PHARMACOKINETIC MODELS FOR ACTIVE LEARNING OF DIFFERENTIAL EQUATIONS

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Abstract: We present adaptable activities for models of drug movement in the human body – pharmacokinetics – that motivate the learning of ordinary differential equations with an interdisciplinary topic. Specifically, we model aspirin, caffeine, and digoxin. We discuss the pedagogy of guiding students to understand, develop, and analyze models, progressing in complexity to a system of differential equations. We investigate the effects of parameter values that distinguish various health levels, and dosing that may have toxic effects. Our assignments include modeling in a student centered, active, and increasingly inquiry-oriented setting through which the mathematics and biology inform and reinforce each other. We include supplemental information regarding inquiry methods, student learning outcomes, a student's commentary about our activities, and support through mathematical communities such as POGIL and SIMIODE.

Keywords: differential equations, mathematical modeling, SIMIODE, pharmacokinetics, drug models, real-world context, active learning, inquiry-based learning, POGIL

1 OVERVIEW AND RATIONALE

We discuss a sequence of three scaffolded assignments that guide students to a modeling-first approach to learning differential equations with an increasing level of inquiry-learning and mathematical complexity. All activities engage students in an interplay between mathematics and *pharmacokinetics,* "the science of the kinetics of drug absorption, distribution, and elimination (ie[sic], metabolism and excretion)" [22, p. 4]. A different drug is used in each model: Aspirin$^{\text{TM}}$, caffeine, and digoxin. The familiarity of most students with the first two drugs enables them to draw from previous experience and understanding. Digoxin is derived from foxglove, or digitalis plants, and is commonly used to treat heart failure, but can have toxic effects [7]. This drug allows for richer analyses and interconnections with a system of ordinary differential equations

that represents the concentrations of drugs in two theoretical compartments of the body for two sets of parameter values, one of which is for an individual with less functional kidneys. We investigate the toxic levels for such a patient.

These models are appropriate for a course in elementary differential equations or in a calculus-based modeling course. The first two models involve accessible differential equations; these and portions of the third model could be implemented in a first-semester calculus course.

Our modules offer active pedagogy that can be effective for both students and faculty. In this paper, we offer some portions of our assignments, mixed with direct discussion of other portions of the models and analyses. We present the primary modeling portions of the student worksheet for the first drug model on bodily absorption of Aspirin$^{\text{TM}}$. We describe the second drug model on bodily elimination of caffeine, and discuss balancing mathematical content with the pharamacokinetic content. For digoxin, we state some analysis and provide some portions of the student activities. We use labels such as "Activity D3.2" for the second activity for the third drug.

Our class modules are designed in a manner that weaves SIMIODE and POGIL. SIMIODE, or "Systemic Initiative for Modeling Investigations and Opportunities with Differential Equations" [27], focuses on a modeling-first approach to differential equations, and has a wealth of modeling scenarioss. Process-oriented guided inquiry-learning [17], or POGIL, provides a structure for crafting and implementing materials to facilitate active learning, although the content can be reframed in other styles. For more about the POGIL style, including important metacognitive student activities, see [2] and our appendices. We include specific student learning outcomes and metacognitive assessment, a student's commentary about the activities and the pedagogy, and we relate to multiple mathematical communities and professional organizations.

Our focus in learning differential equations in these activities is on the meaning and formulation of models involving differential equations, the interplay with another discipline, and the development of understanding of how parameters may affect the solution to a given system. Within these activities, we address the process of solving differential equations through the use of technology. In other activities in our differential equations course, students learn some solution techniques for differential equations.

Each instructor must modify activities to her or his style of teaching. "[T]here is a spectrum of [active learning] methods, techniques, and environments in which students can be effectively engaged in the process of learning. Through identification of a wide array of such techniques, mathematics faculty and departments can select those that best fit their needs and that can be adapted for their local context" [5]. Some possible

modifications include a focus on other aspects of differential equations, a greater focus on biology, or inclusion of data from which students can determine parameter values. We indicate several variations throughout our discussion.

In working through all three modules, our students engage in developing communication skills and transferring their mathematical skills into vocabulary from a discipline that was unfamiliar – pharmacokinetics.

2 ASPIRIN ABSORPTION

2.1 Student Module

Activity D1.1: First Thoughts on Modeling Drug Absorption
(D1.1.1) Typically when a drug is administered to an individual, the amount of the drug in mg, A(t), in the body changes over time in minutes. Write an equation that corresponds to a **constant release** of the drug from a tablet into the body over time. $\frac{dA}{dt} =$
(D1.1.2) Identify the following for your equation, or write "none": independent variable(s); dependent variable(s); constant(s); parameter(s).
(D1.1.3) For a drug that is released into the body at a constant rate, would you expect the amount of drug in the body to increase, stay the same, or decrease with time, at least for a while? What value would you expect for the initial amount of drug in the body?
Activity D1.2: A General Model
(D1.2.1) One general model of drug amount is given by $Eqn\ D1.1 : \frac{dA}{dt} = k$. Use your mathematical background: $\frac{dA}{dt}$ represents the _____ __ _____ of the amount of drug in the body over time, in units of _____ .
(D1.2.2) $Eqn\ D1.1$ is referred to as a zero-order reaction in pharmacokinetics [22]. Classify this equation using mathematical terms. Determine a general solution.
Activity D1.3: ASA Model and Specific ASA Situation. ASA stands for acetylsalicylic acid, which can be used to treat pain and some other conditions. It is the primary ingredient in Bayer®Aspirin™. A patient swallows a tablet that contains 325 mg of ASA. A specific model of drug amount in this case is given in [22], $Eqn\ D1.2 : A(t) = 0.86t - 0.04$.
(D1.3.1) Is this a zero-order reaction?
(D1.3.2) The tablet takes awhile to dissolve. What are the smallest and largest amounts of ASA in the body? At what times do these occur? Determine a realistic time interval for $Eqn\ D1.2$, and graph the resulting realistic A(t).
(D1.3.3) Give the differential equation form (like $Eqn\ D1.1$) and provide a realistic initial condition. Create a "phase plane", which in the context

of our differential equation, is a graph with $A(t)$ on the horizontal axis and the rate of change of the drug amount $\frac{dA}{dt}$ on the vertical axis.

2.2 Comments to Our Reader and Variations

The phase planes for this model and for the next, shown in Figure 1, clearly reveal the meaning of, and distinction between, zero-order and first-order reactions in a single compartment. Differential equations analysis adds to the description in the pharmacokinetic sources [21, 22]. The phase plane for the system in our third model is quite different and more interesting.

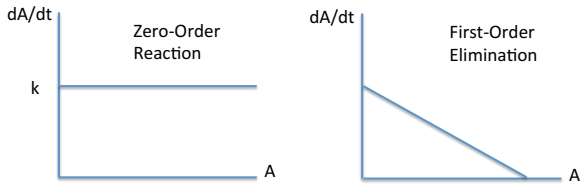

Figure 1. Phase Planes for Zero-Order and First-Order Reactions.

The specific aspirin situation would be more accurately modeled with a piecewise defined function to account for the time for the tablet to release medication into the body. We chose to have students discuss the realistic time interval for which the given model might apply. Another assignment style could have students derive the model for the specific situation rather than beginning with a given solution.

Other substances follow zero-order kinetics in a single compartment model, including blood alcohol; see [22, Ch. 4 Learning Questions]. Alcohol can also incorporate different parameters based upon the sex of the drinker and whether or not food is consumed. The slides from [14] discuss blood alcohol kinetics without differential equations, and [26] has information about alcohol using pre-college mathematics.

3 CAFFEINE ELIMINATION, FOR OUR READER

3.1 Basics

The activity to model a single dose of caffeine is parallel to that of the aspirin activity in structure, but yields a different model. The focus changes to the *concentration* of the drug, C(t), as it is *eliminated from* the body at a rate that is **proportional to** the concentration of the drug in the body; this proportionality indicates a *first-order reaction* in pharmacokinetics [22]. Students translate the following claim

into a simplifying assumption and a boundary condition: "Caffeine is rapidly and almost completely absorbed in humans." Aspirin and caffeine are different, as we assume the amount of caffeine consumed equals the amount of caffeine in the blood at t=0. Students argue about body weight being considered constant. However, "[t]he plasma volume in the healthy state is relatively constant because water lost through the kidney is rapidly replaced with fluid absorbed from the gastrointestinal tract." [22, p. 81] The diuretic effect is negligible. For this and other information on caffeine, also see [11]. Our students noticed that the model indicates caffeine is never completely eliminated from the body, but Aspirin is.

3.2 Deciding on Details

The quote above is an example of a complexity that mathematicians must deal with in pharmacokinetics or other applied areas. We must decide how much detail of the "other" discipline to include. Concentration is usually defined as mass per unit volume. In a pharmacokinetic model, the "apparent volume of distribution" represents the "space" that the drug occupies in the body. Is this concept, incredibly important for a pharmacy student, a distraction for the mathematics student – or faculty – who is already delving into vocabulary in another field? "Volume of distribution is a direct measure of the extent of distribution. It rarely, however, corresponds to a real volume. ... Drugs distribute to various tissues and fluids in the body. Furthermore, binding to tissue components may be so great that the volume of distribution is many times the total body size." [21] Generally, this volume is equivalently described as a percent of body weight. "[C]affeine binds reversibly to plasma proteins, and protein-bound caffeine accounts for about 10 to 30 percent of the total plasma pool." [12] Plasma generally accounts for 4.5% of a person's body weight. [22, p. 80] "The distribution volume [of caffeine] within the body is 0.7 L/kg [of body weight]" [12]. From these, we could express drug concentration in terms of mg/L and convert using a person's weight and volume of plasma. Instead, we can use mg of substance per kg of body weight as an equivalent and often more convenient way to represent concentration. In our implementations, we reveal the detail for caffeine to the student as an aside, and we use known parameter values without explanation for the volumes of distribution needed in the digoxin module. Now, let's return to the caffeine model.

3.3 Specifics, Half-Life, and Variations

Caffeine is a drug that can be used to enhance safety and performance in military situations, among other uses. Consider the following specific

situation for caffeine [12]: *A healthy adult male soldier is administered a form of caffeine that is estimated to yield an initial concentration of 4 mg/(kg BW), meaning four milligrams of caffeine per kilogram of body weight.*
Students state the initial first-order reaction model for the specific situation, as much as possible, including initial conditions, graph the phase plane, and state a solution. Additional information allows the student to solve for the model parameter. The half-life of a drug, $t_{1/2}$, is the time it takes for one half of the amount of the drug to be eliminated. A reasonable half life for caffeine for the specific caffeine situation is 3.0 hours. "[T]he average half-life of caffeine in the blood of adult men given 280 mg (4 mg/kg BW) is between 2.5 and 4.5 hours..." [12] Few of our mathematics students have encountered a half-life outside of the more usual radioactive decay examples.

Students write the initial value problem: $\frac{dC}{dt} = -k\,C(t),\ C(0) = C_0$. Students can plot solutions for multiple values of the half-life to examine the sensitivity of the model to a parameter value. Here, they consider the amount by which the solution changes with a small change in the half-life.

For a non-military application, we might consider a truck driver instead of a soldier, or a student studying for an exam, though without seeming to promote caffeine dosing. Students can engage in comparing caffeine content in popular drinks and snacks, or in some over-the-counter drugs, using a chart like [3]. (Some faculty might be sensitive to students who avoid stimulants for personal or religious reasons.) Which beverage has the most? and what is meant by that? This highlights the difference between *amount of drug*, as with the Aspirin activity, and *concentration.* For instance, 2 ounces of Starbucks®Espresso has 150 mg caffeine and 20 ounces of Dunkin' Donuts®Coffee with Turbo Shot has 398 mg. A creative alternative assignment could have the students outline computations for a mobile app to track caffeine usage, as with Caffeine Zone™ [19, 20]. The focus could be monitoring caffeine for healthy levels and could raise awareness of adverse affects, such as interruption of sleep cycles, with overuse of caffeine. Here, one must include the body weight of the subject, though we would avoid having the student reveal his or her own weight.

Other substances can be used in the activities. See [22, Ch. 4 Learning Questions] for antibiotics that follow first-order kinetics in a single compartment model.

4 DIGOXIN

4.1 Comments to Our Reader

The last activity set that we present has a more interesting model and analyses because this drug behaves differently in parts of the body, though we can still model some parts together for simplification. For digoxin, we consider first-order kinetics in two compartments, implemented from [22]. We later remark that the drug levels here are high and even toxic, given recent considerations in [7]. In the following subsections, we show a mix of some student tasks interspersed with answers, as well as analyses for our readers without the student tasks explicitly stated.

4.2 Student Tasks with Answers

In our previous models, the entire human body was treated as a single unit through which the drug moved. Sometimes, it is useful to think of how drugs distribute in different parts of the body, though we still simplify by combining some. Two main compartments of interest are the "tissue compartment" (like fat and muscle where proteins might bind to the drug), and the "plasma compartment."

Activity D3.1: Modeling Drug Transfer and Elimination

(D3.1.1) 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}.

Answer: See Figure 2.

(D3.1.2) 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.

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

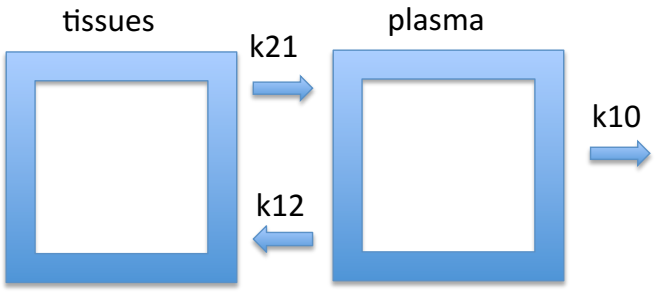

Figure 2. Diagram for Digoxin.

Answer:

$$\begin{aligned} \frac{dC_p}{dt} &= -(k_{12} + k_{10})\, C_p(t) + k_{21}\, C_t(t) \\ \frac{dC_t}{dt} &= \quad k_{21}\, C_p(t) - k_{12}\, C_t(t) \end{aligned} \tag{2}$$

Activity D3.2: 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 [22], 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 should be used to treat a patient with renal failure? Explain, and briefly mention specific parameters.

Answer: Parameter set A is for a patient with reduced renal function. Someone with less functional kidneys would experience a slower rate k_{10} of elimination of the drug from the body.

Activity D3.3: A Specific Model
Consider the following pharmacokinetic model for a specific patient.

$$\begin{aligned} \frac{dC_p}{dt} &= -1.20\ C_p(t) + 0.15\ C_t(t) \\ \frac{dC_t}{dt} &= \ \ 1.02\ C_p(t) - 0.15\ C_t(t) \end{aligned} \tag{3}$$

(D3.3.1) Determine the values for the parameters k_{10}, k_{12}, k_{21} in (3) to represent a two compartment model as in Activity 1 for digoxin.
Answer: This represents parameter set B for the subject with functional kidneys.
(D3.3.2) 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 in the next task.
Answer: $\frac{-(k_{12}+k_{10})\ C_p(t)+k_{21}\ C_t(t)}{k_{21}\ C_p(t)-k_{12}\ C_t(t)} = \frac{-1.20\ C_p+0.15\ C_t}{1.02\ C_p-0.15\ C_t}$ represents the rate of change of the concentration of digoxin in the tissues as a function of the concentration in the plasma compartment.
(D3.3.3) 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. Recall that a concentration can be expressed as an amount per unit volume. State initial conditions in general. State the conditions specifically for (3) to treat a 70-kg patient with an initial dose of 3.6 micrograms (mcg) of digoxin per kg of body weight.
Answer:

$$C_p(0) = \frac{D_0}{V_p} = 4.61 mcg/L, \quad C_t(0) = 0. \tag{4}$$

4.3 Analysis for Our Reader for Activity D3.4

Here, we replace the student instructions with some of the resulting analysis through which the students are guided. Note the great interplay between equations, graphics, mathematical interpretations, and pharmacokinetics.

The C_p-nullcline is $C_t = (k_{12} + k_{10})/k_{21}C_p$, and the C_t-nullcline is $C_t = k_{12}/k_{21}C_p$. Digoxin has a net transfer out of the plasma compartment when $C_p'(t) < 0 \Leftrightarrow C_t < (k_{12} + k_{10})/k_{21}C_p$; we never cross the

C_p-nullcline for our parameter sets. Drug is transferring into the tissue compartment when the ratio of tissue concentration to plasma concentration, C_t/C_p, exceeds the ratio k_{21}/k_{12}, which is the rate at which drug transfers from the tissue compartment to the plasma compartment, divided by the rate at which drug transfers from the plasma compartment to the tissue compartment. Note that one could lead with this sort of description to have students develop the differential equation model in (1), as an alternative to using the diagram approach.

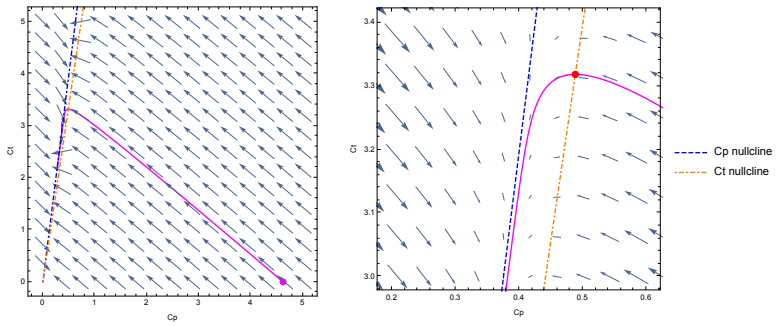

Figure 3. Normal Parameters: Phase Portrait (left), Focus on Maximal Tissue Concentration (right).

Figure 3 shows the phase portrait for the specific digoxin situation in (3, 4) with $\frac{dC_t}{dt}$ ploted against $\frac{dC_p}{dt}$. On the left graph, we see unscaled vectors of $\frac{dC_t}{dC_p}$ in a direction field, nullclines differentiated as dashed and dot-dashed, a point to mark the initial value, and a solution curve as a parametric function $\{C_p(t), C_t(t)\}$. Because the concentration in the plasma is always decreasing, we move on the parametric curve from right to left as time increases. More specifically, our solution begins on the lower right of the phase portraits, progresses up and to the left until the time of maximum tissue concentration, and then the curve shifts down. The slopes of the C_p-nullcline, $C_t = 8.0C_p$, and the C_t-nullcline, $C_t = 6.8C_p$, are visualized in Figure 3.

On the right graph in Figure 3, we see a zoomed-in version that helps distinguish the nullclines, with a point to mark the maximal tissue concentration. The scaled direction vectors on the right graph indicate where the rate of change of tissue concentration with respect to plasma concentration is greater. The solution curve appears smooth on the zoomed-in graph, even though the turn appears quite sharp on the zoomed-out graph; $\frac{dC_t}{dC_p}$ is well-defined.

The highest point on the trajectory in each view indicates the maximum tissue concentration. This occurs when the rate of change of the

tissue concentration is zero, i.e., where the parametric curve crosses the C_t-nullcline. This transition separates the *distribution phase*, with a rapid decline of drug from the plasma compartment and a rapid increase into the tissue compartment, from the *elimination phase* with a slower decline from the plasma compartment. The nullclines divide the phase portrait into regions; vectors are similar within a region but differ across regions. For instance, vectors point down and to the left between the two nullclines in Figure 3, as both plasma concentration and tissue concentration decrease, corresponding to negative values of $\frac{dC_p}{dt}$ and $\frac{dC_t}{dt}$ in the elimination phase.

The system is mathematically tractable for solution via an eigensystem, decoupling, or Laplace Transforms. Our students practice solution techniques in other assignments and use a computer algebra system in this activity to allow them to focus on the pharmacokinetic content. Our students will have seen vector fields for systems of differential equations, but not nullclines.

In the next section, we provide the scaffolded assignment in which the students develop further analyses.

4.4 Student Tasks with Answers

Activity D3.5: Meaning of the Solutions in Time
(D3.5.1) Solve the initial value problem for our specific digoxin situation (3, 4). Consider the magnitude of the coefficients within the resulting exponential functions; let α represent the value with the larger magnitude, and β the smaller.
Answers: The digoxin levels are described by (5) with $\alpha = -1.3297, \beta = -0.02031$.

$$\begin{aligned} C_p(t) &= 4.1582e^{-1.3297t} + 0.4571e^{-0.02031t} \\ C_t(t) &= -3.5953e^{-1.3297t} + 3.5953e^{-0.02031t} \end{aligned} \tag{5}$$

(D3.5.2) Graph the concentration (also known as the "level") of drug in the plasma for 24 hours after the intraveneous 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 behaviors of the different concentrations in calculus terms. Label the maximum on the drug tissue level-time curve with a large dot. From the graph, estimate the time at which maximum tissue concentration occurs, the maximum value of tissue concentration, and the corresponding concentration in the plasma. Record and label the values with appropriate units. Indicate the *distribution phase* and the *elimination phase* on each curve and consider the coefficients within the bi-exponential solutions. Why is the distribution phase also referred to as the *alpha phase*?

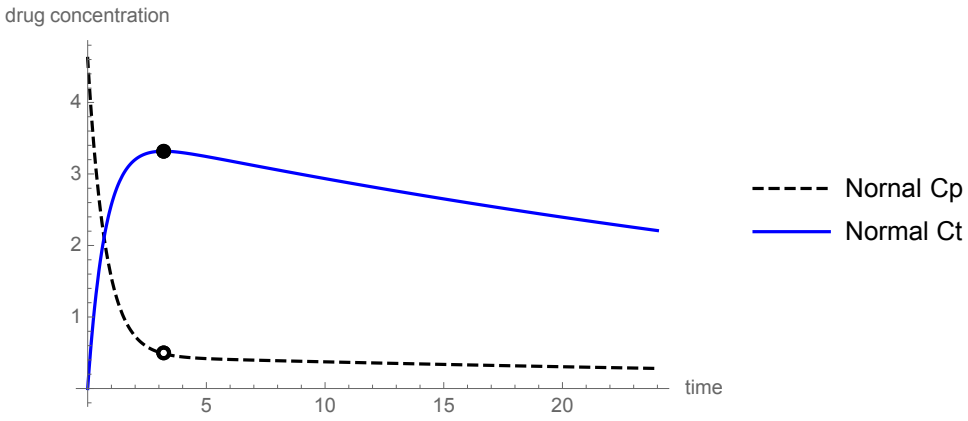

Figure 4. Drug Level-Time Curves with Normal Parameters.

Answers and comments: Figure 4 shows the drug level-time curves and points to mark maximal tissue concentration and the corresponding plasma concentration. At first, the drug distributes quickly to the tissues, so the tissue concentration increases rapidly during the alpha phase. Tissue concentration has its greatest value of 3.32 mcg/L at t=3.2 hours, with corresponding plasma concentration 0.49 mcg/L. After this time, the tissue concentration decreases, which marks the elimination phase. Our students often estimate the maximal tissue concentration to the left of its accurate placement, perhaps focusing on the greater curvature. The bi-exponential form of the solutions in (5) corresponds beautifully to the description of the distribution and elimination phases. Those who wish to connect more to solution techniques can have the students discuss the superposition of solutions using the eigenvalues of this linear system, as well as the stable nature of the isolated critical point at (0,0) as indicated by the negative values for α and β.

It can be worthwhile to have students reconcile the parametric representation of solutions $\{C_p(t), C_p(t)\}$ in Figure 3 with the nonparametric representation of solutions in Figure 4.

4.5 Sensitivity to Parameter Values, for Our Reader

Our students repeat the analyses with the other parameter set to see how the same dose would affect someone who weighs the same, but whose kidneys do not function as well. Students connect the various representations of the model: pharmacokinetics, differential equations, solutions, and graphs. The analyses emphasize the importance of pa-

rameter values in distinguishing renal functionality and the sensitivity of a model to parameter values. The activity reinforces understanding and communication of mathematics and of pharmacokinetics.

Figure 5 shows both solution trajectories; "RF" indicates "renal failure." Here, time increases from right to left; time values cannot be determined from the graph. Figure 6 shows the drug-level curves for each patient. Here, time increases from left to right.

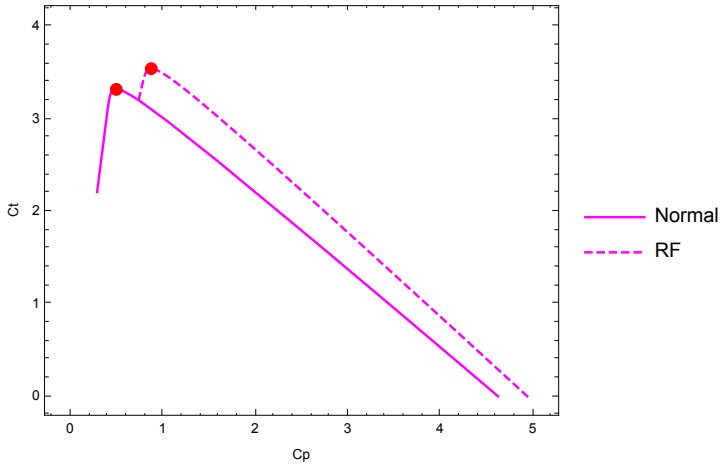

Figure 5. Parametric Representation of Sensitivity to Parameters.

Although the dose is the same for each patient, the initial plasma concentration is higher for the subject with renal failure. The distribution phase for each patient appears on Figure 5 to the right of each maximal tissue concentration; on Figure 6, this appears to the left of each maximal tissue concentration. The patient with renal failure experiences a longer time until maximal tissue concentration, as seen in Figure 6. This is also captured with the smaller distribution rate constant, $\alpha = 0.5926$ in the analytic solution. In Figure 5, the slopes of each portion of the solution curve on either side of the maximal tissue concentration, are apparently greater for the patient with renal failure. Drug transfers into the tissue compartment when the ratio C_t/C_p, exceeds k_{21}/k_{12}, which is 0.15 for the subject with unimpaired kidneys and 0.24 in the subject with less functional kidneys. Similar comparisons can be made regarding the elimination phase. All of the comparisons help explain the significantly higher tissue concentration for the subject with renal failure at the end of the first twenty-four hours.

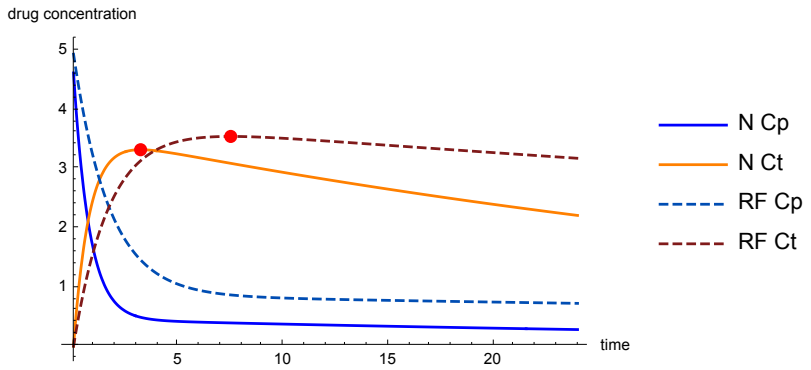

Figure 6. Drug-Level Curve Representation of Sensitivity to Parameters.

4.6 Additional Considerations for Digoxin

There are many quantities of pharmaceutical interest in drug models, including rates per minute of various quantities, such as the amount in mcg of drug eliminated by the body, number of mL of body fluid cleared of drug, and fraction of drug eliminated [22], to name a few. A third variable can account for the concentration of drug that is eliminated from the body, extending the analysis to a 3X3 system of ordinary differential equations. We could determine the amount of drug per kg body weight of the subject, or scale the drug amount in any compartment by the body mass of the individual to obtain the actual amount of the drug in mcg.

In the healthcare profession, specific values of effective and non-toxic drug concentrations are of enormous importance and define the *therapeutic window*. This can be expressed in terms of the drug concentrations, as in [14]. According to [7], digoxin has a narrow therapeutic range, and subjects over sixty-five years of age, in particular, can experience potentially fatal toxicity. Currently recommended plasma concentrations of digoxin are between 0.5 and 1.0 mcg/L to treat congestive heart failure in the elderly – half the level that was previously recommended [7]. Elderly patients generally have decreased renal function, by as much as 50%, as a result of the aging process. This and other factors make older patients more sensitive to drug dosing. However, digoxin is so widely used to manage congestive heart failure, which occurs in about 80% of the elderly, that it is one of the most frequently prescribed medications for those over sixty-five.

In our implementation from [22], the plasma concentrations are mostly

between 2.5 and 4.5 mcg/L – up to 450% of current recommendations. The initial plasma concentrations in our model for the patient with less functional kidneys is almost five times the recommended level. This demonstrates the power of mathematical modeling by virtually investigating a situation that could have toxic effects in reality.

Investigating a wider variety of the parameter values and initial conditions could be a worthy student project. Those who wish to expand the DE model of digoxin may be interested in the diagram in [7] that could be treated as a four-compartment model with two additional parameters, though no parameter values are provided.

5 CONCLUSION

The pharmacokinetic modules we present contribute to the body of materials and active learning approaches to undergraduate mathematics. They provide positive, contextualized experiences in modeling and differential equations that enhance students' mathematical and communication skills in the manner of SIMIODE. The structured style of the materials, written in the POGIL style, has facilitated student conversation and has drawn our students to contribute questions and comments to the group. Some students have been able to contribute ideas from other disciplines, and the resulting dialogue has been amazingly rich for the whole group. Our students have definitely been more engaged with the drug model context, which has been novel to them, than with problems from the text. Through these modules, students can "get a taste of what it might be like to work as a mathematician in an interdisciplinary group," according to our student who wrote of about her perspective. See the Appendices for the full student commentary, for student learning outcomes and self assessment activities, a discussion of inquiry methods, and for more on SIMIODE, POGIL, and other mathematical communities.

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A. 1. INQUIRY AND THE POGIL STYLE

Process-oriented guided inquiry-learning [17], or POGIL, provides a structure for the careful crafting and implementation of materials to facilitate active learning. *Active learning* means "classroom practices that engage students in activities, such as reading, writing, discussion, or problem solving, that promote higher-order thinking" [5]. There is a wide variety of ideas regarding what constitutes inquiry learning. By *inquiry learning* – also known as *inquiry-based learning (IBL)* or *inquiry-oriented learning* – we mean "deep engagement in rich mathematics" in a collaborative setting [8] that adheres to the following principles: "generating student ways of reasoning, building on student contributions, developing a shared understanding, and connecting to standard mathematical language and notation" [13]. The latter article gives a great overview of inquiry-oriented practices, as well as an overview of evidence from multiple research studies of the efficacy of such practices.

The POGIL structure purposely develops *process* skills of teamwork, information processing, critical thinking, oral and written communication, problem solving, and self-awareness of one's learning for students and of one's teaching for faculty.

The instructor can observe student learning better, especially in a larger class, when the students are actively talking to each other in small groups. Furthermore, "[w]hen students are required to express their mathematical ideas in their own words, inadequacies can be identified and addressed" [23]. The instructor facilitates the conversation, when needed, and answers some questions, often with another question, but is not directly leading the students or lecturing to them.

Each instructor must modify activities to her or his style of teaching, and other styles of implementing the modules are appropriate. Indeed, "there is a spectrum of [active learning] methods, techniques, and environments in which students can be effectively engaged in the process of learning. Through identification of a wide array of such techniques, mathematics faculty and departments can select those that best fit their needs and that can be adapted for their local context" [5].

The POGIL framework begins with an explicit statement of the rationale, learning objectives, and student learning outcomes for the activity. The activity author can glean wording for the objective and for student learning outcomes from any source material for the activity or from other sources that focus on educational content and pedagogy. The example included in this paper includes wording specific to pharmacokinetics and differential equations. In addition to those mentioned elsewhere, our sources include [2], [1], and [15] on active and inquiry learning, as well as [9] and [16] for general modeling curriculum and assessment information. We also used [22] for the pharmacokinetic-related objectives.

Finally, students engage in a wrap-up activity that includes a quick qualitative assessment that we adapted from [25]. For specific data for the efficacy of POGIL within a Calculus setting, see [2].

In the next section are the non-modeling portions of our assignments for the students. These are adaptable for the specifics of almost any topics. We include notes for the faculty and a student perspective.

A. 2. METACOGNITION IN OUR POGIL-LIKE FRAMEWORK

General Activity Guidelines

(note for faculty: Provide a rationale - engage, motivate or interest students in the activity. Indicate how this activity relates to concepts that they have learned or will soon be learning. This can include pre-requisites and specific stylistic instructions.)

Rationale: This activity is designed to enhance your understanding of several fundamental concepts needed in mathematical modeling and to

engage you in an interdisciplinary topic. In your answers to questions, use modeling terms, although you should mix them with general English sentences.

This activity is designed to be student centered, active, and inquiry-oriented. You will reflect upon both content skills (what you learn) and process skills (how you acquire, interpret, and apply knowledge). This is designed to help you become lifelong learners and prepare you to be more competitive in a global market.

If appropriate, as you progress through this module, you may wish to revisit a portion and modify your response. Do not erase previous efforts, but add to your response. Indicate what you changed and why.

Primary Content Learning Objective

Students will explore some mathematical aspects of molecular biology dealing with a body's method of processing various molecules. Specifically, we will consider the pharmacokinetics of zero order processes in drug absorption.

(note for faculty: Provide information that can be used by students and faculty to assess the level of success.)

Student Learning Outcomes

Upon successful completion of the activity, the student should:

- be able to apply mathematical expertise to deal with an interdisciplinary topic (content and process)
- have increased their science and technology literacy (content and process)
- have developed modeling techniques and the mathematics necessary to model and analyze these situations (content)
- engage in critical thinking by interpreting and processing information (process)
- communicate mathematical modeling effectively orally and in writing (content and process)
- deal with multiple representations of a concept, including verbal/written, graphical, and symbolic (content and process)
- realize that "mistakes" can be as valuable as an initially correct answer (process)

Student Wrap-Up

(note for faculty: Part of the POGIL style includes eliciting awareness of one's learning from the students. This may be unfamiliar

to quite a few mathematics instructors.

Provide closure with self-assessment and reflection presented in a meaningful and interesting manner consistent with the learning objectives.)

Learning Reflection

Part of learning can include a self assessment. A *good* response indicates honest evaluation and shows clearly that you have actually *read* and *thought about* the Student Learning Outcomes. Discuss strengths and areas for improvement. This segment is to provide some closure for you and to engage you in *metacognition*, awareness of your own learning.

- Summarize the content objectives of this assignment. Assess how well you mastered the objectives.
- Do you know more about mathematical modeling, differential equations, and molecular biology than you did prior to this assignment? Briefly provide evidence. Indicate any questions regarding the content or the rationale for the activity that you may have.
- Did you work effectively to this assignment? If so, explain how. If not, identify what needs to happen to enhance active and positive participation.

Self-Assessment

For each question, on a scale of 1 for "Strongly Disagree" to 5 for "Strongly Agree," indicate your agreement.

- The activity added to my understanding of
  - a real-world context for a differential equation
  - the derivation of a differential equation model
  - initial value or boundary value conditions
- The activity added to my appreciation of applied mathematics and mathematical modeling
- The model and analysis enhanced my educational experience in this class

A. 3. IMPLEMENTATION SPECIFICS

The material outlined above was the first in a sequence of three modules written in this POGIL-like style. Through each, we strove to foster shared understanding as in [13]. We describe three formats in which we implemented our materials.

We used two modules that were written with this POGIL framework in the beginning of a senior modeling course. We had students assume

specific roles within their group, which is advocated by POGIL. This aided effective team dynamics with students of different backgrounds. Not everyone had taken differential equations, but the modules focus on the modeling aspects and effective communication.

We implemented all three activities in differential equations course with small groups without pre-defined roles. In the third model, the groups of students were able to work through the materials primarily outside of the instructor's presence, although groups were able to confer with the instructor when needed.

Student Perspective

One person completed the two preliminary group activities within the senior modeling course. Immediately after graduation, she worked through the third module completely on her own. She had taken an elementary differential equations course that did not cover systems of differential equations but learned about this topic through the third module. Here is her reflection on these experiences.

Working in small groups made the setting intimate and allowed for ease of suggestions. This open and easy flow of ideas generated potential approaches, which had us all thinking out loud about the advantages and disadvantages of strategies. We even included variables that I would not have considered, and we thought of practical constraints that made logical sense. With my background being partially in biology, I was able to contribute to the discussions about the body, caffeine, and the removal therein. Other members of the group contributed their ideas which were similarly integral, and sometimes the instructions gave us wiggle room to decide how detailed we wanted to be. Additionally, we had multiple different working problems of differential equations for each scenario. The problem-solving strategy was stressed more than solution techniques, and through that, we discovered the solutions. I realized that finding the solutions was much more intuitive than I originally considered them to be. There was, and always is, a great feeling to know that the answer is logical and we can get there with reason.

I made a conscious effort to read the instructions carefully because I did not want to miss anything. I encountered a question for which I was supposed to refer to my previous answer. I did not realize this at first and looked at the question for a long time. This experience taught me to be more careful about determining what the question was asking. I made sure to write down my thoughts and my thought processes while working through the problems. This was important to me because the questions were doing a great job at guiding my thoughts, and I wanted to document the path the instructions took me on.

We were all able to bounce around ideas, and we had to explain our reasoning and thinking to each other. This was an outward manifestation of the internal process that happens during metacognition, a tool which has helped me tremendously. I had to think about not only **what** I was thinking, but also **how** I was thinking. Without even knowing it, I was doing something deeply powerful and impactful, which helped me take ownership of my identity as a mathematician.

While working on the digoxin problems by myself, I was able to approach them with a certain level of confidence because of the positive role that inquiry-based learning and metacognition had previously played in my mathematics modeling experience with the preliminary models. Drawing the diagram definitely clarified the generation and progress of the equations, which made sense because of the context. Although I did not have the specific solution techniques to unravel the problems completely on my own, I was able to internalize the fact that there was a system of differential equations and come to a reasonable conclusion. Having this reaction is essential in learning mathematics in general, but I think it can be a powerful tool for learning differential equations. It allows students to come to the right conclusion via a somewhat intuitive path whose steps can be internalized, and this makes the content relevant.

A. 4. ANSWERING CALLS FOR IMPROVEMENTS

We have presented the framework that we used in three student modules for enhancing a modeling-first approach to differential equations, as well as one student's perspectives about the experiences. Now we share a faculty perspective and place this work in a broader context.

When working in groups on our assignments, our students conjectured different models or explanations, the merits of which they discussed in the group. The accessible nature of the differential equations and questions in the first two activities benefitted the discussion among students from a variety of backgrounds. Some upper level students found these tasks challenging, in part because of being more accustomed to performing computations than engaging in meaningful dialogue about a topic using mathematics in a specific context. Throughout, students were actively engaged in connecting to standard notation and language in mathematics. This experience, aided by the POGIL-like framework, students came to a shared understanding of the modeling, mathematics, and the interdisciplinary context.

According to the Conference Board of the Mathematical Sciences (CBMS), active learning methods "have been shown to strengthen student learning and achievement in mathematics, to foster students' confidence in their ability to do mathematics, and to increase the diversity

of the mathematical community." [5] The CBMS report provides a wonderful overview of such methods, an acknowledgement of the increased preparation time and overall investment by faculty, and a call for broad participation in supporting and expanding active learning throughout all levels of mathematics. The CBMS statement outlines the need for materials and supporting communities for active learning throughout mathematics.

We mention some of the communities that have been helpful along our journey and could support others in their journeys. Multiple contributed paper sessions, workshops, and minicourses have been – and will be – available venues for faculty development in the summer and at national meetings by these groups.

A. 5. ENGAGING MATHEMATICAL COMMUNITIES

There are several groups involved with differential equations. The community "Systemic Initiative for Modeling Investigations and Opportunities with Differential Equations" (SIMIODE) [27] includes an online, peer-reviewed bank of adaptable materials. A new grant from the National Science Foundation (NSF) will support additional workshops and production of materials with a modeling-first approach. SIMIODE also sponsors a new modeling contest, SCUDEM. The group "Inquiry-Oriented Differential Equations" (IODE) produced materials for differential equations [18] through a recent NSF grant that included other inquiry-oriented mathematics sub-disciplines. The grant enabled online support groups, "Teaching Inquiry-oriented Materials: Establishing Supports" (TIMES) that tested and discussed materials that are now available. The Community of Ordinary Differential Equations Educators CODEE [4] sponsors a peer-reviewed, open access journal. See the upcoming special issue that considers social justice and environmental concerns.

Regarding general modeling activities, the Society for Industrial and Applied Mathematics (SIAM) [24] has a helpful report [16], Guidelines for Assessment and Instruction in Mathematical Modeling Education (GAIMME) [9], and a new activity group on Applied Math Education with planned conferences. Students can also engage in the MCM/ICM modeling contests [6].

There are several groups involved with active learning in general. Math Learning By Inquiry [15] (MLI) is the new face of the former "Legacy of RL Moore Conference" that supported IBL for twenty years. MLI will work in conjunction with the Academy of Inquiry-Based Learning (AIBL) [1] and the IBL Special Interest Group of the MAA [10]. As we said, we adapted the activity style from the POGIL mathematics group [2].

Involvement with these communities directly benefited the development of our pharmacokinetic materials. The drug model context was novel and interesting to the students. The structured style of the materials facilitated student conversation, drawing students to contribute questions and comments to the group. Some were able to contribute ideas from other disciplines. The resulting dialogue was amazingly rich. Students were definitely more engaged than with problems from the text, and they enhanced their communication skills.

Whether guided or more open, the overarching goal of an inquiry-oriented, modeling-first approach is expressed in this statement: "[w]hile specific mathematical skills from a college course may be easily forgotten, the powerful experience of tackling a real world problem can help students develop a lasting tenacity and confidence such that they are better equipped to address the ill-defined challenges found outside of the classroom." [9] Moreover, in the progressive nature of these three activities, we see "a structured approach to learning mathematics, leading students through a succession of ever more challenging problems ... that force them to build a coherent understanding of mathematical ideas and concepts." [15]

BIOGRAPHICAL SKETCHES

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