Large deviations for models in Systems Biology

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Stochastic processes in systems biology

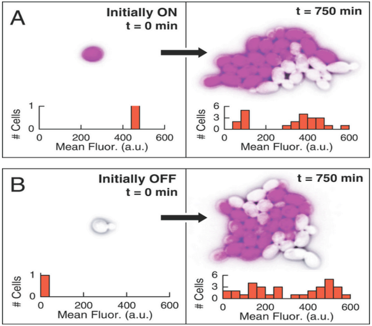
- chemical reaction networks describing basic cellular processes
- stochasticity arises from molecular interactions and environmental noise
- different amounts of molecular abundances and interaction rate magnitudes implies some stochastic features are essential and persistent in the long-term dynamics

Rare events in systems biology

- ⋆ departure from typical behaviour ($\pm$ 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):

$$X_t = X_0 + \int_0^t \left(\frac{c_0^{\pm} + c_{0\star}^{\pm} X_s}{c_1^{\pm} + c_2^{\pm} X_s} - c_3 X_s\right) ds$$
$$+ \epsilon \int_0^t \left(\frac{c_0^{\pm} + c_{0\star}^{\pm} X_s}{c_1^{\pm} + c_2^{\pm} X_s}\left[\frac{c_4^{\pm} + c_{4\star}^{\pm} x}{(c_1^{\pm} + c_2^{\pm} X_s)^2} + c_5^{\pm}\right] + c_3 X_s\right) dW_s + \delta \sum_{s \le t} \Delta X_s$$

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

$$X_t = X_0 - \int_0^t \frac{X_s}{c_1 + c_2 X_s} ds + \epsilon \int_0^t \frac{c_3 X_s}{(c_4 + c_5 X_s)^2} dW_s + \delta \sum_{s \le t} \Delta X_s$$

Short-term behaviour

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

when noise contribution (ϵ, δ) is small

- ⋆ FLLN: $(X_t)_{[0,T]} \to (x_t)_{[0,T]}$ 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: $\mathbf{P}(\sup_{t\in[0,T]} |X_t - \tilde{x}_t| \leq \epsilon) \approx e^{-\epsilon I((\tilde{x}_t)_{[0,T]})}$

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

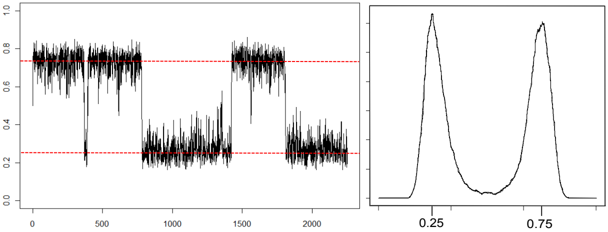
calculating the rate function $I(\tilde{x})$

- from limiting non-linear exponential operator:

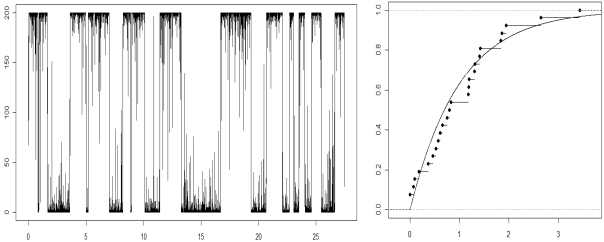
$$Hf = \lim_{\epsilon\to 0} \log \mathbf{E}[e^{\frac{1}{\epsilon} f((X_t)_{[0,T]})}], \quad I(\tilde{x}) = \sup_{f\in\mathcal{C}_b([0,T])} [f(\tilde{x}) - Hf]$$

- 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)

(McSweeney and Popovic, Ann.Appl.Prob. 2014)

Long-term behaviour

on long time intervals $t \to \infty$

with sizeable contribution from diffusion and jumps

- ⋆ assuming V_t is ergodic, stationary measure π, gives average:

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

- ⋆ fluctuations for f with $\mathbf{E}_\pi[f(x)] = 0$ 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 $\delta(x,y) = 0\,\mathbf{1}_{x+y\leq 0} + (x+y)\mathbf{1}_{x+y\in(0,b)} + b\,\mathbf{1}_{x+y\geq b}$

Generalized occupation time

- consider the Additive process - generalization of local time

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

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

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

$$\frac{1}{t}\mathbf{E}[e^{\theta\Lambda_t}] \underset{t\to\infty}{\to} \psi(\theta)$$

exists for ψ such that

- $0 \in \mathrm{int}(D_\psi)$, $D_\psi = \{\theta : \psi(\theta) < \infty\}$
- ψ is lower semi-conts, differentiable on $\mathrm{int}(D_\psi)$
- $D_\psi = \mathbb{R}$ 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 $\theta \to$ pair $(u_\theta(x), \psi_\theta)$

- Suppose there exist $u_\theta(x) \in \mathcal{C}^2_{\geq 0}$ 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_θ is bounded) and for each θ

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

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

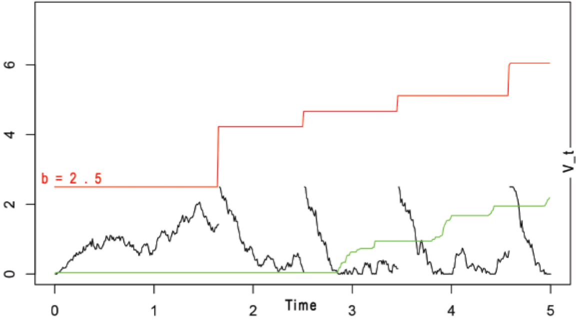
$$\frac{1}{t} \log \mathbf{P}[\Lambda_t \geq at] \underset{t\to\infty}{\to} \psi(\theta^*) - \theta^* a,$$

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

⋆ numerically solving for ψ $\Rightarrow$ 'verifying' needed assumptions only numerically $\Rightarrow$ estimating probabilities of rare events

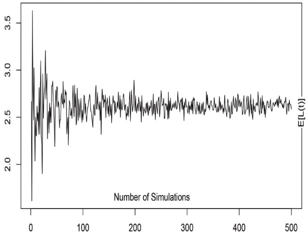
Simulations

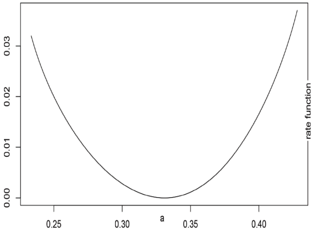
- V_t is jump-diffusion reflected at: 0 and $b = 2.5$ with drift and diffusion: $\mu(x) = 2.62(1.61 - x), \sigma(x) = 0.62\sqrt{x}$ jump rate and measure: $\lambda(x) = x, \nu(x, dy) = \frac{1}{2}\mathbf{1}_{0.72} + \frac{1}{2}\mathbf{1}_{2.87}$



U_t = **local time at** b **and** L_t = **local time at** 0

- $\Lambda_t = L_t$ is local time at 0





$\frac{1}{t}\mathbf{E}[L_t] \sim \min_a \psi^*(a)$ **LDP rate function** ψ^*

$t = 1000$				
θ	$\psi(\theta)$	a	$\psi^*(a)$	$P(\Lambda_t \geq at)$
0	0	0.3401	0	1
0.1	0.0346	0.3555	0.0008	0.4493
0.2	0.0708	0.3653	0.0023	0.1003
0.3	0.1075	0.3697	0.0034	0.0334
0.4	0.1446	0.3714	0.0040	0.0183
0.5	0.1818	0.3721	0.0043	0.0136
0.6	0.2190	0.3724	0.0044	0.0123
0.7	0.2563	0.3725	0.0045	0.0111
0.8	0.2935	0.3726	0.0045	0.0111
0.9	0.3308	0.3726	0.0046	0.0101
1	0.3680	0.3726	0.0046	0.0101