

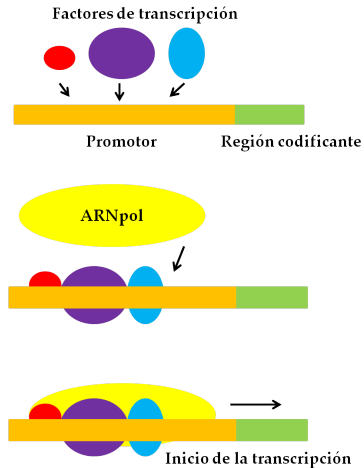
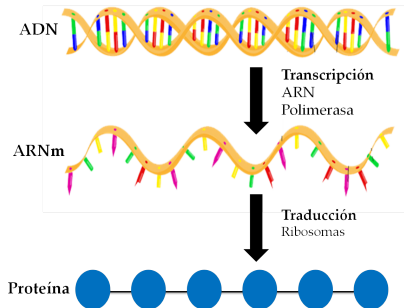
Modelos estocásticos de circuitos genéticos

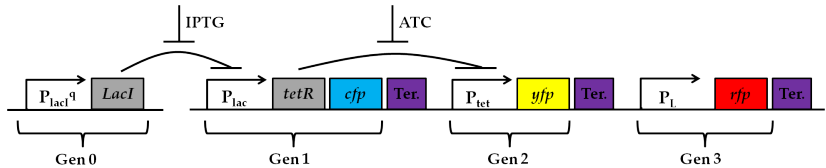
Luis Alberto Gutiérrez López

Director: Juan Manuel Pedraza Leal

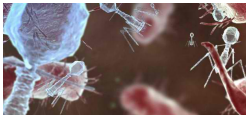
Universidad de los Andes
Departamento de Física

Mayo 23, 2016

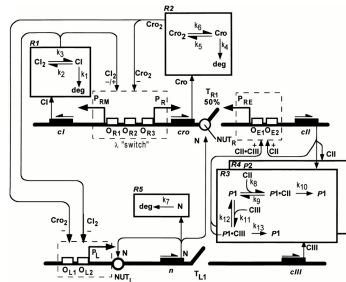




Pedraza y van Oudenaarden (2005).



Tomado de phages.org.



Arkin y col. (1998).

- ▶ 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

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

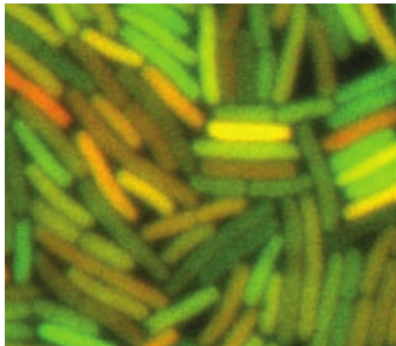
$$\langle p \rangle_s \approx 3000 \text{ proteínas}$$

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

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

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

- Los efectos del ruido son muy notorios.



Elowitz y col. (2002).

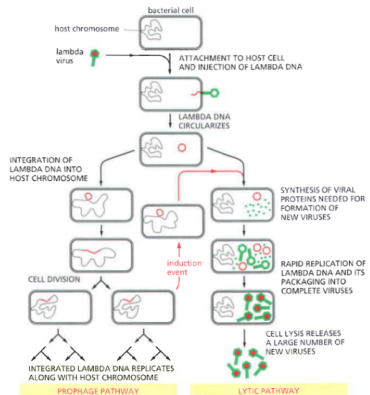
► Estrategias ante el ruido

Robustez

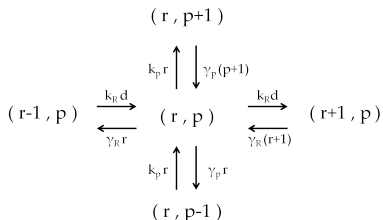
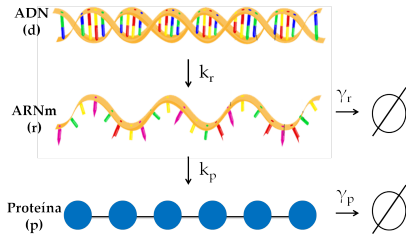


Embrión de *D. melanogaster* (mosca de la fruta). Tomado de: https://en.wikipedia.org/wiki/Drosophila_embryogenesis.

Variabilidad



Alberts y col. (2008).



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

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

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

Promedio

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

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

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

Ruido

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

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

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

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

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

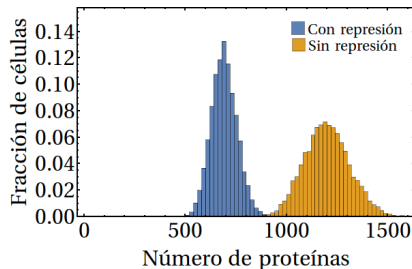
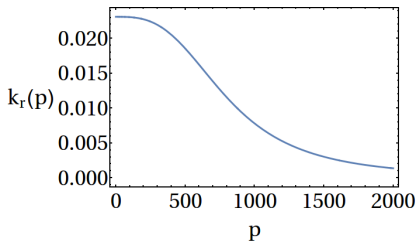
$$\dot{f} = \sum_i \sum_j [(A_{ij} q_j) (f_{q_{i-1}} - f_{q_i})] + \Gamma_{ii} (q_i + 1) f_{q_{i+1}} - \Gamma_{ii} q_i f_{q_i}.$$

Al realizar todo el procedimiento obtenemos en estado estacionario

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

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

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



► Ecuación de Hill.

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

► Linearizar alrededor del promedio en estado estacionario.

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

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

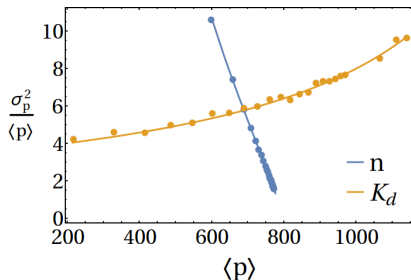
Promedio

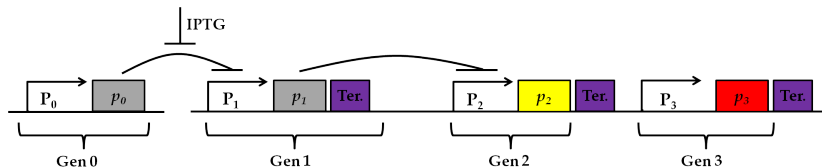
$$\langle p \rangle = \frac{1}{1 + b\phi} \cdot \frac{k_0 b}{\gamma_P}.$$

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

Ruido

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





Pedraza y van Oudenaarden (2005).

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:

$$\eta_0^2 = \frac{b_0 + 1}{\bar{p}_0} + \eta_G^2 := \eta_{0\text{int}}^2 + \eta_G^2$$

Ahora para el gen 1

$$\dot{p}_1 = f_1(p_0) - \gamma p_1 + \mu_1 + \xi_1$$

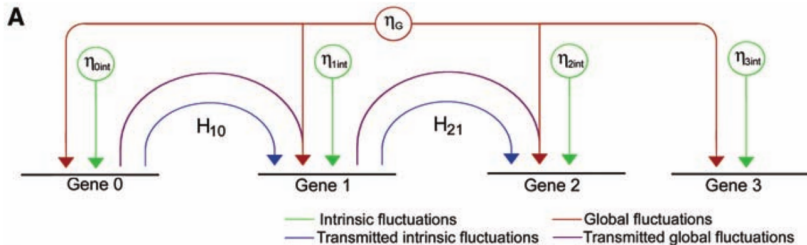
Además de las anteriores autocorrelaciones, hay que incluir:

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

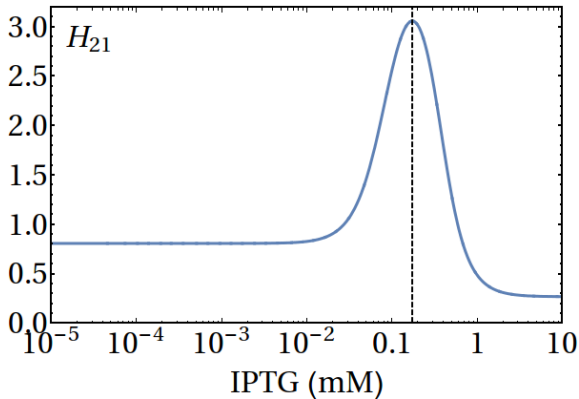
$$\langle \mu_0(t) \mu_1(t + \tau) \rangle = 0.$$

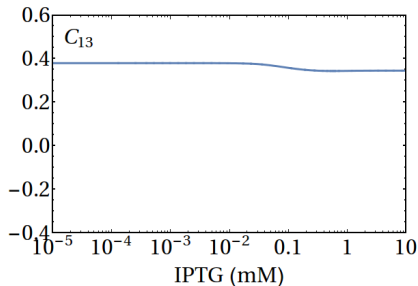
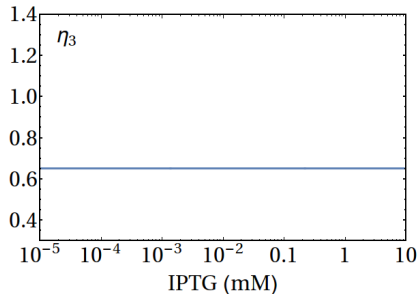
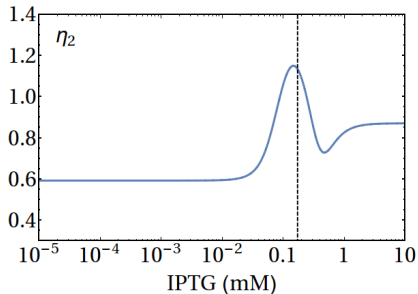
Se obtiene al final

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

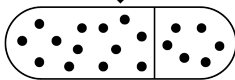
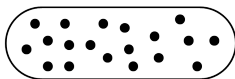


Pedraza y van Oudenaarden (2005).

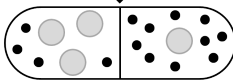
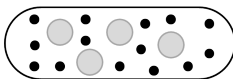




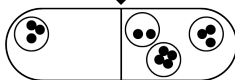
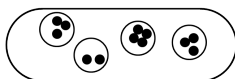
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Sitio de división

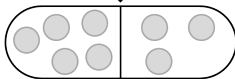
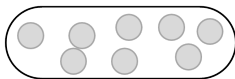


Volumen accesible

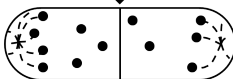
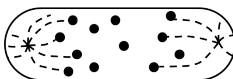


Segregación en grupos

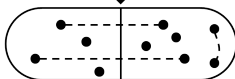
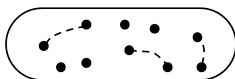
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Exclusión por volumen



Segregación mediante husos



Formación de pares

Para un componente X , donde L y R copias se segregan a cada hija, el error en la partición está dado por

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

Para segregación independiente:






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






Para los mecanismos considerados






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






- ▶ Ecuación maestra vs. ecuación de Langevin.
- ▶ Dificultad para identificar las fuentes de ruido.
- ▶ Técnicas experimentales para medir con mayor resolución.






- ▶ Analizar el ruido por partición mediante simulaciones que lo integren con transcripción y traducción.
- ▶ Analizar la aleatoriedad en el volumen de la célula.

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