Modelos de ruido en circuitos genéticos

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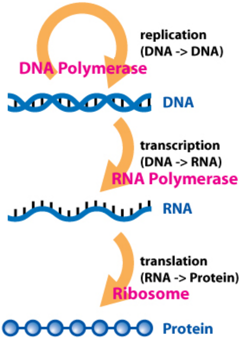
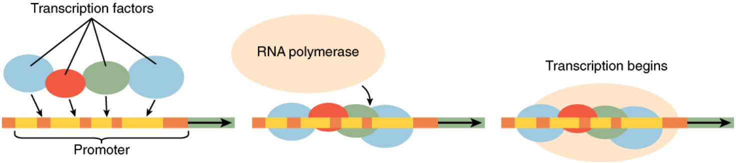
Expresión genética

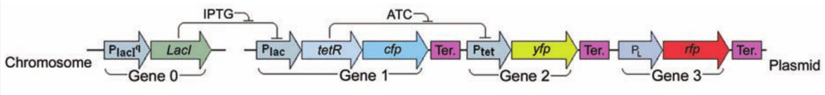


Tomado de: `https://en.wikipedia.org/wiki/Central_dogma_of_molecular_biology`.

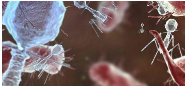


Tomado de `http://oerpub.github.io/epubjs-demo-book/content/m46036.xhtml`.

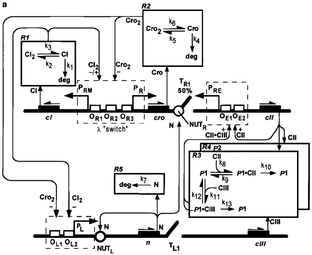
Circuitos genéticos



[Pedraza & van Oudenaarden, 2005].



Tomado de: phages.org.



[Arkin et al., 1998].

Biología de sistemas

- Holismo (SysBio.) vs. reduccionismo (Bio.).
- Interacciones entre partes vs. estructura y funcionamiento de elementos individuales.
- Ingeniería (e.g. motifs).

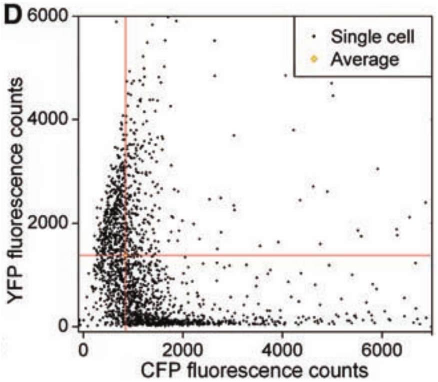
Ruido en circuitos genéticos

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

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

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

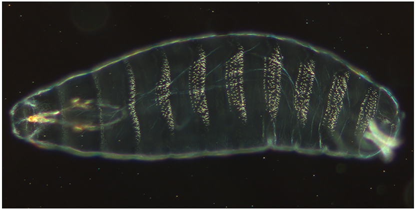
Manifestaciones del ruido



[Pedraza & van Oudenaarden, 2005].

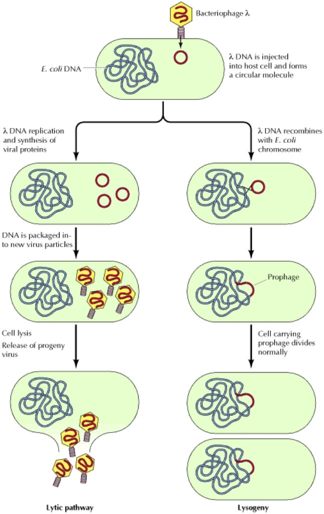
Estrategias ante el ruido

Robustez



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

Variabilidad



[Cooper, 2000].

Ruido intrínseco en circuitos genéticos

Intrinsic noise in gene regulatory networks

Mukund Thattai and Alexander van Oudenaarden*

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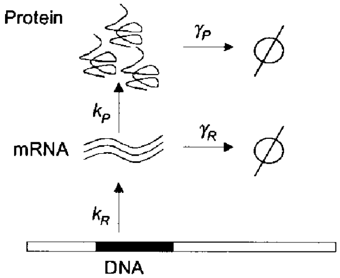
Edited by Peter G. Wolynes, University of California at San Diego, La Jolla, CA, and approved May 18, 2001 (received for review December 12, 2000)

[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.
- $k_R \sim 1 \frac{\text{RNA}}{\text{min}}$.
- $k_P \sim 60 \frac{\text{proteínas}}{\text{RNA min}}$.
- $\gamma_R \sim \frac{1}{5 \text{ min}}$.
- $\gamma_R \sim \frac{1}{30 \text{ min}}$.



[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

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

Ecuación maestra

$$f_{r,p} \xrightarrow{k_R} f_{r+1,p}$$

$$f_{r,p} \xrightarrow{rk_P} f_{r,p+1}$$

$$f_{r,p} \xrightarrow{r\gamma_R} f_{r-1,p}$$

$$f_{r,p} \xrightarrow{p\gamma_P} f_{r,p-1}$$

[Thattai & van Oudenaarden, 2001].

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

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

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

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

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

[Thattai & van Oudenaarden, 2001].

la ecuación maestra queda

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

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: $\left(|_1 := |_{z_1,\dots,z_n=1}\right)$

$$F\big|_1 = 1.$$

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

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

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

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. y derivando respecto a z_l

$$\begin{aligned} 0 = &\sum_{i=1}^{n} (1 - z_i) \left(\Gamma_i \frac{\partial^2 F}{\partial z_i \partial z_j} - \sum_{j=1}^{n} A_{ij} \left(z_j \frac{\partial^2 F}{\partial z_j \partial z_l} + \delta_{lj} \frac{\partial F}{\partial z_j} \right) \right) \\ &- \delta_{il} \left(\Gamma_i \frac{\partial F}{\partial z_i} - \sum_{i=1}^{n} A_{ij} z_j \frac{\partial F}{\partial z_j} \right) . \end{aligned}$$

Evaluando en 1

$$0 = -\Gamma_l \langle q_l \rangle + \sum_{j=1}^{n} A_{lj} \langle q_j \rangle .$$

$$\sum_{j=1}^{n} \left(A_{lj} - \delta_{ij}\Gamma_{lj}\right) \langle q_j \rangle.$$

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

Derivando y evaluando en 1

$$0 = \left(\Gamma_{ii} \left. \frac{\partial^2 F}{\partial z_i \partial z_j} \right|_1 - \sum_{j=1}^{n} Aij z_j \left. \frac{\partial^2 F}{\partial z_j \partial z_l} \right|_1 - A_{il} \left. \frac{\partial F}{\partial z_l} \right|_1 \right) + \left(\Gamma_{ll} \left. \frac{\partial^2 F}{\partial z_l \partial z_i} \right|_1 - \sum_{j=1}^{n} Alj z_j \left. \frac{\partial^2 F}{\partial z_j \partial z_i} \right|_1 - A_{li} \left. \frac{\partial F}{\partial z_i} \right|_1 \right).$$

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

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

Un sólo gen - Resultados

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

Promedio

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

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

Ruido

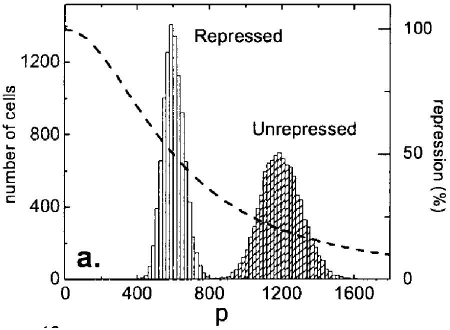
$$\nu_r = \frac{\sigma_r^2}{\langle r \rangle} = 1.$$

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

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

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

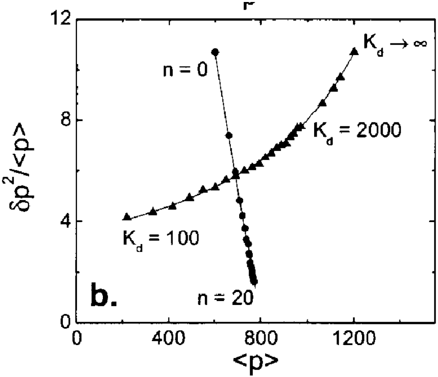
Promedio

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

Ruido

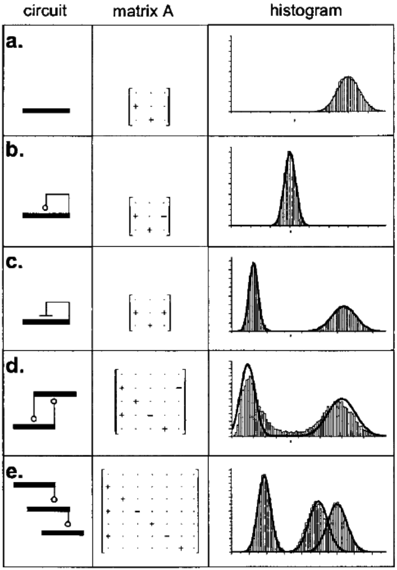
$$\nu_p = \frac{1-\phi}{1+b\phi} \cdot \frac{b}{1+\eta} + 1.$$

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



[Thattai & van Oudenaarden, 2001].

En general



[Thattai & van Oudenaarden, 2001].

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

Problemas

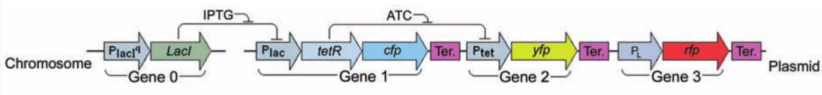
- Hay muchas otras fuentes de ruido que no se consideran.
- Modelo linearizado.
- No sirve para explicar el comportamiento lejos de los puntos fijos si el sistema es no lineal.

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

$$\dot{p_0}(t) = k - \gamma p_0(t) + \mu_0(t) + \xi_{0G}(t).$$

$$\begin{aligned}
\langle \mu_0 \rangle &= \langle \xi_{0G} \rangle = 0, \\
\langle \mu_0(t)\mu_0(t+\tau) \rangle &= 2\gamma \tilde{b_0} \overline{p_0} \delta(\tau), \\
\langle \xi_{0G}(t)\xi_{0G}(t+\tau) \rangle &= 2\gamma \eta_G^2 \overline{p_0}^2 \delta(\tau).
\end{aligned}$$

Escribiendo $\Delta p_0 := p_0 - \bar{p_0}$,

$$\begin{aligned}
\dot{\Delta p_0} &= k - \gamma \Delta p_0 - \gamma \overline{p_0} + \mu_0 + \xi_{0G} \\
&= -\gamma \Delta p_0 + \mu_0 + \xi_{0G}.
\end{aligned}$$

Aplicando transformada de Fourier

$$i\omega(\Delta p_0) = -\gamma(\Delta p_0) + \mu_0 + \xi_{0G}.$$

Despejando Δp_0, tomando norma al cuadrado y promediando

$$\langle|\Delta p_0|^2\rangle = \frac{\langle|\mu_0|^2\rangle + \langle|\xi_{0G}|^2\rangle}{\omega^2 + \gamma^2}.$$

Del teorema de Wiener-Khinchin

$$\langle|\Delta p_0|^2\rangle = \left(2\gamma\tilde{b_0}\overline{p_0} + 2\gamma\eta_G^2\overline{p_0}^2\right)\frac{1}{\omega^2 + \gamma^2}$$

Antitransformando

$$\langle \Delta p_0^2 \rangle = \sigma^2(p_0) = 2\gamma \overline{p_0} \left(\tilde{b_0} + \eta_G^2 \overline{p_0} \right) \frac{1}{2\pi} \int_{-\infty}^{\infty} \frac{d\omega}{\omega^2 + \gamma^2}$$

.
La integral es $2i\pi \frac{1}{2i\gamma}$. Entonces

$$\sigma^2(p_0) = \overline{p_0} \left(\tilde{b_0} + \eta_G^2 p_0 \right)$$

.
Y el ruido es

$$\eta_0^2 = \frac{\tilde{b_0}}{\overline{p_0}} + \eta_G^2 = \eta_{0_{\text{int}}}^2 + \eta_G^2$$

.

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