

# Stochastically Induced Bistability

## in Interacting Population Processes

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## Motivation

- ★ Interacting Populations systems:  
models for **ecology, epidemiology** and **molecular reaction networks**
- ★ Dynamics leading to **on/off** or **all/nothing** values:  
switching between them - (quasi)**bistability**
- ★ In gene expression (cellular differentiation, development) and cell signaling (enzyme kinetics, metabolic pathways):  
modeled **deterministically** using positive feedback switches
- ★ **Stochastic models** for reaction systems in biology:  
- needed due to visibly **noisy** outcomes

**Time-scales for switching** vary over:

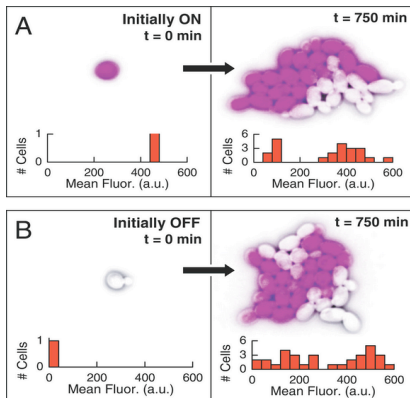
- ★ 1 per  $10^8$  generations (lysogenic state of *E.coli*)
- ★ 1 per 8.33 generations (epigenetic states of *S.cerevisiae*)

**Memory of previous state** vanishes within:

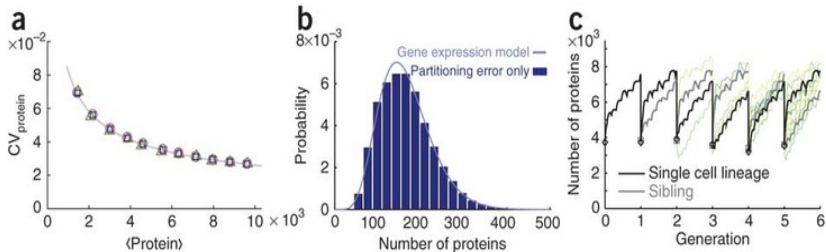
- ★ single generation; to
- ★ thousands of generations

Relevant questions:

- ★ **How long** will a cell **stay in the same state** before spontaneously switching to an alternative one?
- ★ What **features** of the underlying **interaction network** determine this stability?
- ★ Is stability **independent of** specific **details of interaction network**?



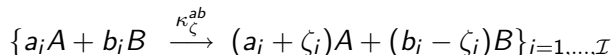
Yeast cells switch between expressing and nonexpressing states –  
*'Heritable Stochastic Switching Revealed by Single Cell Genealogy'*,  
 Kaufmann, B.B., Yang, Q., Mettetal, J.T., van Oudenaarden, A.,  
**PLOS Biology**, 5(9), 2007



Additional noise in gene expression from partitioning of the cells –  
*'Non-genetic heterogeneity from stochastic partitioning at cell division'*,  
 Huh, D., Paulsson, J., **Nature Genetics**, 43(2), 2011

## Reaction Networks

- Simple **interaction system**:



1-dim system in terms of the population size of species  $A$

- $\{1, \dots, \mathcal{I}\}$  = set of different interactions
  - conservation law between  $A$  and  $B$  - environment or space limitations; or species can only one of two forms
- Density dependent **Markov chain model**:

$$X(t) = X(0) + \sum_{i=1}^{\mathcal{I}} \zeta_i Y_i \left( \int_0^t \lambda_i(X(s), N - X(s)) ds \right)$$

- $\{Y_i\}_{i=1, \dots, \mathcal{I}}$  independent Poisson processes
- $\lambda_i(\cdot, \cdot)$  interaction rate - depends on the population size of  $A$

- **Additional noisy mechanism:**

$$X(t) = X(0) + \int_0^t (Z(X(s-), s) - X(s-)) dY_\gamma(s)$$

error due to **resampling/splitting**

- $Y_\gamma$  a counting process with state-dependent rate  $\gamma(x, N)$
  - $\{Z(x, s)\}_{0 \leq x \leq N, s \geq 0}$  independent with distribution  $p_x$ .
- **Effects of additional noisy mechanism** examined based on:
    - different orders of magnitude of **rate**  $\gamma(x, N)$
    - different variance of **'resampling' distributions**  $p_x$

## Assumptions on interaction dynamics:

1. the amount of species  $X(t) \in \{0, \dots, N\}$  has finite capacity;
2. the drift at the boundaries 0 and  $N$  is reflecting

$$\frac{d}{dt} \mathbf{E}[X_A(t) | X_A(t) = 0] > 0, \quad \frac{d}{dt} \mathbf{E}[X_A(t) | X_A(t) = N] < 0;$$

3. the form of rate for  $a_i A + b_i B \xrightarrow{\kappa_i} (a_i + \zeta_i) A + (b_i - \zeta_i) B$  is

$$\lambda_i(X(t)) = \kappa_{\zeta}^{ab}(X_A(t))_{a_i}(X_B(t))_{b_i}$$

where  $(x)_a = x(x-1)\cdots(x-a+1)$  is the falling factorial

4. the effect of any other species on an interaction is reflected only in the value of its interaction rate  $\kappa_{\zeta}^{ab}$ ;



## Assumptions on splitting/resampling mechanism:

5. overall rate is  $\gamma(x, N)$ , which depends both on current state  $x$  and on the scaling parameter  $N$
6. the distribution  $p_x$  has absorbing boundaries  $p_0(0) = 1, p_N(N) = 1$  and is unbiased  $\sum_y y p_x(y) = x$

For some results we will also assume:

- 7\*: the jump sizes are asymptotically uniformly bounded

$$\Delta > 0, \sup_x \gamma(x, N) \sum_{y: N^{-1}|y-x| \geq \Delta} p_x(y) \rightarrow 0 \text{ as } N \rightarrow \infty$$

the variance is asymptotically given by

$$\sup_x \left| \gamma(x, N) N^{-2} \sum_y (y-x)^2 p_x(y) - \tilde{\gamma}^2 \tilde{\sigma}^2(N^{-1}x) \right| \rightarrow 0 \text{ as } N \rightarrow \infty,$$

where  $\tilde{\sigma}^2$  is continuous  $\tilde{\sigma}^2(x) \geq 0$ , and  $\tilde{\sigma}^2(0) = \tilde{\sigma}^2(1) = 0$ .

## Conventional Scaling

- Rescaled species amounts:  $X_N(t) = N^{-1}X(t)$
- Balanced** interactions:  $\mathcal{I}^{\text{bal}} \subset \mathcal{I}$

$$\sum_{(a,b,\zeta) \in \mathcal{I}^{\text{bal}}} \zeta \lambda_{\zeta}^{a,b}(x) = 0 \quad \forall x \Leftrightarrow \exists (a,b) \in \mathcal{I}^{\text{bal}} : \sum_{(a,b,\zeta) \in \mathcal{I}^{\text{bal}}} \zeta \kappa_{\zeta}^{ab} = 0.$$

- Biased** interactions:  $\mathcal{I}^{\text{bia}} \subset \mathcal{I} = \mathcal{I} - \mathcal{I}^{\text{bal}}$
- Relationship between **mean** and **variance**:

$$\frac{d}{dt} \mathbf{E}[X_N(t) | \mathcal{F}_t] = \sum_{(\zeta,a,b) \in \mathcal{I}^{\text{bia}}} N^{a+b-1} \zeta \kappa_{\zeta}^{ab} X_N(t)_{a,N} (1 - X_N(t))_{b,N}$$

$$\begin{aligned} \frac{d}{dt} \mathbf{E}[(X_N(t) - \mathbf{E}[X_N(t)])^2 | \mathcal{F}_t] &= \sum_{(\zeta,a,b) \in \mathcal{I}^{\text{bal}} \cup \mathcal{I}^{\text{bia}}} N^{a+b-2} \zeta \kappa_{\zeta}^{ab} X_N(t)_{a,N} (1 - X_N(t))_{b,N} \\ &\quad + \int_0^t N^{-2} (Z(NX_N(s-), s) - NX_N(s-))^2 dY_{\gamma}(s) \end{aligned}$$

**constrains** the possibilities for limiting behavior

## LLN:

$$\tilde{\kappa}_{\zeta}^{ab} := \lim_{N \rightarrow \infty} N^{a+b-1} \kappa_{\zeta}^{ab}(N) \quad (\text{'mass-action' scaling})$$

$$\forall T > 0, \forall \epsilon > 0 \quad \mathbf{P} \left[ \sup_{0 \leq t \leq T} |X_N(t) - X(t)| \geq \epsilon \right] \rightarrow 0$$

$$dX(t) = \tilde{\phi}(X(t))dt, \quad \tilde{\phi}(x) = \sum_{(\zeta, \mathbf{a}, \mathbf{b}) \in \mathcal{I}^{\text{bia}}} \zeta \tilde{\kappa}_{\zeta}^{ab} x^{\mathbf{a}} (1-x)^{\mathbf{b}}$$

## FCLT:

$$\tilde{\gamma}^2 \tilde{\sigma}^2(x) := \lim_{N \rightarrow \infty} \gamma(Nx, N) \sum_y (y-x)^2 p_{Nx}(Ny) \quad (7^* \text{ holds})$$

$$(X_N(t))_{0 \leq t \leq T} \Rightarrow (\tilde{X}(t))_{0 \leq t \leq T}$$

$$d\tilde{X}(t) = \tilde{\phi}(\tilde{X}(t))dt + \tilde{\gamma} \tilde{\sigma}(\tilde{X}(t))d\tilde{W}(t)$$

## Effects of additional mechanism

- nonlinear dynamics needs to have **2 stable equilibria**:

$$0 < x_1 < x_2 < x_3 < 1 : \tilde{\phi}(x_i) = 0, \tilde{\phi}'(x_1) < 0, \tilde{\phi}'(x_2) > 0, \tilde{\phi}'(x_3) < 0$$

moving between enabled by noise of **additional mechanism**

- if  $\tilde{\gamma} := \varepsilon$  is small (perturbation) then **LD for diffusions** apply:

$$I_{x_i, x_2}(\tilde{\phi}, \tilde{\sigma}) = \inf_{s > 0} \inf_{\varphi} \left\{ \int_0^s L(\varphi(u), \varphi'(u)) du \mid \varphi \in C^1([0, s]), \right. \\ \left. \varphi(0) = x_i, \varphi(s) = x_2 \right\}$$

is the 'quasipotential' with the action functional

$$L(\varphi, \varphi') = \left( \frac{\varphi' - \tilde{\phi}(\varphi)}{\tilde{\sigma}(\varphi)} \right)^2$$

- have explicit form:

$$I_{x_i, x_2}(\tilde{\phi}, \tilde{\sigma}) = - \int_{x_i}^{x_2} \frac{\tilde{\phi}(x)}{\tilde{\sigma}^2(x)} dx, \quad i = 1, 3$$

## LD for diffusion

◦ **transitions**  $\tilde{T}_0 = \inf\{t \geq 0 : X_N(t) = B_c(x_3)\}$ , for  $i \geq 1$ :

$$T_i = \inf\{t > \tilde{T}_{i-1} : \tilde{X}(t) \in B_c(x_1)\}, \quad \tilde{T}_i = \inf\{t > T_i : \tilde{X}(t) \in B_c(x_3)\}$$

◦ **time scales**  $\beta_{\tilde{\gamma}}$ , and  $\tilde{\beta}_{\tilde{\gamma}}$ :

$$\mathbf{P}[T_1 > \beta_{\tilde{\gamma}} | \tilde{X}(0) = x_3] = e^{-1}, \quad \mathbf{P}[\tilde{T} > \tilde{\beta}_{\tilde{\gamma}} | \tilde{X}(0) = x_1] = e^{-1}$$

### Theorem (Wentzell '78 + Galves-Olivieri-Vares '87)

If  $\tilde{\phi}$  has two stable equilibria  $x_1 < x_3$  and one unstable equilibrium  $x_2$ , then transitions of  $\tilde{X}$  from  $D_3 = (x_2, 1]$  and  $D_1 = [0, x_2)$  satisfy:

$$(i) \quad \lim_{\tilde{\gamma} \rightarrow 0} \mathbf{P}[T > t \beta_{\tilde{\gamma}} | \tilde{X}(0) \in D_3] = e^{-t}, \quad \lim_{\tilde{\gamma} \rightarrow 0} \mathbf{P}[\tilde{T} > t \tilde{\beta}_{\tilde{\gamma}} | \tilde{X}(0) \in D_1] = e^{-t}$$

$$(ii) \quad \lim_{\tilde{\gamma} \rightarrow 0} \tilde{\gamma}^2 \ln \beta_{\tilde{\gamma}} = I_{x_3, x_2}(\tilde{\phi}, \tilde{\sigma}), \quad \lim_{\tilde{\gamma} \rightarrow 0} \tilde{\gamma}^2 \ln \tilde{\beta}_{\tilde{\gamma}} = I_{x_1, x_2}(\tilde{\phi}, \tilde{\sigma}).$$

- o **occupation measure:** bdd conts  $f$ ,  $R_{\tilde{\gamma}} \rightarrow \infty$  s.t.  $\frac{R_{\tilde{\gamma}}}{\beta_{\tilde{\gamma}}} \rightarrow 0$

$$\nu_t^{\tilde{\gamma}}(f) = \frac{1}{R_{\tilde{\gamma}}} \int_{\beta_{\tilde{\gamma}} t}^{\beta_{\tilde{\gamma}} t + R_{\tilde{\gamma}}} f(\tilde{X}_{\tilde{\gamma}}(s)) ds$$

Theorem (Wentzell '78 + Galves-Olivieri-Vares '87)

- (i) (Metastability) If  $-\int^{x_1} \frac{\tilde{\phi}(x)}{\tilde{\sigma}^2(x)} dx < -\int^{x_3} \frac{\tilde{\phi}(x)}{\tilde{\sigma}^2(x)} dx$ , then  $(\nu_t^{\tilde{\gamma}})_{t \geq 0} \Rightarrow (\nu_t)_{t \geq 0}$  where, with  $T$  an exponential mean 1 r.v.

$$\nu_t = \begin{cases} \delta_{x_3}, & t < T \\ \delta_{x_1}, & t \geq T \end{cases}$$

- (ii) (Bistability) If  $-\int^{x_1} \frac{\tilde{\phi}(x)}{\tilde{\sigma}^2(x)} dx = -\int^{x_3} \frac{\tilde{\phi}(x)}{\tilde{\sigma}^2(x)} dx$ , then  $(\nu_t^{\tilde{\gamma}})_{t \geq 0} \Rightarrow (\nu_t)_{t \geq 0}$  where, with  $T_i, i \geq 0$  Poisson rate 1 times

$$\nu_t = \begin{cases} \delta_{x_3}, & T_{2i} \leq t < T_{2i+1} \\ \delta_{x_1}, & T_{2i+1} \leq t < T_{2i+2} \end{cases} \quad i = 0, 1, 2, \dots$$

## Effects of finite system size

- transitions between equilibria can be due to **finite system size**

assume  $X_N(t)$  is birth-death chain with rates  $N\tilde{r}_+(\frac{x}{N}), N\tilde{r}_-(\frac{x}{N})$

- if  $N$  is large then **LD for Markov jump processes** apply:

$$I_{x_1, x_2}(\tilde{r}_+, \tilde{r}_-) = \inf_{T>0} \inf_{\varphi} \left\{ \int_0^T \ell(\varphi(u), \varphi'(u)) du \mid \varphi \in C^1([0, T]), \right. \\ \left. \varphi(0) = x_1, \varphi(T) = x_2 \right\}$$

is 'quasipotential' with action functional in variational form

$$\ell(x, y) = \sup_{\theta} \left\{ \theta y - (\tilde{r}_+(x)(e^{\theta} - 1) + \tilde{r}_-(x)(e^{-\theta} - 1)) \right\}$$

- for birth-death process have explicit form:

$$I_{x_1, x_2}(\tilde{r}_+, \tilde{r}_-) = \int_{x_1}^{x_2} \log \left( \frac{\tilde{r}_-(x)}{\tilde{r}_+(x)} \right) dx, \quad x = 1, 2, 3$$

## LD for jump Markov process

### Theorem (Wentzell '78 + uniform conv rates)

If the transition rates of birth-death process  $X_N$  satisfy

$$r_+(Nx)/N \rightarrow \tilde{r}_+(x), \quad r_-(Nx)/N \rightarrow \tilde{r}_-(x) \quad \text{uniformly in } [0, 1]$$

and  $\tilde{\phi} = \tilde{r}_+ - \tilde{r}_-$  has two stable equilibria  $x_1 < x_3$  and one unstable  $x_2$ , then transitions of  $X_N$  from  $D_3 = (x_2, 1]$  and  $D_1 = [0, x_2)$  have mean times  $\beta_N$  and  $\tilde{\beta}_N$ , respectively, which satisfy:

$$(i) \lim_{N \rightarrow \infty} \mathbf{P}[T > t\beta_N | X_N(0) \in D_3] = e^{-t}, \quad \lim_{N \rightarrow \infty} \mathbf{P}[\tilde{T} > t\tilde{\beta}_N | X_N(0) \in D_1] = e^{-t}$$

$$(ii) \lim_{N \rightarrow \infty} \frac{1}{N} \ln \beta_N = \iota_{x_3, x_2}(\tilde{r}_+, \tilde{r}_-), \quad \lim_{N \rightarrow \infty} \frac{1}{N} \ln \tilde{\beta}_N = \iota_{x_1, x_2}(\tilde{r}_+, \tilde{r}_-).$$



## Comparison of effects

- ★ are the transitions more often due to **additional (small noise) mechanism** or due to **finite system size effects**?

### Theorem

If the **rates of interactions scale** as '**mass-action**' and have limiting drift  $\tilde{\phi}$  with two stable and one unstable equilibria, and if additional **resampling/splitting** mechanism has rate  $\frac{1}{N}\gamma(x, N)$  where  $\gamma(x, N)$  satisfies Assumption 7\*: then, transitions between stable equilibria are more often due to finite system size effects than due to the effects of additional mechanism, that is,

$$v_{x_1, x_2}(\tilde{r}_+, \tilde{r}_-) \leq I_{x_1, x_2}(\tilde{\phi}, \tilde{\sigma}).$$

- ★ **threshold** is when perturbation parameter  $\tilde{\gamma}^2 = \frac{1}{N}$ 
  - when parameter  $\tilde{\gamma}^2 \ll \frac{1}{N}$  - interaction noise wins
  - when parameter  $\tilde{\gamma}^2 \gg \frac{1}{N}$  - noise of additional mechanism wins

Proof.

Let  $r_+^N(x) = r_+(Nx)/N$ , and  $r_-^N(x) = r_-(Nx)/N$  then

$$r_+^N(x) = \sum_{(a,b,1) \in \mathcal{I}} N^{a+b-1} \kappa_1^{ab}(N) x_{a,N} (1-x)_{b,N} + \frac{1}{2} N^{-2} \gamma(Nx, N),$$

$$r_-^N(x) = \sum_{(a,b,-1) \in \mathcal{I}} N^{a+b-1} \kappa_{-1}^{ab}(N) x_{a,N} (1-x)_{b,N} + \frac{1}{2} N^{-2} \gamma(Nx, N).$$

Since by Assumption 7\*,  $|N^{-2} \gamma(Nx, N) - \tilde{\sigma}^2(x)| \rightarrow 0$  uniformly, the birth-death rates converge uniformly to

$$\tilde{r}_+(x) = \sum_{(a,b,1) \in \mathcal{I}} \tilde{\kappa}_1^{ab} x^a (1-x)^b + \frac{1}{2} \tilde{\sigma}^2(x)$$

$$\tilde{r}_-(x) = \sum_{(a,b,-1) \in \mathcal{I}} \tilde{\kappa}_{-1}^{ab} x^a (1-x)^b + \frac{1}{2} \tilde{\sigma}^2(x)$$

Let  $\omega(x) = 1 - \frac{\tilde{r}_-(x)}{\tilde{r}_+(x)}$ , since  $\iota_{x_i, x_2}(\tilde{r}_+, \tilde{r}_-) = \int_{x_i}^{x_2} \log(1 - \omega(x)) dx$

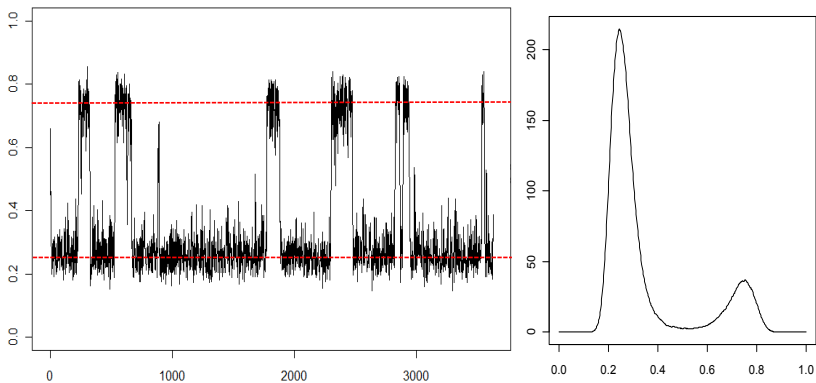
$$\begin{aligned}
 & - \int_{x_i}^{x_2} \frac{\tilde{\phi}(x) dx}{\sum_{(a,b,-1) \in \mathcal{I}} \tilde{\kappa}_{-1}^{ab} x^a (1-x)^b + \frac{1}{2} \tilde{\gamma}^2 \tilde{\sigma}^2(x)} \\
 & \leq \iota_{x_i, x_2}(\tilde{r}_+, \tilde{r}_-) \leq - \int_{x_i}^{x_2} \frac{\tilde{\phi}(x) dx}{\sum_{(a,b,1) \in \mathcal{I}} \tilde{\kappa}_1^{ab} x^a (1-x)^b + \frac{1}{2} \tilde{\gamma}^2 \tilde{\sigma}^2(x)}.
 \end{aligned}$$

hence

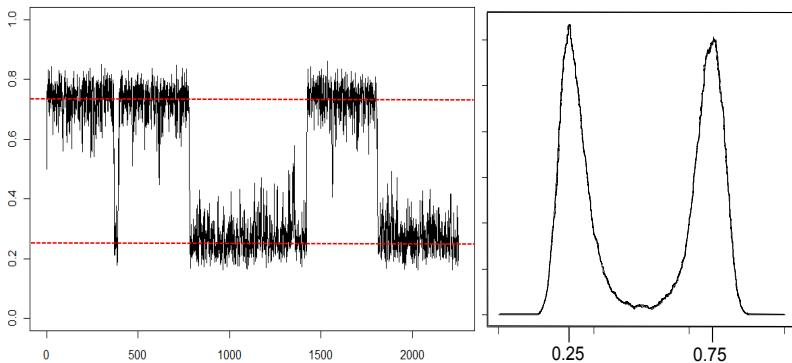
$$\iota_{x_i, x_2}(\tilde{\phi}, \tilde{\sigma}) = - \int_{x_i}^{x_2} \frac{\tilde{\phi}(x) dx}{\frac{1}{2} \tilde{\gamma}^2 \tilde{\sigma}^2(x)} \geq \iota_{x_i, x_2}(\tilde{r}_+, \tilde{r}_-)$$

and the expected values of the time scales satisfy

$$\ln \beta_{\tilde{\gamma}} \approx \frac{1}{\tilde{\gamma}^2} \iota_{x_i, x_2}(\tilde{\phi}, \tilde{\sigma}) \gtrsim N \iota_{x_i, x_2}(\tilde{r}_+, \tilde{r}_-) \approx \ln \beta_{\epsilon_N}.$$



**Figure:** Sample path of  $X_N$  for a system of interactions with double-well potential drift and small perturbative resampling/splitting mechanism.  
**parameters:**  $N = 500$ ,  $\tilde{\gamma}^2 = 2 \cdot 10^{-4}$ ,  $\gamma(x, N) = \frac{1}{2}\tilde{\gamma}^2 N^2 = 25$ :  $\tilde{\gamma}^2 \ll \frac{1}{N}$



**Figure:** Sample path of  $X_N$  for a system of interactions with double-well potential drift and small perturbative resampling/splitting mechanism.  
**parameters:**  $N = 1500$ ,  $\tilde{\gamma}^2 = 2 \cdot 10^{-2}$ ,  $\gamma(x, N) = 22.5 \cdot 10^3$ :  $\tilde{\gamma}^2 \gg \frac{1}{N}$

## Features of Bistability

Bistability due to small additional noise or finite size effects:

- ★ occupation time has **'smooth' bimodal distribution**
- ★ exponentially **long time scale of transitions** (in  $N$  or  $1/\tilde{\gamma}^2$ )
- ★ almost **no correlation** between the **transition times** in **parent/daughter cells**

Can bistability be stochastically induced in other ways?

- ★ the interaction drift may **not be a double-well** potential
- ★ the occupation time may have **sharp two state distribution**
- ★ the parent/daughter cells may have **transition times that are highly correlated**

## Unconventional Scaling

- Rates of **(unscaled) Markov jump process  $X$** :

$$r_{i,j} = \sum_{(a,b,j-i) \in \mathcal{I}} \kappa_{j-i}^{ab}(N) i_a (N-i)_b + \gamma(i, N) p_{i,j}.$$

- By Assumption 2. the boundary is not absorbing,  $\exists j, j'$  s.t.:

$$r_{0j} = \sum_{(0,b,j) \in \mathcal{I}} \kappa_j^{0j}(N) N_b \neq 0, \quad r_{Nj'} = \sum_{(a,0,N-j') \in \mathcal{I}} \kappa_{N-j'}^{a0}(N) N_a \neq 0$$

- **Excursions between boundaries**,  $\tau_{0,N} = \inf\{t \geq 0 : X_A(t) \in \{0, N\}\}$ :

$$e_{j0} := \mathbf{E}[\tau_{0,N} | X_A(0) = j, X_A(\tau_{0,N}) = 0]$$

$$e_{jN} := \mathbf{E}[\tau_{0,N} | X_A(0) = j, X_A(\tau_{0,N}) = N]$$

$$\pi_{jN} := \mathbf{P}[X_A(\tau_{0,N}) = N | X_A(0) = j]$$

## Conditions on $\gamma(i, N)$

( $\star$ ): for some  $\omega_N \rightarrow \infty, \beta_N > 0, \exists \tilde{r}_+, \tilde{r}_-, \tilde{r}_{01}, \tilde{r}_{10} \in (0, \infty)$

$$\frac{1}{\omega_N} \sum_j r_{0j} \rightarrow \tilde{r}_+, \quad \frac{1}{\omega_N} \sum_j r_{Nj} \rightarrow \tilde{r}_-$$

$$\beta_N \sum_j r_{0j} \pi_{jN} \rightarrow \tilde{r}_{01}, \quad \beta_N \sum_j r_{Nj} \pi_{j0} \rightarrow \tilde{r}_{10}$$

$$\frac{1}{\beta_N \omega_N} \sum_j r_{0j} e_{jN}, \quad \sum_j r_{0j} e_{j0}, \quad \frac{1}{\beta_N \omega_N} \sum_j r_{Nj} e_{j0}, \quad \sum_j r_{Nj} e_{jN} \rightarrow 0$$

- transition times  $\tilde{T}_N^0 = \inf\{t \geq 0 : X(t) = 0\}$ , for  $i \geq 1$   
 $T_N^i = \inf\{t > \tilde{T}_N^{i-1} : X(t) = N\}$ ,  $\tilde{T}_N^i = \inf\{t > T_N^i : X(t) = 0\}$
- occupation measure: any  $f, \rho_N > 0$  s.t.  $\frac{\rho_N}{\beta_N} \rightarrow 0$

$$\nu_t^N(f) = \frac{1}{\rho_N} \int_{\beta_N t}^{\beta_N t + \rho_N} f(X_N(s)) ds$$



## Theorem

If the rates of  $X$  satisfy  $(\star)$ , then

$$\lim_{N \rightarrow \infty} \mathbf{P}[T_N^i - \tilde{T}_N^{i-1} > t\beta_N] = e^{-\tilde{r}_{01}t}; \quad \lim_{N \rightarrow \infty} \mathbf{P}[T_N^{i+1} - \tilde{T}_N^i > t\beta_N] = e^{-\tilde{r}_{10}t}$$

and  $(\nu_t^N)_{t \geq 0} \Rightarrow (\nu_t)_{t \geq 0}$  where

$$\nu_t = \begin{cases} \delta_0, & T_{2i} \leq t < T_{2i+1} \\ \delta_1, & T_{2i+1} \leq t < T_{2i+2} \end{cases} \quad i \geq 0$$

with  $\{T_{2i+1} - T_{2i}\}_{i \geq 0}$ ,  $\{T_{2i+2} - T_{2i+1}\}_{i \geq 0}$  independent sequences of i.i.d exponential variables with rates  $\tilde{r}_{01}$  and  $\tilde{r}_{10}$  respectively.

- ★ occupation measure of  $X \Rightarrow$  **2-state Markov jump process**
- ★ not pathwise,  $X$  makes almost successful transition attempts

## Lemma

If  $X$  is a birth-death chain whose rates  $r_+, r_-$  satisfy:

$$\begin{aligned} \frac{r_+(0)}{N} &\rightarrow \tilde{r}_+ \in (0, \infty), & \frac{r_-(N)}{N} &\rightarrow \tilde{r}_- \in (0, \infty) \\ \sum_{i=1}^{N-1} \left| \frac{r_-(i)}{r_+(i)} - 1 \right| &\rightarrow 0 \\ \sum_{i=1}^{N-1} \frac{N-i}{r_+(i)} &\rightarrow 0, & \sum_{i=1}^{N-1} \frac{i}{r_-(i)} &\rightarrow 0. \end{aligned}$$

then  $(\star)$  holds with  $\omega_N = N$ ,  $\beta_N = 1$  and  $\tilde{r}_{01} = \tilde{r}_+$ ,  $\tilde{r}_{10} = \tilde{r}_-$ .

## Theorem

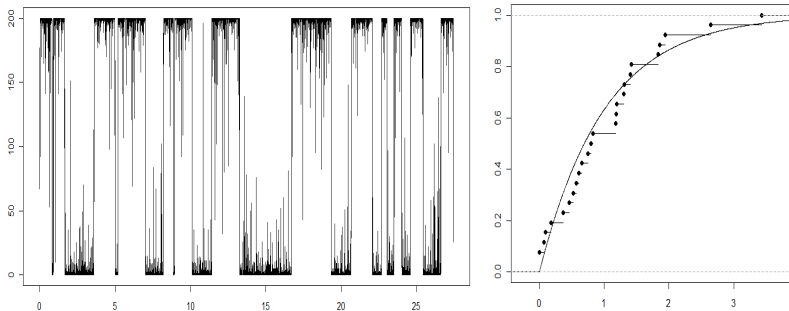
If the rates of interactions scale as '**mass-action**' with drift away from the boundary, and if the additional resampling/splitting mechanism has rates  $\gamma(\mathbf{i}, \mathbf{N}) = \mathbf{p}_i \gamma(\mathbf{N})$ ,  $\mathbf{p}_i = \mathbf{O}(1)$ ,  $\gamma(\mathbf{N})$  satisfies:

$$\frac{N}{\gamma(\mathbf{N})} \sum_{i=1}^{N-1} \frac{1}{p_i} \rightarrow 0, \quad \frac{1}{\gamma(\mathbf{N})} \sum_{i=1}^{N-1} \frac{i}{p_i} \rightarrow 0, \quad \frac{1}{\gamma(\mathbf{N})} \sum_{i=1}^{N-1} \frac{N-i}{p_i} \rightarrow 0$$

then results based on conditions  $(\star)$  hold with

$$\beta^N = 1, \text{ and } \tilde{r}_{01} = \sum_{(0,b,1) \in \mathcal{I}} \tilde{\kappa}_1^{0b}, \quad \tilde{r}_{10} = \sum_{(a,0,-1) \in \mathcal{I}} \tilde{\kappa}_{-1}^{a0}$$

- ★ **time scale** of transitions is  $\beta^N=1$
- ★ the only rates whose **precise value** is relevant are **at the boundary**



**Figure:** Sample path of  $X_N$  for the same system of interactions as before, with additional fast noisy resampling/splitting mechanism.

**parameters:**  $N = 200$ ,  $\gamma(N) = 4N^2$ ,  $p_i = \frac{1}{2}$ ,  $\gamma(i, N) = 8 \cdot 10^4$ :  $\gamma(N) \gg N^2$

## Summary

Rates of additional mechanism lead to different features of bistability: if system has increments of size  $\{+1, -1\}$  only and the rate  $\gamma(x, N) = p_x \gamma(N)$  with  $p_x = O(1)$ , then

- if  $\gamma(N) \ll N$  bistability is caused by large deviations of the Markov jump process, transitions between neighbourhoods of **drift equilibrium points** on a time scale of order  $e^{N(\gamma(N))^{-1}z_{x_1, x_2}}$ , **no correlations** in transition times;
- if  $\gamma(N) \sim \tilde{\gamma}^2 N^2$  bistability is caused by large deviations of a diffusion with a small perturbation coefficient, transitions between neighbourhoods of **drift equilibrium points** on a time scale of order  $e^{\epsilon^{-2}z_{x_1, x_2}}$ , **no correlations** in transition times;
- if  $\gamma(N) \gg N^2 \log N$  bistability is caused by excessive noise, and transitions between the **boundaries** on a time scale of order **1**, **highly correlated** transition times