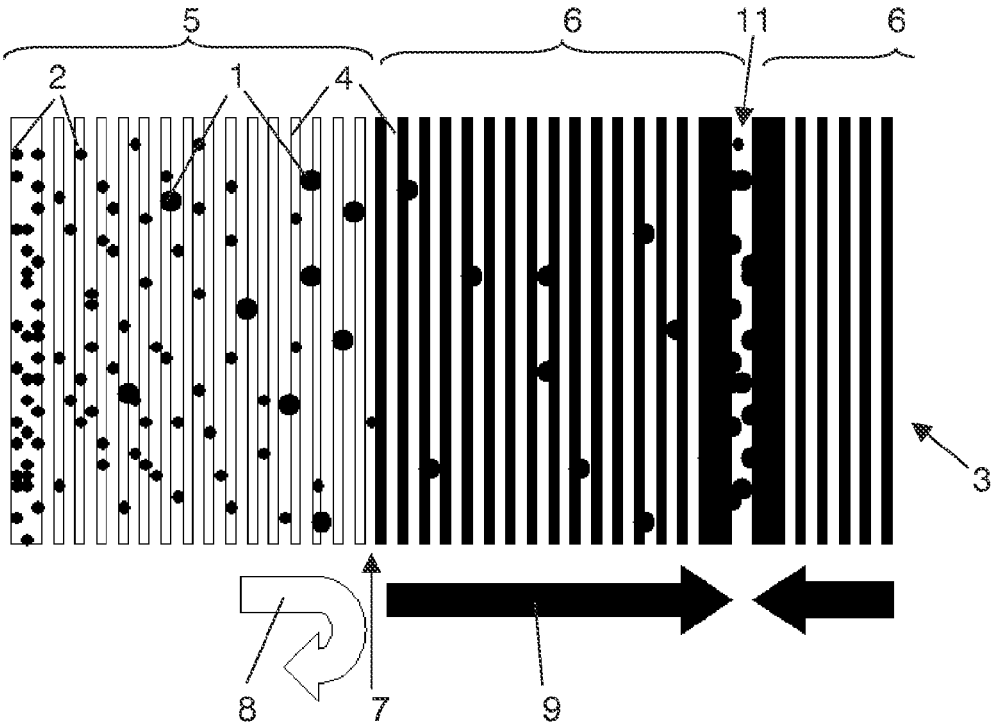

FIG. 3

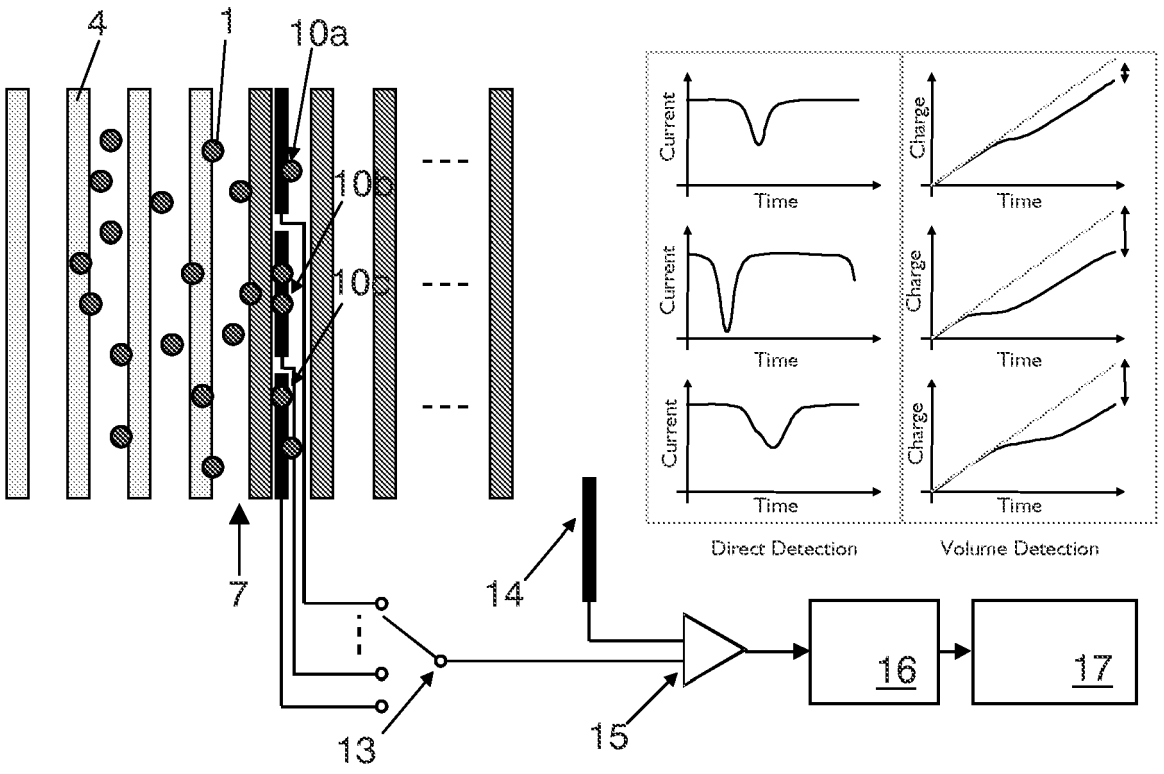
4
1
10a
10b
10c
7
14
13
15
16
17
Current
Time
Charge
Time
Direct Detection
Volume Detection

FIG. 4

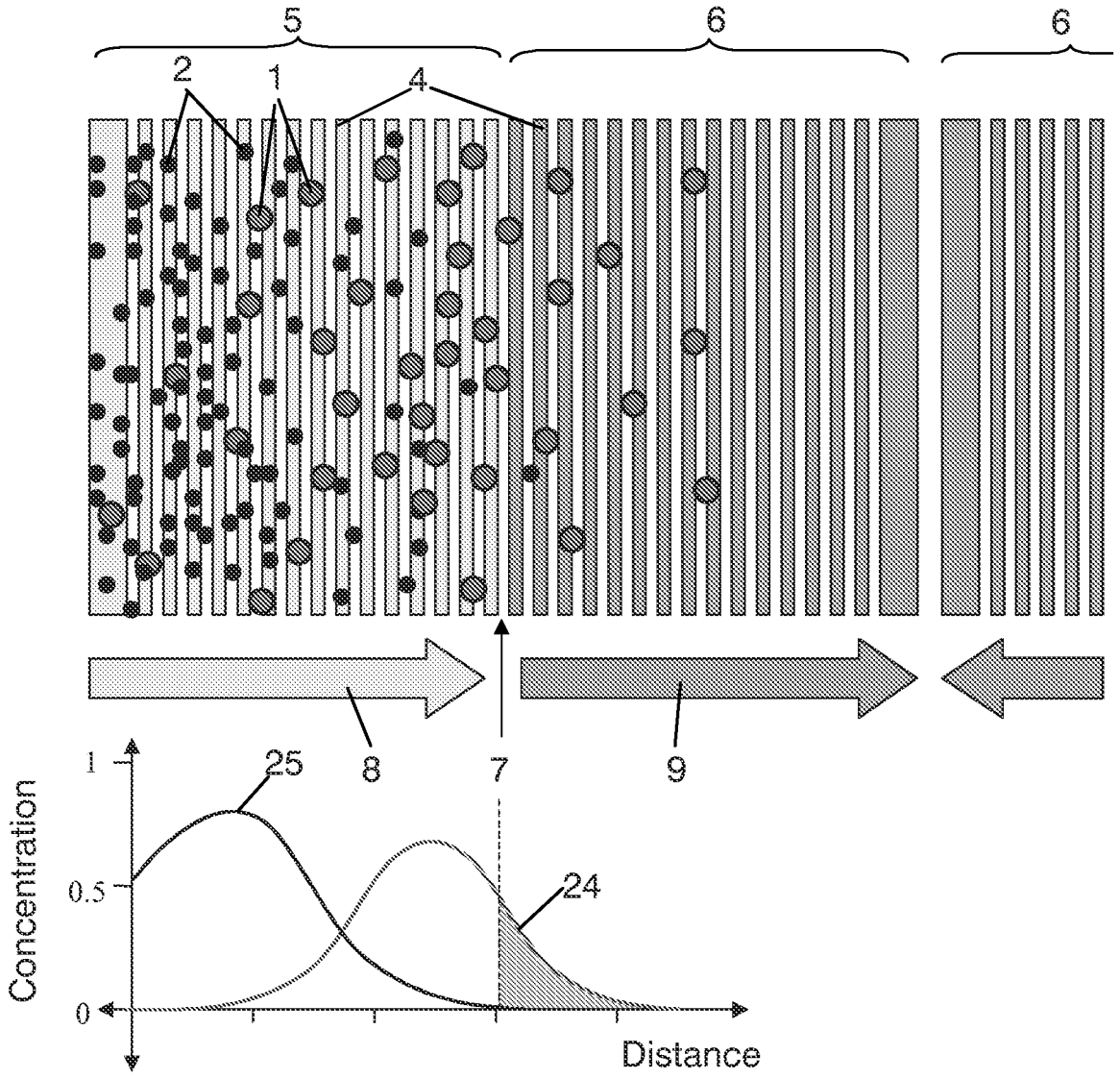

FIG. 5

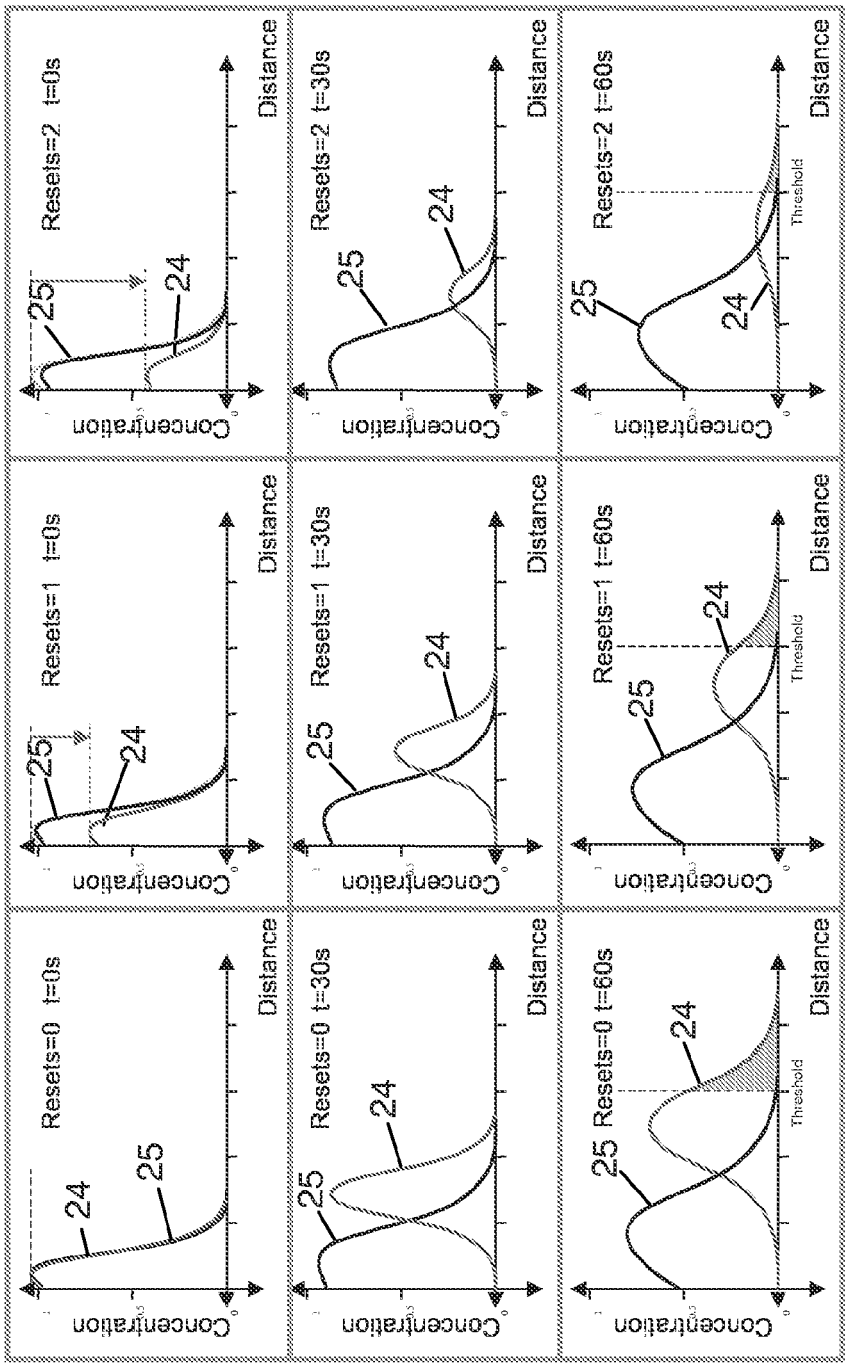
Resets=0 t=0s
Resets=1 t=0s
Resets=2 t=0s
Resets=0 t=30s
Resets=1 t=30s
Resets=2 t=30s
Resets=0 t=60s
Resets=1 t=60s
Resets=2 t=60s
Concentration
Distance
Threshold
24
25

FIG. 6

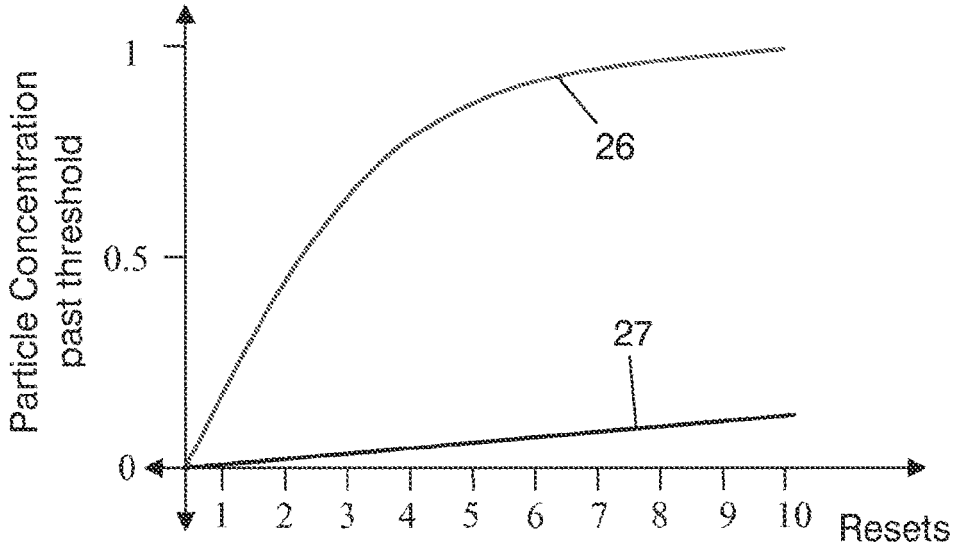
Particle Concentration past threshold
1
0.5
0
26
27
1
2
3
4
5
6
7
8
9
10
Resets

FIG. 7

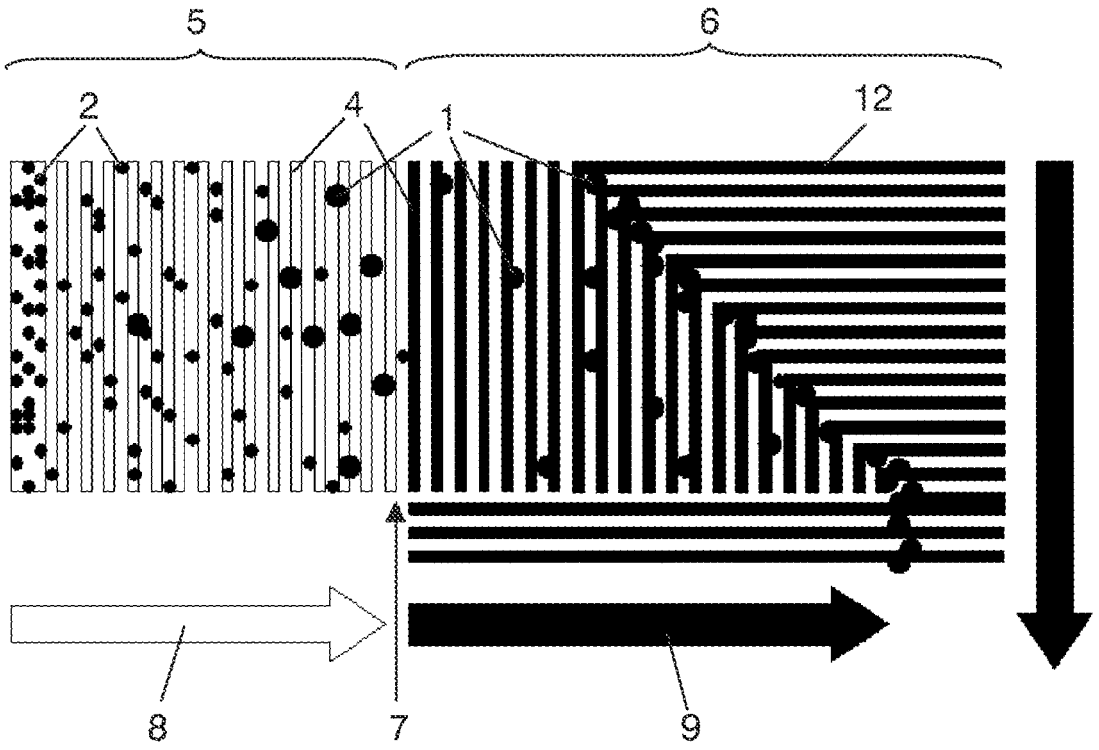
5
6
2
4
1
12
8
7
9

FIG. 8

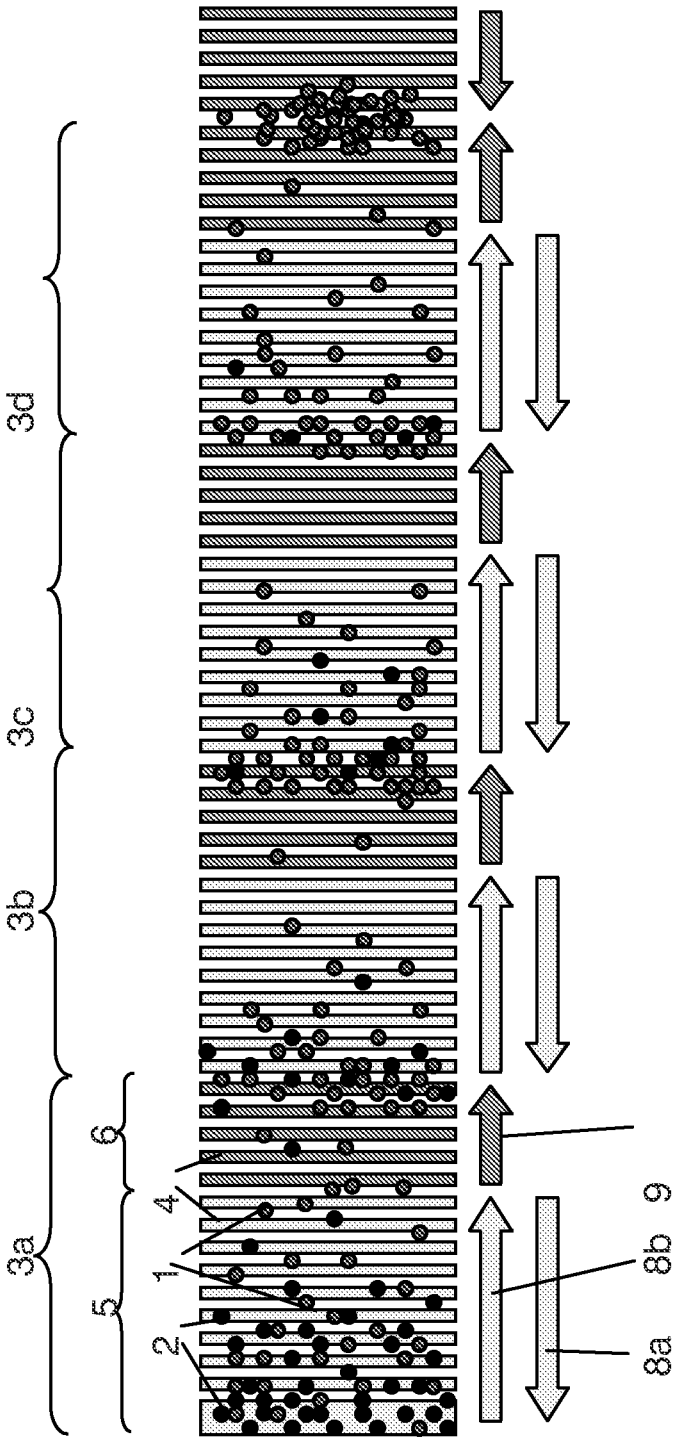

FIG. 9

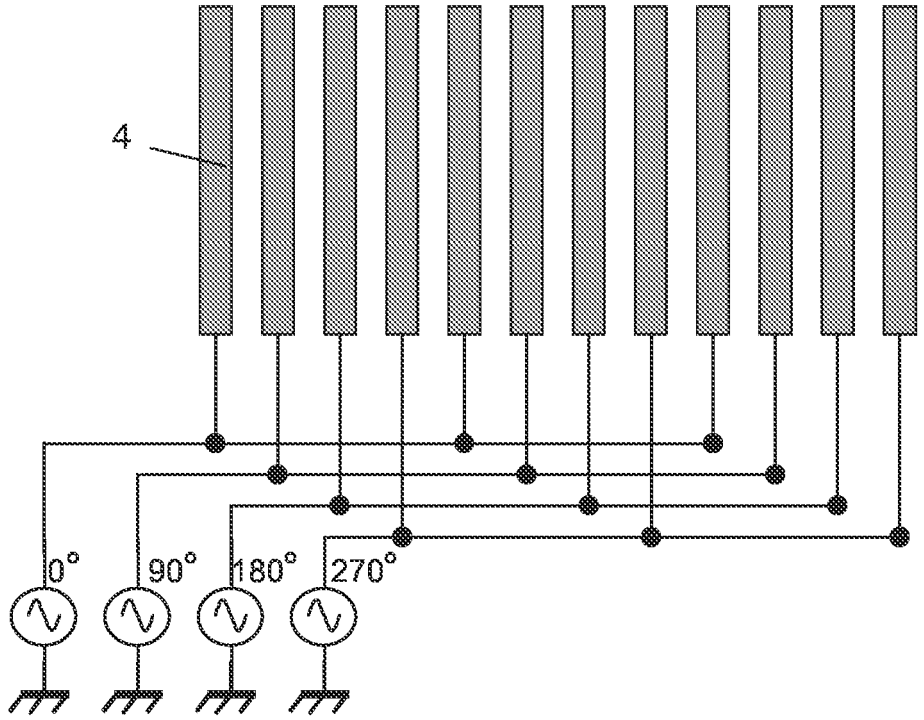

FIG. 10

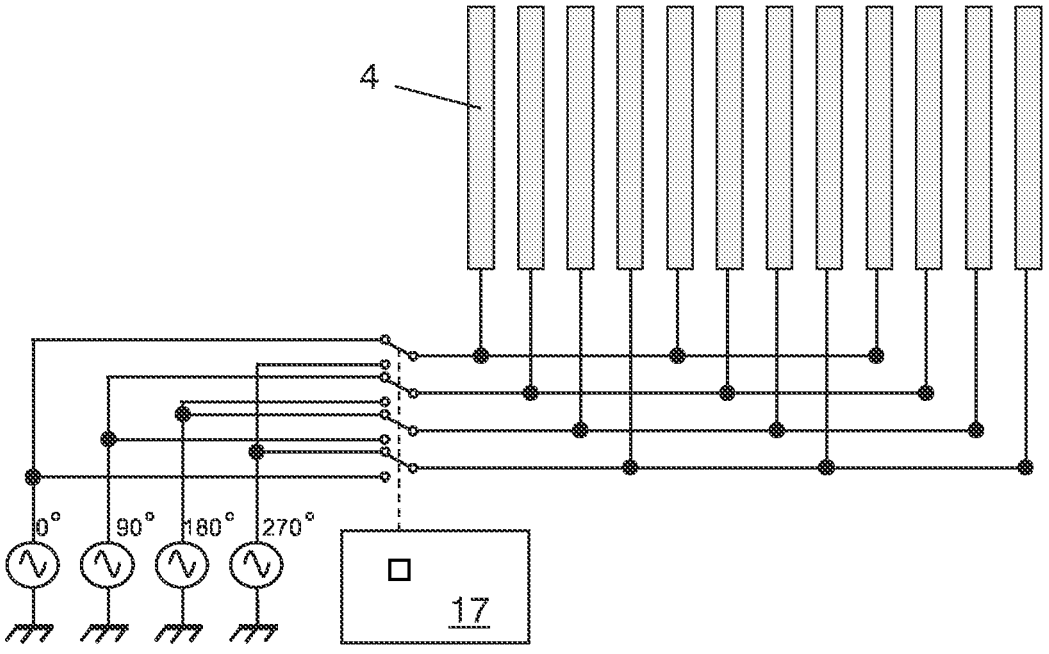

FIG. 11

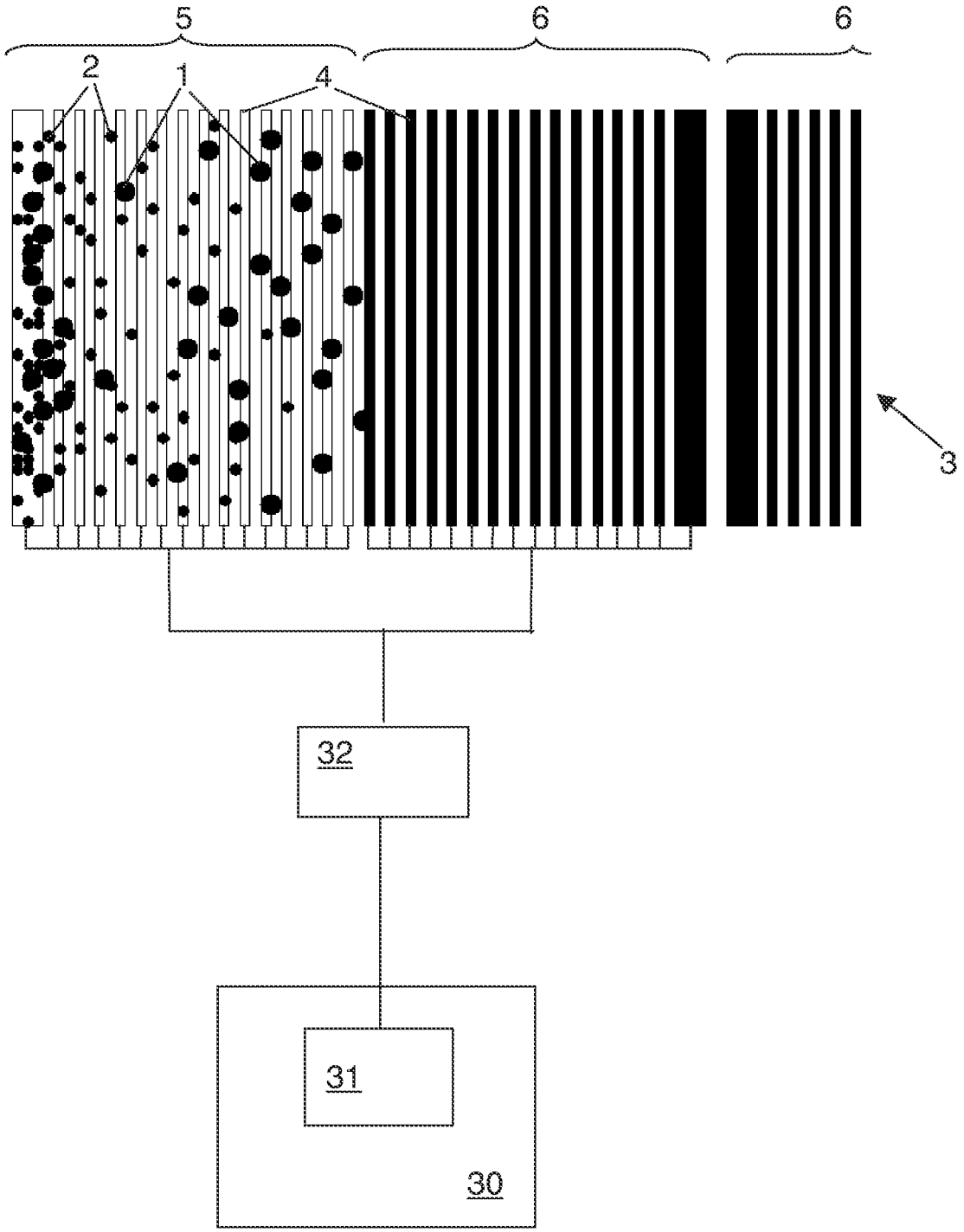

FIG. 12

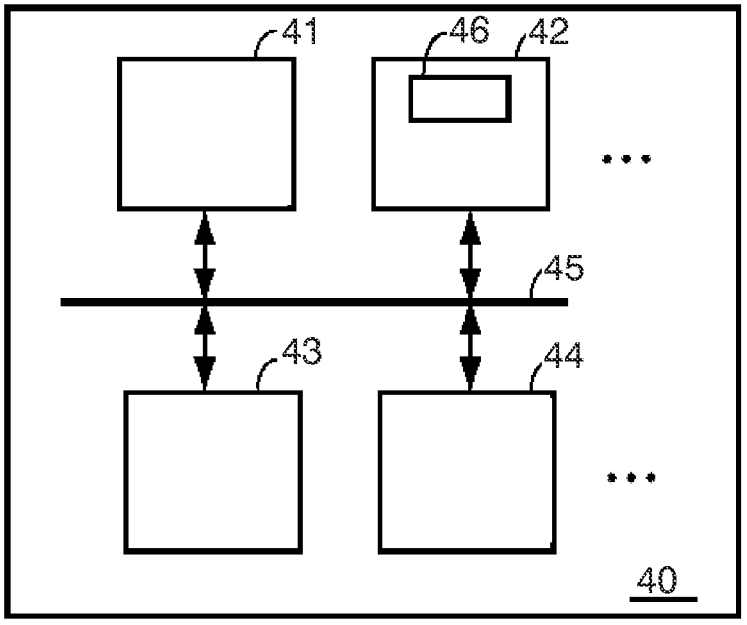

FIG. 13

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 63 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 07 11 9025

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 6 596 143 B1 (WANG XIAO-BO [US] ET AL) 22 July 2003 (2003-07-22) * column 20, line 61 - column 21, line 32; claim 53 *	1-25	INV. B03C5/02
X	US 2005/123992 A1 (VOLKEL ARMIN R [US] ET AL VOELKEL ARMIN R [US] ET AL) 9 June 2005 (2005-06-09) * paragraph [0055] *	1-25	
X	WO 01/05512 A (UNIV WALES BANGOR [GB]; LOCK GARY MICHAEL [GB]; PETHIG RONALD [GB]) 25 January 2001 (2001-01-25) * page 12, line 6 - line 11 *	1-25	
X	US 6 185 084 B1 (TAI YU-CHONG [US] ET AL) 6 February 2001 (2001-02-06) * column 4, line 34 - line 60 *	1-25	
X	WO 97/34689 A (UNIV NORTH WALES [GB]; PETHIG RONALD [GB]; BURT JULIAN PAUL HILLHOUSE) 25 September 1997 (1997-09-25) * page 12, line 24 - line 27 *	1-25	TECHNICAL FIELDS SEARCHED (IPC) B03C

-/--

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
The Hague	7 August 2008	Demol, Stefan

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

EPO FORM 1503 03.82 (P04E07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 07 11 9025

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	US 5 653 859 A (PARTON ADRIAN [GB] ET AL) 5 August 1997 (1997-08-05) * column 12, line 18 - column 13, line 10 *	1-25	
X	US 2005/148064 A1 (YAMAKAWA MINEO [US] ET AL) 7 July 2005 (2005-07-07) * paragraph [0045] *	27,28	
X	US 2006/070879 A1 (BECKER FREDERICK F [US] ET AL) 6 April 2006 (2006-04-06) * paragraphs [0090], [0091] *	27,28	
X	US 2002/056640 A1 (SOANE DAVID S [US] ET AL) 16 May 2002 (2002-05-16) * paragraphs [0040] - [0042] *	27,28	TECHNICAL FIELDS SEARCHED (IPC)
X	US 2003/173223 A1 (GASCOYNE PETER R C [US] ET AL) 18 September 2003 (2003-09-18) * paragraph [0020] *	27,28	
X	US 2006/177815 A1 (SOH HYONGSOK T [US] ET AL) 10 August 2006 (2006-08-10) * paragraph [0086] *	27,28	

EPO FORM 1503 03.82 (P04C10) 2

European Patent Office

INCOMPLETE SEARCH SHEET C

Application Number
EP 07 11 9025

Claim(s) searched completely:
1-25-27-28

Claim(s) not searched:
26

Reason for the limitation of the search (non-patentable invention(s)):

See Guidelines Part C-IV,2.3.6 (Computer programs) and Guidelines Part C-II,4.11 (Insufficient disclosure)

European Patent Office

Application Number
EP 07 11 9025

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing claims for which payment was due.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

☐ The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 07 11 9025

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-25

dielectrophoretic separation:
Independent claim 11: use of a a dielectrophoretic device
Independent claim 12: method of forming a dielectrophoretic device
Independent claim 17: method for separating particles using a dielectrophoretic device
Independent claim 24: a controller for a dielectrophoretic device

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2. claims: 26*-28

computerised operation:
Independent claim 26: a computer program
Independent claim 27: data storage device
Independent claim 28: transmission of a computer program

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 07 11 9025

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.

07-08-2008

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US 2002056640 A1	16-05-2002	NONE	

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 07 11 9025

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07-08-2008

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003173223 A1	18-09-2003	NONE	
US 2006177815 A1	10-08-2006	NONE	

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82