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BioE 10

Introduction to Biomedicine for Engineers

Take-home Final Assignment

Fall 2010

Due Monday, December 13 at 4:30pm to
Department of Bioengineering Office, Stanley 306

Name	
SID	
Signature* (required)	

SCORE (for instructors only)

Question 1:		/40
Question 2:		/35
Question 3:		/35
Question 4:		/30
Question 5:		/25
Question 6:		/20
Question 7:		/20
Question 8:		/20
TOTAL		/225

*Your signature affirms that you understand and have followed the rules listed on page 2, and that you have worked completely independently on this assignment.

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RULES FOR FINAL ASSIGNMENT

- To facilitate grading, please print out this assignment and write your answers in the spaces provided, similar to the midterm exams. If you need additional pages, feel free to attach them.

- As always, show your work and clearly mark your final answer.

- A hard copy of the assignment will be due to the Bioengineering office (306 Stanley Hall) by **4:30 pm on Monday, December 13**.

- The assignment is "open book, open notes," which means you may freely consult your textbook, notes, problem sets, exams, and online resources and databases. Note that this does not include personal communications of any kind, including email (except to Prof. Kumar and/or the GSIs for clarification).

- All answers must be expressed in your own words and show reasoning and calculations. For example, if you are given a circuit and asked to calculate total current, it is unacceptable to say that you arrived at your answer by plugging the circuit into a piece of software. Similarly, unit conversions must be carried through manually. As a rule: when in doubt, show your calculations.

- **No consultation of any kind with others is permitted.** This includes but is not limited to discussing strategies to solve problems, discussing interpretations of questions, and comparing solutions.

- The assignment is designed to take 2-3 hours from beginning to end, but you may spend as much time working on it as you wish prior to the deadline. I would recommend clearing off a block of time in your schedule to complete the assignment in one sitting.

Good luck!

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1. Lifeact is a 17-amino acid peptide sequence that binds to actin filaments in living cells. When Lifeact is fused to a fluorescent protein, it can be used to visualize actin networks in living cells. The sequence of Lifeact is as follows:

MGVADLIKKFESISKEE

A. Consider a solution of this peptide. What will be the net charge on most molecules at (1) pH 7 and (2) pH 11? Assume that the N-terminal amine and C-terminal carboxylic acid have pKa values of 9 and 2, respectively, and that the side chains have the following pKa values: Arg – 12, Asp – 4, Cys – 8; Glu – 4; His – 6; Lys – 10; Tyr – 10. (10)

B. At pH 4, what fraction of Lifeact molecules will have negative charges on all three glutamate residues? (10)

C. Write out an mRNA sequence that could be used to encode the first six amino acids above (MGVADL). You do not need to include start and stop codons. Be clear about the polarity of the mRNA (5' end vs 3' end) (10)

D. Suppose you convert the mRNA in (C) to a cDNA molecule using reverse transcriptase, with a yield of 1 nanogram (ng) of double-stranded (ds) cDNA. Suppose you then generate PCR primers for this sequence. How many cycles of PCR would you need to run in order to amplify this ds cDNA up to at least 2 μg of ds cDNA? Assume that the molecular weight of one nucleotide in a single-stranded DNA molecule is ~330 g/mol. (10)

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2. The enzyme HMG CoA reductase converts HMG CoA to mevalonic acid. It is centrally involved in the metabolism of cholesterol and is the target of the "statin" drugs widely used to treat atherosclerotic disease.

A. Suppose the entropy change of unfolding at 25 C is +1 J/K/mol. If two-thirds of the protein molecules are folded under these conditions, what is the enthalpy per mole of unfolding under these conditions? (10)

B. In the folded structure of HMG CoA reductase, would you be more likely to find an arginine residue on the interior or exterior of the protein, and why? (5)

C. Identify whether each the following quantities increases or decreases when a protein spontaneously folds and briefly explain why: protein conformational entropy, protein enthalpy, water (solvent) entropy, system free energy. (10)

D. Suppose the K_m of HMG CoA reductase is 8 mM and the V_{max} is 12 mmol mevalonic acid/L/min. What concentration of HMG CoA would you need in solution to generate mevalonic acid at an initial rate of 8 mmol/L/min? (10)

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3. A 2008 paper in the *Journal of Clinical Investigation* (Dorfman et al., JCI 118: 1040-9) examined the influence of two genes, mannose-binding lectin 2 (MBL2) and transforming growth factor 1 (TGFB1) on the clinical manifestations of cystic fibrosis.

A. Imagine that two alleles exist for each gene in the population, with allelic frequencies given in parentheses: M (0.6) and m (0.4) for MBL2; and T (0.75) and t (0.25) for TGFB1. Assuming these genes segregate independently, what fraction of the population would be expected to have the MmTt genotype? (10)

B. As the name would imply, mannose-binding lectin 2 is a protein that binds mannose; suppose the dissociation constant for this binding interaction is 38 nM. In a solution with an analytical (nominal) concentrations of mannose-binding lectin of 1 nM and an analytical (nominal) mannose concentration of 10 nM (note that mannose is in large excess of mannose-binding lectin 2), calculate the concentration of free (unbound) mannose-binding lectin 2 in solution. (10)

C. Below is an internal portion of the coding (non-template) strand of the TGFB1 gene:

5′-CCCCGCCGCCGCCGCCCTTCGCGCCCTGGGCCATCTCCCTCC-3′

1. Write the sequence of the non-coding (template) DNA sequence. (5)

2. Assuming the 5'-most nucleotide is the first nucleotide in a codon (i.e., it defines a reading frame), write the amino acid sequence encoded by this sequence. (5)

3. Suppose the underlined C mutates to an A. What would be the amino acid sequence now? (5)

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4. Suppose you have a strip of an unknown biomaterial of length 50 cm and cross-sectional area 10 cm^2. Suppose you then do an experiment in which you hang one end of the strip from a ledge and allow the other end to dangle free.

A. Suppose you grab the free end of the strip and instantaneously stretch it to a total strip length of 60 cm. If the material is a linearly elastic solid with a Young's modulus of 1 MPa, sketch the force against your hand as a function of time. (5)

B. How much force will you need to apply to hold the strip in place? (10)

C. What is the strain energy (in J/m^3) associated with this deformation? (10)

D. Suppose you repeat this experiment with a Voigt-model viscoelastic material that has such a strong viscous component as to be almost fluid-like. Sketch the force on your hand as a function of time and explain how and why (in molecular terms) this differs from what you observed for the elastic material. (5)

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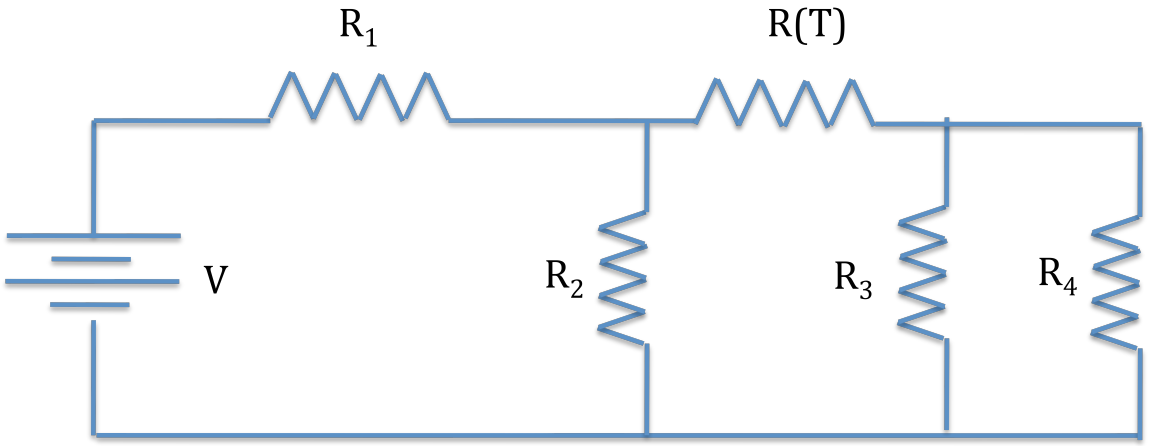
5. Consider the following thermistor circuit, where R_1 – R_4 represent resistors of fixed resistance and R(T) is a temperature-dependent resistor.



A. Derive a formula for the total current through the circuit in terms of V, R_1, R_2, R_3, R_4, and R(T). Express your answer as a simple fraction with fully distributed sums and differences in the numerator and denominator. (15)

B. Suppose V = 1 V, R_1 = 1 kOhm, R_2 = 3 kOhm, R_3 = 2 kOhm, R_4 = 0.5 kOhm, and R(T) = 1.5 kOhm for a given temperature. Calculate the current flowing through R_1. (10)

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6. Suppose you are interested in using a spectrophotometer to measure the concentration of a solution of bovine serum albumin (mol wt. 66399 g/mol, extinction coefficient 44000 M^{-1} cm^{-1}). The detector of the spectrophotometer can reliably measure sample absorptions as small as 1% of the illuminator lamp intensity; i.e., if the lamp intensity is 1 W, the detector can reliably detect sample absorptions of 0.01 W or greater. The path length of the cuvette is 1 cm.

A. What is the smallest protein concentration you can measure? (10)

B. For highly concentrated BSA solutions, you find that your spectrophotometer no longer provides accurate measurements of concentration even though the protein does not precipitate out of solution under these concentrations. Explain why this is the case. (10)

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7. Imagine that you are interested in measuring the ability of a renal countercurrent hemodialysis system to remove a specific toxin from the bloodstream. Suppose that blood is flowing from a patient's bloodstream to the hemodialyzer at 500 mL/min with a toxin concentration of 10 mg/dl, and that it is leaving the hemodialyzer and returning to the bloodstream at the same flow rate but a toxin concentration of 2.5 mg/dl.

A. If the dialysate stream is flowing at 750 mL/min, calculate the toxin concentration in the dialysate output (i.e., after it has exchanged solutes with the bloodstream. Assume that the input dialysate stream contains no toxin. (10)

B. Calculate the extraction ratio of the toxin. (5)

C. If the dialysis membrane was doubled in thickness, by what factor would the membrane permeability change? (5)

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8. Short answer questions:

A. Explain the difference between the following surgical procedures for cancer: biopsy, palliative surgery, and curative surgery. (5)

B. Describe a strategy involving tissue microarrays to determine whether a specific surface protein is a biomarker for a particular type of tumor. (5)

C. Describe two strategies to focus application of radiation to a specific anatomical location. (5)

D. When a particular drug is injected into the bloodstream, it distributes into all tissues in the body. When the same drug is conjugated to polyethylene glycol (PEG) and injected into the bloodstream, it distributes everywhere but the central nervous system. Give a plausible explanation for this difference. (5)

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