

### **Reaction and Diffusion in a Microchannel**

A revolution is occurring in the pharmaceutical industry: the reduction of the chemical laboratory to the micro scale through the development of chip based microlaboratories. In such systems the importation of reactants, buffers, mixing, reactions, separation, and analysis are all done on a microscopic scale leading to tremendous reductions in the volumes of chemicals required for analysis, and in the analysis times. One key application is in the area of pharmaceutical screening, in which pharmaceutical companies test compounds in their drug libraries (sometimes on the order of a million compounds) for activity against newly discovered proteins and enzymes. Such combinatorial screening is often the first step in discovering a drug for treatment of diseases.

In this project we will examine one aspect of the design of a chip-based microlaboratory. Suppose we are interested in determining the activity of drug A against protein B. The first step in such an analysis is to see if A binds with B to form a complex AB - with such a complex usually detected optically via fluorescence microscopy or other techniques. On a macroscale, we would simply take an equal number of moles of A and B, pore them into a beaker, stir them up, and then see what the concentration of AB was as a function of time. In a microlaboratory we do essentially the same thing by bringing a stream containing A together with a stream containing B in a microchannel, and then looking for the product AB. The problem is that we can't just mix the streams together in the microchannel, but rather they must intermix due to diffusion which, for proteins at least, is a very slow process even on a micron scale. Thus it is important to design strategies which allow us to mix (and react) as fast as possible - the object of this project.

The geometry we are considering is depicted below. The stream containing A and that containing B combine in a channel of width  $h$ . Typical microchannels are quite thin relative to their width (around 1:10 aspect ratio), so the transport problem can be regarded as two dimensional to leading order. A second consequence of the very small size and large aspect ratio is that the flow is essentially what is called plug flow: there is very little convective mixing in the flow direction.

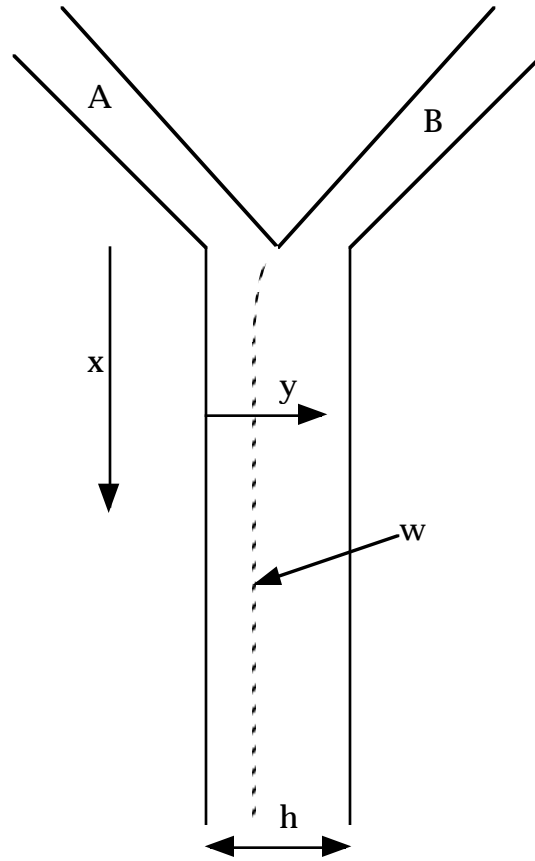
The concentration distributions of each species are governed by the parabolic differential equations:

$$U \frac{\partial c_A}{\partial X} = D_A \frac{\partial^2 c_A}{\partial y^2} + R \quad ; \quad U \frac{\partial c_B}{\partial X} = D_B \frac{\partial^2 c_B}{\partial y^2} + R \quad ; \quad U \frac{\partial c_{AB}}{\partial X} = D_{AB} \frac{\partial^2 c_{AB}}{\partial y^2} - R$$

where  $R$  is the reaction rate given by:

$$R = -k_f c_A c_B + k_r c_{AB}$$

The quantities  $D_A$ ,  $D_B$ , and  $D_{AB}$  are the diffusion coefficients of the three species A, B, and AB, respectively. The quantities  $k_f$  and  $k_r$  are the forward and reverse rate constants.



We can simplify the above equations by introducing dimensionless variables. We shall use as our basis for rendering the equations dimensionless the diffusion rate and concentration of species A. Thus we define:

$$y^* = y/h ; x^* = x/(U h^2 / D_A) ; R^* = R / (k_f \langle c_{A0} \rangle^2)$$

$$c_A^* = c_A / \langle c_{A0} \rangle ; c_B^* = c_B / \langle c_{A0} \rangle ; c_{AB}^* = c_{AB} / \langle c_{A0} \rangle$$

where  $\langle c_{A0} \rangle$  is the average initial concentration ( $x = 0$ ) of reactant A across the channel.

In terms of these dimensionless variables we have the equations:

$$\frac{\partial c_A^*}{\partial x^*} = \frac{\partial^2 c_A^*}{\partial y^{*2}} + Ha^2 R^* ; \frac{\partial c_B^*}{\partial x^*} = \lambda_B \frac{\partial^2 c_B^*}{\partial y^{*2}} + Ha^2 R^* ; \frac{\partial c_{AB}^*}{\partial x^*} = \lambda_{AB} \frac{\partial^2 c_{AB}^*}{\partial y^{*2}} - Ha^2 R^*$$

$$R^* = -c_A^* c_B^* + \frac{1}{K^*} c_{AB}^*$$

where Ha is the Hatta number (the ratio of reaction to diffusion) defined as:

$$Ha = \left[ \frac{k_f \langle c_{A0} \rangle h^2}{D_A} \right]^{1/2}$$

The other dimensionless parameters which appear in these equations are the diffusivity ratios:

$$\lambda_B = D_B / D_A ; \lambda_{AB} = D_{AB} / D_A$$

and the dimensionless equilibrium constant  $K^*$ :

$$K^* = \frac{k_f \langle c_{A0} \rangle}{k_r}$$

We also have the dimensionless boundary conditions at  $y^* = 0, 1$ :

$$\left. \frac{\partial c_A^*}{\partial y^*} \right|_{y^*=0,1} = \left. \frac{\partial c_B^*}{\partial y^*} \right|_{y^*=0,1} = \left. \frac{\partial c_{AB}^*}{\partial y^*} \right|_{y^*=0,1} = 0$$

We'll get to the initial conditions ( $x^* = 0$ ) in a bit.

Far down the channel diffusion will cause the concentrations of all of the species to be uniform, and their relative concentrations will be determined by the reaction equilibrium  $R^* = 0$ . This leads to the equilibrium relationship:

$$c_{AB}^* = K^* c_A^* c_B^*$$

Combining this relation with stoichiometry (and assuming that  $c_{AB} = 0$  at  $x = 0$ ) yields the equilibrium concentration of  $\langle c_{AB}^* \rangle_{eq}$ :

$$\langle c_{AB}^* \rangle_{eq} = \frac{1 + \langle c_{B0}^* \rangle}{2} + \frac{1}{2 K^*} - \sqrt{\left( \frac{1 + \langle c_{B0}^* \rangle}{2} + \frac{1}{2 K^*} \right)^2 - \langle c_{B0}^* \rangle}$$

which is in terms of the ratio  $\langle c_{B0}^* \rangle$  of the average initial concentration of B to that of A, yet another dimensionless parameter which appears in the problem.

All of this brings us to the problem we want to solve: What initial distributions of the two streams gives rise to the most rapid (shortest  $x^*$ ) reaction of A and B? For a fixed  $\langle c_{B0}^* \rangle$  the two streams can be introduced such that:

$$c_A^* \Big|_{x^*=0} = \begin{cases} 1/w^* & 0 < y^* < w^* \\ 0 & w^* < y^* < 1 \end{cases} ; \quad c_B^* \Big|_{x^*=0} = \begin{cases} 0 & 0 < y^* < w^* \\ \frac{\langle c_{B0}^* \rangle}{1-w^*} & w^* < y^* < 1 \end{cases}$$

This basically corresponds to (for  $w^*$  small) a thin, concentrated stream of A of width  $w^*$  and a wide, dilute stream of B of width  $(1-w^*)$ , or (for  $w^*$  approaching 1), the reverse.

We may define as a metric the ratio  $\langle c_{AB}^* \rangle / \langle c_{AB}^* \rangle_{eq}$  (the fraction of approach to equilibrium) and determine the distance  $x^*$  at which this ratio reaches, say, 80%. The question then becomes for what value of  $w^*$  does this distance approach a minimum.

In order to solve this problem, we have to choose values for the various dimensionless parameters. Typically, A might be a low molecular weight drug and B might be a much larger protein or enzyme. Thus we shall take the diffusivity ratios to be:

$$\lambda_B = 0.1 \ ; \ \lambda_{AB} = 0.1$$

We take the equilibrium constant to be  $K^* = 100$ , such that most of A and B complex to AB (about 90% or so). We also take  $\langle c_{B0}^* \rangle = 1$ , a stoichiometric ratio of B to A. The Hatta number is also fairly large, even for microchannels. We shall take  $Ha = 10$ .

Using all of these parameters, write a code which solves for the concentration distribution as a function of  $x^*$  and  $y^*$  for different values of the initial distribution parameterized by  $w^*$ . Determine, based on your numerical results, what strategy we should use for picking an optimal  $w^*$ , e.g., whether  $w^*$  should be close to zero, close to one, or around 0.5.

#### **What to do:**

- 1). You need to turn the PDE's into systems of ODE's in the x-direction. This is easily accomplished by discretizing the domain in the y direction, and then tracking the evolution of the concentrations at each y as a function of x. Thus, you need to write a function which returns the x-derivatives of the concentrations for all of these y locations as arrays.
- 2). Couple this function with an integration routine to obtain the concentration distribution over y as a function of x (e.g., evolution down the channel).
- 3). Calculate the average dimensionless concentration of AB,  $\langle c_{AB}^* \rangle$ , across the channel, and determine the value of  $x^*$  for which it reaches 80% of the equilibrium value.
- 4). Repeat this for different values of  $w^*$ , generating a plot of this distance as a function of  $w^*$ . Based on these results, suggest an optimum strategy for getting rapid mixing and reaction of two species with significantly different diffusivities.

#### **What to turn in:**

- 1). Your program, which should be well commented and readable.
- 2). Studies of the concentration profile contours for each species as a function of x and y (the contour plot works well here) for  $w^* = 0.2, 0.5, \text{ and } 0.8$ . Also include a plot of the approach to equilibrium  $\langle c_{AB}^* \rangle / \langle c_{AB}^* \rangle_{eq}$  as a function of  $x^*$  for each of these values of  $w^*$  (put these on the same plot).
- 3). A graph of the distance at which  $\langle c_{AB}^* \rangle / \langle c_{AB}^* \rangle_{eq} = 0.8$  as a function of  $w^*$ , and your conclusions regarding the optimum design strategy. You should determine the possible degree of improvement (e.g., decrease in required channel length) of the optimal strategy vs. a uniform introduction of the two streams ( $w^* = .5$ ).

## Final Project Evaluation Criteria:

The final project will be evaluated according to the following criteria:

10 points: Were you able to discretize the domain properly and write a function which determined the derivatives?

10 points: Did you deal with the spatial boundary conditions at  $y^* = 0$  and 1 properly?

10 points: Were you able to develop contour plots of the concentration for the different specified values of  $w^*$ ?

10 points: Could you determine the distance at which the reaction approached 80% of equilibrium?

10 points: Did you come up with the optimal design strategy?

20 points: Quality of your algorithms. Did you integrate the concentrations as vectors rather than sequentially? Does your program automatically determine the step size in the  $x$  direction as a function of the spatial discretization in the  $y$  direction? Did you determine the average concentration across the channel in an efficient and accurate manner? Was the value of  $x^*$  at which concentration approached 80% of equilibrium determined in an accurate manner? Is your program robust to changing parameters: could you easily change the values of the dimensionless parameters without having to extensively rewrite your program? Would the integration process remain stable? This is not an exclusive list, just some of the ideas to consider in writing a high quality program.

20 points: Clarity of programming. Did you make effective use of functions, or did you try to cram everything into the main script? Did you use the global command in a restrained manner (remember that the global command is a meat axe - while it is extremely useful, it should also only be used when it significantly simplifies the program)? Is your program easy for us to follow? Is it well commented? Often you will have to pass your programs on to someone continuing your project in the future. If it is not clear and well commented, a program is useless to others and loses much of its value.

10 points: Clarity of presentation of graphical results (e.g., labelled axes & graphs, legend, title, etc.)

I hope that these criteria will make it easier for you to prepare the final versions of your program. Remember, do not discuss this with classmates until after 6:00PM on Thursday! You may talk to me or the TA's, however. Good Luck!