Written Homework 1

Reactions, equilibrium, and enzyme kinetics • 100 points

Explain your reasoning, show calculations, and include units. Handwritten or typed answers are welcome. Use a calculator as needed; no coding is required. Submit your written work through Canvas. Demo 1 is a separate submission.

1 Medicine entering and leaving the body 15 points

In class, $dA/dt = -kA$ described elimination with no additional input. Now consider a continuous IV infusion delivering medicine at a constant rate I directly into the bloodstream. Treat the body as one well-mixed compartment with elimination rate kA. Use hypothetical values A(0) = 100 mg, I = 10 mg/h, and k = 0.20 h^{-1}. These values are for modeling practice only.

(a) Using 'rate of change = rate in − rate out,' write the differential equation for A(t). Define A, I, and k and give the units of every term in the equation. (4 points)

(b) Calculate dA/dt at t = 0. Is the amount initially increasing or decreasing? Explain how it can decrease even though medicine is entering. (3 points)

(c) Find the steady amount A* by setting dA/dt = 0. Explain what happens when A is above or below A*. At A*, do input and elimination stop, or balance? (4 points)

(d) Sketch A(t) with continuous infusion and with no input, starting from the same 100 mg. Label the axes, initial value, and long-term amounts. If the infusion is then stopped after A has approached A*, what equation describes the subsequent change, and what happens to A? No explicit solution is required. (4 points)

2 Reversible binding and conservation 25 points

Two identical protein monomers A bind to form a dimer B in a closed, well-mixed compartment of constant volume. Let a = [A] and b = [B]. Use the reaction rates given below; the definition of k_+ already includes any convention for identical reactants.

$$A + A \rightleftharpoons B \qquad \text{forward rate} = k_+ a^2 \qquad \text{reverse rate} = k_- b$$

(a) Write da/dt and db/dt. Explain why forming one dimer changes the monomer concentration by twice as much. (7 points)

(b) State the units of k_+ and k_- when concentrations are in µM and time is in seconds. (4 points)

(c) Identify a conserved quantity and use it to express da/dt using a alone. Define every new symbol. (6 points)

(d) Let a(0) = 4 µM, b(0) = 0, $k_+ = 0.10\ \mu M^{-1}\ s^{-1}$, and $k_- = 0.20\ s^{-1}$. Calculate the initial da/dt and db/dt. Does a negative da/dt mean the concentration is negative? (4 points)

(e) Both the number of monomers and the solution volume are doubled before the reaction starts. Does the initial forward reaction rate per unit volume increase fourfold? Explain. (4 points)

3 Receptor occupancy and equilibrium 30 points

Use a simplified version of our coffee example: a ligand L binds reversibly to a receptor R, forming a complex C. A ligand is a molecule that binds to a target; a receptor is the binding target. This model considers one ligand and one type of binding site, without competition from other molecules.

$$L + R \rightleftharpoons C$$

Let l = [L], r = [R], and c = [C]. The total receptor concentration is Rtotal = r + c. Assume that free ligand concentration l is held constant by a large reservoir. All numbers below are illustrative; they do not represent a specific number of cups of coffee or a dosing recommendation.

(a) Write dc/dt using k_+, k_-, l, and c by substituting r = Rtotal − c. Explain the formation and dissociation terms. (5 points)

(b) At equilibrium, dc/dt = 0. Rearrange your equation to show that receptor occupancy θ satisfies the expression below, with Kd = k_-/k_+. Explain what θ measures. (7 points)

$$\theta = c / Rtotal = l / (Kd + l)$$

(c) For Kd = 2 μM, calculate θ at l = 1, 2, and 4 μM. Report each result as a percentage. Does doubling l always double occupancy? Explain using your results. (6 points)

(d) Two ligands have Kd values of 1 μM and 5 μM. Which has greater equilibrium occupancy at the same positive free concentration? Explain what a smaller Kd means in this model. (4 points)

(e) A student says, “Kd = 2 means the reverse reaction is twice as fast as the forward reaction.” Explain why this statement is incorrect. Refer to units and to the concentrations in the reaction rates. (4 points)

(f) At equilibrium, are binding and dissociation still occurring? Are free receptor and complex concentrations necessarily equal? Explain. (4 points)

Connect the model to physiology

Your answers should distinguish receptor occupancy from a physiological outcome such as alertness or pain relief. Occupancy describes binding; a complete physiological response can depend on additional processes. No additional submission is required for this note.

4 Enzyme saturation and model interpretation 30 points

An enzyme E binds a substrate S to form a complex C, which can release product P. For this problem, the initial reaction rate v follows the Michaelis–Menten model. The table contains idealized teaching data, not experimental measurements.

$$E + S \rightleftharpoons C \rightarrow E + P \qquad v = V_{max}\, s / (K_m + s)$$

Here s is free substrate concentration, Vmax is the maximum rate at the given enzyme concentration, and Km is the substrate concentration at half the maximum rate.

Substrate s (mM)	Initial rate v (mM/s)
0.25	0.10
0.50	0.167
1.00	0.25
2.00	0.333
4.00	0.40
9.00	0.45

(a) Sketch v against s with labeled axes and units. Explain why the curve supports a saturating enzyme model rather than a rate directly proportional to s at every concentration. (5 points)

(b) Use the rows s = 1.00 mM and s = 4.00 mM to solve for Km and Vmax. Check your values against one other row, allowing for rounding. (8 points)

(c) Calculate v at s = 0.50 mM and at s = 1.00 mM using your parameters. Explain why doubling substrate does not double the rate here. (4 points)

(d) The total enzyme concentration doubles while the rate constants and free substrate concentration remain unchanged. Predict the effects on Vmax, Km, and v. Explain your reasoning. (5 points)

(e) Write the approximate rate expressions when $s \ll K_m$ and when $s \gg K_m$. Explain their physiological meaning in terms of substrate availability and enzyme saturation. (4 points)

(f) An enzyme has a nearly constant complex concentration while continuing to produce product. Is this necessarily chemical equilibrium? Explain the distinction between a quasi-steady complex concentration and equilibrium. (4 points)

Suggested review: lecture slides and notes on mass action and binding; Keener and Sneyd, Mathematical Physiology I, Chapter 1, biochemical and enzymatic reactions.