MULTI-LEVEL FILTER
BASED ON H SHAPED CHANNELS

by

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Micro and nano filtration is a crucial fundamental process in biological, biomedical and chemical engineering fields. By elimination of irrelevant factors, nanofiltration is able to improve the accuracy, efficiency and reliability of experiments. It is essential for treatments and preparation of high quality specimens, separation and purification of specific components, and control of reaction processes. However, it is difficult to separate complex mixtures such as blood into multi groups in chip level. The nanofilters are under threat of adhesion and clogging. This project aims to establish a multilevel filter for separation and purification complex bio-components mixtures by size in both micro and nano scales; generalize the design methodology of this multi level filter; optimise traditional nanofilter and eventually develop a multi level filter for rapid micro volume sample filtration.

During the study and improvement of traditional filter, a new type of multi level filter for sequential separation based on H shaped channels were put forward in this thesis. The methodology of designing this type multi level filter was built and verified with simulations. A general path for multi level filter chip design was established and demonstrates with examples and experiments. A new fabrication process for multi depths channel on the same surface was put forward during the examples design. The fabrication experiments on photolithography, Inductively Coupled Plasma Reactive Ion Etching (ICP RIE), and Focused Ion Beam (FIB) milling demonstrated the feasibility of this fabrication process and the recipes of these three fabrication processes were given by the experiments. Simulations on both 2D and 3D filters were described and discussed. The angle effect of angular H shaped channels was studied with COMSOL Multiphysics® Modelling Software.
ACKNOWLEDGEMENTS

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Last but not least, I would like to thank my parents. Your love is the power supporting me to explore this beautiful big world. Thanks.
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<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<tr>
<td>$a_i$</td>
<td>Width of the $i^{th}$ level sieves’ channel, assuming its width equals to its depth;</td>
</tr>
<tr>
<td>$a_j$</td>
<td>Diameter of component $j$;</td>
</tr>
<tr>
<td>$[B]$</td>
<td>Matrix function of inverted binary diffusion coefficients;</td>
</tr>
<tr>
<td>$c_j$</td>
<td>Molar concentration of component $j$;</td>
</tr>
<tr>
<td>$c_{Capture}^{i,j}$</td>
<td>Capture concentration of component $j$ at the $i^{th}$ level;</td>
</tr>
<tr>
<td>$c_{Sample}^{i,j}$</td>
<td>Inlet sample concentration of component $j$;</td>
</tr>
<tr>
<td>$d$</td>
<td>Depth of inlet channel;</td>
</tr>
<tr>
<td>$D_j$</td>
<td>Diffusion coefficient for component $j$;</td>
</tr>
<tr>
<td>$D_{ij}$</td>
<td>Diffusion coefficient component $j$ in the $i^{th}$ level sieve;</td>
</tr>
<tr>
<td>$D_r$</td>
<td>Hydraulic diameter of the microchannel;</td>
</tr>
<tr>
<td>$F$</td>
<td>Faraday constant;</td>
</tr>
<tr>
<td>$F_b$</td>
<td>Body force;</td>
</tr>
<tr>
<td>$F_{D}$</td>
<td>Dean drag force;</td>
</tr>
<tr>
<td>$F_{L}$</td>
<td>Inertial lift force;</td>
</tr>
<tr>
<td>$h_i$</td>
<td>The length of the $i^{th}$ level sieve channel</td>
</tr>
<tr>
<td>$i$</td>
<td>Number of sieves’ level;</td>
</tr>
<tr>
<td>$j$</td>
<td>Species of components;</td>
</tr>
<tr>
<td>$J_j$</td>
<td>Flux of component $j$;</td>
</tr>
<tr>
<td>$J_{diff}$</td>
<td>Diffusion flux;</td>
</tr>
<tr>
<td>$J_{conv}$</td>
<td>Convection flux;</td>
</tr>
<tr>
<td>$l_i$</td>
<td>Distance between two levels of sieves;</td>
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$L$ Length of the channel;

$n$ Number of different species components;

$N_i$ The minimum number of the $i^{th}$ level sieves in H shaped channel series;

$P$ Pressure;

$Q$ Volume flow rate of laminar flow in a straight channel;

$R$ Gas constant;

$R_j$ Net mass production rate in chemical reactions;

$R_h$ Hydrodynamic resistance of the microchannel;

$t$ Time;

$T$ Temperature;

$T_{i,j}$ Response time of component $j$ at $i^{th}$ level in a multi-level filter;

$v_c$ Convective velocity field;

$w$ Width of the sample inlet entrance

$w_i$ Distance between two adjacent sieves;

$z_j$ Valence of component $j$;

$\gamma$ Constant;

$[\Gamma]$ Matrix of thermodynamic factors;

$\delta_i$ Error of capture concentration in level $i$;

$\delta_{ij}$ Constrictivity, defined as $\frac{a_j}{a_i}$;

$\varepsilon_t$ Porosity, which equals $\frac{a_i^2}{d(a_i+w_i)}$;
\( \eta \quad \text{Viscosity;} \)

\( \theta \quad \text{Angle;} \)

\( \mu \quad \text{Viscosity of the liquid;} \)

\( \rho \quad \text{Density of fluid;} \)

\( \phi \quad \text{Electric potential;} \)

\( \psi \quad \text{Electric potential due to surface charge;} \)

\( \varphi \quad \text{Electric potential caused by stream;} \)

\( \nabla \quad \text{Gradient operator;} \)

\( \Delta \quad \text{Difference operator.} \)
1.1 Background

Microminiaturization is undoubtedly one of the most significant achievements of humans in recent decades. The development of nanotechnology provides powerful tools to scientists and engineers. The volume produced of economic[1], safe[2], clean[3], accurate and fast response[4-6] micro and nano devices has already changed peoples’ lives. In the area of medical science, bioscience, bio-medical engineering and chemical engineering; nanofiltration is an essential process for treatment and preparation of high quality specimens[7, 8], separation and purification of specific components[9, 10], and control of reaction processes. By elimination of irrelevant factors, nanofiltration is able to improve the accuracy, efficiency and reliability of experiments [4, 11]. Therefore nanofilters are widely used for microdetermination, single molecule detection and precise reaction process control.

The multi-level nanofilter research project described in this thesis is a subproject of a Transdermal Patchlab Blood Analyzer System project which is a collaboration project among University of Birmingham, University of New South Wales (Australia) and Harbin Institute of Technology (China). The transdermal patchlab blood analyzer system project aims at developing a Lab-On-Chip system which is able to detect multi bio-markers with painless blood sample collection. This system is designed for rural area medical care and early diagnoses. It is able to work under low gravity in space as well. Figure 1.1 shows a concept
1.1 Background

drawing of the Transdermal Patchlab Blood Analyzer System. It consists of microneedles collecting human blood; multi-level filtration module diluting blood and separating bio-components; bio-marker detection module and pump module. The microneedles fabrication is another PhD project of Miss Zahra Faraji Rad, who is a U21 joint PhD student of University of Birmingham and University of New South Wales.

Consequently a multi-level micro and nano filter for whole human blood separation is demanded for the transdermal patchlab blood analyzer system. The diameter of blood cells, microvesicles, proteins and other components in blood varies from microns to several nanometres. It is difficult to microminiaturize filters for separation in such a large range of scales down to chip level. Considering the differences of micro and nano fabrication techniques, the varieties of diameters result in a complex fabrication process. Pumping for fine channels needs high pressure while for coarse channels low pressure is enough, thus an appropriate pumping strategy for multi-level filtration is desired. For filtration of complex
1.2 Aims and Objectives

The aims of this research project are to establish a multilevel filter for separation and purification complex bio-components mixtures by size in both micro and nano scales; generalize the design methodology of this multi-level filter; optimise traditional nanofilter and eventually develop a multi-level filter for rapid micro volume sample filtration.

Consequently the objectives of this project are set out as below:

1. Review the current development of nanofilters, including but not limited to the transport theory, fabrication techniques, and relevant applications.

2. Analyse and optimise traditional filters to reduce the possibility of clogging and adhesion which block the sieves of filter.

3. Analyse and optimise the traditional filter to seek for a solution of multi-level separation in chip level, where the diameters of target components cover from nanometres to microns.

4. Study the interaction among each level of filter.

5. Generalize the design principles of multi-level filter with mathematical formulas. All physical features of a filter should be able to be described by mathematics.

6. Verify the mathematical formulas by simulations.
1.3 Thesis Structure

7. Generalize the methodology of multi-level filter chip design. Design multi-level chips following the flow process to demonstrate the feasibility of design path.

8. Give a feasible fabrication process of multi-level filter chip.

1.3 Thesis Structure

This thesis contains seven chapters. Chapter 1 introduces the background, aims and objectives of multi-level nanofilter research project. A reading guide for this thesis is set out in this chapter.

Chapter 2 reviews the applications and development progress of micro and nano filtration technology, theory for transport phenomena in nanochannels, guidelines for micro- and nanofluidic chip design and fabrication techniques of lab on a chip micro and nano filter. In the review, answers for the following questions are given: why micro and nano filters are necessary, what kind of micro and nano filter is desired for bio-medical application, and how to design and fabricate a micro and nano filter chip?

Chapter 3 analyses and optimises the model of nanofilter step by step, and then introduces the H shaped channels which is the fundamental basis of the research in thesis. Based on the H shaped channels, a new design of multi-level nanofilter for sequence filtration process is put forward. The theoretical design principles related to this multi-level micro- and nano-filter are discussed in this section.

To improve the capture concentration in the multi-level filter, sieve channel series are applied. Chapter 4 studies the mass transfer process and flow properties of semi-H, H and angular H shaped channels series with finite element software COMSOL. Based on these
analyses, models of multi-level nanofilter is built and simulated. The theoretical design
principles are verified with these simulations.

Chapter 5 describes the 3D infinite element modelling of angular H shaped channels series
and studies their flow properties. Slip boundary condition is applied with same models for
more accurate simulations. Then a 3D model of a three-level nanofilter based on semi-H
shaped channels is discussed; the results of simulation demonstrate the feasibility and
disadvantage of semi-H shaped channel series.

Chapter 6 illustrates a general chip design path for a multi-level micro- and nano-filter. Two
patterned multi-level nanofilter chips are designed as examples following this design flow. A
new fabrication process for multi-level nanofilter chip is put forward in these designs.
Experiments are made to verify the feasibilities of fabrication process. Reasonable recipes
for each step of fabrication process are given by experiments as well. At the end of this
chapter, alternative fabrication paths are introduced.

Overall discussions and conclusions are made in Chapter 7. Then the whole thesis is
summarized and the future work is introduced briefly.

1.4 Summary

This chapter illustrates the importance of microminiaturization a multi-level nanofilter down
to chip level. The aims and objectives of this research project are introduced. An overview of
this thesis is given. Although the main motivations of this research are to establish and
verify a design methodology for multi-level nano filter separating multi bio-components,
develop a multi-level filter and its fabrication process; it also opens up new applications of
bio-medical and chemical engineering.
2.1 Introduction

In this chapter, the applications and development progress of micro and nano filtration technology, theory for transport phenomena in nanochannels, and fabrication techniques of lab on a chip micro and nano filter are reviewed. The questions: why micro and nano filters are necessary, what kind of micro and nano filter is desired for bio-medical applications, and how to design and fabricate a micro and nano filter; are answered.

2.2 Review on Traditional Accurate Size Separation Techniques

Accurate size separation and size measurement of various kinds of particles, including polymer beads, ceramics, cells, pharmaceutical emulsions, proteins and DNA molecules, are one of the most important technologies in the fields of analytical and bio-analytical chemistry, biology and bio-medical research, industrial production, and environmental assessment. A lot of studies have developed and demonstrated methods on particle separation, such as field flow fractionation (FFF) [14-18], split flow thin fractionation (SPLITT) [19-21], hydrodynamic chromatograph (HDC) [22-24], capillary hydrodynamic fractionation (CHDF) [25-28], ultracentrifugation [29, 30], and electrokinetic methods [31]. In this section, brief reviews on these methods will be taken.
2.2 Review on Traditional Accurate Size Separation Techniques

2.2.1 Field Flow Fractionation (FFF)

Field flow fraction (FFF) was first conceptualized and reported by JC Giddings et al in 1976[32]. An external physical field perpendicular with the parabolic flow in a long narrow channel is applied to separate particles into different streams. Thus each group of particles achieves a different velocity based on their position (field direction) in the parabolic flow. These differences of velocity separate the particles into different groups by the end of the channel. (Figure 2.1) The fields or gradients can be flow field (flow FFF), thermal gradients (thermal FFF), centrifugal forces (sedimentation FFF or centrifugal FFF), electrical field (electrical FFF)[14] and magnetic field (magnetic FFF)[33]. Species which range in size from $\sim 10^{-3}$ to $10^2 \mu m$ can be accurately separated with FFF technology. FFF is a measurement method as well. Currently, various commercial FFF systems are widely used in laboratories for particle analysis. Although FFF is an extremely versatile technique, it has some disadvantages. The first disadvantage is that the separation time is relatively long. The second is that FFF is not a continuous separation method. Thus it is not a powerful tool for particle preparation. Thirdly, FFF requires a complicated outer device for small volume sample injection. What is more, comparing with microfluidics separation devices, a FFF system is comparatively complex and expensive.

![Figure 2.1 Field Flow Fractionation with cross flow field][34]
2.2.2 Split Flow Thin Fractionation (SPLITT)

Split flow thin fractionation is a continuous separation method for micro particles. It was developed based on flow FFF by JC Giddings as well [19]. Figure 2.2 illustrates the principle of SPLITT. There are two inlets, one for sample solution while the other is for a buffer fluid (carrier flow). The carrier stream normally injects with a higher flow rate than the sample inlet. So the sample stream is focused to a narrow band along the inlet splitting plane. Without an external field, all particles go with the sample stream and exit from the outlet opposite the inlet. When an external field (gravity, electric field, or magnetic field) is applied, susceptible particles are pushed towards the outlet splitting plane. Consequently the sample is separated to two groups. Comparing with the FFF method, SPLITT achieves a continuous separation thus it is used for particle preparation rather than measurement. However, SPLITT can only separate micro or submicron particles. Both FFF and SPLITT require external fields and so they become complicated systems. Recently, some studies demonstrated the miniaturization of SPLITT as microfluidics devices, reducing the cost of the SPLITT system and achieving a relatively high flow rate [20, 35].

Figure 2.2 Principle of Split Flow Thin Fractionation [36]
2.2 Review on Traditional Accurate Size Separation Techniques

2.2.3 Hydrodynamic Chromatograph (HDC)

In 1974, Small showed that colloid particles in an aqueous suspension emerged from packed beds of spherical particles according their size sequence, the largest first while the smallest last [22]. This is because that in a narrow conduit, larger particles (size range from 0.002 to 0.2 of the conduit size [23]) cannot fully access the stream near the conduit walls. Due to the properties of parabolic flow, the flow rate towards the boundary is lower. Thus larger particles achieve a higher velocity than smaller ones. However, the absorption and clogging of colloidal particles in the packing columns limit its application [37]. By using a capillary channel (diameter is 250 μm) rather than a bed packed by solid nonporous particles, capillary hydrodynamic chromatograph (CHDC) was developed [38, 39]. Silebi et al pointed out that “the separation mechanism results from the eluant’s parabolic velocity profile rather than through the partitioning of the species to be fractionated between two phases, as in typical chromatographic separations, this technique is not a chromatographic separation” [25]. Thus they rephrased capillary hydrodynamic chromatograph (CHDC) as capillary hydrodynamic fractionation (CHDF). Both HDC and CHDF are separation methods without external fields. Although the CHDF increases the separation efficiency comparing with HDC, there are no apparent improvements on resolution. Comparing with the FFF methods, the resolution of HDC and CHDF is their main disadvantage.

2.2.4 Ultracentrifugation

Since Svedberg and his collaborators first introduced the method of centrifugation (1923) [40] and ultracentrifugation (1924) [29], the huge developments of this technique have made ultracentrifugation a common and important tool in analytical chemistry and bioscience, especially Proteomics [30]. There are three areas of ultracentrifugation based on
the transport process and detection methods: sedimentation velocity, sedimentation equilibrium and the approach to sedimentation. Very high resolution of molecular mass can be achieved by analytical ultracentrifuge. Preparative ultracentrifuges are used for pelleting of fine particulate fractions and gradient separation. However, ultracentrifugation is a time consuming process. The high price and complicated systems also limited its applications. For a small volume (nL) sample, the sample needs to first be diluted to a larger volume before ultracentrifugation can take place, which is not necessary for lab-on-chip devices.

2.2.5 Electrophoresis and Electro-osmosis

Electro-osmosis and electrophoresis are two typical electrokinetic separation processes. According to the electrical double layer theory (EDL), if a plane charged surface is in contact with liquid and an electric field is applied parallel to the solid surface, liquid adjacent to the interface moves [31]. This phenomenon is called electro-osmosis. Electrophoresis, in contrast, is the converse process of electroosmosis. It can be viewed as ions movement in fixed liquid. The thickness of the electrical double layer affects the electrophoretic mobility. Schoch made an outstanding review on electrokinetic phenomena in nanofluidics [31]. More details can be referred to that review.

2.2.6 Discussion and Conclusions

In this section, several techniques for particle separation have been reviewed. Each technique has its advantages and disadvantages. In these methods, FFF, HDC, CHDF, ultracentrifugation and electrokinetic method are mainly used for particle or molecule analysis. Except the ultracentrifugation and electrokinetic techniques; FFF, HDC and CHDF are based on the flow rate distribution in parabolic flow. Ultracentrifugation, FFF, electrophoresis and electro-osmosis require external fields such as centrifuge, cross-flow or
electric field. In contrast, external fields are not necessary for HDC and CHDF. Although the separation accuracy is high in these techniques, the time for separation is relatively long. Meanwhile, as these separation methods are not continuous (some preparative ultracentrifuges are continuous with complicated outer injection and collection devices, while most ultracentrifuges are not), they are not used for preparation of particles. The advantages of continuous flow separation were summarised by Pamme as: continuous introduction of sample, continuous readout of separation efficiency, lateral separation of sample components, potential for integration, and Label-free [20].

SPLITT fractionation, however, is a continuous separation technique which requires external physical field as FFF, ultracentrifugation and electrokinetic methods. Thus SPLITT fractionation is mainly used for particle preparation. As the microfluidics chips show significant advantages on their low cost, safety, high efficiency and accuracy; some researchers focused on the microminiaturization of these methods [23, 31]. Even though the miniaturized chips showed enhancements comparing with the traditional machines, the disadvantages of these techniques are still problems. Thus simple label-free continuous flow separation methods for micro and nano components without external fields are demanded. In the next section, micro and nano filters will be reviewed and discussed.

2.3 Review on Micro and Nano Filtration

2.3.1 Classifications of Micro and Nano Filter

Generally, separation by size (mass) and separation by charge are the common ways of classifying micro and nano components separation. Another way of classification is by active and passive separation techniques based on whether external physical fields are applied.
Filtration is a typical separation by size process and in most time is passive. Electrophoresis [41-43] and electroosmosis [44-46] are widely used methods for separation by charge and they are typical active methods. However, the boundaries of these two types of separation are not clear nowadays. A lot of designs of filter take advantages of both of active and passive methods [47, 48].

There are several different classifications of filtration methods; by the filtration process difference, there are two types, filtration with barriers and continuous flow separation. One way to classify the filters with barriers is based on the differences of their structures. There are (1) weir [49-51], (2) pillar [51-53], (3) membrane [54, 55], types of barrier filters. Another way is according to the direction of flow and filter surface, when the flow direction is perpendicular with filter surface it is called dead-end filtration. In contrast, if the flow direction is parallel with the filter, it is classified as cross-flow filter. Filtration with weir and pillar is a typical dead-end filtration process. Membrane can be used for both dead-end and cross-flow filtration. In lots of articles, membrane filter refers in particular to the membrane filter for dead-end filtration [12].

Continuous separation is generally classified into two types, passive and active. Some continuous separation techniques are able to separate mixtures into plural groups by size. Passive structures such as pinched channels (pinched flow fractionation)[20, 56, 57], obstacles array (obstacle induced separation)[58-61], hydrodynamic filtration[20, 62, 63] and spiral channel (inertia flow) [64, 65], are able to separate multi micro components continuously without external physical fields. When external physical fields, such as electric[66], magnetic[67], gravity[16] or sound field[68], are applied; it is the active continuous separation. More details will be discussed in following section for each method.
2.3 Review on Micro and Nano Filtration

2.3.2 Filtration with Barriers

2.3.2.1 Weir, pillar and membrane

A weir in a micro- or nano- channel reduces the depth of the channel, thus it can block the flow of large particles (Figure 2.3a). The weir filter is applied for nano volume separation especially for single molecule separation (entropic trapping[31]). Filters with a row of pillars perpendicular with the flow direction reduce the width of flow path (Figure 2.3b). Comparing with the weir filter, the pillars filter is more easily fabricated and it has a longer working time and larger separation volume. Some publications reported filters which combined the weir and pillar, in these reports both the width and depth of flow pathway were declined [51, 69]. Some continuous separation methods (such as obstacles array) took advantages of array of pillars (more than one row) [58, 69, 70], which are distinct from pillars filters. A membrane with arrays of holes to reduce the width of the flow pathway is also used for barrier filtration (Figure 2.3c). A lot of membrane filters are not patterned such

Figure 2.3 Principle of filter with barriers: (a) Weir, (b) Pillar and (c) Membrane.
2.3 Review on Micro and Nano Filtration

as gel and some polymer membranes [71] which means the holes are not uniform and the channels are windy. This kind of membrane filter is more easily to be blocked and the filtration efficiency is lower than the well patterned membrane filter. Comparing with the pillars filter, a membrane filter can deal with a larger volume filtration as the overall flow cross-section is considerable higher.

2.3.2.2 Dead-end and cross-flow filtration

As normally the flow directions in weir, pillar and membrane filter are perpendicular with the filters and large particles are blocked by the filters, they are called dead-end filtration [72, 73]. Dead-end filters are easily blocked due to clogging and jamming [12, 51, 55, 73, 74]. A cake layer that consists of large particles will cover the filter during the filtration and will progressively stop the filtration. In addition some deformable particles such as blood cells can squeeze into the small channels, again blocking the filters and making the filtration becomes less effective over time [51]. P. Bacchin et al (2002) described the mathematic modelling of deposit formation and compaction of the cake layer[74]. The concentration of solute has an important role during the deposit process. Lower concentration of solute can slow down the deposit formation process and reduce the thickness of the cake layer[75]. External physical fields such as, pulsed electric field, high voltage electrical discharges and ultrasound, are able to improve the performance of dead-end filters [75-78]. However, these external physical fields only slow down the process but are not able to stop the deposition process completely. Cross-flow filtration is a better solution for avoiding the cake layer.
In a cross-flow filtration the flow direction is parallel with the filter surface, which is shown in Figure 2.4b. Small particles are trapped in the filter due to the mass transfer. As the majority of the feed flow travels tangentially across the surface of the filter, it washes away large components; hence the cross-flow filtration avoids the filter cake layer so that it enhances the useful time and throughput of a filter. However, many reports [79-81] demonstrated that the filter cake layer was gradually but finally formed after a long term of filtration. The reason is that some large components are captured on the surface of filter. Luis Seminario (1997) et al studied the pore blocking and permeability reduction in a cross-flow membrane filter and built a mathematic model [82]. For small volume diluted solution separation, the cake layer can be ignored. What’s more, because the majority of feed flow is along the surface of the filter, there are very weak forces to push the large components through the holes. Therefore the cross-flow filter is able to achieve high filtration efficiency and long useful time for deformable particles. External physical fields are able to enhance the cross-flow filtration process as well[83, 84]. It should be pointed out that the electric field enhanced filtration is only acceptable when the membrane and all solute particles have
the same sign of $\zeta$-potentials. Surface modification of filters such as, to produce a hydrophobic surface, is an alternative way to improve the cross-flow filtration[85]. Consequently, the cross-flow filter has a better performance than the dead-end filter under similar conditions.

All of these three types of barrier filters (weir, pillar and membrane, dead-end or cross-flow) separate the components in solution into two groups: small group and mixture group. The weir, pillar and membrane filters are suitable for different volume separations. Fine patterned filters show better selectivity. The membrane filters without uniform patterns are not able to separate similar sized particles. Cross-flow filtration improves the useful time and filtration efficiency comparing with the dead-end filtration. When there are multi species of components which need to be separated, barrier filters become less effective tools. The filtration efficiency of middle sized components is low due to the Brownian movement of smaller particles. Thus other treatments such as external physical fields, dilution and concentration are necessary.

2.3.3 Continuous Flow Separation Techniques

2.3.3.1 Pinched Flow Fractionation

Pinched flow fractionation uses two inlets; one is a liquid stream with particles and one is a buffer stream without particles. (Figure 2.5) By controlling the laminar flow rate of each inlet, the particles in the pinched segment move aligned to one side wall. Due to the different force exerted on larger and smaller particles at the outlet of pinched segment, larger particles move towards the middle of the microchannel while smaller particles move towards the side wall of microchannel. Thus the position difference of different sized particles separates the particles perpendicularly with the flow direction. This method was
2.3 Review on Micro and Nano Filtration

developed by Seki and Yamada (2004).[56] Pinched flow fractionation is a high throughput, label free, and particle sized based separation method. As the dimension of the pinch segment relates to the size of particles, a significant amount of design work is necessary to arrange for different size particles separation. The outlets which collect the different sized particles are all distributed on the upper half of the microchannel. Therefore limited amounts of outlet groups are possible due to space restrictions.

2.3.3.2 Obstacles Induced Separation

In obstacles induced separation (also called deterministic lateral displacement), the pillars or posts are not acting as barriers to block components anymore. The distance between adjacent pillars is fixed and slightly bigger than the diameter of the largest component; and each row of pillars is shifted a little to the next. After a few rows, the pillars repeat as the first row. If the diffusion can be neglected, the small particles move with the laminar flow and exit the obstacles array at same position on x direction (Figure 2.6). However, as a comparison, the large components enter the array at centre of a gap between posts; then
the inertia force will push them to the shifted side of next gap. Thus the large components move out of the original laminar stream and exit the obstacles array with the neighbouring stream. The mixture is thus separated into different positions on y direction. The paths of all particles are pre-designed with the geometry of the obstacle array, which results in a narrow outlet stream band. Consequently obstacles induced separation is a very accurate and very fast separation method without any labelling. David W. Inglis et al made the relevant theoretical analysis as a guidance for posts arrays design[61]. As the diffusion results in some off-path particles, higher flow rate is demanded for a better resolution. It is necessary to carefully design the arrays for different mixtures separation missions. And the gap between particles size are limited.

![Figure 2.6 The principle of particle separation via lateral displacement around obstacles.](image)

Small particles follow the laminar flow streams (shaded in grey) in the y-direction, whereas large particles are continuously forced to change the laminar flow stream and are thus continuously displaced in the x-direction. [20]

As the diffusion coefficient is positively related with molecule mass, there is another way to separate particles by size with obstacles arrays which is called “Brownian ratchet” [86]. A typical application of Brownian ratchet is DNA separation. Different sized molecules are pumped into the array under low flow rate (y direction). Small molecules which have higher diffusion coefficient diffuse faster. Therefore small molecules achieve larger average
movement on x direction while large molecules experience less average movement on x direction during same periods. Comparing with the obstacles induced separation, Brownian ratchet asks for a very slow inlet flow rates (few μm s\(^{-1}\)) so that the separation process is slow as well. Because Brownian ratchet separates particles based on probability of diffusion movement, the path of each sized group is not pre-designed. So the band of each sized components is wide.

### 2.3.3.3 Hydrodynamic Filtration

Hydrodynamic filtration (HDF) was first reported and demonstrated by Masumi Yamada and Minoru Seki in 2005[62]. The principle of hydrodynamic filtration is shown in Figure 2.7. When the diameter of the side channel is small, the majority of the parabolic-flow flows from left to right in main channel and only a small portion flows into the side channels. All particles of solutes cannot enter the side channels; therefore the side channels concentrate and align the micro particles along the side walls of main channel eventually. Then the particles can be selected and collected by size sequence in different sized outlet channels positioned sequentially after the small side channels.

The volume flow rate of laminar flow in a straight channel is described as, 

\[
Q = \Delta P \times \left(\frac{D_r^2 wd}{32 \mu L}\right) = \Delta P \times \left(\frac{1}{R_h}\right),
\]

where \(\Delta P\) is the pressure loss between channel ends, \(L\) is the length of the channel, \(\mu\) is the viscosity of the liquid, \(D_r\) is the hydraulic diameter of the microchannel, and \(R_h\) is the hydrodynamic resistance of the microchannel. Considering the situation at a cross section, only the flow near the side walls can enter the side channel which is the grey section in Figure 2.8. Thus the particles of which their centre is outside of the grey section (the diameter is larger than \(w_1\)) cannot flow into the side channel due to the property of laminar flow; even if the diameter of particles is smaller than the entrance of
side channel. Sari Sugaya et al studied the situation when the particles were nonspherical and which may rotate [63]. This paper demonstrated that HDF can be used for continuous shaped based separation.

Figure 2.7 The principle of hydrodynamic filtration (a) shallow side channels align particles against the main channel wall. (b) Due to the higher flow rate in larger side channels, small particles are able to enter side channels. (c) Finally, if a relatively large portion of the flow enters the side channels, both small and large particles can enter the side channels. (d) Design of hydrodynamic filtration channel network for enrichment of small and large particles. [62]

Consequently, hydrodynamic filtration is a high throughput (100 000s particles per hour), label free, continuous separation or concentration method for micro and sub-micron particles. In the HDF scheme, the particles are viewed as solid phase and the diffusion of particles in two-phase flow is ignored. However, for nano particles, the diffusion flux of the mass transfer is so significant therefore HDF scheme is not suitable to solve nano particles separation. Although its filtration efficiency cannot be as high as 100%, it needs minimal tuning for different situation so that the devices are easy to operate as compared with the
2.3 Review on Micro and Nano Filtration

pinched flow fractionation, pinched flow fractionation and obstacles induced separation methods.

![Diagram of microchannel structure](image)

Figure 2.8 Relation between the channel geometry, filtered particle size, and flow rate distribution. (a) Flow rate distribution at a branch point. (b) Diagram of a resistive circuit corresponding to the microchannel structure. [62]

### 2.3.3.4 Inertia Flow Filtration

Lateral migration due to inertial lift forces was first experimentally shown by Segré and Silberberg[87]. Under the influence of the inertial forces, neutrally buoyant particles flowing in a microchannel migrate to stable equilibrium positions. Di Carlo et al. showed that by employing a curvilinear channel the Dean vortices can be used to reduce the number of equilibrium positions to one[64, 88]. Sathyakumar et al made improvements by adding a cross section at the inlet[65]. Figure 2.9 describes the principle of inertia flow in spiral channels. Where $F_L$ is the inertial lift force and $F_D$ is the Dean drag force. The ratio of $F_L$ and $F_D$ determined the position of different diameter particles.
Inertia flow in a spiral micro channel is able to separate label free micro particles with a high throughput. The separation efficiency is around 90% [65]. Some publications reported applications of inertia flow on cell sorting and alignments [89, 90]. The significant amount of tuning required for different diameter components limits its application. It is also not suitable for nano-particles.

Figure 2.9 The principal of inertia flow filtration (a) Schematic of the spiral microparticle separator. The randomly dispersed particles equilibrate at different equilibrium positions along the inner wall (IW) of the spiral microchannel under the influence of $F_L$ and $F_D$. Separation between individual particle streams is enhanced by opening the spiral channel into a wider straight channel before extracting the individual streams using a multiple outlet design. (b) Microchannel cross-section illustrating effects of $F_L$ and $F_D$ on particles. The ratio of forces ($F_L/F_D$) is the determining factor in where a particle of given size (diameter) equilibrates. [65]

### 2.3.3.5 Active Continuous Flow Separation

There are a lot of reports on blood cells separation with continuous separation techniques [91, 92]. Rapid, high throughput, multi components purifications can be achieved by these methods. However, when the mixtures are complex and contain various diameters components, a large area for filtration is needed but it is still difficult to separate similar
diameter components. For a better filtration, an external field is introduced, which are the active continuous separation methods.

There are various active continuous separation techniques; such as split thin flow fractionation[19], acoustophoresis[93], dielectrophoresis[66], and magnetophoresis[67]; which need an external field applied [36]. These fields can enhance the selectivity; however, more complex devices are needed. For a lot of situations, such as electroneutral or antimagnetic particles separation, or space application, external fields do not help. There are also problems when the size order and charge order of components are different in complex mixtures such as whole blood. As the external fields may harm the bio-activity of cells and other bio-components, the active continuous separation is limited for some particular applications. Thus a passive continuous separation method which is label free and without any external physical field has more comprehensive applicability and thus is demanded. In this thesis, filtration without external fields is mainly concerned. For more information about active continuous separation please refer to the references.

2.3.3.6 Discussion and Conclusions

In this section 2.3.3, several continuous separation techniques have been reviewed. It was mentioned in section 2.2.6 that simple label-free continuous separation methods for micro and nano components without external fields are desired. Therefore this thesis mainly concerns the passive continuous separation. The accuracy and efficiency of separation, throughput, particle size area, output band numbers, complexity of the device, and tolerance of the sample composition variation are key issues for continuous flow separation.
2.3 Review on Micro and Nano Filtration

The PFF, HDF and obstacles induced separation (except the Brownian ratchet) view particles as solid phase thus the diffusion can be neglected. The separation accuracy of pinched flow fraction (PFF) and obstacles induced separation is very high (can be almost 100%). Meanwhile the inertia flow filtration achieves higher flow rate but lower separation accuracy. The throughput of hydrodynamic filtration (HDF) is the highest in these four techniques, while the separation accuracy is the lowest.

The PFF, HDF and inertia flow filtration are all passive continuous methods for micro and sub-micron components separation with high throughput. In contrast, the obstacles induced separation is able to separate nano-particles such as DNA molecules or micro components.

Although the PFF and inertia flow filtration are able to achieve high separation accuracy, the narrow area for the species band limits the complexity of carrier liquid composition. In other words, only a few amounts of species can be separated with these two methods. By careful design and increasing the number of rows and columns of obstacles, the obstacle induced separation can distinguish more species of components. Similarly, the HDF method is able to collect more species of particles by simply adding different size outlet capillaries. Therefore HDF can deal with very complex mixtures separations (but not complete separation).

Except hydrodynamic filtration, all other methods require numerous tuning (geometry design, injection or collection) to adjust to different separation conditions such as flow rate, carrier liquid composition or instrumental parameters. Thus the HDF method is simple for design and use with the highest tolerance of separation conditions.
Consequently, the comparisons of these techniques are not straightforward. There is no “one size fits all” method. A simple high throughput continuous flow separation method for complex mixture which contains both micro and nano particles is still a blank area.

### 2.3.4 Development Progress of Micro and Nano Filters

Before the patterned nanofilters can be easily fabricated, gel was widely used as a nanofilter in biological and biomedical research which can be found in various publications. A lot of applications of gel filters have still been reported in last two decades. [4, 94-96] Gel can be easily and economically achieved without expensive nanofabrication equipments. Although some applications take advantage of it absorption[97], the irregular poles and the winding channels limit the application of gel filter. What is more, it is complex to use gels for the fabrication of micro structures which are desired on chips. All these reasons limit the applications of gel filter and push scientists and engineers to chase well patterned nanofilters.

The membrane filter is one option to replace the gel filter. The studies of transport theory in nanopores date back to early in 20th century. Ferry (1936) derived the hindrance factor (partition coefficient Φ) at the nanopore entrance[54], and Pappenheimer et al. (1951)[98] and Renkin (1954)[99] derived the other factors representing hydrodynamic hindrance. Deen published an outstanding review paper in 1987 which listed all the relevant experimental and theoretical references in the field up to that time.[100] The review made by Han (2008) presented the progress of membrane research in the 1990s and early 21st century.[101] The recent research was focused on the applications of different material and sized membranes. Various materials, such as Si, polymer, anodic alumina, were used for membranes with different applications especially in the biomedical field.
With the development of nanofabrication technology, well patterned nanochannels are capable to be fabricated fast with low cost [101, 102]. The accurate geometric sizes and low surface roughness of patterned filters offer a more controllable filtration process. Single molecule separation in a nanochannel has been reported by Fu[103], Park[103], Diehl[104] and others.

The other important achievements are the various separation methods which have been introduced in the former section. Lots of gel-free continuous separation devices were developed in the last ten years. Figure 2.10 shows an anisotropic nanosieve array filter designed by Fu as an example of active continuous separation[47].

![Diagram of anisotropic nanofilter array](image_url)

Figure 2.10 Concept of the anisotropic nanofilter array (ANA) [47, 101]
2.3.5 Applications of Micro and Nano Filters

Filtration of micro or nano components is a fundamental operation in biological, biomedical [2] [5] and chemical engineering fields [105]. For clinical diagnoses, many of the detection techniques need to remove the blood cells before detection. There are various filter chips designed for blood cell separation. [106-108] Escosura-Muniz et al. reported a membrane sensor for cancer bio-marker CA15-3 detection in 2011.[4] Nanofilter applied on other biomarker detections can also be seen in other numerous reports. [1, 109-111] Membrane filtration is also one of the key processes of water purification [10, 105, 112].

Typical pore diameter of commercial membrane filters using in bio-laboratories are 0.1, 0.2, 0.45, 0.65, 0.8, 1, 1.2, 3, 5, 8, 12um. Table 2.1 lists the sizes of human blood cells and other components in blood which gives the concept of what filter to use for bio-components separation.

<table>
<thead>
<tr>
<th>Typical Particles</th>
<th>General Size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>7,000~20,000</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>2,400~8,000[114]</td>
</tr>
<tr>
<td>Platelets</td>
<td>4000[115]</td>
</tr>
<tr>
<td>Microvesicles</td>
<td>100~1,000[116]</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>6</td>
</tr>
<tr>
<td>Insulin</td>
<td>5</td>
</tr>
<tr>
<td>DNA diameter</td>
<td>2</td>
</tr>
<tr>
<td>Glucose</td>
<td>1</td>
</tr>
<tr>
<td>Sodium</td>
<td>0.102</td>
</tr>
</tbody>
</table>

Table 2.1 Size Table of blood components[113]
2.4 Review on Transport Phenomena in nano channels

2.4.1 Electrical Double Layer Theory

The fixed surface charge on the solid-liquid interface causes an opposite charged layer in the liquid to keep electro neutrality. This screening layer is known as the Electrical Double Layer (EDL). Schoch published a review paper on transport phenomena in nanofluidics 2008 where summarized the theory for EDL.[31] The Gouy-Chapman-Stern model is commonly used to describe EDL. (Figure 2.1) (Reprinted figure with permission from Schoch, R.B., J.Y. Han, and P. Renaud, *Transport phenomena in nanofluidics*. Reviews of Modern Physics, 2008. 80(3): p. 839-883. Copyright (2008) by the American Physical Society.) This model contains three layers. The first layer is at the inner Helmholtz plane. The co-ions and counter ions are not hydrated on this layer and are specifically adsorbed to the surface. The second layer consists of a layer of bound, hydrated and partially hydrated counter ions. The third layer is the diffuse layer at the outer most part of the EDL, composed of mobile co-ions and counter ions. Equations for the surface potential, Debye length of EDL, surface change density and surface conductance were introduced clearly in that review paper. The EDL layer is the fundamental effect for understanding the transport process in a nanochannel.
2.4 Review on Transport Phenomena in nano channels

Figure 2.11 Gouy-Chapman-Stern model of the solid-electrolyte interface, with the corresponding potential distribution $\psi$ vs the distance $z$ from the wall. The solid is illustrated with a negative surface potential $\psi_s$, described by three layers in solution. The inner Helmholtz plane layer ($\psi_i$) consists of nonhydrated co-ions and counterions, whereas the outer Helmholtz plane layer ($\psi_d$) is built up of only hydrated counterions. The diffuse layer is defined beyond the outer Helmholtz plane. At the slip plane, the $\zeta$ potential can be experimentally investigated, and as the distance between the outer Helmholtz plane and the slip plane is negligible in most cases, the $\zeta$ potential is usually equal to $\psi_d$. [31]

http://dx.doi.org/10.1103/RevModPhys.80.839

2.4.2 Mass Transfer in nanochannels

The mass transfer process consists of diffusion and convection. Fick’s laws illustrate the diffusion progress. The First Fick’s Law is,[117]

\[ J_{diff} = -D \nabla c \]  
Equation 2.1

And the Second Fick’s Law is,

\[ \frac{dc}{dt} = -D \nabla^2 c \]  
Equation 2.2
2.4 Review on Transport Phenomena in nano channels

The convection flux is,

\[ J_{\text{conv}} = \pm v_c c \]  \hspace{1cm} \text{Equation 2.3}

Considering the EDL theory, there is a flux generated by electric potential which is:

\[ J_\Phi = -\frac{z_j F}{RT} D_j \cdot c_j \nabla \Phi \]  \hspace{1cm} \text{Equation 2.4}

Consequently, the transport progress of component \( j \) is able to be described by the extended Nernst-Planck equation [31]

\[ J_j = -D_j \nabla c_j \pm v_c c_j - \frac{z_j F}{RT} D_j \cdot c_j \nabla \Phi \]  \hspace{1cm} \text{Equation 2.5}

Where \( J_j \) is the flux of component \( j \),

\( \nabla \) represents gradient,

\( c_j \) is the molar concentration of component \( j \),

\( v_c \) is convective velocity field,

\( z_j \) is the valence of component \( j \),

\( F \) is the Faraday constant,

\( R \) is the gas constant,

\( T \) is the temperature,

\( \Phi \) is the electric potential,

\( D_j \) is the diffusion coefficient for component \( j \).

The continuity equation of mass transfer is:

\[ \frac{\partial c_j}{\partial t} + \nabla \cdot ( -D_j \nabla c_j ) + u \cdot \nabla c_j = R_j \]  \hspace{1cm} \text{Equation 2.6}

Where \( u \) is the velocity vector;

\( R_j \) is the net mass production rate in chemical reactions and \( \sum_j R_j = 0 \).
2.4 Review on Transport Phenomena in nano channels

2.4.3 Diffusion Coefficient for Multicomponent Mass Transfer

For a mixture of components in a porous medium the diffusion coefficient \( D_{ij} \) for the component \( j \) in the \( i^{th} \) level sieve should be used instead of \( D_j \), which is defined as:[118, 119]

\[
D_{ij} = \frac{\varepsilon_{ij} D_j}{\delta_{ij} \frac{a_i a_j}{d(a_i+w_i)}} D_j \quad \text{Equation 2.7}
\]

Where \( a_j \) is the diameter of component \( j \);

\( a_i \) is the width of the \( i \) level sieves’ channel, assuming its width equals to its depth;

\( d \) is the depth of inlet channel;

\( w_i \) is the distance between two adjacent sieves;

\( \varepsilon_i \) is the porosity, which equals \( \frac{a_i^2}{d(a_i+w_i)} \);

\( \delta_{ij} \) is the constrictivity, defined as \( \frac{a_j}{a_i} \);

\( \tau \) is the tortuosity.

With the tortuosity equal to 1 in this case, we have,

\[
D_{ij} < D_j \quad \text{Equation 2.8}
\]

This means that components are less likely to do Brownian movement in a narrow space. Thus we can answer why it is time consuming to filter small particles. It is not only due to the low flow rate in finer channels, but also the lower diffusion coefficient.

When similar diameter components are mixed together, the interactions among similar components result in a multicomponent Fick diffusion coefficient of liquid mixtures. This diffusion coefficient can be estimated by the formula \([D_{ij}] = [B]^{-1}[\Gamma] \), where \([B]\) is the matrix function of inverted binary diffusion coefficients, \([\Gamma]\) is the matrix of thermodynamic factors. [117](Taylor, R. and R. Krishna, Multicomponent mass transfer, section 4.2.2)
2.4 Review on Transport Phenomena in nano channels

2.4.4 Continuity and Navier-Stokes Equations

For incompressible Newtonian fluids and assuming constant viscosity, the continuity equation and the Navier-Stokes equation describe the laminar flow in channels, which are:

\[\nabla v_c = 0\]  \hspace{1cm} \text{Equation 2.9}

\[\eta \nabla^2 v_c - \nabla P - F_b \sum_{j=1}^{n} z_j c_j \nabla \psi - F_b \sum_{j=1}^{n} z_j c_j \nabla \varphi = \rho \frac{\partial v_c}{\partial t}\]  \hspace{1cm} \text{Equation 2.10}

Where \(P\) is the external pressure,

\(\eta\) is the viscosity,

\(F_b\) is the body force,

\(n\) is the number of different species components,

\(\psi\) is the electric potential due to surface charge,

\(\varphi\) is the electric potential caused by stream,

\(\rho\) is the density of fluid,

\(t\) is the time,

other terms are as introduced previously.

Equation 2.9 is the continuity equation. Momentum conservation equation 2.10 describes the viscous force results from convective movement of fluid, and three other forces working on any volume elements of the flow. The first term is the viscous force. The second term shows a mechanical force due to the pressure gradient. The third term illustrates body forces caused by the polarization of EDL, and the forth part relates to another body force due to the streaming potential. For a steady flow, the viscous force balances all the other three forces. If the components are electro neutral, Equation 2.9 can be simplified as

\[-\nabla P + \eta \nabla^2 v_c = 0\]  \hspace{1cm} \text{Equation 2.11}
2.4 Review on Transport Phenomena in nano channels

2.4.5 Casson fluid

For non-Newtonian fluids such as Casson fluid, however, the Navier-Stokes equation is not able to describe the flow properties accurately. Casson fluid was defined as a shear thinning liquid which is assumed to have an infinite viscosity at zero rate of shear, a yield stress below which no flow occurs and a zero viscosity at an infinite rate of shear. Blood is viewed as one of the typical Casson fluids[121]. Casson’s constitutive equation is shown below:

\[ \sqrt{\tau} = \sqrt{\tau_y} + \sqrt{-\mu_x \frac{du}{dr}}, \quad \text{if } \tau \geq \tau_y \]
\[ \frac{du}{dr} = 0, \quad \text{if } \tau \leq \tau_y \]

Where \( \tau \) is the shear stress; \( \tau_y \) is the yield stress; \( \mu_x \) donates the Casson viscosity; \( u \) is the axial velocity; and \( r \) is the distance towards axes of tube. The boundary condition is:

\[ u = 0, \quad \text{when } r = R \]

where \( R \) is the radius of tube. In this thesis, the Newtonian fluid is mainly concerned at a start point of multi-level nanofilter. As the blood is too complex for a design verifying, the aqueous dextran solution is selected as a test solution which is Newtonian fluid [122].
2.5 Review on Fabrication Techniques Used in This Thesis

The fabrication techniques used in this thesis are photolithography, ICP Reactive Ion Etching, and Focused Ion Beam machining.

2.5.1 Photolithography

Photolithography is a process which transfers the 2D geometric patterns from a mask to 3D light sensitive chemical photoresist modules[123]. It is easy to fabricate micro structures with photolithography.[124, 125] The whole process is: pre-treatments, photoresist coating, soft bake, exposure, hard bake (post-exposure bake), develop and clean. During the soft bake, the solvent that the photoresist is dissolved in evaporates and the photoresist loses its liquidity and adheres with substrate the wafer. [126]

Photochemical reaction takes place in photoresist during the exposure to UV light. For positive photoresist, such as MICROPOSIT S1800 SERIES photoresist [127], the exposure area is soluble in developer. For negative photoresist, such as SU-8 [128], cross-link structures forms during the photochemical reaction and post exposure. These cross-link structures are not soluble in developer. The hard bake improves the adhesion force between photoresist and the substrate, and reduces the standing wave phenomena caused by the destructive and constructive interference patterns of the incident light. After development, the modules of photoresist are fabricated.

2.5.2 Inductively Coupled Plasma Reactive Ion Etching

Inductively coupled plasma reactive ion etching is widely applied in industry for fabrication of MEMS systems. Figure 2.12 illustrates the main structure of the ICP RIE system. The
inductively coupled plasma has high density ion fluxes for anisotropic dry etching under low pressure.[129] A RF source is applied on a coil wrapped around the RIE plasma discharge region, to generate inductively coupled plasma. As the density of the plasma and the momentum imparted to the ions can be controlled separately, high aspect ratio structures are achievable by ICP RIE.

![Figure 2.12 Schematic figure of STS ICP system (www.stsystems.com)](Click to view image)

The reactive ion etching proceeds with chemistries which are classified as etching gas and passivate gas. Etching chemistries are normally sulfur-hexafluoride (SF₆) or the combination of tetrafluoromethane (CF₄) mixed with oxygen (O₂). For SF₆, the ICP controls the density of F ions in the plasma while the electrode power of capacitive coupled plasmas (CCP) (Forward Power) controls the momentum applied. In this situation, there are three basic etching mechanisms for silicon: firstly F ions reach attach and chemically combine with the Si to form a volatile SiF₄, and then are pumped away (chemical etching); secondly F ions impinge on the substrate and hit Si ions away (mechanical etching), and thirdly F ions impinge on the substrate, chemically bind with the Si (ion assisted etching).[130, 131]
passivate cycle, octafluorocyclobutane ($C_4F_8$) forms a passivation layer on the surface of substrate and protects the side walls during the etch periods. [85] As the photoresist has a high etch resistance, there is a high etch selectivity.

2.5.3 Focused Ion Beam

The Focused Ion Beam was developed in late of 1970s as a microscope[132]. Currently FIB is wildly used in semiconductor research, processing environments, failure analysis TEM treatments and chip-design centres. As the FIB system enables localized milling and deposition of conductors and insulators in nanoscale, it shows advantages at device modification[133], mask repair[134], process control[135] and failure analysis[136].

Figure 2.13 Schematic diagram of Focused Ion Beam ion column
(http://www.wikiwand.com/en/Focused_ion_beam)
2.6 Summary

Figure 2.13 shows the focused ion beam system. It consists of the liquid metal ion source[137], and focusing lens columns with mass separation capability[138] etc. There are various ion species for the liquid metal ion source; such as Ga, Au, Si, Be, B, As, P, etc. [139] [140, 141]. When the ion incidents on a solid surface; the sputtering of ions, emitting of electrons and chemical reactions all occur. Some atoms move away from their equilibrium positions, and ions implant into the solid, altering solid properties. The sputtering and implantation are widely used in semiconductor device fabrication [142-144] and in other fields[145]. FIB is able to induce deposition with chemical vapour assistance. [142] It is convenient and flexible to milling various sized nanochannels with FIB systems [146-148].

2.6 Summary

In this chapter, several traditional accurate size separation methods were reviewed and discussed. Due to the demand of continuous flow separation without external physical field and the development of microfluidics, numerous micro and nano devices were investigated and reported in the last two decades. The classifications of these separation methods were illustrated. References relating to each type of filter were given. The filters with barriers which are weir, pillar or membrane were discussed. According to the direction of inflow and outflow, there are two kinds of filtration process with barriers, dead-end and cross-flow. The clogging issues related were reviewed. The cross-flow filtration can reduce the cake layer significantly. For similar reason, the continuous flow separation methods avoid the severe problem caused by clogging. The filter with barriers can separate mixture into two groups: small group and the mixture.
Then continuous separation technologies were introduced, some of which can separate mixtures into plural bands. These methods exhibit advantages of high throughput, low blocking possibilities, and accurate label-free multi targets separation. What’s more, with these methods, the continuous introduction of sample, continuous readout of separation efficiency, and lateral separation of sample components were realized and showed great potential for integration. However most of the structures of continuous separation devices are complex and need to be designed and tuned carefully to adjust to different separation conditions; and there are still problems to separate complex mixtures containing both micro and nano particles, such as human blood. Due to the wide range of component diameters, various and complex properties of particles; continuous separation devices are difficult to be designed. The properties of particles limited the application of external physical field. The complicated outer devices on the other hand increase the cost thus reducing the demand of active continuous flow separation. The reviews on transport theory offered mathematic tools to analyse transport process in nanofilters, which is essential for the multi-level filter design. The brief review on photolithography, ICP RIE and FIB is a basis fundamental for fabrication process design.
3.1 Introduction

This chapter builds analyses and optimises the model of a nanofilter aiming at a new design of multi-level nanofilter for sequence filtration process. The theoretical design principles related to this multi-level micro- and nano-filter are discussed.

The study in this chapter starts from an analysis of transport phenomena in dumbbell shaped channels (Figure 3.1b&c), which is the basis of traditional filtration by size. The dumbbell shape channel can be viewed as a unit of a pillar or membrane filter, or two symmetric weirs (dead-end filter). Then the dumbbell shaped channels were improved to semi-H (cross-flow filter) and H shaped channels (Figure 3.1d&e). After studying the static and dynamic properties of H shaped channels (Figure 3.1f), an angular is introduced to the H shaped channels. The effects of angle were analysed and confirmed with COMSOL Multiphysics® finite element software. Based on these results, theoretical design principles of this type of multi-level micro- and nano-filters are discussed. Then a new model of a multilevel filter is built with these principles.
3.2 Transport Phenomena in Dumbbell and Semi-H Shaped Channels

3.2 Transport Phenomena in Dumbbell and Semi-H Shaped Channels

Traditionally a filter is something porous which is able to separate mixture components by size. Ideally it can be viewed as a union of uniform pores. Each pore is combined with two volumes beside it as a dumbbell shape, which is the basis of H shaped channels that are discussed in this chapter. (Figure 3.1a, b&c) Here these three channels from left to right were named as: sample inlet channel (I), sieve channel (II) and capture channel (III) respectively. The study of dumbbell and H shaped channels is helpful to understand the filtration process.

In the following study it is assumed that there are \(i\) \((i = 1, 2, \ldots, n)\) levels of filter and \(j\) \((j = 1, 2, \ldots, n)\) levels of components in the mixture. However, additionally before building the model of dumbbell channels, certain other assumptions must be made. These are, that...
all particles in the mixture are spheres, the diameter of the biggest particles are smaller than the distance between adjacent pores’ centre which is \( w_i \), and the smallest particles are smaller than the diameter of the pore \( a_i \) (otherwise it cannot be simplified to a dumbbell model). All entrances of channel I, II and III are square. As not all mixture components are able to separate by charge and sometimes electric fields mix different sized particles together by their electric properties, it is assumed in this chapter that the components studied are electro neutral.

Then the particles were separated into two groups; a big group for which the diameters are bigger than the pore size and a small group in which the diameters are smaller than the pore size. It was also assumed that during the filtration process the big group is blocked, while the small group can pass through the pore or sieve channel II. For both groups, their transport progress of component \( j \) is able to be described by the extended Nernst-Planck equation (Equation 2.5), when the particles are electro natural (\( Z_j = 0 \)), the equation can be simplified as follows:

\[
J_j = -D_j \nabla c_j \pm \nu_c c_j
\]  
\text{Equation 3.1}

For the big group, the diffusion coefficient in the sieve channel (II) must be 0. That is,

\[
D_{\text{big}} = 0
\]  
\text{Equation 3.2}

Thus the big group particles are blocked by sieve channel (II), and their movements are limited to the sample inlet channel (I). Navier-Stokes equations are used to illustrate the steady laminar flow in channels, and with a no slip boundary condition applied are

\[
\nabla \nu_c = 0
\]  
\text{Equation 2.9}

\[
\eta \nabla^2 \nu_c - \nabla p = 0
\]  
\text{Equation 3.3}
3.2 Transport Phenomena in Dumbbell and Semi-H Shaped Channels

COMSOL Multiphysics® Modelling Software is a finite element simulation software. The Laminar Flow module and Transport of Dilute Species module were used to assist the analysis in all simulation results in this thesis. The Navier-Stokes equation is used in the laminar flow module.

3.2.1 Static Properties of Dumbbell Channels

In this model, the pressure difference between inlet and outlet was 100 Pa; the density of liquid was 1050 kg/m$^3$; the dynamic viscosity was 0.03 Pa·s; the diffusion coefficient was 3.28e-10 m$^2$/s; the inlet and outlet channels (I and III) was 1x1.5 μm$^2$; and the sieve channel (II) was 0.5x0.5 μm$^2$. The free triangular mesh was drawn by COMSOL Multiphysics®, of which the maximum element size was 20nm while the minimum size was 3 nm. No-slip boundary condition was used in this simulation.

The typical velocity and its streamline graphs of Newtonian liquid flow through a dumbbell channel are exhibited in Figure 3.2, which represents the small group transport as well. The concentration after filtration reaches the same value as the inlet. The flux and flow rate through the sieve channel of the big group are zero, while the concentration is raised in channel I. A problem, however, is produced due to the big group concentration magnitude. The high concentration of big particles on the interface between channel I and II may block the entrance of channel II, which means the transport of the small group may be stopped by the filtration process naturally. To avoid this potential blocking, the direction of the fluid inlet and outlet of channel I were changed to the y-axis orientation. As a result semi-H shaped channels were achieved which is the basis of cross flow filtration (Figure 3.1d), these will be discussed in the next section.
3.2 Transport Phenomena in Dumbbell and Semi-H Shaped Channels

![Figure 3.2 Dumbbell channels (a) velocity streamline; (b) velocity magnitude.](image)

### 3.2.2 Transport Properties of Semi-H Shaped Channels

In this model, the pressure difference between inlet and outlet was 100 Pa; the density of liquid was 1050 kg/m$^3$; the dynamic viscosity was 0.03 Pa-s; the diffusion coefficient of small group in the sieve was 3.28e-10 m$^2$/s; the inlet and outlet channels (I and III) was 1x1.5 μm$^2$; and the sieve channel (II) was 0.5x0.5 μm$^2$. The free triangular mesh was drawn by COMSOL Multiphysics®, of which the maximum element size was 20 nm while the minimum size was 3nm. No-slip boundary condition was used in this simulation. All initial values were zero.

The velocity streamline of semi-H shaped channels (Figure 3.3) shows that due to the initial inlet velocity the big group and parts of the small group flow down along the sample inlet channel (I). Comparing with the dumbbell shaped channels; the semi-H shaped channels result in the big group moving along channel I and eliminating the dead volumes; thus reducing the probability of clogging. However, the bifurcation of streamlines towards channel II illustrates a tendency of sieve channel (II) to concentrate the big group components[62]. As the particle size is more similar with the pore diameter, there is a higher probability of the particle to be trapped. In other words, the more similar the size of
3.2 Transport Phenomena in Dumbbell and Semi-H Shaped Channels

the particle blocked by a filter to the filter pore diameter, the higher chance it has to block the filter. This result fits the former study of cross-flow filtration [149]. So that semi-H shaped channels are not able to eliminate cluster but to ease the blocking. This result answers why cross-flow filtration still forms a cake layer after long term use and therefore fits the reports[79, 80, 150]. A smaller pore size and a higher inlet velocity are helpful to reduce blocking. The right part of the semi-H shaped channels showed an extension of streams which potentially can be used for continuous separation[56, 62].

For the small group, a multi-component mass transfer (convection) takes place in channels. A same concentration of small group as the inlet sample is achieved at the end of the capture channel (III). Comparing with dumbbell channels, the convection flux and especially the flow rate in the capture channel III reduce. It is because portions of small particles escape from capture and flow through the new outlet of channel I. So that it takes longer time for the concentration in channel III to get same level as in the dumbbell model.
Consequently, semi-H shaped channels (cross-flow filtration) have a potential to reduce cluster; but sacrifice target amounts of substance collected after filtration, and extend response time. A more important disadvantage is the difficulty of pumping flow through the sieves due to the pressure drop during the fluid flow through orifices [151, 152]. Next to improve the fluid kinetics properties, an H shaped channels model is studied.

### 3.3 Transport Phenomena in H Shaped Channels

#### 3.3.1 Static Flow Properties of H Shaped Channels

As is shown in Figure 3.1e, H shaped channels consist of two parallel inlet channels and one connected channel perpendicular to them, which are geometrically symmetric. In the sample inlet channel, channel I, the input solution is awaiting separation; and the capture channel, channel III, inputs a buffer solution. If there is no electric field or components in solution are electro neutral (as assumed in these studies), there is purely multicomponent mass transfer between these two inlet channels. If the two inlet flows have the same velocity or are under the same pressure, in other words, the flows in these two channels are symmetric; there is only diffusion in channel II. This phenomenon can be explained by the symmetry. For the big group, the flow is similar to the semi-H shaped channels result. It can be seen from the velocity streamline shown in Figure 3.4 clearly that the two inlets flow separately.
The flux streamlines of the small group are shown in Figure 3.5. Components enter the sample inlet channel, diffuse through the sieve channel, and then diffuse to the lowest concentration part which is the inlet of the capture channel. That is why U shaped (or sometimes shallow w shaped) flux streamlines appear.
The velocity magnitude and contour pressure are shown in Figure 3.6 and 3.7 respectively. The force generated by the pressure gradient along channel I and III pushes fluid to flow along these two channels and eliminates the dead volumes both sides. Thus relieves the adhesion and clogging around the sieve channel. As the pressure gradient is symmetric, no flow is seen in channel II. For steady laminar flow, the static and dynamic results on velocity and pressure are same. In this model, the pressure difference between the inlet and outlet was 100 Pa; the density of liquid was 1050 kg/m$^3$; the dynamic viscosity was 0.03 Pa·s; the diffusion coefficient of small group in the sieve was 3.28e-10 m$^2$/s; the inlet and outlet channels (I and III) was 1 x 3 μm$^2$; and the sieve channel (II) was 0.5 x 0.5 μm$^2$. The free triangular mesh was drawn by COMSOL, of which the maximum element size was 20 nm while the minimum size was 3 nm. No-slip boundary condition was used in this simulation.
3.3 Transport Phenomena in H Shaped Channels

3.3.2 Static Concentration vs. Channel Size of H Shaped Channels

Figure 3.8 exhibits the concentration magnitude in H shaped channels. The big group keeps its concentration after filtration while parts of the small group diffuse into the buffer flow. Now considering purely the small group, it can be seen that the concentration at the outlet of the capture channel is not able to reach the same level as was seen in the dumbbell or semi-H shaped model anymore. Based on Fick’s Second Law (Equation 2.2), the width and depth of sieve channel, \(a_i\); the length of the sieve channel which is \(h_i\) and diffusion coefficient \(D_j\) decide the concentration diffusing to the capture channel. It was assumed that the inlet concentration of channel I is unit one, and the inlet concentration of channel III is zero, that is:

\[
\begin{align*}
C_{0j}^{\text{Sample}} &= 1, \\
C_{0j}^{\text{Capture}} &= 0.
\end{align*}
\]

Equation 3.4
To simplify the model, it is assumed that the diffusion coefficient is constant everywhere in the model. Table 3.1 exhibits the outlet concentration of channel III \( \frac{c_{i,j}^{\text{Capture}}}{c_{0,j}^{\text{Sample}}} \times 100\% \) with different \( a_i \) and \( h_i \), while \( w = 1\mu m \). When \( a_i \geq w \), H shaped channels does not function as a filter anymore, and under this condition \( D_{ij} = D_j \). The highest concentration of small group in channel III without external field assistance is 50% of the input. This is due to its symmetry. It can be explained by Fick’s Second Law or the Second Law of Thermodynamics.

### Table 3.1 Concentration at the outlet of capture channel with different sieve size (%)

<table>
<thead>
<tr>
<th>( h_i )</th>
<th>( a_i = 0.5 )</th>
<th>( a_i = 1 )</th>
<th>( a_i = 4 )</th>
<th>( a_i = 8 )</th>
<th>( a_i = 10 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( h_i = 0.5 )</td>
<td>47.37</td>
<td>48.76</td>
<td>49.97</td>
<td>50.00</td>
<td>50.00</td>
</tr>
<tr>
<td>( h_i = 1 )</td>
<td>45.89</td>
<td>47.97</td>
<td>49.90</td>
<td>50.00</td>
<td>50.00</td>
</tr>
</tbody>
</table>
3.3 Transport Phenomena in H Shaped Channels

It is understandable that due to the inlet convection velocity, components are more likely to move along the sample inlet channel rather than enter the sieve channel. The analysis of Equation 2.8 in the previous chapter illustrated that the diffusion is anisotropic in porous medium. These are two reasons why H shaped channels used as a filter cannot capture as much as 50% of the inlet target components. To achieve a concentration as high as 50% of the inlet at the capture side, higher integration of flux on the cross sectional area is demand. Hence higher flux or larger cross-section area are required. A shorter sieve channel can increase the concentration gradient in the sieve channel thus increases the diffusion flux. The larger pore area (no larger than the sample inlet) can be achieved by adding the number of sieve channels which is the H shaped channel series (Figure 3.9). Further discussions on the sieve series will be illustrated in the next chapter.

Figure 3.9 (a) a single sieve H shaped channels; (b) H shaped channel series
3.3 Dynamic Model of H Shaped Channels

For a steady fully developed laminar flow, the time dependent solution is the same as the static result. The response time of the filter which is defined as the time taken by the capture channel to achieve a steady outlet concentration, marked as $T_{i,j}$. Therefore there is,

$$\frac{dc_{i,j}}{dt} = 0, \text{ when } t \geq T_{i,j} \quad \text{Equation 3.5}$$

It is difficult to give a generalized solution of $T_{i,j}$, but CFD software is helpful to give a numerical result for specific models. In this model, there are $w = 100 \text{ nm}, a_i = 50 \text{ nm}, h_i = 100 \text{ nm}$, and $D_{i,j} = 3.28e-10 \text{ m}^2/\text{s}$. The simulation settings were the same as the one in section 3.4, besides the solver was time dependent rather than stationary.

Figure 3.10 exhibits a curve of $c_{i,j}^{\text{Capture}}(t)$, which was drawn by COMSOL finite element software. For this curve, the mass transfer process took only a second to reach a steady concentration output, in other words a steady flux of component $j$. Figure 3.11 illustrates the total flux changing at the outlet of the capture channel, which is $f_{i,j}^{\text{Capture}}(t)$.

![Figure 3.10 Concentration in capture channel corresponding with time (s)](image)
3.3 Transport Phenomena in H Shaped Channels

As a higher flux is able to expedite the mass transfer process, according to the extended Nernst-Planck equation (Equation 2.5) a larger gradient of concentration and a higher diffusion coefficient should be chosen to create a higher flux. For H shaped sieves, most geometric sizes and the diffusion coefficient are fixed by the application except for the length of the sieve channel. Thus a shorter sieve channel can be used to reduce response time.

3.3.4 Conclusions

H shaped channels are high throughput filters. The flows along the interface between channel I & II, II & III reduce the possibility of adhesion at the solid-liquid interface. In addition as the concentration in the capture channel (II) is always lower than the concentration in the channel I, the concentration of the small group in the sample inlet channel reduces (thus there is a negative concentration gradient) during the mass transfer.
3.4 Transport Phenomena in Angular H Shaped Channels

process (due to the Fick’s law); hence the chance of clogging further declines due to this dilution phenomenon. However, a filter based on H shaped channels cannot capture the target components to a level as high as 50% of the concentration of the inlet sample. Thus for applications which ask for keeping the target concentration, a concentration process is necessary. By extending the sieves of H shaped channels, an H shaped channels series is able to improve the capture concentration with the same inlet sample concentration.

3.4 Transport Phenomena in Angular H Shaped Channels

To enhance the convection in the sieve channel (channel II) of H shaped channels, an angle is introduced to make the channels asymmetric (Figure 3.12). Choosing the position sieve channel of the standard previously discussed symmetric H shaped channels as the positive x-axis, and the sample inlet flow direction as the negative y-axis; the angle that the sieve channel is rotated through is defined as $\theta \in (-90^\circ, 90^\circ)$. The angle $\theta$ for H shaped channels is zero. Thus angular H shaped channels are built when angle $\theta$ is not equal to zero. This subsection introduces the transport phenomena in angular H shaped channels, especially the changes caused by the angle.

![Diagram of Angular H shaped channels](image.png)

Figure 3.12 Angular H shaped channels
3.4 Transport Phenomena in Angular H Shaped Channels

In this model, the pressure difference between inlet and outlet was 100 Pa; the density of liquid was 1050 kg/m$^3$; the dynamic viscosity was 0.03 Pa·s; the diffusion coefficient of small group in the sieve was 3.28e-10 m$^2$/s. The free triangular mesh was drawn by COMSOL Multiphysics®, of which the maximum element size was 20nm while the minimum size was 3nm. No-slip boundary condition was used in this simulation. All initial values were zero.

3.4.1 Static Flow Properties of Angular H Shaped Channels

The angle $\theta$ destroys the geometric symmetry of the H shaped channel; so if the inlet keeps the same conditions as subsection 3.2.3, convection appears in sieve channel II (Figure 3.13). This convection is caused by the inertia of fluid and the concentration gradient around channel II. There are 20 streamlines in Figure 3.13. Thus the flow rate through the sieve channel is around fifth of the inlet flow rate.

![Figure 3.13 Velocity streamline of angular H shaped channel](image)
In Figure 3.14, that shows contour pressure, it can be seen that the pressure in channel I and II drops down nonlinearly. The sieve channel connects the two channels and there is a tendency to equilibrate the pressure beside its two entrances. Comparing with the contour pressure of H shaped channels (Figure 3.7), the angular sieve channel changes the pressure gradient in channel I and II, and reduces the pressure difference at the two ends of the sieve channel (if there were no sieve channels, the pressure difference between the start point and end point of sieve channel should be higher). Due to the inertia of the fluid and the additional pressure gradient on the sieve channel, a bigger angle magnitude results in a higher y direction velocity component. Thus a higher convection velocity is achieved in channel II with a larger angle magnitude. For no slip boundary condition, fine sieve channels reduce or even prevent the convection in them.
3.4 Transport Phenomena in Angular H Shaped Channels

The direction of convection is dependent on whether the angle is positive or negative. A positive angle results in convection from the capture channel to the sample inlet channel. It is helpful to reduce adhesions on the interface between channel I and II and adhesions inside sieve channel as well, while dilute the sample solution in channel I. For a negative angle the convection is from channel I to III, which is helpful for the capture progress in the capture channel and reduces the response time. However the extended length of channel II increases the chance of clustering inside it. According to the Navier-Stokes equation, the convection in the sieve channel reduces by the diameter of sieve channel. Hence the angle effect declines with the diameter of sieve channel.

Figure 3.15 illustrates the velocity magnitude in the angled H shaped channels. A weak convection flow in the sieve channel can be seen. While the flux streamline of the small group is shown in Figure 3.16a. Comparing with the U shaped flux streamline of H shaped channel (Figure 3.5), a shift to an asymmetric U shape is seen. This asymmetry results in a different outlet concentration. Figure 3.16b illustrates the situation when the sieve channel is wide enough, where the bottom flux streamline is U shape. However, it cannot work as a filter because all particles injected are able to pass through the sieve channel.
3.4 Transport Phenomena in Angular H Shaped Channels

![Figure 3.15](image1.png)

**Figure 3.15** Velocity Magnitude of Angular H shaped channels (m/s)

![Figure 3.16](image2.png)

**Figure 3.16** Flux Streamline of Small Group (a) Inlet channels are $1 \times 3 \, \mu m^2$, the distance between two inlet channels is $0.5 \, \mu m$, and the width of sieve channel is $0.5 \, \mu m$; (b) Inlet channels are $1 \times 8 \, \mu m^2$, the distance between two inlet channels is $0.5 \, \mu m$, and the width of sieve channel is $2 \, \mu m$. All the other settings of these two models are the same.
3.4 Transport Phenomena in Angular H Shaped Channels

3.4.2 Static Concentration VS. Angle

If the same assumptions regarding the inlet concentration are made as in section 3.2 and 3.3.2 (Equation 3.4), the flux streamlines start from the sample inlet and end at the capture inlet. As the flux streamlines are separated evenly almost everywhere (except the area near the wall and around the cross sections, Figure 3.16), concentration can be approximated as a linear reduction along the flux streamline (uniform concentration gradient). Then the concentration distribution issue shifts to a length issue of flux streamline (based on Equation 2.1). Furthermore, it can be approximated by the boundary condition of angled H shaped channels, which are the three red line sections shown in Figure 3.17. Thus a different angle results in a different concentration output, which can be seen in Table 3.2 \[ \left( \frac{c_{\text{Capture}}}{c_{\text{Sample}}} \times 100\% \right) \].

<table>
<thead>
<tr>
<th>$\theta$</th>
<th>(0.5, 0.5)</th>
<th>(8, 0.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$60^\circ$</td>
<td>47.07</td>
<td>48.19</td>
</tr>
<tr>
<td>$45^\circ$</td>
<td>47.14</td>
<td>49.54</td>
</tr>
<tr>
<td>$30^\circ$</td>
<td>47.20</td>
<td>49.75</td>
</tr>
<tr>
<td>$0^\circ$</td>
<td>47.37</td>
<td>50.0</td>
</tr>
<tr>
<td>$-30^\circ$</td>
<td>47.78</td>
<td>50.21</td>
</tr>
<tr>
<td>$-45^\circ$</td>
<td>48.08</td>
<td>50.46</td>
</tr>
<tr>
<td>$-60^\circ$</td>
<td>48.47</td>
<td>51.81</td>
</tr>
</tbody>
</table>

It shows clearly that the target concentration increased when the angle decreased. If the sieve channel is big enough (U shaped flux streamline), in the simulation the outlet concentration of the capture channel is not only limited to 50% of input sample. Here the
entrance length of inlet lamina flow is ignored, and the concentration at the sample inlet was fixed as 1 mol/m$^3$ while at the capture inlet was fixed as 0 mol/m$^3$. For the continuous flow, in reality, the backward flux in capture channel rise the concentration at the inlet of capture channel thus the concentration cannot be always zero. Moreover, the entrance is much longer than a micro or nano channel; thus these effects are difficult to be observed.

3.4.3 Dynamic Model

As it was mentioned the response time of a filter is related to the length of the sieve channel, angled H shaped channels extended the sieve channel length and thus extended the response time. In addition, in a positive angle sieve, convection is in an inverse direction with the flux which decreases the flux and delays the response time. In contrast the convection in a negative angle sieve channel, increases the flux slightly. However the decrease of flux due to the extended length dominates the total flux, the response time $T_{i,j}$ increases with the magnitude of angle $\theta$,

$$T_{i,j} \propto |\theta|$$

Equation 3.6
3.5 A New Design of Multi-Level Filter Based on H shaped Channel Series

3.5.1 Introduction of a New Design of Multi-Level Filter

Based on the former discussion, a new multi-level filter is designed as shown in Figure 3.18. The filter is a connection of different sized H shaped channels from the smallest to the biggest in series along the sample inlet channel. So it separates components \( j \ (j = 1,2, ..., n) \) by size sequence which marked as \( i \ (i = 1,2, ..., n) \) into \( n \) groups. The diameter of component \( j \) is marked as \( a_j \) and the width of the \( i \) level sieves’ channel is marked as \( a_i \), assuming its width equals to its depth. It is assumed that \( a_i < a_{i+1}, \ a_j < a_{j+1} \) and when \( i = j, \ a_j < a_i \). In the sample inlet channel, when \( i \geq j, \) component \( j \) can diffuse through the sieve channels of level \( i \); in contrast when \( i < j, \) the component \( j \) is blocked by the sieves. Their concentrations drop down at each level, if diffusion occurs. So that concentrations of the small group drops down in sequence, and the amount of the substance of the bigger components remains unchanged until their first diffusion; which is:

\[
C_{i,j,i}^{\text{Capture}} > C_{i+1,j,i}^{\text{Capture}} \quad \text{and} \quad C_{i,j,i}^{\text{Capture}} = 0. \quad \text{Equation 3.7}
\]

Thus for each spices of component \( j \), we have:

\[
C_{i,j=i}^{\text{Capture}} > C_{i,j\neq i}^{\text{Capture}}. \quad \text{Equation 3.8}
\]

In other words, each capture channel mainly captures the same number particle group, while removing all of the bigger particle groups and most of the smaller ones. This means particles are purified by size.

As the capture concentration of H shaped channels is lower than 50% of the target components sample inlet concentrations (section 3.3.2); aiming at a higher capture
3.5 A New Design of Multi-Level Filter Based on H shaped Channel Series

concentration, a series of sieve channels are applied at each level, which is the H shaped channel series. The maximum capture concentration is 50% of sample inlet concentration for a sufficient diffusion (maximum entropy). Table 3.3 shows the ideal concentrations of component $j$ at the outlet of the $i^{th}$ level capture channel compared with the concentration of inlet sample in an n-level filter based on H shaped channels $(c_{i,j}^{\text{Capture}}/c_{0,j}^{\text{Sample}} \times 100\%)$.

![Scheme for multi-level filtration in sequence.](image)

**Table 3.3 The concentration table of multilevel filter (%)**

<table>
<thead>
<tr>
<th>$j$</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>$i = 1$</td>
<td>50.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$i = 2$</td>
<td>25.0</td>
<td>50.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$i = 3$</td>
<td>12.5</td>
<td>25.0</td>
<td>50.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$i = 4$</td>
<td>6.25</td>
<td>12.5</td>
<td>25.0</td>
<td>50.0</td>
<td>0</td>
</tr>
<tr>
<td>$i = n$</td>
<td>$\frac{1}{2^n} \times 100%$</td>
<td>$\frac{1}{2^{n-1}} \times 100%$</td>
<td>$\frac{1}{2^{n-2}} \times 100%$</td>
<td>$\frac{1}{2^{n-3}} \times 100%$</td>
<td>50.0</td>
</tr>
</tbody>
</table>

The concentration of component $j$ after the $i^{th}$ level filtration in the capture and sample channel is able to be written in geometric progression.

$$c_{i,j}^{\text{Capture}} = c_{i,j}^{\text{Sample}} = \frac{1}{2^i} \cdot c_{0,j}^{\text{Sample}} \quad (i = 1, 2, ..., n) \quad \text{Equation 3.9}$$
As it was mentioned previously, one disadvantage of filtration by size is that it is only able to purify the small group from a mixture but not big ones. Comparing with a typical filter, the new design of multilevel filter achieves a purer big group also (Figure 3.18). In order to purify each group further, a dilute channel is added in parallel with the sample inlet channel (Figure 3.19). After each level of capture sieve and before the next level, same size sieves repeat again but between the sample inlet channel and the dilute channel. These sieves dilute particle groups which are smaller than the sieves size, and after these diluted sieves the concentrations of these particles drop down to 50% (if they are first time diluted). Thus in the outlet of each capture channel, the concentration of similar but smaller impurities reduces. Table 3.4 shows the concentrations of component \( j \) at the outlet of the \( i \)th level capture channel with a dilute channel added \((c_i^{C_{ij}} / c_{0,j}^{S_{sample}} \times 100\%)\), assuming that sieve channels of each level are isolated.

<table>
<thead>
<tr>
<th>( j )</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>( n )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( i = 1 )</td>
<td>50.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>( i = 2 )</td>
<td>12.50</td>
<td>50.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>( i = 3 )</td>
<td>9.38</td>
<td>12.50</td>
<td>50.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>( i = 4 )</td>
<td>7.03</td>
<td>9.38</td>
<td>12.50</td>
<td>50.0</td>
<td>0</td>
</tr>
<tr>
<td>( i = n )</td>
<td>( \frac{3^{n-2}}{2^{n-1}} \times 100% )</td>
<td>( \frac{3^{n-3}}{2^{n-2}} \times 100% )</td>
<td>( \frac{3^{n-4}}{2^{n-3}} \times 100% )</td>
<td>( \frac{3^{n-5}}{2^{n-4}} \times 100% )</td>
<td>50.0</td>
</tr>
</tbody>
</table>
3.5 A New Design of Multi-Level Filter Based on H shaped Channel Series

The concentration of component $j$ after $i$ level filtration in the capture, sample inlet and dilute channel is able to be written in a geometric progression.

$$c_{i,j}^{\text{Capture}} = c_{i,j}^{\text{Sample}} = \begin{cases} \frac{1}{2} \cdot c_{0,j}^{\text{Sample}} & i = 1 \\ \frac{2}{9} \cdot \left(\frac{3}{4}\right)^i \cdot c_{0,j}^{\text{Sample}} & i > 1 \end{cases}$$  
Equation 3.10

$$c_{i,j}^{\text{Dilute}} = \begin{cases} \frac{1}{4} \cdot c_{0,j}^{\text{Sample}} & i = 1 \\ \frac{1}{3} \cdot \left(\frac{3}{4}\right)^{i-1} \cdot c_{0,j}^{\text{Sample}} & i > 1 \end{cases}$$  
Equation 3.11

Because the common ratio $\left(\frac{3}{4}\right)$ is higher than the one without the dilute channel where the common ratio is $\left(\frac{1}{2}\right)$; if the particles were diluted by more than three levels of sieves, their concentrations in the capture channel should be no lower than the ones without the dilute channel. Both concentration percentages are lower than 7.03% after three levels dilution. Based on these analyses, a dilute filter is helpful to purify similar sized particles while it declines the concentrations of all components $j$ in all level $i \neq j$.

In this design of multilevel filter, all channels are pumped independently. Laminar streams flow along each channel, which reduces the possibility of adhesion on the surface of the sieves. What’s more, small group is diluted during the filtration, which relieves clustering in sieve channels [75]. Filtration in series makes this filter high throughput and it is able to expand levels easily. It is a general well patterned filter that fulfils most application of
3.5 A New Design of Multi-Level Filter Based on H shaped Channel Series

separation by size in a huge range of scale, such as blood cells separation and bio-marker detection. All features of this multilevel filter are able to be designed and controlled. So it is reasonable to build standard commercial chips of different range of scale. However, it is difficult to separate components of which sizes are extremely similar or even the same. In this kind of situation, other methods, such as electrophoresis and electroosmosis, can be combined with this filter for further precise purification.

3.5.2 Principles for Multi-Level Filter Design

During the design of this type of multi-level filter, several parameters should be considered. i) First is the number of channels that are enough for each level of sieves to achieve a sufficient diffusion. Considering the entrance of the sample inlet shall be big enough for all components to pass through; what is the relation among entrance channel size, filter sieve size and the number of filter sieves? This relates to the entrance area of sample inlet channel and the total area of the sieves entrance surface. In this design, the width of all sieves in the \( i \)th level is equal to their depth which is \( a_i \), and the distance between two adjacent sieve channels is \( w_i \). It is understandable that the minimum number of the \( i \)th level sieves, \( N_i \), is proportional to the width of the sample inlet entrance \( w \) and the depth of the inlet entrance \( d \) whereas inversely related to the width and depth of the sieve channel \( a_i \), where \( \gamma \) is a constant.

\[
N_i \propto \gamma \frac{wd}{a_i^2} \quad \text{Equation 3.8}
\]

Because during the same time 50% of particles entered from the sample inlet diffuse to sieves channel, \( \gamma \) cannot be lower than 0.5. Considering the size effect in nanochannels, finer sieves need a higher \( \gamma \). That means that \( \gamma \) is a function of the sieve channel geometric scale and the particle size \( a_j \) according to the effective diffusion coefficient function
3.5 A New Design of Multi-Level Filter Based on H shaped Channel Series

(Equation 2.7). When \( \gamma = 1 \), the sample inlet entrance area is equal to the total sieves entrance area of this level. \( \gamma \) is a complex function so, a better way to understand it is to find \( \gamma \) for a typical fine nanochannel and examine it for different size sieves. Simulation results on \( \gamma \) are shown in the next chapter.

ii) In a continuous flow diffusion always happens when a concentration difference exists. The second question therefore is that if we want adjacent levels that are independent, how long of a distance between two adjacent levels is enough to ignore the diffusion between them? Considering two adjacent level of sieves \( i \) and \( i + 1 \) (Figure 3.20), the concentration of component \( j \) at the end of the \( i^{th} \) level is \( c_{i,j}^{\text{Sample}} \), and the distance between two levels of sieves is \( l_i \), and the distance between the end point of either sieve is \( L_i \). It can be viewed that the later level sieve introduces an additional concentration gradient on the former level. This extra gradient results in a concentration decrease \( \Delta c_{i,j}^{\text{Sample}} \), where \( \Delta \) is the difference operator. If \( \Delta c_{i,j}^{\text{Sample}} \) is small enough, the two levels can be viewed as independent, that is \( c_{i,j}^{\text{Sample}} \approx 2c_{i+1,j}^{\text{Sample}} \). The average gradient of concentration of component \( j \) on \( l_i \) is smaller (negative) than the average value on \( L_i \), thus the average concentration gradient of component \( j \) on \( l_i \) is able to be used to estimate the extra gradient \( \Delta c_{i,j}^{\text{Sample}} \) sufficiently.

That is,

\[
\Delta c_{i,j} \approx N_i w_i \cdot \frac{c_{i,j}^{\text{Sample}} - c_{i+1,j}^{\text{Sample}}}{l_i} \approx \frac{1}{2} N_i w_i \cdot \frac{c_{i,j}^{\text{Sample}}}{l_i}
\]

Equation 3.9

So the error caused by the additional concentration gradient is estimated as,

\[
\delta_i = \frac{\Delta c_{i,j}^{\text{Sample}}}{c_{i,j}^{\text{Sample}}} \approx \frac{N_i w_i}{2l_i}
\]

Equation 3.10
Where now $\delta_i$ can be decided by technical requirements or the measurement error demand. Based on this equation the minimum distance between two adjacent level sieves can be estimated under a given error:

$$l_i \geq \frac{N_i w_i}{2\delta_i}$$

Equation 3.11

![Diagram of distance between two adjacent levels](image)

Figure 3.20 Scheme about the distance between two adjacent levels.

iii) Another question to be answered is that if engineers use droplet instead of continuous flow, aiming to take advantages of the angle effect, what angle shall be chosen. A positive angle is better for dilution process while a negative angle is helpful for the capture progress. As the entrance width of the sieve channel and the length of the sieve channel increase with angle magnitude ($-90^\circ < \theta < 90^\circ$); the extended sieves due to the angle in one side reduce adhesions inside channels because of the convection introduced, in other side it gives particles which are bigger than the diameter of sieve channels more chance to blocking the at the cross-section[153]. If engineers shorten the sieve channels, more precise fabrication methods would be needed. Normally this means a higher cost. For some fabrication techniques related with removed substrate volume, a bigger angle magnitude needs longer working time or higher energy when the distance between sample inlet and capture channels kept the same. In other words the fabrication cost increases slightly with angle magnitude.
3.6 Summary

There are some general guidelines for microfluidics chips design as well, which will be discussed in Chapter 6; such as chip’s size and material, connection interface and biocompatibility. These issues are not related with the filtration process; so that more specific analyses of these issues are discussed in Chapter 5 where the design of the mask for this multi-level filter is presented.

3.6 Summary

In this chapter, different models of filter element were built and discussed step by step, which is helpful for understanding of the transport phenomena in nano sieves especially the mass transfer process. Then a sequence filtration process was put forward, and a new design of multilevel filter base on H shaped channels was illustrated.

This filter showed potential advantages to reduce adhesion and clustering inside the filter and to purify each group of components by size order in a relatively large scale. The design parameters which affect the performance of the filter were also studied. They will be investigated more specifically in the next chapter through calculation on Semi-H shaped, H shaped and angular H shaped channels series with the finite element simulation software COMSOL Multiphysics®.
4.1 Introduction

This chapter studies the transport process and flow properties of sieve channel series which forms each level of a multi-level filter and verifies, by simulations, the design principles put forward in the last chapter. Based on these analyses, a three-level nanofilter is designed, modelled and discussed.

This chapter start the analyses from semi-H shaped channels, and then simulations of multi-level filter based on semi-H shaped channels are presented. The transport process and flow properties of H and angular H shaped channels are simulated sequentially. Then a model of a multi-level filter based on H shaped channels was the simulated with the finite element software COMSOL Multiphysics®. During these discussions the estimate formulas illustrated in Chapter 3 were examined. In these simulations the Transport of Diluted Species module and the Laminar Flow module were used to study the flow properties and the mass transfer process. The no-slip flow boundary condition was applied in this.

Dextran is a complex branched glucan which is widely used in bio-medical and bioscience. Commercial dextrans with different standard molecular mass are easily obtained. Numerous publications applied dextran as a bio-label. Thus dextran of which the aqueous solution is
Newtonian fluid is a good option for bio-filter testing [122]. Hence in this chapter and the next chapter, all simulations were applied with dextran solutions. In section 4.2-4, all models were applied with 1 mol/m$^3$3kDa dextran aqueous solution. The density of liquid was 1050kg/m$^3$; the dynamic viscosity was 0.03Pa·s; the diffusion coefficient was 7.5e-10m$^2$/s. The pressure difference between inlets and outlets was 100Pa. 500 and 2,000 kDa dextran were applied in section 4.5. The diffusion coefficient can be calculate by the Equation 2.7

4.2 Simulation on Semi-H Shaped Channels Series

4.2.1 Meshing

This model contained an inlet channel and a capture channel whose size were both 2x25 μm. Between these two channels, there were 100 2 μm x 40 nm sieve channels. The distance between two adjacent sieve channels is 120 nm. The free triangular mesh was drawn by COMSOL Multiphysics® physical-controlled mesh automatically (Fine size option).

![Figure 4.1 Free triangular mesh built by COMSOL Multiphysics® (nm)](image-url)
4.2.2 Static Flow Properties of Semi-H Shaped Channels series

Figure 4.2a&b exhibit the velocity streamline and velocity magnitude of a semi-H shaped channels series. The main convection took place in the sample inlet channel (I), while few fluids convect through the series of sieves into the capture channel (III). It is well known that the velocity in the sieve channels reduces with channel size, thus for fine sieves the velocity in capture channel is extremely low. The capture channel worked as a reservoir. This is the ‘pumping problem’ of the semi-H shaped channel series. Contour Pressure is shown in Figure 4.3 which explains this problem. In the sieve channels, pressure dropped rapidly and increasing the inlet pressure did not help significantly with the flow through the sieve channels. One way to solve this problem is to pump both sides of the sieve channels independently, which is achieved in H shaped channels series shown in a later section 4.3.

Figure 4.2 Semi-H shaped channels series, (a) Velocity streamline; (b) Velocity magnitude
4.2 Simulation on Semi-H Shaped Channels Series

Static concentration of target components (Figure 4.4) on both sides of the sieve channels is the same due to the continuous sample input. So a semi-H shaped channel series filter cannot drop down the target component concentration in the sample inlet channel. This phenomenon disables the ability of a multi-level semi-H shaped channels series to purify components except for the smallest target group.

Figure 4.3 Contour pressure in Semi-H shaped channel series (Pa)

Figure 4.4 Concentration magnitude of 3kDa dextran (mol/m$^3$)
4.2 Simulation on Semi-H Shaped Channels Series

4.2.3 Multi-level Semi-H shaped channels series

The sample inlet channel was 2 $\mu$m x 28 $\mu$m and the three capture channels were all 2$\mu$m x 8$\mu$m. There were 400 20 nm sieves, 100 40 nm sieves and 25 80 nm sieves respectively in each level. The spacing between the sieve channels in each level was 20, 40 and 80 nm respectively. All outlet pressures were 0 Pa and the inlet pressure was 100 Pa. The free triangular mesh was drawn by COMSOL physical-controlled mesh automatically (Fine size). Figure 4.5a&b illustrates the velocity streamline and velocity magnitude of 1 mol/m$^3$ 3 kDa dextran aqueous solution in a three-level semi-H shaped channels series filter. Comparing with the capture channels, the sample inlet channel achieved a significantly faster flow which pushed components to keep moving along the inlet channel. Thus it helps to reduce adhesions on the interface between the sieves and the inlet channel. Table 4.1 shows the static flow rates of each channel. It can be seen clearly that there is low flow rate in the capture channels, which means low efficiency of filtration process. The low flow rate also caused a problem in multi-level filtration regarding the concentration, which will be described later.

<table>
<thead>
<tr>
<th>Channel</th>
<th>Sample inlet</th>
<th>Capture 1</th>
<th>Capture 2</th>
<th>Capture 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow rate</td>
<td>88.56</td>
<td>0.4895</td>
<td>0.7411</td>
<td>0.9612</td>
</tr>
</tbody>
</table>
The response time of the three level semi-H shaped channels series are exhibited in Figure 4.6. The red line shows the concentration $c_{1,1}$ (component 1, the 3kDa dextran, in the first level) at the end of the capture channel 1, the green line represents $c_{2,1}$ of capture channel 2 and the blue line is $c_{3,1}$ of capture channel 3. The initial concentration in the three-level filter was zero. At the beginning the stream flowed into the sieves according to the sequence order. Thus the increasing of concentration in the three-level filter started in spatial sequence. During this period both convection and diffusion occurred. Thus the first level responds fastest. By the end of the simulation, all levels achieved a similar concentration. During the mass transfer process, the outlet concentration increases; this results in the concentration gradient of the small group across the sieve channels reducing until almost zero due to the equilibrium of the concentration. The diffusion flux,
4.2 Simulation on Semi-H Shaped Channels Series

correspondingly, decreases to almost zero. Finally the static concentration of the small
group is almost uniform everywhere. The response time relates to the input flow rate and
concentration of the sample, the diffusion coefficient and the sieve length. Hence the
component 1 (3kDa dextran) responds fastest as it has the highest diffusion coefficient.

![Figure 4.6 Curve of the outlet of each capture channel](image)

The static concentration of 3kDa dextran in the three levels of semi-H shaped channels
series is shown in Figure 4.7. The concentration in each capture channel was similar, and did
not drop down by 50% after each level of filtration as it was hoped for the multi-level filter
based on H shaped channels. This behaviour is because in the semi-H channel series with
single inlet, the convection dominates the mass transfer. As the convections of solvent and
the small solute are the same; although the diffusion coefficient of each component is
different, a uniform concentration is observed. Therefore it is not able to purify the medium
or large components from the small ones. The diffusion coefficient only affects the response time of each component in the same level significantly. For the micro components there is a concentrating effect along the surface of the filter[62], however, the concentrated components at each outlets mixed together again due to the Fick’s law. Thus the outlet concentration does not increase due to the concentrating.

Figure 4.7 Static concentration distribution of a three-level semi-H shaped filter (mol/m$^3$)

4.3 Simulations on H Shaped Channels Series

As it was introduced in previous section 3.3.2, the simulations on H shaped channels series were studied in this section. In these simulations the similar geometry model were used as the one in section 4.2.1. The sample inlet channel and capture channel were both 2 x 50 μm. The number of the sieve channels will be discussed with different sieve diameter in section
4.3.1. The settings of the laminar flow module were also the same as section 4.2.1 except that there two parallel inlets both with 100 Pa pressure and two outlets with 0 Pa, which are shown in Figure 4.8. The concentration of the 3 kDa dextran solution at the sample inlet was 1 mol/m$^3$ while 0 mol/m$^3$ at the capture inlet. The free triangular mesh was drawn by COMSOL Multiphysics® physical-controlled mesh automatically (Fine size option).

![Figure 4.8 The scheme of the H shaped channel series](image)

**4.3.1 Statistic concentration vs. Number of H Shaped Channels series**

As it was discussed in the previous chapter, the relationship of channel size and number of channels can be described by Equation 3.12, which is

$$N_i \propto \gamma \frac{wd}{a_i^2}$$

Where $N_i$ is the minimum number of $i$ level sieves;
4.3 Simulations on H Shaped Channels Series

\(w\) is the width of sample inlet entrance;

\(d\) is the depth of inlet entrance;

\(a_i\) is the depth and width of sieve channel;

\(\gamma\) is a constant.

For finding an appropriate value of \(\gamma\), a group of simulations was designed which are shown in Table 4.2.[154, 155] Because \(N_i\) is a natural number, in the group \(N6\), \(N_i = 1\). When \(\gamma = 1\), the total area of the entrances of sieves is equal to the area of the sample inlet; and the capture concentrations are close to the ideal value from Table 4.2. Thus the Equation 3.12 mostly makes a close but insufficient estimation (except \(N9\)) for \(N_i\) when \(\gamma = 1\). This is because of the isotropic diffusion in porous medium (Equation 2.8). In contrast when \(\gamma = 2\), sufficient estimations are achieved in all groups of the table.

<table>
<thead>
<tr>
<th>No.</th>
<th>(\gamma)</th>
<th>(a_i) (nm)</th>
<th>(w = d) (nm)</th>
<th>(N_i)</th>
<th>(c_{i,1}) (mol/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N1)</td>
<td>1</td>
<td>20</td>
<td>20</td>
<td>1</td>
<td>0.49858</td>
</tr>
<tr>
<td>(N2)</td>
<td>1</td>
<td>200</td>
<td>200</td>
<td>1</td>
<td>0.48467</td>
</tr>
<tr>
<td>(N3)</td>
<td>1</td>
<td>2000</td>
<td>2000</td>
<td>1</td>
<td>0.42026</td>
</tr>
<tr>
<td>(N4)</td>
<td>2</td>
<td>20</td>
<td>200</td>
<td>200</td>
<td>0.5</td>
</tr>
<tr>
<td>(N5)</td>
<td>2</td>
<td>200</td>
<td>2000</td>
<td>200</td>
<td>0.5</td>
</tr>
<tr>
<td>(N6)</td>
<td>2</td>
<td>2000</td>
<td>20</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>(N7)</td>
<td>0.5</td>
<td>20</td>
<td>2000</td>
<td>500</td>
<td>0.49882</td>
</tr>
<tr>
<td>(N8)</td>
<td>0.5</td>
<td>200</td>
<td>2000</td>
<td>50</td>
<td>0.49879</td>
</tr>
<tr>
<td>(N9)</td>
<td>1</td>
<td>20</td>
<td>200</td>
<td>100</td>
<td>0.5</td>
</tr>
</tbody>
</table>
4.3 Simulations on H Shaped Channels Series

When is $\gamma = 1$ a sufficient index number for the estimation equation 3.12? Table 4.3 studies the relationship between the number of the sieve channels and the concentration of 3 kDa dextran at the capture outlet with different sieve channel sizes; when $\gamma = 1$, $w = 2000$ nm and $d = a_i$. It can be seen that the concentration drops when the diameter of the sieve channel increased over a point between 100 and 200 nm. This is because the distance from the first sieve channel to the last decreases with the increasing sieve diameter. As the flow rate in the sample channel is the same in every simulations in this table, the time cost by the inflow to pass the sieve area declines meanwhile. So less amount of substance of dextran can diffuse through the sieve channels. Hence at the outlet of the capture channel, the capture concentration of the dextran drops down.

Table 4.3 Concentration of 3 kDa dextran at the outlet of capture channel with different size sieves ($\gamma=1$) (mol/m$^3$)

<table>
<thead>
<tr>
<th>$a_i$ (nm)</th>
<th>20</th>
<th>40</th>
<th>80</th>
<th>100</th>
<th>200</th>
<th>400</th>
<th>800</th>
<th>1000</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c_{1,1}$</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.4981</td>
<td>0.4729</td>
<td>0.4613</td>
<td>0.4273</td>
<td>0.4203</td>
</tr>
</tbody>
</table>

4.3.2 Static Flow Properties of H Shaped Channels series

After determining the sufficient amount of sieve channels to achieve a maximum concentration in the capture channel, the static flow properties were studied. A 200 40nm H shaped sieve series was simulated. The velocity streamline and velocity magnitude of H shaped channels series are exhibited in Figure 4.9a&b. Comparing with semi-H shaped channels series (Figure 4.2), the flow properties of the inlet sample channels are similar. The only difference is that there is no convection in the sieves channels. It also achieved same velocity in the capture channel as in the sample inlet channel. Thus H shaped channels
series solves the pump problem of semi-H shaped channels series which was discussed in section 4.2 by providing a flow in the capture channel.

The flux streamline which is shown in Figure 4.10a appeared as a U shape. Thus there were back fluxes towards the inlet of the capture buffer solution (here the buffer is water). The bottom U shape flux streamlines ends at the middle of the sieve series. As the flux streamline starts from the sample inlet where the concentration is 1 mol/m$^3$ and ends at the capture inlet where the concentration is 0 mol/m$^3$; obviously the concentration at the middle (bottom) of this flux streamline is 0.5 mol/m$^3$. After this point, the concentration of downstream flows keeps the same 0.5 mol/m$^3$. Thus there was sufficient diffusion between the sample inlet channel and capture channel. Whereas the W shaped flux streamline of a single H shaped channel represented insufficient diffusion (Figure 3.5). This is why a single H

Figure 4.9 H shaped channel series (a) Streamline, (b) Velocity magnitude.
shaped channel is not able to achieve a concentration as high as 50% of the inlet concentration. Thus a U shaped flux streamline can be used as a criterion for $N_i$ besides the Equation 3.12.

The contour pressure is shown in Figure 4.10b. Due to the same pressure difference between inlets and outlets, the pressure between two sides of the sieve channels is zero. This is why there is no convection in the sieve channels. If the pressure were asymmetric, there should be convection from the higher pressure side to the lower pressure side. The contour pressure explains the reason of the fast flow in the sample inlet and capture channels as well.

![Figure 4.10 H shaped channel series (a) Flux streamline; (b) Contour pressure (Pa).](image)
4.4 Simulation on Angular H Shaped Channels Series

As it was introduced in previous section 3.4, the simulations on angular H shaped channels series were studied in this section. In these simulations the similar geometry model were used as the one in section 4.3. The sample inlet channel and capture channel were both 2 x 50 μm. The angle and number of the sieve channels will be discussed with different sieve diameter in section 4.4.1. The settings of the laminar flow module were also the same as section 4.3 where both inlets pressure were 100 Pa and both outlets were 0 Pa. The concentration of the 3 kDa dextran solution at the sample inlet was 1 mol/m³ while 0 mol/m³ at the capture inlet. The free triangular mesh was drawn by COMSOL Multiphysics® physical-controlled mesh automatically (Fine size option).

4.4.1 Concentration vs. Number vs. Angle

As it was mentioned that for a single angular H shaped channel the concentration in the outlet of the capture channel should vary with the angle θ (section 3.4.2) if the inlet length was ignored, the question is now what would happen when there is a series of angular H shaped channels? If the upper limit of concentration is not 50%, what number of sieve channels shall be used to achieve a maximum concentration? Table 4.4 shows the relationship of concentration \( c_{1,1} \), angle \( \theta \) and number of sieve channels; which is \( c_{1,1}(\theta, N) \). Here the entrances of the sample inlet channel and the capture channel are both 2 m x 40 nm and the entrance of sieve channel is 40nm x 40nm. It can be seen from the table that for H shaped channels series (\( \theta = 0^\circ \)), the upper limit of concentration is 0.5 mol/m³. When reaching the upper limit, adding sieve channels was not able to increase concentration anymore. For angular H shaped channels series, the concentration increased when the angle decreased, and the minimum channels for sufficient diffusion (maximum
4.4 Simulation on Angular H Shaped Channels Series

Outlet concentration) increased as well. For the 400 channels group, concentration decreased comparing with 300 channels group. There was longer time for the inflow to diffuse due to the increased length of cross section. The capture concentration $c_{1,1}$ in the table i.e. $c_{1,1} (-80, 400) = 0.5603$, exceeds the upper limit which is 50% of the H shaped channel series; due to the entrance length was ignored (Referring to section 3.4.2, Figure 3.17). If the amount of sieve channels are kept increasing, the concentration will finally become 0.5 mol/m$^3$. Therefore for the number of sieve channels it is not the more the better. Besides the parameters in Equation 3.12; the parameters which affect the best amount of sieve channels are the angle, the distance between the sample inlet channel and capture channel, and the distance between the sieves and the entrance of inlet channel.

Table 4.4 Capture concentration with different angle and number of sieves (mol/m$^3$)

<table>
<thead>
<tr>
<th>N</th>
<th>-80°</th>
<th>-70°</th>
<th>-60°</th>
<th>-45°</th>
<th>-30°</th>
<th>-15°</th>
<th>0°</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0.4977</td>
<td>0.5158</td>
<td>0.5177</td>
<td>0.5139</td>
<td>0.5082</td>
<td>0.5021</td>
<td>0.4955</td>
</tr>
<tr>
<td>200</td>
<td>0.5388</td>
<td>0.5250</td>
<td>0.5223</td>
<td>0.5157</td>
<td>0.5091</td>
<td>0.5035</td>
<td>0.50</td>
</tr>
<tr>
<td>300</td>
<td>0.5637</td>
<td>0.5378</td>
<td>0.5261</td>
<td>0.5162</td>
<td>0.5097</td>
<td>0.5046</td>
<td>0.50</td>
</tr>
<tr>
<td>400</td>
<td>0.5603</td>
<td>0.5360</td>
<td>0.5250</td>
<td>0.5155</td>
<td>0.5093</td>
<td>0.5044</td>
<td>0.50</td>
</tr>
</tbody>
</table>

4.4.2 Static Flow Properties of Angular H Shaped Channels Series

The main difference of flow properties between the H shaped channels series and the angular H shaped channels series is the flow rate in the angular sieve channels. The relationship is similar as H shaped channels (section 3.3.1) and angular H shaped channels (section 3.4.1). The convection is caused by the inertia and pressure gradient on the sieve channel series. Although the sieve channels change the pressure distribution in both sample inlet channel and capture channel to reduce the pressure gradient on sieve channels, there
are corresponding increases of pressure gradients on sieve channel series with the angle magnitude, which is shown in Figure 4.11a. It has been mentioned that fine sieve channels are possible to prevent the convection. Here an example of very low convection in sieve channels is exhibited in Figure 4.11b&c. (Figure 4.11b describes the velocity streamlines and Figure 4.11c exhibits the velocity magnitude of angular H shaped channels series.) The flux streamline is shown in Figure 4.11d, which formed an asymmetric U shape. The bottom of U shaped flux streamline does not reach the bottom of sieve channel area, which represents that there is sufficient diffusion.

However, it should be mentioned that due to the no slip boundary condition, the 2D modelling assuming the depth of channels are infinite. Further studies of the 3D modelling of angular H shaped channels series flow properties are discussed in Chapter 6.

Figure 4.11 Angular H shaped channel series when $\theta = -60^\circ$ (a) Contour Pressure, (b) Velocity streamline, (c) Velocity magnitude and (d) Flux streamline.
4.4.3 Dynamic Properties of Angular H Shaped Channels series

It was mentioned that the response time relates to the volume of sample solution, the diffusion coefficient of target components and the length of the sieve channels. There are no apparent relation among response time, with the size and number \( N \) of sieve channels. So the question is, what is the effect of the amount of sieves? Table 4.5 shows response time \( T_{i,j} \) of component \( j \) with different size of sieve \( a_i \) and different number of sieve channels \( N \); where \( w = 2,000 \) nm, \( d = 80 \) nm. It is seen that a stable output is able to be achieved in one minute. This shows the potential of real time applications.

Table 4.5 Response time for different size and number of sieve channels

<table>
<thead>
<tr>
<th>( a_i ) (nm)</th>
<th>( N )</th>
<th>( c_{i,j} ) (mol/m³)</th>
<th>( T_{i,j} ) (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>100</td>
<td>0.4754</td>
<td>33</td>
</tr>
<tr>
<td>40</td>
<td>200</td>
<td>0.4895</td>
<td>42</td>
</tr>
<tr>
<td>80</td>
<td>100</td>
<td>0.4866</td>
<td>48</td>
</tr>
<tr>
<td>80</td>
<td>200</td>
<td>0.4902</td>
<td>35</td>
</tr>
</tbody>
</table>

4.5 Simulation on Multi-level Filter

For the properties of H shaped channel series discussed above, it is able to be applied with both microcomponents and nanocomponents. Based on the design and analysis of multi-level filters in the last chapter, a 2D three-level filter design is built and simulated with COMSOL Multiphysics® software in this section to examine the design and show its practicability. The amounts and sizes of the three-level sieve channels were \( 1000 \ a_1 = 20 \) nm, \( 200 \ a_2 = 40 \) nm and \( 40 \ a_3 = 80 \) nm respectively. (In the 2D simulation the depth is infinite; the number of sieve channels was calculated assuming the depth equal to its
4.5 Simulation on Multi-level Filter

width) For the sample inlet channel and capture channel, there were \( w = 2 \mu \text{m} \) and \( d = 1 \mu \text{m} \). 1 mol/m\(^3\) 3 kDa, 500 kDa and 2000 kDa dextrans were applied as the target components, marking as \( j = 1, 2 \) and 3 respectively. The diffusion coefficient of 3, 500 and 2000kDa dextran are 7.5e-10, 3.28e-10, and 8.4-e-11 m\(^2\)/s respectively. The density of fluid is 1050g/L and the dynamic viscosity is 0.3 Pa·s. All inlets pressures were 100 Pa while outlets pressures were zero. The inlet of capture channel 1, 2 and 3 is water where concentration of dextrans was zero. The free triangular mesh was drawn by COMSOL physical-controlled mesh automatically (normal size). The no-slip boundary condition was applied for the laminar flow modules.

Figure 4.12 shows the static concentration distribution \( c_{i,1} \) \((i = 1, 2, 3)\) of 3 kDa dextran in the three-level filter model. The concentration at each outlet of capture channel is 0.37, 0.05 and 0.01 mol/m\(^3\) respectively. It was mentioned in section 3.5.2 that the ideal outlet concentration should be 0.5, 0.25 and 0.125 mol/m\(^3\) respectively. The difference can be answered by the interaction among different levels. In other words, the distance \( l_i \) between adjacent levels is too short. Thus a two level model was simulated first to examine the estimate equation (Equation 3.15) described in section 3.5.2.

![Figure 4.12 Concentration of 3kDa dextran in a three-level filter](image_url)
4.5 Simulation on Multi-level Filter

4.5.1 Concentration vs. Distance between Adjacent Levels

In this analysis, four different designed errors $\delta_i = \frac{\Delta c_{\text{Sample}}^{i}}{c_{\text{Sample}}^{i}} = \frac{c_{\text{Designed}}^{i} - c_{\text{Sample}}^{i}}{c_{\text{Sample}}^{i}}$ (Equation 3.14) were given which were 0.5%, 1%, 5% and 10%. $c_{\text{Sample}}^{i}$ can be calculated with Equation 3.8. The distance $l_i$ between two adjacent levels $(i = 1, 2)$ was calculated with Equation 3.15,

$$l_i \geq \frac{N_i w_i}{2\delta_i}.$$  

Table 4.6 shows the simulation results where the $N_1 = 250, w_1 = 80\, \text{nm}, N_2 = 40$ and $w_2 = 160\, \text{nm}$. Comparing with the demanded error $\delta_i$, the simulated error ($\delta_{\text{simulate}} = \frac{c_{\text{Simulated}}^{i} - c_{\text{Sample}}^{i}}{c_{\text{Sample}}^{i}}$) shows the same tendency. The estimate equation is accurate when $\delta_i = 10%$. When $\delta_i = 0.1\%$, the result is even better than the designed error.

<table>
<thead>
<tr>
<th>$\delta_i$</th>
<th>0.5%</th>
<th>1%</th>
<th>5%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$l_i$ (mm)</td>
<td>2</td>
<td>2</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>$c_{1,1}^{\text{Simulated}}$</td>
<td>0.4985</td>
<td>0.4901</td>
<td>0.4651</td>
<td>0.4505</td>
</tr>
<tr>
<td>$c_{2,1}^{\text{Simulated}}$</td>
<td>0.0145</td>
<td>0.0735</td>
<td>0.1651</td>
<td>0.2339</td>
</tr>
<tr>
<td>$\delta_{\text{simulate}}$</td>
<td>0.3%</td>
<td>1.98%</td>
<td>6.98%</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

If the application were asked for $\delta_i = 5\%$, a three-level filter is able to be designed based on Equation 3.15 which is shown in Figure 4.13 (using the same settings as Figure 4.12). The capture concentrations of 3kDa, 500kDa and 2000kDa dextran in each level are exhibited in Table 4.7. The errors were similar with the design value. Consequently, Equation 3.15 is suitable for the multi-level filter design.
Table 4.7 Captured concentration of each components when $\delta_i=5\%$ (mol/m$^3$)

<table>
<thead>
<tr>
<th>$c_{i,j}$</th>
<th>$i = 1$</th>
<th>$i = 2$</th>
<th>$i = 3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$j = 1$</td>
<td>0.4586</td>
<td>0.2330</td>
<td>0.1678</td>
</tr>
<tr>
<td>$j = 2$</td>
<td>0</td>
<td>0.4651</td>
<td>0.1651</td>
</tr>
<tr>
<td>$j = 3$</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Figure 4.13 Concentration in a three-level filter (a) 3 kDa, (b) 500 kDa, (c) 2,000 kDa dextran

4.5.2 Static Flow Properties of Multi-level Filter

The contour pressure is exhibited in Figure 4.14a. It can be seen that the pressures beside each end of the sieve channels are not equal. Due to the same pump pressure of each channel but different channel length, the pressure gradient varies each channel. Thus there is convection in sieve channels which causes a higher velocity around cross sections. A uniform pressure gradient can be achieved by designing the pump pressure and length of each channel to get steady flow. Figure 4.14b shows the velocity magnitude. A high flow rate in the sample inlet channel and all capture channels can be viewed clearly, which
contributes to adhesion reduction on sieves surface. Hence, comparing with traditional filtration it shows advantages for high throughput applications.

![Image of three-level filter](image)

**Figure 4.14** The three-level filter (a) Contour pressure, (b) Velocity magnitude m/s.

### 4.5.3 Multi-level Filter with a Dilute Channel

To improve the performance of a multilevel filter, a dilute channel was added as discussed in section 3.5. So a dilute channel was added on the model which built in last section by creating an additional ‘dilate’ inlet channel running parallel to the existing inlet and then placing sieves between the new channel and the original inlet (Figure 4.15). The dilute sieves are the same size and number as the former level filter sieves. The simulation result of 3 kDa dextran concentration is illustrated in Figure 4.15 (the inlet pressure of the dilute channel was the same as the other channels i.e. 100 Pa, the outlet pressure was zero, and other conditions are the same as Figure 4.10). Table 4.8 compares the simulation results with ideal values (Equation 3.9), the ones without dilute channel and their ideal values.
(Equation 3.8). It can be seen that a dilute channel is able to reduce the concentration of small species \((i < j)\) significantly while only decreasing the concentration of the target component \((i = j)\) slightly, therefore improving the separation. As the small species are diluted, the chance of clustering reduces as well. Whereas there is a decrease of target component due to the shortened distance between adjacent sieves which is caused by the additional sieves, \(l_i\) should be redefined as the distance between the filter sieves and the followed same size dilute sieves. Then the target concentration can keep same level as the ones without a dilute channel which fits the design demands. Consequently the dilute channel is a low cost and efficient tool to assist the multi-level filter to achieve a purer separation.

**Table 4.8 Capture concentrations with or without a dilute channel (mol/m\(^3\))**

<table>
<thead>
<tr>
<th></th>
<th>Without dilute channel</th>
<th>Ideal (c_{i,j}^{\text{Sample}})</th>
<th>With a dilute channel</th>
<th>Ideal diluted</th>
</tr>
</thead>
<tbody>
<tr>
<td>(c_{1,1})</td>
<td>0.4586</td>
<td>0.5</td>
<td>0.4482</td>
<td>0.5</td>
</tr>
<tr>
<td>(c_{2,1})</td>
<td>0.2330</td>
<td>0.25</td>
<td>0.1634</td>
<td>0.125</td>
</tr>
<tr>
<td>(c_{3,1})</td>
<td>0.1678</td>
<td>0.125</td>
<td>0.1338</td>
<td>0.0313</td>
</tr>
<tr>
<td>(c_{\text{Sample},1})</td>
<td>0.1817</td>
<td>0.125</td>
<td>0.1502</td>
<td>0.0313</td>
</tr>
<tr>
<td>(c_{1,2})</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(c_{2,2})</td>
<td>0.4168</td>
<td>0.5</td>
<td>0.3677</td>
<td>0.5</td>
</tr>
<tr>
<td>(c_{3,2})</td>
<td>0.3002</td>
<td>0.25</td>
<td>0.2122</td>
<td>0.125</td>
</tr>
<tr>
<td>(c_{\text{Sample},2})</td>
<td>0.3249</td>
<td>0.25</td>
<td>0.2297</td>
<td>0.125</td>
</tr>
<tr>
<td>(c_{1,3})</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(c_{2,3})</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(c_{3,3})</td>
<td>0.4203</td>
<td>0.5</td>
<td>0.4201</td>
<td>0.5</td>
</tr>
<tr>
<td>(c_{\text{Sample},3})</td>
<td>0.4550</td>
<td>0.5</td>
<td>0.4548</td>
<td>0.5</td>
</tr>
</tbody>
</table>
4.5 Simulation on Multi-level Filter

Figure 4.15 Concentration of 3kDa dextran in the three-level filter with a dilute channel

Figure 4.16a shows the contour pressure of a three-level filter with a dilute channel. Because of the pressure difference beside the sieves, convection through the sieve channels dominates the velocity in the sample inlet, capture and dilute channels. So in Figure 4.16b a higher velocity around sieves was observed.

Figure 4.16 The three-level filter with a dilute channel (a) Contour pressure, (b) Velocity magnitude.
4.6 Summary

In this chapter the models discussed in chapter 3, i.e. semi-H shaped channels, H shaped channels and angular H shaped channels; were extended to their series. The mass transfer process was simulated with finite element software COMSOL Multiphysics®. The estimate equations introduced in Chapter 3 were examined as well. Consequently the H shaped channels series showed advantages on relief of adhesion, high throughput and extendibility. Furthermore, simulations on the multi-level filter based on H shaped channels series illustrated the practicability of a filter which consist of H shaped channels series as its basic elements. The principles of a multi-level filter based on H shaped channels series are able to be applied to the design and fabrication of a lab-on-chip multi-level filter. Based on the simulation results in this chapter, chips of multi-level filter are able to be designed. The next chapter will present the progress of multi-level chip design and its fabrication.
CHAPTER 5

3D MODELLING RESULTS

5.1 Introduction

As 2D modelling assumes the depths of each channels are infinite, it is not able to describe the flow properties accurately. In this chapter, further studies on 3D models of one level filters (angular H shaped channels series) are built and analysed with finite element software COMSOL Multiphysics® 4.1a. The results are still given under no-slip boundary condition. Then 3D simulations with slip boundary condition are illustrated and compared with the no-slip results. Finally a 3D model of a three-level filter based on angular semi-H channels is described. It is a model of a simplified angular version of the verification chip designed in chapter 6. The settings of Transport of Diluted Species module and Laminar Flow module are described. The static results of velocity, flow streamline, pressure and concentration distributions are presented and discussed.

5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

5.2.1 Settings and Meshing

In this section, the only variable factor was the angle ($\theta = 0^\circ, -15^\circ, -30^\circ, -45^\circ, -60^\circ$ and $-75^\circ$) of sieve channels. The widths of the sample inlet channel and capture channel were both 5 $\mu$m and the depths were both 500 nm. The distance between these two channels was 2 $\mu$m. Sixteen sieve channels were applied and the width and depth of them were both 400 nm.
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

The density, dynamic viscosity and diffusion coefficient of sample fluid were 1050 kg/m$^3$, 0.03 Pa·s and 1e-9 m$^2$/s respectively.

The continuity and the Navier-Stokes equations (Equation 2.9 & 2.10) were solved by the Laminar Flow module. The boundary condition in this section is the no-slip condition which means the velocity on the boundary interface is zero. The entrance pressures of both sample inlet and capture channels were 100 Pa, while the exit pressures were 0 Pa. Both the entrance and exit lengths were 1 cm.

The Transport of Dilute Species module was used to solve the continuity and the Nernst-Planck equations (Equation 2.6 & 2.5) with an impenetrable boundary. No reaction and all initial values were set up as zero. The Inlet concentration was 1 mol/m$^3$ for sample inlet channel and 0 mol/m$^3$ for the capture channel.

After these settings, the model was meshed by COMSOL. Firstly, free triangular meshes were drawn on the interface between inlet channel and sieve channels. The element sizes were from 50 nm to 200 nm. Then secondly the triangular meshes were swept along the x-axis to form the meshes of sample inlet channel and sieve channels. The swept sizes ranged from 100 nm to 1,000 nm. The third step was drawing the free triangular meshes on the interface between capture channel and sieve channels (50-200 nm). Finally this triangular mesh was swept along the x-axis to form the meshes of capture channel (100-1,000 nm). Figure 5.1 demonstrates the meshes of the 3D model of angular H shaped channel series.
5.2.2 Pressure

Figure 5.2a-f shows the contour pressure of the angular H shaped channels series when the angle $\theta$ is $0^\circ$, $-15^\circ$, $-30^\circ$, $-45^\circ$, $-60^\circ$ and $-75^\circ$ respectively. When $\theta=0^\circ$, the pressure is symmetric on the other side of the sieve channels, which is same as the 2D simulation results. It can be seen that the pressures beside each end of the sieve channel are still similar when the angle magnitude increases, whereas the angle changes the pressure gradient in the sample inlet channel and capture channel. Comparing the results for different angles, there is limited corresponding increase of pressure difference when the angle increased. As finer channels need higher pumping pressure; it is understandable why it is still possible that no convention across in the sieve channel due to the viscose resistance even if the pressure gradient is not zero. More details on the velocity can refer to section 5.2.3 and 5.2.4.
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

- Inlets
- Capture in flow
- Sample in flow
- Out flow
- Outlets

- a $\theta = 0^\circ$
- b $\theta = -15^\circ$
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

c $\theta=-30^\circ$

d $\theta=-45^\circ$
Figure 5.2 3D contour pressure of no-slip flow with different angle $\theta$. 

$\theta = -60^\circ$

$\theta = -75^\circ$
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

5.2.3 Velocity Streamline

The velocity streamlines of different angle angular H shaped channels series are illustrated in Figure 5.3. The streamlines deviate towards the sieve channels on the interfaces between sample inlet channel and sieve channels, and capture channel and sieve channels. A vortex is clearly seen in the sieve channels. This is because of the high aspect ratio of the sieve channel (2 \( \mu m \)/ 400 nm = 5). No vortex was observed in section 3.3.1 due to the low aspect ratio of the sieve channel which was 0.5 \( \mu m \)/0.5 \( \mu m \) = 1. When the angle decreases, the centre of the vortex moves down on the left of the sieve channel and moves up on the right side; accompanied by a decrease of the vortex area.

However, still no convection in the middle of the sieve channels was observed in the streamline. The pressure gradient caused by the angle with a small magnitude was not enough to overcome the viscous resistance. For the large angle magnitude, the increase of the convection in the sieve channels cannot be observed straightforwardly through the streamline pictures compared with the high velocity main flow. Thus more information about convection across the sieve channels refers to the next section about velocity.
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

a  $\theta = 0^\circ$

b  $\theta = -15^\circ$
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

\[ c \quad \theta = -30° \]

\[ d \quad \theta = -45° \]
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

Figure 5.3 3D no-slip flow streamline for different angle $\theta$. 

$\theta = -60^\circ$

$\theta = -75^\circ$
5.2.4 Velocity

Figure 5.4 shows the middle slice (xy-planes) of the velocity magnitude in angular H shaped channel series ($\theta = 0^\circ, -15^\circ, -30^\circ, -45^\circ, -60^\circ, \text{ and } -75^\circ$). It is similar with the 2D results. However, velocity magnitude cannot fully describe the flow. For a more specific study, the velocity field is introduced. Figure 5.5 describes the x component of velocity. Although the pressures beside the sieve channel were the same when $\theta = 0^\circ$, the x direction velocity $u$ was not zero in the sieve channel (Figure 5.5a) due to the osmosis process and trap effect. The trap effect has been shown as the streamlines deviate towards the entrances of the sieve channels in Figure 5.3. Figure 5.6 exhibits the x direction velocity when there is zero inlet concentration at both inlets thus avoiding the osmosis effects. This picture also gives evidence that the x direction vortex occurs in the sieve channels. By calculating the surface integration of $u$ on all area of the cross-section with the capture channel, total flow rates out of the sieve channels were achieved which is shown in Table 5.1. Meanwhile, the sample inlet flow rate was $6.38 \times 10^{-20} \text{ m}^3/\text{s}$, and the average outlet velocity was 25.5nm/s. The negative value when $\theta = 0^\circ$ demonstrates the osmosis phenomenon.

<table>
<thead>
<tr>
<th>Angle</th>
<th>0°</th>
<th>-15°</th>
<th>-30°</th>
<th>-45°</th>
<th>-60°</th>
<th>-75°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow out</td>
<td>-2.31e-23</td>
<td>6.51e-23</td>
<td>2.69e-22</td>
<td>2.84e-22</td>
<td>4.31e-22</td>
<td>6.50e-22</td>
</tr>
</tbody>
</table>
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

\[ \theta = 0^\circ \]

\[ \theta = -15^\circ \]
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

c  θ = -30°

d  θ = -45°
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

Figure 5.4 Velocity magnitude of no-slip flow with different angles.

\[\text{\(\theta = -60^\circ\)}\]

\[\text{\(\theta = -75^\circ\)}\]

Figure 5.4 Velocity magnitude of no-slip flow with different angles.
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

![Diagram showing flow in angular H shaped channels]

(a) $\theta = 0^\circ$

(b) $\theta = -15^\circ$
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

Figure 5.5 Velocity x direction component $u$ of no-slip flow with different angle $\theta$.

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The \( y \) direction velocity \( v \) is shown in Figure 5.7, which is the main velocity component. So these figures are very similar with the velocity magnitude figures. The pressure difference between inlets and outlets of the sample inlet channel and capture channel decides the \( y \) direction velocity component \( v \).

\( Z \) direction velocity component \( w \) is exhibited in Figure 5.8. The trap effect is clearly shown in the figure as the rainbow colour stripes. This effect takes place because the depth of the sieve channels is smaller than the depth of the sample inlet and capture channel.

Consequently, due to the inertia of fluid and improvement of pressure gradient on sieve channels caused by angle, higher but limited convection in sieve channels is able to be achieved with bigger angle magnitude.
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

a  $\theta = 0^\circ$

b  $\theta = -15^\circ$
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

c $\theta = -30^\circ$

d $\theta = -45^\circ$
Figure 5.7 Y direction velocity components of no-slip flow with different angles.
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

\[ a \quad \theta = 0^\circ \]

\[ b \quad \theta = -15^\circ \]
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

c \theta = -30^\circ

d \theta = -45^\circ
5.2 3D No-Slip Modelling of Angular H Shaped Channels Series

Figure 5.8 Z direction velocity components of no-slip flow with different angles.
5.3 Slip Boundary Condition Results

The no-slip boundary condition has been used to solve Navier-Stokes equation since the 19th century[156]. However, a lot of publications reported experimental evidences of slip in variety of situations[157, 158]. For non-Newtonian fluids, such as blood, apparent slips were observed in various experiments[159, 160]. Thus slip boundary condition was applied in this section for more accurate simulations. The boundary condition in laminar module is:

\[ u \cdot n = 0, K - (K \cdot n)n = 0, K = \mu(\nabla u + (\nabla u)^T)n \]

Where \( u \) is the velocity vector, \( n \) is the outer normal vector on \( \partial\Omega \), and \( \Omega \) is a domain. The geometric model and software settings (including the mesh) are the same as section 6.2 except the boundary condition of Laminar Flow module. Thus the simulations in this section can be viewed as the control group of section 6.2. The control variable is the boundary condition of flow.

5.3.1 Velocity

The surface velocity is not zero under slip boundary condition. Comparing with the no-slip simulation results, flow rates in all channels increase significantly. Figure 5.9 exhibits the velocity magnitude (on xy-planes) when \( \theta \) is \(-0^\circ, -15^\circ, -30^\circ, -45^\circ, -60^\circ, \) and \(-75^\circ\). Whereas large increases of flow velocity in sample inlet channel and capture channel are seen, relative low velocity layers are observed on the cross sections due to the vortices in the sieve channels. Table 5.2 exhibits the flow rate in single sieve channel when the slip boundary condition was applied. The sample inlet flow rate was 2.55e-15 m³/s (inlet Pressure 100 Pa), and the average velocities at both outlets were 1.01 mm/s. Comparing with the no-slip results, appreciable increase of flow rate is achieved in all different angle
simulations. It can be seen from the table that the flow rate in the sieve channels increased with the angle magnitude. This relationship is the same as for the no-slip simulation results.

Table 5.2 Total flow rate across the sieve channels (m$^3$/s) (slip boundary condition)

<table>
<thead>
<tr>
<th>Angle</th>
<th>Flow rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0°</td>
<td>2.67e-19</td>
</tr>
<tr>
<td>-15°</td>
<td>8.83e-18</td>
</tr>
<tr>
<td>-30°</td>
<td>2.47e-17</td>
</tr>
<tr>
<td>-45°</td>
<td>3.68e-17</td>
</tr>
<tr>
<td>-60°</td>
<td>6.15e-17</td>
</tr>
<tr>
<td>-75°</td>
<td>8.58e-17</td>
</tr>
</tbody>
</table>

Figure 5.10 shows the $x$ component of velocity ($u$). The trap effect reduces compared with the no-slip results. Thus a slip flow in filters based on H shaped channels takes a lower possibility of clustering at the entrances of the sieve channels than no-slip flow. The high $x$ direction velocity at the top and bottom of the cross section means that the flow goes around the low velocity layer area. This phenomenon further reduces the possibility of clustering at the cross section.

Figure 5.11 introduces the $y$ direction component of velocity. As the $y$ component is distinct higher than $x$ and $z$ direction components, this figure is similar with Figure 5.9. $Z$ direction velocity component is illustrated in Figure 5.12. The $z$ direction movements are caused by the depth changes (sudden contraction and sudden expansion) in the $z$ direction at the cross-section.
5.3 Slip Boundary Condition Results

a. $\theta = 0^\circ$

b. $\theta = -15^\circ$
5.3 Slip Boundary Condition Results

c \(\theta = -30^\circ\)

d \(\theta = -45^\circ\)
Figure 5.9 Velocity magnitude of angular H shaped channel series with slip boundary condition.
5.3 Slip Boundary Condition Results
5.3 Slip Boundary Condition Results

\[ \theta = -30^\circ \]

\[ \theta = -45^\circ \]
Figure 5.10 X direction velocity components (Slip boundary condition)
5.3 Slip Boundary Condition Results
5.3 Slip Boundary Condition Results

c $\theta = -30^\circ$

d $\theta = -45^\circ$
5.3 Slip Boundary Condition Results

Figure 5.11 Y direction velocity components (Slip boundary condition)

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5.3 Slip Boundary Condition Results
5.3 Slip Boundary Condition Results

c. $\theta = -30^\circ$

d. $\theta = -45^\circ$
5.3 Slip Boundary Condition Results

Figure 5.12 Z direction velocity components (Slip boundary condition)
5.3.2 Velocity Streamline

When $\theta = 0^\circ$ (Figure 5.13a), the two vortexes occupy almost the whole area of a sieve channel. By raising the angle magnitude, higher convection appears across the sieve channels while the vortex in the sieve channels decreases. When the angle magnitude is large (Figure 5.13 e & f), streamlines across the sieve channel are obvious while the vortexes disappears. These phenomena were not observed in the simulations under no-slip boundary condition in section 5.2.3. The convection in the sieve channels reduces the possibility of clogging and jamming inside the channels.

The velocity streamlines shown in Figure 5.13 clearly present the low velocity layer. The flow goes around the cross sections and leaves a blank area which is the low velocity layer. The low velocity area is formed due to the vortices in the sieve channels. Comparing with the simulation results in section 5.2.3, the streamlines are still concave towards sieve channels around the cross section but much smoother.

5.3.3 Pressure

Figure 5.14 shows the contour pressure for different angles. The pressures beside the sieve channel are equal, although the value of the pressure varies rapidly at the cross section. There are apparent overpressures at the top edges of the sieve entrances. It is able to be seen that the pressure at the bottom of a sieve channel entrance is lower than the pressure at the top of the adjacent sieve channel entrance. Therefore the pressure gradient along the interface of the cross section slows down the flow along the interface. This is why there is a low velocity layer at the cross section.
5.3 Slip Boundary Condition Results

(a) $\theta = 0^\circ$

(b) $\theta = -15^\circ$
5.3 Slip Boundary Condition Results

c $\theta = -30^\circ$

d $\theta = -45^\circ$
Figure 5.13 Velocity streamlines of angular H shaped channels series with slip boundary condition
5.3 Slip Boundary Condition Results

a $\theta = 0^\circ$

b $\theta = -15^\circ$
5.3 Slip Boundary Condition Results

c \( \theta = -30^\circ \)

d \( \theta = -45^\circ \)
Figure 5.14 Contour pressure of angular H shaped channels series (Slip boundary condition)
5.3.4 Conclusions

When the slip boundary condition is applied for studies of filters based on H shaped channels, the surface velocity at the solid-liquid interface is not zero. Overall higher velocity is achieved. However, a low velocity layer occurs on the interfaces of the sample inlet channel-sieve channels and capture channel-sieve channels. This is because of the high roughness of the interface [161]. In the low velocity layer area, diffusion is the main transport process. The flow goes around the low velocity layer reducing the contact of component with the sieve surface. Considering the slip on the filter interface, the H channel series therefore reduce the possibility of adhesion at the entrances of the sieve channels. The vortexes in the sieve channel with small angle magnitude acts as a mixer thus increase the diffusion flux. On the other hand, the dead volume increases the chance of clogging. Although the flow rate in the sieve channel increases with the angle magnitude and is higher than the flow rate in the no-slip situation; the proportion of fluid flows into the sieve channel drops down (When $\theta = -75^\circ$, the sieve channels occupy 3.36% of the inlet sample solutions flow under the slip condition; while 10.19% under the no-slip boundary condition), therefore the concentrating effect is weakened. As the value of flow velocity in the sieve channel is still low, diffusion still dominates the transport process in the sieve channels. Thus the improvements caused by the convection across the sieves are still limited under the free slip boundary condition. As the flow rate in the sieve channel with no-slip boundary condition is even lower, only large magnitude angle is valuable to be applied with slip flow filtration.
5.4 3D Modelling of Three-Level Angular Semi-H Shaped Filter

5.4.1 Model settings and meshing

The three-level filter consisted of one \(20 \mu m \times 270 \mu m \times 800 \text{ nm}\) sample inlet channel; \(200 200 \text{ nm} \times 2 \mu m \times 200 \text{ nm}\), \(20 400 \text{ nm} \times 2 \mu m \times 400 \text{ nm}\) and \(2 800 \text{ nm} \times 2 \mu m \times 800 \text{ nm}\) sieve channels; and also three capture channels of which the depths were all \(800 \text{ nm}\). The angle of the sieve channels was set as -60°. The density and dynamic viscosity were 1.50 kg/m\(^3\) and 0.03 Pa·s respectively. Transport of Diluted Species (chds) and Laminar Flow (spf) modules were used in this simulation. Figure 5.15 shows the settings of those modules.

![Figure 5.15 Static concentration of particles smaller than 200 nm](image-url)
User control mesh was selected to build the mesh. Figure 5.16 shows the mesh of this model. The meshing process was similar as section 5.2. Firstly the 2D free triangular mesh was drawn on the interface between the sample inlet channel and the sieve channels (yz-plane). This was then swept along the x-axis to build the 3D triangular prism mesh of the sample inlet channel and sieve channels. Thirdly a free triangular mesh was drawn on the interface between the sieve channels and capture channels (yz-plane). Then this free triangular mesh was swept along the x-axis to form the mesh of the capture channels. The size of the free triangular mesh was from 100 nm to 625 nm and the size of swept element was from 200 nm to 1,000 nm.

Figure 5.16 3D Mesh of the three-level angular semi-H shaped filter.
5.4.2 Velocity magnitudes

Table 5.3 exhibits the velocity magnitudes in different positions of the three-level filter. For the sieve channels and capture channel, the highest velocity value is found in the third level. However, in the sample inlet channel, the velocity reduces when the diameter of the sieve channel entrance increases. By calculating the surface integration of velocity at the inlet and outlets, the flow rate of each channel can be found and is given in Table 5.4. As the sample inlet flow separates sequentially into three levels of capture channels, it is understandable that the flow rate in the sample inlet channel drops down during every level of filtration. Among the capture channels, level 3 has the biggest sieve size. Even if the number of third level sieve channels is the least (two), the flow rate of Level 3 is still the highest of the capture channel due to the high flow rate allowed by the big entrance of the sieve channels. Figure 5.17 exhibits the velocity magnitude on yz-planes. The x component of velocity on yz-planes around level 1 & 2; and 2 & 3 are shown in Figure 5.18 a & b.

<table>
<thead>
<tr>
<th>Level</th>
<th>Sample inlet channel</th>
<th>Sieve channel</th>
<th>Capture channel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.28e-8</td>
<td>1.87e-8</td>
<td>2.95e-9</td>
</tr>
<tr>
<td>2</td>
<td>3.08e-8</td>
<td>8.44e-8</td>
<td>9.8e-9</td>
</tr>
<tr>
<td>3</td>
<td>2.57e-8</td>
<td>4.77e-7</td>
<td>5.97e-8</td>
</tr>
</tbody>
</table>

Table 5.4 rate at each outlet of the three-level semi-H shaped filter (m³/s)

<table>
<thead>
<tr>
<th>Sample inlet</th>
<th>Capture 1</th>
<th>Capture 2</th>
<th>Capture 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.57139e-19</td>
<td>1.00056e-19</td>
<td>1.59884e-19</td>
<td>4.97199e-19</td>
</tr>
</tbody>
</table>
5.4 3D Modelling of Three-Level Angular Semi-H Shaped Filter

Figure 5.17 Magnitude of the three-level semi-H shaped filter.
Figure 5.18 X direction velocity component on yz-planes slices:
(a) level 1 and 2; (b) level 2 and 3.
5.4.3 Flow Streamline

Figure 5.19a shows the streamline of the velocity field of the three-level filter based on semi-H shaped channels. Figure 5.19b and c describes the streamline at the second and third level respectively. It can be seen that most streamlines which start from the inlet flow across the third level sieve channels. Thus the flow rate in capture channel 3 is the highest of the three capture channels. The first level captures the least flow due to the small diameter of the sieve entrances in spite of the number of sieve channels being the most for level 1.

Figure 5.19 Velocity streamline of the three-level semi-H shaped filter
5.4.4 Pressure

The pressure distribution in the three-level filter based on semi-H shaped filter is exhibited in Figure 5.20. Although the initial outlet pressure is 0Pa; the pressure at the end of capture channel 1, 2 and 3 is 53, 51 and 47 Pa respectively. It has been mentioned in section 4.2.1 that the pressure drops down quickly in the sieve channels. For that model of a one level semi-H shaped channel series, the pressure at the bottom cross section of the sample inlet channel and last sieve channel is low. Thus the last sieve channel which connects the sample inlet channel and capture channel drags the pressure at each end into equilibrium. The pressure in the sieve channels decrease rapidly because the pressure in the sample channels drops down heavily. In Figure 5.20 there is a clear contour pressure line which shows the pressures at each end of the last sieve channel of the first level are the same. That is why the pressures at the outlets are not zero.

Figure 5.20 Pressure in the three-level filter based on semi-H shaped channels. (Pa)
5.4.5 Concentration

The inlet concentrations of all three components are $1 \text{ mol/m}^3$; the concentrations at each outlet are described in Table 5.5. The results are the same as for three different sized filtrations with paper filters or membrane filters used in the laboratory. Thus this three-level filter is one feasible way to microminiaturize the filtration process down to the chip level. However, it is not able to purify middle diameter components from the mixtures of small, middle and big particles. This problem limits its application for multi component purification when pure middle sized components are wanted. A multi-level filter based on H shaped channels is able to meliorate the purification process.

<table>
<thead>
<tr>
<th></th>
<th>$i = 1$</th>
<th>$i = 2$</th>
<th>$i = 3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$j = 1$</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$j = 2$</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$j = 3$</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

5.4.6 Conclusions

Firstly, there is relatively high flow in the sample inlet channel which is helpful to reduce adhesion on the sample inlet channel-sieve channels interface.

Secondly, the closed sample inlet channel (no outlet) results in a lower flow comparing with an open sample inlet channel (one outlet at the bottom of sample channel). Thus closed sample inlet should be avoided in design.
Thirdly, the concentration results illustrate that multi-level filter based on semi-H shaped channels is able to separate mixtures into multi group. However, it can only remove the bigger group from target components, but cannot remove the smaller group. Thus multi-level filters based on semi-H shaped channels have a limited capability for multi sized component separation. A multi-level filter based on H shaped channels is able to improve the purification process further.

5.5 Summary

Aiming at more accurate simulation of filter based on H shaped filter, 3D models of angular H shaped channel series were built and studied in this chapter. The flow properties and angle effects were analysed. This study was helpful for understanding the flow process in filter based on H shaped channels. Overall the angle was shown to have limited improvement of flow rate in sieve channels. However the possibility of adhesion increases because the angle enhances the trap effect around cross section area by enlarging the cross section.

Then slip boundary condition was applied with the same models. The flow rates were improved comparing with the ones with no-slip boundary condition. Low velocity layers were observed around cross section among sample inlet channel, sieve channels and capture channel. This layer protected the cross section from unwanted contact with big components therefore reducing the chance of adhesion and clustering. The convection in sieve channels was observed when the angle magnitude was bigger than 30°. Thus large angle showed potential improvements of adhesion and clustering inside sieve channels.
A 3D simulation on a three-level filter based on semi-H shaped channels was reported as well. The pattern simulated was designed for the verification chip in Chapter 6. A closed sample inlet channel resulted in a pumping difficulty comparing with an open one. What is more, the simulation results illustrated the limited capability of separation of multi sized components mixture.
6.1 Introduction

This chapter illustrates the methodology of filter chip design. A whole multi-level nanofilter design path contains application demand analysis, detection requirement analysis; geometric design, interface design, material selection and fabrication process design six steps. Two multilevel filter test chips for dextran and dyed nano spheres separation were designed by this path as examples to demonstrate the methodology of filter chip design.

A new applicable fabrication process for micro- and nano- filter chips was described and demonstrated. In this manufacturing process, firstly photolithography was applied to achieve the 2D pattern of micro structures which were the sample inlet, capture and dilute channels; and then RIE was used to build the 3D pattern of these channels. The fine channels, nanosieve channels, were etched by Focused Ion Beam. After bonding the silicon substrate with a glass cover, a chip of multilevel filter was finally made. Fabrication experiments were described in this chapter and the recipes of each step were given. Other alternative fabrication routes were introduced briefly by the end of this chapter.
6.2 Design Flow of Multi-level Nanofilter Chip

Based on the three-level filter models analysed in section 4.5.1 which were the core and main pattern of the filter chips, two test versions of three-level filter chips were designed in this section. Whereas the geometric model of a multi-level filter has been already built based on the demand of the application, during the design several questions still should be answered. The first question is how to detect the flow and components in it? Then secondly besides the core pattern of the channels of multi-level filters, how to design the connection interface with other devices such as pumps and detection instruments, the question is, what kinds of materials are suitable for these applications? And finally the fourth to be answered is how these materials should be fabricated to build a patterned chip? After these questions are answered, combining with the geometric model of a multi-level filter, a design of chip is able to be developed. Figure 6.1 shows the whole design progress.

![Flow process diagram for multilevel filter design](image-url)
6.2 Design Flow of Multi-level Nanofilter Chip

6.2.1 Detection Requirement Analysis

A straightforward way to show the filtration is by separating different size and colour dyed particles, such as commercial dyed nanospheres and fluorescent dextran. The capture solution of each level will show a different colour, which is a rainbow filtration. If the rainbow was observed, the sample inlet channel and capture channels should be visible. This is an example that detection methods affect geometric features design. The concentration is able to be detected under a microscope or more precisely by absorption photometry[162, 163]. For optical detection, the chip is desired to be transparent on at least one side, which should be considered during material selection. If a fluorescent microscope was applied for a real-time detection, the chip diameter and connection interface should be designed to allow adjustment of the stage of microscope.

6.2.2 Geometric features design

By analysing the components in the solutions for separation, main geometric features of multilevel filter chips can be designed. The width and depth ($a_i$) of $n$ ($0 < i \leq n$) level sieve channels can be decided under the condition $a_j < a_i < a_{j+1}$. For a three-level filter, $n = 3$, maximally four different size component groups can be purified. The minimum width ($w$) and depth ($d$) of the sample inlet channel is governed by the size of the largest component, which is ($w > a_{j=n+1}, d > a_{j=n+1}$). The diameter of dextran is as shown in Table 6.1, thus the sieve size $a_i$ for each level can be 2.33-29.4 nm, 29.4-54 nm and bigger than 54 nm respectively. Considering the EDL of channels and the fabrication method used, a set of value is able to be decided. For example, one set of $a_i$ are 20, 40 and 80 nm respectively, which are suitable for Focused Ion Beam milling. The width ($w$) and depth ($d$) of the sample inlet channel could be 2,000 nm and 1,000 nm, which are easily achieved by
photolithography and RIE etching. These values were used in some simulations in Chapter 4. It should be noticed that there are no experimental data for an accurate fluorescent dextran diameter. What is able to found is that the dyed particles are small (molecule weight comparing with 3kDa dextran), thus the theoretical diameter (imagining the shape of component is a sphere) of fluorescent dextran conjugate is similar with but bigger than the dextran itself. Therefore the diameter values in Table 6.1 are still to be referenced when designing the filter.

<table>
<thead>
<tr>
<th>$j$</th>
<th>Molecule Weight</th>
<th>Diameter $a_j$ (nm)</th>
<th>Fluorescent Label</th>
<th>Colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3kDa</td>
<td>2.33</td>
<td>ThermoFisher Dextran Texas Red Neutral</td>
<td>Red</td>
</tr>
<tr>
<td>2</td>
<td>500kDa</td>
<td>29.4</td>
<td>ThermoFisher Dextran Fluorescein</td>
<td>Blue</td>
</tr>
<tr>
<td>3</td>
<td>2,000kDa</td>
<td>54</td>
<td>ThermoFisher Dextran Tetramethylrhodamine</td>
<td>Green</td>
</tr>
</tbody>
</table>

The details of the dyed micro and nano spheres are shown in Table 6.2, and from these it is able to design and test three-level filters to show the design process and fabrication process in a more straight forward way, i.e. a rainbow filtration. For example, Visiblex™ Visible Dyed Nanospheres 1008(30nm red), 1011(300nm yellow), 1012(500nm purple) and 1004(800nm blue) can be used for a three-level filter test, in which the three-level sieves size are 200, 400 and 600nm respectively. Comparing with dextran conjugates, dyed nanosphere can be applied more easily with a uniform geometric shape and diameter. What is more, the detection of dyed nanosphere does not demand a fluorescent microscope which is not available in Micro-engineering and Nano-technology Research Group. For a verification experiment, dyed nanospheres are a better choice, while the dyed dextran conjugates are more suitable for bio-particles filtration. In this section, two chips were designed. One was a
chip aiming at demonstrating the fabrication process and observing the filtration phenomena. This chip was designed for dyed nanospheres. The other one was a three-level filter design for bio-particles separation and fluorescent microscope detection. Commercial dextran has a set of standard molecular masses and is widely used in bioscience, so that it is undoubtedly a good indicative component for filtration studies.

<table>
<thead>
<tr>
<th>Name</th>
<th>Size (nm)</th>
<th>Colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible Dyed Nanospheres 1001</td>
<td>30</td>
<td>Blue</td>
</tr>
<tr>
<td>Visible Dyed Nanospheres 1002</td>
<td>200</td>
<td>Blue</td>
</tr>
<tr>
<td>Visible Dyed Nanospheres 1003</td>
<td>500</td>
<td>Blue</td>
</tr>
<tr>
<td>Visible Dyed Nanospheres 1004</td>
<td>800</td>
<td>Blue</td>
</tr>
<tr>
<td>Visible Dyed Nanospheres 1008</td>
<td>30</td>
<td>Red</td>
</tr>
<tr>
<td>Visible Dyed Nanospheres 1009</td>
<td>500</td>
<td>Red</td>
</tr>
<tr>
<td>Visible Dyed Nanospheres 1011</td>
<td>300</td>
<td>Yellow</td>
</tr>
<tr>
<td>Visible Dyed Nanospheres 1012</td>
<td>500</td>
<td>Purple</td>
</tr>
</tbody>
</table>

6.2.3 Connection Interface Design

At beginning, a test chip aiming at demonstrating the fabrication process and filtration was designed. Here it is named as verification chip. It was designed to be as simple as possible. The sample inlet was a hole on the silicon substrate which connected with a polycarbonate or silica tube. However it is hard to avoid leaking by sealing to the silicon wafer with pipes. One way to solve this problem is packaging the chip and pipe together with PDMS. Another solution is connecting the tubes with the glass side, which is applied on most commercial microfluidic chips. Thus in the later design of multi-level filter chip a commercial connector was used. All pipes were connected with the inlet holes on glass cover (Figure 6.2).
6.2 Design Flow of Multi-level Nanofilter Chip

6.2.4 Materials Selection

As it was mentioned in the literature review, several materials are widely used for Lab-on-Chip devices, which are silicon, glass, PDMS, metal and other polymers.[164] For microfluidics devices, glass is a common choice for substrates, especially in industry, due to the low cost, fabrication accuracy, and harshness of environment that it will withstand. Another reason is that the transparency of glass makes optical detection to be realisable, which is crucial for biomedical applications. However, the fabrication techniques limit the application of glass for nanostructures. Whereas the multi-level filter contains several different depth structures, it is difficult to make each level sieve channels on the same surface by wet etching which is currently the main fabrication method for glass due to the low cost and high throughput. Femtosecond laser machining and other alternative techniques are able to manufacture 3D nano structures on glass; however the cost is relatively high. Thus glass is a candidate substrate material. PDMS and other polymers are not suitable for nano channels due to their low mechanical strength. What’s more the possibility of reaction with sample fluid also limits the application of polymers.

For nanofluidics devices, a silicon wafer is one of the best substrate materials due to the difficulty of reaction of the silicon with the fluidic samples, the low cost, good mechanical properties and the highly developed silicon fabrication techniques. Considering the widely
accessible equipments in laboratories, especially in the clean room of University of Birmingham, the silicon wafer is a great option for a patterned nanofilter demonstration. Meanwhile, glass was selected as the cover material for the compatibility with optical detection.

6.2.5 Fabrication Process Design

When the materials have been selected, fabrication methods and their recipes can be given based on the geometry conditions. For the multi-level filter based on H shaped channels fabrication process, various 3D fabrication techniques, such as Focused Ion Beam milling, femtosecond laser machining, gray scale e-beam lithography, nanoimprint lithography and scanning probe lithography are able to be used. The main difficulty is the fabrication of all levels of channels with different sizes on one chip. Considering the size map of components in human blood, the size of channels shall need to cover nanometres to microns.

Focused Ion Beam (FIB) is one way to manufacture 3D nano structures which was introduced in chapter 2.[132, 133, 135] The disadvantages are that FIB milling is expensive and time consuming. Thus it is not an economic way for large volume structure milling such as micro channels.

Laser machining is an alternative technique for micro channels fabrication. The etch rate of silicon can be more than $2 \times 10^5 \, \mu m/s$ for micro channels.[165] The single femtosecond laser pulses technique can be used for nano channel fabrication on glass substrates or transparent polymer layer with a high repetition rate (GHz)[166] for a rapid writing speed (400m/s, the depth of channel depends on the laser pulse fluence [167]). The principle of femtosecond laser machining is the laser induced breakdown caused by the optical energy transferring to the material (glass or transparent polymer). The ionizations during this
6.2 Design Flow of Multi-level Nanofilter Chip

transfer process permanently change the phase or structure of the material so that the exposure area can dissolve in solvent.[168] (For silica glass the solvent is water[169]). However, due to the strong two-photon absorption of semiconductors such as silicon at the fundamental wavelength of commonly used femtosecond lasers, this technique currently cannot be used for nano scale silicon modification.[170]

Another alternative technique for the 3D nano structures manufacturing on one chip is electron beam (e-beam) greyscale lithography of which the resolution can be 20nm [171, 172]. Comparing with FIB milling, on one hand e-beam lithography is faster and more economic; on the other hand e-beam lithography requires a resist layer. If 3D silicon structures are demanded, RIE could be applied to transfer the structures from the resist mould to the silicon substrate. During the transfer process (such as RIE etch and wet etch), there are unavoidable degradations of structures such as edge smoothing. If the accurate different thickness resist mould was achieved, for some applications (for example, when the fluids do not react with the resist and the mechanical strength requirement is low) there should be no necessity of a silicon mould.

Nanoimprint lithography is another option for batch fabrication, which is a potential way for commercial manufacturing [173-175]. The basic principle of nanoimprinting is to transfer the structures from the mould to the resist layer under pressing; and then transfer the structures from the resist to substrate, typically by anisotropic etching. As nanoimprint lithography needs a mould, it has the geometric accuracy degradation problems during the transfer of structures, which is similar to grey scale e-beam lithography. When the moulds for nanoimprint are ready, for trial experiments, the moulds are applicable thus there are no
necessity of the later imprint process if the amounts of experiment on each sized are little. Therefore nanoimprint is not an economic way for laboratory study.

Scanning probe lithography was reported as a top-down 3D manufacturing method for nanostructures by Yongda Yan et al [176]. In this report, a $20 \mu m \times 20 \mu m$ portrait, in which peak-valley height was 120 nm, was machined with an atomic force microscope on a polished aluminium disc in 10 min. Thus the scanning probe lithography is a low cost technique with high accuracy. This method is only suitable for nano scale structures and requires a precision-stage system. Mostly, scanning probe lithography is used as a bottom-up method for self-assembly manufacturing.[177-179] The basic principle is using the probe tip (scanning tunnelling microscopy or atomic force microscopy) to modify the surface and then proceeding the self-assembly fabrication. The materials and the relatively low geometric accuracy of patterns limit this bottom-up scanning probe lithography to be applied in nanofluidics.

No matter which fabrication techniques are chosen, the final manufacturing step is bonding the silicon chips with glass covers. Then a multi-level filter chip will be achieved. Here is an example fabrication path which was designed to fulfil the conditions in University of Birmingham. Considering the accessible facilities (mask aligner, DRIE and FIB) in clean room here, the femtosecond laser machining, greyscale e-beam lithography and probe scanning lithography are not available. Due to the high cost and low efficiency of FIB system, the micro and nano structures are designed to be fabricated separately for trial experiments of multi-level filter based on H shaped channels. For the micro channels, such as the sample inlet channel and all capture channels, photolithography combined with RIE is a common fabrication process for silicon which was introduced in section 2.5. After micro structures
manufacturing with photolithography and RIE, the nano structures can be etched by FIB on diced chips. Then the silicon chip can be bonded with a glass cover. It should be highlighted that this fabrication process has not been seen in other publications. The reason why not combine photolithography with e-beam lithography is the difficulty of spinning resist on an uneven surface. The greyscale e-beam lithography, femtosecond laser machining and scan probe lithography are not available with the machine in the laboratory here. Figure 6.3 shows this fabrication process. Photolithography is applied first with a silicon wafer to build a photoresist mask for shallow RIE etching. After the shallow RIE etching, a photoresist mask is fabricated on the back side of silicon substrate. Then DRIE is used for a penetration etch from the back side of the wafer. Then the substrate is cleaned and the nano channels are fabricated by FIB milling. Finally a glass cover is bonded with the silicon substrate by anodic bonding. This fabrication process was verified with experiments described below.
6.3 Photolithography

6.3.1 Mask for Photolithography

For both the verification chip and the multi-level filter chip, two masks were needed. One was designed for the micro channels, and the other was for the inlet and outlet connection. The first question that needed to be answered is which type of photoresist is suitable for each mask application. Key factors are the etch resistance and thickness of photoresist. For different depth RIE etching, different type and different thickness of photoresist are available. Considering the depth of micro channels which is around 1μm and the etching rate of silicon and photoresist, a thin photoresist layer is enough. Therefore MICORPOSIT™ S1800 G2 series negative photoresist was used for the micro channels fabrication. As the penetration etchings on back side asked for a thick photoresist layer and high etch resistance, negative photoresist MEGAPOSIT SPR 220-7.0 was chosen for the back side photolithography.

Software AutoCAD2008 was used to draw masks. Figure 6.4 shows the four inch chromium mask designed for the top side of the verification chip. This mask was fabricated by Delta Mask B.V¹. There were two symmetric three-level filters on one chip which were designed for contrast experiments. The round reservoir in the middle was designed for connection with the penetrated inlet hole etched from back the side of the silicon wafer. The width of the wall between the inlet channel and capture channels was 2 μm which was the minimum size that can be achieved by the Canon PLA-501FA mask aligner available in the Birmingham clean room. The width of the sample inlet channel and capture channels is 20 μm and 1 mm

¹ Delta Mask B.V. Nijmansbos 56, 7543 GJ ENSCHEDE, The Netherlands. Website: www.deltamask.nl
respectively (visible by human eyes). There were two special chips with a dilute channel as well.

Figure 6.4 (a) Top side mask for the verification chip photolithography; (b) Top view of a chip.

Figure 6.5 illustrates the back side mask for the verification chip which was printed on transparency film. The photoresist used for this mask was MEGAPOSIT SPR 220 which was a negative resist and had a high etch resistance. The round holes were designed for penetration etching from the back side of the silicon wafer; the produced through hole would then connect with the round reservoir on the top side. The radius of the through hole was smaller than the radius of the reservoir to enhance the tolerance of alignment error.

Figure 6.6 exhibits the mask drawing of the top side of a multi-level filter chip design (not to scale otherwise some details cannot be seen). The size of this chip is the same as a microscope slide (15 mm x 45mm). The U shaped channel at the bottom is the sample inlet. The other three channels are capture channels 1, 2 and 3 from bottom to top respectively. The diameter of four channels is 2 μm and the width of the wall left for the sieves is 2 μm.
The hole for connection was designed to be fabricated on the glass cover with another mask which is shown in Figure 6.7.

Figure 6.5 Back side mask drawing for the verification chip.

Figure 6.6 Three-level nanofilter chip micro channel map.

Figure 6.7 Interface map for glass cover.
6.3.2 Photolithography Experiments

Several experiments were carried out with the masks designed for the verification chip to find the appropriate photolithography recipes. All these experiments were made with EMS 1000-1 hot plate, EMS Model 4000 Photoresist Spinner and Canon PLA-501FA Mask Aligner in the clean room of the Micro-engineering and Nano-technology Research Group (Figure 6.8).

![EMS 1000-1 hot plate (Left), EMS Model 4000 Photoresist Spinner (Right); (b) Canon PLA-501FA Mask Aligner](image)

Table 6.3 records the experiments of the top side photolithography of the verification chip with S1805photoresist. All reused wafers were cleaned before use. It can be seen that pre-treatment with primer is necessary for a good coating. The wafer should be cooled down on a hot plate rather than in air after soft bake, otherwise the resist peeled off easily during developing. The wafer can be agitated slightly and carefully during the dip in developer.
### Table 6.3 Photolithography recipe exploration on photoresist S1805

<table>
<thead>
<tr>
<th>No.</th>
<th>VT1</th>
<th>VT2</th>
<th>VT3</th>
<th>VT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>New wafer, none primer</td>
<td>New wafer, none primer</td>
<td>Reused wafer, none primer</td>
<td>Reused wafer, none primer</td>
</tr>
<tr>
<td>Spin speed</td>
<td>3000 rpm</td>
<td>3000 rpm</td>
<td>3000 rpm</td>
<td>3000 rpm</td>
</tr>
<tr>
<td>Spin time</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Softbake</td>
<td>115°C, 60s</td>
<td>115°C, 60s</td>
<td>115°C, 60s</td>
<td>115°C, 60s</td>
</tr>
<tr>
<td>Cool down</td>
<td>On hot plate</td>
<td>On hot plate</td>
<td>On hot plate</td>
<td>On hot plate</td>
</tr>
<tr>
<td>Exposure time</td>
<td>7s</td>
<td>3s</td>
<td>3s</td>
<td>2.9s</td>
</tr>
<tr>
<td>Develop</td>
<td>MF&lt;sup&gt;TM&lt;/sup&gt;-319, Dip</td>
<td>MF&lt;sup&gt;TM&lt;/sup&gt;-319, Dip</td>
<td>MF&lt;sup&gt;TM&lt;/sup&gt;-319, Dip</td>
<td>MF&lt;sup&gt;TM&lt;/sup&gt;-319, Dip &amp; spray wash</td>
</tr>
<tr>
<td>Result</td>
<td>Over exposure, good adhesion</td>
<td>Lack of develop</td>
<td>Over exposure, Weak adhesion</td>
<td>2μm wall peeled off, Weak adhesion</td>
</tr>
<tr>
<td>NO.</td>
<td>VT5</td>
<td>VT6</td>
<td>VT7</td>
<td>VT8</td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>Reused wafer, none primer</td>
<td>Reused wafer, none primer</td>
<td>Reused wafer, none primer</td>
<td>Reused wafer, 2min primer</td>
</tr>
<tr>
<td>Spin speed</td>
<td>3000 rpm</td>
<td>4000 rpm</td>
<td>4000 rpm</td>
<td>4000 rpm</td>
</tr>
<tr>
<td>Spin time</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Softbake</td>
<td>115°C, 60s</td>
<td>115°C, 60s</td>
<td>115°C, 60s</td>
<td>115°C, 60s</td>
</tr>
<tr>
<td>Cool down</td>
<td>In air</td>
<td>On hot plate</td>
<td>On hot plate</td>
<td>On hot plate</td>
</tr>
<tr>
<td>Exposure time</td>
<td>2.9s</td>
<td>3s</td>
<td>2.5s</td>
<td>2.4s</td>
</tr>
<tr>
<td>Develop</td>
<td>MF&lt;sup&gt;TM&lt;/sup&gt;-319, dip</td>
<td>MF&lt;sup&gt;TM&lt;/sup&gt;-319, Dip</td>
<td>MF&lt;sup&gt;TM&lt;/sup&gt;-319, Dip</td>
<td>MF&lt;sup&gt;TM&lt;/sup&gt;-319, Dip</td>
</tr>
<tr>
<td>Result</td>
<td>Over exposure, Weak adhesion</td>
<td>Over exposure, Weak adhesion</td>
<td>Over exposure, Insufficient &amp; development, good adhesion</td>
<td>Appropriate exposure &amp; development, good adhesion</td>
</tr>
</tbody>
</table>
The recipe used in experiment No. VT8 gave the best result and its reproducibility was very good in later RIE experiments. Consequently, the progress of top side photolithography can be operated with the recipe of No. VT8. The spinner was broken once when these experiments were taken. During the broken period the spin speed was not available at 3000rpm so 4000rpm was used instead. Thus there were two different spin speeds in this table. The thickness of coated S1805 photoresist at 4000rpm was acceptable for shallow RIE etching, which will be described in the RIE experiment section.

The recipe for the back side photolithography of verification chip with photoresist SPR 220-7.0 is shown in Table 6.4. From the results, group No. VB2 shows a best exposure and development.

<table>
<thead>
<tr>
<th>No.</th>
<th>VB1</th>
<th>VB2</th>
<th>VB3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>2min primer</td>
<td>2min primer</td>
<td>2min primer</td>
</tr>
<tr>
<td>Spin speed</td>
<td>3000rpm</td>
<td>3000rpm</td>
<td>3000rpm</td>
</tr>
<tr>
<td>Spin time</td>
<td>30s</td>
<td>30s</td>
<td>30s</td>
</tr>
<tr>
<td>Softbake</td>
<td>30s step-down to 115°C, 90s</td>
<td>30s step-down to 115°C, 90s</td>
<td>30s step-down to 115°C, 90s</td>
</tr>
<tr>
<td>Cool down</td>
<td>On hot plate</td>
<td>On hot plate</td>
<td>On hot plate</td>
</tr>
<tr>
<td>Exposure time</td>
<td>7.7s</td>
<td>7.5s</td>
<td>7.3s</td>
</tr>
<tr>
<td>Develop</td>
<td>Dip in MF-24A</td>
<td>Dip in MF-24A</td>
<td>Dip in MF-24A</td>
</tr>
<tr>
<td>Result</td>
<td>Over exposure, good adhesion, sufficient development</td>
<td>Appropriate exposure,</td>
<td>Lack of exposure</td>
</tr>
</tbody>
</table>

6.3 Photolithography
6.4 Reactive Ion Etch

When the photoresist pattern on the top side of the silicon wafer was achieved, RIE was applied to transform the photoresist pattern to the silicon substrate. The system used here was a STS Multiplex ICP DRIE etcher (Figure 6.9) which was designed for deep RIE etching. A group of experiments were made to explore an appropriate recipe for shallow etching with the STS Multiplex ICP DRIE etcher.

![Figure 6.9 STS Multiplex ICP DRIE etcher](image)

First a group of experiments without a passivate step were designed to figure out a recipe as a start point which could be optimized with further experiments. The RF power was 600W for all experiments. Table 6.5 describes the results where the depth value was detected by AMBIOS XP-200 Surface Profiler (Figure 6.10). Before surface profiler detection, the photoresist was removed by MICROPPOSIT REMOVER 1165 and the wafer was dried in nitrogen gas. It can be seen that No. ET1 and ET6 show results which are desired. However the etch rate is slightly high for etching a 1 m shallow pattern when SF₆ Flow is 130sccm. Thus the etch time should be well controlled. The RF platen power affects the etch rate slightly. For a lower etch rate, a lower power is better.
Table 6.5 RIE experiment without passivate process

<table>
<thead>
<tr>
<th>NO.</th>
<th>SF$_6$ Flow (sccm)</th>
<th>RF Platen Power (W)</th>
<th>Etch time (s)</th>
<th>Depth (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET1</td>
<td>130</td>
<td>12</td>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>ET2</td>
<td>130</td>
<td>12</td>
<td>60</td>
<td>2.5</td>
</tr>
<tr>
<td>ET3</td>
<td>130</td>
<td>12</td>
<td>120</td>
<td>4.7</td>
</tr>
<tr>
<td>ET4</td>
<td>130</td>
<td>12</td>
<td>180</td>
<td>5.8</td>
</tr>
<tr>
<td>ET5</td>
<td>130</td>
<td>12</td>
<td>240</td>
<td>All photoresist removed</td>
</tr>
<tr>
<td>ET6</td>
<td>130</td>
<td>30</td>
<td>20</td>
<td>1.1</td>
</tr>
<tr>
<td>ET7</td>
<td>130</td>
<td>30</td>
<td>60</td>
<td>2.5</td>
</tr>
<tr>
<td>ET8</td>
<td>130</td>
<td>30</td>
<td>120</td>
<td>All photoresist removed</td>
</tr>
<tr>
<td>ET9</td>
<td>130</td>
<td>30</td>
<td>180</td>
<td>All photoresist removed</td>
</tr>
<tr>
<td>ET10</td>
<td>130</td>
<td>30</td>
<td>40</td>
<td>1.9</td>
</tr>
<tr>
<td>ET11</td>
<td>130</td>
<td>12</td>
<td>40</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Then a C₄F₈ passivation step was introduced to the etch process. The RF platen power for the passivation was zero to create an isotropic deposition. Table 6.6 records the results. It is apparently that the etch rate is not steady when there are several cycles. By observing the real time value in the Progress Control-ICP window, it was seen that the SF₆ and C₄F₈ flow rate was not steady in each cycle whereas the long term average value was steady. That is why a longer process time is necessary. Thus reducing the SF₆ Flow and increasing the cycle numbers are options for a more steady etch.

Table 6.6 RIE experiment with 130sccm SF6 Flow

<table>
<thead>
<tr>
<th>No.</th>
<th>SF₆ Flow (sccm)</th>
<th>RF Platen Power (W)</th>
<th>Etch time (s)</th>
<th>C₄F₈ flow (sccm)</th>
<th>Passivate time (s)</th>
<th>Cycle</th>
<th>Depth (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPT1</td>
<td>130</td>
<td>12</td>
<td>10</td>
<td>100</td>
<td>7</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>EPT2</td>
<td>130</td>
<td>12</td>
<td>10</td>
<td>100</td>
<td>7</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>EPT3</td>
<td>130</td>
<td>12</td>
<td>10</td>
<td>100</td>
<td>7</td>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>EPT4</td>
<td>130</td>
<td>12</td>
<td>10</td>
<td>100</td>
<td>7</td>
<td>6</td>
<td>2.1</td>
</tr>
<tr>
<td>EPT5</td>
<td>130</td>
<td>12</td>
<td>10</td>
<td>100</td>
<td>7</td>
<td>12</td>
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<td>EPT6</td>
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<td>EPT7</td>
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<td>10</td>
<td>100</td>
<td>7</td>
<td>6</td>
<td>3.2</td>
</tr>
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<td>EPT8</td>
<td>130</td>
<td>12</td>
<td>8</td>
<td>100</td>
<td>7</td>
<td>5</td>
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<tr>
<td>EPT9</td>
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<td>100</td>
<td>7</td>
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</tr>
<tr>
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<td>6</td>
<td>100</td>
<td>5</td>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td>EPT11</td>
<td>130</td>
<td>12</td>
<td>6</td>
<td>100</td>
<td>5</td>
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<td>130</td>
<td>12</td>
<td>6</td>
<td>100</td>
<td>5</td>
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<td>0.7</td>
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<tr>
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<td>6</td>
<td>100</td>
<td>5</td>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>EPT14</td>
<td>130</td>
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<td>6</td>
<td>100</td>
<td>5</td>
<td>7</td>
<td>1.5</td>
</tr>
</tbody>
</table>
The depth values in No.EPT10-14 show the possibility that there was a thin SiO$_2$ layer on the silicon substrate due to the dip in developer. Therefore it is necessary to bake the wafer after developing and do the RIE etching as soon as possible afterward.

Table 6.7 exhibits experiments which reduced the SF$_6$ flow. After each etching, a 5 min O$_2$ clean (45sccm O$_2$ flow, RF coil 600W, RF platen 30w) was applied on EPT15-30 to remove the photoresist instead of using a chemical remover. The depth varies when SF$_6$ flow is 100sccm (No.EPT15-17) and 80sccm (No.EPT18-22), so that the SF$_6$ flow was reduced again to 60sccm. No.EPT23-28, 29-34 are two groups of repeat experiments which etched three and four cycles respectively with 60sccm SF$_6$ flow. The variances are 0.0077 and 0.0308 m$^2$ respectively. The recipe used in experiment No.EPT35-37 achieved a steady and appropriate depth by increasing the cycle number to five. Figure 6.11 shows the SEM picture of No. EPT37. The silicon structures were well patterned. The bottom of the etching area was very smooth while the side wall was straight but rough. A little photoresist is observed to remain in Figure 6.11b, therefore a longer O$_2$ clean is desired. The dust which can be viewed in 6.11a & c was introduced during the chip transfer from clean room to the SEM centre.
Table 6.7 RIE recipe explore experiments

<table>
<thead>
<tr>
<th>No.</th>
<th>SF$_6$ Flow (sccm)</th>
<th>RF Platen Power (W)</th>
<th>Etch time (s)</th>
<th>C$_2$F$_8$ flow (sccm)</th>
<th>Passivate time (s)</th>
<th>Cycle</th>
<th>Depth (m)</th>
</tr>
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<td>EPT15</td>
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<td>8</td>
<td>80</td>
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<td>4</td>
<td>1.2</td>
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<td>EPT16</td>
<td>100</td>
<td>12</td>
<td>8</td>
<td>80</td>
<td>7</td>
<td>4</td>
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<td>1.3</td>
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<td>2.3</td>
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<td>EPT22</td>
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<td>60</td>
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<td>16</td>
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<td>7</td>
<td>4</td>
<td>0.7</td>
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<td>0.6</td>
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<td>50</td>
<td>7</td>
<td>5</td>
<td>1.2</td>
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<td>1.2</td>
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<td>EPT38</td>
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<td>8</td>
<td>50</td>
<td>7</td>
<td>6</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Figure 6.11 SEM pictures (a) Wall separate sample inlet and capture channel; (b) Side view of the wall; (c) Inlet hole which was designed to connect a penetration hole etched from back side; (d) Open outlet of capture channel and dicing boundary.

The recipe for back side etch is described in Table 6.8. For a 200 m thickness wafer it takes about 145min.

Table 6.8 DRIE recipe for penetration etching

<table>
<thead>
<tr>
<th></th>
<th>Flow</th>
<th>RF coil</th>
<th>RF platen</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etch</td>
<td>SF₆</td>
<td>130 sccm</td>
<td>600 W</td>
<td>12 W</td>
</tr>
<tr>
<td>Passivate</td>
<td>C₄F₈</td>
<td>85 sccm</td>
<td>600 W</td>
<td>0 W</td>
</tr>
</tbody>
</table>
6.5 Focused Ion Beam Milling

After RIE etching the micro structure of the verification chip had been achieved, then FIB was applied to mill the fine sieve channels. Equation 6.1 defines the milling rate \( R \) which can be found in user manual of FEI Dual-Beam Strata 235 Focused Ion Beam.

\[
R = \frac{dA}{lt}
\]

*Equation 6.1*

Where \( d \) is the milling depth,

\( A \) is the scanning area,

\( l \) is the beam current,

\( t \) is the milling time.

The 30keV gallium beam milling rate for silicon is \( R = 0.15 \mu m^3/\mu A \cdot s \). Table 6.9 describes the beam current and its corresponding milling spot size. As the diameter of sieve channels on the verification chip are 200, 400 and 600nm respectively; the beam current for each level of sieves can be decided. The length of sieve channels is 2000nm. Therefore the milling time is able to be calculated using Equation 6.1.

Table 6.10 exhibits the recipe for each size of sieves and the corresponding milling time needed. The quantity of channels were calculated with Equation 3.12 when \( \gamma = 1 \). The whole milling process takes 84.5min and 96.5min for the verification chip and multi-level filter chip respectively. However this time does not consider the time cost for cross section clean which is necessary for a nanochannel FIB milling. If the milling area was same as the aimed channel area, the two entrances of the nanochannel should be over milling one side and lack of milling the other side due to the alignment error. To avoid this phenomenon, a two steps milling are normally applied for cross section milling. A smaller area is milled with high beam current first. Then the edges left of cross section are cleaned with a low beam
current milling. Normally the ion beam current used for each cross section clean is a quarter of its milling beam current. The sieve channels pattern is able to be designed and edited using the xP V2.25 software for FEI Dual-Beam Strata 235 FIB. Figure 6.12 exhibits the FEI Dual-Beam Strata 235 FIB system.

Table 6.9 Different beam currents and the corresponding milling spot size

[Source: FIB manual for FEI Dual-Beam Strata 235]

<table>
<thead>
<tr>
<th>Beam current (pA)</th>
<th>Milling spot size (nm)</th>
<th>Best use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>Very high-resolution imaging, High aspect ratio holes, High-resolution imaging</td>
</tr>
<tr>
<td>10</td>
<td>10.0</td>
<td>Quick imaging</td>
</tr>
<tr>
<td>30</td>
<td>12.5</td>
<td>Navigation imaging</td>
</tr>
<tr>
<td>50</td>
<td>15.0</td>
<td>Milling submicron holes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Final milling on cross sections</td>
</tr>
<tr>
<td>300</td>
<td>25.0</td>
<td>Milling micron-sized holes</td>
</tr>
<tr>
<td>500</td>
<td>30.0</td>
<td>Intermediate/final milling on cross sections</td>
</tr>
<tr>
<td>3000</td>
<td>60.0</td>
<td>Initial milling for small cross sections</td>
</tr>
<tr>
<td>5000</td>
<td>100.0</td>
<td>Initial milling for medium cross sections</td>
</tr>
<tr>
<td>7000</td>
<td>150.0</td>
<td>Initial milling for medium-large cross sections</td>
</tr>
</tbody>
</table>
6.5 Focused Ion Beam Milling

Table 6.10 FIB milling time for different level sieves

<table>
<thead>
<tr>
<th>$d = a_i$ (µm)</th>
<th>$A$ (µm$^3$)</th>
<th>Milling beam current $I$ (pA)</th>
<th>Milling time for one channel (s)</th>
<th>Quantity of channels</th>
<th>Total pattern time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0.4</td>
<td>1000</td>
<td>0.53</td>
<td>6000</td>
<td>53.33</td>
</tr>
<tr>
<td>0.4</td>
<td>0.8</td>
<td>3000</td>
<td>2.13</td>
<td>1500</td>
<td>17.78</td>
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<tr>
<td>0.6</td>
<td>1.2</td>
<td>4000</td>
<td>1.2</td>
<td>667</td>
<td>13.34</td>
</tr>
<tr>
<td>0.02</td>
<td>0.04</td>
<td>10</td>
<td>0.53</td>
<td>6000</td>
<td>53.33</td>
</tr>
<tr>
<td>0.04</td>
<td>0.08</td>
<td>10</td>
<td>1.94</td>
<td>1500</td>
<td>35.56</td>
</tr>
<tr>
<td>0.08</td>
<td>0.16</td>
<td>70</td>
<td>1.22</td>
<td>375</td>
<td>7.62</td>
</tr>
</tbody>
</table>

Figure 6.12 FEI Dual-Beam Strata 235 Focused Ion Beam

A trial milling was made on the verification chip (No.EPT10) and its results are shown in Figure 6.13. The current of 30 keV gallium beam used in this trial milling was 5nA and dwell time of 10 µs. Milling time was 5.87s and a 2 × 2.2 × 1 µm$^3$ cross section was achieved. The
RIE etch depth was 0.7 μm. As the width of milling area is wider than the wall (2 μm), it is clearly shown in the picture that at the bottom besides the wall there was milled two holes. The holes beside sieve channels can trap components therefore increase the possibility of clogging. Thus a better alignment is necessary.

The two steps milling is helpful to improve the geometry features of cross section. High ion beam current and long dwell period results in a sloped side wall in the sieve channel which is shown clearly in the figure. The sediment caused by chemical photoresist remover can be
viewed along the wall. After the chemical removal of photoresist, a nitrogen flow was applied to dry the surface. The silicon wall blocked the nitrogen flow thus kept the remover solution near the bottom of wall which presented as the dirty vestige under SEM. Therefore a physical removal method, O₂ clean taken by STS Multiplex ICP DRIE etcher, was applied to avoid the photoresist pollution. Consequently this is not a successful fine channel milling experiment; however, it demonstrates the feasibility to fabricate a nanofilter combining RIE etching and FIB milling and points out the cautions for nanochannel milling. Due to the machine failure of FEI Dual-Beam Strata 235 Focused Ion Beam and STS Multiplex ICP DRIE etcher, experiments on FIB milling was stopped at this point. Further fabrication on the recipes shown in Table 6.10 will be made in the future.

6.6 Wet Etch and Bonding

6.6.1 Wet Etch of Glass

After FIB milling, the silicon structure part of the chip is all fabricated. Then the glass covers with connection holes for the multilevel filter chip are made by wet etching. A typical glass wet etching process flow that could be used for fabricating the glass covers is described as below. First a hard resist mask is coated with the glass wafer. Hard bake is recommended for photoresist mask to enhance the adhesion of photoresist to glass wafer. Secondly prepare glass etching solution. Add 85ml DI water, buffered HF (5ml), and 9-10ml HCL into a Teflon container sequentially and stir with a plastic stirrer carefully. Thirdly, put the glass substrate into the etching solution and stir constantly. The etch rate is approximately 1μm/min at room temperature. Fourthly after etch rinse the substrate in DI water and then remove the resist. Finally clean up all materials.
6.7 Alternative fabrication routes

6.6.2 Anodic Bonding

The last step of the fabrication process is bonding the silicon substrate with the glass cover. Several techniques are able to bond silicon with glass. Most methods applied adhesives or soft material to seal two wafers together, such as adhesive bonding (epoxies, silicones, photoresist, etc.), glass frit bonding and solder bonding. However this changes the dimensions of the micro and nanostructures at the interface, especially nanoscale structures, due to flow of adhesive into the features. Anodic bonding is one way to bond silicon and glass without adhesives. The silicon and glass wafers are heated (300-500°C, depending on glass type) to mobilize the ions in the glass. When a high voltage is applied, the ions migrate from the interface forming a depletion layer. The high electric field attract silicon and glass to contact firmly where an anodic reaction takes place. Due to the permanent high strength bond, accurate alignment, free thermally matched stress, no flow of glass, no adhesives and low cost; anodic bonding is widely used in research and industry, especially in the microfluidics area. It is also able to be applied on chip level which is necessary for the application in this section. Commercial bonding services are available. For example, Applied Microengineering Limited (AML) is a company in Oxfordshire offering various bonding services including anodic bonding. The chips fabricated in this section were planned to be bonded in this company.

6.7 Alternative fabrication routes

As it was introduced in section 6.2.5, various alternative fabrication routes are available for manufacturing of multi-level filter based on H shaped channels. In this section, more details on the alternative fabrication routes are given.
For silicon substrate, greyscale e-beam lithography combined with etch (dry or wet), dicing and anodic bonding technique is one option for multi-level filter based on H shaped channels. The first step is coating the wafer with resist and soft baking. The pattern is drawn in the e-beam pattern control system and this is then used to control the greyscale e-beam writing process to form exposed features. Finally the development process results in different depth micro and nano channels on the resist. No mask is needed. Then reactive ion etch or wet etch is able to transfer the pattern on resist mould to the silicon substrate. O₂ clean or chemical remover can be used for removing the various thicknesses of resist. After cleaning the silicon wafer, a glass cover wafer is bonded onto it. Finally filter chips are achieved after dicing. This method requires well controlled RIE process to minimize the structure degradations during structure transfer. Apparently, the use of greyscale e-beam lithography avoids the need for alignment process of different masks to create the features and so increases the accuracy of cross section and the fabrication efficiency. By choosing resists with high etch selectivity; the writing time can be further reduced. However the depth errors of e-beam writing will be amplified after RIE step if thin resists are used.

Imprint lithography requires a mould (silicon or metal) as a stamp which can be fabricated by the e-beam lithography or FIB milling (silicon) and lift-off (metal).[180, 181] When the mask has been fabricated, the silicon wafer needs to be coated with a layer of imprint polymer. Then the imprint stamp is pressed against the polymer layer accompanied with heating or UV light exposure. For a silicon filter, RIE shall be applied to transfer the structure on polymer mould to silicon wafer, which is similar with the process of e-beam lithography. For a metal filter, lift-off method is used for the final manufacturing.[182] The metal layer on the substrate needs to be coated before the polymer layer. The anodic bonding and
6.7 Alternative fabrication routes

dicing are the last two steps of this fabrication route. Nanoimprint lithography with RIE and anodic bonding suits for large volume manufacturing of filter chips. Once the stamp has been made, the pattern cannot be changed easily. Thus for trial experiments of multi-level filter based on H shaped channels, the imprint stamps can fulfil the requirements of experiments with higher flexibility.

For use of glass as a substrate, femtosecond laser machining is a convenient method for 3D fabrication. As it was mentioned in section 6.2.5, femtosecond laser pulses change the phase or structure of silica glass. The exposure area is able to dissolve in water. Theoretically, bonding is not necessary. All 3D structure of multi-level filter can be machined inside one glass bulk after femtosecond laser writing and then dipping in water to dissolve the modified glass area. However, the dissolving process of nanochannels in this situation will be extremely slow. It is better to machine the channels on the surface of glass substrate and then bonding with a glass cover. This fabrication route can produce totally transparent chips which are applicable for more optical detection method comparing with the silicon-glass chips.

If the micro and nano channels are fabricated separately, besides the example fabrication route, there are various options. Laser machining, electro discharge machining, powder blasting (glass only), casting, injection moulding (polymer only) and hot embossing (polymer only) etc can be used to replace the photolithography step for microchannel manufacturing[164]. Femtosecond laser machining (glass), e-beam lithography, greyscale e-beam lithography and scanning probe lithography etc are capable for the fabrication of nanochannels.
The greyscale e-beam lithography, nanoimprint lithography and femtosecond laser machining can manufacture all channels in one step. Due to their high resolution, the distance among channels can be sub-micron or even less. Therefore the shorter length of sieve channels results in shorter fabrication time and shorter transport time comparing with the two steps (microchannel and nanochannel) fabrication routes. The nanoimprint lithography suits for large volume chips manufacturing with medium set up cost, while the greyscale e-beam lithography and femtosecond laser machining can be applied for medium volume produce.

6.8 Summary

In this chapter the methodology the design of the multi-level filter based on H shaped channel was described, which contains six steps: application demand analysis, detection requirement analysis; geometric design, interface design, material selection and fabrication process design. For each step, examples were given and analysed based on the multi-level filter. One verification chip aiming at demonstrating fabrication process and basic filtration was designed as an example of the design flow. Another example was a three-level nanofilter chip.

A new path to fabricate a nanofilter was designed as an example of fabrication route design considering the cost and the accessible facilities in University of Birmingham. Then experiments were made to explore recipes for each step of fabrication. Reliable and reproducible recipes for S1805 and SPR 220 photolithography were achieved. RIE experiments gave a recipe which resulted in a $1.2\mu m$ depth etching for the top side of both verification and three-level nanofilter chips. Penetration etch from the back side of the
verification chip had been done as well. Recipes for different level sieve channel FIB milling were discussed. The discussion of a trial milling experiment demonstrated the feasibility of a fabrication process of multi-level nanofilter combining ICP RIE and Focused Ion Beam, and pointed out cautions for FIB nanochannel milling. Nevertheless the failure of equipments halted the following fabrication later fabrication process. The wet etch progress for the glass cover of three-level nanofilter chips and available bonding technique were briefly illustrated. Finally, alternative manufacturing processes were illustrated briefly. Further fabrication will be made in near future.
CHAPTER 7

DISCUSSION AND CONCLUSIONS

7.1 Introduction

In this chapter, firstly the validation of the simulations exhibited in the former chapters is introduced. Based on the validated results, overall discussions on the flow properties and the mass transfer are made to link all former chapters together. The comparisons between multi-level filter based on H shaped channel and other published methods, and the methodology of chip design are discussed as well. The chapter concludes with a summary of the thesis followed by the presentations of the main conclusions of the research and the ideas for future work.

7.2 Validation of the Simulations

7.2.1 Dumbbell channel model

The dumbbell channel contains a sudden contraction and a sudden expansion in width. The flow stream of Newtonian fluid through a dumbbell channel can be calculated by Navier-Stokes equations (Equation 2.9 & 10). The flow properties in channel with sudden contraction [151, 152, 183, 184] and sudden expansion [185-193] were studied and verified by many researchers. The contraction structure contracts the flow while the expansion structure expands the flow in contrast. The researches demonstrated that there is a pressure drop after pass a sudden contraction. Figure 7.1 draws the simulation result of
7.2 Validation of the Simulations

contour pressure in dumbbell channel of section 3.2.1. The pressure drop can be seen clearly, which fits the published results of sudden contraction [152, 184, 194].

Vortices forms near the corners of the barriers and the wall (before the contraction and after the expansion). The turbulent flow caused by the barriers is affected by Reynolds number [183, 184, 186, 187, 190]. In the micron and nano scale, the Reynolds number (Re = ρνl/μ) is low, typically Re < 1.[195, 196] Thus in micro- and nano- dumbbell channels, the transition from laminar to turbulent flow cannot occur.[151, 189] What’s more, the convections of the vortex around the corner of the barrier and wall are so weak, that the eddy (dead-volume) length is small and the weak vortex cannot be seen in the coarse streamline graph (Figure 3.2a). Figure 7.2 redraws the streamline with a density of 400 (the density of Figure 3.2a is 20). Four closed eddy regions were formed around the corner of the barrier and the wall. The vortex near the entrance wall of sieve channel cannot appear due to the low Reynolds number.

Similar results can be found in lot of publications such as Mills[197], Bullen et al [184], Pike et al [185], Hawa [187], and Biswas et al [191] etc. The separated flow after the expansion is applied in Pinched Flow Fractionation (PFF) for micro components separation (Figure 2.5)[56]. The angle of expansion used in PFF is designed to eliminate the dead-volumes (vortex area). The angle issue was discussed in Jeremy and Stefan’s review [190]. If the length of sieve channel is small, the barrier can be viewed as a symmetric channel with an orifice plate inside. Laminar flow through an orifice plate is a classic fluidic case and has been studied by numerous scholars[194, 197].
7.2 Validation of the Simulations

Figure 7.1 Contour pressure of dumbbell channel

Figure 7.2 Velocity streamline through dumbbell channel
7.2 Validation of the Simulations

7.2.2 Semi-H shaped channel model

The left part of semi-H shaped channel is a T junction (bifurcation) while the right part is a channel with extension in width which was introduced in last section (7.2.2). The vortices (maximum around 1.2e-5m/s) in dead-volume region are too weak to be shown in streamline graph (Figure 3.3). For the bifurcation part, comparing with the studies when \( Re > 1 \) [198, 199], the main difference is the vortex region. Due to the low Reynolds number, vortices cannot develop in the sieve channel and main channel. Similar streamlines with low Reynolds number were published in the article of Lin et al [200] and Sugaya et al [63]. The diameter of each branch of the T channel in Lin’s work was the same, whereas in section 3.2.2 of this thesis the size of sieve channel is smaller than the sample inlet channel. Thus in the semi-H shaped channel fewer stream flows into the sieve branch by contrast with the inlet flow. Rainer et al reported a bifurcation blood cell filter which was h-shaped [201]. The bifurcation described the same principle of the semi-H shaped channel. Sugaya analysed the separation process in HDF, which is an application of semi-H channel series. Other similar results about laminar flow around a sharp edge in microchannel can be found in Todd’s review[196].

The right part which is an extension channel was used for continuous separation in the PFF method[56]. Similar separation phenomenon was also observed in the HDF [62]. In that report the micro components flowed through the long sieve channel into the outlet with different directions. However, due to the alignment effect missing in the long sieve channel, the separation efficiency of the extension stream was low. These results support the analysis of semi-H shaped channels in this thesis.
7.2 Validation of the Simulations

When the semi-H channel is extended to semi-H channel series (section 4.2), a model of cross-flow filtration is built. Kim et al studied the particle trajectories and sieving in a two dimensional cross-flow filtration process (without the capture channel) [153]. The results of simulation in section 4.2 show consistency of flow properties comparing with Kim’s results. Detailed analysis of the cake layer formation was introduced in Kim’s paper.

Similar structure of semi-H channel series was also applied in hydrodynamic filtration (HDF Figure 2.7) [62, 202, 203]. The fine capillary in Figure 2.7a allows liquid to flow though under a low flow rate while blockings any micro components. In contrast, the capillary in Figure 2.7b illustrates a typical cross-flow filtration process, similarly with the simulation in section 4.2. The streamline towards the sieve channel concentrates and aligns the particles. Experiment results of Yamada’s work exhibited the fluorescent flow stream and filtration of blood cells.[62] Consequently the COMSOL simulations about semi-H shaped channel and its series are validated theoretically and experimentally.

7.2.3 H shaped, angular H shaped channel model and multi-level filtration

For the symmetric H shaped channel, apparently there is no convection in the sieve channel connecting the three channels. Thus the model can be viewed as two symmetric channels with two symmetric rectangular traps (expansion and then contraction in width). Thus the streamlines in Figure 3.4, 4.7a and 5.3a are the same kind of the streamline of laminar flow passing a trap[203, 204]. They are similar to the trace of the big group in semi-H shaped channel as well. When the depth of the trap increases, vortex is possible to occurs [151]. The streamlines in Figure 5.3&13 demonstrate the vortices in the sieve channels.
Østergaard et al reported an application of active H-shaped channel separation with magnetic enhanced selectivity[205]. In this report, the magnetic particles pass the sieve channel under a magnetic force to realize the single particle detection. No publication about passive filtration based on H-shaped channel has been seen, neither the angular H-shaped channel applications. However, based on the results on H shaped channel and H shaped channel series, the properties of angular H shaped channel are easy to understand with the basic fluidic principles.

The stream in H shaped and angular H shaped channel series with slip flow showed higher resistance (shear stress) of flow near the cross section (Figure 5.9 & 13). Here the cross section can be viewed as a rough surface. Comparing with the smooth side wall, the shear stress increases with roughness. Similar numerical simulation results on gaseous flow were given by Ji et al [206] and Cao et al [207]. Kunert and Harting gave a similar conclusion in their numerical research on fluid flow in microchannel[208]. Lilly et al demonstrated this phenomenon with experimental evidence[209]. Bonaccurso et al validated the relationship of roughness and shear rate of liquid flow in completely wetting microchannel[161].

Consequently, in this section 7.2, by comparing with all these validated publications, the simulations of dumbbell, semi-H and H shaped channel and their series are validated. Therefore the settings of the simulation software COMSOL Multiphysics® are correct. Because the simulations of multi-level filtration used the same settings and the structure of multi-level filter is combination of semi-H or H shaped channel series which have already been validated, therefore the simulations on multi-level filters have a reliable basis. What’s more, the hydrodynamic filtration demonstrates the applicability of multi-level separation in sequence; and the Brownian ratchet[86] and the hydrodynamic cell trapping[210] gives
examples of filtration based on diffusion rather than convection. So the results of multi-level filter simulation presented in this thesis are both meaningful and reliable.

7.2.4 Summary of the validation

Over all, this section validates the simulations in chapter 3-6 with analytical models, numerical models and published experiment results. The results about dumbbell channel, which is the basis of the dead-end filtration, fitted the studies of dead-end filtration and flow properties in a channel with an orifice (sudden contraction and sudden expansion in width) (section 7.2.1). Then the model of semi-H channel was validated by the research results on cross-flow filtration, bifurcation of flow and sudden expansion of flow in width (section 7.2.2). The H shaped channel was also demonstrated by the publications on trap effects, surface roughness effects and example of H shaped channel applications (section 7.2.2). Based on these analyses, the series of dumbbell, semi-H and H shaped channel were also demonstrated. Related research and publication were introduced in section 7.2.3. The three-level filter based on the semi-H channel series was also validated in section 7.2.3 by the reports on cross-flow filtration and HDF. Hence the settings and results of the COMSOL Multiphysics® were confirmed to be correct and reliable. Thus the simulations of multi-level filter based on H shaped channels which used the same modules and settings can be inferred as meaningful and reliable ones. After validated the models used in this thesis, discussions with more details can be made.
7.3 Discussions

7.3.1 Laminar flow

In this thesis, three models, dumbbell, semi-H and H channel were studied as fundamental elements of the filter with barrier. In structure, the right parts of the dumbbell channel and the semi-H channel are the same (sudden expansion) which was mentioned in section 3.1. And the structures of the left part of semi-H channel and the left part of H channel are same, while the left and right parts of H channel are symmetric. In section 3.2 and section 7.2, it can be seen that the same expansion structure results in a similar expansion flow.

As the dead volume regions besides the cross section in the left part of the dumbbell channel (dead-end filtration) (Figure 7.2) are eliminated by switching the structure to a semi-H channel (cross-flow filtration) (Figure 3.3), the semi-H structure (cross-flow) significantly improves the usage time of the filter with less clogging in contrast with dumbbell structure (dead-end) [211, 212].

The streamlines from the inlet towards the sieve channel in the semi-H model (Figure 3.3) illustrates the flow bifurcation at the cross section (structure bifurcation). This phenomenon results in a concentrating and an alignment of micron and submicron particles towards the side wall of the inlet channel. It is more obvious when there are a set of bifurcations (Figure 5.19). This concentrating phenomenon is the main principle of hydrodynamic filtration[62] and hydrodynamic cell trapping[210].

For the H shaped channel, two parallel symmetric inlet channels were set up with the same inlet/outlet pressure. There is no convection across the sieve channel due to the symmetric pressure besides the sieve channel. The concave streamline towards the cross section
exhibits the trap effect. On the one hand, there is no dead volume in the sample inlet and capture channel of the H channel model, which reduces the cake layer formation in both sides of a filter; but on the other hand, the concentrating effect is not available in the symmetric H shaped channel.

Vortices were observed in the sieve channels. In section 3.3.1, no vortex was seen in the H channel model, due to the low aspect ratio (length/width) of the sieve channel (Figure 3.4).

If the pressure in the sample inlet channel and the capture channel are not symmetric, there are convections through the sieve channel from the higher pressure region to the lower pressure region. For the particles with low diffusion coefficient, the higher pressure on the sample side can increase the total flux in the sieve channel; what’s more it also concentrates and aligns the micro particles along the cross section, in a similar manner to the angular H shaped channels.

Because the angle of angular H channel destroys the symmetry of the structure, the pressures on either side of the sieve channel are not equal anymore. Consequently the fluid convection across the sieve channel occurs under a pressure gradient (Figure 3.13 & 14). Comparing with the semi-H channel, however, the pressure difference on either side of the sieve channel of an angular H-shaped channel is small. In other words, the convection across the sieve channel is low. In contrast to the symmetric H channel model, this low convection potentially can be taken advantaged of concentrating and alignment of the particles.

In structure, the semi-H channel series (section 4.2 & 5.4) is a periodic sequence of semi-H channels. Thus the flow in a semi-H channel series has similar properties as for a single semi-H channel. However, due to the bifurcations of flow at each cross section, the flow can be
separated into several layers corresponding to each sieve channel. The convection in sieve channel can be estimated by studying these streamline layers. As the streamlines flow into the sieve channels occupy a large proportion of the total inlet stream when there is a large amount of the sieve channels, the semi-H channel series enhance the concentrating and alignment effect in the sample inlet channel compared with a single semi-H channel.

Similarly, in structure, the H shaped channel series is a periodic series of H shaped channels. Because there is no convection transfer across the sieve channel, in contrast with the semi-H channel series, the laminar flow in H shaped channel series shows strict periodicity (section 4.3 & 5.2-4). Due to the low convection in the sieve channel of angular H-shaped channel series (section 4.4 & 5.2-4), each angular sieve channel corresponds with a thin layer of streamline. When the angle is positive, the convection flux is backward against the diffusion flux. Therefore the trap effect at the cross section can be weakened. When the angle is negative, inversely, the trap effect is enhanced. The variation of convection is slight when the magnitude of angle is small for both situations.

As the same pressure settings were used for the dumbbell, semi-H and H shaped channel simulations, the flow rates of the capture outlets can be compared and it was found that the highest to the lowest were the H shaped channel, dumbbell channel and the semi-H channel. This rank relates to the amount of pressure drop in the sieve channel of dumbbell and semi-H channels. In industry, commonly both dead-end filtration and cross-flow filtration require a high pressure at the original solution side for higher efficiency [213-215].

The simulations on H and angular H shaped channel series with slip boundary condition exhibited significantly higher flow rate both in the inlet channels and the sieve channels comparing with the no-slip ones. The asymmetric laminar flow in the sample inlet and
capture channel reduces the chances of components to contact with the filter surface. The trap and alignment effect at the cross section were weakened as well (Figure 5.13).

The multi-level filter consisting of different semi-H channel series can be analysed by the streamline layers. The different width and depth of sieves result in different convection flow rate into the sieve channel.[62] The multi-level filter based on H shaped channels is a sequence of several periodic H shaped channel series with different periods. Thus the flow correspondingly shows periodicity with different periods.

7.3.2 Mass transfer in the sieve channels

The static flux in a dumbbell channel, semi-H channel and the semi-H channel series mainly refers to the convection flux. The main reason is that there is only one inlet of these three models. The gradient of concentration is zero. Based on the Equation 2.5, the streamline of velocity can be used to describe the principle of the separation process. For the semi-H channel series and the multi-level filter based on semi-H channels, the diffusion flux dropped down till the concentration of the small group was uniform during the passive filtration. Here it was assuming that the volume of the inlet is large enough thus the sample concentration is fixed at the inlet. For a small volume multi-level filtration of micro components, such as the HDF, the diffusion can be neglected however the concentration may not be uniform due to the concentrating effect [62, 63].

For the micro components in a microchannel, components can be viewed as a solid phase so that the diffusion can be neglected. (That is why HDF are applicable for micro-particles.) For the nano-particles which cannot simply be viewed as solid phase in microchannel, the
7.3 Discussions

diffusion cannot be neglected. Therefore the phenomenon of the concentrating and alignment towards the filter interface is weakened by reducing the particle sizes.

In contrast, the H shaped channel has two inlets, the sample inlet and the buffer (capture channel) inlet. The concentration difference of the two inlets causes diffusion between the sample and buffer inlets (Figure 3.5 & 3.16). As there is no convection linking the two parallel channels, the mass transfer process is dominated by diffusion.

For the semi-H filter, Yamada and other researchers reported that even if the micro particle is smaller than the diameter of the branch sieve channel, particles cannot enter the sieve channel due to the particles’ shape and rotation, and the low flow rate into the sieve channel[62, 63]. The width of streamline band was used in these reports to analyze the separation process. By adding sieve channels, in other words, adding the flow rate into capture channel, the small particles can finally transfer into the capture channel by convection. When the diffusion cannot be neglected, the velocity streamline is only able to estimate the convection flux. In the sieve channel of the symmetric H shaped model, only diffusion occurs. The diffusion flux can be calculated with the Fick’s law. For the asymmetric H shaped channel such as the angular H shaped channel, both convection and diffusion should be considered. The smaller that the magnitude of angle is, the lower the convection is.

In section 3.3, it was demonstrated that when the entrance diameter of the sieve channel is smaller than the entrance diameter of the inlet channel, the diffusion flux is lower than half of the total flux of the small group. Thus H shaped channel series was introduced to overcome this. The integration of flux on the total cross section increases with the number of sieve channels until the integration value equal to half of the integration of flux on the
7.3 Discussions

sample inlet (Figure 3.5 & 4.8). Also the reason why \( \gamma = 1 \) is an insufficient estimation for Equation 3.12 is because the diffusion is anisotropic therefore there is a lower flux through the sieve channels [161].

The mass transfer process in the angular H shaped channel series contains the diffusion flux and the convection flux which is caused by the asymmetric pressure distribution. The convection flux relates to the angle and pump pressure settings. Meanwhile the diffusion flux can be analysed by the same principle of the H shaped channel series. As the diffusion coefficient declines with the increasing diameter of particles, the convection flux occupies a higher proportion in the mass transfer of larger components. The angular effect on the capture concentration is weakened however, due to the lower convection towards the sieve channel. Thus the convection caused by the angle shows potential for the concentrating and alignment of micro components or reducing the adhesion.

One of the basic principles of the multi-level sequence filtration is to collect particles from the sample solution by size sequence. So the amount of each substance in the main channel reduces by the size order. It is an easy way to sort the particles by size. For the particles which can pass through more than one level of sieves, the highest concentration of them is always obtained at the first level where they can enter. For the aim of multi species purification, the concentration at later levels (where the species can pass through) is demanded to be as low as possible; so that the effects of these particles on later levels can be minimized. The HDF is an example of the sequence filtration principle. However the small group cannot be completely removed from the main channel, therefore the separation efficiency is below 100% [62, 63]. The Alignment along the main channel side wall varies the concentration distribution. The concentrating and alignment effects of micro-particles in the
main channel of HDF increase the separation efficiency comparing with the multi-level filter based on the H shaped channels.

The multi-level filter based on semi-H shaped channels is a similar device as HDF. However, the sizes of particles are not limited to microns. The section 4.2.2 and 5.4 studied the properties of a three-level filter based on the semi-H channels. For the nanoparticles, concentrating towards the cross section was not observed in the simulations. Because the transfer of solutes accompanies with the transfer of solvent, the static concentrations of all groups were uniform everywhere where they can enter. The simulations on semi-H shaped channel and its series illustrated this issue as well.

Apparently the multi-level filter based on semi-H shaped channels cannot fit the requirement of purification just mentioned which asks for the concentrations of the components (besides the target component) to be as low as possible. If the particles were transferred independently from the solvent, however, the reduced amount of substance in one side should result in a correspondingly reduced concentration. Typically, external fields are implemented for the independent transfers of some species (section 2.2 & 2.3.3.5). The diffusion is another transfer phenomenon of which the solute transfers separately from the solvent. H shaped channel is one design for passive diffusion separation. Thus the multi-level filter based on H shaped channels is applicable for the purification. This design was put forwards in section 3.5 and analyzed in section 4.5.

Due to the diffusion flux among each level of the multi-level filter based on H shaped channels, the concentration for the component \( j \) at each level \( i \) \((i \geq j)\) is not exactly the geometric sequence described by the Equation 3.9. The Equation 3.14 was put forwards to estimate the error of Equation 3.9 and was verified by simulation in section 4.5.1.
7.3 Discussions

Simulation results shown in Table 4.6 demonstrate that the concentration $c_{i,j}$ of a component $j$ at level $i$ ($i = j$) increases with the distance $l_i$ between adjacent levels ($i$ and $i + 1$). In contrast, the concentration $c_{i+1,j}$ decreases with the increasing distance $L_i$.

Figure 7.3 exhibits the concentration curve along the sample inlet channel of the model in section 4.5.1. The first sieve channel starts at $x = -40\mu$m and ends at $x = 0\mu$m. When the demanded error $\delta_i$ is small (0.5%), the distance $l_i$ is the longest in the figure thus the concentration gradient (negative) at the section between adjacent levels $i$ and $i + 1$ is the highest. The concentration decline is limited by the condition $c_{i,j}^{\text{Sample}} \leq c_{i+1,j}^{\text{Sample}} \leq 2^{-i} c_{0,j}^{\text{Sample}}$; $i,j = 1,2,\ldots,n$. Even though the magnitude of concentration gradient is low, the total concentration variation is the largest due to the long $l_i$. That is why the $c_{2,1}^{\text{Simulated}}$ obtained is the lowest value when $\delta_i = 0.5\%$. When the distance reduces, the interaction among each level is enhanced; thus the magnitude of concentration gradient increases. Due to the continuous condition, the concentration gradient before level $i$ decreased as well. As the entrance length is fixed, the concentration at the entrance of level $i$ drops down. Overall, the estimate function reflects the tendency of concentration changing with the distance $l_i$ accurately. It fits the results of simulations and gives sufficient estimate of the error in Equation 3.9 when the design error is small.

As the distances among each level of a multi-level filter based on H shaped channel can be designed based on the Equation 3.9, models of multi-level filter were built and verified in section 4.5. The simulation on the multi-level filter with a dilute channel illustrates that higher filtration efficiency can be achieved. For this principle, the small groups ($j < i$) can be washed out from the sample inlet channel by adding dilute levels. Figure 7.4 is a percentage stacked chart describing the concentration composition of each level (without or with dilute
Figure 7.3 (a) The concentration along the sample inlet channel $c_{ij}^{\text{Sample}}(x)$; (b) the concentration variation around level 1 (the red region in (a))

channel) according to Table 4.8. The concentration variation can be seen straightforwardly. Apparently the dilute channel increased the separation efficiency. The short distances among each levels resulted in a low separation efficiency in level 2 and 3. The values in the
outlet of level 3 and the main channel show that the amount of sieve channels in the third level in insufficient.

Figure 7.4 The ratios of components at the outlets of three-level filters without (original) or with a dilute channel (dilute model)

The results and discussions in section 3.4, 4.4, and 5.2-4 shows that the angular effect on the mass transfer is weak. The convection introduced by the angle is low comparing with the main flow in the inlet channels. This convection flux can vary the time for mass transfer. The static concentration is not affected by the angle in continuous separation process. The angular H shaped channels are potentially able to align and concentrate the micro particles. Slip flow weakens the angular effect on concentrating the flow.
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7.3.3 The chip design methodology

The design work is crucial for transferring from a geometric model to an applicable device. A design methodology was discussed in section 6.2. According to this methodology, two types of multi-level filter chip which had been simulated in section 4.5 and 5.4 were designed as demonstrations. Alternative fabrication routes and test plans were introduced and discussed. The fabrication was unfinished due to facilities failure in the clean room.

7.3.4 Comparing with other methods

Nicole reviewed the continuous flow separation in microfluidics devices and summarized a table to compare different techniques (Table 7.1)[20]. The first seven techniques are passive continuous separation methods without external fields, while the others are active continuous separation methods. The flow rate of passive continuous separation mainly relates to the channel diameter and pumping methods. In these methods, only the lateral displacement and Brownian ratchet are applicable for nano particles. The pinched flow fractionation, filtration obstacles are strict separation methods with specific designed structures for specific composition of solutions while the others are not strict separation methods. Although the hydrodynamic filtration cannot separate micro-components completely, it achieves a very high throughput and adjusts to composition variation easily. Generally, the comparisons of these methods are not straightforward. There are no “one size fits all” separation methods currently.
Table 7.1 Listing of continuous flow separation methods with details of the forces utilised, the basis of separation and the applicable samples. The data for flow rates and throughput were taken from the selected reference, if provided.

<table>
<thead>
<tr>
<th>Method</th>
<th>Separation induced by</th>
<th>Separation based on</th>
<th>Sample</th>
<th>Flow rate /throughput</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinched flow fractionation</td>
<td>Laminar flow regime</td>
<td>Size</td>
<td>Microparticles, cells</td>
<td>70 cm/s</td>
<td>[56]</td>
</tr>
<tr>
<td>Hydrodynamic filtration</td>
<td>Laminar flow regime</td>
<td>Size</td>
<td>Microparticles</td>
<td>1 mm/s</td>
<td>[62]</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>Laminar flow regime</td>
<td>Size, shape</td>
<td>Blood</td>
<td>5 mL/h</td>
<td>[201]</td>
</tr>
<tr>
<td>Filtration</td>
<td>Diffusion and obstacles</td>
<td>Size</td>
<td>Blood</td>
<td>5–12 μL/min</td>
<td>[216]</td>
</tr>
<tr>
<td>Lateral displacement</td>
<td>Obstacle array</td>
<td>Size</td>
<td>Particles (0.8, 0.9, 1.0 μm)</td>
<td>20 μm/s</td>
<td>[60]</td>
</tr>
<tr>
<td>Brownian ratchet</td>
<td>Diffusion and obstacles</td>
<td>Size</td>
<td>DNA</td>
<td>2 μm/s</td>
<td>[86]</td>
</tr>
</tbody>
</table>

Flow rate: 70 cm/s, 1 mm/s, 5 mL/h, 5–12 μL/min, 20 μm/s, 2 μm/s

Throughput: 40 000 particles/h, 100 000s, 10–20 mm/s
### 7.3 Discussions

<table>
<thead>
<tr>
<th>Method</th>
<th>Pressure Gradient</th>
<th>Size</th>
<th>Microparticles</th>
<th>Flow Rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophoretic separation</td>
<td>pressure gradient from slanted obstacles</td>
<td>1 to 3 cm/s</td>
<td>10 000s beads h⁻¹</td>
<td>[217]</td>
<td></td>
</tr>
<tr>
<td>DNA prism</td>
<td>DNA array and electric field</td>
<td>Size DNA</td>
<td>10 ng/h</td>
<td>[218]</td>
<td></td>
</tr>
<tr>
<td>Entropic trap array</td>
<td>Dams and electric field</td>
<td>Size DNA</td>
<td>10 pg/h</td>
<td>[69]</td>
<td></td>
</tr>
<tr>
<td>Repulsion array</td>
<td>Dams, electric size ratio double layers</td>
<td>Charge to Proteins</td>
<td>300 pg/h</td>
<td>[69]</td>
<td></td>
</tr>
<tr>
<td>Free-flow electrophoresis</td>
<td>homogeneous electric field</td>
<td>Charge to Proteins, amino acids</td>
<td>6 mm/s</td>
<td>[219]</td>
<td></td>
</tr>
<tr>
<td>Free-flow isoelectric focusing</td>
<td>pH gradientIsoelectric point</td>
<td>Size Proteins and cells</td>
<td>9 mm/s</td>
<td>[220]</td>
<td></td>
</tr>
<tr>
<td>Magnetophoresis</td>
<td>inhomogeneous magnetic field</td>
<td>Size, magnetic particles, cells</td>
<td>1.2 mm/s</td>
<td>[67]</td>
<td></td>
</tr>
<tr>
<td>Method</td>
<td>Force</td>
<td>Size, Density, Compressibility</td>
<td>Microparticles, up to</td>
<td>Flow Rate</td>
<td>Ref.</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------</td>
<td>---------------------------------</td>
<td>------------------------</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>Dielectrophoresis</td>
<td>Inhomogeneous electric field</td>
<td>Size, polarisability</td>
<td>Micro-particles, up to 4 mm/s</td>
<td>100 000 cells h⁻¹</td>
<td>[66]</td>
</tr>
<tr>
<td>Acoustophoresis</td>
<td>Acoustic pressure</td>
<td>Size, density, compressibility</td>
<td>Microparticles, 11 cm s⁻¹</td>
<td>11 cm s⁻¹</td>
<td>[221]</td>
</tr>
<tr>
<td>Optical lattice</td>
<td>Optical force</td>
<td>Size, refractive index</td>
<td>Micro-particles, 30 μm s⁻¹</td>
<td>90 000 particles h⁻¹</td>
<td>[222]</td>
</tr>
<tr>
<td>Sedimentation</td>
<td>Gravity</td>
<td>Density, size</td>
<td>Micro-particles, 6 mm s⁻¹</td>
<td>Slowed to 1 mm s⁻¹</td>
<td>[223]</td>
</tr>
</tbody>
</table>

The multi-level filter based on H channels is applicable for both micron and nano particle passive separations by size. It is not a complete separation device but has a very high flow rate dealing with more than two sized target components separation. The separation efficiency can be improved by adding dilute levels and extending the distance between each level.

For the multi-level filter based on H shaped channel, theoretically the maximum flow rate is dominated the sample composition (concentration), the diffusion coefficient and the area of cross section. Therefore by adding to the amount of sieve channels, the flow rate is able to reach a very high level. The flow rate/throughput (1.01 mm/s, section 5.3.1) in the slip
models of H shaped channel series under a low pump pressure (100Pa) is similar as the one of hydrodynamic filtration[62].

**7.4 Summary**

In this thesis, a new type multi-level micro and nano filter based on H shaped channels was developed. The design methodology of this type multi-level micro and nano filter was built. A new fabrication process for multi-level filter chip was put forward and verified by experiment. 2D and 3D modelling simulations on filters based on H shaped channels were presented and discussed.

The research started at analysis of dumbbell channels which were the basic constituents of traditional dead-end filters (section 3.2.1). Then the inlet flow direction was changed from perpendicular with the filter surface to parallel with the filter surface aiming for a higher flow rate and a lower possibility of blocking. Therefore semi-H shaped channels (cross-flow filtration) were introduced as an improvement of dumbbell channels (section 3.2.2). For further improvements upon semi-H shaped channels, the flow properties and transport process in H shaped channels were studied (section 3.3), which is the fundamental basis of the research in this thesis. After discussions about angle effect of angular H shaped channels (section 3.4), a new design of multi-level filter based on H shaped channels was put forwards. The theoretical concentrations after sufficient diffusion were given by analytical formulas. Based on the geometric diameter of filter channel, an estimate equation about the number of sieve channels for sufficient diffusion was put forward. The relationship of capture concentration error and the distance between two adjacent levels was described by a formula as well.
It is meaningful to understand the transport process in each level of multi-level filter which consists of one sample inlet channel, one capture channel and a plurality of parallel same sized sieve channels. Chapter 4 studied the flow properties and mass transfer process of the filters based on semi-H shaped channels, H shaped channels and angular H shaped channels. During these studies, the estimate equation on quantities of sieve channel was verified (section 4.3.1 and 4.4.1). Then the multi-level filters were simulated by finite element software COMSOL Multiphysics®. Meanwhile, the formula describing capture concentration error which is introduced by the distance between two adjacent levels was verified. Therefore the main features of a multi-level filter based on H shaped channels can be designed with mathematic tools.

For a better understanding of the flow properties in nanofilter based on H shaped channels and the angle effects, 3D modelling of H shaped and angular H shaped channels series were made as reinforcement (section 5.2). Whereas the no-slip boundary condition does not reflect the real flow movement on solid-liquid interface in various situations, slip boundary condition was applied with the 3D models in section 5.3 as a control group of the simulations in section 5.2. The angular H shaped channels series showed higher flow rate and lower possibilities of adhesion and clustering in slip boundary condition simulations. The improvements of flow rate in sieve channels due to angle effect were observed in both conditions, especially no slip condition. After all, a simulation of a three-level filter based on angular semi-H shaped channels was studied and discussed. A multi-level filter based on semi-H shaped channels is a feasible way to microminiaturize several filtration processes down to chip level. This simulation can be viewed as a verification of the verify chip designed in section 6.2.
A six steps design flow of multi-level filter chips based on H shaped channels was put forward and verified, which is i) application demand analysis, ii) detection requirement analysis, iii) geometric design, iv) interface design, v) material selection and vi) fabrication progress design. Two multi-level filter chips were designed following this design path as examples (section 6.2). For fabricating the pattern of multi-level filters which consist of multi depth structures, a new fabrication process was put forward (section 6.2.5). Fabrication experiments on photolithography (section 6.3), Reactive Ion Etch (section 6.4) and Focus Ion Beam (section 6.5) were taken and reported. The wet etch and bonding processes were introduced. These experiments demonstrated the feasibility of this fabrication process and gave reasonable recipes for this fabrication process.

The simulations in chapter 3-5 were validated in chapter 7. Then the overall discussions were illustrated. Comparisons with other continuous separation techniques were discussed. Consequently, the main conclusions of the research were summarised in the following section along with suggestions for future work (in section 7.6) to take the research forward.

7.5 Conclusions

The conclusions obtained during this research are summarized as following:

The dumbbell channel is the basis of dead-end filters. Dead volumes form before and after the barriers thus easily to be blocked by clogging. (Section 3.2.1 & 7.2.1)

Semi-H shaped channels, which are the basis of cross-flow filters, using the bifurcation structure to eliminate the dead volume before the barriers hence reducing the possibility of clogging and jamming. (Section 3.2.2)
The flow rate in the sample inlet channel is high; however, the pressure drops severely across the sieve channel and the flow rate in the capture channel is low, which is the pumping problem. (Section 3.2.2)

Convection is the main mass transfer process in semi-H shaped channels. (Section 3.2.2)

The static capture concentration is the same as the inlet concentration. (Section 3.2.2)

H shaped channels eliminate all dead volumes around the barriers therefore further reduce the possibility of adhesion on both cross-sections and slow down the cake layer formation process. (Section 3.3.1)

High flow rate are achieved in both the sample inlet and capture channels compared with the semi-H shaped channels. (Section 3.3.1)

Diffusion is the main transport phenomenon in the sieve channel while there is no convection across the sieve channel in a symmetric H shaped channels. (Section 3.3.2&3)

The capture concentration of single H shaped channel filter is less than 50% of sample concentration (the second law of thermodynamics) (Section 3.3.2&3).

For a higher capture concentration, more than one sieve channels are needed, which is the H shaped channels series. (Section 3.3.2)

The angular H shaped channels enhance the convection in sieve channel due to the asymmetric structure, thus both convection and diffusion occur in the sieve channel. (Section 3.4.1)

The semi-H shaped channel series are typical cross-flow structures. The H shaped channel series improve the flow rate in the capture channel. (Section 4.2.2 & 4.3.2)
Osmosis was observed in H shaped channel series. (Section 5.2.4 & 5.3.1)

The sufficient numbers of sieves in H shaped channel series for the maximum capture concentration (50% of the sample inlet concentration) can be estimate by the formula $N_i \geq \gamma \frac{wd}{a_i^2}$ (Equation 3.12). One typical value is $\gamma = 1$ which means that the pore area equals to the sample inlet area. (Section 4.3.1)

The length of the cross-section area affects the diffusion. Longer length is helpful to increase the capture concentration (up to 50% of the inlet concentration). (Section 4.3.1)

Vortices were observed in the sieve channels of H shaped channel series. When the no-slip boundary condition was used, the areas of vortices were small. (Section 5.2.3) When the boundary condition was set as slip, the vortices developed bigger and occupied whole sieve channels. (Section 5.3.2) The vortices increase the diffusion flux.

The increasing magnitude of the angle of the sieve channels enhances the convections through the sieve channels while reduces the vortices area, especially when the flow slips on the boundary interface. (Section 5.2.3 & 5.3.2)

The convection through the negative angular sieve channels concentrates and aligns micro particles along the cross section. It is also helpful to increase the total mass transfer flux in the multi-level filter; therefore higher flow rate is applicable. (Section 5.2.3 & 5.3.2)

The flow rate across the sieve channels increase with the angle magnitude. This angle effect reduces when the width and depth of the sieve channel reduce. (Section 5.2.4 & 5.3.1)

By connecting different level filters (semi-H or H shaped channels series) sequentially; a multi-level micro- and nano- filter is built. (Section 3.5.1)
7.5 Conclusions

For the multi-level filter based on semi-H shaped channels, the flow rates are low in the capture channels compared with the flow rate in the sample inlet channel (Table 4.1); hence a high pumping pressure and long filtration time are required. (Section 4.2.3 & 5.4.2-4)

The capture concentration can be described as $c_{i,j}^{\text{Capture}} = 0, \ i < j; \ c_{i,j}^{\text{Capture}} = c_{0,j}^{\text{Sample}}, \ i \geq j$. Therefore the multi-level filtration based on the semi-H shaped channel is not a complete separation method. (Section 4.2.3 & 5.4.5)

For the multi-level filter based on H shaped channels, the flow rates in both the sample inlet and capture channel are high compared with the multi-level filter based on Semi-H shaped channels; therefore solving this pumping problem. (Section 4.5.2)

The capture concentration in multi-level filter based on semi-H shaped channels fulfills the condition $c_{i,j}^{\text{Capture}} > c_{i+1,j}^{\text{Capture}}$ and $c_{i,j}^{\text{Capture}} = 0$. (Section 3.5.1 & 4.5.1)

Assuming each level is isolated from the others, the ideal concentration in each level is

\[
 c_{i,j}^{\text{Capture}} = c_{i,j}^{\text{Sample}} = 2^{-i} \cdot c_{0,j}^{\text{Sample}} \quad (i = 1, 2, ..., n) \quad (\text{Equation 3.9}).
\]

When a dilute channel is added, the concentration is described as below (Equation 3.10 and 3.11),

\[
 c_{i,j}^{\text{Capture}} = c_{i,j}^{\text{Sample}} = \begin{cases} \frac{1}{2} \cdot c_{0,j}^{\text{Sample}} & \text{if } i = 1 \\ \frac{2}{9} \cdot \left(\frac{3}{4}\right)^i \cdot c_{0,j}^{\text{Sample}} & \text{if } i > 1 \end{cases},
\]

\[
 c_{i,j}^{\text{Dilute}} = \begin{cases} \frac{1}{4} \cdot c_{0,j}^{\text{Sample}} & \text{if } i = 1 \\ \frac{1}{3} \cdot \left(\frac{3}{4}\right)^{i-1} \cdot c_{0,j}^{\text{Sample}} & \text{if } i > 1 \end{cases}
\]

Consequently no matter whether there is a dilute channel, $c_{i,j}^{\text{Capture}} > c_{i,j \neq i}^{\text{Capture}}$. (Section 3.5.1)

The dilute channel and dilute sieves are simple but efficient way to increase the separation efficiency. (Section 3.5.1)
The interaction among each level, actually, introduces an error in Equation 3.9-11. The error and the distance between two adjacent levels can be described by the estimation function:

\[ l_i \geq \frac{N_i W_i}{2 \delta_i} \]  (Equation 3.15). Apparently, a long distance \( l_i \) can reduce the error of Equation 3.9-11. This estimation function fits the results of simulations and gives sufficient estimate of the error in Equation 3.9 when the design error is small.

Overall the multi-level filter based on H shaped channels obtains a rapid, high throughput, large scale range (nanometres to microns) purification of complex mixtures on chip level. The high flow rates in this filter reduce the adhesion on the solid-liquid interface, which reduces the possibility of blocking of the sieves. During the filtration process, the mixture sample is diluted level by level thus also reducing the possibility of clogging. The inlet fluid of the captures channels is able to be a buffer to keep the pH value and osmotic pressure during the filtration process. Thus it is propitious for keeping the cytoactivities, while traditional filtration is not capable to keep the bio-environment for cells. This type of multi-level filter is easily extended by connecting different size filter chips in series. With additional dilute channel and dilute sieve channels, higher size selectivity can be achieved.

The methodology of designing a multi-level filter chip based on H shaped channels was established. It is a six steps path which is i) application demand analysis, ii) detection requirement analysis, iii) geometric design, iv) interface design, v) material selection and the last step vi) fabrication progress design. (Section 6.2)

Among the alternative fabrication process which are able to fabricate different widths and depths channels on the same chip, a new fabrication process was introduced and demonstrated. During this fabrication progress of a chip, it is flexible to design and modify
7.6 Future Work

A new fabrication process has been put forward in this thesis. Although most parts of this process have been demonstrated with experiments, the anodic bonding process is still waiting to be done.

After the multi-level filter chips are fabricated, test experiment of these chips need to be done. Dyed nanospheres and dyed dextran can be uses as indicators. Further phase demonstrations on separation of blood cells and serum, microvesicles, and proteins etc shall be taken to demonstrate the filter chips.

As the fabrication process which was put forward in thesis is not suitable for industry fabrication, other fabrication processes are desired, such as nano-imprint[173]. The recipes of these fabrication processes are crucial for commercialization of multi-level filter chips based on H shaped channels.

For the boundary condition of flow, surface roughness [161, 224, 225] and wetting [226, 227]are key factors. As the SEM figure of ICP RIE results showed a rough side wall, the study of its nano-roughness may introduce potential improvements of the filter. When the surface of sieve channels is super-hydrophobic[52, 53, 85], there is layer of gas[228]. How will this air layer affect the filtration process needs to be assessed?

When most components in the mixture are approximate sphere, the sieve channels are able to be replaced by a long weir. It is helpful to accelerate the transport process across the sieve channel and enhance the tolerance of clogging around cross section. How to design
the length of the weir and what will be happened for the deformable components? What is the advantage of the multi-level filter based on long weir compared with the pillars?

Droplets in micro channels is a hot topic recently[229]. If the inlet flow is droplets rather than continuous flow, the length of the sieve channel is considerable comparing with the scale of droplets. Thus the angle effect on connection could be observed in angular H shaped channels. So it is a potential improvement of micro- or nano- filters based on H shaped channels. Hence the effects of droplet flow should be studied.
List of References


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