Mathematics of Multistationarity

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OPEN PROBLEMS
**Gene Network**

- "Gene A activates (resp. inhibits) gene B": activated gene A produces a protein that has a positive (resp. negative) effect on the expression of gene B.

- Several such interacting genes form a gene network.

- Multistationarity (or, multistability), is the capacity to achieve multiple internal steady states in response to a single set of external inputs.

- When considered as biological switches, essential for differentiation.
**BIOLOGICAL EXAMPLE**

Lactose utilization network in *E. Coli*.

Experimental result

(Left panel) *E. Coli* grown in 18 μM TMG / 0μM Glucose; (Right panel) Bimodal distribution of Lactose utilization.

**Gene Network: Graphical Representation**

- A gene network can be represented by an interaction graph $G$.
- $G(V, E, s)$ is a finite oriented graph $(V, E)$ with a map $s : E \rightarrow \{\pm 1\}$.
- Each edge $e \subset E$ has an origin $o(e) \subset V$ and an endpoint $t(e) \subset V$.
- $s$ may be concentration dependent, i.e. $s(e)$ may depend on the magnitude of $o(e)$ and $t(e)$.
CIRCUITS

- A circuit, $C \subset G$ is a sequence $\{e_1, ..., e_k\}$, $e_i \in E$ with $o(e_{i+1}) = t(e_i)$ and $t(e_k) = o(e_1)$.

- Sign of a circuit is the product of the signs of its edges: $s(C) = \prod_{e \in C} s(e)$.

- A hooping is a collection $C = \{C_1, ..., C_k\}$ of circuits such that, for all $i \neq j$, $C_i$ and $C_j$ do not have a common vertex. We take $s(C) = (-1)^{p+1}$, where $p$ is the number of positive circuits in $C$. 
René Thomas is a Belgian biologist who specializes in biological control phenomena.

He proposed the following (now known as Thomas’ Rule):

Assume a gene network has several non-degenerate stationary states. Then its interaction graph contains, somewhere in phase space, a positive circuit.
DIFFERENTIAL MODEL OF A GENE NETWORK

- Let $n \geq 1$ be an integer and $\Omega = \mathbb{R}^n$, consider the differentiable map $F = (F_i) : \Omega \to \Omega$ and the system of differential equations:

$$\frac{dx}{dt} = F(x), \quad (*)$$

where $x : \mathbb{R} \to \mathbb{R}^n$ is any differential path in $\Omega$.

- This is a model for a network of $n$ genes: for every $i = 1, \ldots, n$, the number $x_i(t)$ is the concentration of the protein $i$ at time $t$. By $(*)$, the variation of $x_i(t)$ is a function of all the concentrations of $x_j(t)$, $j = 1, \ldots, n$.

Example: Let $x = (x_1(t), x_2(t))$, with $\{x_1 = x_2, x_2 = x_1^2 - 1\}$. We have $F(x) = (x_2, x_1^2 - 1)$ and

$$J_F = \left( \frac{\partial F_i}{\partial x_j} \right) = \begin{bmatrix} 0 & 1 \\ 2x_1 & 0 \end{bmatrix}$$
DIFFERENTIAL MODEL OF A GENE NETWORK

- Taking \( x \in \Omega \), we define \( G(x) \): its set of vertices is \([x_1, ..., x_n]\) and there is a positive (or negative) edge from \( j \) to \( i \) when the partial derivative \( \frac{\partial F_i}{\partial x_j}(x) \) is positive (or negative).

- \( G(x) \) for our example (\( \{\dot{x}_1 = x_2, \dot{x}_2 = x_1^2 - 1\} \)) is as follows.

- Note that \( C = \{x_1, x_2\} \) is positive if \( x_1 > 0 \) and negative if \( x_1 < 0 \).
Differential model of a gene network

- A stationary state of the network is a zero of $F$, i.e. $x \in \Omega$ such that $F(x) = 0$. The zero is non-degenerate when $\det(\frac{\partial F_i}{\partial x_j}(x)) \neq 0$.

- In our example, we find non-degenerate stationary states when $x_2 = 0$, and $x_1^2 = 1$. Therefore, we have two stationary states: $(1, 0)$ and $(-1, 0)$.

Theorem

(Soulé, 2003) Assume that $F$ has at least two non-degenerate zeros. Then there exists $x \in \Omega$ such that $G(x)$ contains a positive circuit.
DIFFERENTIAL MODEL OF A GENE NETWORK

Theorem

(Soulé, 2003) Assume that $F$ has at least two non-degenerate zeros. Then there exists $x \in \Omega$ such that $G(x)$ contains a positive circuit.

Preliminaries

- A principal minor of a matrix $A$ is defined to be the determinant of the sub-matrix that is obtained from $A$ by restricting the indices to some subset $I$ ($\det(A_I)$).

- (Leibniz formula for determinants) For $A_{n \times n} = (a_{ij})_{i,j=1,...,n}$, the formula is

  $$\det(A) = \sum_{\sigma \in S_n} \epsilon(\sigma) \prod_{i=1}^{n} a_{i,\sigma(i)}$$

  where $\epsilon$ is the sign function of permutations in the permutation group $S_n$.

- Then, we have a formula for $\det(A_I)$:

  $$\det(A_I) = \sum_{\sigma \in \Sigma_I} \epsilon(\sigma) \prod_{i \in I} a_{i,\sigma(i)} = \sum_{\sigma \in \Sigma_I} a(\sigma)$$
DIFFERENTIAL MODEL OF A GENE NETWORK

Theorem  
*(Soulé, 2003)* Assume that $F$ has at least two non-degenerate zeros. Then there exists $x \in \Omega$ such that $G(x)$ contains a positive circuit.

If $F$ has several zeros, it is not one-to-one. If we can identify sufficient conditions such that $F$ is one-to-one ($S$), then the negation of $S$ will give us necessary (not sufficient) conditions for $F$ to have several zeros.

Theorem  
*(Gale-Nikaido)* A function $F(x)$ will be one-to-one if all of the principal minors of $J(x)$ are non-negative, and if the determinant of $J(x)$ is positive for all $x$.

Theorem  
*(Gale-Nikaido’, Soulé 2003)* If all the principal minors of $-J(x)$ are non-negative, then $-F(x)$ has at most one non-degenerate zero.
DIFFERENTIAL MODEL OF A GENE NETWORK

Theorem
(Soulé, 2003) Assume that $F$ has at least two non-degenerate zeros. Then there exists $x \in \Omega$ such that $G(x)$ contains a positive circuit.

Theorem
(Gale-Nikaido’, Soulé 2003) If all the principal minors of $-J(x)$ are non-negative, then $-F(x)$ has at most one non-degenerate zero.

- Any permutation produces a decomposition of the network into disjoint cycles.
- Each term in a principal minor corresponds to a permutation $\sigma$, and each such permutation defines a natural ‘hooping’, $C(\sigma)$, of the graph $G(x)$.
- Can show that $\det(-A_I) = - \sum_{\sigma \in \Sigma_I} s(C(\sigma)) |a(\sigma)|$, and if $\det(-A_I) < 0$, the sign of at least one hooping in $G(x)$ has to be positive, which occurs only if the graph contains a positive circuit.
Other Models of Gene Networks

- **Boolean**: genes are considered to have binary (on/off) states.
- **Differential model with decay**: proteins have decay rates.
- **Piecewise-linear**: assume effect of genes on other genes is switch-like.
- **Discrete**: discretize protein levels.

A model-appropriate version of Thomas’ rule has been proven for all the models above, giving support to the validity of the rule in biology.
**Open Problems**

- Develop more biologically-realistic mathematical gene-interaction models. Can include
  - Epigenetic factors (chromatin conformation, alternative splicing).
  - Interaction of gene networks with biochemical or protein networks.
  - Consider spatial component: can diffusion in space lead to differentiation in the absence of a positive circuit?
  - Consider gene regulation from a stochastic viewpoint: can a stochastic representation lead to differentiation without a positive circuit?
- Can one find upper bounds for the number of possible stationary states in a gene network?
- Reinterpret mathematical definition of 'stationary state'.
Thank you!

Main references:
