Modelos estocásticos en circuitos genéticos

Luis Alberto Gutiérrez López

Universidad de los Andes
Departamento de Física
Seminario de Biofísica

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Ruido en circuitos genéticos

- Fluctuaciones aleatorias en expresión genética.
- En transcripción y traducción: Colisiones aleatorias entre moléculas que se encuentran en bajo número.
- Otros factores como la división celular, la variablidad del ambiente.

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

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

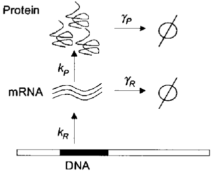
Intrinsic noise in gene regulatory networks

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

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

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

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

Generalización - Ec. maestra

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

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

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

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

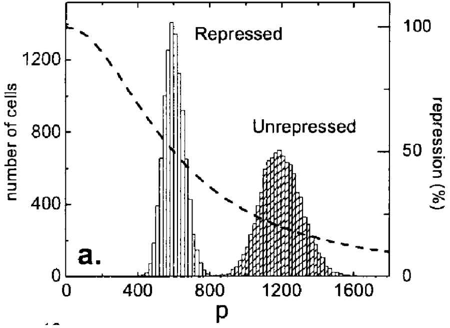
[Thattai & van Oudenaarden, 2001].

la ecuación maestra queda

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

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

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

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

- Posibilidad de biestabilidad.
- Linearizar alrededor de cada punto de equilibrio.

Promedio temporal - Teorema de fluctuación-disipación

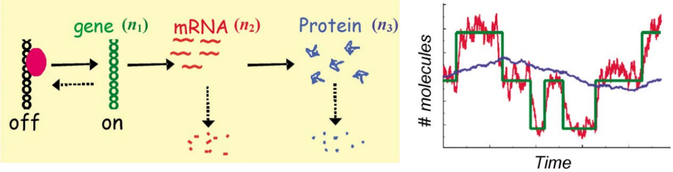
analysis

Summing up the noise in gene networks

Johan Paulsson

Department of Molecular Biology, Princeton University, Washington Road, Princeton, New Jersey 08544-1014, USA, and Department of Applied Mathematics and Theoretical Physics, Centre for Mathematical Sciences, Wilberforce Road, University of Cambridge, Cambridge CB3 0WA, UK

[Paulsson, 2004].



[Paulsson, 2005].

$$\frac{d\boldsymbol{\sigma}}{dt} = \boldsymbol{A\sigma} + \boldsymbol{\sigma A^T} + \boldsymbol{B}$$

Donde $\boldsymbol{\sigma}$ es la matriz de covarianzas. $\boldsymbol{A}$ y $\boldsymbol{B}$ dependen de las tasas.

Promedio temporal en el ruido

$$\frac{\sigma_1^2}{\langle n_1\rangle^2} = \frac{1}{n_1^{\max}}\frac{\lambda_1^-}{\lambda_1^+} = \frac{1-P_{\mathrm{on}}}{\langle n_1\rangle}.$$

[Paulsson, 2005].

$$\frac{\sigma_2^2}{\langle n_2\rangle^2} = \frac{1}{\langle n_2\rangle} + \frac{1-P_{\mathrm{on}}}{\langle n_1\rangle}\frac{\tau_1}{\tau_2+\tau_1}.$$

[Paulsson, 2005].

$$\overbrace{\frac{\sigma_3^2}{\langle n_3\rangle^2}}^{\substack{\text{Total}\\ \text{protein noise}}} = \overbrace{\underbrace{\frac{1}{\langle n_3\rangle}}_{\text{Poisson}}}^{\substack{\text{From individual}\\ \text{births and deaths}}} + \overbrace{\underbrace{\frac{1}{\langle n_2\rangle}}_{\text{Poisson}}\underbrace{\frac{\tau_2}{\tau_3+\tau_2}}_{\substack{\text{One-step}\\ \text{time-averaging}}}}^{\substack{\text{From spontaneous}\\ \text{mRNA noise}}} + \overbrace{\underbrace{\frac{1-P_{\mathrm{on}}}{\langle n_1\rangle}}_{\text{Binomal}}\underbrace{\frac{\tau_2}{\tau_2+\tau_3}\frac{\tau_1}{\tau_1+\tau_3}\frac{\tau_1+\tau_3+\tau_1\tau_3/\tau_2}{\tau_1+\tau_2}}_{\substack{\text{Two-step}\\ \text{time-averaging}}}}^{\substack{\text{From forced mRNA noise, originating}\\ \text{in gene activation-inactivation}}}.$$

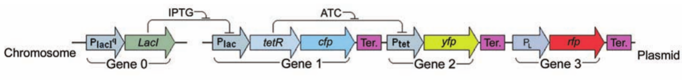
[Paulsson, 2005].

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:

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

$$\langle \mu_0(t)\mu_0(t+\tau) \rangle = q_{0_{\text{int}}}\delta(\tau) = 2\gamma \tilde{b_0} \bar{p_0} \delta(\tau),$$

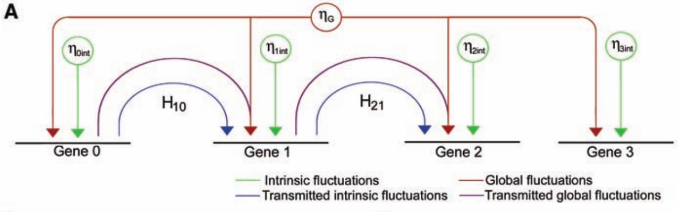
$$\langle \xi_0(t)\xi_0(t+\tau) \rangle = q_{0_G}\delta(\tau) = 2\gamma \eta_G^2 \bar{p_0}^2 \delta(\tau),$$

$$\langle \mu_0(t)\xi_0(t+\tau) \rangle = 0.$$

Luego de hacer el proceso:

$$\eta_0^2 = \eta_{0\,\text{int}}^2 + \eta_{0G}^2$$

Distintas fuentes de ruido y su propagación



[Pedraza & van Oudenaarden, 2005].

Ec. de Langevin - Gen 1

Ahora para el gen 1

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

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

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

Ec. de Langevin - Gen 2

Y similarmente para el gen 2

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

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].

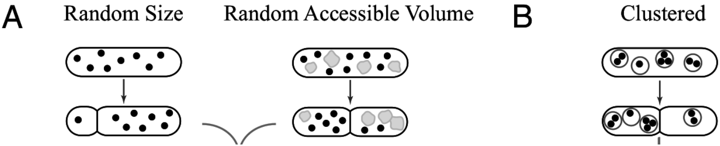
Para un componente X, donde L y R copias se segregan a cada hija:

$$Q_X^2 = \frac{\langle (L-R)^2 \rangle}{\langle X \rangle^2}$$

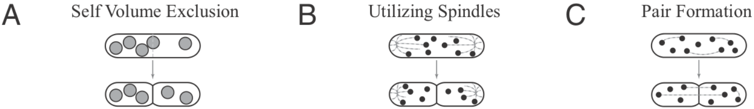
Para segregación independiente:

$$Q_X = \frac{1}{\sqrt{X}}$$

Segregación ordenada y desordenada



[Huh & Paulsson, 2011b].

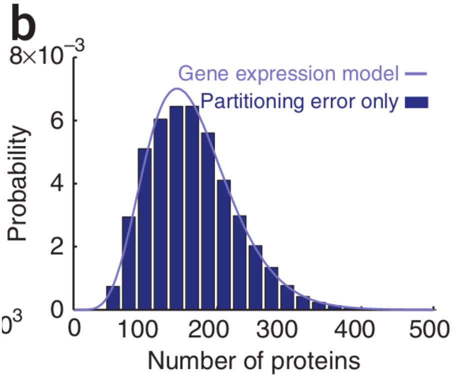


[Huh & Paulsson, 2011b].

Para los mecanismos considerados

$$Q_X^2 = \frac{A}{X}, \quad \text{donde} \quad \begin{cases} A = 1 & \text{para segregación independiente,} \\ A < 1 & \text{para segregación ordenada,} \\ A > 1 & \text{para segregación desordenada.} \end{cases}$$

Consecuencias de errores de partición



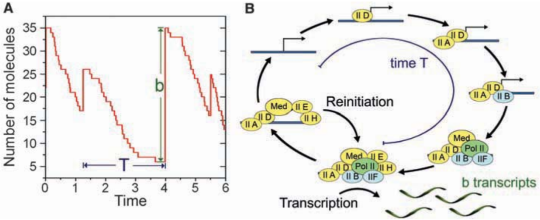
[Huh & Paulsson, 2011a].

- Error por segregación desordenada vs. correcciones por ordenada.
- Hay que controlar cada componente por separado (vs. *feedback* negativo para expresión genética) e.g. segregación en clusters.

Effects of Molecular Memory and Bursting on Fluctuations in Gene Expression

Juan M. Pedraza[1] and Johan Paulsson[1,2]*

[Pedraza & Paulsson, 2008].



[Pedraza & Paulsson, 2008].

$$\frac{\sigma_p^2}{\langle p \rangle^2} = \frac{1}{\langle p \rangle} + \frac{1}{\langle r \rangle} \cdot \frac{\tau_r}{\tau_r + \tau_p} \cdot \frac{\langle b \rangle (\sigma_T^2 / \langle T \rangle^2 + \sigma_b^2 / \langle b \rangle^2) + 1}{2}$$

Futuras investigaciones

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

- Contar moléculas individuales.
- Seguir la dinámica temporal de los componentes celulares.

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