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ABSTRACT

The controlled transport of individual particles and single cells to addressable compartments is a fundamental aim in the emerging fields of lab-on-a-chip and single cell biology. Toward this goal, magnetophoretic circuits, by providing precise control over individual particles in a highly parallel manner, have shown to be a unique competitor for the rivals in the field. In these matter transport platforms, magnetic thin films provide a predefined trajectory for the magnetic microbeads and magnetically labeled cells toward the desired spots. These magnetic paths, called magnetophoretic conductors, are usually placed in horizontal or vertical directions in a circuit; however, we have made no prior attempts to optimize the design of the junctions and the bends in the conductors. Here, we provide an optimization analysis of the bends based on variation in the particle’s size. Considering the achieved results, we designed multiple bends with high performance in transporting magnetized particles and cells. Applying these designs to the magnetophoretic circuits results in a robust, multiplexed platform capable of manipulating microbeads and single cells with important applications in biology, immunology, and drug screening.

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I. INTRODUCTION

Controlled transportation of microparticles in colloids, such as microbeads or living cells, has numerous applications in single-cell analysis,\textsuperscript{1–5} bioprinting,\textsuperscript{6,7} and tissue and organ engineering.\textsuperscript{8,9} For example, in single-cell analysis tools, which are able to reveal the heterogeneity buried among the cell populations, the ability to sort single cells, put one cell type next to another, and study cell-cell, cell-extracellular matrix (ECM), and cell-drug interactions are considered as significantly important aims. These tools are useful in studying diseases such as human immunodeficiency virus (HIV) infection and cancer, where rare and dormant cells show different behavior compared to the other cells and define the patient’s destiny. For particle manipulation, various techniques based on optical,\textsuperscript{10,11} acoustic,\textsuperscript{12–14} electric,\textsuperscript{15,16} and magnetic\textsuperscript{17–21} forces are used. Although each method has its own advantages, finding a robust technique for transporting particles in a massively parallel and highly controllable manner is challenging.

Recently, we have introduced magnetophoretic circuits,\textsuperscript{22–26} composed of passive (e.g., diodes, conductors, and capacitors) and active (e.g., transistor) circuit elements. These building blocks resemble the ones in the electronic circuits; however, they manipulate matter (e.g., magnetized particles and cells), as opposed to electrons. While passive elements provide the opportunity to transport a large number of single particles in parallel, active elements allow us to precisely control the trajectory of individual particles. Furthermore, we demonstrated a random access memory (RAM) into which we “wrote” single living cells and “read” them as biological data.\textsuperscript{24} We implemented this technology in magnetomicrofluidic chips,\textsuperscript{27,28} used as a novel single-cell analysis tool for performing phenotypic and genotypic studies.

Similar to the electronic circuits, the magnetophoretic chips are fabricated using the micro- and nanofabrication techniques. The conductors, made of magnetic thin films, are one of the basic building blocks. In other magnetic transport techniques, shifting magnetic particles along curved paths has been demonstrated.\textsuperscript{20,29} However, in working with magnetophoretic circuits, we have noted that offsets in conducting paths are challenging. When two conductors connect perpendicularly, a corner forms, in which particles may be trapped. In this work, for the first time, we perform an extensive study on this issue and propose a few solutions. We run computer
II. RESULTS AND DISCUSSIONS

In the linearly magnetizable thin films exposed to an in-plane external magnetic field, the field maxima form at positions where the outward convex normal component of the film curvature is aligned parallel to the direction of the external field. Since the energy is proportional to the magnetic field intensity, by designing the magnetic thin films as microdisks connected in series, energy minima appear on opposite sides of the disks (i.e., the north and south poles). These energy minima play the role of microenergy wells capturing the magnetic particles and magnetically labeled cells on the chip. In other words, a magnetic particle exposed to a magnetic field can be modeled as a point dipole at its center, the magnetic force on which is approximated to be $F = (\mathbf{m} \cdot \nabla)\mathbf{B}$, toward the energy wells.

Gradient: When the energy wells on opposite sides of the two neighboring disks overlap, the follower particles move from one magnetic disk to the other one.

The spherical particles, such as magnetic beads and magnetically labeled cells, can be treated as a point dipole at their center. Thus, to evaluate the magnetic energy acting on them, we need to simulate energy at the center of the particle. Hence, we ran a finite element method (FEM) analysis using COMSOL software to simulate the energy landscape in a plane above the magnetophoretic conductors, at the center of the particle, the results of which are shown in Fig. 1 (top view). In this simulation, the particle, shown with the black circle, follows the energy wells, depicted with the blue regions.

Now, we consider a right-angle bend conductor, composed of micromagnets (disks) with a radius of 10 $\mu$m, which is exposed to a 60 Oe external rotating magnetic field. In Figs. 2(a)–2(d), the energy landscapes for various field angles are shown, while in Figs. 2(e)–2(h), the corresponding experimental results are presented. In this illustration, the trajectory of a single particle at the corner and the
desired particle trajectory are depicted by the dotted line and the gray arrow, respectively. As opposed to moving along the magnetic tracks, the particle of interest is circulating in the corner. The simulations suggest that this problem arises from the energy well overlapping and particle switching between the disks numbered 1 and 3 in Fig. 2(b).

To better understand this phenomenon, we evaluated the energy distribution at various heights (i.e., for different bead sizes) and for different magnetic disk sizes. We realized that the energy well overlapping phenomenon depends on (i) the distance of the disks numbered 1 and 3 in Fig. 3(a) [i.e., pq in Fig. 3(a)] and (ii) the particle size. Hence, we define $\alpha$ as the ratio of the pq length and the particle radius ($\alpha = \frac{pq}{r_p}$). For $\alpha < \alpha_{\text{critical}}$, such as the case shown in Fig. 3(a), the energy wells around disks 1 and 3 overlap and merge; however, for $\alpha > \alpha_{\text{critical}}$, such as the case presented in Fig. 3(b), the wells are distinct. For this geometry, we have $\alpha_{\text{critical}} \approx 3$. So, based on our analysis, while the bend shown in Fig. 3 can move small particles appropriately, it has difficulties in transporting large particles.

In designs with larger disks, the pq length is longer [see Fig. 3(d), where the pq length for a bend composed of small disks is compared with the one for a bend composed of large disks], which results in a more appropriate $\alpha$ and better transport of large particles. In the supplementary material, a case in which this design has difficulties in transporting a single cell is shown.

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longer than the one of the previous methods. Hence, the $\alpha$ values achieved here are larger, the energy wells are distinct for larger particles [see Fig. 4(b) for the energy landscape], and a smooth transport is achieved [see Fig. 4(c) for the experimental result]. We ran our analysis for the conductors with corner disks with various radii and for particles of different sizes, the results of which are illustrated in Fig. 4(d). In this geometry, we have $\alpha_{critical} \approx 2$. Table II compares the maximum particle sizes for errorfree transport in bends with various corner disks. We see that increasing the size of the disk at the corner moves the energy wells apart and allows appropriate transportation of the larger particles. Movie 2 of the supplementary material shows the energy distribution for this geometry in an external rotating magnetic field. It will be explained in Sec. II B that although a large corner disk would help in transporting large particles, it lowers the allowed operating frequency.

B. Obtuse bends

In Sec. II A, we explained that we could improve the operation of the bends by using a large disk at their corner and enlarging the pq line, which splits up the energy wells of disks 1 and 3 in Fig. 3. However, widening the bend angle (i.e., using an obtuse bend), as shown in Fig. 5, in addition to enlarging the pq length (p1q length vs p2q length), helps in enhancing the ability of the magnetic track in transporting particles using another important phenomenon, explained here. Figure 5(a) illustrates a 90° bend, depicted by solid black lines, and its 135° bend version, shown by dashed black lines. The simulation results for these two cases are illustrated in Figs 5(c) and 5(d). In Fig. 5(a), we also have overlaid the schematic of the design geometry with the energy simulation for disk 2, where red stands for high energy areas, while blue shows low energy regions [see Fig. 5(b) for better illustration of the energy simulation of disk 2]. Line p1q moves over the red area produced by the disk numbered 2, while line p2q moves over the yellow area. That means between the energy wells, generated with disks 1b and 3 in the obtuse bend, a strong energy barrier [i.e., red in Fig. 5(a)] is produced by the disk numbered 2, which prevents unwanted switching of the trapped particle between the two wells. However, the weak energy barrier in line p2q (i.e., yellow) can easily be overcome by the energy wells generated by disks 1a and 3, and these two energies may merge. Because of this fact, it is not easy to define a for the obtuse bends, where in addition to the distance of the energy wells of the disks on sides [i.e., disks 1 and 3 in Fig. 5(a)] and the particle size, the energy barrier produced with the disk on the corner (i.e., disk 2 on the corner) is a key parameter.

We ran the simulations at various bend angles and various heights, some of which are illustrated in Figs. 5(c)–5(f). Comparing the blue regions around the disks next to the one on the corner in these figures, one realizes that the wider the bend angle, the farther the energy wells of the disks (which is the goal). However, based

| Corner disk radius ($\mu m$) | Maximum particle radius ($\mu m$) |
|-----------------------------|---------------------------------|
| 10                          | 4                               |
| 15                          | 8.5                             |
| 20                          | 11                              |
on Table III, the 135° bend can transport a wide range of particles of interest in bioapplications (e.g., most of the cells). Moreover, as shown in Fig. 5(g), widening the bend angle increases the area used by the bend on the chip. Thus, for a compact design, a 135° bend is a good candidate, the simulation results of which for various field angles [See Figs. 6(a)–6(d)] and the corresponding experimental results [See Figs. 6(e)–6(h)] prove that this geometry transports the particles smoothly. Thus, as opposed to a 90° bend, we suggest the use of two or more obtuse bends, forming a miter bend or a long radius elbow. Figure 1 of the supplementary material shows the energy distribution along the p1q line in Fig. 5(a) for a 135° bend, where an energy barrier is seen for the plots at various heights. Similar to our analysis in the 90° bends, increasing the disk size in obtuse bends helps further optimizing the bend efficiency. However, since (i) increasing the bend angle enhances the efficiency well enough, eliminating the need for disk size increment, and (ii) as it will be discussed later in this work, increasing the disk size may not be the best strategy, we skip performing a careful analysis of particle transports based on the disk diameters in this design.

We used different bead sizes and magnetically labeled cells to run multiple experiments on several geometries composed of the introduced bends (see Fig. 7). In our experiments, we used both magnetic beads with size ranges of 5–5.9 μm (named 5 μm in Fig. 6), 10–13.9 μm (named 10 μm in Fig. 6), and 14–17.9 μm (named 15 μm in Fig. 6) and magnetized cells as the test particles, the results of which are illustrated in Fig. 6. Each experiment was performed for 20 particles (n = 20). As explained before, using a large disk at the corner helps transporting particles with different sizes [see Fig. 7(a) and black bars in Fig. 7(e)]. Also, we mentioned that wide angle bends are good alternatives for overcoming the well overlapping problem. In Fig. 7(b), a bend composed of six 165° bends is shown, which, as expected, transports various particles smoothly [see black bars in Fig. 7(f)]. This nice transport is also seen in the example composed of two 135° bends, as illustrated in Fig. 7(c) [see black bars in Fig. 7(g) for performance analysis]. Movies 3–5 of the supplementary material show the operation of a few offsets based on obtuse bends.

The achieved results in this study are valid for the junctions, where two conductors meet, as well. In Fig. 7(d), a junction, composed of two original 90° bends [compare Figs. 7(a) and 2], is shown. In fact, the particle moves around the disks along the bend [e.g., disks numbered 1, 2, and 3 in Fig. 7(a)] and the disks on the other side of the bend [e.g., disk numbered 4 in Fig. 7(a)] is too far to have a noticeable effect on the particle. In other words, the energy produced with the far disk [disk number 4 in Fig. 7(a)] is strong around that disk, but is too weak far away from it, at the particle spot. Figure 5(b) can again be seen to realize how energy drops far away from the disk. We achieved similar results for the 90° bend and the junction, confirming the similarity. As expected, this design

### Table III. Maximum particle size for an errorfree transport based on obtuse bends.

| Bend angle (deg) | Maximum particle radius (μm) |
|-----------------|-----------------------------|
| 90              | 4                           |
| 105             | 7                           |
| 120             | 9                           |
| 135–180         | 14                          |

FIG. 5. Obtuse bend design. (a) A 90° bend, composed of disks 1a, 2, and 3, and a 135° bend, composed of disks 1b, 2, and 3, are illustrated. The schematic is overlaid with energy simulation of disk 2. p1q and p2q depict the connecting lines for the energy wells of the corresponding disks. (b) The energy landscape for disk 2 is illustrated. The energy simulation results for (c) 90°, (d) 135°, (e) 120°, and (f) 165° bends are presented (γ stands for the bend angle). The field direction is illustrated with a black arrow. Blue and red stand for regions with minimum and maximum energies. (g) Various bends for producing a turn are compared.
transports the majority of small particles, while it has difficulties in moving the large ones [see Fig. 7(h)].

The motion of the particles around magnetic disks exposed to an external in-plane rotating magnetic field can be in “phase-locked,” “phase-slipping,” or “phase-insulating” regimes. Magnetophoretic circuits operate in the phase-locked regime, where the magnetic particle rotates synchronously around the perimeter of the magnetic disks with a fixed phase lag with respect to the external field direction, resulting from the balance between the driving magnetic force and the viscous and frictional drag forces. Hence,
the particles travel exactly around two disks at each external rotating field cycle. This fundamental principle in these circuits provides the opportunity to manipulate all the particles in parallel in an automatic manner with a known timing. However, in an external rotating magnetic field with a fixed frequency, the energy wells (and their following particles) moving around larger magnetic disks travel a longer distance compared to the ones moving around smaller disks, at time t. Thus, to follow the energy wells around the larger disks, the particles need to travel faster around them, compared to the ones that move around small disks. The higher particle velocity results in a stronger viscous drag force on them and increases their phase lag. Also, when working with large particles, the viscose drag force is even higher, as shown in the following equation:

\[ F_D = 6\pi \eta r_p v, \]

where \( F_D \) is the drag force, \( \eta \) is the viscosity of the surrounding liquid, \( r_p \) is the particle radius, and \( v \) is the particle velocity, respectively. Thus, to prevent shifting from the phase-locked to the phase-slip regime, in which particles cannot follow the external magnetic field anymore, we need to reduce the operating frequency (i.e., lower the external field frequency). So, the maximum operational speed in the bends with a larger disk or the ones with a large disk at the corner is lower than the one in the obtuse bends.

To verify this finding experimentally, we performed a set of statistical analyses on success rates of the various bend types, shown in Fig. 7, in transporting particles. As expected, our proposed designs transported the particles smoothly at low frequencies (e.g., 0.2 Hz). At higher frequencies (e.g., 0.5 Hz), the bend with a large disk at the corner could not transport them well; however, the designs based on the obtuse bends could perform well [see gray bars in Figs. 7(c)– 7(h)]. Since the magnetization of the cells is lower than the one for the magnetic beads, at high frequencies, they could not follow the external magnetic field very well, and so not all of them moved along the desired magnetic tracks.

The external field intensity in our experiments was 60 Oe. Increasing the field intensity, other than widening the allowed operating frequency range, does not change the design efficiencies. Although the results are not shown here, we repeated both experiments and simulations with an external field intensity of 1000 Oe. The simulation results show that increasing the magnetic field intensity, other than deepening the energy wells, does not change the energy landscape.

It is important to note that the energy overlapping problem mentioned in this study applies to the concave side of the bends. However, on their convex side, where energy wells are far away from each other, in appropriate conditions, they can manipulate the particles smoothly. An example of particle transport on the convex side of a bend is shown in Movie 5 of the supplementary material.

III. MATERIALS AND METHODS

The microfabrication steps are explained elsewhere. In short, silicon wafers (University Wafer, Boston, MA, USA) were cleaned with acetone and isopropanol. Photoresist NFR16-D2 (JSR Micro Inc., Sunnyvale, CA) was spin-coated onto the chips for 5 s at 500 RPM and then for 30 s at 3000 RPM. Then, they were baked at 90 °C for 2 min on a hotplate. Next, the wafers were exposed to ultraviolet light for 12 s at an illumination power of 13.5 mW at a wavelength of 365 nm (Karl Sus MA6/BA6). Then, they were baked at 90 °C for 2 min. Next, after keeping the chips in Microposit MF-319 (Shipley, Marlborough, MA) for a minute, they were rinsed with deionized water and dried with nitrogen. A 5 nm thick Ti layer, as an adhesion layer, was formed under a 100 nm thick permalloy (Ni80Fe20) film on the chips using electron-beam evaporation (Kurt Lesker PVD 75) at an operating pressure of 1 \times 10^{-7}. Next, a 1165 resist remover (NMP) was used for the lift-off process. After rinsing with acetone and isopropanol, the chips were dried with nitrogen. The chips where spin-coated with a Teflon thin film to prevent the particle to surface adhesion.

The experiments with the magnetic beads (Spherotech CM-50-10, Spherotech CM100-10, Spherotech CM-150-10, Bangs Laboratories UMDG003, and Bang Laboratories UMF003) and the cell were performed in deionized water and phosphate buffered saline (PBS), respectively. The CD4 cells were magnetically labeled with anti-CD4 antibody conjugated magnetic nanoparticles (StemCell Technologies, Vancouver, Canada).

The rotating field was applied by a custom designed four-pole structure wrapped with wire (20 AWG). The coils were connected to programmable power supplies (Kepco BOP 20-5) and controlled by a customized LabVIEW program (National Instruments).

The simulations were based on COMSOL Multiphysics® 5.3. First, the geometry of the models was created. Then, the study domain was chosen (Stationary) and the physical parameters and materials were allocated. An appropriate mesh was chosen (maximum element size: 2 μm, minimum element size: 0.2 μm) to ensure convergent and accurate results. Using the Magnetic Field module, the problem was solved.

IV. CONCLUSIONS

In designing magnetophoretic circuits, one of the basic building blocks is the bend conductor used to make offsets in the trajectory of the particles. Our experimental results and the energy simulations showed that a normal right-angle bend has difficulties in transporting large particles. To overcome this challenge, in this work, we proposed two designs. One solution is to use a large magnetic disk at the bend corner. This design works well at low frequencies; however, it cannot move the particles at high frequencies. The other solution is to use obtuse bends and their combinations. Our simulations and experiments showed that designs based on the obtuse bends work well at frequencies up to 0.5 Hz. Transporting magnetic beads and magnetically labeled cells with the bend structures introduced in this work for the first time opens the window for designing error-free circuits based on magnetophoretic circuits with applications in cell biology and medicine.

SUPPLEMENTARY MATERIAL

See the supplementary material for the energy distribution along the p1q line in Fig. 5(a) for a 135° bend (Supplementary Fig. 1), in which the 90° bend has difficulties in transporting a single cell (Supplementary Movie 1), the energy distribution for the bend with a large disk at the corner in an external rotating magnetic field (Supplementary Movie 2), and the operation of an offset based on obtuse bends (Supplementary Movies 3–5).
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