La geometría algebraica en las redes de reacciones bioquímicas

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Resumen

Un paper

Structural Sources of Robustness in Biochemical Reaction Networks

Guy Shinar[1] and Martin Feinberg[2]*

In vivo variations in the concentrations of biomolecular species are inevitable. These variations in turn propagate along networks of chemical reactions and modify the concentrations of still other species, which influence biological activity. Because excessive variations in the amounts of certain active species might hamper cell function, regulation systems have evolved that act to maintain concentrations within tight bounds. We identify simple yet subtle structural attributes that impart concentration robustness to any mass-action network possessing them. We thereby describe a large class of robustness-inducing networks that already embraces two quite different biochemical modules for which concentration robustness has been observed experimentally: the *Escherichia coli* osmoregulation system EnvZ-OmpR and the glyoxylate bypass control system isocitrate dehydrogenase kinase-phosphatase–isocitrate dehydrogenase. The structural attributes identified here might confer robustness far more broadly.

Biological systems require robustness, that is, the capacity for sustained and precise function even in the presence of structural or environmental disruption (*1*–*11*). Examples of robustness exist over multiple scales of biological

We identify simple yet subtle structural attributes that will impart ACR to any mass-action network that includes them. We provide a mathematical theorem that precisely delineates a very large class of ACR-possessing

the system's equilibration time scale. Under this assumption, the differential equations governing the time evolution of the molar concentrations of A and B, denoted c_A and c_B, are

$$\begin{aligned} \dot{c}_A &= -\alpha c_A c_B + \beta c_B \\ \dot{c}_B &= \alpha c_A c_B - \beta c_B \end{aligned} \qquad (2)$$

The positive steady states of Eq. 2 are given by

$$\begin{aligned} c_A &= \frac{\beta}{\alpha} \\ c_B &= \Theta - \frac{\beta}{\alpha} \end{aligned} \qquad (3)$$

where Θ is the conserved total protein concentration: $\Theta = c_A + c_B = c_A(0) + c_B(0)$. Eq. 3 shows that system (1) has ACR: There is a positive steady state for each value of Θ exceeding β/α, and in each of these steady states c_A has precisely the same value.

In contrast, consider the simple module

$$A \underset{\beta}{\overset{\alpha}{\rightleftarrows}} B \qquad (4)$$

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Redes de reacciones químicas.

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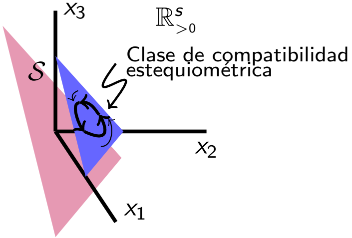

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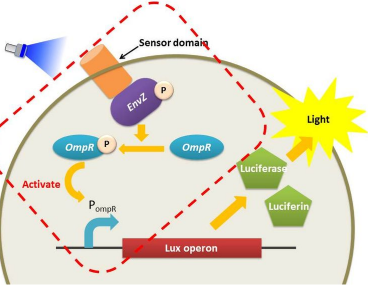

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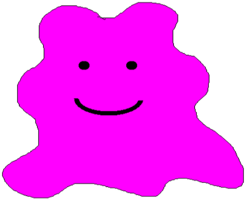

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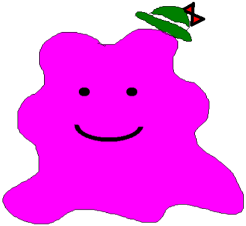

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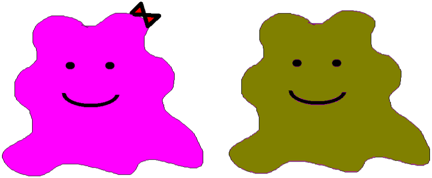

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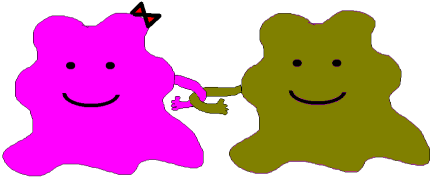

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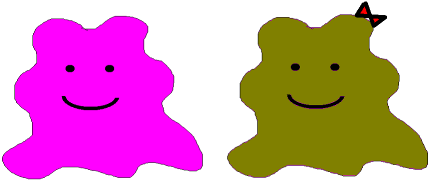

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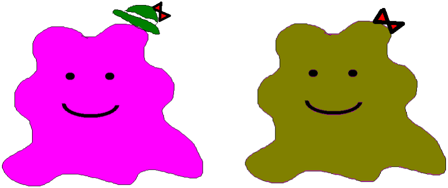

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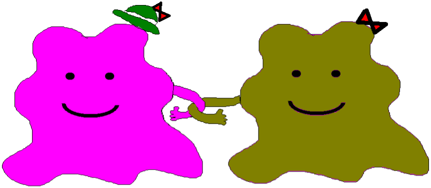

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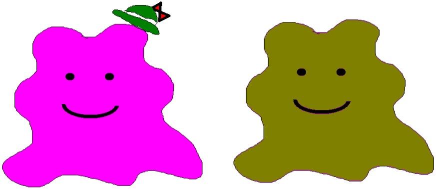

Complejos terminales y no terminales

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Clases fuertemente conexas

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Clases fuertemente conexas no terminales

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Enfoque clásico:

$$\mathbf{f}(\mathbf{x}) = \underbrace{M}_{\substack{\text{matriz de}\\ \text{coeficientes}}} \ . \ \underbrace{\psi(\mathbf{x})}_{\substack{\text{vector de}\\ \text{monomios}}}$$

Son los $\mathbf{x}$ tales que $\psi(\mathbf{x})$ pertenece al núcleo de M.

Deficiencia

$$\mathbf{f}(\mathbf{x}) = Y.\mathcal{L}(G).\psi(\mathbf{x}) = Y.\overbrace{C_G.K}.\psi(\mathbf{x})$$

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$$\delta_D = \dim(\ker(Y) \cap \operatorname{im}(\mathcal{L}(G)))$$

$$\delta_D \leq \delta$$

$$\ker(\mathcal{L}(G)) = \langle \rho_1, \dots, \rho_t \rangle$$

$$\begin{matrix} \rho_1 & \rho_2 & \rho_3 \\ \downarrow & \downarrow & \downarrow \end{matrix}$$
$$\begin{pmatrix} 0 & 0 & 0 \\ \dots & \dots & \dots \\ 0 & 0 & 0 \\ * & 0 & 0 \\ 0 & * & 0 \\ 0 & 0 & * \end{pmatrix}$$

(*Matrix-tree Theorem*)

Resultado de Shinar-Feinberg (Science 2010)

Teorema

Sea un sistema de cinética de acción de masas que admite un equilibrio positivo, y supongamos que la deficiencia de la red de reacciones subyacente es uno. Si, en la red, hay dos nodos no terminales que difieren solo en la especie $\mathfrak{s}$, entonces el sistema tiene "absolute concentration robustness" en la especie $\mathfrak{s}$.

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Una "base" del núcleo de $Y.\mathcal{L}(G)$:

$$\begin{pmatrix} * & 0 & 0 & 0 \\ * & 0 & 0 & 0 \\ * & 0 & 0 & 0 \\ * & 0 & 0 & 0 \\ * & 0 & 0 & 0 \\ * & 0 & 0 & 0 \\ * & 0 & 0 & 0 \\ 0 & * & 0 & 0 \\ 0 & 0 & * & 0 \\ 0 & 0 & 0 & * \end{pmatrix}.$$

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Una "base" del núcleo de $Y.\mathcal{L}(G)$:

$$\begin{pmatrix} B_{11} & 0 & 0 & 0 \\ B_{21} & 0 & 0 & 0 \\ * & 0 & 0 & 0 \\ * & 0 & 0 & 0 \\ * & 0 & 0 & 0 \\ * & 0 & 0 & 0 \\ * & 0 & 0 & 0 \\ 0 & * & 0 & 0 \\ 0 & 0 & * & 0 \\ 0 & 0 & 0 & * \end{pmatrix}.$$

$$\begin{pmatrix} x_1 \\ x_1 x_2 \end{pmatrix} = \lambda \begin{pmatrix} B_{11} \\ B_{21} \end{pmatrix} \longleftrightarrow \quad \det \begin{pmatrix} x_1 & B_{11} \\ x_1 x_2 & B_{21} \end{pmatrix} = B_{21} x_1 - B_{11} x_1 x_2 = 0$$

$$\begin{pmatrix} x_1 \\ x_1x_2 \end{pmatrix} = \lambda \begin{pmatrix} B_{11} \\ B_{21} \end{pmatrix} \longleftrightarrow \quad \det \begin{pmatrix} x_1 & B_{11} \\ x_1x_2 & B_{21} \end{pmatrix} = B_{21}x_1 - B_{11}x_1x_2 = 0$$

$$\longleftrightarrow \qquad \frac{x_1x_2}{x_1} = \frac{B_{21}}{B_{11}}.$$

$$\begin{pmatrix} x_1 \\ x_1 x_2 \end{pmatrix} = \lambda \begin{pmatrix} B_{11} \\ B_{21} \end{pmatrix} \longleftrightarrow \quad \det \begin{pmatrix} x_1 & B_{11} \\ x_1 x_2 & B_{21} \end{pmatrix} = B_{21} x_1 - B_{11} x_1 x_2 = 0$$

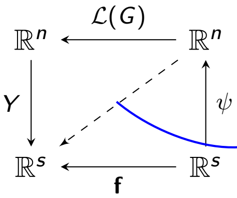
$$\longleftrightarrow \qquad \frac{\cancel{x_1} x_2}{\cancel{x_1}} = \frac{B_{21}}{B_{11}}.$$

$$x_2 = \text{constante}$$

"Absolute Concentration Robustness"

Contribuciones

Complex-linear invariants of biochemical networks, con R. Karp, T. Dasgupta, A. Dickenstein y J. Gunawardena. J. Theor. Biol., 311, pp. 130–138 (2012).



$$\underset{s \times n}{\begin{pmatrix} M \end{pmatrix}} \times \underset{n \times d}{\begin{pmatrix} \quad B \quad \end{pmatrix}} = \underset{s \times d}{\begin{pmatrix} 0 \end{pmatrix}}$$

las columnas de B forman una base de $\ker(M)$

$$B = \overset{n \times d}{\begin{pmatrix} B' \\ \hline * \end{pmatrix}} \begin{matrix} m \times d \\ \\ \end{matrix} \xrightarrow[\text{por col.}]{\text{op. elementales}} \overset{m \times \ell}{\begin{pmatrix} B' & 0 \\ \hline * & * \end{pmatrix}}$$

$\text{rango}(B') = \ell$

$$\rightsquigarrow \overset{m \times (\ell+1)}{\begin{pmatrix} \psi(\mathbf{x})_m & B' \end{pmatrix}} \quad \text{rango} = \ell$$

Contribuciones

Chemical reaction systems with toric steady states, con A. Dickenstein, A. Shiu y C. Conradi. B. Math. Biol., 74:5, pp. 1027–1065 (2012).

- Damos condiciones *suficientes* para que un sistema tenga un ideal de estados estacionarios *binomial*.
- También analizamos la capacidad de multiestacionariedad.
- Nuestro principal ejemplo es la red de fosforilaciones y defosforilaciones secuenciales:

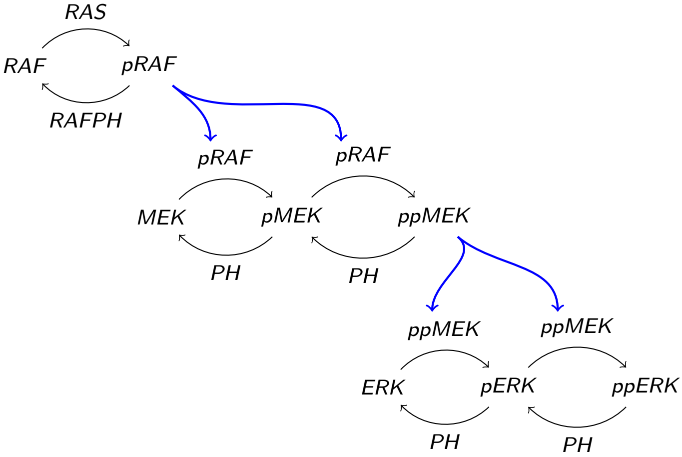
$$S_0 + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES_0 \overset{k_2}{\to} S_1 + E \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} ES_1 \overset{k_4}{\to} S_2 + E$$

$$S_2 + F \underset{h_{-1}}{\overset{h_1}{\rightleftarrows}} FS_2 \overset{h_2}{\to} S_1 + F \underset{h_{-3}}{\overset{h_3}{\rightleftarrows}} FS_1 \overset{h_4}{\to} S_0 + F$$

Contribuciones

MAPK's networks and their capacity for multistationarity due to toric steady states, con A. G. Turjanski. arXiv:1403.6702 (2014).

Aplicamos el resultado anterior a las cascadas de señalización de MAPK.



Contribuciones

Enzymatic networks and toric steady states, con A. Dickenstein. (En preparación.)
Buscamos un método gráfico para determinar si una red tiene estados estacionarios tóricos:

$$S_0 + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES_0 \overset{k_2}{\to} S_1 + E \qquad // \qquad S_1 + F \underset{h_{-1}}{\overset{h_1}{\rightleftarrows}} FS_1 \overset{h_2}{\to} S_0 + F$$

G_T:

$$* \underset{k_{-1}+k_2}{\overset{k_1.[S_0].[E]}{\rightleftarrows}} ES_0$$

$$* \underset{h_{-1}+h_2}{\overset{h_1.[S_1].[F]}{\rightleftarrows}} FS_1$$

- (débilmente) reversibles ✓
- único camino del correspondiente $*$ a cada intermedio ✓

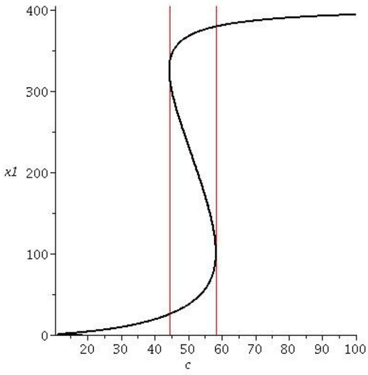
G_S:

$$S_0 \text{ ——— } S_1$$

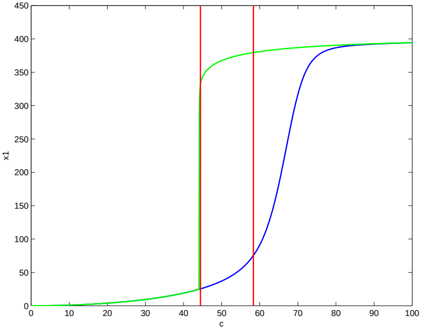
- bosque ✓

Contribuciones

Implicit dose-response curves, con A. Dickenstein. J. Math. Biol. (2014).



$\{(c, x_1) \in \mathbf{R}^2_{>0} / p(c, x_1) = 0\}$



simulación con MATLAB

$(\dim I = 1 \Rightarrow \exists\, p(c, x_1) \in I\ )$

Contribuciones

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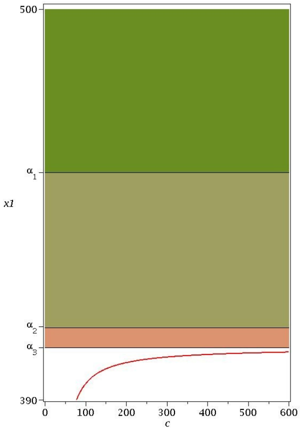
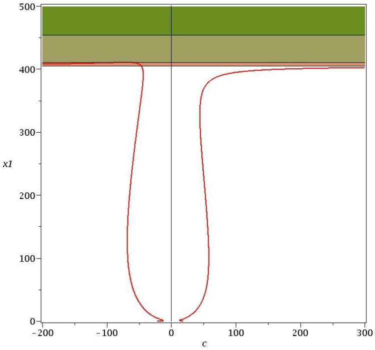




Distiguimos los ceros de

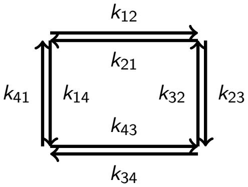
$$\mathrm{Res}_{4,3}\left(p, \frac{\partial p}{\partial c}, c\right)$$

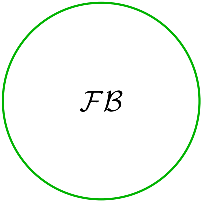
Contribuciones

How far is complex balancing from detailed balancing?, con A. Dickenstein. B. Math. Biol., 73:4, pp. 811–828 (2011).

Variedades algebraicas en $\mathbb{R}^r_{>0}$:

$\mathcal{FB}_Y = \{k = (k_{ij})$: el sistema es formalmente balanceado$\}$





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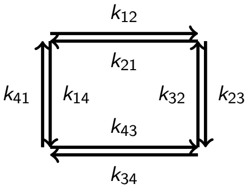
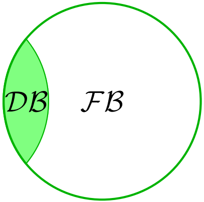


$\mathcal{FB}_Y = \{k = (k_{ij})$: el sistema es formalmente balanceado$\}$

$\mathcal{DB}_Y = \{k = (k_{ij})$: el sistema es "detailed balanced"$\}$

(Por [Feinberg '89].)



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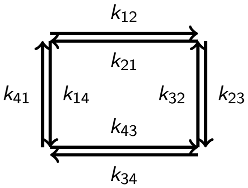

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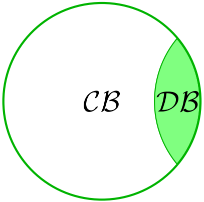

(Por [Craciun, Dickenstein, Shiu, Sturmfels '08], llamada el *espacio de moduli de sistemas dinámicos tóricos*.)

Contribuciones

How far is complex balancing from detailed balancing?, con A. Dickenstein. B. Math. Biol., 73:4, pp. 811–828 (2011).

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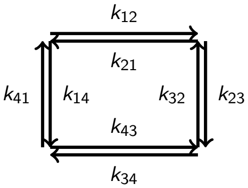

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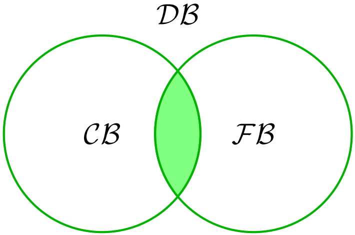

(Por [Craciun, Dickenstein, Shiu, Sturmfels '08], llamada el *espacio de moduli de sistemas dinámicos tóricos*.)

Algunos avances matemáticos

http://reaction-networks.net

Algunos avances matemáticos

- David F. Anderson
  palabras clave: *Markov chain, quasi-stationary distributions, stochastic analysis,etc.*
- Badal Joshi
  p.c.: *stochastic switching, noise in bistable systems, neuronal networks, synchronized oscillations, etc.*
- Gheorghe Craciun
  p.c.: *global attractor conjecture, power-law systems, algebraic statistical model, polyhedral geometry, dimension reduction,etc.*
- Matthew Johnston
  p.c.: *Markov chain, absolute concentration robustness, deficiency, weak reversibility, linear programming, dynamical equivalence, etc.*
- Gilles Gnacadja
  p.c.: *probability, A. I. Vol'pert's Theorem, futile cascaded enzymatic network, etc.*

Algunos avances matemáticos

- Manoj Gopalkrishnan
  p.c.: *combinatorial geometry of reaction diagrams, Birch's theorem, persistence, global attractor conjecture, etc.*

  A geometric approach to the Global Attractor Conjecture, with Ezra Miller and Anne Shiu. (2013)
- Anne Shiu
  p.c.: *monomial parametrization, monotone systems, Descartes' rule of signs, oriented matroid, etc.*

  Sign conditions for injectivity of generalized polynomial maps with applications to chemical reaction networks and real algebraic geometry, with S. Muller, E. Feliu, G. Regensburger, C. Conradi, and A. Dickenstein. Submitted.
- Elisenda Feliu
  p.c.: *explicit analytical expressions, numerical simulations, power-law kinetics, stability, etc.*

Algunos avances matemáticos

- Jeremy Gunawardena
  p.c.: *Perturbation methods, algebraic elimination, linear framework, Matrix-Tree Theorem, quasi-steady state assumption, time-scale separation, etc.*

- Eduardo Sontag
  p.c.: *Neumann eigenvalues of elliptic operators, Turing instabilities, diffusion, partial differential equations, synchronization, small-gain theorem, monotone systems, etc.*

  Quantifying the effect of interconnections on the steady states of biomolecular networks. In Proc. IEEE Conf. Decision and Control, Los Angeles, Dec. 2014, 2014. Note: Submitted, under review.

Algunas revistas

- *Journal of Mathematical Biology*
- *Journal of Theoretical Biology*
- *SIAM Journal on Applied Mathematics*
- *Advances in Applied Mathematics*
- *Journal of the Royal Society Interface*

¿Y usted?

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¡Gracias por su atención!