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(54) **Magnetic separation system comprising flexible magnetic pins and corresponding method**

Magnetisches Trennsystem mit flexiblen magnetischen Stiften und zugehöriges Verfahren

Système de séparation magnétique comportant des tiges magnétiques flexibles et procédé
correspondant

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Description

Field of the invention

[0001] The present invention belongs to the field of analytics, particularly the separation and/or isolation of biological materials such as nucleic acids or proteins in or from complex mixtures. Within that field, the present invention relates to magnetic separation.

Background of the invention

[0002] The separation of magnetic or magnetizable components such as magnetic particles on the basis of magnetic forces has been of considerable significance particularly in the field of analytics.

[0003] Magnetic particles can, for instance, be used as a binding support for biological materials such as proteins or nucleic acids. In an exemplary typical analytical setting, the magnetic particles are contacted with a liquid sample containing an analyte in a multiwell plate, under conditions that facilitate binding of the analyte to the magnetic particles. The latter can then be subsequently separated from the liquid by means of magnetic forces generated by magnetic pins. US 5,779,907, GB 2 300 258 A and EP 1 681 570 A2 disclose devices in which such magnetic pins are attached to a base plate, wherein the multiwell plate containing sample and magnetic particles is exposed to a magnetic field generated by the magnetic pins upon physical combination of the pin-bearing base plate with said multiwell plate. In order to invoke a significant magnetic field within the sample fluids, the magnetic pins are moved into close vicinity to the wells by means of being introduced into preadapted recesses in locations of the multiwell plate not containing any samples.

[0004] However, the coupling of the above-mentioned plates to each other gives rise to the following problem: When the magnetic pins are being placed into the preadapted recesses within the multiwell plate, tolerances with respect to size and position of the pins and recesses frequently lead to jamming of the system or breakage of the pins as the latter cannot be easily inserted into and/or removed from the recesses.

[0005] In the prior art, this problem has been tackled in various manners:

- The diameter of the recesses within the multiwell plate has been increased in relation to the diameter of the magnetic pins
- The above-mentioned tolerances have been controlled more strictly
- Deformability of the multiwell plate has been enhanced.

[0006] For instance, US 2006/0269385 A1 describes a control system for transferring a sample from a source

vessel to a target vessel. The system employs primary and secondary magnetic plates and relies on a relatively complex interaction of encased ferromagnetic pistons with energized electromagnets.

[0007] The present invention provides an alternative solution displaying several advantages.

Description of the invention

[0008] The present disclosure describes a magnetic separation plate including flexible or flexibly fastened magnetic or magnetizable pins. New methods and uses comprising this plate are further provided. According to the invention, which is defined by claim 1, the plate is part of magnetic separation system further comprising a multiwell plate. Also, one aspect of the invention is an analytical system for the processing and/or analysis of a sample, wherein the aforementioned magnetic separation system is a part of the analytical system. In a first aspect, the present disclosure is related to the following: A magnetic separation plate for use in methods employing magnetic particles, said magnetic separation plate comprising a support plate and magnetic pins in a predetermined geometrical arrangement, said magnetic pins having a fastening portion, an intermediate portion and a separation portion and being fastened to said support plate at their fastening portion, wherein said magnetic pins are individually displaceable at their separation portion.

[0009] The present invention features an advantageous possibility to establish reliable and automatable methods for magnetic separation, as the latter require the process of coupling a multiwell plate and the magnetic separation plate to be reversible.

[0010] Especially upon reduction of the size of a magnetic separation device or system, or the reduction of well diameter due to the presence of a higher number of wells in medium or high throughput systems, measures like widening the multiwell recesses or strictly controlling the production-caused tolerances in the recesses' diameter become considerably more difficult to achieve and thus less appropriate to remedy the technical problem set out supra.

[0011] The solution according to the present invention, on the other hand, is particularly useful in the context of striving to minimize the dimensions of separation devices in favor of enhancing sample throughput. Inherent flexibility and/or flexible fastening of the magnetic pins are not negatively affected by reducing the device's or system's size and therefore the distances between the distinct elements.

[0012] Multiwell plates with recesses of comparatively small diameters with relatively high tolerances may be used in the system according to the invention, which simplifies the production of such plates and reduces the respective costs.

[0013] Furthermore, mechanical stress exerted upon the magnetic pins due to the technical problem described

above is compensated for according to the present invention, thus increasing their stability and duration. Moreover, the flexibility and/or flexible fastening of the pins generally reduce the force that is required to insert them into the recesses of the multiwell plate.

[0014] In some of the alternative solutions to the technical problem mentioned above, the homogeneity and/or overall intensity of the magnetic field acting on the magnetic particles can be affected in a negative manner. For example, recesses that are significantly wider than the magnetic pins to be inserted inevitably lead to an increase of the distance between pin and sample, thus decreasing the magnetic force the particles are exposed to. Further, the tolerances in the positions of the wells may cause an inhomogeneous magnetic field, since the distances between distinct pins and recesses may vary compared to each other. The present invention enables the artisan to apply a homogeneous field throughout the wells of the multiwell plate, said field being close to its maximum possible intensity, since small recesses can be used with the magnetic pins adapting the position of their separation portion to possible deviations of the geometrical arrangement of the recesses.

[0015] A "magnetic separation plate" is a device useful for the separation of magnetic particles. It comprises a "support plate" and "magnetic pins", wherein the "support plate" is typically an essentially flat device for bearing and holding the "magnetic pins" in a defined position which is usually perpendicular to the support plate. Said plate can be made of one or more parts and different materials such as metal or plastic. In a preferred embodiment, the plate is made of metal. Preferably, the support plate comprises an upper and a lower plate fastened to each other.

[0016] In preferred embodiments, the "magnetic pins" are essentially rod-shaped magnetic or magnetizable structures. The length of the magnetic pins is preferably 2-100 mm, more preferably 15-50 mm. Their diameter is preferably 1-20 mm, more preferably 2-6 mm. The pins comprise a "fastening portion", an "intermediate portion" and a "separation portion". However, in the context of the invention, this tripartite structure is not necessarily to be understood as an assembly of morphologically distinct and visually clearly separable or distinguishable structures. It is rather preferred that the different portions are integrally linked to each other in a manner such that there is no visible transition between them.

[0017] The "fastening portion" is the portion at the end of the pin at which it is fixed to the support plate. If the "support plate" comprises an upper and a lower plate fastened to each other, the "fastening portion" is preferably embedded in between the upper and the lower plate.

[0018] The "separation portion" is located at the end of the pin opposite to the fastening portion and separates the magnetic particles within the wells of a multiwell plate. A part or all of said "separation portion" is inserted reversibly into recesses within a multiwell plate. Said "separation portion" is morphologically preadapted to fit into

said recesses. Therefore, in a preferred embodiment, the "separation portion" has a rounded-off tip at the end of the pin opposite of the fastening portion. The "separation portion" can be made of flexible and/or rigid material. Preferably, it is made of the same material as the remainder of the magnetic pin.

[0019] The "intermediate portion" designates an integral portion of the magnetic pin located between and physically coupling the "fastening portion" and the "separation portion". The "intermediate portion" is functionally distinct from the "fastening portion" and the "separation portion". The "intermediate portion" can further be magnetic or magnetizable even though it does not directly contribute to the magnetic separation, and it can further be made of flexible and/or rigid material. It has preferably the same diameter and is preferably made of the same material as the "separation portion". The length of the intermediate portion is variable and can be very short.

[0020] In the absence of external forces acting on the magnetic pins, the angle between the pins and the support plate is essentially a right angle. In a preferred embodiment of the invention, the angle is between 80 and 100°, more preferably between 85° and 95°, most preferably 90°.

[0021] A "predetermined geometrical arrangement" in the context of the invention means a defined spatial and directional relation between elements of a group of physical objects such as magnetic pins.

[0022] "Individually displaceable" means that elements of a group of physical objects such as magnetic pins can be displaced independently from each other, i.e. moving one element does not affect other elements of this group. In the context of the invention, the magnetic pins are preferably laterally displaceable up to 5 mm from their default position at their separation portion, more preferably up to 1 mm.

[0023] In a preferred embodiment, the magnetic pins return to their default position when external forces (as e.g. exerted by a microwell plate) are removed. Said return to the default position is caused by reset forces exerted by their specific structure and/or fastening to the support plate.

[0024] At their fastening portion, the magnetic pins can be laterally displaceable up to 2 mm distance from their default position, more preferably up to 0.2 mm.

[0025] A further aspect described herein is the magnetic separation plate described above, wherein the magnetic pins are flexibly fastened to said support plate.

[0026] "Flexibly fastened" means that the pins are not attached to the support plate in a rigid manner, but can be tilted with respect to the support plate such that the pins can be laterally displaced at their separation portion.

[0027] In order to achieve this, there are different advantageous possibilities.

[0028] In a preferred embodiment, the magnetic pins are fastened to the support plate via a holder containing one or more flexible elements.

[0029] A "holder" in the context of the invention is a

mount for the magnetic pins and can for example be a plug, a cone, or a ball or any other object capable of holding a magnetic pin at its fastening portion.

[0030] A "flexible element" is an element made of any material that is compressible and/or extendable in a reversible manner. Such material can be intrinsically flexible like e.g. silicone rubber or polysulfide rubber or any other type of rubber, a polyurethane compound, latex, but it can also be flexible due to its geometrical construction or shape, like e.g. a spring made of metal. A ball joint made of rigid material such as metal is also to be considered a flexible element in the context of the present invention, since it allows for individual displacement of the magnetic pins at their separation portion.

[0031] In a preferred embodiment, said one or more flexible elements are an outer layer made of flexible material, wherein said outer layer covers a rigid core. More preferably, said outer layer comprises one or more O-rings as flexible elements. Most preferably, said outer layer consists of one or more O-rings as flexible elements. In a preferred embodiment, said holder is a plug. Said O-rings are preferably made of rubber.

[0032] In another preferred embodiment, the magnetic pins are fastened to the support plate via a ball joint.

[0033] In a preferred embodiment of the invention, the magnetic pins of the magnetic separation plate are flexible.

[0034] The terms "flexible" or "flexible magnetic pins", respectively, mean that the pins comprise one or more "flexible elements" at one or more of its portions.

[0035] In a further embodiment, the magnetic pins comprise a core containing two or more rigid elements that are displaceable with respect to each other, said magnetic pins further comprising a covering made of flexible material and embedding said rigid elements. Preferred rigid elements are balls or rings. More preferably, said rigid elements are cylinder-shaped discs.

[0036] In a further aspect of the invention, said flexible elements are wires.

[0037] It must be understood that combinations of the features relating to the magnetic separation plate are possible. Thus, in a preferred embodiment of the invention, the magnetic separation plate comprises magnetic pins that are intrinsically flexible as well as flexibly fastened.

[0038] Furthermore, the pins contain magnetic material or magnetizable material.

[0039] As the magnetic separation plate described above can be used in a system comprising other elements it interacts with, the following is an aspect of the invention:

A magnetic separation system for use in methods employing magnetic particles, said system comprising

- a magnetic separation plate as described above
- a multiwell plate comprising wells for receiving fluids containing said magnetic particles, said multiwell

plate further comprising recesses in positions corresponding to a predetermined geometrical arrangement of the magnetic pins of said magnetic separation plate,

wherein the separation portions of said magnetic pins are reversibly inserted into said recesses in a separation position.

[0040] A "magnetic separation system" means a device or combination of devices suitable for the separation of components in a mixture by means of magnetic forces.

[0041] A "multiwell plate" is a device for receiving liquid substances or mixtures in receptacles, the "wells". The latter are usually arranged in a defined geometrical pattern. The "multiwell plate" can e.g. have 6, 12, 24, 48, 96, 384, 480 or 1536 "wells", but is not restricted to these numbers. The plate can further be made of transparent material, allowing for the passage of light e.g. for detection purposes in a photometric assay. Typically, a "multiwell plate" is made of plastics. In a preferred embodiment, the plastic is polypropylene. A "multiwell plate" does not have any specific restrictions with regard to the shape, size or volume of its "wells". Thus, a "multiwell plate" can be e.g. a deep-well plate, a microwell plate etc.

[0042] "Magnetic particles" are a magnetic or magnetizable solid phases. These particles may be preadapted to bind specific materials such as biological materials. Preadaptation can for example be achieved chemically (e.g. adding functional groups like amino groups to the particle surface) or biologically (e.g. coating the particle surface with antibodies or specific nucleic acid binding motives). Further, the "magnetic particles" preferably comprise a silica surface such as glass, thus facilitating binding of e.g. nucleic acids in the presence of chaotropic agents.

[0043] As an example for the application of such particles, their use in immobilizing nucleic acids after precipitation by adding salt and ethanol is described e.g. in Alderton R. P. et al., S., Anal. Biochem. 201 (1992) 166-169 and WO 91/12079. In this procedure, the nucleic acids are agglutinated along with the magnetic particles. The agglutinate is separated from the original solvent by applying a magnetic field and performing a wash step. After one wash step, the nucleic acids are dissolved in a Tris buffer.

[0044] Magnetic, porous glass is also available on the market that contains magnetic particles in a porous, particular glass matrix and is covered with a layer containing streptavidin. This product can be used to isolate biological materials, e.g., proteins or nucleic acids, if they are modified in a complex preparation step so that they bind covalently to biotin. Magnetizable particular adsorbents proved to be very efficient and suitable for automatic sample preparation. Ferrimagnetic and ferromagnetic as well as superparamagnetic pigments are used for this purpose. The most preferred MGPs and methods using magnetic glass particles are those described in WO 01/37291. Particularly useful is the method according to

R. Boom et al. (J Clin Microbiol. 28 (1990), 495-503).

[0045] "Reversibly" means that a process can be reverted without damaging components of a system. In particular, in the magnetic separation system according to the invention, the magnetic pins are "reversibly" inserted into the recesses of the multiwell plate, which means that pins and the recesses can be separated from one another by applying essentially the same force required as for insertion of the pins.

[0046] The "separation position" is a position in which the separation portion of the magnetic pins is inserted into the recesses of the multiwell plate with all or a part of their separation portion such that a magnetic field caused by the pins acts upon the magnetic particles within the wells of the multiwell plate.

[0047] The magnetic separation system according to the invention can advantageously be implemented into a larger analytical system. Thus, another aspect of the invention is an analytical system comprising the magnetic separation system according to the invention, said analytical system further comprising a pipetting module comprising a pipettor.

[0048] An "analytical system" is an arrangement of components such as instruments interacting with each other with the ultimate aim to analyze a given sample.

[0049] The "pipetting module" is one such component of an analytical system, wherein the pipettor, which may e.g. a robotic pipetting device, accomplishes aspirating and dispensing the sample, reagents or mixtures and thus transferring them between the other different components of said system.

[0050] For advantageous manipulation of the multiwell plate being part of the magnetic separation system, one aspect of the invention is the following:

An analytical system comprising the magnetic separation system as described above, said analytical system further comprising a multiwell plate handling module and/or a magnetic separation plate handling module.

[0051] A "multiwell plate handling module" is a device for moving the multiwell plate in spatial relation to the magnetic separation plate. It comprises a holder for the multiwell plate such as a drawer, and further a component like a robotic pivot arm to move said holder with or without the multiwell plate.

[0052] The "magnetic separation plate handling module" is a device for the handling of the magnetic separation plate described herein.

[0053] The handling modules set out above may also comprise DC-motors for movement of the plates and opening/closing/pressing a plate cover, sensors to identify the type of plate, or a barcode reader for identifying the sample.

[0054] In a preferred embodiment, the analytical system according to the invention further comprises one or more elements selected from the following group:

- A reaction module containing the components of a chemical and/or biochemical reaction

- A detection module for detecting signals evoked by an analyte
- A storage module for reagents and/or disposables.

[0055] A "reaction module" can comprise a variety of vessels like tubes or plates, in which a reaction for the analysis of the sample such as Polymerase Chain Reaction or hybridization of antibodies takes place. The outer limits or walls of such vessels are chemically inert such that they do not interfere with the analytical reaction taking place within. Details of the Polymerase Chain Reaction are described infra.

[0056] A "detection module" can e.g. be an optical detection unit for detecting the result or the effect of the analysis procedure. An optical detection unit may comprise a light source, e.g. a xenon lamp, optics such as mirrors, lenses, optical filters, fiber optics for guiding and filtering the light, one or more reference channels, or a CCD camera.

[0057] A "storage module" module stores the necessary reagents to bring about a chemical or biological reaction important for analysis of the sample in question. It can also contain further components useful for the method of the invention, e.g. disposables such as pipet tips or vessels to be used as reaction receptacles within the reaction module.

[0058] Advantageously, the analytical system according to the invention further comprises a control unit for controlling system components.

[0059] Such a "control unit" may comprise a software for ensuring that the different components of said analytical system work and interact correctly and with the correct timing, e.g. moving components such as the pipettor to the multiwell plate in a coordinated manner. The control unit may also comprise a processor running a real-time operating system (RTOS), which is a multitasking operating system intended for real-time applications. In other words the system processor is capable of managing real-time constraints, i.e. operational deadlines from event to system response regardless of system load. It controls in real time that different units within the system operate and respond correctly according to given instructions.

[0060] A further aspect of the present invention is a method as defined by claim 6 for the separation of magnetic particles, said method comprising the steps:

- a) providing a multiwell plate containing magnetic particles and a biological sample in one or more wells,
- b) providing a magnetic separation plate comprising a support plate and magnetic pins in a predetermined geometrical arrangement, said magnetic pins having a fastening portion, an intermediate portion and a separation portion and being fastened to said support plate at their fastening portion, wherein said

magnetic pins are individually displaceable at their separation portion,

c) reversibly inserting said magnetic pins into recesses of said multiwell plate in positions corresponding to the predetermined geometrical arrangement of the magnetic pins of said magnetic separation plate for applying a magnetic field to said magnetic particles in said wells.

[0061] This method can be advantageously carried out with the magnetic separation plate described herein and/or the magnetic separation system or analytical system according to the invention as described supra.

[0062] In a preferred embodiment, the method according to the invention further comprises the step of retracting the magnetic pins from the recesses of the multiwell plate for removing the magnetic field from the magnetic particles after step c).

[0063] Another aspect described herein is the use of the magnetic separation plate disclosed herein for the separation of magnetic particles.

[0064] If the material to be analyzed with the help of the plate described herein, or the systems or method according to the invention is nucleic acids, there are various methods applicable in this context, one very significant method being the Polymerase Chain Reaction (PCR).

[0065] The "Polymerase Chain Reaction" (PCR) is disclosed, among other references, in U.S. Patent Nos. 4,683,202, 4,683,195, 4,800,159, and 4,965,188. PCR typically employs two or more oligonucleotide primers that bind to a selected nucleic acid template (e.g. DNA or RNA). Primers useful for nucleic acid analysis include oligonucleotides capable of acting as a point of initiation of nucleic acid synthesis within the nucleic acid sequences of the microbial nucleic acid or quantitative standard nucleic acid. A primer can be purified from a restriction digest by conventional methods, or it can be produced synthetically. The primer is preferably single-stranded for maximum efficiency in amplification, but the primer can be double-stranded. Double-stranded primers are first denatured, i.e., treated to separate the strands. One method of denaturing double stranded nucleic acids is by heating. A "thermostable polymerase" is a polymerase enzyme that is heat stable, i.e., it is an enzyme that catalyzes the formation of primer extension products complementary to a template and does not irreversibly denature when subjected to the elevated temperatures for the time necessary to effect denaturation of double-stranded template nucleic acids. Generally, the synthesis is initiated at the 3' end of each primer and proceeds in the 5' to 3' direction along the template strand. Thermostable polymerases have been isolated from *Thermus flavus*, *T. ruber*, *T. thermophilus*, *T. aquaticus*, *T. lacteus*, *T. rubens*, *Bacillus stearothermophilus*, and *Methanothermobacter fervidus*. Nonetheless, polymerases that are not thermostable also can be employed in PCR assays pro-

vided the enzyme is replenished. If the template nucleic acid is double-stranded, it is necessary to separate the two strands before it can be used as a template in PCR. Strand separation can be accomplished by any suitable denaturing method including physical, chemical or enzymatic means. One method of separating the nucleic acid strands involves heating the nucleic acid until it is predominately denatured (e.g., greater than 50%, 60%, 70%, 80%, 90% or 95% denatured). The heating conditions necessary for denaturing template nucleic acid will depend, e.g., on the buffer salt concentration and the length and nucleotide composition of the nucleic acids being denatured, but typically range from about 90°C to about 105°C for a time depending on features of the reaction such as temperature and the nucleic acid length. Denaturation is typically performed for about 30 sec to 4 min (e.g., 1 min to 2 min 30 sec, or 1.5 min). If the double-stranded template nucleic acid is denatured by heat, the reaction mixture is allowed to cool to a temperature that promotes annealing of each primer to its target sequence on the microbial nucleic acid and/or quantitative standard nucleic acid. The temperature for annealing is usually from about 35°C to about 65°C (e.g., about 40°C to about 60°C; about 45°C to about 50°C). Annealing times can be from about 10 sec to about 1 min (e.g., about 20 sec to about 50 sec; about 30 sec to about 40 sec). The reaction mixture is then adjusted to a temperature at which the activity of the polymerase is promoted or optimized, i.e., a temperature sufficient for extension to occur from the annealed primer to generate products complementary to the nucleic acid to be analyzed. The temperature should be sufficient to synthesize an extension product from each primer that is annealed to a nucleic acid template, but should not be so high as to denature an extension product from its complementary template (e.g., the temperature for extension generally ranges from about 40° to 80°C (e.g., about 50°C to about 70°C; about 60°C). Extension times can be from about 10 sec to about 5 min (e.g., about 30 sec to about 4 min; about 1 min to about 3 min; about 1 min 30 sec to about 2 min). The newly synthesized strands form a double-stranded molecule that can be used in the succeeding steps of the reaction. The steps of strand separation, annealing, and elongation can be repeated as often as needed to produce the desired quantity of amplification products corresponding to the microbial nucleic acid and/or quantitative standard nucleic acid. The limiting factors in the reaction are the amounts of primers, thermostable enzyme, and nucleoside triphosphates present in the reaction. The cycling steps (i.e., denaturation, annealing, and extension) are preferably repeated at least once. For use in detection, the number of cycling steps will depend, e.g., on the nature of the sample. If the sample is a complex mixture of nucleic acids, more cycling steps will be required to amplify the target sequence sufficient for detection. Generally, the cycling steps are repeated at least about 20 times, but may be repeated as many as 40, 60, or even 100 times.

[0066] Nucleic acid amplification reactions apart from PCR comprise the Ligase Chain Reaction (LCR; Wu D. Y. and Wallace R. B., *Genomics* 4 (1989) 560-69; and Barany F., *Proc. Natl. Acad. Sci. USA* 88 (1991) 189-193; Polymerase Ligase Chain Reaction (Barany F., *PCR Methods and Applic.* 1 (1991) 5-16); Gap-LCR (WO 90/01069); Repair Chain Reaction (EP 0439182 A2), 3SR (Kwoh D. Y. et al., *Proc. Natl. Acad. Sci. USA* 86 (1989) 1173-1177; Guatelli J.C., et al., *Proc. Natl. Acad. Sci. USA* 87 (1990) 1874-1878; WO 92/08808), and NASBA (US 5,130,238). Further, there are strand displacement amplification (SDA), transcription mediated amplification (TMA), and Q β -amplification (for a review see e.g. Whelen A. C. and Persing D. H., *Annu. Rev. Microbiol.* 50 (1996) 349-373; Abramson R. D. and Myers T. W., *Curr Opin Biotechnol* 4 (1993) 41-47).

[0067] Suitable nucleic acid detection methods are known to the expert in the field and are described in standard textbooks as Sambrook J. et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989 and Ausubel F. et al.: *Current Protocols in Molecular Biology* 1987, J. Wiley and Sons, NY. There may be also further purification steps before the nucleic acid detection step is carried out as e.g. a precipitation step. The detection methods may include but are not limited to the binding or intercalating of specific dyes as ethidium bromide which intercalates into the double-stranded DNA and changes its fluorescence thereafter. The purified nucleic acid may also be separated by electrophoretic methods optionally after a restriction digest and visualized thereafter. There are also probe-based assays which exploit the oligonucleotide hybridization to specific sequences and subsequent detection of the hybrid. It is also possible to sequence the nucleic acid after further steps known to the expert in the field. A useful template-dependent nucleic acid polymerase is the ZO5 DNA polymerase and mutations thereof. Other template-dependent nucleic acid polymerases comprise e.g. Taq polymerase and Tth Polymerase.

Figure legends

[0068]

Fig. 1: Perspective view of a magnetic separation plate.

Fig. 2: Bottom view of a multiwell plate.

Fig. 3: Schematic cross section of a multiwell plate and a magnetic separation plate interacting with each other.

Fig. 4: Schematic side view of an analytical system comprising a magnetic separation system.

Description of the figures

[0069] Fig. 1: Perspective view of a magnetic separation plate.

[0070] In this embodiment, the support plate (1) consists of a lower plate (2) and an upper plate (3) that are combined with each other. The magnetic pins (4) are fastened to the support plate at their fastening portion (5) via plugs (6) with the plate, the plugs each having two O-rings (7) made of flexible material. The pins protrude from the plate towards the outside via openings (8) in the upper part of the support plate. The O-rings confer flexibility to the magnetic pins relatively to the support plate such that their separation portions (9) are individually displaceable. The presence of two separate rings causes a reset force upon displacement of the pins' separation portion and therefore provides for a defined default position of the latter. The magnetic pins further possess an intermediate portion (10) between the fastening and the separation portion. The latter two portions are different in shape, thereby avoiding the risk of confusing the magnetic poles when assembling the magnetic separation plate. A potentially resulting alternating pole arrangement would inevitably lead to a weaker magnetic field, thus the preferred pattern of the poles is that all of them are arranged in the same orientation.

[0071] Fig. 2: Bottom view of a multiwell plate.

[0072] The magnetic pins of the magnetic separation plate (not shown) are inserted into preadapted recesses (11) within the multiwell plate (12). In this arrangement, every four wells (13, seen from below) are positioned around a recess for a magnetic pin causing a magnetic field (14) in the surrounding wells.

[0073] Fig. 3: Schematic cross section of a multiwell plate and a magnetic separation plate in three different positions interacting with each other.

[0074] In a first (inactive) position (Fig. 3a), the sample (15) within the wells (13) of the multiwell plate containing essentially homogeneously distributed magnetic particles (16) is not exposed to the magnetic field (14). The magnetic pins (4) are fastened to the support plate (1). The magnetic separation plate and the multiwell plate (12) are not in contact with each other.

[0075] In a second (separation) position (Fig. 3b), the magnetic pins (4) are inserted into the preadapted recesses (11) within the multiwell plate. The sample (15) is exposed to the magnetic field homogeneously throughout its entire height. The pins do not protrude higher than the fluid surface in order to avoid retraction of the magnetic particles (16) from the fluid. The magnetic particles are attracted to the walls of the wells.

[0076] In a third (separation) position (Fig. 3c), the magnetic pins (4) are inserted into the preadapted recesses (11) to a lesser extent, thus causing a stronger magnetic field (14) at the bottom of the wells than in the upper part. In this position, the magnetic particles (16) are attracted closer to the well bottom and are less prone to being accidentally retrieved from the well during re-

moval of the supernatant.

[0077] Fig. 4: Schematic side view of an analytical system comprising a magnetic separation system.

[0078] The analytical system comprises a moveable robotic pipettor (17) for aspirating and dispensing the sample, reagents or mixtures and thus transferring them between the other different components of said system. The system further comprises a multiwell plate handling module (18) for moving the multiwell plate in spatial relation to the magnetic separation plate, and a magnetic separation plate handling module (19) with an analogous function with respect to the magnetic separation plate. The multiwell plate (not depicted) is, in this embodiment, also the reaction module. The system also contains a storage module for reagents (20) necessary to bring about a chemical or biological reaction important for the analysis of the sample in question, and further a storage module for disposables (21) such as pipette tips. Further present in this embodiment is an optical detection unit (22) with a light source (23). Also comprised by the system is a control unit (24) for controlling the other system components.

Claims

1. A magnetic separation system for use in methods employing magnetic particles, said system comprising

- a magnetic separation plate for use in methods employing magnetic particles, said magnetic separation plate comprising a support plate (1) and magnetic pins (4) in a predetermined geometrical arrangement, said magnetic pins (4) having a fastening portion (5), an intermediate portion (10) and a separation portion (9) and being fastened to said support plate (1) at their fastening portion (5), wherein said magnetic pins (4) are individually displaceable at their separation portion (9)
- a multiwell plate (12) comprising wells (13) for receiving fluids containing said magnetic particles, said multiwell plate (12) further comprising recesses (11) in positions corresponding to the predetermined geometrical arrangement of the magnetic pins (4) of said magnetic separation plate,

wherein the separation portions (9) of said magnetic pins are morphologically preadapted to fit reversibly into said recesses (11) in a separation position.

2. An analytical system comprising the magnetic separation system of claim 1, said analytical system further comprising a pipetting module comprising a pipettor (17).

3. An analytical system comprising the magnetic separation system of claim 1, said analytical system further comprising a multiwell plate handling module (18) and/or a magnetic separation plate handling module (19).

4. An analytical system comprising the magnetic separation system of claim 1, said analytical system further comprising one or more elements selected from the following group:

- A reaction module containing the components of a chemical and/or biochemical reaction
- A detection module (22) for detecting signals evoked by an analyte
- A storage module for reagents (20) and/or disposables (21)

5. The analytical system of any of the claims 2 to 4, further comprising a control unit (24) for controlling system components.

6. A method for the separation of magnetic particles, said method comprising the steps:

- a) Providing a multiwell plate (12) containing magnetic particles (16) and a biological sample (15) in one or more wells (13)
- b) Providing a magnetic separation plate comprising a support plate (1) and magnetic pins (4) in a predetermined geometrical arrangement, said magnetic pins (4) having a fastening portion (5), an intermediate portion (10) and a separation portion (9) and being fastened to said support plate (1) at their fastening portion (5), wherein said magnetic pins (4) are individually displaceable at their separation portion (9)
- c) Reversibly inserting said magnetic pins (4) into recesses (11) of said multiwell plate (12) in positions corresponding to the predetermined geometrical arrangement of the magnetic pins (4) of said magnetic separation plate for applying a magnetic field (14) to said magnetic particles (16) in said wells (13).

7. The method of claim 6, further comprising the step of retracting the magnetic pins (4) from the recesses (11) of the multiwell plate (12) for removing the magnetic field (14) from the magnetic particles (16) after step c).

Patentansprüche

1. Magnetisches Trennsystem zur Verwendung in Verfahren, die magnetische Partikel einsetzen, wobei das System Folgendes umfasst

- eine magnetische Trennplatte zur Verwendung in Verfahren, die magnetische Partikel einsetzen, wobei die magnetische Trennplatte eine Trägerplatte (1) und magnetische Stifte (4) in einer vorbestimmten geometrischen Anordnung umfasst, wobei die magnetischen Stifte (4) einen Befestigungsabschnitt (5), einen Zwischenabschnitt (10) und einen Trennabschnitt (9) aufweisen und an ihrem Befestigungsabschnitt (5) an der Trägerplatte (1) befestigt sind, wobei die magnetischen Stifte (4) an ihrem Trennabschnitt (9) individuell verschiebbar sind,
 - eine Multiwellplatte (12), umfassend Wells (13) zur Aufnahme von Fluiden, die magnetische Partikel enthalten, wobei die Multiwellplatte (12) ferner Vertiefungen (11) an Stellen, die der vorbestimmten geometrischen Anordnung der magnetischen Stifte (4) der magnetischen Trennplatte entsprechen, umfasst,
- wobei die Trennabschnitte (9) der magnetischen Stifte morphologisch so vorangepasst wurden, dass sie in einer Trennposition reversibel in die Vertiefungen (11) passen.
2. Analysesystem, umfassend das magnetische Trennsystem nach Anspruch 1, wobei das Analysesystem ferner ein Pipettiermodul umfasst, das einen Pipettierer (17) umfasst.
 3. Analysesystem, umfassend das magnetische Trennsystem nach Anspruch 1, wobei das Analysesystem ferner ein Multiwellplatten-Handhabungsmodul (18) und/oder ein Handhabungsmodul für eine magnetische Trennplatte (19) umfasst.
 4. Analysesystem, umfassend das magnetische Trennsystem nach Anspruch 1, wobei das Analysesystem ferner ein oder mehrere Elemente umfasst, die ausgewählt sind aus der folgenden Gruppe:
 - ein Reaktionsmodul, das die Komponenten einer chemischen und/oder biochemischen Reaktion enthält,
 - ein Nachweismodul (22) zum Nachweisen von Signalen, die von einem Analyten hervorgerufen werden,
 - ein Lagerungsmodul für Reagenzien (20) und/oder Wegwerfartikel (21).
 5. Analysesystem nach einem der Ansprüche 2 bis 4, ferner umfassend eine Steuerungseinheit (24) zum Steuern von Systemkomponenten.
 6. Verfahren zur Trennung magnetischer Partikel, wobei das Verfahren die Schritte umfasst:

a) Bereitstellen einer Multiwellplatte (12), ent-

haltend magnetische Partikel (16) und eine biologische Probe (15) in einem oder mehreren Wells (13),

b) Bereitstellen einer magnetischen Trennplatte, umfassend eine Trägerplatte (1) und magnetische Stifte (4) in einer vorbestimmten geometrischen Anordnung, wobei die magnetischen Stifte (4) einen Befestigungsabschnitt (5), einen Zwischenabschnitt (10) und einen Trennabschnitt (9) aufweisen und an ihrem Befestigungsabschnitt (5) an der Trägerplatte (1) befestigt sind, wobei die magnetischen Stifte (4) an ihrem Trennabschnitt (9) individuell verschiebbar sind,

c) reversibel Einführen der magnetischen Stifte (4) in Vertiefungen (11) der Multiwellplatte (12) an Stellen, die der vorbestimmten geometrischen Anordnung der magnetischen Stifte (4) der magnetischen Trennplatte entsprechen, um ein Magnetfeld (14) an die magnetischen Partikel (16) in den Wells (13) anzulegen.

7. Verfahren nach Anspruch 6, ferner umfassend den Schritt des Herausziehens der magnetischen Stifte (4) aus den Vertiefungen (11) der Multiwellplatte (12) zum Entfernen des Magnetfeldes (14) von den magnetischen Partikeln (16) nach Schritt c).

Revendications

1. Système de séparation magnétique pour une utilisation dans des procédés employant des particules magnétiques, ledit système comprenant

- une plaque de séparation magnétique pour une utilisation dans des procédés employant des particules magnétiques, ladite plaque de séparation magnétique comprenant une plaque de support (1) et des tiges magnétiques (4) dans un agencement géométrique prédéterminé, lesdites tiges magnétiques (4) ayant une partie d'attache (5), une partie intermédiaire (10) et une partie de séparation (9) et étant attachées à ladite plaque de support (1) au niveau de leur partie d'attache (5), lesdites tiges magnétiques (4) étant déplaçables individuellement au niveau de leur partie de séparation (9)

- une plaque multipuits (12) comprenant des puits (13) pour recevoir des fluides contenant lesdites particules magnétiques, ladite plaque multipuits (12) comprenant en outre des évidements (11) dans des positions correspondant à l'agencement géométrique prédéterminé des tiges magnétiques (4) de ladite plaque de séparation magnétique,

dans lequel les parties de séparation (9) desdites

tiges magnétiques sont pré-adaptées morphologiquement pour s'ajuster de façon réversible dans lesdits évidements (11) dans une position de séparation.

2. Système analytique comprenant le système de séparation magnétique selon la revendication 1, ledit système analytique comprenant en outre un module de pipettage comprenant un pipeteur (17). 5
3. Système analytique comprenant le système de séparation magnétique selon la revendication 1, ledit système analytique comprenant en outre un module de manipulation de plaques multipuits (18) et/ou un module de manipulation de plaques de séparation magnétique (19). 10
4. Système analytique comprenant le système de séparation magnétique selon la revendication 1, ledit système analytique comprenant en outre un ou plusieurs éléments choisis dans le groupe suivant : 15
 - un module de réaction contenant les composants d'une réaction chimique et/ou biochimique
 - un module de détection (22) pour la détection de signaux induits par un analyte 25
 - un module de stockage pour des réactifs (20) et/ou des consommables (21).
5. Système analytique selon l'une quelconque des revendications 2 à 4, comprenant en outre une unité de commande (24) pour la commande des composants du système. 30
6. Procédé de séparation de particules magnétiques, ledit procédé comprenant les étapes : 35
 - a) fournir une plaque multipuits (12) contenant des particules magnétiques (16) et un échantillon biologique (15) dans un ou plusieurs puits (13) 40
 - b) fournir une plaque de séparation magnétique comprenant une plaque de support (1) et des tiges magnétiques (4) dans un agencement géométrique prédéterminé, lesdites tiges magnétiques (4) ayant une partie d'attache (5), une partie intermédiaire (10) et une partie de séparation (9) et étant attachées à ladite plaque de support (1) au niveau de leur partie d'attache (5), lesdites tiges magnétiques (4) étant déplaçables individuellement au niveau de leur partie de séparation (9) 45
 - c) insérer de façon réversible lesdites tiges magnétiques (4) dans les évidements (11) de ladite plaque multipuits (12) dans des positions correspondant à l'agencement géométrique prédéterminé des tiges magnétiques (4) de ladite plaque de séparation magnétique pour appliquer 50

un champ magnétique (14) auxdites particules magnétiques (16) dans lesdits puits (13).

7. Procédé selon la revendication 6, comprenant en outre l'étape de rétraction des tiges magnétiques (4) des évidements (11) de la plaque multipuits (12) pour retirer le champ magnétique (14) des particules magnétiques (16) après l'étape c). 55

Fig. 1

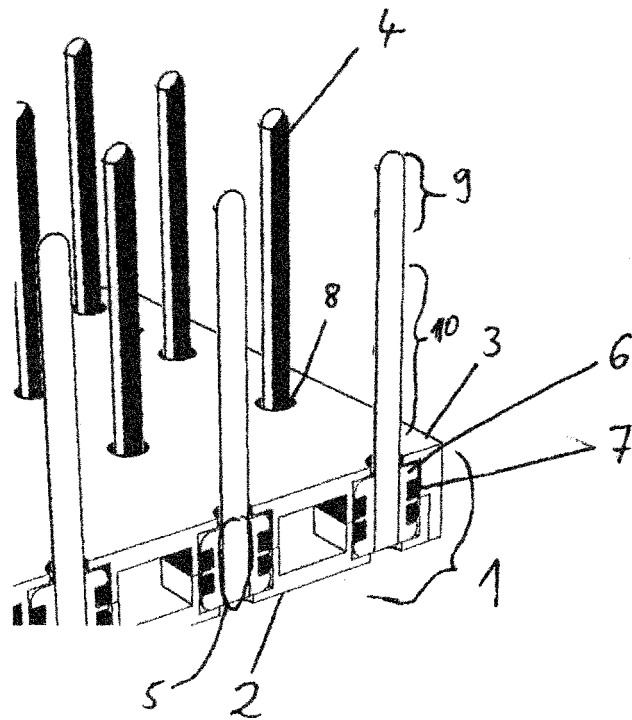


Fig. 2

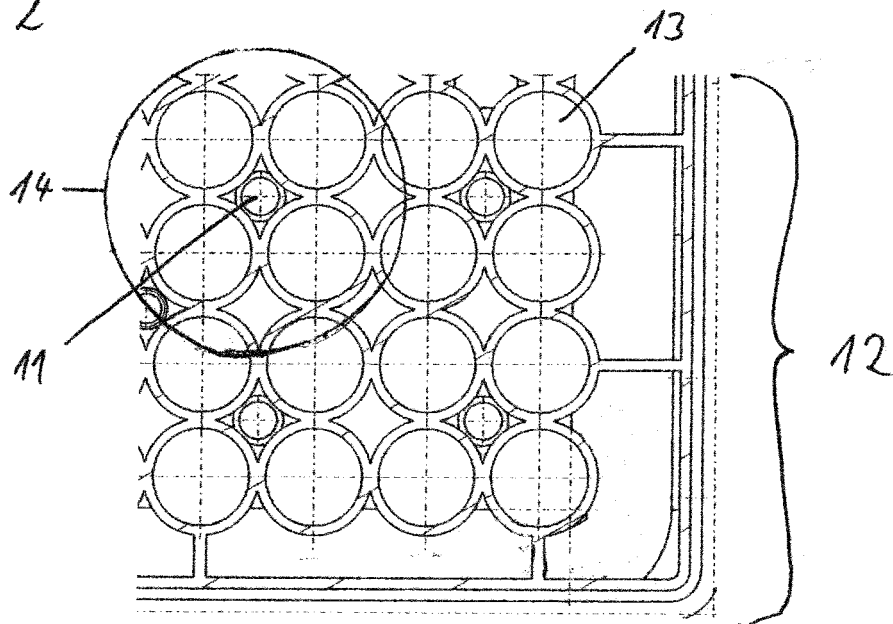


Fig. 3

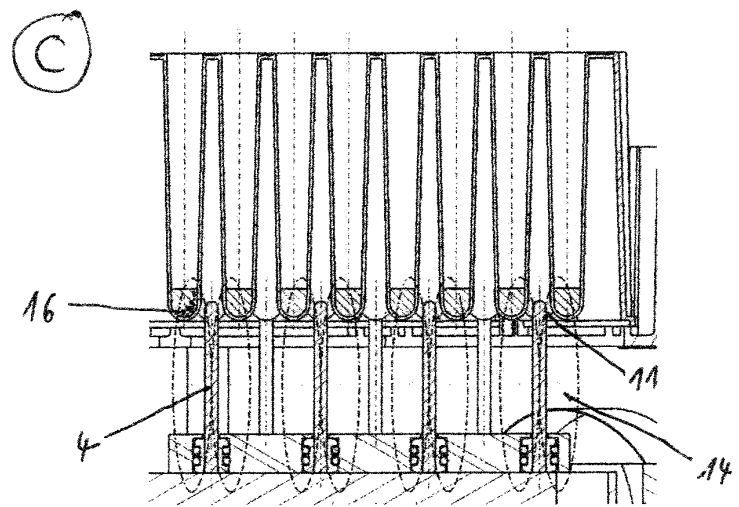
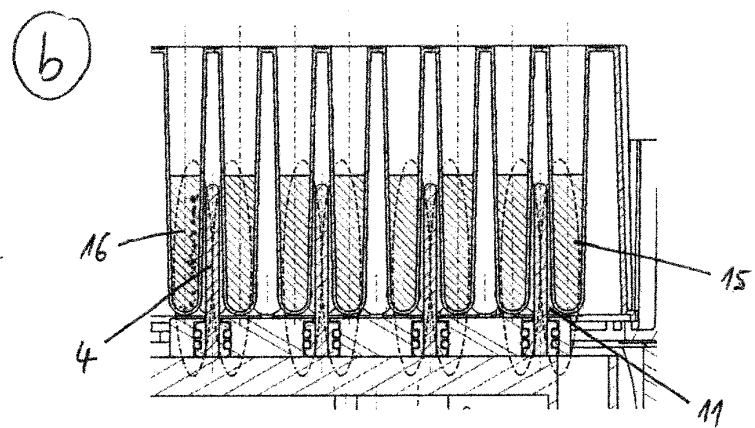
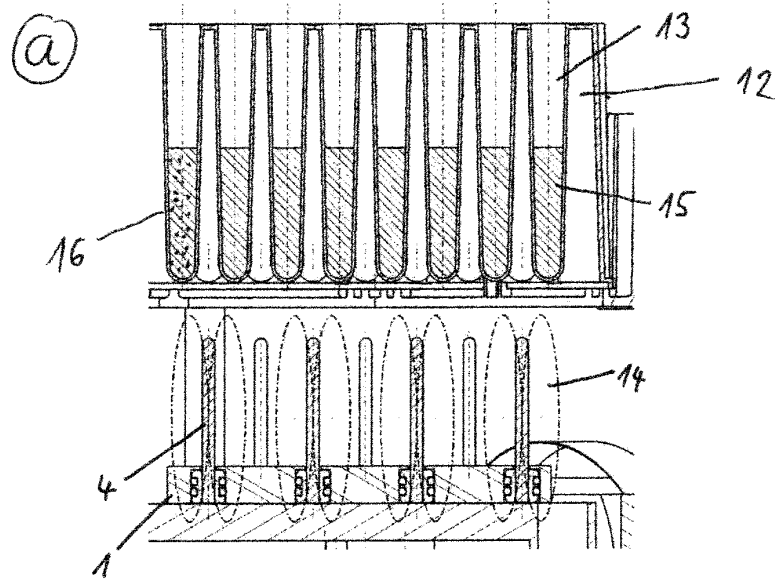
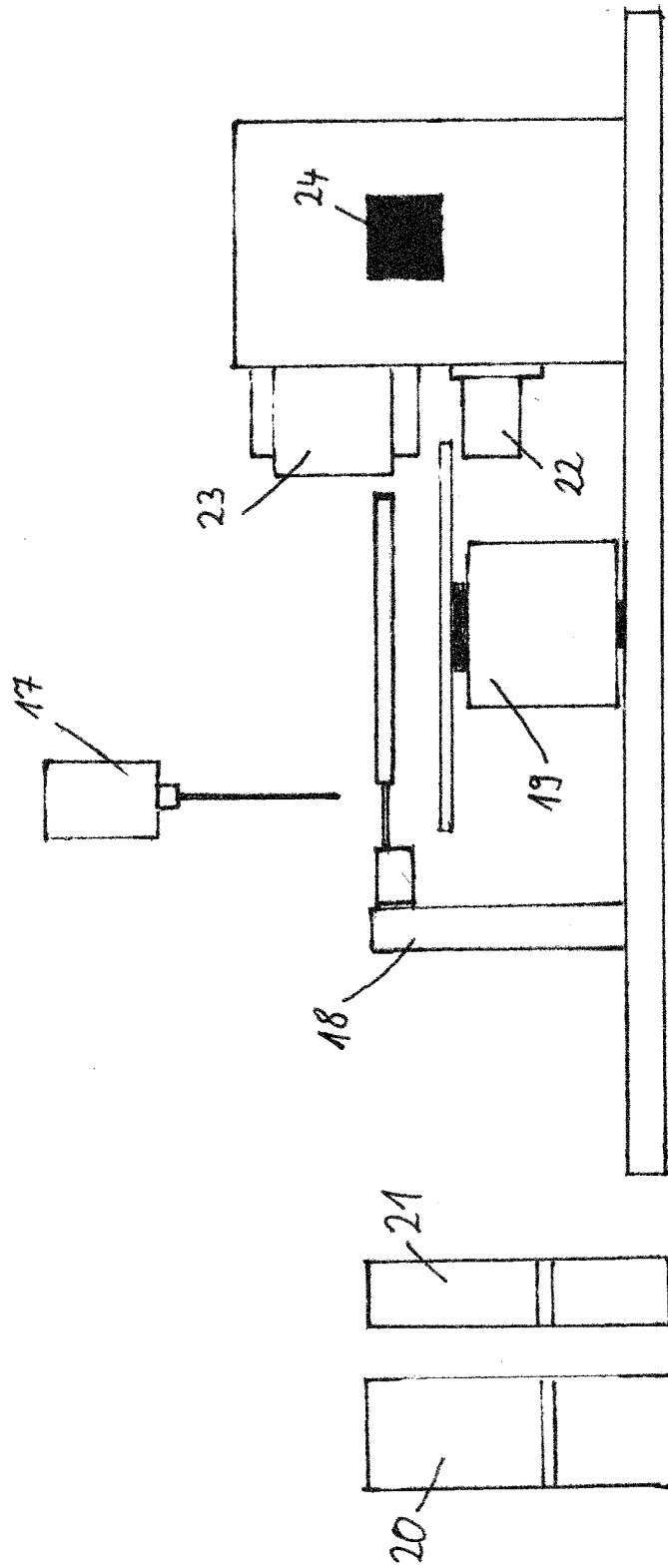


Fig. 4



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