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Using ODEs to Model Drug Concentrations within the Field of Pharmacokinetics

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In 2009, the Food and Drug Administration discovered that individuals taking over-the-counter pain medications containing acetaminophen were at risk of unintentional overdose because these patients would supplement the painkillers with other medications containing acetaminophen. This resulted in an increase in liver failures and death over the years. To combat this problem, the FDA decided to lower the dosage from 1000 mg to 650 mg every four hours, thus reducing this risk (U.S. Food and Drug Administration). The measures taken in this example demonstrate the concepts behind the field of Pharmacology. Pharmacology is known as the study of the uses, effects, and mode of action of drugs ("Definition of Pharmacology"). Knowledge of drug concentrations is of extreme importance when determining the dosage and frequency in which patients are administered medication. By ascertaining how much time is required to eliminate a drug, pharmacists are able to decide when the next dosage should be administered. By diving into this field, we are able to answer questions such as "how much intravenous fluid should be administered to each individual patient?" or "Why should Tylenol only be taken every 4 hours?". Specifically, the concepts within pharmacokinetics and pharmacodynamics aim to explain these answers using specific mathematical systems.

To begin, we must first understand the basic principles of pharmacokinetics. According to the *2011 Nurse's Drug Handbook*, *pharmacokinetics* is a branch of Pharmacology. It is currently defined as the study of a drug's actions as it passes through the body during absorption, distribution, metabolism, and excretion (2). These four parts all play a significant role in the movement of drugs in the human system. Absorption implies the medication is able to be biologically passed through a bi-lipid cell membrane either actively or passively. The drug can enter via three methods of administration, with enteral (oral), parenteral (intravenous), or transcutaneous (topical) drugs. Distribution is the process of the drug being transferred to other regions of the body, or action sites, by bodily fluids such as one's plasm. The conversion

of the drug into useful molecules and compounds is known as metabolism and occurs mainly in the liver, or hepatic system. Finally, excretion is the elimination of the drug from the body, usually taking place in the kidneys, or renal system (*2011 Nurse's Drug Handbook* 4).

Furthermore, clinical pharmacokinetics is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient (Spruill et al. 1). Though it is not possible to directly access the sites where the drug becomes effective, such as in human organs, we are able to successfully measure the concentration of a drug at any given time via the blood, saliva, or urine. Concentration is defined as the amount of the drug divided by the volume where the drug is distributed (Spruill et al. 10). This is very useful when determining how a drug is distributed throughout a person's plasma. A large volume of distribution indicates the drug dosage has been distributed fully into the body fluids (Spruill et al. 11). The volume of distribution varies considerably between patients given the fact that genetic differences as well as illnesses can affect the plasma concentration within that body. Thus, patients with a lower plasma concentration amount would require a lower dosage of a drug to achieve a full distribution throughout the body; something important to note when servicing patients hemorrhaging while receiving medication. The concentration used to calculate the volume distribution is constantly changing as well due to excretion (Spruill et al. 11). Therefore, concentration of the drug in the bloodstream is directly proportional to the concentration in the tissue; higher doses of the drug implies a higher dose in the bloodstream and therefore higher dose diffused into the tissue.

Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects (*2011 Nurse's Drug Handbook* 5). There are a few variables that influence the relationship. Time course is one of the variables defined as the length of time a drug stays at the receptor site which in turn determines the length of its effect. Another is tolerance, which states an increased concentration over time at a receptor site can actually cause the drug's

effectiveness to decrease. As demonstrated in the graph to the left, when the number of doses increases, the drug concentration must also increase to get the same desired effect because the
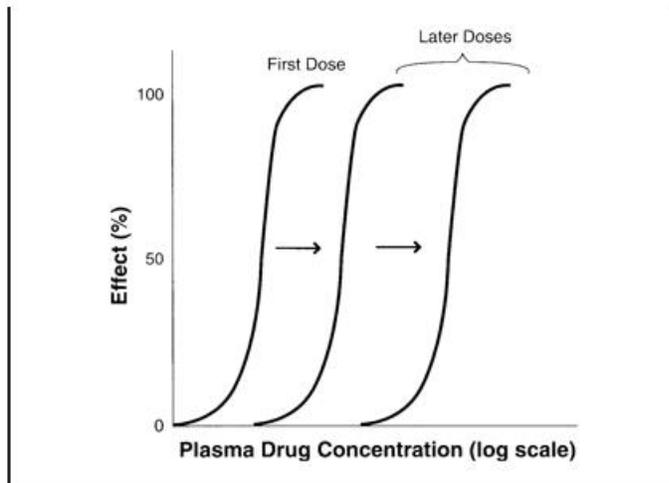
human body develops a resistance to the drug (Spruill et al. 3). Human bodies increase its metabolism so a drug is excreted from the body quicker and its time in the body decreases. Conversely, bacteria have internal survival responses that allow the bacteria to create protective barriers that provide a resistance to certain drugs the more it is exposed. This is why the long term use of non-steroidal anti-inflammatory drugs, such as ibeprophen, and repeated use of antibiotics may actually be detrimental to the human body.

The ways in which drugs are received by the body differ by the type of drug and the drug's mode of action. For example, a medication that aids in lowering blood pressure will target the autorhythmic cells in the human heart to block the release of calcium, thereby slowing contractions in the heart and lowering mean arterial pressure. But an antibiotic like penicillin, that targets foreign bacteria in the body, will attach to the bacterial cell, preventing the cell from forming a protective cell wall and causing it to die. Each drug has different mechanisms because receptor sites vary (Spruill et al. 2).   As a result, the concentration at the receptor site must vary accordingly, proving the importance of understanding these biological processes.

Given this knowledge of pharmacokinetics and pharmacodynamics, we can now look into some mathematical systems. We will soon be able to predict the amount of drugs in the bloodstream, and therefore tissue, at any given time and determine the rate at which it is leaving. This is achieved through compartment models (Spruill et al. 8). The compartments in a given model represent the locations where the drug travels throughout the body, for instance,

the blood stream, and organ tissues, or urine. The simplest form is the one-compartment

model and is in fact a first order model.

In this instance, the drug is administered

into the body, enters the plasma, and is excreted

from the compartment. This can also be looked at

in mathematical terms. There is the initial amount
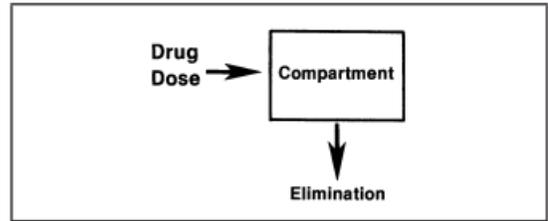
of the dosage, the compartment, which is the

FIGURE 1-13.
Simple compartmental model.

concentration of the drug in the body, and the movement out is the rate at which the drug is

leaving, or the rate of change. Since this rate is decreasing exponentially, we can utilize the

exponential decay function to determine the amount of the drug at any given time. The rate of

change in the concentration is proportional to the current concentration so we start off with

the equation $\frac{dP}{dt} = Pk$ where k is the growth rate, P is the current amount, and dP/dt is the rate

of change. This equation is separable so $\frac{1}{P}dP = kdt$

$$\rightarrow \int \frac{1}{P}dP = \int kdt$$
$$\rightarrow ln|P| = kt + C$$
$$\rightarrow P = e^{kt+C} = e^{kt}e^{c}$$
$$\rightarrow P = P_{o}e^{kt}$$

According to Calculus: Single Variable, "Every solution to the equation dP/dt = kP can be

written in the form P = $P_{o}e^{kt}$, where P_{o} is the value of P at t = 0, and k>0 represents growth,

whereas k <0 represents decay"(Gleason, Hughes-Hallett, McCallum 13).   By utilizing this

equation, we can solve real life applications. For instance, "The rate at which a drug leaves the

bloodstream and passes into the urine is proportional to the quantity of the drug in the blood

at that time. If an initial dose of Q_{o} is injected directly into the blood, 20% is left in the blood

after 3 hours. Write an equation and solve for the quantity Q of the drug in the blood after t

hours" (Gleason, Hughes-Hallett, McCallum 618). Since 20% is left, we know $Q_{o} = 1$ and

$Q(3) = 0.2$ so we can use our decay function $Q = Q_{o}e^{kt}$ and solve for k. Therefore, we can

plug

$$0.2 = e^{k3}$$

➔ $ln|0.2| = k3$

➔ k= -.536479

➔ $Q = Q_o e^{-0.536479t}$

Additionally if we plug in a time value and initial dosage amount, we can determine how much of a drug is in a patient's body at that time.

Also, "The half-life of an exponentially decaying quantity is the time required for half of it to decay" (Gleason, Hughes-Hallett, McCallum 14). It correlates with the duration of action in the hepatic and renal systems. The longer the half-life, the less often the drug needs to be administered and the longer it remains in the body (Spruill et al. 33). Half-life is useful in the medical field for two reasons: it reveals how long it takes for the body to completely eliminate the drug from the body as well as how frequent the doses should be given out (Gordon). Within the biological setting, it takes 4.5 half-lives for a drug to be 95% eliminated so by multiplying the half-life time by 4.5, the time span before the next dosage is revealed (Gordon).

After being introduced to the concept of one compartment models, we can now dive into two compartment models. This is a situation in which the drug passes through two separate locations within the body including the blood, organs and tissues, or urine. This effects the amount of the drug in the body because now it is being metabolized in two places at different rates. The right hand picture demonstrates this process and gives us the following system of equations to model it accordingly (Koch-Noble 237).
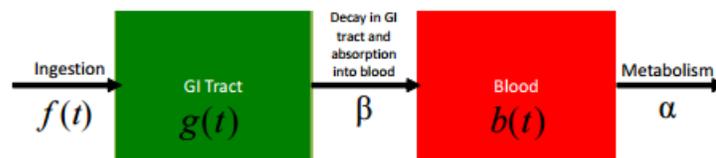

Figure 7: A representation of a two-compartment pharmacokinetics model.

$$\frac{dg}{dt} = f(t) - \beta g(t).$$

$$\frac{db}{dt} = \beta g(t) - \alpha b(t).$$

In this instance,

$f(t)$= initial dosage of ingestion at time 0

$b(t)$= amount of drug in the bloodstream at time t

$g(t)$= amount of drug in the gastrointestinal tract (GI tract) at time t

α, β= the metabolism of the drug in the bloodstream and GI tract, respectively

This is a non-homogeneous equation because $f(t)$ does not play a direct role on the other functions. So to solve, we want to turn the system into a second order linear equation.

Generally, a second order linear equation is written in the form of $Ay'' + By' + Cy = 0$. To solve, let $y = e^{rt}$ and insert into the general formula.

$$\Rightarrow r^2 e^{rt} + re^{rt} + e^{rt} = 0$$

$$\Rightarrow r^2 + r + 1 = 0$$

This last equation is the characteristic equation which we will utilize later. When the quadratic is solved, if we get distinct real roots for r, the general solution for a homogeneous equation is

$$y_h = C_1 e^{-r_1 t} + C_2 e^{-r_2 t}.$$

Furthermore, the solution to a non-homogeneous equation is $y = y_h + y_p$ where p is the particular solution. We can use this to solve our system modeling the two compartments. We start with the system,

$$\frac{dg}{dt} = f(t) - \beta g(t).$$

$$\frac{db}{dt} = \beta g(t) - \alpha b(t).$$

We rewrite these equations to factor out g(t),

$$[D + \beta][g(t)] = 1$$

$$-\beta[g(t)] + [D + \alpha][b(t)] = 0$$

(Note D represents derivative in terms of t and $f(t) = 1$)

We want the g(t) terms to have the same "coefficients" to solve by elimination so we multiply the top equation by $D + \beta$ and the bottom equation by β,

$$\beta[D + \beta][g(t)] = \beta$$

$$[D + \beta](-\beta[g(t)] + [D + \alpha][b(t)]) = 0$$

Adding the two equations will eliminate the g(t) terms and give us,

$$\Rightarrow [D + \beta][D + \alpha][b(t)] = \beta$$

When we foil, we get

$$\Rightarrow b'' + (\beta + \alpha)b' + \beta\alpha b = \beta$$

Now we use the characteristic equation discussed earlier,

$$\Rightarrow r^2 + (\beta + \alpha)r + \beta\alpha = 0$$

$$\Rightarrow (r + \beta)(r + \alpha) = 0 \text{ so } r = -\beta \text{ and } -\alpha$$

The homogeneous solution is then,

$$b_h = Ae^{-\alpha t} + Be^{-\beta t}$$

We must also consider the particular solution since this system is non-homogeneous. To do so, we let the particular solution be represented by a variable,

$$b'' + (\beta + \alpha)b' + \beta\alpha b = \beta$$

$$Let \; b_p = K$$

We plug this in and get,

$$\beta\alpha K = \beta$$

$$\Rightarrow K = \frac{1}{\alpha}$$

So our complete equation is,

$$b(t) = Ae^{-\alpha t} + Be^{-\beta t} + \frac{1}{\alpha}$$

Here $b(t)$ is the amount of drugs in the bloodstream in terms of time, t. A and B are the drug amounts of the first and second compartment, respectively. α and β are the decay rate constants for each compartment(Spruill et al. 78). Using this model, we can determine the amount of the drug in the blood at any given time when the drug passes into two compartments.

In this final portion on the paper, we will look at how multiple injections can be modelled over time by using ordinary differential equations (ODEs). In these cases, a patient would be receiving drug doses at regular intervals and between each injection, the drug would be metabolized. This creates a model in which a discrete function is a part of a continuous function (Koch-Noble 235). We can start off with the equation,

$$\frac{db}{dt} = f(t) - \alpha b(t)$$

$b(t)$= amount of drug in the bloodstream at time t

$f(t)$= dosing pattern of injections at time t (This is a discrete value since dosages will remain constant)

α = metabolism of the drug

It is interesting to note in the absence of another injection, or when $f(t)$= 0, the model will function just as the exponential decay function examined earlier in this paper. In this case, the drug will be fully excreted from the bloodstream as expected. However, the constant injections force the concentration of the drug to spike back up to the initial value and the decay cycle restarts.

The given ODE indicates that the rate at which the amount of a drug in the bloodstream is changing over a period of time (continuous) while injections of the drug are being administered (discrete). We want to transform this into a function that will tell us the amount of the drug in the bloodstream at any given time. To do so, we will utilize the Laplace transform.

First, we will look at the basic properties of three elements needed to solve the equation: the Laplace transform, step function, and Dirac delta function. The Laplace transform of a function is a way to evaluate ODE's in a simpler manner. It is defined as

$$\mathcal{L}\{f(t)\} = \int_0^\infty e^{-st} f(t) dt$$

so long as the integral converges and $f(t)$ doesn't grow larger than the exponential. Then when the integral is evaluated, we get a new function *F(s).* Thus,

$$\mathcal{L}\{f(t)\} = F(s) \text{ where s is similar to a frequency space}$$

This model also utilizes the step function, designated by $u(t)$. The definition of the step function states that,

$$u(t) = \begin{cases} 0, & t < 0 \\ 1, & t > 0 \end{cases}$$

This essentially means that when t is equivalent to a_n we get a value of 1 and the function is turned on. Practically speaking, this means if the time when the drug amount is measured is the same as the time when the drug is injected, we will get a value. It is also important to note that the derivative of the step function is the delta function,

$$\frac{d}{dt} u(t) = \delta(t)$$

The Dirac delta function is defined as a linear functional from a space of test functions f. The action of δ on f gives the value at 0 of f for any function f ("Dirac Delta Function"). By definition,

$$\int_{-\infty}^{\infty} g(t)\delta(t-a)dt = g(a)$$

Identities include,

$$\delta(t) = \begin{cases} 0, & t \neq 0 \\ \infty, & t = 0 \end{cases}$$

$$\int_{-\infty}^{\infty} \delta(t)dt = 1.$$

When time is not equal to 0 the resulting value is 0, but when t = 0, or any time a, the impulse occurs and we get a value. Whenever we have $\delta(t-a)$, we have an impulse shift to time a, but the area is still 1 ("Dirac Delta Function").

$$\delta(t-a) = \begin{cases} 0, & t \neq a \\ "\infty", & t = a \end{cases}$$

Since $f(t)$ is defined as the discrete pulse function, it is actually a delta function. So,

$$f(t) = \delta(t - a_1) + \delta(t - a_2) + \cdots + \delta(t - a_n)$$

where a_n is the time when dosage number, n, is administered.

With those in mind, we can solve the ODE. We start off with the equation,

$$\frac{db}{dt} = f(t) - \alpha b(t).$$

We can utilize the Laplace transform to solve this ODE. So we take the Laplace transform of the left and right hand side of our equation.

$$\mathcal{L}\left\{\frac{db}{dt}\right\} = \mathcal{L}\{f(t) - \alpha b(t)\}.$$

Linearity properties allow us to take the Laplace transform on both sides, from each component on the right hand side, and factor out α as a constant,

$$\mathcal{L}\left\{\frac{db}{dt}\right\} = \mathcal{L}\{f(t)\} - \alpha\mathcal{L}\{b(t)\}.$$

To evaluate, we can look at each side separately. When looking at a table of Laplace transforms (Dawkins), we can use the Laplace transform definition to solve $\mathcal{L}\left\{\frac{db}{dt}\right\}$,

$$\mathcal{L}\left\{\frac{db}{dt}\right\} = \int_0^\infty e^{-st}\frac{db}{dt}dt$$

We solve this by using integration by parts which says $\int uv' = uv - \int vu'$, so we can assign u and v' to parts of our integral and evaluate,

$$u = e^{-st} \qquad v' = \frac{db}{dt}dt$$

$$u' = -se^{-st}\,dt \qquad v = b(t)$$

$$\Rightarrow e^{-st}b(t)|_{t=0}^{t=\infty} \quad + \int_0^\infty se^{-st}b(t)dt$$

$$\Rightarrow -b(0) + s \cdot B$$

Therefore we get number 35 on our Laplace transform table,

$$s \cdot B - b(0)$$

where B is our new function and $b(0)$ is our initial amount of the drug.

We then use the Laplace transform for both functions on the right hand side, utilizing the table once again (Dawkins).

$$\mathcal{L}\{f(t)\} - \alpha\mathcal{L}\{b(t)\}.$$

$$\Rightarrow \mathcal{L}\{\delta(t - a_1) + \delta(t - a_2) + \cdots + \delta(t - a_n)\} - \alpha\mathcal{L}\{b(t)\}.$$

When we take the Laplace transform of the delta function, the definition of the Laplace transform gives us the solutions through a simple substitution of variables,

$$\mathcal{L}\{\delta(t - a)\} = \int_0^\infty e^{-st}\delta(t - a)dt = e^{-as}$$

So our right hand side solution turns out to be,

$$\Rightarrow (e^{-a_1s} + e^{-a_2s} + \cdots + e^{-a_ns}) - \alpha \cdot B \text{ (by 26 and the definition)}$$

Finally, both sides are combined and algebra is used to rearrange the terms so the B terms are on the left and the s terms are on the right.

$$s \cdot B - b(0) = (e^{-a_1s} + e^{-a_2s} + \cdots + e^{-a_ns}) - \alpha \cdot B$$

$$\Rightarrow s \cdot B + \alpha \cdot B = (e^{-a_1s} + e^{-a_2s} + \cdots + e^{-a_ns}) + b(0)$$

$$\Rightarrow B(s + \alpha) = (e^{-a_1s} + e^{-a_2s} + \cdots + e^{-a_ns}) + b(0)$$

$$\Rightarrow B = \frac{(e^{-a_1s} + e^{-a_2s} + \cdots + e^{-a_ns}) + b(0)}{(s+\alpha)}$$

Now we use the inverse Laplace transform to convert our equation for B back into $b(t)$, applying the inverse transform it to each component.

$$\mathcal{L}^{-1}\{B\} = \mathcal{L}^{-1}\left\{\frac{b(0)}{(s+\alpha)}\right\} + \mathcal{L}^{-1}\left\{\frac{e^{-a_1s}}{(s+\alpha)}\right\} + \mathcal{L}^{-1}\left\{\frac{e^{-a_2s}}{(s+\alpha)}\right\} + \cdots + \mathcal{L}^{-1}\left\{\frac{e^{-a_ns}}{(s+\alpha)}\right\}$$

Note,

$$\mathcal{L}^{-1}\left\{\frac{e^{-a_n s}}{(s+\alpha)}\right\} = \mathcal{L}^{-1}\{e^{-a_n s} \cdot F\} \text{ where } F = \frac{1}{(s+\alpha)}$$

There are four steps to solve. First, identify F which we set equal to $\frac{1}{(s+\alpha)}$. Then we take the inverse Laplace transform of F to get $f(t)$ by the definition. After, we replace t with $t - a_n$ and finish by multiplying $f(t)$ by the step function. We can do this because as stated earlier, the derivative of the step function is the delta function. After doing so, we get,

$$\mathcal{L}^{-1}\{e^{-a_n s} \cdot F\} = f(t - a_n) \cdot u(t - a_n) \ (27)$$

We use the Laplace transform table again and plug in

$$f(t) = e^{-\alpha t}(2)$$

Once this is done for every component, we get the final equation,

$$b(t) = b(0)e^{-\alpha t} + u(t - a_1)e^{-\alpha(t-a_1)} + u(t - a_2)e^{-\alpha(t-a_2)} + \cdots + u(t - a_n)e^{-\alpha(t-a_n)}$$

With the use of this equation, we can now determine the amount of the drug in the body at time, t. As time goes on, more of the function is turned on and the result is a temporary spike in the concentration. This spike cannot increase much though because the exponential decay function is attached to it, causing a decrease in the drug concentration. When $b(t)$ is graphed, the result is exactly as we would expect.
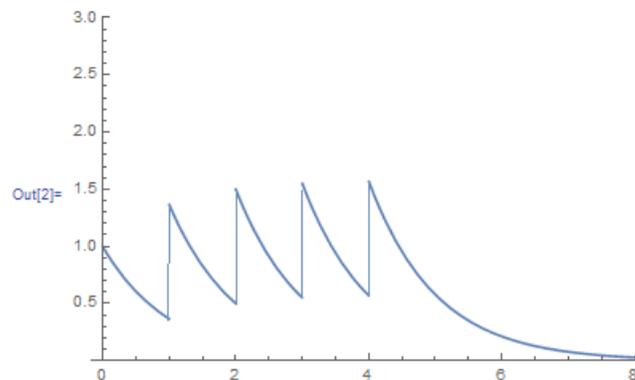
In this graph, the bottom of the curve is when the drug reaches its minimum effective concentration, the peak is its minimum toxic concentration, and the whole curve is the

therapeutic window which is the range in which the drug is working effectively (Koch-Noble 238). As discussed previously, every individual drug has its own chemical properties and are effected by factors in the body differently. For some drugs, it is preferable to give smaller doses more frequently while with others it is preferable to give larger doses over longer time intervals. Larger, less frequent doses cause the therapeutic range to be greater (longer time from peak to pit). This can be a disadvantage because there is a greater chance of staying in the toxic range or subtherapeutic range longer. Likewise, smaller, more frequent doses may not be practical when it comes to administering (Spruill et al. 60).

To conclude, we have looked at just a few of the models that aid in modeling drug injection types within the field of pharmacokinetics. While the complexity of each formula varies, the result is the same; we are able to determine the amount of a drug within the body at any given time. However, it is important to note there are multiple other factors that play a role in this amount. One's ability to metabolize a single drug fluctuates between patients. Interactions between two or more medications may also influence the rate of decay. With an insight into the workings of pharmacodynamics, these factors can be considered and may be adjusted for in our mathematical interpretations. By generating these models, we can develop a deeper understanding of how drugs operate in order to further the effectiveness of their administration, thus accomplishing the ultimate goal of improving the patient's well-being.

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