Assignment #2 – Compartmental PK models

Due: Thursday 2018-02-15, 11:59pm

Submit to Blackboard: one zipped folder that includes the solution (this document, filled out) as a PDF and a set of code files for Question 2.

Your codes must work; that means we must be able to open and run your Matlab code to obtain the results (graphs) for questions 2e & 2f. Label the code filenames appropriately, e.g. "yourname_Q2e_runcode.m"

Example codes and figures should also be included in this report document as requested below. Figures should be annotated with a brief figure caption. Graphs should have **legible** and informative axes.

* Use this document to insert your solutions, then convert to PDF and submit. Expand the space between each question as needed to incorporate your solution.

* Fonts: use Arial 12 for text; use Courier 11 for code.

* If you draw or handwrite parts of this assignment (e.g. equations), you can scan it in using your phone (or similar). Make sure that any solution is clear and readable! I strongly suggest learning to use Equation Editor, MathType or similar to enter equations.

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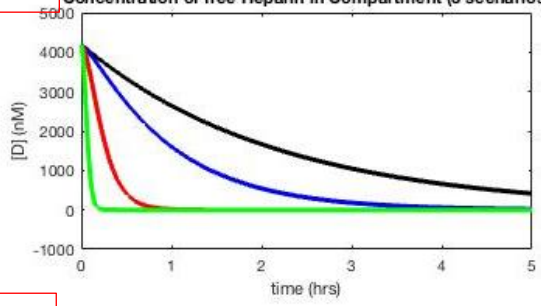
Question 1 (30 points): Heparin is an important and potentially life-saving drug, used as a blood thinner. However, it can cause severe issues when overdosed. A drug called protamine is used to bind and deplete heparin in overdose situations. First, download and install MATLAB. Then, download the MATLAB codes for the heparin-protamine binding simulation from Blackboard.

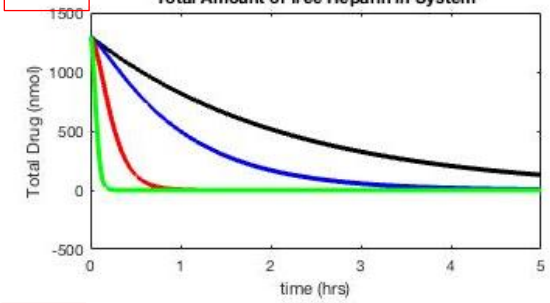
Open the code "m1C_main_Heparin.m". Read through the code and the green comments/annotations – see the units and the derivation of the real parameter values. Open the code "m1C_eqns_Heparin.m". This is a simpler code that only contains the actual equations being simulated. Read through to see the form of the equations.

1a. Run the code ("m1C_main_Heparin.m") as it is, which should give you six graphs, each with four lines – one for each of three rates of infusion of protamine sulfate, plus a line for no protamine at all. Paste the six-panel figure below and describe (in words) what's happening to the (toxic) heparin and (therapeutic) protamine levels over time as the infusion rate of protamine increases.

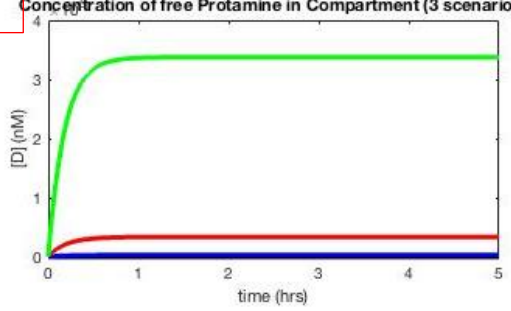
A1



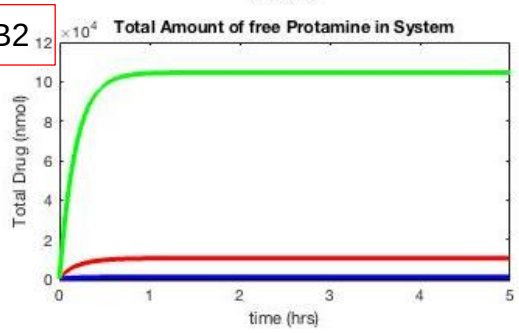
A2



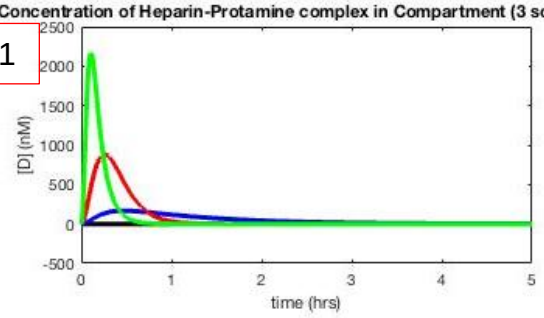
B1



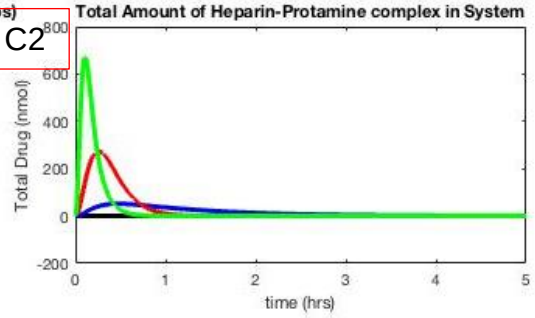
B2



C1



C2

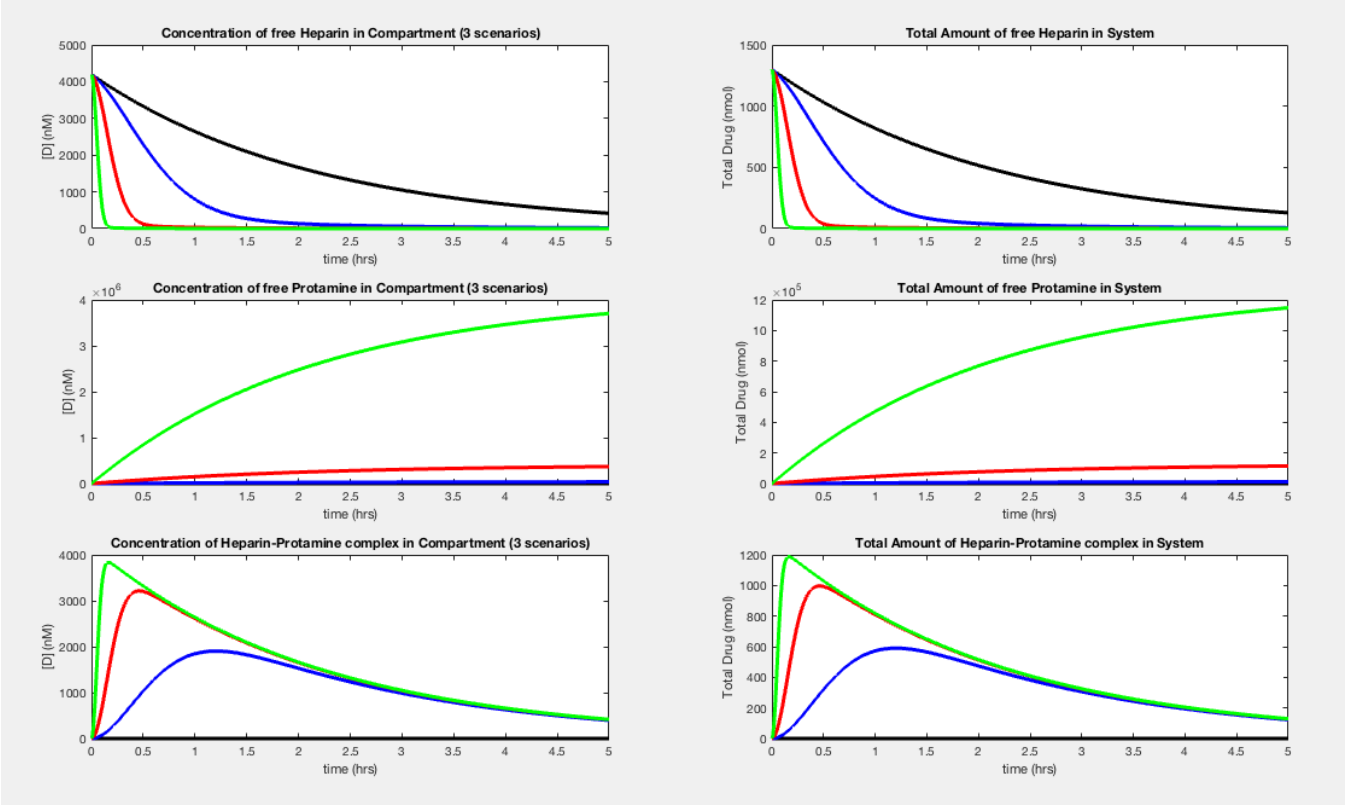


The (toxic) heparin level over time decreases as the infusion rate of protamine increases, as shown in figure A1 and A2. The higher the protamine infusion rate is, the more heparin is depleted from the system because the heparin binds to the protamine and forms the complex. Later in time as we can see in figure C1 and C2, the complex will be execrated from the system as well.

The (therapeutic) protamine levels over time increase as the infusion rate of protamine increases, as shown in figure B1 and B2. When the protamine increases above a certain threshold which all heparin binds to protamine, the protamine which is left over will be accumulated in the system and reaches a steady state.

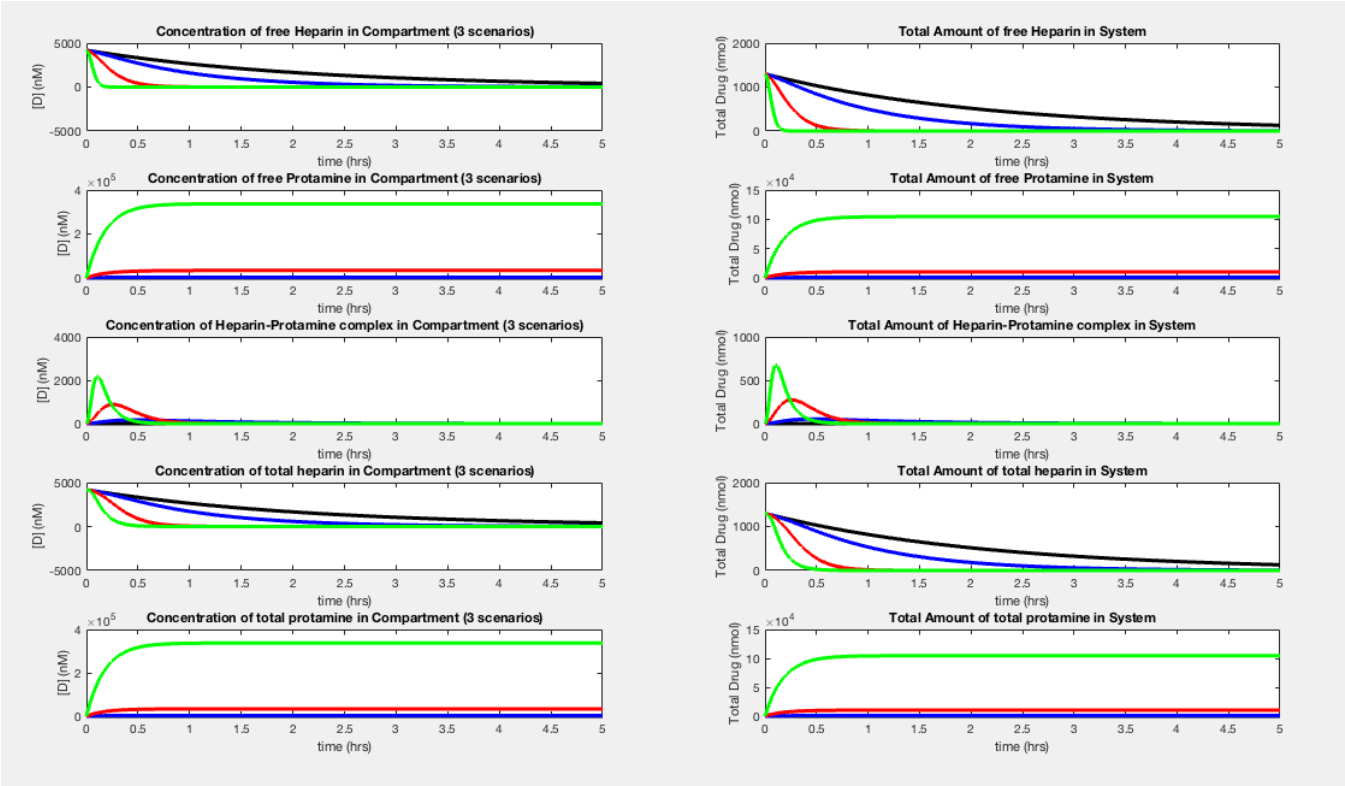
1b. Now take the code and change the rate constants of clearance of protamine sulfate and the protamine-heparin complex. Change them both to be the same as the clearance rate of heparin, which you will note is much slower (longer half-life).

Run the simulation and paste the resulting six-panel figure below and describe (in words) whether the clearance makes a difference to the rate at which the heparin is being removed from the system? Also, what happens to the protamine, and why?



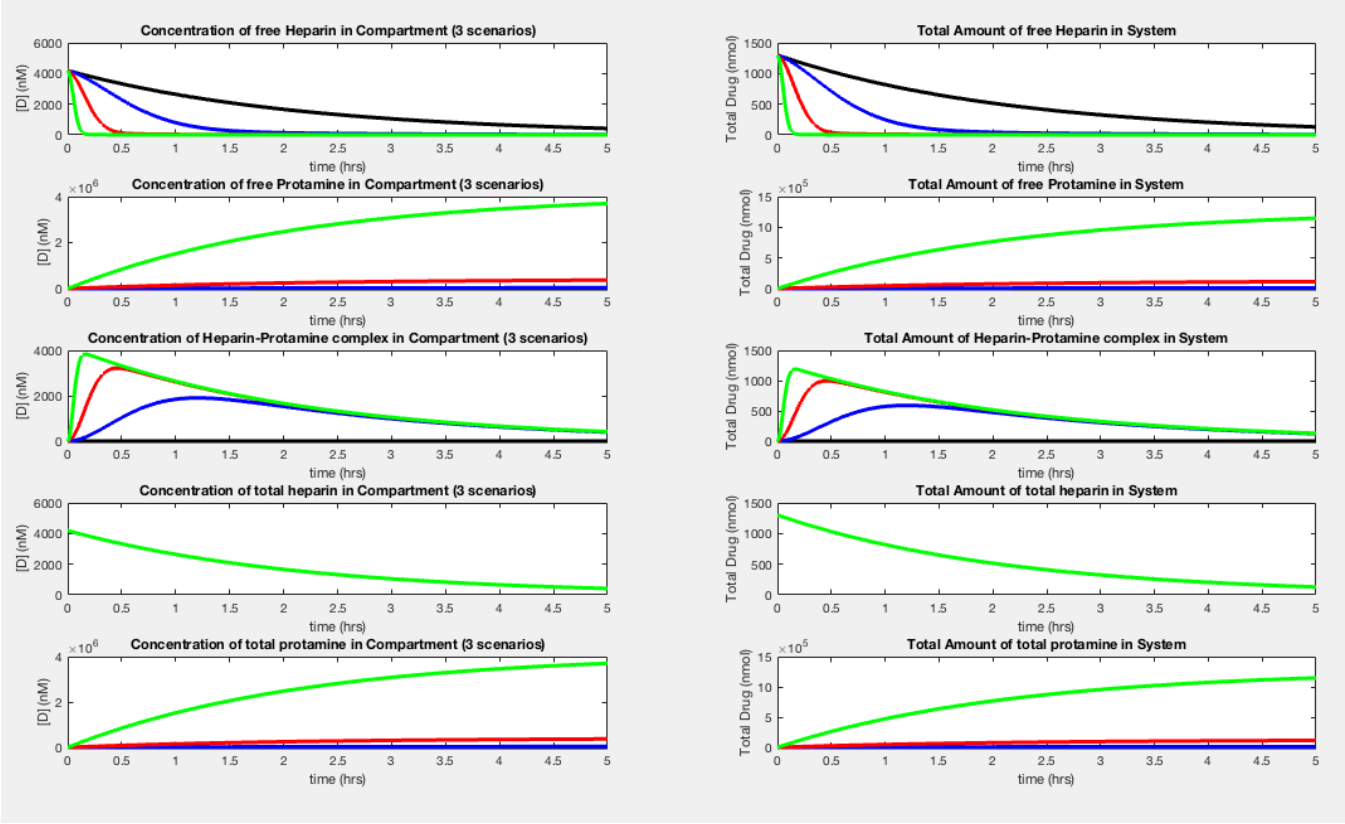
The clearance does not make a big difference to the rate at which the heparin is being removed from the system. However, there are more protamine in the system. This is because the protamine's elimination happens slower, so protamine cannot be excreted from the system; therefore, the larger amount of protamine gets into the system, the more protamine stays in the system (as shown in the green curve); However, if the amount of protamine which gets into the system is low, the difference between the earlier cases and this case is inconspicuous. It is also noticeable that the complex formation happens faster for the higher protamine infusion rate, but the depletions of the complex are similar for all different protamine infusion rates.

1c. Modify the code to include graphs for "total heparin" (i.e. free heparin + heparin-protamine) concentration and amount in the body, and "total protamine" (i.e. free protamine + heparin-protamine) concentration and amount in the body vs time – that's four additional graphs. Run it for the two cases above and paste the now ten-panel figures below. Describe (in words) what is happening to the "total heparin" and "total protamine" concentrations.



The total heparin level is being eliminated gradually. The more protamine intakes into the system, the faster the heparin can be eliminated out of the system; This is because the heparin binds to the protamine and forms a complex with a fast elimination rate. So the complex can leave the system quickly and eliminate the heparin in the system.

If there is too much protamine intake, it is likely to cause execration problem for the protamine. As the green line shows, the total protamine just stays in the system and reaches a positive steady state. However, with a reasonable protamine infusion rate, the drug does get eliminated in time, as shown in the blue curve.

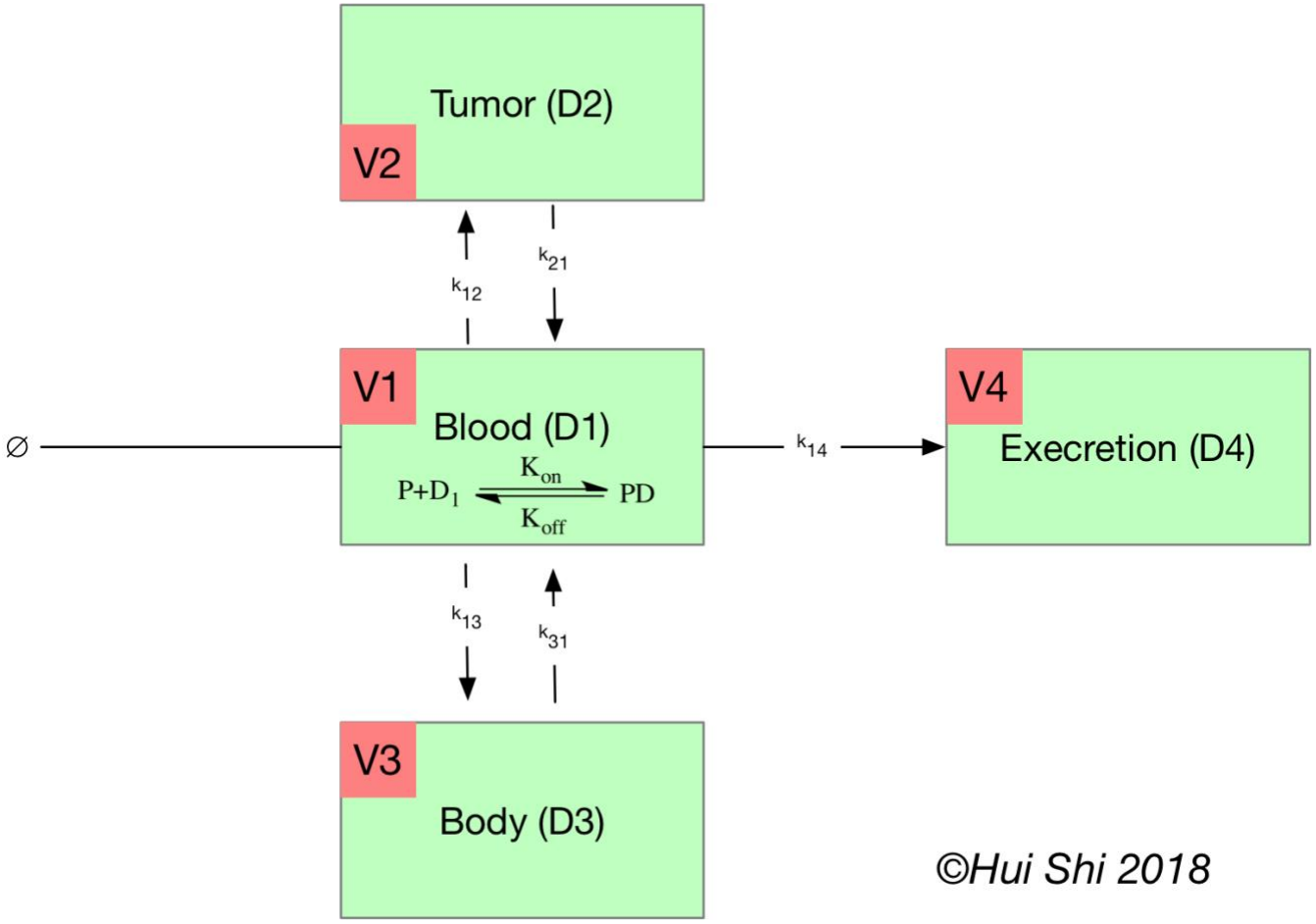


The total heparin level is being eliminated gradually compared to the earlier case, with the different protamine infusion rate overlapped together. This is because the total heparin includes the protamine-heparin complex with a slow elimination rate.

If there is too much protamine intake, it is likely to cause execration problem. As the green line shows, the total protamine just stays in the system and reaches a positive steady state. However, with a reasonable protamine intake, the drug does get eliminated in time, as shown in the blue curve.

Question 2 (70 points). Scenario: A drug that acts on tumor cells is administered as a bolus dose D_0 (fast injection) intravenously. The drug doesn't enter red blood cells, and undergoes first-order clearance (200 mL/hr) from the blood plasma (assume = 3 L). The drug can distribute from the bloodstream into the large tumor (.25 L) and from the bloodstream into the rest of the body (50 L) with transport rate constants of 0.1 hr^{-1} and 0.4 hr^{-1}, respectively. The reverse transport rate constants (i.e. from the peripheral compartments to the bloodstream) have the same values. The drug is not cleared from the two tissue compartments (i.e. the tumor and the rest of the body), only from the blood. In the blood, there is a protein that binds the drug with an equilibrium constant (Kd) of 10 nM and an unbinding (off) rate constant of 0.1 hr^{-1}. The plasma protein is large, and neither the plasma protein nor the bound form of the drug can leave the bloodstream (by clearance or by distribution). The plasma protein itself is initially present at 75 nM in the blood, and is not cleared (i.e. does not undergo clearance).

2a. Draw a schematic for a <u>three-compartment</u> model that represents the above scenario. Use arrows for processes and label each with its associated rate constant(s).



2b. Write out the differential equation(s) that represent the model described above. Be sure that the rate constant notation matches the schematic.

$$\frac{dD_1}{dt} = -k_{12}D_1 + k_{21}D_2\left(\frac{V_2}{V_1}\right) - k_{14}D_1 - k_{13}D_1 + k_{31}D_3\left(\frac{V3}{V1}\right) - k_{on}PD_1 + k_{off}PD_1$$

$$\frac{dD_2}{dt} = k_{12}D_1\left(\frac{V1}{V2}\right) - k_{21}D_2$$

$$\frac{dD_3}{dt} = k_{13}D_1\left(\frac{V1}{V3}\right) - k_{31}D_3$$

$\frac{dD_4}{dt} = k_{14}D_1$ *--- Assuming V4 = V1*

$$\frac{dP}{dt} = -k_{on}P * D_1 - k_{off}PD$$

$$\frac{dPD}{dt} = k_{on}P * D - k_{off}PD$$

2c. Write a complete list of the <u>variables</u> in your equations and a complete list of the <u>parameters</u> in your equations, and the units for each. The list should give both the 'symbol' for the variable/parameter used in your equations above and a short description of it.

V1 = 3 L

V2 = 0.25 L

V3 = 50 L

V4 = V1=3 L

$k_{12} = 0.1\ hr^{-1}$

$k_{21} = 0.1\ hr^{-1}$

$k_{14} = \frac{2}{30} hr^{-1}$

$k_{13} = 0.4\ hr^{-1}$

$k_{31} = 0.4\ hr^{-1}$

$k_{on} = 0.01\ hr^{-1}$

$k_{off} = 0.1\ hr^{-1}$

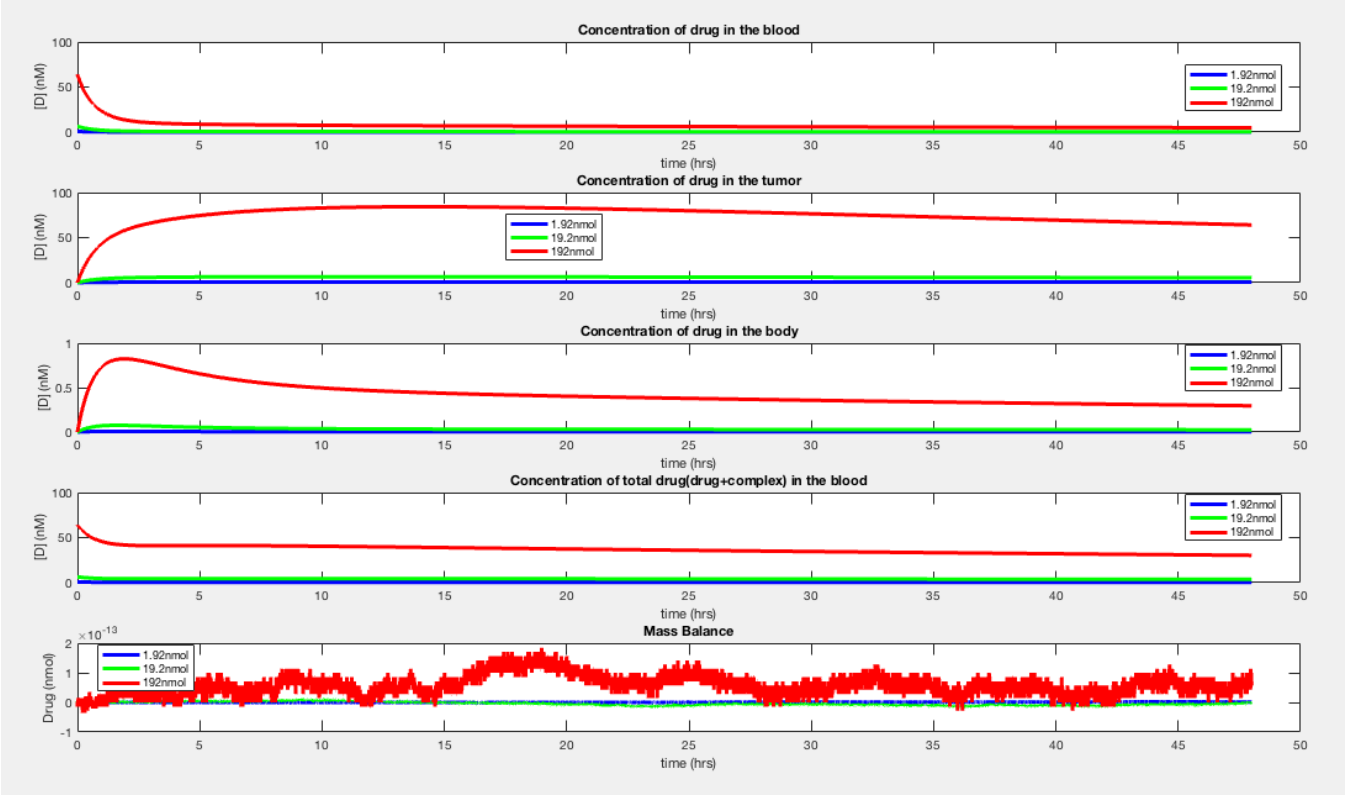
2d. Write Matlab code, based on the codes used in class, that solves the above compartmental model. Include a mass (or mole) balance in order to ensure that the model is working. Include code files that, when run, outputs the results as needed for parts 2e and 2f (i.e. one code for part 2e and one code for part 2f).

DO NOT paste in your code here. Paste it in part 2g below. Also, include the code files with this PDF file in one zipped file.

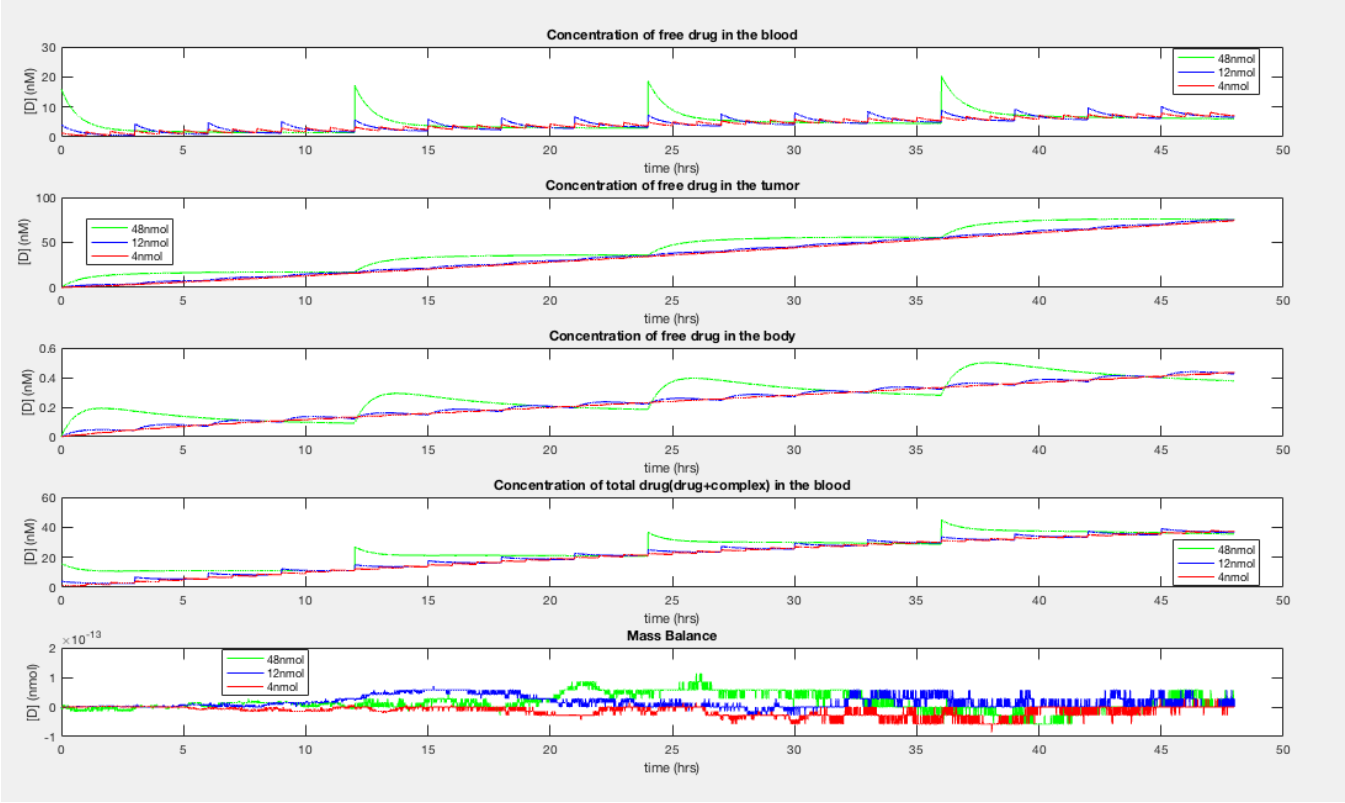
*** Note** that you will have a larger y0 vector than in the previous codes. Comment the code to note which vector element corresponds to which molecule (e.g. y(1) = drug in blood, y(2) = drug in tumor…)

2e. Results 1: Run your model for D_0 = 1.92 nmol, 19.2 nmol, 192 nmol, showing results for 48 hours. Show graphs for: concentration of free drug in blood over time; and concentration of total (free + bound) drug in blood over time; concentration of free drug in the tumor over time; concentration of free drug in the rest of the body over time; and the mass/molecular balance for the drug.

Note: by setting the code up right, you should be able to run it just once to capture all the data you need, and output the figure plots (we listed 5 above) together on one large figure. Graph the three D_0 conditions on the same graphs (e.g. three color lines).



2f. Results 2: Assuming 192 nmol in total is given every 48 hours, simulate repeated bolus injections of 48 nmol every 12 hours, 12 nmol every 3 hours or 4 nmol every hour (simulate a total of 48 hours in each case). What effect does metronomic dosing have on the drug time profiles in the blood and in the tumor? You should present a similar format of figures as 2e. You may have to concatenate results vectors from sequential runs of the solver to make it easier to plot.



2g. Paste codes from part 2d here.

Use Courier Size 11 (it's easier to read code written in monospaced fonts) to paste in your code here.

=======equation========

```
function dydt = hw2_2_eqn(t,y,p)

V1  = p(1);
V2  = p(2);
V3  = p(3);
V4  = p(4);

k12 = p(5);
k21 = p(6);
k14 = p(7);
k13 = p(8);
k31 = p(9);
kon = p(10);
koff= p(11);

dydt = zeros(6,1); % make it a column vector corresponding to 6 equations

dydt(1) = -k12*y(1) + k21*y(2)*(V2/V1) - k14*y(1) - k13*y(1) +
k31*y(3)*(V3/V1) ...
          - kon*y(5)*y(1) + koff*y(6); %D1
dydt(2) =  k12*y(1)*(V1/V2) - k21*y(2); %D2
dydt(3) =  k13*y(1)*(V1/V3) - k31*y(3); %D3
dydt(4) =  k14*y(1); %D4
dydt(5) =  -kon*y(5)*y(1)+koff*y(6); %P
dydt(6) =  kon*y(5)*y(1)-koff*y(6); %PD
end
```

=========2e================

```
clear all;

V1  = 3; %L
V2  = 0.25; %L
V3  = 50; %L
V4  = V1; %L
k12 = 0.1; %hr-1
k21 = 0.1; %hr-1
k14 = 200/3000; %hr-1
k13 = 0.4; %hr-1
k31 = 0.4; %hr-1
kon = 0.01; %hr-1
koff = 0.1; %hr-1

Q = cell(1,3);
com = NaN(10000,3);
for i = 1:3
    D0 = [1.92 19.2,192]; %nmol
    y0 = [D0(i)/V1 0 0 0 75 0]'; % nM
```

```
    p = [V1 V2 V3 V4 k12 k21 k14 k13 k31 kon koff]';
    options = odeset('MaxStep',5e-2, 'AbsTol', 1e-5,'RelTol', 1e-
5,'InitialStep', 1e-2);

    [T1,Y1] = ode45(@hw2_2_eqn,linspace(0,48,10000),y0,options,p);
    Q{i} = Y1;
    TotalD1 = Y1(:,1)*V1 ; % Total of drugs in compartment 1
    TotalD2 = Y1(:,2)*V2 ; % Total of drugs in compartment 2
    TotalD3 = Y1(:,3)*V3 ; % Total of drugs in compartment 3
    TotalD4 = Y1(:,4)*V4 ; % Total of drugs in compartment 4
    TotalP = Y1(:,5)*V1 ; % Total of protein in compartment 1
    TotalPD = Y1(:,6)*V1 ; % Total of protein-drug complex in compartment 1

    com(:,i) = D0(i) - TotalD1- TotalD2- TotalD3- TotalD4-
TotalPD;%conservation of mass
end
%====================Mass Balance=========================================
figure;
ax1=subplot(5,1,1);
plot(ax1,T1,Q{1,1}(:,1),'b',T1,Q{1,2}(:,1),'g',T1,Q{1,3}(:,1),'r','linewidth
',3)
title(ax1,'Concentration of drug in the blood')
ylabel(ax1,'[D] (nM)')
xlabel(ax1,'time (hrs)')
legend('1.92nmol','19.2nmol','192nmol','Location', 'Best')

ax2=subplot(5,1,2);
plot(ax2,T1,Q{1,1}(:,2),'b',T1,Q{1,2}(:,2),'g',T1,Q{1,3}(:,2),'r','linewidth
',3)
title(ax2,'Concentration of drug in the tumor')
ylabel(ax2,'[D] (nM)')
xlabel(ax2,'time (hrs)')
legend('1.92nmol','19.2nmol','192nmol','Location', 'Best')


ax3=subplot(5,1,3);
plot(ax3,T1,Q{1,1}(:,3),'b',T1,Q{1,2}(:,3),'g',T1,Q{1,3}(:,3),'r','linewidth
',3)
title(ax3,'Concentration of drug in the body')
ylabel(ax3,'[D] (nM)')
xlabel(ax3,'time (hrs)')
legend('1.92nmol','19.2nmol','192nmol','Location', 'Best')


ax4=subplot(5,1,4);
plot(ax4,T1,Q{1,1}(:,6)+Q{1,1}(:,1),'b',T1,Q{1,2}(:,6)+Q{1,2}(:,1),'g',...
         T1,Q{1,3}(:,6)+Q{1,3}(:,1),'r','linewidth',3)
title(ax4,'Concentration of total drug(drug+complex) in the blood')
ylabel(ax4,'[D] (nM)')
xlabel(ax4,'time (hrs)')
legend('1.92nmol','19.2nmol','192nmol','Location', 'Best')

ax5=subplot(5,1,5);
plot(ax5,T1,com(:,1),'b',T1,com(:,2),'g',T1,com(:,3),'r','linewidth',3)
```

```
title(ax5,'Mass Balance')
ylabel(ax5,'Drug (nmol)')
xlabel(ax5,'time (hrs)')
legend('1.92nmol','19.2nmol','192nmol','Location', 'Best')
```

=====2f========

```
clear all;

V1  = 3; %L
V2  = 0.25; %L
V3  = 50; %L
V4  = V1; %L
k12 = 0.1; %hr-1
k21 = 0.1; %hr-1
k14 = 200/3000; %hr-1
k13 = 0.4; %hr-1
k31 = 0.4; %hr-1
kon = 0.01; %hr-1
koff = 0.1; %hr-1
D0 = 192; %nmol
p= [V1 V2 V3 V4 k12 k21 k14 k13 k31 kon koff]';

%% 48nmol
num =D0/48;
y0 = [(D0/num)/V1 0 0 0 75 0]';
Ytotal=y0';
Ttotal=0;
comt=0;


for b=1:num
    options = odeset('MaxStep',5e-2, 'AbsTol', 1e-5,'RelTol', 1e-
5,'InitialStep', 1e-2);
    [T1,Y1] = ode45(@hw2_2_eqn,[0:.01:12],y0,options,p);
    TotalD1 = Y1(:,1)*V1;
    TotalD2 = Y1(:,2)*V2;
    TotalD3 = Y1(:,3)*V3;
    TotalD4 = Y1(:,4)*V4;
    TotalP = Y1(:,5)*V1;
    TotalPD = Y1(:,6)*V1;

    com=-TotalD1-TotalD2-TotalD3-TotalD4-TotalPD+((D0/num)*b);

    y0=Y1(end,:);
    y0(1,1)=y0(1,1)+(D0/num)/V1;

    T1=T1+(12*(b-1));

    Ttotal=[Ttotal;T1(2:end)];
    Ytotal=vertcat(Ytotal,Y1(2:end,:));
    comt=[comt;com(2:end)];
end
```

```
%% 12nmol
num =D0/12;
y0 = [(D0/num)/V1 0 0 0 75 0]';
Ytotal2=y0';
Ttotal2=0;
comt2=0;


for b=1:num
options = odeset('MaxStep',5e-2, 'AbsTol', 1e-5,'RelTol', 1e-
5,'InitialStep', 1e-2);
[T1,Y1] = ode45(@hw2_2_eqn,[0:.01:3],y0,options,p);


TotalD1 = Y1(:,1)*V1;
TotalD2 = Y1(:,2)*V2;
TotalD3 = Y1(:,3)*V3;
TotalD4 = Y1(:,4)*V4;
TotalP = Y1(:,5)*V1;
TotalPD = Y1(:,6)*V1;
com=-TotalD1-TotalD2-TotalD3-TotalD4-TotalPD+((D0/num)*b);

T1=T1+(3*(b-1));
y0=Y1(end,:);
y0(1,1)=y0(1,1)+(D0/num)/V1;

Ttotal2=[Ttotal2;T1(2:end)];
Ytotal2=vertcat(Ytotal2,Y1(2:end,:));
comt2=[comt2;com(2:end)];
end

%% 4 nmol
num =192/4;
y0 = [(D0/num)/V1 0 0 0 75 0]';
Ytotal3=y0';
Ttotal3=0;
comt3=0;


for b=1:num
options = odeset('MaxStep',5e-2, 'AbsTol', 1e-5,'RelTol', 1e-
5,'InitialStep', 1e-2);
[T1,Y1] = ode45(@hw2_2_eqn,[0:.01:1],y0,options,p);


TotalD1 = Y1(:,1)*V1;
TotalD2 = Y1(:,2)*V2;
TotalD3 = Y1(:,3)*V3;
TotalD4 = Y1(:,4)*V4;
TotalP = Y1(:,5)*V1;
TotalPD = Y1(:,6)*V1;
com=-TotalD1-TotalD2-TotalD3-TotalD4-TotalPD+((D0/num)*b);
```

```
y0=Y1(end,:);
y0(1,1)=y0(1,1)+(D0/num)/V1;

T1=T1+(b-1);
Ttotal3=[Ttotal3;T1(2:end)];
Ytotal3=vertcat(Ytotal3,Y1(2:end,:));
comt3=[comt3;com(2:end)];
end



% for i = 1:3
%     init_conc = D0(i)/V1;
%     y0 = [init_conc 0 0 0 75 0]'; % nM
%     timelapse = 48/(192/D0(i));
%     comt = [];
%     Ttotal = [];
%     Ytotal = [];
%     njump = 48/timelapse;
%     initialtime = 0;
%         for j = 1:njump
%             options = odeset('MaxStep',5e-2, 'AbsTol', 1e-5,'RelTol', 1e-
5,'InitialStep', 1e-2);
%             [T1,Y1] =
ode45(@hw2_2_eqn,linspace(0,timelapse,10000),y0,options,p);
%             initialtime = T1(end);
%             y0 = Y1(end,:);
%             TotalD1 = Y1(:,1)*V1 ; % Total of drugs in compartment 1
%             TotalD2 = Y1(:,2)*V2 ; % Total of drugs in compartment 2
%             TotalD3 = Y1(:,3)*V3 ; % Total of drugs in compartment 3
%             TotalD4 = Y1(:,4)*V4 ; % Total of drugs in compartment 4
%             TotalP = Y1(:,5)*V1 ; % Total of protein in compartment 1
%             TotalPD = Y1(:,6)*V1 ; % Total of protein-drug complex in
compartment 1
%             com = D0(i) - TotalD1- TotalD2- TotalD3- TotalD4-
TotalPD;%conservation of mass
%             T1=T1+(timelapse*(j-1));
%             comt = [comt;com(1:end)];
%             Ytotal = vertcat(Ytotal,Y1);
%             Ttotal = [Ttotal;T1(1:end)];
%          end
%         Tcell{i} = Ttotal;
%         Ycell{i} = Ytotal;
%
% end
%====================Mass Balance=========================================
figure(1)
ax1=subplot(5,1,1);
plot(ax1,Ttotal,Ytotal(:,1),'g',Ttotal2,Ytotal2(:,1),'b',Ttotal3,Ytotal3(:,1
),'r')
title(ax1,'Concentration of free drug in the blood')
ylabel(ax1,'[D] (nM)')
xlabel(ax1,'time (hrs)')
legend('48nmol','12nmol','4nmol','Location','Best')
```

```
ax2=subplot(5,1,2);
plot(ax2,Ttotal,Ytotal(:,2),'g',Ttotal2,Ytotal2(:,2),'b',Ttotal3,Ytotal3(:,2
),'r')
title(ax2,'Concentration of free drug in the tumor')
ylabel(ax2,'[D] (nM)')
xlabel(ax2,'time (hrs)')
legend('48nmol','12nmol','4nmol','Location','Best')


ax3=subplot(5,1,3);
plot(ax3,Ttotal,Ytotal(:,3),'g',Ttotal2,Ytotal2(:,3),'b',Ttotal3,Ytotal3(:,3
),'r')
title(ax3,'Concentration of free drug in the body')
ylabel(ax3,'[D] (nM)')
xlabel(ax3,'time (hrs)')
ax1=subplot(5,1,1);
legend('48nmol','12nmol','4nmol','Location','Best')


ax4=subplot(5,1,4);
plot(ax4,Ttotal,Ytotal(:,1)+Ytotal(:,6),'g',Ttotal2,Ytotal2(:,1)+Ytotal2(:,6
),'b',Ttotal3,Ytotal3(:,1)+Ytotal3(:,6),'r')
title(ax4,'Concentration of total drug(drug+complex) in the blood')
ylabel(ax4,'[D] (nM)')
xlabel(ax4,'time (hrs)')
legend('48nmol','12nmol','4nmol','Location','Best')


ax5=subplot(5,1,5);
plot(ax5,Ttotal,comt,'g',Ttotal2,comt2,'b',Ttotal3,comt3,'r')
title(ax5,'Mass Balance')
ylabel(ax5,'[D] (nmol)')
xlabel(ax5,'time (hrs)')
legend('48nmol','12nmol','4nmol','Location','Best')
```