Physiological Models and Computations

Exercises

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0. Introduction to MATLAB and SIMULINK

Solve the following exercises using MATLAB. These exercises are inspired by or fully extracted from *EDA017: Föreläsningsanteckningar, OCTAVE/MATLAB* by Christian Söderberg.

0.1

a. Plot $y(x) = e^{-x/2}\cos(2\pi x)$ when $-6 \le x \le 3$. Give your plot a title as well as labels on the axes.

b. Modify your code such that you only show values $-4.5 \le x \le -1$ and $-10 \le y \le 10$.

c. Integrate the function for $-4.5 \le x \le -1$.

d. Find the solution to $f(x) = 0$ when $f(x) = x^3 + 2x - 1$. Comment on the answer.

0.2 Write a function which for every matrix A gives you the sum of the diagonal elements of that matrix.

0.3 Solve the differential equation

$$\begin{aligned} \ddot{y} + 7\dot{y} - 3y &= 0 \\ y(0) &= 0 \\ \dot{y}(0) &= 1 \end{aligned}$$

in the interval $0 \le t \le 5$ by using a solver of your choice.

0.4 Try to fit a first order polynomial $ax + b$ to the following measurements

x	y
1	3.9286
2	5.4059
3	6.0771
4	7.7145

Solve the following exercises using SIMULINK in MATLAB. These exercises are taken from *Exercises in MATLAB/Simulink, Signals and Systems* by Thomas Munther.

0.5 Investigate the bacterial growth in a jam pot. Assume that the number of born bacteria is increasing proportional to the existing number of bacteria x and the number dying is proportional to the existing number in square. This gives the following differential equation

$$\frac{dx}{dt} = bx - px^2$$

where $b = 1$ [1/hour] is the birth rate constant and $p = 0.5$ [1/(bacteria·hour)] is the death rate constant. Assume $x(0) = 100$ [bacteria]. Use SIMULINK to show how the solution to the differential equation looks like.

0.6 Some physiological systems are better described in discrete time which gives rise to difference equations. Show the behavior of y in the two following difference equations

a.

$$y_t = -0.5 \cdot y_{t-1} + x_t$$

b.

$$y_t = 0.5 \cdot y_{t-1} + x_t$$

where x is the input signal to the system, in shape of a step starting in $t = 0$ with amplitude 1 and $y_{-1} = 1$. y_t is the value of y in time step t.

1. Biochemical Reactions

1.1 Use the law of mass balance to derive the differential equations govering the production of X and Y:

a.

$$X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Y$$

b.

$$X + X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Y$$

1.2 Simulate and plot the concentrations for the substrate S, enzyme E, substrate-enzyme complex C and the end product P for the basic enzymatic reaction

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} P + E$$

using the following set of parameters; $k_1 = 0.1$, $k_{-1} = 0.01$ and $k_2 = 0.02$, and with the following initial conditions $[S]_0 = 0.15$ [mmol/l], $[E]_0 = 0.01$ [mmol/l], $[C]_0 = 0$ [mmol/l] and $[P]_0 = 0$ [mmol/l]. What happens if the initial concentration of the enzyme is doubled? What happens if the initial concentration of the substrate is doubled? How does these results correspond to the Michealis-Menten parameters?

1.3 The data in Table 1.1 describes the concentration and reaction rates of a chemical process. Is it an enzymatic reaction following the Michaelis-Menten relationship? Can you give some rough estimates of V_{max} and K_m from this graph? Plot the inverse of the concentration versus the inverse of the reaction rate. This plot is commonly reffered to as a Lineweaver-Burk plot. Can you give some rough estimates of V_{max} and K_m from this graph as well?

1.4 Competetive Inhibition: Some enzymes may bind other substances than the target substrate to the binding site, thereby inhibiting the formation of the intended substrate-enzyme complex and the subsequent end-product. Such a situation is characterized by the following reaction dynamics:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \xrightarrow{k_2} P + E$$

$$I + E \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2$$

Table 1.1 Reaction Data for problem 3

Substrate Concentration [mM]	Reaction Velocity [mM/s]
0.1	0.04
0.2	0.08
0.5	0.17
1.0	0.24
2.0	0.32
3.5	0.39
5.0	0.42

Derive the following relationship for the reaction velocity of the product reaction, considering steady-state conditions for the enzyme and enzyme complexes and preservation of the total enzyme content:

$$V = \frac{V_{max}[S]}{[S] + K_m(1 + [I]/K_I)}$$

where $[I]$ is the concentration of the inhibitor, $K_m = (k_{-1} + k_2)/k_1$ and $K_I = k_{-3}/k_3$.

1.5 Alcohol metabolism: Clearance of the blood alcohol level (BAL) $[A]$ [mg/dl] from the liver is metabolized by more than 20 different enzymes. From experimental data the total clearance effect of these enzymes has been lumped into a common Michaelis-Menten relationship with population average $V_{max} = -15[\text{mg}/(\text{dl}\cdot \text{ h})]$ and a $K_m = 5$ [mg/dl].

$$\frac{d[A]}{dt} = \frac{V_{max}[A]}{K_m + [A]}$$

To calculate the BAL, the total distribution volume of the body for alhocol has to be known. The following relationship between the total water volume, representing this distribution volume V_D $[l]$, and the weight m_{BW} [kg], gender and age Y [years] of the person has been suggested.

$$\begin{aligned} V_D &= 20 + 0.36 m_{BW} - 0.1Y, \quad Men \\ V_D &= 14 + 0.25 m_{BW}, \qquad\quad Women \end{aligned}$$

Assuming that a 25 year old man of 80 kg consumes a drink containing 2 cl of alcohol (density 800 kg/m^3) at a fasting state. Digestion of alcohol is very rapid on an empty stomach, and you may assume that the total alcohol content has reached the blood stream after 20 minutes whereafter metabolization is considered to start. Simulate and plot the BAL level for the four hours following the drink.

Solutions to Chapter 0. Introduction to MATLAB and SIMULINK

Solve the following exercises using MATLAB. These exercises are inspired by or fully extracted from *EDA017: Föreläsningsanteckningar, OCTAVE/MATLAB* by Christian Söderberg.

0.1

```
% a

y = @(x) exp(-x/2)*cos(2*pi*x);
figure
fplot(y,[-6 3])
title('My fancy plot')
xlabel('x')
ylabel('y')

% b
axis([-4.5 -1 -10 10])


% c
% Rewrite y to be accepted by quad/integral
y = @(x) exp(-x/2).*cos(2*pi*x);

integral(y,-4.5,-1)
% or
quad(y,-4.5,-1)

% d
f = @(x) x^3+2*x-1;
sol = fsolve(f,0);
```

The answer is 0.4534. Write `format long` in the command window to get more decimals in the answer. Due to it being numerically calculated $f(0.4534)$ is approximately zero.

0.2 Go to new → function.

```
function sumOfDiag = sumOfDiagonal(A)
[n,m] = size(A);

if n ≠ m
    error('A is not a square matrix')
end

sumOfDiag = sum(diag(A));
end
```

0.3 Introduce $y_1 = y$ and $y_2 = \dot{y}$. The differential equation can then be rewritten as follows

$$
\begin{aligned}
\dot{y}_1 &= y_2 \\
\dot{y}_2 &= 3y_1 - 7y_2 \\
y_1(0) &= 0 \\
y_2(0) &= 1
\end{aligned}
$$

To solve this system of differential equations we define the following function

$$f(t, \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}) = \begin{pmatrix} y_2 \\ 3y_1 - 7y_2 \end{pmatrix}$$

In `MATLAB` this can be written as

```
f = @(t,y) [y(2); 3*y(1)-7*y(2)];
```

Or by matrix multiplication

```
f = @(t,y) [0 1; 3 -7]*y;
```

To solve the differential equation write the following code

```
[t Y] = ode45(f,[0 5],[0 1]);
```

`Y` is a matrix with two colons, the first colon corresponds to our initial variable y.

0.4 The first order polynomial means that

$$
\begin{aligned}
b + a &= 3.9286 \\
b + 2a &= 5.4059 \\
b + 3a &= 6.0771 \\
b + 4a &= 7.7145
\end{aligned}
$$

In matrix form this becomes

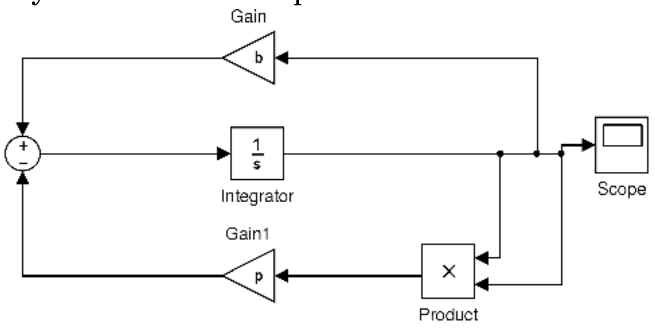
$$\begin{pmatrix} 1 & 1 \\ 2 & 1 \\ 3 & 1 \\ 4 & 1 \end{pmatrix} \cdot \begin{pmatrix} a \\ b \end{pmatrix} = \begin{pmatrix} 3.9286 \\ 5.4059 \\ 6.0771 \\ 7.7145 \end{pmatrix}$$

If this is seen as $S \cdot \begin{pmatrix} a \\ b \end{pmatrix} = T$, the following code will return the values of a and b

```
x = S\T;
a = x(1)
b = x(2)
```

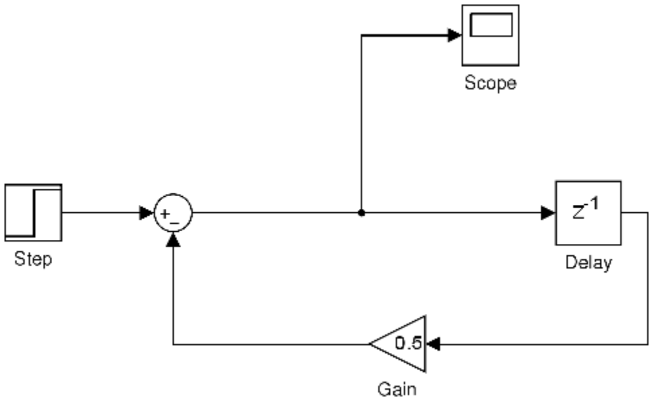
Solve the following exercises using SIMULINK in MATLAB. These exercises are taken from *Exercises in* MATLAB*/*Simulink*, Signals and Systems* by Thomas Munther.

0.5 Start SIMULINK by writing simulink in the MATLAB command window. This makes the SIMULINK Library Browser window pop up. Go to File → New → Model. In this window you can start to create your SIMULINK model. Use the Library Browser to find appropriate blocks and drag them into the model sheet. You can connect two blocks by their connection spots.

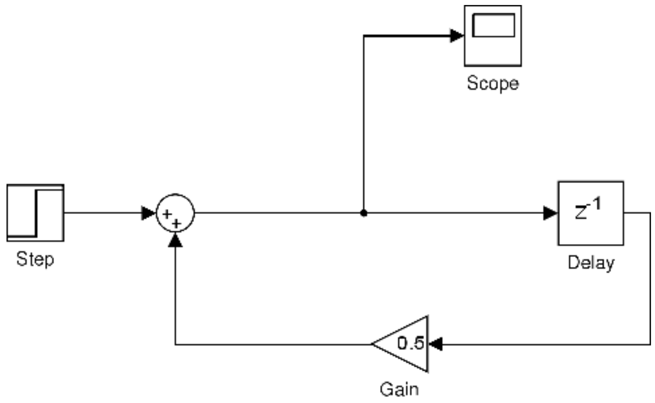


p and b can be defined in the current workspace.

0.6 a. Before running the simulation go to Simulation → Configuration Parameters. In Solver Options choose Fixed-step and Solver → Discrete. Set the sample time in each block to 1 [sec].



b. The only difference from the previous model is that the minus sign in the sum-block is changed to a plus sign.


Scope
Step
+
+
z^{-1}
Delay
0.5
Gain

Solutions to Chapter 1. Biochemical Reactions

1.1 a. Denote the concentrations $x = [X]$ and $y = [Y]$

$$\frac{dx}{dt} = -k_1 x + k_{-1} y$$
$$\frac{dy}{dt} = k_1 x - k_{-1} y$$

b. Denote the concentrations $x = [X]$ and $y = [Y]$

$$\frac{dx}{dt} = -2k_1 x^2 + 2k_{-1} y$$
$$\frac{dy}{dt} = k_1 x^2 - k_{-1} y$$

1.2 A matlab script may look as follows:

```
% Simulation of the substrate, enzyme and product concentrations in a MM
% example
% ds/dt = -k_1 *(se) + k_{-1}*c
% de/dt = -k_1 *(se) + (k_{-1} + k_2)*c
% dc/dt = k_1 *(se) - (k_{-1} + k_2)*c
% dp/dt = k_2 c
%--------------------
% Initial conditions
s(1) = 0.15; % mmol/L
e(1) = 1e-2; % mmol/L
c(1) = 0; % mmol/L
p(1) = 0; % mmol/L
%--------------------
% Parameters
k1 = 0.1;
k3 = 0.01; % k_{-1}
k2= 0.02;
%--------------------

% Run discretized simulation
for k = 2:10000
    s(k) = s(k-1) + k3*c(k-1) - k1*s(k-1)*e(k-1);
    e(k) = e(k-1) + (k3+k2)*c(k-1) - k1*s(k-1)*e(k-1);
    c(k) = c(k-1) - (k3+k2)*c(k-1)  + k1*s(k-1)*e(k-1);
    p(k) = p(k-1) + k2*c(k-1);
end

figure(1)
[ax,h1,h2] = plotyy(1:10000,[s' p'],1:10000,[e' c'])
legend('Substrate','Product','Enzyme','Complex')
xlabel('time [s]')
ylabel(ax(1),'Substrate/Product Concentration [mmol/L]')
ylabel(ax(2),'Enzyme/Complex Concentration [mmol/L]')
title('Simulation of enzymatic reaction')
```

```
% Run ode-solver simulation
% y = [S E C P]

dAll = @(t,y) [-k1*y(1)*y(2)+k3*y(3); ...
    -k1*y(1)*y(2)+(k3+k2)*y(3); ...
    k1*y(1)*y(2)-(k3+k2)*y(3); ...
    k2*y(3)];

[t Y] = ode45(dAll,[0 10000],[0.15 1e-2 0 0])

figure(2)
[ax,h1,h2] = plotyy(t,[Y(:,1) Y(:,4)],t,[Y(:,2) Y(:,3)])
legend('Substrate','Product','Enzyme','Complex')
xlabel('time [s]')
ylabel(ax(1),'Substrate/Product Concentration [mmol/L]')
ylabel(ax(2),'Enzyme/Complex Concentration [mmol/L]')
title('Simulation of enzymatic reaction')
```

Doubling the enzymatic concentration doubles the production rate since $V_{max} = k_2 \cdot e_0$. Likewise since $K_m = (k_2 + k_{-1})/k_1 = 0.3$ and $V = V_{max}s/(K_m + s)$, a doubling of s_0 from $K_m/2$ to K_m means that the initial reaction rate will become 1.5 times greater.

1.3 The plot indicates that the relationship between the reaction rate and the substrate concentration goes to saturation in a M-M-like behavoir, see Fig. 1.1. V_{max} and K_m are estimated as shown in the plot.

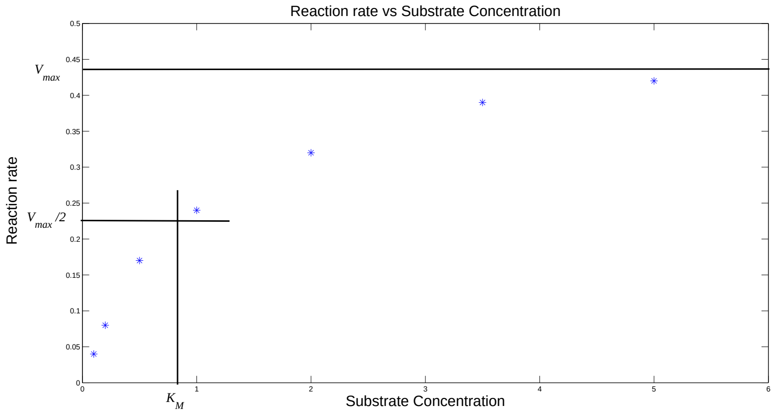


Figure 1.1 Graphical estimation of V_{max} and K_M

Lineweaver-Burke plot: The Michaelis-Menten relationship between substrate concentrations $[S]$ states that:

$$v = \frac{V_{max}[S]}{K_m + [S]}$$

Taking the inverse yields:

$$\frac{1}{v} = \frac{K_m}{V_{max}} \frac{1}{[S]} + \frac{1}{V_{max}}$$

Now, the parameters K_m/V_{max} and $1/V_{max}$ for this linear relationship may be estimated from the plot as seen in Fig. 1.2.

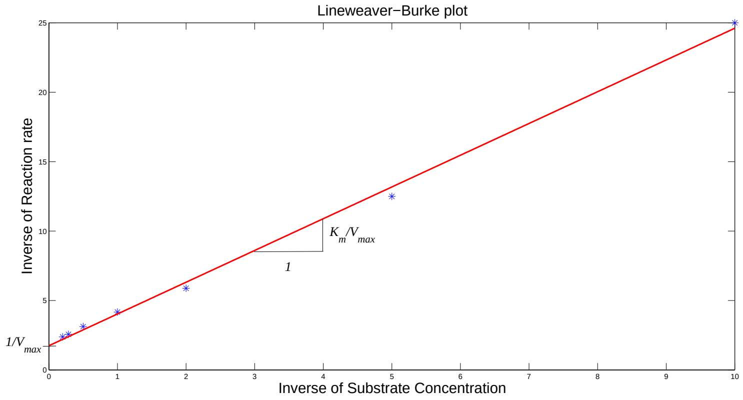


Figure 1.2 Graphical estimation of V_{max} and K_M using the Lineweaver-Burke plot.

1.4 Draw a graph of the compartment representation, see Fig 1.3. Next, determine the differential equations governing the reaction dynam-

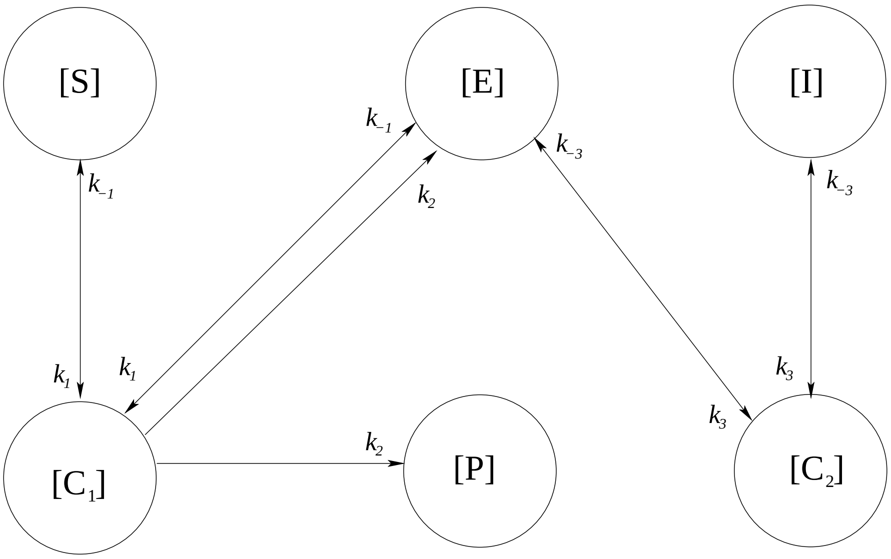


Figure 1.3 Compartment model representation of the enzyme inhibition dynamics.

ics:

$$\frac{d[S]}{dt} = -k_1[S][E] + k_{-1}[C_1] \tag{1.1}$$

$$\frac{d[I]}{dt} = k_{-3}[C_2] - k_3[E][I] \tag{1.2}$$

$$\frac{d[C_1]}{dt} = k_1[S][E] - (k_{-1} + k_2)[C_1] \tag{1.3}$$

$$\frac{d[C_2]}{dt} = k_3[E][I] - k_{-3}[C_2] \tag{1.4}$$

$$\frac{d[E]}{dt} = (k_2 + k_{-1})[C_1] + k_{-3}[C_2] - k_1[S][E] - k_3[E][I] \tag{1.5}$$

$$\frac{d[P]}{dt} = k_2[C_1] \tag{1.6}$$

Next, use the steady-state assumptions; $d[C_1]/dt = d[C_2]/dt = 0$ to get

$$[C_1] = \frac{k_1}{k_{-1} + k_2}[S][E] \tag{1.7}$$

$$[C_2] = \frac{k_3}{k_{-3}}[E][I] \tag{1.8}$$

The conservation of enzymatic mass gives

$$[E_0] = [E] + [C_1] + [C_2] = [E](1 + \frac{k_1}{k_{-1} + k_2}[S] + \frac{k_3}{k_{-3}}[I]) \tag{1.9}$$

Put Eq. (1.6), Eq. (1.8) and Eq. (1.9) together:

$$V = \frac{d[P]}{dt} = \frac{k_2[E_0][S]}{[S] + \frac{k_1}{k_{-1}+k_2}(1 + \frac{k_3}{k_{-3}}[I])} \tag{1.10}$$

1.5 Blood alcohol level
A matlab script may look as follows:

```
% BAL simulation
V = -15;% mg/(l*h)
K_m = 5;% mg/dl
%-----
VD = 10*(20 + 0.36*80-0.1*25); %dl
BAL(1:20) = zeros(20,1);
BAL(20) = 0.02*1000*0.8*1000/VD; % mg/dl
der = 0;
for k=21:1:240
    BAL(k) = BAL(k-1) + der;
    der = V/60*BAL(k)/(K_m + BAL(k));
end
plot([1:length(BAL)]/60,BAL)
title('Blood Alcohol Level after ingesting 2 cl alcohol ...
(about one pint of beer) in 20 minutes','Fontsize',10)
ylabel('BAL [mg/dl]','Fontsize',10)
xlabel('time [h]','Fontsize',10)
```

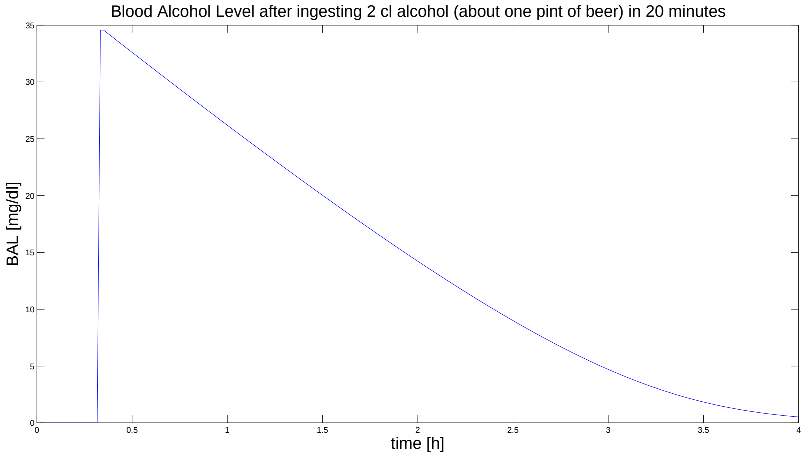


Figure 1.4 Blood alcohol content according to the simulation example.

Running the code generates the plot in Fig. 1.4.

Another possibility is to use `MATLAB`s built in solvers for odrinary differential equations, such as `ode45`. The `MATLAB`-script would then look something like

```
% BAL simulation
V = -15;% mg/(l*h)
K_m = 5;% mg/dl
VD = 10*(20 + 0.36*80-0.1*25); % dl

% The 'initial value' of the concentration [A] is actually
% the concentration in t = 20 min when the metabolization
% of the alcohol starts.

initial_value_A = 0.02*1000*0.8*1000/VD; % mg/dl

% Define the differential equation y(t) = [A](t)
dAdt = @(t,y) V/60*y/(K_m+y);

% Solve the differential equation
[t, Y] = ode45(dAdt, [0 220], initial_value_A);

t = (t+20)/60; % Shifting the time vector 20 min, and changing into
% hours instead of minutes.
Y = [zeros(size(0:0.1:(t(1)-0.01))) Y']; % Adding zeros to the
% value-vector for time 0-20 min.
t = [0:0.1:(t(1)-0.01) t']; % Adding the time between 0-20 minutes
% to the time vector.

plot(t,Y)
title('Blood Alcohol Level after ingesting 2 cl alcohol ...
(about one pint of beer) in 20 minutes','Fontsize',10)
ylabel('BAL [mg/dl]','Fontsize',10)
xlabel('time [h]','Fontsize',10)
```