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Chapter 3

Magnetic Field-Based Technologies for Lab-on-a-Chip Applications

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Additional information is available at the end of the chapter

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Abstract

In the last decades, LOC technologies have represented a real breakthrough in the field of in vitro biochemical and biological analyses. However, the integration of really complex functions in a limited space results extremely challenging and proper working principles should be identified. In this sense, magnetic fields revealed to be extremely promising. Thanks to the exploitation of external magnetic sources and to the integration of magnetic materials, mainly high aspect ratio micro-/nanoparticles, non-contact manipulation of biological and chemical samples can be enabled. In this chapter, magnetic field-based technologies, their basic theory, and main applications in LOC scenario will be described by foreseeing also a deeper interaction/integration with the typical technologies of microrobotics. Attention will be focused on magnetic separation and manipulation, by taking examples coming from traditional LOC devices and from microrobotics.

Keywords: Lab-on-chip, microrobotics, magnetic nanoparticles, magnetophoresis, magnetic manipulation

1. Introduction

The need of reliable, precise, and fast techniques for biochemical and biological analysis has fostered the search for miniaturized systems integrating multiple laboratory techniques, assays, and procedures into a really small chip, up to few square centimeters in size. These small platforms, named lab-on-a-chip (LOC) or, less frequently, micro total analysis systems (μTAS), have historically been fabricated in silicon and/or glass using semiconductor processing techniques. More recently, polymer-based devices emerged, thanks to the introduction of soft

lithography [1]. LOC devices can be considered as sophisticate microsystems embedding mechanical, electronic, and fluidic functions [2], aiming at mixing, pumping, and manipulating samples. It is possible to identify a wide literature concerning LOC systems, in which a variety of applications ranging from biological assays, drug sorting and testing, DNA extraction, cell manipulation, etc., have been explored.

The use of LOC devices for laboratory tasks execution offers several advantages: reduced sample and reagent volumes, fast sample processing, high sensitivity and spatial resolution, increased detection accuracy, low contamination, high throughput, and reliability thanks to the possibility to automate some processes, without depending on human operator skills [3].

Due to the really small dimensions of LOC devices, the major role is played by surface effects with respect to inertial ones. Consequently, traditional actuation strategies cannot be exploited for actuation in LOCs. Fluidic actuation is the most commonly employed strategy, but electrostatic, magnetic, and chemical motion has been reported as well.

LOC systems can be distinguished in continuous-flow and stationary devices, depending on the role played by the fluidic actuation in the execution of the desired tasks. In continuous-flow devices, microfluidic forces are responsible for the effects experienced by the sample (e.g., beads, liquids, or droplets). In static flow devices, although the working environment is still a fluid, additional actuation strategies, such those based on magnetic fields, are exploited for effectively executing the desired task.

Depending on the working environment and on the object lengthscale, the most effective physical principle to be exploited in order to achieve the desired objective can change significantly. **Figure 1** shows the trend of different physical effects at varying of the manipulated object dimension. At the microscale, due to the capillary forces and to low Reynolds numbers, it is quite hard to manipulate or mix liquids and particles by exploiting only fluidic forces or direct manipulation, and the exploitation of other actuation strategies showing high efficiency at the microscale is required. In this sense, magnetic field-based strategies exploitation could be a valid solution. In LOC scenarios, in fact, the magnetic field sources can be really close to the working environment, thus compensating the rapid decay of magnetic force with the distance between the source and the object [4]. Furthermore, the exploitation of magnetic fields enables non-contact manipulation [5] also for biological samples, thus paving the way for a wide variety of applications in biology and medicine. In this chapter, the force balance acting on a micro-object in a LOC will be analyzed with a particular focus on magnetism basic theory. The exploitation of magnetic fields for torque and force generation will be considered, especially for magnetic separation and magnetic manipulation applications. Techniques employed both to endow an object with magnetic properties and to characterize it will be described. Finally, potential applications of magnetic field-based strategies in LOCs will be reviewed. Throughout the chapter, technologies and examples not typical of LOCs but deriving, for example, from the world of microrobotics will be introduced, thus foreseeing a deeper and deeper interaction/integration between these two fields.

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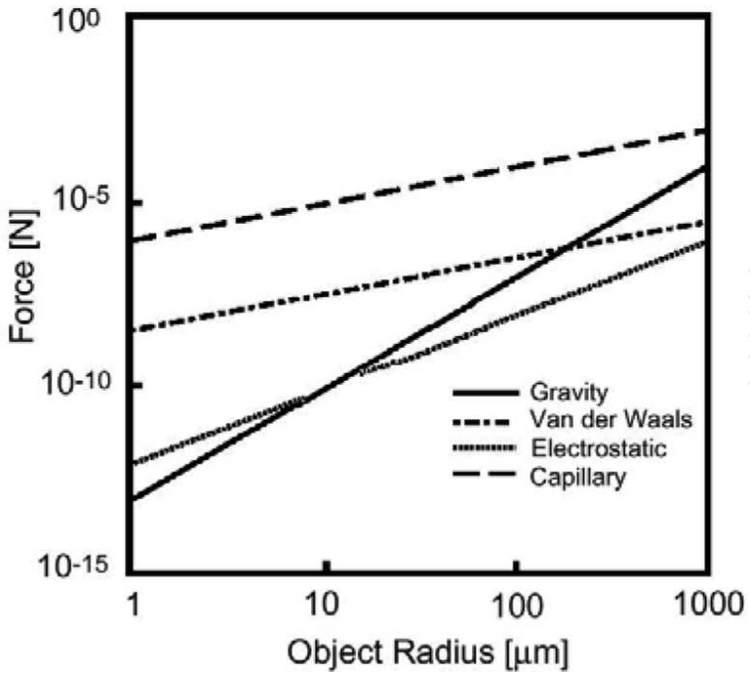

Figure 1. Scaling of different forces in function of the size of the object.

2. Physics at the microscale: key principles

According to Newton's second law, when considering a magnetic microcarrier with mass m_p and moving in a fluidic environment with velocity v, the following equilibrium equation should be considered:

$$m_p \frac{dv}{dt} = \boldsymbol{F}_m + \boldsymbol{F}_g + \boldsymbol{F}_d + \boldsymbol{F}_b \tag{1}$$

Several physical effects, including the magnetic force F_m, the fluidic drag force F_d, the net gravitational force F_g that take into account also the fluidic lift effect, and the Brownian interaction force F_b contribute to the force balance of the moving object. In the following, the Brownian force, representing fluid-object and inter-objects interactions, will be neglected as it is really weak with respect to the other contributions. The other forces contributing to the equilibrium will be analyzed more in detail.

2.1. Fluidic drag force

Navier–Stokes equations completely define a fluid velocity in space and time. From these equations, it is possible to derive the Reynolds number (*Re*), a dimensionless quantity that is proportional to the ratio between the fluid's inertia and its viscosity and that allows to define a fluid's behavior when it flows around an object. Given the fluid density ρ, the dynamic

viscosity η, the object maximum velocity with respect to the fluid v and a characteristic linear dimension L, Re can be defined as:

$$Re = \frac{\rho v L}{\eta} \tag{2}$$

Usually, in both microrobotics and LOC applications, a low-Re regime, typically defined for $Re < 10$, applies. At low Re, surface and capillary forces play an important role compared to inertia and temporal variations of the flow pattern. Due to the relative importance of surface effects, flow at low Re-number strongly depends on object geometry. Thus, it is interesting to derive the viscous drag force acting on the object. By approximating the object to a sphere with radius r put in an infinite extent of fluid, the viscous drag force can be calculated as a linear function of the sphere's velocity through the fluid:

$$\boldsymbol{F}_d = 6\pi\eta r(\boldsymbol{v}_f - \boldsymbol{v}_p) \tag{3}$$

where v_f and v_p are the fluid and the sphere velocity, respectively.

2.2. Gravitational force

Inertial and gravitational forces play a minor role at low Re. When considering a micro-object immersed in a liquid, usually net gravitational force is taken into account. In fact upthrust forces, responsible for body buoyancy, should be considered in addition to gravitational force, which acts in the opposite direction:

$$\boldsymbol{F}_g = -V_p\left(\rho_p - \rho_f\right)\boldsymbol{g} \tag{4}$$

In Eq. (4), V_p and ρ_p are object volume and density, ρ_f is the fluid density, and g is the gravity acceleration.

2.3. Magnetic force

The force acting on an object immersed in a magnetic field depends both on the field features and on the object properties. The magnetic force acting on a magnetic microstructure can be modeled by using the "effective" dipole moment method, in which a magnetic object is replaced by an "equivalent" point dipole with a moment $m_{p,eff}$ [6]. The force on the dipole is given by:

$$\boldsymbol{F}_m = \mu_f(\boldsymbol{m}_{p,eff} \cdot \nabla)\boldsymbol{B} \tag{5}$$

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where μ_f is the magnetic permeability of the medium, $m_{p,eff}$ is the "effective" dipole moment of the object, and B is the magnetic field produced by an external source acting at the center of the target object, where the equivalent point dipole is located.

The dipole moment ***m*** strictly depends on object volume and magnetic properties and it can be defined as:

$$\boldsymbol{m} = \boldsymbol{M} \cdot V \tag{6}$$

where M and V are the magnetization and the volume of the dipole, respectively.

As mentioned, the force exerted on such dipole varies upon the features of the magnetic field sources. It also depends on the distance between the source and the target object. If considering a permanent magnet, the magnetic field density at a generic point P can be expressed as:

$$\boldsymbol{B} = \frac{\mu_0}{4\pi}\left(\frac{3(\boldsymbol{m}\cdot\boldsymbol{r})\boldsymbol{r}}{|r|^5} - \frac{\boldsymbol{m}}{|r|^3}\right) \tag{7}$$

with *r* being the distance vector connecting the field source and the point P.

3. Classification of magnetic materials, magnetization, and characterization of micro-objects

One of the greatest advantages of magnetic actuation lies in the possibility to transfer powering and actuation in a wireless fashion. Remote magnetic actuation relies on the coupling, namely the creation and maintenance of a magnetic link, between two objects showing magnetic properties. Typically, an external control platform, based on permanent magnets, electromagnets, or a combination of them, and a micro-object, that could be a magnetic bead, a magnetized cell, or a microrobot, constitute the key elements. Materials behavior in response to a magnetic field depends on the material atomic organization. In particular, the spatial organization of the material microscopic domains and the possible changes in this organization produced by the presence of an external magnetic field determine the material response. Indeed, the magnetization induced in a material is proportional to the ability of these domains to align or to form cooperative structures when a magnetic field is applied. This ability can be described by means of the magnetic susceptibility χ, a non-dimensional parameter defined by the ratio of the magnetization M induced in the material and the applied magnetic field H.

$$\boldsymbol{M} = \chi \boldsymbol{H} \tag{8}$$

Depending on this parameter, it is possible to classify magnetic materials in three main categories: diamagnetic, paramagnetic, and ferromagnetic (**Figure 2**) [7]. Diamagnetic mate-

rials, such as bismuth or brass, have no net atomic or molecular magnetic moment and do not retain magnetization when the external magnetic field is removed. When these materials are subjected to an applied field, atomic currents generate and produce a bulk magnetization antiparallel to the field H, thus resulting in negative and negligible susceptibility χ levels (~10^{-6} to ~10^{-3}). Paramagnetic materials have a net magnetic moment at the atomic level which shows a random orientation when no magnetic field is acting. When the magnetic field H is applied, the moment tends to align with it. The susceptibility of such materials is in the range 10^{-6}–10^{-1}. Ferromagnetic materials, such as iron, nickel, and cobalt, on the other hand, have a net magnetic moment at the atomic level, but unlike paramagnetic materials, they show a strong coupling between neighboring moments as they align all in the same direction and parallel to each other to produce a larger magnetization state. This coupling gives rise to a spontaneous alignment of the moments over macroscopic regions, called domains, which undergo further alignment when the material is subjected to an applied field. Ferromagnetic materials can be permanently magnetized since they are able to retain residual magnetization after the removal of the applied magnetic field. They can be furtherly classified as soft or hard materials: The first ones are featured by a high permeability and a low coercivity H_c (the coercivity is defined as the magnetic field intensity needed to reduce the magnetization of a ferromagnetic material from its complete saturation to zero). This makes them easy to be magnetized and demagnetized. The second ones have a relatively low permeability and high coercivity which make them more suitable for the fabrication of permanent magnets [8, 9].

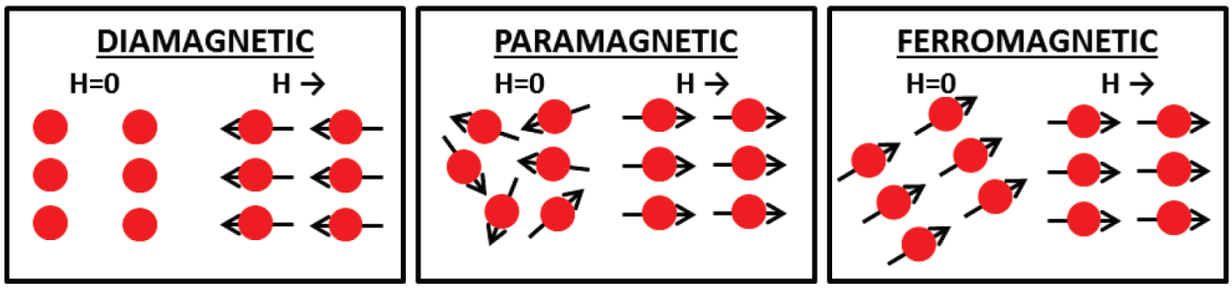

Figure 2. Schematic representation of diamagnetic, paramagnetic, and ferromagnetic materials microscopic structures at rest and in the presence of a magnetic field H.

To enable magnetic field-mediated task execution in a LOC, it is necessary to provide the objects to be manipulated with magnetic properties. In some cases, magnetic manipulation relies on the intrinsic magnetic properties of the sample, as in the case of red blood cells [10]. More frequently, labeling and internalization of magnetic material, or fabrication of magnetic microcarriers, are required. To this aim, magnetic micro- and nanoparticles have gained growing attention in LOC systems and in microrobotics in general. Usually, polymeric or silica microparticles with embedded iron oxide nanoparticles are used. Simple iron oxide nanoparticles are also used, mainly magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) ones. Due to the reduced dimensions of the magnetic core (diameter <1 μm), these particles usually consist of single magnetic domains showing a superparamagnetic behavior. The main advantages of using magnetic particles are that they have a large surface-to-volume ratio; they can be

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conveniently biofunctionalized, thus favoring their coating or enabling labeling molecules. To provide a micro-object with magnetic properties, two main strategies can be employed: (1) labeling with magnetic particles or (2) particle internalization. In both cases, sample incubation in the presence of a relatively high concentration of particles is required.

Sample magnetic labeling relies on the possibility to properly functionalize particle surface to enable the binding with functional groups exposed on sample surface. This applies, for example, for cell labeling: functional micro- or nanoparticles are conjugated with antibodies corresponding to specific cell surface antigens [11].

In the case of internalization, the magnetic particles are included in the sample structure itself by embedding the magnetic material during the micro-object fabrication process or exploiting transfection and magnetofection techniques in the case of biological samples. In this case, superparamagnetic iron oxide nanoparticles (SPIONs), usually properly modified to promote internalization, for example, through polystyrene or dextran coatings, or exploiting other transfection agents, such as peptides or antibodies [12], are widely employed.

An alternative to sample magnetization through labeling or internalization is the exploitation of magnetic carriers or manipulation systems that avoid a direct contact between sample and magnetic material.

In this case, magnetic properties can be imparted to a carrier, by simply including magnetic materials in its structure. To this aim, not only SPIONs have been employed: the integration of ferromagnetic materials, for example, in the form of powder, has been investigated in applications in which high magnetic responsivity and residual magnetization were required. Ferromagnetic materials, such as Ni, have been employed also in the form of surface coating, obtained through sputtering or evaporation techniques, with the aim to provide micro-objects showing complex geometries, fabricated, for example, through 2D or 3D lithography techniques, with magnetic properties [13].

Once identified the methods allowing to magnetize the samples to be manipulated, it can be useful to briefly describe some techniques allowing to properly characterize a magnetic micro-object. When designing the hardware for a magnetic manipulation or separation platform, it is useful (in some cases even mandatory) to precisely know the magnetic properties of the beads or structures to be manipulated. Particularly, interesting parameters, most commonly evaluated, are the magnetic susceptibility χ, the saturation magnetization M_s and the coercivity field H_c. Considering that small entities usually show weak magnetic properties, traditional technologies employed at the macroscale, such as Hall sensor-based probes, do not result suitable for their characterization. Microstructured magnetic materials can be properly characterized through both inductive- and force-based techniques. Inductive methods, such as the vibrating sample magnetometry (VSM) and the superconducting quantum interference device (SQUID) magnetometry, are usually employed for magnetic characterization at the micro-/nanoscale. In both cases, the measurement can be carried out at variable temperature and by applying different magnetic fields, thus allowing to obtain the typical material magnetization curves in a specific range of temperatures. In VSM, a magnetic sample is vibrated within a uniform magnetic field: sample vibration induces a current in dedicated

sensing coils; by measuring the resulting voltage induced into the coil, it is possible to obtain sample magnetic moment and to magnetically characterize it. The sensitivity of this kind of technique can reach 10^{-6} emu. When the samples are really diluted or show really weak magnetic properties, thus claiming for higher sensitivities, SQUID-based magnetometry can be a suitable solution, enabling to reach sensitivities up to 10^{-8}–10^{-12} emu. The magnetic properties of the material are measured by detecting quantum mechanical effects in conjunction with superconducting detection coils. In both VSM and SQUID magnetometry, however, the duration of a single measurement is in the order of some hours. This obviously represents a strong limitation for all cases in which the characterization of a large number of samples is needed. On the other hand, force-based methods, such as Gouy and Faraday balances, rely on the change in weight of a magnetic material when it is subjected to a uniform magnetic field. Commercial systems based on the Faraday method, such as the alternating gradient magnetometer (AGM), provide sensitivities in the 10^{-8}–10^{-9} emu range with really fast measurement procedures [14, 15].

4. Magnetic actuation in LOC: principles and exploited hardware

Some applications of magnetic fields in LOCs have already been mentioned and range from magnetic separation for chemical and biological analyses to sample manipulation for drug screening and cell sorting. In terms of magnetic actuation of samples, it is possible to classify the various applications in two main categories: (1) magnetic separation and (2) magnetic manipulation. In the first case, two or more classes of objects are separated depending on their magnetic properties, but without any need to properly drive them along complex paths or to guarantee the execution of specific tasks; in this case, magnetic fields are responsible for separation, but transportation is usually provided by fluidic forces. In the second case, a more accurate control is required to enable a single magnetic object or a swarm of them to follow a planned trajectory or to perform a specific task; larger magnetic fields and forces are required in this case, as they are responsible also for object transport.

4.1. Magnetic separation

Magnetic separation, often defined as magnetophoresis, is widely exploited in LOC applications. Magnetophoresis is a nondestructive method for the selective collection or separation of magnetic particles, by moving them in a viscous medium under the influence of an applied magnetic field [16]. Usually, in LOC applications, we refer to free-flow magnetophoresis, since the separation of particles or magnetic objects takes place in a liquid environment where magnetic particles are deflected from the direction of laminar flow by a perpendicular magnetic field (**Figure 3**); the extent of the deflection depends mainly on flow rate and on the susceptibility of the magnetic particle, or more precisely, on the susceptibility mismatch between the particle and the fluid.

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The vector u_{defl}, which represents the deflection of magnetic particles due to the applied magnetic field, is the result of two contributions: the flow velocity induced on the particle by the applied magnetic field $u_{mag,}$ and the hydrodynamic flow velocity u_{hyd}:

$$\boldsymbol{u}_{defl} = \boldsymbol{u}_{mag} + \boldsymbol{u}_{hyd} \tag{9}$$

The magnetically induced flow velocity $u_{mag,}$ can be expressed as the ratio of the magnetic force F_m exerted on the particle to the viscous drag force:

$$\boldsymbol{u}_{mag} = \frac{\boldsymbol{F}_m}{\boldsymbol{F}_d} = \frac{\boldsymbol{F}_m}{6\pi\eta r} \tag{10}$$

In a magnetophoresis application, the magnetic force depends on the particle features, mainly its volume V_p, on the mismatch in terms of magnetic properties between the particle and the fluid, and on the applied magnetic field B. Eq. (5) becomes consequently [17]:

$$\boldsymbol{F}_m = \frac{V_p \cdot \Delta\chi}{\mu_0}\left(\boldsymbol{B}\cdot\nabla\right)\boldsymbol{B} \tag{11}$$

Eq. (11) is suitable for both paramagnetic and superparamagnetic particles, since soft magnetism approximation, and lack of magnetic memory is considered for the particles, and for relatively high magnetic field strengths, able to induce in the particles a magnetization close to the saturation one. To this aim, macroscopic permanent magnets and electromagnets can be exploited, since they produce sufficiently strong fields (>0.5 T), able to saturate superparamagnetic particles.

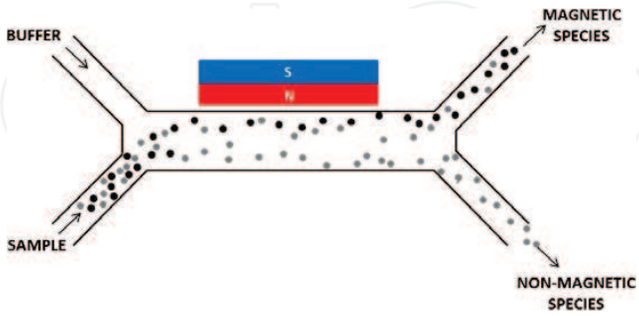

Figure 3. Typical schematization of a magnetophoresis scenario in which a magnetic field perpendicular to the flow direction is exploited to deviate magnetic particles from the trajectory imposed by fluidic forces and thus to separate them from the rest of the sample. Complete separation of the species can be obtained through some consecutive steps.

It is possible to distinguish between positive and negative magnetophoresis depending on the sign of the susceptibility mismatch: if $\Delta\chi$ is positive, for example, in the case of magnetic micro-/

nano-objects in a non-magnetic fluid, we talk about positive magnetophoresis and the particles are attracted by the externally applied magnetic field. On the other hand, when the susceptibility mismatch $\Delta\chi$ is negative, for example, in the case of diamagnetic particles in a magnetofluid, the particles are repelled from the magnetic field and negative magnetophoresis occurs. When designing a magnetophoresis device, it is necessary to assure the dominance of magnetic forces respect to the other physical contributions. Considering Eq. (11), F_m results proportional to the magnetic field gradients and to the susceptibility mismatch. Several strategies aiming at optimizing magnetophoresis have been investigated and proposed, and they may be essentially classified in two categories distinguishing between those aiming at maximizing the magnetic field gradients and those acting on the susceptibility mismatch [18].

In the attempt to increase the magnetic field gradient, many solutions have been proposed in literature, all aiming at the generation of a nonuniform magnetic field distribution. In some cases, uniform external magnetic field sources, such as permanent magnets, were combined with wires [19], ferromagnetic strings [20], or magnetic microparticles embedded in the chip structure itself [21], whereas in other cases, the integration of small electromagnets produced intense magnetic field gradients [22]. Alternatively, permanent magnets can be actuated to generate a time-dependent magnetic field, for example, through the use of a rotating magnetic wheel [23], or arranged in an asymmetric configuration, thus generating spatial field variation or multiple magnetic separation stages [24]. One of the most commonly employed magnet configuration in magnetophoresis applications, able to maximize field distribution anisotropy, is the quadrupolar arrangement which creates a magnetic gradient radially outward from the center of the flow column [25]. In a variant of this, the fluid is static, while an applied magnetic field is moved up the container [26]. The particles move in the resulting field gradient at a velocity dependent on their magnetophoretic mobility. At the top of the container, they enter a removable section and are held here by a permanent magnet. The bottom section of the container moves to the next section where a magnetic field with different strength to the first is applied and the process repeats. The result is a fractionation of the sample into aliquots differing for magnetophoretic mobility [27].

The alternative strategy to enhance the magnetic separation capabilities of the device lies in increasing the susceptibility mismatch by modifying either the susceptibility of the particle, or the one of the surrounding fluid. This can be accomplished (1) by labeling the cells or the desired microstructure with higher magnetic susceptibility beads (2) by internalizing higher quantity of magnetic material, and (3) by using a ferrofluid medium, for example, by adding gadolinium, and diamagnetic particles instead of the para/ferromagnetic ones [28].

4.2. Magnetic micromanipulation

Magnetic fields can be employed in LOC for the non-contact manipulation of biological samples or other magnetically labeled substances/structures. Apart from applications in which it is necessary to separate different types of samples or specific entities from the medium (tasks that can benefit from techniques mainly based on magnetophoresis), in some cases, precise manipulation or transport along defined paths is required. This kind of task is more complex

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in terms of extent of magnetic fields required and of control, considering that for 3D manipulation, torque equilibrium must be taken into account, in addition to force balance.

It has been demonstrated that biological systems or chemical samples labeled with magnetic nanoparticles can be micro-/nano-manipulated or transported in three dimensions, by exploiting combinations of electromagnets or permanent magnets, possibly moved or rotated along three axes. Permanent magnets offer the advantage to produce large fields without the need of any electrical current, thus avoiding powering, heating and control issues, which have to be faced instead when using electromagnets. On the other hand, electromagnets offer the possibility to tune magnetic field gradients and field intensities by simply varying the currents across the coils. By properly combining electromagnets, it is possible to produce in the workspace both varying magnetic fields, without the need of moving parts, and spatially uniform magnetic fields and gradients. This makes possible to accomplish also quite complex manipulation and locomotion paradigms. Several architectures have been proposed, presenting different magnet and electromagnet arrangements. In LOC applications, due to the need to finely control the locomotion of small-scale entities, electromagnets are the most commonly employed solution.

Generally, when an electrical current flows in a wire, a magnetic field is generated according to the Biot–Savart theory [9]. When considering a single circular coil in which a current with magnitude I is flowing, the magnetic field along the central axis of the coil can be defined as:

$$\boldsymbol{B} = \quad d\boldsymbol{B} = \frac{\boldsymbol{I}r^2}{2(r^2+z^2)^{\frac{3}{2}}} \tag{12}$$

where r is the radius of the coil, and z is the coordinate along the central axis.

Often, specific coil pairs arrangements, namely Helmholtz and Maxwell coils, are exploited in micromanipulation applications. They consist of two identical circular magnetic coils symmetrically placed along a common axis, one on each side of the workspace, and separated by a distance d corresponding to coil radius (r_H) in the case of Helmhotz coils and to $\sqrt{3}r_M$ in the case of Maxwell coils. In Helmholtz arrangement, each coil carries an equal electric current in the same direction, whereas in Maxwell coils currents flow in opposite directions. The magnetic flux density in case of Helmholtz and Maxwell coils can be derived from Eq. (12):

$$\boldsymbol{B}_H = \frac{\mu_0 r_H^2 N_H \boldsymbol{I}_H}{2}\left(\frac{1}{\left[r^2+\left(\frac{d}{2}-z\right)^2\right]^{\frac{3}{2}}}+\frac{1}{\left[r^2+\left(\frac{d}{2}+z\right)^2\right]^{\frac{3}{2}}}\right) \tag{13}$$

$$\boldsymbol{B}_M = \frac{\mu_0 r_M^2 N_M \boldsymbol{I}_M}{2}\left(\frac{1}{\left[r^2+\left(\frac{d}{2}-z\right)^2\right]^{\frac{3}{2}}}-\frac{1}{\left[r^2+\left(\frac{d}{2}+z\right)^2\right]^{\frac{3}{2}}}\right) \tag{14}$$

$N_{H,}$ $I_{H,}$ r_H, $N_{M,}$ $I_{M,}$ r_M are the numbers of windings, current, and radius of Helmholtz and Maxwell coils, respectively.

When considering a combination of Helmholtz and Maxwell coils (**Figure 4A**), the magnetic field B and magnetic field gradient ∇B in the workspace can be derived analytically by Eqs. (13) and (14) as follows:

$$\boldsymbol{B} = \frac{8\mu_0 N_H \boldsymbol{I}_H}{5\sqrt{5} r_H} \tag{15}$$

$$\boldsymbol{B} = \frac{48\sqrt{3}\mu_0 N_M \boldsymbol{I}_M}{49\sqrt{7} r_M^2} \tag{16}$$

Equations (15) and (16) clearly show that Helmholtz coils are able to generate a uniform magnetic field, whereas Maxwell coils produce a uniform magnetic field gradient along its axis. For this reason, combinations of Helmholtz and Maxwell coils have been exploited to obtain both a uniform field gradient and magnetic field uniformity [29].

Nonuniform field setups have been developed as well. Despite the major complexity both in terms of design/fabrication and control, they enable an increase in the number of controlled degrees of freedom. In this sense, a representative example is the OctoMag system [30, 31] (**Figure 4B**), designed for the control of intraocular microrobots for minimally invasive retinal therapy and diagnosis, but showing also potentialities for use as a wireless micromanipulation apparatus. It consists of eight stationary electromagnets with soft-magnetic cores able to generate predefined values of magnetic field and gradient, providing the manipulated object with five degrees of freedom; this system can operate closed-loop position control by exploiting computer-assisted visual tracking or in open loop by relying only on the operator microscope-mediated visual feedback. Alternative approaches aim at exploiting other sources of nonuniform magnetic fields: Martel et al. [32] demonstrated the effectiveness of using an MRI scanner for the control of a swarm of magnetotactic bacteria in executing a manipulation task on micro-objects. Micro-assembly of micro-objects using a cluster of microparticles (with average diameter of 100 μm) and a magnetic-based manipulation system has also been shown in [33].

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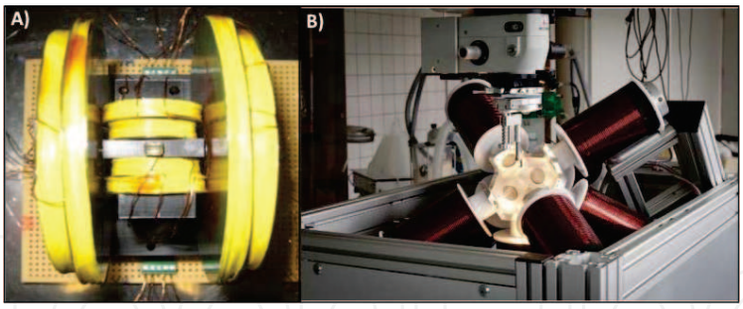

Figure 4. Different magnetic field generation setup exploited for magnetic manipulation. (A) Combination of Helmholtz and Maxwell coils; (B) OctoMag system [31].

5. Applications of magnetic fields in lab-on-a-chip

Once provided the reader with an overview of physics at the microscale, as well as of magnetic materials properties and principles to be exploited, some real applications of LOCs will be described, where using magnetic fields. Such applications range from biological samples handling to chemical reactions and other manipulation tasks. As a consequence, in order to better analyze the potential of using magnetic fields in this context, it is useful to classify the applications in three main areas: (1) on-chip bioanalysis; (2) cell separation or manipulation; and (3) non-conventional manipulation techniques.

5.1. On-chip bioanalysis

A vast number of reactions in genomics, proteomics, and clinical medicine need molecular mixing of fluids or recognition events between single strands of DNA, between antibodies and antigens, or between receptors and cells. Such reactions usually require a number of steps that must be performed sequentially, such as isolation, washing, or purification. In this kind of applications, the introduction of automation could lead to higher throughput and the use of magnetic fields, commonly mediated by the use of magnetic particles, has revealed to be extremely useful in some on-chip functions such as the mixing of fluids, selective capture of analytes, later to be transferred for further analysis steps, or the performance of stringency and washing. Usually two main properties of magnetic particles are exploited in analytical assays: the possibility to biofunctionalize them, thus enabling selective binding and related applications, and the capability to form supra-particle structures, such as chains, exploited mainly in fluid mixing and analytes capture applications [5].

Usually, magnetic particles are labeled with molecules, for example, antibodies, showing high affinity for the target species and able to mediate the binding with them. Often multistep binding processes are carried out to bind the particle–analyte complex, for example to fluorescent dies, thus to enable target detection [34]. In other cases, for additional purification steps after labeling, magnetic separation, mediated by magnetophoresis phenomena, or transfer processes are required to enable further purification/washing steps or analysis. This

kind of procedures can be exploited both for the in vitro purification of nucleic acids or proteins and for biomolecules separation, as well as DNA sequencing. For example, in case of DNA extraction and separation processes, magnetic particles are firstly held in place by exploiting external magnetic fields, thus exposing their functional groups to specific DNA strands. Magnetic separation steps can consequently be performed to isolate the strands of interest from the rest of the sample [35]. In other cases, the target-binding capabilities, with analytes showing at least two epitopes, have been exploited to create large aggregates for albumin detection in buffer [36]: The binding between particles is mediated by the target molecule and thus the extent of the aggregate represents a measure of analytes concentration within the solution and the magnetic properties of the aggregate allow their detection. In this case, non-specific particle clustering should be avoided.

Another interesting application is in the field of biosensing or surface binding bioassays: In this context, magnetic particles can be exploited as binding mediators between the target species and a functionalized surface. The most common configuration in this field is the sandwich one, in which the target molecule binds first the magnetic particles dispersed in the solution. Later, by exploiting magnetic field gradients, the complex can be moved toward the surface of the sensor where interactions at the molecular scale occur [37].

Whereas in detection applications, non-specific magnetic interaction within particles has to be avoided, there are applications in which the capability of magnetic particles to interact each other thanks to magnetic forces to form supra-particle structures can be advantageously exploited. When working with really precious/expensive fluids, really small volumes and microfluidic devices are employed. Due to the small scale and to the strong viscous force, fluid mixing is not straightforward. In this case, magnetic particles can be exploited to steer fluids. This is done specifically for supra-particle structures such as chains created by the dipole–dipole interactions between magnetic particles, and actuated, for example, by means of rotating magnetic fields [38].

5.2. Magnetic cell separation

Cell manipulation by means of magnetic fields relies on cells magnetic labeling or, alternatively, on magnetic particles internalization through magnetic field-mediated transfection mechanisms (magnetofection). In a typical in vitro magnetofection system, target cells are located at the bottom of a fluidic chamber well of a culture plate, and a permanent magnet beneath the chamber provides a magnetic force that attracts the biofunctional particles toward the cells.

Separation and isolation of rare cell populations from a heterogeneous suspension is essential for many applications, ranging from disease diagnostics to drug screening. Various separation techniques have been proposed, but magnetic fields emerged as very promising also in this kind of application thanks to the exploitation of the magnetic separation principles presented in the previous section.

Magnetic cell sorting can be operated in either a serial or a parallel manner, resulting in higher throughput with up to 10^{11} cells processed in 30 min. This process can be operated in both

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batch and continuous flow mode. In batch processing, the hardware is very simple, including a magnetic field source placed close to a column containing the cells to be separated. Several architectures were developed to this aim both at large scales, exploiting for example ferromagnetic columns [39] and at smaller scales with arrays of electrical wires exploited to produce local magnetic fields [40]. In the case of continuous flow cell sorting, instead, typical magnetophoresis principles are exploited.

Multicell sorting systems rely on the variation in the uptake of magnetic material between different cell populations and thus on the different path deviation produced by magnetic field gradients. They can be also used for the separation of different cell species from heterogeneous samples [41].

The separation of a specific class of cells from a certain sample is extremely important for some applications, for example, for the detection of pathology or for the testing of a therapeutic strategy. For example, diagnosis and treatment of HIV disease rely on the efficient separation of human T-lymphocytes from whole blood [42], whereas in the diagnosis and treatment of malaria, the detection of infected red blood cells (RBCs) and their separation from healthy cells is mandatory [43]. Separation of neuronal cells has gained interest for its potential applications in cell replacement therapy of neurodegenerative disorders such as Parkinson's disease, multiple sclerosis, and Alzheimer's disease [44]. Cell separation methods are also needed for separating nucleated RBCs from the peripheral blood of pregnant women, for monitoring maternal, fetal, and neonatal health [45].

Magnetic field-based cell counting techniques have also been developed. One method estimates the location and number of cells tagged by measuring the magnetic moment of the microsphere tags [46], while another uses a giant magnetoresistive sensor to measure the location of microspheres attached to a surface layered with a bound analyte [47].

5.3. Non-conventional manipulation strategies based on magnetic fields

When high sensitivity, not compatible with magnetophoretic techniques is required, and independence on the human operator are desirable, microrobotic manipulators acting at the cellular scale can offer significant benefits. Wirelessly controlled (i.e., untethered) cell-sized robots are highly noninvasive. At this length scale, where viscous fluid forces dominate inertial ones, mobile microrobots cause very little mixing or agitation of the surrounding environment. This is a significant advantage, for example, over suction pipetting for life scientists, since pipettes cause relatively large fluid disturbances [48]. Magnetic control of microrobots and microgrippers is gaining growing importance in micro-object manipulation: in addition to increasing the manipulation accuracy, the exploitation of such micro-systems avoids sometimes the direct magnetization of the sample, through internalization or labeling, thus helping in keeping its integrity. Many challenges have to be faced to enable single cell manipulation. When working with single cells or with really fragile samples, in fact, it is essential to have microstructures with sizes comparable to those ones of the target, to be able to finely control them within the workspace, and to avoid to affect cell viability or samples integrity due to the microrobot exploitation.

Some research groups focusing on microtechnologies have been working toward a high efficiency in vitro fertilization (IVF) process [49] (**Figure 5A**). The IVF goal is to fertilize oocytes, and it consists of several manually or teleoperated manipulation steps that require important practical skills. Sakar et al. [50] developed microtransporters using a simple, single-step microfabrication technique allowing parallel fabrication. They demonstrated that the microtransporters can be navigated to separate individual targeted cells with micron-scale precision and deliver microgels without disturbing the cells in the neighborhood and the local microenvironment. Yamanishi et al. [51] presented an innovative driving method, devised for cell sorting, for an on-chip robot actuated by permanent magnets in a chip, where a piezoelectric ceramic is applied to induce ultrasonic vibration to the microfluidic chip and the high-frequency vibration reduces significantly the effective friction on a magnetically driven microtool.

Other interesting magnetic microstructures, devised for cell manipulation in in vitro environments for LOC applications, but finally eligible in the future for in vivo applications, have been recently proposed. Examples are novel microgrippers, in which both the navigation and the gripper actuation rely on magnetic fields [52] (**Figure 5B**), 3D laser lithography microcages devised to act as cell carriers (**Figure 5D**) [53] or thin magnetic films working at the air fluid

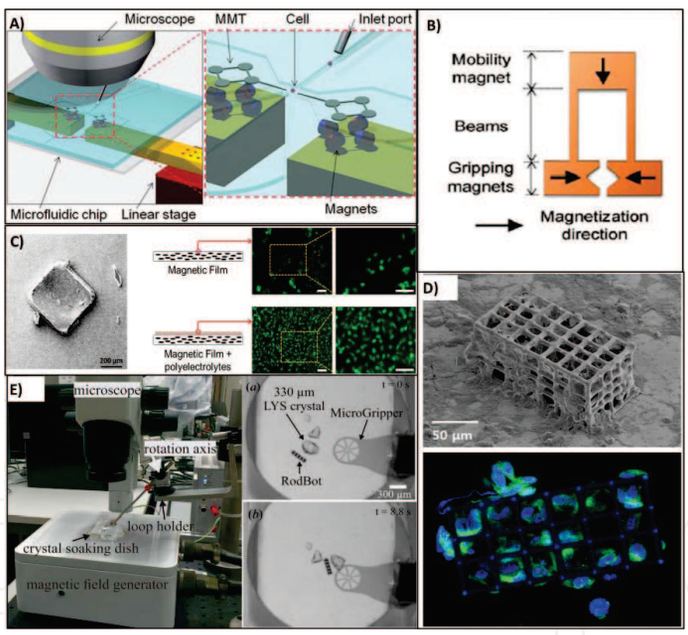

Figure 5. Overview of non-conventional manipulation systems for microrobotics and LOC applications. (A) Conceptual overview of a microfluidic cell manipulation system based on magnetically driven microtools and exploited for oocytes handling [49] (reproduced with permission from Royal Society of Chemistry); (B) Schematic representation of a remotely controlled microgripper exploiting magnetic fields both for navigation and for gripper actuation (adapted from [52] and reproduced with permission from Royal Society of Chemistry); (C) SEM image of a magnetic thin film devised for cell manipulation (left) and schematic representation of the film structure with microscope images showing T24 cell compatibility with the magnetic structure (right) [13] (reproduced with permission from Springer); (D) SEM image (above) and confocal microscope image of a magnetic microcage after cell culture [53]; (E) Experimental setup for magnetic micromanipulation (left) and microscope images of the magnetic microrobot during christal manipulation tasks (adapted from [55] and reproduced with permission of the International Union of Crystallography).

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interface and exploiting surface tension phenomena together with magnetic navigation and showing compatibility with cell manipulation applications [54] (**Figure 5C**). Interesting is also the development of manipulation strategies for precise non-contact handling of small and fragile samples based on complex control algorithms aiming at creating vortexes, as demonstrated for crystal harvesting applications (**Figure 5E**) [55].

6. Conclusions

LOC technologies represented a real breakthrough in the last decades for in vitro laboratory analyses. However, the integration of really complex functions in a limited space results extremely challenging and further efforts are required to make LOC systems accurate and operating in an automated fashion. Magnetic fields exploitation revealed to be extremely promising and effective in the execution of certain tasks, with the aim of overcoming some of the limitations connected to human operators and enabling procedures impossible with traditional laboratory techniques.

In this sense, the role played by magnetic nanoparticles is extremely important, but alternative techniques providing the samples to be manipulated with magnetic properties have been investigated and show great potentialities.

In some cases, magnetic field-based technologies appear more advantageous compared with other LOC actuation strategies, first of all the fluidic one. However, in view of more reliable systems, a possible future trend, already investigated in many applications focuses on combining several effects, including chemical binding, microfluidic actuation, magnetic and electric fields, to obtain more efficient analytical and biological testing platforms. A further enhancement of LOC devices, and especially of those exploiting magnetic fields, may derive from the integration of technologies that are typical of the microrobotics world. Some examples have been reported in the Section 5.3 and an interesting contribution could derive from microrobotics, both in terms of cell carriers and manipulation systems fabrication, and in terms of control strategies.

The development of cheaper and more reliable LOCs could enable many steps forward in really important fields, such as nanomedicine, personalized medicine, and cellular studies. The advantages and technological progresses offered by magnetic technologies at all the scales and in different fields could surely help to reach this goal.

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