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Guided self-assembly of magnetic beads for biomedical applications

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ABSTRACT

Micromagnetic beads are widely used in biomedical applications for cell separation, drug delivery, and hyperthermia cancer treatment. Here we propose to use self-organized magnetic bead structures which accumulate on fixed magnetic seeding points to isolate circulating tumor cells. The analysis of circulating tumor cells is an emerging tool for cancer biology research and clinical cancer management including the detection, diagnosis and monitoring of cancer. Microfluidic chips for isolating circulating tumor cells use either affinity, size or density capturing methods. We combine multiphysics simulation techniques to understand the microscopic behavior of magnetic beads interacting with soft magnetic accumulation points used in lab-on-chip technologies. Our proposed chip technology offers the possibility to combine affinity and size capturing with special antibody-coated bead arrangements using a magnetic gradient field created by Neodymium Iron Boron permanent magnets. The multiscale simulation environment combines magnetic field computation, fluid dynamics and discrete particle dynamics.

1. Introduction

The analysis of circulating tumor cells (CTCs) supports the monitoring of tumor growth and can be used to control the success of therapies. Microfluidic chips help to detect, to identify and to count these cells in peripheral blood. First time observed in 1869 [1] it becomes possible to gain a better understanding of how metastases form through the analysis of CTCs with the advance of technology platforms. Due to their rare appearance existing microfluidic filters [2] cannot find every single CTC in the blood flow. In these devices the distinct properties (size, affinity, density) of the tumor cells are used to filter them. The technical challenge is to detect, count and isolate one CTC over one billion cells [3] (1–100 tumor cells per ml blood).

A promising approach from Saliba et al. uses self-organizing chains of ferromagnetic biofunctionalized beads [4]. An array of magnetic traps is prepared by microcontact printing in a microfluidic channel. Single particle chains line up which create a sieve-like structure. This method has a limitation of flow rate due to decreasing stability with higher velocity. Our proposed chip technology uses thin soft magnetic seeding points with a diameter several times larger than the bead diameter. We will analyze the microfluidic behavior of soft magnetic beads attracted by this seeding points in multiphysics simulations.

1.1. Multiscale simulation environment

A microfluidic chip (Fig. 1A) is placed on the top of a single or multiple permanent magnets. On the bottom of the chip a hexagonal array of soft magnetic cylinders is placed. The cylinders act as a accumulation point (seeding point) for soft magnetic particles in the fluid flow. When applying the permanent magnets on the microfluidic chip the soft magnetic particles self-organize according to the field created by the seeding points and the permanent magnets. The behavior of magnetic beads close to a single seeding point is discussed in Section 3.3. Cuboidal or cylindrical NdFeB permanent magnets are the magnetic source for the given scenario. Akoun [5] showed the analytic calculation of the magnetic field created by a cuboidal permanent magnet. Derby [6] did the same for cylindrical permanent magnets. To get a higher magnetic field $\vec{H}$ several magnets are combined having superposition of the field values (Fig. 1A). In order to reduce simulation time and computational cost we are focusing on special areas in the microfluidic channel. Fig. 1B shows the microfluidic chip with the seeding point array at the bottom. The light green seeding points will be taken into account for further investigation. The simulation boundaries are set according to the results of Section 3.1.

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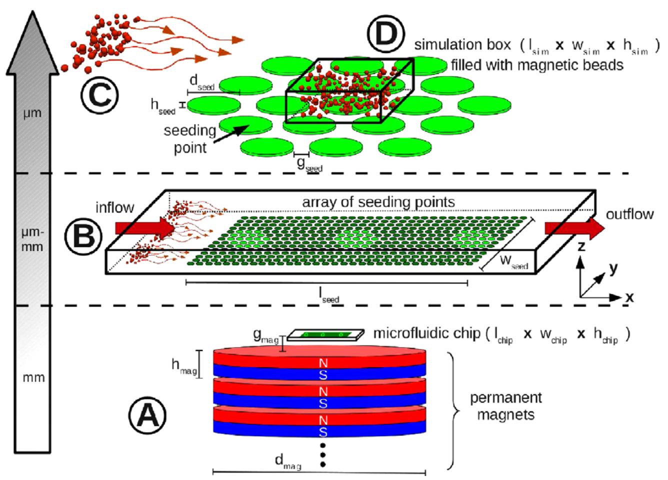

Fig. 1. Multiscale simulation environment: (A) magnetic field source: *N* permanent magnets, (B) zoom into the microfluidic chip: hexagonal array of soft magnetic seedings points with light areas of interest, (C) trajectories of soft magnetic particles, (D) magnetic field from permanent magnets and soft magnetic disks for a closed simulation box filled with soft magnetic beads.

The magnetic field $\vec{H}$ magnetizes the interacting seeding points. They create a highly non-homogeneous magnetic field in the microfluidic chip. Fig. 1D shows the simulation area close to a single seeding point. Soft magnetic particles are randomly filled into the simulation box and interact with each other, the permanent magnets and the seeding points.

Looking at a larger scale the trajectories of the magnetic beads to the seeding points are calculated with the software package Comsol [7] (Fig. 1C). The particle distribution, i.e. the number of beads close to a single seeding point, depends on the fluid velocity, the applied magnetic field, the chip geometry as well as the seeding material.

2. Methods

2.1. Magnetic particle dynamics

Under the influence of a magnetic field a magnetic moment $\vec{m}$ is created in every particle. With the moments of two nearby beads and the vector $\vec{r}$ pointing from bead 1 to bead 2 we got a formulation (Eq. (1)) of the interaction force F_i for bead 2 and vice versa for bead 1 [8]:

$$\vec{F}_{1\to 2} = \frac{3\mu_0}{4\pi r^5}\Big[(\vec{m}_1\cdot\vec{r})\vec{m}_2 + (\vec{m}_2\cdot\vec{r})\vec{m}_1 + (\vec{m}_1\cdot\vec{m}_2)\vec{r} - \frac{5(\vec{m}_1\cdot\vec{r})(\vec{m}_2\cdot\vec{r})}{r^2}\vec{r}\Big] \quad (1)$$

The gradient force $\vec{F}_g$ on a bead is given by the negative gradient of the energy of the magnetic dipole moment $\vec{m}$ in the field $\vec{B}$. Eq. (2) shows this 3-dimensional vector with the assumption of homogeneous magnetization inside the beads ($\partial_{\vec{r}}\,\vec{m} = 0$):

$$\vec{F}_g = \nabla\left(\vec{m}\cdot\vec{B}\right) = \begin{pmatrix} m_x\partial_x B_x + m_y\partial_x B_y + m_z\partial_x B_z \\ m_x\partial_y B_x + m_y\partial_y B_y + m_z\partial_y B_z \\ m_x\partial_z B_x + m_y\partial_z B_y + m_z\partial_z B_z \end{pmatrix} \quad (2)$$

In our preliminary work we assumed that the external field is inhomogeneous only in one dimension and also the field itself has only a single direction [9]. This assumption reduces computational time a lot. We derived only the z-field in the *y*-direction leaving a resulting force $F_{g,y} = m_z\partial_y B_z$. But if we want to have a complex magnetic field from several permanent magnets and thin soft magnetic disks, we have to consider all three dimensions.

During simulation this force could be calculated in every timestep for every single bead which slows down the simulation. Another possibility is the initial calculation of the external field $\vec{H}$ and its derivatives $\partial_i B_j$ at the beginning of the simulation in a Cartesian grid. And during the simulation this fixed values are interpolated according to the non-fixed position of the bead.

We implemented both methods, the direct calculation in every timestep, and the particle-in-cell method for faster computation in the open-source particle simulator Yade [10].

2.2. Particle-in-cell method

The particle-in-cell method works with a fixed Cartesian grid (Fig. 2a). In our case the simulation box in Fig. 1D is the boundary of the particle simulation and contains the fixed grid with uniform grid length $l_{g,\mathrm{sim}}$. Before the actual simulation of interacting magnetic beads, initial values for the external field $\vec{H}$ and all derivatives $\partial_i B_j$ need to be calculated in every single grid node. To get the magnetic field values in the grid several steps are performed.

1. Analytic calculation of the magnetic field from permanent magnets at seeding points of interest using Ref. [5] for cuboidal and Ref. [6] for cylindrical permanent magnets.
2. Numerical calculation of the field $\vec{H}$ in every grid point of the simulation box using the finite element micromagnetic package FEMME [11]. The amount of seeding points taken into account for the field calculation in the simulation box is derived in Section 3.1.
3. Numerical differentiation of the grid to get all values of $\partial_i B_j$ using three point formulas [12]. They include the point before and after the calculated point (centered difference formula). At the edge points a forward or backward difference formula is used as there are no points outside the grid. The differentiation generates a second-order accurate approximation with a truncation error of $O(l_{g,\mathrm{sim}}^2)$.

During the simulation in every timestep the following tasks are performed to get the magnetic induced force on the beads:

1. Interpolate magnetic field $\vec{H}$ and derivatives $\partial_i B_j$ for every single magnetic bead according to the position in grid cell using tricubic interpolation [13] (Fig. 2b).
2. Calculate magnetic moment in every single bead ($\vec{M} = \chi\vec{H}$) using interpolated field $\vec{H}$ from the grid.
3. Calculate and add force on bead due to magnetic particle interaction (Eq. (1)).
4. Calculate and add force on bead due to magnetic gradient field (Eq. (2)) using interpolated derivatives $\partial_i B_j$ from the grid.

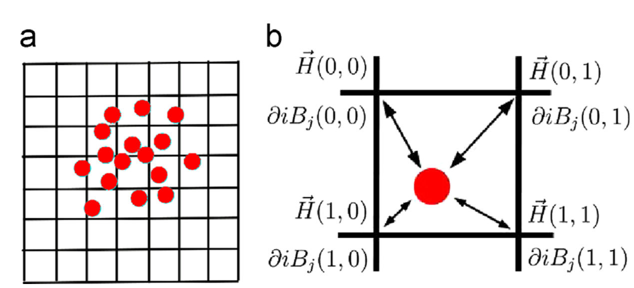

Fig. 2. (a) Fixed Cartesian grid with magnetic particles. (b) Interpolation of field and derivatives according to particle position.