Abstract—A numerical study is carried out on the fluid dynamics and mass transfer in a microchannel perfusion bioreactor. The bioreactor channel has a porous wall for the co-culture of two types of cells which are distributed randomly and uniformly. A group of dimensionless parameters is proposed, which can be applied to correlate the numerical data and characterize the mass transfer in the bioreactor. The normalized numerical data, for the concentration at the porous-fluid interface and concentration difference between the interface and the base, show satisfactory correlation when presented as a function of the effective distance parameter.

Index Terms—Transport phenomena in porous media, numerical methods in fluid flow, mass transfer.

I. INTRODUCTION

In a type of perfusion bioreactor design, a porous layer partially occupies the channel [1], [2]. It was found [3] that the shear stress in this bioreactor was significantly lower than others, which made their bioreactor suitable for cell cultures sensitive to shear stress. A model was developed [4], [5] for mass transport in the perfusion channel partially filled with a porous layer, in which the flow convection in the porous layer has been neglected. The model was improved [3] by applying Brinkman’s model in the porous layer. By assuming the continuities of velocity and shear stress at the porous-fluid interface, the improved model was numerically solved by the Lattice-Boltzmann method. More recently, a two-domain approach [6] was applied to simulate flow and mass transport in this type of bioreactor. The Navier-Stokes equations and the generalized Darcy-Brinkman-Forchheimer extended equations were applied to govern the flows in the fluid and porous regions, respectively.

The present paper numerically investigates flow and mass transfer in a perfusion channel partially filled with a porous layer, which is suitable for co-culture applications. One of the main objectives of the present study is to propose a group of combined-parameters that are useful for the design of this type of bioreactor.

II. NUMERICAL MODEL

The bioreactor modelled in the present study consists of a channel partially filled with a porous medium as shown in Fig. 1. The width of the channel, being much larger than the depth, has negligible effect [7]. Thus the numerical model considered here is simplified into a two-dimensional one like that of a previous study [4]. The length of the channel is $L$. The depths of the porous and homogenous fluid regions are $h$ and $H$, respectively. In the present configuration, the length scale is much larger than the depth scale so that the inlet effect can be neglected.

The culture medium flows through the channel along the $x$ direction. The absorption and release cells adherent to the porous medium scaffold consume and secrete the substrate respectively, forming the reactions in the porous scaffold. The incoming flow with substrate concentration $c_{in}$ is steady, laminar and incompressible. The fully developed velocity profile is imposed at the inlet.

The porous medium is assumed to consist of the scaffold structure and the attached cells, with volume fractions $\varepsilon_s$ and $\varepsilon_c$ occupied by the scaffold and cells respectively. The porosity of the porous medium $\varepsilon$, which is the void fraction, can be calculated as $\varepsilon = 1 - \varepsilon_s - \varepsilon_c$. The cells are assumed to be uniformly distributed in the scaffold. The porous medium is considered to be rigid, homogeneous and isotropic, and saturated with the culture medium. The dimensions of the cells are more than one order smaller than the channel gap and are not considered. Typical cell parameters are given in Tables I and II.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D$</td>
<td>$3.29 \times 10^{-7}$ m$^2$/s</td>
<td>[8]</td>
</tr>
<tr>
<td>$D_{c,0}$</td>
<td>$1.59 \times 10^{-7}$ m$^2$/s</td>
<td></td>
</tr>
<tr>
<td>$D_{m}$</td>
<td>$2.3 \times 10^{-10}$ mol/ml</td>
<td>[5]</td>
</tr>
<tr>
<td>$V_{max}$</td>
<td>$1.25 \times 10^{-7}$ mol/cell/s</td>
<td></td>
</tr>
<tr>
<td>$k_{m}$</td>
<td>$1.1 \times 10^{-9}$ mol/mol</td>
<td></td>
</tr>
<tr>
<td>$\gamma_{c}$</td>
<td>$5.4 \times 10^{-7}$ cells/ml</td>
<td></td>
</tr>
</tbody>
</table>

For the cell reactions, the consumption reaction is assumed to follow the Michaelis-Menten model [13] and the release reaction is assumed to be constant [14]. The governing
equations for the flow and mass transport [15]-[18] can be written as given below.

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

\[ \bar{u} \cdot \nabla \bar{u} = -\frac{1}{\rho} \nabla p + \nu \nabla^2 \bar{u} \]

\[ \bar{u} \cdot \nabla c = D \nabla^2 c \]

where \( \bar{u} \) is the velocity vector; \( p \) is the pressure; \( \rho \) and \( \nu \) are the density and fluid viscosity of the culture medium, respectively; and \( c \) and \( D \) are the concentration and diffusivity of the substrate respectively.

For porous scaffold region:

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

\[ \bar{u} \cdot \nabla \bar{u} = -\frac{1}{\rho} \nabla (\varepsilon p) + \nu \nabla^2 \bar{u} - \frac{\varepsilon C_f \| \bar{u} \|}{\sqrt{K}} \bar{u} \]

\[ \bar{u} \cdot \nabla c = D_{ef} \nabla^2 c - \gamma_a V_{ma} \left( \frac{c}{c + k_m} - a \right) \]

where \( \bar{u} \) is the local average velocity vector (Darcy velocity); \( p \) is the local average pressure; \( \rho \) and \( \nu \) are the density and the fluid viscosity of the culture medium, respectively; \( \varepsilon \) is the porosity; \( K \) is the permeability; \( C_f = 1.75/\sqrt{150} \varepsilon^3 \) is the Forchheimer coefficient; \( c \) and \( D_{ef} \) are the equilibrium weighted average concentration and the effective diffusivity of the substrate in the porous medium region, respectively; \( \gamma_a \) is the volume density of the absorb cells; \( V_{ma} \) is the maximal substrate uptake rate (SUR); \( k_m \) is Michaelis-Menten constant or substrate concentration at which the SUR is half-maximal; and \( a \) is the ratio of release rate over absorb rate, which is defined as:

\[ a = \frac{V_{ma} \gamma_a}{V_{ma} \gamma_a} \]

where \( \gamma_a \) is the volume density of the secretion cell, \( V_{ma} \) is the maximal substrate release rate (SRR) for secretion cell. In the present study, we only consider the condition \( \frac{c}{c + k_m} - a > 0 \), which indicates that the cell absorption rate is larger than the release rate, and the concentration in the porous scaffold decreases along the flow direction.

For the concentration boundary conditions, zero mass flux condition is imposed on the upper and bottom solid-walls. Uniform concentration of \( c_{in} \) is set at the inlet. As for the outlet, the condition \( dc/dx = 0 \) is not satisfied because of the above condition \( \frac{c}{c + k_m} - a > 0 \), which indicates that the cell absorption rate is larger than the release rate. Thus, \( \partial c \partial x^2 = 0 \) is imposed at the outlet, which assumes that the concentration drops at a constant rate near the outlet boundary region. At the interface between the homogeneous fluid region and porous media scaffold, continuities of mass and mass flux [19] are imposed.

For the velocity boundary conditions, the non-slip condition is imposed on the solid upper and bottom walls. As we are considering the steady laminar channel flow, to reduce computation cost, a fully-developed flow condition is imposed for the channel inlet. At the interface between the homogeneous fluid region and porous media scaffold, besides the continuity of velocity, the shear stress jump condition [20] and the continuity of normal stress condition are imposed:

\[ \beta \frac{\partial u_t}{\varepsilon} \bigg|_{\text{porous}} - \beta \frac{\partial u_t}{\varepsilon} \bigg|_{\text{fluid}} = 0 \]

where \( n \) is a coordinate normal to the interface with its direction from porous medium to homogenous fluid; \( v \) is the velocity component perpendicular to the interface; \( t \) is a coordinate perpendicular to \( n \) with its direction determined by the right-handed system; \( v \) is the velocity component tangential to the interface; \( \beta \) is a coefficient associated with an excess viscous stress, and \( \beta_1 \) is a coefficient related to an excess inertial stress.

The Peclet number for the homogeneous fluid region is defined as

\[ Pe_e = \frac{u_{av\cdot H}}{D} \]

where \( u_{av\cdot J} \) is the average flow velocity in the homogeneous fluid region. The porous Damkohler number for cell absorption is defined as:

\[ Dam_{pa} = \frac{V_{ma} \gamma_a h^2}{D_{ef} c_{in}} \]

which characterizes the ratio of the time scales of substrate absorb reaction to substrate diffusion in the porous medium. The fluid Damkohler number for cell absorption is defined as:

\[ Dam_{fl} = \frac{V_{ma} \gamma_a h}{u_{av\cdot S} c_{in}} \]

which characterizes the ratio of the time scales of substrate absorb reaction to substitute convection in the fluid domain.
to be fine enough to obtain the grid independent results by a preliminary study. The jump parameters $\beta$ and $\beta_1$ was both set to be zero because the previous studies have indicated that these two parameters have relatively minor effect on the concentration distribution.

The concentration difference parameter $\kappa$ can be expressed as:

$$\kappa = \frac{C_{int} - C_{bot}}{Dam_{pa}(1-a)} = \frac{D_{eff} (c_{int} - c_{bot})}{h} = \frac{h}{V_{ma} \gamma_a h (1-a)}$$

The study proposes two combined parameters which may be useful for correlating the interface concentration at various $Pe_a$, $Dam_{pa}$ and $K_m$:

Effective distance parameter:

$$\zeta = \frac{h}{H Pe_f} = \frac{X}{H Pe_f}$$

Interface concentration reaction parameter:

$$\xi = \frac{C_{int} - 1}{Dam_{pa} \lambda}$$

where $\lambda$ is reaction rate parameter:

$$\lambda = \frac{H}{h} \left( \frac{1 + K_m}{1 + 3K_m - a} \right)$$

To quantify the mass transfer resistance of the porous medium, an effectiveness factor is defined [22] as the ratio of actual reaction rate to that which would be obtained if the enzyme or cells were at the interface (that is without the porous medium diffusion resistance). In the present study, this definition is followed and the actual reaction rate is expressed as:

$$\lambda = \frac{H}{h} \left( \frac{1 + K_m}{1 + 3K_m - a} \right)$$

The concentration difference parameter $\xi$ at different release and consumption rates is plotted as a function of effective distance $\zeta = x(HPe_f)$ in Fig. 2. The results show that the concentration reaction parameter decreases with increasing effective distance parameter. The numerical results agree with the general trend of the analytical solution except the gradient is steeper. The variations of $Dam_{pa}$ and $a$ do not significantly change the non-dimensional results, except for one case at large $Dam_{pa}$ of 0.5 and zero release ratio $a$. The normalization of the interface concentration by $Dam_{pa}$, and plotted against effective distance $xH(Pe_f)$, is effective in collapsing the numerical data.

The concentration reaction parameter $\zeta$ at different release and consumption rates is plotted as a function of effective distance parameter when $c = 0.8$ and $K_m = 0.128$ at different $a$ and $Dam_{pa}$.

The concentration difference parameter $\kappa$ at different release and consumption rates is plotted as a function of effective distance parameter $x(HPe_f)$ in Fig. 3. All the data collapse together except that at large $Dam_{pa}$ of 0.5 and zero release ratio $a$. The spread of data is less at smaller effective distance smaller than 2. The effects of $Dam_{pa}$ and $a$ have been incorporated in the concentration difference parameter. It is noted that away from the inlet, the concentration difference parameter is around 0.5 which agrees with the analytical solution (Equation 19).

$$\eta = \frac{1 - \bar{C}_{out}}{Dam_{pa} \left( \frac{1}{1 + K_m} - a \right) L/H} = \frac{u_{f, av} H (c_{in} - \bar{C}_{out})}{h L V_{ma} \gamma_a c_{in} + k_m - V_{ma} \gamma_a}$$

where $\bar{C}_{out}$ is the average outlet concentration in plain fluid region and $C_{in}$ is inlet concentration.

To evaluate the wastage of substrate in bioreactors, the utilization efficiency (or conversion rate) is defined as the ratio of actual utilized mass rate over the inlet mass rate:

$$\eta_u = \frac{u_{f, av} H (c_{in} - \bar{C}_{out})}{u_{f, av} H c_{in}} = 1 - \bar{C}_{out}$$

Combining the above two equations, the utilization efficiency is expressed as:

$$\eta_u = \eta \cdot Dam_{pa} \left( \frac{1}{1 + K_m} - a \right) \frac{L}{H}$$

III. RESULTS AND DISCUSSION

The concentration reaction parameter $\zeta$ at different release and consumption rates is plotted as a function of effective distance parameter $x(HPe_f)$ in Fig. 2. The results show that the concentration reaction parameter decreases with increasing effective distance parameter. The numerical results agree with the general trend of the analytical solution except the gradient is steeper. The variations of $Dam_{pa}$ and $a$ do not significantly change the non-dimensional results, except for one case at large $Dam_{pa}$ of 0.5 and zero release ratio $a$. The normalization of the interface concentration by $Dam_{pa}$, and plotted against effective distance $xH(Pe_f)$, is effective in collapsing the numerical data.

Fig. 2. Concentration reaction parameter as function of effective distance parameter when $c = 0.8$ and $K_m = 0.128$ at different $a$ and $Dam_{pa}$.
Fig. 3. Concentration difference parameter as function of effective distance parameter when $\varepsilon = 0.8$ and $K_m = 0.128$ at different $a$ and $Dam_{pa}$.

Fig. 4 presents effectiveness factor $\chi$ as a function of effective distance $\zeta$. It shows that away from the inlet, the effectiveness factor varies from around 0.9 to 0.6. The effectiveness is lower at large $Dam_{pa}$ and small release ratio $a$. With large $Dam_{pa}$ (relatively large consumption), the concentration in the porous medium is much lower than that at the interface. Thus the actual reaction in the porous medium compared to that at the interface is smaller; and hence the porous medium is less effective for mass transfer across the interface. The effectiveness factor is a local parameter and it becomes lower far away from the inlet due to the lower concentration in the porous medium.

Fig. 5 presents the bioreactor efficiency $\eta_u$ as a function of effective channel length $\zeta_L = L/(H \cdot Pe_f)$ at different $Dam_{pa}$ and $a$. The bioreactor efficiency varies from around 0.85 to 0.6. The efficiency is lower at larger $Dam_{pa}$ and smaller $a$ due to the smaller concentration in the porous medium. At longer bioreactor length the efficiency is smaller. This is because of the decreasing interface concentration with length, which gives a lower concentration in the porous medium and hence the average reaction is low.

Fig. 6 presents utilization efficiency $\eta_p$ as a function of effective channel length $\zeta_L = L/(H \cdot Pe_f)$ at different $Dam_{pa}$ and $a$. The utilization efficiency varies from around 0 to 0.8. The utilization efficiency is very low at small $L/(H \cdot Pe_f)$; that is either small $L/H$ or large $Pe_f$. This is because the convection time scale is relatively short compared to the diffusion time. Hence the substrates further away from the interface are not utilized. At larger $Dam_{pa}$, the consumption is larger and hence it gives better utilization. At smaller release ratio $a$ there is a requirement for more flux and hence larger utilization. The utilization efficiency highlights the importance of effective length to achieve good utilization.

IV. CONCLUSION

The present work has investigated the mass transfer in a microchannel bioreactor with a porous wall in which there is a co-culture of two types of cells distributed randomly and uniformly. A group of dimensionless parameters, which can be applied to correlate the numerical data and characterize the mass transfer in the bioreactor, have been proposed based on a simplified analysis.

The velocity and concentration fields in the bioreactor have been calculated by using the LBM. It is shown that the concentration should be normalized by a parameter combining the Damkohler number $Dam_{pa}$, Michaelis-Menten constant $K_m$ and release ratio $a$. The normalized numerical data, of the interface concentration and concentration
difference, show satisfactory correlation when presented as a function of the effective distance $x/(H Pe)$. The efficiency of the present bioreactor has been evaluated. Based on the numerical simulation, it is found that the effectiveness factor varies from around 0.9 to 0.6, the bioreactor efficiency varies from around 0.85 to 0.6, and the utilization efficiency varies from around 0 to 0.8. The utilization efficiencies are very low at small $L/(H Pe)$, that is either small $L/H$ or larger $Pe_f$. This is because the convection time scale is relatively short compared to the diffusion time.

REFERENCES


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