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STUDENT VERSION
Two Compartment Pharmacokinetic Model with First-Order Drug Interactions

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STATEMENT

The human body eliminates some drugs, particularly digoxin, with transfer rates that depend on which part of the body we consider.

1 DIGOXIN ELIMINATION

Activity 1: First Thoughts

(1.1) Typically when a drug is administered to an individual, the concentration of the drug $C(t)$ in the body changes over time. The drug is gradually eliminated from the body. The concentration is usually amount per unit volume, though we will see an alternative idea of concentration. A first-order drug reaction is one in which the rate of change is proportional to the concentration of the drug in the body.

Sometimes it is useful to think of how drugs distribute throughout the various parts of the body, particularly tissues (like fat and muscle where proteins might bind to the drug) and the plasma. Even though there are many tissues throughout the body, and they are all different, we can make a simplification of treating some as a single compartment. Two main compartments of interest are the "tissue compartment" and the "plasma compartment."

(1.2) Draw a diagram with two rectangles, each labeled to represent the drug concentration in the theoretical compartments. Include arrows on the diagram, and label each with an appropriate rate constant to indicate first-order drug reactions (that is, in which the transfers of the drug occur at rates proportional to the concentration) as follows.

- From the plasma compartment, the drug can move out of the body entirely, with proportionality constant k_{10}, and the drug can move into the tissue compartment, with proportionality constant k_{12}.
- From the tissue compartment, the drug can move back into the plasma compartment with proportionality constant k_{21}.

(1.3) Now write a system of differential equations relating the rates of change of the concentrations of the drug in the plasma, C_p, and in the tissues, C_t. Keep in mind all constants are positive.

$$\begin{aligned} \frac{dC_p}{dt} &= (\qquad\qquad\qquad)C_p + (\qquad\qquad\qquad)C_t \\ \frac{dC_t}{dt} &= \end{aligned} \tag{1}$$

Activity 2: Types of Patients and Model Parameter Values

The way a drug interacts with the body is highly affected by certain health conditions. Kidneys are responsible for a great deal of drug elimination, so a person with renal failure has a lower rate of overall elimination. A person without conditions that require special consideration has "normal parameters" and a person with reduced kidney function has "renal failure parameters." A great deal of research that is beyond the scope of our assignments is needed to properly treat different patients, so we use published results. According to [2], Table 1 gives some pharmacokinetic parameters of *digoxin*, a drug used to treat congestive heart failure. Here, h^{-1} means "per hour" and "per kg" means "per kg of body weight."

Parameter	Unit	Set A	Set B
k_{10}	h^{-1}	0.04	0.18
k_{12}	h^{-1}	0.45	1.02
k_{21}	h^{-1}	0.11	0.15
V_p per kg	L/kg	0.73	0.78

Table 1. Parameter Sets of Digoxin for Subjects with Different Renal Functions.

Which set of parameters, A or B, in Table 1 could be used to treat a patient with renal failure? Explain, and briefly mention specific parameters.

Activity 3: A Specific Model

Consider the following pharmacokinetic model for a specific patient.

$$\begin{aligned} \frac{dC_p}{dt} &= -1.20C_p(t) + 0.15C_t(t) \\ \frac{dC_t}{dt} &= 1.02C_p(t) - 0.15C_t(t) \end{aligned} \tag{2}$$

(3.1) Determine the values for the parameters k_{10}, k_{12}, and k_{21} in (2) to represent a two compartment model as in Activity 1 for digoxin.
(3.2) The concentration of the drug in each of the two compartments depends upon time, and they are interdependent upon each other. Find an expression for $\frac{dC_t}{dC_p}$, and interpret this as a rate of change. We will visualize this on the phase plane.
(3.3) A drug administered intravenously as a "bolus dose", meaning over a short period of time, distributes so quickly throughout the plasma that it is modeled as being instantaneous. The "volume of the plasma compartment" is V_p and is considered to be constant for the time interval of interest. The initial amount of the drug given in the intraveneous bolus dose is D_0. A concentration can be expressed as an amount per unit volume, or as amount per kg body weight. State initial conditions in general. State conditions specifically for (2) to treat a 70-kg patient with an initial dose of 3.6 micrograms (mcg) of digoxin per kg of body weight, based on the information provided. (It can be shown that this dosage is actually too high by current standards.)

Activity 4: Phase Plane Analysis

We can use our first order 2×2 system of autonomous (independent of time) differential equations as a vector field and analyze the *phase plane*.
(4.1) Use technology to create a well-labeled vector field for (2, **??**). Begin with a scale so that drug concentrations in either compartment might be as high as 5 mcg/L, micrograms per litre. You may adjust this scale if needed.
(4.2) A "C_p nullcline" is a curve on which C_p does not change. Determine the C_p nullcline, solving for C_t if possible. Sketch on the phase plane using a dashed line.
(4.3) Complete the inequality condition that describes when the drug has a net transfer *out of* the plasma compartment: C_p _____ 0. Determine this condition for (2). Which side of the C_p nullcline represents a net transfer of drug out of the plasma compartment?
(4.4) Determine the "C_t nullcline". Determine the C_t nullcline, solving for C_t if possible. Sketch on the phase plane using a dot-dashed line.
(4.5) Complete the inequality condition that describes when the drug has a net transfer *into* the tissue compartment: C_t _____ 0. Determine this condition for (2). Which side of the C_t nullcline represents a net transfer of drug into the tissue compartment?

(4.6) These nullclines break the first quadrant into three regions. In one region, the vectors all point up and to the left. Remembering that $\frac{dC_p}{dC_t} = (\frac{dC_p}{dt})/(\frac{dC_t}{dt})$, this means that C_p is _____ (increasing or decreasing?) and that C_t is _____. Describe this in terms of the net drug transfer into/out of the two compartments.

(4.7) Give the specific initial conditions for an initial drug concentration of 4.6 mcg/L. Sketch a solution curve on the phase plane using these initial conditions. Indicate a direction on the curve. Estimate the coordinates for the highest point on the curve.

Activity 5: Meaning of the Solution of the IVP - as functions of time

(5.1) Use a DE solver, and record the results: Solve the initial value problem with (2) and initial conditions

$$C_p(0) = 4.616, C_t(0) = 0.000 \tag{3}$$

(5.2) Consider the magnitude (absolute value) of the coefficients within the exponential functions. Let α be the larger magnitude and β the smaller: $\alpha =$ _____, $\beta =$ _____,

(5.3) Graph the concentration (also known as the "level") of drug in the plasma for 24 hours after the IV bolus dose. The graph of $C_p(t)$ is called the "drug plasma level-time curve." Graph the drug tissue level-time curve on the same set of axes. Describe the behavior of the curve in calculus terms.

(5.4) In a two-compartment first-order-reaction pharmacokinetic model from an IV injection, the drug declines rapidly from the plasma compartment in a period of time called the *distribution phase*, followed by a slower decline in the *elimination phase*.

Indicate the phases on the drug plasma level-time curve. (An approximate distinction will suffice.) Consider the coefficients within the exponential functions. Why is the distribution phase also referred to as the *alpha phase*?

(5.5) Graph the drug tissue level-time curve. Describe the behavior of the curve in calculus terms.

(5.6) Graph the drug plasma level-time curve on the same set of axes as the drug tissue level-time curve. Label each axis, including units, and include a title.

(5.7) Label the maximum on the drug tissue level-time curve with a large dot.

From the graph, estimate the time at which this occurs, the maximum tissue concentration, and the corresponding concentration in the plasma. Record and label the values here, with units:

$$t_{max} = \_\_\_\_\_ \qquad C_t(t_{max}) = \_\_\_\_\_ \qquad C_p(t_{max}) = \_\_\_\_\_$$

(5.8) Use the solutions and/or the IVPs to calculate these values to 4 decimal places.

Activity 6: Solution as a parametric function

Use technology to plot the curve formed by the parametric expression $\{C_p(t), C_t(t)\}$ and the vector field. Label the point of maximum tissue concentration with a large dot.

Activity 7: Model 2

Consider the following pharmacokinetic model

$$\begin{aligned} \frac{dC_p}{dt} &= -0.49C_p(t) + 0.11C_t(t) \\ \frac{dC_t}{dt} &= 0.45C_p(t) - 0.11C_t(t) \end{aligned} \tag{4}$$

$$C_p(0) = 4.932,\ C_t(0) = 0.000 \tag{5}$$

(7.1) Determine the values for the parameters k_{10}, k_{12}, k_{21} in (4) to represent a two compartment model as in (1).

(7.2) Use technology to solve the initial value problem for (4, 5). Record the results:

(7.3) Use the solutions and/or the IVPs to calculate these values to 4 decimal places.

$$t_{max} = \_\_\_\_\_ \qquad C_t(t_{max}) = \_\_\_\_\_ \qquad C_p(t_{max}) = \_\_\_\_\_$$

(7.4) Plot the parametric drug-level curve and the vector field. Label each axis, including units, and include a title. Label the point of maximum tissue concentration with a large dot.

(7.5) Plot both the drug plasma level-time curve and the drug tissue level-time curve on the same set of axes here. Label each axis, including units, and include a title. Label the point of maximum tissue concentration with a large dot.

(7.6) Compare Model 1 and Model 2. Use these questions to help formulate your response, but other comments are also appropriate. Does one have a longer distribution phase? Which has the higher maximum tissue concentration? Does that take longer to achieve in one model? Which one might be used for a patient with renal failure?

REFERENCES

[1] Currie, G. M., J. M. Wheat and H. Kia. 2011. Pharmacokinetic Considerations for Digoxin in Older People. *The Open Cardiovascular Medicine Journal*. 5: 130-135. `http://doi.org/10.2174/1874192401105010130`. Accessed 12 August 2018.

[2] Shargel, L. and A. Yu 2016. *Applied Biopharmaceutics and Pharmacokinetics, 7th ed*. New York: McGraw Hill.