Calculus + Functions Application in Pharmacokinetics

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This project uses the single compartment model applied to oral dosing of various pharmaceuticals in pharmacokinetics. This model assumes an absorption rate, dependent on an absorption rate constant k_a, to represent the transfer of the drug from the stomach to the bloodstream where the elimination process begins. The elimination process, dependent on an elimination rate constant k_e, models the removal of the drug from the bloodstream, thus eliminating it from the body. The amount of drug remaining in the stomach that has not yet been absorbed into the blood will be represented by the variable A, and the drug in the bloodstream awaiting excretion will be represented by E. This model avoids factors such as blood volume, concentration, and bioavailability. Here is a background to the equations I will be using:

The equations that model the rate of absorption and elimination of the drug:

dA/dt = -k_a * A
dE/dt = [k_a * A] - [k_e * E]
For all values of k_a and k_e.

To calculate k_a:
k_a = ln2 / t_1/2 where t_1/2 represents the absorption half-life of the drug (the time it takes for the drug to go from its maximum blood plasma concentration to half of its maximum blood plasma concentration)

It is possible to find k_e by taking the slope of the line on a semi-log graph plotting concentration vs. time, but for the sake of time I will be gathering sample k_e values from literature to use in my calculations.

Integrating to find the amount of drug that has not been absorbed/eliminated as a function of time:

For absorption as a function of time:
$\frac{dA}{dt} = -k_a * A$
$\frac{dA}{A} = -k_a * dt$ (Rearrange for dA/A in order to integrate)
$ln(A) = -k_a * t + C_0$ (Integrate both sides of the equation in order to isolate A)
$A = e^{-k_a * t} * e^{C_0}$ (Taking the inverse of ln(A) to isolate A and using exponent laws)
$A(t) = D * e^{-k_a * t}$ (Given A_0 = D, e^C_0 = D where C_0 = initial concentration; I am not entirely sure how this is true, but it is what makes sense mathematically)

For elimination as a function of time:

$\frac{dE}{dt} = [k_a * A] - [k_e * E]$
$\frac{dE}{dt} = [k_a * D * e^{-k_a * t}] - [k_e * E]$
$\frac{dE}{dt} + [k_e * E] = k_a * D * e^{-k_e * t}$

Set integrating factor as $\mu = e^{\int k_e * dt} = e^{k_e * t}$
From this point forward I am unclear on how the final equations were found, but I will include it for any required reference.
$E = \frac{1}{\mu} \int_0^t \mu * k_a * D * e^{-k_a * s} * ds$
$E = D * e^{-k_e * t} * k_a \int_0^t e^{(k_e - k_a) * s} * ds$
$E(t) = D * k * e^{-k_e * t} * t$ where $k = k_a = k_e$

$E(t) = D * \frac{k_a}{k_a - k_e} * (e^{-k_e * t} - e^{-k_a * t})$ where $k_a \neq k_e$
This project will only be exploring the case where $k_a \neq k_e$, but it's interesting to see how the other case comes about as well.

To demonstrate how these equations can be used, I will show how medical professionals determine the frequency of oral administration of sample drugs. In this example, I use the dosage guidelines for acetaminophen in children, as outlined in the pediatric dosing charts provided by Tylenol. According to this chart, it is recommended that children aged 2-3 years old take 1 tablet (160 mg) of acetaminophen every 4 hours as needed. Numerically and graphically, it can be shown that 4 hours (240 minutes) is ample time for the dose to be absorbed and to be eliminated from the body, thus making it safe for another dose to be taken without risk of overdose. According to a kinetic study of drug elimination, a sample elimination rate constant (k_e) of acetaminophen is $0.27h^{-1}$.

For the absorption rate constant (k_a) of acetaminophen:
$k_a = \frac{ln(2)}{t_{1/2}}$
$k_a = \frac{ln2}{2}$
$k_a \approx 0.35$

```
# values of variables used in analysis of Tylenol dosing chart
drug_dosage = 160
k_a = 0.35
k_e = 0.27
K = k_a/(k_a - k_e)

# defining absorption as a function of time (A(t))
absorption <- function(time) {
  return( drug_dosage * exp(-k_a*time) )
}

# library calling for packages that contain graphing functions
library(tidyverse)
```

```
## -- Attaching packages --------------------------------------- tidyverse 1.3.1 --

## v ggplot2 3.3.6     v purrr   0.3.4
## v tibble  3.1.7     v dplyr   1.0.9
## v tidyr   1.2.0     v stringr 1.4.0
## v readr   2.1.2     v forcats 0.5.1

## -- Conflicts ------------------------------------------ tidyverse_conflicts() --
## x dplyr::filter() masks stats::filter()
## x dplyr::lag()    masks stats::lag()
```

```
require(ggthemes)
```

```
## Loading required package: ggthemes
```

```
# graphing + designing the absorption over time graph
ggplot() +
  stat_function(fun = absorption, geom = 'line', colour = '#b04ede', size = 0.5) +
  stat_function(fun = absorption, geom = 'point', size = 1) +
  xlim(0, 240) + theme_minimal() +
```

```
  labs(title = "Amount of Drug in Stomach",
       x = "Time (m)",
       y = "Amount in Stomach (mg)") +
  theme(
    axis.title = element_text(family = 'Helvetica', size = 14, color = 'black'),
    axis.text = element_text(family = 'Helvetica', size = 14, color = 'black'),
    plot.title = element_text(family = 'Helvetica', size = 20, color = 'black')
  )
```

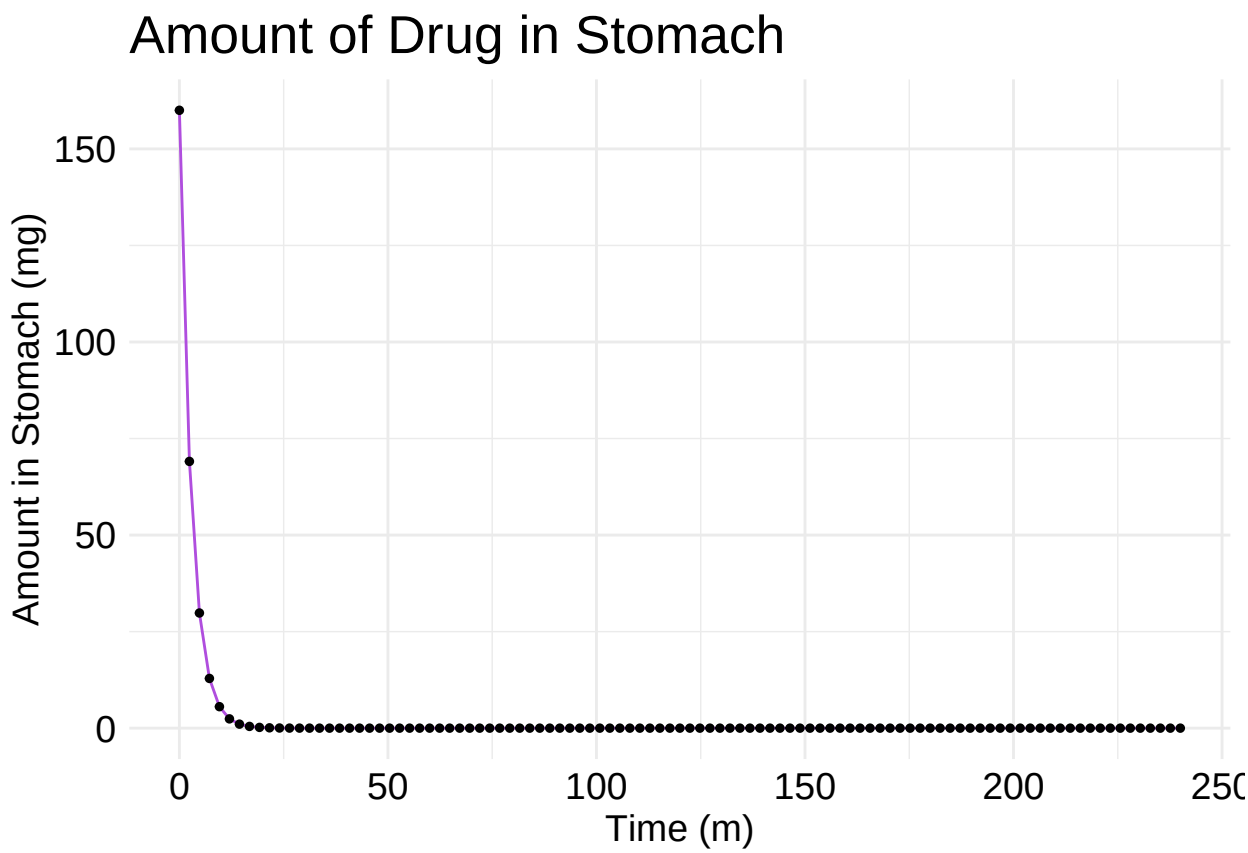

Figure 1.1: Graph portraying the transfer of acetaminophen from the stomach to the bloodstream over time.

$A(t) = D * e^{-k_a * t}$
$A(t) = 160 * e^{-0.35 * t}$ $A'(t) = -56 * e^{-0.35 * t}$
$A(24) = 160 * e^{-0.35 * 240}$
$A(240) \approx 0$

```
# defining the derivative of absorption as a function of time (A'(t))
absorpderiv <- function(time) {
  return(drug_dosage * -k_a * exp(-k_a * time))
}

# graphing + designing the derivative of absorption
ggplot() +
  stat_function(fun = absorpderiv, geom = 'line', color = 'red', size = 0.5) +
  stat_function(fun = absorpderiv, geom = 'point') +
  xlim(0, 240) + theme_minimal() +
```

```
  labs(title = "Rate of Absorption",
       x = "Time (m)",
       y = "A'(t)") +
  theme(
    axis.title = element_text(family = 'Helvetica', size = 14, color = 'black'),
    axis.text = element_text(family = 'Helvetica', size = 14, color = 'black'),
    plot.title = element_text(family = 'Helvetica', size = 20, color = 'black')
  )
```

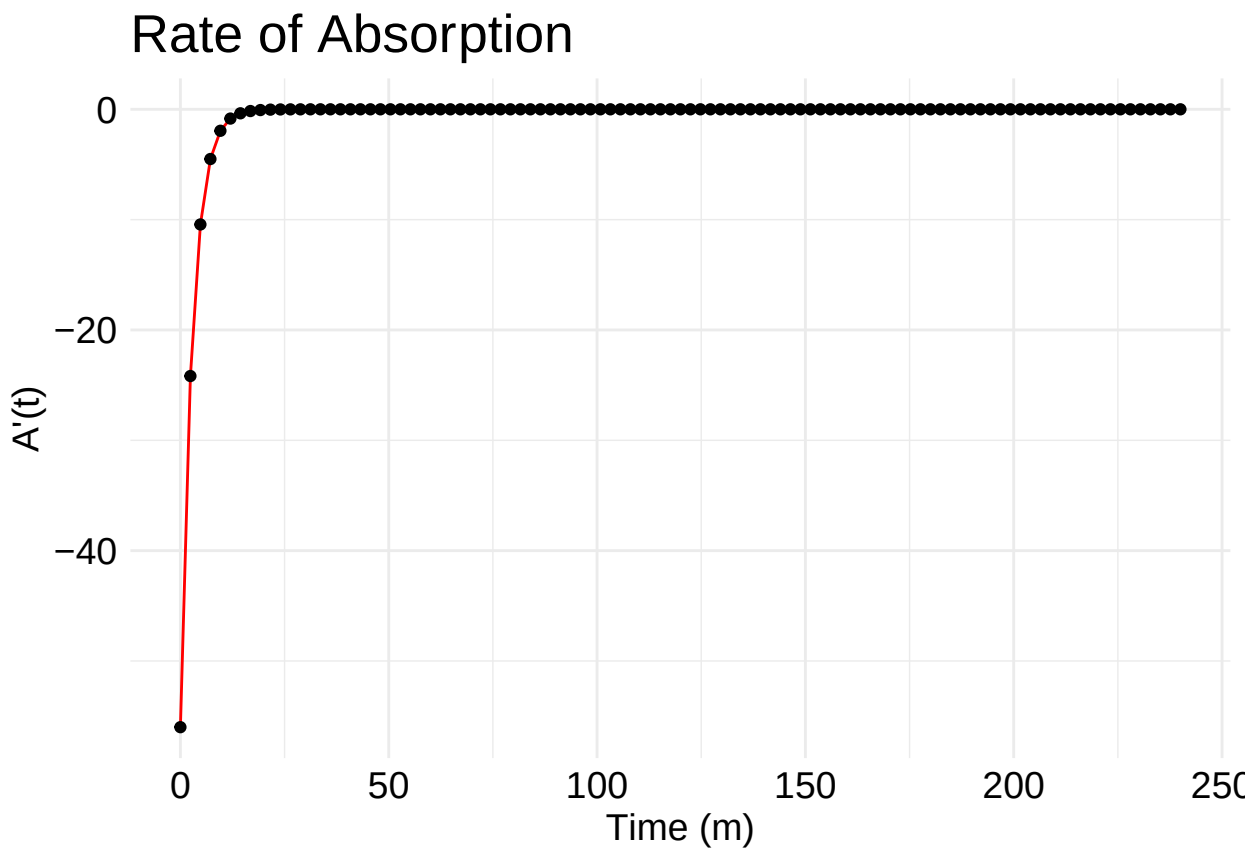

Figure 1.2: Graph of A'(t) showing the rate of drug absorption in the body.

```
# defining elimination as a function of time (E(t))
elimination <- function(time) {
  return((drug_dosage * K) * ((exp(-k_e*time)) - (exp(-k_a*time))))
}

# graphing + designing the elimination over time graph
ggplot() +
  stat_function(fun = elimination, geom = 'line', colour = '#b04ede', size = 0.5) +
  stat_function(fun = elimination, geom = 'point') +
  xlim(0, 240) + theme_minimal() +
  labs(title = "Amount of Drug in Blood Stream",
       x = "Time (m)",
       y = "Amount in Blood Stream (mg)") +
    theme(
      axis.title = element_text(family = 'Helvetica', size = 14, color = 'black'),
```

```
    axis.text = element_text(family = 'Helvetica', size = 14, color = 'black'),
    plot.title = element_text(family = 'Helvetica', size = 20, color = 'black')
  )
```

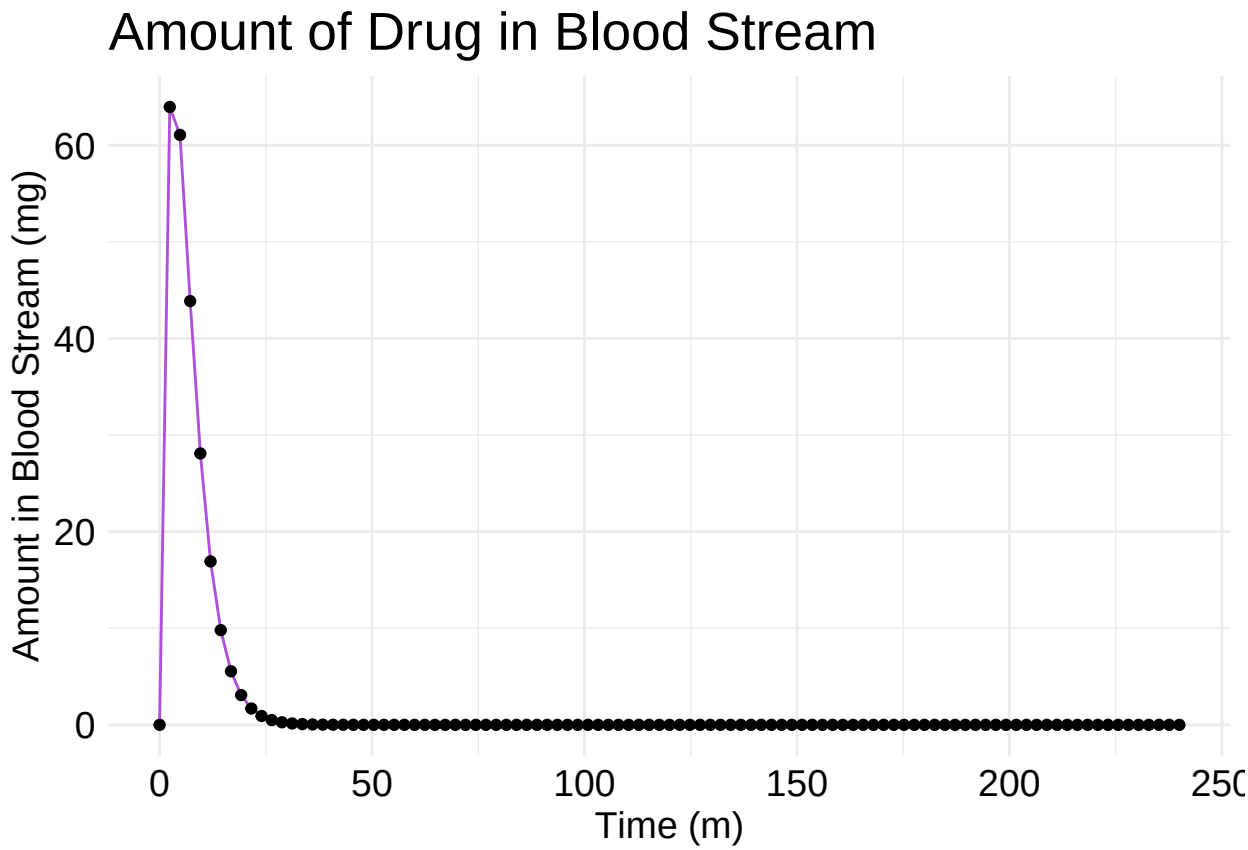

Figure 2.1: Graph portraying the process of acetaminophen being eliminated from the bloodstream.

$E(t) = D * \frac{k_a}{k_a - k_e} * (e^{-k_e * t} - e^{-k_a * t})$, since $k_a \neq k_e$
$E(t) = 160 * \frac{0.35}{0.35 - 0.27} * (e^{-0.27 * t} - e^{-0.25 * t})$
$E(240) = 160 * \frac{0.35}{0.35 - 0.27} * (e^{-0.27 * 240} - e^{-0.35 * 240})$
$E(240) \approx 0$

To find the point where the volume of drug in the bloodstream changes from increasing to decreasing:

$E'(t) = 160 * \frac{0.35}{0.35 - 0.27} * (-0.27e^{-0.27 * t} + 0.35e^{-0.35 * t})$
$0 = 160 * \frac{0.35}{0.35 - 0.27} * (-0.27e^{-0.27 * t} + 0.35e^{-0.35 * t})$
$0.27e^{-0.27 * t} = 0.35e^{-0.35 * t}$
$e^{0.08 * t} = \frac{0.35}{0.27}$
$0.08 * t = ln\frac{0.35}{0.27}$
$t = \frac{ln\frac{0.35}{0.27}}{0.08} \approx 3.24$ min

The drug present in the bloodstream will start decreasing after approximately 3.24 minutes. Realistically, when factors such as bioavailability, concentration, blood volume, the patient's mass, and the patient's metabolism are taken into consideration, this process will be much slower.

As can be seen from the graphs, the drug volume approaches 0 in the body as it is processed in the stomach and the blood stream, so there is an asymptote at y = 0 for both absorption and elimination.

```r
# defining the derivative of elimination as a function of time (E'(t))
elimderiv <- function(time) {
  return(drug_dosage * K * (-k_e*exp(-k_e*time) + k_a*exp(-k_a*time)))
}

# graphing + designing the derivative of elimination
ggplot() +
  stat_function(fun = elimderiv, geom = 'line', color = 'red', size = 0.5) +
  stat_function(fun = elimderiv, geom = 'point') +
  xlim(0, 240) + theme_minimal() +
  labs(title = "Rate of Elimination",
       x = "Time (m)",
       y = "E'(t)") +
  theme(
    axis.title = element_text(family = 'Helvetica', size = 14, color = 'black'),
    axis.text = element_text(family = 'Helvetica', size = 14, color = 'black'),
    plot.title = element_text(family = 'Helvetica', size = 20, color = 'black')
  )
```

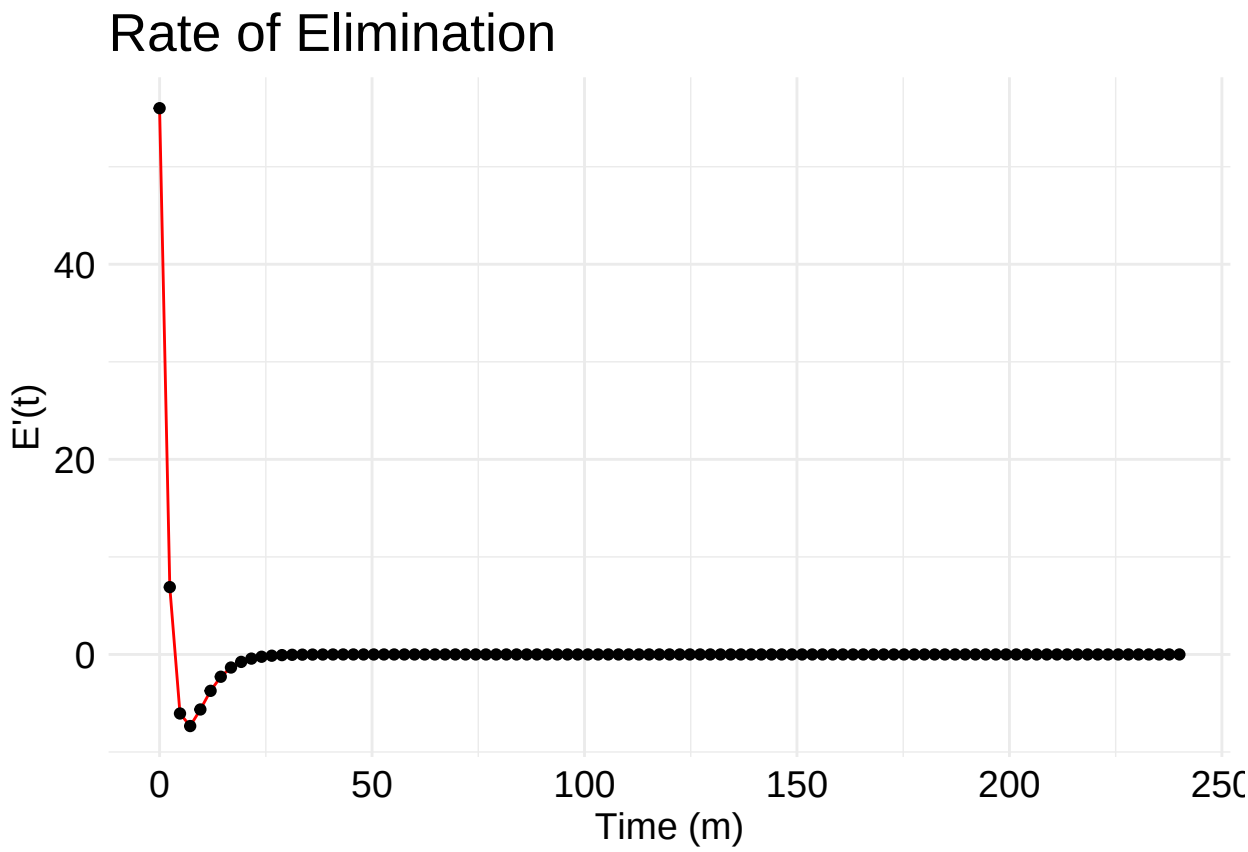

Figure 2.2: Graph of E'(t) showing the rate of drug elimination from the body.

As proven numerically and graphically, A(240) and E(240) ≈ 0, therefore proving that 4 hours is a safe amount of time before another dose of acetaminophen can be administered without risk of overdose.

Using our equations and graphical analysis, we can now determine how much time is needed in between doses of other pharmaceuticals for safe consumption. Let's explore ibuprofen dosages in adults. For osteoarthritis patients, 400 mg is recommended as a single dose. The elimination constant (k_e) for ibuprofen is 0.4 h^{-1},

while the absorption constant (k_a) is 0.5 h^{-1}.

Since the volume of drug in the stomach and the bloodstream approaches 0 but will never truly be 0, I will find the time required for 5^{-26} mg of the drug to be remaining, as that is how much would be remaining in the bloodstream after 4 hours of acetaminophen consumption; I will use the assumption that 5^{-26} mg is also sufficient volume of ibuprofen that renders it safe to take another dose (Figure 1.3).

$E(t) = D * \frac{k_a}{k_a - k_e} * (e^{-k_e * t} - e^{-k_a * t})$
$5^{-26} = 400 * \frac{0.5}{0.5 - 0.4} * (e^{-0.4 * t} - e^{-0.5 * t})$
Using the console, I find that it takes approximately 165 minutes for this equation to be true.

Therefore, after approximately 165 minutes (2.75 hours), it is likely safe to take another dose of ibuprofen according to the single compartment model. However, this value may vary according to the patient's physical build and genetic makeup.

In conclusion, the single compartment model for oral dosing is effective in showing the basics of how dosing intervals of pharmaceuticals are calculated without taking into account factors such as physical makeup of the individual, blood volume, concentration, and bioavailability. Factors such as basal metabolic rate would affect dosing intervals, as they would play a role in how fast an individual absorbs and eliminates the drug. This model assumes only the dose and rate constants affecting dosing intervals, and it sufficiently achieves the purpose of demonstrating at a base level how such intervals are determined to be safe for patients worldwide.