Exam I **BE.462J/3.962J**
Model Solutions **Spring 2003**

(60 points total)

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1. (5 points) Explain the following observation: autocatalysis generally has a smaller influence on the degradation rate of surface-eroding polymers than bulk-eroding polymers.

Oligomers formed by chain hydrolysis in surface-eroding polymers are rapidly solubilized into the surrounding medium, thus minimizing the influence of acidic chain ends of these oligomers on hydrolysis of the remaining matrix. In contrast, acidic by-products forming deep within bulk-eroding polymers are largely trapped within the matrix until significant erosion has occurred, thus providing ample opportunity for these species to catalyze further chain cleavage.

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2. (5 points) Explain why knowing the spatial distribution of adhesion ligands at a surface in addition to the average total density is a key part of understanding cellular responses to ligand-modified biomaterials.

Adhesion receptors on the cell surface, particularly the integrin family of adhesion receptors, are known to interact with intracellular signaling components and have modulated signaling on clustering of the receptors. Clustering of integrins initiates assembly of actin filaments and signaling complexes at the site of the receptors, forming focal contacts. Thus ligands in close spatial proximity on the substrate (with separations on the order of the size of receptors, e.g. ~5-20 nm) will have the ability to induce different signaling in adhesion receptors by driving receptor clustering than would be obtained if ligands are separated by greater distances. Two surfaces with the same total density of ligand but with different local densities (i.e. clustered vs. unclustered distribution of ligand across the surfaces) will elicit different levels of cell adhesion strength and migration speeds, and may have other cell function effects.

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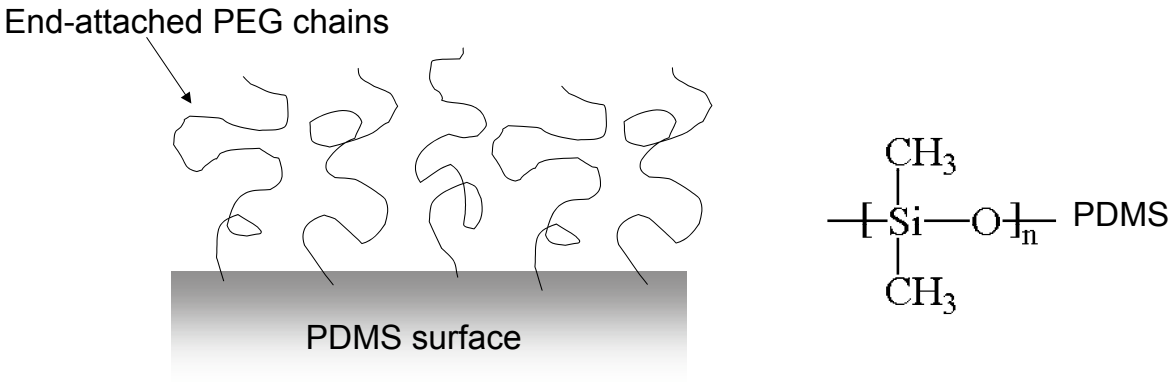
3. (5 points) A synthetic vascular graft fabricated from the synthetic rubber poly(dimethyl siloxane) (PDMS) is surface modified with poly(ethylene glycol) as illustrated schematically below. In platelet adhesion tests carried out for 48 hrs at 37°C, platelets were completely unable to adhere to the modified surface. From other tests it is known that PDMS and the covalently bonded PEG layer are chemically stable for years under physiological conditions. However, when tested in animals, the graft is found to occlude after 5 months due to platelet binding to the graft surface. Explain this result.



End-attached (grafted) layers of poly(ethylene glycol) or dextran can prevent proteins from adsorbing to the polymer-modified surface. Cell adhesion is thus eliminated if proteins fail to adsorb. However, experimentally, protein resistance may be either kinetic or thermodynamic: Kinetic resistance implies that a free energy minimum is reached when protein binds the surface: the energy barrier to reach this minimum is large, implying a long time-scale for achievement of equilibrium and a window of time over which the surface resists adsorption. Physically, this is due to the highly dynamic nature of the PEG/dextran chains that sterically interfere with the approach of proteins to the underlying surface. Thermodynamic protein resistance is only obtained with high chain densities and/or long grafted chain lengths, and implies permanent protein resistance- free energy is minimized with proteins repelled from the substrate.

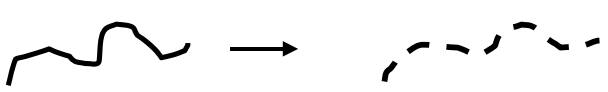
Observation of protein resistance over time-scales of a few days may only reflect kinetic protein resistance: and over longer time-scales adsorption may occur as equilibrium is finally attained. Slow protein adsorption in a vascular graft may lead to eventual platelet deposition and ultimately graft occlusion.

4. (10 points) Show how the following hydrogel network would degrade *in vivo*, if at all, by showing what bonds break, the chemical structure of the resulting chain break, and schematically illustrate the ultimate structural changes. An example of this analysis is shown to demonstrate:

Example: $-(CH_2)_5-\overset{O}{\overset{\|}{C}}-O)_n-$

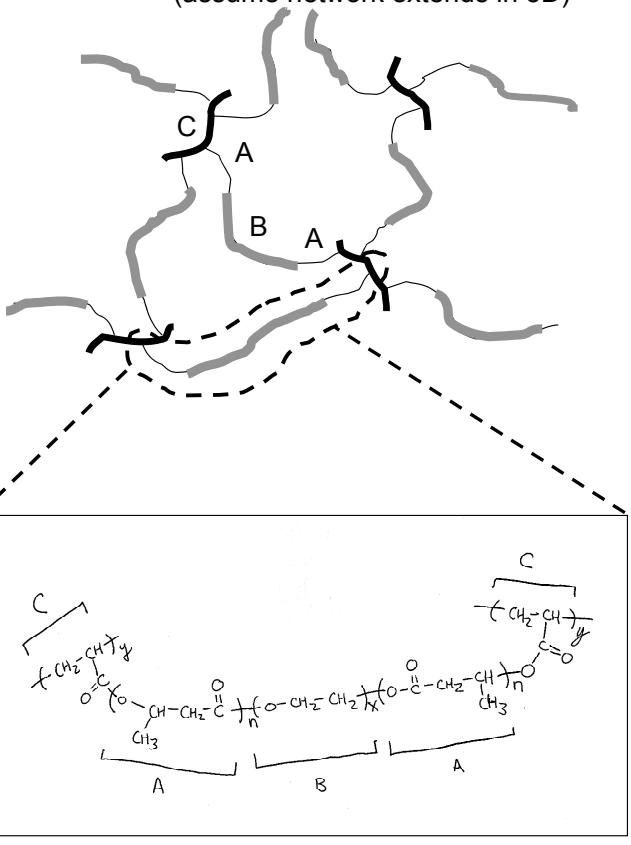
Answer:

$-(CH_2)_5-\overset{O}{\overset{\|}{C}}-O)_n-$ → $-(CH_2)_5-\overset{O}{\overset{\|}{C}}-OH$ $\quad$ $HO-(CH_2)_5-\overset{O}{\overset{\|}{C}}-O-$

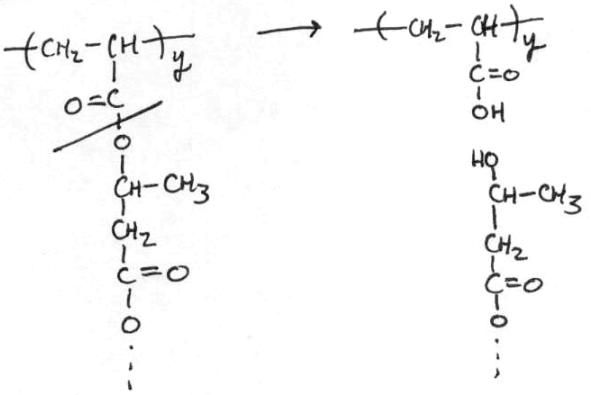


The network is composed of 3 different types of repeat units, designated A, B, and C in the schematic.

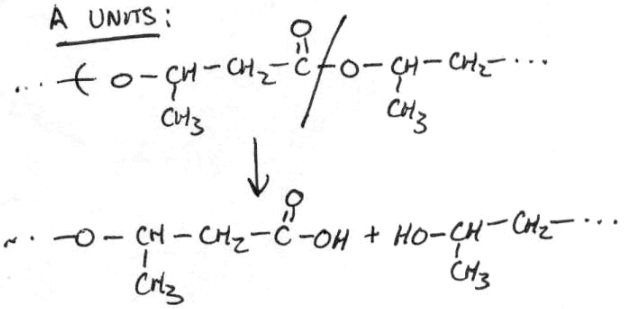
(assume network extends in 3D)



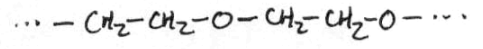
C UNITS:



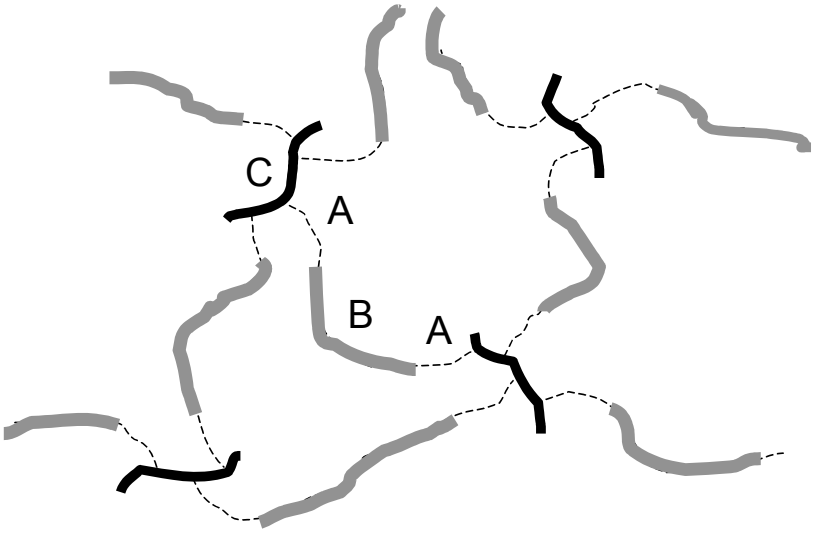
A UNITS:



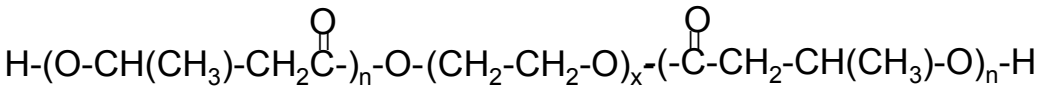
B UNITS:



... NO UNSTABLE BONDS

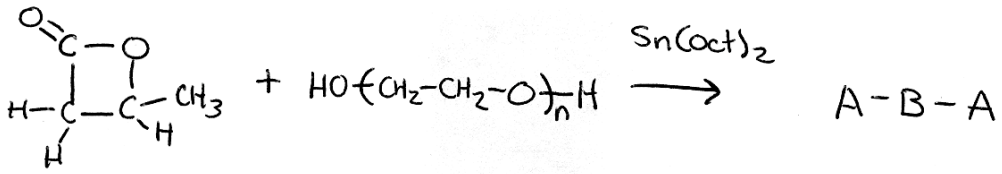


5. (5 points) A precursor of the network shown in question 2 has the chemical structure:



Propose a route for synthesis of this material and show the chemical structures of the monomer and state what initiator you would use.

The simplest solution is to use poly(ethylene glycol) as an initiator and ring-opening polymerization catalyzed by stannous octoate:



It is also possible to propose a di-lactone ring monomer for the polymerization. However, the high ring strain in the monomer shown actually helps polymerization proceed (the ring strain is relaxed by polymerization); it is quite difficult in contrast to obtain high yields of polymerization of an 8-member ring due to its relative stability.

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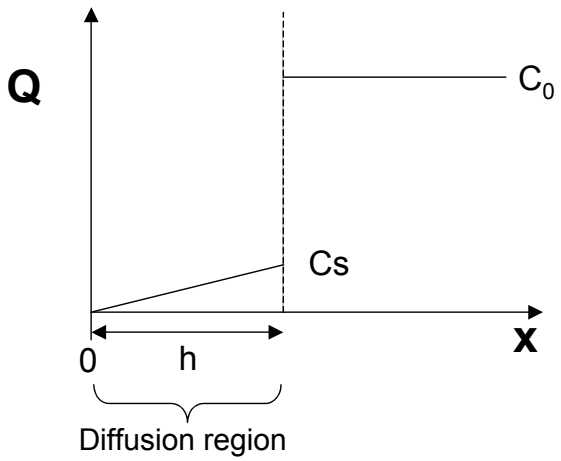
6. (10 points) The Charlier model for controlled release discussed in class was developed to describe the kinetics of drug release from bulk-eroding degradable polymers. The model concentration profile is shown below as a reminder. Describe in as much detail as possible why the model as we developed it is inappropriate to describe release from surface-eroding degradable polymers. Make specific suggestions of how the model might be modified to attempt to describe surface-eroding devices.



The Charlier model cannot accurately predict the release of encapsulated drugs from surface-eroding polymer matrices on several points:

a. *The Charlier model assumes the diffusion constant of drug in the matrix is increasing with time throughout the device, due to water infiltration throughout the device and homogeneous bulk degradation of chains throughout the matrix. However, chain degradation occurs only at the surface of surface-eroding polymers, and the diffusion constant in the interior of the matrix will remain constant.*

b. *The diffusion constant for drug releasing from the surface-eroding polymer will also quantitatively have a much lower value, as transport will be by direct diffusion of the drug molecule through the polymer instead of drug transport through water+polymer.*

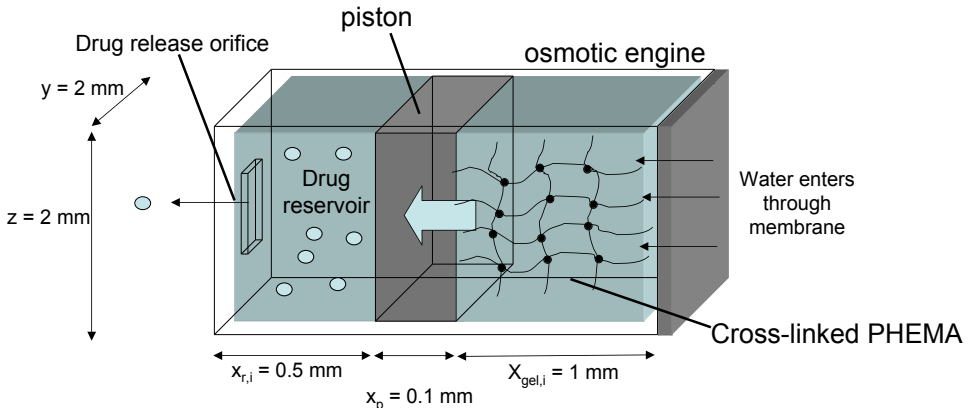
c. *The Charlier model, in accordance with the behavior of bulk erosion, assumes the dimensions of the device remain constant as degradation proceeds. (Of course, this assumption breaks down at the point where the matrix collapses). Surface-eroding polymers, by contrast, will continuously shrink as degradation proceeds into the device.*

Modications to consider:

   a. *One possibility is to neglect diffusion of the drug through the matrix and only consider the kinetics of drug release at the surface due to erosion. This would require an entirely new model but could account for the changing dimensions of the device and the dominance of surface erosion on drug release.*

   b. *Another alternative is to maintain the pseudo-steady-state concentration profile approximation for drug diffusion toward the surface and include a second term of drug release in the equation for dQ that is due to motion of the erosion front into the sample. The difficulty here is that the kinetics of the erosion front motion and drug diffusion will be quite different- and an analytical solution may not be obtainable except for approximations such as described in (a). In this case, the diffusion constant for drug motion through the polymer would remain a constant (water penetration does not occur in surface-eroding polymers).*

7. (10 points) Osmotic pump drug-delivery devices can be based on the swelling thermodynamics of hydrogels. Consider the device shown below: The osmotic engine is to be composed of poly(hydroxyethyl methacrylate) (PHEMA) chains with molecular weight M (given below), cross-linked into a network. Calculate the molecular weight between cross-links, M_c, necessary if the device must eject 80% of the solution in the drug reservoir when the osmotic engine reaches equilibrium. Assume the piston moved by the osmotic engine is frictionless, the drug solution exerts negligible pressure against the piston, and the network swells isotropically. The volume fraction of PHEMA in the engine prior to cross-linking is 0.4. For the calculation, use the other necessary physical and thermodynamic parameters given below.



initial volume of gel: $V_{gel,i} = x_{gel,i}^3$ (gel is a cube that does not fill y and z dimensions of engine chamber)

initial volume of drug reservoir: $V_0 = x_{r,i}yz$

$\lambda^3 = V_{gel,f}/ V_{gel,i}$

$\lambda = 0.5$

specific volume of PHEMA = 0.869 cm^3/g

molar volume of water = 18 cm^3/mole

M = 150,000 g/mole

$$\frac{1}{M_c} = \frac{2}{M} - \frac{v_{sp,2}}{v_{m,1}\phi_{2,r}} \frac{\left[\ln(1-\phi_{2,s}) + \phi_{2,s} + \chi\phi_{2,s}^2\right]}{\left[\left(\frac{\phi_{2,s}}{\phi_{2,r}}\right)^{1/3} - \frac{1}{2}\left(\frac{\phi_{2,s}}{\phi_{2,r}}\right)\right]}$$

The final volume in the drug reservoir must be $0.2V_0$. This can be achieved by moving the piston toward the release orifice by a distance $0.8x_{r,I} = 0.4$ mm. This implies the swelling of the gel must be such that $x_{gel,f} = x_{gel,i} + 0.2x_{r,I} = 1.4$ mm. Since we are asked to assume the gel can isotropically swell in the 'engine' chamber, we have $\lambda = (x_{gel,f})^3/ V_{gel,I} = 2.744$. Now:

$$\lambda^3 = \frac{V_{gel,f}}{V_{gel,i}} = \frac{\phi_{2,r}}{\phi_{2,s}}$$

$$\left(\frac{x_{gel,f}}{x_{gel,i}}\right)^3 = 2.744 = \frac{\phi_{2,r}}{\phi_{2,s}}$$

We are given that $\phi_{2,r}$ = 0.4, thus $\phi_{2,s}$ = 0.145. Turning to the equation relating M_c to $\phi_{2,r}$, $\phi_{2,s}$, χ, M, the polymer specific volume and water molar volume, we obtain:

$$\frac{1}{M_c} = \frac{2}{M} - \frac{v_{sp,2}}{v_{m,1}} \frac{\left[\ln(1-\phi_{2,s}) + \phi_{2,s} + \chi\phi_{2,s}^2\right]}{\left(\frac{\phi_{2,s}}{\phi_{2,r}}\right)^{1/3} - \frac{1}{2}\left(\frac{\phi_{2,s}}{\phi_{2,r}}\right)} = 2.72257\text{x}10^{-04}$$

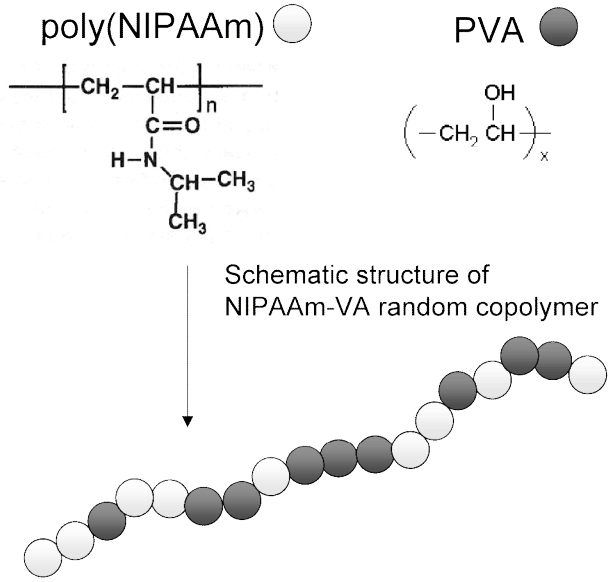
Therefore M_c = 3673 g/mole.

8. (10 points) An approach for controlled drug release to treat arthritis has been investigated by injecting concentrated poly(vinyl alcohol) (PVA) solutions into the knee of patients experiencing inflammation. It is found that the gel rapidly dissolves over a period of a few days. To improve the stability of the gel at 37°C, a proposed solution is to copolymerize PVA with N-isopropyl acrylamide (NIPAAm) to obtain copolymers with a random distribution of PVA and poly(NIPAAm) units along the chain, as illustrated below.

    a. Why would the PVA gel have such a short lifetime *in vivo*?

    b. Will the proposed change in molecular structure (synthesis of a copolymer as illustrated schematically below) improve the stability of the gel? Why or why not?

    c. How would you modify this PVA/PNIPAAm copolymer strategy to make the gel more stable while retaining an injectable formulation?



a. *A poly(vinyl alcohol) gel forms by hydrogen bonding between groups of adjacent repeat units in the chains. Because each repeat unit of the polymer can also strongly hydrogen bond with water, water competes for binding and the net lifetime of any single polymer-polymer bond is very short. This leads to the general instability of these physical gels at 37°C, where thermal energy further limits the lifetime of each polymer-polymer bond.*

b. *Provided that enough NIPAAm repeat units are incorporated into the chains to allow cooperative interchain NIPAAm-NIPAAm associations, this approach may work to strengthen the gel. Poly(NIPAAm) is an LCST polymer that dehydrates its isopropyl group with increasing temperature. Association of NIPAAm groups, being driven by hydrophobic association, becomes stronger with increasing temperature and will thus strengthen the gel with increasing temperature (the opposite trend occurs for the H-bonding PVA groups).*

c. *To improve this strategy, one might seek to synthesize block copolymers, where instead of randomly placing NIPAAm groups along the polymer chains, blocks of poly(NIPAAm) alternate with blocks of PVA. A block copolymer structure will more readily allow cooperative bonding of multiple adjacent NIPAAm groups to their neighbors in an opposing chain, providing stronger physical cross-links in the gel.*