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Periodic convection of superparamagnetic beads within a microfluidic channel by interlocked, electroplated structures activated by a static field

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ABSTRACT

To enhance point-of-care analysis by means of lab-on-a-chip devices, functionalized superparamagnetic beads can be used in combination with micro-sensing. Prior to detection of specific low-concentrated biomarkers a pretreatment step is necessary in most cases. Here we present a novel approach for the periodic convection of superparamagnetic beads for intensified up-concentration and biomarker labeling. In contrast to previous approaches, where dynamic switching fields were applied, our system can be activated within a static field, but still allows a controlled movement in two directions. By introducing softmagnetic structures, the magnetic field as well as the field gradient can be periodically modulated along the microfluidic channel. Suitable shapes of pole pieces were analyzed using Finite Element Method simulation before the microsystem was microfabricated and tested. Experiments show how the flow rate within the channel and the magnetic field cooperate to establish an operational regime in which periodic convection can be established and controlled.

1. Introduction

The interest in lab-on-a-chip systems, also known as micrototal analysis systems, has gained remarkable attention since these miniaturized devices enhance the emerging trend in point of care diagnostics [1]. Based on a variety of microfluidic techniques they are enabled to carry out standardized laboratory tasks [2]. Furthermore, these devices can be used for the detection of protein markers or nucleic acid markers to diagnose for instance cardiac diseases or infectious diseases. Besides the sensing technology, which is required for the detection process, a pretreatment of the sample is often necessary, due to low concentrations of biomarkers in a complex sample [3]. Molecular selective detection of antigens or protein biomarker particularly can be achieved by the use of antibodies and immunoassays. In order to obtain higher sensing accuracy, an up-concentration pretreatment with biochemical amplification labels can be applied [4].

A variety of microfluidic processing tasks can be realized by employing magnetic particles. Their high potential of application in microfluidic devices is not restricted to mixing and pumping [5]. In addition, these particles can be functionalized and act as labels in an immunoassay, using established biomolecular surface linking strategies [6]. The multiple advantages of the magnetic particles derive from micro- and nano-scale effects, such as a large surface-to-volume ratio, a relatively fast reaction time and a superparamagnetic behavior [7–8]. Moreover, the superparamagnetic beads can be manipulated by a magnetic field, allowing a contact free external control. Thus, they are able to accomplish important functions inside a lab-on-a-chip system [9].

In the past years a variety of approaches have been developed by many research groups in order to manipulate superparamagnetic beads within a microfluidic channel as shown in the excellent review by Cao et al. [7]. In some cases macroscopic external magnets had been applied [10–11]. Others used a more complex manipulation set-up consisting of microfabricated integrated electromagnets [12,13,14]. To combine the benefits of the strong external magnets and the integrated magnets, which are closer aligned to the microchannel, both techniques have been combined. In a hybrid arrangement softmagnetic structures were integrated on the chip and magnetized by an external magnet for bead immobilization [15].

Here we present a novel method that allows a periodic convection of superparamagnetic beads by hydrodynamic and magnetic actuation forces only. In a flow-through microfluidic system, superparamagnetic beads will be used to capture specific antigens e.g. insulin. Once, the antigen is tied to the functionalized surface of the bead it can be controlled and guided through the microfluidic channel. In order to measure the antigen's concentration, an additional microsystem based on quartz crystal microbalances (QCMs) can be employed [16,17,18]. In this combination the superparamagnetic beads can be used for sample up-concentration and amplification of the signal.

The microsystem is kept very simple. It consists of a microfluidic channel, surrounded by softmagnetic, interlocked pole pieces.

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Therefore, it can be integrated easily in a lab-on-a-chip application or in other analytical application devices.

2. Theory for the manipulation of superparamagnetic beads

Superparamagnetic beads are microsized polymer spheres containing dispersed nano scaled iron oxide grains. They are characterized by a superparamagnetic behavior, which means that they become magnetic in the presence of a magnetic field, but do not exhibit magnetic remanence [9].

In order to move a superparamagnetic bead within a microfluidic channel the hydrodynamic force needs to be counteracted by the magnetic force $\vec{F}_{mag}$. The force, acting on a magnetic dipole moment $\vec{m}$ in a field $\vec{B}$, can be described as: [19]

$$\vec{F}_{mag} = \left(\vec{m}\nabla\right)\vec{B}. \quad (1)$$

According to this expression it becomes clear that a magnetic field gradient is essential for a translational motion of the beads. Furthermore no motion can be obtained by homogenous fields. The formula can also be expressed in a more intuitive form, using standard vector notation. For an unsaturated particle it is defined as: [11]

$$\vec{F}_{mag} = \frac{1}{2\mu_0}\chi V_m \nabla \vec{B}^2 \quad (2)$$

where μ_0 is the permeability in vacuum, Δ (dimensionless) the magnetic susceptibility of the particle relatively to the surrounding medium and V_m the volume of the magnetically active fraction of the bead. Additionally, a magnetically saturated bead experiences a constant dipole moment. Hence the magnetic force $\vec{F}_{mag}$ can be seen as proportional to the magnetic field gradient $\nabla\vec{B}$ [20]. Once the beads are exposed to a magnetic field they also interact with one another. Since each individual bead functions as a micromagnet they are bilaterally attracted and start to form chains. A comprehensive study of the interactions and forces acting on superparamagnetic chains is given by Singh et al. [21].

Within a viscous medium the displacement of a superparamagnetic bead, that moves with the velocity $\vec{v}$, creates a hydrodynamic drag force $\vec{F}_D$ that is defined as:

$$\vec{F}_D = -6\pi\eta r\vec{v} \quad (3)$$

where r is the radius of the bead and η the dynamic viscosity of the medium. Under dynamic circumstances, where the magnetic particles retain in flow, the magnetic force has to be counterbalanced with the hydrodynamic drag force. Further, the magnetic force acts perpendicularly to the flow direction. Considering that the superparamagnetic beads are not supposed to be immobilized at the channel wall, the interaction between the magnetic actuation force and the flow rate is crucial.

For our experiments, first an evaluation of the field strength was made, based on Eq. (2), concerning the saturation of the actual magnetization of the beads. However, for a more detailed mathematical analysis of the forces acting on beads, chains of beads or even more complex clusters, a more elaborate evaluation is required.

3. Materials and methods

3.1. Working principle and FEM simulation

The goal of this study was to develop a flow-through microsystem that allows a periodic up-and-down movement of superparamagnetic beads. At low Reynolds numbers, where laminar flow dominates, the interaction between antigens and beads is limited by diffusion. Hence, an intensified convection of the beads needs to be obtained to increase the amount of binding events of specific antigens to the antibody coated surface of a bead. That comprises in detail the deceleration of the magnetic particles and a periodic movement oblique to the stream flow, as demonstrated in Fig. 1.

After the antigens are tied to the beads, the microspheres can be manipulated and sorted for a sample up-concentration. Further, they can be guided to an analytical instrument like a QCM to measure the concentration. With the beads attached to the antigens the measuring signal can be amplified.

In order to realize a periodic convection of the magnetic beads a complex setup for dynamic field switching, as attempted by other research groups [20], is not required here. In lieu thereof we take advantage of the hydrodynamic forces. In combination with magnetic actuation forces a novel function principle is achieved.

Prior to fabrication, the magnetic poles were designed and evaluated by Finite Element Method (FEM) simulation created with the open source program femm 4.2. With these results a microsystem can be designed and the modulated magnetic field can be tested and analyzed under different flow conditions.

Out of different designs that were tested, only the most suitable shape is presented. This design has interlocked fingerlike poles, made of a softmagnetic alloy. The 14 poles pieces lie on both sides of the microfluidic channel. Each has a width of 100 μm but different lengths. The longer pole pieces have a length of 3600 μm and are around 250 μm apart from the microfluidic channel. The shorter pieces are only 3200 μm long and have a distance of 650 μm to the channel. Both types are alternatingly placed so that each long pole piece is on the opposite site of a short piece. The configuration of pole pieces can be seen on the density plot (FEM simulation) shown in Fig. 2.

The simulation shows the modulated magnetic field obtained by placing softmagnetic structures in a static field. These structures are excited by two external permanent magnets each having a magnetic strength, as measured with a teslameter (FH55 from MAGNET-PHYSIK Dr. Steingroever GmbH) of around 620 mT at the tip. Without these softmagnetic structures the magnetic field would be distributed symmetrically to the microfluidic channel center axis. Their function is thus to focus the magnetic flux und generate local high field gradients in order to obtain high actuation forces. This can be observed by analyzing the tip of the oblong structures shown in Fig. 2, where a local magnetic field is generated at the tip of each pole. Through the alternating length of the poles a relatively high magnetic field is created in a zigzag pattern. This permits the manipulation of the beads in a periodic seesaw manner. Furthermore, the field values of the flux density were extracted for a quantitative examination and plotted in Fig. 3. The chart shows the distribution of the magnetic flux density ($|B|$) in Tesla along the lower and upper microchannel wall. The scale placed in Fig. 2 is plotted on the x-axis of the chart and shows the position of the poles.

The magnetic flux density along the upper channel wall as well as the lower site lies in the range of about 400–525 mT and rises toward the center. In the area of the first pole, at x-position 0.3 mm, the lower pole is located closer to the microchannel. Thus, the field is stronger in this area. The second pair of poles ($x = 0.5$ mm) has a reversed arrangement, where the upper pole generates a stronger magnetic field. This alternating configuration continues and results in a modulation of the magnetic field, based on displacement and size of the magnetic poles.

In order to fulfill a translational movement of the superparamagnetic beads the magnetic field gradient, as described in Eq. (1) needs to be considered. The graph in Fig. 4 shows the deviation of the magnetic flux density in x direction along the lower and upper microfluidic channel wall. The vertical axis of the graph shows the field gradient in mT per 100 μm, whereas on the horizontal axis the position of the poles, as defined in the FEM-simulation (Fig. 2) is plotted. Further the two lines show the alteration of the field gradient along the channel walls. Similar to the above mentioned alternating magnetic field this chart emphasizes the magnetic effect of the interlocked structures. Right before the