20.430/6.561/10.539/2.795
Fields, Forces, and Flows in Biological Systems
Fall 2015

Problem Set # 2 (Chemical Sub-System)

Issued: Friday 9/25/15
Due: Friday 10/02/15 at 5pm

Problem Sets should be turned in to the 20.430 FFF drop-off boxes, located to the right of the elevators on the 2nd floor of Building 16. Please turn Problem 1 into Box 1, and Problem 2 into Box 2.

Reading Assignment – Chapter 1.4-1.7 from FFF by AJ Grodzinsky

Problem 1: The time constant for equilibration of $c_1(t)$ and $c_2(t)$ across the tissue.

In the figure below, we generally assume that the concentration of the two baths, c_1 and c_2, are constants independent of time. In reality, if we wait long enough, and assume the tissue section is small compared to the baths, the concentrations will equilibrate such that $c_1 = c_2 = \frac{c_1(t=0)+c_2(t=0)}{2}$. This problem asks you to find an expression for the "chamber equilibration" time constant.

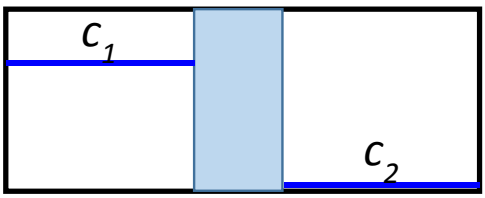


Fig. 1A

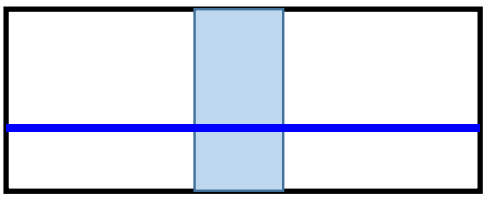


Fig. 1B

a) Assume that c_1 and c_2 are uniform within each respective bath compartment for all time (i.e., the compartments are well stirred) and that initially, $c_1 \neq c_2$ (Fig. 1A). Assume that the left and right chamber volumes are much greater than that of the tissue. Thus, after a sufficient time has passed that a linear concentration profile from left to right exists within the tissue, c_2 will not have increased much during this intra-tissue equilibration process. At this time-point, find an expression for the solute flux across the tissue in terms of c_1, c_2, L, and D.

(Assume that the partition coefficient K = 1; the right- and left-hand-side chambers both have volume V, and that the area of the membrane/tissue is A)

b) Using conservation of mass, derive a differential equation for the time rate of change of the average bath concentration $c_1(t)$ as solute moves from left to right across the tissue.

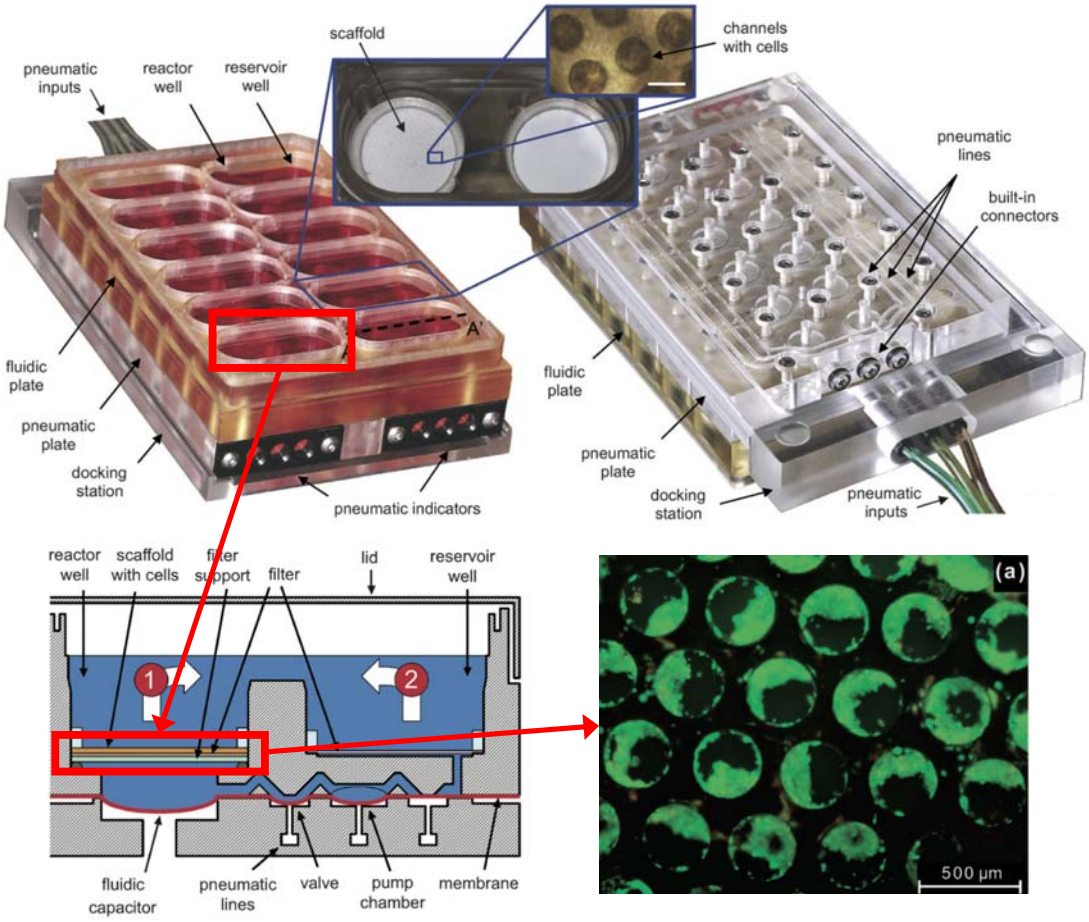
c) Find the solution to the preceding differential equation (it should consist of a simple exponential decay), and show that your solution satisfies the expected infinite-time response $c_1(t \to \infty) = \frac{c_1(t=0) + c_2(t=0)}{2}$ (as drawn in Fig. 1B) assuming that the intervening membrane/tissue has negligible thickness.

d) Compare your chamber exponential decay time constant from part (c) to the characteristic diffusion time for a solute moving across a the tissue length L, $\tau_{diff} = L^2 / (\pi^2 D)$. State the conditions under which the assumption of a "steady-state" linear concentration profile is valid.

e) Based on your answer to Problem 4, part (b) of PSet 1, find an analytical expression for the flux of solute evaluated at the right-hand edge of the tissue, $x = L$, at any time t during the initial transient diffusion process across the tissue (i.e., for times much less than the total chamber decay time of part (c) above). By integrating the flux with respect to time, t, find the total amount of solute that has moved across the tissue into the right-hand chamber after time t. (If you divide by the volume, V, of the right-hand chamber, you'll have an expression for the concentration $c_2(t)$. While $c_2(t)$ may be small enough to approximate as zero for the purposes of solving PSet1 Problem 4, $c_2(t)$ can still be measured quantitatively, i.e., using radiotracers or fluorescently tagged solutes.)

f) As $t \to \infty$, the graph of $c_2(t)$ versus time approaches a straight line as a function of t. Find the extrapolated intercept of the line on the t-axis, and **<u>show that</u>** this time-intercept is related to the solute diffusivity, D, by the value $\boldsymbol{L^2/6D}$.

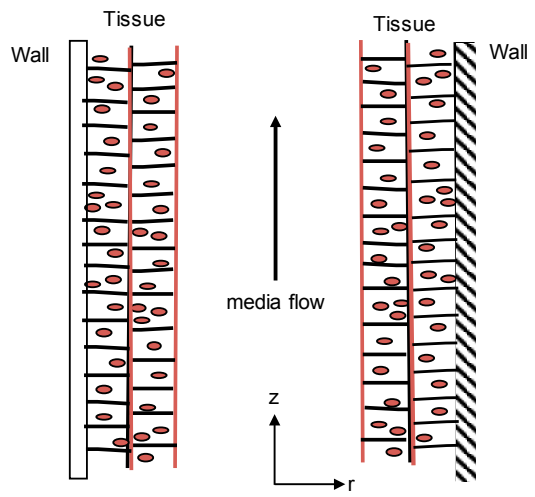
Problem 2: Analysis of a bioreactor



Adapted from Domansky et al. *Lab on a Chip* 2009.

Traditional 2D culture of cells *in vitro* places cells on a hard plastic surface covered by nutritional media. This system in many cases does not accurately represent the physiological environment, and therefore many non-cancerous cell types do not survive or proliferate in these conditions. For example, one of the most difficult-to-culture cell types is hepatocytes, the primary functional cells of the liver. Hepatocytes, while demonstrating extraordinary regenerative capacity in vivo, fail to maintain function and survival beyond 1 week in 2D culture. The LiverChip bioreactor seeks to overcome this issue through the use of perfused 3D culture. In this reactor (see above), media is continually pumped through a scaffold in which hepatocytes rest in cylindrical wells. This setup allows several benefits: 1) Higher amount of tissue aggregation, and hence better autocrine and paracrine signaling, 2) Modifiable scaffold properties to facilitate attachment and tissue formation, and 3) Increased oxygen delivery to the cells.

Consider a simplified single-channel system, where hepatocytes are attached to the walls of a cylinder, and flow is traveling through the center:



Assume our flow allows an approximately constant oxygen concentration $[O_2]_0$ at the tissue-media boundary in the z-direction. Inside the tissue, assume that oxygen is irreversibly consumed and described by a first-order rate constant k_o. Also assume that oxygen travels through the tissue only via diffusion, and that the length of the channel is long compared to its diameter.

a) Inside the tissue, apply a mass balance of oxygen within a thin cylindrical shell, ignoring edge effects. Let the thickness of the shell approach zero, and show that this result yields Fick's Second Law with reaction – please state your assumptions.

b) Apply boundary conditions that you deem reasonable and explain qualitatively the result that you expect. Do not solve the equation. To gain quantitative insight into the solution, we want to consider switching to a different reference frame. Recast the system in Cartesian coordinates (including modified boundary conditions), and solve for the explicit steady-state solution. It may help to non-dimensionalize your variables.

c) What is the expression for the Damköhler number (Da) in this system? Plot your solution using values of Da = 100, Da = 1, Da = 0.01 and contrast the behaviors. Explain the competing processes, what aspects of the system determine the value of Da, and how this informs the parameters you would use to design the channel.

d) From a literature search, you estimate the following constants: Diffusion through tissue = $2 \times 10^{-5} cm^2/s$, hepatocyte oxygen consumption rate constant = 0.25/s, blood oxygen concentration=0.13mM. Additionally, we estimate that under conditions where the oxygen concentration drops to about $[O_2]_0/4$, cells become hypoxic and die off. With

this constraint, estimate the maximum tissue thickness that can be obtained in this system in μm. Replot your solution with these numbers and compare with part (c).

e) In reality, what other factors do you need to consider? Note that the length of the channel is typically 200um, and the diameter is 250um. How does this geometry affect the system? It is observed experimentally that in certain areas of the cell wells, the cell layer thickness on the walls is both uneven and much thinner than our estimate calculated in part (d). Discuss what factors could lead to this non-uniformity.

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