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Rotating magnetic particles for lab-on-chip applications – a comprehensive review

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Magnetic particles are widely used in lab-on-chip and biosensing applications, because they have a high surface-to-volume ratio, they can be actuated with magnetic fields and many biofunctionalization options are available. The most well-known actuation method is to apply a magnetic field gradient which generates a translational force on the particles and allows separation of the particles from a suspension. A more recently developed magnetic actuation method is to exert torque on magnetic particles by a rotating magnetic field. Rotational actuation can be achieved with a field that is uniform in space and it allows for a precise control of torque, orientation, and angular velocity of magnetic particles in lab-on-chip devices. A wide range of studies have been performed with rotating MPs, demonstrating fluid mixing, concentration determination of biological molecules in solution, and characterization of structure and function of biomolecules at the single-molecule level. In this paper we give a comprehensive review of the historical development of MP rotation studies, including configurations for field generation, physical model descriptions, and biological applications. We conclude by sketching the scientific and technological developments that can be expected in the future in the field of rotating magnetic particles for lab-on-chip applications.

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Introduction

Magnetic nano- and micro-particles (MPs) can be actuated in fluids using applied magnetic fields. Their large surface-to-

volume ratio and the availability of a wide range of particle types and methods for surface functionalization have enabled the application of MPs as carriers (*e.g.* for biomolecule and cell extraction), as labels (*e.g.* for biomolecule detection) and as probes in biophysical studies (*e.g.* to quantify mechanical properties of molecules and cells). Several reviews have discussed principles and applications of magnetic actuation, see *e.g.* Gijs *et al.* 2010 (MPs in microfluidics),¹ Van Reenen *et al.* 2014 (lab-

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$$\vec{\tau} = \vec{m} \times \vec{B}. \quad (1)$$

Fig. 1 sketches five experimental configurations in which rotational actuation of MPs is exploited for different functionalities, namely for mixing (Fig. 1A), for determining the concentration of biological molecules (Fig. 1B and C) or for biophysical characterization of cells or molecules (Fig. 1D and E). In the following paragraphs we will summarize the main application areas based on these experimental

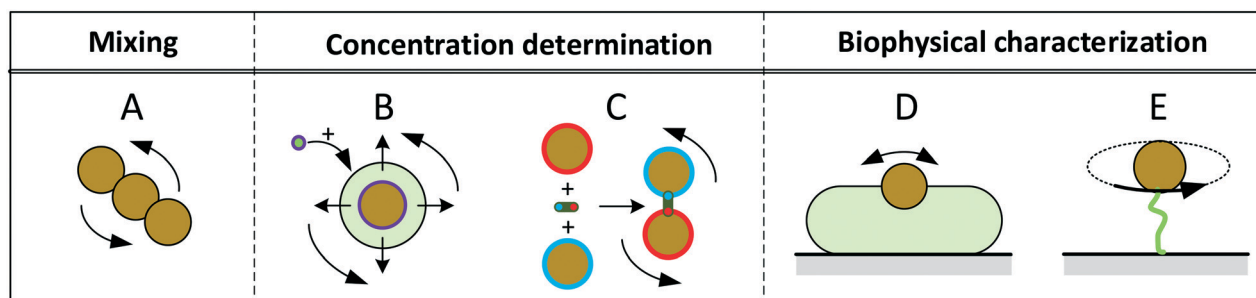
The rotational force on an object, the torque, is represented with symbol $\bar{\tau}$ and is expressed in the unit N m (New-



and continuous monitoring of biomolecules. To stimulate education and innovation in the field of biosensing, he founded and organizes SensUs, the annual international student competition on biosensors for health (www.sensus.org).

In the following sections we will discuss how torque is generated in MPs, the magnetic field actuation systems that have been used, and subsequently we will review lab-on-chip studies based on application and control of torque and rotation.

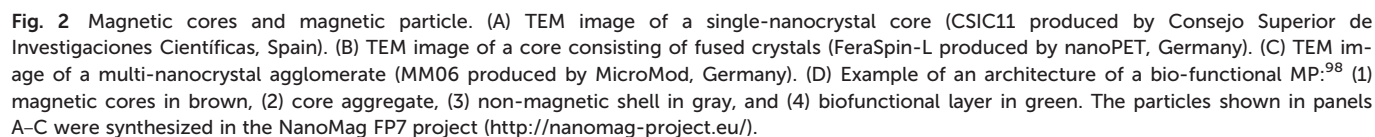
The magnetic content of a magnetic particle typically consists of ferro- or ferri-magnetic nano-crystals. These nano-crystals



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A MP that is placed in a magnetic field can respond by internally changing its magnetization direction, called Néel relaxation, or by changing its physical orientation, called Brownian relaxation.¹⁰¹ Both processes lower the magnetic energy by orienting the magnetic moments of the cores toward the external field. There are two limiting cases of Néel relaxation, namely fast relaxation for superparamagnetic particles and slow relaxation for magnetically blocked particles (particles with a barrier for re-magnetization that exceeds the thermal energy). In the superparamagnetic limit the re-magnetization barrier of the cores is smaller than the thermal energy so the magnetic relaxation time is short, *i.e.* shorter than the timescale of the lab-on-chip experiment. The magnetization of an ensemble of superparamagnetic cores in thermal equilibrium can be modeled like atomic paramagnets, only with a significantly larger magnetic moment. This implies that the magnetic moment of the MP is zero in absence of an external field. For the small field regime (B typically < 50 mT) the magnetization is approximately linear with the external field and occurs on a timescale that is short

Core-core interactions such as dipolar and/or exchange interactions are not taken into account in the Néel model, but these can also have a strong influence on the magnetic relaxation time.⁹³ The core-core interactions are defined by the mesoscopic structure of the MP. Three types of mesoscopic structures can be distinguished. The simplest case is a single nanocrystal that behaves as a single magnetic domain (Fig. 2A). The second type consists of multiple fused single crystals that behave as a single magnetic entity due to the strong magnetic (exchange) coupling (Fig. 2B). The third type consists of an agglomerate of single nanocrystals that do not have exchange coupling but do have strong dipolar interactions due to their close proximity (Fig. 2C). Such nanocrystal-



For an ensemble of MPs, the total remnant moment can be measured using a commercially available magnetometer, for example a superconducting quantum interference device (SQUID) or a vibrating sample magnetometer (VSM). For an individual MP, the remnant moment can be quantified *via* the magnetic torque by tracking the rotation of a single particle in an optical microscope.¹⁰⁶ For a particle that is not attached and that can freely rotate in solution at the same frequency as the applied magnetic field, the torque on the particle is approximately equal to its rotational hydrodynamic drag. The hydrodynamic drag of a smooth sphere with radius R in a fluid with dynamic viscosity η , is given by the Stokes equation, which together with eqn (1) gives the following equation for the angular motion of the particle:

where $\bar{\theta}$ is the angular orientation of the particle.¹⁰⁷ Inertial forces have been ignored since these can be neglected for small particles (between 10 nm and 10 μ m).¹⁰⁶ When a particle is bound to a substrate *via* a cell or a molecular complex (*cf.* Fig. 1D and E), the rotational motion is restricted by the elastic properties of the biological matter. A general analytical expression is not available for the torsional elasticity of biological matter due to its complex structure. In case of small deformations of a biological macromolecule, the response can be approximated by a linear torsional spring, $\vec{\tau} = -k\vec{\theta}$, where typically $\tau < 1$ pN μ m (*i.e.* 1 pN using a 1 μ m arm).⁷⁰

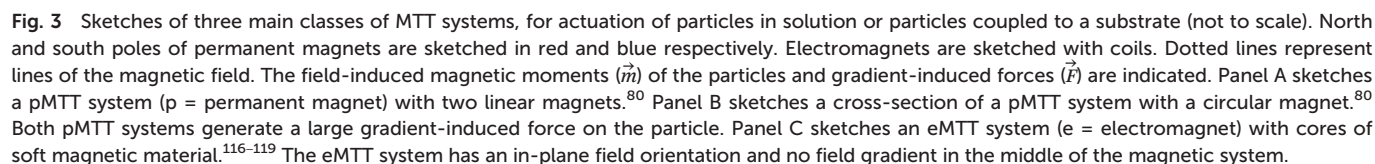
cle.^{106,108} The torque of single superparamagnetic particles with a diameter of 2.8 μm has been calibrated in small fields (<5 mT on Dynal M-280 particles¹⁰⁶) as well as in larger fields (10–100 mT on Dynal M-270 particles¹⁰⁸). For the small fields, the magnetic torque was calibrated based on the known hydrodynamic drag of a smooth sphere, which revealed a linear dependence of the torque on the applied field. This linear dependence of the torque was attributed to a small remnant moment in the superparamagnetic particles.¹⁰⁶ For larger magnetic fields (10–100 mT), the angular thermal motion of surface-coupled particles was recorded to calibrate the magnetic torque. A quadratic scaling of the magnetic torque with field was found,¹⁰⁸ indicating that there is a net anisotropy in the MP,¹⁰³ or in other words, an easy-axis and a hard-axis.¹⁰⁴

A quadratic scaling of torque with field was also found for two-particle clusters of superparamagnetic particles. Clusters of particles have a non-spherical shape and thus a magnetic shape anisotropy. For such clusters a quadratic scaling of torque with field was observed, also for small fields,⁴¹ caused by the shape anisotropy of the clusters. The torque of clusters of particles depends only on the magnetic moment and diameter of the particles. In contrast, the magnetic torque of single particles depends on the size distribution and arrangement of nanocrystals within the particle, which can vary strongly between particles.^{109,110} The torque varies by 30–60% between particles of the same type and even more, up to a factor 100, between particles of different types.²⁷

In this section we discuss various systems to generate magnetic fields for rotational actuation of magnetic particles in lab-on-chip applications. Two main categories can be distinguished: permanent-magnet actuators and electromagnetic actuators. The geometry and type of magnetic actuator depends on the required field strength, field frequency, and sometimes the need for an additional field gradient. An instrument that can control the field direction and magnitude in two or three dimensions is typically referred to as magnetic torque tweezers (MTT),¹¹¹ a term that was introduced around the year 2000. A fundamental difference between magnetic tweezers and for instance optical- or mechanical tweezers, is that magnetic fields tend to spread out in space and therefore typically many particles are actuated at the same time. The torque that can be generated in a MTT system is comparatively large. Values for the torque generated in a MTT system using micrometer-sized MPs are between 1 and 100 pN μm .^{84,106,108} In optical torque tweezers the torque is between 0.1 and 1 pN μm ;^{84,112,113} higher torques could in principle be achieved using stronger optical fields, but limiting factors are the optical power, the generated heat inside the particles and heat that biological systems can withstand.

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Electromagnetic MTT systems (eMTT) generate fields using current-carrying coils in combination with optional soft-magnetic materials. eMTTs typically have smaller fields than pMTTs, but eMTTs are much more flexible for modulating the magnitude-, orientation-, and frequency of the field. eMTT systems were already used three decades ago in magnetic twisting cytometry experiments (Fig. 1D). Uniaxial fields (AC fields) were used to apply mechanical stress on cell membranes.^{54,55} Later, eMTTs were also used to study single biological molecules.⁷⁰ Typically a single coil or a set of two coils is used to control the magnetic field amplitude along a single axis. By adding pairs of coils, field control is extended to two or three spatial dimensions. The systems are typically designed to have a homogenous, gradient free, magnetic field in the center of the system. Fig. 3C sketches an example with a single pair of coils. The coils can be equipped either with or without a soft-magnetic material inside the coil. Rotating fields are created by applying phase-shifted currents through orthogonal sets of coils in the system. No physical movement



is needed to create field modulation or field rotation, therefore high frequencies can be achieved (>100 Hz without a soft magnetic material inside the coils). For creating high frequency fields, a limiting factor is the currents and heating induced by time varying fields, due to Faraday's law of induction and eddy currents.

For creating high amplitude fields the limiting factors are the Joule heating of the coils and/or the electric current that the power supply can deliver. The maximum field strengths for coils without a soft-magnetic material are in the order of a few milli Tesla at the sample location. If larger magnetic fields are required active cooling of the coils is needed. Another approach to enhance the field strength is to add a soft-magnetic material inside the coils.^{116,119} This enhances the field strength significantly (approximate 50 times) due to the high magnetic susceptibility of the soft-magnetic material. A disadvantage is that soft-magnetic materials have a remnant moment, typically 0.5–5% of the saturation magnetization, limiting the accuracy and the maximum frequency at which the field can be changed. Depending on the pole tip geometry, fields of 10 to 100 mT can be reached, with almost no field gradient. Table 1 summarizes the typical magnetic fields and rotation frequencies that can be achieved with the different magnetic systems. Typical values for the torque generated by an MTT and micrometer sized MPs are between 0 and 100 pN μm .^{84,106,108}

Applications of rotating MPs

In this section we highlight early works and recent publications describing applications of rotating MPs as sketched in Fig. 1. We will discuss (1) the physical measurement principles, (2) the used detection methods (magnetic or optical), (3) the used types of particles (ferro- or superparamagnetic, size), (4) the used magnetic systems (eMTT or pMTT), and (5) we give examples of the physical systems that have been studied. An overview of this section is given in Table 2.

Mixing

Fluid mixing is important in lab-on-chip devices because a homogeneous composition of fluid ensures efficient reactions with low variability. However, mixing on a micrometer scale is difficult due to the low Reynolds numbers. Magnetic particles can be used to induce mixing in a lab-on-chip system (*cf.* Fig. 1A) by applying rotating gradient-free magnetic fields to particles in solution. Chains of particles are formed

due to dipole–dipole interactions between the MPs. These chains align themselves along the field lines due to the large shape anisotropy of the self-assembled chains.

When the magnetic field is rotated the chains act as rotors in the fluid. The average size of the rotors can be controlled by the magnitude of the field. Due the absence of a gradient the rotors remain in the same position and induce local mixing. Studies have shown that rotational chain mixing can enhance the capturing rate of molecular targets by about a factor 4.^{10,13,15} An early publication describing the use of self-assembled chains for mixing was written by Vuppu *et al.* in 2003,⁶ based on superparamagnetic MPs in combination with a motorized permanent magnet.

One year later the same group published a paper showing that these rotating magnetic particle chains can be used to capture biological molecules.⁹ This principle has been extensively studied in the years thereafter¹¹ and was used in many bio-sensing applications^{35,37,38,42,43} (Fig. 1B and C) to significantly shorten assay times, typically from 60–120 min to 15–30 min. In later studies by Gao *et al.* an octopole magnetic tweezer was developed (Fig. 4A).¹⁵ The system can create 3D rotating magnetic fields with and without field gradient, which can for example be used to create particle chains, pull these to a substrate (Fig. 4B), and subsequently redisperse the chains to achieve distributed single particles¹⁴ (Fig. 4C). A more recent trend is to integrate magnetic micro-mixers on a chip, which gives compact systems for fluid mixing in very small volumes.⁷

Biomarker detection and concentration determination

An important application field of MPs in lab-on-chip applications is the detection and concentration determination of biomarkers for point-of-care medical diagnostic purposes. Typically the biomarkers to be measured are captured onto MPs and thereafter a secondary process is applied to detect the captured substance. Commonly chemiluminescent labels and reagents are used for detection² but a disadvantage of this method is that additional reagents and fluidic processing steps are needed.

To simplify the assay and allow direct detection in solution,³ measurement concepts are being studied based on particle rotation. One method is to measure a change of the hydrodynamic size of magnetic particles, as in Fig. 1B. The surface of the particles is functionalized with specific capture molecules, *e.g.* antibodies or aptamers that target the antigen

Table 1 Characteristics of magnetic torque tweezer systems as sketched in Fig. 3. pMTT refers to MTT with permanent magnet. eMTT refers to MTT with electromagnet. The eMTT can be built either with or without a soft magnetic material core inside the coil. The reported values are typical values rather than hard limitations. Note that for an eMTT system, a higher field typically implies a lower frequency

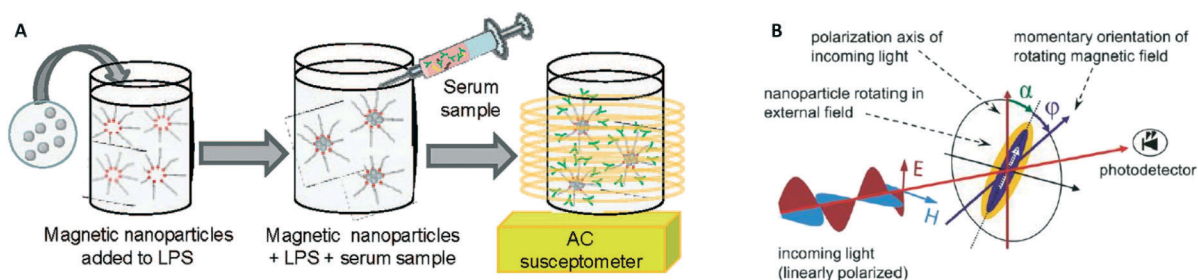
	Typical field (mT)	Typical frequency (Hz)	Field gradient
pMTT	100	1	Large, out of plane
eMTT with core	10	10	Small, in plane
eMTT without core	1	1000	Small, in plane



via the magnetic response and the second by optical scattering.

Application	Cluster or single particle	Magnetic Particle (type & size range)	Magnetic tweezer	Detection method	Studied system	Measurement principle	Early publication	More recent works
Mixing (Fig. 1A)	Cluster	SP μm	eMTT	n.a.	n.a.	n.a.	2003 Vuppu ⁶	2009 Bruls ¹¹ actuation of clusters increases mixing at a surface 2014 Gao ¹⁵ actuation of clusters enhances mixing and capture in solution 2014 Van Reenen ² review paper
Concentration detection (Fig. 1B)	Single	FP nm	eMTT	Magnetic	Protein	Out-of-phase field component	2004 Astalan ¹⁶	2008 Fornara ²⁴ antibody concentration in undiluted serum
		SP/FP nm and μm	eMTT	Optical scattering or transmission	Cell/protein	Oscillation frequency or phase lag	2007 McNaughton ²²	2017 Schrittwieser ²¹ protein detection in diluted serum and saliva
Concentration detection (Fig. 1C)	Cluster	SP μm	eMTT	Optical scattering or transmission	Protein	Oscillation frequency or amplitude	2006 Baudry ⁸	2012 Ranzoni ⁴³ PSA in undiluted blood plasma 2016 Uddin ³⁸ Lab on a disc 2018 Van Vliembergen ¹²⁴ inter-particle distance
		FP nm	eMTT	Magnetic	Protein	In-phase component	2007 Hong ³¹	2010 Chieh ⁴⁰ VEGF in buffer, measured using a SQUID
Biophysical characterization (Fig. 1D)	Single	FP μm	pMTT and eMTT	Magnetic	Cell	Oscillation frequency	1987 Valberg ⁴⁷	2001 Puig-De-Morales ⁵⁷ frequency demodulation to measure mechanical cell properties
		SP/FP μm	eMTT	Optical microscopy	Cell	Spatial position and/or angular position	1993 Berg ⁴⁸	2008 del Alamo ⁵⁰ anisotropy in mechanical properties of cells 2012 Irmischer ⁵¹ torsional and translational mechanical properties of cell membranes
Biophysical characterization (Fig. 1E)	Single	SP μm	pMTT	Optical microscopy	DNA	Distance to surface or angular position	1996 Strick ⁶¹	2000 Strick ⁸³ DNA-protein interactions 2005 Koster ⁸⁶ enzyme-induced uncoiling of DNA 2012 Bryant ⁶⁵ review 2016 Berghuis ⁷⁹ high-throughput probing of DNA-protein interactions
		SP μm	eMTT	Optical microscopy	Protein	Angular position	2013 Van Reenen ⁷⁰	2016 Gutiérrez-Mejía ⁸¹ conformation changes in cardiac troponin

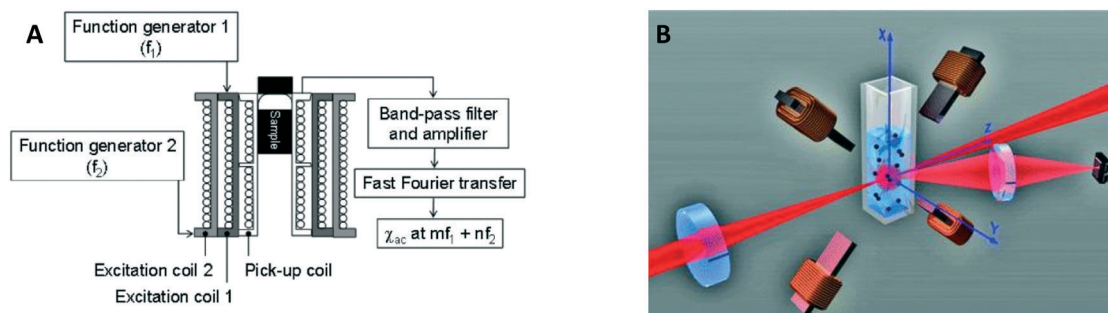
The abovementioned techniques involve a change of hydrodynamic radius. Another approach for measuring the concentration of biological molecules makes use of the analyte-induced formation of clusters of particles, as in Fig. 1C. In

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In 2006 Baudry *et al.* showed the detection of a biological target by optically measuring the change of the rotational Brownian relaxation speed of clusters of MPs.⁸ A magnetic field was applied to form chains of MPs and the redispersion time of particles was measured upon removal of the magnetic field. The redispersion time is larger when target-induced clusters are present than when such biochemically-formed clusters are absent, due to the slower Brownian motion of clusters compared to single particles. The cluster assay was accelerated by the magnetic chain formation, to a time on the order of 5 min. The formation of chains can also be measured by recording the modulation of scattered light in a rotating magnetic field, as demonstrated around 2010 by Park *et al.*¹²³ and Donolato *et al.*^{36,38} who monitored the transmission of light, and by Ranzoni *et al.*^{41–43} who monitored the scattered light under an angle (see Fig. 6B). In these experiments spherical 100–1000 nm superparamagnetic MPs were used. Only clusters or chains of particles cause the scattered light to fluctuate in a rotating magnetic or AC field, because single particles possess no optical anisotropy. The magnitude of the oscillations of the scattered or transmitted light is proportional to the number of clusters, which in turn depends on the target concentration. The transmission-based measurement principle in combination with AC actuation along the optical axis, as demonstrated by Donolato *et al.*, led in

BluSense combines magnetic actuation with existing blue-ray technology, where the rotational motion of a disk-shaped cartridge gives microfluidic actuation and optical detection is used to measure cluster formation.³⁸ With a detection angle of the scattered light at 90 degrees, Ranzoni *et al.*⁴³ demonstrated that the concentration of PSA in undiluted blood plasma could be measured in the low picomolar range, by recording the amplitude of the 2f signal (at twice the driving frequency). Vliembergen *et al.*^{124,125} have extended the optical detection method by analyzing the rotation-angle dependent scattering signals. Sharp peaks in the spectrum allowed them to measure nanometer-scale inter-particle distances within the clusters. The results show that particle roughness is an important factor in the data. In the future this approach can lead to novel ways to distinguish between specific and non-specific binding in lab on chip cluster assays.

One of the first applications of rotating MPs was for studying the mechanical properties of cell membranes (Fig. 1D), by so-called magnetic twisting cytometry (MTC).⁴⁷ An experiment done by Valberg *et al.* in 1987 is shown in Fig. 7. Typically ferromagnetic MPs were used in combination with an AC field generated by an eMTT. The magnetic relaxation time of these ferromagnetic MPs is chosen to be significantly



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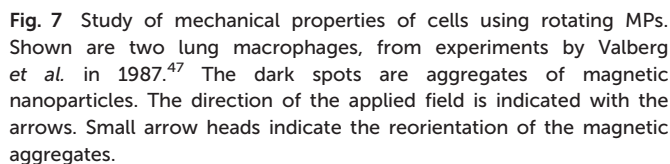


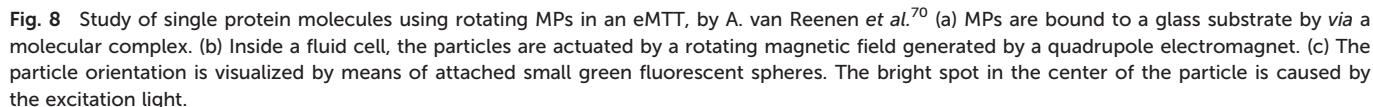
Fig. 7 Study of mechanical properties of cells using rotating MPs. Shown are two lung macrophages, from experiments by Valberg *et al.* in 1987.⁴⁷ The dark spots are aggregates of magnetic nanoparticles. The direction of the applied field is indicated with the arrows. Small arrow heads indicate the reorientation of the magnetic aggregates.

In later work, researchers switched from detecting the magnetic signal to optically tracking the spatial position and/or angular orientation of individual particles. Both ferromagnetic and superparamagnetic particles, typically larger than 1 μm , have been used in these experiments. An example of early work using optical detection was a study on the torque generated by a flagellar motor of *Escherichia coli* by Berg *et al.* in 1993.⁴⁸ They tracked the rotation speed of the particle and compared it for different magnetic field strengths.

Rotating MPs are also well-suited for studying the torsional properties of biological systems at the single-molecule level^{69,80} (Fig. 1E). Typically, a molecular system is captured between a planar substrate and a MP, and the rotation of the MP is recorded using optical microscopy. The first molecule to be studied was double-stranded DNA (dsDNA), where the

Later studies involved direct tracking of the angular orientation of the MP. Angular tracking can be achieved by attaching an optical marker that breaks rotational symmetry, *e.g.* a small non-magnetic particle. One solution is to attach a small nonmagnetic bead as marker to the DNA molecule itself. This labelling technique has allowed for studying the local structure, sequence specific effects and dynamical effects in supercoiled DNA.⁷¹ Another technique to track MP rotation is by using a circular magnet, as in Fig. 3B. The magnet creates a displacement of the center of the MP with respect to the anchoring point of the DNA in the fluid cell. As a consequence, rotation of the MP becomes related to the off-center spatial position of the MP. This technique has been used to monitor changes in the twist of nucleic acids at minimal torque.⁶⁴ If required the DNA can be torsionally actuated by adding a set of coils or a small linear magnet.^{63,66}

More recently the torque properties of proteins have been studied using MPs. The mechanical properties of proteins are very different from DNA: proteins are globular molecules (rather than filaments) with a size of around 10 nm. This gives a number of important differences: (i) there is no need to apply a stretching force when studying proteins, (ii) proteins are small and stiff, so angular and spatial displacements of the MP are small, and (iii) in the experiment the MP is close to the substrate, so artefacts due to particle-surface interactions need to be carefully ruled out. Janssen *et al.* developed an eMTT system with minimal field gradients.^{131,132} The system was used to study the torsional properties of proteins as a function of the angle of rotation⁷⁰ and as a function of the concentration of surfactants.⁷⁷ Fluorescent nanoparticles were attached to the MP for angular tracking, see Fig. 8. Panel C shows a microscopy image of an MP with a single fluorescent marker. By applying a continuously rotating magnetic field and recording the maximum angular deformation, the torsional rigidity of protein G-IgG and IgG-IgG complexes could be quantified.⁷⁰ This technique has also been used to study the torsional rigidity of a heterotrimeric protein complex, namely the cardiac troponin complex that regulates muscle contraction of the heart. Using antibody targeting of



Another approach that has seen strong development is the biophysical probing of biomolecules and cells using rotating MPs (Fig. 1D and E). Methodologies were first developed for studying cells, but in recent years the focus has shifted completely to studying single molecules. Single-molecule studies (Fig. 1E) have given unique insights into the properties and function of macromolecules such as DNA, DNA-protein interactions, and also native protein complexes.

Single-molecule techniques are important for answering scientific questions but the methodologies also penetrate into bioanalytical sciences. Commercial analytical instruments are now available based on earlier academic studies on single-molecule methodologies for the quantitation of proteins^{126,127} and for DNA sequencing.^{128,129} The same trend can be expected for sensing based on magnetic rotation and torque, when the single-molecule methods will become suited to test unknown biological samples. As an example, the rotation-based methodologies based on target capturing by affinity molecules such as aptamers or antibodies⁸¹ will enable the detection and characterization of native proteins in biological samples. Due to the fact that unmodified native proteins are measured, the methods can have impact beyond research only. Proteins and their functional response can be characterized straight from industrial processes (for biotechnological process monitoring) and from patient samples (for diagnostics and patient monitoring). We foresee that this paves the way for biomarker response fingerprinting at the single-molecule level, with the prospect to lead to lab-on-chip systems with high specificity and high sensitivity, *e.g.* particle-based point-of-care testing devices² and devices for continuous biomarker monitoring.¹³⁰

In summary, the controlled application of torque and rotation to magnetic particles has developed strongly and steadily over the past decades, delivering a range of unique actuation and probing functionalities of fluids, molecules and cells in lab on chip systems. The field is set to further develop innovative approaches for characterizing biomolecular and biological systems as well as for integrating lab on chip functionalities into advanced bio-analytical tools.

Nanometer and micrometer sized magnetic particles combined with gradient-free magnetic fields allow for the generation of well-defined mechanical torques and rotations in lab on a chip devices. Foundations of the field were laid in the previous century, when superparamagnetic behavior of magnetic particles was observed and monodisperse micrometer-sized superparamagnetic particles were developed. More recently, lab on chip functionalities have been studied with rotating magnetic particles, ranging from fluid mixing, detection of biomolecules, to biophysical studies of molecules and cells. These applications could be developed due to the large and well-controlled torques and rotation, the inherent spatial uniformity, and the bio-orthogonal nature of magnetic fields.

The mixing functionality (Fig. 1A) has been well-developed in terms of experiments as well as theory. Many basic studies have been performed and fluid-mechanical models exist to describe the development of flow by rotating particles. Biomarker quantification (Fig. 1B and C) is being studied using rotation of single particles as well as clusters of particles. These applications involve biofunctionalization of the particles, capture of target molecules by the particles, and readout *via* magnetic or optical signals. An advantageous feature is that the detection is performed in solution, without a fluidic washing process or other separation steps, which strongly simplifies assay integration into lab on chip devices. Further developments can be expected, particularly in the field of cluster assays (Fig. 1C), to achieve high analytical performance in a wide range of assays, by designing new particles, biofunctionalizations and assay implementations, with the prospect to enable affinity-based biosensing that is fast, reliable, integrated, cost-effective, and broadly applicable.

Conflicts of interest

There are no conflicts to declare.

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