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**BE.430/2.795//6.561/10.539/HST.544**

**Final Exam**

**Handed out: Monday, Dec. 6, 2004**

**Due: Thursday, Dec. 9 by 5pm**

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## **Problem 1 (30 %)**

ALG Notes Problem 2.6.3 – Parts a – f (not g) (Page 199)

## **Problem 2 (35 %)**

When patients are on hemodialysis therapy for enhancement of subpar renal function, their blood must be treated with the anticoagulant heparin so that potential problems with clotting within the dialysis device can be minimized. However, the heparin concentration in the blood returned to the patient must be carefully controlled in order to diminish the risk of bleeding. One approach to accomplishing this is use of an enzyme reactor, in which porous spherical beads whose channels throughout are coated with heparinase. The beads are packed tightly into a cylindrical vessel, through which the blood flows; the fluid flow may be considered to be governed by the Darcy Equation, so that the flow velocity profile is uniform across the radial cross-section of the reactor and is proportional to the pressure drop across the axial dimension of the reactor. The rate of transport of heparin from the flowing blood to the beads is governed by a convective mass transport coefficient, with the heparin concentration driving force being the difference between its local concentration in the fluid and its concentration at the bead surface. From the surface, heparin diffuses into the bead and undergoes irreversible degradative reaction (governed by Michaelis-Menten enzyme/substrate kinetics) due to the activity of the heparinase coating the interior pore channels.

The objective for use of this enzyme reactor is to reduce the concentration of heparin in the outlet to below a specified critical level, so we need to determine key parameters for its proper design.

- a. Develop a comprehensive set of model equations for this situation, which can be employed to determine the heparin concentration at the reactor outlet as a function of all other system parameters, including: heparin concentration at the reactor inlet, blood flow rate, heparin diffusion coefficient (assume it is the same in both the bulk blood fluid and the bead pore channel fluid).
- b. Explain justifications for making the following simplifications in the problem: [i] restriction to analysis of steady-state operation; [ii] neglect of radial heparin concentration gradients; [iii] assumption of 1<sup>st</sup>-order heparinase/heparin reaction within the beads.

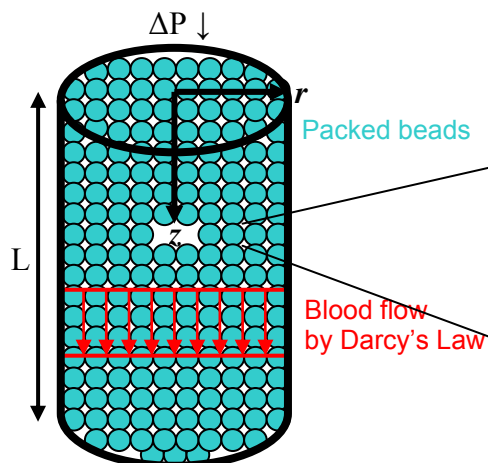
- c. Elucidate parameter relationships under which axial diffusion of heparin within the bulk blood fluid can be neglected relative to the convective flow.
- d. Ascertain an expression for the outlet heparin concentration as a function of the blood flow velocity through the reactor.
- e. Repeat part d under conditions that heparin diffusion within the bulk blood fluid cannot be neglected relative to the convective flow.
- f. Plot the dependence of outlet heparin concentration on fluid flow rate numerically for the following set of parameter values: inlet heparin concentration =  $10^{-3}$  M; volumetric flow rate range =  $10^{-4}$  to  $10^2$  ml/min; column radius = 3 cm; column length = 10 cm; bead radius = 500 microns; heparin diffusion coefficient =  $3 \times 10^{-7}$  cm<sup>2</sup>/sec; Darcy permeability =  $10^{-11}$  m<sup>2</sup>;  $V_{\max} E_T = 10^{-6}$  M/sec;  $K_M = 10^{-3}$  M. Also determine the pressure drop needed to obtain the blood flow velocity range prescribed. (You are requested to do this calculation for the low and high extreme volumetric flow rate volumes; the number of intermediate flow rates for which you might also do the calculation is optional.)

For the convective mass transfer coefficient characterizing heparin transport from the bulk fluid to the bead surfaces, you may use an appropriate Sherwood number expression from the literature (if you do, please describe your source and justify its validity); if you cannot find one, you are welcome to use the following expression as discussed in class lecture:

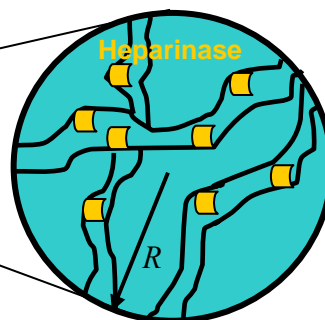
$$Sh = \frac{hR}{D} = 2 + Pe^{0.33}$$

where R is the bead radius.

**Cylindrical Enzyme Reactor**



**Heparinase coated, porous spherical bead**



### Problem 3 (35 %)

The diagnostic microfluidics chip shown schematically in the Figure below models vascular endothelial cell lining of a blood vessel, in which the cells are exposed to both physiologic fluid shear and to the introduction of the inflammatory agent, TNF- $\alpha$ . These chemical and mechanical stimuli, in vivo, can induce cellular production of a variety of cytokines, chemokines, and proteinases, thereby simulating inflammation at an infection in a local tissue site.

In the diagnostic chip, the TNF- $\alpha$  is introduced at the inlet port in the channel behind the cell layer and diffuses across a semi-permeable membrane to the cells at the channel wall, mimicking production of this inflammatory cytokine at a local infection site in peripheral tissue (e.g., skin).

TNF- $\alpha$  and fluid shear both trigger the recipient endothelial cells (ECs) to secrete proteins into the “bloodstream” channel as part of the next step of the inflammatory cascade, and the chip is designed to measure the concentration and identity of the EC-secreted protein factors as a function of time.

#### **Chip Configuration:**

The TNF- $\alpha$  is injected via electroosmotic fluid flow, by means of the applied voltage  $V_2$ . The stimulated cells secrete proteins into the “bloodstream” microfluidics channel, which is flowing at physiologic velocity induced by the applied pressure drop ( $P_1 - P_0$ ). Channel depths in the  $z$ -direction are very large compared to  $L_2$  and  $L_3$ . *Therefore, assume that the fields and flows do not vary with  $z$ .*

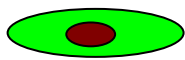
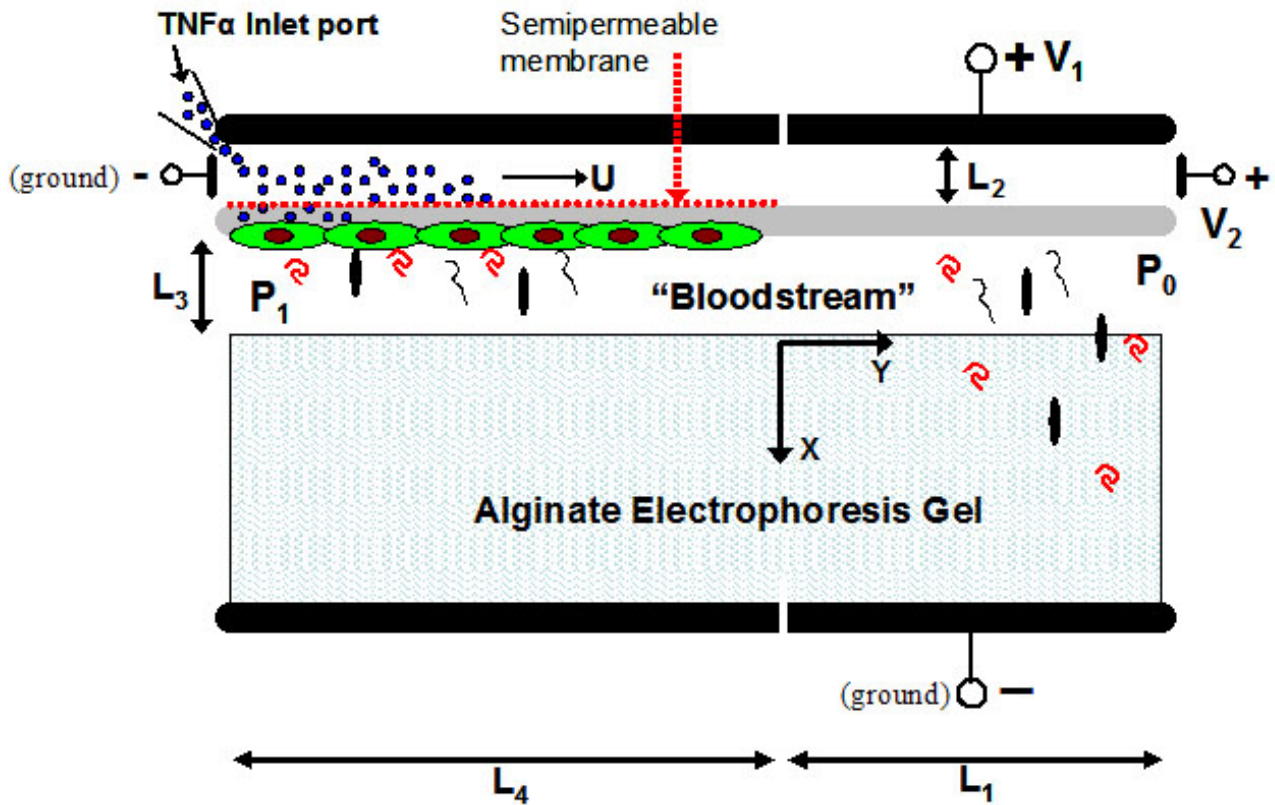
An alginate gel used for electrophoresis forms the opposite wall of the “blood vessel.” As the secreted proteins are convected to the right, they can enter the gel due to the positive voltage  $V_1$  and the associated E-field in the  $x$ -direction within the gel. The pI (isoelectric pH's) of two secreted proteins of interest are interleukin-6, IL-6, (pI = 8.7) and matrix metalloproteinase-1, MMP-1, (pI = 5.2); it is hoped that in-line electrophoresis can be used to separate and collect them at the channel bottom. Various additional in-line assays are used to determine the quantity and identity of the proteins. All channel fluids are buffered at pH = 7.2. (Assume that TNF- $\alpha$  is neutral at pH 7.2)

(a) The surface charge density,  $\sigma_s$ , on all the walls of the TNF inlet channel is negative. Channel width

$$L_2 = 100 \mu\text{m}.$$

- (i) Find the sign of the voltage  $V_2$  needed to induce electroosmotic flow to the right.
- (ii) Find an analytical expression and sketch the fluid velocity profile within the “TNF channel”, and find the mean velocity  $U$  as a function of fluid viscosity, dielectric permittivity, surface charge density, and other necessary parameters.
- (b) Find an expression and sketch the fluid velocity profile within the “bloodstream” channel caused by the applied pressure drop. Find an expression for the fluid shear stress acting on the cell layer.
- (c) Write the flux and continuity transport equations for the  $i^{\text{th}}$  protein species within the bloodstream channel. Include all sources of flux. Assume that diffusion in the x-direction, but *not* the y-direction, is important. Also, assume for now that the proteins do not bind to anything. State appropriate boundary conditions at  $x = 0$  and  $x = -L_3$ . (DO NOT SOLVE the EQNS.)
- (d) Derive an expression for the effective dimensionless Peclet number describing protein transport in the bloodstream channel (i.e., the dimensionless ratio of non-diffusive to diffusive transport, but including all contributions to non-diffusive transport). Represent the effective Peclet number as a ratio of characteristic time constants.
- (e) Do both IL-6 and MMP-1 make it into the gel region for analysis?
- (f) Write the flux and continuity transport equations for the transport of the  $i^{\text{th}}$  protein species within the gel region. Include all sources of flux. (Neglect binding; DO NOT SOLVE the EQNS.)
- (g) IL-6 produced by ECs in response to TNF- $\alpha$  can re-bind to the endothelium in an autocrine manner.
- Using the additional data given below, recast the transport equations and boundary conditions of parts (c) and (e) to account for IL-6 binding to endothelial cells as it is transported along the channel. (DO NOT SOLVE the EQNS.)

$K_D$ of IL-6 binding to IL-6 heterodimer receptor:	2.25 nM
$k_{\text{on}}$	$0.013 \text{ nM}^{-1} \text{ min}^{-1}$
$k_{\text{off}}$	$0.029 \text{ min}^{-1}$
number of receptors per endothelial cell:	400



= EC = endothelial cell



= inflammatory agent (TNF- $\alpha$  molecules; 17.5 kDa)



= secreted cytokines, chemokines, and proteinases, including IL-6 and MMP-1

where  $L_4$  = length of cell channel

$L_1$  = length of electrophoresis channel section,

$L_3$  = Bloodstream channel width

$L_2$  = TNF channel width

**Note:**  $L_1 \gg L_4$  (not drawn to scale)

$L_1, L_4$  are both  $\gg L_3$  and  $L_2$  (Channels are very narrow compared to length)