Quantitative modeling of forces in electromagnetic tweezers

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This paper discusses numerical simulations of the magnetic field produced by an electromagnet for generation of forces on superparamagnetic microspheres used in manipulation of single molecules or cells. Single molecule force spectroscopy based on magnetic tweezers can be used in applications that require parallel readout of biopolymer stretching or biomolecular binding. The magnetic tweezers exert forces on the surface-immobilized macromolecule by pulling a magnetic bead attached to the free end of the molecule in the direction of the field gradient. In a typical force spectroscopy experiment, the pulling forces can range between subpiconewton to tens of piconewtons. In order to effectively provide such forces, an understanding of the source of the magnetic field is required as the first step in the design of force spectroscopy systems. In this study, we use a numerical technique, the method of auxiliary sources, to investigate the influence of electromagnet geometry and material parameters of the magnetic core on the magnetic forces pulling the target beads in the area of interest. The close proximity of the area of interest to the magnet body results in deviations from intuitive relations between magnet size and pulling force, as well as in the force decay with distance. We discuss the benefits and drawbacks of various geometric modifications affecting the magnitude and spatial distribution of forces achievable with an electromagnet. © 2010 American Institute of Physics. [doi:10.1063/1.3510481]

I. INTRODUCTION

Magnetic tweezers have become an important tool for analysis of mechanical behavior of individual cells^{1–3} or single biomolecules under tension or torsion.^{4–6} In magnetic tweezers, the forces are applied to molecules via superparamagnetic spherical probes using an external magnetic field. By using multiple switchable magnetic poles^{7,8} or by moving permanent magnets^{9,10} it is possible to achieve controlled manipulation (repositioning or rotation) of individual probes. Due to the ability to perform measurements from many molecules in parallel,^{11–13} significantly improving statistical treatment of the single molecule data, magnetic tweezers stand out among other implementations of single molecule force spectroscopy and are attractive for application in force spectroscopy-on-a-chip devices. Both permanent magnets and electromagnets have been used in the design of magnetic tweezers. The magnetic field and forces generated by permanent magnets in various arrangements have been treated theoretically,^{6,14,15} while rigorous theoretical modeling of electromagnetic tweezers has not received much attention.¹⁶

Electromagnets are an attractive option for force generation in even the simplest of configurations (e.g., when force is applied in the direction normal to the plane of biomolecular attachment), since it is possible to control the magnetic field easily via changes in the current applied to the electromagnet coil. The ramp of the magnetic field to generate a force-extension curve using an electromagnet does not require mechanical motion (only variable current), thus, yielding better environmental noise characteristics for magnetic

tweezers, while preserving a straightforward setup for force spectroscopy. The obvious drawback of having nonlinear changes in the field generated by the electromagnet in the course of the current ramp, due to inductance of the coil, can be minimized by selecting an appropriate rate for changes in the coil current.

Force spectroscopy experiments that perform single molecule stretching or unbinding require high field gradients in the normal (z) direction and, preferably, negligible gradients in the lateral (x, y) directions. Unfortunately, high gradients, needed for manipulation of the superparamagnetic probes, can lead to loss of the highly parallel nature of the stretching experiments with multiple probes in a relatively large area of the sample. Therefore, the design of the electromagnet needs to balance these two requirements. In this paper, we investigated the magnetic fields produced by the electromagnet formed by a coil of wire wound on a core machined from a soft ferromagnetic material.

II. METHODS

A. Geometry

For single molecule stretching experiments with no application of torque or three-dimensional manipulation, a field gradient along only one dimension (in the direction of stretching) is needed. We are specifically interested in forces that are applied normal to the plane of attachment of biomolecules because one can detect changes in molecular size with a high (potentially subnanometer) resolution using detection schemes based on evanescent field¹⁷ or optical interference.^{7,9,12} The magnetic tweezers for this type of force spectroscopy application usually consist of a solenoid

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FIG. 1. (Color online) (a) Typical geometry of the electromagnet that can be used in magnetic tweezers (not drawn to scale). (b) Geometry with the magnet showing conformal inner and outer surfaces for placement of auxiliary sources. EM field sources are placed on these auxiliary surfaces and aligned along the corresponding surface tangents (or normals). (c) Body of revolution magnet with surface tangents. The area of interest (hosting an array of biomolecules having length of $\sim 50\text{--}100$ nm with magnetic beads of radius $\sim 1\text{--}3$ μm attached to their ends) is $0.2\text{--}0.4$ mm below the tip of the magnet.

with a cylindrical magnetic core.^{17,18} Rods of various diameters made from several ferromagnetic materials are commercially available but for optimal performance they must be machined to concentrate the magnetic field and provide the largest possible field gradient in the area of interest. For experiments where the active area of the probe array is hundreds of microns in size (field of view for a high magnification objective of a typical optical microscope), one of the simplest suitable designs of the core is shown in Fig. 1—it represents a rounded tip, several millimeters in diameter, pointing toward the sample connected to a wider diameter rod (the core) via a conical section. The wide section of the core supports the coil of electrical wire and optional liquid cooling elements. The electromagnetic (EM) problem is then to find the magnetic field distribution in the area below the tip, and further fine-tune the tip geometry, in order to ensure the highest possible uniform vertical pulling forces for the magnetic beads in the area of interest. In order to use the numerical simulations, generally, the geometry of the system has to be smoothed to avoid sharp edges [as shown in Fig. 1(a)] and be able to define a normal uniquely, at any point on the target surface.

B. Field and force modeling

We based the numerical simulations in this study on the method of auxiliary sources (MAS). The MAS is a robust, easy to implement, and accurate numerical technique developed for solving a large range of EM radiation and scattering problems. It has been successfully applied to the investigation of waveguide structures, antennas, complex media, etc.^{19,20} In the MAS, the boundary value problems are solved

numerically using a representation of the EM field in each domain of the structure of interest by a finite linear combination of analytical solutions of the relevant field equations. These solutions correspond to the fields created by auxiliary EM field sources (individual set for each domain), and are usually chosen to be elementary dipoles (or charges), located on fictitious surfaces that conform to the actual boundaries of the structure of interest. Knowledge of the detailed mesh structure of the modeled objects is not required, which is one of the advantages of the MAS over finite element methods.

There are two layers of auxiliary sources set up for each physical boundary in the problem: the inner layer of sources describes EM fields outside of this boundary, while the outer layer describes the fields in the space confined by the boundary. The only constraint placed on the fields is to satisfy the boundary conditions for Maxwell's equations. These conditions can be evaluated at a finite number of collocation points across the object boundaries, leading to a system of linear equations binding together the amplitudes of the auxiliary sources. Thus, the scattering problem is solved once these amplitudes have been found: any other EM parameter of interest can be derived through the fields created by the auxiliary sources. This scheme also provides an easy way of monitoring the accuracy of the solution by observing the boundary conditions mismatch in the area between the collocation points.

In this paper, we used the MAS in a limiting case of the magnetostatic regime to evaluate the distribution of the magnetic field in the vicinity of the tip of the electromagnet as a function of the magnetic core geometry. We used the axial symmetry of the system to reduce the dimensionality of the problem.^{21,22} For our purposes, the auxiliary sources can be electric dipoles, oriented along the tangent $\vec{v}$, or magnetic dipoles, oriented along the normal $\vec{n}$ or the tangent $\vec{u}$ (Fig. 1). The distance of the inner auxiliary surface from the real surface is limited by the smallest radius of curvature present in the magnet geometry.

The main objective of this work is to understand how the distribution and magnitude of the magnetic force inside the area of interest (Fig. 1) depends on the magnet geometry and material properties of the electromagnet core. Assuming no remanent magnetization of the probe, the analytical expression for force pulling a superparamagnetic bead in an inhomogeneous magnetic field is well-known:^{23,24}

$$\vec{F} = V(\vec{M} \cdot \vec{\nabla})\vec{B} = \phi V M_d L(\alpha) \frac{(\vec{B} \cdot \vec{\nabla})\vec{B}}{|B|} \quad (1)$$

where V is the volume of the bead, $\vec{M} = \phi M_d L(\alpha) (\vec{B}/|B|)$ is the induced magnetic moment per unit volume, M_d the domain magnetization of the magnetic material, ϕ is the loading (volume fraction) of magnetic material, and $L(\alpha) = \coth(\alpha) - 1/\alpha$ is the Langevin function, which asymptotically approaches unity for high magnetic fields [$\alpha(B) = (\pi M_d B D^3 / 6 k_B T)$, with D being the diameter of the magnetic nanoparticles and k_B being the Boltzmann constant]. The force on the beads in the saturation regime (high B) then reduces to:

FIG. 2. (Color online) (a) Magnetic B field distribution inside and outside of the magnet, (b) $\log_{10}(B)$ distribution, (c) magnetic force distribution pulling the beads below the tip. Magnet tip radius=1.5 mm, tip length=10 mm, core radius=6 mm, core length=5 cm.

$$\vec{F} = \varphi V M_d \frac{(\vec{B} \cdot \vec{\nabla}) \vec{B}}{|B|}. \quad (2)$$

The magnitude of the pulling force is proportional to the magnetic field gradient. Therefore, it is important to optimize the shape of the magnet to achieve the highest possible field gradient (normal to the surface of the substrate) in the area of interest.

The highest pulling forces will arise in the vicinity of the sharp edges of the magnetic core. The presence of a single tip of the magnet, therefore, ensures the existence of a stable equilibrium position for all the beads tethered to the surface underneath. On the other hand, any other sharp edges away from the axis of the core would disturb the local field distribution, destroying the stable equilibrium at the axis of symmetry of the magnet. For example, a flat tip will produce a magnetic field having the highest inhomogeneities around the rim of the tip. Small misalignment of the population of beads with respect to the axis of the magnet will then result in uncontrollable shifts due to lateral gradients (which we detected experimentally as lateral jerking of the beads when the field is turned on). For the rounded tip, the field and force distributions change smoothly, providing the stable equilibrium position at the axis of symmetry of the system with significantly higher forces under the same conditions [i.e., with the same product of (current) $\times$ (number of wiring turns)].

With the goal of achieving high forces in experimentally accessible configurations ($100 \times 100 \mu\text{m}^2$ region of interest, 0.2–0.4 mm distance from the sample surface), we selected a single-tip geometry for detailed analysis of magnetic field distributions. As a starting point for our simulations, we have chosen a magnet with a mu-metal core (relative permeability $\mu_r = 20\,000$) with a radius of 6 mm and length of 5 cm. The core was excited by 1360 turns of wire carrying 0.94 A current, arranged in a single layer around the cylindrical section of the magnet core. For simplicity, the distance between the magnet surface and wiring was always set to 1.5 mm, except in the calculation used for direct comparison with the experimental data where we closely replicated the actual dimensions of all elements. The probe in the area of interest was a

spherical bead with a radius of $1.0 \mu\text{m}$, frequently found in force spectroscopy applications, loaded with 10% volume fraction of magnetite (Fe_3O_4) with domain magnetization of $M_d = 4.46 \times 10^5 \text{ A/m}$. The results for other compositions and sizes of the superparamagnetic beads can be readily rescaled using Eq. (2).

The typical magnetic field distribution, along with the magnetic force experienced by the beads, is illustrated in Fig. 2. The accuracy of our simulations was controlled by monitoring the matching of boundary conditions in the MAS simulation. For all simulations in this paper, the boundary mismatch of the normal component of the magnetic B field was kept below 1%. The mismatch of the tangential components of the magnetic H field was higher; however, the boundary values of H_t themselves are on the order of 1% of the corresponding B_n values (due to the high magnetic permeability of the magnet core), and, therefore, the mismatch in H_t components can be ignored. The following sections discuss the behavior of magnetic fields and pulling forces in the area of interest as functions of magnetic core radius and length, magnet tip length and radius, and magnetic permeability of the core material.

III. RESULTS AND DISCUSSION

A. Effect of tip length and radius

The geometry of the magnet strongly affects the field distribution around the tip. Namely, the tip length and tip radius of curvature are expected to be the most critical parameters defining the details of the field configuration in the area of interest, due to its close proximity to the tip. With the same reasoning, we may neglect the effects of exact local configuration of the parts of the magnet away from the tip—any field inhomogeneities introduced by these parts will quickly decay before reaching the area of interest.²⁵

Our simulations revealed that magnetic forces are, indeed, relatively immune to small variations (factor of 3) of the tip length (Fig. 3). The change in the tip length from 5 to 10 mm results in a 20% increase in the local magnetic force near the tip, while a further increase in the tip length to 15 mm does not provide significant benefits. Thus, the magnetic

FIG. 3. (Color online) (a) Magnetic field and (b) magnetic force distribution along the magnet symmetry axis as a function of the distance from the tip with magnetic tip length varying from 5 to 15 mm. Magnet tip radius is fixed at 1.5 mm.

core, as expected, is very effective in delivering a concentrated magnetic field to a location a significant distance away from the coil carrying the current.

While variations in the tip length do not produce significant field changes, our simulations confirmed that the sharpness (radius) of the magnet tip can have a dramatic effect on the local field distribution in the vicinity of the tip. Figure 4 compares the decay of magnetic fields with distance from magnets having the same tip length but different tip curvatures. At short distances, up to several hundred micrometers away from the tip, the magnets with the smaller tip radii provide greater fields. Decreasing the magnet tip radius from 3 to 1 mm can increase the magnetic field by $\sim 100\%$ – 50% at the surface-tip separations of 0.2–0.4 mm. In terms of magnetic force, which is more relevant for magnetic tweezers applications, decreasing the tip radius by a factor of 3 can result in a factor of 5 increase in the pulling force in this range.

In the range of the highest forces (0.1–2.0 mm), the force-distance dependence is represented very closely ($<1\%$ maximum error) by a power law with a position offset:

$$F = F_0 \frac{1}{\left(\frac{z}{z_0} + 1\right)^p}. \quad (3)$$

Exponent p increases from 2.3 to 2.8 when the tip radius changes from 0.5 to 2.0 mm, empirically approaching a power of 3 dependence theoretically expected for magnetic dipoles. When the tip radius is increased from 0.5 to 2.0 mm, the range of distances where the magnetic force is well described by the power law dependence [Eq. (3)] also increases from 2 to 9 mm. The fitted value of the offset z_0 for each geometry is on the order of the corresponding tip radius (0.3 to 2.6 mm), while F_0 grows from 25 to 530 pN with the decrease in tip radius. The rough estimate (within 1%–5%) of the force in the region of 0.1–1.0 mm from the tip can be

obtained by setting the exponent to a mid-range value $p=2.5$ and using F_0 (piconewtons) and z_0 (millimeters) that depend on the tip radius R_{tip} (millimeters): $F_0 = 156/(R_{tip})^{1.69}$ and $z_0 = 0.79 R_{tip} - 0.06$.

The advantages of using sharp tips disappear, if the observation point (sample) is moved further from the magnet [Fig. 4(c)]. For example, at a distance of 0.5 mm from the tip of the magnet, the reduction in the tip radius from 3 to 1 mm almost triples the force, while a further decrease in the tip radius below 1 mm provides limited improvements with an apparent leveling off in the magnetic force, especially for tips with radii <0.6 mm. At a distance of 1.5 mm away from the magnet, a similar plateau starts at even greater values of tip radii (~ 1.5 mm), and if the tip radius is further reduced below 1.0 mm, the pulling force decreases. Finally, for microspheres located 2.5 mm from the magnet tip, the peak pulling force is provided by the magnets with tip curvatures in the range of 1.0–2.0 mm. The presence of such a peak in pulling force versus tip radius relation is associated with a rapid spatial decay of magnetic fields created by sharp tips. The sharper the tip is—the shorter becomes the spatial range of high gradients in magnetic fields and high pulling forces that this tip produces. Very short distances (<0.5 mm) between the tip and the sample surface, however, are not readily compatible with the instrument designs that use a flow cell and an external magnet. Therefore, depending on the exact position of the area of interest, the decrease in the magnet tip radius below a certain threshold is not beneficial for increases in field gradients and forces normal to the plane of attachment of biomolecules.

Our simulations indicate that for every fixed distance between the magnet and the sample we can find an optimal value of the curvature for the tip (R_{tip}) of the magnet, which provides the highest possible pulling force at that specific point, keeping the same all other characteristics of the magnet and magnetic beads. As evident from Fig. 5(a), this op-

FIG. 4. (Color online) (a) Magnetic field and (b) magnetic force distribution along the magnetic core axis as a function of the distance from the tip with magnetic tip radius varying from 0.5 to 3 mm. Magnet tip length is fixed at 10 mm. (c) Pulling force, acting on magnetic beads positioned 0.5, 1.5, and 2.5 mm away from the magnet tip, as a function of the tip radius.

FIG. 5. (Color online) (a) Dependence of the radius of the magnet tip that provides highest pulling forces at a specific fixed location on the distance of this point from the magnet tip; (b) highest pulling force attainable by varying tip radius at a fixed distance from the sample for magnets with tip lengths of 5, 10, 15, and 20 mm. All other dimensions of the magnet core, coil parameters, and properties of magnetic beads are the same in all cases.

timal tip radius depends linearly on the fixed location (z) of the point of interest. The exact dependence is not universal and differs for magnets with different tip lengths. For long tips, the limiting relationship scales as $R_{tip} = 0.60z$. The magnitude of the highest possible pulling force (F_{max})—delivered by the magnets with tip radii optimized for a fixed sample location—decreases with the distance from the sample surface. A qualitatively similar result was previously obtained during the analysis of microscopic magnetic poles.²⁶ Figure 5(b) shows the magnitude of this force as a function of the position of the tip from the area of interest. The force has a limiting scaling relationship $F_{max}/(IN) \approx 0.015/z^{1.7}$ for the magnets with long tips (I is the current in amperes, N is the number of turns in the coil, z is in millimeters, and F_{max} is in piconewtons). Evidently, in order to provide the highest pulling forces in the region of 0.5–1.0 mm away from magnet tip, the magnet tip curvature should also be chosen to be around 0.5–1.0 mm.

The main reason, however, to keep the magnet tip radius large enough is to provide highly uniform pulling forces over the broad spatial range comprising the area of interest in the single molecule array around the axis of the magnet. Since we are interested in applications of force spectroscopy in an array format, rather than micromanipulation, blunt tips and wide cores are more appropriate than sharp needles.¹⁶ Figure 6 demonstrates that sharper tips result in a quick build up of a substantial lateral force component acting on the beads placed off-axis. Keeping the magnitude of the lateral component under $\sim 5\%$ of the total forces for the region of interest (50–100 μm around the magnet axis) requires relatively blunt tips and tip curvatures of 1 to 1.5 mm tend to be the best for these purposes. Therefore, we focused all further simulations on the magnets with the tip radius equal to 1.5 mm. With such a magnet, the deviation of the total force magnitude should be within 1%–2% of the average value over a $100 \times 100 \mu\text{m}^2$ field of view typical for high magnification, high numerical aperture objectives [Fig. 6(b)]. Given that the superparamagnetic beads usually are 1–2 μm in diameter and should be separated by a distance comparable to their size to avoid bead-bead interactions, a total of about 400 beads (20×20 array) could be pulled with a

highly uniform force and observed simultaneously. Since most common approaches to attachment chemistry result in random single molecule arrays and, therefore, Poisson rather than regular bead distributions, the maximum number of beads is probably an order of magnitude lower (as we indeed observed in our experiments).

B. Effect of magnet core length and diameter

While the exact field configuration and the rate of decay in the area of interest depend on the local magnet geometry, the magnitude of the magnetic field can be affected by the overall magnet configuration, including parameters describing parts remote from the tip, such as the total length and radius of the magnetic core. Figure 7 illustrates the results of the calculation for the magnetic field and magnetic force behavior near the tip of the magnet for different lengths of the core. The local fields and their gradients in the vicinity of the magnet tip do not change significantly even when the length of the core is tripled.

Although the magnetic field in the vicinity of the magnet tip is higher for the magnets with shorter cores, as seen on Fig. 7(a), the situation does, in fact, change at higher distances from the tip. We observed that the magnetic field from the 15-cm-core magnet becomes greater than that of 5-cm-core magnet 10–25 mm away from the tip, as expected qualitatively, since the total magnetic dipole moment excited inside a large volume of the longer magnet core is higher than the total moment inside a small volume of the shorter core. Similarly, the magnets with a greater radius of the core have larger volume and, therefore, higher magnetic dipole moment resulting from the excitation by the coil than small radius cores. Therefore, the wider the magnet, the higher the magnetic fields should be. By comparing fields from the cores having radii between 3 and 12 mm, we observed that in this case, indeed, at the distances 5–7 mm from the tip and greater, the wide core radius magnet displays higher fields than the ones having lower radii. Unfortunately, the very low magnitude of the magnetic field and its gradient at these distances are impractical in force spectroscopy applications.

FIG. 6. (Color online) Ratio of the lateral pulling force to vertical force in the area of interest below the magnet tip, for magnetic tweezers with tip radii of (a) 0.5 mm, (b) 1.5 mm, and (c) 3 mm. Tip length=10 mm. Color map level step corresponds to 5% magnitude change in F_{xy}/F_z .

FIG. 7. (Color online) (a) Magnetic field and (b) magnetic force distribution along the magnet symmetry axis as a function of the distance from the tip with magnet core length of 5, 10 and 15 cm. Magnet tip length is fixed at 10 mm, while the tip radius is 1.5 mm. Magnet core radius equals 6 mm. The coil is stretched to cover the entire length of the magnet core.

Our simulations, however, revealed an interesting dependence of the fields in close proximity of the magnet tip, on the radius of the magnet core. As Fig. 8 indicates, the narrower the magnet core—the larger are the fields and pulling forces outside the magnet, in the vicinity of its tip. Decreasing the magnet core radius by a factor of 4 (from 12 to 3 mm) results in doubling of the bead pulling force. More drastic are the changes in the magnetic field distribution inside the magnet, as shown in Fig. 8(c). As with the fields in the close proximity to the tip, the fields inside the magnet are higher for narrower magnets. The reduction in the magnet radius from 6 mm to 3 mm results in the doubling of the maximum magnetic field inside the magnet core. This result is due to the deviation of the real magnet coil from an ideal solenoid, in which the magnetic field would be constant inside the entire solenoid volume and independent of its radius. For a single loop of wire carrying current I , however, the magnetic field at its center is inversely proportional to its radius R_{loop} : $B = \mu_0 I / 2R_{loop}$. The actual magnet coil used in our simulations of magnetic tweezers is effectively in the regime between these two limiting cases, which leads to an increase in the magnetic B field with the decrease in the coil radius. Apparently, the changes in magnet core length and radius are having a stronger impact on the magnetic field inside the magnet than on the fields in the vicinity of the magnet tip.

Similarly, despite the weak dependence of the magnetic fields on the magnet core length, our simulations show that the fields inside the magnet grow significantly with the increase in the magnet length: from a maximum field of 0.6 T for a 5 cm core to a maximum of 0.9 T for a 15 cm core (the wiring is spread out over the entire length of the core to provide uniform coverage). This increase in the internal field needs to be accounted for in the experimental implementation of the magnetic tweezers due to the saturation of the magnetization observed in actual materials used for the fabrication of magnetic cores. With the coil parameters and cur-

rent used in our simulation, the magnetic core 5 cm in length already approaches conditions of the magnetic field saturation inside the core made from mu-metal.

C. Effect of the core material

Magnetic materials are characterized by magnetic permeability and saturation induction.²⁷ The observation of how magnetic field changes with the size of the core is very important, since it indicates that, for example, any further reduction in the core radius below a certain threshold will bring no additional benefits, due to the saturation effects in the material of the core. After the saturation magnetic B field is reached within the core of the electromagnet, a further increase in external magnetic field (via higher coil current) will not lead to a significant B -field increase both inside and outside of the core. Therefore, in order to achieve higher magnetic fields and field gradients, one has to select magnetic materials with higher saturation induction.

As seen from Fig. 8(c), the magnet with a core radius of 6 mm and specified coil parameters and current, already approaches conditions of the magnetic field saturation ($B = 0.6$ T) in the middle of the core. Therefore, any other attempts to excite a higher field (e.g., by driving the coil current higher) will result in nonlinear effects that will neutralize the potential benefits of further magnet core elongation, increase in coil current or the number of turns in the coil. We confirmed these conclusions by fabricating two electromagnets with the same diameter (24.5 mm), tip length, and radius but different core lengths—5 and 16 cm. With the short core, we did not observe the saturation of the external field with magnetomotive force as high as 1220 ampere-turns, whereas an electromagnet with a longer core displayed a clear saturation behavior above 960 ampere-turns. The effect of saturation induction could also be responsible for observed leveling in the force-current response reported in magnetic tweezers experiments on protein unfolding.¹⁷

FIG. 8. (Color online) (a) magnetic field near the magnet tip, (b) magnetic force on the beads and (c) magnetic field inside and outside of the magnet, distributed along the magnet symmetry axis as functions of the distance from the tip with magnet core radius of 3, 6, 9, and 12 mm. Magnet tip length is fixed at 10 mm, while the tip radius is 1.5 mm. Magnet core length equals 5 cm.

FIG. 9. (Color online) (a) Magnetic field outside of the magnet, in the vicinity of its tip and (b) magnetic field inside the magnet. Fields are along the magnet symmetry axis. The relative magnetic permeativity of the core material is taking the values of 10, 100, 1000, and 10 000. Magnet tip radius=1.5 mm, tip length=10 mm, core radius=6 mm, core length=5 cm.

Generally, the materials with higher relative magnetic permeability will result in higher magnetic fields. Our simulations indicate, however, that after the value of $\mu_r=1000$ is reached for the core material, any further increase in permeability does not significantly change the field distribution in the area of interest outside of the magnet, as seen from Fig. 9(a). Same is true for the fields inside the magnet [Fig. 9(b): magnetic fields grow by a factor of 3 when μ_r increases from 10 to 1000, while a further increase in μ_r up to 10 000 does not lead to a significant B field increase ($\sim 5\%$).

Therefore, for the core of the electromagnet, it is advantageous to select soft magnetic materials that have high saturation induction, even though they might have small magnetic permeability ($\mu_r \sim 1000$). This will allow one to effectively manipulate the magnetic forces by increasing the coil currents, and reach high magnetic B field values in the area of interest, while staying below the saturation of the core magnetization. Designing a magnetic core that stays below saturation in the wide range of coil current ensures that forces acting on magnetic beads change linearly with current, therefore, providing for a straightforward interpretation of the experimental results obtained with EM tweezers.

D. Application to magnetic tweezers

We used the optimized geometry of the magnetic core to design the electromagnet for our magnetic tweezers instrument. Clearly, relatively short length and wide diameter ferromagnetic cores are preferable from the point of view of achieving comparably high fields in the region of a linear current response. The magnetic core was fabricated from mu-metal and had a 5.67-cm-long cylindrical section (with a radius of 0.635 cm) and 9.92 mm 28° conical section terminating in a tip with a radius of 1.5 mm. Measurements of the

B field at 0.5 mm from the tip showed a linear dependence of the field magnitude on current in a wide range of currents of interest (Fig. 10). As evident from the field-versus-coil-current loop data in Fig. 10, the remanent magnetization of the soft ferromagnetic core can be safely neglected for this geometry (as assumed in our simulation). At high currents (above 0.8–0.9 A), one can detect the onset of the effects of saturation of magnetic induction of the core.

A comparison between theory and experiment for magnetic B field versus distance data is shown in Fig. 11. Overall, there is a very good agreement between observed and predicted field magnitude and its rate of decay with the distance from the tip. The discrepancy is possibly due to (i) differences in the actual and simulated area used for averaging these highly concentrated fields, (ii) small misalignments between the axes of the magnet and the sensor, (iii) magnetic induction in the core approaching saturation, and (iv) not precisely known actual z position of the sensing chip embedded within plastic packaging.

These magnetic tweezers were used to stretch single stranded DNA oligomers (Biosynthesis, Lewisville, TX, USA) having a random nonrepeating (no doublets) sequence with a nominal length of 150 nucleotides [5' $H_2N-(CH_2)_6$ -TTT TTT TTT TTT TTT ATG CTA TCA GCA GAG AGT ACA CAG TGC TAC GTA CTG AGT GAT GCA GAT GCG TAT GCT AGC TCA CTG CAC GCG TCA TAT ACT ACA TCG ACT CGC AGT GTC TTG TGC TAC GAT GTG CGA TGA TTT TTT TTT TTT TTT-(CH_2)₃-SH 3']. One end of the DNA molecule was covalently attached to the surface of the 2.6 μ m diameter magnetic-fluorescent bead (10 vol % nominal magnetite content, Bangs Laboratories, Inc., Fishers, IN, USA), whereas the other end was covalently linked to the surface of the

FIG. 10. (Color online) Linear response of magnetic B field with current applied to the coil. Hall-effect sensor is located at a distance of 0.5 mm from the tip of the core. Inset: a region of the field-current loop near the origin magnified ($10\times$) to illustrate low remanence observed for the ferromagnetic core.

FIG. 11. (Color online) Comparison of the simulated and experimentally evaluated magnetic B fields in the area of interest below the tip of the electromagnet. Simulated curve represents the vertical component of the magnetic B field, averaged over the circular area of the diameter of 1.2 mm, in order to account for data acquisition by a finite size Hall-effect sensor (1.2×1.2 mm²). The sensing chip is buried inside plastic packaging at the depth specified as 0.5 mm from the surface. Simulation took into the account the actual coil geometry, consisting of seven layers of AWG 30 wires (total of 1359 turns) carrying the current of 0.94 A.

FIG. 12. (Color online) (a) A scheme for the general experimental setup for magnetic tweezers in single molecule stretching experiments. (b) Colorized image of the magnetic bead illuminated by the evanescent wave (532 nm laser) in a TIRF microscope. Upon applying force (F) to the magnetic probe, the intensity of the bead fluorescence changes due to an increase in the distance (z) from the sample surface. (c) Applied electromagnet current and (d) raw probe intensity data (normalized to the intensity observed when no current is applied to the coil) vs time. These data can be converted into force-extension curves with proper calibration.

transparent solid support [Fig. 12(a)]. For this purpose, the opposing termini of the synthetic DNA were modified with amine and thiol functional groups to enable coupling to carboxyl terminated magnetic beads and transparent solid substrates (glass coverslip coated with 2 nm Ti and 10 nm Au film). When the fluorescent bead is observed in the total internal reflection fluorescent (TIRF) microscope, the total intensity of the bead image [Fig. 12(b)] decreases with increase in bead-surface separation because intensity of the illuminating optical field decreases exponentially away from the solid-buffer interface.

In such a setup, we can generate a force-extension curve for a single DNA molecule by ramping the current in the coil of the electromagnet. As shown in Fig. 12, the increase in the applied magnetic force reduces the brightness of the fluorescence, indicating that the bead moves away from the surface of the sample. This behavior appears to be fully reversible and reducing the coil current (force) brings the bead back toward the surface. Through proper calibration of bead magnetic properties and decay length of the evanescent wave one can convert these data into a true force-extension curve, but these considerations are beyond the scope of this paper. Given the results of our simulation for magnetic forces [Fig. 2(c) and Eq. (2)], we expect that stretching forces of 15 to 25 pN have been reached with this electromagnet-bead pair. Stretching behavior of the single stranded DNA molecule is well described by the extensible freely joined chain model of

FIG. 13. (Color online) Individual force-extension curve for 150-mer single stranded DNA obtained from one of the intensity-current cycles in Fig. 12(d).

a polymer molecule.^{28,29} Using parameters of this model under our experimental conditions (phosphate buffer saline containing 150 mM NaCl, $pH=7.4$), one can describe the curves in Fig. 12(d) in terms of the linear dependence of B field on coil current (Fig. 10) and exponential decay of the fluorescence from the bead³⁰ with respect to extension of the DNA molecule (for detailed description see Ref. 31). Such fits for intensity versus current curves in Fig. 12(d) produced a decay length of 97.5 ± 0.9 nm for the evanescent field and force sensitivity of 16.9 ± 0.5 pN/A for the magnetic bead. The resulting force-distance curve shown in Fig. 13 is consistent with previously reported stretching behavior of single stranded DNA molecules.^{28,29} This experiment demonstrates that electromagnets with properly designed magnetic cores can be used in magnetic tweezers.

IV. CONCLUSIONS

We investigated spatial distributions of the magnetic field and forces produced by the EM tweezers having various geometrical configurations of the soft ferromagnetic core. We determined that these magnetic tweezers can exert pulling forces, up to 200 pN in magnitude, uniformly over relatively large sample areas ($>100 \times 100 \mu m^2$). The numerical studies were done using the MAS technique. The simulation results were validated by a favorable comparison with the experimental data on magnetic field decay with distance from the tip of the magnet and by monitoring how well the boundary conditions for the magnetic field were satisfied across the physical surface of the magnetic core (to better than 1%).

In analysis of the results from the simulations, it is convenient to consider separately effects due to the tip and body of the core. The magnetic field distributions inside and outside of the magnet do not change noticeably due to varying tip length, however, the field as well as the distribution of forces exerted on magnetic microspheres depend significantly on the tip radius. Namely, for a fixed tip length, at short distances, up to several hundreds micrometers away from the tip, the magnets with smaller tip radii provide greater fields than those with higher radii. Even more pronounced effects are observed on forces, which are more relevant for magnetic tweezers applications than B field. We determined that, for a fixed distance from the sample, the

optimal tip radius is slightly less than the tip-sample separation, with forces decreasing when the radius is reduced further. Our study shows that decreasing the tip radius from 3 to 1 mm can result in a factor of 3 increase in the pulling forces at distances 0.2–0.4 mm from the magnet tip, while any further decrease in the tip radius creates a highly nonuniform lateral field distribution and diminishing improvements in the force magnitude. Thus, in order to provide the high pulling forces that are uniform over the broad spatial range comprising the area of interest around the axis of the magnet, one should choose an optimal (compromise) tip radius of 1 to 1.5 mm.

Further, we investigated how the distributions of magnetic field and pulling forces depend on the core length and radius. Our results showed that both field and force in the vicinity of the magnetic tip depend significantly on the core radius: by reducing the magnet core radius, both the magnetic fields and pulling forces increase in the vicinity of the tip. On the other hand, significant changes in B field are also observed inside the magnet and diminish any gain in performance for small cores, because then saturation induction is reached at smaller currents. By reducing the magnet radius by a factor of 2, the maximum magnetic field inside the magnet core is doubled, thus, the total dynamic range of the linear response (to coil current) is reduced by a factor of 2 as well. Overall, our results show that the length and radius of the magnet core affect the magnetic field inside the magnet more than the fields in the vicinity of the magnet tip. Since each of the magnetic materials is characterized by a specific magnetic saturation induction, this increase in the internal field needs to be avoided in the course of experimental implementation of the EM tweezers: once the internal magnetic field exceeds the saturation level, any further attempts to achieve higher field outside of the tip will result in nonlinear effects that will neutralize the potential benefits of further magnet core elongation, increase in the coil current or the number of turns.

To demonstrate the utility of these considerations to the design of the electromagnet for magnetic tweezers, we built an EM tweezers instrument using optimized core geometry obtained in our simulations. The experimental results showed that a relatively short length and wide diameter ferromagnetic cores are preferable for achieving comparably high fields in the region of a linear current response. The magnetic tweezers were used successfully to stretch single stranded DNA attached to a 2.6 μm superparamagnetic bead by adjusting the electromagnet current with a linear ramp. The design considerations for the choice of the magnetic core

parameters and materials characteristics should be useful to researchers working on the experimental implementations of magnetic tweezers using electromagnets.

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