Enhanced Capture of Magnetic Microbeads Using Combination of Reduced Magnetic Field Strength and Sequentially Switched Electroosmotic Flow—A Numerical Study

Magnetophoretic immunoassay is a widely used technique in lab-on-chip systems for detection and isolation of target cells, pathogens, and biomolecules. In this method, target pathogens (antigens) bind to specific antibodies coated on magnetic microbeads (mMBs) which are then separated using an external magnetic field for further analysis. Better capture of mMB is important for improving the sensitivity and performance of magnetophoretic assay. The objective of this study was to develop a numerical model of magnetophoretic separation in electroosmotic flow (EOF) using magnetic field generated by a miniaturized magnet and to evaluate the capture efficiency (CE) of the mMBs. A finite-volume solver was used to compute the trajectory of mMBs under the coupled effects of EOF and external magnetic field. The effect of steady and time varying (switching) electric fields (150–450 V/cm) on the CE was studied under reduced magnetic field strength. During switching, the electric potential at the inlet and outlet of the microchannel was reversed or switched, causing reversal in flow direction. The CE was a function of the momentum of the mMB in EOF and the applied magnetic field strength. By switching the electric field, CE increased from 75% (for steady electric field) to 95% for lower electric fields (150–200 V/cm) and from 35% to 47.5% for higher electric fields (400–450 V/cm). The CE was lower at higher EOF electric fields because the momentum of the mMB overcame the external magnetic force. Switching allowed improved CE due to the reversal and decrease in EOF velocity and increase in mMB residence time under the reduced magnetic field strength. These improvements in CE, particularly at higher electric fields, made sequential switching of EOF an efficient separation technique of mMBs for use in high throughput magnetophoretic immunoassay devices. The reduced size of the magnet, along with the efficient mMB separation technique of switching can lead to the development of portable device for detection of target cells, pathogens, and biomolecules. [DOI: 10.1115/1.4029748]

Keywords: electroosmotic flow, magnetophoretic separation, magnetic microbeads, capture efficiency, sequential switching

1 Introduction

Research in the field of microfluidics has led to the development of tools that enable biochemical assays to be conducted on portable devices with faster response times compared to experiments on a laboratory scale [1]. Microfluidic devices have potential applications in the development of diagnostic devices for immunoassays that help detect biomolecules, cells, and pathogens in throughput screening. One such method of immunoassay is magnetophoretic separation that uses mMBs conjugated with antibodies against specific cell surface epitopes (antigens) and are used to tag cells of interest [2–8].

1.1 Application of EOF in Magnetophoretic Separation. In magnetophoretic separation, the mMBs are carried in a fluid which can be either pressure or electrokinetically driven. Electrokinetically driven flows, such as EOF, have advantages in microfluidics as EOF does not require mechanical pumps to drive the flow [9–11]. EOF is driven by an external electric field. The electric field in the microchannel is achieved by placing electrodes in the inlet and outlet reservoirs and applying a voltage potential across them. The flow rate is in direct proportion to the applied electric field.

Several analytical [12,13] and computational models [14–17] have been developed to study the magnetophoretic separation of mMBs. The magnetic fields were modeled by simulating permanent magnets [18,19], electromagnets [20,21], or quadrupolar Halbach arrays [22]. During the capture of mMBs, the magnetic force and drag force dominate over Brownian force and sedimentation [23]. Numerical studies have also demonstrated the effects of L- and T-shaped microchannels in enhancing the capture of mMBs [24,25]. The results from these numerical models enabled the design and fabrication of microelectromechanical system-based biosensors for magnetophoretic separation [26]. The mMBs coated with glycine, streptavidin, and protein A were used by Bronzeau and Pamme [27] to perform multiple assays.

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simultaneously. Teste et al. [28] used the intrinsic magnetic field of mMBs, in channels with restricted flow, to trap magnetic nanobeads. In other applications, Wang et al. [29] used mMBs for rapid mixing in microchannels.

1.2 Advantages of mMBs as Antigen–Antibody Diagnostic Tool. The micron-sized spherical mMBs consist of iron oxide nanospheres (Fe₃O₄ or Fe₂O₃) embedded in a polystyrene substrate, with the antibodies attached to the outer surface of the polymer matrix. Cell separation is achieved by applying an external magnetic field to impart magnetophoretic mobility to the tagged cells. These functionalized mMBs can be manipulated independently of the microfluidic medium and chip substrate, which have contrasting magnetic properties [30]. The tagged cells or biomolecules experience minimal disturbance during the manipulation process by external magnetic field [31,32]. Also, the manipulation of target cells or biomolecules using mMB is effective since the magnetic interactions are not generally affected by surface charges, pH, ionic concentrations, or temperature [33].

1.3 Significance of mMB CE in Magnetophoretic Separation. The reduced CE of mMBs affects the sensitivity of the device to detect target pathogens from dilute samples [34]. Also, imperfect mMB retention leads to the loss of samples and expensive reagents. While several studies, discussed earlier, have tried to develop novel techniques for capturing mMBs using different channel and magnetic field configurations, very few among these have focused on the techniques to improve the mMB CE without additional complications in the flow path and magnetic field configurations. While some devices and models rely on elaborating a magnetic field to improve the CE, others rely on very low flow rates for successful mMB separation. There is, therefore, a need to improve the mMB CE in microfluidics by focusing on the type of flow, without additional complications to the design.

1.4 Current Study: Capture of mMBs in Switched EOF. Most studies have used pressure driven flow to demonstrate CE of mMBs. However, the capture of mMBs in EOF has not been reported in current literature. The transport of liquids and samples through the microchannels is critical in microfluidic immunoassays and the quality of the fluid-driving system can directly affect the results of these assays. EOF has been recently used as a liquid transport strategy because it offers precise control over media velocity, sample volume, and provides automation of sample handling in a microfluidic system [35], when compared to pressure driven flow. Because of these advantages, EOF has been used in microfluidic devices for clinical applications. For example, Gao et al. [36] developed an EOF-driven microfluidic device for simultaneous detection of multiple microbial targets (E. coli and H. pylori). Using droplet-based microfluidic devices, the application of electrokinetic flows has also been demonstrated for clinical diagnostics of human physiological fluids [37]. Enzyme assays, deoxyribonucleic acid (DNA) separation immunoassay, and polymerase chain reaction amplification are some additional processes that have been integrated in microfluidics using EOF [38,39].

EOF also offers a unique advantage over pressure-driven flows as the flow direction can be altered rapidly by reversing or switching, the polarity of the applied potential at the inlet and outlet. To achieve flow reversal in pressure driven systems, additional pumps, and conduits with complex designs would be required. Flow reversal to enhance CE has not been investigated by researchers. The reversal in EOF flow direction within the channel could cause a momentary drop in the mMB velocity which could allow the magnetic force to overcome the momentum of the flowing mMB, resulting in their capture. Also, reversing the flow near the miniaturized magnet could increase the residence time of the mMBs in a region of higher magnetic field, thus increasing their probability of getting captured.

Accordingly, the goal of this study was to develop a numerical model to demonstrate the CE of mMBs by sequential switching of the external electric field that drives the EOF. Due to disadvantages of using electromagnets, i.e., Joule heating and weak magnetic field [31], the strongest known magnetic material, permanent earth magnet or neodymium (NdFeB) [40], was simulated as a source of external magnetic field in our model. The reduced size of the magnet in our model led to lower values of magnetic field strength (T, Tesla) within the channels. Despite the reduced field strength, sequential switching of EOF ensured efficient mMB capture when using miniaturized magnets. Integrating such magnets with an efficient mMB capture method will help in developing smaller scale portable device for field testing. The important design-variable studied in the model was the effect of the applied electric field, both constant and time varying (switching), on the mMB CE under constant magnetic force. In this study, we were particularly interested in improving the CE at higher electric fields, since flow at high electric fields, i.e., higher flow rates, could help design a high throughput microfluidic device with improved mMB retention and high CE.

2 Methodology

This section describes the governing equations for magnetophoretic flow, the numerical schemes used to compute the trajectories of the mMBs, and the validation of our numerical model. The classical Navier–Stokes equation of fluid mechanics was modified to account for the influence of external electric field as a driving force for the flow [9,10]. The transport of mMBs in the channel was affected by the flow field and the external magnetic field. The mMBs were tracked in the computational domain using Eulerian–Lagrangian approach. The primary figure-of-merit of our model, called the CE, was calculated as the ratio of the number of mMBs captured by the magnetic field to the number of mMBs injected through the channel inlet (Eq. (12)).

2.1 Governing Equations. The governing equations for EOF were derived based on the assumptions given in Krishnamoorthy et al. [41] and Comandur et al. [9], and are listed below

Conservation of mass: \( \nabla V = 0 \) \hspace{1cm} (1)

Conservation of momentum: \( \rho \frac{DV}{Dt} = -\nabla p + \mu \nabla^2 V + f_e \) \hspace{1cm} (2)

Coulomb force: \( f_e = \rho_e E \) \hspace{1cm} (3)

Poisson’s equation: \( \nabla^2 \phi = 0 \) \hspace{1cm} (4)

Electric field: \( E = -\nabla \phi \) \hspace{1cm} (5)

where \( V \) represents the fluid velocity, \( \rho \) is the fluid density, \( \mu \) is dynamic viscosity, \( \phi \) is the applied potential, \( \varepsilon \) is the permittivity of fluid, and \( E \) is the applied electric field. In the momentum equation (Eq. (2)), \( f_e \) represents the Coulomb force exerted by the external electric field. Additionally, the pressure drop term, \( \nabla p \), in our model was zero because a constant pressure was maintained at the inlet and outlet of the channel during EOF in the channel. The Poisson’s equation (Eq. (4)) was then coupled with the momentum equation (Eq. (2)). The electric field in the channel was solved using Eq. (5).

The governing equations for the magnetic field, velocity of the mMBs and the magnetic force experienced by them are given below

Magnetostatic equation: \( M = \frac{B}{\mu_0 H} (\mu_r - 1) \) \hspace{1cm} (6)
Magnetic force on mMB:  \[ F_m = \frac{1}{2\mu_0} \chi \left( \frac{4}{3}\pi r_b^3 \right) \mathbf{B} \mathbf{V} \]  
\[ (7) \]

Drag force on mMB:  \[ F_d = 6\pi \mu_0 \rho_b (V - v_b) \]  
\[ (8) \]

Newton’s second law  
(force balance on mMB):  
\[ \left( \frac{4}{3}\pi r_b^3 \right) \frac{d\mathbf{v}_b}{dt} = F_m + F_d + F_{g} + F_{t} \]  
\[ (9) \]

Velocity of mMB:  
\[ v_b = V + \frac{F_m}{6\pi \mu_0 \mu} \]  
\[ (10) \]

Particle relaxation time:  
\[ \tau = \frac{m_b}{6\pi \mu_0 \mu} \]  
\[ (11) \]

CE(%) = \frac{\text{No. of mMB captured by magnet}}{\text{No. of mMB injected in channel}} \times 100  
\[ (12) \]

where \( \mathbf{B} \) represents the magnetic field intensity, \( M \) is the magnetization of NdFeB material, \( \chi \) is the susceptibility of the mMB, \( F_m \) is the magnetic force, \( \mu_0 \) is magnetic permeability of vacuum, \( \mu_r \) is relative permeability of NdFeB material, \( F_d \) is the viscous drag force on the mMB, \( v_b \) is the mMB velocity, \( r_b \) is the mMB radius, \( \rho_b \) is the mMB density, and \( m_b \) is the mass of the mMB.

Based on the equations above, several parameters such as the magnetic field strength and the external electric field driving the flow can be simulated and optimized for the design of an efficient mMB separator. In our model, the magnetic field was kept constant and the electric field was varied to evaluate the changes in CE, for a fixed design of the miniaturized magnet. The list of parameters used in our model and their quantitative values are listed in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid density (( \rho ))</td>
<td>997 kg/m(^3)</td>
</tr>
<tr>
<td>Dynamic viscosity (( \mu ))</td>
<td>8.6 \times 10^{-3}Pa\cdot s</td>
</tr>
<tr>
<td>Relative permeability (( \mu_r ))</td>
<td>78.8</td>
</tr>
<tr>
<td>Zeta potential (( \zeta ))</td>
<td>-95.6 mV</td>
</tr>
<tr>
<td>Debye-layer thickness (( \lambda_d ))</td>
<td>0.1 \mu m</td>
</tr>
<tr>
<td>EOF electric field</td>
<td>150–450 V/cm</td>
</tr>
<tr>
<td>Radius of mMB (( r_b ))</td>
<td>1.42 \mu m</td>
</tr>
<tr>
<td>Density of mMB (( \rho_b ))</td>
<td>1800 kg/m(^3)</td>
</tr>
<tr>
<td>Susceptibility (( \chi ))</td>
<td>1.42</td>
</tr>
<tr>
<td>Magnetic coercive field (( H_c ))</td>
<td>9.79 \times 10^3 A/m</td>
</tr>
</tbody>
</table>

Previous studies have shown that mMB having a radius greater than 40 nm experience a significantly larger drag force (\( F_d \)) and magnetic force (\( F_m \)) compared to the Brownian force (\( F_B \)) and gravitational force (\( F_g \)) [23]. Also, based on the properties of the mMBs used in our model, the value of particle relaxation time (\( \tau \)) was found to be significantly small, and consequently the term \( d\mathbf{v}_b/dt \) was nearly zero. Thus, Newton’s Second Law simplified to \( F_m + F_d = 0 \) or \( F_m = -F_d \). The velocity of the mMBs, under the influence of the flow and magnetic fields, was computed using Eqs. (7)–(10). The mMBs are only affected by the flow field and magnetic field. The mMBs are not influenced by the electric field or the gradient of the electric field because they do not possess any electrical charge.

The magnetic field, simulated using a miniaturized magnet, was computed based on the properties of a typical NdFeB magnet. In our model, a one-way momentum coupling of the mMBs and fluid was asserted into the numerical method, i.e., the velocity of the fluid (\( V \)) affected the velocity (\( v_b \)) of the mMBs, but not vice versa. The boundary conditions for the flow (EOF) and magnetic field are shown in Fig. 1. The boundary conditions for driving the EOF, i.e., zeta potential (\( \zeta \)) and Debye layer thickness (\( \lambda_d \)), were applied to the walls of the microchannel (solid–fluid interface in Fig. 1). The velocity driving the EOF was specified at the inlet and outlet of the channel. The magnetization of NdFeB was specified initially for the magnetic volume and an extrapolation boundary condition was applied at the walls for computing the magnetic field.

For each simulation, a fixed number of mMBs (20) were injected into the microchannel from the inlet. The mMBs were modeled as discrete phases (or microparticles) using the spray module of the solver and were injected uniformly from the inlet. From the values of magnetic force and drag force, the trajectories of the mMBs were computed using Newton’s second law (Eq. (9)) in a Lagrangian frame of reference. The CE of the microfluidic device, based on the number of mMBs injected and the number of mMBs that escaped through the outlet was computed using Eq. (12). A flow chart of the overall algorithm used to compute the mMBs trajectories is illustrated in Fig. 2. The region in the channel where the mMBs were immobilized was referred to as the capture zone.
For EOF driven by a steady electric field, the input electric field (150–450 V/cm) was applied at the channel inlet while the outlet was set to ground (0 V). For flow with sequential switching, the boundary conditions for the electric field were reversed periodically, i.e., the inlet was set to ground and the outlet was set to the applied electric field (150–450 V/cm). The Debye layer thickness was set to 0.1 \( \mu \)m and the zeta-potential was set to 95.6 mV.

This value of zeta potential was based on experimental values obtained from polydimethylsiloxane (PDMS)–glass microchannels in our laboratory [43] and was similar to the values reported in literature, shown in Table 3 [44–46]. The magnetic field in the computational domain was simulated from the input values of intrinsic mMB susceptibility (\( \chi \)) equal to 1.42 and magnetic coercive field (\( H_c \)) of the permanent NdFeB magnet equal to 9.79 \( \times \) 10^5 A/m.

For the magnetic field, extrapolation boundary condition was applied in the computational domain.

### 2.3 Validation of Simulation Results

#### 2.3.1 Validation of EOF Velocity

When EOF is driven by a uniform electric field in a channel, the flow field will have a plug profile. The analytical solution for steady-state EOF, given by the Helmholtz–Smoluchowski (H–S) equation (Eq. (13)), correlates the applied electric field, zeta potential of the channel wall (\( \zeta \)), fluid permittivity and viscosity to the magnitude of EOF velocity (\( U_e \)). This analytical solution is used to validate the velocity vector (\( \mathbf{V} \)) computed by Eq. (2) in the finite volume solver (Fig. 3).

As a baseline analysis, we numerically evaluated the velocity profile of a fully developed EOF in the channel using the finite-volume solver. As shown in Fig. 3, the numerical solution, for an applied electric field of 275 V/cm, agreed within 0.1% of the analytical EOF profile given by the H–S equation.

### Table 2 Comparison of magnetic field intensity of miniaturized NdFeB magnets in capture of mMBs in a microchannel

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Distance between magnet and channel (( \mu )m)</th>
<th>Magnetic field intensity (T) at channel wall</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 ( \mu )m × 150 ( \mu )m</td>
<td>750 ( \mu )m</td>
<td>0.0084 T</td>
<td>Current model</td>
</tr>
<tr>
<td>200 ( \mu )m × 200 ( \mu )m</td>
<td>50 ( \mu )m</td>
<td>0.35 T</td>
<td>Gassner et al. [18]</td>
</tr>
<tr>
<td>20 ( \mu )m × 60 ( \mu )m</td>
<td>0 ( \mu )m</td>
<td>1.1 T</td>
<td>Munir et al. [19]</td>
</tr>
</tbody>
</table>

#### 2.3.2 Validation of Magnetic Field

The magnetic field, computed by the solver, was validated with experimental data and by a finite element solver. In order to compare and validate the magnetic field computed by the finite volume solver, we used the experimental data for a 3/8 in. cubic NdFeB magnet (K&J Magnetics, Jamison, PA) and numerical results using a finite element solver called finite element method magnetics (FEMM) [47]. The magnet was assumed to be magnetized along the \( y \)-axis in the computational domain. The variation of the magnetic field intensity was plotted from the surface of the magnet. As shown in Fig. 4, the results obtained from the finite-volume solver compared well with both the experimental data and the finite element solver. The maximum error in the computational results with respect to experimental data and finite element solver (at \( y = 6 \) mm) was 5.1% (\( |0.138_{\text{Finite volume}} - 0.131_{\text{Experimental}}| \times 100/0.138_{\text{Finite volume}} \))% and 7.3% (\( |0.138_{\text{Finite volume}} - 0.148_{\text{Finite element}}| \times 100/0.138_{\text{Finite volume}} \))%, respectively.

#### 2.3.3 Validation of Model Grid Independence

In order to demonstrate the grid independence of our model, the trajectory of a single mMB was plotted when released from the center of the channel under an applied electric field of 200 V/cm. As shown in Fig. 5, grid independence was tested for four mesh configurations.
having: (1) 8910, (2) 19,650, (3) 36,000, and (4) 56,523 cells. The trajectory of the captured mMB was similar in all the four mesh configurations tested. This trajectory was quantified based on the final position \( (x) \) coordinate of the mMB on the upper wall of the channel \( (y = 100 \text{ lm}) \). The final \( x \) coordinate of the mMBs at \( y = 100 \text{ lm} \) were 1189.2 \( \text{lm} \), 1219.7 \( \text{lm} \), 1235.8 \( \text{lm} \), and 1260.5 \( \text{lm} \) for Grids 1, 2, 3, and 4, respectively. Accordingly, the average difference in this final \( x \) coordinate (at \( y = 100 \text{ lm} \)) with respect to Grid 3 was 2.36\% \( \left( \frac{3.77 \text{ Grid 1} + 1.31 \text{ Grid 2} + 2.00 \text{ Grid 4}}{3} \right) \). Grid independent results obtained for the current mesh (Grid 3: 36,000 nodes) were used for subsequent simulations. This grid size enabled simulations of complex steady-state and transient coupled electric, magnetic, and fluid flow fields for capture of mMBs.

Table 3 Comparison of zeta potential values with the literature

<table>
<thead>
<tr>
<th>Channel type:</th>
<th>Zeta potential value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDMS–glass</td>
<td>−95.6 mV</td>
<td>Current study</td>
</tr>
<tr>
<td>PDMS–glass</td>
<td>−110 mV to −68 mV</td>
<td>Sze et al. [44]</td>
</tr>
<tr>
<td>PDMS–glass</td>
<td>−92 mV to −49 mV</td>
<td>Almutairi et al. [45]</td>
</tr>
<tr>
<td>Fluoropolymer–glass</td>
<td>−91 mV to −42 mV</td>
<td>Werner et al. [46]</td>
</tr>
<tr>
<td>PDMS–silica</td>
<td>−95 mV</td>
<td>Al-Rjoub et al. [43]</td>
</tr>
</tbody>
</table>

Fig. 3 Comparison of numerically calculated EOF profile with analytical solution of Helmholtz–Smoluchowski equation (electric field applied: 275 V/cm)

Fig. 4 Magnetic field produced by 3/8 in. cubic NdFeB magnet: comparison between experimental data (K&J Magnetics, Jamison, PA), finite volume solver (CFD-ACE+) and finite element solver (FEMM); Inset: magnetic field contour, IBI, computed by the finite volume solver.
3 Results

The magnetic field that immobilizes the mMBs, the electric field that drives the flow and their coupled effects on the CE of the mMBs in the microchannel are discussed in this section. First, the magnetic field generated by a miniaturized magnet placed above the microchannel and its effects on the trajectory of mMB transported within the channel are described. Second, the CE of the mMBs using EOF is characterized under two applied electric field conditions: (a) steady electric field (constant inlet electric field, outlet grounded) and, (b) electric field altered by sequential switching of applied potential at inlet and outlet. The enhancement of CE by the periodic changes in flow direction, caused by switching, is discussed in further detail. The characteristics of the EOF velocity profile are also assessed for flows driven by steady and sequentially switched electric field.

3.1 Effect of Magnetic Field. The magnetic field produced by permanent earth magnets, such as NdFeB have been found to be effective in immobilizing mMBs in millitubes during immunoassays [48]. Figure 6 shows the magnetic field contours around a microchannel when simulated using the properties of NdFeB miniaturized magnet. From the surface of the magnet, the magnetic field decreases exponentially in space. The magnetic field strength used in this study is significantly lower than the ones reported in previous studies (Table 2). The magnetic force exerted due to the external magnetic field is critical in determining the number of mMB immobilized in the microchannel. To study the effect of this force on the trajectory of the mMB, 20 mMBs, equally spaced along the inlet, were injected into the microchannel.

As an example, the trajectory of the mMBs is plotted for an applied EOF electric field of 275 V/cm (Fig. 7). Out of the 20 mMBs injected, 10 were captured by the magnetic field. Since...
the magnetic force, similar to the magnetic field, decays as one moves away from the surface of the miniaturized magnet, the mMBs injected from the top of the channel (closer to the magnet) were more susceptible to being captured than those injected from the bottom. Therefore, the remaining 10 mMBs, injected near the bottom of the channel, overcame the force exerted by the magnet and eventually reached the outlet. For an applied EOF electric field of 275 V/cm, the CE, calculated using Eq. (12), was 50%.

3.2 CE Without Switching. The CE at an applied EOF electric field was evaluated for the without switching case by keeping the polarity of electric field constant at the inlet and outlet of the microchannel. At all times during the simulations the EOF had a plug profile. The CE of the system decreased with increase in EOF electric field driving the flow (Fig. 8). This decrease was because of increase in fluid velocities at higher electric fields (from Eq. (13), \( U_e \propto E \)). With the increased flow rates, the mMBs in the channel acquired higher momentum. Consequently, the mMBs escaped through the outlet after overcoming the stronger magnetic force in the capture zone. For the without switching case (steady electric field), the maximum CE obtained was 85% at 150 V/cm. The average CE at lower electric fields (150–200 V/cm) was 75% (\( (85_{150 \text{ V/cm}} + 75_{175 \text{ V/cm}} + 65_{200 \text{ V/cm}})/3 \)). At higher electric fields (400–450 V/cm), this average decreased to 35% (\( (35_{400 \text{ V/cm}} + 35_{450 \text{ V/cm}})/2 \)).

3.3 Variation of EOF Field During Switching

3.3.1 Dynamics of the Debye Layer. As discussed earlier, a fully developed EOF velocity in a microchannel has a plug profile and its magnitude is governed by the H–S equation (\( U_e \), Eq. (13)). When the electric potential between the inlet and outlet of the microchannel was reversed, the flow was first altered within a small region near the Debye layer. This flow reversal near the Debye layer was due to the instantaneous response of the counter ions, concentrated near the Debye layer, to the changed electric field. The motion of these ions affected the fluid flow in their immediate vicinity and this localized flow reversal was in the direction of the applied electric field but against the flow field in the core of the channel. The subsequent flow reversal in the core region of the microchannel was delayed due to the existing inertia of the fluid in the core region of the microchannel against the applied electric field. Eventually, the fluid in the core region was reversed by the counter-ions in the Debye layer responding to the switched electric field.

3.3.2 Electric Field and Velocity Variation During Switching. To study the effect of switching on CE, the applied voltage potential was reversed and the duration of this reversal was varied. Reversing the polarity at the inlet and outlet terminals led to the switching of the flow direction within the channel. It also caused the mMBs to travel in reverse direction toward the inlet for the duration of the switching or electric field reversal. The potential was switched when the uncaptured mMB began to pass the capture zone moving toward the outlet. The distance traveled by the mMBs during the electric field reversal was proportional to the duration of switching. As shown in Table 4, the flow was initialized with the potential at the inlet set to the applied electric field (275 V/cm) and the outlet kept at ground (0 V) from \( t = 0 \) s to \( t = 0.51 \) s. When the electric potentials at the inlet and the outlet were reversed from \( t = 0.51 \) s to \( t = 0.61 \) s, a reversal in flow direction was achieved, i.e., the flow was switched. For an applied electric field of 275 V/cm, the corresponding voltage signals at the input and the output terminals are shown in Fig. 9.
Table 4  Applied electric field conditions for sequential switching of flow

<table>
<thead>
<tr>
<th>Time (s)</th>
<th>Inlet</th>
<th>Outlet</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0–0.51</td>
<td>275</td>
<td>0</td>
</tr>
<tr>
<td>0.51–0.61</td>
<td>0</td>
<td>275</td>
</tr>
<tr>
<td>0.61–1.2</td>
<td>275</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 10 shows an example of the axial velocity profile for an applied electric field of 275 V/cm (corresponding to an EOF voltage of 55 V across 2 mm), before the flow was switched (inlet at 275 V/cm, outlet at ground: indicated by arrows showing age of 55 V across 2 mm), before the flow was switched (inlet at 275 V/cm, outlet at ground: indicated by arrows showing −55 V).

(i) Forward flow (inlet at 275 V/cm, outlet at ground): Initially \( t = 0 \) s to \( t = 0.51 \) s the EOF had a plug profile with the axial velocity equal to \( 2.13 \times 10^{-3} \) m/s in the forward direction (+x).

(ii) Backward flow (inlet at ground, outlet at 275 V/cm): When the electric field was switched at \( t = 0.51 \) s, the flow in the Debye layer immediately aligned itself with the direction of the applied electric field (−x). However, at this instance, the velocity in the core of the channel still had a magnitude of \( \sim 2.13 \times 10^{-3} \) m/s in the direction (+x) opposite to the reversed electric field (−x). Eventually, the flow in the Debye layer overcame the momentum in the core toward the direction of the electric field (−x); thus, completely overcoming the forward (+x) inertia of the fluid within the channel.

(iii) Forward flow (inlet at 275 V/cm, outlet at ground): When the flow was switched back at \( t = 0.61 \) s in the +x direction, the ions in the Debye layer again reversed the flow from −x direction to the direction of applied electric field (+x). About \( 6 \times 10^{-3} \) s after switching, a steady state velocity field was attained in the +x direction.

3.4 CE With Switching

3.4.1 CE With Switching Compared to Without Switching. For flow without switching, the CE decreased with an increase in electric field. A similar trend was observed for flow with switching. However, for the same magnitude of applied electric field, switching the flow led to an increase in the CE (Fig. 8). The initial results of CE with switching indicated that the mMBs which initially escaped the magnetic field could be captured if the flow field was reversed. At lower electric field (150–200 V/cm) the CE with switching increased to 95% (\([100_{150 \text{ V/cm}} + 100_{275 \text{ V/cm}} + 85_{200 \text{ V/cm}}]\%) compared to 75% for flow without switching. At higher electric field (400–450 V/cm) CE increased from 35%, for flow without switching, to 47.5% (\([50_{400 \text{ V/cm}} + 45_{500 \text{ V/cm}}]\%2) for flow with switching. The enhancement in CE due to switching was significant and was further investigated by varying the duration of electric field reversal.

3.4.2 Enhancement of CE by Increased Switching Distances. To further enhance the CE with switching, we increased the time period for which the polarity at the inlet and outlet terminals was reversed. This time period \( t’ \) was based on the time it took for a particle to travel a given distance \( d \) in the backward (−x) direction (toward inlet). The time \( t’ = d/U \) was calculated at each electric field (150–450 V/cm) for a specified distance \( d = 200 \mu m \) (case A), 300 μm (case B), and 450 μm (case C) using the corresponding values of EOF velocity \( U_e \). When the period of switching was prolonged, the residence time of the mMB in the capture zone increased. For example, at an electric field of 275 V/cm, increasing the distance traveled by the mMB in the backward direction \( d \) from 200 μm to 450 μm increased the residence time \( t’ \) from \( 9.4 \times 10^{-2} \) s to \( 2.1 \times 10^{-1} \) s. This allowed the magnetic force to exert its effect on the mMB in the capture zone for a longer period to overcome the momentum of the mMBs. Due to this increased period of switching, the corresponding CE increased from 65% to 80%. During this switching, velocity magnitude momentarily acquired a nearly zero value. Consequently, the magnetic force was able to pull the mMB closer to the regions of strong magnetic fields under the reduced forward (+x) inertia of
systems has not been explored extensively [49]. The present driven microfluidic systems employ external pumps such as studies have focused on the improvement of CE of the devices to values of slope for the linear correlations (Fig. 11) showed that effect increase) at higher electric field (400–450 V/cm). The similar val-
ues of 15.8% (400 V/cm: 15% increase and 450 V/cm: 16.7% increase, and 350 V/cm: 13.6% increase), which further increased at intermediate electric field (225–350 V/cm) the relative increase in CE was 15.1% (225 V/cm: 12.5% increase, 275 V/cm: 19.2% increase, and 350 V/cm: 13.6% increase), which further increased to 15.8% (400 V/cm: 15% increase and 450 V/cm: 16.7% increase) at higher electric field (400–450 V/cm). The similar values of slope for the linear correlations (Fig. 11) showed that effect of electric field on CE remained generally similar for different switching distances.

4 Discussion

Unique methods have been developed to immobilize function-
alized mMBs for microfluidic immunoassays. However, very few studies have focused on the improvement of CE of the devices to minimize the loss of samples and reagents [6]. Most pressure driven microfluidic systems employ external pumps such as syringe pumps. The use of EOF for the mMB immobilization systems has not been explored extensively [49]. The present numerical model studied the effects of steady and switched applied EOF electric field on the CE of mMBs, by simulating micron-sized permanent magnets under reduced magnetic field strength. These magnets have potential application when integrated in miniaturized devices. The study showed that the flow direction can be changed using periodic switching of EOF which can significantly improve the CE of mMBs in microfluidic systems. Such switching of the applied electric field also enabled better control over flow rate and its direction. Additionally, the plug profile of EOF ensured uniform distribution of mMBs in the flow through the microchannel. The rationale behind switching was to increase the residence time of the mMB in the region of higher magnetic fields. This was achieved by changing the direction of applied electric field, causing the escaped mMBs to return to the capture zone. The numerical results also showed that flow reversal significantly improved the CE (Fig. 11) as discussed in further details below.

4.1 Effect of Steady and Switched EOF Electric Field on mMB Capture. To improve throughput of the device, higher flow rates are desired. However, such higher flow rates lead to loss of samples and reagents, such as mMBs that escape the magnetic field due to higher momentum. In the present study, the CE decreased with increase in applied electric field in both steady electric field and with switching. Figure 8 shows that the CE decreased linearly with the increase in applied EOF electric field. The trajectory of the mMBs in the microchannel was governed by the combined effects of flow field velocity, V, and the magnetic force term, \( F_m/\beta r_{w} \), shown in Eq. (10). The mMBs escaped when the fluid momentum was greater than the magnetic force in the momentum equation (\( V > F_m/\beta r_{w} \)). For the miniaturized magnet to capture the mMBs, the term \( F_m/\beta r_{w} \) needs to be greater than fluid momentum. The static magnetic field produced by the miniaturized magnet led to a constant magnetic force in the computational domain (Fig. 6). As a result, the mMBs could be captured if, (a) the mMBs were in a region of high magnetic field, and (b) if the EOF velocity of the fluid medium containing the mMBs was lower. For the flow without switching, the miniaturized magnet could immobilize the mMBs, only when the transverse (+y) magnetic force was greater than the force due to steady-state momentum of EOF in the axial direction (+x). The resultant velocity acquired by the mMB \( v_{y} \) was due to the combination of forward (+x) EOF force and transverse (+y) magnetic force components. The captured mMBs traveled in a region closer to the magnet and were immobili-
ized due to the higher magnetic force. The mMBs which remained uncaptured did not acquire sufficiently high transverse velocities due to relatively lower magnetic force away from the magnet. These mMBs failed to overcome the axial momentum exerted by the EOF and eventually escaped through the outlet.

In the case of switching, residence time increased due to decel-
eration of particles during reversal of the voltage potential. Due to the static magnetic field, the magnetic force in the channel remained constant, while the momentum due to the fluid velocity did decrease. The resultant mMB velocity \( v_{r} \), which was the combined effect of the magnetic force term \( F_m/\beta r_{w} \), and the flow velocity \( V \) decreased due to the reduced flow velocity. Thus, the magnetic force in conjunction with the reversal of flow during switching reduced the net velocity of the captured mMBs in comparison to flow without switching. During the switching period, the magnetic force in the channel was able to overcome the reduced momentum of the flow field, thus, immobilizing additional mMBs which would have otherwise escaped. In addition to mMB captured during the period of switching, some mMBs were also captured by the miniaturized magnet when the polarity was reinstated and forward flow was restored from the inlet to the outlet (inlet: applied electric field, outlet: ground). This was due to mMBs being pulled closer toward the magnet in the capture zone during the period of switching. As the flow attained its steady state plug profile, the higher magnetic force near upper wall of the microchannel was able to overcome the momentum of the flow field and immobilized additional mMB. Most of the mMBs during switching were captured before the flow attained its steady state plug profile \( U_c \).

4.2 Advantages of Switching in Improving CE. Previous designs demonstrating high CE were sometimes effective but required additional manufacturing steps or complex setup of magnetic field in the channel. The method of EOF switching can be implemented by using commercially available off-the-shelf
systems allowing improved CE of mMBs. Using EOF power supplies the polarity of the electrodes placed in the inlet and outlet reservoirs can be sequentially changed for altering the flow direction. Replicating the process of switching in pressure driven systems would require additional pumps, instrumentation and tubing which may not be trivial to setup. To compare the proposed method with conventional systems, capture of mMBs in a pressure driven flow was modeled (average velocity equal to \( U_h \) for comparison), as shown in Fig. 12. The CE for pressure-driven flow was comparable to flow without switching, but was lower than what was obtained with EOF switching.

4.2.1 Assumptions and Limitations. In this research, the computational model demonstrates the capture of mMBs tagged with antibodies. The binding kinetics of the target cells (antigens) with the immobilized microbeads (tagged with antibodies) and any flow of cell-microbead complex are not modeled in this study. Thus, this study evaluated the event of capture of mMBs tagged with antibodies in the microchannels, prior to the injection of cell samples. Also, our current computational model is based on certain assumptions. The model assumes that the particles are sufficiently small compared to channel width so that the fluid momentum is not significantly affected due to presence of the particles thereby neglecting the two-way coupling between particles and fluid. In two-way coupling, the interplay between the magnetic and particle-induced fluid momentum may enhance the CE [17]. A superparamagnetic microbead when exposed to an external magnetic field generates an intrinsic magnetic field [50]. This phenomenon enhances the magnetic field in the microchannel. As a result, the particles which may have escaped could be captured by weaker magnetic fields or their trajectories could be altered. The altered trajectory could primarily lead to mMBs being captured by the external miniaturized magnet and thus enhance the CE of the device. Also, particle–particle interactions were not modeled in the current numerical method. In this study, the mMBs were treated as discrete particles without their intrinsic magnetic fields. The particle collisions were not modeled. This assumption is generally valid for low concentration of particles. The mMBs sticking to the walls were assumed not to ricochet back into the flow field. We anticipate that these assumptions should not affect the accuracy of the simulations.

Despite the limitations in the model, we demonstrated that sequential switching of electric field in EOF under reduced magnetic field strength has the potential to minimize the loss of mMB samples and reagents in immunoassays. The optimization of sequential switching of EOF in conjunction with reduced size of magnets, or magnetic field strengths, will help fabricate a device on a smaller scale and improve the portability as a hand-held monitoring unit for field testing. The method can also be extended to immobilize mMBs for other applications in microfluidics such as mixing. The future scope of this work is to integrate the results of the mMBs immobilized with bacteria or pathogens injected into the channels and study the antigen–antibody kinetics of mMBs and target pathogens. The detection of bacteria from a sample can subsequently be modeled using antigen–antibody kinetics.

5 Conclusions

In this study, we presented a numerical model which demonstrated a simple technique of sequential switching which can be used in EOF systems for efficient capture of mMBs using miniaturized magnet. The unidirectional flow of mMBs from inlet to outlet in a steady electric field showed a linear decrease in CE with increase in applied electric field. The sequential switching of this EOF electric field caused the direction of the flow field to reverse periodically, that led to an increase in CE due to the capture of the mMBs that initially escaped the magnetic field. The sequential switching of EOF improved the CEs at both high (400–450 V/cm) and low (150–200 V/cm) electric field ranges evaluated by the model. The CE also improved significantly with increase in switching distances. The increase in CE was due to decreased velocity of flow field and increased residence time of mMBs in the capture zone. The improvements in CE were more significant at higher electric field (400–450 V/cm) where relative increase in CE due to prolonged period of switching was 15.8% compared to 4.9% at lower electric field (150–200 V/cm). The method of switching efficiently captured the mMBs and overcame the reduced magnetic field strength (T) in the channel due to the smaller size of the magnet. The technique of sequential switching of EOF under reduced magnetic field strength can reduce the loss of samples and reagents during magnetophoretic immunoassays in high throughput microfluidic devices. In conclusion, the reduced size of magnet and mMBs capture with switching can enable the fabrication of efficient and portable devices for field testing.

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Nomenclature

\( A_e \) = magnetic vector potential, Wb/m
\( B \) = magnetic field intensity, Wb/m² or T
CE = capture efficiency, %
\( d \) = switching distance, m
\( E \) = electric field, V/m
EOF = electroosmotic flow
\( F_d \) = viscous drag force, N
\( F_e \) = Coulomb force, N
\( F_g \) = gravitational force, N
\( F_m \) = magnetic force, N
\( F_B \) = Brownian force, N
\( H \) = height of microchannel, \( \mu \)m
\( H_c \) = magnetic coercive field, A/m
\( L \) = length of microchannel, \( \mu \)m
\( M \) = magnetization of NdFeB, A/m
\( m_0 \) = mass of mMB, kg
NdFeB = neodymium alloy
\( p \) = pressure, Pa
\( r_b \) = radius of mMB, m
\( t' \) = switching time, s
\( U_e \) = EOF velocity magnitude, m/s
\( V \) = fluid velocity, m/s
\( v_b \) = velocity of mMB, m/s

Fig. 12 Comparison of CE in pressure driven flow with flows with and without switching

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Greek Symbols

ε = permittivity, C/V-m
ζ = zeta potential, V
ξP = Debye layer thickness, μm
μ = dynamic viscosity of fluid, Pa·s
µm = magnetic permeability of vacuum, Wh/A·m
ρ = relative permeability of NdFeB, unitless
ρ = fluid density, kg/m³
p = density of mMB, kg/m³
ρe = bulk charge density, C/m³
τ = particle relaxation time, s
φ = applied EOF voltage, V
ζ = susceptibility of mMB, unitless

References


