COURSE DESCRIPTION: A monotone dynamical system is just a dynamical system, arising from an ode, delay equation, or pde, for which a comparison principle holds so that “bigger” initial states give rise to bigger future states in some sense. Monotone systems of odes are often called “cooperative systems” and their time-reversals are called “competitive systems”. Such systems have SIMPLER dynamics than general ode systems: for cooperative systems the typical solution converges to equilibrium-periodic orbits and chaotic invariant sets may exist but their domains of attraction are insignificant; a Poincare-Bendixson theory holds for THREE dimensional competitive systems. Moreover, these systems arise naturally in biological settings such as population dynamics, gene regulatory networks, epidemiology, and physiology. Even when systems are not monotone, they can sometimes be imbedded in larger systems that are monotone from which useful information may be derived. Cyclic feedback systems, related to monotone systems, often arise in neural networks or gene regulatory networks. Such systems will also be considered in the course.

I intend to present the basic results of the theory (proofs are given in references below). The main focus will be the application of the theory to systems of ordinary, delay, and partial differential equations, such as:

1. 3-species-Lotka-Volterra Competition Model

2. Competition between 2 bacterial strains in spatially heterogenous bio-reactors

3. Testosterone Dynamics in vivo

4. Virus Dynamics in vivo

5. The Repressilator: Two genes whose protein products repress each others transcription

6. $S \rightarrow E \rightarrow I \rightarrow R$ Epidemic Model
7. Chemical Reaction Networks

8. 2-sex $S \rightarrow I \rightarrow S$ Sexually Transmitted Disease model

9. Antibiotic treatment of a bacterial infection

10. Microbial growth in a gradostat

REQUIREMENTS: Homework and presentation of homework problems or presentation of a project.

REFERENCES:


• SIAM Review Article, on my web page below syllabus.

• Differential Inequality appendix to ”Theory of the Chemostat”, on my web site.


Topics

• Perron-Frobenius Theory

2
- irreducible matrix,
- incidence graph of matrix
- $A$ quasi-positive $\Rightarrow e^{At} \geq 0$, $t \geq 0$
- dominant eigenvalue-positive eigenvector
- Linear Compartmental Models-Mean Residence Time

- Partial order relations and Cones
- Monotonicity Properties of Maps
- Kamke-Müller Theorem for ODEs
- Competitive & Cooperative Systems of ODEs
  - Planar Periodic Competitive & Cooperative Systems of ODEs
  - Generic convergence to equilibrium for Cooperative Systems
  - Poincaré-Bendixson Theory for 3D competitive & cooperative system
  - The Carrying Simplex and Invariant Manifolds
- Monotone Cyclic Feedback Systems
- Competitive & Cooperative Systems of Delay Equations
- Reaction Diffusion Equations-Traveling Waves
1 Partial Orders & Monotone Maps

We want a partial order relation on a normed vector space $X$. A partial order, compatible with vector space operations and the metric, must satisfy:

(1) $x \leq x$

(2) $x \leq y \& y \leq x \Rightarrow x = y$

(3) $x \leq y, \ y \leq z \Rightarrow x \leq z$

(4) $x \leq y, \ u \leq v \Rightarrow x + u \leq y + v$

(5) $x \leq y, \ a \in \mathbb{R}_+ \Rightarrow ax \leq yz$

(6) $x_n \leq y_n, \ x_n \rightarrow x, \ y_n \rightarrow y \Rightarrow x \leq y$

Of course, these should hold for all values of the indicated variables. Note that (4) implies: $x \leq y \Rightarrow −y \leq −x$.

The set of **positive vectors**

$$C = \{ x \in X : x \geq 0 \}$$

is often called a **cone**. We can see from the above that $C$ has the following properties:

(a) $0 \in C$

(b) $C + C = C$

(c) $\mathbb{R}_+ C = C$

(d) $C$ is closed.

(e) $C \cap (−C) = \{ 0 \}$

Most importantly:

$$x \leq y \Leftrightarrow y − x \in C \quad (1)$$

If set $C$ has properties (a)-(e) and we define $\leq$ by (1), then $\leq$ satisfies (1)-(6). There is a one-to-one relation between partial order relations on $X$ satisfying (1)-(6) and cones $C$ satisfying (a)-(e).
Example 1: $X = \mathbb{R}^n$, $C = \mathbb{R}^n_+$, and $x \leq y \iff x_i \leq y_i$, $1 \leq i \leq n$.

Example 2: $X = \mathbb{R}^n$, given $1 \leq k \leq n$

$$C_k = \{x : x_i \geq 0, 1 \leq i \leq k, x_i \leq 0, k + 1 \leq i \leq n\}$$

so

$$x \leq_{C_k} y \iff x_i \leq y_i, 1 \leq i \leq k, x_i \geq y_i, k + 1 \leq i \leq n.$$

Example 3: $X = C([0,1],\mathbb{R})$, $C = \{f \in X : f(t) \geq 0, 0 \leq t \leq 1\}$, and $f \leq g \iff f(t) \leq g(t), 0 \leq t \leq 1$.

A map $F : (X, \leq_X) \to (Y, \leq_Y)$ is **monotone** if

$$x_1 \leq_X x_2 \Rightarrow F(x_1) \leq_Y F(x_2)$$

Since our interest is dynamics, we will be primarily interested in maps from a space into itself.

Since $X$ is a normed linear space $L(X) = \{T : X \to X : T \text{ is continuous and linear}\}$ is also a normed linear space. If $X$ is ordered by cone $C$, define

$$L(X)^+ = \{T \in L(X) : T(C) \subset C\}$$

A linear operator $T$ in $L(X)^+$ takes positive vectors to positive vectors. We call $T$ a **positive linear operator** and write $T \geq 0$ (see below).

If $X = \mathbb{R}^n$ and $C = \mathbb{R}^n_+$ then $L(X)$ consists of the $n \times n$ matrices and the positive linear operators $L(X)^+$ consist of the nonnegative matrices.

A linear operator generates a monotone map if and only if it is positive.

**Proposition 1.** $T \in L(X)$ defines a monotone map $x \to Tx$ if and only if $T \in L(X)^+$.

**Proof.** If $x \leq y$ we want to show that $Tx \leq Ty$, or equivalently, $0 \leq Ty - Tx = T(y - x)$. Since $y - x \geq 0$ and $T \in L(X)^+$, this last inequality holds. \qed

It is interesting and useful that $L(X)^+$ is typically a cone in $L(X)$.
Proposition 2. \( L(X)^+ \) satisfies all the properties (a)-(e) of being a cone in \( L(X) \) except possible (e). Property (e) holds if \( X = \overline{C - C} \).

Proof. It is easy to check that the 0 operator belongs to \( L(X) \), that sums of positive operators are positive operators, and the positive multiples of positive operators are positive operators. If \( \{T_n\} \) is a sequence of positive operators and \( T_n \to T \), then for any \( x \geq 0 \) we have \( Tx = \lim_n T_n x \). Since \( T_n x \in C \) and \( C \) is closed, we see that \( Tx \geq 0 \). If \( T \) belongs to both \( L(X)^+ \) and \( -L(X)^+ \) and \( x \geq 0 \), then \( Tx \geq 0 \) and \( -Tx \geq 0 \) so \( Tx \leq 0 \leq Tx \). Consequently, \( Tx = 0 \), and since \( x \geq 0 \) is arbitrary, we have shown that \( TC = 0 \). To show \( T = 0 \) we must show \( TX = 0 \). If every vector can be written as the difference of two positive vectors, \( X = C - C \), this is obvious. You should be able to see it also holds if \( C - C \) is dense in \( X \). \qed

In \( X = \mathbb{R}^2 \) with the usual order generated by \( C = \mathbb{R}^2_+ \) we have
\[
(-3, 2) = (0, 2) - (3, 0)
\]
and, obviously \((0, 2), (3, 0) \in C\). This can clearly be generalized:
\[
\mathbb{R}^n = \mathbb{R}^n_+ - \mathbb{R}^n_-
\]

Lemma 1. If \( T : [0, 1] \to L(X)^+ \) is continuous then \( \int_0^1 T(t)dt \in L(X)^+ \).

Proof. The integral is a limit as \( N \to \infty \) of partial sums
\[
S_N = \sum_{n=1}^N T(n/N) \frac{1}{N}
\]
Since each \( S_N \in L(X)^+ \) and \( L(X)^+ \) is closed, the result follows. \qed

Here is the main result. Just like in ordinary calculus, a function is monotone (increasing) if its derivative is positive. We just need to interpret "positive derivative" as "positive operator".

Theorem 1. Let \( F : X \to X \) be continuously differentiable on the normed linear space \( X \) ordered by cone \( C \). If for every \( x \in X \), \( F'(x) \in L(X)^+ \), then \( F \) is monotone with respect to \( \leq_C \).
Proof. Use the above Lemma, the definitions, and 

\[ F(y) - F(x) = \int_0^1 \frac{d}{dt} F(ty + (1 - t)x) dt = \int_0^1 F'(ty + (1 - t)x) dt (y - x) \]

\[ \square \]

We remark that it is not necessary for the above proof that \( F \) is defined on all \( X \). It suffices for \( F \) to be defined on \( D \subset X \) and \( D \) to have the convexity property that \( ty + (1 - t)x \in D \) for \( 0 \leq t \leq 1 \) whenever \( x, y \in D \) and \( x \leq y \).

Example: \( X = \mathbb{R}^2 \) with the competitive order generated by the fourth (southeast) quadrant \( Q = \{ (x, y)^T : x \geq 0, y \leq 0 \} \). Recall \( u \leq_Q v \) means \( v \) is southeast of \( u \). Check that \( L(X)^+ \) consists of matrices of the following type

\[
\begin{pmatrix} + & - \\ - & + \end{pmatrix}
\]

since

\[
\begin{pmatrix} + & - \\ - & + \end{pmatrix} \begin{pmatrix} + \\ - \end{pmatrix} = \begin{pmatrix} + \\ - \end{pmatrix}
\]

Consider the mapping \( F : \mathbb{R}_+^2 \to \mathbb{R}_+^2 \) given by

\[ F(x, y) = \left( \frac{r_1 x}{1 + x + c_{12} y}, \frac{r_2 y}{1 + c_{21} x + y} \right) \]

where \( r_i, c_{ij} > 0 \). It is easy to verify that its Jacobian matrix has the requisite sign structure for \( (x, y) \in \mathbb{R}_+^2 \). Therefore \( F \) is monotone with respect to the “southeast ordering”.

2 Graph theoretic issues related to Competitive and Cooperative systems

The test for a \( C^1 \) system \( x' = f(x) \), whose jacobian is sign stable and sign symmetric on a convex domain, to be cooperative with respect to some partial order \( \leq_m \), where \( m \in \{0, 1\}^n \), and \( \leq_m \) is defined by

\[ x \leq_m y \iff (-1)^{m_i} x_i \leq (-1)^{m_i} y_i, \ 1 \leq i \leq n \]
requires solving the equations
\[ m_i + m_j = s_{ij}, \quad \text{mod } 2, \ i < j \] (2)
for \( m \in \{0, 1\}^n \) where
\[ s_{ij} = \begin{cases} 
1 & \frac{\partial f_i}{\partial x_j}(x) + \frac{\partial f_j}{\partial x_i}(x) < 0, \text{ some } x \\
0 & \frac{\partial f_i}{\partial x_j}(x) + \frac{\partial f_j}{\partial x_i}(x) > 0, \text{ some } x
\end{cases} \]

Note that the number of equations is exactly the number \( e \) of edges in the signed influence graph for the system \( x' = f(x) \), with \((-1)^{s_{ij}}\) being the sign on the edge joining vertex \( i \) to vertex \( j \). When \( f_i \) is independent of \( x_j \) and vice-versa, we have no edge for vertex \( i \) to vertex \( j, \ i \neq j \).

If we rewrite (2) in matrix-vector format as
\[ Gm = s \] (3)
then \( G \) is an \( e \times n \) matrix whose rows \( g_1, g_2, \cdots, g_e \) characterize the edges of the graph since each contains precisely two ones in the components corresponding to the vertices connected by that edge. We can identify the graph with the matrix. This is not the usual influence matrix used to codify the graph which is an \( n \times n \) and contains a one in the \( i - j \)-th entry if an edge connects vertex \( i \) and vertex \( j \).

As an example, consider the influence graph below

```
+  
/  
x1 ————> x2
 
|         |
|         |
|x4 ————> x3
|         |
|         |
+  
```
The corresponding equations are
\[
\begin{align*}
m_1 + m_2 &= 0 \\
m_1 + m_4 &= 1 \\
m_2 + m_3 &= 1 \\
m_2 + m_4 &= 1 \\
m_3 + m_4 &= 0
\end{align*}
\]
and the matrix-vector form of the equations is
\[
\begin{pmatrix}
1 & 1 & 0 & 0 \\
1 & 0 & 0 & 1 \\
0 & 1 & 1 & 0 \\
0 & 1 & 0 & 1 \\
0 & 0 & 1 & 1
\end{pmatrix}
\begin{pmatrix}
m_1 \\
m_2 \\
m_3 \\
m_4
\end{pmatrix}
= s
\]
where \(m = (m_1, m_2, m_3, m_4)^T\) and \(s = (0, 1, 1, 0)^T\). We may readily solve these equations to get \(m = (0, 0, 1, 1)\) or \(m = (1, 1, 0, 0)\). Consequently, the cone is given by \(K = \{x : x_1, x_2 \geq 0, x_3, x_4 \leq 0\}\).

We will always assume our influence graph is connected (path between any two vertices). Disconnected influence graphs correspond to disconnected systems; for example if there are two connected components in the influence graph then our system has the form
\[
x' = f(x), \quad y' = g(y)
\]
In this case, we deal with each subsystem separately.

We begin by finding the kernel of \(G\) which we view as finding all partial orders \(\leq_m\) that are preserved when the system has only positive edges: \(s = 0\). The answer is that only the standard order \(\leq\) corresponding to \(m = 0\) or its opposite work.

**Lemma 2.** If the graph is connected then the null space of \(G\) is \(N(G) = \{\vec{0}, \vec{1}\}\) where \(\vec{0}\) is the \(n\)-vector of zeros and \(\vec{1}\) is the \(n\)-vector of ones.

**Proof.** Obviously \(\{\vec{0}, \vec{1}\} \subset N(G)\). Suppose \(Gm = 0\) and there is a proper subset \(A\) of \(\{1, 2, \ldots, n\}\) such that \(m_i = 0, i \in A\) and \(m_i = 1, i \in A^c\). But from the equations (2) we see that there cannot be an edge from a vertex in \(A\) to one in \(A^c\) since such an edge joining \(j \in A\) to \(k \in A^c\) yields the equation \(m_j + m_k = 0 + 1 \neq 0\). We have a contradiction to the connectedness of the influence graph. \(\square\)
If $h \in \{0, 1\}^e$ then $q = h^T g = \sum_{i=1}^e h_i g_i$ may be viewed formally as the union of edges $g_i$ for those $i$ for which $h_i = 1$. As such, $q$ is a union of paths. It vanishes if and only if each vertex appears an even number of times in each path. But a path in which each vertex appears an even number of times is a loop. This means that $q$ is a disjoint union of loops. This is the key idea in the following.

**Lemma 3.** Let $h \in \{0, 1\}^e$. Then $h^T G = 0$ if and only if the formal union $q = \sum_{i=1}^e h_i g_i$ is a disjoint union of loops in the influence graph.

Our main result is the following.

**Proposition 3.** (2) has a solution $m \in \{0, 1\}^n$ if and only if

$$h^T s = 0, \forall h \ni h^T G = 0$$

Equivalently, if and only if each loop has an even number of $-$ edges.

**Proof.** The standard solvability criteria for $Gm = s$ apply: vector $s$ must be orthogonal to $N(G^T)$. Since each $h$ for which $h^T G = 0$ corresponds to a formal union of loops in the graph and $h^T s$ counts the number of $-$ edges in the loop, the parity assertion follows.

Proposition 3 says our system is cooperative if and only if every loop has an even number of negative edges. Our example apparently derives from a cooperative system.

To test for a competitive system, we see if the time-reversed system $x' = -f(x)$ is cooperative. As the influence graph of this system is related to the influence graph of $x' = f(x)$ by having all signs flipped, we must focus on the positive edges of the influence graph of $x' = f(x)$ as they become the negative edges of the influence graph of $x' = -f(x)$. Every loop of the influence graph of $x' = f(x)$ must have an even number of $+$ edges for the system to be competitive relative to some order relation $\leq_m$. 


3 Homework Problems

Exercise 1. Let $A \geq 0$ be a square matrix and denote by $a_{ij}^{(q)}$ the $ij$-th entry of $A^q$ where $q = 1, 2, \cdots$. Show $a_{ij}^{(q)} > 0$ if and only if there is a directed path with $q$ edges from vertex $j$ to vertex $i$ in $G(A)$.

Exercise 2. Let $A$ be a quasipositive square matrix with $s(A) < 0$. Show that

$$-A^{-1} = \int_0^\infty e^{At} dt > 0$$

Exercise 3. Let $A$ be a square matrix and $G(A)$ its directed graph. Vertex $i$ is equivalent to vertex $j$ if either $i = j$ or there is a directed path from $i$ to $j$ AND a directed path from $j$ to $i$. This defines an equivalence relation on the vertices: the equivalence class of vertex $i$ is denoted as usual by $[i]$—the collection of all vertices that one can get to from $i$ and get back from. Now lets define a new graph with vertices these equivalence classes. A directed edge goes from class $[i]$ to class $[j]$ if there is a directed edge in $G(A)$ from SOME member of $[i]$ to SOME member of $[j]$. Observe that this graph has NO LOOPS!! It also has at least one vertex with no edges to it! I think it is called a TREE. If $A$ is irreducible then this graph is trivial—only one vertex!

This construction tells us how to permute the standard basis vectors so that the new matrix obtained from $A$ is in ”canonical form” with irreducible submatrices down the main diagonal. Try this out on

$$
\begin{pmatrix}
0 & 0 & 1 & 0 \\
0 & 0 & 1 & 1 \\
1 & 0 & 0 & 0 \\
1 & 1 & 0 & 0
\end{pmatrix}
$$

This construction is related to Conley’s Fundamental Theorem of Dynamical Systems. See p 404 of “Dynamical Systems”, 2nd ed., Clark Robinson.

Exercise 4. Consider $n$ tanks, each containing growth medium of volume $V$, in a linear array with nearest neighbor two-way flows between vessels:

$$
\Rightarrow \bigcirc \Rightarrow \bigcirc \Rightarrow \cdots \Rightarrow \bigcirc \Rightarrow
$$

The circles represent the tanks and the arrows denote the flow between tanks and between the first and last tanks and the environment. Each arrow represents a flow of rate $F$ in units of volume per unit time (e.g., gallons per
minute) of growth medium. The material of interest here is a nutrient supplied at concentration $N^0$ (weight per unit volume) in the inflow from the external environment to the left-most tank. The inflow from the environment to the right-most vessel contains only growth medium with no nutrient. Each tank is assumed to be well-mixed so its contents are homogeneously distributed. The outflow from the two end-tanks to the environment contains just the well-mixed contents of each vessel. We want to determine equations for

$$N_i(t) = \text{concentration of nutrient in tank } i \text{ at time } t$$

(a) Write down the linear system of equations for $N_i$ in case $n = 2$. Show that it is a linear compartmental system with inputs. Calculate $s(A)$ and determine the Mean Residence Time for nutrient in the gradostat. Find the steady state values of $N_i$. Why is this called a gradostat?

(b) Can you repeat (1) for the general case $n \geq 2$?

**Exercise 5.** Particularly in pharmacology, it is common to administer drugs in a periodic fashion: take 2 tablets every 6 hours. Therefore it is natural to consider compartmental systems

$$x' = Ax + r(t)$$

where $r(t + T) = r(t)$ is periodic of period $T$ and, of course, nonnegative $r(t) \geq 0$. Suppose that $A$ is a compartmental matrix as described in the pdf on my web site with $s(A) < 0$. Show that there is a unique $T$-periodic solution $x(t) \geq 0$. Hint: by the variation of constants formula

$$x(t) = e^{AT}x(0) + \int_0^t e^{A(t-s)}r(s)ds.$$  

We want to find initial data $x(0)$ so that $x(0) = x(T)$, which will guarantee that the corresponding solution is $T$-periodic. Therefore we seek a solution $x(0)$ of the equation

$$x(0) = e^{AT}x(0) + \int_0^T e^{A(T-s)}r(s)ds$$

Show that there exists a unique solution $x(0) \geq 0$ and provide a formula for it.
Exercise 6. Consider the discrete-time Juvenile-Adult population model

\[ J_{n+1} = \frac{r A_n}{b + A_n} \]
\[ A_{n+1} = p A_n + q J_n \]

where \( 0 \leq p, q < 1 \), \( 0 < q \) are survival probabilities and \( r, b > 0 \) have to do with adult fecundity. Find all fixed points and determine their stability. In the case \( p = 0 \), find all period-two points and determine their stability. Hint: They are fixed points of \( P^2 \) where \( P \) is the map defined by the right side.

A 2 \times 2 matrix \( A \) has \( |\lambda| < 1 \) for all \( \lambda \in \sigma(A) \) if and only if

\[ |\text{tr}(A)| < 1 + \det A < 2 \]

and \( |\lambda| > 1 \) for some eigenvalue if any one of the three inequalities

\[ \text{tr}(A) > 1 + \det A, \quad \text{tr}(A) < -1 - \det A, \quad \det A > 1 \]

holds.

When \( q = 0 \) and \( qr > b \), the fixed point \((J, A) = (0, 0)\) is unstable and \((J^*, A^*) = (rq - b)(1, q^{-1})\) is asymptotically stable. In addition, there is the period-2 orbit \( \{(J^*, 0), (0, A^*)\} \) where \( J^*, A^* \) are the components of the positive fixed point. The period-2 orbit is of saddle type since the eigenvalues of the Jacobian of the second iterate map are \( rq/b > 1 \) and \( b/rq < 1 \). This periodic orbit attracts all orbits starting at points \((J, A) \neq (0, 0)\) where either \( J = 0 \) or \( A = 0 \). You can easily check this. All orbits starting at points \((J, A)\) with \( J > 0 \) and \( A > 0 \) converge to the positive fixed point!

Exercise 7. Consider two competing species in an seasonally changing environment

\[ x'_1 = x_1[e(t) - a(t)x_1 - b(t)x_2] \]
\[ x'_2 = x_2[f(t) - c(t)x_1 - d(t)x_2] \]

where \( a, b, c, d, e, f \) are \( T \)-periodic, continuous functions: \( a(t) = a(t + T) \) for all \( t \). Assume that \( a, b, c, d \geq 0 \) for all \( t \) making this a “competitive system”.

Let \( P : \mathbb{R}^2_+ \rightarrow \mathbb{R}^2_+ \) be the “period map” defined by \( P(x(0)) = x(T) \).

(a) Show that \( P \) is a competitive map in the sense that \( x(0) \leq_C y(0) \) implies that \( P(x(0)) \leq_C P(y(0)) \) where \( \leq_C \) is the “southeast ordering”. 

13
(b) Show that $P$ satisfies $\det P'(x) > 0$, $x \in \mathbb{R}^2_+$ and that $P$ is injective. Recall Abel’s formula (Thm 2.3 Brauer & Nohel)! Therefore $P$ satisfies $(H+)$ from the notes.

(c) Show that if $\int_0^T e(t) dt \neq 0$ and $a(t)$ is not everywhere zero then there can be at most one $T$-periodic solution $(x_1(t), 0)$ satisfying $x_1(t) \geq 0$ and $x_1$ not identically zero. Hint: let $y(t) = 1/x_1(t)$.

Recall that $P(x_0) = x(T, x_0)$ so $P'(y) = \frac{\partial x}{\partial x_0}(T, y)$. We know that $\Phi(t) = \frac{\partial x}{\partial x_0}(t, y)$ is the $2 \times 2$ fundamental matrix for

$$z' = \frac{\partial F}{\partial x}(t, x(t, y))z$$

satisfying $\Phi(0) = I$. Here, $F(t, x)$ denotes the right hand side of our competing species system, $x = (x_1, x_2)^T$. By Abel’s formula

$$\det \Phi(t) = \det \Phi(0) \exp\left(\int_0^t \text{trace}A(s) ds\right)$$

where $A(s) = \frac{\partial F}{\partial x}(s, x(s, y))$. In any case, $\det \Phi(T) = \det P'(y) > 0$.

Exercise 8. A model of bacteria growing in a two-vessel gradostat on a nutrient $S$ is given by the following equations (which have been scaled to simplify them) in which $S_i$ denotes scaled nutrient concentration in vessel $i$ and $u_i$ denotes scaled bacterial density in vessel $i$, $i = 1, 2$.

$$S'_1 = 1 - 2S_1 + S_2 - f(S_1)u_1$$
$$S'_2 = S_1 - 2S_2 - f(S_2)u_2$$
$$u'_1 = u_1f(S_1) - 2u_1 + u_2$$
$$u'_2 = u_2f(S_2) - 2u_2 + u_1$$

The specific growth rate of the organism is

$$f(S) = \frac{mS}{a + S}$$

The leading 1 in the equation for $S'_1$ signifies fresh nutrient entering vessel one of the gradostat at scaled concentration one.

This system has an equilibrium $(S_1, S_2, u_1, u_2) = (2/3, 1/3, 0, 0)$ called the “washout equilibrium” because all bacteria are washed out.
(1) Show that $\mathbb{R}_+^4$ is positively invariant for the system: solutions that start nonnegative stay nonnegative in the future.

(2) Show that if $S(0) \leq (2/3, 1/3)$, then $S(t) \leq (2/3, 1/3)$ for $t \geq 0$.

(3) Show that every solution with $S(0) \leq (2/3, 1/3)$ converges to the washout equilibrium if the Jacobian matrix there has all eigenvalues with negative real part.

For part (3), we assume the $4 \times 4$ variational equation at the washout state $z' = Az$, where

$$A = \begin{pmatrix} -2 & 1 & f'(2/3) & 0 \\ 1 & -2 & 0 & f'(1/3) \\ 0 & 0 & f(2/3) - 2 & 1 \\ 0 & 0 & f(1/3) - 2 \\ \end{pmatrix}$$

has all eigenvalues with negative real part. Note that this holds precisely when the $2 \times 2$ block $B$ in the lower right has negative eigenvalues since the upper left $2 \times 2$ block has negative eigenvalues. Now, by part (2), since if $S(0) \leq (2/3, 1/3)$, then $S(t) \leq (2/3, 1/3)$ for $t \geq 0$ we have

$$u_1' \leq u_1 f(2/3) - 2u_1 + u_2$$
$$u_2' \leq u_2 f(1/3) - 2u_2 + u_1$$

or

$$u' \leq Bu$$

If $\bar{u}$ satisfies

$$\bar{u}' = B\bar{u}, \quad \bar{u}(0) = u(0)$$

then we may compare: $0 \leq u(t) \leq \bar{u}(t)$, $t \geq 0$. But $B$ has negative eigenvalues so $\bar{u}(t) \to 0$ as $t \to \infty$. It follows that $u(t) \to 0$ too since it is squeezed between 0 and $\bar{u}(t)$! It is now not hard to see that $S(t) \to (2/3, 1/3)$ at $t \to \infty$. One way is to notice that $v_1 = S_1 + u_1$ and $v_2 = S_2 + u_2$ satisfy

$$v' = \begin{pmatrix} -2 & 1 \\ 1 & -2 \\ \end{pmatrix} v + \begin{pmatrix} 1 \\ 0 \\ \end{pmatrix}$$

and thus $v(t) \to (2/3, 1/3)$ as $t \to \infty$. 

15
Exercise 9. Perhaps the simplest model of antibiotic treatment of a bacterial infection is the following system

\[
\begin{align*}
B' &= rB(1 - B/K) - cAB \\
A' &= d(A^0 - A) - cAB
\end{align*}
\]

where \(B\) denotes bacteria (cells/ml) and \(A\) denotes antibiotic (gms/ml). Bacteria grow logistically in the absence of antibiotic: \(r, K > 0\). Antibiotic is supplied at concentration \(S^0\), \(d > 0\) is removal rate, and antibiotic kills at rate proportional to its concentration (\(c > 0\)).

(a) Show that the system is competitive in the first quadrant.

(b) Show that solutions are bounded. Therefore, all solutions converge to equilibrium since the system is competitive.

(c) Find all equilibria and describe the global behavior of all solutions.

The trivial equilibrium \((B, A) = (0, A^0)\) is locally asymptotically stable if \(cA^0 > r\) and unstable when \(cA^0 < r\). Positive equilibria \((B, A)\) must satisfy \(0 < B < K\) and \(0 < A < A^0\). Letting \(x = B/K \in (0, 1)\) we find that \(x\) satisfies

\[
p(x) = x^2 + \left(\frac{d}{cK} - 1\right)x + \frac{d}{cK}(A^0 - \frac{1}{c}) = 0.
\]

Case I: \(cA^0 - r < 0\). In this case \(p(0) < 0 < p(1)\) and there is a unique root \(x \in (0, 1)\). Therefore there is a unique positive equilibrium \((0, A^0) \leq_K (B^*, A^*)\) in this case (here \(\leq_K\) is the southeast order). Using the equilibrium conditions, the Jacobian at \((B^*, A^*)\) is

\[
\begin{pmatrix}
-rB^*/K & -cB^* \\
-cB^* & -dA^*
\end{pmatrix}
\]

which has negative trace and positive determinant. Thus \((B^*, A^*)\) is asymptotically stable. It attracts all solutions not on the A-axis.

Case II: \(cA^0 - r > 0\). In this case \(p(0), p(1) > 0\) so we expect zero, one or two roots of \(p(x) = 0\) in \((0, 1)\). \(p'(x) = 0\) gives \(x_0 = \left(1 - \frac{d}{cK}\right)/2\) which belongs to \((0, 1)\) only if \(d < cK\). If \(d \geq cK\) or if \(d < cK\) and \(p(x_0) > 0\) then there are no other equilibria. Note that \(p(x_0) = \frac{d}{K}(A^0 - \frac{1}{c}) - \frac{1}{4}(1 - \frac{d}{cK})^2\). In this case, \((0, A^0)\) is globally asymptotically stable since it is the only equilibrium and every solution converges to equilibrium.
If $d < cK$ and $d = \frac{d}{K} (\frac{A^0}{r} - \frac{1}{c}) - \frac{1}{4} (1 - \frac{d}{cK})^2 < 0$ (in addition to $cA^0 - r > 0$) then there are two positive steady states $(B_1, A_1), (B_2, A_2)$ where

$$(0, A^0) \ll_K (B_1, A_1) \ll_K (B_2, A_2)$$

$(0, A^0)$ and $(B_2, A_2)$ are asymptotically stable and $(B_1, A_1)$ is a saddle point whose stable manifold forms the separatrix boundary between the basins of attraction of the two attractors. This case is biologically interesting because a small inoculum of bacteria (initial data near $(0, A^0)$) results in eradication of the infection while a larger inoculum of bacteria will end up at $(B_2, A_2)$ with the infection not contained!

**Exercise 10.** Decide whether each of the following is competitive, cooperative, or neither. Cooperative (competitive) should be interpreted in the broad sense that there is some ordering, generated by an orthant, that is preserved in the future (past). Find the appropriate ordering in each case. Unless otherwise specified, the domain of each system is the positive cone.

1. A model of two genes which interact with each other:

$$
x_1' = \beta_1 (y_1 - x_1)
\]
$$

$$
y_1' = \alpha_1 f_1 (x_2) - y_1
\]
$$

$$
x_2' = \beta_2 (y_2 - x_2)
\]
$$

$$
y_2' = \alpha_2 f_2 (x_1) - y_2
\]

where $f_i > 0$ satisfy $f_1' \neq 0$, $f_2' \neq 0$. $x_i = \text{mRNA}$, $y_i = \text{protein product of gene } i$. Consider the different cases depending on the signs of the interaction terms $f_i'$.

2. $S \rightarrow E \rightarrow I \rightarrow R$ epidemic model.

$$
S' = \mu N - \mu S - \beta IS/N
\]

$$
E' = \beta IS/N - (\mu + \gamma) E
\]

$$
I' = \gamma E - (\mu + \alpha) I
\]

Here the domain is $\{(S, E, I) : S, E, I \geq 0, S + E + I \leq N\}$.

3. Virus dynamics model:

$$
T' = \delta - \alpha T - kVT
\]

$$
(T^*)' = -\beta T^* + kVT
\]

$$
V' = -\gamma V + N \beta T^* - kVT
\]
Here, \( V \) denotes virus density, \( T \) denotes target cell density, and \( T^* \) denotes infected target cell density in the blood.

(4) A two-sex, two strain STD model boils down to the following equations:

\[
\begin{align*}
\dot{I}^m_i & = -\sigma^m_i I^m_i + \alpha^m_i (p^m - I^m_i - I^m_2) I^f_i \\
\dot{I}^f_i & = -\sigma^f_i I^f_i + \alpha^f_i (p^f - I^f_i - I^f_2) I^m_i, \quad i = 1, 2
\end{align*}
\]

\( I^f_i \) denotes the females infected with strain \( i \) of the disease. The domain is \( \{(I^m_1, I^m_2, I^f_1, I^f_2) \geq 0 : I^x_1 + I^x_2 \leq p^x, \ x = m, f \} \).

Exercise 11. Let \( x_0 \) be an equilibrium of the cooperative system \( x' = f(x) \), \( x \in D \) where \( f \in C^1(D) \) and \( D \subset \mathbb{R}^n \) is open and convex. For simplicity, let’s assume the cooperativity is relative to the usual ordering since we can always change variables so that this is so.

(a) Show that \( \{x \in D : x \geq x_0\} \) and \( \{x \in D : x \leq x_0\} \) are positively invariant.

(b) If \( s = s(Df(x_0)) > 0 \) and \( Df(x_0)v = sv \) where \( v \gg 0 \), which holds for example if \( Df(x_0) \) is irreducible, show that \( f(x_0 + rv) \gg 0 \) for all sufficiently small \( r > 0 \). This means, by our convergence theorem, that \( x(t, x_0 + rv) \to p \) for some equilibrium \( p \gg x_0 \) provided this solution has compact orbit closure in \( D \). A similar conclusion \( f(x_0 - rv) \ll 0 \) holds implying that \( x(t, x_0 - rv) \to q \ll x_0 \). Hint: Taylor series with remainder!

(c) Suppose that \( x_0, y_0 \) are two equilibria satisfying \( x_0 \ll y_0 \) with \( s(Df(x)) > 0 \), \( x = x_0, y_0 \). If the Jacobian is irreducible at these two points, show that there must exist an equilibrium \( p \) with \( x_0 \ll p \ll y_0 \).

(d) If \( s = s(Df(x_0)) < 0 \) and \( Df(x_0)v = sv \) where \( v \gg 0 \), show that for all small \( r > 0 \) we have \( f(x_0 + rv) \ll 0 \ll f(x_0 - rv) \). Therefore, the solution starting at any point of the box

\[ [x_0 + rv, x_0 - rv] = \{y : x_0 - rv \leq y \leq x_0 + rv\} \]

converges to \( x_0 \).
Part (b) simply uses the definition of differentiability of \( f \):

\[
f(x_0 + rv) = f(x_0) + rDf(x_0)v + o(r) = r[sv + O(r)] \gg 0
\]

where the last inequality holds for all small \( r > 0 \) since all components of \( sv \) are positive and \( O(r) \to 0 \) as \( r \to 0^+ \).

Part (c) uses that \( x(t, x_0 + rv_1) (x(t, y_0 - rv_2)) \) is increasing (decreasing) in all its components, where \( v_i \gg 0 \) is the eigenvector associated with \( Df(x_0) \) for \( i = 1 \) and \( Df(y_0) \) for \( i = 2 \), and \( r > 0 \) is sufficiently small that \( x_0 + rv_1 \ll y_0 - rv_2 \). Therefore:

\[
x_0 \ll x(t, x_0 + rv_1) \ll x(t, y_0 - rv_2) \ll y_0, \quad t > 1
\]

Since \( x(t, x_0 + rv_1) \nearrow p \) and \( x(t, y_0 - rv_2) \searrow q \) where \( p, q \) are (not necessarily distinct) equilibria by the convergence criterion, we conclude that:

\[
x_0 \ll p \leq q \ll y_0.
\]

Exercise 12. Consider the example graph in the section of these notes on Graph theoretic issues related to Competitive and Cooperative systems above. Find the set of vectors \( h \in \{0, 1\}^e \) such that \( h^T G = 0 \) and show that these \( h \) correspond to loops in the graph as stated in Proposition 3 of that section. Find \( m \) such that the system preserves the order relation \( \leq_m \) in forward time.

Exercise 13. The system

\[
\begin{align*}
x'_1 &= \frac{1}{1 + x_3^n} - \gamma x_1 \\
x'_2 &= x_1 - \gamma x_2 \\
x'_3 &= x_2 - \gamma x_3
\end{align*}
\]

arises in gene regulation (see my web page pdf on gene regulatory networks). Its domain is \( \mathbb{R}^3_+ \); \( \gamma > 0 \) and \( n > 0 \). Find conditions on \( \gamma \) and \( n \) for the existence of a periodic orbit.

See the pdf file on “gene regulatory networks” for answers.

Exercise 14. You et al. (Nature 428 22Apr 2004) build a gene circuit to control the density of E. coli. \( x_1 \) denotes bacterial density, \( x_3 \) denotes the density of a quorum sensing molecule emitted by these cells. As this molecule
builds up it activates a "killer" gene circuit for a protein $x_2$ which promotes programmed cell death in the bacteria. The model system is given by:

$$
x'_1 = k_1 x_1 (1 - x_1) - dx_1 x_2 \\
x'_2 = x_3 - \gamma_1 x_2 \\
x'_3 = x_1 - \gamma_2 x_3
$$

where all parameters are positive and $x \in \mathbb{R}^3_+$. Analyze the dynamics of this system as completely as you can. Can it have a periodic orbit?

Equilibria are $0$ and $p \gg 0$. $0$ is unstable and its stable manifold consists of the $x_1 = 0$ plane. $\mathbb{R}^3_+$ is positively invariant and orbits are bounded by a standard argument using differential inequalities. If $D = \{ x : x_i > 0, i = 1, 2, 3 \}$, then the Butler-McGehee lemma shows that every orbit that starts in $D$ has compact closure in $D$. $D$ contains only one equilibrium $p$. Our system is competitive and irreducible. The determinant of the jacobian $J$ at $p$ satisfies $\det J = -k_1 \gamma_1 \gamma_2 < 0$ so $J$ either has all eigenvalues with negative real part or precisely two with positive real part and one negative eigenvalue. We use Routh-Hurwicz test to show that the latter can occur. The characteristic polynomial $\lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_3 = 0$ satisfies $a_i > 0$ so the stability test fails if

$$
[a_1 a_2 - a_3] / \gamma_1 \gamma_2 = \left( \frac{k_1^2 \gamma_1 \gamma_2}{k_1 \gamma_1 \gamma_2 + d} + \gamma_1 + \gamma_2 \right) \left( \frac{k_1^2}{k_1 \gamma_1 \gamma_2 + d} + 1 \right) - k_1
$$

is negative. One can see that this holds, for example, if the $\gamma_i$ are sufficiently small since the product of the first two terms in parentheses goes to zero with $\gamma_i$. In this case, Prop. 6.1 of the notes on competitive and cooperative systems implies that the omega limit set of every orbit starting off the one-dimensional stable manifold of $p$ is a periodic orbit.

**Exercise 15.** Species $x$ competes with species $y$ but species $x$ has a refuge where it can hide from species $y$. We assume there are two habitats, species $y$ is restricted to habitat one but species two can wander between the two habitats. Here is the model system where $x_i$ denotes species $x$ in habitat $i$, same for $y$.

$$
x'_1 = r_1 x_1 (1 - ax_1 - by_1) + \delta(x_2 - x_1) \\
x'_2 = r_1 x_2 (1 - cx_2) + \delta(x_1 - x_2) \\
y'_1 = r_2 y_1 (1 - cx_1 - dy_1)
$$
Assume all parameters are positive. Is this a cooperative and irreducible system? If so what is the appropriate order relation? Determine the behavior of this systems as completely as you can. This should include the stability of all steady states and identifying subsets of their basin of attraction. There are several cases but you may assume that the determinant of the jacobian at each equilibrium is not zero!

**Exercise 16.** Species $x_1$ competes with species $x_2$ and species $x_3$ competes with species $x_2$ but species $x_1$ and $x_3$ do not interact.

\[
x_1' = r_1 x_1 (1 - x_1 - c_{12} x_2) \\
x_2' = r_2 x_2 (1 - c_{21} x_1 - x_2 - c_{23} x_3) \\
x_3' = r_3 x_3 (1 - c_{32} x_2 - x_3)
\]

where $r_i, c_{ij} > 0$. assume further that $c_{ij} < 1$ and $c_{21} + c_{23} < 1$

Is this a cooperative and irreducible system? If so what is the appropriate order relation? Determine the behavior of this systems as completely as you can. This should include the stability of all steady states and identifying subsets of their basin of attraction. You may assume that the determinant of the jacobian at each equilibrium is not zero!

In this and the previous problem, use our results that if two equilibria are related but there are no other equilibria in between them, then all trajectories starting at a point strictly between them converges to the stable equilibrium.

**Exercise 17.** A model of bacterial growth in the chemostat with delay between nutrient uptake and conversion to biomass is given by:

\[
S'(t) = 1 - S(t) - f(S(t)) x(t) \\
x'(t) = e^{-r} f(S(t-r)) x(t-r) - x(t)
\]

where $f(S) = m S / (a + S)$ and $x, S \geq 0$. Assume that $m / (1 + a) > e^r$ and $m, a, r > 0$. The factor $e^{-r}$ accounts for a suppression in growth rate due to substrate stored inside cells that washes out of the culture vessel before giving rise to new growth.

(a) Show that solutions corresponding to nonnegative initial data remain nonnegative.
(b) Show that \( u(t) = x(t) + e^{-r}S(t-r) \to e^{-r}, \ t \to \infty \).

(c) Using b., obtain a scalar delay equation satisfied by \( x(t) \), called the limiting equation. Change variables to let \( y(t) = e^{r}x(t) \) and write the equation using this variable. Notice that there is a biological restriction on the domain of this delay equation.

(d) Show that the limiting system generates a strongly monotone dynamical system. Describe the behavior of its solutions as completely as you can.

Exercise 18. Recall that \( x_0 \in X \) is a super-equilibrium (sub-equilibrium) for monotone semiflow \( \Phi : X \times [0, \infty) \to X \) if \( \Phi(x_0, t) \geq x_0, \ t \geq 0 \) (\( \Phi(x_0, t) \leq x_0, \ t \geq 0 \)). Monotonicity of \( \Phi \) then implies that \( t \to \Phi(x_0, t) \) is non-decreasing (non-increasing) and, if \( \{\Phi(x_0, t) : t \geq 0\} \) has compact closure in \( X \), that \( \Phi(x_0, t) \nearrow p \) (\( \Phi(x_0, t) \searrow p \)) for some equilibrium \( p \). Obviously, every equilibrium is both a sub-equilibrium and a super-equilibrium.

A point \( x_0 \in \mathbb{R}^n \) is a super-equilibrium for \( x' = f(x) \), where \( f \) satisfies the quasimonotone condition, if and only if \( f(x_0) \geq 0 \). This last condition is both necessary and sufficient (by convergence criterion from notes)!

How do we identify a super-equilibrium for the delay differential systems \( x'(t) = f(x(t), x(t-1)) \) where \( \frac{\partial f}{\partial x}(x, y) \) is quasi-positive and \( \frac{\partial f}{\partial y}(x, y) \geq 0 \)? Assume \( f : \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}^n \) is continuously differentiable. Recall that a super equilibrium must be a state so it must by a \( \phi \in C([-1, 0], \mathbb{R}^n) \).

(a) Given \( x_0 \in \mathbb{R}^n \), find sufficient conditions such that \( \phi = \hat{x}_0 \), the function identically equal to \( x_0 \), is a super-equilibrium and justify your conditions. Hint#1: try to reformulate the problem as one of positive invariance of a certain set; hint#2: consider the special case \( x_0 = 0 \); hint#3: make your conditions as weak as possible by using the above hypotheses on \( f \).

(b) In problem 17 (d) show that \( \hat{1} \) is a sub-equilibrium. Show that \( \{y_t(\hat{1}) : t \geq 0\} \) has compact closure in \( C([-r, 0], \mathbb{R}_+) \) and therefore \( y_t(\hat{1}) \searrow e \) for some equilibrium \( e \). Determine \( e \).
Exercise 19. The initial boundary value problem for \( u(x,t) \):

\[
\begin{align*}
    u_t &= d\Delta u + f(u), \ x \in \Omega, \ t > 0 \\
    0 &= \frac{\partial u}{\partial n}(x), \ x \in \partial\Omega \\
    u(x,0) &= u_0(x), \ x \in \Omega
\end{align*}
\]

where \( u_0 \in C(\overline{\Omega}, \mathbb{R}) \), generates a monotone semiflow \( \Phi(u_0,t) = u(\bullet,t) \). Here, \( n \) is the outer normal vector to the boundary of \( \Omega \subset \mathbb{R}^n \), assumed to be smooth, and \( \Omega \) is bounded.

(a) Let \( a \in \mathbb{R} \) and \( \hat{a} \) be the element of \( C(\overline{\Omega}, \mathbb{R}) \) whose value at every \( x \) is \( a \). Give conditions for \( \hat{a} \) to be a super-equilibrium and justify your conditions.

(b) If \( f(u) = u(u-0.5)(1-u) \), find all constant equilibria, all stable equilibria, all constant sub-equilibria, and all constant super-equilibria. Determine the largest set \( B \subset C(\overline{\Omega}, \mathbb{R}) \) such that \( \Phi(t,b) \rightarrow \hat{1} \) as \( t \rightarrow \infty \) for each \( b \in B \) that you can.