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Analytical model of batch magnetophoretic separation

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Magnetophoresis (the motion of magnetic particles driven by the nonuniform magnetic field), that for a long time has been used for extracting magnetically susceptible objects in diverse industries, now attracts interest to develop more sophisticated microfluidic and batch techniques for separation and manipulation of biological particles, and magnetically assisted absorption and catalysis in organic chemistry, biochemistry, and petrochemistry. A deficiency of magnetic separation science is the lack of simple analytical models imitating real processes of magnetic separation. We have studied the motion of superparamagnetic (generally, soft magnetic) particles in liquid in the three-dimensional field of the diametrically polarized permanent cylindrical magnet; this geometry is basically representative of the batch separation mode. In the limit of the infinite-length magnet, we found the particle magnetophoresis proceeds independently of the magnet polarization direction, following the simple analytical relation incorporating all the relevant physical and geometrical parameters of the particle-magnet system. In experiments with a finite-length magnet we have shown applicability of the developed theory as to analyze the performance of the real batch separation systems in the noncooperative mode, and finally, we have presented an example of such analysis for the case of immunomagnetic cell separation and developed a criterion of the model limitation imposed by the magnetic aggregation of particles.

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I. INTRODUCTION

Simple by nature, the idea of magnetic separation, the use of which has been known for decades in diverse industries [1], nowadays arouses wide interest integrating with modern sophisticated, primarily biomedical, technologies. Is seems that the germination of new approaches in the field of magnetic separation is marked by introducing two concepts. First is the concept of high-gradient magnetic separation [2,3], proposed in the search for magnetic monopole, and second, the concept of magnetic particle functionalization (for magnetic control of cell separation [4] and biocatalysis [5]). A vast amount of publications in this field is necessitated by the variety of realized and potential applications and by the complex nature of the problem related with various branches of chemistry, biology, physics, and engineering. There are several reviews analyzing recent advances in magnetic separation as whole [6,7], and also in its different branches including traditional (glass and ceramic production [8], water purification [9], food processing [10]), and novel applications such as immunomagnetic cell separation [11,12], analytical biochemistry [13,14], and organic synthesis [15]. Chemical and biochemical laboratories have proposed a wide spectrum of functionalized magnetic carriers intended for separation and manipulation of biological particles (cells, proteins, amino acids) [11–14], and magnetically assisted absorption [16,17] and catalysis in organic chemistry [18–20], biochemistry [21], and even petrochemistry [22]. A distinct area is composed of a few studies of the old but still attractive idea of direct (label-free) magnetic separation of submagnetic microparticles, primarily biological particles, using differences between magnetic susceptibility of the particles and the liquid carrier [23–31].

The scope of problems relating to the applied physics is wide. In the field of label-free separation of submagnetic microparticles and cells from liquid we indicate research and development of magnetophoretic measuring methods for determining individual magnetic characteristics of particles [32–34] and studies of the diamagnetic separation mode [35–38], the effectiveness of which can be dramatically enhanced [39–43] by employing, in the capacity of liquid carrier, the stable magnetic colloids (magnetic fluids [44,45]) having incomparably stronger magnetic susceptibility than ordinary liquids. Moreover, magnetic fluids have relatively slow magnetic relaxation, the rate of which is limited by the rotation of colloidal magnetic particles in viscous carrier [44]. This dramatically changes the character of interaction with magnetic fields of both magnetic fluids [44,46] and suspended nonmagnetic particles [47]. The symmetry of the Maxwell stress tensor is violated, the electrodynamic bulk torque and the dissipative addition to the bulk electrodynamic force appear, and nonmagnetic particles acquire regular internal rotation. A complicated combination of these factors was found to create new possibilities for magnetic manipulation of nonmagnetic particles [48–50]. Also, magnetic separation, with its specific problems, calls for reexamination of the cooperative behavior of the systems of interacting magnetic particles, which for decades have been an important issue of the above mentioned magnetic fluids and magnetorheological suspensions [51,52]. In magnetic fluids, the size of magnetic nanoparticles is limited from above to prevent aggregation [45], and the long-range particle-particle magnetic interactions may affect their macroscopic properties either at the local level (via formation of chains [53,54]), or at the thermodynamic level. The latter manifests itself in the magnetic fluid separation into dilute and concentrated phases [55–58] and anisotropy of the particle mass diffusion [59–61]. In the case of magnetic separation, it may be desirable to increase the active specific

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surface of particles. This suggests decreasing of the particle size, and hence, the driven magnetic force. When estimated for an isolated particle, magnetic separation of particles smaller than 50 nm appears impractical [62]. But magnetically induced aggregation of unstabilized (in contrary to magnetic fluids) magnetic nanoparticles makes it possible, with the use of rather moderate magnetic field gradients, to extract from liquid even much smaller (∼12 nm) particles [63]. Magnetic aggregation can accelerate the batch separation 100-fold [64,65]. Cooperativity also may be important in separation of nonmagnetic particles in magnetic fluids. In the case of uniform magnetic fields, cooperativity was studied long ago [66], and was found strong enough to considerably influence the magnetic fluid/nonmagnetic particle system fluidity in magnetic fields [67,68].

Theoretical studies have always been an important ingredient of magnetic separation science, providing practically useful patterns of relationship between the process characteristics and physical and geometrical properties of the separation systems. As can be seen from recent overviews [69,70] of magnetic separation models, as well as from recent theoretical studies of particular systems [65,71–74], the behavioral complexity due to magnetic (and to some extend hydrodynamic [34]) interactions of particles is widely recognized, but the dominant approach since the early studies [1,75–79] remains noncooperative, relying on calculations of single-particle motion under given magnetic and hydrodynamic conditions. Basically a different (continuous) approach is under development to account for the thermal diffusion influential in the case of colloidal magnetic nanoparticles [80,81]. The proposed model is also noncooperative by nature, and is applicable to very dilute systems, as far as it takes the Stokes-Einstein diffusion constant for the mass diffusion coefficient and ignores the coupling between the volume distribution of particles and that of the magnetic field intensity, due to which the particle mass diffusivity in magnetic field becomes anisotropic and dependent upon the field intensity even in ideally stable magnetic colloids [59,60], let alone the particle chaining. In most cases, quantification of even single-particle behavior in real systems involves numerical simulations, which, considering the multiplicity of involved physical and geometrical parameters, are not very suitable for the system optimization [82]. Analysis can be simplified with the use of magnetic field sources having analytical representation. Magnetized by the uniform external field cylindrical wire is a classical model for magnetic trapping studies. Recently, more complex but still analytically representable magnetic fields have been employed created by systems of either externally magnetized or permanent-magnet rectangular rods [43,72,83–86]. Still, the magnetic field is rather complicated which excludes the possibility of deriving analytical description imitating real separation systems. More simplification should be employed to obtain such results. The lack of analytical solutions as an essential drawback of the magnetic separation science was recently cited to develop an analytical single-particle model of batch magnetic separation in the uniform magnetic field gradient [65].

Here we study magnetophoresis and magnetic separation in the three-dimensional nonuniform field created by a diametrically magnetized permanent cylindrical magnet. We consider this geometry the basic one, embodying key characteristics of the typical batch immunomagnetic columns consisting of the set of a transversely magnetized rod and the adjacent container with the suspension to be separated. As for any permanent magnet, magnetic field distribution around the cylindrical one is rather complicated. Still, there is an encouraging advantage, determining the methodological importance of this geometry. Namely, in the limiting case of infinite length, a diametrically polarized cylindrical magnet creates the field with a simple analytical presentation. So the first issue of our studies is magnetophoresis of a single magnetic particle in this field. We will show that for the case of superparamagnetic (in general, soft magnetic) particle, the driving magnetic force around the permanent diametrically polarized cylindrical magnet does not depend on the magnet polarization direction. This fact, which seems to have never been appreciated in the relevant literature, has important consequences. It implies that the motion (and hence, separation) of magnetically noninteracting particles proceeds homogeneously from any direction. Furthermore, the problem of the particle magnetophoresis turns out to be one dimensional. Under reasonable assumptions, this problem has a simple analytical solution, which incorporates all the relevant physical and geometrical parameters of the particle-magnet system.

To clarify the relevance of the developed model as to finite-length magnets, we perform experiments with a single magnetic particle at different sites near a cylindrical magnet with a length to diameter ratio typical for applications. On establishing reasonable relevance, we apply the developed model to analyze some performance characteristics of the immunomagnetic batch system constituted by a cylindrical magnet and adjacent cylindrical vessel. Considering the limitation imposed upon the developed single-particle model by the possible magnetic chaining in real magnetic columns, we introduce a simple dynamic criterion based upon comparing the time of full separation with the time of the magnetic chaining initiation.

II. SINGLE-PARTICLE MAGNETOPHORESIS

A. Analytical model: Magnetophoresis near the infinite-length magnet

We consider a diametrically polarized cylindrical magnet of infinite length with radius R_m and with uniform magnetization I_m along the unit vector $\mathbf{e}$. The magnetic field intensity $\mathbf{H}$ around such a magnet does not vary along the magnet axis, and in the transverse plane is given by the relation

$$\mathbf{H} = -\frac{2\pi I_m R_m^2}{R^2}\left[\mathbf{e} - \frac{2}{R^2}(\mathbf{e}\cdot\mathbf{R})\mathbf{R}\right]. \tag{1}$$

Here $\mathbf{R}$ is the radius vector drawn in the transverse plane from the magnet axis to the referring point. Equation (1) can be obtained as follows. Inside the uniformly magnetized cylinder there exist the uniform demagnetizing self-field $\mathbf{H}^i = -2\pi I_m\mathbf{e}$ (which follows from the well-known uniformity of the demagnetizing field of the uniformly magnetized body with quadric surface [87]) and its scalar magnetic potential $\psi^i = 2\pi I_m(\mathbf{e}\cdot\mathbf{R})$. The magnetic potential of the outer field, that satisfies the Laplace equation $\Delta\psi = 0$ and coincides with ψ^i at the cylinder boundary is given by the relation $\psi = 2\pi I_m R_m^2 R^{-2}(\mathbf{e} \cdot \mathbf{R})$, from which Eq. (1) follows.

According to the continuous media electrodynamics [87], in a nonuniform magnetic field, a body of any magnetic complexity with the total magnetic moment **M**, given the size of the body is small as compared to the scale of the field nonuniformity (here, the magnet radius), is acted upon by the magnetic force,

$$\mathbf{F} = (\mathbf{M} \cdot \nabla)\,\mathbf{H}. \tag{2}$$

Equation (2) is valid for any small object to be magnetically separated, including cells labeled by magnetic beads with the total magnetic moment **M**. Let us denote the whole object as "particle," and its magnetizable part as "magnetic carrier." The basic assumption of our consideration is that the total moment **M** of the magnetic carrier is a single-valued function of the applied magnetic field, which we write as follows:

$$\mathbf{M}(\mathbf{H}) = M(H)\mathbf{H}/H, \quad M(H) = M_s f(H), \quad M_s = I_s V_c. \tag{3}$$

Here I_s is the magnetic carrier saturation magnetization, V_c its volume. Note that Eq. (3) suggests alignment of magnetic moment $\boldsymbol{M}$ in the field direction, which obviously holds for any isolated particle in liquid. But the single-valuedness of magnetization function $f(H)$ excludes particles with magnetic hysteresis, retaining soft magnetic (including superparamagnetic) particles. Now, with the use of Eq. (3) and the magnetostatic equation rot$\mathbf{H} = 0$, we reduce Eq. (2) to the form

$$\mathbf{F} = M_s f(H) \boldsymbol{\nabla} H, \tag{4}$$

which shows, that under assumption (3), the driving magnetic force is related with the field intensity only through the vector **H** magnitude. Further, addressing Eq. (1) we find that in the case of an infinite-length diametrically polarized permanent cylindrical magnet, the spatial distribution of magnetic field magnitude is axially symmetric, and is given by the following simple function of the distance to the magnet axis:

$$H = \frac{2\pi I_m R_m^2}{R^2}. \tag{5}$$

Equation (5) allows us to write down the driving magnetic force (4) as follows:

$$\mathbf{F} = -4\pi I_m R_m^2 M_s f[H(R)] R^{-4} \mathbf{R}. \tag{6}$$

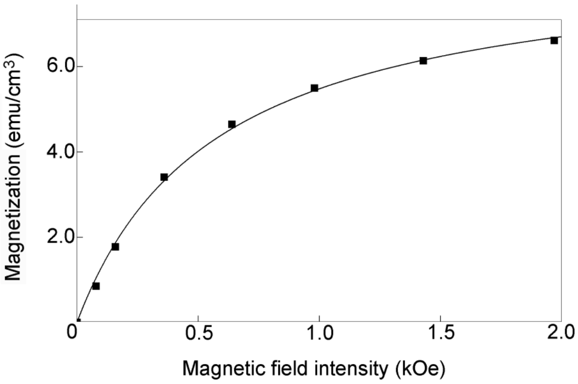

FIG. 1. Magnetization curve of the particle material (dispersion of magnetite nanoparticles in plasticine).

This result implies that magnetophoresis, and hence, magnetic extraction of soft magnetic particles by the infinite-length diametrically polarized cylindrical magnet does not depend on the magnet polarization direction. The particles are attracted towards the magnet axis equally from all directions. To completely quantify the driving magnetic force (6) we have to specify magnetization function $f(H)$. Remind that the quantity H in Eq. (6) stands for the external magnetic field intensity. This means that if proceeding from the magnetization law of the magnetic carrier material, we have to take into consideration its demagnetizing field. Otherwise, function $f(H)$ can be obtained experimentally, from the magnetization curve, $J(H)$, of a dilute (preferably solid) suspension of magnetic carrier particles. Given that all carrier particles are of the same shape and magnetic material, we can relate the sought function $f(H)$ with the measured function $J(H)$ as follows:

$$J(H) = J_s f(H), \quad J_s = cI_s. \tag{7}$$

Here c stands for the volume fraction of the carrier particles in the suspension; J_s is the suspension saturation magnetization. As one more assumption, we represent the suspension magnetization function $J(H)$ by the following simple relation, incorporating only two basic magnetic characteristics of soft magnetic materials, the initial magnetic susceptibility χ, and the saturation magnetization J_s:

$$J(H) = J_s \left(1 + \frac{J_s}{\chi H}\right)^{-1}. \tag{8}$$

This relation is known as the Fröhlich-Kennelly law primarily introduced to approximate magnetization of ferromagnetic materials near saturation [90]. Equation (8) gives correct values of magnetization on the linear section of the magnetization curve and in the saturating fields, and agreeably approximates magnetization in the intermediate fields. This statement is supported below in Sec. II B (Fig. 1).

Using Eqs. (7) and (8) we write down the magnetization function in the form

$$f(H) = \left(1 + \frac{J_s}{\chi H}\right)^{-1} \equiv \left(1 + \frac{I_s}{\chi_c H}\right)^{-1}. \tag{9}$$

The identity in Eq. (9) is written under the assumption that both the saturation magnetization and the initial magnetic susceptibility of the suspension are proportional to the volume fraction of carrier particles, $\chi_c = \chi/c$, standing for the initial susceptibility of a single carrier particle (magnetic bead).

Now, on substituting Eqs. (9) and (5) in Eq. (6) we arrive at the following representation for the magnetic force that affects the particle around the infinite-length cylindrical magnet:

$$F = -\frac{4\pi I_m R_m^2 M_s}{R^3} \left(1 + \frac{I_s}{2\pi \chi_c I_m} \frac{R^2}{R_m^2}\right)^{-1}. \tag{10}$$

Using the final assumption, namely, remaining within the inertialess approximation, we obtain the equation of particle motion in liquid from the condition of compensation of the above magnetic force and the force of viscous friction,

$-3\eta d_h(dR/dt)$, in the form

$$\frac{dR}{dt} = -\frac{4\pi I_m R_m^2 M_s}{3\eta d_h}\frac{1}{R^3}\left(1+\frac{I_s}{2\pi\chi_c I_m}\frac{R^2}{R_m^2}\right)^{-1}. \quad (11)$$

Here η stands for the liquid viscosity; d_h is the particle effective (hydrodynamic) diameter.

Equation (11) is integrable in explicit form, and its solution with the initial condition $R|_{t=0} = R_0$ can be presented as follows:

$$t = \frac{\eta d_h}{16\pi I_m^2 \chi_c R_m^4 V_c}\left(R_0^6 - R^6\right) + \frac{3\eta d_h}{16 I_m R_m^2 I_s V_c}\left(R_0^4 - R^4\right). \quad (12)$$

It determines the time interval t it takes the particle to move along the radial direction from the distance R_0 to the distance R (from the magnet axis). A special case arises when the magnetic field is large enough to magnetically saturate the magnetic carrier over the entire volume of the container. In this case, the bracketed term in Eq. (11) is unity, and instead of Eq. (12) we arrive at

$$t = \frac{3\eta d_h}{16 I_m R_m^2 I_s V_c}\left(R_0^4 - R^4\right). \quad (13)$$

Equation (12) allows simple calculation of the performance characteristics of batch magnetic separation systems with all physical and geometrical properties accounted for, with the exception of the finite length of magnets in real systems. The relevance of the obtained simple solution as to the real systems could be studied numerically. But we choose a more illustrative experimental method.

B. Experimental: Particle motion near the finite-length magnet

In experiments we used a cylindrical diametrically polarized NdFeB (N45) magnet with the length $L = 80$ mm, the radius $R_m = 7.5$ mm, and the remanent magnetization $I_m = 1070$ emu/cm^3. The single spherical magnetic particle of rather large diameter ($d = 2.3$ mm) was used, made by hand from a plasticine of density 1.05 g/sm^3 with dispersed superparamagnetic (~10 nm) magnetite particles, obtained by evaporation of a stable magnetic fluid. The magnetization law of the used particle material, measured by a homemade vibrating sample magnetometer and approximated by Eq. (8), is presented in Fig. 1.

From these data we find the saturation magnetization $I_s = 8.62$ emu/cm^3, and the initial magnetic susceptibility $\chi = 0.016$. The initial magnetic susceptibility of the particle, $\chi_c = 0.015$, was calculated with account for the demagnetizing field of sphere from the relation $\chi_c = \chi(1 + 4\pi\chi/3)^{-1}$.

The particle was placed in the middle of the 10-mm-thick layer of a very viscous ($\eta = 660$ P) polymethylsiloxane liquid put in a cylindrical container. The particle motion occurring on bringing the container in contact with the magnet was recorded by a video camera. The motion was investigated starting from three different vertical positions, $z = 0, L/4, L/2$ (along the magnet axis), and three different azimuthal positions, $\varphi = 0, \pi/4, \pi/2$ (with respect to the magnet polarization direction), as depicted in Fig. 2.

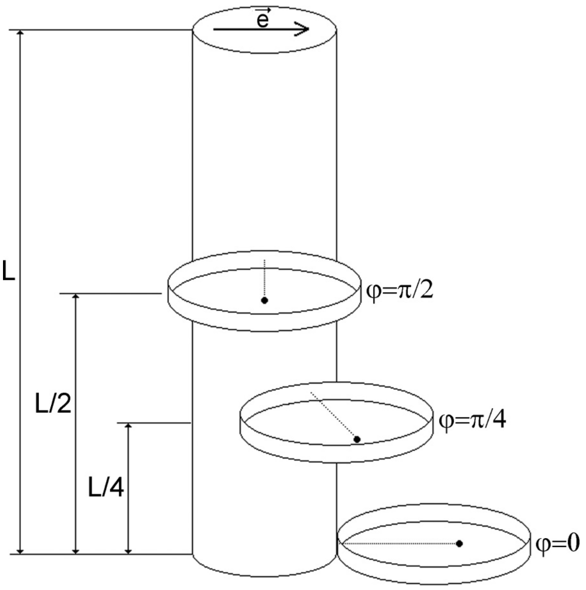

FIG. 2. The particle motion in liquid was recorded from above, starting from three different vertical positions $z = L/2$, $L/4$, and 0 along the magnet axis and three different azimuthal positions $\varphi = 0$, $\pi/4$, and $\pi/2$ with respect to the magnet polarization direction **e**.

First of all, it should be noted that in all cases we did not observe any azimuthal motion of the particle, which traveled straight to the magnet axis. At the same time, some elevation of the particle, on approaching the magnet, was registered in experiments at the magnet lower end. The set of time-varying positions of the moving particle for each case was established by handling the set of successive video frames. The results of measurements are dotted in Fig. 3 in the form of function $t(R_0)$, relating the particle travel time t to the final position at the inner wall of the container ($R = 0.965$ cm) with its initial position R_0 (from the magnet axis). Solid curves in Figs. 3(a)–3(c) depict the analytical function

$$t = \frac{3\eta}{8\pi^2 I_m^2 \chi_c R_m^4 d^2}\left(R_0^6 - R^6\right) + \frac{9\eta}{8\pi I_m R_m^2 I_s d^2}\left(R_0^4 - R^4\right), \quad (14)$$

which follows from Eq. (12) in the considered case of the particle with the hydrodynamic diameter equal to the physical diameter d, and $V_c = \pi d^3/6$.

It can be seen that in the near-magnet zone (within the distance from the magnet surface equal to one and a half of the magnet radius) the measured time of the particle separation practically does not depend on the particle's both vertical and azimuthal positions and is closely fitted by the calculated function (14). Moreover, a significant increment [as compared to the function (14)] of the separation time is registered only at the direction normal to the magnet polarization direction at the magnet end. It seems that the model of infinite-length magnet may serve as the reasonable instrument for practical calculations within cylindrical volume at one diameter distance from the magnet ends and one diameter distance from the magnet lateral surface.

In conclusion of this section let us support the compliance of the above experimental conditions with the hydrodynamic model assumptions. The inertial forces can be neglected indeed, as far as the Reynolds number, $\mathrm{Re} = \rho v d/\eta$, at the pick registered particle velocity $v \approx 0.1$ cm/s (near the magnet)

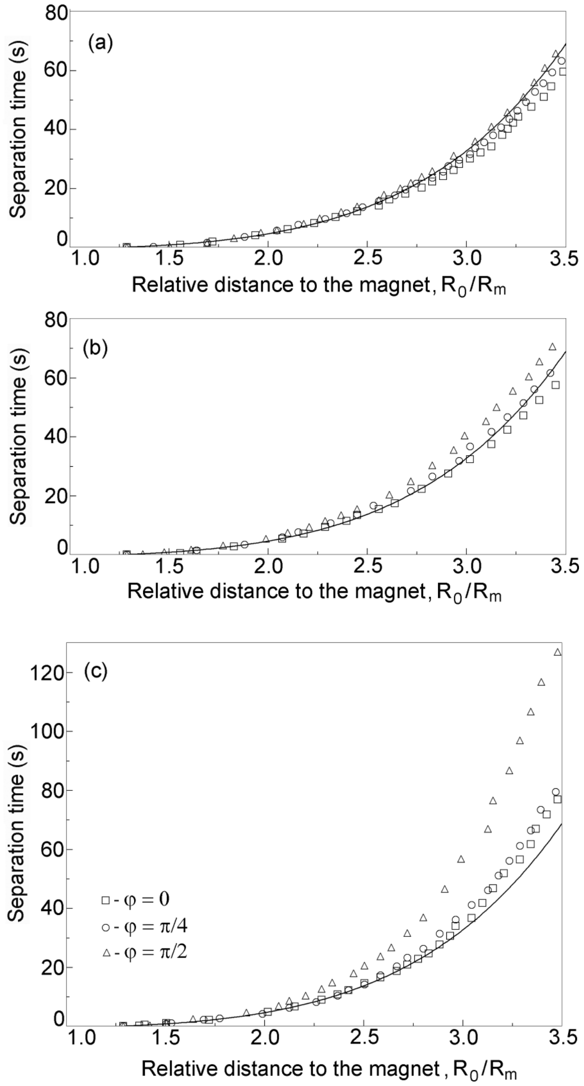

FIG. 3. The time of the particle magnetophoretic transition from relative distance R_0/R_m (with respect to the magnet axis) down to the container wall measured at different sites around the cylindrical magnet (see Fig. 2). (a), (b), and (c) correspond to different vertical positions: $z = L/2$, $L/4$, and 0 respectively; points 1, 2, and 3, to different azimuthal positions, $\varphi = 0$, $\pi/4$, and $\pi/2$, respectively.

in the liquid with density $\rho = 0.96$ g/cm^3, and viscosity $\eta = 660$ P is of the order 10^{-5}. The velocity of the gravitational motion of the particle with density 1.12 g/cm^3 (with account of the dispersed magnetite) in the used liquid is estimated as $\sim 8 \times 10^{-7}$ cm/s, so that the biggest gravitational drift in the longest of the performed experiments ($t = 120$ s) is of about 10^{-3} mm.

III. APPLICATION TO ANALYZE A BATCH MAGNETIC COLUMN PERFORMANCE

Consider a widespread scheme of immunomagnetic separation, namely, precipitation of labeled cells on the lateral surface of a vertical test tube in the nonuniform magnetic field created by a transversally magnetized rodlike permanent magnet positioned right up against the tube. The first practical implication of our studies is that in the case of a cylindrical magnet, it is possible to use several tubes set regularly around the magnet. Let us apply the developed theory to find the optimal radius of the magnet when the radius of the tubes, R_c, is chosen. By "optimum" we mean such a magnet which ensures the minimum separation time in a given tube. Quite realistically, we can disregard the tube wall thickness and accept this time as equal to the pass time of a labeled cell between the farthermost, $R_0 = R_m + 2R_c$, and the nearest, $R = R_m$, points of the tube. Consider first the limiting case of magnetically saturated beads. Proceeding from Eq. (13) we write the corresponding separation time in the form

$$T_s = \frac{3\eta d_h}{2M_s I_m}\left[R_c R_m + 3R_c^2 + 4\frac{R_c^3}{R_m} + 2\frac{R_c^4}{R_m^2}\right]. \tag{15}$$

For the optimum magnet radius, from condition $\partial T_s/\partial R_m = 0$, we find the equation

$$1 - 4(R_c/R_m)^2 - 4(R_c/R_m)^3 = 0.$$

Kordano's solution of this equation gives $R_m \approx 2.38 R_c$. Therefore, in the magnetically saturated system, the fastest separation occurs when the magnet is almost two and a half times bigger in diameter than the container, and the separation time at this condition is given by the relation

$$T_s^{\min} = \frac{11.1\eta d_h R_c^2}{M_s I_m}. \tag{16}$$

In the general case, from Eq. (12), the separation time is given by the relation

$$\begin{aligned} T = {} & \frac{3\eta d_h R_c^2}{2M_s I_m} \times \left[3 + 5k + (k+1)\left(\frac{R_c}{R_m}\right)^{-1}\right. \\ & + \left(\frac{40}{3}k + 4\right)\frac{R_c}{R_m} + (20k+2)\left(\frac{R_c}{R_m}\right)^2 + 16k\left(\frac{R_c}{R_m}\right)^3 \\ & \left. + \frac{16}{3}k\left(\frac{R_c}{R_m}\right)^6\right]. \end{aligned} \tag{17}$$

Here the dimensionless value

$$k = \frac{I_s}{2\pi\chi_c I_m} \tag{18}$$

is introduced composed of the magnetic characteristics of the beads and the magnet. Note that Eq. (15) is the limiting form of Eq. (17) given $k \to 0$. So parameter k represents the effect of incomplete magnetization of beads. For the optimum magnet radius from Eq. (17) it follows

$$\begin{aligned} & k + 1 - \left(\frac{40}{3}k + 4\right)\left(\frac{R_c}{R_m}\right)^2 - (40k+4)\left(\frac{R_c}{R_m}\right)^3 \\ & - 48k\left(\frac{R_c}{R_m}\right)^4 - \frac{64}{3}k\left(\frac{R_c}{R_m}\right)^5 = 0. \end{aligned} \tag{19}$$

Equation (19) determines the optimum ratio R_m/R_c as a function of the beads' magnetic unsaturation parameter k. Numerically found, this function is depicted in Fig. 4. For the system used in the above experiments (the NdFeB magnet with remanent magnetization $I_m = 1070$ emu/cm^3 and the superparamagnetic filler of beads with $I_s/\chi_c = 575$ emu/cm^3)

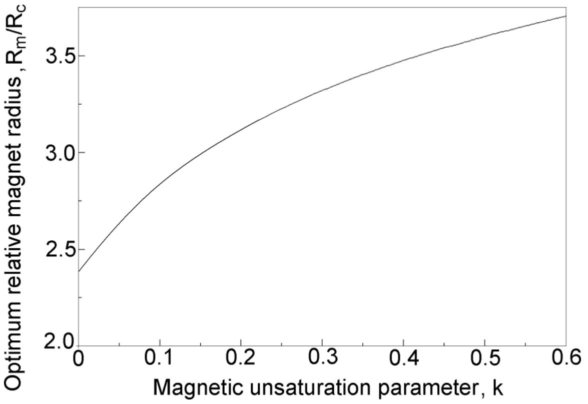

FIG. 4. The optimum magnet to container radii ratio vs the magnetic unsaturation parameter.

Eq. (18) yields $k = 0.085$, and from Fig. 4 the optimum magnet radius $R_m = 2.78R_c$. In such a case, the most distant position of separated particles from the magnet axis ($R = R_m + 2R_c = 1.72R_m$) is inside the area where our model works well (Fig. 3).

It is worth noticing that for beads with superparamagnetic filler, the ratio I_s/χ_c, and hence parameter k, should depend on the filler volume fraction just slightly, increasing due to the filler particles' magnetic interactions and the bead demagnetizing field. Neglecting these factors, from the Langevin magnetization law of filler we have $I_s/\chi = 3k_B\theta/m$, and hence $k = 3k_B\theta/(2\pi m I_m)$, k_B being the Boltzmann constant, θ the temperature, and m the magnetic moment of the superparamagnetic nanoparticles of the filler. That is, the magnetic moment m is the only characteristic of the magnetic filler involved with the magnetic unsaturation parameter k. Consider now how the deviations of the system from the magnetic saturation and from the optimum ratio R_m/R_c influence the separation time. As it follows from Eqs. (16) and (17), and is illustrated in Fig. 5, the relative separation time, $T/T_s^{\min}$, depends on just two nondimensional system parameters, the relative magnet radius, R_m/R_c, and the magnetic unsaturation parameter k. As seen, with the magnet radius increment over its optimum (minimizing the separation time for a given k) value, the separation time grows slowly. With the decrease of the magnet radius, the separation time grows rapidly. From the data of Fig. 5 we can conclude, that for systems with $k < 0.1$, the magnet diameter should not be smaller than that of the container.

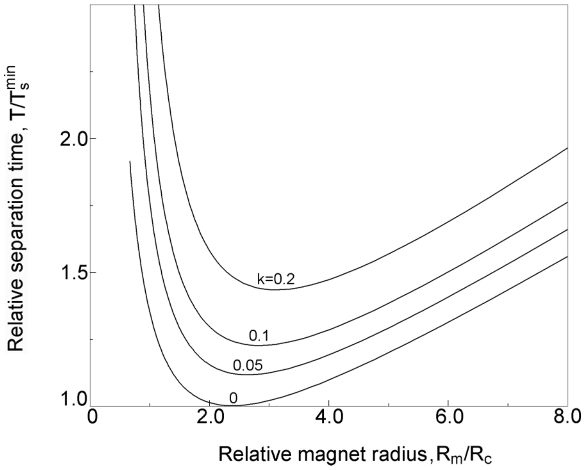

FIG. 5. The relative separation time vs the relative magnet radius for different magnetic unsaturation parameters: $k = 0$, 0.05, 0.1, and 0.2.

Now let us consider the properties of magnetic beads for the batch immunomagnetic cell separation. Under proper conditions, the separation time, as follows from Eq. (16), is inversely proportional to the total magnetic moment of conjugated beads. With the other involved parameters being more or less restricted, and the separation time of a reasonable value, Eq. (16) allows simple estimation of the minimum necessary magnetic moment $M_s^{\min}$. Given the test tube radius $R_c = 0.5$ cm, the cell hydrodynamic diameter $d_h = 10\ \mu$m, the magnet magnetization $I_m = 1000$ emu/cm^3, the liquid viscosity $\eta = 0.01$ P, and the desirable separation time $T_S^{\min} = 600$ s, Eq. (16) yields $M_s^{\min} = 4.63 \times 10^{-11}$ emu. Due to the high cost of antibodies, it is best if a cell can be extracted by a single bead, as small as possible. The latter suggests, by the way, that the beads preferably should be monodisperse. The minimum diameter $d_{\min}$ of such a bead is defined by the relation $M_s^{\min} = (\pi/6)I_{\rm spm}c_{\rm spm}d_{\min}^3$ where $c_{\rm spm}$ is the volume content of superparamagnetic material in beads, and $I_{\rm spm}$ is its saturation magnetization. The above estimate of $M_s^{\min}$ implies that the diameter of beads for the batch immunomagnetic separation of cells cannot be too small. Even for the hypothetic content $c_{\rm spm} = 1$ of the typical magnetic material (magnetite, $I_{\rm spm} = 500$ emu/cm^3) we find $d_{\min} = 0.56\ \mu$m. More realistic content $c_{\rm spm} = 0.5$ gives $d_{\min} = 0.71\ \mu$m, more typical $c_{\rm spm} = 0.1$ requires $d_{\min} = 1.2\ \mu$m, and poor 1% content suggests $d_{\min} = 2.6\ \mu$m.

One more remark is about the possible influence that magnetic interaction between thus big magnetic beads exerts on the extraction of labeled cells. There exist numerous studies of magnetic structuring of both nanosized and micron-sized magnetic particles in relation to magnetic and magnetorheological fluids. Recently, as was mentioned in the Introduction, this problem attracted attention in magnetic separation studies as well. In this regard we should say that there is not quite appreciated fundamental difference between separation systems and those considered in magnetic fluids. Namely, a magnetic separation system never exists in stationary conditions. It is known [68], that given enough time, non-Brownian magnetic particles would build chains of any length. This is valid for the above considered beads for immunomagnetic separation. To estimate the possibility of chaining to influence the considered separation it would be not appropriate to apply either the recently proposed criterion [88] or the much older statistical results [53,54], as far as they have been obtained for stationary Brownian systems. The proper criterion can be derived by answering the question whether or not magnetic chains appear before the separation is completed. A simple but quite reliable answer may be found by comparing the above calculated separation time with the characteristic initiation time of the chaining. The latter can be estimated as the approaching time of two labeled cells, the initial distance between the centers of the cells being equal to the characteristic distance $r_0 = n^{-1/3}$ determined by the concentration number n of target cells. In the conditions most favorable for chaining (the pair of beads is aligned along the vector of magnetic field) the approaching of cells is governed by the equation [89]

$$\frac{dr}{dt} = -\frac{4M_s^2}{r^4 \pi \eta d_h}, \tag{20}$$

which represents the balance of the magnetic dipole force, and that of viscous friction. From Eq. (20) it is easy to find that the time interval it takes the cells to come into contact is given by the relation

$$t_P = \frac{\pi \eta d_h}{20 M_s^2}\left(n^{-5/3} - d_h^5\right) \approx \frac{\pi \eta d_h}{20 M_s^2} n^{-5/3}. \tag{21}$$

Now, the dynamic criterion allowing us to neglect the chaining effects in the magnetic separation column can be written in the form of the following relation:

$$\frac{t_p}{T_s^{\min}} = \frac{0.014 I_m}{M_s R_c n^{5/3}} > 1. \tag{22}$$

Note that both the cell size and the liquid viscosity are not involved in the chaining-imposed limitation (22), so this result can also be applied for any batch magnetic separation, say, in relation with chemical and biochemical reactors. As for the above considered optimum immunomagnetic separation system, it follows from Eq. (22) that the effect of chaining can be neglected up to the target cell concentration $n = 1.14 \times 10^7\ \mathrm{s\,m^{-3}}$. It is quite an appreciable number concentration for extraction of rare cells. We expect that the relation (22), obtained disregarding the different-velocity motion of particles towards the magnet, in fact overrates the role of chaining.

IV. CONCLUSION

In this study, under reasonable simplifications, an analytical solution is derived describing noncooperative magnetophoretic separation of soft magnetic (including superparamagnetic) particles from liquid in the field of a diametrically polarized permanent cylindrical magnet of infinite length. Experiments with a finite-length magnet demonstrated that this solution is applicable to analyze real systems apart from the magnet ends. Our application of the model as to the magnetic separation column consisting of a cylindrical magnet and adjacent cylindrical container(s) has disclosed the relation of the main performance characteristic of the system, the total separation time, with all the relevant geometrical and physical parameters, including characteristics of superparamagnetic particles dispersed in immunomagnetic beads. We propose a dynamic criterion of the model limitation due to magnetic aggregation of particles, which is based upon comparing the time of full separation with the initiation time of the particle chaining. We believe that our findings are of utility for analyzing and designing batch systems with different shape of magnets, as well as a starting point for studying complications connected with the magnetic interaction of particles and with the hydrodynamic drag of unlabeled cells by the moving labeled cells [90].

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