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

Problem Set # 5 (Electrochemical Coupling) **Issued: Monday 10/19/15**
Due: Monday, 5pm – 10/26/15

Reading Assignment: Textbook, sections in **Chapter 3**: Sections 3.1 and 3.4

Turn in Problem set in dropbox to the right of elevators on the 2nd floor of Building 16. Please turn in Problems 1 & 2 into Box 1 and 3 into Box 2.

Problem 1: Centric Dipole Model of the Heart: A Simple Model for Electrocardiography

Do Problem 2.4 in the text, page 66-67 Parts (a)-(c), as well as additional part (d) below.

Hints:
(i) Along the way, you'll want to compare the "current dipole" derived in this problem with the "charge dipole" of Example 2.5.1 on page 50.

(ii) Check out Appendix Table B.7, page 297, which lists all the solutions to Laplace's Eqn. in spherical coordinates that you will need to consider: the first term corresponds to the potential of a uniform field; the second term corresponds to the potential of a dipole; the third term is the potential of a point charge; and last is a constant. In this problem, you'll make the analogy from point charges to point current sources, but the form of the Laplacian solutions should be the same.)

(iii) For all parts (a)-(c) of the problem, you can assume that all the "point current" and "dipole current" sources are steady state. (This limit is equivalent to the assumption that *the charge relaxation time is very fast; i.e., almost instantaneous for the slow heart rate of interest*.)

(iv) For part (b), it will be helpful to recognize that for small values of x, the Taylor Series expansions of the following functions are:

$$\sqrt{1+x} \approx 1 + \frac{x}{2}$$

$$\frac{1}{1-x} \approx 1 + x$$

(d) At the end of part (c), argue that your solutions are correct for the case in which the heart beats at ~1 Hz (i.e., it is NOT steady). You will need to estimate charge relaxation time constants and compare to characteristic times of interest.

Problem 2: Electrical conductivity as a measure of charge density and of the isoelectric point of the material (Modified Problem 3.11 in the Text)

(a) Modified Part (a): Write an expression for the electrical conductivity σ inside the RNase plug in terms of the concentrations and ionic mobilities of Na+ and Cl- inside the RNase plug.

(b) Skip part (b) of the problem in the Text.

(c) Do part (c) as in the Text.

Problem 3: Donnan Equilibrium of positively charged drug delivered in culture medium to cells cultured in negatively charged Matrigel

Here we refer to a paper published in *Nature* to motivate the concept of Donnan partitioning of charged drugs into charged extracellular matrix. In this case, cells are in 3D culture in "Matrigel," which consists of a dense population of extracellular matrix proteins including highly negatively charged heparan sulfate proteoglycans (which we mentioned previously in lecture). **Your objective is to add a drug to the culture medium which prevents these cells from producing amyloid proteins associated with Alzheimer's disease.** (***This was not done in the paper, but here's your chance to extend their results.***)

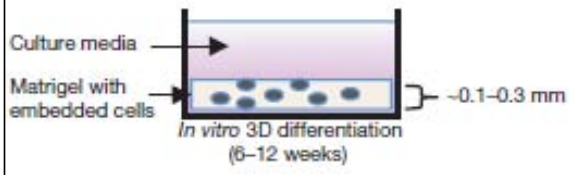
LETTER

Nature, 10/12/2014

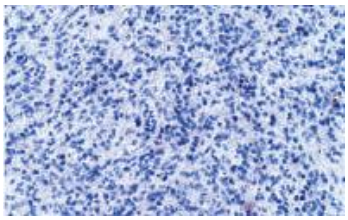
doi:10.1038/nature13800

A three-dimensional human neural cell culture model of Alzheimer's disease

Se Hoon Choi[1]*, Young Hye Kim[1,2]*, Matthias Hebisch[1,3], Christopher Sliwinski[1], Seungkyu Lee[4], Carla D'Avanzo[1], Hechao Chen[1], Basavaraj Hooli[1], Caroline Asselin[1], Julien Muffat[5], Justin B. Klee[1], Can Zhang[1], Brian J. Wainger[4], Michael Peitz[3], Dora M. Kovacs[1], Clifford J. Woolf[4], Steven L. Wagner[6], Rudolph E. Tanzi[1] & Doo Yeon Kim[1]



Matrigel contains many extracellular matrix proteins including highly negatively charged heparan sulfate proteoglycans….

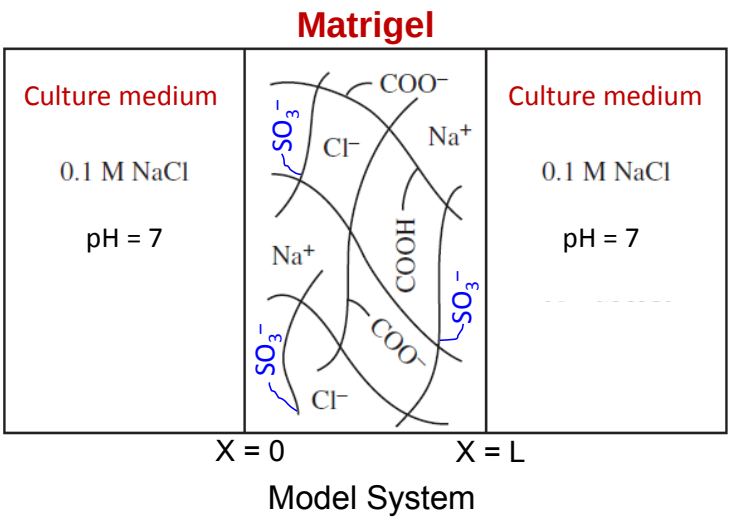


Immunohistochemistry shows amyloid protein deposits in this 3D cell culture system

Source: Choi, Se Hoon et al. "A three-dimensional human neural cell culture model of Alzheimer/'s disease." Nature 515, no. 7526 (2014): 274-278.

Background from paper: Human neural progenitor cells (hNPCs) that can produce high levels of toxic amyloid-β proteins were cultured in 3D Matrigel. In their new Nature paper (above, the authors state, "In conventional 2D cultures, secreted amyloid-β diffuses into a large volume of media (and thereby are lost). We hypothesized that a 3D culture would accelerate amyloid-β *deposition* by limiting diffusion of amyloid-β out of the gel, allowing for aggregation near the cells. We chose BD Matrigel (BD Biosciences) as a 3D support matrix since it contains high levels of brain extracellular matrix proteins."

For the purposes of this problem, you can forget about the relatively small population of cells, and model the gel as a matrix having fixed charge density ρ_m, which is highly negative due to the sulfate and carboxyl groups of the matrix proteoglycans and glycoproteins: see the Figure below:



Model System

Assume that the gel and fixed charge density are uniform, and that the culture medium is a simple bath having concentration C_o = 0.1M NaCl at pH 7 (for simplicity). The bath has a volume that is much, much greater than that of the gel. You now add your positively charged drug to the medium at a concentration of 10 nM, and let the system come to complete equilibrium. (In equilibrium, the concentration of all species inside the gel is assumed here to be spatially uniform)

(a) Write an expression for electroneutrality inside the gel. (Include all relevant solute species of interest including the drug concentration, C_d. (Hint: see equation 3.99 in the text)

(b) Write an expression that describes the Boltzmann partitioning of each species into the gel (Hint: see equation 3.100 in the text)

(c) Find an expression for the Na+ concentration inside the gel phase in terms of C_o and gel charge density ρ_m. NOTE: In general, this can be a difficult and tedious problem; however, if you

make judicious engineering approximations considering the relative values of the various ion and drug concentrations involved, the solution will be mathematically much simpler!

(d) While you only used 10 nM drug concentration in the bath (to simulate using a very low drug concentration that would minimize systemic side effects), you would like to achieve much higher drug concentration inside the gel, where the cells would be. You therefore make the drug highly positively charged, having valence +Z. Find an expression for the drug concentration inside the gel in terms of the drug bath concentration, and the concentration of Na+ inside the gel and in the bath.

(e) Now find an expression for the valence of the drug, Z, in terms of the concentrations of drug and Na+ ions inside the gel and the bath.

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