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(54) Dielectrophoretic device for manipulation of particles

(57) The present invention provides a dielectrophoretic device comprising an array (10) of electrodes (1), there being a space (2) in between every two neighboring electrodes (1), and driving means for driving the electrodes (1) of the array (10) to generate a traveling wave dielectrophoretic force. The array (10) of electrodes (1) is formed such that the space (2) in between every two neighboring electrodes (1) has a decreasing width in a longitudinal direction of the electrodes (1). The dielectrophoretic device according to embodiments of the invention can be sued for performing manipulation of particles (5) in small, non-flowing volumes of particles suspensions. The present invention furthermore provides a method for manufacturing such a dielectrophoretic device and a method for manipulating particles (5) by using such a dielectrophoretic device.

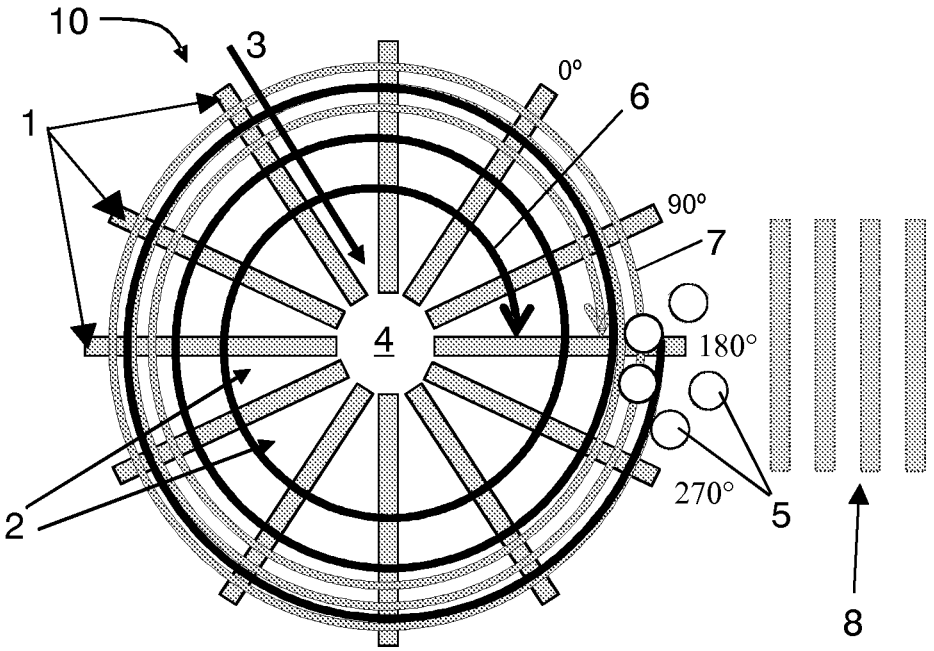


FIG. 2

EP 2 039 433 A1

Description

FIELD OF THE INVENTION

[0001] The present invention relates to dielectrophoretic devices. More particularly the present invention relates to a dielectrophoretic device for manipulating particles, to a method for forming such a device and to a method for manipulating particles using such a device. The methods and devices according to embodiments of the invention may, for example, be used for identifying and/or separating and/or sorting particles, e.g. cells, or for lysis or electroporation of cells.

BACKGROUND OF THE INVENTION

[0002] The ability to identify and separate cell sub-populations from a heterogeneous cell mixture is essential in many biomedical applications. The simplest methods known for such purposes are based on filtration and centrifugation and rely on differences in cell size or density. More advanced methods exploit specific binding of antibodies to antigens on a cell surface to target a particular cell population. Examples of such methods are magnetically activated cell sorting (MACS), where antibody-functionalized magnetic beads are attached to the cells and sorted in a magnetic field, or fluorescence-activated cell sorting (FACS), where cells are labeled with fluorescent antibodies and separated by electrostatically deflecting charged liquid droplets containing the cells. Current FACS analyzers are very versatile instruments and allow cell separation on the basis of multiple simultaneous markers, cell size, and scattering properties. However, they are large and expensive instruments and can only be operated by trained personnel.

[0003] Recently, considerable effort has been put into transferring cell analysis to microfabricated systems. The advantages of lab-on-a-chip devices include ease of use and low fabrication costs (ultimately leading to disposable chips), low fluid volumes and reagents consumption, large integration of functionalities, high-throughput analysis via massive parallelization and increased process control due to the faster response of the system. Electric field based approaches are particularly suited for miniaturization because micropattemed electrodes are easy to fabricate and result in high electric fields at modest voltages.

[0004] One of the most promising methods to separate and manipulate cells in microsystems is dielectrophoresis (DEP), i.e. the movement of dielectric particles in a nonuniform, usually AC, electric field. Unlike electrophoresis, DEP relies on field-induced polarization effects and is independent of the net charge of the particle. The DEP force depends on the electrical properties of the particle and of the surrounding medium, on the size and shape of the particle and on the spatial distribution and frequency of the applied field. Depending on these factors, the particle 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).

[0005] DEP has 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.

[0006] Most reported experiments are proof-of-principle applications of DEP, in which cells that undergo positive DEP are separated from those experiencing negative DEP on the microscopic level. Practical applications, however, require cell separation on a macroscopic scale. This is usually achieved by combining DEP with liquid flow. The particles that are attracted by the electrodes are retained in the device, while the others are washed away. Such devices are, however, unable to separate cells with different degrees of positive or negative DEP, unless the experiment is repeated several times in succession, e.g. by varying the amplitude or frequency of the applied field or by varying the strength of the liquid flow.

[0007] Hyperlayer dielectrophoretic field-flow fractionation (DEP-FFF) is a significant step towards a more refined separation of cell populations. In this method, a linear array of microelectrodes is used to levitate cells by negative DEP. A non-constant flow profile causes cells levitated at different heights to emerge from the separation channel at different times. A similar method, which is referred to as electrosmear, has been developed to allow collection of cells onto characteristic zones on a substrate. Similarly to DEP-FFF, this method is also based on the combination of liquid flow and cell levitation by negative DEP. The cells are introduced at one end of an electrode array, which provides a levitation force that opposes cell sedimentation and prevents cells from adhering to the substrate. The voltage applied to the electrodes varies along the array. The cells flow along the channel until the DEP forces are no longer sufficient to levitate them, at which point they touch down and adhere to the substrate, which is coated with a binding agent.

[0008] The DEP methods described above rely on liquid flow to achieve cell separation on a macroscopic level. This is a disadvantage, as it requires the use of an external pump or, alternatively, requires the microsystem to be equipped with a MEMS or electro-osmotic pump. In addition to considerably complicating the device, the need for liquid flow and, consequently, a pumping mechanism results in larger suspension volumes where more cells have to be used.

[0009] In EP 0 815 942 a device is described comprising a channel defined by two rows of electrodes separated by the channel and wherein the width of the channel progressively decreases in the direction of particle migration. According to embodiments of the invention, the

spacing between successive electrodes in each of the rows may be the same (Fig. 1(a)) or the spacing between successive electrodes in each of the rows may progressively decrease in the direction of particle migration (Fig. 1(b)). Traveling wave dielectrophoresis (twDEP) is used to transport the particle through the channel. A particle moving under twDEP, in EP 0 815 942 referred to as traveling wave field migration, will be accelerated as a result of the field increasing as the channel width decreases. Particles with different properties will be spatially separated as they move along the channel. However, a drawback of the configuration described in EP 0 815 942 is that the device is symmetric with respect to the direction of travel of the particles. As a consequence, only a one-dimensional smear (distribution) of the particles can be obtained. This does not allow, for example, collecting the particles into separate microfluidic channels for subsequent analysis or processing.

SUMMARY OF THE INVENTION

[0010] It is an object of embodiments of the present invention to provide a good dielectrophoretic device for manipulating particles, a good method for forming such dielectrophoretic device and a good method for manipulating particles using such a dielectrophoretic device.

[0011] The above objective is accomplished by a method and device according to the present invention.

[0012] In a first aspect, the present invention provides a dielectrophoretic device for manipulation of particles. The device comprises:

> an array of electrodes, there being a space in between two neighboring electrodes, the array of electrodes being formed such that the space in between the two neighboring electrodes, preferably in between every two neighboring electrodes, has a width which is decreasing in a longitudinal direction of the electrodes, or, in other words, is funnel-shaped, and driving means adapted for driving the electrodes of the array to generate a traveling wave dielectrophoretic force to be exerted on the particles.

[0013] An advantage of embodiments of the invention is that different types of particles even with small differences in properties may be manipulated, e.g. separated, with the dielectrophoretic device according to embodiments of the invention. The dielectrophoretic device according to embodiments of the invention is efficient and sensitive. The dielectrophoretic device according to embodiments of the invention can be used for performing particle manipulation from small, non-flowing volumes of particle suspensions.

[0014] The array of electrodes may be a one-dimensional array.

[0015] The direction of decrease of the width of the space in between two neighboring electrodes, preferably in between every two neighboring electrodes, may be oriented in the direction of the average longitudinal direction of the neighboring electrodes. For radial arrays the direction may be a radial direction, for linear arrays, the direction may be the longitudinal direction of the electrodes.

[0016] The electrodes may be funnel-shaped.

[0017] According to embodiments of the invention, the array of electrodes may be a radial array in which the electrodes are arranged as segments of a circle extending from a center of the circle to its circumference.

[0018] According to other embodiments of the invention, the array of electrodes may be a linear array and the electrodes are funnel-shaped.

[0019] The driving means may be adapted for driving the electrodes with a mutual phase difference of 360°/n between two neighboring electrodes, preferably between every two neighboring electrodes, with n being higher than 2.

[0020] According to embodiments of the invention, n may be 4 and the driving means may be adapted for driving the electrodes with a mutual phase difference of 90° between two neighboring electrodes.

[0021] According to embodiments of the invention, the dielectrophoretic device may furthermore comprise transport means for transporting particles toward the array of electrodes. The transport means may be formed by a linear array of parallel electrodes.

[0022] According to further embodiments of the invention, the dielectrophoretic device may furthermore comprise collection means for collecting particles. The collection means may be formed by an array of collection channels. The collection channels may be microfluidic channels.

[0023] According to embodiments, the collection means may furthermore comprise impedance measurement means for determining an amount of particles in the collection means.

[0024] According to embodiments of the invention, the particles may be biological particles (e.g. cells), solid dielectric particles, or engineered particles.

[0025] The present invention also provides the use of the dielectrophoretic device according to embodiments of the invention for particle separation or sorting.

[0026] The present invention also provides the use of the dielectrophoretic device according to embodiments of the invention for cell lysis or cell electroporation.

[0027] In a further aspect of the invention, a method is provided for forming a dielectrophoretic device for manipulation of particles. The method comprises:

> providing an array of electrodes with a space in between two neighboring electrodes such that the array of electrodes is formed such that the space in between the two neighboring electrodes, preferably in between every two neighboring electrodes, has a width which is decreasing in a longitudinal direction of the electrodes, or in other words is funnel-shaped, and

providing driving means adapted for driving the electrodes of the array to generate a traveling wave dielectrophoretic force to be exerted on the particles.

[0028] An advantage of the method according to embodiments of the invention is that it allows forming a dielectrophoretic device in which different types of particles even with small differences in properties may be manipulated, e.g. separated, with the dielectrophoretic device according to embodiments of the invention.

[0029] Providing an array of electrodes may be performed such that the array is a one-dimensional array.

[0030] Providing an array of electrodes may furthermore be performed such that the direction of decrease of the width of the space in between two neighboring electrodes, preferably in between every two neighboring electrodes is oriented in an average longitudinal direction of the two neighboring electrodes. For radial arrays the same direction may be a radial direction, for linear arrays, the same direction may be the longitudinal direction of the electrodes.

[0031] According to embodiments of the invention, providing an array of electrodes may be performed such that a radial array is formed in which the electrodes are arranged as segments of a circle extending from a center of the circle to its circumference.

[0032] According to other embodiments of the invention, providing an array of electrodes may be performed such that a linear array is formed with electrodes having a funnel-shape.

[0033] The method may furthermore comprise providing transport means for transporting particles toward the array of electrodes.

[0034] The method may furthermore comprise providing collection means for collecting particles.

[0035] The method may furthermore comprise providing impedance measurement means to the collection means for determining an amount of particles in the collection means.

[0036] In still a further aspect of the invention, a method is provided for manipulating particles using a dielectrophoretic device comprising an array of electrodes wherein the space in between two neighboring electrodes, preferably in between every two neighboring electrodes, has a decreasing width in a longitudinal direction of the electrodes. The method comprises applying a voltage signal to the electrodes with a mutual phase difference of 360°/n between two neighboring electrodes, preferably between every two neighboring electrodes, with n being higher than 2.

[0037] According to specific embodiments, n may be 4 and a voltage signal may be applied to the electrodes with a phase difference of 90° between two neighboring electrodes, preferably between every two neighboring electrodes.

[0038] The method may furthermore comprise transporting the particles towards the array of electrodes for allowing them to be manipulated.

[0039] The method may furthermore comprise collecting particles in a collection means after manipulation of the particles.

[0040] The method may furthermore comprise counting the amount of particles in the collection means.

[0041] Manipulating particles may comprise separating particles based on a difference in dielectric properties.

[0042] Manipulating particles may comprises lysis or electroporation of cells.

[0043] The present invention also provides the use of the method according to embodiments of the invention in molecular diagnostics, biological sample analysis or chemical sample analysis.

[0044] The present invention also provides the use of the method according to embodiments of the invention for particle separation.

[0045] The present invention also provides the use of the method according to embodiments of the invention for cell lysis or cell electroporation.

[0046] In yet a further aspect of the invention a controller is provided for controlled driving of electrodes of an array wherein the space in between two neighboring electrodes, preferably in between every tow neighboring electrodes, has a decreasing width in a longitudinal direction of the electrodes. The controller comprises a control unit for controlling a driving means for applying a voltage to the electrodes with a mutual phase difference of 360°/n between two neighboring electrodes, preferably in between every tow neighboring electrodes, with n being higher than 2.

[0047] According to specific embodiments, n may be 4 and the controller may be adapted for controlling the driving means such that a voltage signal is applied to the electrodes with a phase difference of 90° between two neighboring electrodes, preferably between every two neighboring electrodes.

[0048] The present invention furthermore provides a computer program product for performing, when executed on a computing means, a method according to embodiments of the invention.

[0049] The present invention also provides a machine readable data storage device for storing the computer program product according to embodiments of the invention.

[0050] The present invention also provides a transmission of the computer program product according to embodiments of the invention over a local or wide area telecommunications network.

[0051] The dielectrophoretic device according to embodiments of the invention is efficient and sensitive.

[0052] The dielectrophoretic device according to embodiments of the invention can be used for performing manipulation of particles in small, non-flowing volumes of particle suspensions.

[0053] The dielectrophoretic device according to embodiments of the invention may be used for manipulating different types of particles. According to embodiments of the invention, different types of particles can be separat-

ed, even with small differences in properties, e.g. shape, size, or composition. The dielectrophoretic device according to embodiments of the invention can also be used to separate particles with different degrees of positive or negative dielectrophoresis. Hence the present invention can be used for cell sorting.

[0054] 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.

[0055] 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

[0056]

Fig. 1 shows configurations of dielectrophoretic devices according to the prior art.

Fig. 2 illustrates a dielectrophoretic device according to embodiments of the invention.

Fig. 3 illustrates a dielectrophoretic device according to embodiments of the invention.

Fig. 4 illustrates the principle of embodiments of the present invention using a dielectrophoretic device according to embodiments of the invention.

Fig. 5 and 6 illustrate the principle of embodiments of the present invention using dielectrophoretic devices according to embodiments of the invention.

Fig. 7 illustrates the application of cell lysis using a dielectrophoretic device according to embodiments of the invention.

Fig. 8 schematically illustrates a system controller for use with a dielectrophoretic device according to embodiments of the present invention.

Fig. 9 is a schematic representation of a processing system as can be used for performing a method according to embodiments of the present invention.

[0057] In the different figures, the same reference signs refer to the same or analogous elements.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0058] 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.

[0059] 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.

[0060] The terms top, bottom and the like in the description and the claims are used for descriptive purposes and not necessarily for describing relative positions. 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 orientations than described or illustrated herein.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] The present invention provides a dielectrophoretic device for manipulation of particles, a method for manufacturing such a dielectrophoretic device and a method for manipulating, e.g. identifying, sorting, separating, lysis or electroporation, of particles, e.g. cells using such a dielectrophoretic device.

[0067] The device 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 suitable 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, large molecules e.g. large proteins, complexes of molecules.

[0068] The device and method for manipulation of particles according to embodiments of the present invention need only rely on electric field induced effects to achieve manipulation of particles, e.g. separation of particles, on a macroscopic level. In the 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 is 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. The device and methods according to embodiments of the invention may be used in a variety of applications including molecular diagnostics, biological sample analysis or chemical sample analysis.

[0069] For example, the device and methods according to embodiments of the invention may 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. In the dielectrophoretic device and method for manipulation of particles according to embodiments of the invention, dielectric particles, e.g. cells, may be separated according to their dielectric properties into distinct zones on the device. This facilitates visual or automatic inspection of a sample under investigation. Alternatively, particles, e.g. cells can be collected into separate microfluidic channels for subsequent analysis or processing. This includes, for example, counting cells in various collection channels, statistically analyzing particle distributions, or further fractionating a target sub-population.

[0070] Compared to devices that can only separate cells undergoing either positive or negative dielectrophoresis (DEP), the dielectrophoretic device according to embodiments of the invention allows a more refined particle, e.g. cell, separation. In particular, particles, e.g. cells, with different degrees of positive (or negative) DEP can be separated in a single step. With particles having a different degree of positive (negative) DEP is meant that these particles undergo positive (or negative) DEP, but the force has a different magnitude. Due to long interaction distances achieved with the dielectrophoretic device according to embodiments of the invention, even small variations in the dielectric properties of particles, e.g. cells, can be resolved. Furthermore, the dielectrophoretic device and method for manipulation of particles, e.g. cells, according to embodiments of the invention may be used for lysis or electroporation of cells.

[0071] In a first aspect of the invention, a dielectrophoretic device is provided for manipulation of particles. The dielectrophoretic device comprises an array of electrodes, there being a space in between every pair of neighboring electrodes. The array of electrodes can be a one-dimensional array. The array may be a linear array or a radial array. According to embodiments of the invention, the dielectrophoretic device may comprise at least two one-dimensional arrays placed next to each other.

[0072] Each electrode has a longitudinal direction. Two neighboring electrodes, e.g. every pair of neighboring electrodes, have an average longitudinal direction, being a direction defined by the average of the longitudinal directions of the two neighboring electrodes. The array of electrodes is formed such that the space between two neighboring electrodes, for example between every two neighboring electrodes, has a width which is decreasing in the longitudinal direction of the electrodes. The width may be decreasing continuously. Preferably the width of the space between two neighboring electrodes may be measured in a direction perpendicular to the average longitudinal direction of the neighboring electrodes. The space in between two neighboring electrodes, e.g. every two neighboring electrodes, may be funnel-shaped. The direction of the decrease of the width of the spaces in between the two neighboring electrodes may be oriented in a same direction, i.e. the average longitudinal direction of the two neighboring electrodes may be the same (linear array). Alternatively, the direc-

tion of the decrease of the width of the spaces in between every two neighboring electrodes may be radially oriented to a center point of the array (radial array).

[0073] The dielectrophoretic device according to embodiments of the invention is based on traveling wave dielectrophoresis (twDEP) in combination with either negative (repulsive) or positive (attractive) DEP. Therefore, the dielectrophoretic device furthermore comprises driving means adapted for driving the electrodes of the array to generate a twDEP force to be exerted on the particles.

[0074] An array of electrodes, e.g. microelectrodes, is used to transport particles, e.g. cells, over a relatively long distance by twDEP. Instead of using an array of parallel electrodes with parallel spaces in between, as commonly done in devices based on twDEP, the present invention proposes the use of an electrode array with a space in between every two neighboring electrodes having a width which is decreasing in a longitudinal direction of the electrodes. The space in between every neighboring electrode may be referred to as funnel-shaped, hence the space may also be referred to as a funnel. Configurations of the array according to embodiments of the invention allow, in addition to generating a propelling twDEP force, generating a weaker DEP component perpendicular to the traveling direction. The magnitude and direction of such component varies for different types of particles with differences in dielectric properties, e.g. subpopulations of cells, and allows them to be manipulated, e.g. transported or separated or sorted. When a voltage is applied to the electrodes of the array, configurations of electrode arrays according to embodiments of the invention may generate a strongly inhomogeneous electric field. Particles experiencing a positive DEP force may be pulled towards locations in the space in between neighboring electrodes where the width of the space is smaller, and thus where the electric field is stronger. The degree or extent to which they move to the smallest part of the space, also referred to as bottom of the funnel, depends on the strength of the positive DEP force, which in turns depends strongly on the characteristics and properties of the particles, e.g. cells, for example on their size, shape and/or composition. Particles, e.g. cells, undergoing negative DEP on the contrary, are directed towards the entrance of the funnel, or where the space in between neighboring electrodes is broadest, and thus where the electric field is weaker.

[0075] Hereinafter, the dielectrophoretic device according to the present invention will be described by means of different embodiments. The dielectrophoretic device will be described by means of the particles being cells. It has to be understood that this is not intended to limit the invention in any way and that the invention also applies for particles other than cells, such as e.g. microparticles, nanoparticles, solid dielectric particles, engineered particles or biological particles, as described above.

[0076] In all embodiments described hereinafter, the electrodes 1 may have a length which is at least 2 times larger than their average width. The longitudinal direction of the electrodes 1 is in their length direction.

[0077] According to a first embodiment, which is illustrated in Fig. 2, the dielectrophoretic device may comprise a radial array 10 of electrodes 1. With radial array 10 is meant that the electrodes 1 are arranged as segments of a circle extending from a center 4 of the circle to its circumference, thereby forming spaces 2 in between every two neighboring electrodes 1, the spaces 2 having a width which is decreasing along the longitudinal direction of the electrodes 1. The width of the space 2 between every two neighboring electrodes may be measured in a direction perpendicular to the average longitudinal direction of the neighboring electrodes, being a direction defined by the average of the longitudinal direction of the two neighboring electrodes. The space 2 in between neighboring electrodes 1 may also be referred to as funnel-shaped space or as funnel. The decreasing width of the space 2 in between every two neighboring electrodes 1 may be radially oriented to a center point of the radial array 10, as indicated by arrow 3. The electrodes 1 may have a length of between 50 μm and 1 mm. The average distance between neighboring electrodes 1 may be such that high electrical fields of between 10^3 V/m and 10^6 V/m may be obtained by applying acceptable voltages of between 1V and 10V. The average distance between neighboring electrodes 1 may be between 10 μm and 500 μm.

[0078] According to the present embodiment, the funnel-shaped space 2 in between neighboring electrodes 1 results from the radial arrangement of the electrodes 1. As a consequence of the changing width of the space 2 in between neighboring electrodes 1, the electric field generated when driving the electrodes 1 will vary along the longitudinal direction of the electrodes 1, i.e. in the direction indicated with reference number 3. More particularly, the electrical field will become stronger toward the center 4 of the electrode array 10.

[0079] Neighboring electrodes 1 in the array 10 may be energized or 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 neighboring electrodes, with n being higher than 2. For example, n may be chosen to be 3 or 4. n may kept low because in these cases less different signals are required and thus simpler electronics is needed to drive the dielectrophoretic device. According to the embodiment illustrated in Fig. 2, n may be 4 and neighboring electrodes 1 in the array 10 may be energized or driven with power signals, e.g. voltage signals, with a mutual phase difference of 90° in order to obtain twDEP. The phase differences of voltage signals applied to four of the electrodes 1 are indicated in Fig. 2. Because of these applied voltage signals, cells 5 present at the electrode array 10 will experience a tangential twDEP force. Simultaneously to the tangential twDEP force, the cells 5 will also experience a radial force due to the inhomogeneity

of the electric field. For cells 5 undergoing positive DEP, the radial force may be directed towards the center 4 of the array 10, where the electric field is stronger, as the electrodes 1 are closer to each other. As a result, the cells 5 will be propelled along a spiral trajectory, indicated by arrows 6 and 7. In other words, cells 5 undergoing positive DEP will follow a contracting spiral towards the center 4 of the array 10. The trajectory, and in particular, the degree of penetration into the 'spiral', will, for a fixed driving voltage amplitude, depend on the cell characteristics, such as shape, size and/or composition. Cells 5 undergoing negative DEP will be attracted towards the outside of the radial array 10, where the electric field is weaker, and will therefore follow an expanding spiral, i.e. the cells 5 will be propelled along a spiral trajectory in the opposite direction as indicated by arrows 6 and 7. For clarity reasons, this case is not illustrated in Fig. 2. As a consequence, cells 5 of different types may be collected on distinct zones of the substrate on which the electrode array 10 is formed.

[0080] The dielectrophoretic device may comprise driving means for driving or energizing the electrodes 1 of the array 10. The driving means may be adapted for driving the electrodes 1 with a mutual phase difference of 360°/n between every two neighboring electrodes 1, with n being higher than 2. According to embodiments of the invention, n may be 4 and the driving means may be adapted for driving the electrodes with a mutual phase difference of 90° between every two neighboring electrodes 1. The electrodes 1 of the array 10 may, according to embodiments of the invention, be driven by active matrix electronics, e.g. LTPS (low-temperature polycrystalline silicon) technology.

[0081] The dielectrophoretic device may furthermore comprise transport means 8 for transporting cells 5 toward the array 10 of electrodes 1. Several methods can be envisaged to transport the cells 5 onto a specific location of the electrode array 10. According to embodiments of the invention, the transport means 8 may comprise a linear array of parallel electrodes to transport the cells 5 by twDEP, as indicated in Fig. 2. This linear array 8 may also be referred to as conveyor array. The conveyor array 8 may comprise any suitable number of electrodes as is required to transport the cells 5 toward the electrode array 10. For example, the conveyor array 8 may comprise between at least 3 electrodes, and may, for example, comprise 20 electrodes.

[0082] According to embodiments of the invention, the dielectrophoretic device may comprise collection means 16 for collecting cells 5 (not shown in Fig. 2; however, illustrated in the embodiment of Fig. 3). The collection means 16 may comprise collection channels, e.g. microfluidic collection channels. Such channels 16 can, for example, be placed adjacent the electrode array 10. According to embodiments of the invention, the collection channels 16 may comprise additional electrodes for performing impedance measurements. Such additional electrodes may, for example, form particle or cell counters sometimes called Coulter counters to count the cells 5 collected in each of the collection channels 16. In case of a large number of channels, active matrix electronics (based on large area electronics, e.g., LTPS technology) can be used to provide the readout electronics to perform the impedance measurements. According to embodiments of the present invention, the same active matrix electronics may also be used to drive the electrodes 1 of the electrode array 10 of the dielectrophoretic device.

[0083] The radial arrangement of the electrodes 1 in the array 10 in the dielectrophoretic device according to the first embodiment of the invention provides an interaction distance of the cells 5 with respect to the electrodes 1 in the array 10 in the order of millimeters or even centimeters while maintaining a compact size of the dielectrophoretic device in the order of, for example, 100 mm^2. Because of the high interaction distance achievable with the radial design, the dielectrophoretic device according to the first embodiment may be able to resolve even small variations in the dielectric properties of the cells 5.

[0084] For example, the device according to the first embodiment of the invention may be used for the following experiment. The experiment may be started with a homogeneous distribution of particles 5, e.g. cells. Then the device is turned on by applying a voltage signal to the electrodes 1 as described above. The distribution of particles in the device can be monitored by taking images of the device at certain time intervals (e.g. 1 s) or by recording a video. The particles 5, e.g. cells will start to rotate but particles 5, e.g. cells of different types will follow different trajectories. Video processing can be used in real time to detect when a fractionation, i.e. separation in sub-groups between different types of particles 5, e.g. cells is visible. At that point the assay can be stopped and the device can be turned off. By means of suitable software, particles 5, e.g. cells present in each of the subgroups can be counted and statistics can be performed. Alternatively, various populations or sub-groups can be examined e.g. by means of a microscope by a pathologist. If necessary, the various populations or sub-groups can be fixed to a slide and stained with standard histochemical techniques to facilitate identification.

[0085] According to a second embodiment of the invention, the dielectrophoretic device may comprise a linear array 10 of funnel-shaped electrodes 1, also referred to as triangular-shaped electrodes. This is illustrated in Fig. 3. The electrodes 1 may have a length of between 50 μm and 1 mm. The average distance between neighboring electrodes 1 may be such that high electrical fields of between 10^3 V/m and 10^6 V/m may be obtained by applying acceptable voltages of between 1V and 10V. The average distance between neighboring electrodes 1 may be between 10 μm and 500 μm.

[0086] According to the second embodiment, the funnel-shaped space 2 in between neighboring electrodes 1 results, differently from the first embodiment, from the

shape of the electrodes 1. Similarly to the first embodiment, as a consequence of the changing width of the space 2 in between neighboring electrodes 1, i.e. a width which is decreasing in a longitudinal direction of the electrodes, the electric field generated when driving the electrodes 1 will vary along the longitudinal direction of the electrodes 1. More particularly, the electrical field will become stronger toward the location in the array 10 where the width of the electrodes 1 is the highest and thus where the electrodes 1 are closest together, in the example given at the top 9 of the electrode array 10.

[0087] Similar to the first embodiment, every two neighboring electrodes 1 in the array 10 are driven or energized with voltage signals which are phase-shifted by 90° with respect to each other, as indicated in Fig. 3, in order to obtain twDEP. Therefore, the dielectrophoretic device may comprise driving means which may be adapted for driving the electrodes 1 with a mutual phase difference of 90° between every two neighboring electrodes 1. In general, the driving means may be adapted for driving the electrodes 1 with a mutual phase difference of 360°/n between every two neighboring electrodes 1, with n being higher than 2. According to embodiments of the invention, the electrodes 1 of the array 10 may be driven by active matrix electronics such as e.g. LTPS (low-temperature polycrystalline silicon) technology.

[0088] Under the influence of twDEP (indicated by arrow 12 in Fig. 3), cells 5 are transported along the electrode array 10. Simultaneously to the lateral twDEP force, the cells 5 will experience a second force substantially perpendicular to the twDEP force and due to the inhomogeneity of the electrical field in between every two neighboring electrodes 1. For cells 5 undergoing positive DEP, the second force is directed towards the location where the electrical field is the strongest, in the example given towards the top 9 of the electrode array 10. For cells 5 undergoing negative DEP, the second force is directed towards the location of the electrode array 10 where the electrical field is weaker, in the example given, towards the bottom 11 of the electrode array 10. As a result of the twDEP and the second force perpendicular to the twDEP force and depending on the type of cell 5, the trajectory of the cell 5 may, for example, be indicated by arrows 13 (cells 5 undergoing strong positive DEP), 14 (cells 5 undergoing strong negative DEP) and 15 (cells 5 undergoing weak positive DEP).

[0089] Similar to the dielectrophoretic device described in the first embodiment, the dielectrophoretic device according to the second embodiment may comprise transport means 8 for transporting cells 5 toward the array 10 of electrodes 1 (not shown in Fig. 3). Several methods can be envisaged to transport the cells 2 onto a specific location of the electrode array 10. According to embodiments of the invention, the transport means 8 may comprise a linear array of substantially parallel electrodes to transport the cells 5 by twDEP. This linear array 8 may also be referred to as conveyor array. The conveyor array 8 may comprise any suitable number of electrodes as is required to transport the cells 5 toward the electrode array 10. For example, the conveyor array 8 may comprise at least 3 electrodes, and may, for example, comprise 20 electrodes.

[0090] According to embodiments of the invention, the electrode array 10 can extend over a relatively long distance, i.e. in the order of millimeters or even centimeters. Due to such long interaction distance, even small variations in the dielectric properties of the cells 5 can be resolved. Cells 5 of different types, i.e. with different dielectric properties, can then be trapped onto characteristic zones on the dielectrophoretic device.

[0091] Alternatively, the dielectrophoretic device may comprise collection means 16 for collecting cells 5. For example, different cell sub-populations, or cells 5 with different dielectric properties, may be sorted into subsequent microfluidic collection channels 16, as illustrated in Fig. 3. Such channels 16 can, for example, be placed adjacent the electrode array 10. According to embodiments of the invention, the collection channels 16 may comprise additional electrodes (not shown in the figure) for performing impedance measurements. Such additional electrodes may, for example, form Coulter counters to count the cells 5 collected in each of the collection channels 16. In case of a large number of channels, active matrix electronics (based on large area electronics, e.g., LTPS technology) can be used to provide readout electronics for performing the impedance measurements. According to embodiments of the present invention, the same active matrix electronics may also be used to drive the electrodes 1 of the electrode array 10 of the dielectrophoretic device.

[0092] In a second aspect of the invention, a method is provided for manipulating particles 5 using a dielectrophoretic device according to embodiments of the present invention. The method comprises applying voltage signals to the electrodes 1 with a mutual phase difference of 360°/n between every two neighboring electrodes 1, with n being higher than 2. As described above, applying voltage signals with a mutual phase difference of 360°/n between every two neighboring electrodes 1 is performed to obtain twDEP. For example, according to embodiments of the invention, n may be 4 and neighboring electrodes 1 may be driven with a mutual phase difference of 90°. Under the influence of twDEP the cells 5 are moved over the electrode array 10 and, based on their properties, e.g. size and/or dielectric properties are differently manipulated. For example, according to embodiments of the invention, the particles 5 may be separated and collected, e.g. sorted, in collection means 16 where they can be counted or treated. According to other embodiments, the particles 5 may be moved towards a location, such as a electric field processing region (see further), in the array 10 where the electric field is the highest and where electric lysis or electroporation of cells 5 can be performed.

[0093] According to embodiments of the invention, the method for manipulating particles 5 may furthermore

comprise transporting the particles 5 towards the array 10 of electrodes 1. This may be done by transport means 8. Several methods can be envisaged to transport the particles 5 to a specific location of the electrode array 10. According to embodiments of the invention, the transport means 8 may comprise a linear array of parallel electrodes to transport the particles 5 by twDEP. The linear array of parallel electrodes may comprise any suitable number of electrodes as is required to transport the particles 5 toward the electrode array 10.

[0094] Experiments have been performed to demonstrate the efficient working of the dielectrophoretic device and method according to embodiments of the present invention. These experiments were performed using a suspension of cells 5 of a single type. Nonetheless, differences due to individual cell variations could readily be detected.

[0095] In a first experiment, an electrode array 10 similar to the one described in the second embodiment was used. This configuration allowed verification that cells 5 undergoing positive DEP are pulled towards the location on the array where the electric field is the highest, i.e. to the top 9 of the electrode array 10 as illustrated in Fig. 3, while cells 5 undergoing negative DEP are pulled towards locations on the electrode array 10 where the electric field is the smallest, i.e. to the bottom 11 of the electrode array 10 as illustrated in Fig. 3. Fig. 4 illustrates the principle of the dielectrophoretic device according to embodiments of the invention for mouse cancer cells 5 undergoing positive DEP. For this experiment, a signal with a voltage of 3V and a frequency of 1 MHz was applied to the electrodes 1 surrounding the cells 5 present in the space 2 in between the electrodes 1. In order to have twDEP, the frequency should be such that the imaginary part of the clausius-mossotti (CM) factor, which indicates changes in dielectric properties of the particles, is different from zero. Suitable ranges of frequencies thus depend on the type of particles 5, e.g. cells, and the conductivity of the medium in which the particles 5, e.g. cells are present. In general, the imaginary part of the CM factor peaks around the DEP cross-over frequency. For conductivities of between 100 μS/cm and 1 mS/cm a suitable frequency range may be between 10 kHz and 5 MHZ. It has to be noted that it is difficult to obtain twDEP at high conductivities. Therefore, preferably particles 5, e.g. cells are suspended in a low conductivity medium.

[0096] For the purpose of clarity, the cells 5 that were looked at are surrounded by a white circle. The electrodes 1 were driven with a mutual phase difference of 90° between neighboring electrodes 1. It can be seen from the subsequent figures (a), (b) and (c) of Fig. 4 that the cells 5 are moved along the longitudinal direction of the electrodes 1. The cells 5 are pulled towards locations in the space 2 between two neighboring electrodes 1 where the width is smallest, i.e. where the electric field is the highest.

[0097] In a further experiment, a radial array 10 of electrodes 1 according to the first embodiment was used with mouse cancer cells 5. The experiment is illustrated in Fig. 5 which shows successive steps 1 to 4 in the movement of mouse cancer cells 2 in a radial electrode array 10. Several important points could be verified with the dielectrophoretic device. Cells 5 move in a circle (indicated with arrow 17) when the electrodes 1 in the array 10 are energized or driven with twDEP voltage signals as described above. The movement was observed to be fast, i.e. cells 5 close to the center 4, for example less than 10 μm from the center 4, of the radial array 10 (indicated by circles) can do one revolution in 10 à 20 seconds when the electrodes 1 are driven at a voltage of 2V which may lead to an electric field of about 400 kV/m for a distance between the electrodes 1 of about 5 μm, whereas cells 2 located further away from the center 5 of the radial array move slower. For example, for cells 5 which are 50 μm away from the center 4, about 1 minute is required to move them toward the center 4.

[0098] The movement of the cells 5 was observed to depend strongly on the properties of the cells 5, such as their size, shape and/or composition. Changes in the dielectric properties of the cells 5 also had an effect on the cell trajectory. For example, in several occasions cells 5 were observed to invert the sense of rotation immediately prior to lysis. This is due to the fact that a strong electric field disrupts the cell membrane. This dramatically changes the dielectric properties of the cell (also expressed by means of the Clausius-Mossotti (CM) factor (see above)). If the imaginary part of the CM factor changes sign, the rotation sense is inverted.

[0099] The direction of the rotation of the cells 5 (indicated with arrow 17) can be inverted by varying the relative phase of the applied voltage signals or, alternatively, by varying the frequency of the signals across the DEP cross-over frequency, i.e. the frequency where a cell 5 makes the transition from negative to positive DEP.

[0100] The existence of a force substantially perpendicular to the twDEP force, also referred to as perpendicular DEP component, which is due to configuration of the electrode array 10 according to embodiments of the invention, was also verified during this experiment. Although spiral trajectories (both expanding and contracting) could be observed for short periods of time, the perpendicular component was in general too weak to lead to a consistent spiral trajectory over several revolutions when using cells. To overcome this problem, the dimensions of the device may be optimized.

[0101] Consistent spiral trajectories over several revolutions could be observed with the dielectrophoretic device according to embodiments of the invention using micron-sized latex beads (see Fig.6). By varying the relative phases of the applied voltage signals, both expanding and contracting spirals could be induced. The left part of Fig. 6 shows the situation at 0 seconds while the right part of Fig. 6 shows the situation after 70 seconds. Fig. 6 illustrates the case for an expanding spiral, indicated by arrow 18. At t=0 seconds, the beads are evenly spread over the device; at t=70 seconds, the beads are moved

away from the center 4 of the radial array towards the outside thereof.

[0102] The dielectrophoretic device according to embodiments of the invention can be used to separate cells 5, or in general to separate particles 5, on the basis of their dielectric properties, e.g. to collect or sort such cells or particles. As already described above, particles, e.g. cells, can differ in size, shape and/or composition, which will lead to different dielectric properties and thus to different dielectrophoretic responses. For example, cell separation or sorting on the basis of cell type has important applications, such as the isolation of stem cells from blood or bone marrow for regenerative therapy, or the isolation of circulating tumor cells from blood, so that they can be further examined in detail by e.g. a pathologist.

[0103] Often, the differences in dielectric properties between the particles 5, e.g. cells that are to be separated are small. An advantage of the dielectrophoretic device according to embodiments of the present invention compared to other separation or sorting methods based on DEP is that the interaction time of the particles 5, e.g. cells, with the electrical field is much longer in case of the device according to embodiments of the invention, i.e. may be from 10s up to several minutes. Hence, even particles 5, e.g. cells, with very small differences in dielectric properties can be separated.

[0104] The application area of the dielectrophoretic device according to embodiments of the invention can be expanded greatly in cases where the differences in the dielectrophoretic properties of the particles 5, e.g. cells can be artificially enhanced, e.g. by labeling specific cells with polymeric beads. This allows particles 5, e.g. cells, to be sorted on the basis of the presence of certain proteins on the membrane. This approach could be useful in clinical applications, such as stem cell enrichment and tumor cell isolation, but also in biotech applications such as protein engineering. For instance, libraries of (genetically altered) cells can be screened to develop peptide and antibody affinity reagents.

[0105] The dielectrophoretic device according to embodiments of the invention can also be used in electrical field lysis or electroporation of cells 5.

[0106] Cell lysis, i.e. breaking open a cell membrane to release sub-cellular material, is a key step in biochemical and biomedical assays based on the analysis of proteins, nucleic acids (DNA and RNA) or organelles. In some cases, a total homogeneous lysate, i.e. contents released from a lysed cell, is sufficient for the analysis. Often, however, sub-cellular fractionation is necessary and complete homogenization of cellular components should be avoided. The requirements for a device suitable for cell lysis include speed, high efficiency, selectivity (e.g. breaking down cell membranes while protecting organelles) and integration with other micro fluidic devices.

[0107] Conventionally, cells 5 are lysed by either chemical or mechanical means. The cell membrane consists of a lipid double-layer, which can be dissolved by buffers containing detergents. In general, such buffers also dissolve the organelle membranes and are therefore not suitable for assays where organelle integrity is critical. Moreover, additional steps are needed to introduce and/or remove the lysis buffer. Mechanical breakdown of the cell membrane can be induced by shear stress, wear or by applying ultrasound (sonication). Such methods also do not generally provide the discrimination needed for organelle analysis and are difficult to integrate into microfluidic systems. Thermal lysis can also be used but is only compatible with nucleic acids analysis because proteins are denatured by heat.

[0108] Recently, electric field lysis has attracted considerable attention as it enables sub-cellular fractionation without the complications of chemical and mechanical lysis and can be easily integrated into microfluidic systems. In electric field lysis, an external electric field disrupts the cell membrane by inducing changes in the trans-membrane potential. Depending on the voltage applied, the membrane can be disrupted permanently (lysis) or reversibly (electroporation). In the last case, transient pores are created in the membrane, either to release intracellular material or to introduce macromolecules such as DNA or drugs. By exploiting differences in the trans-membrane potentials of the cell membrane (-60 mV) and organelle membranes (-160 mV for e.g. mitochondria) cells 5 can be lysed with minimal impact on organelles. The applied voltage can be a pulsed DC voltage or an AC voltage to avoid electrolysis and gas formation.

[0109] The dielectrophoretic device according to embodiments of the invention has several advantages for electric field lysis. The principle of cell lysis will be described by means of a dielectrophoretic device wherein the electrodes 1 of the array 10 are arranged radially as described with respect to the first embodiment (see Fig. 7). However, it has to be understood that also the dielectrophoretic device according to the second embodiment of the invention can be used for electric cell lysis.

[0110] Due to the decreasing width of the space 2 in between neighboring electrodes 1, the magnitude of the electrical field created by the electrodes 1 increases gradually towards the center 4 of the electrode array 10 as illustrated in Fig. 2 and Fig. 7. When operating under positive (attractive) DEP conditions, the cells 5 will experience a radial force directed towards the center 4 of the array 10. As they move towards the center 4 of the array 10, the cells 5 are exposed to a stronger and stronger electric field until they arrive in the high field region (indicated with reference number 19), also referred to as lysis region, and are eventually lysed. Lysed cells are indicated in Fig. 7 with reference number 20. Electric lysis of cells 5 using the dielectrophoretic device according to embodiments of the invention may have the following advantages:

[0111] Cells 5 can be collected over a large area and transported to the processing region such as a lysis region 19, resulting in high efficiency.

[0112] To create high electrical fields on the order of

10^6 V/m with acceptable voltage signals, i.e. with voltage signals of between 1V and 10 V, it is necessary to have electrodes 1 close together. For example, for a voltage signal of 1V the distance between neighboring electrodes may be 1μm and for a voltage signal of 10V the distance between neighboring electrodes may be 10 μm. This can have two negative effects for the device. A first one is that the chance of electrolysis may increase because the resistance between the electrodes 1 is low and a second one is that the capacitance may increase which results in higher power consumption. Unlike conventional structures for electric lysing, such as e.g. castle electrodes, the configuration according to the first embodiment of the invention only has electrodes 1 close together near the center 4 of the radial array 10. Similarly, for the dielectrophoretic device according to the second embodiment of the invention, because of the funnel-shape of the electrodes 1, the electrodes 1 are only close together at one end, in the example of Fig. 3 at the top 9 of the array 10. Hence, the average electrode distance of the configurations according to embodiments of the invention may be larger than in prior art devices, the overall capacitance may be lower and therefore lower power may be required. The larger average distance also increases the resistance and therefore reduces the likelihood of electrolysis.

[0113] The proper voltage for cell lysis is obtained automatically, and does not have to be adjusted for different types of cells 5. Once the cell membrane is lysed, the intracellular material is released. The electric field amplitude at the location of the lysis region 19 will not be sufficient to disrupt organelles membranes, which will therefore remain intact. With the configurations according to embodiments of the invention, a determination is made of the position where lysing of individual cells 5 occurs. In cases of radial arrays 10, the radial coordinate where lysing occurs defines the electric field that is required. By measuring this parameter for all cells 5 in a population, a histogram of "Electrical field required for lysing" versus "number of cells in the population" can be constructed. This is a very interesting plot as it is indicative of the viability of a cell population. Measuring the radial coordinate where lysing occurs may be done optically, for example with a microscope and a camera. Other approaches may also be possible, e.g. by means of integrated sensor electrodes.

[0114] In a further aspect, the present invention also provides a system controller 30 for use in dielectrophoretic device for controlling driving of the electrodes 1 of an array 10 in a dielectrophoretic device according to embodiments of the present invention. The system controller 30, which is schematically illustrated in Fig. 8, may comprise a control unit 31 for controlling driving means 32 for applying a voltage signal to the electrodes 1 with a mutual phase difference of 360°/n between every two neighboring electrodes 1, with n being higher than 2. According to embodiments of the invention, n may be 4 and the controller may be adapted for controlling driving means 32 for applying a voltage signal to the electrodes 1 with a mutual phase difference of 90° between every two neighboring electrodes 1

[0115] 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 microfluidic system, 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.

[0116] The method described above according to embodiments of the present invention may be implemented in a processing system 40 such as shown in Fig. 9. Fig. 9 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. 9. The various elements of the processing system 40 may be coupled in various ways, including via a bus subsystem 45 shown in Fig. 9 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.

[0117] 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, pro-

vides 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 fiber optics, including the wires that comprise a bus within a computer.

[0118] 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 particles (5), the device comprising:

- an array (10) of electrodes (1), there being a space (2) in between two neighboring electrodes (1), the array (10) of electrodes (1) being formed such that the space (2) in between the two neighboring electrodes (1) has a width which is decreasing in a longitudinal direction of the electrodes (1), and
- driving means (32) adapted for driving the electrodes (1) of the array (10) to generate a traveling wave dielectrophoretic force to be exerted on the particles (5).

2. A dielectrophoretic device according to claim 1, wherein the array (10) of electrodes (1) is a one-dimensional array.

3. A dielectrophoretic device according to claim 1 or 2, wherein the direction of decrease of the width of the space (2) in between two neighboring electrodes (1) is oriented in the direction of the average longitudinal direction of the neighboring electrodes.

4. A dielectrophoretic device according to any of the previous claims, wherein the electrodes (1) are funnel-shaped.

5. A dielectrophoretic device according to any of claims 1 to 3, wherein the array (10) of electrodes (1) is a radial array in which the electrodes (1) are arranged as segments of a circle extending from a center of the circle to its circumference.

6. A dielectrophoretic device according to any of claims 1 to 3, wherein the array (10) of electrodes (1) is a linear array and the electrodes (1) are funnel-shaped.

7. A dielectrophoretic device according to any of the previous claims, wherein the driving means (32) is adapted for driving the electrodes (1) with a mutual phase difference of 360°/n between two neighboring electrodes (1), with n being higher than 2.

8. A dielectrophoretic device according to claim 7, wherein the driving means (32) is adapted for driving the electrodes (1) with a phase difference of 90° between two neighboring electrodes (1).

9. A dielectrophoretic device according to any of the previous claims, furthermore comprising transport means (8) for transporting particles (5) toward the array (10) of electrodes (1).

10. A dielectrophoretic device according to claim 9, wherein the transport means (8) is formed by a linear array of parallel electrodes.

11. A dielectrophoretic device according to any of the previous claims, furthermore comprising collection means (16) for collecting particles (5).

12. A dielectrophoretic device according to claim 11, wherein the collection means (16) is formed by an array of collection channels.

13. A dielectrophoretic device according to claim 12, wherein the collection channels are microfluidic collection channels.

14. A dielectrophoretic device according to any of the previous claims, wherein the collection means (16) furthermore comprises impedance measurement means for determining an amount of particles (5) in the collection means (16).

15. A dielectrophoretic device according to any of the previous claims, wherein the particles (5) are cells, solid dielectric particles, engineered particles or biological particles.

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

17. Use of the dielectrophoretic device according to any of claims 1 to 15 for cell lysis or cell electroporation.

18. Method for forming a dielectrophoretic device for manipulation of particles (5), the method comprising:

providing an array (10) of electrodes (1) with a space (2) in between two neighboring electrodes (1) such that the array (10) of electrodes (1) is formed such that the space (2) in between the two neighboring electrodes (1) has a width which is decreasing in a longitudinal direction of the electrodes (1) and
providing driving means (32) adapted for driving the electrodes (1) of the array (10) to generate a traveling wave dielectrophoretic force to be exerted on the particles (5).

19. Method according to claim 18, wherein providing an array (10) of electrodes (1) is performed such that the array (10) is a one-dimensional array.

20. Method according to claim 18 or 19, wherein providing an array (10) of electrodes (1) is performed such that the direction of decrease of the width of the space (2) in between two neighboring electrodes (1) is oriented in an average longitudinal direction of the two neighboring electrodes.

21. Method according to any of claims 18 to 20, wherein providing an array (10) of electrodes (1) is performed such that a radial array (10) is formed in which the electrodes (1) are arranged as segments of a circle extending from a center of the circle to its circumference.

22. Method according to any of claims 18 to 20, wherein providing an array (10) of electrodes (1) is performed such that a linear array (10) is formed with electrodes (1) having a funnel-shape.

23. Method according to any of claims 18 to 22, furthermore comprising providing transport means (8) for transporting particles (5) toward the array (10) of electrodes (1).

24. Method according to any of claims 18 to 23, furthermore comprising providing collection means (16) for collecting particles (5).

25. Method according to claim 24, furthermore comprising providing impedance measurement means to the collection means (16) for determining an amount of particles (5) in the collection means (16).

26. Method for manipulating particles (5) using a dielectrophoretic device comprising an array (10) of electrodes (1) wherein the space (2) in between two neighboring electrodes (1) has a decreasing width in a longitudinal direction of the electrodes (1), the method comprising:

applying a voltage signal to the electrodes (1) with a mutual phase difference of 360°/n between two neighboring electrodes (1), with n being higher than 2.

27. Method according to claim 26, wherein n is 4 and a voltage signal is applied to the electrodes (1) with a phase difference of 90° between two neighboring electrodes (1).

28. Method according to claim 26 or 27, furthermore comprising transporting the particles (5) towards the array (10) of electrodes (1) for allowing them to be manipulated.

29. Method according to any of claims 26 to 28, furthermore comprising collecting particles (5) in a collection means (16) after manipulation of the particles (5).

30. Method according to claim 29, furthermore comprising counting the amount of particles (5) in the collection means (16).

31. Method according to any of claims 26 to 30, wherein manipulating particles (5) comprises separating particles (5) based on a difference in dielectric properties.

32. Method according to any of claims 26to 30, wherein manipulating particles (5) comprises lysis or electroporation of cells (5).

33. Use of the method according to any of claims 26 to 32 in molecular diagnostics, biological sample analysis or chemical sample analysis.

34. Use of the method according to any of claims 26 to 30 for particle separation.

35. Use of the method according to any of claims 26 to 30 for cell lysis or cell electroporation.

36. A controller (30) for controlled driving of electrodes (1) of an array (10) wherein the space (2) in between two neighboring electrodes (1) has a decreasing width in a longitudinal direction of the electrodes (1), the controller (30) comprising: a control unit (31) for controlling a driving means (32) for applying a voltage to the electrodes (1) with a mutual phase difference of 360°/n between two neighboring electrodes

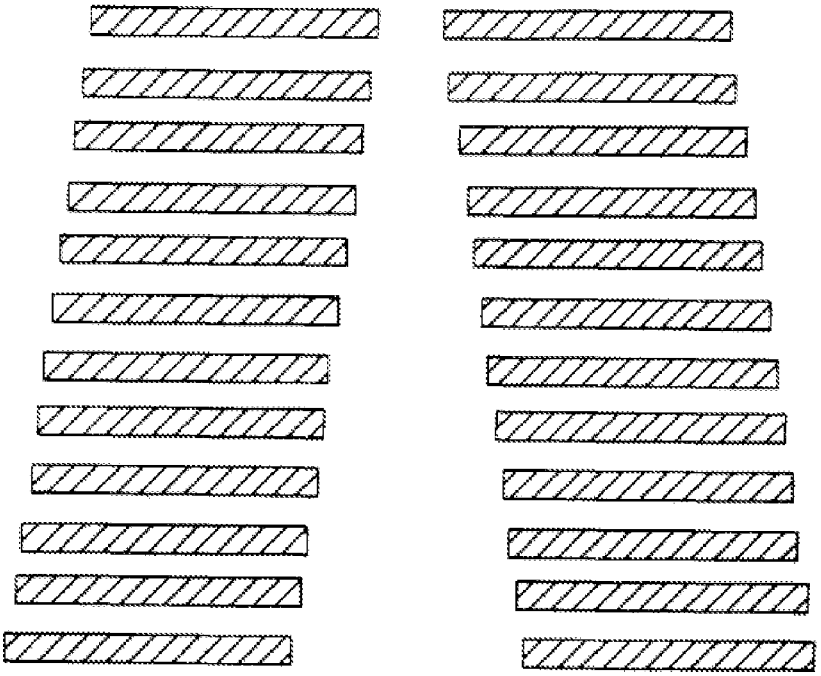
(1), with n being higher than 2.

37. A controller according to claim 36, wherein n is 4 and a voltage signal is applied to the electrodes (1) with a phase difference of 90° between two neighboring electrodes (1).

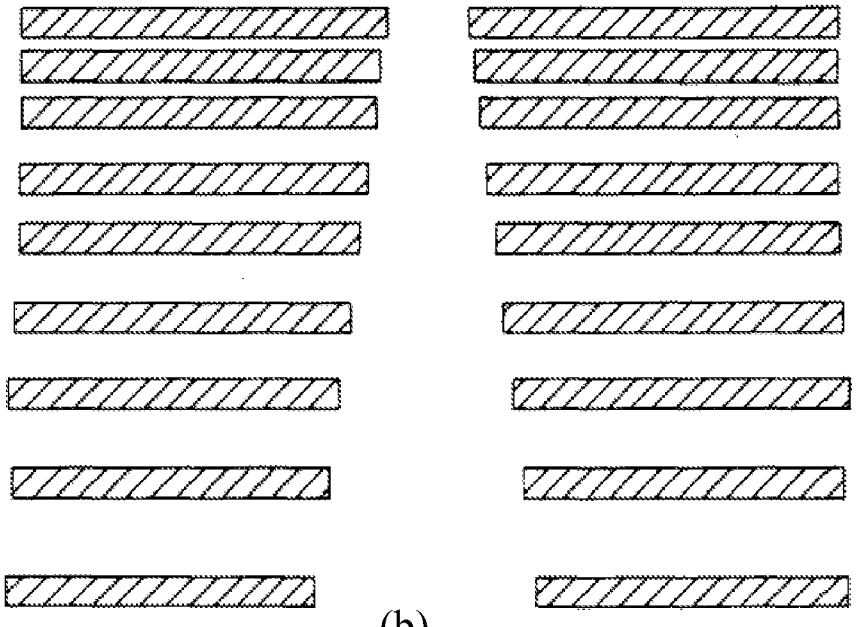
38. Computer program product for performing, when executed on a computing means, a method as in any of claims 26 to 32.

39. A machine readable data storage device for storing the computer program product of claim 38.

40. Transmission of the computer program product of claim 38 over a local or wide area telecommunications network.



(a)



(b)

FIG. 1 PRIOR ART

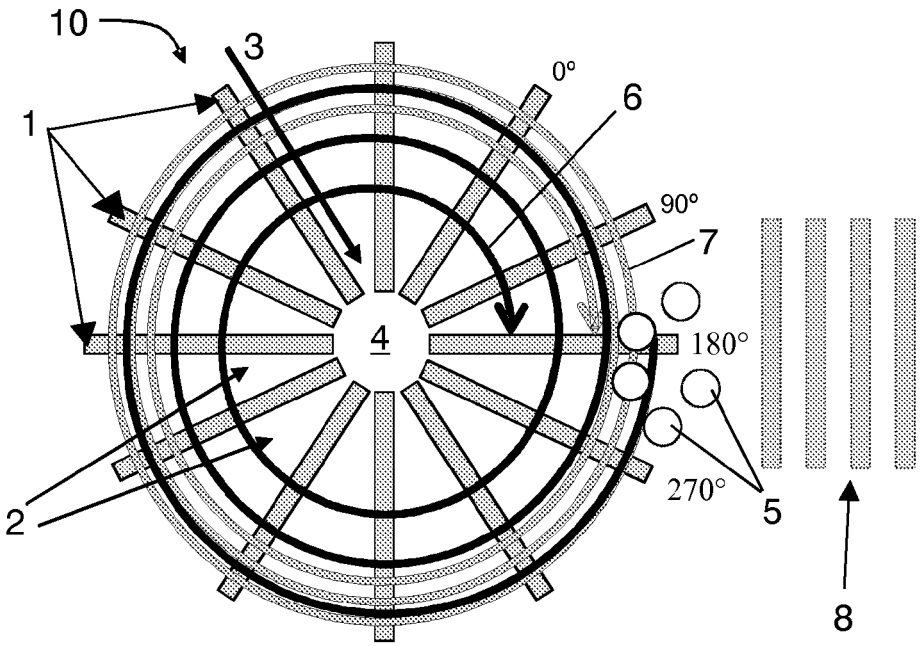


FIG. 2

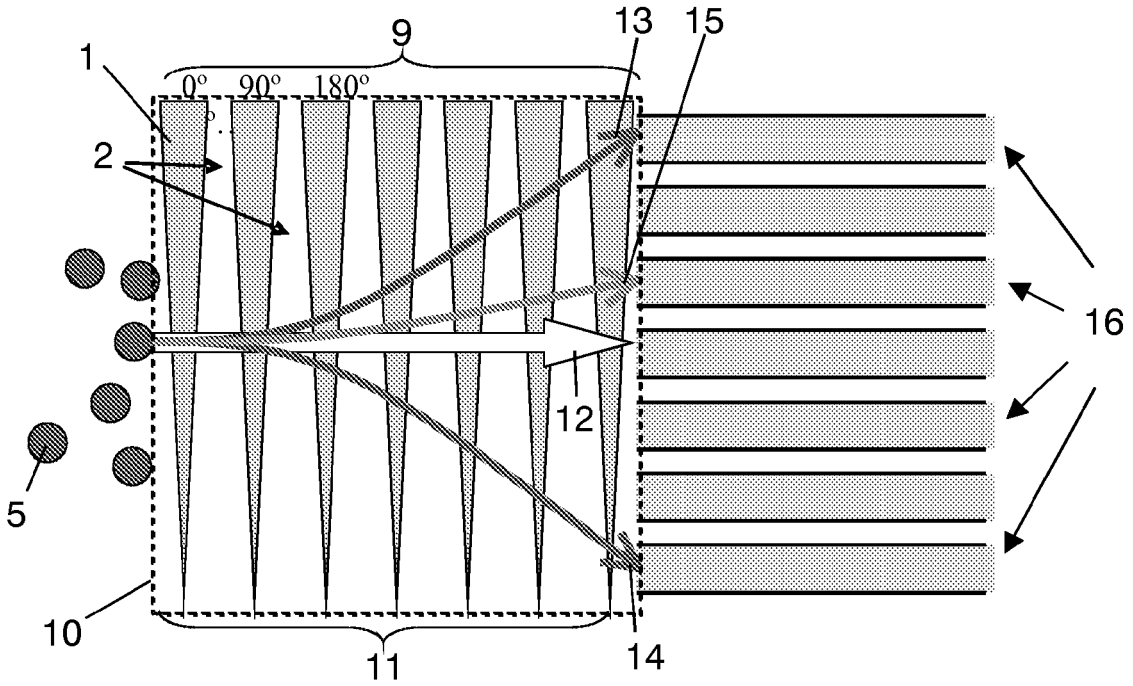


FIG. 3

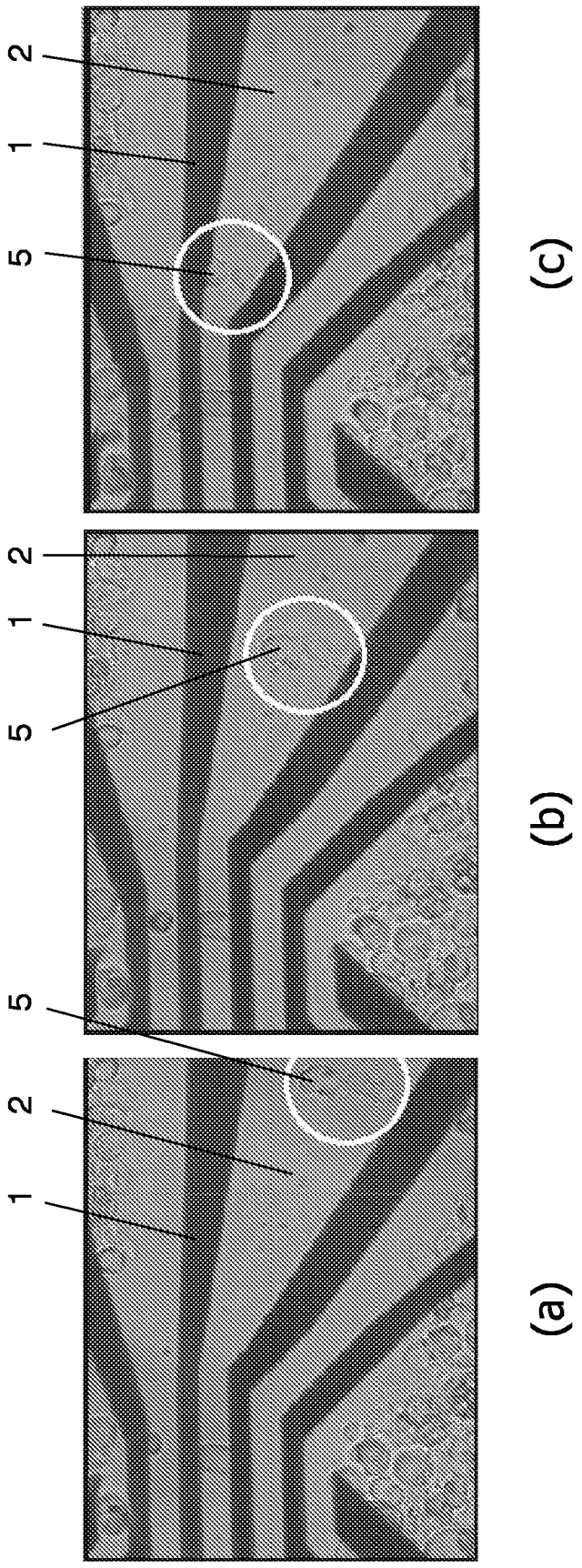


FIG. 4

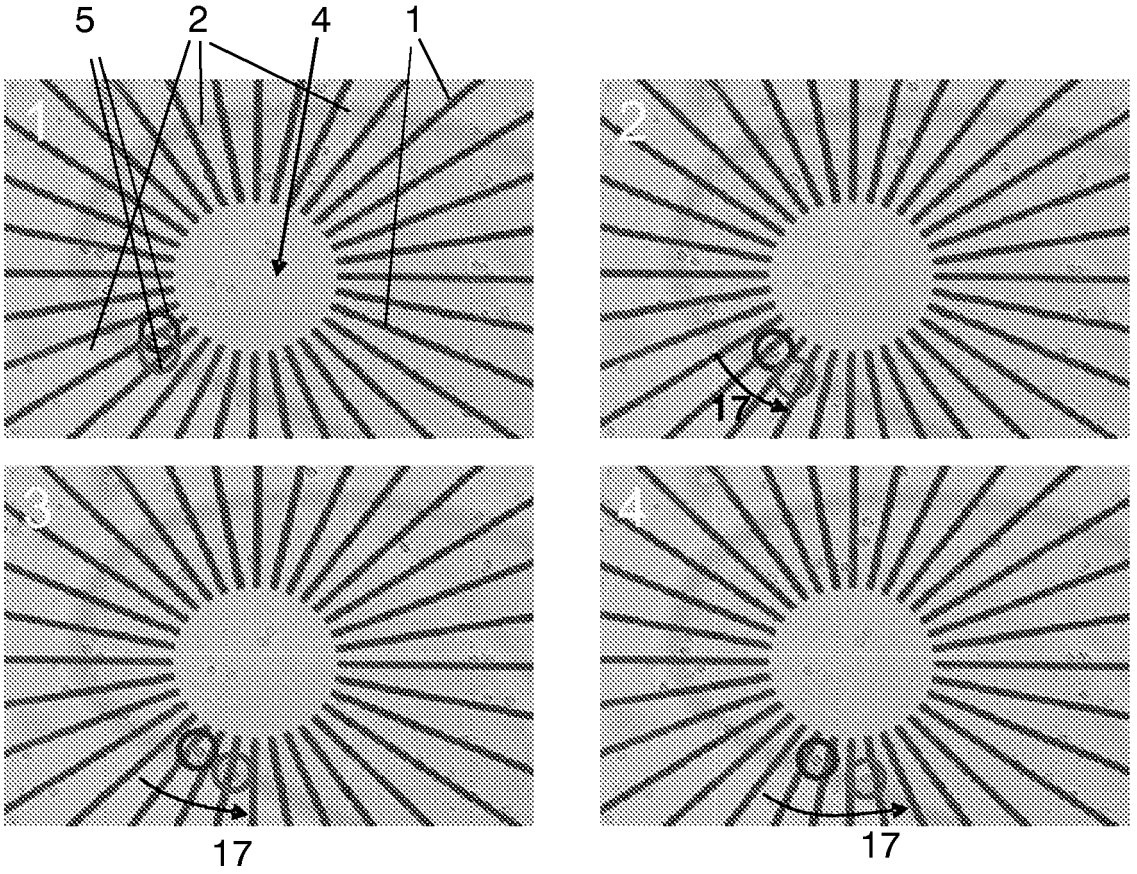


FIG. 5

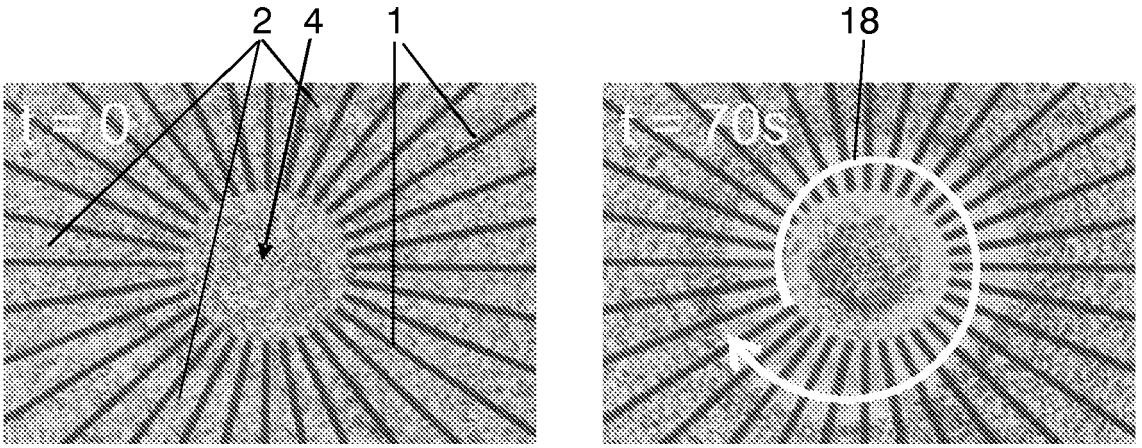


FIG. 6

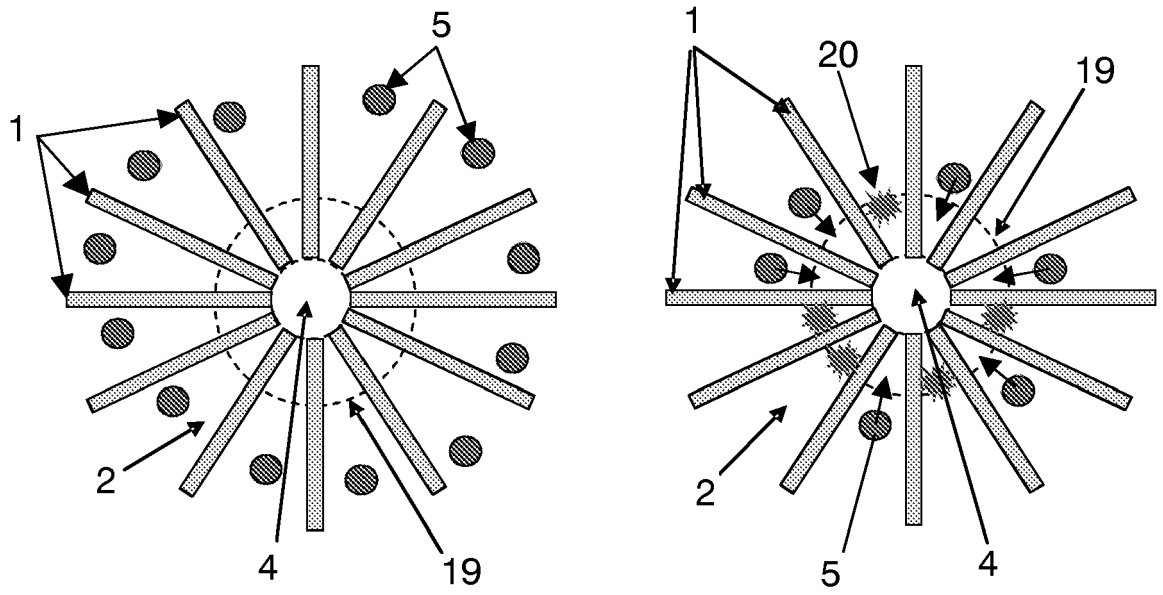


FIG. 7

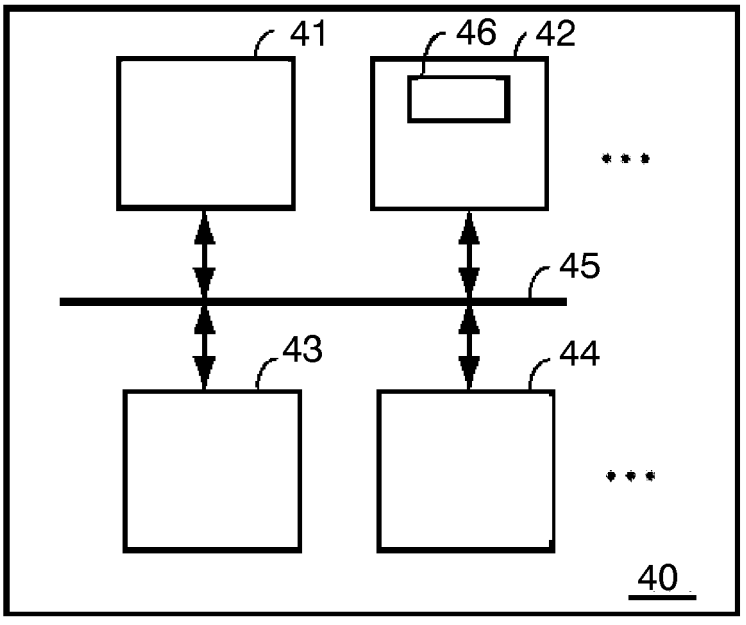


FIG. 9

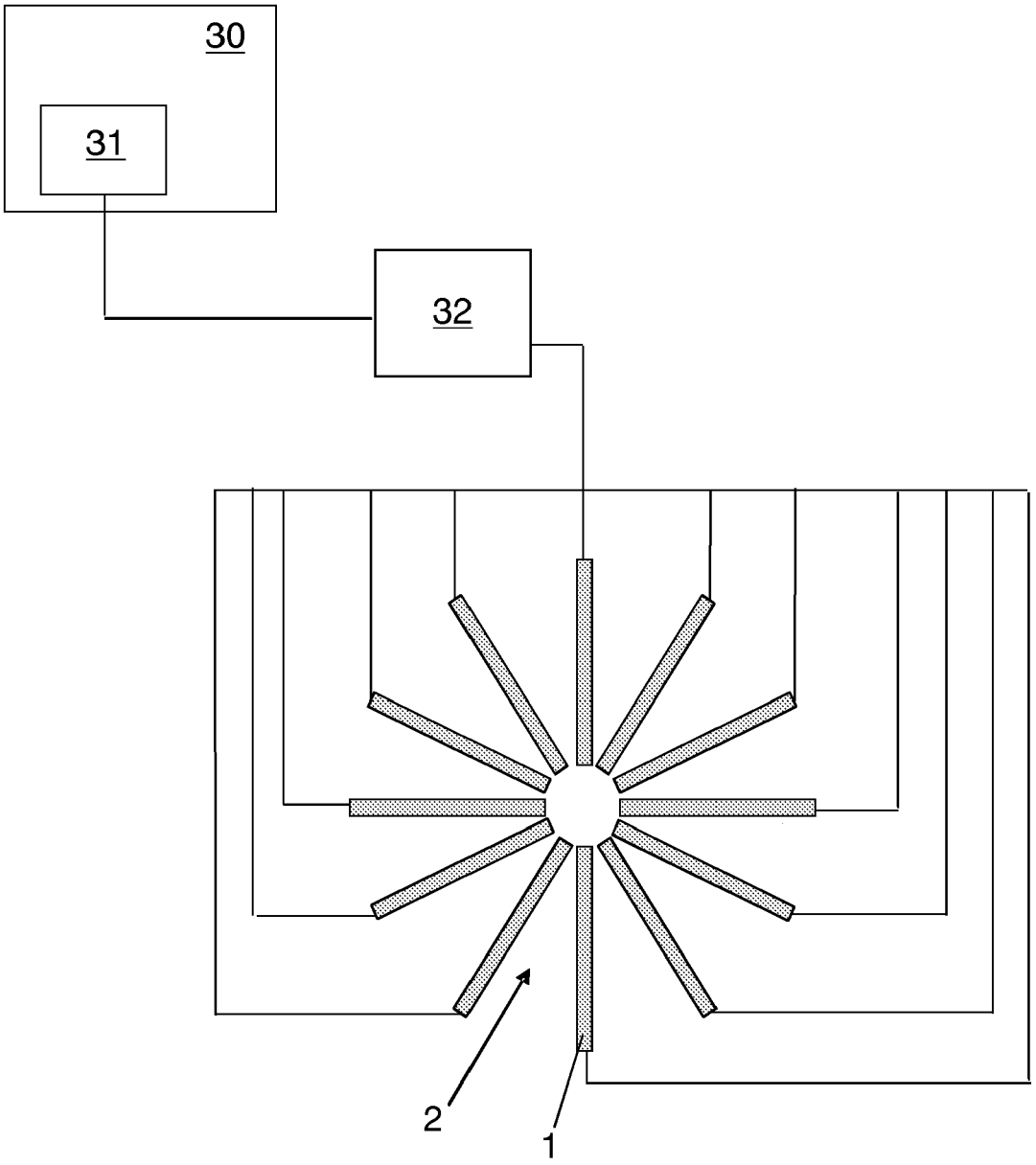


FIG. 8

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EUROPEAN SEARCH REPORT

Application Number
EP 07 11 5462

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 6 149 789 A (BENECKE WOLFGANG [DE] ET AL) 21 November 2000 (2000-11-21) * column 3, line 66 - column 4, line 3; figure 7 *	1-36	INV. B03C5/02 B03C5/00
X	US 2005/211557 A1 (CHILDERS WINTHROP D [US] ET AL) 29 September 2005 (2005-09-29) * paragraphs [0053], [0054] *	1-36	
X	US 6 596 143 B1 (WANG XIAO-BO [US] ET AL) 22 July 2003 (2003-07-22) * column 37, line 6 - line 11; figures 19a,19b *	1-36	
X	WO 99/17883 A (CALIFORNIA INST OF TECHN [US]) 15 April 1999 (1999-04-15) * figure 3a *	1-36	
D,A	EP 0 815 942 A (SCIENT GENERICS LTD [GB]) 7 January 1998 (1998-01-07) * abstract *	1-40	

TECHNICAL FIELDS SEARCHED (IPC)

B03C

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	28 February 2008	Demol, Stefan

CATEGORY OF CITED DOCUMENTS

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28-02-2008

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

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- EP 0815942 A **[0009] [0009] [0009]**