

**A DEVICE, SYSTEM AND METHOD FOR WASHING AND ISOLATING
MAGNETIC PARTICLES IN A CONTINUOUS FLUID FLOW**

Description

5 [001] The present invention relates to the field of magnetic separation systems, and specifically, to a device, system and a method of washing and isolating magnetic particles from a continuous fluid flow in at least one fluidic channel having an inlet at one end and an outlet at another end.

10 [002] In many bio-analytical assays magnetic nano and/or micro particles are used as a solid phase carrier for bio-analyzed targets (also known as analytes including, but not limited to, cells, DNA, RNA, mRNA and proteins, for example). In the course of said bio-analytical assays, the solid phase, including its analyte attached thereto, is typically separated from the liquid phase in which it is
15 contained in, and is subsequently washed in a buffer solution, for example.

[003] Conventional methods of washing the solid phase include pipetting a defined amount of buffer solution into a reaction vessel containing the solid phase to suspend the solid phase in the buffer solution. This is followed by a suction step
20 that separates the solid phase from the liquid phase. During the suspension and suction steps mentioned above, a washing cycle of the solid phase takes place, and if needed, said steps are repeated to carry out a required 'n' number of cycles till the analyte is of a suitable purity. Each washing cycle usually includes the steps of carrying out a suspension of the solid phase, a separation (via suction) of the
25 solid phase from the buffer solution and an aspiration.

[004] Magnetic separation of an analyte from a solution using magnetic particles as the solid phase is another well known and popular method employed in many biological assays such as immunoassays, nucleic acid hybridization assays and
30 sample purification assays, for example. In these assays, it is common to use the magnetic particles in connection with a reagent. The magnetic particles are typically coated with the reagent, which has a specific affinity for a targeted analyte. Subsequently, once the magnetic particle coated with the reagent is

introduced into a solution containing the analyte, the reagent coating on the magnetic particle forms a complex with the target analyte thereby binding the target analyte to the magnetic particle. Following this, the magnetic particles (and its attached analyte) are separated from the solution using a permanent and/or
5 electro magnet. The magnetic particles are then typically washed, and further separated in another medium or alternatively, the targeted analyte may be removed from the magnetic particles for further analysis.

[005] One example of an automated magnetic separation device is disclosed in
10 US patent 5,536,475. This device includes both a means for a stationary capture of magnetic particles followed by a capture of magnetic particles during continuous flow. The device also includes a means for collecting most of the magnetic particles in a stationary reservoir above a first magnet. The remaining solution is then channeled over a second magnet to remove any magnetic particles that may
15 not have been captured by the first magnet.

[006] Another example of a magnetic particle separation device is disclosed in international application WO92/05443A. This application describes a device for separating magnetic particles from a plurality of reaction vessels, each of which
20 contain a mixture (that includes magnetic particles) in a static state. The reaction vessels containing the magnetic particles are positioned in an array. The array is supported by a supporting means. Also included in the support is an array of stationary permanent magnets arranged such that each magnet exerts a magnetic force on a specific reaction vessel, thereby holding the magnetic particles in said
25 reaction vessels at a fixed position relative to the permanent magnets. Following the fixing step of the magnetic particles, the remaining mixture may be removed from the reaction vessels thereby leaving behind the magnetic particles and the analyte attached thereto.

30 [007] Another magnetic particle separation device is disclosed in US patent 6,159,378. This magnetic particle separation device employs a stationary magnetic flux conductor made of monolithic porous foam. The magnetic flux conductor is permeable and thus, permits magnetic particles and fluid to flow

through it. The magnetic flux conductor is magnetized by an external magnetic field from a permanent or an electromagnet and generates a magnetic field gradient within the magnetic flux conductor. When the magnetic field gradient is sufficiently high enough, the magnetic particles present in any fluid passing
5 through the magnetic flux conductor are retained on walls of the porous foam. Conversely, when the magnetic field gradient is reduced to sufficiently low value the magnetic particles are allowed to pass through the magnetic flux conductor again.

10 **[008]** Although the above-mentioned devices are capable of extracting magnetic particles with analyte attached thereto from mixtures, as many diagnostic tests are carried out after said extraction, it is necessary, as mentioned above, to wash the analyte in order to improve its purity. In this respect, the above – mentioned devices do not provide any means for washing the analyte obtained during the
15 extraction process. As such, if the aforesaid devices are used, it is necessary to carry out subsequent washing steps before the analyte may be analyzed further. However, in carrying out said subsequent washing steps, there exists the necessity to repeat the washing steps several times to achieve an analyte with a high level of purity. In doing so, therein lies the risk that quantities of analyte may
20 be lost during transfers between different washing containers, evaporation and adsorption to the wall of the containers during these washing steps.

[009] In the case of a low concentration of analyte in the starting sample, carrying out the extraction and washing of said analyte as described above may cause the
25 complete lose of analyte, or a sharp decrease in the amount such that it may become undetectable. Besides the above mentioned drawbacks, these washing steps (or additional manipulation methods) are expensive and expand a lot of time, which renders it unpractical in many industrial applications such as the detection of pathogenic micro organisms in biological, environmental or industrial samples, for
30 example.

[010] In order to overcome the aforesaid difficulties, PCT application WO 2002/43865 A discloses a method for separating magnetic particles from a mixture

and a washing means. In this method, a solution where the analyte (attached to magnetic particles) is suspended in a first container connected via a bottle-neck to a second container. The analyte attached to the magnetic particles are dragged from the first container to the second container by a permanent magnet and the
5 washing of the magnetic particles and its analyte then takes place in the second container.

[011] Another such device is described in PCT application WO 2006/010584 A1. In this PCT application, the solution containing the analyte is contained in a
10 reaction vessel with a large upper compartment having a funnel shape and an elongated lower compartment with a constant cross-sectional area. The process consists of subjecting the magnetic particles to two magnetic fields applied simultaneously to separate magnetic particles present in the upper compartment of the vessel from the fluid. This transfers magnetic particles from the upper part to
15 the elongated lower compartment and removes the solution from the vessel. This is followed by adding washing buffer to the lower part. The rest of the washing buffer containing the magnetic particles is then subjected to two magnetic fields applied with different directions to wash the magnetic particles.

20 **[012]** Further examples of magnetic particle separation devices are also disclosed in US patents 6,346,196, 6,355,491, US patent application 2004/0023273, and PCT applications WO 2007/044642 A2 and WO 2006/021410 A1.

25 **[013]** However, the aforesaid devices and/or processes still have drawbacks such as the capture the magnetic particles occurring only mainly at the walls of reservoirs, a low concentration of magnetic particles (which leads to low analyte yields) being captured, a general inability to release all the magnetic particles because of the residual magnetism that remain in the magnetic structures and
30 finally, all the above devices require a lot of processing time before all the magnetic particles are separated from the liquid phase. In addition to the above difficulties, further disadvantages include a high loss of analyte during transfers

from one container to another during the washing steps, and an inability to handle a large volume of samples.

[014] As such, there still exists a need for a device for washing and isolating
5 magnetic particles from a continuous fluid flow in at least one fluidic channel having an inlet at one end and an outlet at another end. Such a device should also be capable of being utilized together with existing laboratory infrastructure and be simple and yet cost-effective to implement. In this respect, the device, system and method, according to the present invention, of washing and isolating magnetic
10 particles from a continuous fluid flow in at least one fluidic channel having an inlet at one end and an outlet at another end, overcomes the aforesaid difficulties.

[015] The device of the present invention for washing and isolating magnetic particles from a continuous fluid flow in at least one fluidic channel having an inlet
15 at one end and an outlet at another end includes at least one magnetic source carrier. The magnetic source carrier is arranged proximate to the at least one fluidic channel. The at least one magnetic source carrier is moveable between a first position and a second position and itself comprises at least one magnetic source. The magnetic source carrier does not move in a translational motion but
20 rather rotates around its axis. A movement of the at least one magnetic source carrier to the first position places the at least one first magnetic source at a first spatial location along the at least one fluidic channel. In doing so, said at least one first magnetic source generates a maxima magnetic field at said first spatial location. The generated maxima magnetic field at the first spatial location attracts
25 the magnetic particles from the continuous fluid flow and assembles said magnetic particles at said first spatial location. Conversely, a movement of the at least one magnetic source carrier to the second position places the at least one first magnetic source distal from the first spatial location such that said magnetic field at said first spatial location is at a minima, and the magnetic particles disperse
30 from said first spatial location back into the continuous flow. The maxima magnetic field is between about 200 mT to about 500 mT. The minima magnetic field is between about 0 mT to about 50 mT.

[016] In one exemplary embodiment, the at least one magnetic source carrier may further include at least one second magnetic source. In this exemplary embodiment, said at least one second magnetic source is arranged in a spatial arrangement with respect to the at least one first magnetic source such that the movement of the at least one magnetic source carrier to the second position places the at least one second magnetic source at a second spatial location along the fluidic channel. The second spatial location is located downstream from the first spatial location. The at least one second magnetic source generates a maxima magnetic field at said second spatial location. The generation of a maxima magnetic field at the second spatial location attracts the magnetic particles from the continuous fluid flow and assembles said magnetic particles at said second spatial location. The second magnetic source has a maxima magnetic field when the first magnetic source has a minima magnetic field. Therefore after the particles are released from the first position (when the first position has changed from a maxima magnetic field to a minima magnetic field) and flow downstream with the continuous flow, the particles will be trapped again at the second position where second position has changed from a minima magnetic field to a maxima magnetic field.

[017] In this embodiment, it may be the case that the at least one magnetic source carrier moves again, to either a third position or back to the first position. In either case, the at least one second magnetic source is then distal to the second spatial location and hence generates a minima magnetic field at said second spatial location resulting in a dispersal of the magnetic particles assembled there. Concurrently, the at least one first magnetic source is then placed at the first spatial location along the at least one fluidic channel. In doing so, said at least one first magnetic source once again generates a maxima magnetic field at said first spatial location and that attracts the magnetic particles from the continuous fluid flow and assembles said magnetic particles at said first spatial location again.

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[018] In one exemplary embodiment of the invention, the magnetic source carrier may include a cylinder. In this embodiment, the cylinder may be arranged proximate to the fluidic channel, such that the cylinder is moveable via a rotation

about its central longitudinal axis. In this embodiment, the at least one magnetic source carrier, which is a cylinder, may include, as previously mentioned, at least one first magnetic source and at least one second magnetic source. Where there are two magnetic sources, the at least one first and second magnetic sources are
5 in an equidistant alternating spatial arrangement with respect to each other along the central rotational axis of the cylinder. In addition, each of the at least one second magnetic source is oriented to be perpendicular to its adjacent at least one first magnetic source. This embodiment, especially the orientation of the magnetic sources, is further described in detail below with respect to **Figure 2a**.

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[019] In another embodiment, the magnetic source carrier may include a disc arranged concentric (or simply directly beneath) to the fluidic channel. In this embodiment, the disc may be moveable via a rotation about its origin. The disc may include at least one circular ring and the at least one circular ring may include
15 the at least one first magnetic source arranged along its circumference.

[020] In another exemplary embodiment where the magnetic source carrier is a disc, the disc may further include another circular ring. In this embodiment, the another ring is arranged to be concentric to the at least one circular ring. The
20 another circular ring includes the at least one second magnetic source arranged along its circumference as well. The at least one circular ring and the another circular ring may be moveable independent of each other or moveable as a single entity. This embodiment is further described in greater detail with respect to **Figure 5a – Figure 5c below**.

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[021] In yet another exemplary embodiment, the magnetic source carrier may include a platform arranged parallel to the fluidic channel. In this embodiment, the platform is moveable via an oscillation about a median axis. In this embodiment, the platform may include a first and a second magnetic source carriage arranged
30 such that the fluidic channel is positioned in parallel between the first and second magnetic source carriage. In other words, the fluidic channel lies along the median axis about which the platform oscillates.

[022] In the above embodiment where the platform includes a first and a second magnetic source carriage, the at least one first magnetic source may be arranged at discrete points along the first magnetic source carriage and the at least one second magnetic source may be arranged at discrete points along the second magnetic source carriage. The arrangement of each consecutive at least one first magnetic source is such that it is distal (opposite) to a gap between two consecutive at least one second magnetic sources of the second magnetic source carriage. The first and the second magnetic source carriages may be adapted to oscillate independently of each other or in unison. In any case, at any one time, only one magnetic source carriage is proximate to the fluidic channel.

[023] All the preceding embodiments of the device of the invention may further include a motor that drives the movement of the magnetic source carrier. The motor may be an AC or a DC motor, for example. In the case of an AC motor, the motor may be a stepper motor, synchronous motor or an induction motor, for example. In the case of a DC motor, the motor may be a shunt wound motor, a series wound motor, a permanent magnet motor or a servomotor, for example.

[024] In addition, all the embodiments as described above may also have the at least one first magnetic source and/or the at least one second magnetic source embedded within the at least one magnetic source carrier. Alternatively, the respective magnetic sources may be arranged on the surface of the magnetic source carrier. The at least one first and second magnetic sources may include permanent magnets or electromagnets, or a combination thereof, for example.

[025] In addition to the above, all the preceding embodiments of the invention may also further include at least one capture magnetic source proximate to the outlet of the fluidic channel. The capture magnetic source is constant and does not vary as it is intended to capture all the magnetic particles having undergone the previous washing steps which are the result of the assembly and dispersal due to the varying magnetic fields.

[026] Another aspect of the invention relates to a system for washing and isolating magnetic particles in a continuous fluid flow. The system essentially includes at least one fluidic channel having an inlet at one end and an outlet at another end and any one of the embodiments of the device of the invention as
5 previously described.

[027] In one embodiment of the system the at least one fluidic channel may be a straight channel that extends across the length of the device as previously described. In another embodiment, the channel may be a meandering shape. In
10 yet another embodiment, the channel may have between two to four arms, for example, extending from a central core channel therefore effectively creating anywhere between two to four channels, each of which may be individually processed using any of the various embodiments of the device of the present invention previously described.

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[028] Yet another aspect of the present invention relates to a method of washing and isolating magnetic particles from a continuous fluid flow in at least one fluidic channel having an inlet at one end and an outlet at another end. The method includes the application of a magnetic field from a first magnetic source at a first
20 spatial location along the fluidic channel. This attracts the magnetic particles from the continuous fluid flow and assembles said magnetic particles at the first spatial location. Subsequently the first magnetic source is moved relative to the fluidic channel such that the magnetic field at said first spatial position decreases sufficiently to result in a dispersal of the assembled magnetic particles from the
25 first spatial location back into the continuous fluid flow.

[029] The assembly and dispersal of the magnetic particles is analogous to the washing cycle as previously mentioned. During the assembly and dispersal of the magnetic particles, said magnetic particles rotate and oscillate as they move from
30 a stationary position during assembly to a translational and rotational movement that includes oscillations. These movements during the dispersal of the magnetic particles have the effect of removing impurities that may be still attached to the analyte. Accordingly, the assembly and dispersal of the magnetic particles may be

taken to constitute one washing cycle, which serves to improve the purity of the analyte.

[030] In one embodiment, the above method may further include the application of a magnetic field from a second magnetic source at a second spatial location. The second spatial location is located downstream from the first spatial location along the fluidic channel. As in the application of the first magnetic field, the application of the second magnetic field attracts the magnetic particles from the continuous fluid flow and assembles said magnetic particles at the second spatial location. Subsequently, moving the second magnetic source relative to the fluidic channel such that the magnetic field at said second spatial position decreases sufficiently results in a dispersal of the assembled magnetic particles from the second spatial location back into the continuous fluid flow. This may be considered as an application of a second washing cycle. Using this same method, repeatedly, results in 'n' number of washing cycles being applied to the mixture containing the magnetic particles.

[031] Both embodiments of the method as described above include the application of a magnetic field from an at least one capture magnetic source at a capture spatial location proximate to the outlet of the fluidic channel. The magnetic field from the capture magnet, as described above, is constant and attracts and assembles the magnetic particles from the continuous fluid flow at the capture spatial location. The constant magnetic field is necessary in order to facilitate the subsequent removal of said magnetic particles assembled at the capture spatial location so that the analyte attached thereto may be further processed.

[032] Various aspects of the present invention will now be described with reference to the following illustrated exemplary embodiments of the present invention in which:

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[033] Figures 1a – 1c shows the effects of different configurations of the channel-magnet pole interface and its corresponding effect on a magnetic particle within the channel;

[034] **Figure 2a** shows a cylindrical shaped magnetic source carrier with a number of magnetic sources inserted in it, each adjacent magnetic source being perpendicular to each other; **Figure 2b** shows cross-sectional view about the line 5 X – X of the cylindrical shaped magnetic source carrier of **Figure 2a**;

[035] **Figure 3a** shows a magnetic source carrier with a fluidic channel on top of it; **Figure 3b** shows a meander shaped channel as used in conjunction with the magnetic source carrier of **Figure 2a**; **Figure 3c** shows a spiral shaped channel as
10 used in conjunction with the magnetic source carrier of **Figure 2a**;

[036] **Figure 4a** shows a schematic illustration of a trapping and releasing sequence of magnetic particles due to a magnetic field; **Figure 4b** is an illustration of a magnetic source carrier, a fluidic channel, and a motor to generate the
15 spinning motion of the magnetic source carrier;

[037] **Figure 5a** is a circular shaped magnetic source carrier with a number of permanent magnet inserted in it; **Figure 5b** is a top view of the magnetic source carrier of **Figure 5a**; **Figure 5c** illustrates concentric magnetic source carriers for
20 programmable transport of magnetic particles;

[038] **Figure 6a** and **6b** are illustrations of an embodiment of the invention;

[039] **Figure 7a** illustrates an embodiment of the invention where the magnetic
25 source carrier includes concentric rings, a fluidic channel and a motor to generate the rotation motion in the magnetic source carrier; **Figure 7b** is a diagram that illustrates the washing and isolation sequence of magnetic particles as carried out by the embodiment of **Figure 7a**;

30 [040] **Figure 8a** and **8b** are a schematic diagram and an illustration, respectively, of another embodiment of the invention;

[041] **Figure 9a and Figure 9b** are alternative embodiments of magnetic source carriers;

[042] **Figure 10** is another illustration of an alternative embodiment where a magnetic source carrier has a dual pole magnetic structure.

[043] **Figure 11a, 11b and 11c** are photographs of the embodiment of the invention as illustrated in **Figures 3a, 7a and 3c**, respectively;

10 [044] **Figure 12** shows snap shots of magnetic particle concentrations using the embodiment of **Figures 2, 3 and 11a** at different flow rates (200 $\mu\text{l}/\text{min}$, 300 $\mu\text{l}/\text{min}$ and 500 $\mu\text{l}/\text{min}$;

[045] **Figure 13** shows snap shots of magnetic particles concentration using the 15 embodiment of **Figures 5, 6, 7 and 11b**;

[046] **Figure 14a** shows a concentration efficiency of the system described by **Figures 2, 3 and 11a** at different flow rate of the sample in the fluidic channel and **Figure 14b** shows estimated purification efficiency as measured by the system 20 described by **Figures 2, 3 and 11a**; and

[047] **Figure 15** shows a series of graphs that illustrate concentration efficiency as a function of the oscillation frequency at different flow rates using the embodiment of **Figure 8**.

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[048] **Figures 1a – 1c** shows the effects of different configurations of the channel – magnet pole interface and its corresponding effect on a magnetic particle within the channel. In **Figures 1a – 1c**, the magnetic source **1** is shown at different orientations with respect to the fluidic channel **10**. In **Figure 1a**, the magnetic 30 source **1** is at a vertical orientation with its south pole directly beneath the fluidic channel **10**. At this time, the magnetic field produced by the magnetic source **1**, as experienced in the fluidic channel **10**, is at a maximum. Accordingly, the magnetic

particles **12** are illustrated as being assembled or trapped at the bottom of the fluidic channel **10**.

[049] In **Figure 1b**, the magnetic source **1** is rotated such that it is at an angle ϕ to the fluidic channel **10**. At this instant, the magnetic field produced by the magnetic source **1**, as experienced in the fluidic channel **10**, is no longer at a maximum. As such, a magnetic particle **12a** is seen to be dispersed as the decreased magnetic field is no longer able to hold all the previously assembled magnetic particles **12** any longer in view of the force exerted on the magnetic particles **12** due to the shear forces from the continuous flow within the fluidic channel **10**.

[050] In **Figure 1c**, the magnetic source **1** is oriented horizontal to the fluidic channel **10**. At this instant, the magnetic field, as produced by the magnetic source **1**, and as experienced in the fluidic channel **10**, is at a minimum. Accordingly, the magnetic field is no longer strong enough to trap the magnetic particles **12a** and said magnetic particles **12a** disperse and rejoin the continuous flow.

[051] **Figures 2a** and **2b** show a cylindrical shaped magnetic source carrier **22** with a number of magnetic sources **1** and **2** inserted in it, each adjacent magnetic source **1** and **2** being perpendicular to each other. In the cylindrical magnetic source carrier **22**. The magnetic sources **1** and **2** are inserted inside the magnetic source carrier **22** with their longitudinal axis being perpendicular to the longitudinal axis of the carrier **22**. In addition, and as shown, each consecutive magnetic source **1** is arranged in a manner such that it is perpendicular to its adjacent magnetic source **2** and, at the same time, both magnetic sources **1** and **2** are perpendicular to the longitudinal magnetic source carrier **22**.

[052] **Figure 3a** shows a magnetic source carrier **22** with a fluidic channel **10** on top of it. The magnetic source carrier **22** is positioned directly beneath the fluidic channel **10** with its longitudinal axis parallel to that of the channel **10** as shown in **Figure 3a**. The magnetic source carrier **22** is actuated by a motor (not shown) and spins in the direction indicated. When the magnetic source carrier **22** spins, this

causes the magnetic field to vary between maxima and minima values along the length of the fluidic channel **10**. The maxima and minima values occur between any two adjacent perpendicular magnets as shown in **Figure 2a** and **Figure 3a**, for example. Accordingly, magnetic particles **12** follow the magnetic field maxima, which shift between any two adjacent perpendicular magnets due to this spinning.

[053] It should be noted that the magnetic particles accumulate (or concentrate) at the magnetic field maxima at locations when the poles of the magnetic sources (either **1** or **2**) are facing the base of the fluidic channel **10**. As such, when the cylinder spins and the poles of the magnetic sources **1** and **2** are no longer facing the base of the fluidic channel **10**, the magnetic field experienced by the magnetic particles drops. Thus, the magnetic particles **12** are demagnetized and disperse back into the continuous flow system and are carried along till they reach the next magnetic field at maxima where said magnetic particles **12** are re-magnetized and assembled.

[054] The magnetic particles **12** are typically made of super paramagnetic materials and as such, are capable of rapid re-magnetization and demagnetization. This is important as said it is optimal that the magnetic particles **12** exhibit no magnetic hysteresis or "magnetic memory" as this would prevent (work against) any applied magnetic field from assembling or dispersing the magnetic particles and translating across the fluidic channel in general. This translational motion of the particles is an advantageous effect of the device of the present invention as the magnetic particles **12**, when translating between two adjacent magnetic sources **1** and **2**, within a period of time (washing time T_w) provide a washing step for the particles (and hence the analyte) and this washing step is repeated continuously as the magnetic particle translates along the fluidic channel **10**.

[055] Efficiency of the device may be further increased by using, as shown in **Figure 3b**, a meander shaped channel as used in conjunction with a plurality of magnetic source carriers **22**. This embodiment of the fluidic channel **10** serves to increase the efficiency of the device of the present invention as the fluidic channel

10 is now elongated, i.e. a greater volume of analyte may be processed with more washing cycles thereby increasing the purity of the analyte obtained. Alternatively, a spiral form of the channel may also be used as shown in **Figure 3c**. **Figure 3c** shows a spiral shaped channel as used in conjunction with the magnetic source carrier of **Figure 2a**. A magnetic source carrier **22** rotates in a central core of the spiral shaped fluidic channel **10**.

[056] **Figure 4a** shows a schematic illustration of a trapping and releasing sequence of magnetic particles due to a magnetic field. The magnetic sources **1a**, **1b** and **1c** are orientated such that their respective south poles are facing the base of the channel **10**. As mentioned above, at the particular locations of the magnetic sources **1a**, **1b** and **1c** along the length of the channel **10**, a maxima magnetic field is established. Correspondingly, the respective maxima magnetic fields assemble the magnetic particles **12**. As the magnetic source carrier (not shown) spins, the magnetic field at these locations drops sharply to a minimum until the magnetic sources are oriented with their north poles facing the channel, thereby generating a maxima magnetic field at these locations again.

[057] During the transition time between the regeneration of the maximum magnetic field, the magnetic particles **12a** behave as weak magnetic particles. In other words, this transition time allows the particles to be detached from each other, thereby decreasing the total concentration and consequently allows for a washing of each magnetic particle **12a** releasing any impurity that may have been trapped during the magnetic particle assembly processes. **Figure 4b** is an illustration of an embodiment of the invention that includes a magnetic source carrier **22**, a fluidic channel **10** above the magnetic source carrier **22**, and a motor **42** to generate the spinning motion of the magnetic source carrier **22** in order to vary the magnetic field applied to the fluidic channel **10**. As in the embodiment of the magnetic source carrier shown in **Figure 2a**, the magnetic source carrier **22** shown here also has magnetic sources **1** and **2** arranged in a similar fashion as described with respect to **Figure 2a**.

[058] **Figure 5a** is a circular disc-shaped magnetic source carrier **52** with a number of magnetic sources **5** inserted in it and around its circumference. Unlike the magnetic source carrier **22** in the previous embodiment, a rotation of this magnetic source carrier **52** will maintain the orientation of the magnets and will
5 translate them instead of rotating them with respect to the fluidic channel. **Figure 5b** is a top view of the magnetic source carrier of **Figure 5a** and shows the equidistant and uniform distribution of the magnetic sources **5** around the circumference of the magnetic source carrier **52**. The use of this embodiment if the magnetic source carrier **52** in an alternative embodiment of the invention will be
10 described later below with respect to **Figure 6**.

[059] **Figure 5c** illustrates another embodiment of the magnetic source carrier **52** where the carrier **52** comprises a plurality of concentric rings **52a – 52d** that carry magnetic sources **5a – 5d**, respectively. The use of this embodiment if the
15 magnetic source carrier **52** in an alternative embodiment of the invention will be described later below with respect to **Figure 7**.

[060] **Figure 6a** and **6b** are illustrations of the magnetic source carrier **52** with a fluidic channel **10** on top of it. The magnetic source carrier **52** includes a plurality
20 of magnetic sources **5** uniformly distributed around the circumference of the magnetic source carrier **52**. In this embodiment, the magnetic source carrier **52** is supported by a supporting base **62**. The fluidic channel **10** on top of the magnetic source carrier **52** is in the form of a cross, i.e. a central portion with four arms extending from said central portion. The arms extend over the magnetic source
25 carrier **52** and therefore, also over the magnetic sources **5** carried by the magnetic source carrier **52**, causes the fluidic channel **10** to be subject to any (maximum) magnetic field generated/applied by the magnetic source carrier **52**.

[061] In **Figure 6b**, the fluidic channel **10** is rotated about its centre of rotation
30 such that the axis Y – Y is also rotated, as compared to **Figure 6a**. The fluidic channel **10** no longer extends over the magnetic sources **5** and is thus, also no longer subject to the maximum strength of the magnetic field. Instead, it may be expected that the magnetic field strength as applied to the now rotated fluidic

channel **10** is at a minimum. It should be noted that the essential principle illustrated in this embodiment of the invention is one where the rotating/translating mechanism modulates the strength of the magnetic field (and therefore, the magnetic force) on the magnetic particles **12** in the fluidic channel **10** from maxima to minima.

[062] Figure **7a** illustrates the above-described embodiment of the invention where the magnetic source carrier **52** includes concentric rings, a fluidic channel **10** and a motor **42** to generate the rotation motion in the magnetic source carrier **52**. Referring to Figure **7b**, which illustrates a step-by-step operation of this embodiment of the invention, initially the magnetic particles **12** are trapped at the most inner ring **(A)**. By rotating the magnetic source carriers **52a – 52d** together by an angle ϕ , for example, the magnetic source **5a** in the most inner concentric ring of the magnetic source carrier **52a** will shift from its location beneath the channel to a new location far enough from the channel while concurrently, the magnetic source **5b** in the second carrier **52b** will then be situated beneath the channel at **(B)**. As such, the magnetic force vanishes at the first location **(A)** to be minima and increases to maxima at the location **(B)**.

[063] The magnetic particles **12** then move, as described earlier, from **(A)** to **(B)**. This trapping/assembling, followed by releasing, constitutes a washing step and is repeated by the continuous rotation of the magnet carriers **52a – 52d**. After the magnetic particles **12** are released from the outermost magnetic source at **(D)**, said magnetic particles **12** may be trapped in a reservoir with a stationary magnetic particle capture magnet (not shown).

[064] Figure **8a** and **8b** are a schematic diagram and an illustration, respectively, of another embodiment of the invention. In this embodiment, the magnetic source carrier **84a** and **86a** oscillates about a mean position to modulate the magnetic field strength applied to the fluidic channel **10**. The magnetic source carrier **86a** may function in solo or in tandem with an additional carrier **84a**, as illustrated in Figure **8b**. The start position of the carriers **84a** and **86a** may be with one carrier, such as carrier **84a** for example, proximate to the fluidic channel **10** while the other

(carrier **86a**) is distal from said channel **10**. By this arrangement, a maximum magnetic field is only applied on one side (either topside or lateral side) of the fluid channel **10**, and correspondingly, the magnetic particles **12** will tend to assemble at the locations at which the maximum magnetic fields are applied (due to the 5 magnetic sources **1a** and **1b**).

[065] Subsequently, the carrier **84a** will oscillate and move away from the fluidic channel **10** while concurrently, the carrier **86a** oscillates and moves proximate to the channel **10**, thereby applying a magnetic field on a corresponding (opposite) 10 side of the channel **10**. As such, since the maximum magnetic field is now applied to a corresponding side of the channel **10**, the magnetic particles will be attracted towards said side. Thus, a dispersion of the magnetic particles takes place from the original side at which the maximum magnetic field (due to carrier **84a**) was applied towards the present side of the channel where carrier **86a** now applies the 15 magnetic field. During the dispersion, as the concentration of magnetic particles **12** is lower, and due to the shear forces exerted on the magnetic particle **12** from the fluid flow in the channel **10**, the magnetic particles **12** get "washed", i.e. any impurities that are attached to the analyte to which the magnetic particle is bound to get washed away during the translation from one point of a maximum magnetic 20 field to the next along the channel **10**.

[066] Figure **8a** is a schematic diagram of the path of the magnetic particles **12** in this embodiment of the invention. The magnetic sources **1a** – **1e** may be from carrier **84a** and magnetic sources **2a** – **2d** may be from carrier **86a**, for example. 25 As such, and as described above, the washing step takes place as the magnetic particles **12** translate between the points at which the various magnetic sources (**1a** – **1e** and **2a** – **2d**) apply maximum magnetic fields across the channel **10**. In this embodiment, a magnetic particle capture magnet (or a fixed unmodulated magnetic source) **82** is placed at the end of the channel **10**, or proximate to the 30 outlet, or at any other location along the channel that is convenient for extraction. This magnet **82** assembles all the magnetic particles **12** previously washed and is adapted to be removable from the channel such that the magnetic particles (and

their analytes) are also removed along with it, thereby completing the isolation step.

[067] **Figure 9a** and **Figure 9b** are alternative embodiments of magnetic source carriers. In the alternative embodiment of **Figure 9a**, the magnetic source carrier **150** includes a magnetic source **152**. The carrier **150** is initially at position **150a** at one end of the channel **10**. At this position **150a**, the magnetic source **152** is oriented vertically such that its south pole is closest to the channel **10** thereby applying a maximum magnetic field to the channel **10**. Magnetic particles **12** are correspondingly attracted and assembled at the spatial location along the fluidic channel at which the maximum magnetic field is generated.

[068] Subsequently, the carrier **150** rolls along the fluidic channel through positions **150b** – **150d** before reaching position **150e**. During the transition between position **150a** and **150e** (i.e. at positions **150b** – **150d**), the magnetic field applied to the channel **10** is less than the maximum, and also ought to be insufficient to hold the assembled magnetic particles **12** at position **150a** in place any longer. As such, the magnetic particles **12** will disperse into the continuous fluid flow and undergo the washing step as previously described with respect to the previous embodiments above.

[069] Upon reaching position **150e**, the magnetic particles **12** are once again subject to a maximum magnetic field as applied by the carrier **150**, which is also at said position **150e**. Accordingly, the magnetic particles **12** reassemble at the spatial location **150e**, thus completing one washing cycle. This cycle may be repeated over the entire length of the channel **10** in order to improve the purity of any analyte attached to the magnetic particles **12**.

[070] **Figure 9b** is an illustration of a further alternative embodiment where a magnetic source carrier **156** has a quadruple pole magnetic structure. In other words, it has four magnetic sources **154** uniformly distributed, each at ninety degrees to its preceding magnetic source. As above, when one of the four is oriented in the vertical position, it generates a maximum magnetic field, which

functions as described above. Also as mentioned above, the magnetic source carrier **156** in this embodiment translates along the length of the fluidic channel **10**. Unlike the previous embodiment, since the carrier **156** of this embodiment has four magnetic sources **154**, the rate of modulation of the magnetic field, i.e. the frequency of successive maximum magnetic fields occurs at a higher rate than in the previous exemplary embodiment. Accordingly, more washing cycles may be generated with a single rotation of the magnetic source carrier **156** as compared to say the magnetic source carrier **150**, for example.

[071] Figure **10** is another illustration of an alternative embodiment where a magnetic source carrier **160** has a dual pole magnetic structure. Essentially this means that there are two magnetic sources **1** located on the magnetic source carrier **160**. Accordingly, about fifty percent less washing cycles may be generated with a single rotation of the magnetic source carrier **160** as compared to say the magnetic source carrier **156**, for example.

[072] Figure **11a**, **11b** and **11c** are photographs of actual embodiments of the invention as illustrated in Figures **3a**, **7a** and **3c**, respectively. As described above, each embodiment includes the basic feature of a magnetic source carrier **22** and **52** including at least one magnetic source (not shown), wherein the magnetic fields generated by the respective magnetic sources, and as applied to their respective fluid channels **10**, are modulated by a movement (spinning, rotation or oscillation) of the magnetic source carriers.

[073] To test the devices efficiency for magnetic beads concentration and purification three solutions were prepared. These solutions are:

1. Magnetic particles suspension of specified dilution;
2. Non-magnetic particles suspension of specified dilution;
3. 1:1 mixture of magnetic & non magnetic suspension of above specified solutions

[074] The concentration efficiency test has been done by passing solution (1) through the system and collecting the waste at outlet. To quantify the concentration efficacy, the relative absorbance of the waste samples was measured against the control sample (taken from the sample prior passing through 5 the magnetic system) using a spectrophotometer. Alternatively, the number of beads before in the sample before and after injection to the system was counted using a haemocytometer. The concentration efficiency can be given by:

$$\text{Concentration} = \left(1 - \frac{Q3}{Q1}\right) \times 100\%$$

Q1: Number of the magnetic beads in the sample before the injection into the 10 system

Q2: Number of magnetic particles that trapped in the system (concentrated)

Q3: Number of un-trapped magnetic particles

[075] To measure the sample loss through the fluidic channel, a normalization 15 test was done by passing sample (2) through the channel and collecting the waste at the outlet. The number of particles was quantified by counting the number of particles in the samples (from the outlet) and comparing it with a control sample using a haemocytometer. This gives an approximate measure of the loss of particles during typical run of immunomagnetic separation (IMS) experiment.

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[076] The purification efficiency of the system was measured by passing solution (3) through the system and collecting the waste sample at the outlet and using the haemocytometer the non-magnetic particles were counted and compared to the control sample by considering the loss. The purification efficiency can be given 25 by:

$$\text{Purification} = \left(1 - \frac{Q2 - q}{Q1}\right) \times 100\%$$

30 Q1: Number of the non-magnetic beads in the sample before the injection into the system

Q2: Number of non-magnetic particles in the waste sample

q: Number of beads lost in system during the IMS experiments

[077] Figure 12 shows snap shots of magnetic particle concentrations using the embodiment of Figures. 2, 3a , and 11a at different flow rates (200 μ l/min, 300 μ l/min and 500 μ l/min;

[078] Figure 13 shows snap shots of magnetic particles concentration using the embodiment of Figures 5, 6, 7 and 11b;

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[079] Figure 14a shows a concentration efficiency of the system described by Figures 2, 3 and 11a at different flow rate of the sample in the fluidic channel and Figure 14b shows estimated purification efficiency as measured by the system described by Figures 2, 3 and 11a.

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[080] Figure 15 shows a series of graphs that illustrate concentration efficiency as a function of the oscillation frequency at different flow rates using the embodiment of Figure 8.

20 [081] It should be noted that the exemplary embodiments described above merely serve to aid in the understanding of various aspects of the present invention. Accordingly, said various aspects of the present invention are not to be construed to as being limited to said exemplary embodiments, but rather, as defined by the claims that follow.

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Claims

What is claimed is:

1. A device for washing and isolating magnetic particles from a continuous fluid flow in at least one fluidic channel having an inlet at one end and an outlet at another end, said device comprising:

at least one magnetic source carrier arranged proximate to the at least one fluidic channel, wherein the at least one magnetic source carrier is moveable between a first position and a second position; said at least one magnetic source carrier comprising:

at least one first magnetic source, and

at least one second magnetic source;

wherein a movement of the at least one magnetic source carrier to the first position places the at least one first magnetic source at a first spatial location along the at least one fluidic channel such that said at least one first magnetic source generates a maxima magnetic field at said first spatial location that attracts the magnetic particles from the continuous fluid flow and assembles said magnetic particles at said first spatial location;

wherein a movement of the at least one magnetic source carrier to the second position places the at least one first magnetic source distal from the first spatial location such that said magnetic field at said first spatial location is at a minima and the magnetic particles disperse from said first spatial location; and

wherein the at least one magnetic source carrier further comprises at least one second magnetic source, wherein said at least one second magnetic source is arranged in a spatial arrangement with respect to the at least one first magnetic source such that the movement of the at least one magnetic source carrier to the second position places the at least one second magnetic source at a second spatial location, which is downstream from the first spatial location, such that said at least one second magnetic source generates a maxima magnetic field at said second spatial location that attracts the

magnetic particles from the continuous fluid flow and assembles said magnetic particles at said second spatial location..

2. The device according to claim 1, wherein the magnetic source carrier comprises a cylinder arranged proximate to the fluidic channel, wherein the cylinder is moveable via a rotation about its central longitudinal axis.

3. The device according to claim 1, wherein the magnetic source carrier comprises a disc arranged concentric to the fluidic channel, wherein the disc is moveable via a rotation about its origin.

4. The device according to claim 1, wherein the magnetic source carrier comprises a platform arranged parallel to the fluidic channel, wherein the platform is moveable via an oscillation about a median axis.

5. The device according to claim 2, wherein the at least one first magnetic source and the at least one second magnetic source are in an equidistant alternating spatial arrangement along the central rotational axis of the cylinder with respect to each other, and each of the at least one second magnetic source is oriented to be perpendicular to its adjacent at least one first magnetic source.

6. The device according to claim 3, wherein the disc comprises at least one circular ring.

7. The device according to claim 6, wherein the at least one circular ring includes the at least one first magnetic source arranged along its circumference.

8. The device according to claim 6 or 7, wherein the disc further comprises another circular ring, concentric to the at least one circular ring, wherein said another circular ring includes the at least one second magnetic source arranged along its circumference.

9. The device according to claim 8, wherein the at least one circular ring and the another circular ring are moveable independent of each other.

10. The device according to claim 4, wherein the platform comprises a first and a second magnetic source carriage arranged such that the fluidic channel is positioned in parallel there between, and the fluidic channel lies along the median axis about which the platform oscillates.

11. The device according to claim 10, wherein the at least one first magnetic source is arranged at discrete points along the first magnetic source carriage and the at least one second magnetic source is arranged at discrete points along the second magnetic source carriage such that the arrangement of each consecutive at least one first magnetic source is distal to a gap between two consecutive at least one second magnetic sources of the second magnetic source carriage.

12. The device according to claim 11, wherein the first and the second magnetic source carriages oscillate independently of each other.

13. The device according to any of the preceding claims, further comprising a motor that drives the movement of the magnetic source carrier.

14. The device according to any of the preceding claims, wherein the at least one first magnetic source and the at least one second magnetic source are embedded within the at least one magnetic source carrier.

15. The device according to any of the preceding claims, wherein the at least one first and second magnetic sources comprise permanent magnets or electromagnets.

16. The device according to any of the preceding claims, further comprising at least one capture magnetic source proximate to the outlet of the fluidic channel.

17. A system for washing and isolating magnetic particles in a continuous fluid flow, said system comprising:

- at least one fluidic channel having an inlet at one end and an outlet at another end; and

- at least one magnetic source carrier arranged proximate to the at least one fluidic channel, wherein the at least one magnetic source carrier is moveable between a first position and a second position; said at least one magnetic source carrier comprising:

- at least one first magnetic source, and

- at least one second magnetic source,

- wherein a movement of the at least one magnetic source carrier to the first position places the at least one first magnetic source at a first spatial location along the at least one fluidic channel such that said at least one first magnetic source generates a maxima magnetic field at said first spatial location that attracts the magnetic particles from the continuous fluid flow and assembles said magnetic particles at said first spatial location;

- wherein a movement of the at least one magnetic source carrier to the second position places the at least one first magnetic source distal from the first spatial location such that said magnetic field at said first spatial location is at a minima and the magnetic particles disperse from said first spatial location; and

wherein the at least one magnetic source carrier further comprises at least one second magnetic source, wherein said at least one second magnetic source is arranged in a spatial arrangement with respect to the at least first magnetic source such that the movement of the at least one magnetic source carrier to the second position places the at least one second magnetic source at a second spatial location, which is downstream from the first spatial location, such that said at least one second magnetic source generates a maxima magnetic field at said second spatial location that attracts the magnetic particles from the continuous fluid flow and assembles said magnetic particles at said second spatial location.

18. The system according to claim 17, wherein the magnetic source carrier comprises a cylinder arranged proximate to the fluidic channel, wherein the cylinder is moveable via a rotation about its central longitudinal axis.

19. The system according to claim 17, wherein the magnetic source carrier comprises a disc arranged concentric to the fluidic channel, wherein the disc is moveable via a rotation about its origin.

20. The system according to claim 17, wherein the magnetic source carrier comprises a platform arranged parallel to the fluidic channel, wherein the platform is moveable via an oscillation about a median axis.

21. The system according to claim 18, wherein the at least one first magnetic source and the at least one second magnetic source are in an equidistant alternating spatial arrangement along the central rotational axis of the cylinder with respect to each other, and each of the at least one second magnetic source is oriented to be perpendicular to its adjacent at least one first magnetic source.

22. The system according to claim 19, wherein the disc comprises at least one circular ring.

23. The system according to claim 22, wherein the at least one circular ring includes the at least one first magnetic source arranged along its circumference.

24. The system according to claim 22 or 23, wherein the disc further comprises another circular ring, concentric to the at least one circular ring, wherein said another circular ring includes the at least one second magnetic source arranged along its circumference.

25. The system according to claim 24, wherein the at least one circular ring and the another circular ring are moveable independent of each other.

26. The system according to claim 20, wherein the platform comprises a first and a second magnetic source carriage arranged such that the fluidic channel is positioned in parallel there between, and the fluidic channel lies along the median axis about which the platform oscillates.

27. The system according to claim 26, wherein the at least one first magnetic source is arranged at discrete points along the first magnetic source carriage and the at least one second magnetic source is arranged at discrete points along the second magnetic source carriage such that the arrangement of each consecutive at least one first magnetic source is distal to a gap between two consecutive at least one second magnetic sources of the second magnetic source carriage.

28. The system according to claim 27, wherein the first and the second magnetic source carriages oscillate independently of each other.

29. The system according to any of claims 17 - 28, further comprising a motor that drives the movement of the magnetic source carrier.

30. The system according to any of claims 17 – 29, wherein the at least one first magnetic source and the at least one second magnetic source are embedded within the at least one magnetic source carrier.

31. The system according to any of claims 17 - 30, wherein the at least one first and second magnetic sources comprise permanent magnets or electromagnets.

32. The system according to any of claims 17 - 31, further comprising at least one capture magnetic source proximate to the outlet of the fluidic channel.

33. The system according to any of claims 17 - 32, wherein the at least one fluidic channel is straight or meandering in shape between its inlet and outlet.

34. A method of washing and isolating magnetic particles from a continuous fluid flow in at least one fluidic channel having an inlet at one end and an outlet at another end, said method comprising:

applying a magnetic field from a first magnetic source at a first spatial location along the fluidic channel thereby attracting the magnetic particles from the continuous fluid flow and assembling said magnetic particles at the first spatial location;

moving the first magnetic source relative to the fluidic channel such that the magnetic field at said first spatial position decreases sufficiently to result in

a dispersal of the assembled magnetic particles from the first spatial location back into the continuous fluid flow;

applying a magnetic field from a second magnetic source at a second spatial location, downstream from the first spatial location along the fluidic channel, thereby attracting the magnetic particles from the continuous fluid flow and assembling said magnetic particles at the second spatial location; and

moving the second magnetic source relative to the fluidic channel such that the magnetic field at said second spatial position decreases sufficiently to result in a dispersal of the assembled magnetic particles from the second spatial location back into the continuous fluid flow.

35. The method of claim 34 further comprising:

applying a magnetic field from an at least one capture magnetic source at a capture spatial location proximate to the outlet of the fluidic channel thereby attracting and assembling the magnetic particles from the continuous fluid flow at the capture spatial location; and

removing said magnetic particles assembled at the capture spatial location.