Large deviations for models in Systems Biology

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Stochastic processes in systems biology

• chemical reaction networks describing basic cellular processes
• stochasticity arises from molecular interactions and environmental noise
• different amounts of molecular abundances and interaction rate magnitudes implies some stochastic features are essential and persistent in the long-term dynamics

Rare events in systems biology

★ departure from typical behaviour (± st.dev. fluctuations)
★ in bistable systems leads to transitions to new stable state
★ deviations can arise from intrinsic stochasticity of the system (rather than from external perturbations)
Bistable examples in systems biology

- competing positive-negative feedback, enzymatic futile cycle, de/phosphorylation cycle, bistable repressible switch

Yeast cells switch between expressing and nonexpressing states
(Kaufmann, Yang, Mettetal, and van Oudenaarden, PLOS Bio. 2007)

- cell growth + division: rare events have many trials to occur not rare on the level of the cell population
Stochastic models for reaction network system

- continuous-time Markov chains and their rescaled versions
- multi-scale properties can lead to various limiting processes: jump diffusions with state-dependent coefficients

\[ X_t = X_0 + \int_0^t \mu(X_s) ds + \int_0^t \sigma(X_s) dW_s + \sum_{s \leq t} \Delta X_s \]

jumps have rate \( \lambda(X) \) and jump measure \( \int |y| \nu(X, dy) < \infty \)

- reflection of \( X_s \in [0, b] \) at the boundaries \( 0, b \leq \infty \)

\[ V_t = V_0 + X_t + L_t - U_t \]

\( L_t \) and \( U_t \) are local times at the lower and upper boundary

- intrinsic constraints in reaction systems give processes with reflection

(Leite and Williams, www.math.ucsd.edu 2017)
Examples

- **self-regulated gene expression w/ protein bursts** (due to protein translation + transcription):

\[
X_t = X_0 + \int_0^t \left( \frac{c_0^+ + c_0^- X_s}{c_1^+ + c_2^- X_s} - c_3 X_s \right) ds \\
+ \epsilon \int_0^t \left( \frac{c_0^+ + c_0^- X_s}{c_1^+ + c_2^- X_s} \left[ \frac{c_4^+ + c_4^- X_s}{(c_1^+ + c_2^- X_s)^2} + c_5^- \right] + c_3 X_s \right) dW_s + \delta \sum_{s \leq t} \Delta X_s
\]

- **enzymatic (Michaelis-Menten) kinetics w/ substrate bursts** (due to cell division):

\[
X_t = X_0 - \int_0^t \frac{X_s}{c_1 + c_2 X_s} ds + \epsilon \int_0^t \frac{c_3 X_s}{(c_4 + c_5 X_s)^2} dW_s + \delta \sum_{s \leq t} \Delta X_s
\]
Short-term behaviour

on a finite time interval \( t \in [0, T] \)

when noise contribution \((\epsilon, \delta)\) is small

\* **FLLN:** \((X_t)[0, T] \rightarrow (x_t)[0, T]\) with \(dx_t = \mu(x_t)dt\)

\* **FCLT:** \(\frac{1}{\epsilon}(X_t - x_t)[0, T] \Rightarrow (U_t)[0, T]\) with \(U\) Gaussian

\* **PLDP:** \(P\left(\sup_{t \in [0, T]}|X_t - \tilde{x}_t| \leq \epsilon\right) \approx e^{-\epsilon I((\tilde{x}_t)[0, T])}\)

(Freidlin and Wentzell; Anderson and Orey - for reflected processes)

calculating the rate function \(I(\tilde{x})\)

- from limiting non-linear exponential operator:
  
  \[ Hf = \lim_{\epsilon \to 0} \log \mathbb{E}[e^{\frac{1}{\epsilon}f((X_t)[0, T])}], \quad I(\tilde{x}) = \sup_{f \in C_b([0, T])} [f(\tilde{x}) - Hf] \]

- operator \(H\) has additional term on the boundary for reflection

(Feng and Kurtz ‘Large Deviations for Stochastic Processes’ 2006)
sample path and occupation measure for $\delta \ll \epsilon^2$

sample path and switching times for $\delta \gg \epsilon^2$ (same system)

Long-term behaviour

on long time intervals $t \to \infty$

with sizeable contribution from diffusion and jumps

assuming $V_t$ is ergodic, stationary measure $\pi$, gives average:

$$\frac{1}{t} \int_0^t f(V_s) ds \to \infty \ E_\pi[f(x)]$$

fluctuations for $f$ with $E_\pi[f(x)] = 0$ can be calculated using solution $g$ of the Poisson equation:

$$f(x) = \mu(x)g'(x) + \frac{1}{2}\sigma^2(x)g''(x)$$

$$+ \lambda(x) \int (g(\delta(x, y)) - g(x))\nu(x, dy), \quad g'(0) = g'(b) = 0$$

where $V_s = \delta(V_{s-}, \Delta X_s)$ if $\Delta X \neq 0$

for $\delta(x, y) = 0 \ 1_{x+y\leq 0} + (x + y) \ 1_{x+y\in(0,b)} + b \ 1_{x+y\geq b}$
Generalized occupation time

- consider the **Additive process** - generalization of local time

\[ \Lambda_t = \int_0^t f(V_s)ds + \sum_{s \leq t} \tilde{f}(V_{s-}, \Delta X_s) + f_0 L_t^c + f_b U_t^c \]

- \( f \) bdd, \( \tilde{f}(x, 0) = 0, \int e^{\theta \tilde{f}(x, y)}\nu(x, dy) < C \ \forall x, \ f_0, f_b \in \mathbb{R}_+ \)

- \( L^c, U^c \) are the continuous parts of local times at 0, b

- e.g. \( \Lambda_t = L_t \) with \( f = 0, \tilde{f} = -[x + y]^-, f_0 = 1, f_b = 0 \)

this gives the *fraction of time* a protein is *not expressed in*, or *fraction of time* enzymatic substrate is at **extremely low level**
**Gaertner-Ellis theorem**

for stochastic process on $\mathbb{R}^d$

- Suppose
  \[ \frac{1}{t} \mathbb{E}[e^{\theta \Lambda_t}] \xrightarrow{t \to \infty} \psi(\theta) \]

  exists for $\psi$ such that

- $0 \in \text{int}(D_\psi), \ D_\psi = \{ \theta : \psi(\theta) < \infty \}$
- $\psi$ is lower semi-continuous, differentiable on $\text{int}(D_\psi)$
- $D_\psi = \mathbb{R}$ or $\lim_{\theta \to \partial D_\psi} |\psi'(\theta)| = \infty$

Then $\frac{\Lambda_t}{t}$ satisfies the **Large Deviation Principle**
with ‘speed’ $t$ and ‘good’ convex rate function

\[ \psi^*(a) = \sup_{\theta \in \mathbb{R}} [a\theta - \psi(\theta)] \]
Integro-differential equation

each fixed $\theta \rightarrow$ pair $(u_\theta(x), \psi_\theta)$

- Suppose there exist $u_\theta(x) \in C^2_{\geq 0}$ and $\psi_\theta \in \mathbb{R}$ satisfying the integro-differential equation

$$0 = \mu(x)u'_\theta(x) + \frac{1}{2}\sigma^2(x)u''_\theta(x) + (\theta f(x) - \psi_\theta)u_\theta(x)$$

$$+ \lambda(x) \int (e^{\theta \tilde{f}(x,y)} u(\theta, \delta(x, y)) - u_\theta(x)) \nu(x, dy)$$

subject to boundary conditions

$$u_\theta(0) = 1, \ u'_\theta(0) = -f_0 \theta, \ u_\theta(b) = 1, \ u'_\theta(b) = f_b \theta$$

- the integral term makes it somewhat more difficult to solve the differential equation boundary problem numerically
Martingale argument

Then (under assumptions on \(\mu, \sigma, \lambda, \nu\))

\[ M_t(\theta) = e^{\theta \Lambda_t} u_\theta(V_t) \]

is a martingale (\(u_\theta\) is bounded) and for each \(\theta\)

\[ \frac{1}{t} \log E[e^{\theta \Lambda_t}] \to_{t \to \infty} \psi_\theta \]

Assuming \(\psi(\theta) := (\psi_\theta)_{\theta \in \mathcal{D}_\psi}\) satisfies Gaertner-Ellis theorem

\[ \frac{1}{t} \log P[\Lambda_t \geq at] \to_{t \to \infty} \psi(\theta^*) - \theta^* a, \]

for any \(\theta^* > 0\) such that \(\psi \in C^1\) around \(\theta^*\), \(a = \partial_\theta \psi(\theta^*)\)

\(\star\) numerically solving for \(\psi\) ⇒ ‘verifying’ needed assumptions only numerically ⇒ estimating probabilities of rare events
Simulations

- $V_t$ is jump-diffusion reflected at: $0$ and $b = 2.5$ with drift and diffusion: $\mu(x) = 2.62(1.61 - x), \sigma(x) = 0.62\sqrt{x}$
jump rate and measure: $\lambda(x) = x, \nu(x, dy) = \frac{1}{2}1_{0.72} + \frac{1}{2}1_{2.87}$

$U_t =$ local time at $b$ and $L_t =$ local time at $0$
\[ \Lambda_t = L_t \text{ is local time at 0} \]

\[ \frac{1}{t} E[L_t] \sim \min_a \psi^*(a) \]

LDP rate function \( \psi^* \)

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