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Biosensing utilizing the motion of magnetic microparticles in a microfluidic system

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Abstract

The study for the design of a compact and inexpensive biosensing device, which can be operated either by primary care personnel or by patients as opposed to skilled operators, is presented. The main parts of the proposed device are a microfluidic channel, permanent magnets and functionalized magnetic microparticles. The innovative aspect of the proposed biosensing method is that it utilizes the volumetric increase of magnetic microparticles when analyte binds to their surface. Their velocity decreases drastically when they are accelerated by an externally applied magnetic force within a microfluidic channel. This effect is utilized to detect the presence of analyte e.g. microbes. Analytical calculations showed that a decrease in velocity of approximately 23% can be achieved due to the volumetric change of a magnetic microparticle of 1μm diameter when HIV virions of approximately 0,135 μm are bound to its surface and by keeping its magnetic properties the same. Preliminary experiments were carried out utilizing superparamagnetic microparticles coated with streptavidin and polystyrene microparticles coated with biotin.

Keywords: Microfluidics, magnetic microparticles, biosensors, on chip

1. Introduction

The research and development of biosensing devices has drastically increased in the recent years driven by the impressive advances in microtechnology and biotechnology which enable the integration of a variety of analytical functions on a single chip. Microfluidic systems are chosen due to their potential to perform quick and reliable measurements from small volumes of fluids. Magnetic microparticles (MAPs) in combination with magnetic means are utilized because techniques employing magnetism in biomedicine are amenable to automation and miniaturization. Hand held analysis instrumentation can be operated either by primary care personnel or by patients

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as opposed to clinical lab technicians. Additionally, they can be used for field studies without the need for bulky laboratory equipment and yields much faster analysis results and saves costs significantly.

Nomenclature

F_{mag}	magnetic force
m	magnetic moment
B	externally applied field gradient
μ_0	permeability of vacuum
χ	effective magnetic susceptibility
n	viscosity of the medium surrounding the microparticle
Δv	velocity difference between the magnetic microparticle and the liquid
r	radius of the magnetic microparticle
r_p	radius of the attached particle
V	volume of magnetic microparticle

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2. Working principle

In the proposed system, MAPs, having a volume V, are coated with ligands of specific affinity to the analyte to be detected and are mixed with the fluid under investigation in a microfluidic system. If analyte is present and binds to the coated MAPs loaded magnetic microparticle compounds are formed (LMAPs). These are compounds with total volume V´ (see Fig.1a, b). Upon the application of an external magnetic force, MAPs and LMAPs show different velocities due to the difference in volume. Thus the difference of the velocities determines the presence of the analyte in the fluid under examination. The discrimination method is based on the fact that the LMAPs need more time to travel a certain distance than MAPs.
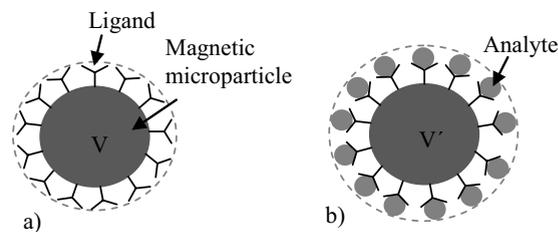

Fig. 1. (a) Magnetic microparticle coated with ligands exhibits a certain volume V; (b) magnetic microparticle coated with ligands and attached analytes exhibits a bigger volume V´.

3. Analytical Calculations

In order to use a magnetic field to transport magnetic microparticles a magnetic field gradient is required to exert a translational force. A uniform field gives rise to a torque, but no translational action [1-3]. The magnetic force F_{mag} acting on a single microparticle, approximated by a point-like magnetic dipole with a magnetic moment m is proportional to the gradient of the field $\boldsymbol{B}$ and is given by:

$$\vec{F}_{mag} = \frac{1}{\mu_0}\nabla\left(\vec{m}\cdot\vec{B}\right) \approx \frac{1}{\mu_0}\left(\vec{m}\cdot\nabla\right)\vec{B} \qquad (1)$$

The magnetic moment of a superparamagnetic microparticle, in a nonmagnetic medium, is induced by a field $B=\mu_0 H$ and can be expressed $m = V\mu_0\chi H$. Because the magnetic susceptibility of the surrounding medium is assumed to be zero, we can adapt Eq. 1 to the case of a superparamagnetic microparticle as:

$$\nabla \times \vec{B} = 0 \ \rightarrow \ \vec{F}_{mag} = \frac{V\chi}{2\mu_0}\nabla \vec{B}^2 \tag{2}$$

The hydrodynamic drag force acting on the magnetic microparticle is a consequence of the velocity difference between the magnetic particle and the fluid Δv. In our case the fluid is static. For a spherical particle with radius r it is:

$$\vec{F}_d = 6\pi n r \Delta v \tag{3}$$

By equalizing Eqs. (2) and (3) one can determine the maximum flow rate that a microparticle can withstand when exposed to a magnetic immobilization force, or the maximum particle flow rate that can be generated by a magnetic force in a surrounding static liquid:

$$\Delta v = \frac{r^2\chi}{9\mu_0 n}\nabla \vec{B}^2 \tag{4}$$

If analytes are attached around the coated magnetic microparticle (see Fig. 1a, b) then the total radius r' of the magnetic microparticle will increase. This increase will only have an influence in Eq. (3) thus:

$$\vec{F}_d = 6\pi n r' \Delta v \tag{5}$$

Therefore Eq. (4) is then given by:

$$\Delta v = \frac{r^3\chi}{9\mu_0 n r'}\nabla \vec{B}^2 \qquad \text{where } r'= r + 2r_p. \tag{6}$$

A calculation example of an HIV detection system utilizing the suggested method is given in the following (the values for sizes have to be understood as being approximations). HIV particles show a size of 0.135 μm in diameter. Each virion posses 72 glycoprotein projections on their surface and the gp120 is utilized as receptor by the help of MAb YZ-23 antibodies [4-5]. Paramagnetic microparticles of 1 μm in diameter covalently coated with MAb YZ-23 antibodies are utilized for the detection. Each coated microparticle typically shows 104 antibodies (1 μm SPHERO^{TM} magnetic particles). The antibodies have a size of 12.5 nm. This results in a magnetic microparticle size of 1.025 μm in diameter. Taking into account the size of a virion, a maximum number of 181 virons can be bound by one microparticle. The radius r of the coated magnetic microparticle is 0,5125 μm. The radius r_p of the HIV particle is 0,0675 μm. If HIV particles are present in the liquid under examination they will bind to the coated magnetic microparticles during mixing in a microfluidic channel. Assuming that only one layer of particles binds around the coated magnetic microparticle, the resulting total radius of the microparticle (see Fig. 1a, b) will be: $r' = 0, 5125 + 0,135 \leftrightarrow r'= 0, 6475$ μm.

By replacing these numbers in Eq. (6) the velocity of the magnetic microparticle can be calculated before and after binding with the virions. A decrease in velocity of approximately 23% can be achieved due to the volumetric change of the microparticle. This percentage velocity decrease can be optimized if microparticles of smaller diameter (nm range) are utilized.

4. Experiments

Preliminary experiments were carried out in order to measure the velocity decrease due to the volumetric increase of the MAPs. Superparamagnetic microparticles plain and coated with streptavidin (6,2 μm in diameter) and polystyrene microparticles coated with biotin (0,97 μm in diameter) were utilized. The streptavidin coated MAPs

and the biotin coated polystyrene microparticles were bound with each other forming the LMAP compounds (~ 8,1 µm in diameter). This way, an increase in the total volume of the MAPs was ensured (see Fig. 2a, b). Both the LMAPs and the MAPs are introduced into a microfluidic channel using a syringe [6]. The MAPs and LMAPs can be accelerated using permanent magnets of 5 x 5 x 1 mm³. The time it takes for the LMAPs and MAPs to move from the inlet to the outlet can be measured using an optical microscope and a manually triggered stopwatch computer program. Fig. 3a, b shows the first experiments of the acceleration of the MAPs inside a microfluidic channel without having introduced the LMAPs.
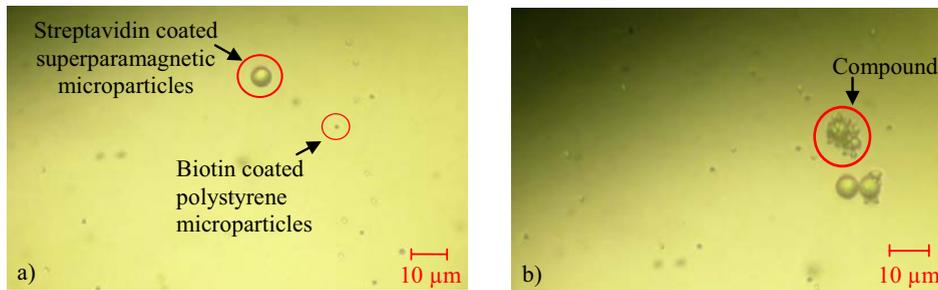

Fig. 2: a) superparamagnetic microparticles coated with streptavidin of radius 3,1 µm and polystyrene microparticles coated with biotin of radius 0,485 µm; b) superparamagnetic microparticles coated with streptavidin and attached polystyrene microparticles coated with biotin of an approximate total radius 4,1 µm. This way, an increase in the total volume of the superparamagnetic microparticles is ensured.
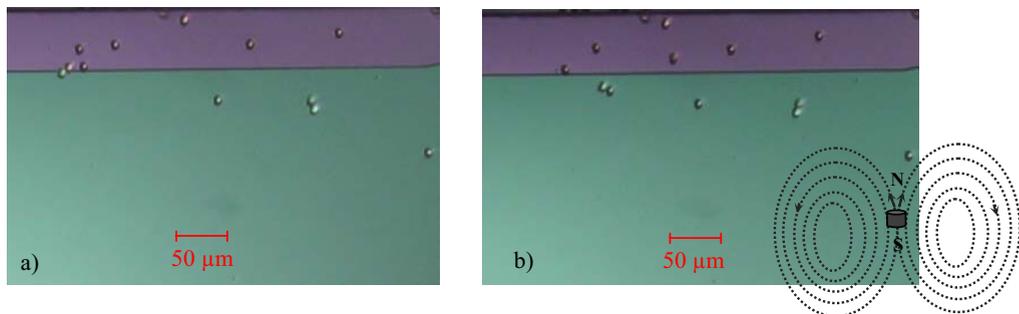

Fig. 3: a) superparamagnetic microparticles inside the microfluidic channel without the application of an external magnetic field; b) superparamagnetic microparticles are accelerated by the external magnetic field.

5. Conclusions

The proposed system can be utilized in multiple scientific fields like microbiology, biochemistry, molecular biology and molecular genetic engineering. It can also be applied in multiple industrial fields such as clinical, forensic and environmental studies.

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