Mathematics of Multistationarity

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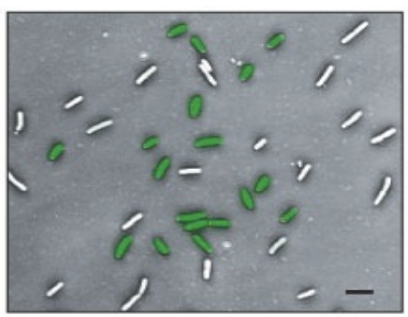

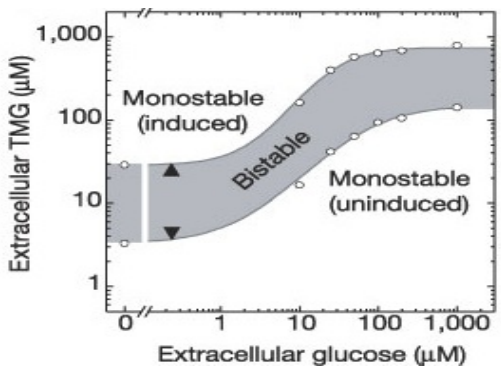

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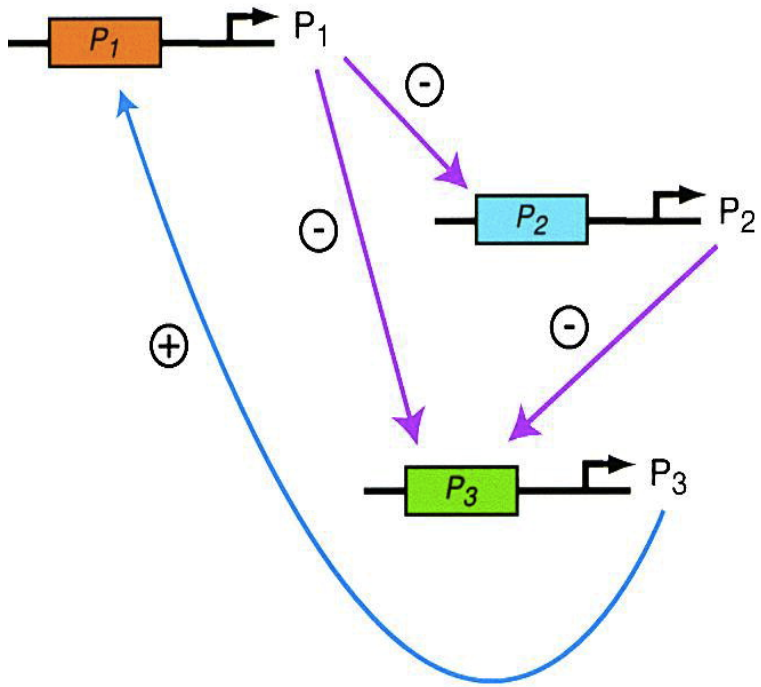
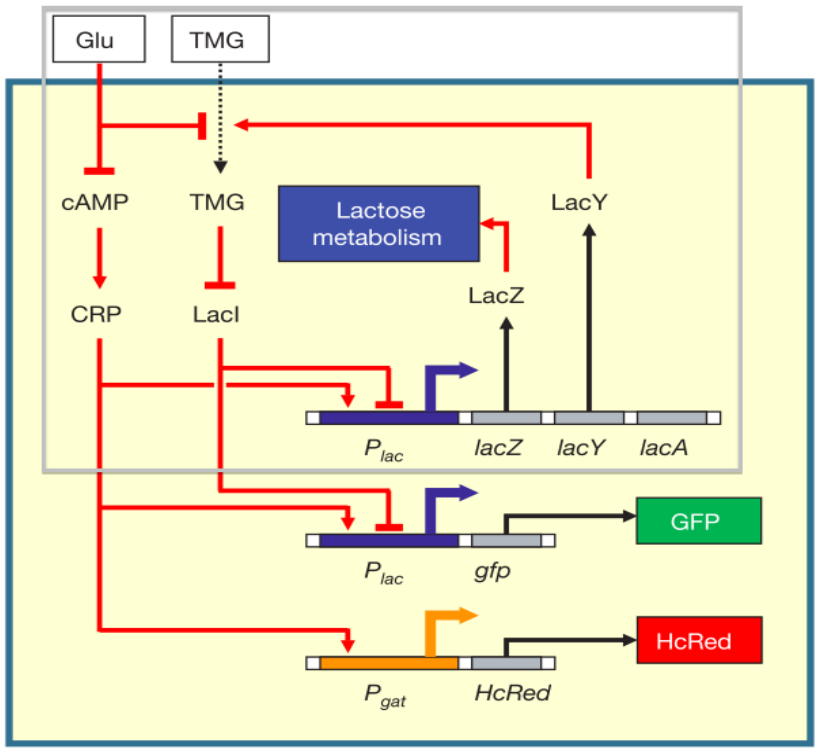
GENE NETWORK

- "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.



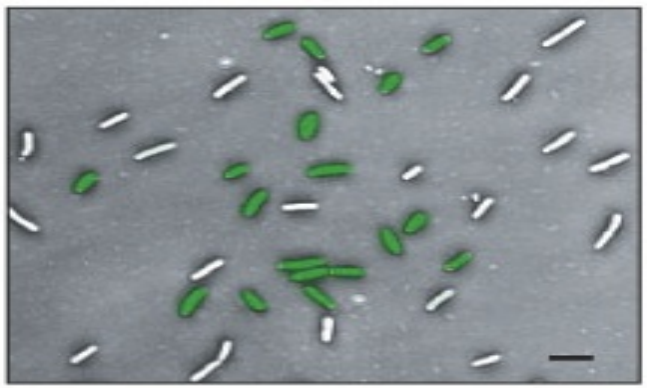
BIOLOGICAL EXAMPLE

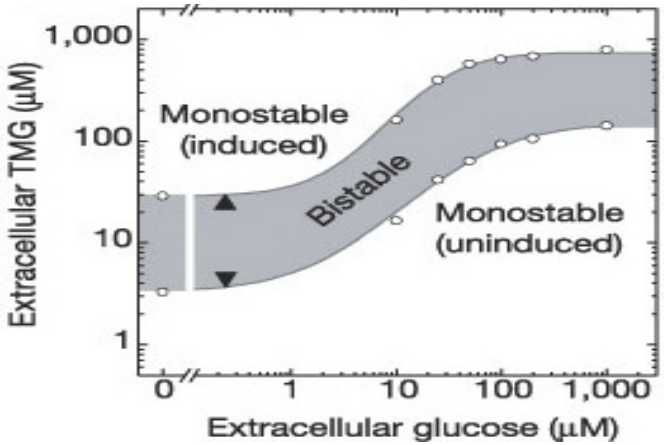


Lactose utilization network in *E. Coli*.

Osbidak et al., (2004) Nature (427) pp. 737-740.

EXPERIMENTAL RESULT



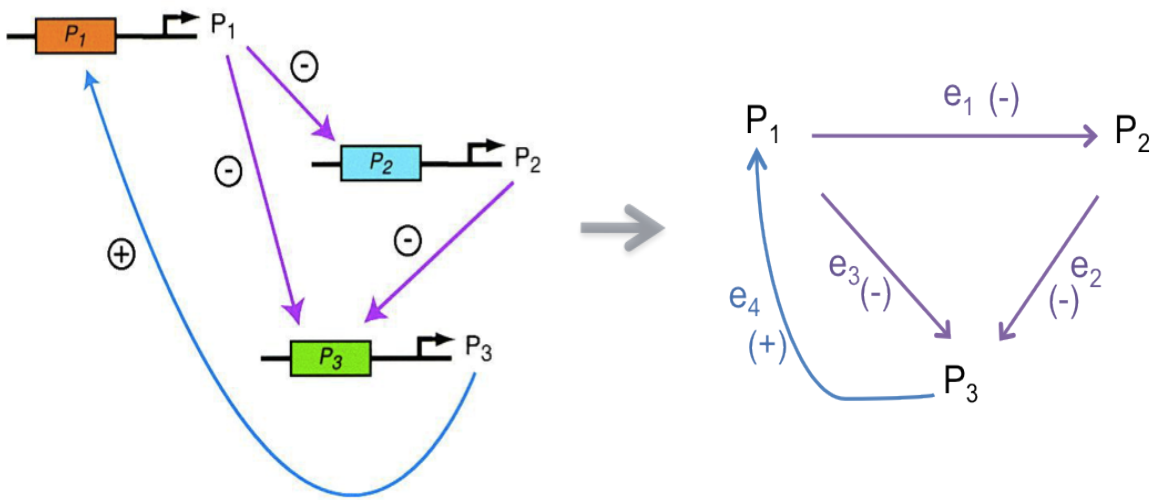


(Left panel) *E. Coli* grown in 18 μM TMG / 0μM Glucose;
(Right panel) Bimodal distribution of Lactose utilizaiton.

Osbidak et al., (2004) Nature (427) pp. 737-740.

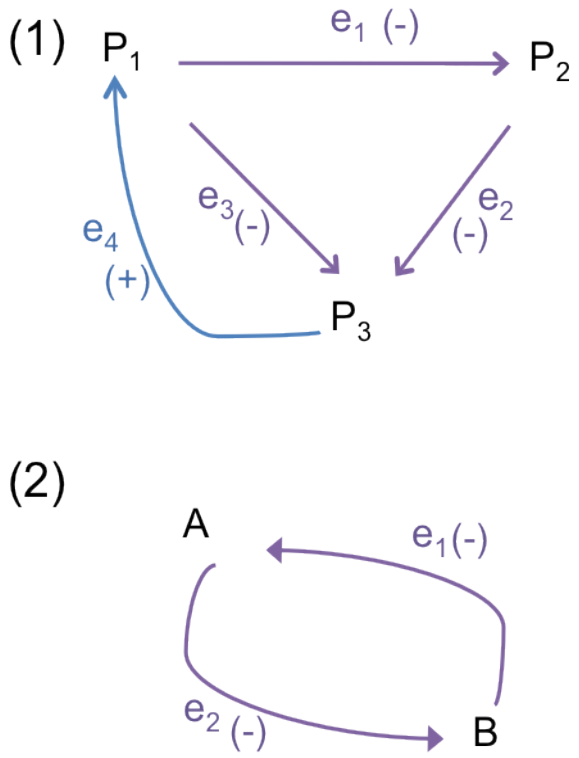
GENE NETWORK: GRAPHICAL REPRESENTATION

- 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 $s : E \to \{\pm 1\}$.
- 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

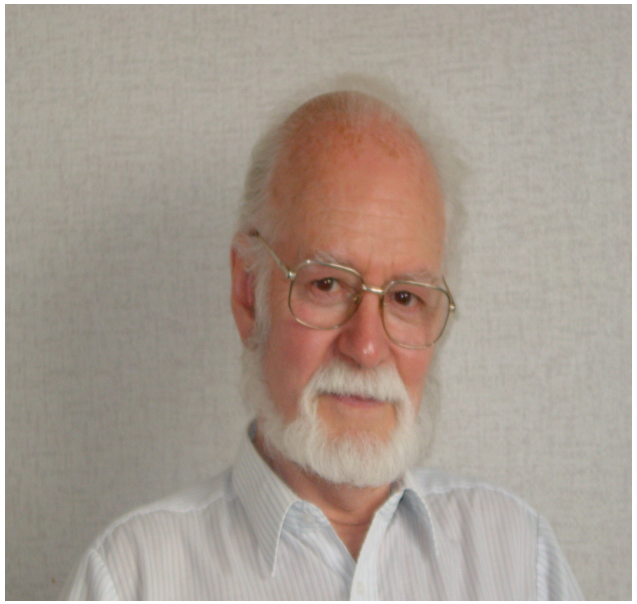
- A *circuit*, $C \subset G$ is a sequence $\{e_1, ..., e_k\}$, $e_i \in E$ with $o(e_{i+1}) = t(e_i)$ and $t(e_k) = o(e_1)$.
- Sign of a circuit is the product of the signs of its edges: $s(C) = \prod_{e \in C} s(e)$.
- A *hooping* is a collection $C = \{C_1, ..., C_k\}$ of circuits such that, for all $i \neq j$, 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.



THOMAS' RULE

- 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 Ω.

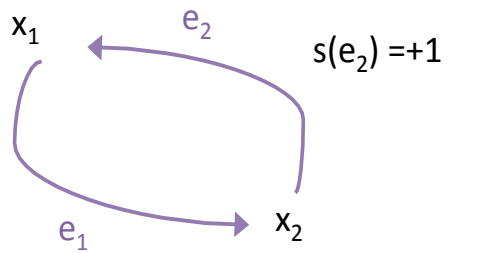
- This is a model for a network of n genes: for every $i = 1, .., n$, the number $x_i(t)$ is the concentration of the protein i at time t. By (*), the variation of $x_i(t)$ is a function of all the concentrations of $x_j(t), j = 1, ..., n$.

Example: Let $x = (x_1(t), x_2(t))$, with $\{\dot{x_1} = x_2, \dot{x_2} = x_1^2 - 1\}$. 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 $\det\left(\frac{\partial F_i}{\partial x_j}(x)\right) \neq 0$.
- 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

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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 $A_{n\times n} = (a_{ij})_{i,j=1,\ldots,n}$, the formula is

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

  where ϵ is the sign function of permutations in the permutation group S_n.
- Then, we have a formula for $\det(A_I)$:

$$\det(A_I) = \sum_{\sigma \in \Sigma_I} \epsilon(\sigma) \Pi_{i\in I} a_{i,\sigma(i)} = \sum_{\sigma \in \Sigma_I} a(\sigma)$$

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 σ, 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?
- Reinterpet mathematical definition of 'stationary state'.

Thank you!

Main references:

Soulé (2003) *Graphic Requirements for Multistationarity*. ComplexUs (1) 123-133.

Soulé (2006) *Mathematical Approaches to Gene Regulation and Differentiation*. C.R. Biologies (329) 13-20.