Spring 2005 (Przybycien) **42-101 Intro to BME** **NAME: ____________________**

EXAM #3 SOLUTIONS and GRADING SCHEME

Part I: Short Answer Questions (48 pts)

Short written-answer and short calculation questions. I'll be looking for significant keywords, equations and/or diagrams. - *No more than two or three sentences in answer to any question in this section please.*

1. (6 pts) Explain how an uncompetitive inhibitor works.

   An uncompetitive inhibitor binds to the enzyme-substrate complex, preventing its dissociation to form product. (6 pts) Both v_{max} and K_M are decreased by a factor of $(1 + [I]/K_I)$

2. (6 pts) The "standard man" transfers 72 kcal/hr of heat to the surroundings at rest as a byproduct of metabolic activity. Given that man generates energy by aerobic respiration and assuming that 50% of the energy generated by respiration is lost as heat to the surroundings (hence the 72 kcal/hr heat transfer rate), estimate the rate of glucose usage by the standard man at rest in moles/hour.

$$\frac{72\text{kcal}}{\text{hr}} \times \frac{100\%\text{total metabolic activity}}{50\%\text{heat loss to surroundings}} \times \frac{1\text{ mol ATP}}{7.3\text{kcal}} \times \frac{1\text{mol glucose}}{36\text{molATP}} = 0.547945\text{mol glucose/hr}$$

$$\approx 0.55\text{mol glucose/hr}$$

   (2 pts ΔG for ATP, 2 pts ATP from respiration, 1 pt #, 1 pt sig figs)

3. (6 pts) What is lymph and what is its purpose?

   Lymph is interstitial fluid that bathes the cells (3 pts); mainly derived from plasma. Lymph, delivers nutrients, collects wastes and helps in the trafficking of cells from the immune system (lymphocytes) (3 pts).

4. (6 pts) What is a nephron and what does it do?

   The nephron is the functional unit of the kidney (3 pts). Nephrons filter the blood, secreting substances to be removed and re-adsorbing substances to be retained, ultimately forming urine (3 pts).

5. (6 pts) Our "walking box" model for gait analysis has both a kinetic energy term and a potential energy term. State explicitly the physical walking phenomenon that each of these terms represents.

   The KE term represents the acceleration of the leading leg forward during a stride (3 pts); the PE term represents the bobbing of body up and down to accommodate leg swing (3 pts).

6. (6 pts) In our "walking box" model for gait analysis, is there an optimum walking velocity? Justify your answer.

   Our model for the rate of energy expenditure on walking is expressed as

   $$\dot{W} = \frac{\alpha m v^3}{2a} + \frac{\beta m g a v}{8L}$$

   To look for an extremum, w.r.t. walking velocity, we take the first derivative and set it equal to zero, solving for the value of v that satisfies this equation (3 pts)

   $$\frac{\partial \dot{W}}{\partial v} = 0 = \frac{3\alpha m v^2}{2a} + \frac{\beta m g a}{8L} \Rightarrow v = imaginary\ number$$

   So, there is no extremum for the mathematical function describing Wdot. But, if look over the range of physical values for v we realize that $v \geq 0$ and that Wdot = 0 when $v = 0$. This makes sense as the minimum energy will be expended when the walking velocity is zero (3 pts), i.e. no walking! This is a so-called "trivial solution" for this system.

7. (6 pts) What criterion would you use to decide if the flow of fluid in a vessel was dominated by viscous or inertial effects? State the criterion and how it may be used to decide.

   The Reynolds number, Re = $\rho v d/\mu$, is the criterion (3 pts). Large values of Re (> 100) indicate that the flow is dominated by inertial effects; small values of Re (< 100) indicates that flows are dominated by viscous effects (3 pts).

8. (6 pts) We've stated multiple times that fluid pressure decreases in the direction of flow. However, in the case of an aneurysm, you showed that the pressure actually increases in the direction of blood flow. Explain why this occurs. [Hint: refer to the relevant energy balance.]

   Applying Bernoulli's equation to the aneurysm (3 pts) where point 1 represents the healthy, upstream portion of the blood vessel and point 2 represent the aneurysm (bulge in the vessel), we go from $P_1 + \rho\frac{v_1^2}{2} + \rho g z_1 = P_2 + \rho\frac{v_2^2}{2} + \rho g z_2$ to $P_2 = P_1 + \frac{\rho}{2}\left(v_1^2 - v_2^2\right)$. We expect $v_2 < v_1$ since $A_2 > A_1$. So, the blood flow has less KE at the aneurysm then it does upstream; the KE from the small (normal) portion of the vessel is converted to flow work (higher pressure) in the expanded (aneurysm) part of the vessel (3 pts).

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Part II: Detailed Questions (52 pts)

1. (26 pts) A drug company has two lead compounds that inhibit a key enzyme involved in the progression of a disease. This enzyme catalyzes the reaction: (S)ubstrate→(P)roduct. Compound A is a competitive inhibitor ($K_{I,A}$ = 2.3 nM compound A); compound B is an uncompetitive inhibitor ($K_{I,B}$ = 5.6 nM compound B). The target enzyme has k_{cat} = 0.00421 mM substrate/(min•μM enzyme) and K_M = 72.9 μM substrate. Typical intracellular enzyme and substrate concentrations are 32 μM and 98 μM, respectively. The maximum concentration that may be used for either compounds A or B in the body without the appearance of side effects is 10.0 nM.

   If the company has the resources to commercialize only one drug compound, is there a preference as to which compound the drug company should pursue, all other things being equal? You must justify your answer with a calculation.

   Equating enzyme activity with enzymatic reaction rate *v* (5 pts)

$$\frac{dP}{dt} = -\frac{dS}{dt} = v(no\ inhibitor) = \frac{v_{\max}S}{K_M + S} = \frac{k_{cat}E_oS}{K_M + S}$$
$$= \frac{(0.00421mMS/(\min\bullet \mu ME))(32\mu ME)(98\mu MS)}{72.9\mu MS + 98\mu MS}$$
$$= 0.077253mMS/\min$$

   Equation for competitive inhibition reaction rate (5 pts), numerical rate value (3 pts)

$$\frac{dP}{dt} = -\frac{dS}{dt} = v(10.0nMA) = \frac{v_{\max}S}{K_M(1 + A/K_{I,A}) + S} = \frac{k_{cat}E_oS}{K_M(1 + A/K_{I,A}) + S}$$
$$= \frac{(0.00421mMS/(\min\bullet \mu ME))(32\mu ME)(98\mu MS)}{(72.9\mu MS)(1 + 10.0nMA/2.3nMA) + 98\mu MS}$$
$$= 0.027062mMS/\min$$

   Equation for uncompetitive inhibition reaction rate (5 pts), numerical rate value (3 pts)

$$\frac{dP}{dt} = -\frac{dS}{dt} = v(10.0nMB) = \frac{v_{\max}S/(1 + B/K_{I,B})}{K_M/(1 + B/K_{I,B}) + S} = \frac{k_{cat}E_oS/(1 + B/K_{I,B})}{K_M/(1 + B/K_{I,B}) + S}$$
$$= \frac{\frac{(0.00421mMS/(\min\bullet \mu ME))(32\mu ME)(98\mu MS)}{(1 + 10.0nMB/5.6nMB)}}{\frac{72.9\mu MS}{(1 + 10.0nMB/5.6nMB)} + 98\mu MS}$$
$$= 0.043851mMS/\min$$

   Since *v*(10 nM A) < *v*(10 nM B) < *v*(no inhibitor), inhibitor A seems a better choice to pursue than B as it's more potent at similar, tolerated concentrations (5 pts). (Note however that the effect on the enzyme is modest in both cases – a factor of ~3 reduction in enzyme activity for inhibitor A versus a factor of ~2 reduction in enzyme activity for inhibitor B; neither A or B would appear to be potential blockbusters.)

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2. (26 pts) A sitting student suddenly stands up, exerting a force of 1.8g's on themselves. Estimate the average blood pressure (gauge pressure), in mmHg, in the arterial and venous portions of the circulation in the brain. You may assume that the average blood pressure (gauge pressure) at the left ventricle is 100 mmHg, that the pressure drop due to resistance to flow in the arterial circulation is 5 mmHg, that the pressure drop due to resistance to flow in the microvasculature (the capillary bed) is 90 mmHg, and that the average distance from the left ventricle to the brain for this student is 0.26 m. The acceleration due to gravity is 9.81 m/s^2; the densities of blood and mercury (Hg) are 1.056 g/mL and 13.55 g/mL, respectively.

   What may the student experience on standing suddenly? Why?

   Add hydrostatic effect to pressure drop in direction of flow to determine average blood pressure on arterial and venous sides of the circulation in the brain:

   On the arterial side

   P_{head} $= P_{left\ ventical} - \Delta P_{flow,arterial} + P_{hydrostatic}$ (3 pts)

   $= P_{left\ ventical} - \Delta P_{flow,arterial} + \rho(1.8g)h$
   (3 pts ρgh, 3 pts 1.8xg)

   = 100mmHg – 5mmHg + (1.056 g/mL)(1.8*9.81m/s2)(-0.26m)
   (3 pts)
   *<kg/1000g><106mL/m3><Pa/kg/(m•s2)><kPa/103Pa><760mmHg/101.325kPa>
   (3 pts)

   = 100mmHg – 5mmHg – 36.3643mmHg
   = 58.63mmHg
   ~ 59 mmHg (1 pt # + sig figs)

   On the venous side

   P_{head} $= P_{left\ ventical} - (\Delta P_{flow,arterial} + \Delta P_{flow,capillary}) + P_{hydrostatic}$ (3 pts)

   $= P_{left\ ventical} - \Delta P_{flow,arterial} + \rho(1.8g)h$

   = 100mmHg – (5 + 90 mmHg) + (1.056 g/mL)(1.8*9.81m/s2)(-0.26m)
   *<kg/1000g><106mL/m3><Pa/kg/(m•s2)><kPa/103Pa><760mmHg/101.325kPa>

   = 100mmHg – 95mmHg – 36.3643mmHg
   = -31.36 mmHg
   ~ -31 mmHg (1 pt # + sig figs)

   Lightheadedness/fainting (3 pts) are possible as blood flow to the brain will be reduced due to pressure-induced constriction when the arterial blood pressure supplying the brain falls below atmospheric pressure (3 pts).