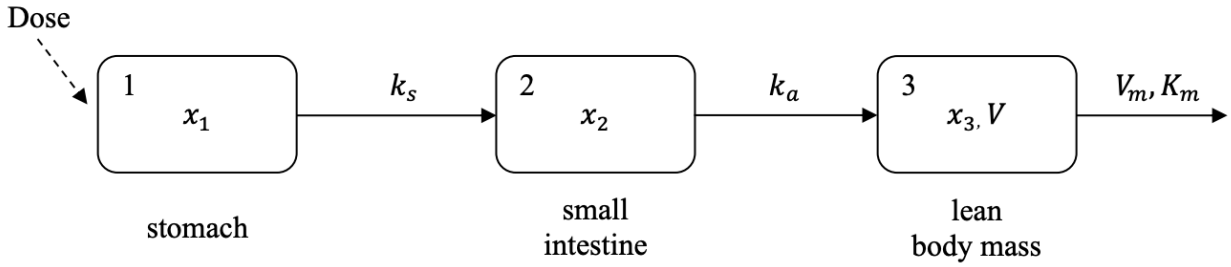
Kevin Shu
Homework 4 Report Summary
BME210, Prof. Kay

Section 1: Compartment Model Simulation Alcohol Pharmacokinetics

Part 1: Report Summary

The science of pharmacokinetics is vital to drug development and the tracking of material through the active sites in the body. To understand how drugs and other substances travel through the body and are absorbed, a number of mathematical models and calculations are used to gain a better understanding of where exactly substances are absorbed and at what rate they are absorbed. In order to track substance absorption within different areas of the body, compartment models and first order equations are used to model the way chemical substances travel throughout the body in an effort to see how much substance accumulates where in the body.

In this part of the report, the absorption of alcohol in the lean body mass will be calculated through a compartment model. The model being used is shown below:



From this compartment model, three first order differential equations can be derived. The movement of contents from the stomach and small intestine can be accurately modeled through first order differential equations where the rate of emptying is proportional to the compartments' contents. However, alcohol metabolism cannot be modeled using a first order equation. Instead, the process is saturable and will be modeled using Michaelis-Menten kinetics. The equation uses Vm, which is the maximum rate of change the compartment achieves while Km is the Michaelis constant. All rate constant (k) values will be in units of per hour while all masses and volumes will be in grams and liters respectively. The three differential equations using these assumptions are listed below where D is the initial alcohol dose in the stomach:

$$\frac{dx_1}{dt} = -k_s x_1, \qquad x_1(0) = D \text{ (dose)}$$

$$\frac{dx_2}{dt} = k_s x_1 - k_a x_2, \qquad x_2(0) = 0$$

$$\frac{dx_3}{dt} = k_a x_2 - \frac{V_m x_3}{K_m + x_3}, \qquad x_3(0) = 0$$

After the implementation of said differential equations, the solved differential equation of blood alcohol content showed that women metabolize alcohol slower than men while the stomach alcohol content was identical. It was also found that as alcohol content decreased, the BAC increased in both men as the alcohol was being moved into the lean body mass. It was also found that when the dosage was increased by a factor of two, the time above 0.08% BAC increased by a factor of larger than two consistently in all four scenarios.

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Section 2: The Program

```
clear; clc; close all;

%define male and female constants
maleV = 13; %L
femaleV = 10; %L
k =[10 11000]; %h^-1 male and female are the same
maleVm = 45; %g/h
femaleVm = 40; %g/h
Km = 50; %g male and female are the same

%initial values
dose1 = 14;
dose2 = 28;
alc01 = [dose1 0 0];
alc02 = [dose2 0 0];
tspan = 0:0.001:8;

%options for ode45
tolerance = 1e-5;
options = odeset('RelTol', tolerance, 'AbsTol', tolerance);

%male 14 g dose
[tm14, maleAlc14] = ode45(@AlcoholPK, tspan, alc01, options, k, maleVm, Km);

%female 14 g dose
[tf14, femaleAlc14] = ode45(@AlcoholPK, tspan, alc01, options, k, femaleVm, Km);

%male 28 g dose
[tm28, maleAlc28] = ode45(@AlcoholPK, tspan, alc02, options, k, maleVm, Km);

%female 28 g dose
[tf28, femaleAlc28] = ode45(@AlcoholPK, tspan, alc02, options, k, femaleVm, Km);

figure (1);
subplot(2,1,1);
hold on;
plot(tm14, maleAlc14(:,1), '--g');
plot(tf14, femaleAlc14(:,1), ':r');
plot(tm28, maleAlc28(:,1), '--b');
plot(tf28, femaleAlc28(:,1), ':k');
title('Alcohol Content in Stomach (g) vs. time (h)');
xlabel('time (h)');
```

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```
ylabel('Alcohol Content in Stomach (g)');
legend('Male 14 g Dose', 'Female 14 g Dose', 'Male 28 g Dose', 'Female 28 g Dose');
subplot(2,1,2);
hold on;
plot(tm14, maleAlc14(:,3)/(10*maleV), '--g');
plot(tf14, femaleAlc14(:,3)/(10*femaleV), ':r');
plot(tm28, maleAlc28(:,3)/(10*maleV), '--b');
plot(tf28, femaleAlc28(:,3)/(10*femaleV), ':k');
title('BAC (%) vs. time (h)');
xlabel('time (h)');
ylabel('BAC (%)');
legend('Male 14 g Dose', 'Female 14 g Dose', 'Male 28 g Dose', 'Female 28 g Dose');

figure (2);
hold on;
plot(tm14, maleAlc14(:,3)/(10*maleV), '--g');
plot(tf14, femaleAlc14(:,3)/(10*femaleV), ':r');
plot(tm28, maleAlc28(:,3)/(10*maleV), '--b');
plot(tf28, femaleAlc28(:,3)/(10*femaleV), ':k');
yline(0.08, 'm');
title('BAC (%) vs. time (h)');
xlabel('time (h)');
ylabel('BAC (%)');
legend('Male 28 g Dose', 'Female 28 g Dose', 'Male 14 g Dose', 'Female 14 g Dose', '0.08 BAC');

function dxdt = AlcoholPK(t, alc, k, Vm, Km)
   %k is rate constants for stomach (1) and intestine (2)
   %Vm is maximum volume rate
   %Km is Michaelis Constant
   dxdt = [-k(1)*alc(1);
      k(1)*alc(1) - k(2)*alc(2);
      k(2)*alc(2) - Vm*alc(3)/(Km+alc(3))];
end
```

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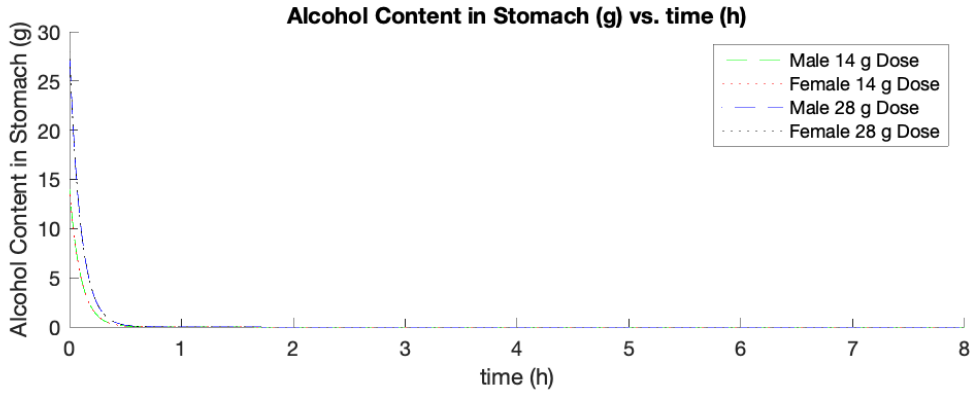

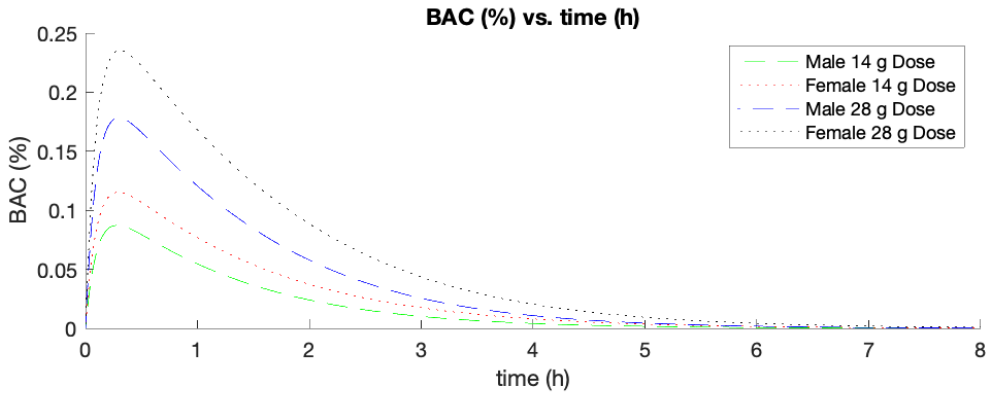

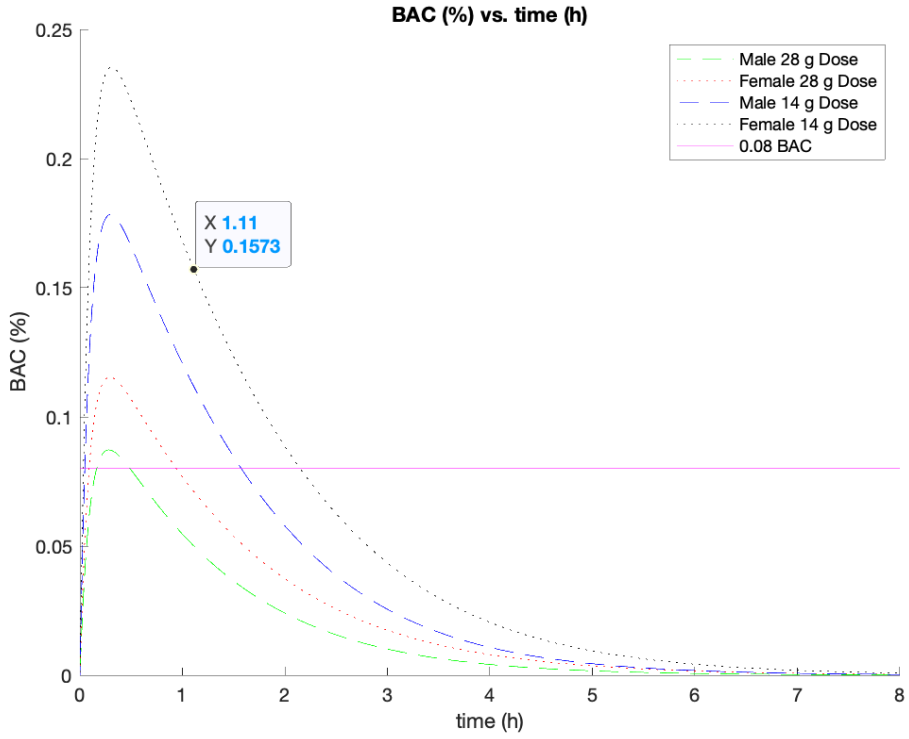

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For both male and female, the time it took for the alcohol to reduce to 3 grams in the stomach was around 0.2 hours. Both male and female times were identical since they both relied on a differential equation that didn't rely on variables that were different between men and women. The differential equation is merely a rate constant multiplied by the alcohol content of the stomach. The rate constant of outflow of the stomach was identical, so the solved differential equation between the two should be identical as well. As the stomach empties, the alcohol gradually moves to the lean body mass, thus increasing the BAC. When the alcohol content of the stomach's rate of decrease is at its largest, the BAC has its largest increase.

The time-above-limit for a male with the 28 gram dose was around 1.5 hours. The time-above-limit for a male with the 14 gram dose was only around 0.5 hours. Therefore, the time-above-limit increases by a factor of around 3. A female with a 28 gram dose took around 2 hours and with the 14 g dose took around 0.9 hours, making the ratio 2.2. Both ratios are greater than 2 because the differential equations are not linear, but create exponential relationships so there shouldn't be a directly proportional relationship between dosage and metabolic time.

Section 2: Compartment Model Estimation

Part 1: Report Summary

Rate constants are integral information needed in order to model pharmacokinetics of drugs. One way that rate constants can be accurately estimated is through least squares estimation. This is done by comparing patient data with the theoretical exponential model. The exponential equation is shown below where D is the dose in milligrams, V is the volume in liters, and K is the rate constant in hr^{-1}:

$$c(t) = \frac{D}{V} e^{-Kt}$$

To estimate the rate constant as accurately as possible, the goal is to minimize the sum of the square differences between the experimental and theoretical data points. When the sum of the squared differences is as close to zero as possible, K has been accurately estimated. The objective function of the least squares model is described below where z(t) represents the experimental measurements at specific times:

$$O(K, V) = \sum_{j=1}^{m} (z(t_j) - \frac{D}{V} e^{-Kt})^2$$

To find the least squares estimation, both Newton's Method and the Nelder-Mead simplex method will be used. The MATLAB function fminsearch() implements the Nelder-Mead simplex method, so that portion of the report will rely on the aforementioned function.

The report finds that the least squares estimate of both the rate constant and the volume creates a much more accurate model that fits the observed data more tightly. This is because fixing the volume creates a fixed y-intercept so that a number of points, especially in the Smoker 2 graph, lie too far above the differential equation. So, when both volume and rate constant are estimated using least squares, the model equation is far more accurate.

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Part 2: Least Squares Estimate of K Using Newton's Method

```
clear; close all; clc;

patients = importdata('Student24.txt');

%defining constants and variables
V = 25; %liters
D = 10; %milligrams
t = [1 3 5 14 18 24]; %time points
nonsmoker1 = patients(1,:); %nonsmoker1
nonsmoker2 = patients(2,:);
smoker1 = patients(3,:);
smoker2 = patients(4,:);

max = 400;
nonsmoke1 = zeros(1,max);
nonsmoke2 = zeros(1,max);
smoke1 = zeros(1,max);
smoke2 = zeros(1,max);

% initial k = ln2/t1/2
nonsmoke1(1) = log(2)/14;
nonsmoke2(1) = log(2)/14;
smoke1(1) = log(2)/18;
smoke2(1) = log(2)/18;

%using the Newton's formula to find the values
i = 2;
while (abs(Fun1(nonsmoker1, t, nonsmoke1(i), D, V))>0.01) && i<max
   nonsmoke1(i) = nonsmoke1(i-1) - Fun1(nonsmoker1, t, nonsmoke1(i-1), D, V)/Fun2(nonsmoker1, t,
nonsmoke1(i-1), D, V);
   if (abs(nonsmoke1(i) - nonsmoke1(i-1)) <0.001)
      nonsmoke1K = nonsmoke1(i);
      break;
   end
   nonsmoke1K = nonsmoke1(i);
   i = i+1;
end



i = 2;
while (abs(Fun1(nonsmoker2, t, nonsmoke2(i), D, V))>0.01) && i<max
```

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```
   nonsmoke2(i) = nonsmoke2(i-1) - Fun1(nonsmoker2, t, nonsmoke2(i-1), D, V)/Fun2(nonsmoker2, t,
nonsmoke2(i-1), D, V);
   if (abs(nonsmoke2(i) - nonsmoke2(i-1)) <0.001)
      nonsmoke2K = nonsmoke2(i);
      break;
   end
   nonsmoke2K = nonsmoke2(i);
   i = i+1;
end

i = 2;
while (abs(Fun1(smoker1, t, smoke1(i), D, V)) >0.01) && i<max
   smoke1(i) = smoke1(i-1) - Fun1(smoker1, t, smoke1(i-1), D, V)/Fun2(smoker1, t, smoke1(i-1), D, V);
   if (abs(smoke1(i) - smoke1(i-1)) <0.001)
      smoke1K = smoke1(i);
      break;
   end
   smoke1K = smoke1(i);
   i = i+1;
end

i = 2;
while (abs(Fun1(smoker2, t, nonsmoke2(i), D, V))>0.01)  && i<max
   smoke2(i) = smoke2(i-1) - Fun1(smoker2, t, smoke2(i-1), D, V)/Fun2(smoker2, t, smoke2(i-1), D, V);
   if (abs(smoke2(i) - smoke2(i-1)) <0.001)
      smoke2K = smoke2(i);
      break;
   end
   smoke2K = smoke2(i);
   i = i+1;
end

%inputting k into our differential equation
tRange = 0:0.01:24;
smoker1est = D/V*exp(-smoke1K*tRange);
smoker2est = D/V*exp(-smoke2K*tRange);
nonsmoker1est = D/V*exp(-nonsmoke1K*tRange);
nonsmoker2est = D/V*exp(-nonsmoke2K*tRange);

%plotting
figure (1)
subplot(2,2,1);
title('Smoker 1');
```

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```
hold on;
ylim([0 0.8]);
xlabel('time (hrs)');
ylabel('plasma concentration (mg/L)');
scatter(t, smoker1, 'x');
plot(tRange, smoker1est);
legend('Observations', sprintf('Newton: %g', smoke1K));

subplot(2,2,2);
title('Smoker 2');
hold on;
ylim([0 0.8]);
xlabel('time (hrs)');
ylabel('plasma concentration (mg/L)');
scatter(t, smoker2, 'x');
plot(tRange, smoker2est);
legend('Observations', sprintf('Newton: %g', smoke2K));

subplot(2,2,3);
title('Nonsmoker 1');
hold on;
ylim([0 0.8]);
xlabel('time (hrs)');
ylabel('plasma concentration (mg/L)');
scatter(t, nonsmoker1, 'x');
plot(tRange, nonsmoker1est);
legend('Observations', sprintf('Newton: %g', nonsmoke1K));

subplot(2,2,4);
title('Nonsmoker 2');
hold on;
ylim([0 0.8]);
xlabel('time (hrs)');
ylabel('plasma concentration (mg/L)');
scatter(t, nonsmoker2, 'x');
plot(tRange, nonsmoker2est);
legend('Observations', sprintf('Newton: %g', nonsmoke2K));

function fofK = Fun1(z, t, K, D, V)
   %this is the f(K)

   pt1 = z.*t.*exp(-K.*t);
   pt2 = (D/V)*t.*exp(-2*K.*t);
```

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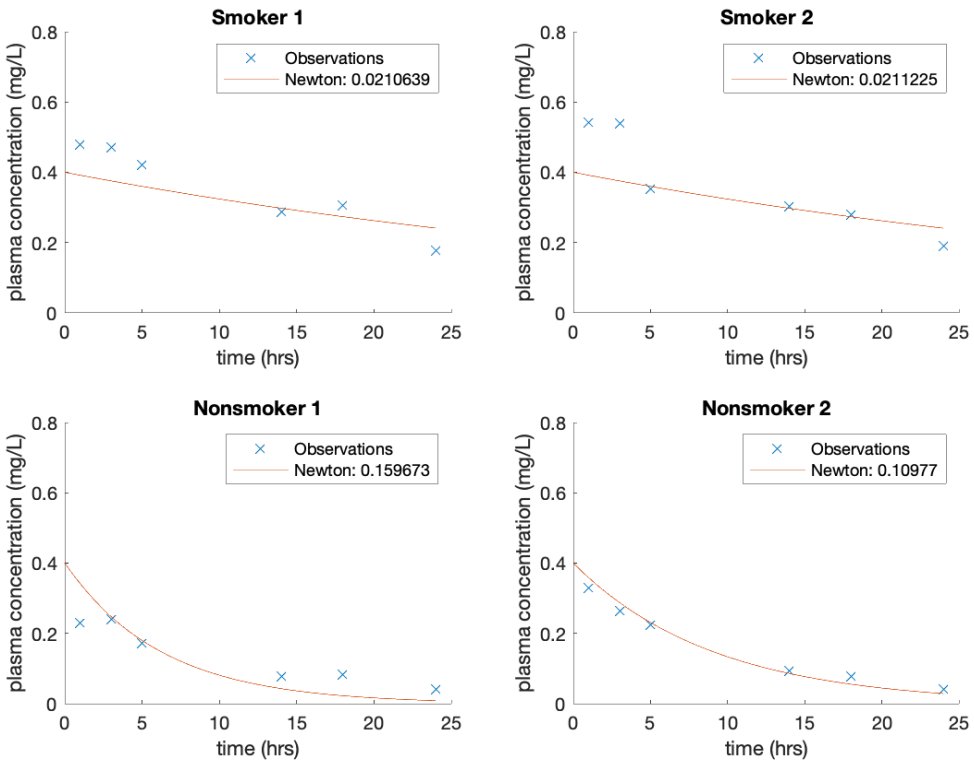
```
    fofK = sum(pt1) - sum(pt2);
end

function fprimeofK = Fun2(z, t, K, D, V)
    %this is f'(K)
    pt1 = -z.*t.^2.*exp(-K.*t);
    pt2 = 2*D/V*t.^2.*exp(-2*K.*t);

    fprimeofK = sum(pt1) + sum(pt2);
end
```



Part 3: Least Squares Estimate of K and V for Each Subject

```
clc; clear; close all;

patients = importdata('Student24.txt');

%defining constants and variables
t = [1 3 5 14 18 24]; %time points
nonsmoker1 = patients(1,:); %nonsmoker1
nonsmoker2 = patients(2,:);
smoker1 = patients(3,:);
smoker2 = patients(4,:);
```

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```
V = 25; %liters
D = 10; %milligrams

%initial guesses of K
nonsmoke1 = log(2)/14;
nonsmoke2 = log(2)/14;
smoke1 = log(2)/18;
smoke2 = log(2)/18;

%initial values K and V
alpha1 = [nonsmoke1 V];
alpha2 = [nonsmoke2 V];
alpha3 = [smoke1 V];
alpha4 = [smoke2 V];

options = optimset();

[a1, hval1] = fminsearch(@Fun3, alpha1,options, nonsmoker1, t, D); %nonsmoker1
[a2, hval2] = fminsearch(@Fun3, alpha2,options, nonsmoker2, t, D); %nonsmoker2
[a3, hval3] = fminsearch(@Fun3, alpha3,options, smoker1, t, D); %smoker1
[a4, hval4] = fminsearch(@Fun3, alpha4,options, smoker2, t, D); %smoker2

%inputting k into our differential equation
tRange = 0:0.01:24;
smoker1est = D/a3(2)*exp(-a3(1)*tRange);
smoker2est = D/a4(2)*exp(-a4(1)*tRange);
nonsmoker1est = D/a1(2)*exp(-a1(1)*tRange);
nonsmoker2est = D/a2(2)*exp(-a2(1)*tRange);

%plotting
figure (1)
subplot(2,2,1);
title('Smoker 1');
hold on;
ylim([0 0.8]);
xlabel('time (hrs)');
ylabel('plasma concentration (mg/L)');
scatter(t, smoker1, 'x');
plot(tRange, smoker1est);
legend('Observations', strcat('K: ', num2str(a3(1)), ' V: ', num2str(a3(2))));

subplot(2,2,2);
```

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```
title('Smoker 2');
hold on;
ylim([0 0.8]);
xlabel('time (hrs)');
ylabel('plasma concentration (mg/L)');
scatter(t, smoker2, 'x');
plot(tRange, smoker2est);
legend('Observations', strcat('K: ', num2str(a4(1)), ' V: ', num2str(a4(2))));

subplot(2,2,3);
title('Nonsmoker 1');
hold on;
ylim([0 0.8]);
xlabel('time (hrs)');
ylabel('plasma concentration (mg/L)');
scatter(t, nonsmoker1, 'x');
plot(tRange, nonsmoker1est);
legend('Observations', strcat('K: ', num2str(a1(1)), ' V: ', num2str(a1(2))));

subplot(2,2,4);
title('Nonsmoker 2');
hold on;
ylim([0 0.8]);
xlabel('time (hrs)');
ylabel('plasma concentration (mg/L)');
scatter(t, nonsmoker2, 'x');
plot(tRange, nonsmoker2est);
legend('Observations', strcat('K: ', num2str(a2(1)), ' V: ', num2str(a2(2))));

function fofK = Fun3(alpha, z, t, D)
   %this is the f(K)
   fofK = sum((z - (D/alpha(2))*exp(-alpha(1)*t)).^2);
end
```

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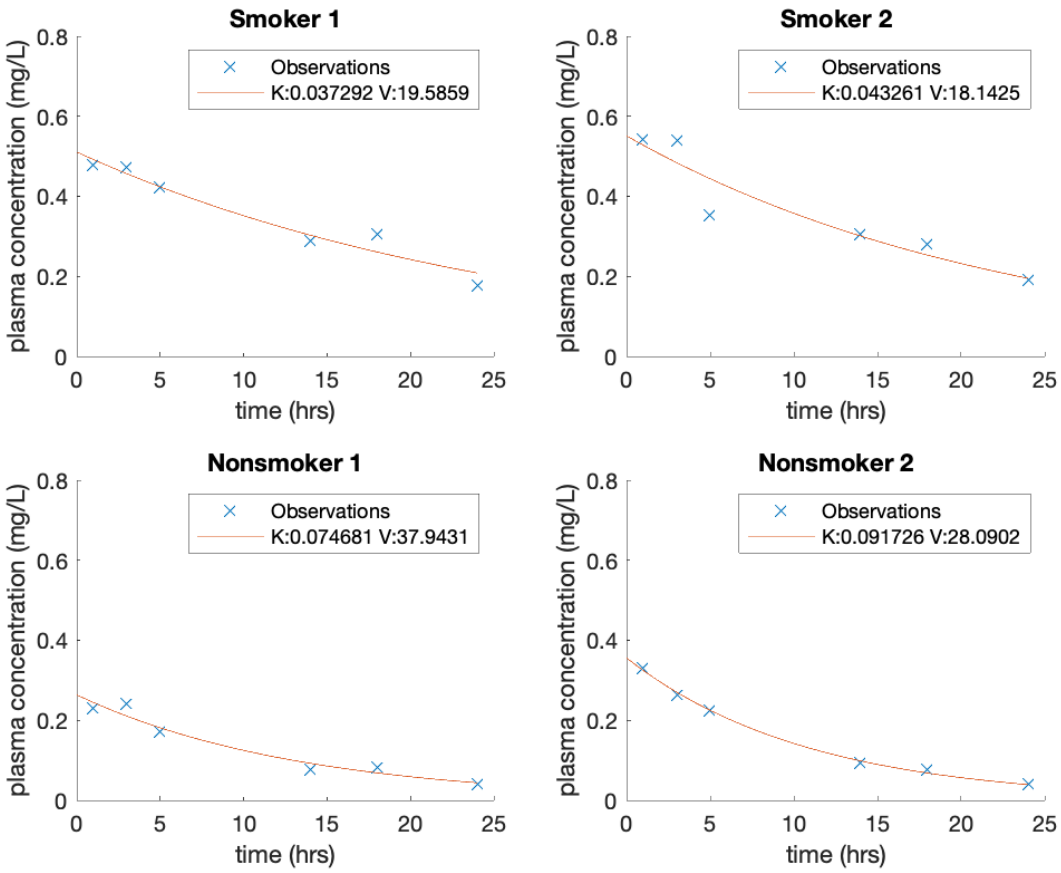

Section 4: Comparison of K Estimates

The least squares estimate of both the rate constant and the volume constant is a much better fit to the observed points. In the Newton's Method estimations, since the volume was fixed at 25 liters, the y-intercept of the graph was also fixed. This means that if the original concentrations aren't close to the y-intercept a number of the observed points will not fit the curve well. The rate constant does not change the volume, so when the volume was also estimated, it was only natural for the curve to fit the observed values better than when it was not.