Problem Set 3 solution **BE.462J/3.962J**
Issued: Day 6 **Spring 2003**
Due: Day 8
(20 pts total)

A recent study of controlled release of a model small-molecule drug from poly(lactide-co-glycolide) microspheres prepared by the single-emulsion method found that the diffusion constant of the drug through the polymer was best related to the polymer's molecular weight according to:

$$D(t) = D_0 + \frac{\square}{M(t)}$$

In this equation, $\square$ and D_0 are constants, and M(t) is the molecular weight of the matrix polymer. From data obtained on PLGA microspheres, the constants were determined to be:

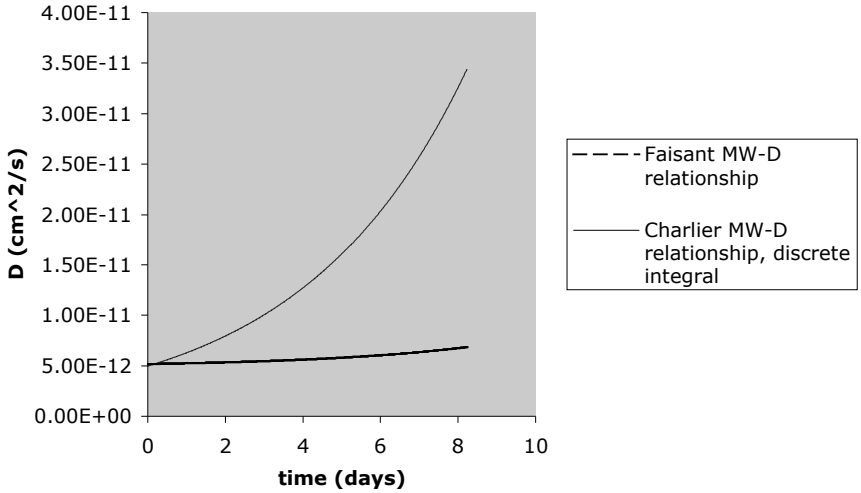
$\square$ = 2.1x10^{-11} cm^2(kg/mole)/s
D_0 = 4.9x10^{-12} cm^2/s

We can use this expression for D(t) in the Charlier controlled release model to obtain modified expressions for h(t) and Q(t) (we'll call this model B, and the expression derived in class model A). Assume that the molecular weight $M(t) = M_0e^{-kt}$, where M_0 is the initial molecular weight and *k* is the degradation rate constant for PLGA hydrolysis. A reasonable estimate for *k* is:

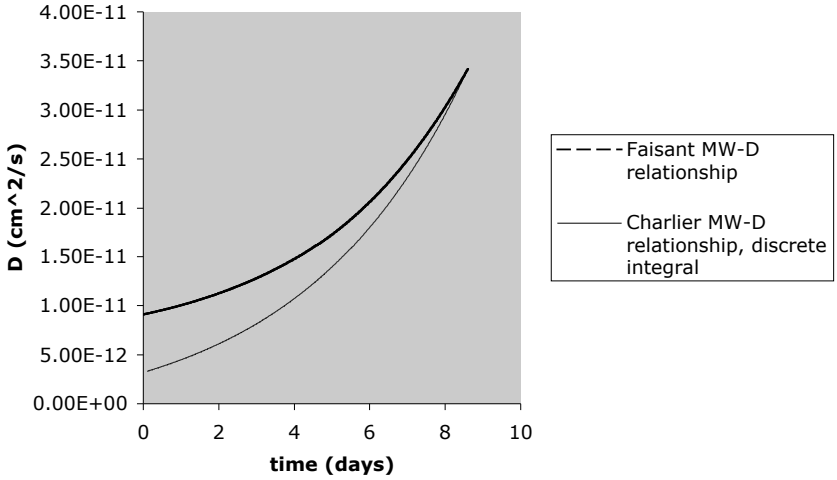
Degradation rate constant for PLGA hydrolysis: k = 9.8E-03 hr^{-1}

1. (5 pts) Quantitatively, will the diffusion constant in model B given above differ significantly from that obtained from model A derived in class over experimentally-relevant timescales?

The difference in diffusion constants depends significantly on the initial value of the molecular weight, M_0. For release from a high molecular weight matrix with M_0 = 80,000 g/mole, we have:



…where the diffusion constant starts similar in both models and becomes greatly disparate after several days of hydrolysis. In contrast, if a low molecular weight matrix is used (e.g., the plot below is for M_0 = 5000 g/mole), the diffusion constant begins quite disparate and becomes similar in each model after several days:



This analysis indicates that for a high molecular weight matrix, the two models will at least initially predict similar release profiles, which will become different as time goes on (after only 24-48 hours). For a low molecular weight matrix, the difference in release profiles will be apparent immediately.

2. (5 pts) Using the model B formula above for the diffusion constant, derive a new expression for the thickness of the diffusion field h(t) in the Charlier model. Assume M(t) has an exponential decay with time as derived in class.

$$D = D_o + \frac{\Phi}{M(t)}$$

FROM THE CHARLIER MODEL:

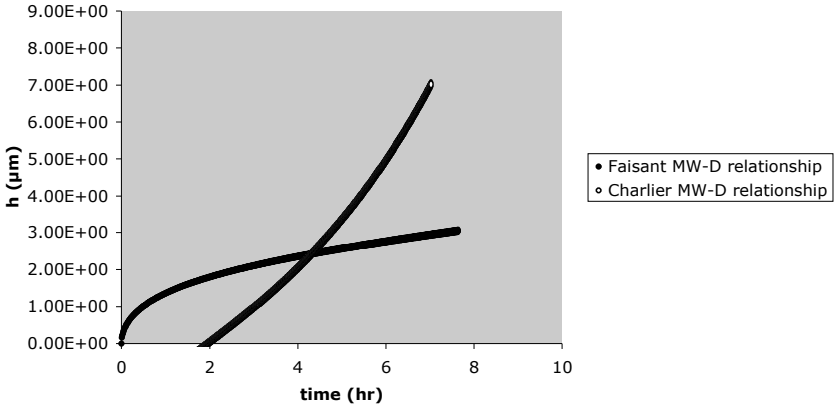
$$D(t)\frac{C_s}{C_o}dt = h'dh'$$

$$\int_0^t \left(D_o + \frac{\Phi}{M_o e^{-kt}}\right)\frac{C_s}{C_o}dt = \int_0^h h'dh'$$

$$\frac{C_s}{C_o}D_o t + \int_0^t \frac{\Phi C_s e^{kt}}{C_o M_o} = \frac{h^2}{2}$$

$$\frac{C_s}{C_o}\left[D_o t + \frac{\Phi}{M_o}\left(\frac{e^{kt}-1}{k}\right)\right] = \frac{h^2}{2}$$

$$\therefore h(t) = \left[2\frac{C_s}{C_o}\left(D_o t + \frac{\Phi}{M_o}\frac{(e^{kt}-1)}{k}\right)\right]^{1/2}$$



3. (10 pts) Using the data above and that given below, determine how long release experiments that measure Q(t) (total amount of drug released at time t) would need to be carried out to distinguish which of the two models for the diffusion constant ($D = D_0 e^{kt}$ as derived in class, or the expression given above) best represents release of HGH from a PLGA matrix in the framework of the Charlier model. (Hint: plot Q(t) for each of the two models; solve for Q(t) in model B by numerically integrating an expression dQ = (…)dt.)

Solubility of HGH in PLGA matrix: C_s = 6.12E-04 g/cm^3
Concentration of HGH encapsulated in the matrix: C_0 = 0.02 g/cm^3
Surface area of release matrix: A = 1.67 cm^2
Initial molecular weight of the matrix: M_0 = 78,000 g/mole

AGAIN USING THE CHARLIER MODEL:

(i) $\frac{1}{A}\frac{dQ}{dt} = \frac{DC_s}{h(t)}$

REARRANGING:

(ii) $Q = \int_0^t \frac{ADC_s}{h(t)}\,dt = \int_0^t C_s A\left(D_0 + \frac{\Phi}{m_0 e^{-kt}}\right)\left[\frac{2C_s}{C_0}\left(D_0 t + \frac{\Phi}{m_0}\left(\frac{e^{kt}-1}{k}\right)\right)\right]^{1/2} dt$

...SINCE (ii) IS NOT STRAIGHTFORWARD TO INTEGRATE, WE CAN OBTAIN A REASONABLE NUMERICAL ESTIMATE FOR Q(t) USING (i) INSTEAD:

(iii) $dQ = \frac{AD(t)C_s\,dt}{h(t)}$

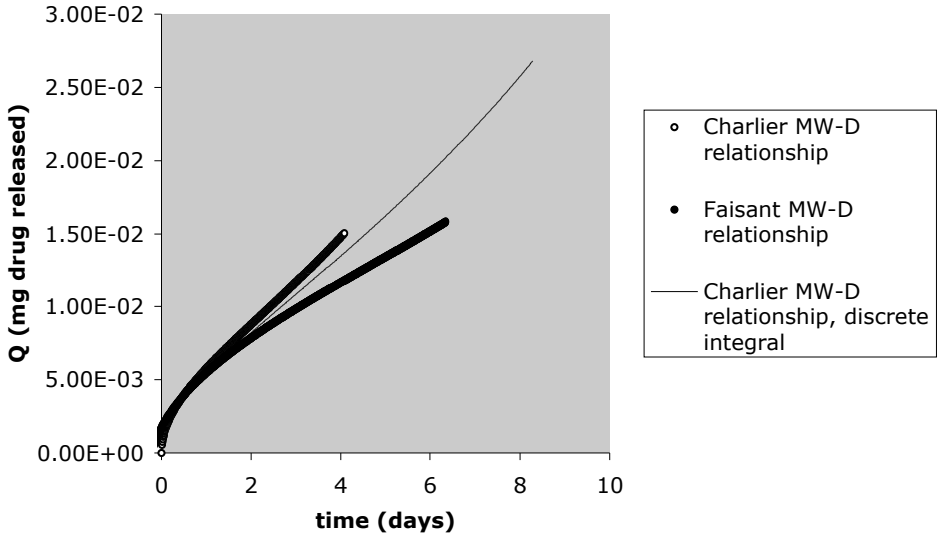
↓ DISCRETE INTEGRATION

(iv) $\Delta Q_i = \frac{AD(t)C_s}{h(t)}\Delta t_i$ WHERE ΔQ_i IS THE AMOUNT OF DRUG RELEASED IN A SMALL TIME INTERVAL Δt_i

AND (v) $Q = \sum_{i=1}^{all} \Delta Q_i$ (Q IS OBTAINED BY SUMMING ALL THE ΔQ_i FROM TIME 0 TO TIME t)

SINCE WE HAVE EXPLICIT EXPRESSIONS FOR D(t) AND h(t), (iv) AND (v) CAN BE IMPLEMENTED IN A SPREADSHEET / MATLAB / CALCULATOR TO NUMERICALLY OBTAIN Q(t) IN MODEL B.

Using the derived expressions, we can compare release predicted by model A and model B:



Thus, for the given parameters, release experiments carried out for at least 2 days would be necessary for the 2 models to deviate from one another significantly. Release experiments carried out for 10 days should allow an unequivocal determination of which model better fits the experimental system.