Dynamics of Genetic Networks
Nonlinear ODE models

Variables
• \( x = (x_1, x_2, ..., x_n) \) Concentrations of mRNA, proteins, and cofactors
• time-dependent, positive, real-valued

Assumptions
• Spatial homogeneity
• Time rate of change of \( x \) is determined by the present value of \( x \):
  \[ \dot{x} = f(x) \]

Behavior
Main features of interest
• Limiting behavior for \( t \to \infty \)
  – fixed points \( x^* \) - solutions of \( f(x^*) = 0 \)
  – stability of fixed points (asymptotically stable, stable, saddle-points, unstable)
  – periodic orbits \( x(t) = x(t + T) \)
  – homoclinic or heteroclinic orbits – trajectories connecting saddle points
  – quasiperiodic or strange attractors
• Basins of attraction – regions of initial conditions that approach the same attractor
• Bifurcations – changes in the number and stability of attractors as a function of a parameter

Increasing dimensionality increases complexity of the behavior:

1-dimensional: Monotone trajectories, Limit sets = fixed points, Bifurcations = saddle-node, transcritical, pitchfork
2-dimensional: Limit sets = fixed points and periodic orbits, New bifurcations – Hopf (fixed point -> periodic orbit), global bifurcations of cycles, orbits, blue-sky catastrophe
3 and higher-dimensional: Limit sets = high-dimensional attractors, strange attractors
• Difficult to analyze
• Sensitive to parameter values
Special systems
• Additional assumptions can simplify behavior

Conservative systems: There is a quantity $E(x)$ that is conserved on trajectories, i.e., $\frac{d}{dt}E(x(t)) = 0$
• no attracting fixed points – only saddles and centers
• dimensional reduction

Reversible systems: $\dot{x} = f(x)$ is invariant under change of variables $t \rightarrow -t, x \rightarrow R(x)$ where $R(R(x)) = x$
• time reversal symmetry – heteroclinic & homoclinic orbits

Gradient systems: $\dot{x} = -\nabla V(x)$
• no periodic orbits or chaos

Systems with Liapunov function: There is a positive definite function $V(x)$ (positive everywhere except the fixed point $x^*$) that decreases on trajectories.
• global asymptotic stability

Classical results on gene regulation
(Goodwin 1963, 1965; Griffith, 1968; Tyson & Othmer, 1978)

\[
\begin{align*}
\dot{x}_1 &= k_1 f(x_n) - \gamma_1 x_1 \\
\dot{x}_2 &= k_2 x_1 - \gamma_2 x_2 \\
&\vdots \\
\dot{x}_n &= k_n x_{n-1} - \gamma_n x_n
\end{align*}
\]

Positive feedback - necessary for multistability, differentiation
Ex: $\dot{x} = kf(x) - \gamma x$ with $f'(x) > 0$, non-monotone

Negative feedback – homeostasis, necessary for oscillations

\[
\begin{align*}
\dot{x}_1 &= \frac{1}{1 + (x_3)^m} - \gamma_1 x_1 \\
\dot{x}_2 &= x_1 - \gamma_2 x_2 \\
\dot{x}_3 &= x_2 - \gamma_3 x_3
\end{align*}
\]
Ex: $\dot{x}_2 = x_1 - \gamma_2 x_2$ oscillates if $m > 8$
Hurwitz criterion

- The stability of a fixed point depends on the matrix $A$ of the linearized system $f(x^*) = 0$
  $$
  \dot{x} = A(x - x^*) + O(|x - x^*|^2)
  $$
- Fixed point $x^*$ is asymptotically linearly stable iff all eigenvalues of $A$ have negative real parts.

Characteristic polynomial:  
$$
\det(\lambda I - A) = \lambda^{n-s}\left(\alpha_0 \lambda^s + \alpha_1 \lambda^{s-1} + \ldots + \alpha_s\right)
$$

Hurwitz array:  
$$
H = \begin{bmatrix}
\alpha_1 & \alpha_3 & \alpha_5 & \alpha_7 & \ldots \\
\alpha_0 & \alpha_2 & \alpha_4 & \alpha_6 & \ldots \\
0 & \alpha_1 & \alpha_3 & \alpha_5 & \ldots \\
0 & 0 & \alpha_0 & \alpha_2 & \ldots \\
0 & 0 & 0 & \alpha_0 & \alpha_2 & \ldots \\
\vdots & \vdots & \vdots & \vdots & \ddots
\end{bmatrix}
$$

Hurwitz determinant:  
$$
\Delta_i = \det(H_{i,i,i})
$$

Routh-Hurwitz Theorem:  
The number of eigenvalues of $A$ with positive real part equals to the sum of the number of sign changes in the sequences

$$
1, \Delta_1, \Delta_3, \Delta_5, \ldots \\
1, \Delta_2, \Delta_4, \Delta_6, \ldots
$$

Corollary:  
$$
\Delta_i > 0 \text{ for all } i \Rightarrow \Re \lambda_j < 0 \quad \forall j \Rightarrow \text{asymptotically linearly stable}
$$

Corollary:  
$$
\exists i \quad \alpha_i < 0 \Rightarrow \exists j \quad \Re \lambda_j > 0 \Rightarrow \text{exponentially unstable}
$$
Monotone systems [Hirsch, Smith]

**Incidence graph** of a dynamical system $\dot{x} = f(x)$ is the graph with edge signs corresponding to the signs of $\frac{\partial f_i}{\partial x_j}$ (assumed independent of $x$)

- $\frac{\partial f_i}{\partial x_j} > 0$ - positive edge,
- $\frac{\partial f_i}{\partial x_j} < 0$ - negative edge,
- $\frac{\partial f_i}{\partial x_j} = 0$ - no edge,
- $\frac{\partial f_i}{\partial x_j}$ no effect

Consistent graph: Every path between two nodes has the same parity (sum of signs along the path)

Consistent

Inconsistent

Monotone systems: Preserve partial order in the state space

$$x(0) \leq y(0) \Rightarrow x(t) \leq y(t) \quad \text{for all } t > 0$$

Order: $x \leq y \iff x - y \in K$ where $K$ is a cone in $\mathbb{R}^n$

Strongly monotone systems:

$$x(0) \leq y(0) \& x(0) \neq y(0) \Rightarrow x(t) < y(t) \quad \text{for all } t > 0$$

**Theorem:** Almost every bounded solution of strongly monotone system converges to the set of equilibria.

**Corollary:** No chaos, strange attractors or periodic orbits exist.

- Monotonicity is *not* obvious
- Proving that a system is monotone is hard
- Testing whether a system is monotone with respect to a particular $K$ is easier

**Theorem:** When $K$ is an orthant, monotonicity with respect to $K$ is equivalent to consistency of the incidence graph of the system
Ex: competitive system
\[ \begin{align*}
\dot{x}_1 &= x_1(k_1 - x_1 - \gamma_1 x_2) \\
\dot{x}_2 &= x_2(k_2 - x_1 - \gamma_2 x_2)
\end{align*} \]

**Input/Output monotone systems** [Sontag]

\[ \begin{align*}
\dot{x} &= f(x, u) \\
y &= h(x)
\end{align*} \]

Monotonicity:
\[ x_1(0) \leq x_2(0) \& u_1(0) \leq u_2(0) \Rightarrow x_1(t) \leq x_2(t) \& u_1(t) \leq u_2(t) \& h_1(t) \leq h_2(t) \text{ for all } t > 0 \]

**Theorem:** For bounded monotone system,
1. for each constant input \( u(t) = u \) there is at least one steady state \( x* \), and if \( x* \) is unique then it is a global attractor (monostable response)
2. for each periodic input there is a corresponding periodic solution.

Utility:
- Monostable systems can be combined
- Inconsistent systems with small number of consistency deficits can be converted to monotone systems with input/output and studied in low-dimensional spaces.
- Results hold for reaction-diffusion systems and systems with delays

Ex: Testosterone dynamics [Enciso & Sontag, JMB 2004] – no oscillations
\[ \begin{align*}
\dot{x}_1 &= f(x_3) - b_1 x_1 \\
\dot{x}_2 &= g_1 x_1 - b_2 x_2 \\
\dot{x}_3 &= g_2 x_2(t - \tau) - b_3 x_3 \\
f(x) &= \frac{A}{K + x}
\end{align*} \]