Numerical Investigation of a time-dependent magnetic actuation technique for tagging biomolecules with magnetic nanoparticles in a microfluidic system

A. Munir[1], J. Wang[1], Z. Zhu[1], and H.S. Zhou[1]

[1]Department of Chemical Engineering, Worcester Polytechnic Institute, Worcester, MA
*Corresponding author: 100 Institute Road, Worcester, MA 01609, E-mail address: szhou@wpi.edu (Susan Zhou)

Abstract: The magnetic body forces that act on mono-dispersed magnetic nanoparticle (MNP) tagged biomolecules in a microfluidic system can be efficiently used in various applications that involve separation and detection including DNA and protein analysis, bio-defense, drug delivery, and pharmaceutical development. However, for microfluidic devices to perform such operations for point-of-care analysis, it is often necessary to tag biomolecule of interest with MNPs on-chip. Tagging various fluid contents continuously in the micro-scale is often difficult due to slow diffusion process where length scale of mixing is large. Therefore, enormous time is needed for the biomolecules to be thoroughly mixed and combined with MNPs. In this work, we report an FEM model to demonstrate a novel method of tagging biomolecules with MNPs on-chip using time-dependent magnetic field, produced due to the electrodes embedded in the device substrate beneath the microchannel. A time-dependent magnetic body forces produces oscillation in MNPs causing agitation in the surrounding fluid that otherwise follow laminar profile and overall speeds up the reaction kinetics of the tagging process. This strategy is easy to implement and can be integrated on a lab-on-a-chip system. The model was employed to quantify the effect of convection, diffusion, reaction and magnetic field on the tagging performance. Overall, the developed COMSOL model demonstrates that time-dependent magnetic actuation is an efficient tool to mix or tag MNPs with biomolecules *in situ* for the development of efficient point-of-care microfluidic systems.

Keywords: microfluidics, magnetic nanoparticles, lab-on-a-chip, modeling, medical diagnostics.

1. Introduction

Microfluidics together with nanotechnology has played a major role in developing micro-total-analysis-systems (μTAS) or lab-on-a-chip systems. These miniaturized systems have found profound application in medical diagnostics, chemical and biological analysis, forensic analysis and even immunoassays and toxicity monitoring [1]-[3]. Miniaturization has offered numerous advantages including shorter analysis times, reduced sample and reagent volume, as well as high selectivity and sensitivity [4].

Recently, functionalized magnetic micro/nanoparticles [5], [6] are advantageously combined with microfluidics for separation and detection of biomolecules such as cells, proteins, DNA's and RNA's from. It is based on very simple principle of isolating biomolecules of interest from the bulk mixture by attaching them to small magnetic micro/nanoparticles and then steering it by using an external magnetic field [7], [8]. Numerious microfluidic systems based on magnetic isolation techniques have been developed in the last few years [9]-[13]. The combination of magnetic micro/nano particles together with microfluidic offered added significant advantages such as, easy implementation and automation, higher surface to volume ratio [5], [6] for chemical binding, superparamagnetic nature [5] i.e., zero magnetization in absence of magnetic field helps them to stay suspended in carrier liquid without agglomerating, and no harmful effect on internal solution containing biomolecules.

However, prior to separation and detection analysis, the biomolecules should be tagged with magnetic nanoparticles using specific antigen-antibody chemistry [6] in-situ before realizing its advantages in a lab-on-a-chip system typically developed for point-of-care analysis. Tagging involves bulk phase reaction between MNPs and biomolecules which greatly depends on the quality of mixing. Due to extremely small channel size the flow regimes are typically laminar therefore diffusion processes limit mixing, reaction rates, biomolecule accumulation times and ultimately, separation or detection

sensitivities of these devices. Therefore, enormous time is needed for the biomolecules to be thoroughly mixed and combined with MNPs for further application. Numerous external/internal actuation strategies have been designed in order to enhance the mixing either in an actively or passively. Some of them include splitting and injecting of fluid flows [14], disturbing the fluid flows with microchannel structures [15] and confining the species in droplets [16], [17]. Other active methods are by inducing external energies including mechanical [18], [19], electrical [20], acoustic [21], ultrasonic [22] or thermal [23] in the microchannel flow. Although these methods have produced excellent result but often require complicated fabrication protocols or energies that can potentially damage cell, biomolecules or DNA [24].

To circumvent this problem, magnetic nanoparticles together with local alternating magnetic field can be used in the microfluidic channels. This novel strategy can produce enhanced mixing which is simple and can be easily integrated in to lab-on-a-chip device for tagging biomolecules of interest with magnetic particles for further processing. However, a more quantitative understanding of the dynamics and kinetics involved in the time-dependent magnetic particle actuated tagging process is required. Therefore, in this work finite-element COMSOL based multi-physics model is developed to investigate a wide range of design parameters involved in the development of novel time-dependent magnetically actuated tagging process on chip. It is demonstrated that a time-dependent magnetic body forces are produced due to the electrodes embedded in the device substrate beneath the microchannel. These forces disturbs the MNPs flow regime causing agitation in the surrounding fluid that otherwise follow laminar profile and overall speeds up the reaction kinetics of the tagging process. This strategy is easy to implement and can be integrated on a lab-on-a-chip system especially for point-of-care analysis. The model was employed to quantify the effect of convection, diffusion, reaction and magnetic field on the tagging performance. Overall, the developed COMSOL model demonstrates that time-dependent magnetic actuation is an efficient tool to mix or tag MNPs with biomolecules in situ for the development of efficient point-of-care microfluidic systems.

2. Numerical model

In this work MNPs are used together with time-dependent magnetic field to enhance the mixing and consequently improve tagging of MNPs with biomolecules. A schematic of the microfluidic system together with integrated copper electrodes for creating time-dependent magnetic field, along with corresponding co-ordinates and dimensions, is shown in Fig. 1.

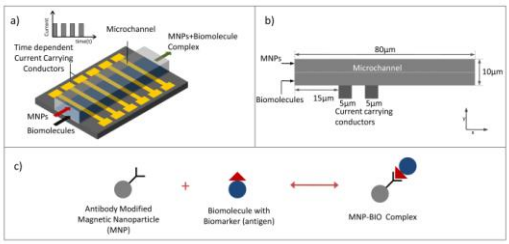

Figure 1. Schematic of time dependent magnetic tagging process: a) a three-dimensional conceptual representation of the microfluidic system, b) a 2D cross-sectional view used to develop finite element COMSOL model, and c) binding reaction between MNPs and biomolecule using antigen-antibody chemistry.

On application of current in the electrodes, large magnetic force and magnetic field gradients are created which disturb the MNP solution flowing within the microchannel. The disturbances are periodically created by turning the current on/ off through the conductors causing agitation in the flow thereby increasing the mixing and consequently the tagging kinetics. A simplified two-dimensional geometry is considered for COMSOL model focusing on the axial cross-section of the microchannel. Although a full three-dimensional simulation would be more accurate but will be more memory intensive. Moreover, qualitative trend would still be the same. Two fluids one containing MNPs and the other biomolecules are loaded in the microchannel via top and bottom inlets respectively. In all the simulations, it is considered that the fluids flow with a constant flow velocity from left to right with a laminar flow. It is considered that both the magnetic nanoparticle and biomolecule solution is transported by convective flow towards the outlet and is also free to diffuse. The surface modified MNPs containing antibody as a

receptor are employed to bind with biomolecules (receptor-antigen) by utilizing specific antigen-antibody chemistry. In order to quantify the tagging performance, mixing cup concentration (C_{MC}) and mixing cup variance (V_{MC}) MNPs-biomolecule (MNPBIO) complex given by Eq. 1 & 2 respectively, are computed at the outlet of the microchannel.

$$C_{MC} = \frac{\int_A uC(x,y)\,dxdy}{\int_A u\,dxdy} \quad (1)$$

$$V_{MC} = \frac{\int_A u(C(x,y) - C_{MC})^2\,dxdy}{\int_A u\,dxdy} \quad (2)$$

Where, $C(x,y)$ is the instantaneous concentration of MNPBIO complex and u is the x-directed flow velocity. The finite element COMSOL model developed is based on Navier-Stokes equations for flow, convection and diffusion equation for concentration profiles, bulk phase reaction kinetics for tagging process, and Maxwell's equation for calculating the magnetic field and magnetic force acting on MNPs. The finite element software package, COMSOL™ Multiphysics (COMSOL AB., Stockholm, Sweden) is used to solve the two-dimensional partial differential Equations obtained in our model. The finite element model consists of three application modes: incompressible Navier-Stokes mode and magnetostatics mode to predict the convective velocity of fluids with and without the influence of magnetic field force, a convection-diffusion mode to predict the concentration of MNPs, biomolecules, and MNPBIO complex solution within the microchannel. A bulk phase reaction term is used in the convection and diffusion mode to realize interaction between MNPs and biomolecules based on antigen-antibody chemistry. The meshing within the microchannel was kept at 10^{-6} except near the centre point of inlet where point meshing parameter of 10^{-7} with growth rate of 1.1 is selected. The model is solved in transient mode in one step using time-dependent solver.

3. Results & Discussion

Time-dependent finite element results were obtained using the above described model and the performance of tagging was predicted using both mixing cup concentration and mixing cup variance described earlier in section 2. The diffusivity of DNA, protein, cells, etc. as reported in literature ranges from 10^{-11}–10^{-14} m^2/s , therefore in convection and diffusion equation, diffusion coefficient, $D=10^{-11}$ m^2/s is used in all the simulations. In magnetic field equation average current of 1A with a switching frequency, $f = 1\,\mathrm{Hz}$ was considered whereas other parameters such as fluid viscosity η $(10^{-3}\,kg/m\cdot s)$ and density ρ $(10^{3}\,kg/m^{3})$ were kept constant throughout. Concentration profiles of MNP-BIO complex formed due to the bulk phase reaction between MNPs and biomolecules having affinity constant of 10^8 M^{-1} [13] were predicted for Peclet Number ranging from 50-300. Fig. 2 gives the concentration profile of MNP-BIO complex within the microchannel at different time points.

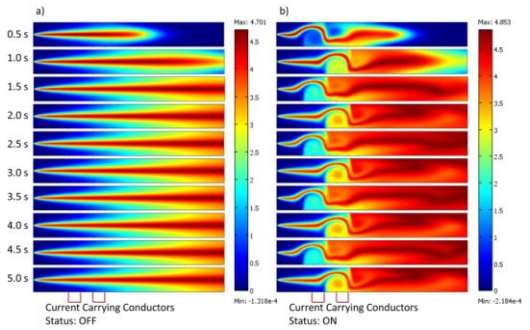

Figure 2. Concentration Profile of MNP tagged biomolecule complex formed during the bulk phase reaction taken at different times with microchannel. (a) no magnetic actuation, and (b) time-dependent magnetic actuation

It can be seen that time-dependent magnetic seems to enhance the tagging process as evident from increase in formation of MNP-BIO complex concentration shown in Fig.2b. It can also be seen that when magnetic actuation is not used the formation (see Fig.2a) of MNP-BIO

complex takes place primarily at the interface (center of microchannel) of MNPs and biomolecule fluids. This is due to low diffusivity of biomolecules and MNPs which limits the bulk phase reaction process. Therefore, it is evident from these simulations that the binding concentration is enhanced when time-dependent magnetic field is used and illustrates that MNP under the influence of magnetic force field causes more mixing, disturbance and provides enhanced tagging of MNPs with the target biomolecules.

In order to further understand the time-dependent magnetic field influenced tagging process, simulations were performed to account for the effect of Peclet and Reynolds Number on the mixing cup concentration and mixing cup variance at the exit of microchannel. Mixing cup concentration is defined as the concentration of fluid if the flow was emptied to a cup that was well stirred basically it determines how well the concentrations of MNP tagged biomolecule is mixed, whereas mixing cup variance gives the overall change of concentration within microchannel. Therefore, smaller the mixing cup variance, lesser will be the diffusion limitation and better will be the mixing and eventually the tagging process. Figure 3 provides the mixing cup concentration of MNP tagged biomolecule with Peclet and Reynolds Number for magnetic and non-magnetic actuated scenarios.

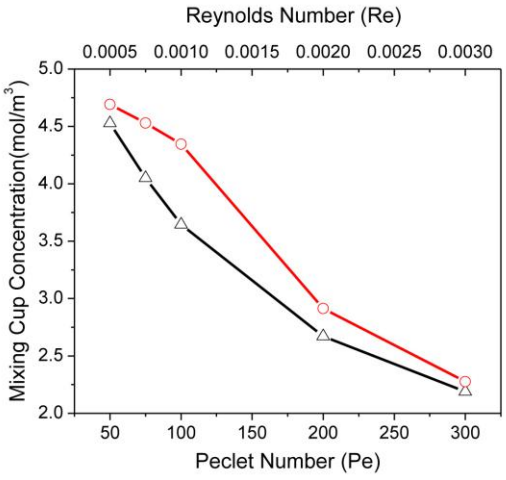

Figure 3. Mixing cup concentration variation with Peclet and Reynolds Number, red line with circle is when magnetic actuation was used whereas, black line with triangle is for no magnetic actuation scenario.

Overall, the mixing cup concentration decreases with increase in convective flow. This is true, because MNPs and biomolecule will get less time to react before they are pulled out of the microchannel, resulting in decrease in formation of MNP-BIO complex. It is found that mixing cup concentration under the influence of magnetic force field is always higher than no magnetic field scenario with the effect being more pronounced in the Pe range of 75-200.

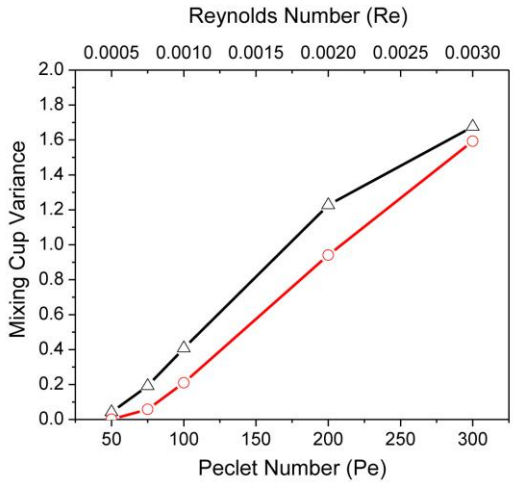

Figure 3. Mixing cup variance variation with Peclet and Reynolds Number, red line with circle is when magnetic actuation was used whereas, black line with triangle is for no magnetic actuation scenario.

At low Peclet Number (Pe~50) we observed that the magnetic actuation does not appreciably influence mixing cup concentration. This is due to the fact that at very low value of Peclet Number convective flow is very small and therefore diffusion dominates the advection time as such even without magnetic field, MNPs and biomolecule get enough time to combine. Similar trend is observed at very high value of Peclet Number (Pe~300). This may be due to the fact that at very high convective flow, magnetic field force is not strong enough to cause cross sectional mixing and overcome diffusion. Therefore, larger magnetic field force will be needed for higher Peclet or Reynolds Number. This can be done by either increasing current or increasing the frequency of current passed through electrodes.

In order to further understand the tagging process, mixing cup variance was predicted as shown in Fig.4. The concentration variation of

MNP-BIO complex is always smaller for magnetically actuated scenario when compared to tagging process without magnetic field force. This proves that magnetic field actuation provides better mixing for bulk phase reaction. Mixing cup variance increases almost linearly with the Peclet Number. This shows that at high convective flow magnetic actuation is not effective enough to overcome diffusion limitation and enhance mixing. In order to be more effective, magnetic field force needs to be adjusted for higher flow rates.

From the above analysis it is found that for the given set of conditions, magnetic actuation technique was very effective if the microchannel is operated at a Peclet Number of 100.Moreover, magnetic actuation can be adjusted based given flow rate and channel geometry. The adjustment can be done either by changing the size or concentration of MNPs or by optimizing current and frequency given to the electrodes in order to obtain time-dependent magnetic field. The numerical simulations results report here indicate that time-dependent magnetic actuation strategy is a useful simple technique for increasing mixing in microchannel, particularly for molecules that have very low diffusivity and will be efficient in tagging process, that can be integrated on lab-on-a-chip systems for point-of-care analysis.

4. Conclusions

A finite element mathematical model for demonstrating an innovative time-dependent magnetically actuated process based on magnetic nanoparticles (MNPs) for enhancing the tagging performance of a microfluidic system was successfully developed. The effect of Peclet and Reynolds Number on mixing cup concentration and mixing cup variance was studied. It was found that in order to have an effective time-dependent magnetically actuated tagging, an optimum convective magnetic field force in the microchannel is required that not only depends on applied magnetic field but also on convective flow velocity, channel's dimension and nanoparticle size. Optimum Peclet Number together with Reynolds Number, was predicted for the given channel configuration for efficiently tagging biomolecule with magnetic nanoparticles. Overall, the simulation performed using the developed COMSOL Model provided an excellent estimate of the potential to use time-varying magnetic field force for efficiently tagging MNPs with target biomolecules in situ for further analysis and detection. The developed model will also be very useful in designing and developing faster integrated lab-on-a-chip devices.

References

[1] M. A. Burns, B. N. Johnson, S. N. Brahmasandra, K. Handique, J. R. Webster, M. Krishnan, T. S. Sammarco, P. M. Man, D. Jones, D. Heldsinger, C. H. Mastrangelo and D. T. Burke, "An integrated nanoliter DNA analysis device," Science, vol. 282, pp. 484-487, Oct 1998.

[2] F. Vinet, P. Chaton and Y. Fouillet, "Microarrays and microfluidic devices: miniaturized systems for biological analysis," Microelectronic Engineering, vol. 61-2, pp. 41-47, Jul 2002.

[3] L. Cao, S. Mantell and D. Polla, "Design and simulation of an implantable medical drug delivery system using microelectromechanical systems technology," Sensors and Actuators a-Physical, vol. 94, pp. 117-125, Oct 2001.

[4] R. Ehrnstrom, "Miniaturization and integration: challenges and breakthroughs in microfluidics," Lab on a Chip, vol. 2, pp. 26N-30N, 2002.

[5] Q. A. Pankhurst, J. Connolly, S. K. Jones and J. Dobson, "Applications of magnetic nanoparticles in biomedicine," Journal of Physics D-Applied Physics, vol. 36, pp. R167-R181, Jul 2003.

[6] M. A. M. Gijs, "Magnetic bead handling on-chip: new opportunities for analytical applications," Microfluidics and Nanofluidics, vol. 1, pp. 22-40, Nov 2004.

[7] C. C. Berry and A. S. G. Curtis, "Functionalisation of magnetic nanoparticles for applications in biomedicine," Journal of Physics D-Applied Physics, vol. 36, pp. R198-R206, Jul 2003.

[8] N. Pamme, "Magnetism and microfluidics," Lab on a Chip, vol. 6, pp. 24-38, 2006.

[9] M. A. Hayes, N. A. Polson, A. N. Phayre and A. A. Garcia, "Flow-based microimmunoassay," Analytical Chemistry, vol. 73, pp. 5896-5902, Dec 2001.

[10] Y. K. Hahn, Z. Jin, J. H. Kang, E. Oh, M. K. Han, H. S. Kim, J. T. Jang, J. H. Lee, J. Cheon,

S. H. Kim, H. S. Park and J. K. Park, "Magnetophoretic immunoassay of allergen-specific IgE in an enhanced magnetic field gradient," Analytical Chemistry, vol. 79, pp. 2214-2220, Mar 2007.
[11] U. Lehmann, C. Vandevyver, V. K. Parashar and M. A. M. Gijs "Droplet-based DNA purification in a magnetic lab-on-a-chip," Angewandte Chemie-International Edition, vol. 45, pp. 3062-3067, 2006.
[12] N. Xia, T. P. Hunt, B. T. Mayers, E. Alsberg, G. M. Whitesides, R. M. Westervelt and D. E. Ingber, "Combined microfluidic-micromagnetic separation of living cells in continuous flow," Biomedical Microdevices, vol. 8, pp. 299-308, Dec 2006.
[13] A. Munir, J. L. Wang, Z. H. Li and H. S. Zhou, "Numerical analysis of a magnetic nanoparticle-enhanced microfluidic surface-based bioassay," Microfluidics and Nanofluidics, vol. 8, pp. 641-652, May 2010.
[14] R. Miyake, T. S. J. Lammerink, M. Elwenspoek, and J. H. J. Fluitman, –Micro mixer with fast diffusion," in proceedings of the 1993 IEEE Micro Electro Mechanical Systems—MEMS, Fort Lauderdale, FL, USA,1993, 248.
[15] A. D. Stroock, S. K. W. Dertinger, A. Ajdari, I. Mezic, H. A. Stone and G. M. Whitesides, "Chaotic mixer for microchannels," Science, vol. 295, pp. 647-651, Jan 2002.
[16] V. Srinivasan, V. K. Pamula and R. B. Fair "Droplet-based microfluidic lab-on-a-chip for glucose detection," Analytica Chimica Acta, vol. 507, pp. 145-150, Apr 2004.
[17] R. B. Fair, A. Khlystov, T. D. Tailor, V. Ivanov, R. D. Evans, P. B. Griffin, V. Srinivasan, V. K. Pamula, M. G. Pollack and J. Zhou, "Chemical and biological applications of digital-microfluidic devices," IEEE Design & Test of Computers, vol. 24, pp. 10-24, Jan-Feb 2007.
[18] L. H. Lu, K. S. Ryu and C. Liu, "A magnetic microstirrer and array for microfluidic mixing," Journal of Microelectromechanical Systems, vol. 11, pp. 462-469, Oct 2002.
[19] K. S. Ryu, K. Shaikh, E. Goluch, Z. F. Fan and C. Liu, "Micro magnetic stir-bar mixer integrated with parylene microfluidic channels," Lab on a Chip, vol. 4, pp. 608-613, 2004.
[20] E. Biddiss, D. Erickson and D. Q. Li, "Heterogeneous surface charge enhanced micromixing for electrokinetic flows," Analytical Chemistry, vol. 76, pp. 3208-3213, Jun 2004.
[21] R. H. Liu, J. N. Yang, M. Z. Pindera, M. Athavale and P. Grodzinski, "Bubble-induced acoustic micromixing," Lab on a Chip, vol. 2, pp. 151-157, 2002.
[22] G. G. Yaralioglu, I. O. Wygant, T. C. Marentis and B. T. Khuri-Yakub, "Ultrasonic mixing in microfluidic channels using integrated transducers," Analytical Chemistry, vol. 76, pp. 3694-3698, Jul 2004.
[23] J. H. Tsai and L. W. Lin, "Active microfluidic mixer and gas bubble filter driven by thermal bubble micropump," Sensors and Actuators a-Physical, vol. 97-8, pp. 665-671, Apr 2002.
[24] M. A. McClain, C. T. Culbertson, S. C. Jacobson and J. M. Ramsey, "Flow cytometry of Escherichia coli on nucrifluidic devices," Analytical Chemistry, vol. 73, pp. 5334-5338, Nov 2001.

Acknowledgements

The author greatly achnowledge the support from National Science Foundation (EEC-0823974).