Large deviations for Gaussian diffusions with delay

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MS52: Stochastic analysis with applications
in biology and evolutionary dynamics

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Outline

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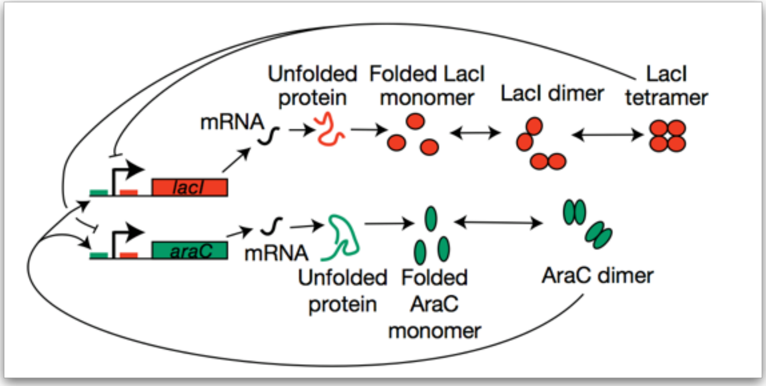
Motivation

- Interplay between delay and stochasticity – subtle and complex
- Can delay act constructively?

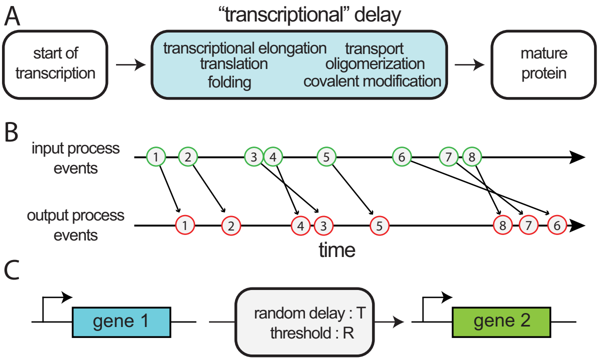
Origin of delay in genetic networks

- 'Transcriptional' delay



Protein synthesis as a queueing system

- Hasty, Mather, Tsimring, and Williams, et al.



Delay acts constructively!

- Accelerates signaling in genetic network pathways
  - Josić, López, Ott, Shiau, Bennett (PCB)
- Stabilizes metastable systems with positive feedback architectures
  - Gupta, López, Ott, Josić, Bennett (PRL)

- Questions
  - How?
  - Quantification?

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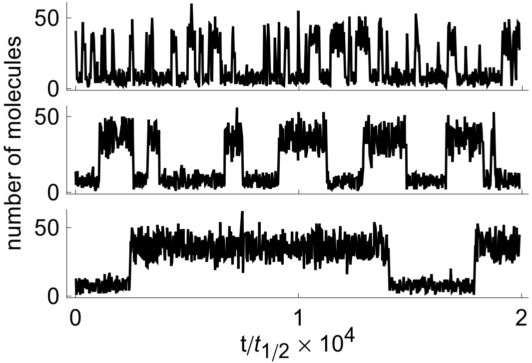
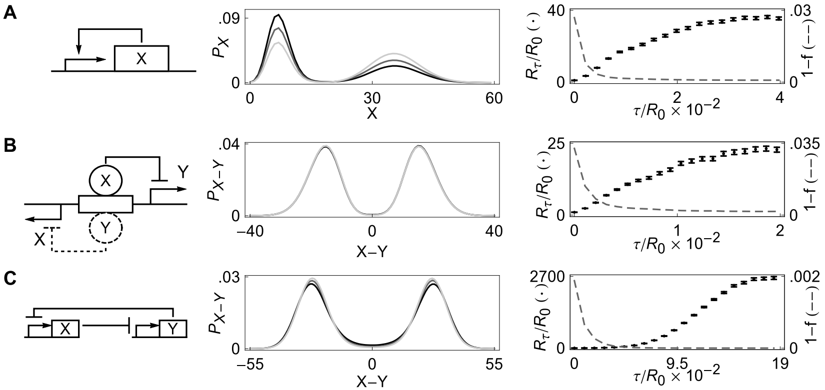
Results from direct simulations

- Traces: single-gene positive feedback circuit

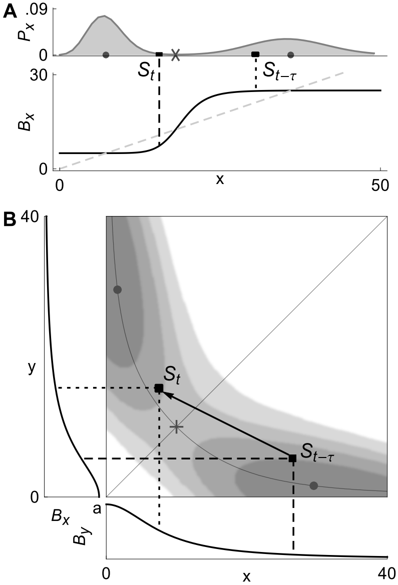


Results from direct simulations

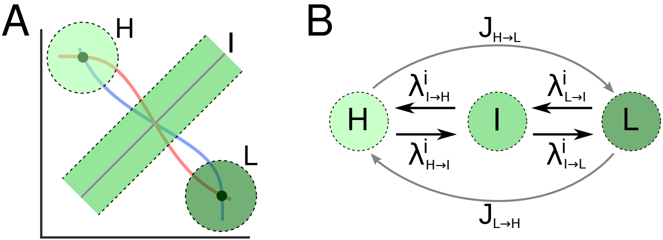
- Delay stabilizes metastable states: Generality



Explanation: Sisyphus



A symbolic reduction



- Examine the $H \to I \to L$ transition
- Key assumptions
  - Rubber band effect

$$p^H_{I\to H} := \frac{\lambda^H_{I\to H}}{\lambda^H_{I\to H} + \lambda^H_{I\to L}} > \frac{\lambda^I_{I\to H}}{\lambda^I_{I\to H} + \lambda^I_{I\to L}} =: p^I_{I\to H}$$

  - Small delay regime

MFPT calculations

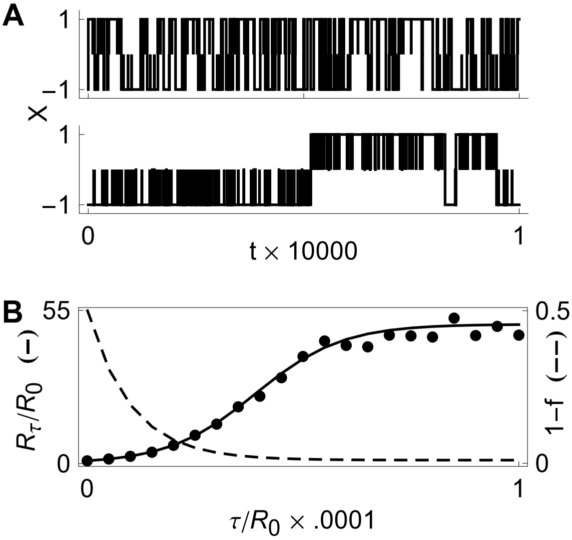
$$
\begin{aligned}
MFPT_{H\to L} \approx\ & \mathbb{E}[\#\text{ failed transitions}] \times \mathbb{E}[\text{failed transition time}] \\
& + \mathbb{E}[\text{successful transition time}]
\end{aligned}
$$

$$
\begin{aligned}
f &:= \mathbb{P}[\text{transition fails}] \\
f &= (1 - Z(\tau))p^{H}_{I\to H} + Z(\tau)p^{I}_{I\to H}
\end{aligned}
$$

$$
Z(\tau) = \exp\big(-(\lambda^{H}_{I\to H} + \lambda^{H}_{I\to L})\tau\big) \quad \text{(rapidly decreasing with } \tau\text{)}
$$

$$
\begin{aligned}
MFPT_{H\to L} \approx\ & \left(\frac{f}{1-f}\right) \times \mathbb{E}[\text{failed transition time}] \\
& + \mathbb{E}[\text{successful transition time}]
\end{aligned}
$$

Symbolic model exhibits desired qualitative behavior



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Model

- Start with Langevin description (Brett and Galla; Gupta et al.)

$$\mathrm{d}x_t = f(x(t), x(t-\tau))\,\mathrm{d}t + \varepsilon g(x(t), x(t-\tau))\,\mathrm{d}W_t$$

- Linearize near a metastable state to obtain Itô delay SDE

$$\begin{cases} \mathrm{d}X_t^\varepsilon = (a + BX_t^\varepsilon + CX_{t-\tau}^\varepsilon)\,\mathrm{d}t + \varepsilon\Sigma\,\mathrm{d}W_t \\ X_t^\varepsilon = \gamma(t) \text{ for } t \in [-\tau, 0] \end{cases}$$

- Goal: solve exit problem

Large deviations framework

$$\mathbb{P}_x \left\{ \sup_{0 \leqslant t \leqslant T} |X^\varepsilon(t) - \psi(t)| \leqslant \delta \right\} \approx \exp\left(-\varepsilon^{-1} S_T(\psi)\right) \qquad \text{(LDP)}$$

- $\psi \in C([0, T], \mathbb{R}^d)$
- S_T: action (or energy) of ψ

- Minimizing over ψ then T produces the quasi-potential
  - Most likely transition pathways
  - Mean first passage times

Azencott, Geiger, Ott: Explicit theory for the linear case

$$\begin{cases} \mathrm{d}X_t^\varepsilon = (a + BX_t^\varepsilon + CX_{t-\tau}^\varepsilon)\,\mathrm{d}t + \varepsilon\Sigma\,\mathrm{d}W_t \\ X_t^\varepsilon = \gamma(t) \text{ for } t \in [-\tau, 0] \end{cases}$$

- Explicit formula for the action (energy) via the Cramér transform
- Fast numerical computation of optimal transition pathways, quasi-potential
- Methods scale nicely with dimension

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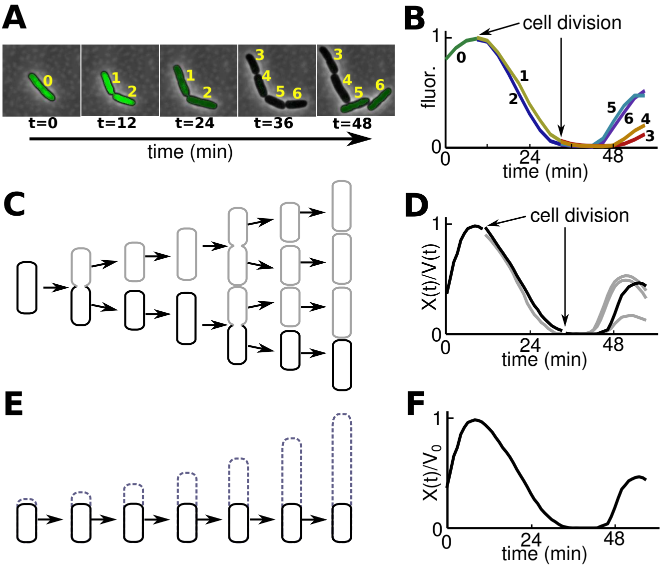
Modeling the cell cycle



A concentration effect