PART V

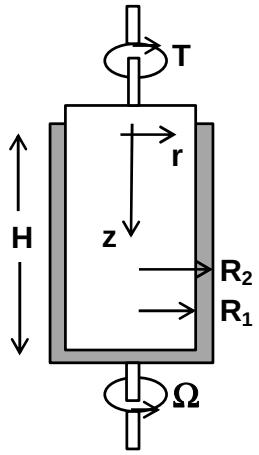
CHAPTER 13

Problem 13-1: Planar Shearing Flow

(a) Starting from Navier-Stokes and continuity equations, derive the fully developed, steady laminar velocity profile (Eq. 13-2-3) for an incompressible Newtonian fluid flow between parallel plates as shown in Fig. 13.2-1. Note that the plate is open at both ends to the atmosphere.
(b) Develop an expression for the x-component of the force F exerted on the bottom plate. The total surface area (x-z plane) of the bottom plate is S.

Problem 13-2: Couette Viscometer

As mentioned in section 12.2 of the book, a simple shearing flow can be produced by placing a fluid in the radial gap between two vertical concentric cylinders. The outer cylinder of radius R_2 spins at a rotation rate Ω[rad/s] in order to produce a shear rate $\gamma_{\theta r}$ [s^{-1}] on the fluid in the gap. The resulting torque T[N-m] is measured on the inner cylinder of radius R_1 that is stationary. The liquid column filling the gap has a height H.



Analyze an incompressible Newtonian fluid in this viscometer using a cylindrical coordinate system. The z axis coincides with the axis of the inner cylinder and points downward from the top of the liquid column. The r axis is perpendicular to the cylinder walls. In a steady laminar shearing flow, u_θ is the only non-zero velocity component. In addition, the kinematics are independent of θ when the flow is axisymmetric flow.

$$u_\theta = u_\theta(r,z),\ u_r = u_z = 0\ ,\ \mathcal{P} = \mathcal{P}(r,z)$$

(a) Given these kinematics, reduce the r, θ and z components of the Navier-Stokes equation.
(b) Integrating the r and z components of the Navier-Stokes equation, determine how pressure P

depends on z. At the fluid surface where z=0, P is equal to atmospheric pressure P_{atm}. Recall that modified pressure is defined as $\mathcal{P} \equiv P + \rho\varphi$ and $-\nabla\varphi = \mathcal{G}$. In this problem, the gravitational vector $\mathcal{G}$ points downward in the positive z direction so that its radial component is zero ($\mathcal{G}_r = 0$) and its axial component is equal to its magnitude.

(c) Express the θ component of the Navier-Stokes equation in dimensionless form. Apply an order-of-magnitude analysis to justify the approximation:

$$\frac{\partial}{\partial r}\left(\frac{1}{r}\frac{\partial(ru_\theta)}{\partial r}\right) = 0$$

(d) State the necessary boundary conditions and apply them to the solution of this equation for $u_\theta(r)$.

(e) From the velocity distribution, determine the nine components of the deviatoric stress tensor, $\boldsymbol{\tau}$. The only non-zero components should be $\tau_{r\theta}$ and $\tau_{\theta r}$.

(f) Explain the following equation fot total torque on the inner cylinder.

$$T = \int_0^H \int_0^{2\pi} R_1 \left[\tau_{\theta r} r\right]_{r=R_1} d\theta dz$$

(g) Describe how you would use T-Ω data to determine the unknown viscosity of a Newtonian fluid. Assume that a fluid standard (*i.e.*, a fluid of known viscosity) is available.

Problem 13-3: Shear Stress in Blood Vessels (courtesy of John Tarbell)

(a) The definition of flow rate in a cylindrical tube is

$$Q = \int_0^0 \int_0^{2\pi} ru_z d\theta dr \qquad (1)$$

Assuming radial symmetry, relate Q to du_z/dr (Hint: use integration by parts). Then, show that the following equation is valid for Newtonian as well as non-Newtonian fluids in a fully-developed, steady, laminar flow.

$$Q = -\frac{2\pi a^3}{\tau_w^3}\int_0^{\tau_w} \gamma\tau^2 d\tau \qquad (2)$$

Here, τ_w is the shear stress at the tube wall, and $\tau \equiv \tau_{zr}$ and $\gamma \equiv \gamma_{zr}$ are the shear stress and corresponding deformation rate component within the fluid. Use the general force balance between wall shear stress and pressure drop (Eq. 13.4-12).

(b) By utilizing the rheological equation for a Casson fluid in a simple shearing flow (Eq. 13.2-16b), eliminate γ from Eq. (2) and integrate to find Q in terms of τ_w. Note the sign of γ and

that the shear stress is at a minimum at the tube centerline.

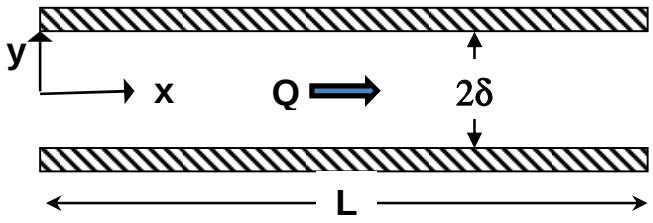
(c) Compute τ_w rate in the four regions of the circulation listed below when blood is modeled as a Casson fluid with μ_∞=0.005 Pa-sec and τ_0=0.004 Pa. Repeat these computations for a Newtonian fluid whose viscosity is 0.005 Pa-sec. What is the effect of the yield stress τ_0 on the results?

Region	Tube Radius (cm)	Average Velocity (cm/sec)
Ascending Aorta(AA)	0.75	20
Femoral Artery(FA)	0.20	10
Arteriole(A)	0.0025	0.75
Capillary(C)	0.0003	0.07

Problem 13-4: Channel Flow

A parallel plate flow chamber with a thin gap δ compared to its width W and length L can be used in *in vitro* experiments to study the effects of shear stress on a cell monolayer. Cells are cultured on the bottom plate and a pressure driven steady flow of nutrient medium over the cells is established in the chamber. Beginning with the Navier-Stokes equation, develop a relationship for the velocity profile and the wall shear stress experienced by the cells in terms of the volumetric flow rate Q and viscosity μ of the nutrient medium and the geometric dimensions of the channel. Assuming fully-developed laminar flow, the kinematics nutrient medium are:

$$u_x = u_x(x,y); \quad u_y = u_z = 0; \quad \mathcal{P} = \mathcal{P}(x,y)$$



Problem 13-5: Flow of a Bingham Plastic Fluid Through a Tube

A Bingham fluid has an apparent viscosity with that incorporates a yield stress τ_o at low shear rates and viscosity μ_∞ at high shear rates.

$$\mu_{app} = \mu_\infty + \tau_o / 2\gamma_{app}$$

(a) Write the relationship between shear stress $\tau \equiv \tau_{rz}$ and shear rate $\gamma \equiv (1/2)du_z/dr$ for a Bingham fluid in steady-state, fully-developed, laminar flow through a circular tube.

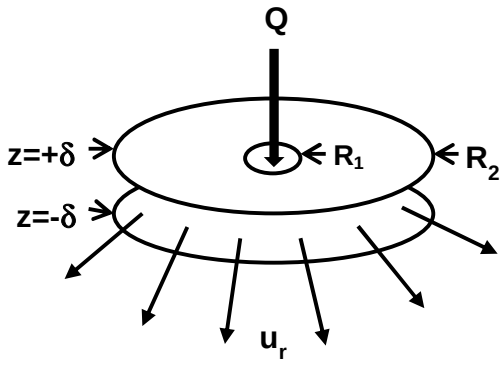
(b) Solve the equation of motion for the velocity distribution $u_z(r)$ of this fluid.

(c) Integrate the velocity distribution to obtain the volumetric flow rate Q_{Bing}. What does this equation indicate about the size of the applied pressure gradient, $\Delta\mathcal{P}/L$, relative to the yield stress τ_o?

(d) Find the ratio of Q_{Bing} to Q_{Newt} for a Newtonian fluid with viscosity $\mu = \mu_\infty$. What is the effect of the yield stress on the flow?

CHAPTER 14

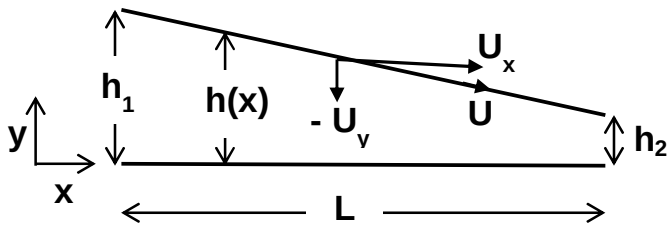
Problem 14-1: Radial Creeping Flow



A disadvantage of a rectangular flow channel design is that it can only subject a cell monolayer to one wall shear stress for a single flow rate (problem 13.4). To overcome this, a design consisting of two parallel circular disks can be used. The fluid enters with a volumetric flow rate Q at the center core with a radius of R_1. It exits at a radial position denoted by R_2. We will assume that the fluid is in steady laminar flow at a low Reynolds number (creeping flow assumption).

(a) State the kinematics you expect in this radial flow field at steady state.
(b) Based on these kinematics, reduce the continuity and components of the Navier-Stokes equation. Further reduce this to a set of linear differential equations by assuming creeping flow.
(c) State the necessary boundary conditions, and solve for $u_r(r,z)$ as a function of $\Delta\mathcal{P}$, the modified pressure drop between $r=R_1$ and $r=R_2$.
(d) Integrate this result between $z=-\delta$ and $z=+\delta$ to formulate Q. Then, rewrite $u_r(r,z)$ as a function of Q.
(e) Derive an expression for the radial shear stress distribution along a cell monolayer placed on the inner wall of one of the disks as a function of Q. Make a sketch of this distribution.

Problem 14-2: Lubrication Creeping Flow



The lubrication of articulating joints by synovial fluid can be modeled by an idealized geometry consisting of two solid surfaces separated by a gap containing a highly viscous Newtonian fluid. The lower surface is stationary while the upper surface slides by at a velocity U. Because the gap h(x) in the joint is so thin, relative to its perimeter around the joint, we can represent the surfaces as flat plates with a local irregularity on the joint surfaces accounted for by a linear variation in the gap thickness: $h(x)=h_1+(h_2-h_1)(x/L)$. We also assume that the width of the plates is so large relative to their length L that we can treat this as a two-dimensional flow such that

$$u_x=(x,y),\ u_y=(x,y),\ u_z=0$$

Using this model, we will show that because of this lubrication flow, a pressure is developed between the plates that keeps them separated.

(a) After eliminating terms by accounting for these kinematics, state the continuity and x,y,z components of the Navier-Stokes equation.
(b) Make these four equations dimensionless using the following variables:

$$x=\frac{x}{h_1},\quad y=\frac{y}{L},\quad u_x=\frac{u_x}{U_x},\quad u_y=\frac{u_y}{U_y},\quad P=\frac{\mathcal{P}}{\mathcal{P}*},\quad h=\frac{h(x)}{h_1}$$

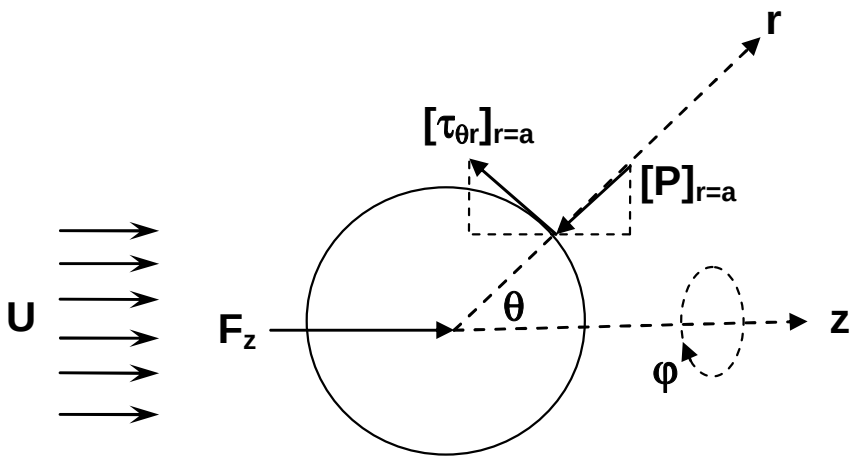
where U_x and U_y are velocity components of U, and $\mathcal{P}*=(\mu U_x/h_1)(L/h_1)$ is a characteristic pressure. It is important to note that the scale factors are chosen so that the dimensionless variables as well as their dimensionless x and y derivatives have values that are of order one.

(c) Simplify the dimensionless equations by realizing that $h_1/L<<1$, and by assuming that this is a creeping flow in which the Reynolds number, $Re= Re\equiv \rho U_x L/\mu$, is much less than one. Your result should be the lubrication equation.

$$\frac{\partial^2 u_x(x,y)}{\partial y^2}=\frac{dP(x)}{dx}$$

(d) Integrate this equation twice using the velocity conditions at $y=0$ and $y=h$ to obtain $u_x(x,y)$. Then integrate this result from $y=0$ to $y=h$ to obtain the local value of the dimensionless volumetric flow per unit width, $Q\equiv\int u_x dy$.
(e) Using the facts that Q is constant at steady state, and $P=P_o$ has the same values at the two open ends of the film, formulate a second order ODE and its boundary conditions for $P(x)$. The only parameters in these relations should be P_o and $\Delta h\equiv(h_1-h_2)/h_1$.
(f) Solve this equation numerically for alternative Δh values of 0, 0.6, 0.8 and 0.9 with a fixed value of $P_o=1$. Plot the resulting pressure distributions, $P(1\geq x\geq 0)$. Can you explain why P exhibits a maximum value when $\Delta h>0$?
(g) The choice of $\mathcal{P}*=(\mu U_x/h_1)(L/h_1)$ is a critical aspect in obtaining the lubrication equation. Explain what this characteristic pressure represents.

Problem 14-3: Mobility of a Sphere in Creeping Flow



A Newtonian liquid of viscosity μ and density ρ is in laminar flow around a sphere of radius 'a'. The liquid impinges on the sphere at a uniform velocity U, and the pressure at the stagnation point (r=a, θ=2π) is P_o. When the characteristic Reynolds number 2UR/υ is very small such that fluid inertia can be neglected, the steady-state solution to the Navier-Stokes equation is

$$u_r = U\left[1-\frac{3}{2}\left(\frac{a}{r}\right)+\frac{1}{2}\left(\frac{a}{r}\right)^3\right]\cos\theta$$

$$u_\theta = -U\left[1-\frac{3}{4}\left(\frac{a}{r}\right)-\frac{1}{4}\left(\frac{a}{r}\right)^3\right]\sin\theta$$

$$u_\phi = 0$$

(a) Excluding the effect of gravity, formulate the pressure distribution $P(r,\theta,\phi)$ due to fluid motion alone.

(b) Integrate the pressure distribution to obtain the net force of pressure on the surface of the sphere in the z direction, $F_{z,p.}$ Note that a spherical surface element is given by $a^2\sin\theta d\theta d\phi$.

(c) Formulate the elements of the viscous stress tensor at the surface of the sphere.

(d) Integrate the shear stress distribution $[\tau_{\theta r}]_{r=a}$ to obtain the net force of friction on the surface of the sphere in the z direction, $F_{z,f.}$

(e) The hydrodynamic mobility δ of a sphere is the velocity at which it moves relative to the frictional force (skin friction) and the pressure force (form drag) that retards that motion. This is equivalent to the ratio $U/(F_{z,f}+F_{sp})$ for a stationary sphere. Formulate δ from the results of parts (b) and (d).

Problem 14-4: Boundary Layer Flow on a Rotating Disk

By approximating the velocity field near the surface rotating disk (Fig. 14.1-2), determine how the mean wall stress depends on radial position r, angular velocity Ω, fluid density ρ and viscosity μ without making use of the numerical solution in section 14.1.

(a) Transform the dimensional continuity equation in cylindrical coordinates (table 13.1-1) using

$$u_r=\Omega F(\xi)r,\quad u_\theta=\Omega G(\xi)r,\quad u_z=(\Omega/\upsilon)^{0.5}H(\xi)$$

where

$$\xi=(\Omega/\upsilon)^{0.5}z$$

Show that for cylindrical symmetry:

$$H'(\xi) = -2\upsilon F(\xi)$$

(b) Show that the r component of the steady-state Navier-Stokes equation in cylindrical coordinates (table B4-5) can be written in terms of F and G as:

$$[F(\xi)]^2 - [G(\xi)]^2 + F'(\xi)H(\xi) = F''(\xi)$$

Note that $(\ldots)'\equiv d(\ldots)/dz$ and $''(\ldots)\equiv d^2(\ldots)/dz$.

(c) Approximate the independent variables F and G in the vicinity of the disk surface as linear functions:

$$F(\xi)\approx b_1+c_1\xi,\quad G(\xi)\approx b_2+c_2\xi$$

State the boundary conditions for the three velocity components at the surface, z=0. Using these boundary conditions, evaluate 'b' constants. Determine an approximation for H in terms of ξ with additional unknown constant.

(d) Use the functions of $F(\xi)$, $G(\xi)$, $H(\xi)$ to express the velocity components in the vicinity of the surface: $u_r(r,\theta,z)$, $u_\theta(r,\theta,z)$ and $u_z(r,\theta,z)$,

(e) Use Newton's law of viscosity with deformation rate components in cylindrical coordinates (table B4-8) to obtain the shear stresses, $\tau_{rz}(r)$ and $\tau_{\theta z}(r)$, acting in the vicinity on the surface. Formulate the mean shear stress on the surface:

$$\tau_{wall}(r) \equiv \sqrt{\tau_{rz}^2(r) + \tau_{\theta z}^2(r)}$$

How does this equation compare with Eq. 14.1-65? What is a practical application of this result?

Problem 14-5: Tube Flow With a Non-Sinusoidal Pressure Distribution

In the pulsatile flow illustration in Section 14-3, the pressure gradient involved a simple sinusoidal function. The pressure gradient can be more complex such as in arterial blood flow. To address this, researchers use a multiharmonic Fourier function to better represent the pressure gradient. In such a case, the pressure gradient is written in terms of a time average gradient X_0 and an oscillating component comprising the sum of N complex harmonics.

$$-\frac{\partial \mathcal{P}}{\partial z} = X_0 + \sum_{n=1}^{N} X_n e^{jn\omega t} \quad ; \quad X_n = X_{cn} - jX_{sn}$$

where X_n is the complex Fourier coefficient associated with the n^{th} harmonic. Using this representation of the pressure gradient, and assuming non-oscillatory transients have died out, we expect the velocity profile, u_z, to have the multi-harmonic form:

$$u_z = u_0 + \sum_{n=1}^{N} u_n e^{jn\omega t}$$

(a) Starting from Eq. 14.3-2, derive separate equations for u_0 and u_n in terms of X_0, X_n, r and t.
(b) Using the results of part(a), integrate u_z over the tube cross-section to formulate the volumetric flow rate Q(t). Your result in dimensionless form should be

$$\frac{Q}{Q_0} = \left\{ 1 + \sum_{n=1}^{10} \frac{16}{Wo_n^2} \left[\frac{1}{2} - \int_0^1 \frac{J_0\left(j^{3/2} Wo_n r\right)}{J_0\left(j^{3/2} Wo_n\right)} r dr \right] \left(\frac{X_{sn}}{X_0} - j\frac{X_{cn}}{X_0} \right) e^{jnt} \right\} \qquad (1)$$

where r=r/a, $t \equiv \omega t$, $Q_0 = (\pi a^4/8\mu)X_0$ and $Wo_n = a\sqrt{n\rho\omega/\mu}$.

Problem 14-6: Fourier Analysis of Blood Flow in a Dog Aorta

In the ascending aorta of a dog, pulsatile blood flow was measured and then expressed as a Fourier series with 10 harmonics (Atinger, et al. p230-246, *Circulation Research* 1966).

$$\frac{Q}{Q_0} = \left(1 + \sum_{n=1}^{10} \frac{Q_n}{Q_0} e^{jn\omega t} \right); \quad Q_n = Q_{cn} - jQ_{sn}$$

n	Q_{cn}/Q_0	Q_{sn}/Q_0	n	Q_{cn}/Q_0	Q_{sn}/Q_0
1	-0.465	1.34	6	0.103	0.079
2	-0.739	-0.268	7	-0.099	0.003
3	-0.043	-0.298	8	-0.037	0.075
4	0.176	-0.228	9	0.0068	-0.115
5	0.052	0.132	10	-0.0272	-0.0139

(a) By equating Eq.(1) from problem 14.4 to above flow equation, find the dimensionless relationship between $(Q_{cn}/Q_0) - j(Q_{sn}/Q_0)$ and $(X_{cn}/X_0) - j(X_{sn}/X_0)$.

(b) With the aid of numerical software such as Mathematica, find the numerical values of X_{cn}/X_0 and X_{sn}/X_0 (n=1,2,…10) from the numerical values of Q_{cn}/Q_0, Q_{sn}/Q_0 given in the table.

(c) Using these X_{cn}/X_0 and X_{sn}/X_0 values, plot the $Q(t)/Q_0$ and $-(1/X_0)\partial\mathcal{P}/\partial z$ waveforms.

CHAPTER 15

Problem 15-1: Alternative Forms of One Dimensional Transport Equations

The one-dimensional transport model for solution (Eq. 15.3-25) is given by:

$$\frac{\partial(\rho A_t)}{\partial t}+\frac{\partial(\rho Q)}{\partial z}=-\rho A_t \phi_t u_{wall}$$

and for solute (Eq. 15.3-27) is given by:

$$\frac{\partial(A_t C_i)}{\partial t}+\frac{\partial(Q C_i)}{\partial z}=\frac{\partial}{\partial z}\left[\left(\mathcal{D}_i+\mathcal{D}_i^*\right)A_t\frac{\partial C_i}{\partial z}\right]+R_i A_t-A_t\phi_t N_{i,wall}$$

(a) Assume constant mass density ρ and combine these two equations to show that

$$A_t\frac{\partial C_i}{\partial t}+Q\frac{\partial C_i}{\partial z}=\frac{\partial}{\partial z}\left[\left(\mathcal{D}_i+\mathcal{D}_i^*\right)A_t\frac{\partial C_i}{\partial z}\right]+R_i A_t-F$$

What is function F ?

(b) Starting with the model of (a), specify the conditions for which model takes the form:

$$\frac{\partial C_i}{\partial t}+\frac{Q}{A_t}\frac{\partial C_i}{\partial z}=\frac{\partial}{A_t\partial z}\left(\mathcal{D}_i^* A_t\frac{\partial C_i}{\partial z}\right)-k_i C_i-\frac{\vartheta_t}{A_t}P_i\left(C_i-C_i^{external}\right)$$

where ϑ_t is the circumference of the tube at position z. Explain $P_i\left(C_i-C_i^{external}\right)$. What is the relation of ϕ_t to ϑ_t/A_t ?

(c) Show that the model of part (b) can be expressed as

$$\frac{\partial C_i}{\partial t}+G\frac{\partial C_i}{\partial z}=H\frac{\partial^2 C_i}{\partial z^2}-k_i C_i-\frac{\vartheta_t}{A_t}P_i\left(C_i-C_i^{external}\right)$$

Define functions G and H.

(d) Transform the spatial derivatives of the part (a) equation into cumulative volume: dV = Adz .

Problem 15-2: Cell Monolayer Oxygenation in a Two-Dimensional Channel

Buffered saline containing a nutrient concentration $C_{s,in}$ flows through a thin rectangular channel of thickness H and Length L>>H. A confluent cell monolayer is adherent to the lower channel

wall at y=0. The cells absorb the nutrient according at a rate given by a Michaelis-Menten type equation. Nutrient is also supplied through a permeable membrane that forms the upper wall of the channel at y=H. The outside surface of this membrane is in contact with a large pool of nutrient at a constant concentration at a constant concentration $C_s^{external}$. The following equation models the steady-state O_2 concentration $C_s(y,z)$ in the channel:

$$u_z(y)\frac{\partial C_s}{\partial z} = \mathcal{D}_s \frac{\partial^2 C_s}{\partial y^2} \qquad (L > z > 0, \quad H > y > 0) \tag{1}$$

where the longitudinal velocity distribution is

$$u_z(z) = U_0 \frac{y}{H}\left(1 - \frac{y}{H}\right)$$

and the boundary conditions are

$$z = 0: \quad C_s = C_{s,in}$$
$$y = 0: \quad \mathcal{D}_s \frac{\partial C_s}{\partial y} = \frac{V_m C_s}{K_m + C_s}$$
$$y = H: \quad \mathcal{D}_s \frac{\partial C_s}{\partial y} = P_s\left(C_s^{external} - \lambda C_s\right)$$

The dimensional parameters of this model are U_0, H, $\mathcal{D}_s$, L, $C_{s,in}$, V_m, K_m, P_s, $C_s^{external}$

(a) Express the model in dimensionless form with the variables:

$$C = \frac{C_s}{C_s^{in}}, \quad u = \frac{u_z}{U_0}, \quad z = \frac{z}{L}, \quad y = \frac{y}{H}$$

Show that the dimensionless parameters are

$$\alpha = \frac{\mathcal{D}_s L}{U_0 H^2}, \quad \beta = \frac{V_m H}{\mathcal{D}_s C_{s,in}}, \quad \gamma = \frac{K_m}{C_{s,in}}, \quad \mu = \frac{P_s H}{\mathcal{D}_s}, \quad C^{external} = \frac{C_s^{external}}{C_{s,in}}.$$

(b) Assuming $\alpha = \mathcal{D}_s L / U_0 H^2 >> 1$, how does the model simplify? Explain the physical significance of this case. Obtain the solution for *C*(*y*,*z*).

(c) Simplify the original model, Eq 1, assuming that *u* is constant and $\gamma << C$. Use the linear transformation $\vartheta = C + ay + b$ to obtain a homogeneous governing equation. Under what conditions will the boundary conditions in the ζ domain also be homogeneous?

Problem 15-3: Dispersion With a Rapid Tracer Input

Often dispersion is studied by the rapid injection of a non-reactive tracer at the entrance of the vascular system. If the system can be modeled as a long cylindrical tube and axial diffusion is negligible, then the convective-dispersion equation (Eq. 15.5-51) is

$$\frac{\partial C_s}{\partial t} + u_z \frac{\partial C_s}{\partial z} = \mathcal{D}_s^* \frac{\partial^2 C_s}{\partial z^2} \qquad (z > 0, t > 0)$$

where the axial velocity u_z and the dispersion coefficient $\mathcal{D}_s^*$ are constants. The appropriate initial and boundary conditions for an injection that creates a concentration pattern $C_o\theta(t)$ are:

$$t = 0: \quad C_s = 0, \qquad z = 0: \quad C_s = C_o\theta(t), \qquad z \to \infty: \quad C_s \to 0$$

(a) Using the dimensionless variables

$$C = \frac{C_s}{C_o}, \quad t = \frac{t}{t_o}, \quad z = \frac{z}{z_0}$$

where t_o and z_o are arbitrary scale factors, show that the dimensionless model can be expressed as:

$$\frac{\partial C}{\partial t} + \frac{\partial C}{\partial z} = \frac{\partial^2 C}{\partial z^2} \qquad (z > 0, \ t > 0)$$

with the conditions

$$t = 0: \quad C = 0, \qquad z = 0: \quad C = \theta(t), \qquad z \to \infty: \quad C \to 0$$

To obtain this result, what must be the relationship of t_o and of z_o to u_z and $\mathcal{D}_s^*$?

(b) Apply the Laplace transforms, $\boldsymbol{L}\{C(z,t)\} = \tilde{C}(z,s)$ and $\boldsymbol{L}\{\theta(t)\} = \tilde{\theta}(s)$, to the governing equations and boundary conditions. From the differential operator of the transformed differential equation obtain the roots, r_1 and r_2. Then, write a general solution for $\tilde{C}(z,s)$.

(c) Apply the boundary conditions to get the transfer function, $\tilde{C}(z,s)/\tilde{\theta}(s)$, for this system.

(d) For a very rapid tracer injection, we can idealize the input as an ideal unit impulse (see section 18.1.2 in the textbook) for which the input is $\tilde{\theta}(s) = 1$. For this case, find the inverse transform. Note that

$$\boldsymbol{L}^{-1}\left\{\exp\left(-b\sqrt{s+a}\right)\right\} = \left[\frac{b}{4\pi t^3}\right]^{0.5} \exp(-at)\exp\left(-\frac{b^2}{4t}\right)$$

Then , obtain the dimensional concentration, C(z,t).

Problem 15-4 Dispersion by Pure Convection in Poiseulle Flow

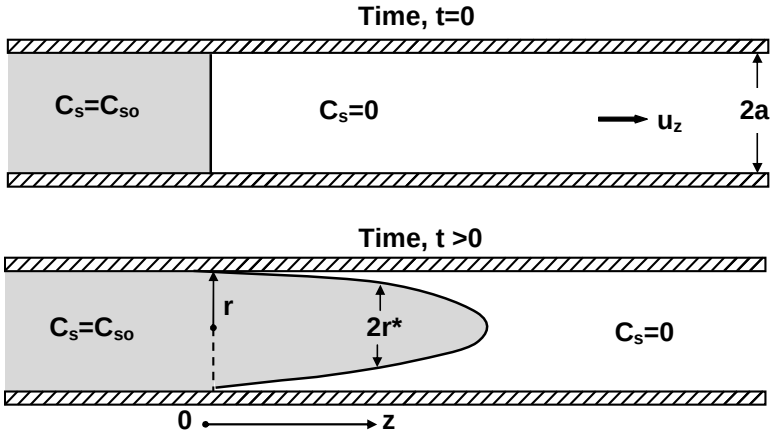
Consider dispersion of solute s by pure convection along a tube in which fluid flows in well-developed laminar flow with an axial velocity distributed from the tube center (r=0) to the tube wall (r=a):

$$u_z = 2\bar{u}\left(1-\frac{r^2}{a^2}\right)$$

A planar dividing front initially separates upstream solution at solute concentration $C_s=C_{so}$ from downstream solvent. Thereafter, solute moves by axial convection at a rate $u_z(r)C_{so}$. At a time t>0, the dividing front assumes a parabolic shape located between z=0 and $z = 2\bar{u}t$; consequently, the solute concentration changes according to

$$C(r,z,t) = \begin{cases} C_{so} & \text{for } r^*(z,t) > r > 0 \\ 0 & \text{for } r > r^*(z,t) \end{cases}$$

Here, r*(z,t) is the radius to which solute molecules are just able to translate to position z during a time interval {0,t}. At r<r*, the solute molecules are fast enough to surpass position z. At r>r* solute molecules are too slow to reach position z.



(a) Solve for r* as a function of axial position z and time t.

(b) Determine the cross-sectional average solute concentration $\bar{C}_i$ as a function of z and t. Obtain the concentration derivative.

(c) Express the average cross-sectional axial solute flux $\bar{N}_{s,z}$ (per tube cross-section area) as a function of z and t:

(d) Starting with the flux equation:

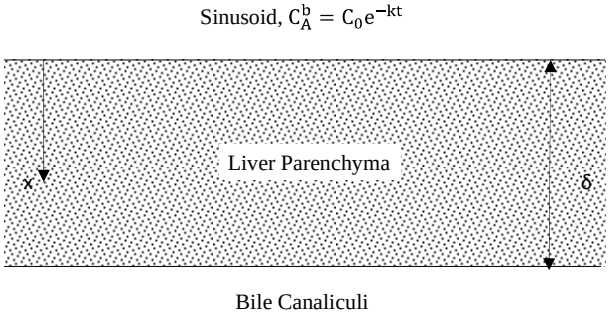
$$\bar{N}_{s,z} = \bar{u}\bar{C}_s - \mathcal{D}_s^* \frac{\partial \bar{C}_s}{\partial z}$$

formulate the dispersion coefficient $\mathcal{D}_i^*$ as a function of z and t.

(e) Describe how $\mathcal{D}_i^*$ changes with z at a particular time t. At what values of z is $\mathcal{D}_i^*$ at a minimum and at a maximum ? What are the minimum and maximum values of $\mathcal{D}_i^*$?

Problem 15-5: Drug Transport in the Liver

Drug transport in liver tissue (Fig. 1.2-7 in textbook) has been modeled as diffusion across a parenchymal layer, which consists of a planar slab of hepatocytes that separate liver sinusoids on one side from bile canaliculi on the other side (Yasui, H *et al.* Hepatocellular diffusion model, J. Pharm. Biopharm. 23:183-203,1995). Consider drugs (*e.g.,* cefixime) that are not metabolized in the hepatocytes and are actively transported in their intact form into the bile. Initially, there is no drug in the liver tissue. Thereafter, the introduction of a drug pulse into the body results in a drug concentration in the sinusoid that can be approximated by $C_A^b = C_0 e^{-kt}$. Develop a model for drug concentration in the parenchymal layer.



(a) Under conditions of constant density and diffusion coefficient $\mathcal{D}_A$, what is the PDE that describes the dynamic drug concentration $C_A(x,t)$ in the parenchymal domain $\delta > x > 0$?

(b) At the x=0 boundary, the diffusion flux of drug from the sinusoids is the product of a mass transfer coefficient k_A and the difference between the concentration in the sinusoid, C_A^b, and that in the parenchyma, $C_A(0,t)$. What is the equation that expresses this boundary condition?

(c) Drug transport across the $x=\delta$ boundary occurs by the facilitated transport rate given by Eq. 11.1-12b. What is the equation representing this boundary condition?

(d) Express the model including initial and boundary conditions in dimensionless form using:

$$t = kt; \quad x = \frac{x}{\delta}; \quad C_A = \frac{C_A}{C_0}.$$

What are the dimensionless parameters in the resulting mathematical model?

(e) Simulate the model by numerical solution with all the dimensionless parameter values set to 1. Plot the concentration profiles as a function of dimensionless distance at different dimensionless times ($10 > t > 0$)

(f) The dimensionless liver excretion rate of the drug into the bile is defined in terms of the flux N_{Ax} at the x=δ boundary.

$$ER \equiv \frac{[N_{Ax}]_{x=\delta}}{\mathcal{D}_A C_0/\delta}$$

Formulate *ER* in terms of $[C_A]_{x=\delta}$ and then plot *ER* as a function of dimensionless time (10>*t*>0).

Problem 15-6: Oxygen Limitation in Tissue Engineering

A tissue-engineered construct consists of a spherical scaffold that is initially loaded with a dilute cell suspension and then cultured in a bioreactor for several days. Experiments have shown that, as they propagate, the cells consume O_2 at a rate, R_{O2}(moles O_2/s/cm^3), that is proportional to the cell number density Ω(cells/cm^3).

$$R_{O2}(r,t) = -k_{O2}\Omega(r,t)$$

(a) Assuming that the construct is so porous that its effect on O_2 diffusion can be ignored, write the dynamic concentration equation.
(b) Formulate the boundary and initial conditions to solve this PDE for a construct of radius 'a', an initial cell number density Ω_o, and O_2 concentration C_o initially in the construct. Oxygen concentration C_o is also maintained at the construct surface for all later times.
(c) Express the PDE and its conditions in terms of the dimensionless variables:

$$t = \frac{t}{T},\quad r = \frac{r}{a},\quad C = \frac{C_{O2}}{C_o},\quad \Omega = \frac{\Omega}{\Omega_o}$$

where T is the characteristic time of cell propagation.
(d) Under what conditions can the transient term be neglected so that simultaneous O_2 diffusion and consumption can be treated as a pseudo-steady process? Under what conditions are the diffusion and consumption terms of equal importance?

Problem 15-7 : Alternative Models of Capillary-Tissue Transport

The following dimensionless models are different representations of solute transport from capillary blood to surrounding extra-vascular tissue. What do these models have in common? Briefly explain the processes and assumptions associated with each model.

Crone Model: The solute concentration in capillary blood C^C changes according to

$$\frac{\partial C^C}{\partial t} + \frac{\partial C^C}{\partial x} = -\left(\frac{PS}{Q}\right)C^C \qquad (1 > x > 0)$$

where PS/Q is the ratio of capillary permeability×surface area to volumetric blood flow. The boundary and initial conditions are

$$t = 0: \; C^{C} = 1$$
$$x = 0: \; C^{C} = 0$$

Sangren-Sheppard Model: The solute concentration in capillary blood C^{C} and in extra-vascular tissue C^{T} change according to

$$\frac{\partial C^{C}}{\partial t} + \frac{\partial C^{C}}{\partial x} = -\left(\frac{PS}{Q}\right)\left(C^{C} - C^{T}\right) \qquad (1 > x > 0)$$
$$\frac{\partial C^{T}}{\partial t} = \left(\frac{PS}{Q}\right)\frac{V^{C}}{V^{T}}\left(C^{C} - C^{T}\right)$$

where V^{C}/V^{T} is the capillary-tissue volume ratio. The boundary and initial conditions are

$$t = 0: \quad C^{C} = 1, \; C^{T} = 0$$
$$x = 0: \quad C^{C} = 0$$

Turner Model: The solute concentration in blood C^{C} and in extra-vascular tissue C^{T} change according to

$$\frac{\partial C^{C}}{\partial t} + \frac{\partial C^{C}}{\partial x} = \left[\frac{(A^{C})^{2}\mathcal{D}}{QV^{C}}\right]\frac{\partial^{2} C^{C}}{\partial x^{2}} - \left(\frac{PS}{Q}\right)\left(C^{C} - C^{T}\right) \qquad (1>x>0)$$
$$\frac{\partial C^{T}}{\partial t} = \left(\frac{PS}{Q}\right)\frac{V^{C}}{V^{T}}\left(C^{C} - C^{T}\right)$$

The boundary and initial conditions are

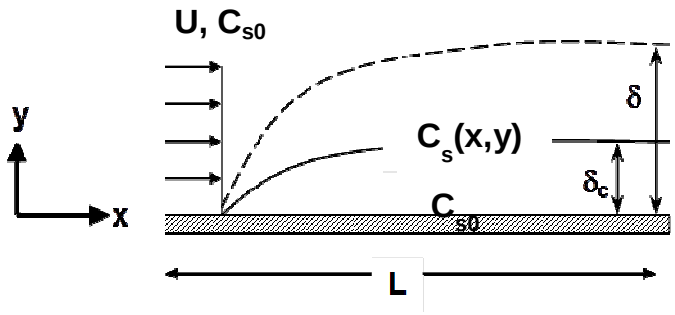
$$t = 0: \quad C^{C} = 1, \; C^{T} = 0$$
$$x = 0: \quad C^{C} = 0$$
$$x = 1: \quad \frac{\partial C^{C}}{\partial x} = 0$$

where $\mathcal{D}$ is the dispersion coefficient and A^{C} the capillary cross-sectional area.

Problem 15-8: Concentration Boundary Layer On a Flat Plate

Consider a wide flat plate with a concentration $C_s(x,y=0)=C_{sw}$ of inert solute at the plate surface and a solute concentration at $C_s(x=0,y)=C_{s0}$ in the impinging flow (Fig. 15.5.4). At a sufficiently rapid impinging velocity $u_x(0,y)=U$, momentum and concentration boundary layers will both be

formed. At a downstream position x=L, the concentration boundary layer thickness δ_c is much less than L.



The objective of this problem is to find the criteria to justify the assumption that $\delta_c << \delta$ under steady state conditions. From an analysis of the velocity field using the Navier-Stokes equation, we know that $\delta \sim \sqrt{L\upsilon/U}$ (Eq. 14.1-29b), and the velocity components near the plate surface are $u_x \sim y\sqrt{U^3/\upsilon x}$ (Eq. 14.1-32) and $u_y \sim y^2\sqrt{U^3/\upsilon x^3}$ (Eq. 14.1-33).

(a) Incorporating the assumptions given above, simplify the governing equation for the solute concentration $C_s(x,y)$ in rectangular coordinates (table 15.2-1):

$$\frac{\partial C_s}{\partial t} + \left(u_x \frac{\partial C_s}{\partial x} + u_y \frac{\partial C_s}{\partial y} + u_z \frac{\partial C_s}{\partial z} \right) = \mathcal{D}\left(\frac{\partial^2 C_s}{\partial x^2} + \frac{\partial^2 C_s}{\partial y^2} + \frac{\partial^2 C_s}{\partial z^2} \right) + R_s$$

(b) Make the governing equation dimensionless using the following scaled variables:

$$C = \frac{C_s - C_{s0}}{C_{sw} - C_{s0}}, \quad x \equiv \frac{x}{L}, \quad y \equiv \frac{y}{\delta_c}$$

(c) From an order of magnitude analysis, simplify the dimensionless equation and find δ_c in terms of U, L, υ and $\mathcal{D}$. Then, relate δ_c to $\delta \sim \sqrt{L\upsilon/U}$. Specify the criterion to justify $\delta_c/\delta << 1$.

Problem 15-9: Diffusion in Central Nervous System : Alternative Models

L-Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Initially, a micropipette containing C_D=5 mM L-glutamate is inserted into the CNS. At the end of the micropipette, a drop is formed by a 10 ms pressure pulse. The drop has a radius around r_D=25 μm. Surrounding the drop is a much larger medium into which the L-glutamate diffuses . The governing equation for concentration of L-glutamate in either the drop or surrounding medium is

$$\frac{\partial C}{\partial t} = \left(\frac{\mathcal{D}}{r^2}\right)\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right) + C_D H(r_D - r)\delta(t) \qquad (r>0,\ t>0)$$

where $H(\ )$ is the unit step function; $\delta()$ is the Dirac delta function; $\mathcal{D}$ is a diffusion coefficient, which is the same in the drop and the external medium. The conditions are

$t<0$: $C=0$
$r=0$: $\partial C/\partial r=0$
$r\to\infty$: $C=0$

(a) What are the key assumptions of the governing equation and their justifications?
(b) Explain the source term, initial condition, and boundary conditions.
(c) What is the number of micromoles m_D of L-Glutamate in the drop?
(d) Use the Laplace transform $L\{C(r,t)\}=\tilde{C}(r,s)$ to show that the following is an alternative form of the governing equation:

$$\frac{\partial C}{\partial t} = \left(\frac{\mathcal{D}}{r^2}\right)\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right) \qquad (r>0,\ t>0)$$

with conditions:

$t=0$: $C=C_D H(r_D-r)$
$r=0$: $\partial C/\partial r=0$
$r\to\infty$: $C=0$

Problem 15-10: Diffusion in Central Nervous System : Model Transformation

Consider the model for the radial diffusion of L-Glutamate in the mammalian central nervous system described in problem 15-9:

$$\frac{\partial C}{\partial t} = \left(\frac{\mathcal{D}}{r^2}\right)\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right) \qquad (r>0,\ t>0)$$

$t=0$: $C=C_D H(r_D-r)$
$r=0$: $\partial C/\partial r=0$
$r\to\infty$: $C=0$

where $H(\ )$ is the unit step function; $\delta()$ is the Dirac delta function; $\mathcal{D}$ is a diffusion coefficient.

(a) Show that the model can be expressed with dimensionless variable in the following form:

$$\frac{\partial C}{\partial t} = \left(\frac{1}{r^2}\right)\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right) \qquad (r>0,\ t>0)$$

$$t = 0: \quad C = U(1 - r)$$
$$r = 0: \quad \frac{\partial C}{\partial r} = 0$$
$$r \to \infty: \quad C = 0$$

What are the scale factors (a, b, c) that relate the dimensionless variables to the dimensionless variables ?

$$C(r,t) = \frac{\mathrm{C(r,t)}}{\mathrm{a}}, \quad r = \frac{\mathrm{r}}{\mathrm{b}}, \quad t = \frac{\mathrm{t}}{\mathrm{c}}$$

(b) Transform the dimensionless problem by letting $\bar{C} = rC$. What simplification occurs ? What are the dimensionless conditions ?

Problem 15-11 : One Dimensional Transport in a Tube with Variable Dimensions

Under some conditions, the one dimensional solute concentration C(z,t) in liquid flowing through a tube surrounded by an external phase with solute concentration C^E changes according to:

$$\frac{\partial \mathrm{C}}{\partial \mathrm{t}} + \frac{\mathrm{Q}}{\mathrm{A}} \frac{\partial \mathrm{C}}{\partial \mathrm{z}} = \frac{1}{\mathrm{A}} \frac{\partial}{\partial \mathrm{z}} \left(\mathcal{D} \mathrm{A} \frac{\partial \mathrm{C}}{\partial \mathrm{z}} \right) - \frac{\mathrm{PS_L}}{\mathrm{A}} \left(\mathrm{C} - \mathrm{C^E} \right) + \mathrm{R}$$

where $S_L(z)$ the tube circumference and A(z) the cross-sectional area vary with axial position z .

(a) Assume that: 1) the solute diffusion coefficient $\mathcal{D}$ is constant; 2) the tube has a circular cross-section whose radius is a function f(z) of axial position z. Express $S_L(z)$ and A(z) in terms of f(z). Then express the dynamic concentration distribution in the form:

$$\frac{\partial \mathrm{C}}{\partial \mathrm{t}} + \mathrm{F} \frac{\partial \mathrm{C}}{\partial \mathrm{z}} = \mathrm{G} \frac{\partial^2 \mathrm{C}}{\partial \mathrm{z}^2} - \mathrm{H} \left(\mathrm{C} - \mathrm{C^E} \right) + \mathrm{R}$$

Specify F, G and H in relation to f(z) and df/dz as needed.

(b) The differential change in volume of the tube lumen between axial positions z and z+dz is dV=A(z)dz. Given f(z), how is the derivate of V with respect to z evaluated ? Using the chain rule of differentiation, transform the result of part (a) from C(z,t) to C(V,t). Express your result in the form:

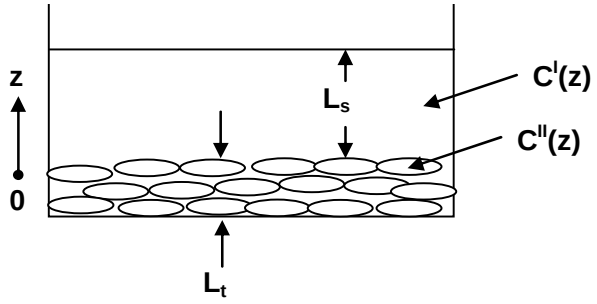
$$\frac{\partial \mathrm{C}}{\partial \mathrm{t}} + \mathrm{F_V} \frac{\partial \mathrm{C}}{\partial \mathrm{z}} = \mathrm{G_V} \frac{\partial^2 \mathrm{C}}{\partial \mathrm{z}^2} - \mathrm{H_V} \left(\mathrm{C} - \mathrm{C^E} \right) + \mathrm{R}$$

Relate F_V, G_V, H_V to f and df/dV as appropriate.

CHAPTER 16

Problem 16-1: Oxygenation of a Tissue Layer

A tissue layer of thickness L_t is being maintained on the bottom of a Petri dish. The tissue is covered with a nutrient solution of height L_s that is in contact with atmospheric air whose oxygen partial pressure is p_o. Oxygen diffuses from the atmosphere through the nutrient layer and into the tissue layer where it is metabolized.

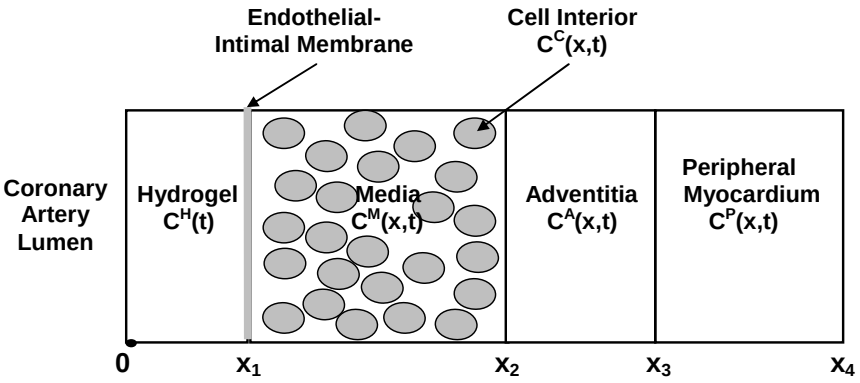


The diffusion domain in this problem can be spatially subdivided into the nutrient layer located at $L_s>z>L_t$ (zone I) and a homogeneous tissue layer located at $L_t>z>0$ (zone II). The O_2 diffusion coefficients, $\mathcal{D}^I$ and $\mathcal{D}^{II}$, as well as the O_2 solubilities, α^I and α^{II}, are different in the two zones. While there is no O_2 reaction in zone I, O_2 in zone II is utilized at a constant molar rate per unit volume, R^{II} .

(a) Write the second-order differential equation for O_2 concentration in the two zones, $C^I(z)$ and $C^{II}(z)$. In each zone, assume a steady-state process, a stationary phase, a constant diffusion coefficient and constant mass density
(b) How many boundary and how many initial conditions are necessary to solve the two ODE found in part (a)? Give the conditions that you would use to solve this problem; write the formulas and state what each one means.
(c) Find the O_2 distributions in the two zones by integrating the differential equations and applying the boundary conditions.
(d) Using the solution for $C^I(z)$, formulate the oxygen transport rate into the surface area S of the monolayer at $z=L_c$. Explain this result.

Problem 16-2 Heparin Distribution in Arterial Wall

Placement of stents in coronary arteries frequently results in lesions on the vessel walls. Locally applied heparin is a possible treatment for suppressing a proliferation response that exacerbates this damage. Consider a mathematical model for heparin delivery through a coronary arterial wall from a locally-applied hydrogel film (Lovich MA, Edelman ER. Am. Physiol. Soc. 271:H2014-H2024, 1996). We represent the arterial wall as a series of endothelial-intimal, medial and adventitial layers bounded by the hydrogel. Between these planar layers, the (uniform) cross-sectional area is S.



One-dimensional diffusion occurs in the x direction through the media ($x_2>x>x_1$), the adventitia ($x_3>x>x_2$) and the myocardium ($x_4>x>x_3$). The hydrogel layer ($x_1>x>0$) is considered to be a well-mixed reservoir of heparin. The endothelium-intimal layer ($x=x_1$) is represented as a membrane with a heparin permeability P^E[mol/s/m^2]. The media is modeled as a uniform, fixed tissue of cells surrounded by interstitial fluid. As free heparin diffuses through the media, it reacts with cell surface receptors to form bound heparin. Once bound, heparin can be internalized across the cell membranes with a permeability P^C. Within the cells, the heparin is metabolized by Michaelis-Menten kinetics at a maximum intensive rate α and a concentration at half maximum of β. Free heparin is also metabolized in the peripheral myocardium with a first-order rate coefficient k^P[s^{-1}]. At the proximal boundary of the arterial wall (x=0), heparin moves into the arterial blood of the lumen with an irreversible loss rate coefficient k^H[s^{-1}]. At the distal boundary ($x=x_4$) of the myocardium, heparin concentration is very small compared to that in the hydrogel. For uniformity of symbols, represent the equilibrium partition coefficients of heparin between any phases I and J as $\lambda^{I,J}$ and the diffusion coefficients of free heparin in phases I=M, A and P as $\mathcal{D}^I$.

(a) For the well-mixed hydrogel layer, derive an equation for the concentration dynamics of free heparin, $C^H(t)$. Account for transport across both the x=0 and $x=x_1$ surfaces.

(b) Develop an equation for the overall formation rate R^M[mol/s/m^3] of free heparin in the medial layer resulting from reversible monovalent binding to unoccupied receptor sites. This equation should depend on the molar concentrations of free and bound heparin, $C^M(x,t)$ and $C_b^M(x,t)$, as well as the total concentration of occupied and unoccupied receptor sites, T^M, which is assumed to be constant. The forward and reverse rate constants for the reaction are k_{on} and k_{off}, respectively.

(c) For the medial layer, derive an equation for the dynamics of free heparin $C^M(x,t)$ and an equation for the dynamics of bound heparin $C_b^M(x,t)$. Since the cells are stationary, the bound heparin does not move through the medial layer.

(d) What are the boundary conditions for the free heparin concentration at the medial boundaries, $x=x_1$ and $x=x_2$?

(e) For the cell interior, derive a concentration dynamics equation for internalized heparin, $C^C(x,t)$.

(f) For the adventitia, derive the PDE for the concentration dynamics of free heparin $C^A(x,t)$. What conditions relate C^A to the myocardial concentration $C^P(x,t)$ at the $x=x_3$ boundary?

(g) For the peripheral myocardium, derive the PDE for the concentration dynamics of free heparin $C^p(z,t)$. What alternative boundary conditions would be appropriate at the distal myocardial boundary $x=x_4$?

(h) Do the number of boundary conditions specified match the number of boundary conditions that are necessary for this model ?

(i) What are reasonable initial conditions?

Problem 16-3: Carbon Dioxide Excretion From Pulmonary Capillaries

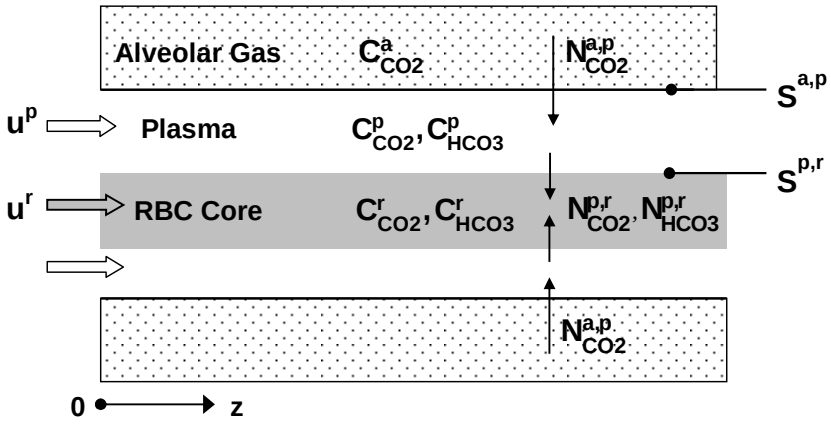
In the pulmonary capillaries, CO_2 is eliminated from flowing blood to the well-mixed alveolar gas. Within the blood, carbon dioxide is transported as dissolved CO_2 molecules as well as in hydrated form as HCO_3^- ions.

$$CO_2 + H_2O \underset{k_r}{\overset{k_f}{\rightleftharpoons}} HCO_3^- + H^+$$

Although this reversible hydration reaction occurs in any aqueous solution, it is greatly accelerated by the action of the carbonic anhydrase, an enzyme that is present in the RBC.

In this problem, we model the transport of CO_2 in pulmonary capillaries in a similar fashion as the blood oxygenation model in section 16.2.3. Blood is treated as a two phase system consisting of a RBC core encircled by a plasma layer. The plasma layer is separated by an alveolar-capillary membrane from a surrounding alveolar gas layer that contains a constant concentration C^a_{CO2} of CO_2.

Additional symbols not shown in the figure are: R_{CO2}, the net formation rate of CO_2 by the hydration reaction per unit RBC volume; $\lambda^{a,p}_{CO2}$, the partition coefficient of CO_2 between alveolar gas and plasma; V^b, the volume of the RBC phase; ε_H, the volume fraction of the RBC phase in blood.



(a) What conditions must be met if the net production rate of CO_2 by the hydration reaction is given by:

$$R^r_{CO2} = k_r C^r_{HCO3} - k_f C^r_{CO2}$$

Here k_r and k_f are constant rate constants for the forward and reverse reactions. If this reaction reaches equilibrium, what is the relationship between C^r_{CO2} and C^r_{HCO3}?

(b) Rewrite Eqs. 16.2-45 and 16.2-46 from the textbook so that they apply to CO_2 transport in the plasma and the RBC phases. For simplicity, assume that the solubility of CO_2 is equal in the plasma and RBC phases.

(c) Develop the corresponding equations for HCO_3^- transport in the RBC and plasma phases. Assume that the solubility of HCO_3^- is equal in the plasma and RBC phases.

(d) As a first step in reducing the two-phase model of blood developed in parts (b) and (c) to a single-phase model, we define the volume average CO_2 and HCO_3^- concentrations in blood as

$$C^b_{CO2} \equiv \varepsilon_H C^r_{CO2} + (1-\varepsilon_H) C^p_{CO2}$$
$$C^b_{HCO3} \equiv \varepsilon_H C^r_{HCO3} + (1-\varepsilon_H) C^p_{HCO3}$$

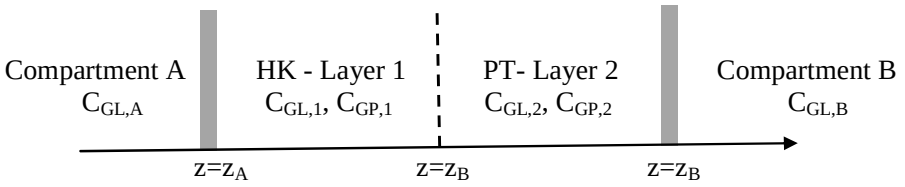
Combine the concentration equations obtained in part (b) for CO_2 transport in the RBC and plasma phases to obtain one concentration equation in which the unsteady and convection terms are given in terms of C^b_{CO2}. Assume that the velocity of the two phases are equal, $u^r = u^p \equiv u^b$.

(e) Repeat this derivation to obtain one equation for C^b_{HCO3} from the separate concentration equations determined in part (c).

(f) In the special case of interfacial equilibrium of CO_2 between the RBC and plasma phases, and reaction equilibrium between CO_2 and HCO_3^- in the RBC phase, combine the results of parts (d) and (e) to obtain a single concentration equation with C^b_{CO2} as the only dependent variable.

(g) If the inlet concentration of CO_2 in blood is C_o, integrate this equation to determine the CO_2 concentration distribution $C^b_{CO2}(z)$ under steady state conditions .

Problem 16-4: Artificial Membrane Model



Broun and colleagues (J. Membrane Biol. 1972. 8:313-332) describe an artificial membrane consisting of two active protein layers enclosed by two selective films located at positions $z=z_A$ and $z=z_B$. The protein layers containing ATP and ADP meet at a dividing surface $z=z_m$. To promote a reaction-driven diffusion of glucose(GL), protein layer 1 incorporates immobilized

hexokinase (HK) whereas layer 2 incorporates phosphatase (PT). Well-mixed, external compartments A and B that surround this artificial membrane both contain GL.

The HK in layer 1 catalyzes the phosphorylation of GL by ATP to form glucose-6-phosphate (GP) by the reaction

$$GL + ATP \xrightarrow{HK} GP + ADP$$

The PT in layer 2 catalyzes the dephosphorylation of GP to form GL and inorganic phosphate (Pi):

$$GP \xrightarrow{PT} GL + Pi$$

The overall reaction occurring in the two layers is given by the sum of these two reactions.

$$ATP \longrightarrow ADP + P_i$$

This hydrolysis of ATP to ADP liberates a bond energy which can possibly promote active transport.

The films at $z=z_A$ and $z=z_B$ are highly permeable to GL but impermeable to GP. Both GL and GP readily pass through the dividing plane at $z=z_m$. Dehosphorylation in layer 1 is limited by the presence of GL while phosphorylation in layer 2 is limited by the presence of GP. In that case, the enzymatic reaction rates follow Michaelis-Menten kinetics that depend only on GL and GP concentrations:

$$R_{GL,1} = -R_{GP,1} = \frac{-\alpha_{HK} C_{GL,1}}{\beta_{HK} + C_{GL,1}}, \quad R_{GL,2} = -R_{GP,2} = \frac{\alpha_{PT} C_{GP,2}}{\beta_{PT} + C_{GP,2}}$$

Initially, GL and GP concentrations, $C_{GL,j}$ and $C_{GP,j}$, in the two layers (j=1,2) are zero. The GL concentrations in the external compartments, $C_{GL,A}$ and $C_{GL,B}$, are constant. The diffusion coefficient $\mathcal{D}$ of GL and GP are equal to each other and are the same in both layers. You can neglect differences in solubility of GL and GP in the two layers and in the external compartments.

(a) Assuming a 1-dimensional diffusion-reaction system with no convection, what are the dynamic mole balance equations for $C_{GL,i}(z)$ and $C_{GP,i}(z)$ in the i=1 and i=2 layers?
(b) State the total of eight boundary conditions for $C_{GL,i}$ and $C_{GP,i}$ in the two layers (i=1,2) at $z=z_A,z_B,z_m$. What are the initial conditions at t=0 in the two layers?
(c) Non-dimensionalize the mole balance equations and their boundary conditions using the dimensionless variables:

$$t = \frac{\mathcal{D}t}{(z_B - z_A)^2} \quad z = \frac{z - z_A}{z_B - z_A}, \quad C_{i,j} = \frac{C_{i,j}}{C_{GL,A}} \ (i = GL, GP, \ j = 1,2)$$

and the dimensionless parameters:

$$z_m \equiv \frac{z_m - z_A}{z_B - z_A}, \quad \gamma \equiv \frac{C_{GL,B}}{C_{GL,A}}$$

$$\alpha_{HK} \equiv \frac{(z_B - z_A)^2}{\mathcal{D} C_{GL,A}} \alpha_{HK}, \quad \alpha_{PT} \equiv \frac{(z_B - z_A)^2}{\mathcal{D} C_{GL,A}} \alpha_{PT}$$

$$\beta_{HK} \equiv \frac{\beta_{HK}}{C_{GL,A}}, \quad \beta_{PT} \equiv \frac{\beta_{PT}}{C_{GL,A}}$$

(d) Simulate the behavior of the dynamic GL and GP concentrations in the i=1 and i=2 layers when the dimensionless parameters have the values:

$$z_m = 0.5, \quad \gamma = 2, \quad \alpha_{HK} = 200, \quad \alpha_{PT} = 100, \quad \beta_{HK} = \beta_{PT} = 1$$

Then make a plot of $C_{GL}(z)$ and $C_{GP}(z)$ between z=0 and z=1 when the simulations reach steady state.

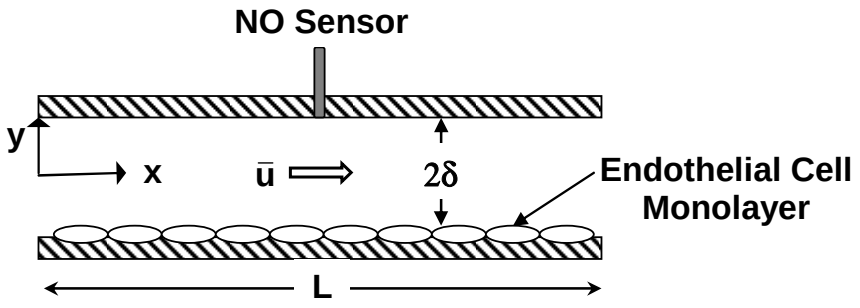
(e) Solve for the dimensionless molar flux of GL across each of the two membrane surfaces.

$$N_{A,z} \equiv -\frac{dC_{GL}}{dz}$$

What should be true of these two values at steady state? Is the GL flux in the same direction as the GL concentration driving force across the membrane, or are they in opposite directions (*i.e.* primary active transport)?

Problem 16-5: Nitric Oxide Generation and Shear Stress

Nitric oxide (NO) is a cell signaling molecule released by endothelium to regulate vascular smooth muscle tone. In an experiment designed to observe the effect of hydrodynamic shear stress on NO generation rate (Kansai *et* all, Circulation Research. 77: 284-293, 1995), a monolayer of bovine aortic endothelial cells was placed on the lower wall of a rectangular channel. While a flow of culture medium produced a desired shear stress τ_{wall} on the monolayer surface, NO concentration C_{NO} was measured by a miniature sensor mounted flush with the upper channel wall and directly above the center of the cell monolayer.



Develop a

mathematical model that relates the shear stress to the NO concentration that would be detected by the NO sensor once steady state is reached. The following additional information is available:

- The flow channel has dimensions of length L, height 2δ and width W.
- Assume steady state, fully-developed laminar flow of a Newtonian medium, the velocity field and wall shear stress are then given by (problem 13-4)

$$u_x = \frac{3}{2}\bar{u}\left(1-\frac{y^2}{\delta^2}\right), \quad u_y = u_z = 0, \quad \tau_{wall} = \frac{3\mu\bar{u}}{\delta}$$

  where $\bar{u}$ is the average velocity.
- In addition to convection and diffusion, NO undergoes oxidation in the medium at an intensive reaction rate $R_{NO}[\text{mol}/(\text{m}^3\text{-s})] = -k_r C_{NO}^2$ (The minus sign indicates that oxidation depletes NO).
- NO generation rate at the monolayer surface $R_{NO,wall}[\text{mol}/(\text{m}^2\text{-s}]$ is only a function of τ_{wall}.

(a) Write the steady state concentration equation for $C_{NO}(x,y,z)$ due to convection, diffusion and reaction if the flowing medium has a constant molar density and constane NO diffusion coefficient $\mathcal{D}_{NO}$.

(b) Make the concentration equation dimensionless using the dimensionless variables:

$$x = \frac{x}{L}, \quad y = \frac{y}{\delta}, \quad z = \frac{z}{W}, \quad C = \frac{\mathcal{D}_{NO}}{\delta R_{NO,wall}} C_{NO}$$

Arrange the equation such that the coefficient of the diffusion term in the y direction is unity. Explain the significance of the two dimensionless parameter groups, $Pe \equiv \bar{u}\delta/\mathcal{D}_{NO}$ and $R \equiv \delta^3 k_r R_{NO,wall}/\mathcal{D}_{NO}^2$.

(c) Based on the dimensionless equation, specify the conditions under which we can neglect diffusion in the x and z directions relative to diffusion in the y direction. Write the dimensionless concentration equation when these conditions are met.

(d) Formulate the dimensional and dimensionless boundary conditions.

(e) In one experiment, the sensor located at (x=L/2, y=+δ) detected an NO concentration of $C_{NO}(L/2,\delta)$=125nM when a shear stress of τ_{wall}=0.1 Pa-s was applied to the cells. Compute the value of $\bar{u}$ required to impose this τ_{wall}? Then, determine the corresponding NO generation rate from numerical simulations of the simplified dimensionless model. The known parameter values are: L=22mm, δ=0.125mm, μ=8.5×10^{-4} Pa-s, $\mathcal{D}_{NO}$= 3.33×10^{-9}m^2/s and k_r=36.0(m^3/mol-s).

(f) For the result found in part (e), plot *C* vs *y* at *x*=0.1, 0.2 and 0.5.

Problem 16-6: One-Dimensional Dispersion With Chemcal Reaction

Rather than being inert, suppose that the tracer described in the convection-dispersion model of section 15.5.3 undergoes a first-order reaction as it flows through a tube of diameter d at velocity u. The cross-sectional average of tracer concentration $C_s(z,t)$ can then be modelled by:

$$\frac{\partial C_s}{\partial t} + u\frac{\partial C_s}{\partial z} = \left(\mathcal{D}_s + \mathcal{D}_s^*\right)\frac{\partial^2 C_s}{\partial z^2} - k_r C_s \qquad (z>0)$$

where the coefficients for diffusion $\mathcal{D}_s$, dispersion $\mathcal{D}_s^*$ and reaction k_r are constants. Initially no tracer is in the tube (z>0). At the tube entrance (z=0), the tracer concentration C_o is a constant at all times. At sufficiently large downstream distances ($z\to\infty$), the tracer concentration can be neglected.

(a) State the mathematical equations for the initial and boundary conditions necessary to solve the differential concentration equation.

(b) Express the differential model equation and its conditions in terms of dimensionless tracer concentration $C(z,t)$ using the same scaling factors and dimensionless group as in section 15.5-3. There should now be an additional dimensionless group (define it as $\alpha=k_r/u$) which is due to the chemical reaction.

(c) Under what conditions can the Laplace transform with respect to time be applied to this model? Obtain the Laplace transform solution for the dimensionless concentration $\tilde{C}(z,s)$.

(d) Invert the Laplace transform to obtain an equation for the dimensionless concentration $C(z,t)$ in the dimensionless time domain. Note that you will have to use three relations obtained from: Roberts GE, Kaufman H, Table of Laplace Transforms, 1966.

$$L^{-1}\left\{\tilde{f}(as+b)\right\} = \frac{1}{a}\exp\left(-\frac{b}{a}t\right)f\left(\frac{t}{a}\right) \qquad \text{p 169, entry 3}$$

$$L^{-1}\left\{\frac{\tilde{f}(s)}{s}\right\} = \int_0^t f(\xi)\,d\xi \qquad \text{p 170, entry 13}$$

$$L^{-1}\left\{\exp\left(-\sqrt{s}\right)\right\} = \frac{1}{2\pi^{1/2}t^{3/2}}\exp\left(-\frac{1}{4t}\right) \qquad \text{p 246, entry 14}$$

(e) The correct result to part (d) is

$$C(z,t) = \sqrt{\frac{Pe_d z^2}{4\pi}}\exp\left(\frac{Pe_d z}{2}\right)\int_0^t \frac{1}{\xi^{3/2}}\exp\left[-\frac{Pe_d}{4}\left(\xi+\frac{z^2}{\xi}\right)-\alpha\xi\right]d\xi$$

Numerically integrate this equation to obtain a plot of C versus z in the domain, $40\geq z\geq 0$, when $Pe=1$, $t=10$ and $\alpha=0.1$. In the same graph, plot the corresponding dimensionless concentration distribution for the case of an inert tracer. What is the effect of the chemical reaction on dispersion?

Problem 16-7: Isotopic Tracers for Kinetic Analysis

Radioactive isotopic tracers can be used to quantify the transport and chemical kinetics of metabolites or drugs in the body. The count rates from an isotope in samples of body fluids or from external detection is a measure of tracer concentration. The purpose of this problem is to determine the physicochemical properties of the isotope and the metabolite or drug (*i.e.*, the tracee) such that tracer kinetics follow the behavior of the tracee.

Let $C^*(\mathbf{z},t)$ be the isotopic tracer concentration at some spatial point $\mathbf{z}$ and time t, and let $C(\mathbf{z},t)$ be the corresponding tracee concentration. By definition, specific activity is $S(\mathbf{z},t)=C^*(\mathbf{z},t)/C(\mathbf{z},t)$. Physical equivalence of the tracer and tracee exists at any point $\mathbf{z}$ in the system if: 1) the same velocity field applies to both; 2) their diffusion coefficients are equal, $\mathcal{D}=\mathcal{D}^*$; 3) the initial and boundary conditions on the concentration of both are the same. Chemical equivalence of the tracer and tracee exist if the chemical reaction rate of tracer R* and of tracee are related by $R^*(\mathbf{z},t) = (C^*/C)R=SR$ at any point $\mathbf{z}$ in the system. In this problem, we assume that that the tracer and tracee are both physically and chemically equivalent.

(a) Show that when the S is independent of time, the relative change of the tracer and tracee concentrations at two different times are equal (*i.e.* $\partial C^*/\partial t = (C^*/C)\partial C/\partial t$).

(b) Let us consider the total reaction rate of the tracee and tracer in a general form:

$$R + R^* = -k_r\left(C + C^*\right)^n$$

For $S<<1$, which is typically the case, show that the tracer kinetics are first order with respect to tracer concentration, even when $n>1$. When $n=1$, show that the rate equations reduce to the analogous forms: $R=-k_rC$ and $R^*=-k_rC^*$.

(c) In that case, the transport equations of tracee and tracer also have analogous forms:

$$\frac{\partial C}{\partial t} + u\bullet\nabla C = \mathcal{D}\nabla^2 C - k_r C$$

$$\frac{\partial C^*}{\partial t} + u\bullet\nabla C^* = \mathcal{D}\nabla^2 C^* - k_r C^*$$

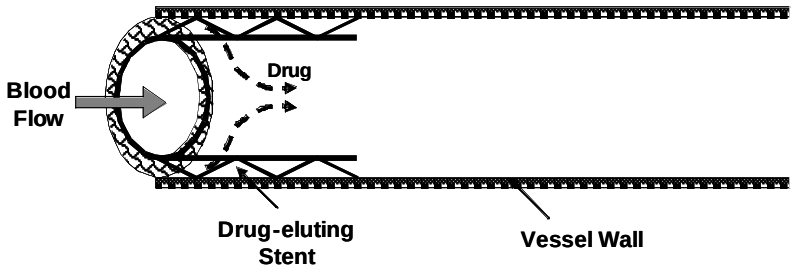
If the specific activity S is constant everywhere, show that the solution for C^* is also the solution for C.

(d) When S is not constant, obtain the dynamic equation that represents the specific activity:

$$\frac{\partial S}{\partial t} = ?$$

Will this equation allow us to compute $C(\mathbf{z},t)$ from $C^*(\mathbf{z},t)$?

Problem 16-8 Drug-Eluting Stent



In a common cardiovascular surgery, a ring-shaped stent is inserted on the surface of a partially blocked artery to increase blood flow. Often, the stent is impregnated with an anticoagulant drug. Time release of the drug into the blood prevents the formation of clots on the device. As drug is transported downstream from the stent, it adsorbs onto to the vessel surface and prevents clot formation on the endothelial wall. For a simplified analysis, assume that the artery can be modelled as a rigid straight tube of radius R and length L. In addition, consider the stent thickness to be negligible compared to R, and the stent length h<<L.

(a) Starting with the appropriate equation from table 15.2-1, write the local drug concentration C(r,z,t) assuming that:
   1) the velocity field in the blood corresponds to Poiseulle flow at a mean velocity u;
   2) C(r,z,t) is axisymmetric;
   3) drug diffuses radially and axially with a constant diffusion coefficient $\mathcal{D}$.

(b) Specify mathematically the five conditions necessary to solve this concentration equation given the following information. Initially, there is no drug in the blood, and drug does not enter at the tube entrance. For the stent surface at h>z>0, the molar flux of drug release N_o is approximately constant. Downstream of the stent at z>h, the flux of drug uptake by endothelial cells is proportional to local drug concentration, $N_r = kC$. Axial diffusion can be neglected at the tube outlet.

(c) Derive the governing equation in the dimensionless form

$$\lambda\frac{\partial C}{\partial t}+\left(1-r^2\right)\frac{\partial C}{\partial z}=\alpha\left[\varepsilon\frac{\partial^2 C}{\partial z^2}+\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C}{\partial r}\right)\right] \qquad (1\geq r>0,\quad 1>z>0)$$

using the scaled variables (where C_o is yet to be determined)

$$C=\frac{\mathrm{C}}{\mathrm{C_o}},\quad z=\frac{\mathrm{z}}{\mathrm{L}},\quad r=\frac{\mathrm{r}}{\mathrm{R}},\quad t=\frac{\mathrm{t}}{\theta}$$

Specify the dimensionless parameters α, λ and ε in terms of the original model parameters.

(d) Explain the physical conditions necessary for the dimensionless concentration equation to be simplified to:

$$\left(1-r^2\right)\frac{\partial C}{\partial z}=\frac{\alpha}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C}{\partial r}\right) \qquad (1\geq r>0,\quad 1>z>0)$$

(c) Show that, with appropriate selection of C_o, the dimensionless boundary conditions to solve the simplified concentration equation of part (d) have the form

$$z=0: \quad C=0$$

$$r=0: \quad \frac{\partial C}{\partial r}=0$$

$$r=1: \quad -\frac{\partial C}{\partial r}=\begin{cases}1 & h>z>0\\ -\beta C & 1>z>h\end{cases}$$

What is the physical significance of β?

Problem 16.9: Spinning Disk With Zeroth Order Surface Reaction

Consider a rotating disk with solute depletion by chemical reaction on the disk surface. Unlike section 16.3.1 in the textbook where the chemical reaction rate was assumed to be first order, we now consider the case when it is zeroth order.

(a) Specify the boundary condition at z=0 for the surface reaction which occurs at a constant molar depletion rate per unit area, $-R_s^S[\mathrm{mol/m^2-s}]$. Using the same dimensionless variables as in section 16.3.1, express this condition in dimensionless form. What is the physical meaning of the Damkohler number , $Da^S \equiv -R_s^S \Big/ \left(C_{s\infty}\sqrt{\upsilon\Omega}\right)$, that appears in this condition?

(b) With this zeroth-order boundary condition at z=0, solve for the dimensionless concentration distribution $C(z)$ by performing two successive integrations of Eq. 16.3-7.

(c) For a mass transfer coefficient defined as:

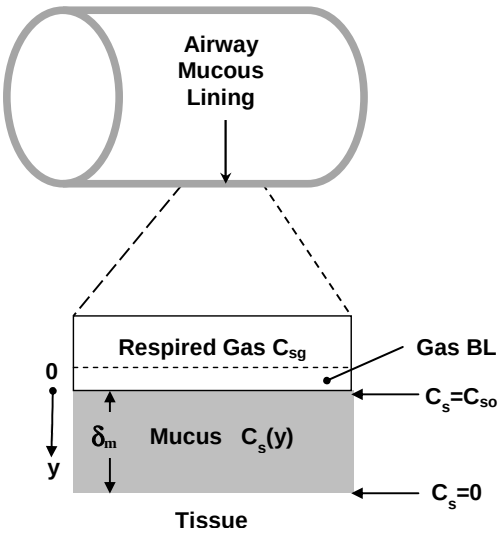
$$k_s \equiv \frac{N_{s,\mathrm{wall}}}{C_s(0)-C_{s\infty}}$$

formulate a dimensionless correlation for the Sherwood number ($Sh_d = k_s d/\mathcal{D}_s$) in terms of the Schmidt number ($Sc = \upsilon/\mathcal{D}_s$) and the Reynolds number ($Re=d^2\Omega/4\upsilon$). Use the following relationship between the integral appearing in the equation for $C(z)$ and the gamma function, $\Gamma(1/3)$, to simplify the correlation as much as possible:

$$\int_0^\infty \exp\left(-\alpha\xi^3\right)d\xi=\frac{\Gamma(1/3)}{3\alpha^{1/3}}=\frac{0.893}{\alpha^{1/3}}$$

(d) Compare your results for zeroth order reaction to those in section 16.3 when the reaction is first order.

Problem 16-10 Gas Phase Resistance to Uptake into Airway Mucous



Transport of an inhaled reactive gas s into an airway wall was modelled in section 16.1.1 as a one-dimensional, steady state, diffusion-reaction process through a stagnant mucous layer of thickness δ_m. More realistically, the transport domain consists of the respired gas phase in contact with the mucous layer. In this two-phase model, convection-diffusion through the gas phase can be modeled as a boundary layer process at the gas side of the air-mucous interface. The molar flux through the boundary layer is given by:

$$\left[N_s\right]_{y=0} = k_s\left[C_{sg} - \lambda C_{so}\right]$$

Here, k_s is a gas-phase mass transfer coefficient; C_{sg} is the molar concentration of s in the bulk gas phase; C_{so} is the concentration of s in mucous at the gas-mucous interface; λ is the equilibrium partition coefficient between the concentration of s in gas relative to mucous. Follow the steps outlined below to analyze this improved model.

(a) Based on Eqs, 16.1.12, 16.1-18 and 16.1-19, formulate the flux of species s in mucous at the gas-mucous interface $[N_s]_{y=0}$ and at the mucous-tissue interface $[N_s]_{y=1}$.
(b) What must be true if there is no accumulation of species s at the gas-mucous interface? Use this concept to relate C_{so} to C_{sg} and the other parameters in the model. Then eliminate C_{so} from the equation for $[N_s]_{y=1}$. From this result, explain how the gas phase boundary layer affects the penetration rate of species s into tissue.
(c) What condition on k_s is necessary for equilibrium to (approximately) exist between C_{sg} and C_{so}? Reduce the equation for $[N_s]_{y=1}$ for this case. Compare this to Eq. 16.1-20 ?

CHAPTER 17

17-1: Tissue Engineered Cartilage

Chondrocytes produce the extracellular matrix protein collagen type II (A) which is known to resist compressive strain in native cartilage. A tissue cartilage construct is produced by seeding chondrocytes onto hyaluronate-based scaffolds. The collagen production rate r_A[g/min] is proportional to the number density of chondrocytes Ω[cells/ml] provided that there is cell-cell contact.

$$r_A = \begin{cases} \lambda\Omega & \text{if} \quad \Omega \geq \Omega_c \\ 0 & \text{if} \quad \Omega < \Omega_c \end{cases}$$

Here, $\lambda=2\times10^{-13}$g collagen/(cell-min) is a rate constant and $\Omega_c=10^7$cells/ml is the critical cell concentration necessary to maintain cell-cell contact (An implicit assumption in this equation is that the porosity of the construct is sufficiently large that it does not interfere with cell-cell contact).

The growth rate of chondrocytes Ξ[cells/ml/day] is expressed by the rate expression:

$$\Xi = \beta\Omega.$$

where $\beta=0.2$ day^{-1}.

(a) Perform a mass balance for type II collagen density ρ_A[g collagen/ml scaffold] and a number balance for chondrocyte number density $\Omega(t)$ in a construct with a porosity greater than 98%. Be sure to state your assumptions.
(b) With Ω_o[cells/ml] signifying the initial seeding density, solve the ODEs formulated in part (a) for $\Omega(t)$ and $\rho_A(t)$.
(c) In an experiment in which 1 million cells are initially seeded per milliliter of the scaffold, what is the time t_c required for cell-cell contact? How long does it take for the collagen density to reach that found in the native cartilage density, which is about 0.1 g/ml.

Problem 17-2: Moments of Axon Migration

Consider an *in vitro* experiment of axon tip migration with taxis in a long tube. When the gradient of the chemotactic agent is constant, the population balance for the number density of axon tips Ω (Eq. 17.3-3) is

$$\frac{\partial\Omega}{\partial t} + \nu\frac{\partial\Omega}{\partial z} - \mu\frac{\partial^2\Omega}{\partial z^2} = 0 \qquad (\infty > z > 0)$$

Here, the transport coefficients μ[m^2/s] for random migration and ν[m/s] for chemotaxis are constants. The initial and boundary conditions are

t=0: $\Omega = 0$

z=0: $\Omega = \Omega_0 e^{-t/\tau}$

$z \to \infty$: $\Omega \to 0$

Note that the boundary condition at z=0 approximates a rapid seeding of the axons at the mouth of the tube during the time interval $\{0,\tau\}$.

(a) Transform the governing differential equation and its conditions in terms of the following dimensionless variables:

$$\Omega \equiv \frac{\Omega}{\Omega_0}, \quad t \equiv \frac{t}{T}, \quad z = \frac{z}{L}$$

The scaling parameters T and L representing the characteristic time and distance of tip migration are, as of yet, not known.

(b) Determine T and L such that the dimensionless governing equation becomes

$$\frac{\partial \Omega}{\partial t} = \frac{\partial^2 \Omega}{\partial z^2} - \frac{\partial \Omega}{\partial z}, \quad \infty > z > 0$$

How are T and L related to μ and ν?

(c) The k^{th} moment of the *dimensionless* axon tip distribution is defined as

$$\lambda_k(t) \equiv \int_0^\infty z^k \Omega(z,t) dz$$

What are the dimensionless initial conditions for the zero and first moments: $\lambda_0(0)$ and $\lambda_1(0)$?

(d) By integrating the equation for $\partial\Omega/\partial t$ in part (b), obtain $d\lambda_0(0)/dt = d(\int \Omega dz)/dt$ and $d\lambda_1/dt = d(\int z\Omega\, dz)/dt$. You should assume that $\partial\Omega/\partial z$ is negligible at the boundaries of the domain.

(e) For k=0 and then k=1, solve for $\lambda_k(\theta)$ using the two ODE's found in part (d) and the initial conditions from part (c)

(f) The mean distance that the axon tips migrate at any time can be represented by

$$\bar{z}(t) = \frac{\int_0^\infty z\Omega dz}{\int_0^\infty \Omega dz}$$

What is the corresponding *dimensionless* mean migration distance $\bar{z} \equiv \bar{z} / L$ in terms of the dimensionless moments , $\lambda_0(t)$ and $\lambda_1(t)$.

(g) Under what physical conditions are the characteristic times very different, that is $\tau << T$? Simplify the dimensionless migration distance $\bar{z}(\theta)$ for this situation. Then formulate the corresponding dimensional migration distance $\bar{z}(t)$ in terms of the parameters μ and ν.

Problem 17-3 Oxygen Limitation in Tissue Engineering

A tissue-engineered construct consists of a highly porous, spherical scaffold of radius 'a' that is initially loaded with a dilute cell suspension and then cultured in a bioreactor for several days. The bioreactor needs to be optimized for adequate delivery of nutrient (oxygen) delivery throughout the scaffold.

(a) By integrating a dynamic cell number balance, formulate an algebraic expression for cell number density $\Omega(t)$ (cells/cm^3) starting with a uniform, initial cell distribution $\Omega_o \equiv \Omega(0)$. The proliferation rate of cells Ξ(cells/ cm^3/time) is given by the following kinetic model:

$$\Xi = k_1 \Omega (k_2 - \Omega)$$

The parameters k_1 and k_2 are constant. Neglect cell transport (migration) in the construct and assume that the construct volume remains constant.

(b) Separate experiments have shown that the oxygen consumption rate of cells $-R_{O2}$ (moles of O_2/sec/cm^3) is proportional to the cell density:

$$R_{O2} = -k_{O2} \Omega$$

Assuming that the oxygen transport can be treated as a pseudo-steady process (see problem 15-5), write the pseudo-steady differential equation that determines the O_2 concentration distribution and specify the boundary conditions.

(c) Obtain the analytical solution from part (b) and show that the oxygen concentration profile is given by

$$C_{O2}(r,t) = C_o - \frac{k_{O2}\Omega(t)}{\mathcal{D}_{O2}} \frac{\left(a^2 - r^2\right)}{6}$$

where $\Omega(t)$ is the time-dependent cell density from part (a), $C_o = C_{O2}(a,t)$ is the oxygen concentration at the periphery of the construct, and $\mathcal{D}_{O2}$ is the diffusivity of oxygen in the construct.

(d) Based on the solution of part (c), formulate the rate of oxygen uptake $\dot{N}_{O2}(t)$ at r=a.

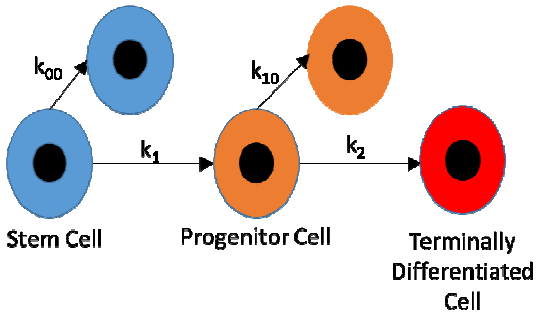
(e) Compute Ω_o for a construct of radius a=1cm that initially contains a uniform distribution of 5 million cells. Then compute $\dot{N}_{O2}(t)$ (μmol/day) as a function of time given the remaining parameter values: $\mathcal{D}_{O2} = 2 \times 10^{-5}$cm^2/sec, k_2=50 million

cells/cm^3, k_1k_2=0.2 day^{-1}, k_{O2}=0.5 x 10^{-12} moles O_2/sec/million cells and C_o=0.12 μmoles/cm^3.

(f) Judging from the oxygen concentration profile expression, where in the construct is C_{O2} at its minimum? Make a plot of this minimum C_{O2} as a function of time. What is the critical time t_c at which oxygen transport can no longer support the cellular oxygen demand? Compute the cell number density $\Omega(t_c)=\Omega_c$ that is reached at t_c.

Problem 17-4: Stem-Cell Differentiation With Replication

In a model of a stem-cell differentiation with replication, a population of stem cells (0) undergoes differentiation into progenitor cells (1) while also undergoing self-renewal to form new stem cells. The progenitor cells propagate to form new progenitor cells or they can become terminally differentiated cells (2) that no longer propagate. The rates of all three cellular rate processes—self-renewal, propagation, terminal differentiation—are first-order with respect to cell number density with the rate constants shown in the figure.



(a) Defining $\Omega_j(t)$ as the number density of cell type j (j=0,1,2) at time t, formulate rate expressions Ξ_i for the cellular fate processes associated with the three cell types.

(b) Consider the case where N stem cells per cm^3 are added to a well-mixed reactor. Develop a cell population model by performing a number balance for three the cell types in the system.

(c) Specify the initial conditions $\Omega_j(0)$ when j=0,1,2.

(d) Apply the Laplace transform $\boldsymbol{L}\{\Omega_j(t)\}=\tilde{\Omega}_j(s)$ to these equations and solve for $\tilde{\Omega}_j(s)$ when j=0,1,2.

(e) Expand $\tilde{\Omega}_3(s)$ as the sum of partial fractions (appendix C.4). Obtain the dynamic change in the cell number density of the terminally differentiated cells, by taking the inverse transform, $\Omega_3(t)=\boldsymbol{L}^{-1}\{\tilde{\Omega}_3(s)\}$.

(f) Consider a chondrogenic differentiation process involving mesenchymal stem cells . The stem cells upon exposure to chondrogenic medium in a closed incubation chamber undergo differentiation to form transitory chondrocytes which terminally differentiate into chondrocytes . During this process, the self- renewal rates are zero, and the rate constants for the differentiation steps are k_1=0.1 day^{-1} and k_2=0.2 day^{-1}. Plot relative cell densities Ω_i/N as a function of time. Determine the relative proportions of the three cell types at the end of 21 days of differentiation. Assume well-mixed conditions.

Problem 17-5: Antibiotic Treatment of an Infected Tissue

A serious infection with bacteria can be treated by continuous infusion of an antibiotic into the blood stream. We can analyze the dynamics of the bacterial distribution using a Krogh model (Fig. 16.2-3) consisting of a representative capillary of radius a_b and a surrounding tissue region of inner radius a_b and outer radius a_t. Within the blood flowing through the capillary, the antibiotic concentration is everywhere constant at a value C_o. In the tissue, the number density of bacteria is $\Omega(r,t)$ and the antibiotic concentration is $C(r,t)$. The bacteria proliferate at a rate per unit volume $k^{prolif}\Omega$[cells/s/m^3]. They randomly migrate at a flux $-k^{rand}d\Omega/dr$[cells/s/m^2] in the r direction, which is much greater than migration in the axial direction. When the local antibiotic concentration is above a critical level, $C>C_{crit}$, the bacteria die at a rate $k^{death}C\Omega$[cells/s/m^3].

Antibiotic diffuses at a flux $-\mathcal{D}dC/dr$ in the r direction that is much greater than diffusion in the axial direction. Further, antibiotic is cleared from the tissue at a rate $k^{ab}C$, which is independent of the bacteria. At the capillary blood-tissue boundary $r=r_b$, the antibiotic is in interfacial equilibrium with partition coefficient $\lambda^{t,b}$. Because it is a local infection, bacterial transport across this boundary is negligible. Initially, the bacterial number density Ω_o is uniform and there is no antibiotic in the tissue.

(a) Formulate the unsteady state governing equation for the number density distribution of bacteria, $\Omega(r,t)$ in the tissue region.
(b) Formulate the unsteady state governing equation for the concentration of antibiotic, $C(r,t)$ in the tissue region.
(c) Formulate the initial and boundary conditions. Assume radial symmetry with adjacent tissue regions at $r=r_b$.
(d) Express the model equations in dimensionless form with the variables:

$$t \equiv \frac{\mathcal{D}}{a_t^2}t, \quad r = \frac{r}{a_t}, \quad \Omega \equiv \frac{\Omega}{\Omega_o}, \quad C \equiv \frac{C}{C_o}$$

(e) Simulate the radial distributions of bacterial number density and antibiotic concentration at t=50, 100 and 200 given the following dimensionless parameter values:

$$\frac{k^{rand}}{\mathcal{D}} = 0.01, \quad \frac{k^{prolif}a_t^2}{\mathcal{D}} = 0.1, \quad \frac{k^{death}a_t^2C_o}{\mathcal{D}} = 0.3, \quad \frac{k^{ab}a_t^2}{\mathcal{D}} = 2$$

$$C_{crit} \equiv \frac{C_{crit}}{C_o} = 0.1, \quad \frac{a_b}{a_t} = 0.1, \quad \lambda^{t,r} = 1$$

(f) In this simulation, is the infection controlled by the antibiotic? What do think would happen if the antibiotic is stopped?

(g) A different class of antibiotic with characteristics that lead to a new value for the dimensionless parameter $k^{death} a_t^2 C_o / \mathcal{D} = 0.2$ is to be tested. Determine whether the infection is treatable with this new antibiotic.