

Repressilator and Toggle Switch

Stochastic simulations

Stochastic simulations allow to take into account the fluctuations due, for example, to the low number of molecules present in a system (intrinsic noise) (Raser & O’Shea, 2005; Kaern et al, 2005; Raj & van Oudenaarden, 2008). Numerical methods have been proposed to simulate such stochastic models (Gillespie 2007; Andrews et al, 2009). The stochastic approach is complementary to deterministic approaches and can be used to address the question of the robustness of dynamical behaviors when the number of molecules is low, to identify molecular mechanisms that affect this robustness, or to highlight possible noise-induced dynamical behaviors.

In this project it is proposed to simulate the stochastic version of the Repressilator (Elowitz & Leibler, 2000) and of the Toggle Switch (Gardner et al, 2000) models using the Gillespie algorithm (Gillespie, 1977).

References

- Andrews SS, Dinh T, Arkin AP (2009) Stochastic models of biological processes” Encyclopedia of Complexity and System Science, Meyers, Robert (Ed.) Vol. 9:8730-8749, Springer.
- Elowitz MB, Leibler S (2000) A synthetic oscillatory network of transcriptional regulators. *Nature* 403:335-8.
- Gardner TS, Cantor CR, Collins JJ (2000) Construction of a genetic toggle switch in *Escherichia coli*. *Nature* 403:339-42.
- Gillespie DT (1977) Exact stochastic simulation of coupled chemical reactions, *J. Phys. Chem.* 81:2340-2361.
- Gillespie DT (2007) Stochastic simulation of chemical kinetics. *Annu Rev Phys Chem.* 58:35-55.
- Kaern M, Elston TC, Blake WJ, Collins JJ (2005) Stochasticity in gene expression: from theories to phenotypes. *Nat Rev Genet.* 6:451-64.
- Raj A, van Oudenaarden A (2008) Nature, nurture, or chance: stochastic gene expression and its consequences. *Cell.* 135:216-26.
- Raser JM, O’Shea EK (2005) Noise in gene expression: origins, consequences, and control. *Science.* 309:2010-3.

Toggle Switch

Equations

Equations of the original model for the Toggle switch (Gardner et al, 2000):

$$\frac{dx}{dt} = \alpha_1 \frac{K_1^n}{K_1^n + y^n} - \delta_1 x \quad (1)$$

$$\frac{dy}{dt} = \alpha_2 \frac{K_2^n}{K_2^n + x^n} - \delta_2 y \quad (2)$$

Parameter values: $\alpha_1 = \alpha_2 = 2$, $K_1 = K_2 = 1$, $n = 4$, $\delta_1 = \delta_2 = 1$.

Modified version of the Toggle switch model, which incorporates the effect of IPTG (S):

$$\frac{dx}{dt} = \alpha_1 \frac{K_1^n}{K_1^n + \left(\frac{y}{(1 + S/K_s)^m} \right)^n} - \delta_1 x \quad (3)$$

$$\frac{dy}{dt} = \alpha_2 \frac{K_2^n}{K_2^n + x^n} - \delta_2 y \quad (4)$$

Additional parameter values: $K_s = 5$, $m = 2$.

Questions

1. The deterministic equations (ODE) for the Toggle Switch are given here above. Write the stochastic version of this model (i.e. a table with each reaction and their corresponding propensity).
2. Simulate the stochastic model using the Gillespie algorithm. In the Gillespie algorithm, a parameter Ω - the system size - allows to control the number of molecules present in the system. Changing Ω means changing the level of noise. Study the robustness of the bistability in the Toggle Switch model with respect to molecular noise.

Hint: The effect of noise can be quantified by computing, as a function of Ω the standart deviation of the level of X (around its mean = steady state value) or, if the level of noise is large, by the frequency of the spontaneous switches between the 2 states.
3. What happens when the system is placed close to a Saddle-Node bifurcation (i.e. for a value of α_1 near the boundary of the bistable region)?
4. Modify the model to incorporate IPTG. Simulate a pulse of IPTG. Run several simulation and compare the results. What do we observe at the level of the cell population? Hint: You can plot on a single graph the same variable (e.g. X) for different simulations and check at which time each cell “switches”. Discuss the effect of the duration and amplitude of the pulse of IPTG. Alternatively you can compute the distribution of the cell state (i.e. the level of X) at different times and show the transient bimodal distribution.

Repressilator

Deterministic equations

Equations of the original model for the Repressilator (Elowitz and Leibler, 2000):

$$\frac{dm_1}{dt} = \alpha_1 \frac{K_1^n}{K_1^n + p_3^n} + \alpha_0 - \gamma m_1 \quad (5)$$

$$\frac{dm_2}{dt} = \alpha_2 \frac{K_2^n}{K_2^n + p_1^n} + \alpha_0 - \gamma m_2 \quad (6)$$

$$\frac{dm_3}{dt} = \alpha_3 \frac{K_3^n}{K_3^n + p_2^n} + \alpha_0 - \gamma m_3 \quad (7)$$

$$\frac{dp_1}{dt} = \beta m_1 - \delta p_1 \quad (8)$$

$$\frac{dp_2}{dt} = \beta m_2 - \delta p_2 \quad (9)$$

$$\frac{dp_3}{dt} = \beta m_3 - \delta p_3 \quad (10)$$

Parameter values: $\alpha_1 = \alpha_2 = \alpha_3 = 100$, $\alpha_0 = 0$, $K_1 = K_2 = K_3 = 1$, $n = 2$, $\gamma = 1$, $\beta = 5$, $\delta = 5$.

Questions

1. The deterministic equations (ODE) for the Repressilator are given above. Write the stochastic version of these models (i.e. a table with each reaction and their corresponding propensity).
2. Simulate this system using the Gillespie algorithm. In the Gillespie algorithm, a parameter Ω - the system size - allows to control the number of molecules present in the system. Changing Ω means changing the level of noise. Study the robustness of the oscillations with respect to molecular noise.
3. Run several simulations starting from the same initial condition. Choose an initial condition on the limit cycle (which you can find by running a deterministic simulation). Compare then the different stochastic times series and observe the phase diffusion.

Hint: You can plot on a single graph the same variable (e.g. M_1) for different simulations and check how fast the oscillations are unsynchronized.

4. In the experiment the authors used pulses of IPTG to synchronize the cells. Adapt the program to account for the effect of IPTG, and run some simulations to assess the effect of the pulse of IPTG on the oscillations (you will need to run several simulations to observe synchronization). Discuss the effect of the duration and amplitude of the pulse on the synchronization.