A Mathematical Model for an Intravenous Bolus Injection

University of California, San Diego
BENG 221: Mathematical Methods in Bioengineering

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1. Introduction and background

Intravenous bolus injections are used for administering drugs short term. The patient usually feels the effect of the drug within 1 – 30 minutes of administration.[2] Therefore, bolus injections are often used in the emergency room, as cancer chemotherapy drugs, and as pain relievers such as morphine. Intravenous Bolus injections allow for very precise control of drug dosage. This report is going to focus on IV bolus injections of morphine. Morphine is an opiate drug that is used to relieve sever pain. It is the golden standard in clinical medicine which means not only is it used in high volumes at hospitals it is also used by the FDA as a benchmark point for approving new pain relieving drugs. Morphine acts directly on the central nervous system and therefore an overdose of morphine can be fatal.

When morphine is administered intravenously, there is an extensive first pass metabolism that results in only about 40-50% of the drug reacheing the central nervous system. The other 50-60% is metabolized by the liver through a process called glucuronidation. During this process, about 60% of the metabolized morphine is converted into morphine -3-glucuronide and 6-10% is converted into the morphine-6-glucuronide.[1] The M3G structure cannot undergo μ-opioid receptor binding. The M6G structure can bind to the receptor but is only half as potent as morphine. The μ-opioid receptors, **Figure 1**, are found in the brain and on terminal axons of the spinal cord. When the receptor is activated it is associated with analgesia, sedation, euphoria, physical dependence, and respiratory depression. The half-life of morphine in the body is 120 minutes and the duration and analgesia is typically 3-4 hours.[7] 87% of the morphine is out of the patients system after 72 hours, or 3 days.[7] It is important to note that these numbers are based off of a typical metabolism rate and that they can vary patient to patient. This paper uses these numbers to validate the model developed to represent a morphine injection in the body.

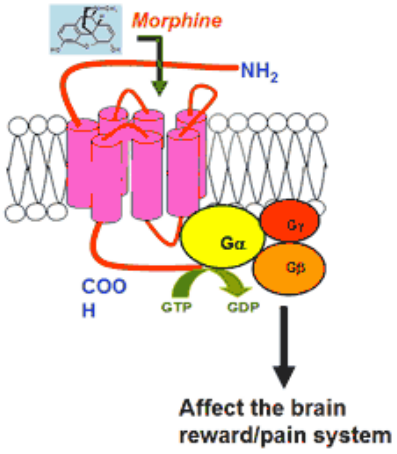

Figure 1 the u-opioid is a trans-membrane receptor that when bound to morphine activated a cascade of events that lead to the promotion of analgesia, sedation, and euphoria

2. Problem Statement

In addition to determining a mathematical model for an IV Bolus Injection, we came up with a sample problem to mimic a real life application. Suppose a post-op patient requires a blood concentration of at least 60ng/mL morphine to feel pain relief. The patient is of average size and the doctor wants to set the IV drip to administer morphine in boluses of 15mg. How often should he inject his patient to keep him pain free?

3. Assumptions

In order to simplify the problem we assumed a two compartment model as shown in Figure 2, which shows the path the drug takes through the body. First into the blood, degrades and is excreted through liver and kidneys. Then, the remainder goes to the tissues where it is further degraded or actually takes effect.

The first compartment mimics the drug in the blood and the second looks at the drug in the central nervous system (CNS). We assumed the bolus is intravenously administered and that the bolus is "well mixed" instantly after being administered. In reality, there is a short time lag from the point the drug is introduced in the body until it is fully mixed in the system. In order to analyze our mathematical model we therefore ignored this time lag by saying that the drug is "well mixed" upon administration.

We also assumed that the compartment volumes and reaction rates are constant and that the flow of morphine travels from the central compartment to the peripheral; there is no diffusion from the peripheral to the central. Our final assumptions were that morphine is degraded constantly in the blood and tissue, all patients have similar reactions to morphine, and there is no renal clearance.

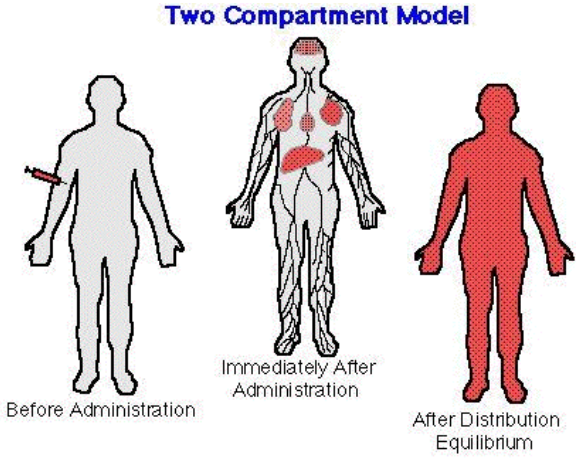

Figure 2: Two Compartment Model

4. Mathematical Analysis

We used Figure 2 to develop the mathematical model shown in Figure 3, where the central compartment represents the blood stream and the peripheral compartment consists of the tissues such as the brain and receptors that the drug binds to.

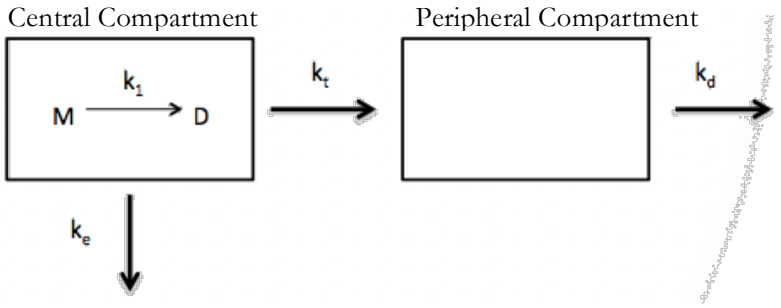

Figure 3: Simplified Representation of Two Compartment Model

The variables are as follows:

- C_1 = Concentration of morphine in central compartment
- C_2 = Concentration of morphine in peripheral compartment
- V_1 = Volume of central compartment
- V_2 = Volume of peripheral compartment
- k_1 = Rate of morphine absorbed in central compartment
- k_t = Rate of drug transferred from central to peripheral compartment
- k_d = Rate of drug degraded in peripheral compartment
- k_e = Clearance rate of drug leaving central compartment

We first need to determine the threshold value for the concentration of the drug in the organs. Using Figure 3, we set up our differential equations **(1)** and **(2)**.

$$\frac{d(C_1V_1)}{dt} = -k_1C_1V_1 - k_tC_1V_1 - k_eC_1V_1 \textbf{ (1)}$$

$$\frac{d(C_2V_2)}{dt} = k_tC_1V_1 - k_dC_2V_2 \textbf{ (2)}$$

Dividing by V_1 and V_2 in **(1)** and **(2)**, respectively, we get:

$$\frac{dC_1}{dt} = -k_1C_1 - k_tC_1 - k_eC_1$$

$$\frac{dC_2}{dt} = k_t\frac{V_1}{V_2}C_1 - k_dC_2$$

We are looking to solve for the usual time, t*, between boluses given the concentration as stated in Section 2.0 so we need **(1)** as a function of time, in order to plug into **(2).**

$$\frac{dC_1}{dt} = -(k_1 + k_t + k_e)C_1$$
$$\frac{dC_1}{C_1} = -(k_1 + k_t + k_e)dt$$

Taking the integral of the above equation we get:
$$lnC_1 = -(k_1 + k_t + k_e)t + K_1$$

Rearranging:
$$C_1 = \exp(K_1)\exp(-(k_1 + k_t + k_e)t)$$
$$C_1 = K_2\exp(-(k_1 + k_t + k_e)t)$$

We now implement our initial conditions:
$At\ t = 0,$
$$C_1 = \frac{\gamma}{V_1}\ where\ \gamma = moles\ of\ drug\ administered\ in\ each\ bolus$$

$$\frac{\gamma}{V_1} = K_2\exp(0)$$
$$K_2 = \frac{\gamma}{V_1}$$
$$C_1 = \frac{\gamma}{V_1}\exp(-(k_1 + k_t + k_e)t)$$ **(3)**

Substitute **(3)** into **(2)**:

$$\frac{dC_2}{dt} = k_t\frac{V_1}{V_2}\frac{\gamma}{V_1}\exp(-(k_1 + k_t + k_e)t) - k_dC_2$$

Bring C_2 terms to the left hand side:
$$\frac{dC_2}{dt} + k_dC_2 = \frac{k_t\gamma}{V_2}\exp(-(k_1 + k_t + k_e)t)$$

Set an integrating factor and solve:
$$IF = \exp\left(\int k_d dt\right) = \exp\left(k_d t\right)$$
$$\frac{d}{dt}(C_2\exp(k_d t)) = \frac{k_t\gamma}{V_2}\exp\big((-k_1 - k_t - k_e + k_d)t\big)$$
$$C_2\exp(k_d t) = \frac{k_t\gamma}{V_2}\int exp\left((-k_1 - k_t - k_e + k_d)t\right)dt + K_3$$

U-Substitution:

$$Let\ u = (-k_1 - k_t - k_e + k_d)t$$

$$\frac{du}{dt} = -k_1 - k_t - k_e + k_d$$

$$C_2 \exp(k_d t) = \frac{k_t \gamma}{V_2} \int \frac{du}{-k_1 - k_t - k_e + k_d} e^u + K_3$$

$$C_2 \exp(k_d t) = \frac{k_t \gamma}{V_2} \frac{1}{(-k_1 - k_t - k_e + k_d)} \exp\big((-k_1 - k_t - k_e + k_d)t\big) + K_3$$

$$C_2 = \frac{k_t \gamma}{V_2} \frac{1}{(-k_1 - k_t - k_e + k_d)} \exp(-(k_1 + k_t + k_e)t) + K_3 \exp(-k_d t)$$

Implement initial conditions for C_2:

$$at\ t = 0, C_2 = 0$$

$$0 = \frac{k_t \gamma}{V_2} \frac{1}{(-k_1 - k_t - k_e + k_d)} + K_3$$

$$K_3 = -\frac{k_t \gamma}{V_2} \frac{1}{(-k_1 - k_t - k_e + k_d)}$$

$$C_2 = \frac{k_t \gamma}{V_2} \frac{1}{(-k_1 - k_t - k_e + k_d)} (\exp(-(k_1 + k_t + k_e)t) - \exp(-k_d t))$$

We then obtain the final solution:

$$C_2{}^* = C_2(t^*) = \frac{k_t \gamma}{V_2} \frac{1}{(-k_1 - k_t - k_e + k_d)} (\exp(-(k_1 + k_t + k_e)t^*) - \exp(-k_d t^*))$$

5. MATLAB Analytical – Clearance Model

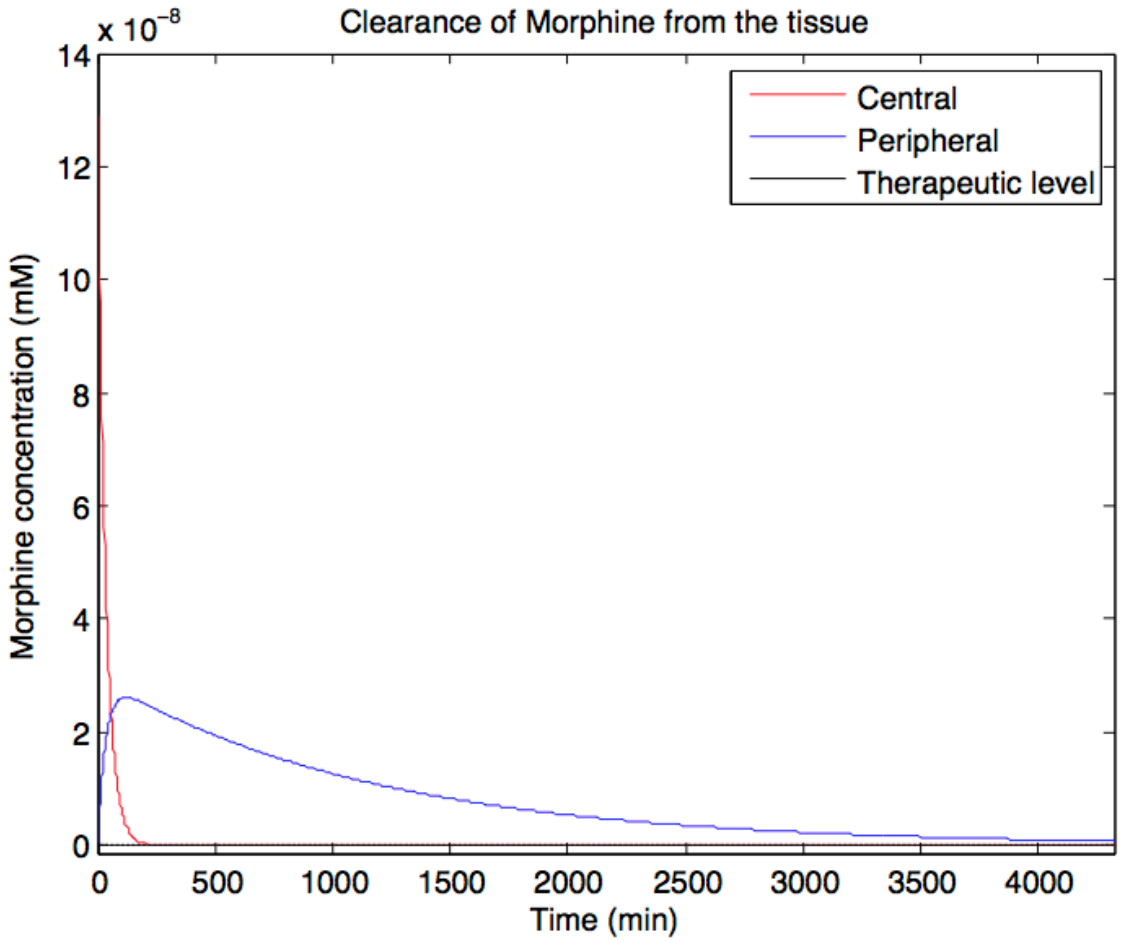

Figure 4

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Figure 4: Analytical plot of morphine clearance from the tissue after an initial IV bolus of 15mg morphine in a two compartment system

6. MATLAB Analytical

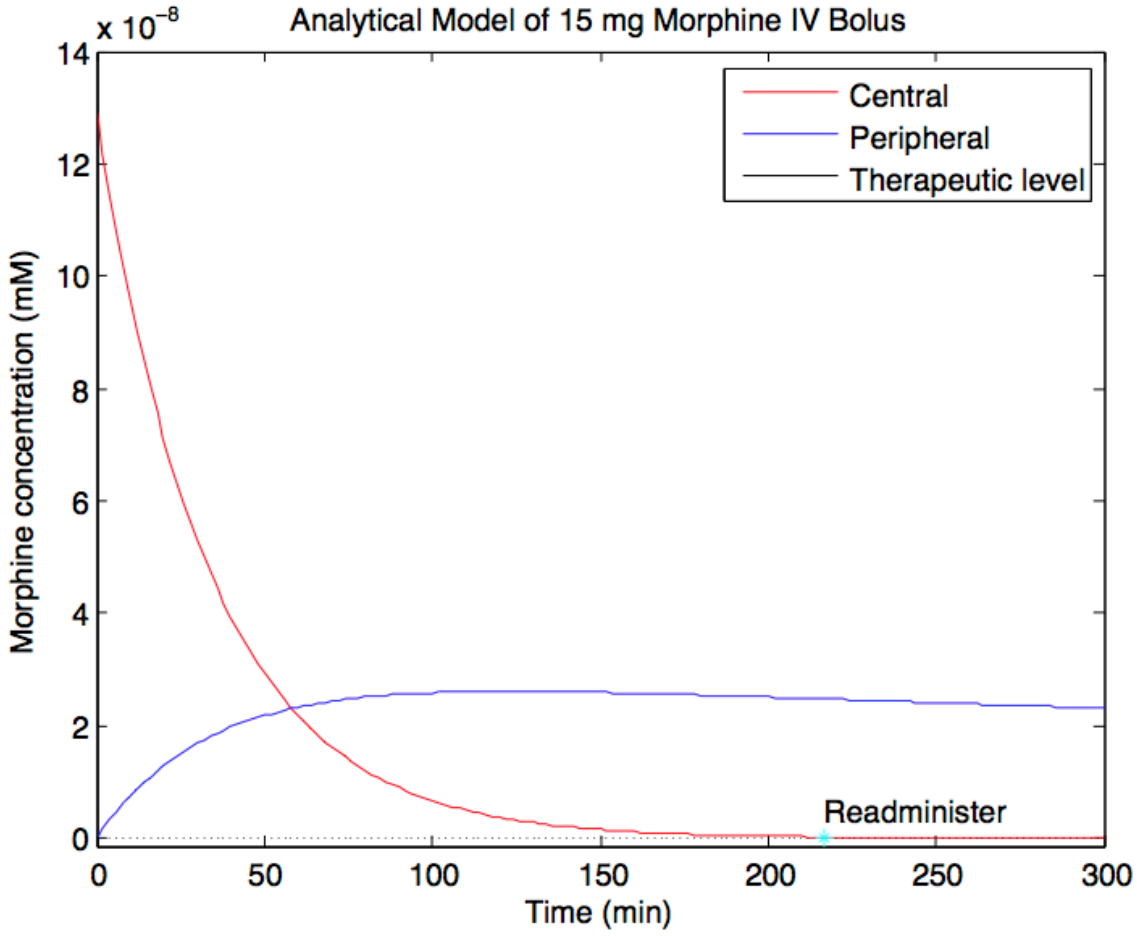

Figure 5 Analytical model of a 15mg morphine IV Bolus injection in a two compartment system

7. MATLAB Numerical

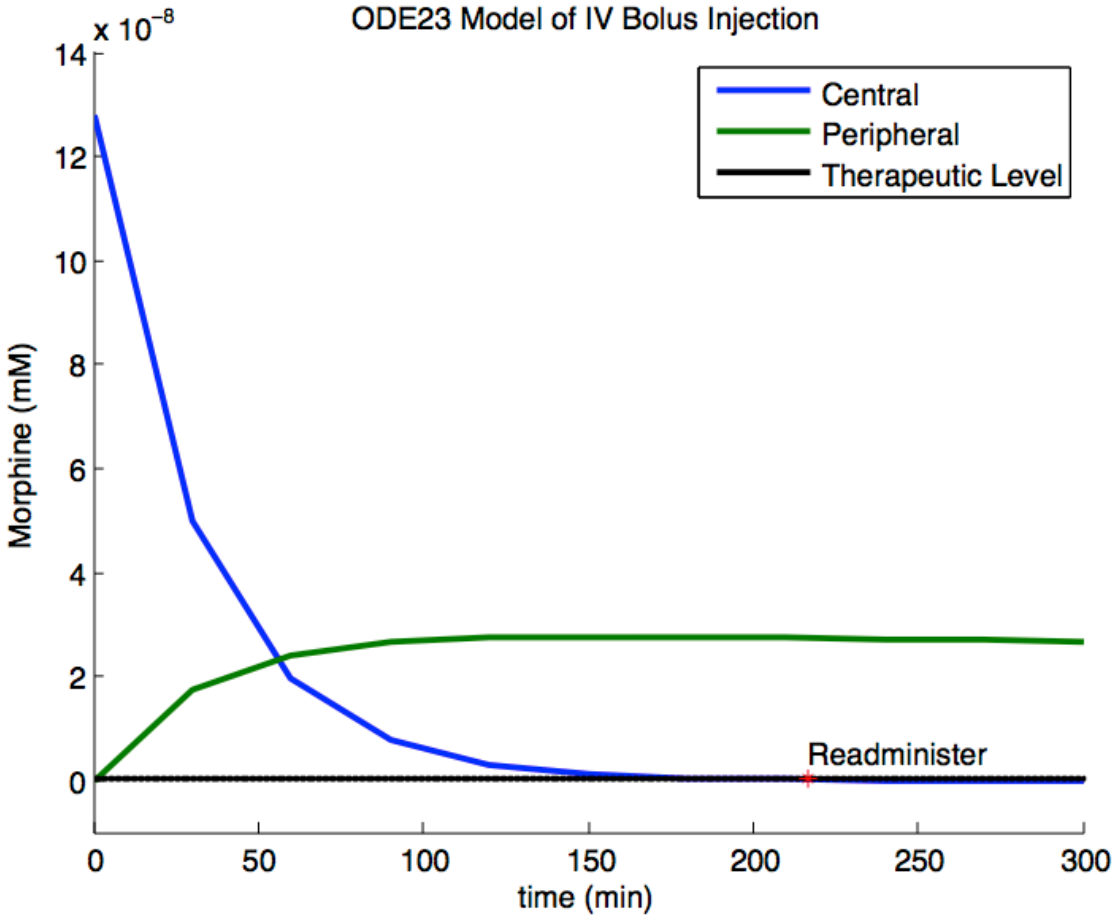

Figure 6 Numerical model of a 15mg morphine IV Bolus injection in a two compartment system

8. Discussion

We modeled the pathway of a morphine IV Bolus injection through the body using a two compartment system. In Figure 4 we modeled the time for the morphine to completely leave the body. Clinically this time is around 72 hours depending on the size and metabolism of the patient. Our model shows that for an average patient the morphine transfers from the blood (central compartment) to the tissues (peripheral compartment) rapidly whereas the clearance of the morphine from the tissues takes 4330 minutes, or 3 days. This shows that our assumption of a constant decay of morphine in the body as an average of its actual decay due to its 120min half life does not create discrepancies in our model.

In Figures 5 and 6 we have modeled the pathway of a morphine IV Bolus injection and determined the longest possible period between boluses to keep the patient pain free. Clinically a blood concentration of 60ng/mL has been determined as the Therapeutic Threshold: the minimum amount of morphine in the body for the patient to feel pain relief. Using our two compartment model at what time this threshold value would be reached using the analytical solution and an ode23 solution. Both solutions agree that the time at which the patient reaches the Therapeutic Threshold after a 15mg morphine IV bolus injection is 220minutes, or 3.7 hours. Clinically the period between boluses is between 3-4hours depending on the size and metabolism of the patient, and our predicted value falls within this range.

9. Conclusions & Future Work

Though the two compartment system we have used to model the pathway of morphine through the body greatly simplifies the actual system, it is still accurate enough to be of use when determining the period between boluses for different sized patients. If a more accurate model were needed a three compartment system including the morphine in the liver or nonlinear rate constants would have to be used. This model could also be used to model the effects of Naloxone, a drug that reverses the effects of morphine if the patient has overdosed. As IV boluses are used for more immediate relief, this model could be used to quickly approximate how often the patient will need morphine by altering the mass of the patient.

References

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10. Appendices: A - MATLAB Code

Appendix A.1: Clearance Model

```
%MATLAB Model Of Morphine IV Bolus Injection: Clearance Model

                                        %Define constants
mg_bolus = 15;                          %mg morphine in the bolus
V_bolus = 10;                           %mL volume of bolus
mw_morphine = 285.34;                   %mg/mmol molecular weight of morphine
mmol_bolus = mg_bolus / mw_morphine; %mmol morphine in the bolus injection
C_bolus = mmol_bolus / V_bolus;      %mmol/mL concentration of bolus
injection
kg_patient = 68;                        % weight of avg patient in kg
V_per_kg = 6000;                        %mL/kg mL compartment per kg person
%kg/mL conversion of kg per compartment liters
V_1 = V_per_kg*kg_patient;              %mL Central compartment volume
V_2 = V_per_kg*kg_patient;              %mL Peripheral compartment volume
C1i = mmol_bolus / V_1;                 %M Concentration of morphine in
peripheral at t=0
C3i = (10/mw_morphine)/V_1;
C5i = (5/mw_morphine)/V_1;
C_therapeutic = 6E-8/mw_morphine;   %M Therapeutic concentrations of morphine
C_toxic = 16E-3/mw_morphine;            %M 16E-3mg/mL is toxic in the blood
renal_clearance = 2;                    %mL/kg/min clearance from central
compartment
to_peripheral = 40;                     %mL/kg/min morphine from central to
peripheral



k1 = 1E-6 * mw_morphine;                 %mmol/min degradation rate of morphine
in the central compartment
kd = 3E-6 * mw_morphine;                 %mmol/min degradation rate in the
peripheral compartment
kt = to_peripheral/V_per_kg;       %1/min rate constant from central to
peripheral
ke = kg_patient*renal_clearance/V_per_kg;     %1/min rate constant from
central out of body

%System of Differential Equations
    %dC2/dt = kt*C1*V1/V2 - kd*C2
    %dC1/dt = -(ke + kt + k1) C1
    %Initial Conditions C1(t=0) = mmol_bolus / V1 ; C2(0)=0;

%Assumptions
    %1. Bolus is intravenously administered
    %2. Body is a two compartment model
    %3. Bolus is "well-mixed" instantly after being administered
    %4. Compartment volumes are constant
    %5. Reaction Rates are constant
    %6. No morphine diffuses from the peripheral to the central compartment
    %7. Morphine is degraded constantly in the blood and the tissue
    %8. All patients have similar reactions to morphine
    %9. No renal clearance

%Analytical Solution
```

```
t_end = 72*60;
t = 0:2:t_end; %mins

%Initial Bolus of 15mg
C1 = C1i * exp(-(k1+kt+ke)*t); %morphine concentration in central compartment
with respect to time
C2 = (kt*mmol_bolus/V_2)*(exp(-(k1+kt+ke)*t) - exp(-kd*t))/(-k1-kt-ke+kd);
t_therapeutic = 217;

%plot(t,C1, 'r',t,C2,'b',t,C_therapeutic,'k')
plot(t,C1,'r',t,C2,'b')
hold on
%yi = interp1(t,C1,t_therapeutic);
%plot(t_therapeutic, yi,'c*');
%xlabel('time (min)');
%ylim( [-1E-8)
ylabel('Morphine concentration (mM)')
title('Clearance of Morphine from the tissue')
legend( 'Central','Peripheral','Therapeutic level')
%text(t_therapeutic,yi+.5E-8,'Readminister')
hold off
```

Appendix A.2: Analytical Code

```
%MATLAB Model Of Morphine IV Bolus Injection: Analytical

                                    %Define constants
mg_bolus = 15;                      %mg morphine in the bolus
V_bolus = 10;                       %mL volume of bolus
mw_morphine = 285.34;               %mg/mmol molecular weight of morphine
mmol_bolus = mg_bolus / mw_morphine; %mmol morphine in the bolus injection
C_bolus = mmol_bolus / V_bolus;     %mmol/mL concentration of bolus
injection
kg_patient = 68;                    % weight of avg patient in kg
V_per_kg = 6000;                    %mL/kg mL compartment per kg person
%kg/mL conversion of kg per compartment liters
V_1 = V_per_kg*kg_patient;          %mL Central compartment volume
V_2 = V_per_kg*kg_patient;          %mL Peripheral compartment volume
C1i = mmol_bolus / V_1;             %M Concentration of morphine in
peripheral at t=0
C3i = (10/mw_morphine)/V_1;
C5i = (5/mw_morphine)/V_1;
C_therapeutic = 6E-8/mw_morphine;   %M Therapeutic concentrations of morphine
C_toxic = 16E-3/mw_morphine;        %M 16E-3mg/mL is toxic in the blood
renal_clearance = 2;                %mL/kg/min clearance from central
compartment
to_peripheral = 40;                 %mL/kg/min morphine from central to
peripheral



k1 = 1E-6 * mw_morphine;             %mmol/min degradation rate of morphine
in the central compartment
kd = 3E-6 * mw_morphine;             %mmol/min degradation rate in the
peripheral compartment
kt = to_peripheral/V_per_kg;       %1/min rate constant from central to
peripheral
ke = kg_patient*renal_clearance/V_per_kg;     %1/min rate constant from
central out of body

%System of Differential Equations
    %dC2/dt = kt*C1*V1/V2 - kd*C2
    %dC1/dt = -(ke + kt + k1) C1
    %Initial Conditions C1(t=0) = mmol_bolus / V1 ; C2(0)=0;

%Assumptions
    %1. Bolus is intravenously administered
    %2. Body is a two compartment model
    %3. Bolus is "well-mixed" instantly after being administered
    %4. Compartment volumes are constant
    %5. Reaction Rates are constant
    %6. No morphine diffuses from the peripheral to the central compartment
    %7. Morphine is degraded constantly in the blood and the tissue
    %8. All patients have similar reactions to morphine
    %9. No renal clearance...for now

%Analytical Solution (without ke)
```

```
t_end = 5*60;
t = 0:2:t_end; %mins

%Initial Bolus of 15mg
C1 = C1i * exp(-(k1+kt+ke)*t); %morphine concentration in central compartment
with respect to time
C2 = (kt*mmol_bolus/V_2)*(exp(-(k1+kt+ke)*t) - exp(-kd*t))/(-k1-kt-ke+kd);
t_therapeutic = 217;

%plot(t,C1, 'r',t,C2,'b',t,C_therapeutic,'k')
plot(t,C1,'r',t,C2,'b',t,C_therapeutic,'k')
hold on
yi = interp1(t,C1,t_therapeutic);
plot(t_therapeutic, yi,'c*');
%xlabel('time (min)');
%ylim( [-1E-8)
ylabel('Morphine concentration (mM)')
xlabel('Time (min)')
ylim([-.14E-8 1.4E-7])
title('Clearance of Morphine from the tissue')
legend( 'Central','Peripheral','Therapeutic level')
text(t_therapeutic,yi+.5E-8,'Readminister')
hold off
```

Appendix A.3: Numerical Code

```
%MATLAB Model Of Morphine IV Bolus Injection: Numerical


t_start = 0;
t_end = 300;

Initials = [1.28E-7;0]
[t,Q] = ode23(@fun1, [t_start; t_end], Initials);
C_therapeutic = 2.1E-10;
hold on
plot(t,Q,'LineWidth',2)
t=0:1:t_end;
plot(t,C_therapeutic,'k','LineWidth',2)
plot(217,C_therapeutic,'r*')
xlabel('time (min)')
ylabel('Morphine (mM)')
ylim( [-1E-8, 1.4E-7])
title('ODE23 Model of IV Bolus Injection')
legend('Central','Peripheral', 'Therapeutic Level')
text(217, C_therapeutic + 0.5E-8, 'Readminister')
```