Dynamical Systems in Biology

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Outline

Dynamical Systems Theory

$$x_i' = f_i(x_1, x_2, \cdots, x_n),\ 1 \le i \le n$$

Goal: characterize the asymptotic behavior, as $t \to \pm\infty$ of every solution, or, of almost every solution, or, of almost every solution of almost every f, or, $\cdots$

ω-limit set of solution $x(t)$:

$$\{y : y = \lim_{m\to\infty} x(t_m),\ t_m \to \infty\}$$

Goal Reached for $n = 1, 2$; Little known for $n \ge 3$.
Restrict to special systems: Hamiltonian, Gradient,etc.

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What's special about systems arising in biology?

$$x_i' = f_i(x_1, x_2, \cdots, x_n) = f_i(x), \quad 1 \leq i \leq n$$

Variables tend to be positive: $x \geq 0$, i.e., all $x_i \geq 0$.

Theorem: Assume:

1. solutions of initial value problems with $x(0) \geq 0$ exist and are unique.
2. $\forall i, \forall x \geq 0 : x_i = 0 \Rightarrow f_i(x) \geq 0.$

Then

$$x(0) \geq 0 \Rightarrow x(t) \geq 0, \; t > 0.$$

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Systems with Defined Feedback Relations

Positivity may lead to defined feedback relations among variables:
Rate of change of x_i depends positively or negatively on x_j, $j \neq i$:

Either

$$\forall x, \ \frac{\partial f_i}{\partial x_j}(x) \geq 0, \ i \neq j$$

"x_j activates x_i"
or

$$\forall x, \ \frac{\partial f_i}{\partial x_j}(x) \leq 0, \ i \neq j$$

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Can we exploit DFR to circumscribe asymptotic behavior of solutions?

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"Signed Influence Directed Graph" for DFR System

1. Vertices: the dependent variables x_i.
2. $+$ directed edge from x_j to x_i if $\frac{\partial f_i}{\partial x_j}(x) \geq 0$.

$$x_j \xrightarrow{\quad + \quad} x_i$$

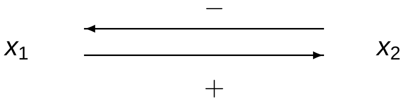
3. $-$ directed edge from x_j to x_i if $\frac{\partial f_i}{\partial x_j}(x) \leq 0$.

$$x_j \xrightarrow{\quad - \quad} x_i$$

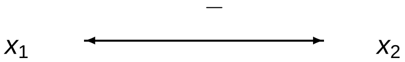
4. No directed edge from x_j to x_i if $\frac{\partial f_i}{\partial x_j}(x) \equiv 0$.

DFR and the Jacobian $Df(x)$

Prey-Predator: $\begin{bmatrix} * & - \\ + & * \end{bmatrix}$



Competition: $\begin{bmatrix} * & - \\ - & * \end{bmatrix}$



Repressilator with 2 genes

x_i = [protein] product of gene i
y_i = [mRNA] of gene i.
x_{i-1} represses transcription of y_i:

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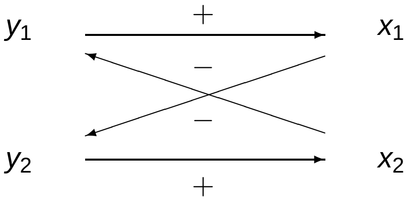
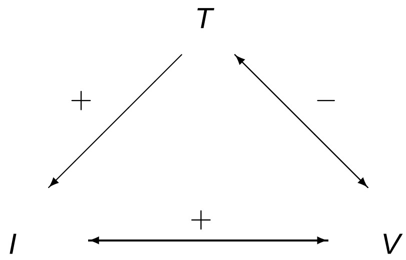
where $\alpha_i, \beta_i > 0$ and $f_i > 0$ satisfies $f_i' < 0$.



HIV-T-cell dynamics

T = T cell density in blood
I = infected T cell-density
V = HIV virus density
N = # virus released

$$T' = \delta - \alpha T + pT(1 - \frac{T}{T_{\max}}) - kVT$$
$$I' = kVT - \beta I$$
$$V' = \beta NI - \gamma V - kVT$$



Cooperative Systems

A system is cooperative if

$$\frac{\partial f_i}{\partial x_j}(x) \geq 0, \quad i \neq j.$$

It is cooperative and irreducible if the Jacobian matrix is irreducible.

Component-wise partial order:

1. $x \leq y \Leftrightarrow \forall i, x_i \leq y_i$.
2. $x < y \Leftrightarrow x \leq y \wedge x \neq y$.
3. $x \ll y \Leftrightarrow \forall i, x_i < y_i$.

A Cooperative Irreducible system is strongly order-preserving in forward time: $x(0) < \bar{x}(0) \Rightarrow x(t) \ll \bar{x}(t),\ t > 0$.

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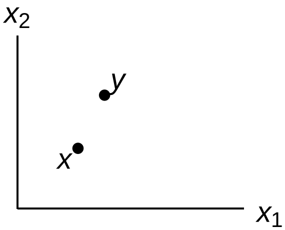

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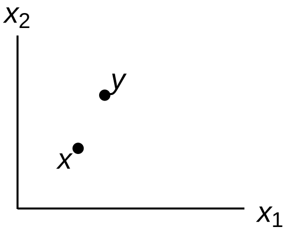

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Behavior of Cooperative Irreducible Systems

Theorem [Non-ordering of Limit Sets] No pair of points of $\omega(x)$ are related by $<$.

Theorem [Limit Set Dichotomy] If $x < y$ then either

(a) $\omega(x) < \omega(y)$, or

(b) $\omega(x) = \omega(y) \subset$ Equilibria.

Theorem (M.W.Hirsch): For almost every $x(0)$, the solution $x(t)$ converges to equilibrium.

Theorem: $\nexists$ an attracting periodic orbit.

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$x' = f(x)$ is competitive $\Leftrightarrow$ $x' = -f(x)$ is cooperative.

Time reversal flips sign on every arrow!

Theorem (Hirsch): The flow on a limit set of an n-dimensional competitive or cooperative system is topologically equivalent to the flow of a general $(n-1)$-dimensional system on a compact invariant set.

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A Generalization of Cooperative Systems

Suppose $x' = f(x)$ can be decomposed $x = (x_1, x_2) \in \mathbb{R}^k \times \mathbb{R}^{n-k}$

$$\begin{aligned} x_1' &= f_1(x_1, x_2) \\ x_2' &= f_2(x_1, x_2) \end{aligned}$$

- diagonal blocks $\frac{\partial f_i}{\partial x_i}(x)$ have nonnegative off-diagonal entries.
- off-diagonal blocks $\frac{\partial f_i}{\partial x_j}(x) \leq 0$ have nonpositive entries.

$$\text{Jacobian} = \begin{bmatrix} * & + & - & - \\ + & * & - & - \\ - & - & * & + \\ - & - & + & * \end{bmatrix}$$

Components cluster into two subgroups. positive within-group interactions, negative between-group interactions.

Then change of variables $y = (y_1, y_2) = (x_1, -x_2)$ yields a cooperative system in the usual sense!

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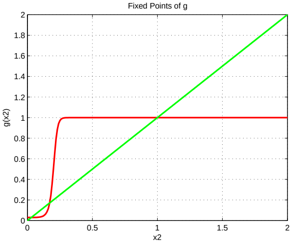
Gardner et al, “Construction of a genetic toggle switch in E. coli", Nature(403),2000.

Dynamics of Repressilator

Equilibria $u = (x_1, y_1, x_2, y_2)$ are in 1-to-1 correspondence with fixed points of increasing map $g \equiv \alpha_2 f_2 \circ \alpha_1 f_1$



Theorem: If g has no degenerate fixed points, $\exists$ odd number of equilibria $u^1, u^2, \cdots, u^{2m+1}$ indexed by increasing values of x_2. u_{2i+1} are stable, u_{2i} are unstable. If $B(u_i)$ denotes the basin of attraction of u_i, then

$$\cup_{\text{odd } i} B(u_i)$$

is open and dense in $\mathbb{R}^4_+$. u_1 is globally attracting if $m = 0$.

Competition in Two Patches yields cooperative system

$$
\begin{aligned}
x_1' &= x_1(r_1 - a_1x_1 - b_1y_1) + d(x_2 - x_1) \\
x_2' &= x_2(r_2 - a_2x_2 - b_2y_2) + d(x_1 - x_2) \\
y_1' &= y_1(s_1 - c_1x_1 - d_1y_1) + D(y_2 - y_1) \\
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Jiang & Liang, Quart. Appl. Math. 64 (2006):

System is cooperative and competitive! Has $2-D$ dynamics-a limit set containing no equilibrium is periodic orbit.

Is my system $x' = f(x)$ Cooperative? Competitive?

For Cooperative:

1. DFR system: no sign change of $\frac{\partial f_i}{\partial x_j}(x)$, $i \neq j$.
2. sign symmetry: $\frac{\partial f_i}{\partial x_j}(x)\frac{\partial f_j}{\partial x_i}(y) \geq 0$, $i \neq j, \forall x, y$.
   - (no predator-prey-like relations.)
3. every loop in undirected*, signed, incidence graph for Jacobian $(\frac{\partial f_i}{\partial x_j}(x))_{i,j}$ has even # of negative edges.

*just drop arrows on signed influence directed graph.

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1. as above
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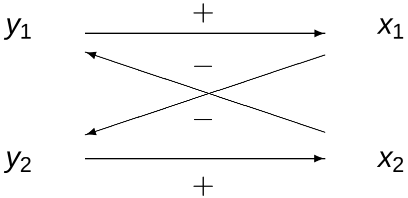
where $\alpha_i, \beta_i > 0$ and $f_i > 0$ satisfies $f_i' < 0$.

even number of $+$ and even number of $-$ edges!



MAPK intra-cellular signaling Cascade is cooperative

$$
\begin{aligned}
x' &= -\frac{v_2 x}{k_2 + x} + v_0 u + v_1 \\
y_1' &= \frac{v_6 (y_{tot} - y_1 - y_3)}{k_6 + (y_{tot} - y_1 - y_3)} - \frac{v_3 x y_1}{k_3 + y_1} \\
y_3' &= \frac{v_4 x (y_{tot} - y_1 - y_3)}{k_4 + (y_{tot} - y_1 - y_3)} - \frac{v_5 y_3}{k_5 + y_3} \\
z_1' &= \frac{v_{10} (z_{tot} - z_1 - z_3)}{k_4 + (z_{tot} - z_1 - z_3)} - \frac{v_7 y_3 z_1}{k_7 + z_1} \\
z_2' &= \frac{v_8 y_3 (z_{tot} - z_1 - z_3)}{k_4 + (z_{tot} - z_1 - z_3)} - \frac{v_9 z_3}{k_9 + z_3}
\end{aligned}
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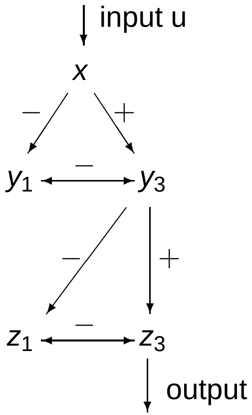
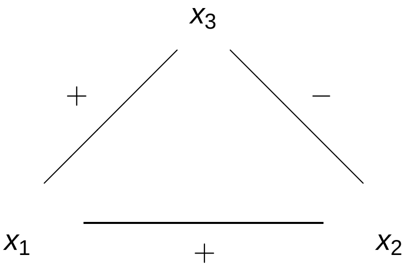


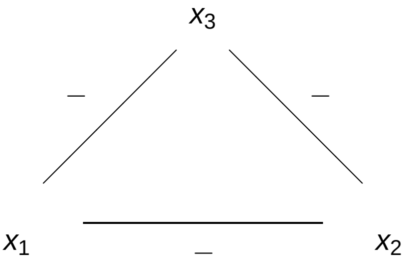
Molecular Systems Biology & Control, E. Sontag

Competitive Systems in $\mathbb{R}^3$

Corollary[Hirsch]: A Limit set containing no equilibria is a periodic orbit

Influence graph must have even # of + edges in each loop.





Classical Lotka-Volterra Competition

$$\begin{aligned} x_1' &= x_1(r_1 - c_{11}x_1 - c_{12}x_2 - c_{13}x_3) \\ x_2' &= x_2(r_2 - c_{21}x_1 - c_{22}x_2 - c_{23}x_3) \\ x_3' &= x_3(r_3 - c_{31}x_1 - c_{32}x_2 - c_{33}x_3) \end{aligned}$$

Hirsch's “Carrying Simplex"

M.L. Zeeman: 33 dynamically distinct phase portraits

How many limit cycles? Three!

Hofbauer & So, Gyllenberg & Ping Yan

Examples with one negative edge (term in red)

classical $S \to E \to I \to R$

$$
\begin{aligned}
S' &= \mu - \mu S - \sigma I S \\
E' &= \sigma I S - (\mu + \gamma) E \\
I' &= \gamma E - (\mu + \rho) I
\end{aligned}
$$

predator-prey with stage structure

$$
\begin{aligned}
x' &= x(r - ax) - bxy_2/(1 + cx) \\
y_1' &= kbxy_2/(1 + cx) - (m + d_1)y_1 \\
y_2' &= my_1 - d_2 y_2
\end{aligned}
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Goldbeter's model for Mitotic Oscillator

$$
\begin{aligned}
C' &= v_i - v_d X \frac{C}{K_d + C} - k_d C \\
M' &= V_{M1} \frac{C}{K_c + C} \frac{1 - M}{K_1 + 1 - M} - V_2 \frac{M}{K_2 + M} \\
X' &= V_{M3} M \frac{1 - X}{K_3 + 1 - X} - V_4 \frac{X}{K_4 + X}
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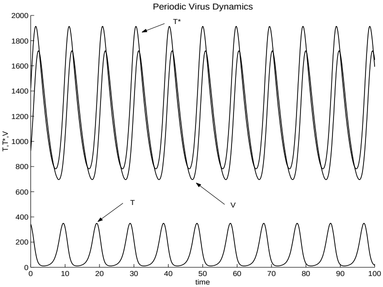
Virus dynamics model is competitive

$$\begin{aligned} T' &= \delta - \alpha T + pT(T_{\max} - T)/T_{\max} - kVT \\ I' &= kVT - \beta I \\ V' &= \beta N I - \gamma V - kVT \end{aligned}$$

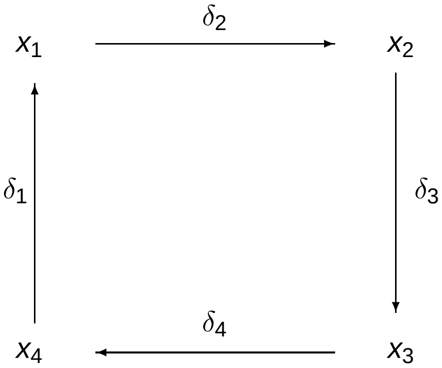


Smith & de Leenheer, SIAM Appl. Math. 63 (2003)

Monotone Cyclic Feedback Systems

single-loop DFR system:

$$\begin{aligned} x_1' &= f_1(x_1, x_n) \\ x_2' &= f_2(x_2, x_1) \\ &\vdots \\ x_n' &= f_n(x_n, x_{n-1}) \end{aligned}$$



where

$$\delta_i \frac{\partial f_i}{\partial x_{i-1}} > 0, \ \delta_i \in \{-, +\}$$

Mallet-Paret & H.S., Poincaré-Bendixson theorem for MCFS, J. Dynam. & Diff. Eqns. (2) 1990

Monotone Cyclic Feedback Systems

Theorem: A limit set L of a bounded solution of a MCFS is either:

- an equilibrium
- a periodic orbit
- a set of equilibria and orbits connecting them.

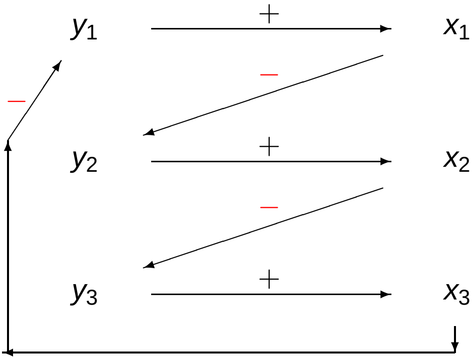
Moreover, $\Pi^i : \mathbb{R}^n \to \mathbb{R}^2$ defined by $\Pi^i x = (x_i, x_{i-1})$ is injective on L.

Repressilator with n genes is a MCFS!

x_{i-1} represses transcription of y_i:

$$\begin{aligned} x_i' &= \beta_i(y_i - x_i) \\ y_i' &= \alpha_i f_i(x_{i-1}) - y_i,\ i = 1,2,3 \mod 3 \end{aligned}$$

where $f_i \geq 0$ satisfy $f_i' < 0$.



Results for *n*-gene repressilator

Theorem:

1. if n even, then almost all orbits converge.
2. n odd, then stable periodic orbits may exist.

Hofbauer et. al., A generalized model of the repressilator. J. Math. Biol. 53 (2006)

Basic Definitions

R. Thomas* formulated conjectures about the possible dynamics a system could have based on its signed directed influence graph. Below are some key points required to formulate his conjectures.

1. Partial derivatives may have different signs in different regions of phase space! The graph G depends on the point x in phase space: $G = G(x)$.
2. G includes signed self-loops $i \to i$ with "+" sign if $\frac{\partial f_i}{\partial x_i}(x) > 0$ and "-" sign if partial derivative is negative.
3. G is a directed graph (edges have direction).
4. A circuit in G is a sequence of distinct vertices $i_1, i_2, \cdots, i_p$ so that there is an edge from i_k to i_{k+1}, $1 \leq k < p$, and from i_p to i_1.
5. the sign of a circuit is the product of signs of its edges.

*On the relation between the logical structure of systems and their ability to generate multiple steady states or sustained oscillation, Springer Ser. Synergetics 9, 180-193, 1981

Thomas's Conjectures

Conjecture 1: A positive circuit (even # negative edges) in $G(x)$, for some x, is a necessary condition for multistationarity (more than one equilibrium).

Conjecture 2: A negative circuit of length at least two is a necessary condition for stable periodicity.

Conjecture 3: Chaotic dynamics requires both a positive and a negative circuit.

More recent reference: Kaufman, Soul, Thomas, A new necessary condition on interaction graphs for multistationarity, T. Theor. Biol. 248 (2007), 675-685

Examples

1. predator-prey system has a negative circuit so cannot have two coexistence equilibria but can have stable periodic solutions.
2. competitive system has positive circuit so can have multistationarity but not stable periodic solutions.

References for competitive and cooperative systems

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