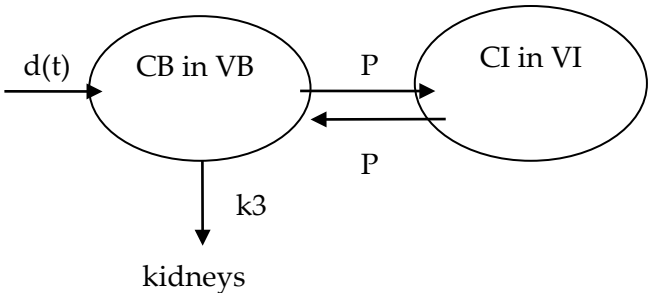
Lecture 4: Linear Systems Analysis, Continued

On Monday we learned to solve linear models using Laplace Transforms by applying both analytic and numeric tools to the transfer function of the system. Today we will learn to solve linear models using the state space representation of the linear system. We will also introduce sensitivity and bifurcation analysis, which are methods to describe how system behavior changes with parameter values.

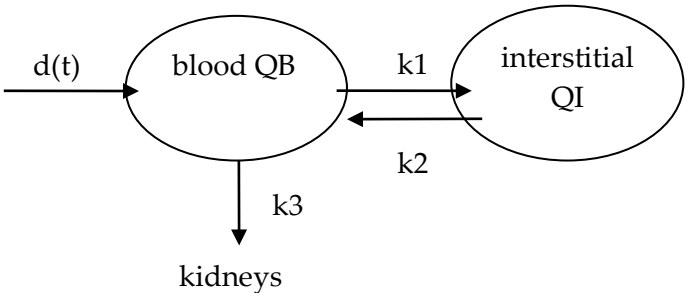
State space models.

The state space representation of a system is the matrix representation of the differential equations. S**tate space techniques make use of linear (matrix) algebra** rather than Laplace transforms.



Recall the pharmacokinetic (PK) model that relates a dosing protocol $d(t)$ to the concentration of drug in the blood, C_B, assuming there is an interstitial compartment as well. PK models are used to design dosing protocols for patients. A good dosing protocol should keep the concentration of drug in the blood above the therapeutic threshold and below the toxic threshold, for as long as possible. This concentration range is referred to as the therapeutic window. A good dosing protocol also needs to be convenient enough for the patients and/or nurses to follow accurately. This usually means that drug should be given as infrequently as possible, as long as the drug remains in the therapeutic window and the doses can be given at the same time(s) each day (so you can dose every 4 or 6 hours, but not every 5 hours).

Our system variables are C_B, C_I, the concentrations in the blood and interstitium. Our parameters are , V_B, V_I, k_3 , and any parameters that describe the dosing, $d(t)$. However, we also converted this to a model in terms of quantities rather than concentrations, using



$$Q_B = V_B C_B$$
$$Q_I = V_I C_I$$
$$k_1 = P/V_B$$
$$k_2 = P/V_I$$

To obtain the ODE model:

$$\frac{dQ_B}{dt} = d(t) - (k_1 + k_3)Q_B + k_2 Q_I$$
$$\frac{dQ_I}{dt} = k_1 Q_B - k_2 Q_I$$

With initial conditions, $Q_B = 0; Q_I = 0$. We will use this form simply to better illustrate all aspects of the state space representation.

The state space model provides a convention about how to relate input to output for linear models. For a state space model, we define $z(t)$ as the vector of system variables that describe the state of the system, $x(t)$ as the vector of inputs, and $y(t)$ as the vector of outputs.

Our goal is to identify matrices A, B, C and D such that:

$$\frac{dz(t)}{dt} = Az(t) + Bx(t)$$
$$y(t) = Cz(t) + Dx(t)$$

That is, A and B give the intrinsic system response and response to the inputs, and C and D convert the state variables to the output of interest. If the system variables are the outputs, then C = 1, and D = 0.

For this model, our input is the quantity of drug per time injected into the blood:

$$x(t) = d(t)$$

Our system is the amounts in the blood, so the ODEs translate to:

$$\frac{dz(t)}{dt} = \begin{bmatrix} dQ_B/dt \\ dQ_I/dt \end{bmatrix} = \begin{bmatrix} -k_1 - k_3 & k_2 \\ k_1 & -k_2 \end{bmatrix} \begin{bmatrix} Q_B \\ Q_I \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \end{bmatrix} d(t) = Az(t) + Bx(t)$$

This gives us $A = \begin{bmatrix} -k_1 - k_3 & k_2 \\ k_1 & -k_2 \end{bmatrix}$ and $B = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$. Our output is the concentration of drug in the blood, because this can be measured directly and determines the therapeutic and toxic effects:

$$y(t) = C_B = \frac{Q_B}{V_B} = \begin{bmatrix} \frac{1}{V_B} & 0 \end{bmatrix} \begin{bmatrix} Q_B \\ Q_I \end{bmatrix} + [0]d(t)$$

This gives us $C = \begin{bmatrix} \frac{1}{V_B} & 0 \end{bmatrix}$ and $D = [0]$.

In Matlab, we can define the four matrices, and then define the system described by them using the "ss" command:

```
A=[-k1-k3, k2;k1, -k2];B=[1;0]; C=[1/VB, 0]; D = 0;
PKmod = ss(A,B,C,D);
```

Finally, we can convert this state space model to a transfer function model if we wish using the "tf" command.

```
PKtf = tf(PKmod);
```

And if we want to know the values for the polynomial coefficients (for the parameters used), we can do this with the "tfdata" command:

```
[num,den] = tfdata(PKtf);
```

This returns two matrices of polynomials. If your H(s) is a scalar, then:

```
den = den{1,1}; num = num{1,1}
```

You can then analyze the stability of your state space model with the roots command, but we will also learn a new way.

Stability Analysis of State-Space Models

The state space representation can be used directly to address the stability and steady state gain of the system using linear algebra.

The stability of the system is determined by the eigenvalues of the A. Recall that the eigenvalues of A are the solutions λ to the equation, $\det(A - \lambda I) = 0$. Indeed, this equation will always be identical to the characteristic equation of the transfer function. Thus, the eigenvalues are identical to the roots of the characteristic equation of the transfer function. You can obtain the numeric values of the eigenvectors, given specific parameters, using the command:

```
lambda = eig(A)
```

For our PK system, $A = \begin{bmatrix} -k_1 - k_3 & k_2 \\ k_1 & -k_2 \end{bmatrix}$, and we assume parameter values $k_1 = 1.0417, k_2 = 0.5, and\ k_3 = 0.3$. The eig(A) command returns eigenvalues -1.7563 and -0.0854. Thus, the PK system is stable, as expected, since all the drug will eventually be excreted through the kidneys.

For a small matrices, the eigenvalues can easily be obtained analytically using the determinant.

Recall that for a 2D matrix, $\det \begin{bmatrix} a & b \\ c & d \end{bmatrix} = \begin{vmatrix} a & b \\ c & d \end{vmatrix} = ad - bc$.

Thus, for a 2D system with $A = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$, the eigenvalues α satisfy the equation:

$$\left| \begin{bmatrix} a & b \\ c & d \end{bmatrix} - \begin{bmatrix} \alpha & 0 \\ 0 & \alpha \end{bmatrix} \right| = 0$$

$$\begin{vmatrix} a - \alpha & b \\ c & d - \alpha \end{vmatrix} = (a - \alpha)(d - \alpha) - bc = \alpha^2 - (a + d)\alpha + ad - bc = 0$$

This can be solved using the quadratic formula, to give: $\alpha = \frac{1}{2}\left(a + d \pm \sqrt{(a - d)^2 + 4bc}\right)$. For our PK model, you can thus calculate analytically that:

$$\alpha = \frac{1}{2}\left(-k_1 - k_3 - k_2 \pm \sqrt{(-k_1 - k_3 + k_2)^2 + 4k_2k_1}\right)$$

We can check the math on this by calculating

```
alpha1 = 1/2*(-k1-k2-k3 + sqrt((-k1-k3+k2)^2+4*k2*k1))
alpha2 = 1/2*(-k1-k2-k3 - sqrt((-k1-k3+k2)^2+4*k2*k1))
```

using the same values for the k's as we used above with the command `lambda = eig(A)`

You may recall that an eigenvector v that corresponds to the eigenvalue λ satisfies the equation

$$Av = \lambda v$$

You obtain the eigenvalues and eigenvectors simultaneously, by using the commands:

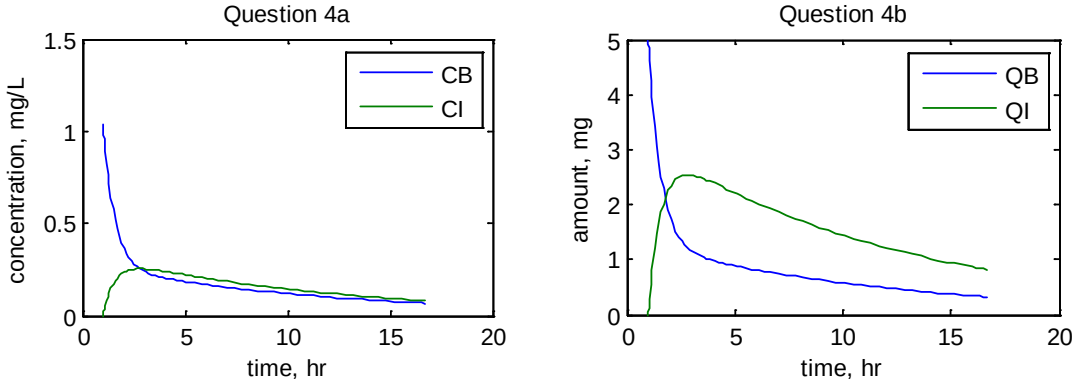
```
[V,D] = eig(A); alpha = diag(D);
```

With two output values, the eig command returns a diagonal matrix, with the eigenvalues on the diagonal, so the diag command extracts the vector of eigenvalues. The V matrix is a matrix with the ith column providing the eigenvector for the ith eigenvalue.

For the PK system, this gives:

```
V =
   -0.7698   -0.3698
    0.6383   -0.9291
D =
   -1.7563         0
         0   -0.0854
```

The eigenvectors tell you how the system approaches its steady state value. For example, you may have noticed that the PK system exhibits a rapid decay during which the concentrations in the two compartments are close to equilibrium (although the quantities are not), then a slow decay where the relative concentrations remain the same:



The slow decay reflects the smaller eigenvalue (-0.085); the time constant for this decay is 1/0.085 = 11.7 hours. Because the smaller eigenvalue is listed second, the eigenvector that corresponds to it is the second column of V. The magnitude of the eigenvectors is irrelevant, since they are always normalized to one. However, the 'direction' of the vector gives you the relative rate of change of the different variables during that slow decay. That is, -0.3698/-0.9291=0.398, which is the same as the ratio of slope near the end of the simulated time. The first eigenvector has opposite signs for the two components, consistent with the fact that one variable increases while the other decreases at early time points.

Steady state solution of state space models.

To obtain the steady state solution of a state space model, simply set all derivatives to zero. This converts each ODE to an algebraic equation, for which it is generally possible to find a solution. (or multiple solutions, for nonlinear models.) This should provide the same result as calculating the steady state solution using Y(0) in the transfer function representation.

Consider our PK model.

$$\frac{dz(t)}{dt} = Az(t) + Bx(t)$$
$$y(t) = Cz(t) + Dx(t)$$

For a steady state solution, we need a constant input, so we let $x(t) = x^0$, so our steady state requirement is $0 = Az_{ss} + Bx^0$, or $z_{ss} = -A^{-1}Bx^0$. Then $y_{ss} = Cz_{ss} + Dx^0$. These can be calculated from the state space matrices using MATLABs simple commands for matrix algebra.

For the PK system, $A = \begin{bmatrix} -k_1 - k_3 & k_2 \\ k_1 & -k_2 \end{bmatrix}$ and $B = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$. You might recall that the inverse of a matrix $A = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$ is $A^{-1} = \frac{1}{ad-bc}\begin{bmatrix} d & -b \\ -c & a \end{bmatrix}$. Thus:

$$z_{ss} = -A^{-1}Bx^0 = -\frac{\begin{bmatrix} -k_2 & -k_2 \\ -k_1 & -k_1 - k_3 \end{bmatrix}\begin{bmatrix} 1 \\ 0 \end{bmatrix}}{k_2(k_1 + k_3) - k_2 k_1}x^0 = \frac{\begin{bmatrix} k_2 \\ k_1 \end{bmatrix}}{k_2 k_3}x^0 = \begin{bmatrix} \frac{1}{k_3} \\ \frac{k_1}{k_2 k_3} \end{bmatrix}x^0$$

That is, if we dose a patient with a continuous infusion of x^0 =1 mg/hr, the amount in the blood will reach a steady state of $\frac{x^0}{k_3} = \frac{1\ mg*hr^{-1}}{0.3\ hr^{-1}} = 3.33\ mg$, while the interstitium will reach $\frac{x^0 k_1}{k_2 k_3} = \frac{1\ mg*hr^{-1}*1.0417\ hr^{-1}}{0.5\ hr^{-1}*0.3\ hr^{-1}}$ =6.9 mg. We really want to know the concentration in the blood, so this is our $y(t) = Cz(t) + Dx(t)$, with $C = \begin{bmatrix} \frac{1}{V_1} & 0 \end{bmatrix}$ and $D = [0]$ since the input dose and the interstitial drug only affect the blood concentration by their effects on the amount in the blood. Thus, $y_{ss} = -CA^{-1}B = \begin{bmatrix} \frac{1}{V_B} & 0 \end{bmatrix} z(t) = \begin{bmatrix} \frac{1}{V_B} & 0 \end{bmatrix}\begin{bmatrix} \frac{1}{k_3} \\ \frac{k_1}{k_2 k_3} \end{bmatrix} = \frac{1}{V_B k_3}$. Thus, if we dose with 1 mg/hr, we get a steady state concentration of $\frac{1\ mg*hr^{-1}}{4.8L*\ 0.3\ hr^{-1}} = 0.69\ mg/L$ of drug in the blood. Since this is a linear system, the perturbation in output is proportional to the perturbation in input. Moreover, the set point is clearly zero if there is no input, so the output is proportional to input, and we can calculate how much to dose the patient to obtain a desired concentration of drug in the blood. Finally, you may want to verify this and learn about the transient response by running the time-dependent simulation to completion.

Complete Time-Dependent solution of state space models.

You can solve the state space model using an ODE solver, and using the vector form of the derivative definition, such as `dy = A*y+B*x`, where `x` is the time-dependent input function. This is exactly what you did in lab last week, except that you are using the matrix form instead of writing out each equation. Alternatively, you can solve the state space model that you defined with the ss commands, using the linear systems commands such as impulse and step.

Bifurcation and Sensitivity Analysis

As parameters change, the system behaviors change. Some changes in parameters cause incremental effects, which we can quantify with sensitivity analysis. Other changes cause dramatic qualitative effects, such as a switch between a stable and unstable system, or whether the system oscillates. The characterization of these sudden switches is called bifurcation analysis. Understanding the responses of engineered systems to changes in parameters is an important aspect of engineering design, while understanding these responses in biological systems is important to physiology, pathology, and therapy.

To perform bifurcation analysis, identify parameters required for the Real or Imaginary components of the roots/eigenvalues to equal zero. This is a bifurcation point. Then analyze the

neighboring parameter values to understand the nature of the bifurcation. This is most powerful if it can be done analytically, but in some cases, you may need to do this numerically.

To verify and illustrate your conclusions about bifurcation, you may want to plot trajectories for parameter conditions at and on either side of a bifurcation.

To perform a sensitivity analysis, we need to identify the outcome of interest, and then calculate how sensitive this outcome is to changes in one or more parameters. If Y is our outcome of interest, and P is the parameter of interest, then the sensitivity of Y to P is: $S = \partial Y/\partial P$. If Y and P have different units, then the magnitude of this calculation of absolute sensitivity is meaningless except in the context of the units. This makes it meaningless to compare the sensitivity to two parameters that have different units, such as force and distance. We thus often express $\partial Y/\partial P$ in a fractional form. That is, what fractional change in output results from a fractional change in input? The fractional sensitivity is $S_f = \frac{\partial Y/Y}{\partial P/P} = \frac{\partial Y/\partial P}{Y/P}$. A parameter is considered insensitive if the absolute value of the fractional sensitivity is much less than 1 $(|S_f| \ll 1)$, sensitive if it is on the order of one $(|S_f| \sim 1)$, and highly sensitive if it is much greater than 1 $(|S_f| \gg 1)$. In general, the sensitivity and fractional sensitivity will depend on the specific values of some or all parameters, as we will see below.

For a numeric calculation, we ask how a small change in a parameter (e.g. 1% so $\partial P/P = 0.01$) affects the output, then calculate ∂Y or $\partial Y/Y$, and divide. When calculating the sensitivity this way, be aware that the code you write to calculate the outcome may involve assumptions about the numeric solution. For example, you may be assuming that the last point in the trajectory is at equilibrium, or that the maximum value of a variables gives the height of a single peak, so you need to make sure that your assumption is valid. e.g. by a graphic inspection.

To illustrate your conclusions about sensitivity, you can plot trajectories for several values of a parameter, plot the outcome versus the parameter value, or provide the sensitivity or fractional sensitivity for outcomes and parameters of interest.

Example of bifurcation and sensitivity analysis in the PK system:

In the PK system, we showed that the eigenvalues are:

$$\alpha_i = \frac{1}{2}\left(-k_1 - k_3 - k_2 \pm \sqrt{(-k_1 - k_3 + k_2)^2 + 4k_2k_1}\right)$$

To find the bifurcation point, we set $\alpha_i = 0$, and manipulate the resulting equation to see if we can find requirements on the parameters, which in this case are $k_1, k_2, and\ k_3$.

$$k_1 + k_3 + k_2 = \pm\sqrt{(-k_1 - k_3 + k_2)^2 + 4k_2k_1}$$

$$(k_1 + k_3 + k_2)^2 = (-k_1 - k_3 + k_2)^2 + 4k_2k_1$$

$$k_1^2 + k_2^2 + k_3^2 + 2k_1k_2 + 2k_1k_3 + 2k_2k_3 = k_1^2 + k_2^2 + k_3^2 - 2k_1k_2 + 2k_1k_3 - 2k_2k_3 + 4k_2k_1$$

$$4k_1k_2 + 4k_2k_3 = 4k_2k_1$$

$$k_2 = 0\ or\ 4k_1 + 4k_3 = 4k_1$$

$$k_2 = 0\ or\ k_3 = 0$$

Thus, the system is marginally stable if $k_2 = 0$ or $k_3 = 0$. We can confirm this analysis with intuition by looking at the diagram. If $k_1 = 0$, then the drug is fully cleared by the kidneys. However, if $k_2 = 0$, then drug is trapped in the interstitial fluid, and if $k_3 = 0$, the drug equilibrates between the blood and interstitial fluid but is not cleared through the kidneys. Thus, both conditions maintain the perturbation in one or both variables.

We learned from calculating the eigenvalues that the system was stable for one set of positive parameter values, and here we see that the only bifurcations occur at $k_2 = 0$ and $k_3 = 0$, so the system must be stable for all sets of positive parameter values. This conclusion makes sense intuitively from the system structure, since all compartments in the system should drain empty if there is no input regardless of parameter values. We can show that the system is unstable for $k_2 < 0$ or $k_3 < 0$, but this has no physiological meaning. In this case, each bifurcation was defined in terms of on a single parameter, but bifurcations often occur at conditions that satisfy an expression of multiple parameters, such as $\frac{\beta}{\gamma} > 1$ or $a + b < c$.

Next we ask how the concentration of drug in the patient's blood after a continuous infusion will depend on the parameter values for that patient. Our outcome is the steady state gain: $Y = \frac{1}{V_B k_3}$, and we want to know fractional sensitivity to P, V_B, V_I, k_3 (where P is permeability, not a general parameter value). By taking partial derivatives of $Y = \frac{1}{V_B k_3}$, we see:

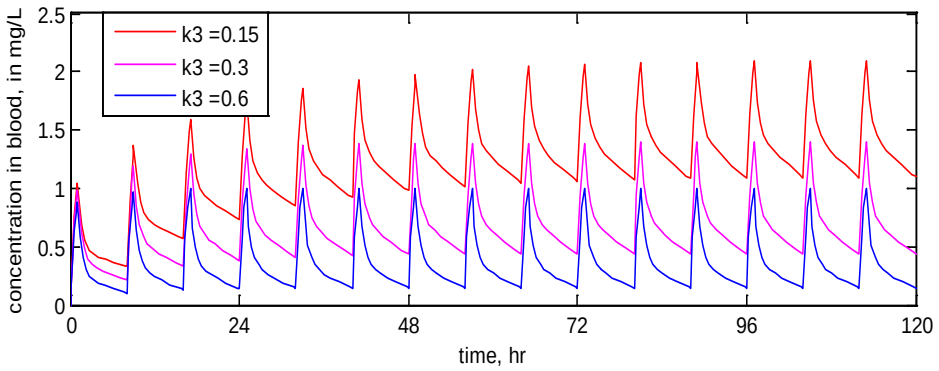
$$\frac{\partial Y}{\partial P} = 0, \frac{\partial Y}{\partial V_B} = -\frac{1}{V_B^2 k_3}, \frac{\partial Y}{\partial V_I} = 0, \frac{\partial Y}{\partial k_3} = -\frac{1}{V_B k_3^2}$$

For V_I and P, the fractional sensitivity is also zero. For blood volume, the fractional sensitivity is:

$$\frac{\partial Y / \partial V_B}{Y / V_B} = -\frac{\frac{1}{V_B^2 k_3}}{\frac{1}{V_B k_3} / V_B} = -1$$

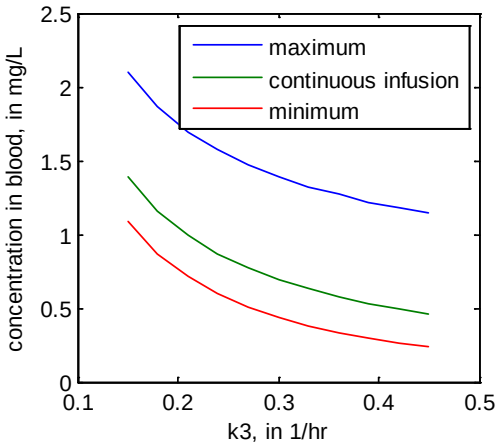
By symmetry, the fractional sensitivity for clearance rate k3 should be the same.

Thus, the steady state levels of drug in the blood during continuous infusion is insensitive to the volume in the interstitium and insensitive to the permeability, but sensitive to the volume in the blood and the clearance rate, in that it decreases proportionally to both. Indeed, we could see that directly from the formula for steady state gain. This analysis explains why doctors estimate the blood volume from height, weight and gender if they are prescribing drugs that have a narrow therapeutic window. Alternatively, doctors may simply measure blood levels of the drug and change the dosage accordingly.



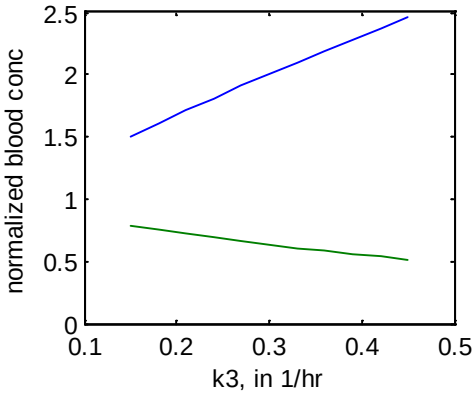
For convenience, we

would rather concentrate the dose into several injections per day, so we want to perform sensitivity analysis on our ability to maintain drug levels within the therapeutic window during such a dosing protocol. We plot the time-dependent solution for blood concentration below using SIMULINK with the transfer function form of the system that we calculated numerically, with a pulse train as the source. Our pulse train injects for 1 hour every 8 hours. We perform these calculations using half and twice the previous value of k3. As expected, the blood levels decreases as k3 increases.



To understand better the effect of k3 on the minimum and maximum blood levels, we calculate these over the last half of our simulation (since the minimum value is zero at the start, we want to wait until this transient response to initial conditions is past.) We can do this for multiple values of k3, in order to obtain a smooth curve as shown here, and also include the analytically calculated steady state value for a continuous infusion. We see that the patient with faster clearance will need more drug to stay above a therapeutic threshold, while one with slower clearance would need less to stay below the toxic threshold.

We can also perform a calculation of sensitivity, by decreasing k3 by 1%. When we do this, the max value increases from 1.3910 to 1.3893, or a gain of 0.52%, and the min value increases from 0.4404 to 0.4468, or a gain of 1.45%. Thus the fractional sensitivity is $\frac{\partial Y/Y}{\partial k_3/k_3}$ is -0.52 and -1.45 for the max and min value respectively.



Finally, we ask what happens if we alter the dosage according to the calculated steady state gain. To see this, in the figure to the right, we plot the min (green) and max (blue) values, normalized by dividing by the steady state gain. The patient with faster clearance has larger swings in blood concentrations. We could only correct this with more frequent dosing. Thus, a patient with higher clearance would require more frequent dosing to stay within the therapeutic window, which makes sense.

Partial sample code used to generate these plots:

```
K3 = [k3*0.5 k3, k3*2]
colors = {'r','m','b','c','g'};
figure(1)
for i = 1:length(K3)
    k3 = K3(i); A=[-k1-k3, k2;k1, -k2];
    PKmod = ss(A,B,C,D); PKtf = tf(PKmod);
    [num,den] = tfdata(PKtf); num = num{1,1}; den = den{1,1};
    tout = sim('lecture4PKsim');
    Qb = PKout.Data;
```

```
    plot(tout,Qb,colors{i}); hold on;
    maxQb(i) = max(Qb);
    minQb(i) = min(Qb(floor(3*end/4):end));
    description{i} = strcat('k3 = ',num2str(k3));
end
legend(description{1},description{2},description{3});
xlabel('time, hr'); ylabel('concentration in blood, in mg/L');
figure(2); plot(K3,maxQb,K3,minQb);
```

Summary of week 2

- The state space representation of a system is $\frac{dz(t)}{dt} = Az(t) + Bx(t)$ and $y(t) = Cz(t) + Dx(t)$. z(t) are the system variables, x(t) are inputs, and A and B are a constant coefficient matrix and vector, respectively. y(t) are the outputs of interest, and C and D are a constant coefficient matrix and vector that tell us how the outputs relate to the system variables and inputs.
- The eigenvalues of the system matrix A, which we call α_i, are the same as the roots of the characteristic equation $den(s) = 0$. The real component of these gives the stability of the system and the imaginary components indicate whether the system oscillates. (see lecture 3 for details).
- The inverse of the roots/eigenvalues α_i give the characteristic time constants of the system which tell how quickly it decays or oscillates, and can be used to identify the time frame needed for the simulation.
- For the state space representation, the steady state gain can be calculated from $G_{ss} = -CA^{-1}B$.
- For the state space representation, the steady state solution can be calculated from $z_{ss} = -A^{-1}Bx^0$ and $y_{ss} = Cz_{ss} + Dx^0$.
- We can simulate linear systems using the linear system toolbox, by creating a ss or tf model, and can interconvert these. We can also use SIMULINK to simulate the response of systems defined in both ways to various input functions.
- Bifurcations are identified by solving for parameter conditions that result in zero values of the roots/eigenvalues: $\alpha_i = 0$.
- Fractional sensitivity is determined by calculating the fractional change in output for a fractional change in a parameter: $S_f = \frac{\partial Y/Y}{\partial P/P}$.
- A parameter is considered <u>insensitive</u> if the absolute value of the fractional sensitivity is much less than 1 $(|S_f| \ll 1)$, <u>sensitive</u> if it is on the order of one $(|S_f| \sim 1)$, and <u>highly sensitive</u> if it is much greater than 1 $(|S_f| \gg 1)$.
- In general, the sensitivity and fractional sensitivity will depend on the specific values of some or all parameters.
- We should always verify our solutions by comparing numeric solutions to the ODEs, analytic calculations, and/or intuition.