1. Numerous population studies of the flour beetle, *Tribolium*, have been done where the amount of flour was limited. These studies were matched with mathematical models. In this problem you explore one of the structured models for some different parameters.

a. The population of *Tribolium* is divided into larva, pupal, and adult numbers. Both the larva and adults cannibalize other larva and adults when the populations become crowded. In the discrete dynamical systems studies we explored Hassell's model, which simulates the crowding effects. Below is one version of an age-structured model for *Tribolium*:

$$\begin{aligned} L_{n+1} &= \frac{bA_n}{(1 + c_{ea}A_n + c_{el}L_n)^4}, \\ P_{n+1} &= s_l L_n, \\ A_{n+1} &= \frac{P_n}{(1 + c_{pa}A_n)^4} + s_a A_n, \end{aligned}$$

which has the population limiting terms from the rational Hassell functions. For this part, take the birth parameter, $b = 15$, survival parameters, $s_l = 0.4$ and $s_a = 0.5$, and population limiting parameters, $c_{ea} = 0.002$ (adults eating eggs), $c_{el} = 0.005$ (larva eating eggs), and $c_{pa} = 0.03$ (adults eating pupa). Simulate this system starting with only two adults $A_0 = 2$ ($L_0 = 0$ and $P_0 = 0$). List the populations at $n = 10$, 20, 30, 50, and 100.

b. Find all (non-negative) equilibria for this system. Linearize this system about the equilibria. Write your Jacobian matrices for each of the equilibria and find the eigenvalues for these matrices. Briefly discuss the stability about these equilibria and describe the limiting age-structure of the population.

c. Let $b = 30$ and repeat Parts a and b. Repeat the simulations and the calculations for the equilibria and eigenvalues.

d. One should see a stability change between Parts b and c with only a change in the parameter b. Find the bifurcation value of b, where this stability changes. (**Hint**: Create a program to find the positive equilibrium as b varies, substitute this into your Jacobian matrix, and find the eigenvalues. A bisection comparing the magnitude of the largest eigenvalue can fairly rapidly be made to converge to the bifurcation value. The bisection can even be done by hand for a few figures of accuracy provided you have a good equilibrium program and Jacobian/eigenvalue program.)

2. A fair die has an equal probability of each number occurring on a roll. This problem examines what happens when a pair of dice are loaded by weighting one die to favor a six and another die loaded to favor a one. (This is often done by putting lead filings in one side of the die.) Assume that for one die it is weighted to favor a six twice as much as the sides two, three, four, and five, and the opposite side with a one having half the probability of the side numbers. That is if p is the probability of a two, three, four, or five, then $2p$ is the probability of a six, and $0.5p$ is the probability of a one. Assume that a second die is weighted oppositely to favor a one with p again the probability of a two, three, four, or five, $2p$ is the probability of a one, and $0.5p$ is the probability of a six.

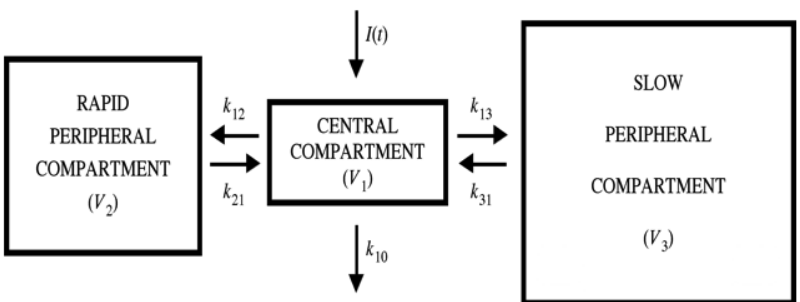
a. Roll these two dice 10,000 times and determine the frequency of the dice totalling 7. Compare this to the expected value for fair dice.

b. Roll the dice twice and add these results. Perform this operation 10,000 times and determine the average and standard deviation of these sums. Compare this mean and standard deviation to what one would obtain with fair dice.

3. A study including 6 dogs were injected with the opioid ^{3}H-fentanyl citrate. Below is a table[1] of the time evolution of plasma concentration (ng/ml), where t is in min.

t	C	t	C	t	C
5	7.42	60	0.95	240	0.24
7	3.87	90	0.67	270	0.21
11	3.21	120	0.52	300	0.20
13	2.80	150	0.42	330	0.17
22	1.86	180	0.32	360	0.16
30	1.46	210	0.27		

We model the fentanyl blood concentration with a three-compartment model.



a. Use the diagram above to create a 3D model for the concentrations in the three compartments:

$$\begin{aligned} \dot{C}_1 &= f_1(C_1, C_2, C_3), & C_1(0) &= I_0, \\ \dot{C}_2 &= f_2(C_1, C_2, C_3), & C_2(0) &= 0, \\ \dot{C}_3 &= f_3(C_1, C_2, C_3), & C_3(0) &= 0. \end{aligned}$$

Find the appropriate functions, f_1, f_2, and f_3 illustrated in the diagram. This diagram assumes that the drug is not metabolized (or lost) inside either peripheral compartment and that the transfer rates are linear and proportional to the kinetic parameters, k_{ij}. This last assumption means, for example, that C_1 leaves the blood compartment to enter the slow peripheral compartment at a rate $k_{13}C_1$, so enters the slow peripheral compartment at the same rate. Assume that the drug is injected into the blood stream, so the $I(t)$ in the diagram simply enters as the initial condition, $C_1(0) = I_0$.

b. Since the experiment only measures blood concentration, explain how your model for the disappearance of fentanyl in Part a can be reduced to a single equation of the form:

$$C_1(t) = a_1 e^{-\lambda_1 t} + a_2 e^{-\lambda_2 t} + a_3 e^{-\lambda_3 t}, \tag{1}$$

[1] Murphy, M. R., Olson, W. A., and Hug, Jr, C. C., Pharmacokinetics of ^{3}H-Fentanyl in the dog anesthetized with enflurane, *Anethesiology*, **50**: 13-19, 1979

which is fit to the data. The parameter λ_1 represents the *rapid distribution phase*, λ_2 represents the *middle distribution phase*, and λ_3 represents the *terminal/elimnation phase*. Connect the solution of your differential equation to the form of the solution above, including why $\lambda_i > 0$. (The general case to show $\lambda_i > 0$ is challenging and not expected for you to show. However, the special cases where either $k_{12} = k_{21}$ and $k_{13} = k_{31}$ or $k_{12} = k_{21} = k_{13} = k_{31} = k$ are readily manageable. Furthermore, physical arguments can justify this result.)

c. The model (1) is simply three decaying exponentials, which we want fit to the data. Begin by plotting the data with the vertical axis having a logarithmic scale, and we see that the data are not in a straight line. However, squinting enough one can see roughly three linear sections over the ranges $t \in [0, 22]$, $t \in [30, 150]$, and $t \in [180, 360]$. We introduce a fitting procedure called **exponential peeling**, where piecewise we fit (1) with decaying exponentials. This procedure is outlined below:

1. Start with the *terminal/elimination phase* and find best fitting exponential model (using a linear least squares fit to the logarithms of the concentrations) with $t \in [180, 360]$ (only these data).
2. Subtract this model from the remaining data.
3. With the *middle distribution phase* find the best fitting exponential model (again using a linear least squares fit to the logarithms of the concentrations) with $t \in [30, 150]$.
4. Once again subtract this model from the remaining modified data.
5. With the *rapid distribution phase* find the best fitting exponential model with $t \in [0, 22]$.
6. Combine these three fits to obtain your model (1).

Give the complete 3-compartment model using this exponential peeling procedure. Include the sum of square errors for this model. In addition, compute the sum of square errors between the logarithms of the data and the logarithm of this model.

d. Start with the 6 parameters from the exponential peeling (3 coefficients and 3 exponents) and use MatLab's `fminsearch` (Nonlinear Least Squares fit) to find the best fitting parameters for the 3-compartment model. This procedure fails with a direct least squares fit of the model to the data, so perform a least squares best fit of the logarithm of the model to the logarithm of the data. Write this best fitting model with its parameters and give the sum of square errors. Write a brief paragraph comparing the exponential peeling model to the nonlinear fit model. Give at least one strength and one weakness of the two models.

4. The HW assignment examined a repression model with delays. This problem examines a modified negative feedback system with delays, where the second reaction has an induction of the production of x_2 by the product of the first reaction. Consider the system of delay differential equations given by:

$$\begin{aligned}
\frac{dx_1(t)}{dt} &= \frac{a_1}{1 + k_1 x_3^2(t-r)} - b_1 x_1(t), \\
\frac{dx_2(t)}{dt} &= \frac{a_2 x_1^2(t)}{1 + k_2 x_1^2(t)} - b_2 x_2(t), \\
\frac{dx_3(t)}{dt} &= a_3 x_2(t) - b_3 x_3(t),
\end{aligned}$$

where a_i are production rates, b_i are decay constants, k_i are kinetic constants, and r is the delay for the various processes.

a. Consider the undelayed case, where $r = 0$. Let all $a_i = 1$, $b_i = 0.5$, and $k_i = 1$. Find all equilibria. Linearize the above system of ordinary differential equations about each of the equilibria. Find the eigenvalues at each equilibrium and discuss the stability for this model.

b. With the same kinetic parameters the equilibria are the same for the delayed model. Linearize the above system of delay differential equations about each of the equilibria. Write the characteristic equation for finding the eigenvalues at each equilibrium. Consider the cases when $r = 1$ and $r = 5$. For each of these cases, create a program to map the perimeter of rectangle in the complex plane bounded by $0 \leq x \leq 4$ and $-3 \leq y \leq 3$ in the counterclockwise direction into the complex image space using the characteristic equation. Using the argument principle, determine how many, if any, eigenvalues are contained in the rectangle described above. With this information, discuss the stability of the delay differential equation for each of these delays. If unstable, include what the analysis says about the period of oscillation.

c. Let $\lambda = i\omega$ in the characteristic equation and find where the Hopf bifurcation occurs. Give the value of both r and ω at the bifurcation.