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Characterising the effect of geometry on a microchamber for producing controlled concentration gradients

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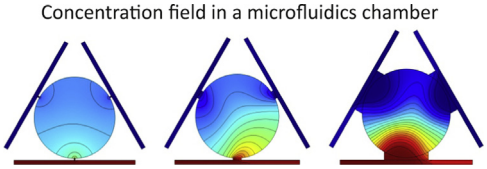
HIGHLIGHTS

- A 2D concentration gradient within a microfluidics device has been characterised.
- The effects of geometry on time to steady-state have been determined.
- The effects of geometry on concentration profile and symmetry have been determined.
- An important recommendation – entrance width to the chamber should be below 80 μm.

GRAPHICAL ABSTRACT

Geometry affects flow and concentration profiles, shown above, and the time to reach steady state. Inlet width has a critical length, above which asymmetries arise.



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ABSTRACT

A microfluidic diffusion chamber with 3 inlets and a circular central chamber allows a 2D concentration gradient to develop. This diffusion chamber has been characterised numerically for the effect geometry has on equilibrium time, the concentration profile and the flow profile within the central chamber. As the Einstein–Smoluchowski relation predicts, the time to reach steady state is proportional to the square of the radius of the chamber but features within the chamber are qualitatively insensitive to the size of the chamber within the range of 100–1000 μm. Inlet width had a much more significant effect on the qualitative behaviour within the chamber, affecting the symmetry of the concentration profile. It is recommended that inlet widths are less than 80 μm to preserve symmetry. In this paper, the effect of geometry on both transient and steady-state behaviour has been explored, providing a basis and criteria for designing chambers for a wide range of applications, including studying the effect of concentration gradients on cell mobility or a rapid assay for biofilm development in a range of concentrations.

1. Introduction

Microfluidic devices can be used to study carefully controlled concentration gradients. Clever geometries allow gradients to be maintained and manipulated (Wegrzyn et al., 2012). Fleming Glass et al. (2008) summarised that microfluidic environments are well suited to vary the concentration of the environment surrounding a cell. Flow-induced shear can be problematic to cells because shear can affect cells' physical development, growth and protein expression (Merchuk, 1991; Metallo et al., 2008), flow can affect motility (Kaya and Koser, 2012) and weakly adherent cells are easily displaced by shear (St. John et al., 1994). Due to the inherently small length scales in microfluidics, flow is often laminar, with a Reynolds number less than 1. Devices have been designed to facilitate diffusion in the absence of convection, allowing concentration gradients to develop without flow-induced shear stress (Du et al., 2009).

Previously published works have used microchannels to study cell suspensions. Kolnik et al. (2012) used many individual chambers with small inlets to a main perfusion channel. Adherent

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shear sensitive mammalian cells within the small chambers are subjected only to low flow velocities. The concentration in the chamber is dependant on the concentration in the main perfusion channel and also the entrance width. Although it was mentioned that the time to equilibrium could be controlled using the entrance width, the control of the concentration gradients through changing the entrance width was not explored. Du et al. (2009) studied attached shear sensitive mammalian cells using evaporation to drive transport and develop a concentration gradient.

Motile cells have also been studied. Ahmed et al. (2010) used diffusion through a hydrogel to create a concentration gradient in a test channel, which had no convective flow within it, particularly suitable for studying bacterial chemotaxis. Mao et al. (2003) produced a device that uses 22 outlets at different positions to capture cells according to their migration. Bulk flow was used to push cells along a relatively long channel, 18 mm, which may have affected a cell's ability to migrate. A common disadvantage of both Ahmed et al.'s (2010) and Mao et al.'s (2003) geometries is the restriction to a one dimensional concentration gradient.

Atencia et al. (2009) used a geometry that allows chemotaxis to be studied in a two-dimensional chemical gradient, within a central chamber, called a microfluidic palette (Fig. 1). Atencia's claimed benefits for the device include not only a 2D gradient, but also a quick equilibrium time. An absence of hydrogels and membranes through which molecules have to diffuse means that even without bulk flow, time to reach steady state is relatively short (Atencia et al., 2009).

Flexibility in the set up is provided by 3 inlet/outlet channels. One source and two sinks allows a gradient to develop in 2D. Source and sink channels are interchangeable to study the effect of a changing concentration gradient on chemotaxis. Although there is scope for more inlets, three provide enough flexibility without over-complication and redundancy. It is possible to have two or three source channels with different chemoeffectors in each, to explore the effect of different combinations across a full range of concentrations. Three inputs are the maximum which allow all combinations of diffusive species to be represented. Flow rates and flow direction in the three channels can be varied independently.

In this paper a numerical model has been developed to find the optimum dimensions of a diffusion chamber for a given application. The effect of the diameter of chamber and inlet width on the time to reach steady state, the flow profile and the shape and range of the concentration gradient have been explored. With a view to fabricating a device for uses in practical experiments, a case study will be provided optimising for short steady state times.

2. Methods

COMSOL Multiphysics 4.3b (COMSOL AB, Stockholm, Sweden) was used to model the chamber, using two physics packages, laminar flow and transport of dilute species. The device was approximated to a 2D system with the following dimensions:

- Radius which varied from 100 μm to 1000 μm.
- Inlet gap a minimum width of 5 μm.
- The maximum ratio between inlet width and radius has been set to 1. As the ratio value increases above 1.7, the inlets overlap each other.

Atencia et al.'s work operated with a typical chamber radius of 750 μm and approximately 500 μm (Atencia et al., 2009).

The following constraints are imposed:

- The fluid is assumed to be water, which is a good approximation of the viscosity and density of many liquid media used in cell growth.
- Two inlets with an input concentration of 0 M and one inlet with an input concentration set to 1 M. It is assumed that the concentration is dilute, so that concentration can be treated as dimensionless.
- The temperature is set to 293.15 K.
- The diffusion coefficient is set to 10^{-9} m^2 s^{-1}, approximately the diffusion coefficient of sugar in water at 293.15 K (Jamshidi-Ghaleh et al., 2004).
- Inlet conditions were fully developed laminar flow.
- Boundary conditions at the wall were no slip and zero pressure at the outlets.
- A physics controlled mesh was chosen, using the preset 'extremely fine' density with a maximum size of 3.76×10^{-5} m.

The Navier–Stokes equations were used for transient flow:

$$\rho\left(\frac{\partial u}{\partial t}+u\cdot\nabla u\right)=-\nabla p+\nabla\cdot[\mu(\nabla u+(\nabla u)^T)] \quad (1)$$

$$\nabla\cdot(\rho u)=0, \quad (2)$$

where ρ is the density, u is the velocity vector and p is the pressure. For steady state simulations the ∂t is suppressed.

The equations used for transport were

$$\frac{\partial c_i}{\partial t}+u\cdot\nabla c_i=\nabla\cdot(D_i\nabla c_i) \quad (3)$$

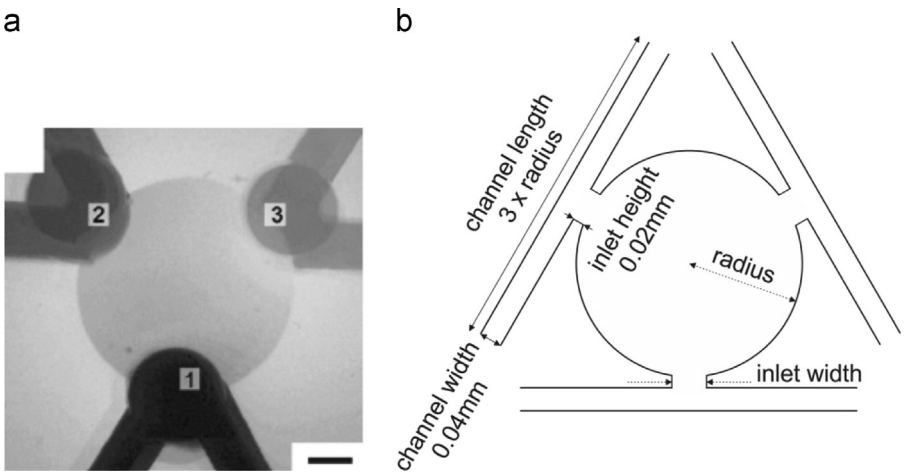

Fig. 1. (a) Atencia et al.'s (2009) working palette, three different coloured dyes, diffuse to create a 2D concentration, and (b) the particular geometry used in this study. Measurements specified with a solid line are fixed for all simulations. Radius and inlet width are adjustable lengths, represented by a dashed line.