Modeling of Particle and Biological Cell Transport in Microchannels

A Thesis

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By

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Abstract

Cell transport in microchannels is very important in biological cell labeling, separation and bio-diagnosis technologies. Other applications include drug delivery, DNA sensing, miRNA transport and water purification. In this thesis, mathematical models of cell transport in microchannels are simulated to understand cell motion as cells travel through micro-devices.

The objectives of the modeling are: to characterize particle or biological cell motion in different control systems, including pressure drop, electric field, and magnetic field-induced transport, to observe cell transport properties in cell labeling, separation and bio-diagnosis technologies, and to determine the channel surface effect on a particle or cell motion and distribution near walls.

Assuming a particle or cell is uncharged, the particle/cell transport in a pressure-driven flow is hindered by the size of the cell while both very small cells and very large cells move slowly. Numerical simulations of pressure-driven flow are applied to the cell labeler (cell-antibody binding enhancement device) design. The improvement of cell-antibody binding brought by oblique grooves embedded within the cell labeler is proved. Furthermore, the optimum geometry of the oblique grooves and the minimum mixing length are found to provide good cell labeling efficiency in a cell labeler with parallel pattern grooves.

When a cell or particle is subjected to an external field, the effect of the cell or particle on the surrounding fluid is due to forces from both the external fields and surfaces acting
on the cell or particle. Dimensional analysis shows that forces from an external electromag-
netic field and forces from particle-fluid friction are the primary forces that control the
motion of a magnetized particle/cell.

Particle transport and cell transport are investigated within electrokinetically-driven
flow. The wall effects of electrophoretic motion on both the particle and cell are negli-
gible, unlike in the uncharged case. The electric double layer repulsion and van der Waals
attraction dominates the wall-to-particle effect, reaching a minimum at the wall-particle
separation $D \approx 70\text{nm}$. These were confirmed by comparing with the experimental data.

The concept of osmotic pressure is investigated in a microscopic setting. A cell keeps
ionic equilibrium through its porous semi-permeable membrane. Using force balance anal-
ysis, the electric and molecular interaction between membrane and solute particles are
found to induces the primary force on solute particles, dragging surrounding fluid away
from the membrane and causing a pressure gradient. The microscopic model is compared
to the classical expression of osmotic pressure, van’t Hoff’s Law, and is found to be in
agreement.
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Chapter 1: Introduction

1.1 MEMS and Microfluidics

In recent years there has been a growing interest in the study of microfluidics due to a wide application of both micro- and nano-technology in medicine, chemistry, engineering and other fields, including micro-electro-mechanical systems (MEMS), lab-on-a-chip micro-devices, drug delivery and cell therapy, DNA sensors, and implantation. The study of the microfluidics focuses on manipulating flows in micro/nano-scale channels and investigating the character of these flows.

Figure 1.1: Pressure-driven flow in a rectangular channel.
1.1.1 Pressure-driven Flow and Electroosmotic Flow

Most of the fundamental theories of macroscale fluid mechanics are still applicable in microscale flow. One method to induce flow through a micro/nano-scale channel is to apply a pressure difference between the inlet and the outlet, called pressure-driven flow. The dominating effects on the flow rate in pressure-driven flow include the pressure drop, the viscosity of the fluid, the boundary conditions and the factors. For example, in a rectangular channel with pressure drop $\Delta p$ (Figure 1.1), the volume flow rate is calculated by

$$Q = \frac{Wh^3}{12\mu L}\Delta p$$  \hspace{1cm} (1.1)

where $W$, $h$ and $L$ are the width, height and length of the channel, respectively, and $\mu$ is the fluid viscosity. If we keep the length of the channel constant but decrease the height and width to the micro/nano-scale, a dramatic increase in the pressure drop is needed to keep the same flow rate. This trend is plotted in Figure 1.2 for changes in height. For this reason, pressure-driven flow is not practical in small-dimension channels.

The electroosmotic flow (EOF) pump has been considered as one of the methods to reduce the loss in the flow rate caused by a decrease in channel dimensions. The EOF pump is used to transport an ionized solution in microchannels. If electroosmotic flow is induced by an external electric field $E$, then the flow rate of the EOF in a rectangular channel can be calculated by electric field strength $E[1]$

$$Q \approx -\frac{\varepsilon_e \zeta_w Wh}{\mu}E$$  \hspace{1cm} (1.2)

where the permittivity of water is $\varepsilon_e = 80 \times 8.854 \times 10^{-12}(F/m)$ at $293K$ and $\zeta_w$ is the $\zeta$-potential of the wall.

Assuming the $\zeta$-potential of the channel wall $\zeta_w = -20mV$, the voltage drop $\Delta V$ required to maintain volume flow rate $Q = 0.1\mu L/min$ as a function of the channel height...
To match the experimental and computational data, the rectangular channel is chosen as $W = 150\text{nm}$ in width and $L = 1\mu\text{m}$ in length and the flow rate is $Q = 0.1\mu\text{L/min}$, and $\zeta_w = -20mV$. The dramatically increase of pressure drop is shown in the range of $h < 40\text{nm}$.

$h$ is plotted in Figure 1.2. As the channel height drops from 70\text{nm} to 8\text{nm}, the required increase of voltage drop is 0.045\text{V}, which is much more practical than the required increase of pressure drop (1.285\text{atm}). The EOF pumps have been widely used in micro- and nano-technologies such as water purification and drug delivery.

1.1.2 Magneto-hydro-dynamic Flow

The third method to enhance flow in micro/nano-scale channels is \textit{magnetically-driven flow}, which has been applied to the development of magnetic drug targeting technologies. Magnetically driven flow refers to the electrically conductive fluid flow that reacts to an magnetic field (a field generated by the moving or the self-spinning of the electric charges, or the moving of the electric fields). If the magnetic field $\textbf{B}$ induced by electric field $\textbf{E}$
(bold denotes a vector) is uniform and normal to two stationary parallel plates, then the flow between these two plates is called Hartmann flow[2]. The Hartmann number \(Ha\) was introduced by Hartmann as the ratio of the electromagnetic force to the viscous force[3]

\[
Ha = Bh_0 \left( \frac{\delta}{\mu} \right)^{\frac{1}{2}}
\]

(1.3)

where \(B\) is the value of magnetic flux density vector \(B\), \(h_0\) is the channel half height, and \(\delta\) is the thickness of the Hartmann boundary layer, the geometry of which is showed in Figure 1.3 (a). The Hartmann layer thickness is calculated by

\[
\delta = \left( \frac{\rho \mu}{\sigma B^2} \right)^{\frac{1}{2}}
\]

(1.4)

where \(\rho\) is the fluid density, \(\sigma\) is the electrical conductivity of the fluid, and \(\mu\) is the dynamic viscosity of the fluid. The velocity of flow of an electrically conductive liquid in a uniform magnetic field is calculated by[4]

\[
u = U_0 \frac{1 - \cosh(\frac{Ha \cdot y}{h_0})}{\cosh(Ha)}
\]

(1.5)

where \(U_0\) is a velocity scale and its value is given by

\[
U_0 = -\frac{1}{\sigma B^2} \frac{\partial p}{\partial x} - \frac{E}{B}
\]

(1.6)

where \(\frac{\partial p}{\partial x}\) is the axial pressure gradient, \(E\) is the value of the electric field. Figure 1.3 shows the velocity profile of Hartmann flow passing between two plates as a function of the magnetic flux density \(B\). When \(B \to 0\),

\[
u = U_0 \left[ 1 - \left( \frac{y}{h_0} \right)^2 \right]
\]

(1.7)

As \(B\) increases, the velocity gradients near walls get sharper and the velocities away from the walls become uniform.
Figure 1.3: Sketches of Hartmann flow. (a) the Hartmann boundary layer $\delta$ and the direction of magnetic field. (b) Hartmann flow velocity profiles at different magnetic field $B$. The channel half height $h_0 = 25 \mu m$, the pressure drop $p - p_0 = 100 Pa$, the electrical conductivity of water at $297 K$ is $72 \times 10^4 S/m$.

It is necessary to mention that magneto-hydro-dynamic flow requires a strong magnetic flux density $B$, which makes it less likely to be applied to the transport of some biological cells that are sensitive to these high magnetic fields.

### 1.2 Interaction Between Particles and Walls

#### 1.2.1 Free Particle Diffusion in Micro-scale Pressure-driven Flow

Consider particles entering and exiting a channel. The particles will interact with its surrounding objects, causing the random motion; and the concentration of particles may decrease. The spread of particles by random motion is called diffusion.

There is a dimensionless number which connects the free particle diffusion efficiency to the Péclet number, defined as the ratio of the rate of convection to the rate of diffusion[5].
For the diffusion of particles based on the particle concentration gradient, the Péclet number is

\[ Pe = \frac{\bar{u}L}{D_i} \]  

(1.8)

where \( \bar{u} \) is the average incoming velocity and \( L \) is the characteristic length. For example, a micro-channel has a \( 30\mu m \times 150\mu m \) cross-section, then \( L \) is chosen as the square root average of channel height \( h \) and channel width \( W \), \( \sqrt{h^2 + W^2}/2 = 76.48\mu m \). Typically \( D_i < 10^{-9}m^2/s \), so the micro-scale particle free diffusion is a slow process. One way to enhance the diffusion is to increase the convective motion of fluid (stirring, stretching and folding fluid). Due to limitations in manufacturing technology, the mixing tools which are widely used to stir macro-scale flow, such as spinning blades, are unlikely to be used in micro-scale. Thus the necessity of passive mixing of fluid is strengthened. The passive mixing method discussed in this thesis is an addition of oblique grooves to a rectangular channel wall, and will be introduced in detail in Chapter 3.

1.2.2 The Electric Double Layer

A surface in an ionized liquid will be charged due to the dissociation of surface groups or the adsorption of charged molecules from the surrounding solution. The charged surfaces include not only channel walls, but also particles such as drug beads, colloidal polystyrene beads, and cells. In cell research, phosphate buffer saline is widely used for keeping cells \textit{in vivo}, which contain ions such as \( K^+ \), \( Na^+ \), \( Cl^- \), \( PO_4^{3-} \), etc. At the same time, channel walls made of biomedical materials such as polymethyl-methacrylate accumulate positive charges on their surface. The region near a surface of enhanced counter ion concentration is called the electric double layer (EDL)[6, 7].
Consider a negatively-charged surface that collects mostly positive ions nearby, forming a cation layer. This cation layer is called the Stern layer. More positive ions are collected and lay on the top of the Stern layer and some negative ions are attracted by the Stern layer, forming a diffuse layer with mixed anions and cations. Ions in the Stern layer have very low mobility while ions in the diffuse layer have some mobility. The Stern layer plus the diffuse layer contribute to the electric double layer, formed at both charged particle surfaces and charged wall surfaces (see Figure 1.4). The thickness scale of the electric double layer is the Debye length (or Debye-Hückel length, denoted by $\lambda$), which is the normal distance from the charged surface to where significant charge separation occurs[8]

$$\lambda = \sqrt{\frac{\varepsilon_e RT}{F^2 \sum_i c_i z_i^2}}.$$  \hspace{1cm} (1.9)

where $\varepsilon_e$ is the permittivity of solution, $R = 8.3145 J/(mol \cdot K)$ is the gas constant, $T$ is the local temperature, $F = 96485.3415 sA/mol$ is the Faraday constant, $c_i$ is the concentration of species $i$, and $z_i$ is the valence of the species.
The electric double layer on a particle and wall may cause interactions when the particle nears the wall, affecting the particle’s motion. This is called electrophoresis. The microfluidic devices discussed in this thesis often transport cells and particles in microscale channels since the channel height is similar to the cell’s diameter. Cells are usually negatively charged[9] and the \( \zeta \)-potential of MCF-7 breast cancer cell is approximately \(-30 mV\). Early research[6, 7, 10] show that the interactions of surfaces may become stronger when two surfaces are close to each other. The effect of this cell-wall interaction is evaluated and compared to particle transport and experimental data in these thesis.

1.2.3 van der Waals Force and Electric Double Layer Force

*van der Waals* force is the additive force of molecular attractions and repulsions after removing the contributions from covalent bonds and the electrostatic interaction between ions and ions/neutral molecules, named for the Dutch physicist Johannes van der Waals who first described these molecular interactions in 1873[11].

Both van der Waals attraction and electrostatic repulsion due to the electric double layers need to be considered to describe the interaction of two charged surfaces within a small distance. The superposition of van der Waals attraction and EDL repulsion is described by the *DLVO* (Derjaguin, Landau, Verwey, and Overbeek) *theory*[6, 7]. When two charged surfaces approach, EDL repulsive energy will grow faster than van der Waals attractive energy, and the total force between these surfaces is repulsive. The net effect of the repulsive double layer interaction energy and the attractive London-van der Waals energy is to be discussed in Chapter 4.
1.3 Automated Cell to Biomolecule Analysis Nanofactory

This project is sponsored by the National Science Foundation for the development of the Automated Cell to Biomolecule Analysis (ACBA) nanofactory platform in the Nanoscale Science and Engineering Center (NSEC), which is developing a high efficiency/low cost lab-on-a-chip medical device for cancer diagnosis. The project is based on the idea of system level integration, combined with bio-nanofactory technology and model technology. The objective of the ACBA nanofactory at the present stage is to realize the early and convenient detection of metastatic cancer cells in the blood of patients with various solid tumor malignancies. The detection of these cells was normally limited to later stages of the cancer progression. Future work will include rare tumor cell detection and the post treatment monitoring.

The ACBA nanofactory project includes 3 stages (shown in Figure 1.5): Stage 1 - cell labeling stage, Stage 2 - cell separation stage, Stage 3 - bio-detection stage. However,
the experimental measurement at the micro-scale has met some difficulties, such as the measurement of local flow rate and particle concentration. Computational simulations are used to supplement the experimental model, investigating the translocation characteristics of specific cells in cell separation devices. These simulations are especially used for developing cancer cell labeling and the magnetic tweezer separation methods. Applications of these models also include micro-scale medical devices intended for lab-on-a-chip cancer cell biomolecule analysis, drug delivery, implantation, and many other areas. The cell labeling stage (Stage 1) of ACBA nanofactory is studied in Chapter 3. The cell magnetic tweezer separation stage (Stage 2) is studied in Chapter 4.

1.4 The Biology of Cancer Cells

Cancer is the general name of more than 100 diseases that cause uncontrolled cell growth[12]. There are several common characteristics that distinguish cancer cells from normal cells. First, cancer cells start forming from genetic abnormalities in the transformed cells. For example, oncogenes can cause hyperactive growth and division of cells which can lead to damage of normal tissue boundaries. Additionally, oncogenes can prevent normal cells from accurately replicating DNA. Second, cancer cells reproduce uncontrollably. Normal cells grow old and die after approximately 50 cycles of proliferation. As a result of genetic degradation due to oncogenes, cancer cells gradually become more immature (i.e. primitive in form) and reproduce more rapidly. Third, cancer cells can invade and destroy surrounding tissue and be spread to other parts of the body via the circulatory or lymphatic systems, called metastasis[13].
1.4.1 Circulating Tumor Cells (CTCs)

The phenomena of cancer cell metastasis is observed in many kinds of cancer. New biomedical studies show that circulating tumor cells (CTCs) carried by the bloodstream (see Figure 1.6) may be the origin of metastatic tumors. For example, Cristofanilli et al[14] have found that the presence of circulating tumor cells (CTCs) in a blood sample is a strong prognostic factor in patients with metastatic breast, colorectal or prostate cancer. Cells detach from the primary tumor and circulate through the blood, spreading to other tissues or organs and forming secondary tumors. These cells are called circulating tumor cells. Paterlini-Brechot[15] has also predicted that CTCs are the origin of metastatic cancer tumors.

CTCs can be detected using the FDA-approved CellSearch system, which detects CTCs using antibody-based labeling techniques on blood samples[16]. The quantity of CTCs in the blood can be as low as 1 in 3,000 cells. These CTCs can also be detected using the diagnostic methods of the ACBA nanofactory.

Figure 1.6: Circulating tumor cells (green) moving with blood cells (red) and antigen (blue). Photo from tataa.com.
The ACBA nanofactory also focuses on detecting three different types of human mammary epithelial cells: the breast cell line MCF-10a, the non-invasive breast cancer cell line MCF-7, and the metastatic breast cancer cell line MDA-MB-231. Recently, the ACBA nanofactory and our modeling are focused on the detection of the widely-studied MCF-7 breast cancer cells. The MCF-7 cells are nearly spherical, which has reduced the difficulty of modeling.

### 1.4.2 MCF-10a Benign Breast Cell Line

The MCF-10a breast cell line (ATCC No. CRL-10317, see Figure 1.7) is a benign epithelial cell line. It does not form tumors, but has been observed to form colonies in a semisolid medium[17]. MCF-10a cells are nearly spherical with an average size of approximately $20 - 30 \mu m$ in diameter[18]. The surface potential of MCF-10a cells is $-31.16 mV$[19].
1.4.3 MCF-7 Breast Cancer Cell Line

The MCF-7 breast cancer cell line (ATCC No. HTB-22, see Figure 1.8) was the first hormone-responsive breast cancer cell line. It was isolated and established in 1973 by Dr. Herbert Soule and co-workers[20]. MCF-7 cells are proliferating breast tumor cells that are estrogen receptor (ER) positive. Research[18] has found that the cytokine tumor necrosis factor alpha (TNF alpha) can inhibit MCF-7 cell’s tumorigenesis. Anti-estrogen treatment can be used to adjust the secretion of the insulin-like growth factor binding protein which has the effect of reducing MCF-7 cell growth[21].

MCF-7 cells are negatively charged with a surface potential of approximately $-20.32 mV$[19]. As seen in the EMS photo (Figure 1.8), MCF-7 cells are nearly spherical. Their diameter varies from $10 \mu m$ to $50 \mu m$, mainly around $30 - 40 \mu m$. 

Figure 1.8: MCF-7 Cells, dispersed (left) and concentrated (right). Photos from atcc.org.
1.4.4 MDA-MB-231 Breast Cancer Cell Line

The MDA-MB-231 breast cancer cell line (ATCC No. HTB-26, see Figure 1.9) is a progressive tumor cell line. The cells have a long and narrow shape, approximately 10 $\mu m$ in width and $70 - 90\mu m$ in length (Figure 1.9). MDA-MB-231 cells are negatively charged, with a surface potential around $-25mV$ to $-31mV$[22].

1.5 Literature Review

The technology of micro medical devices has been developed since the late 1990s, and the surgical and clinical demands of the relevant instruments are growing bigger every day. The sophisticated devices require high precision modeling, design and manufacture, which requires the study of particles traveling through micro-scale channels or cells traveling through narrow pores considering the micro-scale influencing factors that are usually neglected in macro-scale modeling and design.
1.5.1 Studies on The Pressure-driven Particle/cell Transport

Before the development of the microfluidic technology, the pressure-driven particle transport has been studied in sub-micro models. A one-dimensional mass transfer model was given by Anderson and Quinn[23] for particle diffusion in one of a network of sub-micron pores, observing the necessary of considering the steric exclusion and Brownian motion effect to the motion of small-size particles.

Later on, several models have been established in attempt to find the influence from the size of particles. Dechadilok and Deen[24] introduced the hindered diffusion coefficient $K_d$ and convection coefficient $K_c$ to the particle movement between two walls into the particle’s Nernst-Planck diffusion equation. These two coefficients are function of the ratio of the particle radius and the channel half-height. Conlisk et al[25] compared the particle hindered diffusion transport and hindered convection transport between parallel walls under applied electric field, and applied the results to the kidney dialysis technology. They also determined that the streaming potential effect is negligible on the solute flow rate in hindered transport model. Secomb and Hsu[26] developed a model testing the transit time of red blood cells moving through cylindrical nano pores. The red blood cell deformation was assessed since the ratio of the cell radius and the half-height $\chi = a/h$ is greater 1. With lubrication theory applied and shear viscosity and elasticity included, transit time decreases substantially as the pore diameter or the driving pressure goes up, or as the suspending medium viscosity goes down. Comparing the diffusion dependent cell motion in microfluidic channels with cell behavior in traditional macro-scale culture flasks, Yu et al[27] found the microchannel culture systems have reversible growth inhibition influenced by cell seeding density and channel height.
A technology to improve micro-scale particle/cell mixing in pressure-driven flows is investigated by Stroock et al.[28] who developed a passive micro-scale flow mixing method of altering the channel cross-section area and adding crosswise oriented grooves. Since the grooves generates flow with complex velocity profile, the micro-scale channel with these grooves embedded is named chaotic mixer. The chaotic mixer has been widely used in industry and the design of its geometry has been improved. Hassell and Zimmerman[29] have observed that different groove heights results in different transverse flow rate in a staggered herringbone mixer (SHM) as well as the existence of optimal groove height. Their observation indicates the possibility of an optimal groove height for the design of grooved cell labeler. Wang and Yang[30] have observed that the oblique grooves’ efficiency for inducing crosswise flow rate is increased with the total groove number or mixing length increases.

1.5.2 Studies on Particle/cell-wall interaction

The dimensions of micro-scale channels can be very close to the dimensions of the biological cells or particles, therefore the wall effect to the particles or cells may no longer be negligible. The effect of adhesion and friction forces between two surfaces has been first modeled by B.V. Derjaguin[31]. Later on, Bhattacharjee and Elimelech[32] developed the surface element integration (SEI) method which is an improved Derjaguin Landau Verwey Overbeek (DLVO)[6, 7] method to integrate the force and energy between a colloidal particle with an arbitrary geometric shape and a flat plate with infinite area. They claimed that the accuracy of SEI methods, unlike Derjaguin approximation, does not depend on the particle curvature or the restriction of the separation between the particle and wall to small distances. Thus SEI should provide more accurate interaction energy generally along the
domain of integration. The scaled ratio of van der Waals interaction energy to Hamaker constant \( A_H \) (a Van der Waals body-body interaction, \( A_H = \pi^2 C \rho_1 \rho_2 \), where \( \rho_1 \) and \( \rho_2 \) are the number of atoms per unit volume in two interacting bodies and \( C \) is the coefficient in the particle-particle pair interaction\([33]\)) is obtained to verify the SEI results. The SEI method is also appropriate to membrane separation, transport in porous media, etc. Bhattacharjee and Elimelech’s method is applicable to simulate the motionless interaction between the particles and the walls.

With an external electric field applied, it is predicted that the electric double layers on the channel walls will have effect on particles when these small beads are moving near wall. Yariv\([34]\) discussed the electrophoretic motion for colloidal spherical particles moving near wall with applied electrical field parallel to the wall. He argued that when the fluid domain is bounded there may exist a nonzero electric force which gives additional electrophoretic velocity to particle motion in or near the Debye layer. The direction of this force starts from the wall toward the particles near wall and the force will drive those particles away from the wall. The importance of the electrophoretic movement of particles and particle surface charge have been recognized. The structure of the electric double layer(also called Debye layer) has been studied by Debye\([35]\) and the Debye-Hückel approximation of double layer is also investigated by Conlisk\([36]\). Dutta and Beskok\([37]\) shows the Helmholtz-Smoluchowski (HS) velocity - the particle electroosmotic/pressure-driven velocity - can be used as the appropriate slip condition when imposed on the wall. Chen and Conlisk\([38]\) showed that when non-uniform patches carrying charges are applied to the channel wall, the distribution of potential and species concentration resulting from Poisson-Nernst-Planck model is different from the Boltzmann distribution because of the surface potential distribution dependence. Kazoe and Yoda\([39]\) observed that the particle
number density rapidly drops when the particle edge-wall distance is smaller than 60nm. This phenomena is predicted owing to an applied electric field repulsion to the approaching nano-particles.

The electric double layer also forms on the surface of negatively charged biological cells[40]. Thus the theories of wall effect on particles are extended to cells. Lee and Cho[41] found cell lysis device used for extracting intracellular materials such as DNA, RNA and protein is capable of developing samples of cell transport (30µm/s) by electroosmotic flow with generated low electric field strength (30 – 50V over 7mm length). Ahmed and Stocker[42] computed population-scale bacterial transport velocity $V_C$ (1 – 10µm/s) by microscale approach for a range of chemoattractant concentrations and concentration gradients with the experimental results support. Also the transient electrokinetic motion of cylindrical cells has been studied by Ai et al[43] suggests that the dielectrophoretic (DEP) effect should be taken into account to study the electrokinetic transport of cylindrical particles in a straight microchannel. In addition, Oster and Peskin[44] present a micro-scale model that investigates the generation of osmotic pressure, and found that the volume expansion of a cell adjacent to porous membrane is induced by the electric double layer repulsion from the charged membrane to the charged solute particles.

1.5.3 Studies on Magnetic Cell Transport

Recently, studies focusing on magnetically-driven transport of particles and cells in medical devices have appeared. Ehrlich[45] developed a procedure to integrate magnetic field component $H$ from permanent magnetic charge on a circular ring with a line magnetic density $\lambda_R$ using Coulomb’s law. Davidson[4] and Sarris et al[46] introduced Hartmann flow, a magnetic field dominated flow through channel, and discussed the influence to the
velocity profile from $Ha$, the Hartmann number (see Section 1.1). Zhu et al. [47] showed the experimental results for the separation of size-based non-magnetic microparticles in ferrofluid by magnetic buoyancy force. This force had a greater effect on larger particles; it deflected them out of the particle mixture toward the magnetic field gradient direction. Therefore devices that use this technique can separate magnetic particles by size. In their experiment the Stokes drag equation is given a correction (Ganatos et al. [48]) when particle moves near the channel surface.

The studies on simulating the magnetic targeting and manipulating are important in aiding the experimental research. Henighan et al. [49] simulated the magnetic field generating by magnetic tweezer composed by magnetic patch arrays, and showed the strong trapping ability for magnetic particle labeled T-lymphocyte cells artificially controlled magnetic patches. This magnetic tweezer is used in ACBA nanofactory lab. Comsol Multiphysics based models have been developed by Strauss [50] for modeling drug targeting by permanent magnet through blood vessels, which shows the possibility of 3-D model of cell targeting and magnetically separating.

Through the above survey it can be concluded that the engineering analysis on the control of cell motion in synthetic microchannels by external driving fields has begun. However, most of the previous work focuses on particle transport; experimental work by a number of biologists is available but the results are of a qualitative nature. All of these have increased the necessity of research on cell transport process. Since biological cells are porous and their diameter is about hundreds times larger than that of particles (in magnitude, 10 $\mu$m comparing to 100 nm), cell transport shows its own characters. In the present
work, the cell transport processes are compared to the particle transport, firstly investigated under different applied external driving fields, making the modeling of cell transport processes more applicable to biomedical devices.

1.6 Present Work

In this thesis, the particle/cell transport models including a pressure-driven transport model, a magnetic field induced model and an electrophoretic transport model are investigated, respectively, and the results of each model have been discussed. The cell labeling process and its effect are simulated.

In Chapter 2 an analytical model has been developed to determine the influence of the hindered coefficients in both the uncharged particle and the uncharged cell transport model in a straight microchannel. In Chapter 3, three-dimensional computational simulations have been developed by multiphysics analysis software Comsol, calculating cell/antibody array distribution in the cell labeling process.

In Chapter 4 the presence of particles on surrounding fluid is considered. The forces acting on the particle are analyzed, while the magnitude of each force is identified. The magnetically induced velocity of a cell moving by the force balance and in the cell capture process are both discussed. Cell transport velocity/transit time are estimated, based on the distribution of magnetic field. van der Waals attraction force and electrical double layer repulsion force are calculated using Derjaguin approximation and surface element integration method, respectively.

In Chapter 5, the cell transport results are compared with the particle transport in an electrokinetically driven flow. Wall effect on particles and biological cells is investigated and compared with the experimental data.
The force balance model developed in Chapter 4 is also applicable to explain the phenomena of porous semi-permeable membrane absorbing water. The membrane-induced osmotic pressure is discussed in Chapter 6. All the results are summarized and the prospects for future work are discussed in Chapter 7.
Chapter 2: Cell Migration as Hindered Species Transport in Micro-scale Channels

2.1 Introduction

More and more research has been focused on cell diagnosis and cell therapy as well as the manufacture of relevant biomedical micro-devices in recent years. Considering the sensitivity of biological cells to electric and magnetic fields, many of these cell technologies require controlling and manipulating micro-scale cell transport within pressure-driven flow only. Typically the radii \(a\) of animal cells falls into a range between \(a = 3\mu m - 50\mu m\) and this size varies with different cell types and circumstances[51]. In Chapter 1 we discussed the cell categories we are using, including normal blood cells, MCF-7 cells and circulating tumor cells. The radii \(a\) of these cells varies. There are small cells e.g. red blood cells \((a = 4\mu m\) on average) and leukocytes \((a = 3 - 4\mu m)\), while most of the cancer cells are larger. MCF-7 breast cancer cells have radii of \(15 - 20\mu m\). Lymphoma cells and lung cancer cells can be up to \(a = 50\mu m\). The corresponding antibodies of cancer cells have radii with the magnitude of \(nm\), e.g. immunoglobulin G (IgG) antibodies \((a = 33nm)[52]\). Additionally, the membrane of cells is porous, and this membrane often keeps a surface charge because of intracellular acid-base equilibrium. In order to accurately capture and manipulate cells and antibodies, channels in biomedical devices are also designed to be
Figure 2.1: 3D cell migration through a rectangular channel, carried by pressure driven flow, shown in Cartesian coordinates.

micro-scale. All of these requires the study of pressure-driven cell/particle transport in micro-scale.

In this chapter we assume the biological cells are uncharged spherical colloidal particles, then investigate the influence of geometric factors to the migration of a single cell in a micro-channel. Figure 2.1 is an intuitive picture of our model: a cell moving in a rectangular channel. The cell is carried by phosphate buffer saline (PBS), which is a commonly used bio-fluid for keeping cells alive. The general assumption and governing equations for cell migration are discussed. The cell migration velocity is derived from the Navier-Stokes equations and the hindered Nernst-Plank equation in Cartesian coordinates. The migrating velocity of a cell in pressure-driven flow is found to be hindered by the size of the cell.

2.2 General Assumptions and Fluid Nernst-Planck Equations

To simplify the problem several assumptions are made:
The cell, in general, can be modeled as a colloidal particle carried by a fluid. The charge that the cell carries is not considered.

- Steady state, fully-developed pressure-driven flow.
- The channel length and width are much larger than the channel height.
- The fluid is incompressible, and no-slip boundary condition is applied at the walls.

The cell convection and diffusion are hindered by the presence of the walls.

The motion of fluid flow can be described by the Navier-Stokes equations. Assuming incompressible flow, the conservation of mass:

\[
\nabla \cdot \mathbf{u} = 0
\]  

(2.1)

The dimensional Navier-Stokes equations in Cartesian coordinates with no electric field applied are given by

\[
\begin{align*}
\rho \left( \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) &= -\frac{\partial p}{\partial x} + \mu \left( \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) \\
\rho \left( \frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} \right) &= -\frac{\partial p}{\partial y} + \mu \left( \frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) \\
\rho \left( \frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + v \frac{\partial w}{\partial y} + w \frac{\partial w}{\partial z} \right) &= -\frac{\partial p}{\partial z} + \mu \left( \frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \right)
\end{align*}
\]  

(2.2, 2.3, 2.4)

where \( \rho \) is fluid density and \( \mu \) is the fluid viscosity, \( p \) is the pressure, \( u, v, w \) are the bulk velocity in \( x, y, z \) direction, respectively.

In a fully developed pressure driven flow, \( v = w = 0, u = u(y) \). Thus we can simplify equation (2.3) and (2.4) into \( \frac{\partial p}{\partial y} = \frac{\partial p}{\partial z} = 0 \) and the pressure distribution becomes \( p = p(x) \).

Substituting equation (2.1) from equation (2.2) yields

\[
0 = -\frac{\partial p}{\partial x} + \mu \frac{\partial u^2}{\partial y^2}
\]  

(2.5)

If we apply the no-slip boundary conditions

\[
u = 0 \quad \text{at} \quad y = \pm h_0
\]
where $h_0$ is the channel half-height, then integrate $u$ on $y$, equation (2.5) yields

$$u(y) = - \frac{1}{2\mu} \frac{dp}{dx} \left(y^2 - h_0^2\right)$$  \hspace{1cm} (2.6)

From the assumptions we can establish a cell migration model considering cell as a mass carried by fluid. The flow rate in a channel with uniform cross-section areas is

$$Q = \bar{u}A$$  \hspace{1cm} (2.7)

where $A$ is the area of the channel cross-section and $\bar{u}$ is the average velocity. In 2-D Cartesian coordinates

$$\bar{u} = \frac{1}{h} \int_{-h_0}^{h_0} u(y)dy.$$  \hspace{1cm} (2.8)

where $h = 2h_0$ is the channel height and $\mu$ is the fluid viscosity. The average bulk velocity can be calculated by pressure-drop gradient along the channel $\frac{dp}{dx}$ and is given by

$$\bar{u} = - \frac{h_0^2}{3\mu} \frac{dp}{dx}$$  \hspace{1cm} (2.9)

The total volumetric flow rate is estimated by

$$Q = \bar{u}A = \frac{2h_0^3}{3\mu} \frac{dp}{dx} W$$  \hspace{1cm} (2.10)

2.3 The Nernst-Planck Equation and the Hindered coefficients

Figure 2.2 is a two-dimensional picture showing the cell motion in the micro-channel in Cartesian coordinates. Our goal is to determine the geometric factors that influence cell migration in laminar flow through a micro-scale channel. Here we define the cell radius to channel half-height ratio

$$\chi = \frac{\bar{a}}{h_0}$$
as a dimensionless geometry parameter. The average cell radius $\bar{a}$ is used considering various kinds of cells. If we only consider the migration of a single cell, $\bar{a} = a$.

The Nernst-Planck equation is a formula for the molar flux $N_i$ of cells. Considering the size-influence of the particle and the channel geometry, we have to introduce the hindered diffusion and convection coefficients $K_d$ and $K_c$ which are geometry-dependent dimensionless linear corrections to the diffusion term and convection term in the Nernst-Planck equation. The hindered Nernst-Planck equation without considering external electric field is given by\[24\]

$$N_i = -K_d D_i \frac{dc}{dx} + K_c \bar{u}c$$ \hspace{1cm} (2.11)

where $\bar{u}$ is the averaged unperturbed bulk flow velocity, $N_i$ is the molar flux of cells, $c$ is the cell concentration, $F$ is the Faraday constant, and $D_i$ is the diffusion coefficient. The cell velocity can be calculated by the molar flux of cell $N$ over the cell concentration $c$,

$$\frac{N_i}{c} = - \frac{K_d D_i}{c} \frac{dc}{dx} + K_c \bar{u}$$ \hspace{1cm} (2.12)
The hindered coefficients are given by Dechadilok and Deen(2006) considering the motion of the spherical cell in the channel and involve calculation of the hydrodynamic flow field and the drag force on the cell without assuming cells moving along the centerline of the channel[24]

\[ K_c = \frac{1 - 3.02\chi^2 + 5.776\chi^3 - 12.3675\chi^4 + 18.9775\chi^5 - 15.2185\chi^6 + 4.8525\chi^7}{1 - \chi} \] (2.13)

\[ K_d = \frac{1 + \frac{9}{10}\chi \ln(\chi) - 1.19358\chi + 0.4285\chi^3 - 0.3192\chi^4 + 0.08428\chi^5}{1 - \chi} \] (2.14)

We must point out that equation (2.13) is valid in \(0 \leq \chi \leq 0.95\) while equation (2.14) is valid when \(0 \leq \chi \leq 0.8\).

### 2.4 Effect of Hindered Transport to Cell Migration

The hindered convection coefficient \(K_c\) and hindered diffusion coefficient \(K_d\) are plotted in Figure 2.3 as a function of the cell diameter to channel height ratio \(\chi\), where \(\chi = 0.1 - 0.95\) for \(K_c\) and \(\chi = 0.1 - 0.8\) for \(K_d\). The diffusion coefficient \(K_d\) declines as \(\chi\) increase due to the shrink of channel geometry and the decrease of free space. As for the convection coefficient \(K_c\), when \(\chi > 0.41\), \(K_c\) drops as \(\chi\) increases. This is because the hindering surface friction between cells and surrounding fluid is growing with the cell size. Additionally, When \(\chi \to 0.95\), the cell is more likely to collide with the channel walls which largely reduce the migration speed.

In the case that cells are sorted and isolated, we may further simplify our model by neglecting the diffusion term. The hindered biological cell migration velocity from equation (2.12) further simplifies to

\[ \frac{N_i}{c} = K_c \bar{u} \] (2.15)
which indicates that a single cell migration speed is affected by convection (following the similar trend with $K_c$), where both very small cells and very large cells move slowly.

The hindered velocity of biological cells in a $50\mu m \times 150\mu m \times 8mm$ rectangular channel\cite{53} is plotted as function of the cell diameter to channel height ratio $\chi$ and the volume flow rate $Q$ in Figure 2.4, along with the corresponding transit time. The range of the ratio $\chi$ is $0.1 - 0.95$, corresponding to the cell radius range $a = 2.5 - 24.5\mu m$. The input bulk flow has a range of $0.05 - 0.3\mu l/min$\cite{53}, corresponding to the average velocity $\bar{u} = 0.11 - 0.67mm/s$.

Within the range of the volume flow rates considered, the approximate velocity range for the cell carried by fully developed pressure driven flow in the $50\mu m \times 150\mu m$ cross-sectional rectangular microchannel is $0.08 - 0.79\mu m/s$. The corresponding transit time
Figure 2.4: Plots of (a) the hindered cell transport velocity and (b) the corresponding transit time in a $50\mu m \times 150\mu m \times 8mm$ rectangular channel as a function of the cell diameter to channel height ratio $\chi = 0.1 - 0.95$ and volume flow rate $Q = 0.05 - 0.3\mu l/min$. 
for traveling through the 8mm length of the channel has a range of 10.14 – 98.97s. When the flow rate is 0.1µl/min, the time range falls between 30.43s to 51.17s, which is in accordance with the transit time measured in experiments[53]. The cell migration model can help interpret the experimental data and guide future experimental design.

2.5 Summary

In this chapter, a pressure-driven cell transport model has been established for cell migration in micro-channel as mass transport. The cells are modeled as uncharged sphere colloidal particles. The governing equations for bulk flow velocity are derived from the Navier-Stokes equations and the cell migration velocity is derived from hindered Nernst-Planck equation.

The cell migration velocity is found dependent on the bulk flow velocity while hindered by the ratio of two geometric characters: the cell radius and the channel half-height. The cell size is double-edged to the cell migration speed, where both very small cells and very large cells move slowly. It is predicted that the random motion of small cells or collision/adhesion between large cells and channel surfaces are the major influence. The calculation results match the cell transit time range measured from experiments. The results can be used to estimate the mass transport of cells or the delivery of other particles such as drug solute particles, antibodies and RNA.
Chapter 3: 3-D Simulation and Design of An Oblique Groove Cell Labeler

3.1 Introduction

Pressure-driven flow is widely applied in transporting biological cells or particles in micro medical devices, not only owing to the sensitivity of some cells or biological tissues to the electric and magnetic fields, but also because these external fields are applied only in specific part of the device to achieve special functions.

In this project, cancer cells must be separated from non-cancer cells prior to analysis. Using antibodies as arrays to label cancer cells is validated, due to the one-to-one correspondence between the antibodies and the cells (each type of antibody targets a homologous population of cancer cells). The antibodies are magnetized by magnet quantum dots and are expected to attach to certain cancer cells[16]. Such cell to antibody binding is called cell labeling.

One way to achieve effective cell labeling is to mix a laminar cell sample stream and an antibody stream together. Since the streams entering the micro-channel are laminar, a regular rectangular channel requires a very long distance to achieve good cell/antibody mixing, which is not practical in micro-scale medical devices. However, it is possible to reduce the mixing length by generating particle transverse movement passively through a channel with oblique grooves.
The efficiency of passive micro mixers with grooves was tested by Stroock et al. They proved that a grooved channel has the ability to generate complicated crosswise fluid motion in a microscale flow and can strengthen the molecular diffusion across the channel. The development of transverse flow in this kind of mixer is irregular, even a simple groove structure can cause very complex flow; thus Stroock called it a *chaotic mixer*. Grooved channel mixer became popular in applications of bio-medical devices. The phenomenon of the chaotic mixing process is still not well understood and requires further research.

A cell labeler with improved design of oblique grooves is investigated in the ACBA nanofactory using both experiments and computational simulations. The objective of the computational simulation is to study the performance and determine the design parameters of the oblique grooves. We are able to simulate the groove-induced transverse and vertical fluid motion out of an axial bulk stream in the channel as well as tracking particle pathlines using the CFD simulation. The simulations are evaluated based on several geometrical factors that influence the results. The factors include but are not limited to: different arrangements of the grooves, total number of grooves, groove height to channel height ratio, groove thickness and slant angle. Two criteria have been used to justify a good mixing effect in a grooved cell labeler: the scaled average transverse velocity, and the degree of particle dispersion.

### 3.1.1 The Geometries, Objectives and Assumptions

The current design of the cancer detection system in the ACBA nanofactory is shown in Figure 3.1. The cell labeler is adopted in stage 1, right before the process of magnetically separating cancer cells from other cells. The pretreated cell blood sample enters into inlet 1, while the PBS solution carrying magnetized antibodies are fed from inlet 2. The two
Figure 3.1: Geometry of the current design on the system of the micro-device in ACBA nanofactory, top view. A microscale cell labeling and separating device with alternating pattern oblique grooves is adopted after the two inlets in Stage 1.
Figure 3.2: Geometry and multiple-size mesh grids on a cycle of cell labeler, bottom view. The domain is meshed with maximum element size $1.14 \times 10^{-5}m$ and maximum element growth rate is 1.25, which is the maximum ratio of the size of an arbitrary mesh element $A$ to the size of the largest elements among all the elements that are smaller than $A$. The groove boundaries are meshed with maximum element size $7 \times 10^{-6}m$ and maximum element growth rate 1.15. The $\theta = 45^\circ$.

Incoming streams will pass a series of labeling grooves. The specific cancer cells (probability existing in blood $1/3000$) should be attached to corresponding antibodies at the exit of the cell labeler.

Given the details of the oblique groove cell labelers in ACBA nanofactory, the main channel of the labeler has a height $h = 30\mu m$ and a width $W = 150\mu m$. The grooves are embedded 45 degrees to the side walls and are divided into cycles by their repeating arrangement, each cycle aligns 6 parallel grooves with different length. The geometry of a one-cycle cell labeler is shown in Figure 3.2, along with the meshed surfaces. The geometry parameters used in all the simulations in this chapter are summarized in Table 3.1.

The objectives of our 3-D simulations are: 1. Study the crosswise convective motion in a cell labeler. 2. Simulate the particle dispersion process in the cell labeler. We also would like to determine the optimum groove geometry for a given rectangular channel cell.
<table>
<thead>
<tr>
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<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Channel height ($\mu$m)</td>
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</tr>
<tr>
<td>Channel width ($\mu$m)</td>
<td>150</td>
</tr>
<tr>
<td>Groove length ($\mu$m)</td>
<td>depend on location</td>
</tr>
<tr>
<td><strong>Variable: groove height</strong></td>
<td></td>
</tr>
<tr>
<td>Cycle</td>
<td>1</td>
</tr>
<tr>
<td>Groove height ($\mu$m)</td>
<td>10, 15, 20, 25, 30</td>
</tr>
<tr>
<td>Groove width ($\mu$m)</td>
<td>30</td>
</tr>
<tr>
<td>Groove distance ($\mu$m)</td>
<td>10, 15, 20, 25, 30</td>
</tr>
<tr>
<td><strong>Variable: groove width</strong></td>
<td></td>
</tr>
<tr>
<td>Cycle</td>
<td>1</td>
</tr>
<tr>
<td>groove height ($\mu$m)</td>
<td>20</td>
</tr>
<tr>
<td>groove width ($\mu$m)</td>
<td>10, 20, 30</td>
</tr>
<tr>
<td>Groove distance ($\mu$m)</td>
<td>10, 20, 30</td>
</tr>
<tr>
<td><strong>Variable: mixing length</strong></td>
<td></td>
</tr>
<tr>
<td>Cycle</td>
<td>0, 1, 3, 6</td>
</tr>
<tr>
<td>Groove height ($\mu$m)</td>
<td>20</td>
</tr>
<tr>
<td>Groove width ($\mu$m)</td>
<td>30</td>
</tr>
<tr>
<td>Groove distance ($\mu$m)</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 3.1: Geometries of parameters of cell labeler in different simulations.

labeler. Thus three dimensional micro fluidic models of, in this case, pressure driven flow carrying cells and antibodies through the cell labeler are developed.

Several assumptions are made to simplify the 3D simulation:

- Before entering the mixing area, the pressure-driven flow is fully-developed.
- The no-slip boundary condition is applied at all walls.
- Cells and antibodies follow the stream; that is, they are passive marker particles. They do not stick to the boundaries.
- The bio-fluid used is an incompressible Newtonian fluid, in this case, water.

### 3.1.2 Comsol Multiphysics Finite Element Code

*Comsol Multiphysics* software has been chosen to generate finite element code of our 3-D modeling. Comsol Multiphysics is a finite element solver for modeling and simulation.
in engineering and design with a special strength of solving multiple simultaneous physical problems, for example, an electromagnetic flow problem, or a fluid flow with chemical reaction[56]. Comsol Multiphysics contains various module packages and we have used the computational fluid dynamic module and the particle tracing module for our simulations.

Our simulations in this chapter mainly used Comsol Multiphysics version 4.1 and 4.2 sponsored by the Ohio Supercomputer Center, partly on a 2.67 GHz processor, 4.00GB RAM computer. The numerical calculation is based on solving the stationary 3-D Navier-Stokes equations presented in Chapter 2 (time dependent term removed) and incompressible flow condition.

The no-slip boundary condition $u = 0$ is applied on all the channel walls and groove surfaces. The initial condition $u = 0, p = 0$ is applied to the fluid domain. The inlet flow rate is $Q = 0.3 \mu L/min$ (set by the syringe pump), equivalent to the average velocity $\bar{u} = 1.1 \times 10^{-3} m/s$. The boundary condition $p_0 = 0$ is applied at the outlet. The channel length is extended about 20% upstream and downstream from the grooves to avoid inlet and outlet boundary effects on the area of interest.

Multiple sizes of meshes are applied at the domain and the boundaries(refer to Figure 3.2). The geometry is imported from engineering design using the 3-D drawing software Solidworks. Both domain and boundaries use the free tetrahedral mesh elements. The fineness of the elements are decided by the local structure of geometry, which emphasizes the effect of grooves while saving computational time. The domain is meshed with maximum element size $8 \times 10^{-6} m$ and maximum element growth rate 1.25, which is the maximum ratio of the size of an arbitrary mesh element A to the size of the largest elements among all the elements that are smaller than A. The groove boundaries are meshed with maximum element size $6 \times 10^{-6} m$ and maximum element growth rate 1.15. Each simulation consists
of around 100,000 − 200,000 total tetrahedral mesh elements depending on the geometry and the volume of each labeler.

3.2 3-D Motion Induced by Grooves

It is known that the oblique grooves are able to use the expansion of the cross-sectional area and the angular oriented grooves to induce non-axial fluid/particle motion. Now we would like to have an intuitive understanding of this convective motion. It is necessary to observe the profiles of the induced convection velocity (transverse and vertical) and to trace the fluid/particle moving patterns. The CFD module from Comsol Multiphysics is used to obtain the velocity distribution in an oblique groove cell labeler. The main stream entering the cell labeler with a velocity \( \mathbf{u} \) (bold as vector) in 3-D Cartesian coordinates can be noted as \( \mathbf{u} = (u, v, w) \) where \( u, v \) and \( w \) are the fluid velocity components on \( x, y \) and \( z \) axis, respectively. In the laminar incoming flow we have \( v = w = 0 \) thus the velocity of fluid is \( \mathbf{u} = (u, 0, 0) \).

Suppose we are tracing fluid particles A and B. Fluid particle A is just about to enter a groove, while B is just out of the exit of the same groove. These two fluid particles passively obtain non-axial velocity components by passing the groove region, including transverse velocity component \( v \) and vertical velocity component \( w \). Figure 3.3 (a) shows the flow orientation of fluid particles A and B above the 3rd groove with their velocity components in Cartesian coordinates (not to scale).

Viewing at the cross-section marked in Figure 3.3 (a), we found a convective motion of flow across the main channel and the grooves, sketched in Figure 3.3 (b). The induced transverse velocity \( v \) is generated both inside and above the groove. Inside the groove the fluid particles move with the groove orientation, while above the groove the fluid is folded.
Figure 3.3: Flow orientations (a) above the grooves, with the positions of fluid points A and B, angled side view. (b) the crosswise flow velocity distribution (on scale) on the cross section of the 3rd groove (the bold plane), end view. The $\mathbf{u} = (u, v, w)$ is the flow speed at fluid particle A and B. The velocity components $u$, $v$ and $w$ are along x-axis, y-axis and z-axis, respectively, in Cartesian coordinates (not to scale).

Figure 3.4: Simulation of paths of 5 different fluid particles (passive markers) moving directed by certain oblique grooves in angled top-view. If we divide the channel axially into two halves by the center line, all the points are transferred from one half to the other half of the channel. Also, the further fluid point above the grooves, the later the fluid point sinks into a groove.
to the direction which is opposite to the groove orientation. The induced vertical velocity \( w \) concentrates at the entrance and the exit of the groove. With the vertical velocity distributed at the groove’s entrance and exit, fluid particles are able to sink into the entrance and are released from the exit. After that, the particles are merged back into the main stream. By contrast, velocity \( v \) has much stronger influence to the convection, because of its higher magnitude and larger distribution area than \( w \). The evaluation of transverse velocity \( v \) is given in Section 3.3.

Figure 3.4 shows the effect of the parallel grooves on the motion of several fluid particles (passive markers). The dash-dot center line divides the channel into two halves. Five fluid particles concentrated at the upper left corner are released from upstream, each path-line is marked with a number. Each particle is captured by one of the oblique grooves so that the displacement of these fluid particles are no longer axial, similar to the results recorded from the relevant experiments[55], showing the ability of the oblique grooves capturing particles and transport them transversely.

3.3 Optimized Design: Geometry Parameters that Affect the Cell Labeler

According to Stroock et al[54], the amount of transverse flow that can be generated is one of the criteria of a labeler’s efficiency. There are several groove geometry parameters that influence the transverse flow, such as groove height, groove width, and total groove number.
3.3.1 Effect of Groove Height

We define a characteristic dimensionless parameter, the \textit{groove height to channel height ratio}
\begin{equation}
\alpha = \frac{h_g}{h} \tag{3.1}
\end{equation}
where \(h_g\) is the groove height and \(h\) is the channel height. Hassell and Zimmerman[29] observed the influence of the groove height to the transverse velocity in a staggered herringbone mixer (SHM) as well as the existence of an optimal groove height. The transverse flow speed is increased with an increase of \(\alpha\) but eventually reached a limit. This observation shows the possibility of an optimal groove height for the design of grooved cell labeler.

A simple way to visualize and compare the distribution of transverse velocity \(v\) is to plot its profile on a characteristic interface that represents the largest velocity field variation. The characteristic plane is chosen as the \(x-z\) plane, a center plane (3-D view in Figure 3.5) of the labeler which is the interface of two kinds of streams: cell sample stream and antibody stream. The mass exchange of the two streams on the \(x-z\) characteristic interface is strongest.

Figure 3.5 compares the transverse velocity profiles at the characteristic interface with different groove heights. Given a \(h = 30\mu m, W = 150\mu m\) channel, we set the variation of the groove height \(h_g\) from \(5\mu m\) to \(30\mu m\) with step length \(5\mu m\), which corresponds to the ratio \(\alpha = 0.17 - 1\). Other fixed parameters are the groove width \(W_g = 30\mu m\), 6 grooves per cycle, and the incoming average velocity \(\bar{u} = 1.1mm/s\).

Several conclusions can be drawn from the contours. First, the magnitude of transverse velocity is greatly enhanced by the increased groove height both inside and above the
Figure 3.5: The transverse velocity $v$ profiles on the x-z plane (3-D view) in a 1-cycle cell labeler with groove height $h_g = (a) \, 5\, \mu m$, (b) $10\, \mu m$, (c) $15\, \mu m$, (d) $20\, \mu m$, (e) $25\, \mu m$, (f) $30\, \mu m$, corresponding to $\alpha = 0.17, 0.33, 0.5, 0.67, 0.83, 1$. 
Figure 3.6: The absolute value of maximum transverse velocity $v_+$ and $v_-$ profile on the x-z plane in a 1-cycle cell labeler with $\alpha = 0.17, 0.33, 0.5, 0.67, 0.83, 1$.

grooves. Second, the fluid inside the grooves and above the grooves have opposite velocity direction. This is consistent with the velocity distribution in Figure 3.3 (b).

However, we notice that as the groove height increases, the peak value of the velocity $v$ levels off, plotted in Figure 3.6. We denote the absolute value of peak velocity above and inside the grooves as $|v_+|$ and $|v_-|$, respectively. It can be seen that the growth of $|v_+|$ is slowed when $\alpha > 0.67$. Moreover, $|v_-|$ slightly drops when $\alpha > 0.67$. These trends indicate that the improvement of transverse flow by solely adding groove height is limited when $\alpha > 0.67$.

To determine the optimum groove height, we would like to quantitatively measure the average transverse flow velocity. We define a scaled average transverse velocity $f_v$ by averaging the absolute velocity ratio $|v/\bar{u}|$ ($\bar{u}$ is the average inflow speed) onto the volume $V$
Figure 3.7: The scaled transverse velocity $f_v$ as a function of $\alpha$. The velocity growth is clearly slowed down when $\alpha > 0.67$.

The scaled velocity is plotted in Figure 3.7 as a function of $\alpha$ where the step length $\Delta \alpha = \frac{1}{6}$. This plot illustrates that the growth of $f_v$ is not linear but slows down as $\alpha$ increases. The increasing rate percentage of $f_v$ per $\Delta \alpha$ (per $5\mu m$ groove height growth) is measured by

$$I_{f_v,i+1} = \frac{f_{v,i+1} - f_{v,i}}{f_{v,i}} \times 100\%$$

where the subscript $i$ is an integer from 1 to 6 and represents the results that are obtained at a certain groove height $h_{g,i}$, while $i + 1$ represents the results at $h_{g,i+1} = h_{g,i} + 5\mu m$. The $f_v$ and $I_{f_v}$, corresponding groove height $h_g$, and ratio $\alpha$ are listed in Table 3.2. When $\alpha$ increases from 0.17 to 0.33, we obtain the highest $I_{f_v}$ (52.97%). When $\alpha \geq 0.67$, the
<table>
<thead>
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<th>Quantity</th>
</tr>
</thead>
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<tr>
<td>$i$</td>
<td>1</td>
</tr>
<tr>
<td>$h_g (\mu m)$</td>
<td>5</td>
</tr>
<tr>
<td>$\alpha = \frac{h_g}{h}$</td>
<td>0.17</td>
</tr>
<tr>
<td>$f_v (\times 10^2)$</td>
<td>2.25</td>
</tr>
<tr>
<td>$I_{f_v} (%)$</td>
<td>52.97</td>
</tr>
</tbody>
</table>

Table 3.2: Groove height to channel height ratio $\alpha$, scaled transverse velocity $f_v$, and percentage of transverse velocity increase $I_{f_v}$ per $\Delta \alpha$ corresponding to groove height $h_g$.

values of $I_{f_v}$ are very small, only about one-tenth of the highest $I_{f_v}$ (6.88% and 4.90%). The trend of transverse velocity increase appears to level-off (also see Figure 3.7), indicating that excessively increasing the groove height is not desirable when trying to increase the average transverse velocity.

Increasing transverse flow velocity in a cell labeler by deepening grooves individually is limited. This is because not all the regions in a groove are useful. The “dead zones” of fluid field occur at the corners of grooves where flow is hard to develop. The detail views in Figure 3.8 show that the deeper the grooves, the larger the dead zone. Thus over increased groove height is not only a waste of volume, but also adds to the risk that small particles such as antibodies can be trapped in the dead zones.

In conclusion, in a $h = 30 \mu m$ oblique groove cell labeler, the optimum value of groove height to channel height ratio is $\alpha \sim 0.67$, corresponding to the groove height $h_g = 20 \mu m$ (see Figure 3.5 (d)).

### 3.3.2 Effect of Groove Width

The evaluation of labeler efficiency based on measurement of transverse velocity also can be used to decide the optimum groove width. This time we fix the groove height as
Figure 3.8: Comparison of the transverse velocity distribution in cell labeler with (a) $h_g = 20\,\mu m$ and (b) $h_g = 30\,\mu m$ grooves. Higher grooves cause larger dead zones. The space of dead zones grow downstream.

$h_g = 20\,\mu m$. The groove width $W_g$ (see Figure 3.8) is defined as an axial length of the real groove width $W'_g$, $W_g = W'_g\cos(\theta) = \frac{1}{\sqrt{2}} W'_g$ where $\theta$ is the slant angle of the grooves. We vary $W_g$ with 10$\,\mu m$, 20$\,\mu m$ and 30$\,\mu m$.

The transverse velocity profiles at the characteristic interface with different groove widths are compared in Figure 3.9, along with the plot of the scaled average transverse velocity $f_v$. A rapid improvement of $f_v$ is found by enlarging the groove width. At $W_g = 10\,\mu m$, $f_v$ is very weak. At $W_g = 20\,\mu m$, $f_v$ is doubled while at $W_g = 30\,\mu m$ $f_v$ is nearly quadrupled. As a consequence, we can make the conclusion that in the range of $W_g \leq 30\,\mu m$, wider grooves increase the transverse velocity on an oblique groove cell labeler.

However, the groove width cannot be increased without limit. If we keep the total groove number constant and increase the groove width, the mixing length is increased.
Figure 3.9: Left: the transverse velocity $v$ profile on the x-z plane ($y = 0$) in a 1-cycle cell labeler with the groove width $W_g = (a)10 \mu m$, (b)20$\mu m$, (c)30$\mu m$. Right: (d) the scaled average transverse velocity $f_v$ as a function of $W_g$. The $f_v$ is rapidly increased by groove width growing.

Accordingly, which is what we want to avoid. Additionally, in a cell sample, there exists blood cells and cancer cells. Blood cells are small ($d_0 = 6 − 10 \mu m$) and can be transported by the grooves. Unlike blood cells, cancer cells are $3 − 7$ times large. Wider grooves may cause cancer cells sunked and trapped at the corners, not only blocking the grooves but also lowering cancer cell recovery rate. For these reasons, we want to keep $W_g \leq 30 \mu m$.

### 3.4 Dispersion Effect of Mixing Length in Multiple-cycle Parallel Pattern Cell Labeler

In practical applications, biological samples with suspended cells and suspended antibodies are released as two parallel streams into the cell labeler. The ultimate goal of increasing transverse velocity is to induce well-distributed antibody concentration along the cross-section of the labeler, resulting in an increased cell antibody collision frequency[57].
In this section, antibody distributions in different cross-sections are simulated to quantify
the enhancement of cell-antibody binding. Both the CFD module and the particle tracing
module of Comsol Multiphysics are used.

If we align several cycles of grooves parallel to each other, the pattern of the cell labeler
is named parallel pattern. To visualize the moving paths of cells and antibodies through the
parallel pattern cell labeler, we mark cells with large blue dots and antibodies with small
red dots. We also assumed that the ratio of cells to antibodies is approximately 1:100. The
influence of labeling length (or mixing length) of the channel (i.e. the cycle of grooves)
is also considered. We keep channel cross-section $30 \times 150 \mu m$ and groove cross-section
$30 \times 20 \mu m$, but add more cycles to the parallel pattern cell labeler.

Figure 3.10 gives the cell and antibody distributions at various cross-sections along a
parallel pattern cell labeler, i.e. at entrance (cycle 0), after 1 cycle, 3 cycles and 6 cycles.
We quantitatively measure the dispersing effect of the cell labeler as well as intuitively
reading the distribution profile. A clockwise particle trajectory is found in Figure 3.10.

Because of the large antibody to cell ratio, we treat the antibodies as a group. If we
choose the center of the channel cross-section as a reference point, the angular displace-
ment of the antibodies is given by the flare angle $\gamma_a$, measured from the region tip to the
region root. Initially $\gamma_a = 180^o$. When the flare angle $\gamma_a$ reaches $360^o$, antibodies will
be distributed in all four quadrants of the cross-section. Thus we use $\gamma_a = 360^o$ as a
measurement of good dispersion efficiency.

Cycle 0 represents the initial state of the cells and antibodies, distributed on opposite
halves of the channel. Intuitively, both cell 1 and cell 2 are outside of the flare angle $\gamma_a$.
When all the particles are passing the grooves, they start moving clockwise. After cycle
1, the flare angle $\gamma_a = 215^o$. Cell 1 is within the antibody group, allowing cell labeling to
Figure 3.10: Performance of the parallel pattern grooved cell labeler. Cell (blue) and antibody (red) distribution at the cross-section of entrance (cycle 0), after 1 cycle, 3 cycles and 6 cycles of grooves of parallel pattern cell labeler. The $\gamma_a$: the flare angle of the antibody-concentrated region. Channel cross-section $30 \times 150\mu m$, groove cross-section $30\mu m \times 20\mu m$. Cell to antibody concentration ratio: 1 : 100. Cell radius not to scale, antibody radius 0.5$\mu m$. 

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occur. Cell 2 is still outside of the flare angle, where binding is unlikely. Within 3 cycles of grooves, the flare angle $\gamma_a = 240^\circ$. The tip of antibody group has moved further, but the tail of antibody group also has had a clockwise movement so the antibodies still do not cover the whole cross-section. Thus we say the antibodies are further dispersed, but not well distributed. Cell 2 has moved onto the edge of the antibody group, where binding is likely. After cycle 6, the flare angle $\gamma_a = 360^\circ$ and the antibody group covers the whole cross-section. The concentration of antibodies is well dispersed. Both cell 1 and 2 are inside the antibody group. These results suggest that extending the labeling length greatly improves the labeling efficiency of a parallel pattern grooved cell labeler, which is similar to Wang and Yang’s observation of SHM and grooved mixer[30].

It should be noted that only after cycle 6 does $\gamma_a$ reach $360^\circ$. A conclusion can be made: adding cycles of grooves is more likely to enhance antibody dispersion in the $30 \times 150 \mu m^2$ parallel pattern cell labeler, and at least 6 cycles of grooves are preferred to ensure binding. A typical design is shown in Figure 3.11.

### 3.5 Cell Damage Test for Oblique Groove Cell Labeler

The rupture of a cell membrane occurs when large shear stress exists. This phenomena is called cell disruption. It is the main physical cause of cell death. Damage of suspended
Figure 3.12: Contours of shear stress $\tau$ on the surface of the grooves and plots of shear stress $\tau$ on different height. Curve: Plot along center line of the channel-groove interface. Colored dots: Plots with different depth inside of each groove.
cells due to shear stress has been investigated by Born et al.[58], giving the threshold cell
disruption shear stress range $200 - 700 \text{N/m}^2$ in laminar flow.

In a $30 \times 150\mu m$ channel cross-section, $30 \times 20\mu m$ groove cross-section cell labeler,
the shear stress of the bulk flow close to the channel-groove interface is plotted in Figure
3.12. The shear stress is reduced from $0.215 \text{N/m}^2$ upstream to $0.090 \text{N/m}^2$ above grooves,
and reaches the minimum of about $0.027 \text{N/m}^2$ at the half height of the grooves ($z =
-10\mu m$). The range of shear stress along channel-groove interface of the cell-labeler falls
in $0.089 - 0.279 \text{N/m}^2$ which is nearly 0.1% of the critical cell disruption shear stress. The
shear stress in the oblique groove cell labeler is unlikely to cause cell disruption.

3.6 Summary

In this chapter, three-dimensional models have been established to investigate the fluid
and particle transport in a cell labeler and help to design the oblique groove labeler. Cal-
culations show that the optimized groove height to channel height ratio $\alpha = \frac{h_g}{h} \sim 0.67$.
Also, increasing groove width improves labeling effect, yet groove width $W_g \leq 30\mu m$ to
prevent cancer cells becoming stuck. Thus we suggest using $30\mu m \times 20\mu m$ width by height
grooves in a $30\mu m$ channel height rectangular cell labeler. Meanwhile, total mixing length
also enhances labeling. At least six cycles of grooves are suggested in a parallel pattern
cell labeler.

Other parameters contributing to cell labeler efficiency include the oblique angle of the
grooves and alternative patterns of groove arrangement. These parameters will be opti-
mized in future work.
Chapter 4: Forces and Particle Transport

4.1 Force Distribution on a Particle or a Cell

In the COMSOL calculations presented in the previous chapter, the cell was modeled as a passive scalar in the three dimensional flow field defined. That is, it is assumed that there is no effect of the cell on the flow itself. Locally this is certainly not the case and in this chapter we analyze the forces on a cell and how the cell affects the flow through a body force term in the Navier-Stokes equations.

For the purpose of this chapter we refer to forces on a particle that includes a biological cell. Thus there are three objectives of this chapter:

1. To identify the several different forces that may act on a single particle or a single cell;

2. to elucidate how the particle/cell position and velocity may be calculated as a function of time;

3. and to show how the presence of the particle/cell affects the flow field through the body force term in the Navier-Stokes equations.

We begin by writing a force balance on a particle and identify the different forces on the particle. We then write the equation in dimensionless form to show that the acceleration
term in the equation is negligible. This allows the computation of the particle position and velocity as a function of time. For simplicity we restrict the discussion to one dimensional motion in a rectangular channel.

The types of forces on a particle moving in an electrically conducting fluid are divided into three groups: electrostatic force, magnetic force, and gravity (from external fields); Stokes drag and random force (from fluid particles); van der Waals force and electric double layer force (from the channel walls, summarized as DLVO force).

In addition, the companion experiments are exploring the use of magnetic fields to move cells and the nature of this force is explored from a theoretical perspective.

4.2 Forces from External Fields

The first group of forces includes all the forces generated by the external fields, denoted as $F_{\text{ext}}$. These forces include but are not limited to the electrostatic force, the magnetic force, and the force of gravity.

4.2.1 The Electrostatic Force

When an electric field $E$ is imposed on the system, an electrostatic force is induced on a particle in the form of

$$F_e = qE$$ (4.1)

where $q = \int_V \rho_e dV$ is the total electric charge of the particle ($\text{Coul}$) and $\rho_e$ is the volume charge density on a particle ($\text{Coul/m}^3$). The electric force density ($\text{N/m}^3$) is

$$f_e = \rho_e E$$
4.2.2 The Magnetic Force

A magnetic force exists when ferromagnetic materials and/or an artificially-controlled magnetic field are present in the system. A magnetic field is generated by the moving or the self-spinning of the electric charges, or the moving of the electric fields. The ferromagnetic materials that are most frequently used in the micro-scale magnetic particles are iron, magnetite and hematite[59].

In a magnetic field induced by current, the magnetic force density \( (N/m^3) \) on a particle is given by[60]

\[
f_m = \mathbf{J} \times \mathbf{B}
\]

where \( \mathbf{J} \) is the current density. The magnetic flux density \( \mathbf{B} = \mu_0(\mathbf{H} + \mathbf{M}) \) (measured in Tesla) is from the inducing source, where \( \mu_0 = 4\pi \times 10^{-7} (T \cdot m/A) \) is the permeability of a free space, \( \mathbf{H} \) is the magnetic field intensity defined as a modification of \( \mathbf{B} \) due to magnetic fields produced by material media, and \( \mathbf{M} \) is the induced volume density of the total magnetic moment for the magnetic fields (magnetization). With both an electric field

Figure 4.1: Geometrical relationship between an external magnetic field and a magnet.
and magnetic field in the system, the combination of the electric force and magnetic force
gives the Lorentz force \( (N/m^3) \)[4]

\[
f_L = \rho_e E + J \times B
\]  \hspace{1cm} (4.3)

and the total magnetic force \( F_m \) on a magnet is (the geometry see Figure 4.1, the derivation
see Appendix B)

\[
F_m = \int_V (M \cdot \nabla)BdV
\]  \hspace{1cm} (4.4)

The magnetic force between a single magnetic disc and a single magnetized particle/cell
are given in Appendix B. In a magnetic tweezer system, hundreds of magnetic discs are ap-
plied. The disc group generates a total magnetic force on the particle/cell with a maximum
magnitude of \( 10^3pN \), dominating the magnetized particle/cell motion in the tweezer.

4.2.3 Gravity

The force of gravity acts on biological cells and particles. This force is given by Newton’s Second Law, \( F_g = mg \), where \( m \) is the mass of the particle and \( g \) is the gravitational
acceleration towards the surface of the Earth. The force of gravity on a 300\( nm \) radius,
\( 10^3kg/m^3 \) density particle is \( 1 \times 10^{-3}pN \), while on a 5\( \mu m \) radius, \( 10^3kg/m^3 \) density cell
is \( 5pN \), such that the gravitational force \(| F_g | \ll | F_m | \).

4.3 Forces from Surrounding Fluid

The second group of forces comes from the fluid surrounding the particle, including the
random force and the friction force.
4.3.1 The Random Force

The phenomena where a suspended particle interacts with the surrounding fluid and causes a random drifting of the particle is called Brownian motion. The force exerted on the particle by fluid-particle interaction is called the random force, denoted as $R$. Unlike its name, the random force $\rho_R$ distributed on the particle’s surface is presumable by both numerical calculation and experimental measurement. For example the random force on a particle $k$ from the $j^{th}$ surrounding particles can be summed up by a Gaussian random process[61]

$$R_k = \sum_{j=1}^{N} \left[ A_j e^{\frac{2\pi i j k}{N}} + B_j e^{-\frac{2\pi i j k}{N}} \right]$$ (4.5)

where $N$ is the total number of interacting fluid particles, $A_j$ and $B_j$ are arbitrary constants chosen from Gaussian distribution, and $i = \sqrt{-1}$. Experimentally, Yuan et al[62] measured the Brownian motion force exerted on nano-scale particles in a static dilute solution and found the range to be $0.013 - 0.17 \mu N$. The Random force is much weaker compared to the applied magnetic force.

4.3.2 Stokes Drag

The interaction between the particle/cell and its surrounding viscous fluid induces a friction force, found by G. G. Stokes[63] and named Stokes drag. Padmavathi et al[64] and many others gave the Stokes drag for a sphere in the flow with mixed slip-stick boundary conditions as[64]

$$F_S = \begin{cases} 
4\pi \mu a (u_p - u) & \text{for slip boundaries} \\
6\pi \mu a (u_p - u) & \text{for no-slip boundaries}
\end{cases}$$ (4.6)

where $\mu$ is the fluid’s viscosity, $a$ is the radius of the cell, $u_p$ is the particle velocity, $u$ is the fluid velocity.
It is worth mentioning that the Stokes drag exists whenever a difference between the fluid speed and the particle/cell speed exists. In an equilibrium state, it balances any other external forces.

4.4 Forces from the Channel Walls

The third group of forces includes van der Waals attraction force and the electric double layer repulsion force. These are short range forces due to the charged surfaces (the channel walls), and are not usually considered in macro-scale models. According to the DLVO theory introduced in Chapter 1, the combination of the van der Waals and the EDL interactions gives the DLVO force

\[ F_{DLVO} = F_{vdW} + F_{EDL} \]

When the particle-wall separation distance \( D \leq 2a/3 \), it is necessary to consider van der Waals interaction and the electric double layer interaction between particle and wall. The results can be applied to biological cell-wall interaction since we consider cells as negatively charged colloidal particles, moving with electrolytes and placed near walls. Ai et al[43] have observed the increase of oscillatory motion of cylindrical cells when the height of channel decreases, and the reason was predicted as the dielectrophoretic effect from both the electric field and the channel walls. In this section we present results for the parameters of the Kazoe and Yoda [39] since the experimental data exists. In future work, we will apply the theory to the parameters typical of biological cell transport.

4.4.1 van der Waals Force

A particle moving near a channel surface fells van der Waals force: a sum of the attractive and repulsive molecular forces but not including the electrostatic interaction of
Figure 4.2: A spherical particle with radius $a$ close to an infinite flat plate, for both integration analysis of van der Waals attraction and electric double layer repulsion. The integration chooses the ring element $dS = 2\pi r dr$. (a) Derjaguin approximation assumes the particle surface is parabolic; (b) SEI method considers both hemispheres $ABA'$ and $ACA'$.

molecules[11]. B.V. Derjaguin developed a mathematical method in the 1930s to estimate the van der Waals force between spherical or flat surfaces that is termed the Derjaguin approximation[31]. The Derjaguin approximation is available to model the force between two surfaces, e.g. two flat walls, two spherical particles, or a spherical particle and a plane wall. We focus on the model of a spherical particle and a flat wall. According to macroscopic theories and experiments, the molecular interaction energy per unit area between two surfaces 1 and 2 is given by[65, 66]

$$E_{vdW}(z) = -\frac{A_H}{12\pi z^2}$$

(4.7)

where $z$ is the distance from a unit area on surface 1 to surface 2 (shown in Figure 4.2), $A_H = \pi^2 C \rho_1 \rho_2$ is the Hamaker constant and is approximately $A_H \sim 10^{-21} - 10^{-20} J$, the
constant $C$ is the coefficient in the particle-particle pair interaction, and $\rho_1$ and $\rho_2$ are the number densities of the interacting molecules 1 and 2. When $z \to \infty$, $E_{vdW}(z) \to 0$.

Given a particle having radius $a$ and a flat wall, Derjaguin specified that the interaction is confined to the minimum separation distance $D$ between the particle and the wall ($D \ll a$). The Derjaguin approximation integrates the van der Waals interaction energy per unit area on the particle, and assumes that the surface curve of the particle is parabolic (the dash line in Figure 4.2 (a)). The surface element is chosen as the circular ring with an area $dS = 2\pi r dr$ in cylindrical coordinates where $r$ is the radius of the element. The total surface energy of molecular interaction on a particle near a plane wall is thus

$$U_{vdW}^{DA}(D) = \int_S E_{vdW}(z) dS = 2\pi \int_0^\infty E_{vdW}(z) r dr$$

(4.8)

From the geometry shown in Figure 4.2 we have

$$z(r) \approx \frac{r^2}{2a} + D$$

Since

$$r dr = adz$$

equation (4.8) becomes

$$U_{vdW}^{DA}(D) = 2\pi a \int_D^\infty E_{vdW}(z) dz$$

(4.9)

From equation (4.7), this gives the interaction result of sphere-flat wall molecular interaction energy

$$U_{vdW}^{DA}(D) = -\frac{A_H a}{6D}$$

(4.10)

Differentiating the interaction energy $U_{vdW}^{DA}$ with respect to the separation $D$ gives the force in the Derjaguin approximation as

$$F_{vdW}^{DA} = -\frac{dU_{vdW}^{DA}}{dD} = -\frac{A_H a}{6D^2}$$

(4.11)
We need to point out that Derjaguin approximation did not consider the actual shape of the particle since it assumes the shape of the sphere is locally parabolic. Recently, the surface element integration (SEI) method was developed by Bhattacharjee et al.[68, 32]. The SEI method relaxes the assumption that all interactions are local and also makes the model more accurate. The interaction energy is integrated over the whole surface of the particle, i.e. the hemisphere $ABA'$ and $ACA'$ (see Figure 4.2 (b)), such that the total van der Waals attraction energy is

$$U_{vdW}^{SEI} = U_{ABA'} - U_{ACA'}$$  (4.12)

The surface element is again chosen as the circular ring with an area $dS = 2\pi r dr$ where $r$ is the radius of the element. The integrated form of the van der Waals attraction energy by SEI method is given by (Figure 4.2 (b))

$$U_{vdW}^{SEI} = \int_0^a E(f_r)_{ABA'} 2\pi r dr - \int_0^a E(f_r)_{ACA'} 2\pi r dr$$  (4.13)

where $E(f_r)$ is the energy per circular ring and the function $f_r$ represents the area (line integration) of the circular ring[68]

$$f_r(r) = \begin{cases} D + a - a \sqrt{1 - \frac{r^2}{a^2}} & \text{on surface } ABA' \\ D + a + a \sqrt{1 - \frac{r^2}{a^2}} & \text{on surface } ACA' \end{cases}$$  (4.14)

Performing the integration gives the sphere-flat plate interaction energy[68]

$$U_{vdW}^{SEI} = -\frac{A_H}{6} \left( \frac{a}{D} + \frac{a}{D + 2a} + \ln \left( \frac{D}{D + 2a} \right) \right)$$  (4.15)

The van der Waals attraction force between the sphere and the wall is calculated by

$$F_{vdW}^{SEI} = -\frac{dU_{vdW}^{SEI}}{dD} = -\frac{2a^3 A_H}{3D^2(2a + D)^2}$$  (4.16)

We note that the attractive energy has negative values and the repulsive energy has positive values. The scaled van der Waals attractive interaction energy $U_{vdW}/k_B T$ calculated
Figure 4.3: Comparison of scaled van der Waals interaction energy $U_{vdW}/k_BT$ calculated by SEI method (Eq. 4.15) and Derjaguin Approximation (Eq. 4.10) between a wall with surface potential $-130\,mV$ and particle with different radii and surface potentials (listed in Table 4.1).

by the SEI method (Eq. 4.15) and Derjaguin approximation (Eq. 4.10) are compared in Figure 4.3. Without considering the repulsion from the hemisphere $ACA'$ of particle, the Derjaguin approximation overestimated the van der Waals interaction energy[68]. van der Waals interaction energy increases rapidly as the particle-wall separation distance $D$ decreases, indicating the molecular interaction is effective only in a very short range. Calculated by the SEI method (Eq. 4.15), within $D \geq 0.05a$ the maximum value of van der Waals force on a particle with radius $110\,nm$ and surface potential $-60.6\,mV$ from a wall with surface potential $-130\,mV$ reaches approximately $4.6\,pN$.

4.4.2 The Electrostatic Double Layer Force

A particle’s surface or a channel wall may be charged by dissociation of surfaces or by adsorption of charged molecules (e.g. polyelectrolyte) from the surrounding solution,
establishing an electrical double layer (EDL) and inducing electrostatic repulsion between the charged particle and the wall. Hogg et al.[69] derived the energy per unit area based on the Derjaguin approximation by considering the interaction between double layers on spherical particles to be integrated from infinitesimally small parallel rings each of which can be considered as a flat plate (see Figure 4.2). The EDL interaction energy per unit area between surface 1 and 2 with scaled surface potential $\Phi_1$ and $\Phi_2$ is[69]

$$E_{EDL}(z) = \frac{\varepsilon e \kappa}{8\pi} (\Phi_1^2 + \Phi_2^2) \left[ 1 - \coth(\kappa z) + \frac{2\Phi_1 \Phi_2}{\Phi_1^2 + \Phi_2^2} \csch(\kappa z) \right]$$

(4.17)

where $\kappa = \frac{1}{\lambda}$ is the inverse Debye length, $\Phi = \nu e \zeta / k_B T$, $\zeta$ is the surface potential, $\nu$ is the valence, $\varepsilon_e$ is the permittivity of the solution, $k_B$ is the Boltzmann constant, $T$ is the temperature, $e = 1.6 \times 10^{-19} \text{Coul}$ is the unit charge. As with the van der Waals interaction, the EDL interaction energy between a spherical particle and a flat wall can also be calculated by Derjaguin approximation

$$U_{DA}^{EDL}(D) = 2\pi a \int_D^\infty E_{EDL}(z) dz$$

(4.18)

Performing the integration after substituting in the scaled surface potentials of particle and wall $\Phi_p$ and $\Phi_w$ ($p =$surface 1, $w =$surface 2), the double layer interaction energy between a particle and a flat wall has the expression

$$U_{DA}^{EDL}(D) = \frac{\varepsilon e a}{4} \left( \frac{k_B T}{\nu e} \right)^2 \left( \Phi_p^2 + \Phi_w^2 \right) \left[ \frac{2\Phi_p \Phi_w}{\Phi_p^2 + \Phi_w^2} \ln \left( \frac{1 + e^{-\kappa D}}{1 - e^{-\kappa D}} \right) + \ln(1 - e^{-2\kappa D}) \right]$$

(4.19)

the electrostatic force is given by

$$F_{DA}^{EDL}(D) = \frac{dU_{DA}^{EDL}}{dD} = -\frac{\varepsilon e a}{4} \left( \frac{k_B T}{\nu e} \right)^2 \left( \Phi_p^2 + \Phi_w^2 \right) \left( \frac{2\Phi_p \Phi_w}{\Phi_p^2 + \Phi_w^2} e^{\kappa D} - 1 \right) \left( \coth(\kappa D) - 1 \right)$$

(4.20)

The electric double layer force increases as the particle approaches the wall ($D$ decreases). Using the parameters from Kazoe and Yoda (2011), given the permittivity of water $\varepsilon_e =$
7.08 \times 10^{-10} \text{Farad/m}, the wall surface potential $\zeta_w = -0.130V$, the reciprocal Debye length $\kappa = 10^8 m^{-1}$, and within $D \geq 0.05a$, the maximum value of the EDL force reaches $40 pN$ on a particle with radius $a = 110 nm$ and surface potential $\zeta_p = -0.060V$.

The surface element integration method mentioned in the previous section is also applicable in estimating the electric double layer interaction energy and force. The EDL energy using SEI method (equation (4.13) is solved numerically by Bhattacharjee and Elimelech[68] and the results show considerable difference when compared with the Derjaguin approximation.

### 4.5 Wall-Particle Interaction Energy

van der Waals interaction (molecular interaction) and the electric double layer interaction exist when two charged surfaces approach each other, without the support of external electric field. According to the DLVO theory, the net surface-surface interaction energy is the superposition of the van der Waals attraction and electric double layer repulsion energies

$$U_{net} = U_{vdW} + U_{EDL} \quad (4.21)$$

The scaled van der Waals energy $U_{vdW}/k_B T$ (attractive, calculated by equation (4.15)) and the electric double layer energy $U_{EDL}/k_B T$ (repulsive, calculated by equation (4.19)) for a particle moving near a single wall are plotted in Figure 4.4 (a), while the net energy $U_{net}/k_B T$ calculated by equation (4.21) is plotted in (b). The wall surface potential is $\zeta_w = -130 mV$. The concentration of sodium tetraborate/nanopure water solution is $1.0 mM$. The experimental temperature is $292.35 K$. The properties of the particles used in the Kazoe and Yoda[39] experiments are listed in Table 4.1.
Figure 4.4: The scaled energy as a function of the particle-wall separation $D$, (a) van der Waals energy (using SEI method, attractive) and electric double layer energy (using Derjaguin approximation, repulsive), (b) the net energy for a particle moving near a single wall. The particle radii and surface potentials refer to Table 4.1. $\zeta_w = -130mV$.

<table>
<thead>
<tr>
<th>Material</th>
<th>Polystyrene (PS)</th>
<th>Silica ($SiO_2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radius $a$ (nm)</td>
<td>110</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>371</td>
<td>461</td>
</tr>
<tr>
<td></td>
<td>463</td>
<td></td>
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<tr>
<td>$\zeta$-potential (mV)</td>
<td>$-60.6$</td>
<td>$-57.4$</td>
</tr>
<tr>
<td></td>
<td>$-96.2$</td>
<td>$-99.9$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$-91.7$</td>
</tr>
</tbody>
</table>

Table 4.1: Properties of polystyrene and silica particles in experiment, from Kazoe and Yoda (2011).
When the minimum distance between particle and wall is very small, $U_{EDL} \gg U_{vdW}$ and $U_{net} > 0$. Therefore the repulsive electric double layer energy dominates the wall-particle interaction. As the minimum distance $D$ increases, the EDL interaction energy decreases much faster than van der Waals energy. The net energy (DLVO energy) decreases as $D$ increases and approaches zero at $D \approx 60\text{nm}$. As $D$ increases, $U_{EDL} < U_{vdW}$, $U_{net} < 0$, the molecular attraction (van der Waals attraction) becomes the dominant. The nonlinear variation of net energy indicates the synergistic effect of van der Waals attraction and electric double layer repulsion between a wall and a particle.

Kazoe and Yoda[39] have observed that the particle number density reaches a maximum value when the particle-wall separation $D$ decreases, then rapidly drops in the range when particle-wall separation $D < 70\text{nm}$ (not shown). The scaled potential of particle-wall interaction of three types of polystyrene particles with radii $a = 110\text{nm}$, $240\text{nm}$, and $461\text{nm}$ (for corresponding surface potentials see Table 4.1) are measured by Kazoe and Yoda in Figure 4.5 (a)[39], showing a rapid drop of the total interaction energy as the separation $D$ decreases, and a slight recovery of total energy at $D > 70\text{nm}$. The vertical dash lines refer to the corresponding particle radii $a$.

We can calculate the wall-particle interaction energy of a single particle qualitatively by DLVO approach as discussed above. The scaled DLVO energies of the same types of particles as the experiments are calculated by continuum equations (4.21, 4.15 and 4.19), and plotted in Figure 4.5 (b).

Comparing Figure 4.5 (a) and (b), a similar energy variation trend is found in theoretical calculation and experimental results, showing a strong increase of repulsive energy when a particle approaches the wall. This indicates the synergistic effect of van der Waals attraction
and electric double layer repulsion between wall and particle surface could be the primary cause of the particle number density drop near wall.

Moreover, a minimum energy position for all three types of particles is clearly shown by the analytical solutions at particle-wall separation \( D \approx 70 \text{nm} \) \((D \approx 80 \text{nm} \text{ for } a = 461 \text{nm})\) particle). At the lowest energy positions the total force acting on the particle yields \( F = \frac{dU}{dD} = 0 \) while before and after the lowest energy point the value of forces on the particle are both greater than zero, indicating the minimum energy positions are the most stable position for corresponding particles. Surprisingly, the minimum energy separations \( D \approx 70 - 80 \text{nm} \) calculated by our simulation is very close to the separation at the peak particle number density that are observed by Kazoe and Yoda[39].

It is noticeable in the analytical plots that the van der Waals attraction shows a stronger effect on bigger particles, and the minimum net energy is lower, while the experimental data does not show great difference between different particle radii, the reason of which is unknown. Thus comparison to Molecular Dynamics (MD) simulation results are needed to look into non-DLVO forces and verify the DLVO approach to the effect of the walls on the particle and cell motions.

### 4.6 Force Balance on a Particle/cell

The summary of possible forces on a particle or on a biological cell are listed in Table 4.2. In this chapter, biological cell transport is treated as a particular example of particle transport. In what follows we neglect the excluded volume effect except for the fluid thickness \( d \) around a particle or a cell. We also assume in a dilute particle solution (or dilute cell sample) and there are no particle interactions. Thus the equation of motion \( ma = F \) for a
Figure 4.5: The scaled particle-wall interaction potential energy of (a) experimental data from Kazoe and Yoda (2011) and (b) DLVO approach using Derjaguin approximation, as a function of the particle center-wall distance $H$ ($H = D + a$) with particle radii $a = 110\,nm$, $240\,nm$, $461\,nm$. The corresponding particle surface potentials refer to Table 4.1. $\zeta_w = -130mV$. 
<table>
<thead>
<tr>
<th>Force</th>
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<th>Origin</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stokes drag</td>
<td>fluid</td>
<td>speed difference</td>
<td>$F_S$</td>
</tr>
<tr>
<td>Random</td>
<td></td>
<td>Bowmann motion</td>
<td>$R$</td>
</tr>
<tr>
<td>DLVO</td>
<td>wall</td>
<td>molecule interaction</td>
<td>$F_{DLVO}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electric double layer</td>
<td>$F_{vdW}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electric field</td>
<td>$F_{EDL}$</td>
</tr>
<tr>
<td>External field</td>
<td>electromagnetic field</td>
<td>electric field</td>
<td>$F_{ext}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>magnetic field</td>
<td>$F_m$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gravity field</td>
<td>$F_g$</td>
</tr>
</tbody>
</table>

Table 4.2: Summary of forces on a particle.

The particle's position at any time $t$ is (vectors are noted in bold)

$$m\frac{d^2\mathbf{X}(t)}{dt^2} = F_{ext}(t) + \beta \left[ \bar{u}(\mathbf{X}(t), t) - \frac{d\mathbf{X}(t)}{dt} \right] + R(t) + F_{DLVO}(t) \quad (4.22)$$

where $\mathbf{X}(t)$ is the location of the particle at time $t$ (seen in Figure 4.6 in the former section), and $\frac{d\mathbf{X}(t)}{dt}$ is the particle velocity $\mathbf{u}_p$. The velocity of the fluid is estimated by the weighted average fluid velocity $\bar{u}$ surrounding the particle, integrated over the spherical fluid volume $V_i$

$$\bar{u}(\mathbf{X}(t), t) = \frac{1}{V_i} \int \mathbf{u}(\mathbf{x}, t) \delta_d(\mathbf{x} - \mathbf{X}(t))dV_i \quad (4.23)$$

where $\mathbf{X}(t)$ is the particle position at time $t$, $\mathbf{x} = (r, \theta, \phi)$ is a point in the fluid (seen in Figure 4.6), $dV_i = r^2 \sin \theta dr d\theta d\phi$ for a sphere (seen in Figure 4.7), and $\delta_d$ is the weighting function defined by spreading the force out over a fluid volume of thickness $d$ around the solute particle. The function $\delta_d$ can be any approximation to the Dirac function, for example, a 1-D Gaussian sequence

$$\delta_d(x) = \frac{1}{d\sqrt{\pi}} e^{-\frac{x^2}{d^2}} \quad \text{as } d \to 0$$

For an infinite small thickness, $\lim_{d \to 0} \delta_d(x) = \delta(x)$, where in 3-D Cartesian coordinates

$$\delta(x) = \delta(x, y, z) = \begin{cases} +\infty & \text{if } x^2 + y^2 + z^2 = 0 \\ 0 & \text{if } x^2 + y^2 + z^2 \neq 0 \end{cases} \quad (4.24)$$
Figure 4.6: Vector displacement $\mathbf{X}$ of a solute particle $i$ and vector location $\mathbf{x}$ of an arbitrary fluid point, Cartesian coordinates. The position of a point in fluid volume is also defined in spherical coordinates, $\mathbf{x} = (r, \theta, \phi)$.

Figure 4.7: A solute particle (radius $a$) and fluid (thickness $d$) surrounding it, spherical coordinates. The fluid volume element $dV_i = r^2 \sin \theta dr d\theta d\phi$. 

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\[ \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \delta(x, y, z) \, dx \, dy \, dz = 1 \]  

(4.25)

Dimensional analysis is applied to identify the magnitude of the forces in the equation. Dimensional analysis is able to provide reduced parameters for experiments, to assist with the scale-up of microscopic devices, and to investigate the characteristics of the devices[70]. We choose the velocity scale \( U_0 \) as the average bulk flow velocity in a channel. Thus the dimensionless velocity is given by \( \bar{u}^* = \frac{u(X(t), t)}{U_0} \). The dimensionless particle displacement in each of the coordinate directions is defined as \( X^* = \frac{X}{L} \) where \( L \) is the channel length. The dimensionless time is \( t^* = \frac{t}{t_0} \) within scale \( t_0 = \frac{L}{U_0} \).

We may also define the force scale \( \beta U_0 = 6\pi \mu a U_0 \). Therefore all the forces now can be represented by a dimensionless force ratio in the form of \( F^* = \frac{F}{\beta U_0} \). Equation (4.22) can be rewritten in a dimensionless form (the * is dropped) as

\[ \epsilon^2 \frac{d^2 X(t)}{dt^2} = \left[ \bar{u}(X(t), t) - \frac{dX(t)}{dt} \right] + F_{\text{ext}} + R(t) + F_{DLVO} \]  

(4.26)

It is observed that the particle mass \( m \), bulk velocity \( U_0 \), channel length \( L \) and friction coefficient \( \beta \) are summed up by a single parameter - the dimensionless acceleration coefficient, \( \epsilon^2 = \frac{m U_0}{\beta L} \). For instance, a cell is transported in a micro-scale channel. If we choose the channel length \( L = 8mm[53] \), cell radius \( a \sim 5\mu m \) (the size of human blood cells), cell density \( 10^3 \text{kg/m}^3 \), flow speed \( U_0 = 1mm/s \), and fluid viscosity \( \mu = 10^{-3} Pa \cdot s \), the coefficient \( \epsilon \sim 10^{-4} \). Thus the acceleration term is negligible. The magnitude of the forces are listed in Table 4.3.

One application of the force balance analysis is the simulation of biological cell transport in a uniform magnetic field in which the movement of a magnetized biological cell is dominated by the external magnetic field. In some cases, a constant magnetic field in both
<table>
<thead>
<tr>
<th>Force</th>
<th>Symbol</th>
<th>Magnitude (pN)</th>
<th>Importance to cell motion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random</td>
<td>$R$</td>
<td>$0.013 - 0.17$</td>
<td>Secondary</td>
</tr>
<tr>
<td>van der Waals</td>
<td>$F_{vdW}$</td>
<td>$&lt; 4.6$</td>
<td>Secondary</td>
</tr>
<tr>
<td>EDL</td>
<td>$F_{EDL}$</td>
<td>$&lt; 40$</td>
<td>Secondary</td>
</tr>
<tr>
<td>Magnetic</td>
<td>$F_m$</td>
<td>$\sim 10^4$</td>
<td>Primary</td>
</tr>
<tr>
<td>Electrostatic</td>
<td>$F_e$</td>
<td>$\sim 10^3$</td>
<td>Primary</td>
</tr>
<tr>
<td>Gravity</td>
<td>$F_g$</td>
<td>$&lt; 5$</td>
<td>Secondary</td>
</tr>
<tr>
<td>Stokes drag</td>
<td>$F_S$</td>
<td>$\sim 10^4$</td>
<td>Primary</td>
</tr>
</tbody>
</table>

Table 4.3: Summary of the order of magnitude of forces on a cell ($a = 5\mu m$). The van der Waals force and EDL force are calculated in the separation range $D \geq 5.5nm$. The secondary forces are much smaller than the primary forces.

The magnitude and direction is established to enhance the flux of the magnetized particles/cells through micro-scale channels. When the system has reached an equilibrium, the forces acting on the cell are in balance. Figure 4.8 is a sketch of a particle moving in a rectangular channel with an axial magnetic field $B$. The magnetic field can be established by adding two opposite magnetic poles at the inlet and outlet. In equilibrium, magnetic force $F$ has the same direction of magnetic flux density $B$.

According to Table 4.3, the random force and the force of gravity on a single cell are negligible, and DLVO forces are neglected. Thus the only axial forces are the magnetic force and the Stokes drag, and is at equilibrium, the magnetic force and the Stokes drag balance each other and yield

$$F_m = -F_S$$

Since the forces and displacement terms are time independent at equilibrium, using equation (4.26) in the x-direction with the random force and the DLVO force term removed solves the magnetized cell/particle migration velocity in uniform magnetic field

$$\frac{dX}{dt} = \bar{u} + F_m$$  \hspace{1cm} (4.27)
Figure 4.8: Force distribution on a particle inside of a rectangular channel with a uniform magnetic field of steady state. The magnetic force $F_m$ and Stokes drag $F_S$ act in the horizontal direction while van der Waals force $F_{vdW}$ and the electric double layer force $F_{EDL}$ act in the vertical direction. The direction of $R$ is random.

where $\bar{u}$ is the average bulk flow velocity through the channel. The magnetic field adds the scaled force $F_m$ to the scaled bulk flow velocity. Thus given a constant bulk flow velocity, the velocity of a magnetized cell increases as the magnetic force increases, which creates the possibility of sorting magnetized cells by using a micro-scale slit pore as a track and applying an axial magnetic field. The magnetically-labeled cells are more likely to move faster when moving with unlabeled cells along the track.

### 4.7 Effect of a Particle/cell on Fluid Velocity

Since the acceleration term in equation (4.26) is negligible, separating forces given by the fluid from forces given by other objects (e.g. channel walls and external fields) gives the force balance equation

$$\left[ \frac{dX(t)}{dt} - \bar{u}(X(t), t) \right] - R(t) = F_{\text{ext}}(t) + F_{\text{DLVO}}(t)$$

(4.28)

The Navier-Stokes equation describing the fluid momentum without external forces has been given in Chapters 2 and 3. Now we add the external force terms and obtain the
Navier-Stokes equations locally near a fluid particle in the form

\[
\rho \left[ \frac{\partial \mathbf{u}(\mathbf{x}, t)}{\partial t} + (\mathbf{u}(\mathbf{x}, t) \cdot \nabla) \mathbf{u}(\mathbf{x}, t) \right] + \nabla p = \mu \nabla^2 \mathbf{u}(\mathbf{x}, t) + \mathbf{F}
\]  

(4.29)

where the fluid velocity \( \mathbf{u}(\mathbf{x}, t) \) is dependent on the fluid position \( \mathbf{x} \) and time \( t \), \( \rho \) is the fluid density and \( \nabla p \) is the pressure gradient. For incompressible flow we have

\[
\nabla \cdot \mathbf{u}(\mathbf{x}, t) = 0
\]  

(4.30)

The term \( \mathbf{F} \) on the right side of equation (4.29) is the sum of all the forces acting on the surrounding fluid, i.e. the Stokes drag from the particle-fluid friction and the random force from the particle Brownian motion.

The external force \( \mathbf{F} \) for a collection of particles with the weighted 3-D delta function \( \delta_d \left( \mathbf{x} - \mathbf{X}_i(t) \right) \). The mutual forces of action and reaction between the particle and surrounding fluid are equal, opposite and collinear (e.g. \( \mathbf{F}_{p\rightarrow f} = -\mathbf{F}_{f\rightarrow p} \) where the subscript \( f \) is the fluid and \( p \) is the particle). Thus \( \mathbf{F} \) is given in dimensional form

\[
\mathbf{F} = \sum_{i=1}^{N} \delta_d \left( \mathbf{x} - \mathbf{X}_i(t) \right) \left[ \beta \left( \frac{d\mathbf{X}_i(t)}{dt} - \bar{\mathbf{u}}(\mathbf{X}_i(t), t) \right) - \mathbf{R}_i(t) \right]
\]  

(4.31)

where the subscript \( i \) represents the \( i^{th} \) particle. In this example, we choose the solute particle radius \( a \) as the length scale. Considering the delta function, the dimensionless force is (* dropped)

\[
\mathbf{F} = \sum_{i=1}^{N} \delta_d \left( \mathbf{x} - \mathbf{X}_i(t) \right) \left[ \left( \frac{d\mathbf{X}_i(t)}{dt} - \bar{\mathbf{u}}(\mathbf{X}_i(t), t) \right) - \mathbf{R}_i(t) \right]
\]  

(4.32)

Substituting equation (4.28) into equation (4.32) yields

\[
\mathbf{F} = \sum_{i=1}^{N} \delta_d \left( \mathbf{x} - \mathbf{X}_i(t) \right) \left[ \mathbf{F}_{ext,i}(t) + \mathbf{F}_{DLVO,i}(t) \right]
\]  

(4.33)

To further reduce parameters in momentum equation (4.29), Reynolds number \( Re_a = \frac{\rho U_0 a}{\mu} \) is introduced. We also introduce the geometry factor \( f = 6\pi \), scaled pressure \( p^* = \)
\( \frac{P}{\mu U_0} \) for small Reynolds number, and scaled time \( t^* = \frac{t}{a/U_0} \). Thus the dimensionless Navier-Stokes equation becomes

\[
Re_a \frac{Du(x,t)}{Dt} + \nabla p - \nabla^2 u(x,t) = f \sum_{i=1}^{N} \delta_d(x - X_i(t)) \left[ F_{ext,i}(t) + F_{DLVO,i}(t) \right]
\] (4.34)

In micro devices \( Re_a \ll 1 \); for example, with \( a = 2.5 \times 10^{-5} \text{m}, \rho = 10^3 \text{kg/m}^3, \mu = 10^{-3} \text{kg/(s \cdot m)}, \) and \( U_0 = 1 \text{mm/s}, Re_a \sim 10^{-2} \). Thus it is possible to neglect the fluid inertia. Equation (4.34) becomes

\[
\nabla p - \nabla^2 u(x,t) = f \sum_{i=1}^{N} \delta_d(x - X_i(t)) \left[ F_{ext,i}(t) + F_{DLVO,i}(t) \right]
\] (4.35)

We can use equation (4.35) and the continuity equation to determine the fluid velocity \( u \) and the pressure \( p \).

### 4.8 Summary

It is informative to estimate the range of external forces acting on a biological cell or a particle and predicting the cell/particle motion. According to the dimensional calculations, we are able to divide all the forces into two groups by magnitude: the primary forces dominating the magnetic cell/particle transport, including the magnetic force, the electric force and the Stokes friction force; and the secondary forces which have a minor influence on the cell motion, including the random force, gravity, van der Waals attraction force, and the EDL repulsion force.

The van der Waals energy (molecular interaction) is calculated by both Derjaguin approximation and surface element integration method, showing the SEI method is more accurate than the Derjaguin approximation. The EDL energy and force are estimated by Derjaguin approximation. The van der Waals attractive energy and electric double layer repulsive energy both affects the wall-particle interaction, while the net energy changes from
repulsive to attractive at the wall-particle separation $D \approx 60\text{nm}$. A minimum net energy is obtained at $D \approx 70\text{nm}$ where the total force exerted on the particle is zero. This separation is the stable position and is close to the peak particle number density position observed by Kazoe and Yoda (2011).

Dividing by the sources who give the forces, we obtain three groups of forces: the magnetic force, electric force and gravity which are the external forces given from the system fields; the Stokes drag and the random force which are given from the surrounding fluid; the van der Waals force and the EDL force which are from the surface-surface interaction. If all the forces on the particle/cell reach a balance, the forces of external field/surfaces toward particles are transferred to the forces between the particles and their surrounding fluid. When forces given from the external field/surfaces are known, the fluid velocity and the pressure gradient can be determined. The example of force balance model in a constant external magnetic field is given, showing that the speed of the magnetically-labeled cell increases as the magnetic force increases. The expression of magnetic force between a magnetic disc and a magnetized particle (or a labeled cell) are in Appendix B, and is applicable to the future study of magnetic tweezers.
Chapter 5: Electrophoretic Motion of a Single Particle or Cell

5.1 Introduction

Many conditions require an external electric field to enhance charged particle movement in micro or nano-scale channels. Such applications includes water purification, drug delivery, and cell transport by weak electric field. Cells are usually negatively charged because they have a semi-permeable membrane which can not let ATP, organic acids, and other negative molecules inside the cells through. Meanwhile, the PBS solution is hydrolyzed into ions such as $Na^+$, $K^+$, $Cl^-$, $HPO_4^{2-}$, $H_2PO_4^-$, forming the electric double layers on the cell surface and channel surfaces such that the motion of cells can be affected.

In this chapter a theoretical model is developed to describe the transport of particles or cells traveling through micro/nano channels with electric field $E$ existing in the system. These calculations are compared against experimental and previous theoretical results and good agreement is found. Moreover, we complement our theoretical research by performing continuum and atomistic simulations of biological cells surrounded by electrolytes and placed near walls. Surprisingly, the results show that wall effects on electrokinetic motion are weak.
5.2 Electrophoretic Transport of Particles and Cells

Chen et al[71] have developed an electrophoretic model for a long DNA strand passing through a nano-channel. A similar model can be applied to cells and particles. The cells, in general, are considered as colloidal spheres. The diameter of biological cells is $6 - 180 \mu m$; the diameter of antibodies is $100 - 500 \mu m$. The $\zeta$-potential of breast cancer cells is approximately $-20 mV$ to $-40 mV$. The channel walls are also negatively charged.

An electrokinetic model is first applied to polystyrene beads and silica particles (see Figure 5.1). The surface potential $\zeta_p$ for polystyrene beads is $-57.4 mV \sim -99.9 mV$ and for $SiO_2$ particles is $-91.7 mV$[39]. The channel walls have negative charge of $-130 mV$. Consider the case where polystyrene beads enter the channel near the boundaries. Due to the electrostatic forces generated by the negatively charged channel, a negatively charged particle tends to move to the anode at the electrophoretic velocity ($u_{ep}$) relative to the fluid flow. Note that the particle velocity ($u_p$) depends on the electroosmotic flow velocity ($u_{eo}$) and the particle electrophoretic velocity ($u_{ep}$) as

$$ u_p = u_{eo} + u_{ep}. \quad (5.1) $$

The electrophoretic velocity of a single particle with radius $a$ and Debye layer thickness $\lambda_p$ can be calculated by Debye-Hückel expression[72]

$$ u_{ep} = \frac{2 \varepsilon_0 \zeta_p}{3 \mu} E \quad \text{at } \lambda_p >> a \quad (5.2) $$

and by Helmholtz-Smolukowski expression[73]

$$ u_{ep} = \frac{\varepsilon_0 \zeta_p}{\mu} E \quad \text{at } \lambda_p << a \quad (5.3) $$

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Figure 5.1: Electrokinetic motion of a negatively-charged particle near a negatively-charged wall. The $u_{eo}$ is the velocity of the electroosmotic flow; $u_{ep}$ is the particle electrophoretic motion speed.

It is clear that the cell motion is influenced by the ratio of Debye layer thickness to particle radius

$$\varepsilon = \frac{\lambda_p}{a}$$

Based on both Smolukowski’s equation and Debye-Hückel expression, Henry[74] derived the correction formula of the velocity $u_{ep}$ of a charged particle driven by electric field in the absence of walls, considering larger range of $\varepsilon$. Henry’s Law for the particle electrophoretic velocity is given by

$$u_{ep} = \frac{\varepsilon eE\zeta_p}{4\pi\mu} \left(1 - 3\varepsilon + 25\varepsilon^2 - 220\varepsilon^3 + \ldots\right) \quad (5.4)$$

for $\varepsilon < 0.04$, and

$$u_{ep} = \frac{\varepsilon eE\zeta_p}{6\pi\mu} \left(1 - \frac{1}{16\varepsilon^2} - \frac{5}{48\varepsilon^3} - \frac{1}{96\varepsilon^4} + \frac{1}{96\varepsilon^5} - \left(\frac{1}{8\varepsilon^4} - \frac{1}{96\varepsilon^6}\right) e^{\frac{1}{2}} \int_{\infty}^{1/2} \frac{e^{-t}}{t} dt \right) \quad (5.5)$$

for $\varepsilon > 0.2$, where $E$ is the applied electric field, $\varepsilon_e$ is the solution permittivity, $\mu$ is the fluid dynamic viscosity. The full numerical solution is given by O’Brien and White (1978).
Henry’s equation is simplified by Masliyah and Bhattacharjee’s curve fit[75]

\[ u_{ep} = \frac{2\varepsilon e \zeta p E}{3\mu} \left( \frac{3}{2} - \frac{1}{2(1 + A\varepsilon - B)} \right) \] (5.6)

where A=0.072, B=1.13.

To provide evidence that the wall effects are negligible, particle electrophoretic velocity calculated by Henry’s solution has been compared with experimental data by Yoda et al[76]. A 38µm × 306µm × 1mm (height×width×length) channel with −130mV surface ζ-potential is used in both the experiments and the model. The concentration of sodium tetraborate/nanopure water solution \( C_0 \) is 1.0mM. The experimental temperature is 19.2°C. The properties of particles are seen in Table 4.1.

Both the experiment data and the analytical results of particle velocity are plotted in Figure 5.2. The analytical solutions of particle velocity calculated by Henry’s formula are very close to experimental results for polystyrene particle diameters 742nm and 922nm, and for silica particle diameter 926nm. The absolute values of the analytical electrophoretic velocities of particles are slightly lower than experimental results for the 220µm polystyrene beads. These results suggest that wall effects are negligible.

5.3 Wall Effect on Cell and Particle Electrophoretic Velocity

To further show the wall influence on particle electrophoretic motion is negligible, we first define a geometric scale

\[ \eta = \frac{a}{H} \]

where a is the particle radius and \( H = D + a \) is the distance from wall to particle center. The particle velocity is given by the Keh and Anderson’s[77] expression for the velocity of
Figure 5.2: Electrophoretic velocity of particles calculated by Henry’s formula compared with experimental data. The experimental data and analytical results fit well. The diamonds, circles and squares along with the * are the experimental data(Table 4.1). The solid lines are Henry’s Law.
a colloidal particle moving near a single wall or a slit pore

\[ u_p = \frac{\varepsilon_e E}{\mu} (\zeta_p - \zeta_w) f(\eta) \]  

(5.7)

where \( f(\eta) \) is the correction function. For article or biological cell moving near a single wall the correction function is

\[ f(\eta) = 1 - \frac{1}{16} \eta^3 + \frac{1}{8} \eta^5 - \frac{31}{256} \eta^6 + O(\eta^8) \]  

(5.8)

and for the particle velocity in a slit pore (two parallel walls) is

\[ f(\eta) = 1 - 0.268\eta^3 + 0.338\eta^5 - 0.04\eta^6 + O(\eta^8) \]  

(5.9)

The correction function \( f(\eta) \) is plotted in Figure 5.3, showing a slight wall effect as \( \eta \) increases. The wall effect is larger in the slit pore than near the single wall.

The particle velocity \( u_p \) is calculated from equation (5.7) and plotted in Figure 5.4 (a) with the range of the distance \( H = 1.4\mu m - 20\mu m \). The radius of the chosen particle is 500nm. An electric field with an intensity \( E = 15V/cm \) is applied. Results have been
Figure 5.4: Migration velocity as a function of $\eta = \frac{a}{H}$ with the effect of a single wall and a slit pore for (a) a polystyrene particle with radius 500nm and the particle center-wall distance $H = 1.4\mu m - 20\mu m$; (b) a biological cell with radius 15$\mu m$, $H = 50\mu m - 270\mu m$. The velocity does not change much on the range of $0 \leq \eta \leq 0.6$.

produced for values of the $\zeta$-potential of the particle and wall $-60mV$ and $-130mV$, respectively. The thickness of electric double layer on the wall surface is estimated to be 9.6$nm$. A small change is observed in the velocity distribution of a particle near a single wall (decreasing from 72.9$\mu m/s$ to 72.2$\mu m/s$) and in the particle velocity distribution in a slit pore (decreasing from 72.9$\mu m/s$ to 70.5$\mu m/s$) in the range of $\eta = 0.1 - 0.6$, which suggests that the wall effect on particle motion parallel to the surface is relatively weak.

Similarly, velocity distributions $u_c$ of the biological cell (radius $a = 15\mu m$) near a single wall and inside a slit pore ($H = 50\mu m - 270\mu m$) are calculated in Figure 5.4 (b), also using Keh and Anderson’s formulas. A weak electric field with $E = 5V/cm$ is applied since cells are sensitive to large electric field. The $\zeta$-potential of the particle and wall are $-20mV$ and $-70mV$ respectively. The thickness of electric double layer on the wall surface is estimated to be 6.5$nm$. Both distributions (17.2$\mu m/s - 17.4\mu m/s$ near a
single wall and $16.8\mu m/s - 17.4\mu m/s$ in a slit pore) in the range of $\eta$ show that the wall effect on cell motion parallel to the surface is weak.

### 5.4 Summary

We have used a simple model to describe the electrokinetic transport of cells and particles in micro- and nano-channels, and investigated the effect of charged channel walls on different size of particles as the imposed external electric field, the particle-wall distance and the particle surface charge are varied. The analytical solutions of particle electrophoretic motion speed by Henry’s formula (considering no wall effect) is very close to the experimental results from Kazoe and Yoda[39]. Keh and Anderson[77] gave a formula for correction of the particle velocity considering the wall effect and results show the wall effect is relatively weak.

In theoretical calculations, we are not able to include the complex dynamic interplay between solid-liquid interfaces, geometrical heterogeneities, long and short range forces, and ions. Therefore in the future work of this study, we hope to conduct comparison to Molecular Dynamics (MD) simulation results in order to improve our analysis of the effect of the proximity of walls on the particle and cell motions in micro and nano confined electrolytes.
Chapter 6: Osmotic Pressure

6.1 Introduction

In this chapter the effect of solute particles on the surrounding fluid is studied to describe the role of the semi-permeable membrane in generating osmotic pressure and mass transport through the membrane. Figure 6.1 (a) is a macroscopic view of an osmotic pressure equilibrium generated by a semi-permeable membrane placed at the boundary of two reservoirs. The left reservoir is filled with a dilute solution containing solute particles (spherical with radius \( a \)) while the right reservoir is pure water. Oster and Peskin[44] introduced an intuitive microscopic model for osmotic pressure driven flow, considering the chain effect of “membrane→particle→fluid” as the formation of osmotic flow through the micro-scale pores. In this chapter we verify this chain effect by using the force balance analysis from Chapter 4, find the membrane effect to the movement of the solute particles, and compare the micro-scale osmosis model to macro-scale osmosis theories.

A semi-permeable membrane is widely used in water-purification and electrolyte battery systems. The membrane also plays an important role in biological cell actions in vitro, absorbing or expelling water, preserving ionic equilibrium and controlling the exchange of nutrients and RNA. Seen from Figure 6.1 (b), the semi-permeable membrane is a phospholipid bilayer and is covered by many micro-scale pores that connect the interior of the cell to the exterior. This membrane is particularly sensitive to large particles such as proteins.
Figure 6.1: Macro- and micro-scale examples of osmosis, (a) a macroscopic view of induced osmotic pressure. The osmotic pressure drop is $\Delta p = P_{\text{solution}} - P_{\text{water}}$; (b) the cell expansion in pure water reservoir.

and some ions. The solute particles inside a biological cell can be ions (e.g. $H^+$, $K^+$, $Ca^{2+}$, $Na^+$, $Cl^-$, $HCO_3^-$), macromolecular compounds (e.g. glucose, sucrose, proteins) or RNA. If a live cell is inserted into pure water, an expansion of the cell’s volume can be observed, due to the continuous water absorption by the membrane.

6.2 Osmotic Pressure in Dilute Equilibrium Solutions

A semi-permeable membrane usually carries a negative charge and an electric potential accumulates on the membrane, forming an electric double layer. The value of the electric potential can reach $-120mV$ [78]. The distribution of forces on a solute particle and on the particle’s surrounding fluid are sketched in Figure 6.2. At the static equilibrium state, the system is independent of time; the fluid in the system is macroscopically motionless, so the solution flux is zero. Thus using the force balance equation (4.28) in steady state on a
solute particle neglecting the external fields yields

$$\mathbf{R} + \mathbf{F}_S = \mathbf{F}_{DLVO}$$  \hspace{1cm} (6.1)

where \( \mathbf{R} \) is the scaled random force, \( \mathbf{F}_S = \frac{d\mathbf{X}_i}{dt} - \bar{\mathbf{u}}(\mathbf{X}_i) \) is the scaled Stokes Drag, and \( \mathbf{F}_{DLVO} \) is the scaled DLVO force given by the membrane. It is clear that the only force from the system rather than from fluid is the DLVO force term.

The solution particles are assumed to be points, so equation (4.35) of Chapter 4 is still valid. Substituting the DLVO force term into the fluid momentum equation neglecting the external fields the equation (4.35) yields the pressure gradient on the micro pores generated by all the particles (particle total number \( N \))

$$\nabla p = f \sum_{i=1}^{N} \delta_d(\mathbf{x} - \mathbf{X}_i) \mathbf{F}_{DLVO}$$  \hspace{1cm} (6.2)
where $f = 6\pi$ and the DLVO force is normal to the membrane surface, $X_i$ is the position of the $i^{th}$ solute particle, and $x$ is a point in the surrounding fluid. Since $F_{DLVO} = -\nabla U_{net}(X_i)$, where $U_{net}(X_i)$ is the superposition of electric double layer energy and van der Waals energy that exerts on the solute particle, substituting the scaled energy $U^*_i = U_{net}(X_i)/k_BT$ into equation (6.2) we get (* dropped)

$$\nabla p = \xi \sum_{i=1}^{N} \delta_d(x - X_i) \left[ -\nabla U_{net}(X_i) \right]$$

(6.3)

where the coefficient $\xi = \frac{k_BT}{\mu U_0 a^2}$, $a$ is the radius of the solute particle, and the velocity scale $U_0$ can be chosen as the particle moving velocity $\frac{dX_i}{dt}$.

The membrane induced particle drifting process is sketched in Figure 6.3. When a particle inside the solution moves closer to the charged semi-permeable membrane, the DLVO
interaction acting on this particle gets stronger. From the comparison done in Chapter 4, Figure 4.4 we found that when a particle approaches the charged wall the electric double layer energy increases much faster than van der Waals energy, and becomes primary energy. So the net interaction shows as repulsive, that is, it opposes the particle’s motion. This particle will drag surrounding fluid away from the membrane by friction. A local pressure gradient forms at the two sides of the micro-pore on the membrane. If we sum up the pressure gradient generated by all the solute particles which distribute near the whole surface of the membrane, a continuous pressure gradient will drag fluid through the micro-pores from the water side to the solution side. From the macroscopic view, a continuous volume expansion of the solution occurs, called swelling. Integrating the pressure gradient along the surface of the membrane we obtain the total osmotic pressure.

Assuming the solute particles have a random distribution in the solution, the molar concentration of particles can be evaluated by

\[ c = \frac{N}{V_0 N_A} \]

where \( N \) is the total number of particles, \( V_0 \) is the volume of the solution, and \( N_A \) is the Avogadro number. Thus the scaled molar concentration of solute particles is

\[ c^* = c \cdot a^3 N_A \]

where \( a \) is the radius of a solute particle. The average pressure gradient can be written as an integration on the concentration of particles on whole solution area averaged on total particle number (* dropped)

\[ \nabla \bar{p}(x) = -\xi \sum_{i=1}^{N} \int \delta_d(x - X_i) \nabla U_{net}(X_i) \frac{c(X_i)}{N} dX_i \]  

(6.4)

From the macroscopic view, \( p(x) \) is close to the average pressure \( \bar{p}(x) \). Thus we have for non-interacting particles

\[ \nabla p(x) = -\xi \int \delta_d(x - X_i) \nabla U_{net}(X_i)c(X_i)dX_i \]  

(6.5)

Using the shifting property of the delta function yields the scaled pressure gradient

\[ \nabla p(x) = -\xi c(x) \nabla U_{net}(x) \]  

(6.6)
The dimensional concentration of solute particles follows the dimensional Boltzmann distribution

\[ c(x) = c_0 e^{-\frac{U_{\text{net}}(x)}{k_B T}} \]  

(6.7)

where \( c_0 \) is the particle concentration when \( U_{\text{net}}(x) = 0 \). Thus the scaled particle concentration (* dropped)

\[ c(x) = a^3 N_A c_0 e^{-U_{\text{net}}(x)} \]  

(6.8)

Differentiating with respect to \( x \) gives

\[ \nabla c(x) = -c(x) \nabla U_{\text{net}}(x) \]  

(6.9)

The resulting pressure gradient is

\[ \nabla p(x) = \xi \nabla c(x) \]  

(6.10)

which states osmotic pressure gradient is proportional to the solute particle molar concentration gradient. Integrating equation (6.10) on \( x \) yields the scaled osmotic pressure which is proportional to the scaled particle concentration

\[ \Delta p = \xi c \]

It is worth mentioning that the proportional relation between scaled \( \Delta p \) and \( c \) is identical to van’t Hoff’s law, which describes the macroscopic osmotic pressure (denoted as \( \Pi \)) of a dilute solution. In Chapter 4 we have chosen the scaled pressure \( p^* = \frac{p}{\mu U_0/a} \) for small Reynolds number, scaled particle concentration \( c^* = a^3 N_A c \), and the Boltzmann constant \( k_B = R/N_A \) where \( N_A \) is the Avogadro number and \( R \) is the gas constant. Thus we obtain van’t Hoff’s law (dimensional)

\[ \Pi = \Delta p = RT c \]  

(6.11)

which is the classical expression of osmotic pressure.
6.3 Summary

The microscopic solution of osmotic pressure is consistent with the macro-scale theory. The osmotic pressure originates from the electric and molecular interactions between a semi-permeable membrane and charged solute particles which causes the solute particles or ions to drift away from the membrane. The micro-scale model shows the osmotic pressure is proportional to the solute particle concentration, which is in accordance with the classical expression of osmotic pressure.
7.1 Summary

In this thesis, the pressure-driven, magnetically-driven, and electrokinetically-driven transport of a biological cell or particle in rectangular channels have been investigated. Applications are cancer cell separation technology, as well as drug delivery, DNA sensing, miRNA transport, and water purification. Analytical and numerical calculations were used to study the flow field, particle speed and particle trajectory in these biomedical devices. The conclusions are listed below:

1. Pressure-driven transport of uncharged particles/cells is hindered by particle/cell size. A pressure-driven cell transport model has been developed in Chapter 2 to investigate the influence of the hindered coefficients in both the particle and the cell transport model in a straight microchannel. The cell migration velocity was found to be dependent on the bulk flow rate and the ratio of two geometric characters: the channel height and the cell radius. The increase of cell size was found to reduce the cell migration velocity because of the higher friction and higher cell-channel surface adhesion and collision chances. The pressure-driven transport is a basic method delivering particles and biological cells in biomedical devices.

2. Based on the analysis in Chapter 3, the geometry for a $30 \times 150 \mu m$ cross-section rectangular parallel-pattern grooved cell labeler should have at least 6 cycles of grooves with
the groove height $h_g = 20 \mu m$ and groove width $W_g = 30 \mu m$. In Chapter 3, numerical simulations were applied to a 3-dimensional oblique groove cell labeler design. Given an axial pressure-driven flow, 3-D velocity fields and dispersion of particles were observed in and above the oblique grooves of the cell labeler. The increase of the transverse flow velocity induced by increasing either the groove height or groove width are observed. Furthermore, optimum values of both the groove height and groove width in a $30 \times 150 \mu m$ cross-section labeler were found. The optimized groove height to channel height ratio $\alpha = 0.67$, and the optimized groove width $w_g = 30 \mu m$. The $2400 \mu m$ mixing length (equal to 6 cycles of grooves) was proposed to provide good labeling efficiency in a parallel pattern cell labeler.

3. The magnetic force and friction force are the primary forces on a magnetized cell/particle in a magnetic field. The effect of a cell/particle on the surrounding fluid has been evaluated in Chapter 4 by analyzing forces acting on the cell/particle. Based on the magnitude, all forces can be divided into two groups: the forces that dominate the magnetic cell transport, including magnetic force, electric force and Stokes friction force; and the forces that have minor influence on cell transport, including gravity and lifting forces, random force, van der Waals attraction and EDL repulsion forces. In a magnetically-driven transport process, the magnitude of the magnetic force was found to influence the magnetized cell transport speed using the force balance analysis.

4. The net interaction of wall-particle EDL repulsion and van der Waals attraction is the primary wall-particle interaction. The DLVO approach, a superposition of van der Waals and electric double layer interactions, is used in Chapter 4 to describe the wall effect when a particle or a cell approaches the channel wall. van der Waals attraction energy is calculated using both the Derjaguin approximation and the surface element integration method.
and the latter has the higher accuracy, while electric double layer repulsion energy is estimated by Derjaguin approximation. The DLVO energy (van der Waals attraction and EDL repulsion) is found as a primary effect between a channel wall and a particle. Surprisingly, the minimum DLVO energy separation is close to the experimentally[39] observed particle number density peak position (see Figure 4.5).

5. Unlike the uncharged case, effect of a wall on particle/cell electrophoretic motion is weak. In Chapter 5, particle transport and cell transport has been compared within the electrokinetically driven flow. The wall effect on cell or particle transport velocity under electric field has been investigated by Henry’s solution and compared with the experimental data. Also, using Keh and Anderson’s[77] method, the effect of wall surface potential $\zeta_w$ on cell and particle motion was found to be relatively weak.

6. Osmotic pressure mainly comes from the repulsion of the charged membrane. A force balance model is used to model the microscopic osmotic pressure in Chapter 6. The analytical solution of osmotic pressure from the micro-scale model is compared with the classical van’t Hoff’s law and agreement is found. The DLVO theory can also be applied to describe the interaction between the solute particles and the semi-permeable membranes which provides electric double layer repulsion toward charged particles or ions along with the van der Waals attraction, which is a primary cause of osmotic pressure.

7.2 Future Work

The future work of this project are as follows:

1. The simulation and design of 3-D cell labeling process can be improved and extended. Future work includes
a. considering other parameters, such as the adjustment of slant angle of grooves, the optimum groove distances, and precision of outline fabrication;

b. considering other labeler styles, such as the efficiency test of alternating pattern cell labeler and SHM labeler;

c. using the two phase flow model and the chemical reaction model to investigate the cell-antibody binding process.

2. The magnetic force between a magnetic disc and a magnetized cell is derived in Appendix B. Based on the derivation and the force balance analysis used in Chapter 4, we are able to study the manipulation of magnetically labeled cells and simulate the magnetic cell separation process in future.

3. An analytical solution for the electric double layer energy and force may be obtained under the Derjaguin approximation. However, the electric double layer force and energy must be calculated numerically if the SEI method is used. Given the considerable difference in the DA and SEI results for the electrical double layer energy\[68\] it is possible that the results of Figures 4.4 and 4.5 may change considerably.

4. In future, the molecular dynamics (MD) simulation should be combined with continuous simulation and experimental data in order to improve the model of the wall effect to the particle and cell and verify the validity of DLVO approach.
Appendix A: Notation

English

$a$  
radius of a sphere

$ar{a}$  
average radius of a group of spheres

$A$  
channel cross-sectional area

$A$  
vector magnetic potential on a point in space from a point on a magnet

$A_H$  
Hamaker constant, $A_H = \pi C \rho_1 \rho_2$

$a_p$  
average radius of the magnetic particles or the magnetic labels on a cell

$B$  
magnetic flux density

$B_d$  
magnetic flux density induced by a magnetic disc

$c$  
molar concentration of a type of solute particle in a solution

$C$  
coefficient of the particle-particle pair interaction for Hamaker constant

$c_0$  
molar concentration of a solute particle when $U_{net} = 0$

$c_i$  
molar concentration of the $i^{th}$ ion or particle in a solution

$d$  
thickness of fluid surrounding a particle (diameter of spherical volume of fluid when particle radius approaches zero)

$D$  
minimum distance (separation) between two surfaces

$d_0$  
diameter of a sphere or a cylinder

$D_i$  
diffusion coefficient, $m^2/s$

$e$  
unit electric charge, $e = 1.6 \times 10^{-19} Coul$
Electric field intensity and its value

Electric double layer interaction energy per area

Molecular interaction (van der Waals interaction) energy per area

Faraday constant, \( F = 96485.3415 \text{sA/mol} \)

DLVO force, a superposition of van der Waals force and electric double layer force

Volume density of electric force

Electric force and its value

Electric double layer force vector and its value

Forces acting on a particle from external fields

Force of gravity and its value

Lorentz force per volume

Volume density of magnetic force

Magnetic force vector and its value

The line integration on the circular ring, used in surface element integration

Stokes drag vector and its value

Scaled transverse flow velocity in a cell labeler

Van der Waals force vector and its value

Gravity

Height of a rectangular channel

Distance between the center of a sphere to a flat wall

Magnetic field intensity

Half-height of a rectangular channel

Hartmann number, the ratio of the electromagnetic force to the viscous force

Height of a groove in an oblique groove cell labeler
The following are some commonly used symbols and their definitions:

- **J**: current density
- **J_s**: surface current density
- **J_v**: volume current density
- **k_B**: Boltzmann constant, \( k_B = 1.3806503 \times 10^{-23} \text{J} \text{K}^{-1} \)
- **K_c**: hindered convection coefficient
- **K_d**: hindered diffusion coefficient
- **L**: length of a channel
- **m**: particle inertial mass
- **m**: magnetic moment
- **M**: magnetization, an induced volume density of the total magnetic moment for the magnetic fields
- **m_c**: magnetic moment on a magnetized cell
- **m_d**: magnetic moment on a magnetic disc
- **M_s, M_s**: saturation magnetization vector of permalloy and its value, \( M_s = 8.6 \times 10^5 \text{A/m} \)
- **n**: unit vector that has the same direction with saturation magnetization \( M_s \)
- **\hat{n]**: unit vector used in surface integration, normal to a surface
- **N**: total number of a group of particles
- **N_A**: Avogadro constant, \( N_A = 6.02214129(27) \times 10^{23} \text{mol}^{-1} \)
- **N_i**: molar flux of particles or cells
- **p**: local fluid pressure
- **p_0**: outlet pressure
- **\Delta p**: macroscopic osmotic pressure
- **P_e**: Péclet number, the ratio of the rate of convection to the rate of diffusion
- **P_{solution}**: hydraulic pressure of the solution reservoir
- **P_{water}**: hydraulic pressure of the water reservoir
\( q \) total electric charge on a particle

\( Q \) volumetric flow rate

\( R \) gas constant, \( R = 8.3145 \text{Jmol}^{-1}\text{K}^{-1} \)

\( \mathbf{R} \) random force

\( \mathbf{r}_1, r_1 \) vector from the bottom surface of a magnetic disc to a cell and its length

\( \mathbf{r}_2, r_2 \) vector from the top surface of a magnetic disc to a cell and its length

\( Re_a \) Reynolds number, ratio of inertial forces to viscous forces

\( S \) area of the surface in the surface integration on a particle or a magnet

\( t \) time

\( T \) temperature

\( t_0 \) time scale

\( t_d \) the thickness of the magnetic disc

\( u, v, w \) velocity component of a fluid point on \( x, y \) and \( z \) axis, respectively, in Cartesian coordinates

\( \mathbf{u} \) bulk flow velocity vector

\( \bar{u} \) average velocity on the axial velocity \( u \) in a channel in Cartesian coordinates

\( \bar{\mathbf{u}} \) weighted average fluid velocity surrounding a particle

\( U_0 \) a velocity scale, values of which varies in different models

\( u_c \) cell migrating velocity

\( U_{EDL}, U^{DA}_{EDL} \) electric double layer energy, calculated by Derjaguin approximation

\( u_{eo} \) electroosmotic flow velocity

\( u_{ep} \) particle electrophoretic velocity

\( U_{net} \) DLVO energy, net energy of electric double layer repulsion and van der Waals attraction

\( u_p \) particle migrating velocity

\( \mathbf{u}_p \) particle velocity vector
$U_{vdW}, U_{SEI}^{vdW}$ molecular interaction energy calculated by surface element method

$U_{vdW}^{DA}$ molecular interaction energy calculated by Derjaguin approximation

$V$ volume

$\Delta V$ voltage drop of electroosmotic flow

$V_0$ volume of the higher concentration side fluid in osmosis phenomena

$V_i$ spherical fluid volume outside of a solute particle

$|v_+|$ absolute value of transverse velocity that has the same direction with y axis in a cell labeler

$|v_-|$ absolute value of transverse velocity that has the opposite direction with y axis in a cell labeler

$W$ width of a rectangular channel

$W_g$ width of an oblique groove projected on $x$-axis

$W'_g$ width of an oblique groove, $W'_g = \cos(\theta) W_g$

$x$ location vector of a fluid point

$X$ displacement of a particle in fluid on $x$-axis in Cartesian coordinate system

$X$ vector displacement of a particle in fluid

$X_i$ vector displacement of $i^{th}$ solute particle in fluid

$z_i$ valence of the $i^{th}$ species

$z$ normal distance from a point on a particle to a flat wall

**Greek**

$\alpha$ ratio of groove height $h_g$ to channel height $h_c$

$\Delta \alpha$ ratio of per groove height increase to channel height $h_c$

$\beta$ Stokes drag coefficient, particle-fluid friction coefficient

$\chi$ particle radius to channel half height ratio

$\delta$ the thickness of the Hartmann boundary layer
\[\delta_d\] Dirac delta function
\[\eta\] ratio of sphere radius \(a\) to sphere center-wall distance \(H\)
\[\varepsilon\] \(\varepsilon = \lambda_p/a\)
\[\varepsilon_e\] permittivity of the fluid
\[\gamma_a\] flare angle from the tip of the antibody group to the tail, representing the angular displacement of fluid or particle in the cell labeler
\[\kappa\] reciprocal Debye length
\[\lambda_p\] Debye length on a charged particle
\[\lambda_R\] line magnetic density
\[\mu\] fluid dynamic viscosity
\[\mu_0\] magnetic permeability of a free space, \(\mu_0 = 4\pi \times 10^{-7}T \cdot m/A\)
\[\nu\] valence
\[\Pi\] osmotic pressure, \(\Pi = \Delta p = RTc\)
\[\Phi_p\] surface electric potential on spherical particle
\[\Phi_w\] surface electric potential on flat wall
\[\rho\] fluid density
\[\rho_e\] electric charge density
\[\rho_1, \rho_2\] number density of molecules on surface 1 and 2, respectively
\[\sigma\] electrical conductivity of the fluid
\[\tau\] shear stress of fluid on the surface of the grooves
\[\theta\] slant angle between the oblique grooves and the side walls of the rectangular channel
\[\xi\] ratio of osmotic pressure gradient to solute particle concentration gradient
\[\zeta_p\] surface potential of spherical particle
\[\zeta_w\] surface potential of flat wall

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Appendix B: Derivation of Magnetic Force on a Cell

In a magnetic field induced by current, the magnetic force density \( N/m^3 \) on a particle is given by

\[
f_m = J \times B \tag{B.1}
\]

where \( J \) is the current density. The magnetic flux density \( B = \mu_0 (H + M) \) (measured in Tesla) is from the inducing source, where \( \mu_0 = 4\pi \times 10^{-7} (T \cdot m/A) \) is the permeability of a free space, \( H \) is the magnetic field intensity defined as a modification of \( B \) due to magnetic fields produced by material media, and \( M \) is the induced volume density of the total magnetic moment \( m \) for the magnetic fields (magnetization).

The geometry of a magnet in the external magnetic field \( B \) is shown in Figure B.1. The total magnetic force on a micro-scale, current-induced magnet (e.g. a magnetic particle) can be integrated on the volume and the surface of the magnet, respectively

\[
F_m = \int_V J_v \times B \, dV + \int_S J_s \times B \, dS \tag{B.2}
\]

where \( J_v = \nabla \times M \) \( (A/m^2) \) is the volume current density, and \( J_s = M \times \hat{n} \) \( (A/m) \) is the surface current density where \( \hat{n} \) is the normal vector to the surface. Since the magnetic flux \( B \) is from an external source and the magnetization of the magnetic material \( M \) is intrinsic, such that we have \( \nabla \cdot B = 0 \). Also \( \nabla \times B = 0 \) which is always true. If we apply the vector
Figure B.1: Geometrical relationship between an external magnetic field and a magnet.

identity [60]

\[ \int_V (\nabla \times V) \times W \, dV - \int_S (\hat{n} \times V) \times W \, dS = \int_V \left[ V \times (\nabla \times W) - V (\nabla \cdot W) \right] dV + \int_V (V \cdot \nabla) W \, dV \]

and the property of cross product

\[ \hat{n} \times V = -V \times \hat{n} \]

and substituting \( V = M \) and \( W = B \) in equation (B.2) yields

\[ F_m = \int_V (M \cdot \nabla) B \, dV \]  

(B.3)

The magnetic force exerted on a magnetized particle/cell is of great concern to the magnetic tweezer design in the ACBA nanofactory. The micro-scale magnets (disc shape) are embedded in the tweezer to induce the magnetic force. The magnitude and direction of the magnetization on these magnets is determined by the external magnetic sources that are controllable. The geometric relation between a magnetic disc dipole and a magnetic particle dipole is shown in Figure B.2, where \( r \) is the distance vector from the center of the
disc to cell, \( \mathbf{r}_1 \) is the vector from the bottom surface of the magnetic disc to cell, and \( \mathbf{r}_2 \) is the vector from the top surface of the magnetic disc to cell.

Additionally, because of the micro- to nano-scale dimensions, a magnetic disc, a magnetized particle or a magnetically labeled cell can be treated as a magnetic dipole, indicating the magnetic moment \( \mathbf{m} \) is constant while the dimensions of the dipole are reduced to zero. Particularly we have the magnetic force on a magnetized cell from a magnetic disc[4]

\[
\mathbf{F}_{mc} = (\mathbf{m}_c \cdot \nabla) \mathbf{B}_d
\]  

To obtain the magnetic force we need to know the magnetic moment on the magnetic disc and the magnetized particle or cell. The magnetic disc dipole carries induced magnetization \( \mathbf{M}_s = M_s \mathbf{n} \), where \( M_s = 8.6 \times 10^5 (A/m) \) is the saturation magnetization of permalloy material and \( \mathbf{n} \) is the unit vector in the direction of \( \mathbf{M}_s \). The total magnetic moment \( \mathbf{m}_d \) of the disc gives

\[
\mathbf{m}_d = VM_s = \frac{\pi}{4} d_0^2 t M_s \mathbf{n}
\]  

Figure B.2: Geometrical relationship between a magnetized particle/cell and a magnetic disc.
where $t_d$ is the thickness of the disc and $d_0$ is the diameter of the disc (shown in Figure B.2).

Similarly, integrating on the volume of the magnetic particle we find the magnetic moment on a magnetized particle/cell

$$m_c = \frac{4\pi}{3} a_p^3 M_s$$

(B.6)

where $a_p$ is the average radius of the magnetic particle (or the magnetic label on a cell, shown in Figure B.2).

Since $\nabla \times B_d = 0$, the magnetic flux density $B_d$ of the disc can be derived from

$$B_d = \nabla \times A$$

where $A$ is the vector potential on a point in space ($x_1$) from a point on the magnet ($x_2$), and $A$ satisfies

$$\nabla^2 A = -\mu_0 J$$

(B.7)

In free space, the solution for $A$ is given using the Green’s function for the Laplacian

$$G(x_1, x_2) = -\frac{1}{4\pi|x_1-x_2|}$$

[79]

$$A = \frac{\mu_0}{4\pi} \int_V J_v(x_2) \frac{dV}{|x_1-x_2|} + \frac{\mu_0}{4\pi} \int_S \frac{J_s(x_2)}{|x_1-x_2|} dS$$

(B.8)

Thus the magnetic flux density $B_d$ of the disc can be derived

$$B_d = \frac{\mu_0}{4\pi} \int_V J_v \times \frac{x_1-x_2}{|x_1-x_2|^3} dV + \frac{\mu_0}{4\pi} \int_S J_s \times \frac{x_1-x_2}{|x_1-x_2|^3} dS$$

(B.9)

The disc is treated as a magnetic dipole, indicating the magnetic surface charge is concentrated at the top and bottom surfaces of the disc with a value derived from equation (B.5)

$$\frac{\pi}{4} d^2 M_s = \frac{m_d}{t_d n}$$

(B.10)
Substituting the geometric relations $x_1 - x_2 = r_1$ and $x_1 - x_2' = r_2$ into equation (B.9) and integrating on the top and bottom surface of the disc yields

$$B_d = \frac{\mu_0 \pi}{4d^2} M_s \left( \frac{-r_1}{r_1^3} + \frac{r_2}{r_2^3} \right)$$  \hspace{1cm} (B.11)

Assuming $t_d \ll r$ and substituting $r_1 = r - \frac{t_d}{2} n$, $r_2 = r + \frac{t_d}{2} n$ and equation (B.10) into equation (B.11) yields the magnetic flux density from the disc to a magnetized particle[79]

$$B_d = \frac{\mu_0}{4\pi} \left( \frac{3(m_d \cdot r) r}{r^5} - \frac{m_d}{r^3} \right)$$  \hspace{1cm} (B.12)

Substituting equation (B.12), (B.5) and (B.6) into equation (B.4) solves the magnetic force acting on a magnetized particle or a labeled cell from a single magnetic disc[80]

$$F_c = \frac{3\mu_0}{4\pi r^5} \left[ (m_d \cdot m_c) r + (m_d \cdot r) m_c + (m_c \cdot r) m_d - \frac{5(m_d \cdot r)(m_c \cdot r)r}{r^2} \right]$$  \hspace{1cm} (B.13)
Bibliography


