Modelling the Metabolism of Morphine Based Method of Administration

Noreen Altaf, Nadia Breault, Selena Dajani, Justin Gebel,
Alex McMullen, Jackson Timewell

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1 Introduction

Many people depend on prescription drugs in their day-to-day lives, and we must understand how drugs are metabolized within the body to determine how to effectively administer them, and ensure they are administered safely without the risk of overdose.

The concentration of the drug remaining in the bloodstream depends on the process of absorption, excretion, and the clearance rate of the drug. Absorption is the process that moves administered medication to the bloodstream. This process affects how quickly the drugs are transported around the body and at what concentration they are transported. The rate at which absorption occurs depends on the method of administration. Additionally, the mechanism by which drugs are removed from the body is known as excretion, which works to decrease the concentration of drugs in the bloodstream. The kidneys usually facilitate this process, however, other organs may play a role in the removal of drugs from the body. Furthermore, clearance can be defined as the ratio between the elimination rate and the absorption rate. Thus, the clearance rate tells us the rate at which a drug is leaving the body compared to absorption (Grogan & Preuss, 2023). Overall these factors help us to understand the metabolism of drugs and the movement of drugs through the body.

Drug metabolism is the process that assists with the clearance of drugs in the bloodstream (Schaffenburg et al., 2021). Understanding drug metabolism is critical for optimizing drug therapy, and drug efficiency. Additionally, understanding drug metabolism allows us to determine dosages and safe use of drugs (Subramanian, 2023). The rate at which drugs are metabolized depends on the individual and their metabolism rate, and also affects the toxicity and the effectiveness of the drug (Moravek Inc., 2020). For instance, an individual with a slower metabolism will metabolize drugs slowly and will have a buildup of drugs within their body. This may cause health issues for such individuals. Most drugs pass through the liver, where enzymes work to metabolize it. Enzymes in the liver modify the drug's structure and attach it to an endogenous substance that allows it to be excreted easily (Moravek Inc., 2020).

Additionally, there are many methods of administration, and each method affects the rate of absorption. Drugs and medication can be administered orally, intravenously, subcutaneously, transdermally, or via inhalation (Subramanian, 2023). Many drugs are in the form of pills that are taken orally and pass through the stomach as well as the gastrointestinal tract. The absorption rate for these drugs is affected by pH within the stomach and digestive tract, the amount of food present in the stomach, and even the gastric emptying rate (Subramanian, 2023). Intravenous administration is the method of injecting medication directly into the bloodstream. This method is more efficient and allows the drug to take effect at a faster rate. Subcutaneous and intramuscular administration is similar to intravenous administration, however, in this case, medication is injected into the muscle of the recipient. This method allows the drug to be absorbed in a controlled way. Drugs can also be absorbed through the skin and into the bloodstream in the form of a cream or ointment. This is known as transdermal administration. This method is ideal for the continuous absorption and movement of drugs around the body. Finally, inhalation administration is a method in which drugs are inhaled into the lungs. This method also allows for quick absorption and efficient movement around the body (Subramanian, 2023).

While the body's ability to absorb a drug is a crucial factor when optimizing drug design, many factors affect how the body processes the drug and how the drug will break down. How a drug is absorbed affects the speed and concentration of how the drug arrives in the body, including how the drug is released from its dosage form (Grogan & Preuss, 2023). The preparation of the drug determines the absorption rate. The process of preparing the drug includes how it is administered, the size and concentration of the dosage and the degree of protein binding and lipid solubility (Bertram-Ralph & Amare, 2023). An important factor that determines how fast a drug is absorbed

is related to its oil-water partition coefficient. In other words, the more lipophilic a drug is, the faster it may be absorbed. All pharmaceutical products are made of active and inactive ingredients which all affect the body and how the drug is absorbed. The active ingredients include the drug itself, while the inactive ingredients include ingredients and molecules that enhance stability, absorption, flavour and other qualities (Anchordoquy, 2022). No matter the form of dosage, whether that be tablets, capsules or solutions, they all consist of these ingredients (Le, 2022). Many elements in drug absorption affect how drugs are absorbed into the body, it is also important to take these into account when modelling all types of drug intake.

Thus, many factors affect the concentration of drugs within the body. We must consider these factors when designing drugs that are effective, but also efficient. This project aims to examine the absorption and metabolism of morphine within the body, through different methods of administration. In particular, we will model the concentration of morphine in the bloodstream and explore the absorption and clearance rate of morphine administration. Our focus will be on comparing intravenous administration with oral administration through pills.

2 Model

2.1 Base Model

Our model aims to capture the absorption of intravenous treatments into the body. The focus is to be able to balance the dosage rate with the body's processing rate, so that treatment is effective, but does not lead to overdoses. To do this, we use a continuous model to measure the amount of morphine in the body at a given time.

$$\frac{dA}{dt} = D(t) - P(A)$$

where $A(t)$ represents the amount of the morphine in the body at any given time t, $D(t)$ represents the dosage rate and $P(A)$ represents the body's processing rate (which we assume to be proportional to the amount of morphine present). Our state variable is therefore the amount of morphine present, or A.

We also have several parameters. In our first case, it is assumed that morphine is administered intravenously at a constant rate of $0 < r < 10$ (in mg/hr), which ceases after a certain number of hours h. The second case models when morphine is administered by a pill, and so we model the dosage rate by $D(t) = D_{max}e^{-t/h}$ to capture the slow release of the medication as the pill dissolves.

Additionally, we assume that the rate at which the body clears the morphine is a constant $0 < c < 2$ (in mg/hr), and so we model the body's processing rate by $P(A) = cA$. Notice that in this way, we assume that the clearance rate of morphine depends solely on the amount in the body and not on any outside factors like patient health, hydration, food intake, and the interactions of the morphine with any other medications an individual may be taking.

2.2 Analysis of Base Model

We used both mathematical methods and computer simulations to analyze our model. In both cases, the initial configuration of our model was simple enough that we could explicitly find an expression for $A(t)$ which solves our differential equation. Our solution for the intravenous case is

$$A(t) = \begin{cases} \frac{r}{c} + K_1 e^{-ct} & 0 \leq t \leq h \\ K_2 e^{-ct} & t \geq h \end{cases}$$

where K_1 and K_2 are arbitrary constants. For the first time interval, we used the initial condition $t = 0, A = 0$ (since at time 0 there will have been no morphine administered) to find that $K_1 = \frac{r}{c}$. Then for the second time interval, the initial condition was found to be $t = h$ and $A = A(h)$, and so our constant in this case was $K_2 = \frac{r}{c}(e^{ch} - 1)$. This then gives us the complete solution to our model, which is

$$A(t) = \begin{cases} \frac{r}{c}(1 + e^{-ct}) & 0 \leq t \leq h \\ \frac{r}{c}(e^{ch} - 1)e^{-ct} & t \geq h \end{cases}$$

The result to glean from this is that the amount of morphine in the body will roughly follow a decreasing exponential curve according to our model. Note that the curve is shifted upwards in the first time interval, which accounts for the minimum amount of drug guaranteed by the dosing.

Furthermore, in the first interval (before time h), the unique point of equilibrium was found to be $A^* = \frac{r}{c}$, which is stable for positive r and c since that will mean that the slopes approaching A^* from the left will be positive and the slopes approaching from the right will be negative. This finding is supported by our model solution, which is a decreasing exponential curve on this time interval. In this case, the curve has been shifted upwards by $\frac{r}{c}$, and so we would expect A to reach this value in the longer term since e^{-t} normally approached 0 over time.

Moreover, this point represents the solubility of morphine in the bloodstream, so stability makes sense as we would expect the concentration of morphine to steadily approach this value over the course of dosing. We would also expect that excesses of morphine in the body would be cleared by the body to return to this balanced level. The values of r and c disrupt stability in the following ways:

1. If $r < 0$ and $c > 0$, then this point is semi-stable, where solutions below this point will be detracted, and those above will be attracted.

2. If $r > 0$ and $c < 0$, then this point is semi-stable, with the inverse behaviour of the previous case.

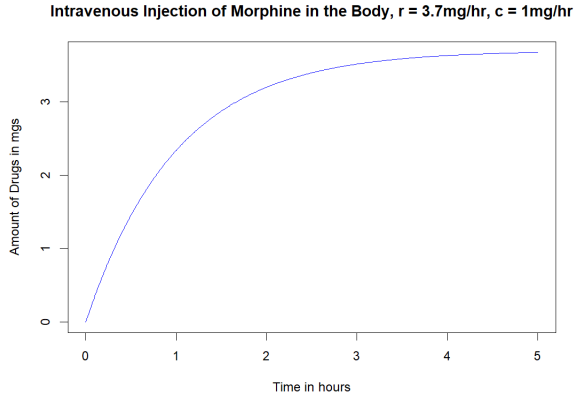
3. If $r < 0$ and $c < 0$, then this point is unstable.

However, these are not feasible as negative intake and clearance rates do not make sense in our real world context. Therefore, we can safely ignore these cases. Alternatively, in the second interval (after time h), we found that the unique point of equilibrium was $A^* = 0$, which is only unstable if $c < 0$. However, as previously discussed, this does not occur, and so this point is always stable in reality. Indeed, this is consistent with the model solution that we found, which is a scaled decreasing exponential curve. We would expect the value of such a function to approach 0 over time, and A certainly exhibits this behaviour. This also makes sense as it represents all of the morphine being cleared from the body, which we would expect to eventually happen after dosing ceases.

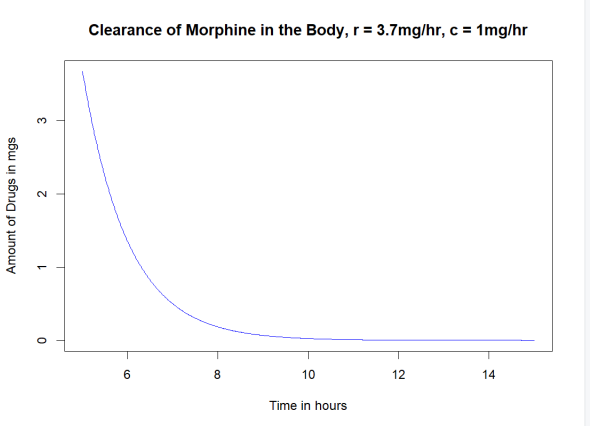
Furthermore, we simulated this model in R and indeed found that the stability of our equilibria matched the above analysis. Using the plot function in R, we modelled our solution over time t from times 0 to h with steps every 0.01 hours. We used parameters r, c and h. The figure below shows a representation of the amount of morphine in the body at time t with injection rate $r = 3.7$ mg/hr, clearance rate $c = 1$ mg/hr, and injection time $h = 5$ hours. These parameters are intended to represent accurate standards of morphine used by medical professionals.

Here we can see that long term, the amount of morphine in the body quickly approaches 3.7 milligrams as expected. It will stay at this value for as long as the morphine is being administered.

Additionally, using the plot function in R, we modelled our solution for when morphine is no longer being administered, over time t from hours h to 15 with steps every 0.01 hours. We used



parameters r, c and h. The figure below shows a representation of the amount of morphine in the body at time t with injection rate $r = 3.7$ mg/hr, clearance rate $c = 1$ mg/hr, and injection time $h = 5$ hours.



As we can see, at time h, the amount of morphine in the body is 3.7 mg/hr, which matches what we saw in the model from 0 to h. As time goes on, since we are no longer administering morphine into the body, we see that the amount of morphine in the body drops to zero. Notice that this is identical to the findings of our mathematical analysis. As we have seen from these models, the morphine takes effect almost instantly, and the amount of morphine in the body can be accurately controlled to a safe level. We can also notice that when the morphine stops being administered, it clears out of the body rapidly.

We were also able to find a solution to our model in the case where morphine is administered via a pill. Recall that our differential equation for this method of administration was

$$\frac{dA}{dt} = D_{max}e^{-t/h} - cA$$

And indeed our solution is

$$A(t) = \frac{h}{hc-1}D_{max}(e^{-t/h} - e^{-ct}) \qquad t \geq 0$$

In this case, there is only one time interval as the dosage time h is variable based on how long the pill takes to dissolve. This is a parameter that is not easily controlled, and so is already accounted for in our model equation. Note that as this is not an autonomous differential equation, there are no equilibrium points to determine. However, we may still analytically determine the behaviour of $A(t)$ in order to gain insight into how the dosage will occur. So note that the derivative of $A(t)$ is

$$\frac{dA}{dt} = \frac{h}{hc-1} D_{max} \left(ce^{-ct} - \frac{1}{h} e^{-t/h} \right)$$

Then we know that $A(t)$ achieves an extremal value whenever this expression is equal to 0. In other words, we must find a time value t^* such that

$$\frac{hc}{hc-1} D_{max} e^{-ct^*} = \frac{1}{hc-1} D_{max} e^{-t^*/h}$$

Most of these constants immediately cancel out, and so we can simplify this expression to $hce^{-ct^*} = e^{-t^*/h}$. Then, gathering like terms gives us $hc = e^{ct^* - t^*/h}$. It is then easy to see that t^* must be

$$t^* = \frac{h \ln(hc)}{hc-1}$$

Therefore, t^* is a critical value of A, and subsequently must be either a maximum or a minimum. It would be unrealistic for t^* to be an inflection point as that would mean that the amount of morphine in the body would increase without bound. For a reasonable choice of h and c, where $h \geq \frac{1}{c}$, we would find that $\frac{dA}{dt}$ is positive at $t = 0$ and negative as t becomes arbitrarily large since ce^{-ct} will approach 0 faster than $\frac{1}{h} e^{-t/h}$. Therefore, we can conclude that the likeliest case is that A achieves a maximum at t^*.

Thus, our model predicts that the amount of morphine in the body will increase until time t^* and then steadily decline afterwords. This would represent the amount of the time it takes for the pill to dissolve, and then the time period after the maximum amount occurs would represent the body clearing out all of the morphine.

Furthermore, we can use our model solution to estimate how much morphine is released by the pill in the time interval $[0, h]$. Indeed, we find that

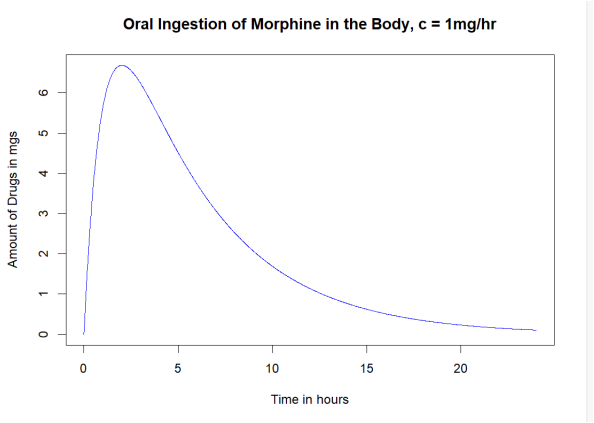
$$\text{Amount released} = \int_0^h \frac{h}{hc-1} D_{max} (e^{-t/h} - e^{-ct}) \, dt = -hD_{max} e^{-t/h} \Big|_0^h = hD_{max} \left(1 - \frac{1}{e} \right)$$

which will give a decent estimate for the amount of morphine released, given specific values of h and D_{max}.

Next, we modelled the effects of the pill in R and confirmed these results. Using the plot function in R, we modelled our solution over time t from times 0 to h with steps every 0.01. We chose parameters $h = 5$ hours, $c = 1$ mg, $D_{max} = 10$ mg. These parameters were chosen to align accurately with the standards of medical professionals and researchers.

This matches the mathematical analysis, as after time h our model is identical to the intravenous case. As expected, the pill causes a spike in the amount of morphine in the body, and then dissolves slowly to approach a concentration of zero. This contrasts the method of intravenous administration as there is increased unpredictability with pills. This is because the maximum amount of morphine achieved could be much higher.

This allows us to conclude that intravenous administration is the safer choice due to the stability of morphine in the body over time. Our model predicts that intravenous methods will result in the amount of morphine in the body approaching a fraction of the intake rate over the clearance



rate. Then at time h the amount of morphine begins to return to zero. We also predict that oral administration methods will cause a spike in the amount of morphine, with the prediction being the same as the IV case in the long run. In a real-world scenario, this shows why intravenous administration methods are the preferred choice in an emergency.

2.3 Model Extension

In this section, we extend our model by assuming that the metabolization of the morphine occurs logistically rather than exponentially. This could potentially be more accurate as the logistic growth can account for absorption stagnating as the bloodstream approaches saturation with the morphine. This is illustrated through analyses similar to what we conducted for the exponential case.

The differential equation we are working with now is:

$$\frac{dA}{dt} = \begin{cases} r - cA(1 - A/K) & 0 \leq t \leq h \\ -cA(1 - A/K) & t \geq h \end{cases}$$

Where A is the amount of drug in the body at time t, c is our clearance rate, and K is our logistic parameter.

We simulated this logistic model in R, by approximating a solution using Euler's method since this differential equation is difficult to explicitly solve. Euler's Method allowed us to visualize and predict the behaviour of the model. Additionally, we can interpret K as the maximum amount of morphine which can be dissolved into the bloodstream. With morphine being such a potent drug it is important to take into account that the average human can only have so much of it. Also, we determined that an appropriate choice for K is 10 milligrams, and our simulations allowed us to determine that a clearance rate of 1 mg/hr is realistic.

This model differs from our base model in that we now have a measure of solubility for the morphine. This means that we can never reach an amount of morphine higher than 10 milligrams in the body. However, if the injection rate were to change in our base model, it would be quite easy to get an amount higher than the solubility. With logistic drug metabolism, we can administer morphine in a more controlled and stable way.

3 Results

Mathematical analysis of this extended model is more challenging due to the logistic component. In the first time interval $[0, h]$, solving the differential equation

$$\frac{dA}{dt} = r - cA\left(1 - \frac{A}{K}\right) = r - cA + \frac{c}{K}A^2$$

is rather difficult. Instead, we notice that this is an autonomous ODE, which prompts us to search for equilibrium points. Then, setting $\frac{dA}{dt} = 0$, we find by the quadratic equation that the two equilibrium points will be

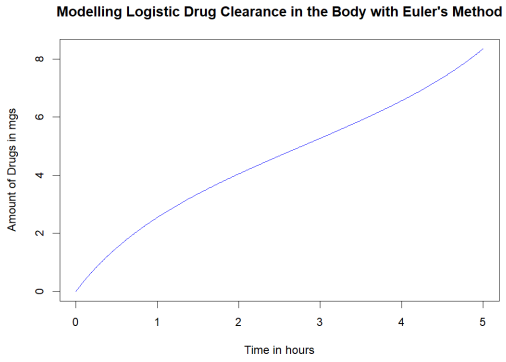
$$A^* = \frac{K}{2} \pm \frac{K}{2c}\sqrt{c^2 - \frac{4cr}{K}}$$

which is not very helpful. However, if we input our test values of $K = 10$, $r = 3.7$, and $c = 1$, we find that $c^2 - \frac{4cr}{K} = 1 - 1.48 = -0.48$, indicating that there will be no equilibrium points in this case, as the quadratic will have no real solutions. This makes sense as pure logistic growth models typically have two equilibrium points, both of which will be difficult to achieve during the dosing phase as the amount of drug will not be growing purely logistically. In contrast to this, we have the following differential equation on the second time interval (h, ∞):

$$\frac{dA}{dt} = -cA\left(1 - \frac{A}{K}\right)$$

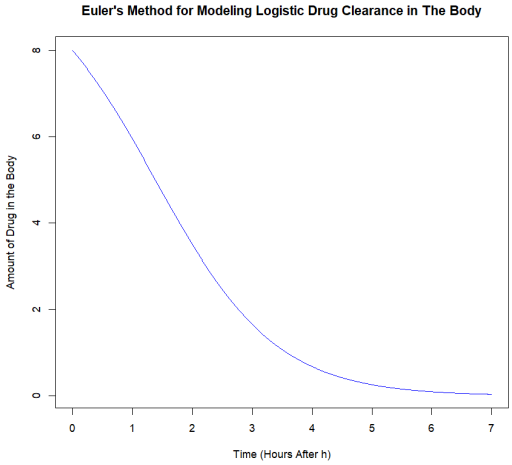
which always has the equilibrium points $A^* = 0$ and $A^* = K$, as is expected with logistic growth. Then, given reasonable values of K and c, we find $A^* = 0$ to be stable and $A^* = K$ to be unstable, which makes sense as we would expect the body to clear the morphine over time, bringing the concentration to zero.

We then also simulated this extended model in R using the methods previously discussed. Looking at the graph for $t < h$ (hours), we can see that the body is metabolizing the drug steadily and does not ever exceed our carrying capacity. Since Euler's Method works better on shorter time steps, we use $h = 5$ hours with a time step of 0.01 hours.



From this plot, we can see that our drug successfully avoids hitting carrying capacity K. This is beneficial because it allows for flexibility in dosing. If we require a higher dosage we can alter h to allow for a longer dosing period. We also have some flexibility in our carrying capacity and make changes based on our patient's needs. This shows that the logistic drug metabolism dosing method provided an extremely stable way of administering morphine.

Next, simulating time $h < t$ in R, we can see that the amount of morphine still drops off drastically similar to our other models. This makes sense since our clearance rate stayed the same through all 3 of our models. This plot begins 5 hours into the dosing period. It is the time that we stopped administering the morphine and it matches the amount of the morphine in the body at time h for $t < h$.



Overall, this model extension verified that intravenous administration remains the safer option regardless of the method/rate of administration. We can see that even considering logistic metabolism, the drug exits the body in a fast, yet controlled manner.

4 Discussion

To summarize, the results of our model show that intravenous administration is a stable and safe method of morphine administration. The amount of morphine in the body can be accurately controlled using this method, and its effects can be seen immediately. This is why this method is commonly used in emergencies by medical professionals. On the other hand, oral administration is a much more convenient method of administering morphine. With this method, the peak amount of morphine in the body is much higher than the IV method, making the oral method a much more dangerous method of administration. Essentially, there is a trade-off between safety and convenience between the two methods. In general, the results have shown that intravenous administration is best, but we still acknowledge that methods of administration should be determined on a case-by-case basis. Finally, when considering logistic metabolization we found this deeper analysis verified the findings of our base model. The long-term behaviour of morphine in the body follows a similar pattern with this extra consideration, exemplifying the safety and flexibility of the administration method. We found that under deeper scrutiny, intravenous administration remains the best.

However, the models that we have created are only a small representation of all that needs to be considered when providing morphine to patients in the real world setting. As the parameters we considered were limited, we expect there to be other factors affecting drug absorption, resulting in a degree of error stemming from our model. Though, since every patient is different, it would be impossible for any model to perfectly represent drug absorption in every case. Drug metabolism is affected by many variables, including hydration, food intake, patient health and individual reactions

to ingredients in the drug. This model is applicable in general cases when looking into a whole population, but should not be used when looking at a specific patient case. This is because the factors that vary from person to person will start adding variation to the model. Moving forward, one should use these models as a base to determine how a patient may intake morphine, but this should always be monitored as these models do not apply well to specific cases.

To further our understanding of drug metabolism and absorption, other methods of administration should be modelled. Additionally, these administration methods should be modelled in more detail, taking into consideration more parameters and variables. This will provide us with more information on the effectiveness of a drug, and the factors affecting the absorption and clearance. Furthermore, each drug is metabolized and absorbed differently by the body, and thus detailed research and models should be conducted on each type of drug. With new research and knowledge, drug administration can be streamlined, optimizing drug effectiveness and efficiency (Subramanian, 2023).

Overall, understanding drug metabolism and absorption is crucial for determining the effectiveness of a drug, and is important for the optimization of drug administration (Subramanian, 2023). Additionally, modelling and performing research on drug absorption and clearance is necessary for determining the dosages and the effectiveness of drugs used every day in hospitals and clinics. Models also provide information on how to safely and effectively use a drug, and what factors affect the success of a drug (Subramanian, 2023). From this, we can see that these models are essential for day to day medical practices, and more specifically, these models can help us improve quality of life through advancing the medical tools that we depend on.

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6 Appendix

6.1 R Code

```
# model for 0 <= t <= h morphine given intravenously
h = 5
t_vals <- seq(0, h, by = 0.01)
r = 3.7
c = 1
soln <- (r/c) - ((r/c) * exp(-c*t_vals))

plot(t_vals, soln, type = "l", col = "blue", xlab = "Time in hours",
ylab = "Amount of Drugs in mgs", main = "Intravenous Injection of Morphine in the Body,
r = 3.7mg/hr, c = 1mg/hr")



#model for t > h morphine given intravenously
h = 5
t_vals <- seq(h, 15, by = 0.01)
r = 3.7
c = 1
soln <- (r/c) * (exp(c*h)-1) * exp(-c*t_vals)

plot(t_vals, soln, type = "l", col = "blue", xlab = "Time in hours",
ylab = "Amount of Drugs in mgs", main = "Clearance of Morphine in the Body,
r = 3.7mg/hr, c = 1mg/hr")



# model for 0 <= t <= h morphine given orally as pill
h=5
t_vals <- seq(0, 24, by = 0.01)
c=1
Dmax=10
soln <- (h/(h*c-1))*Dmax*exp(-t_vals/h) + (h/(1-h*c))*Dmax*exp(-t_vals*c)

plot(t_vals, soln, type = "l", col = "blue", xlab = "Time in hours",
ylab = "Amount of Drugs in mgs", main = "Oral Ingestion of Morphine in the Body,
c = 1mg/hr")



#Logistic Drug Clearance with Euler's Method 0<=t<=h
exp_model <- function(pop, c, r, K) {
val <- r - (c*pop*(1-(pop/K)))
return(val)
}
t_vals <- seq(0, 5, by = 0.01)
p_vals <- rep(NA, times = length(t_vals))
```

```
p_vals[1] <- 0

for (n in 2:length(t_vals)) {
h <- t_vals[2] - t_vals[1]
p_vals[n] <- p_vals[n-1] + h*exp_model(pop = p_vals[n-1], c = 1, r = 3.7, K = 10)
}

plot(t_vals, p_vals, type = "l", col = "blue", xlab = "Time in hours",
ylab = "Amount of Drugs in mgs",
main = "Modelling Logistic Drug Clearance in the Body with Euler's Method")



# model for h < t morphine metabolized logistically
exp_model <- function(pop, c,K,r) {
val <- -(c*pop*(1-pop/K))
return(val)
}
t_vals <- seq(0, 7, by = 0.01)
p_vals <- rep(NA, times = length(t_vals))
p_vals[1] <- 8

for (n in 2:length(t_vals)) {
h <- t_vals[2] - t_vals[1]
p_vals[n] <- p_vals[n-1] + h*exp_model(pop = p_vals[n-1], c = 1, K=10,r=2)
}

plot(t_vals, p_vals, type = "l", col = "blue", xlab = "Time (Hours After h)",
ylab = "Amount of Drug in the Body",
main = "Euler's Method for Modeling Logistic Drug Clearance in The Body")
lines(t_vals, p_vals, col = "blue")
```

6.2 Individual Contributions

- Selena Dajani - Written report (Introduction, Discussion: Future Research and Conclusion), research, computational work (solving differential equations, finding equilibrium points), editing
- Nadia Breault - Presentation Slide, R code, research, written report (Analysis of Extension, and Results)
- Noreen Altaf - Computation work (double checking math), Report (introduction, discussion, references), research, video editing and recording
- Jackson Timewell - Coding in R, notes for presentation, research, written report (analysis, discussion, appendix)
- Justin Gebel - LaTeX formatting, written report (base model/assumptions, analysis of base model/extension), computational work (solving differential equations, finding equilibrium points), editing

- Alex McMullen - research, R code, presentation notes, written report (analysis of base model, discussion: summary of results, appendix)