Modelos estocásticos de circuitos genéticos

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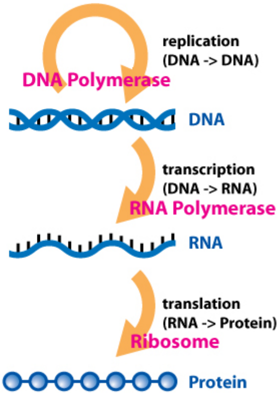
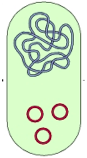
Marzo 9 de 2016

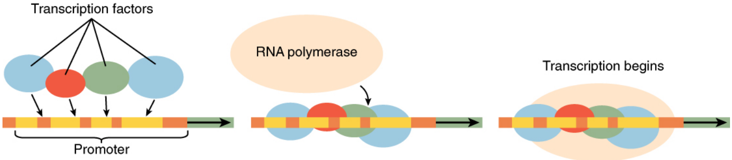
Expresión genética



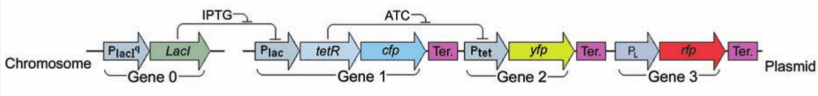
Tomado de:
https://en.wikipedia.org/wiki/Central_dogma_of_molecular_biology.



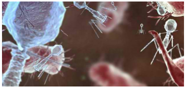
[Cooper, 2000].



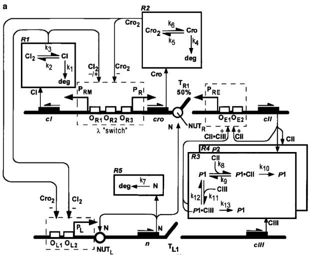
Circuitos genéticos



[Pedraza & van Oudenaarden, 2005].



Tomado de: `phages.org`.



[Arkin et al., 1998].

Ruido en circuitos genéticos

- Fluctuaciones aleatorias en expresión genética.
- En transcripción y traducción: Colisiones aleatorias entre moléculas que se encuentran en bajo número (Intrínseco).
  Para *E. coli* en promedio

$$\langle r \rangle_s \approx 5 \text{ ARNs}$$

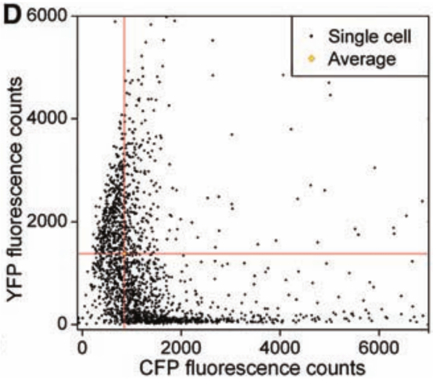
$$\langle p \rangle_s \approx 3000 \text{ proteínas}$$

- Otros factores como la división celular y la variablidad del ambiente (Extrínseco).

$$\eta_X = \frac{\sigma_X}{\langle X \rangle}.$$

$$\nu_X = \frac{\sigma_X^2}{\langle X \rangle}.$$

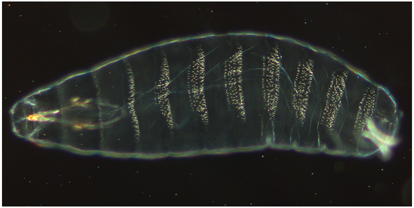
Manifestaciones del ruido



[Pedraza & van Oudenaarden, 2005].

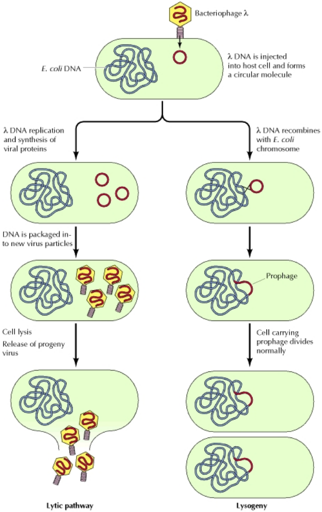
Estrategias ante el ruido

Robustez



Tomado de: `https://en.wikipedia.org/wiki/Drosophila_embryogenesis`.

Variabilidad



[Cooper, 2000].

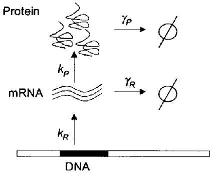
Intrinsic noise in gene regulatory networks

Mukund Thattai and Alexander van Oudenaarden*

Department of Physics, Room 13-2010, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139

Edited by Peter G. Wolynes, University of California at San Diego, La Jolla, CA, and approved May 18, 2001 (received for review December 12, 2000)

[Thattai & van Oudenaarden, 2001].



[Thattai & van Oudenaarden, 2001].

$$f_{r,p} \xrightarrow{k_R} f_{r+1,p}$$
$$f_{r,p} \xrightarrow{rk_P} f_{r,p+1}$$
$$f_{r,p} \xrightarrow{r\gamma_R} f_{r-1,p}$$
$$f_{r,p} \xrightarrow{p\gamma_P} f_{r,p-1}$$

[Thattai & van Oudenaarden, 2001].

$$\dot{r}(t) = k_R - \gamma_R r(t).$$
$$\dot{p}(t) = k_P r(t) - \gamma_P p(t).$$

$$\frac{df_{r,p}}{dt} = k_R f_{r-1,p} - k_R f_{r,p}$$
$$+ k_P r f_{r,p-1} - k_P r f_{r,p} + \gamma_R (r+1) f_{r+1,p}$$
$$- \gamma_R r f_{r,p} + \gamma_P (p+1) f_{r,p+1} - \gamma_P p f_{r,p}.$$

Un sólo gen - Resultados

Promedio

$$\langle r \rangle = \frac{k_R}{\gamma_R}.$$

$$\langle p \rangle = \frac{k_R b}{\gamma_P}.$$

Ruido

$$\nu_r = \frac{\sigma_r^2}{\langle r \rangle} = 1.$$

$$\nu_p = \frac{\sigma_p^2}{\langle p \rangle} = \frac{b}{1+\eta} + 1 \approx b + 1.$$

$$b := \frac{k_P}{\gamma_R}, \quad \eta := \frac{\gamma_P}{\gamma_R}.$$

Generalización - Ecs. deterministas

Las ecuaciones

$$\begin{aligned} \dot{r}(t) &= k_r - \gamma_r r(t), \\ \dot{p}(t) &= k_p r(t) - \gamma_p p(t), \end{aligned}$$

pueden ser escritas como

$$\dot{\mathbf{q}} = (A - \Gamma)\mathbf{q}.$$

Donde $\mathbf{q}^T := (d, r, p)$ y

$$A := \begin{array}{c} \\ (d) \\ (r) \\ (p) \end{array} \begin{array}{c} \begin{array}{ccc} (d) & (r) & (p) \end{array} \\ \begin{pmatrix} 0 & 0 & 0 \\ k_R & 0 & 0 \\ 0 & k_P & 0 \end{pmatrix} \end{array}, \qquad \Gamma := \begin{array}{c} \\ (d) \\ (r) \\ (p) \end{array} \begin{array}{c} \begin{array}{ccc} (d) & (r) & (p) \end{array} \\ \begin{pmatrix} 0 & 0 & 0 \\ 0 & \gamma_R & 0 \\ 0 & 0 & \gamma_P \end{pmatrix} \end{array}.$$

Generalización - Ec. maestra

Se puede realizar en general. Si $\mathbf{q}^T := (q_1, q_2, \ldots, q_n)$,

$$f_{q_i} \xrightarrow{k_i^+(q_j)} f_{q_i+1}$$

$$f_{q_i} \xrightarrow{k_i^-(q_j)} f_{q_i-1}$$

$$k_i^+(q_j) = \Sigma_j A_{ij} q_j \qquad k_i^-(q_j) = \Sigma_j \Gamma_{ij} q_j$$

[Thattai & van Oudenaarden, 2001].

la ecuación maestra queda

$$\dot{f}_{q_i} = \sum_j \left[(A_{ij} q_j) \left(f_{q_{i-1}} - f_{q_i} \right) \right] + \Gamma_{ii}(q_i + 1) f_{q_{i+1}} - \Gamma_{ii} q_i f_{q_i}.$$

Al realizar todo el procedimiento obtenemos

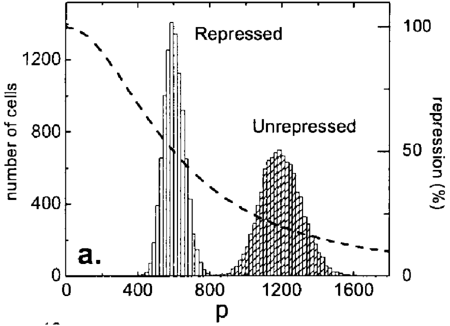
$$\left(\mathbf{A} - \boldsymbol{\Gamma}\right) \langle \mathbf{q} \rangle = 0.$$

$$0 = \Big(\left(\boldsymbol{\Gamma} - \mathbf{A}\right) \nabla\nabla^T F|_1 - A\Theta F|_1 \Big) + \Big(\left(\boldsymbol{\Gamma} - \mathbf{A}\right) \nabla\nabla^T F|_1 - A\Theta F|_1 \Big)^T,$$

$$\Theta_{ij} := \delta_{ij} \frac{\partial}{\partial z_i}.$$

Autorregulación - Modelo

[Thattai & van Oudenaarden, 2001].



[Thattai & van Oudenaarden, 2001].

- Ecuación de Hill.

$$k_R = \frac{k_R^{max}}{1 + (p/K_d)^n}.$$

- Linearizar alrededor del promedio en estado estacionario.

$$k_R \approx k_0 - k_1 p.$$

$$A = \begin{pmatrix} 0 & 0 & 0 \\ k_0 & 0 & -k_1 \\ 0 & k_P & 0 \end{pmatrix}.$$

Autorregulación - Resultados

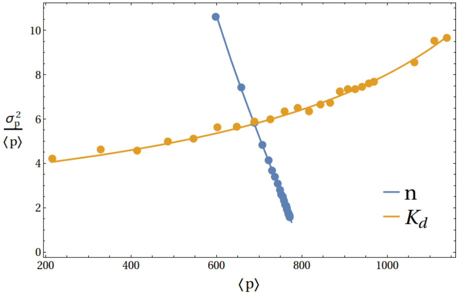
Promedio

$$\langle p\rangle = \frac{1}{1+b\phi}\cdot\frac{k_0 b}{\gamma_p}.$$

Ruido

$$\nu_p = \frac{1-\phi}{1+b\phi}\cdot\frac{b}{1+\eta}+1.$$

$$b := \frac{k_P}{\gamma_R},\quad \eta := \frac{\gamma_P}{\gamma_R},\quad \phi := \frac{k_1}{\gamma_P}.$$

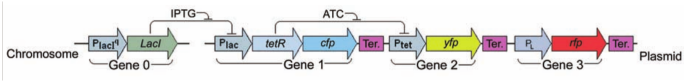


Ruido global y propagación del ruido

Noise Propagation in Gene Networks

Juan M. Pedraza and Alexander van Oudenaarden*

[Pedraza & van Oudenaarden, 2005].



[Pedraza & van Oudenaarden, 2005].

Ecuación de Langevin - Gen 0

Ecuación determinista con términos de ruido. Para el gen 0

$$\dot{p}_0 = k - \gamma p_0 + \mu_0 + \xi_0.$$

Los términos de ruido cumplen:

$$\langle \mu_0 \rangle = \langle \xi_0 \rangle = 0,$$

$$\langle \mu_0(t)\mu_0(t+\tau) \rangle = 2\gamma(b_0+1)\bar{p}_0\delta(\tau),$$
$$\langle \xi_0(t)\xi_0(t+\tau) \rangle = 2\gamma\eta_G^2 \bar{p}_0{}^2\delta(\tau),$$
$$\langle \mu_0(t)\xi_0(t+\tau) \rangle = 0.$$

Luego de hacer el proceso:

$$\eta_0^2 = \frac{b_0+1}{\bar{p}_0} + \eta_{0G}^2 := \eta_{0\,\mathrm{int}}^2 + \eta_{0G}^2$$

Ec. de Langevin - Gen 1

Ahora para el gen 1

$$\dot{p}_1 = Nf_1(p_0) - \gamma p_1 + \mu_1 + \xi_1$$

Además de las anteriores autocorrelaciones, hay que incluir:

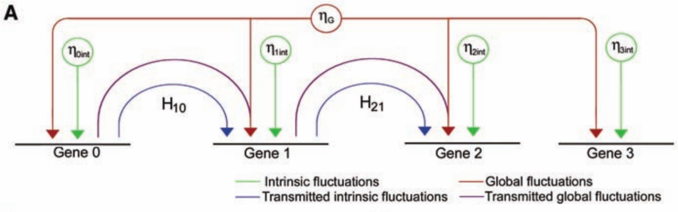
$$\langle \xi_0(t)\xi_1(t+\tau)\rangle = 2\gamma\eta_G^2\bar{p}_0\bar{p}_1\delta(\tau),$$

$$\langle \mu_0(t)\mu_1(t+\tau)\rangle = 0.$$

Se obtiene al final

$$\eta_1^2 = \eta_{1\,\mathrm{int}}^2 + \frac{1}{2}H_{10}^2\eta_{0\,\mathrm{int}}^2 + \eta_G^2\left(1 + \frac{1}{2}H_{10}^2 - H_{10}\right) + \frac{1}{2}\eta_N^2$$

Distintas fuentes de ruido y su propagación



[Pedraza & van Oudenaarden, 2005].

Ec. de Langevin - Gen 2

Y similarmente para el gen 2

$$\eta_2^2 = \eta_{2\,\text{int}}^2 + \frac{1}{2}H_{21}^2\eta_{1\,\text{int}}^2 + \frac{3}{8}H_{21}^2H_{10}^2\eta_{0\,\text{int}}^2 + \eta_G^2\left(1 + \frac{1}{2}H_{21}^2 \right.$$
$$\left. + \frac{3}{8}H_{21}^2H_{10}^2 - H_{21} - \frac{3}{4}H_{21}^2H_{10} + \frac{1}{2}H_{21}H_{10}\right) + \eta_N^2\left(\frac{1}{2} + \frac{3}{8}H_{21}^2 - \frac{3}{4}H_{21}\right).$$

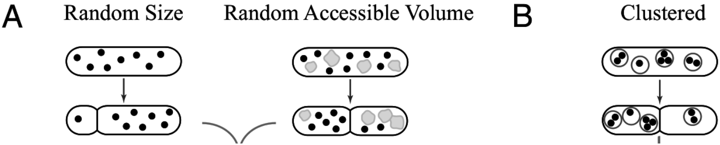
Ruido por partición

Random partitioning of molecules at cell division

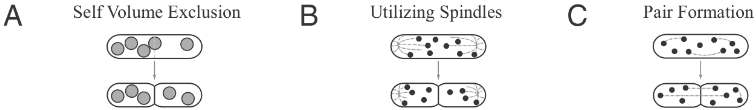
Dann Huh[a,b] and Johan Paulsson[a,1]

[a]Department of Systems Biology, Harvard University, Boston, MA 02115; and [b]Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138

[Huh & Paulsson, 2011b].

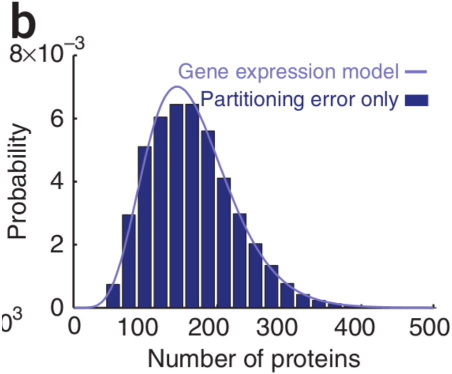


[Huh & Paulsson, 2011b].



[Huh & Paulsson, 2011b].

Consecuencias de errores de partición



[Huh & Paulsson, 2011a].

Futuras investigaciones

- Considerar las no-linealidades.
- Considerar la dinámica temporal del ruido.
- Posibilidad de usar herramientas teóricas adicionales.

Referencias

Arkin, A., Ross, J. & McAdams H. H. (1998).
Stochastic Kinetic Analysis of Developmental Pathway Bifurcation in Phage λ-Infected Escherichia coli Cells.
Genetics 149, 1633 – 1648.

Cooper, G. M. (2000).
The Cell, A Molecular Approach. 2nd Edition.
Sunderland (MA): Sinauer Associates.

Thattai, M. & van Oudenaarden, A. (2001).
Intrinsic noise in gene regulatory networks.
Proc. Natl. Acad. Sci. U.S.A. 98(15), 8614 – 8619.

Paulsson, J. (2004)
Summing up the noise in gene networks.
Nature 427, 415–418.

Kaern, M., Elston, T. C., Blake, W. J. & Collins, J. J. (2005).
Stochasticity in gene expression: from theories to phenothypes.
Nat. Rev. Genet. 6(6), 451 – 464.

Referencias

Pedraza, J. M. & van Oudenaarden, A. (2005).
Noise Propagation in Gene Networks.
Science 307, 1965 – 1969.

Paulsson, J. (2005).
Models of stochastic gene expression.
Phys. Life Rev. 2, 157–175.

Pedraza, J. M. & Paulsson, J. (2008).
Effects of Molecular Memory and Bursting on Fluctuations in Gene Expression.
Science 319, 339–343.

Huh, D. & Paulsson, J. (2011).
Non-genetic heterogeneity from stochastic partitioning at cell division.
Nat. Genet. 43, 95–100.

Huh, D. & Paulsson, J. (2011).
Random partitioning of molecules at cell division.
Proc. Natl. Acad. Sci. U.S.A. 108, 15004–15009.