CFD-Assisted Design and Optimization of a Pharmacokinetic Microfluidic System

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ABSTRACT

A microfluidic system was designed and optimized to study pharmacokinetics of drug candidates in the mammalian liver tissue. Computational fluid dynamics (CFD) was called on to assist in the system design process and was used as a tool to investigate the flow field within the microfluidic passageways. The ultimate goal was to enhance the desired flow characteristics based on the required conditions for cells inside the system. A three-dimensional model was developed and different grid sizes (2~20 microns) were generated for grid independence study. As a result, grids with the edge length of less than 4 microns were found to be proper for further analyses. The commercial CFD code FLUENT was utilized for the numerical solution of the governing equations using the finite volume method and the three-dimensional pressure and velocity fields were obtained. The numerical predictions were verified against experimental results of velocity measurement at different points. Velocity measurements were obtained by image analysis of video streams of 50 vol% McFarland turbidity standard 2.0 solution (Remel) mixed with a 50 vol% culture medium solution flowing from inlet to outlet at a constant pushing pressure within a transparent flow test-section. Good agreement between the two approaches was observed. In conclusion, based on the verified numerical results, the existing flow field and its characteristics were clearly elucidated and feasible modifications were proposed to optimize the microfluidic system. In addition, experimental results showed that cells that are introduced into the cell chamber will remain there (i.e. no cell escape). Therefore, nutrients that reach the cells from the side channels will contribute to the growth of the cells.

Keywords: microfluidic, pharmacokinetic, computational fluid dynamics, design, optimization

1 INTRODUCTION

CFD is an ideal tool to investigate fluid flow and its related phenomena at different scales. In microfluidic systems, CFD has been used to analyze the behavior and features of the flow in numerous cases in the micron scale [1, 2] and can dramatically reduce the time and cost of design process from concept design to analyses of on-chip processes and chip performance evaluation [3]. Weigl et al studied the design and manufacture of laminar fluid diffusion in self-contained microfluidic cartridges used for diffusion-based separation and detection applications [4]. They found that the experimental results largely matched the numerical predictions except for under-prediction of diffusion in higher viscosity solutions. Koo and Kleinstreuer investigated the liquid flow in microchannels experimentally and computationally [5]. Using different computational models, they studied the microfluidics effects such as channel entrance, friction, slip velocity, viscous dissipation, wall roughness and turbulence effects and found good agreement between experimental and model predictions. Lee et al developed a computational model of a piezoelectric-actuated microvalve to study the pressure drop between the inlet and outlet ports as a function of mass flow rate for liquid flow control [6]. Their experimental measurements confirmed the values predicted by the model. Sun et al studied design, simulation and experiment of electroosmotic microfluidic cell-storing chips [7]. Using a combination of CFD model predictions and PIV-measured velocities, they concluded that the resulting velocity in microchannels can be viewed as the superposition of electroosmotic and pressure-induced velocities. Glatzel et al extensively studied the performance of CFD software tools for microfluidic applications [8]. They considered a variety of problems from mixers and rotating platforms to bubble dynamics in microchannels and droplet generators which include surface tension and free surface flows and volume-of-fluid method treatment. They found that for conventional convection diffusion problems most of the commercial codes work well numerically; however, for complicated cases of surface tension and multiphase flows some of them give erroneous results.

Being aware of the abovementioned capabilities in numerical simulation of microfluidic systems, in this research, a microfluidic system was designed and optimized to carry out in-vitro pharmacokinetic studies of drug candidates in the liver, as a substitution for in-vivo studies conventionally performed on mammalian cells including human cells. The configuration of the system was realized to mimic the basic structure observed in the liver, i.e. a row of two cells bordered by two blood vessels providing the nutrients. CFD was used as a predictive tool to investigate the flow field within the microfluidic passageways. The ultimate goal is to enhance the desired flow characteristics

based on the required conditions for cells inside the microfluidic system.

2 MODELING AND GRID GENERATION

In view of the complexity of the flow fields and due to the variable depth of the system at different locations, a three-dimensional model, shown in Figure 1, was developed for numerical simulation. Since a time-dependent periodic flow pattern could emerge under particular conditions, the symmetry of the microfluidic model with respect to plane 2 (Fig. 1) was disregarded. Several three-dimensional unstructured meshes were generated (Fig. 2) with different edge lengths of tetrahedron grids (2~20 microns) to investigate grid independency. Steady-state analyses were performed and the values and variation of different quantities were checked for various grid systems. Variation of the maximum velocity on plane 1 (Fig. 1) and pressure drop in the microfluidic system are shown in Figures 3 and 4, respectively. Based on grid independence study, it was concluded that when the edge length is less than 4 microns, the results are independent of grid size. Therefore, a mesh with 505,000 grids (grid size of 2.5 microns) was selected for production runs. In order to obtain more accurate results, the mesh was denser in the regions with high curvature and around the cells.

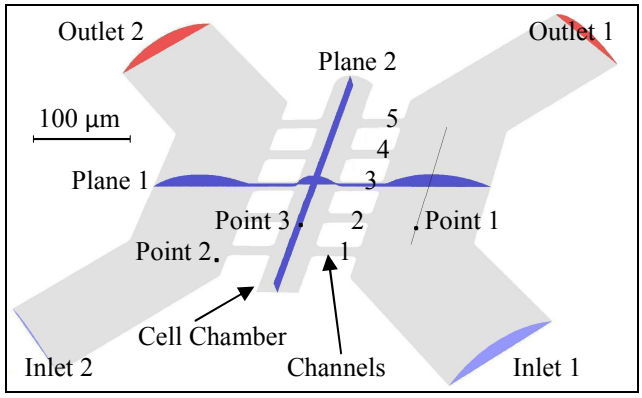

Figure 1: 3-D model of the microfluidic system

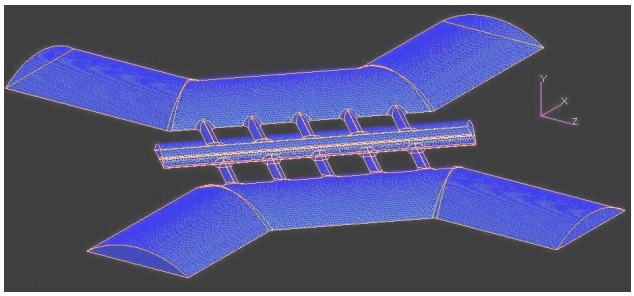

Figure 2: Unstructured tetrahedron grid for CFD analysis

3 NUMERICAL METHOD

The commercial CFD code FLUENT [9] was utilized for steady-state solution of the governing equations (i.e. continuity and momentum) using the finite volume method. The physical properties of the culture solution used for feeding the cells inside the cell chamber were measured and defined as a new material. Based on the hydraulic diameter, the maximum Reynolds number is 0.55 in the passageways and the maximum Knudsen number in the channels is about 5×10^{-5}. Therefore, the flow is laminar and no-slip boundary condition can be applied on the walls. For inlet boundaries, shown in Figure 1, the inlet mass flow rate was fixed to 8.87 µg/s as the boundary condition. Since there is enough channel length before the selected inlet sections in the full microfluidic device, there is no entrance effect at the modeled inlet boundaries. The flow is laminar and fully-developed within the system; therefore, the outlet boundary conditions were set to outflow for outlets 1 and 2. The SIMPLE algorithm was used for numerical procedure and the convergence criteria were fixed to 10^{-12} for continuity and velocity residuals. In order to improve the accuracy, double-precision computation was selected with second order discretization scheme. Finally, the 3-D pressure and velocity fields were obtained.

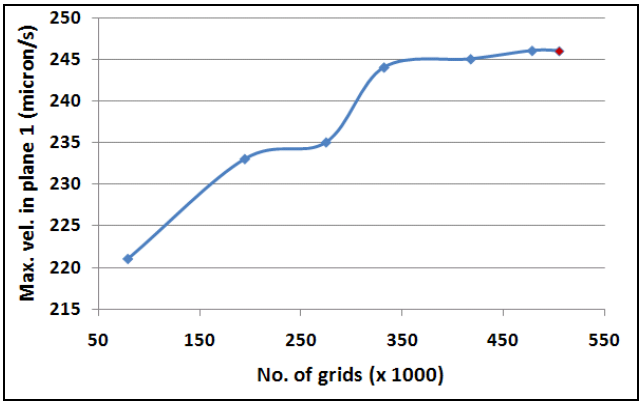

Figure 3: Effect of grid size on the max. velocity on plane-1

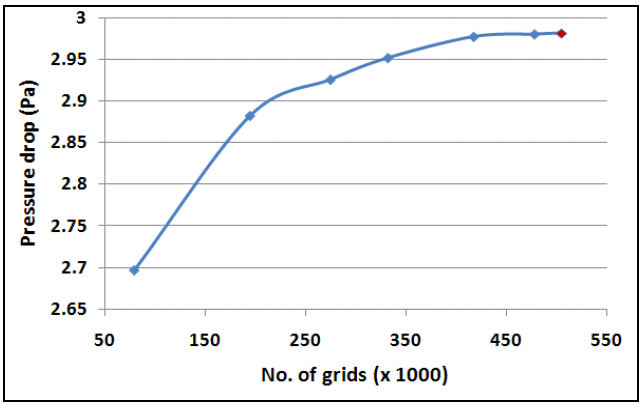

Figure 4: Effect of grid size on the pressure drop

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4 RESULTS AND DISCUSSION

Based on the discussed numerical method, the numerical results of the flow field were obtained in the microfluidic system. The velocity field in channels and cell chamber and the flow pathlines (colored by velocity magnitude) are shown in Figures 5 and 6, respectively. The numerical predictions were verified against experimental results of velocity measurement at three different points presented in Table 1. Velocity measurements were obtained by image analysis of video streams of 50 vol% McFarland turbidity standard 2.0 solution (Remel) mixed with a 50 vol% culture medium solution flowing from inlet to outlet at a constant pushing pressure within a transparent flow test-section shown in Figure 7. A steady-state CFD analysis was performed for this condition and good agreement was observed between the two approaches. As it can be observed from Figure 8, the velocity is much slower in the cell chamber (max. 550 µm/s) compared to passageways (max 2 cm/s). As a result, there is enough diffusion time to transfer nutrients from culture solution to cells located within the cell chamber. The velocity at the two ends of the cell chamber is nearly zero which indicates a quiesent flow at those regions. This means that the cell feeding is noticeably lower there and cell growth rate would be non-uniform in the cell chamber. Therefore, this is a disadvantage for the current design. Another feature of the flow pattern is that the flow rate in the mid-channels (channel 3 at right and left of the cell chamber shown in Figure 1) is nearly zero which means that these channels are not effectively contributing to the solution exchange between passageways and cell chamber. Although these channels can be eliminated, they are necessary for control and sampling purposes. Other influential parameters such as the shear stress applying to the cells due to the flow were checked and compared to the available criteria.

Finally, based on the flow features, some modifications were proposed to improve the circulation of the flow in the two ends of the cell chamber. These modifications included cutting the two ends of the cell chamber (which confines its area and capacity and is not desirable), changing the position of the channels, and changing the shape of the first and the last channels and make them curved to conduct the flow toward the two ends. The feasibility and cost of these optimization strategies is under consideration; then the selected modification(s) will be applied to the current design and further CFD analysis of the optimized system will show possible improvements in making the uniform

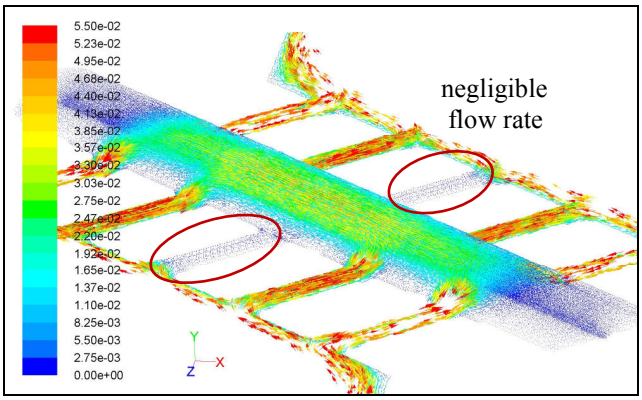

Figure 5: Velocity vectors in channels and cell chamber

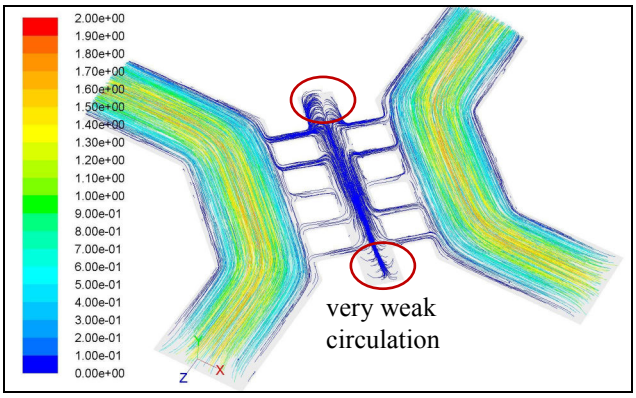

Figure 6: Flow pathlines colored by the velocity magnitude

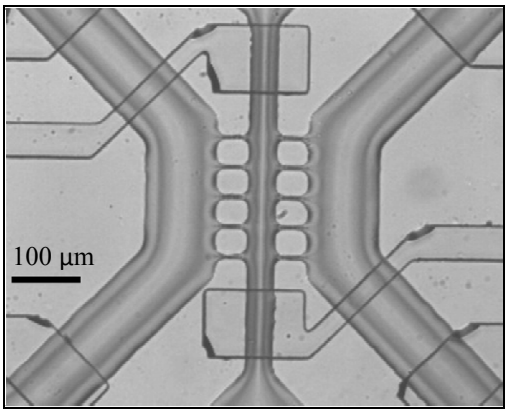

Figure 7: Enlarged picture of the microfluidic system before any loading of culture solution or cells

Table 1: Comparison of the numerical results with measured velocities using particle tracking

Measuring Points (shown in Fig. 1)	Depth (µm)	Measured Velocity (µm/s)	CFD-Predicted Velocity (µm/s)	Deviation (%)
1	14	3851.2	3885	0.88
2	3.5	134.4	139.9	4.09
3	4	165.6	171.8	3.74

condition in the cell chamber as a criterion for cells uniform growth rate. Moreover, it can be confirmed from Figure 6 that there is a laminar parallel flow within the microfluidic system. Contours of static pressure are also displayed in Figure 9 (working pressure=1 atm).

5 CONCLUSIONS

The flow field within a microfluidic device was investigated using CFD as a predictive tool. Based on the dimensions and geometric features of the microfluidic system, a 3-D model was developed. Different unstructured meshes were generated with different grid edge lengths and grid independence study was conducted to determine the proper size of the grid for CFD analyses. Applying boundary conditions, steady-state CFD simulation was conducted under the working condition of the microfluidic system. Then, the model velocity predictions were verified by the experimental measurements of velocity using particle tracking method.

In conclusion, based on the verified numerical results, the existing flow field and its contribution to fluid exchange to the cell chamber and existence of the dead-zones, where the flow is nearly quiescent and cells can not be fed properly, were clearly elucidated. Furthermore, feasible modifications were proposed to optimize the microfluidic system. In addition, experimental results showed that cells that are introduced in the cell chamber will remain there (no cell escape). Therefore, nutrients that reach the cells from the side channels will contribute to the growth of the cells. Further experiments and analyses are underway for the long-term cultural experimental study.

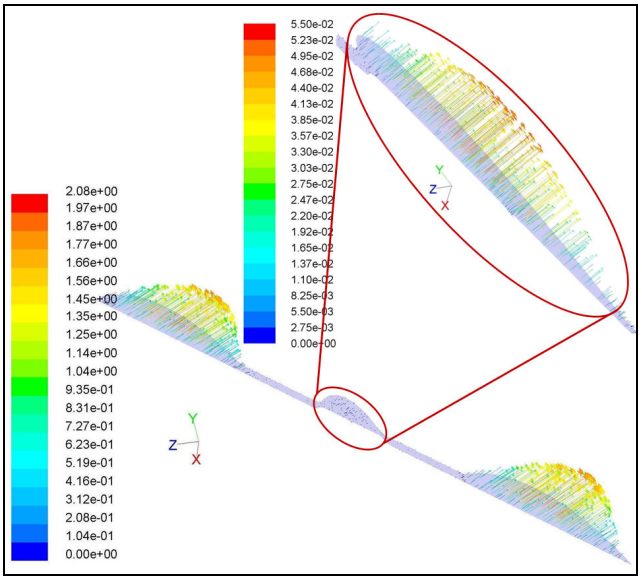

Figure 8: Velocity distribution in plane-1 (identified in figure 1) within the passageways and cell chamber of the microfluidic system

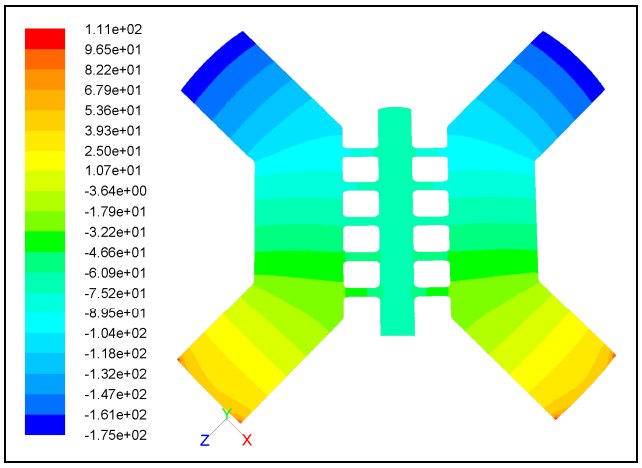

Figure 9: Static pressure distribution in the system

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