You may use Mathematica or Maple for matrix operations where appropriate, and for problems that call for integration of ODEs.

On each problem show sufficient detail so that we can judge your results fairly, and make sure your work is neat, easily read, and understandable. We will not spend time trying to decipher illegible writing.

We will count the best five of the six problems for each person.

(1) Consider the following system for the bifurcation of periodic solutions, written in polar coordinates.

\[
\begin{align*}
\frac{dr}{dt} &= r\left(p_1 + p_2 r^2 - r^4\right) = r\Phi(r) \\
\frac{d\theta}{dt} &= 1
\end{align*}
\]

Here \( p_1 \) and \( p_2 \) are independent real parameters.

(a) Construct an invariant region in the \( r - \theta \) plane.

(b) Determine all the steady states and periodic solutions and their stability.

(c) Plot the curves on which bifurcations occur in the \( p_1 - p_2 \) plane and indicate the type of solution(s) in each distinct region.

(d) Plot a bifurcation diagram showing \( r \) as a function of \( p_2 \) for a fixed \( p_1 > 0 \), and indicate all bifurcation points.

(2) Consider the three-dimensional system

\[
\begin{align*}
\frac{dx}{dt} &= y \\
\frac{dy}{dt} &= -z \\
\frac{dz}{dt} &= -z + x + y \quad \epsilon << 1
\end{align*}
\]

(a) Determine the slow manifold, sketch the manifold in \( \mathbb{R}^3 \), and determine whether or not it is attracting.

(b) Analyze the flow on the slow manifold. In particular, find all steady states and determine their stability.

(c) Determine the asymptotic behavior of all solutions on the slow manifold.

(d) Solve (2) directly by computing eigenvalues and eigenvectors for \( \epsilon = 0.01 \) and verify the results of steps (a)-(c). Plot the trajectory in three space for various choices of the initial condition.

(3) Consider the simple three-step autocatalytic chain

Here \( \phi \) is a constant input, the \( x_i \) are the amounts of each species and the \( p_i \)'s and \( d_i \)'s are positive constants.
(a) Write the governing equations in the form
\[
\frac{dx}{dt} = \mathcal{R}(x)
\] (3)
where \( \mathcal{R} \) is the vector of reaction rates.

(b) Show that the set \( \{ x \in R_3 | x_i \geq 0 \} \) is invariant under (3). (i.e. show that if \( x_i(0) \geq 0 \) \( i = 1, 2, 3 \); then \( x_i(t) \geq 0 \) \( \forall \ t \geq 0 \).

(c) Construct a compact (closed, bounded) invariant set for (3).

(d) Determine the steady state(s) and analyze their stability.

(4) Consider an enzyme that has two binding sites that follow the kinetic scheme
\[
S + \frac{k_2}{k_{-1}} C_1 \rightarrow_k E + P
\] (4)
\[
S + C_1 \frac{k_3}{k_{-3}} C_2 \rightarrow_k C_1 + P
\] (5)
where \( C_1 = ES \) and \( C_2 = ESS \).

(a) Write out the governing equations for all variables and state all conservation conditions that apply.

(b) Show that a the solution remains non-negative if \( S(0) > 0 \) and \( E(0) > 0 \).

(c) Nondimensionalize the equations for \( S, C_1, C_2 \) and the time using suitable definitions for the scaling constants. You should choose them similar (but not identical) to those used in the notes, so that you arrive at a single small parameter that is the ratio of time scales.

(d) Find the equation for the evolution of the product on the outer (slow) time scale.

(5) Consider the gene expression model shown in (a) below, wherein messenger RNA is transcribed to a protein that represses transcription of the DNA.

\[ \begin{array}{ccc}
\text{(a)} & \text{(b)} \\
\end{array} \]

Let \( x \) be the concentration of RNA and \( y \) the concentration of protein, and consider the model equations.
\[
\frac{dx}{dt} = k_0 S \frac{K_2^2}{K_d^2 + y^2} - k_1 x
\] (6)
\[
\frac{dy}{dt} = k_2 x - k_3 E_T \frac{y}{K_m + y}
\] (7)

(a) Set \( x = \alpha u \ y = K_d v \) and \( \tau = \lambda t \) and choose \( \alpha \) and \( \lambda \) to arrive at the dimensionless form
\[
\frac{du}{d\tau} = \frac{1}{1 + v^2} - u
\] (8)
\[
\frac{dv}{d\tau} = \Omega u - \chi \frac{v}{1 + \gamma v}
\] (9)
Show explicitly that for your choice of $\alpha$ and $\lambda$ the resulting parameters $\Omega, \chi$ and $\gamma$ are dimensionless. Assume that all are strictly positive.

(b) Sketch the nullclines in the positive quadrant of the $u$-$v$ plane, show that the positive quadrant is invariant, and show that solutions remain bounded for any initial point $(u_0, v_0)$.

(c) Show that there is exactly one steady state in the positive quadrant and that it is asymptotically stable.

(Hint: Consider using Descartes’ rule of signs.)

(d) Consider the more realistic model shown in (b) in which mRNA is transported to the cytosol and translated there, and then protein is transported into the nucleus to inhibit transcription. Modify the system (7) and (8) above by adding the transport terms, each of which is first-order in the corresponding concentration. Assume that both mRNA and protein are degraded in the cytosol as well, and write the full set of four equations in dimensional form with suitable definitions of the new parameters.

(e) Show, using the Routh-Hurwitz criterion, that a Hopf bifurcation may occur in the 4D system as the transport rate of mRNA is varied.

(f) Choose a set of parameters for which the steady state is unstable, integrate the 4D system numerically, and show the four species as a function of time.

(6) (a) Consider the graph shown below.

\[ \text{A} \rightarrow 1 \quad \text{B} \quad 2 \rightarrow \text{C} \]

Let $X = (a, b, c)^T$ be the state vector giving the ‘amounts’ of $A, B, \text{ and } C$. Suppose that the rate functions $f_i(a, b, c)$ for the three steps are non-negative functions. Write the evolution equation for the amounts in the form

$$\frac{d}{dt}X = KR$$

where $K$ is a suitable matrix and $R$ is a vector, and show that $R$ must vanish component-wise at a steady state. Would the conclusion change if we reverse the direction of the step between A and C? Justify your answer.

(b) Consider the following graph, which shows the possible state transitions for healthy and cancerous (mutated) cells.

\[ \text{Normal Cell} \quad \text{Mutated Cell} \quad \text{Dead Cell} \]

(i) Write out the governing equations for the three populations assuming general rate laws. State and justify particular forms that you might use for the rate laws.

(ii) Analyze the steady state(s) and their stability assuming that proliferation and other processes are first order. Analyze both the case in which $d_N = d_M = 0$ and the case in which they are very small.
(iii) Determine conditions under which the normal cells win \((N >> M)\).

(iv) Determine conditions under which the cancerous cells win \((M >> N)\).

(v) Discuss how realistic this model is, and indicate other factors that may play a role.