1 Introduction

Advances in manufacturing technologies and control of fluid flows on the micron-scale have made possible devices that can be used to great advantage in miniaturizing and automating testing processes in chemical and biological experiments, such as cell analysis [10], immunoassays [5] or DNA analysis [31]. The paradigm has been to reduce an entire laboratory to the size of a computer chip (a “lab on a chip”).

In this project we analyze and try to improve the design for the integrated microfluidic device presented by Chung and co-workers [11] intended to create a better simulated and controlled \textit{in vivo} environment for biological cells by allowing a steady flow-through of nutrients and analyte.

1.1 Lab on a chip

The so called “Lab on a Chip“ has a number of advantages over traditional bioanalysis laboratories. The most obvious advantages are low sample consumption, rapid analysis, good repeatability and high portability of these integrated microfluidic devices. On top of this they mimic biological conditions (ie flow of fluid) and allow “in vivo” observation of cells. The integrated character of the device results in a highly controlled environment where many assays can be run in parallel and without expert knowledge.

The typical “Lab on a Chip“ consists of a number of the following components [3,25]. One or more fluid inlets and outlets provide the interface to the external flow-control devices (typically syringe pumps). Microfluidic mixers and bioreactors perform the biological or chemical processes which we want to study or detect. Finally, the detection component which could work on a number of different principles, e.g. fluorescence or surface plasmon resonance.
1.2 The device: mixing and diffusion

Stem cell growth and differentiation in traditional culture formats requires a large number of cells and the microenvironment of the cells is difficult to control and optimize. Chung et al. [11] present an integrated microfluidic device which is intended to reduce the number of required cells and to create a better controlled *in vivo* environment for biological cells. The device is similar to the one depicted in figure 1 and is comprised of two sections: a mixing region that generates a series of dilutions of nutrients and growth factors and a testing area (“interrogation region”) where multiple cell spots will be exposed to the different nutrients and growth factor concentrations in each of several “uniform testing lanes”.

![Figure 1: Sketch of the overall design for the “Lab on a chip”. The left half contains the “mixer” microchannel network. The right open uniform area is the interrogation region, where several cell samples will be placed within each of the “flow lanes” of controlled analyte concentration.](image)

1.3 Design considerations and goals

The design goals for this project can be split up into two different but connected sets: one for the mixing region and one for the interrogation region. Every mixing element, the small wiggly channels in figure 1, in the mixing region has to achieve good mixing of the two input concentrations. The desired output of the mixer is a set of well calibrated mixtures of nutrients and analyte that will be delivered to each lane of cell samples in the testing region. The concentration range in the interrogation region should be as large as possible. Especially the first requirement puts a limit on the allowed velocity and therefore limits the allowed mass flux.

In the testing region we want to put as many cell colonies as possible in every lane of equal concentration. Each of these cell colonies should be subject to the same nutrient and growth factor concentration, see figure 2. This requires low mixing between neighboring lanes and rapid equilibration of concentration deviations due to cell/analyte reaction. Depending on how much of the analyte is consumed by the cells, the goals of maintaining uniform concentrations along lanes (requiring small flow rates) and minimizing diffusion between lanes (requiring large flow rates) may conflict.

Further restrictions come from the used fabrication techniques [1] at home and the limited area on the wafer. The available area for the interrogation region is 10 cm by 10 cm into which we would like to incorporate 10 lanes of different nutrient concentration.
Figure 2: (left) Desired sharp, piecewise-constant concentration profile across lanes in the testing region, (right) expected concentration along lanes due to cell uptake of analyte.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter</th>
<th>Size</th>
<th>Units</th>
<th>Source</th>
</tr>
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<tbody>
<tr>
<td>$c_i$</td>
<td>Input bulk concentration</td>
<td>$10^{-6} - 10^{-4}$</td>
<td>mol m$^{-3}$</td>
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<tr>
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<td>mol m$^{-2}$</td>
<td>[34]</td>
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<td>$D$</td>
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</tr>
<tr>
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<td>Adsorption rate</td>
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<td>s$^{-1}$</td>
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</tr>
<tr>
<td>$k_a$</td>
<td>Association rate</td>
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<td>[34]</td>
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<tr>
<td>$k_d$</td>
<td>Dissociation rate</td>
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<tr>
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<td>$2 - 5 \times 10^{-6}$</td>
<td>m</td>
<td></td>
</tr>
<tr>
<td>$R_s$</td>
<td>Cell spot radius</td>
<td>$5 \times 10^{-4}$</td>
<td>m</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Parameters for the proposed device

1.4 Parameters and variables

The feasibility of the proposed design much be demonstrated within the constraints set by the known operating parameters. These values (see Table 1) are primarily based on properties of the cells to be tested. The design variables (see Table 2) that we will work with are primarily geometric – they describe the size and shape of elements in the device and transport properties in the fluid flow.

2 Design of the concentration mixer

Mixing of fluids is one of the most basic and important processes in microfluidic devices [28] and since it poses some fundamental problems it has been the focus of extensive recent research. The generally accepted form of good mixing devices takes pure fluids from a small number of

<table>
<thead>
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<th>Symbol</th>
<th>Variable</th>
<th>Size</th>
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</tr>
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<td>$c_s$</td>
<td>Surface concentration</td>
<td>Predicted</td>
<td>mol m$^{-2}$</td>
</tr>
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<td>Interrogator height</td>
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<td>m</td>
</tr>
<tr>
<td>$L$</td>
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<td>m</td>
</tr>
<tr>
<td>$W_l$</td>
<td>Lane width</td>
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<td>m</td>
</tr>
<tr>
<td>$U$</td>
<td>Mean flow speed</td>
<td>$\sim 10^{-5}$</td>
<td>m s$^{-1}$</td>
</tr>
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</table>

Table 2: Variables for the proposed device
inlet sources and feeds them into a network of micron-scale channels, see Fig 3. The presence of junctions yields controlled volume fractions of the fluids to be directed into various channels. The torturous shapes of these channels enhances diffusion through “Lagrangian mixing” to yield a homogeneous mixture before the flow reaches the next junction. The literature falls into two classes: (i) engineering studies of the effectiveness of various overall network designs and (ii) detailed studies of individual elements used to build the network. Several articles described microfluidic mixers with arrays of identical channels by a geometric analogy with networks of electrical resistors [12, 14, 19]. A few articles went further and gave comparisons of the network analogy with experiments and flow calculations in full-scale mixer geometries [8, 33]. It is notable that in [14] experiments showed that if the flow rate through the mixer becomes large, then the fluxes and concentrations predicted by the resistor analogy are no longer accurate. Other articles focused on the mixing with individual channels or junctions using intensive two- or three-dimensional numerical simulations of the fluid flow equations [13, 15, 16, 21, 23, 28], some with further comparisons to experiments [35].

The most promising mixer design for the current project is suggested by the article [19]. There, a symmetric microchannel network of the general form pioneered by Whitesides is modified in terms of the connections to the inlet sources to produce outlet concentrations that follow a geometric progression and hence can easily span a wide range of concentrations, see Fig. 4.
2.1 Evaluating the mixing

This section consists of the relevant non-dimensionalisations on three scales: (I) the mixer bends/junctions scale, (II) the mixer channel scale, and (III) the diffuser scale, see Fig 5. Ideally, the radius of curvature of the bends/junctions should be of the same order as the width of the mixer channels; that also being the depth of the device. This ensures that strong three dimensional flows are set up in the bends, which effectively stir the oncoming concentration distributions. Diffusion then kicks in on the channel length scale (II) and smooths out the high concentration gradients that result from the stirring in the bends. Finally, the flow is slowed and enters the interrogator through a set of diffusers (expanding channels), which join the mixing channels to the interrogator. The governing equations also simplify on this length scale (III).

The dimensional governing equations are the steady Navier-Stokes equation for the fluid

\[
\begin{align*}
\rho(\mathbf{u} \cdot \nabla)\mathbf{u} &= -\nabla p + \mu \nabla^2 \mathbf{u}, \\
\nabla \cdot \mathbf{u} &= 0, \\
u &= 0 \text{ on boundaries.}
\end{align*}
\]

(1)

and the advection-diffusion equation for the nutrient concentration

\[
\begin{align*}
\frac{\partial c}{\partial t} + (\mathbf{u} \cdot \nabla)c &= D \nabla^2 c, \\
\nabla c \cdot \hat{n} &= 0 \text{ on device boundaries.}
\end{align*}
\]

(4)

Relevant non-dimensional parameters are the Reynolds number Re

\[
Re = \frac{UL}{\nu} \approx 10^{-5} \times \frac{0.1}{0.725 \times 10^{-6}} \approx 1.3,
\]

(6)

the Peclet number Pe

\[
Pe = \frac{UL}{D} \approx 10^4
\]

(7)
and the aspect ratio of the interrogator region

\[ \epsilon = \frac{H}{L} \approx 10^{-4}. \]  

(8)

The first task is to non-dimensionalize the governing equations using the relevant scalings. However, there are at least three scales on which the device functions and so we must do this three times. We will obtain the relevant governing equations at each scale, which will be simpler than the original equations. The solutions on each scale will then have to be smoothly matched together to form a composite solution valid throughout the device.

Scaling I

Scaling I applies in the mixer in the vicinity of any junctions or tight bends. The mass flux is taken to be \( q = \frac{Q}{n} \) where \( n \) is the number of channels in parallel at that location. We expect the following scalings to hold

\[ x = H\xi; \quad y = H\eta; \quad z = H\zeta; \]  

(9)

\[ u = \frac{q}{H^2} \hat{u}; \quad v = \frac{q}{H^2} \hat{v}; \quad w = \frac{q}{H^2} \hat{w}; \]  

(10)

\[ P = \frac{\mu q}{H^3 \hat{p}}; \quad c = c_0 \hat{c}; \quad t = \frac{H^3}{q} \hat{t}; \]  

(11)

where a hat denotes the non-dimensional quantity.

Substitution into the governing equations gives the non-dimensional Navier-Stokes equation

\[ \text{Re} n^{-1} (\vec{u} \cdot \nabla) \vec{u} = -\nabla p + \nabla^2 \vec{u}, \]  

(12)

\[ \nabla \cdot \vec{u} = 0, \]  

(13)

\[ u = 0 \text{ on boundaries}. \]  

(14)

where we removed the hats to increase the readability. The non-dimensional advection-diffusion equation is given by

\[ \frac{\partial c}{\partial t} + (\vec{u} \cdot \nabla) c = \frac{n}{\text{Pe}} \nabla^2 c, \]  

(15)

\[ \nabla_c \cdot \vec{n} = 0 \quad \text{on device boundaries}. \]  

(16)

Since the Reynolds number and \( n \) are \( \mathcal{O}(1) \) we cannot neglect the fluid inertia in equation 14. However since the Peclet number is \( \mathcal{O}(10^{-4}) \) we can neglect \( n \text{Pe}^{-1} \) and so we see that on this scale the concentration is simply advected with the fluid and the fluid velocity satisfies the Navier-Stokes equations.

Scaling II

Scaling II applies in the mixing channels between the junctions and bends of the previous section. The idea being that having folded the concentration profile in a bend using lagrangian advection one would like that profile to mix/blur using diffusion. The complexity here being in the upstream boundary conditions emerging from a bend or junction. In any case, we expect the following scaling to hold

\[ x = \frac{L}{n} \hat{x}; \quad y = H \hat{y}; \quad z = H \hat{z}; \]  

(17)
\[ u = \frac{q}{H^2} \dot{u}; \quad v = \frac{\delta q}{H^2} \dot{v}; \quad w = \frac{\delta q}{H^2} \dot{w}; \]

\[ P = \frac{\mu q L}{n} \dot{\rho}; \quad c = c_0 \dot{c}; \quad t = \frac{H^2 L}{q} \dot{\gamma}; \]

with unknown \( \delta \ll 1 \).

Substituting into the governing equations we get

\[ \epsilon \text{Re} u \frac{\partial u}{\partial x} + \frac{\delta}{n} \text{Re} \left( v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) = - \frac{\partial p}{\partial x} + n^2 \epsilon^2 \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \]

\[ \delta \epsilon \text{Re} u \frac{\partial v}{\partial x} + \epsilon \frac{\partial^2 v}{\partial x^2} + \frac{n^2 \rho u}{\partial y} = - \frac{\partial p}{\partial y} + \delta n^2 \epsilon^2 \frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial z^2} \]

\[ \delta n^2 \text{Re} u \frac{\partial w}{\partial x} + \frac{\partial^2 w}{\partial x^2} = - \frac{\partial p}{\partial z} + \delta n^2 \epsilon^2 \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \]

These look somewhat complicated, but if we stick to straight channels as in the current designs there is no reason to suspect that \( \delta > 0 \), since \( \delta = 0 \) is consistent with the governing equations and boundary conditions. For \( \delta = 0 \) we have

\[ p = p(x) = p_0 + x \frac{dp_0}{dx} \]

\[ u = u(y, z) \]

\[ \frac{dp_0}{dx} = \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \]

\[ \epsilon \text{Pe} \left( \frac{\partial c}{\partial t} + u \frac{\partial c}{\partial x} \right) = n^2 \epsilon^2 \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2} \]

Since \( \epsilon \approx 10^{-4} \) and \( \text{Pe} \approx 10^4 \) we have \( \epsilon \text{Pe} \approx 1 \). Since \( \epsilon^2 \approx 10^{-8} \) and \( n^2 \) is smaller than 100 we have \( n^2 \epsilon^2 \ll 1 \) and we can neglected terms with \( n^2 \epsilon^2 \). Therefore we have an advection diffusion problem for \( c \) where \( u(y, z) \) can be found exactly and the pressure \( p(x) \) is at most a linear function of \( x \) and \( u(y, z) \) satisfies Poisson’s equation. For a square channel cross-section we have

\[ \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} = \frac{dp_0}{dx} \]

\[ u(0, z) = u(1, z) = u(y, 0) = u(y, 1) = 1 \]

which can be solved using separation of variables. For this length scale the concentration profile is advected and diffused out by unidirectional pipe flow if the mixing channels are straight and have uniform cross-section.

**Scaling III**

Scaling III applies in the interrogator on a range of length scales but consider it on the largest of these first. On the length scale of the whole device \( L \) we expect the following scalings to hold

\[ x = L \dot{x}; \quad y = L \dot{y}; \quad z = H \dot{z}; \]
\[ u = U \hat{u}; \quad v = U \hat{v}; \quad w = \gamma U \hat{w}; \quad (32) \]
\[ P = \frac{\mu UL}{H^2} \hat{p}; \quad c = c_0 \hat{c}; \quad t = \frac{L}{U} \hat{t}; \quad (33) \]

with unknown \( \gamma \ll 1 \).

Substituting into the governing equations we get

\[
\epsilon^2 \text{Re} \left( u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} \right) + \gamma \epsilon^2 \text{Re} w \frac{\partial u}{\partial z} = - \frac{\partial p}{\partial x} + \epsilon^2 \left( \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) + \frac{\partial^2 u}{\partial z^2} \quad (34)
\]
\[
\epsilon^2 \text{Re} \left( u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} \right) + \gamma \epsilon^2 \text{Re} w \frac{\partial v}{\partial z} = - \frac{\partial p}{\partial y} + \epsilon^2 \left( \frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} \right) + \frac{\partial^2 v}{\partial z^2} \quad (35)
\]
\[
\gamma \epsilon^2 \text{Re} \left( u \frac{\partial w}{\partial x} + v \frac{\partial w}{\partial y} \right) + \gamma \epsilon^2 \text{Re} w \frac{\partial w}{\partial z} = - \frac{\partial p}{\partial z} + \gamma \epsilon^3 \left( \frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} \right) + \epsilon \gamma \frac{\partial^2 w}{\partial z^2} \quad (36)
\]
\[
\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\gamma \epsilon}{\epsilon} \frac{\partial w}{\partial z} = 0 \quad (37)
\]
\[
\epsilon^2 \text{Pe} \left( \frac{\partial c}{\partial t} + u \frac{\partial c}{\partial x} + v \frac{\partial c}{\partial y} \right) + \gamma \epsilon \text{Pe} \frac{\partial w}{\partial z} = \epsilon^2 \left( \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} \right) + \frac{\partial^2 c}{\partial z^2} \quad (38)
\]

For horizontal top and bottom surfaces we can take \( \gamma = 0 \) which simplifies the system.

\[
\epsilon^2 \text{Re} \left( u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} \right) = - \frac{\partial p}{\partial x} + \epsilon^2 \left( \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) + \frac{\partial^2 u}{\partial z^2} \quad (39)
\]
\[
\epsilon^2 \text{Re} \left( u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} \right) = - \frac{\partial p}{\partial y} + \epsilon^2 \left( \frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} \right) + \frac{\partial^2 v}{\partial z^2} \quad (40)
\]
\[
\frac{\partial p}{\partial z} = 0 \quad (41)
\]
\[
\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} = 0 \quad (42)
\]
\[
\epsilon^2 \text{Pe} \left( \frac{\partial c}{\partial t} + u \frac{\partial c}{\partial x} + v \frac{\partial c}{\partial y} \right) = \epsilon^2 \left( \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} \right) + \frac{\partial^2 c}{\partial z^2} \quad (43)
\]

Remember \( \epsilon \sim 10^{-4} \), \( \text{Re} \sim 1 \) and \( \text{Pe} \sim 10^4 \), which means the terms with \( \epsilon^2 \) are negligible in comparison to those of order unity hence the leading order equations are

\[
\frac{\partial p}{\partial x} = \frac{\partial^2 u}{\partial z^2} \quad (44)
\]
\[
\frac{\partial p}{\partial y} = \frac{\partial^2 v}{\partial z^2} \quad (45)
\]
\[
\frac{\partial p}{\partial z} = 0 \quad (46)
\]
\[
\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} = 0 \quad (47)
\]
\[
\frac{\partial^2 c}{\partial z^2} = 0 \quad (48)
\]

These equations govern the flow in the Hele-Shaw cell which we are considering in the next section.
Table 3: Aspect ratios for the different channel dimensions

<table>
<thead>
<tr>
<th>Aspect ratio</th>
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<tr>
<td>$\epsilon = H/L$</td>
<td>$10^{-4} - 10^{-2}$</td>
</tr>
<tr>
<td>$H/W$</td>
<td>$10^{-4} - 10^{-2}$</td>
</tr>
<tr>
<td>$H/R_s$</td>
<td>$1/50 - 1/5$</td>
</tr>
<tr>
<td>$H_c/H$</td>
<td>$1/50 - 1/2$</td>
</tr>
</tbody>
</table>

3 Considerations for the interrogator region

In the interrogation region we have to consider the profile of the fluid flow, the transport of the nutrients through convection and diffusion and the uptake reaction of nutrients at the cell colonies.

3.1 Fluid flow

For the proposed flow speed $U \approx 10^{-5} \text{m s}^{-1}$ the Reynolds number $Re = WU/\nu \approx 1$ which shows that the flow in the interrogation region and therefore in the mixing region as well is dominated by viscous effects due to the slow flow speed and the small device dimensions. For the proposed design the channel width $W$ is much larger than the channel height $H$ which leads to thin film flow [2] so that the viscous term in the Navier-Stokes equation can be approximated by $\nu \partial_z \vec{u}$. We can neglect the inertia term if the following holds

$$\frac{UW}{\nu} \left( \frac{H}{W} \right)^2 \ll 1.$$  \hspace{1cm} (49)

For our design both conditions hold and we can reduce the Navier-Stokes equations 1-3 to the equations for the Hele-Shaw cell. For the no-slip boundary condition at the top and bottom of the channel we get the flow speed in $x$ and $y$ direction

$$\vec{u} = -\frac{1}{2\mu} z(H-z) \nabla p.$$  \hspace{1cm} (50)

The pressure differences across the width of the channel due to different mixing length are negligible, see section 2. Assuming that the pressure is uniform across the channel outlet the pressure is only dependent on $x$ which gives us

$$\vec{u} = u(z) \hat{i}, \quad u(z) = \frac{6Q}{H^3} z(H-z), \quad Q = \int_0^H U(z) \, dz = -\frac{H^3}{12\mu} \frac{\partial p}{\partial x}.$$  \hspace{1cm} (51)

This gives us the typical parabolic flow profile over the height of the channel and a uniform flow speed over most of the width of the channel, see figure 6. At the side walls of the channel the flow profile has a boundary layer with a width of $O(H)$. In this analysis we have neglected the height of the cell colonies which is only reasonable for the larger channel heights.

3.2 Transport of the analyte

In the proposed device the nutrient molecules are transported through the channel by convection with the flow and by molecular diffusion. These processes can be described using the established equation [22]

$$\frac{\partial c}{\partial t} + u(z) \frac{\partial c}{\partial x} = D \left( \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2} \right).$$  \hspace{1cm} (52)
Figure 6: 3D schematic of the fluid flow in the testing region showing the flow profile across the width and height of the channel. Inset: Diffusion and advection timescales for the various length scales in the device. The timescales are calculated for $L = W = 0.1 \text{m}$ and $D = 10^{-10} \text{m}^2 \text{s}^{-1}$.

Using the following variables $x = L \hat{x}$, $y = W \hat{y}$, $z = H \hat{z}$, $c = c \hat{c}$, $u = U \hat{u}$ and $t = \frac{L^2}{D} \hat{t}$, we get a non-dimensional version of equation (52)

$$\frac{\partial \hat{c}}{\partial \hat{t}} + \hat{u}(\hat{z}) \frac{\partial \hat{c}}{\partial \hat{x}} = \frac{DL}{UH^2} \left( \frac{H^2}{L^2} \frac{\partial^2 \hat{c}}{\partial \hat{x}^2} + \frac{H^2}{W^2} \frac{\partial^2 \hat{c}}{\partial \hat{y}^2} + \frac{\partial^2 \hat{c}}{\partial \hat{z}^2} \right).$$

(53)

For the ease of readability we are removing the hat atop the non-dimensional variables from now on. The non-dimensional number on the right side of the equation is the reduced Peclet number $\epsilon^2 \text{Pe}$. The Peclet number and reduced Peclet number for the whole interrogation region, for the lanes and for a cell spot are given in table 4. The reduced Peclet number for the cell spots

<table>
<thead>
<tr>
<th>Location</th>
<th>Pe</th>
<th>$\epsilon$</th>
<th>$\epsilon^2 \text{Pe}$</th>
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<td>$10^{-4} - 10^{-2}$</td>
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<tr>
<td>Strip</td>
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<td>$10^{-3} - 10^{-2}$</td>
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<tr>
<td>Spot</td>
<td>$10^2$</td>
<td>$10^{-2} - 10^{-1}$</td>
<td>$10^{-2} - 1$</td>
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</table>

Table 4: Peclet number and reduced Peclet number for the different device features. The values are calculated for $L = 0.1 \text{m}$ and $W_1 = 10^{-2} \text{m}$.

is of the order 1 or smaller which means that on the scale of the cell spots the diffusion is faster or at least as fast as the convection. The suggested mean flow speed $U$ is therefore reasonable as every nutrient molecule theoretically has the chance to diffuse to the cell surface.

**Taylor dispersion**

For $\epsilon^2 \ll \epsilon^2 \text{Pe} \ll 1$, Taylor’s arguments imply that $c$ is independent of $z$ at leading order. Scaling

$$x \sim R_2, \ y \sim R_s, \ z \sim \epsilon R_s, \ t \sim \frac{\epsilon R_s^2}{Q}, \ c \sim |c|,$$

Taylor dispersion

For $\epsilon^2 \ll \epsilon^2 \text{Pe} \ll 1$, Taylor’s arguments imply that $c$ is independent of $z$ at leading order. Scaling

$$x \sim R_2, \ y \sim R_s, \ z \sim \epsilon R_s, \ t \sim \frac{\epsilon R_s^2}{Q}, \ c \sim |c|,$$
the cross-chamber-averaged concentration \( \bar{c}(x, y, t) \) satisfies (with an error of \( O(\epsilon^2, \epsilon^4 Pe^2) \)) the dimensionless advection-diffusion equation

\[
\frac{\partial \bar{c}}{\partial t} + \frac{\partial \bar{c}}{\partial x} = \frac{1}{Pe} \left( 1 + \frac{\epsilon^2 Pe^2}{210} \right) \frac{\partial^2 \bar{c}}{\partial x^2} + \frac{1}{Pe} \frac{\partial^2 \bar{c}}{\partial y^2},
\]

where for a spot the dimensionless parameters are given by

\[
\epsilon = \frac{H}{R_s} \approx 10^{-2} - 10^{-1}, \quad Pe = \frac{R_s U}{D} \approx 10^2.
\]

For \( H_{cell} \approx H \) it may be important to consider the effect of variations in the thickness of the Hele-Shaw cell on the Taylor dispersion reduction. See appendix A for details.

### 3.3 “Lane maintenance”: minimizing lateral diffusion

The first requirement for the device is a constant nutrient concentration over the whole length of a lane. We can estimate the minimum velocity to keep the diffusive boundary layer out of the lane center by the relationship

\[
U_{\text{min}} \approx \frac{DL}{(W_\ell/2)^2}
\]

which is derived from \( x \sim \sqrt{Dt} \). For \( L = 0.1 \)m and \( W_\ell = 10^{-2} \)m, the minimum velocity is \( U = 10^{-7} \)m\,s\(^{-1} \) which is two orders of magnitude smaller than the desired flow velocity.

Solving equation (53) we can investigate the concentration profile for the chosen flow speed and device dimensions. For this calculation we average the convection-diffusion equation over the \( z \) direction and neglect the diffusion in \( x \) direction. We solved the resulting equation

\[
c_t + uc_x = Dc_{yy}
\]

with top hat initial condition \( c(x, y, 0) = H(y) - H(y-W_\ell) \). A concentration profile for a single lane is shown in figure 7. For \( L = 0.1 \)m, \( W_\ell = 10^{-2} \)m, \( U = 10^{-7} \)m\,s\(^{-1} \) and \( D = 10^{-10} \)m\(^2\)\,s\(^{-1} \) a

![Figure 7: Steady-state concentration profile along a single lane.](image)

1% deviation of the nutrient concentration in the middle of the lane is reached at \( x = 0.293 \)m and a 5% deviation at \( x = 0.554 \)m. This shows that for the given flow speed and channel dimensions the diffusion across lanes is negligible.

### 3.4 Reaction at cell surface

The uptake of nutrients at the cell surface is governed by the rate constants, \( k_a \) and \( k_d \), which are a measure for the speed of the attachment and detachment reaction. Furthermore the reaction
is dependent on the concentration of nutrients and free receptor sites at the cell surface and can be described through the following formula

$$c + c_r \xrightarrow{k_a} c_s \xrightarrow{k_d} c_r$$

(57)

where $c, c_r$ and $c_s$ are the nutrients, cell receptors and attached nutrients, respectively. There are many ways to transfer this into a mathematical model which describes the nutrient uptake. In this section we are looking at two different ways, a bimolecular reaction model and the Michaelis-Menten model. The parameters governing the reaction can vary immensely for different cell lines and nutrients. In this project we are only looking at the worst case for the parameters provided in table 1.

**Bimolecular reaction**

Most bimolecular reactions are dependent on the concentration of both reagents. The change in concentration of the target product can be describe through

$$\frac{\partial c_s}{\partial t} = k_a c c_r - k_d c_s - k_s c_s.$$  
(58)

Using the same non-dimensionalization as in section 3.2 we get

$$\frac{\partial c_s}{\partial t} = \frac{k_a c_i L}{U} \left( c c_r - \frac{k_d + k_s}{k_a} c_s \right).$$  
(59)

The non-dimensional parameter $K = \frac{k_d + k_s}{k_a c_i}$ controls the equilibrium when both the attachment and detachment rate are equal. For $c_i = 10^{-5}\text{mol m}^{-3}$ we get $K = 0.15$. Under the assumption that $c$ is constant we can calculate the equilibrium values for $c_r$ and $c_s$. It follows that in equilibrium $20/23$ of the receptor sites on the cell are occupied. Again keeping $c$ constant and neglecting detachment we can solve equation (59)

$$c_s = 1 - \exp \left( -\frac{k_a c_i L}{U} t \right).$$  
(60)

Equating this to $20/23$ we find a rough, best case estimate for the equilibration timescale of $10^2\text{s}$. We can also calculate the recovery time of the cell surface by setting $c = 0$ and $c_s$ to the equilibrium concentration. It takes about 13min for $c_s$ to drop below 10% and another 13min to drop under 1%.

The flux of nutrients into the cell surface should be equal to the change of surface concentration

$$D \frac{\partial c}{\partial z} = \frac{\partial c_s}{\partial t}$$  
(61)

thus linking the convection-diffusion equation (52) to the boundary condition (58). This equation can be solved numerically and a plot of the steady-state bulk concentration is given in figure 8. The numerical calculation is done with the commercial PDE package COMSOL Multiphysics 3.2 (COMSOL AB, Stockholm, Sweden).

**Michaelis-Menten kinetics**

A disadvantage of using the full, coupled problem (52, 58) is the need to solve it numerically due to the nonlinearity in the boundary condition. We investigated a different reaction model to
Figure 8: Steady-state bulk concentration for an interrogator region with 5 cell spots, $S_1 - S_5$.

Parameters: $c_i = 10^{-5}\text{mol m}^{-2}$, $c_r = 2 \times 10^{-9}\text{mol m}^{-2}$, $k_a = 2 \times 10^3\text{m}^3\text{mol}^{-1}\text{s}^{-1}$, $k_d = 2 \times 10^{-3}\text{s}^{-1}$, $U = 10^{-5}\text{m s}^{-1}$ and $D = 10^{-10}\text{m}^2\text{s}^{-1}$

get some analytical results about the uptake and the bulk concentration. For the case that the maximal surface concentration $c_e$ is the limiting factor we can use Michaelis-Menten kinetics.

The main assumption is that one of the two reacting species is in steady-state. The time for liquid to cross a spot ($10^2\text{s}$) is much smaller than the time needed for a nutrient molecule to adsorb into the cell ($k_s^{-1} \sim 10^3\text{s}$). We modify the surface concentration

$$\frac{dc_s}{dt} = -D \frac{\partial c}{\partial n} - k_s c_s$$

and the accompanying flux into the cell surface

$$-D \frac{\partial c}{\partial n} = k_a (c_e - c_s) + k_d c_i.$$  

Considering the quasi-steady version of equation 58 where $c_s < c_e$ we get a boundary equation for the bulk concentration which is independent of the surface concentration $c_s$

$$-D \frac{\partial c}{\partial n} = \frac{k_a c_e c}{1 + \frac{k_d}{k_s} + \frac{k_a}{k_s}}.$$  

Imposing equation 64 on $z = 0$ and

$$D \frac{\partial c}{\partial z} = 0, \quad \text{on } z = H,$$

we can incorporate the uptake reaction into the Taylor dispersion equation (54)

$$\frac{\partial \bar{c}}{\partial t} + \frac{\partial \bar{c}}{\partial x} = \frac{1}{\text{Pe}} \left( 1 + \frac{e^2 \text{Pe}^2}{210} \right) \frac{\partial^2 \bar{c}}{\partial x^2} + \frac{1}{\text{Pe}} \frac{\partial^2 \bar{c}}{\partial y^2} - \frac{\text{Da}}{e^2 \text{Pe}} \left( \frac{\bar{c}}{\mu_1 + \mu_2 \bar{c}} \right) - \frac{\text{Da}}{60} \frac{\partial}{\partial x} \left( \frac{\bar{c}}{\mu_1 + \mu_2 \bar{c}} \right),$$
where for a spot and typical cell receptor kinetics the dimensionless parameters are given by

\[ \epsilon = \frac{H}{R_s} \approx 10^{-2} - 10^{-1}, \quad Pe = \frac{R_s \bar{U}}{D} \approx 10^2, \quad Da = \frac{k_0 c_H}{D} \approx 10^{-1}, \]

\[ \mu_1 = 1 + \frac{k_d}{k_s} \approx 2, \quad \mu_2 = \frac{k_s[c]}{k_s} \approx 1 - 10^3. \]

Solving equation 65 we can calculate the bulk concentration depending on the various parameters. The flux downstream of cell spots depends on saturation of receptors given controlled by \( \mu_2 \), see figure 9. This model has a low numerical complexity so that it is feasible to simulate the device response for different spot locations and model parameters. It is also possible to change the model for the kinetics if a different reaction type is of interest.

### 3.5 Diffusion of reaction “divot”

Figures 9 and 10 show that the bulk concentration might be significantly depleted after passing over one cell spot. This is especially important for low levels of nutrient concentrations.

For the steady problem in which \( S = Da/\epsilon^2 Pe = O(1) \), the problem reduces to the ODE

\[ \frac{\partial \bar{c}}{\partial x} = - \frac{S \bar{c}}{\mu_1 + \mu_2 \epsilon}. \] (66)

Take the spot to be the unit circle. The concentration to the left of the spot is \( c = 1 \), and hence by continuity of flux \( c = 1 \) on the left-hand boundary \( x = -\sqrt{1-y^2} \), so (for \( x^2 + y^2 < 1 \))

\[ \mu_1 \ln(c(x, y)) + \mu_2 (c(x, y) - 1) + S(x + \sqrt{1-y^2}) = 0. \] (67)
Hence the concentration on the right-hand boundary,
\[ ¨c^*(y) = ˙c(\sqrt{1 - y^2}, y), \]  
(68)
is given by
\[ \mu_1 \ln( ¨c^*(y)) + \mu_2( ¨c^*(y) - 1) = -2S\sqrt{1 - y^2}. \]  
(69)
The drop in average concentration across the spot is given by
\[ \frac{1}{2} \text{ (Flux in} - \text{ Flux out)} = 1 - \frac{1}{2} \int_{-1}^{1} ¨c^*(y) \, dy. \]  
(70)

Down stream of the spot ¨c(x, y) is smoothed out according to the balance (in dimensional variables, with \( \bar{U} = Q/R_s \))
\[ \bar{U} \frac{\partial \bar{c}}{\partial x} \sim D \frac{\partial^2 \bar{c}}{\partial y^2}, \]  
(71)
so that a uniform concentration in the \( y \)-direction is attained on the length scale \( x \) such that
\[ R_s \sim \sqrt{Dx/\bar{U}}, \]  
(72)
giving
\[ x \sim \frac{R_s \bar{U}}{D} \cdot R_s \approx 0.1 \text{ m} \quad \text{for} \quad \bar{U} \approx 10^{-5} \text{ m s}^{-1}. \]  
(73)

4 Conclusions and Design recommendations

For the mixer:
We have analysed the underlying equations for the micro mixer on the various length scales. In the bends and junctions we have to consider the full 3D Navier-Stokes equations because we cannot neglect inertia effects. This leads to secondary flow profiles in the bends which mix the two concentrations. Because the flow is reversible this advective mixing is undone in the next bend. To design an effective serpentine mixer we have to vary the bend configuration: change the curvature or channel shape. In the channels between the bends the flow is unidirectional. The residence time in this channels has to be long enough to smooth the high concentration gradients that result from the stirring in the bends.

Preliminary investigations suggest that the available space is sufficient to incorporate a concentration gradient generator which is capable of delivering 10 different concentrations in a variety of distributions. More research is required in evaluating the mixing for very high flow rates which disrupt the mixing because flow will bypass paths with higher resistance.

For the interrogator:
The evaluation of the diffusion, across lanes and across the height of the channel, shows that the suggested flow velocity of \( U = 10^{-5} \text{ m s}^{-1} \) is a good choice for the interrogator. It is slow enough so that the diffusion time over the height of the channel is of the same size as the convection time over a single cell spot. On the other hand is the flow speed still fast enough so that the diffusion across concentration lanes is negligible.

A drawback of the chosen flow speed is the fact that divots created through the uptake over on cell spot cannot be compensated over the length of the interrogation region. This means that it is not possible to put multiple colonies in series because they would experience vastly different nutrient concentrations. The available space on the other hand is large enough to put at least 5 cell spots in a row across a lane.
Future:

We want to use the governing equations for the mixing region to evaluate existing mixers as well as testing new mixer plan ideas. Especially serpentine channels with varying bends could lead to efficient micro mixers.

Using a combination of numerics and the asymptotic analysis in section 3.4 and 3.5 we want to evaluate the behaviour of the device for a range of model parameters. In particular, the evaluation of worst case scenarios could help us designing a device which is capable of handling a wide variety of different cell/nutrient systems.

A Untangling DNA molecules in micro-channel flows

Another question that we were asked to consider was how microfluidics could be used to stretch-out complicated DNA molecules to allow for optical sequencing in a more convenient linear configuration. Recently there has been a lot of interest in untangling and stretching DNA molecules. In the cell and in vivo the DNA molecules form loops of various sizes and are highly coiled up. This complicates the detection of the base pair sequence through optical means. If the DNA molecule is untangled and stretched the base pairs can be flown past an optical detector sequentially. To achieve the required stretching a tensile force between 5pN and 50pN is necessary [6,7].

So far most methods bring the DNA molecule into contact with a surface to achieve the untangling and stretching; for example stretching through a receding meniscus [4] or attaching one end of the DNA molecule to a surface and pulling the other end with optical tweezers [32]. These methods achieve reasonable untangling and stretching of the DNA but have a low yield and are not as flexible as free flow methods. The use of elongational and shear flow [18,24] is effective in stretching but not in untangling DNA. Szymczak and Cieplak [29] report on the stretching of proteins in a uniform flow and compare it to that in a force-clamp apparatus. Chan et al. [9] extends these ideas to incorporate an untangling region as well. However the untangling region reduces the yield of usable, fully intact molecules to only 28%. Several publications [17,26,27] investigate the conformational behaviour and dynamics of DNA in various flow conditions. A different approach using electrophoretic forces is reported by Tang and Doyle [30].

The complexity of the real structure of DNA makes a direct simulation of the interaction of the macromolecule with fluid forces prohibitively difficult. Many studies have made very good progress by modeling the molecule by an elastic rod, or string. A related but simpler model is to reduce the molecule to lumped point masses connected by springs. Force balances at the point masses due to the molecular structure (the springs) and frictional drag from velocity differences with the surrounding fluid flow field yield evolution equations for the masses,

\[ m \frac{d^2\vec{x}_k}{dt^2} = -f(|\vec{x}_k - \vec{x}_{k+1}| - \ell) \frac{\vec{x}_k - \vec{x}_{k+1}}{|\vec{x}_k - \vec{x}_{k+1}|} - f(|\vec{x}_k - \vec{x}_{k-1}| - \ell) \frac{\vec{x}_k - \vec{x}_{k-1}}{|\vec{x}_k - \vec{x}_{k-1}|} - \beta \left( \frac{d\vec{x}_k}{dt} - \vec{u}(\vec{x}_k(t), t) \right), \]

where \( m \) is a mass, \( \beta \) is a friction coefficient and \( f(s) \) gives the stress-strain relation of the spring model considered. Simple convective transport of small, light test particles would consider only the last term in this equation, eliminating inertia and the spring coupling forces. Many studies also add stochastic forcing, due to thermal fluctuations in the fluid at the molecular scale, which yield Brownian motion. It may be appropriate to consider models that neglect restoring compressional forces, i.e. \( f(s) = 0 \) for \( s \leq 0 \), as buckling is more energetically favorable than compression. Some studies have shown the spring models show dramatic hardening effects for large extensions [26]. Above, \( \ell \) represents an equilibrium rest-length between adjacent masses.
and \( \bar{u}(\mathbf{x}, t) \) is the three-dimensional fluid flow field, which will be parabolic (Poiseuille) in the \( z \)-direction in a Hele-Shaw cell.

A  **Taylor dispersion in a slowly varying domain**

The transport of analyte molecules can be described through the system

\[
\begin{align*}
\alpha_t + u(z)c_x &= D \left( c_{xx} + c_{zz} \right), \\
\n c_z &= 0 \quad \text{on } z = H, \\
\n \nabla c \cdot \mathbf{n} &= \frac{\delta}{2} Dq \quad \text{on } z = h(x).
\end{align*}
\]  

(75)\hspace{1cm}(76)\hspace{1cm}(77)

where \( h(x) \) represents the profile of the bottom surface. The velocity distribution is

\[
u(x, z) = \frac{6Q}{(H-h)^3}(z-h)(H-z).
\]  

(78)

We decompose \( c \) and \( u \) as follows

\[
c(x, z, t) = \bar{c}(x, t) + \epsilon c'(x, z, t), \quad u(x, z) = \bar{u}(x) + u'(x, z),
\]  

(79)

with \( \bar{c} \) and \( \bar{u} \) vertically averaged concentration and velocity, respectively. We then obtain the following two equations for \( \bar{c} \) and \( c' \)

\[
\begin{align*}
\bar{c}_t + \bar{u} \bar{c}_x + <u'c'_x> &= D \bar{c}_{xx} + \frac{D}{H-h} \left( 2h_xc'_x + h_{xx}c' + h^2_z c'_z - c'_z \right)_{z=h}, \\

\epsilon c'_t + \epsilon u' c'_x + \bar{u} c'_x + u' \bar{c}_x - <u'c'_x> &= D \left[ c'_{xx} + c'_{zz} - \frac{1}{H-h} \left( 2h_xc'_x + h_{xx}c' + h^2_z c'_z - c'_z \right)_{z=h} \right].
\end{align*}
\]  

(80)\hspace{1cm}(81)

We make variables non dimensional as

\[
\begin{align*}
\hat{x} &= \frac{x}{L}; \quad \hat{z} = \frac{z}{\varepsilon L}; \quad \hat{h} = \frac{h}{\varepsilon L}; \quad \hat{u} = \frac{u}{Q/(\varepsilon L)}; \quad \hat{t} = \frac{t}{\varepsilon L^2/Q}; \quad \hat{c} = \frac{c}{c},
\end{align*}
\]  

(82)

with \( \varepsilon = H/L \). In the following we skip the hats for simplicity of the notation. \( \bar{u} \) and \( u' \) take the following dimensionless form

\[
\begin{align*}
\bar{u} &= \frac{1}{1-h}, \\
u' &= \frac{6}{(1-h)^3} \left[ (z-h)(1-z) - \frac{1}{6} (1-h)^2 \right].
\end{align*}
\]  

(83)\hspace{1cm}(84)

Equations (80) and (81) take the following dimensionless form

\[
\begin{align*}
Pe \left( \bar{c}_t + \bar{u} \bar{c}_x + <u'c'_x> \right) &= \bar{c}_{xx} + \frac{1}{1-h} \left( 2h_xc'_x + h_{xx}c' + h^2_z c'_z \right)_{z=h} - \frac{1}{\varepsilon^2} \frac{1}{1-h} \left| c'_z \right|_{z=h}, \hspace{1cm} (85)
\end{align*}
\]

\[
\varepsilon^2 Pe \left( \epsilon c'_t + \epsilon u' c'_x + \bar{u} c'_x + u' \bar{c}_x - <u'c'_x> \right) = \epsilon^2 c'_{xx} + c'_{zz} - \frac{\varepsilon^2}{1-h} \left( 2h_xc'_x + h_{xx}c' + h^2_z c'_z \right)_{z=h} + \frac{1}{1-h} \left| c'_z \right|_{z=h}. \hspace{1cm} (86)
\]
The problem for \( c' \) is subject to the following boundary conditions

\[
c'_z = 0 \quad \text{on} \quad z = 1, \quad (87)
\]

\[
c'_z = \varepsilon^2 h_x c'_x + \varepsilon^2 Pe q + O(\varepsilon^4 Pe) \quad \text{on} \quad z = h \quad (88)
\]

We assume \( \varepsilon^2 \ll \varepsilon^2 Pe \ll 1 \) and use the following expansion

\[
c' = c'_0 + \varepsilon^2 Pe c'_1 + \ldots \quad (89)
\]

At leading order we find

\[
c'_0 = 0. \quad (90)
\]

At the order \( \varepsilon^2 Pe \) we find the equation:

\[
u' c'_x = c'_{1zz} + \frac{q}{1 - h}. \quad (91)
\]

The solution for \( c'_1 \) is

\[
c'_1(x, z) = \tau_x F_1(x, z) + q F_2(x, z), \quad (92)
\]

where

\[
F_1 = \frac{6}{(1 - h)^3} \left\{ \frac{-z^4}{12} + \frac{z^3}{6} (1 + h) - \left[ \frac{1}{6} (1 - h)^2 + h \right] \frac{z^2}{2} + \frac{h}{6} (1 + h) z + \frac{1}{6} \left( \frac{h^4}{60} - \frac{h^3}{15} - \frac{2}{5} h^2 - \frac{h}{15} + \frac{1}{60} \right) \right\}, \quad (93)
\]

\[
F_2 = \frac{1}{1 - h} \left( \frac{-z^2}{2} + z + \frac{h^2}{6} - \frac{h}{3} - \frac{1}{3} \right). \quad (94)
\]

From the above equations we find

\[
< u' c'_{1x} > = -\frac{\tau_{xx}}{210} + \frac{q_x}{60} + \frac{\tau_x}{420} \frac{h_x}{(1 - h)} + \frac{q}{60} \frac{h_x}{(1 - h)}. \quad (95)
\]

Substituting in equation (85) and neglecting terms of order \( \varepsilon^2 \) we obtain

\[
\tau_t + \tau_x \tau_x = \frac{1}{Pe} \left( 1 + \frac{\varepsilon^2 Pe^2}{210} \right) \tau_{xx} - \frac{q}{1 - h} - \frac{\varepsilon^2 Pe}{60} q_x + \frac{\varepsilon^2 Pe}{60} h_x \quad \text{for} \quad 1 - h \neq 0. \quad (96)
\]

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