

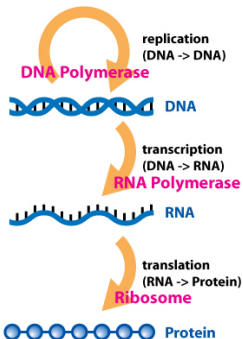
Modelos estocásticos de circuitos genéticos

Luis Alberto Gutiérrez López

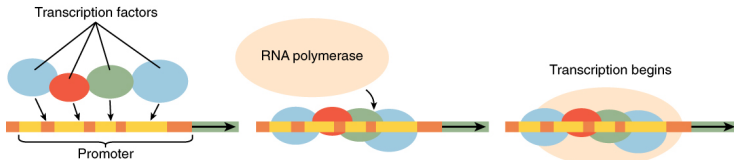
Universidad de los Andes
Departamento de Física

Marzo 9 de 2016

Expresión genética

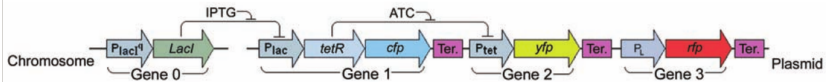


Tomado de: https://en.wikipedia.org/wiki/Central_dogma_of_molecular_biology.

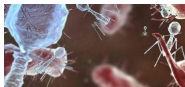


Tomado de <http://oerpub.github.io/epubjs-demo-book/content/m46036.xhtml>.

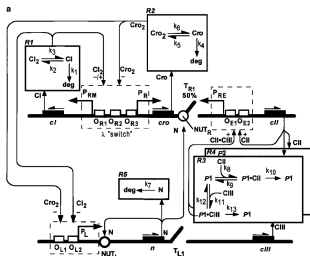
Circuitos genéticos



[Pedraza & van Oudenaarden, 2005].



Tomado de: phages.org.



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

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

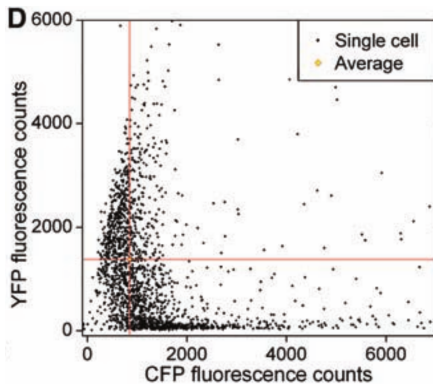
$$\langle p \rangle_s \approx 3000 \text{ proteínas}$$

- Otros factores como la división celular y la variabilidad 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

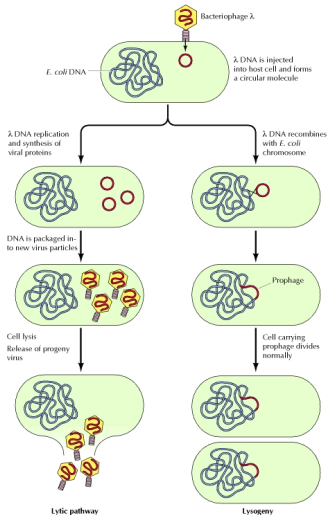
Robustez



Tomado de:

https://en.wikipedia.org/wiki/Drosophila_embryogenesis.

Variabilidad



[Cooper, 2000].

Intrinsic noise in gene regulatory networks

Mukund Thattai and Alexander van Oudenaarden*

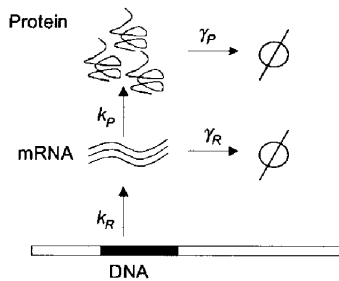
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Edited by Peter G. Wolynes, University of California at San Diego, La Jolla, CA, and approved May 18, 2001 (received for review December 12, 2000)

[Thattai & van Oudenaarden, 2001].

Suposiciones y ecuaciones deterministas

- La tasa de producción de ARN es cte. k_R .
- Tasa de producción de proteínas cte. por cada ARN k_P .
- Tasas de decaimiento γ_R y γ_P .
- $k_R \sim 1 \frac{\text{RNA}}{\text{min}}$.
- $k_P \sim 60 \frac{\text{proteínas}}{\text{RNA min}}$.
- $\gamma_R \sim \frac{1}{5 \text{ min}}$.
- $\gamma_P \sim \frac{1}{30 \text{ min}}$.



[Thattai & van Oudenaarden, 2001].

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

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

Generalización de ecuaciones 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

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

Ecuación maestra

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

[Thattai & van Oudenaarden, 2001].

$$\begin{aligned}\frac{df(r,p)}{dt} &= k_R f(r-1,p) - k_R f(r,p) + k_P r f(r,p-1) - k_P r f(r,p) \\&\quad + \gamma_R (r+1) f(r+1,p) - \gamma_R r f(r,p) + \gamma_P (p+1) f(r,p+1) - \gamma_P p f(r,p).\end{aligned}$$

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

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

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

$$k_i^+(q_j) = \sum_j A_{ij} q_j \quad k_i^-(q_j) = \sum_j \Gamma_{ij} q_j$$

[Thattai & van Oudenaarden, 2001].

la ecuación maestra queda

$$\begin{aligned} \dot{f}(\mathbf{q}) = & \sum_{i=1}^n \sum_{j=1}^n [(A_{ij} q_j) (f(q_i - 1) - f(q_i))] \\ & + \Gamma_{ii} (q_i + 1) f(q_i + 1) - \Gamma_{ii} q_i f(q_i) . \end{aligned}$$

Función generadora de momentos

$$F(z_1, \dots, z_n) := \sum_{q_1, \dots, q_n=0}^{\infty} z_1^{q_1} \dots z_n^{q_n} f(q_1, \dots, q_n).$$

Para todos $i, j = 1, \dots, n$ se cumple que: ($|_1 := |_{z_1, \dots, z_n=1}$)

$$F|_1 = 1.$$

$$\left. \frac{\partial F}{\partial z_i} \right|_1 = \langle q_i \rangle.$$

$$\left. \frac{\partial^2 F}{\partial z_i \partial z_j} \right|_1 = \langle q_i q_j \rangle, \quad i \neq j.$$

$$\left. \frac{\partial^2 F}{\partial z_i^2} \right|_1 = \langle q_i(q_i - 1) \rangle.$$

La ec. para F es

$$\dot{F} = \sum_{i=1}^n (1 - z_i) \left(\Gamma_i \frac{\partial F}{\partial z_i} - \sum_{j=1}^n A_{ij} z_j \frac{\partial F}{\partial z_j} \right).$$

En s.s., derivando y evaluando en 1

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

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

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

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

Promedio

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

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

Ruido

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

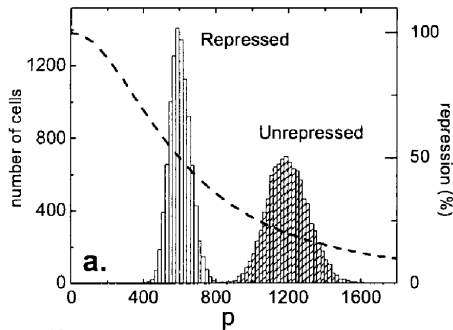
$$\nu_p = \frac{\sigma_p^2}{\langle p \rangle} = \frac{b}{1 + \eta} + 1 \approx b + 1.$$

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

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

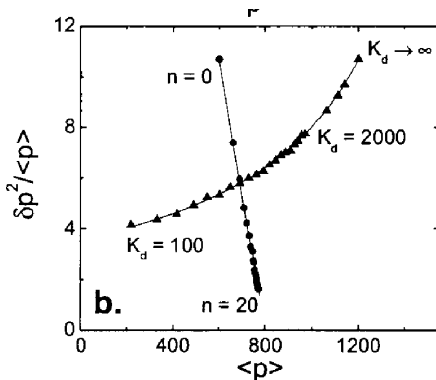
Promedio

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

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

Ruido

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



[Thattai & van Oudenaarden, 2001].

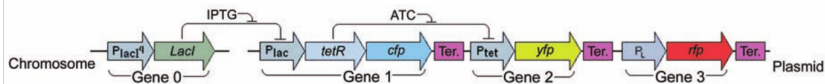
- Hay muchas otras fuentes de ruido que no se consideran.
- Modelo linearizado.
- No sirve para explicar el comportamiento lejos de los puntos fijos si el sistema es no lineal.

Noise Propagation in Gene Networks

Juan M. Pedraza and Alexander van Oudenaarden*

Accurately predicting noise propagation in gene networks is crucial for understanding signal fidelity in natural networks and designing noise-tolerant gene circuits. To quantify how noise propagates through gene networks, we measured expression correlations between genes in single cells. We found that

[Pedraza & van Oudenaarden, 2005].



[Pedraza & van Oudenaarden, 2005].

Ecuación de Langevin

Para el gen 0

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

$$\langle \mu_0 \rangle = \langle \xi_{0G} \rangle = 0,$$

$$\langle \mu_0(t) \mu_0(t + \tau) \rangle = 2\gamma \tilde{b}_0 \overline{p_0} \delta(\tau),$$

$$\langle \xi_0(t) \xi_0(t + \tau) \rangle = 2\gamma \eta_G^2 \overline{p_0}^2 \delta(\tau).$$

El ruido es

$$\eta_0^2 = \frac{\tilde{b}_0}{\overline{p_0}} + \eta_G^2 = \eta_{0_{\text{int}}}^2 + \eta_G^2$$

La ec. para p_1 es

$$\dot{p}_1(t) = k_1(p_{0A}) - \gamma p_1(t) + \mu_1(t) + \xi_1(t).$$

Los distintos ruidos globales están correlacionados

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

El ruido para el gen 1 es

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