Rare switching events in non-stationary and non-Markovian systems

N. Becker, R. Allen, P. R. ten Wolde

Computation of transition trajectories and rare events in in non-equilibrium systems

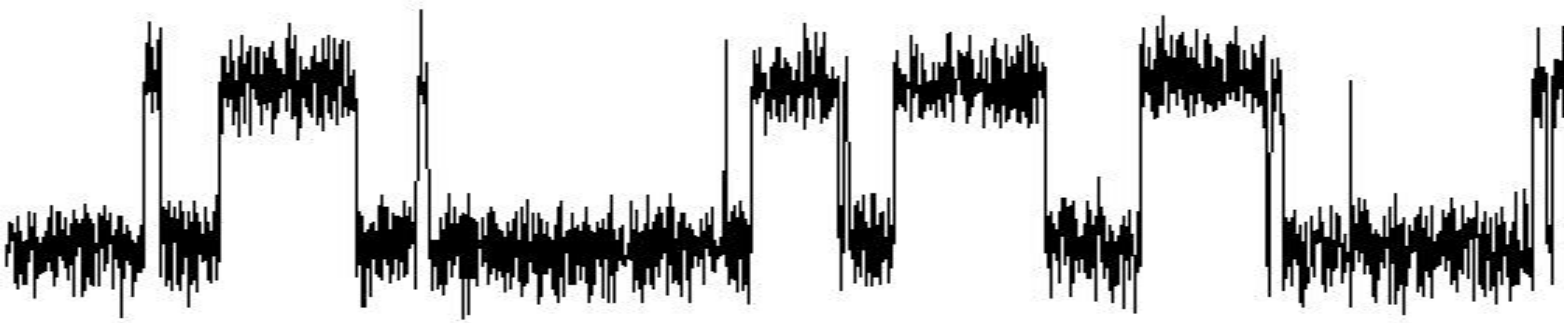
Lyon, June 11-15, 2012

FOM Institute AMOLF

Rare events in non-equilibrium systems

- protein and DNA pulling
- polymer collapse under flow
- crystal nucleation under shear
- traffic jams
- (bio)polymer translocation
- DNA condensation
- switches in biochemical networks

Rare events in stationary, Markovian systems



- Mean waiting time much longer that duration of switching event itself
- Time-homogeneous Markov systems:

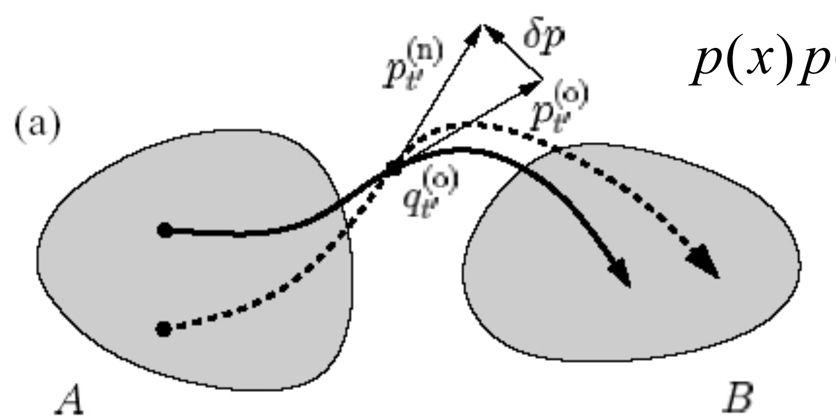
  transitions are independent and intervals are uncorrelated and exponentially distributed

Non-equilibrium systems

- Dynamics do not satisfy detailed balance
- Stationary distribution is not known

Simulating rare events in non-equilibrium systems

- Biasing potentials cannot be used
- Problems with transition path sampling and transition interface sampling



$$p(x)p(x \to y) = p(y)\overline{p}(y \to x)$$

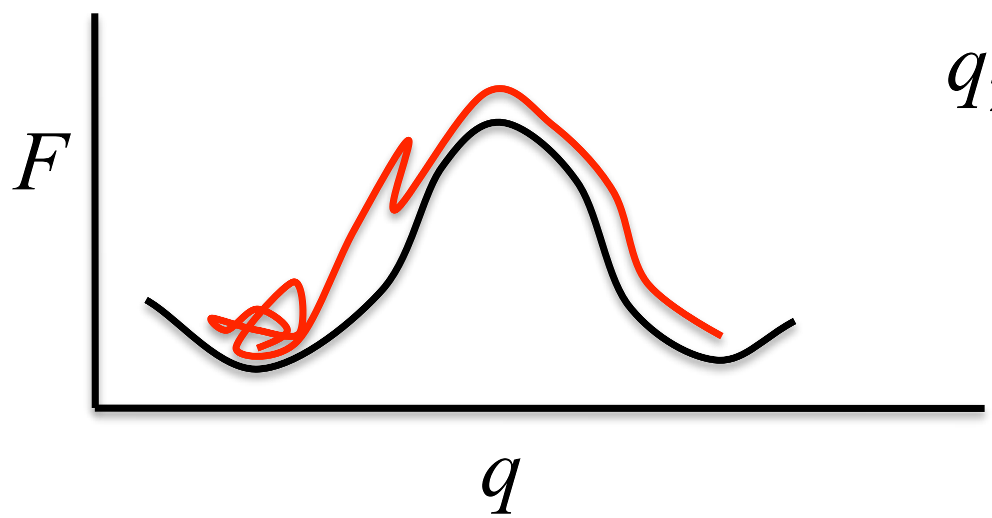
C. Dellago, P. G. Bolhuis, F. S. Csajka & D. Chandler, *J. Chem. Phys.* **108**, 1964 (1998)

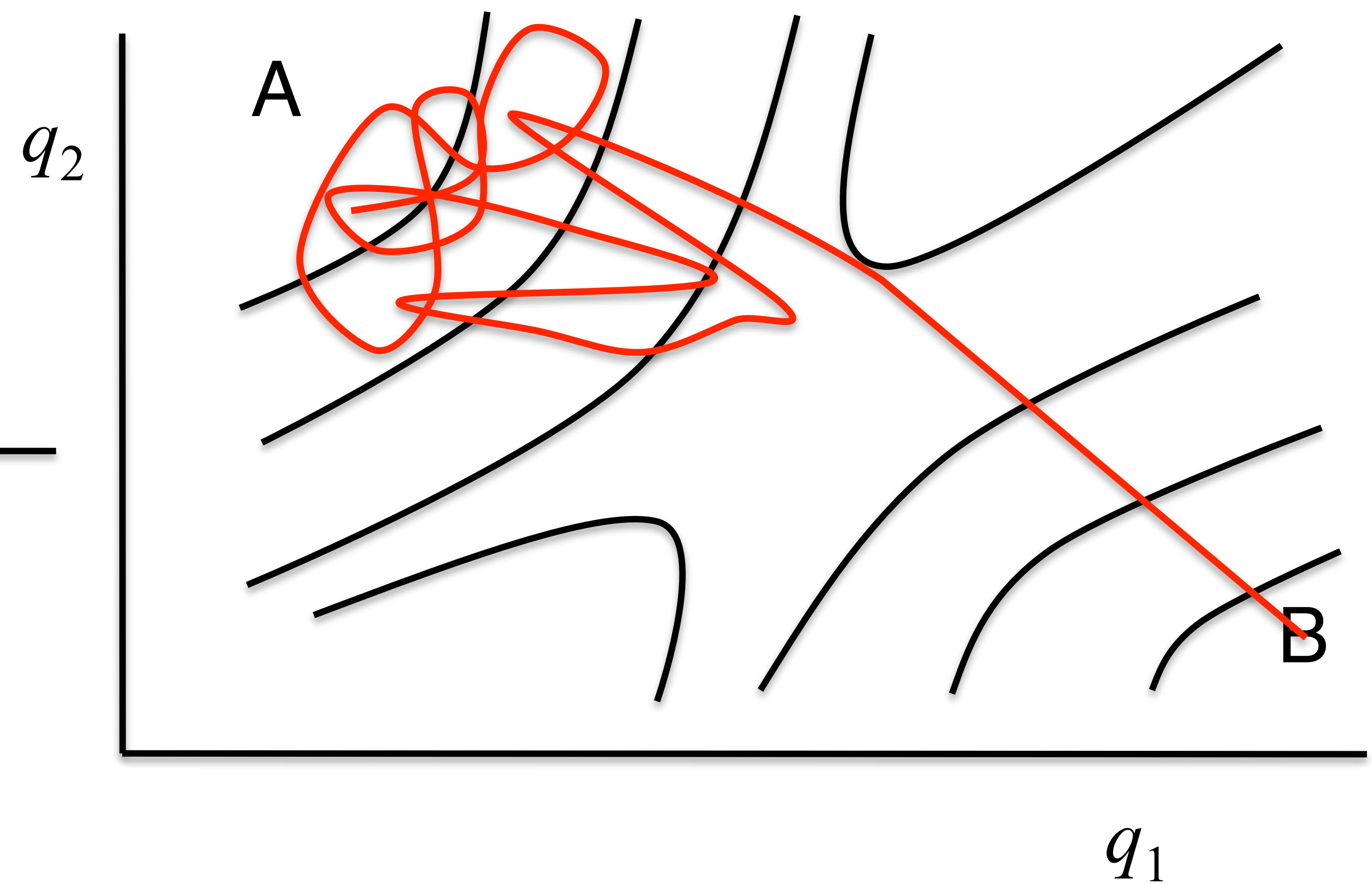
C. Dellago, P. G. Bolhuis & P. L. Geissler, *Adv. Chem. Phys.* **123**, 1 (2002)

Path sampling in non-equilibrium systems

- Often only transition rates between states are known
- Detailed balance is not satisfied
- Phase-space density is not known
- Cannot propagate backwards in time
- Cannot calculate weight of paths

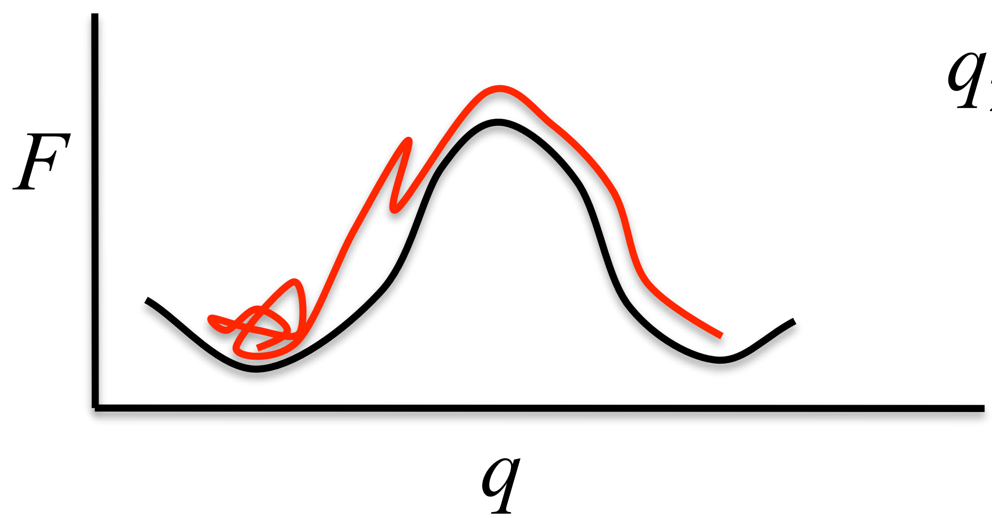
Rare-event problem

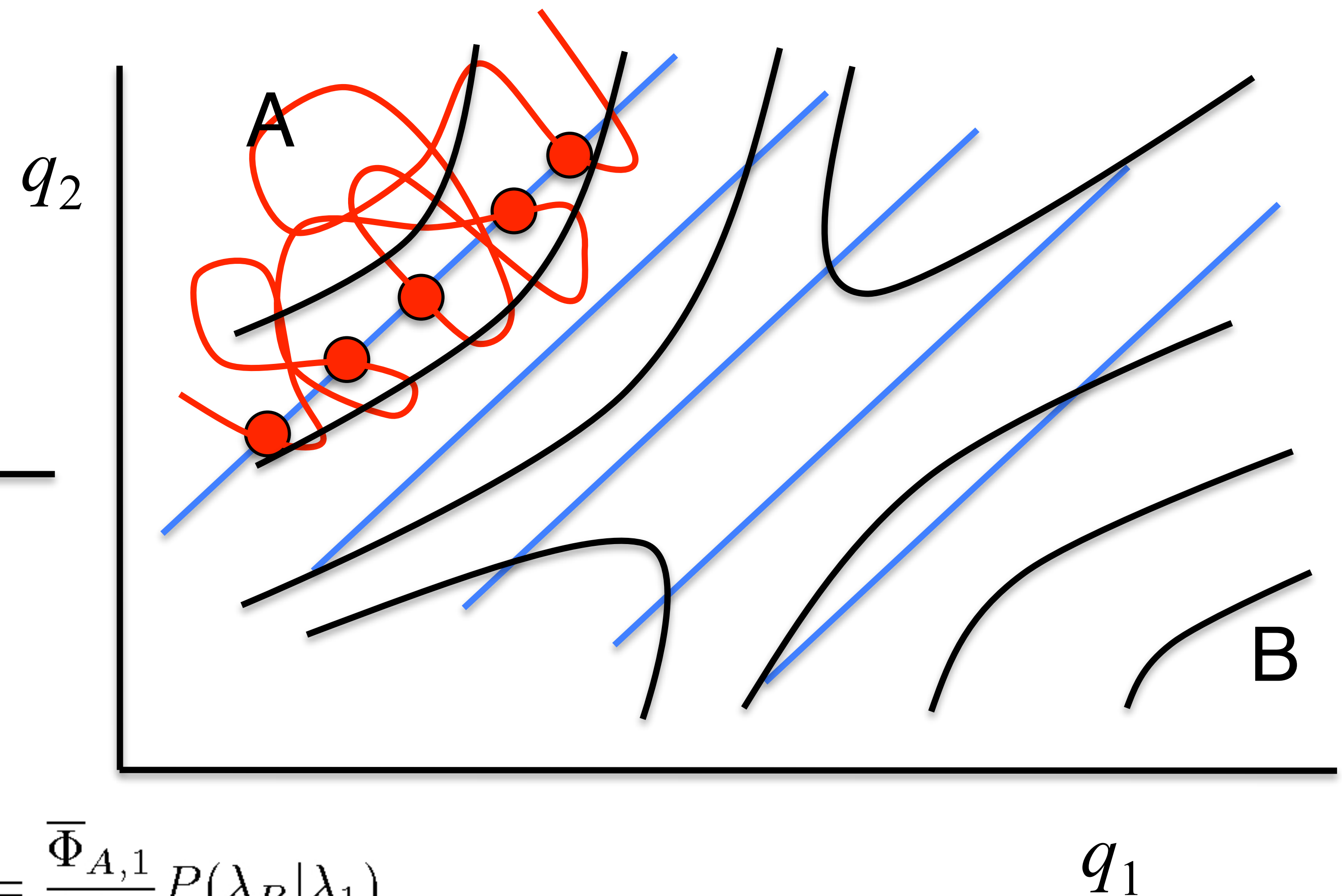




Can we drive the system over the barrier by only propagating forward in time?

Forward-Flux Sampling





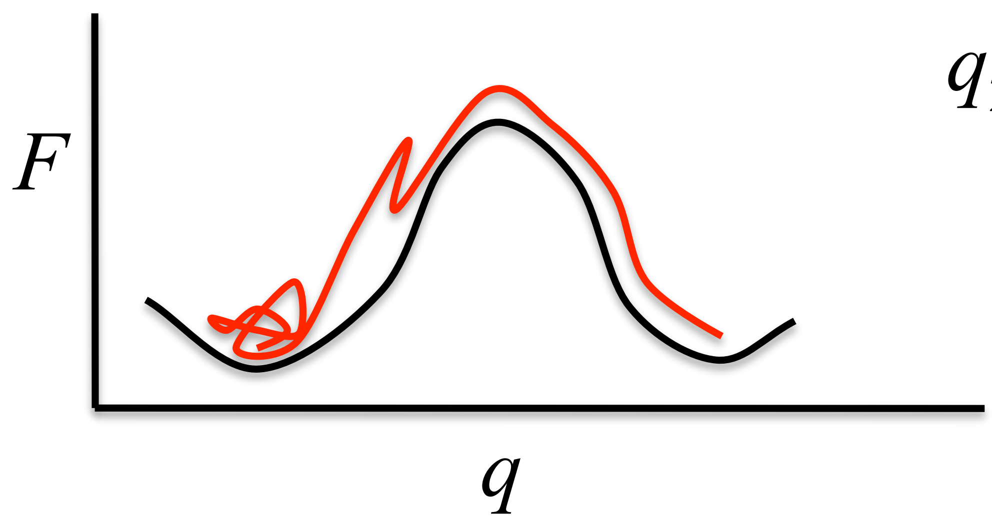
$$k_{AB} = \frac{\overline{\Phi}_{A,B}}{\overline{h}_{\mathcal{A}}} = \frac{\overline{\Phi}_{A,1}}{\overline{h}_{\mathcal{A}}} P(\lambda_B|\lambda_1)$$

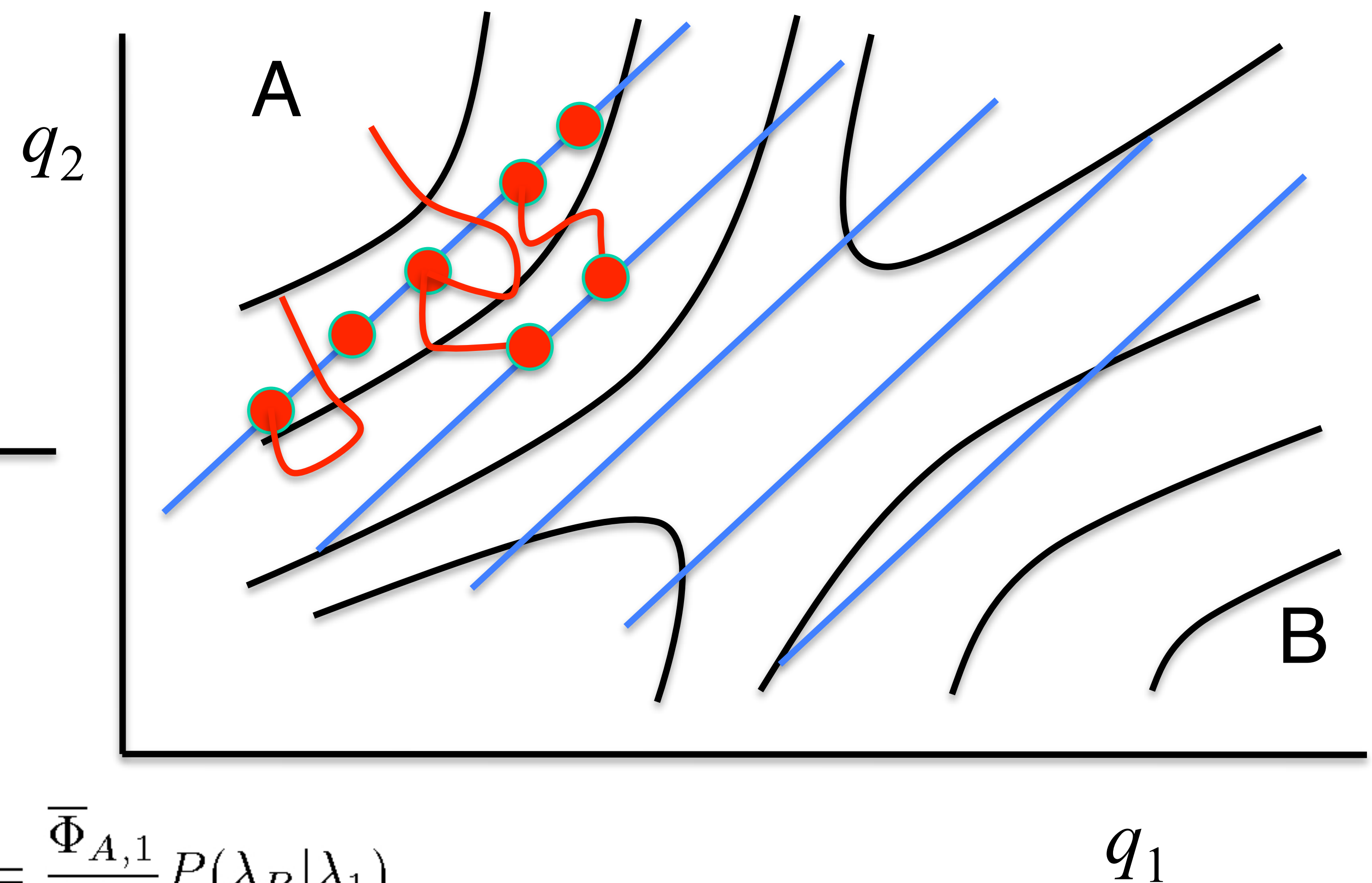
Allen et al, PRL (2005); JCP (2006)

$$P(\lambda_B|\lambda_1) = \prod_{i=1}^{n-1} P(\lambda_{i+1}|\lambda_i) \times P(\lambda_B|\lambda_n)$$

T. S. van Erp, D. Moroni & P. G. Bolhuis, *J. Chem. Phys.* **118**, 7762 (2003)

Forward-Flux Sampling





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Forward-Flux Sampling

- Different versions:
  - Static MC:
    - Direct FFS (just shown)
    - Branched-Growth (BG) FFS (PERM, Grassberger)
  - Dynamic MC:
    - Rosenbluth (RB) FFS
- FFS can be used to compute stationary distributions
- Committors can be extracted on the fly and used to identify reaction coordinates (Borrero & Escobedo)

Review: Allen et al, JPCM (2009)

Forward-Flux Sampling

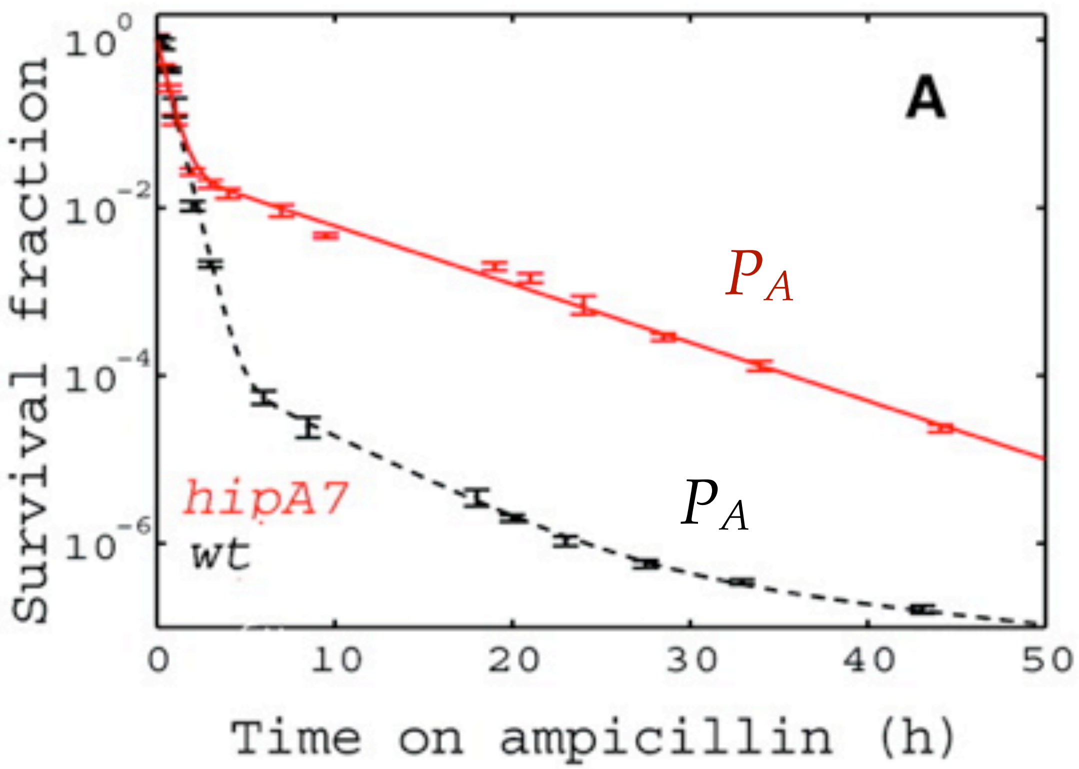
- Widely used:
  - crystal nucleation and gas-liquid nucleation
  - DNA condensation
  - membrane pore formation
  - translocation of DNA and proteins through pores
  - protein folding
  - droplet coalescence
  - polymer collapse under flow
  - diffusion-limited aggregation
  - nucleosome dynamics
  - switches in biochemical networks

Review: Allen et al, JPCM (2009)

Rare events in non-stationary and non-Markovian systems

- Externally driven systems
    - protein folding under force
    - nucleation during temperature quench
- Robustness against transient perturbations
    - power grid
    - traffic jams
    - biological systems
- (In) sensitivity to transient driving or pulses
    - signaling networks, e.g. cell differentiation and cell cycle
    - antibiotics
- Non-Markovian transitions

Resistance against antibiotics: A non-stationary rare event



Balaban et al., Science, 2004

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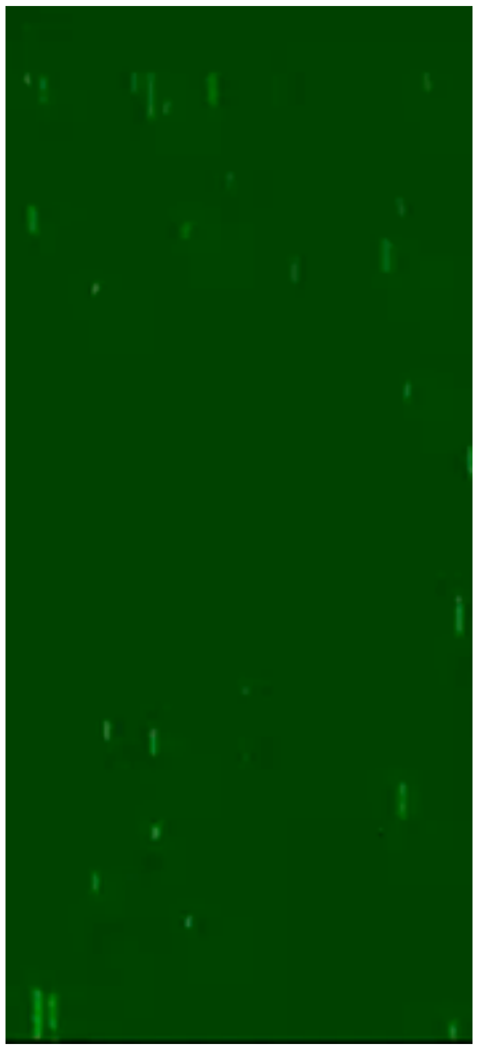

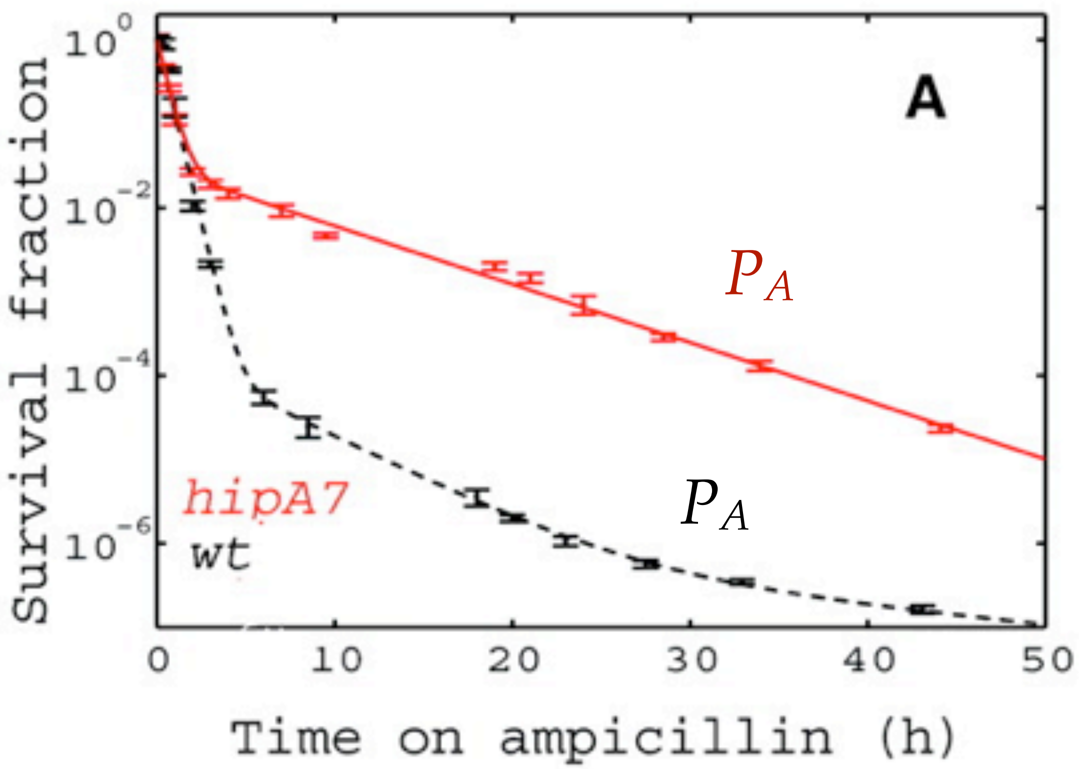

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Resistance against antibiotics:
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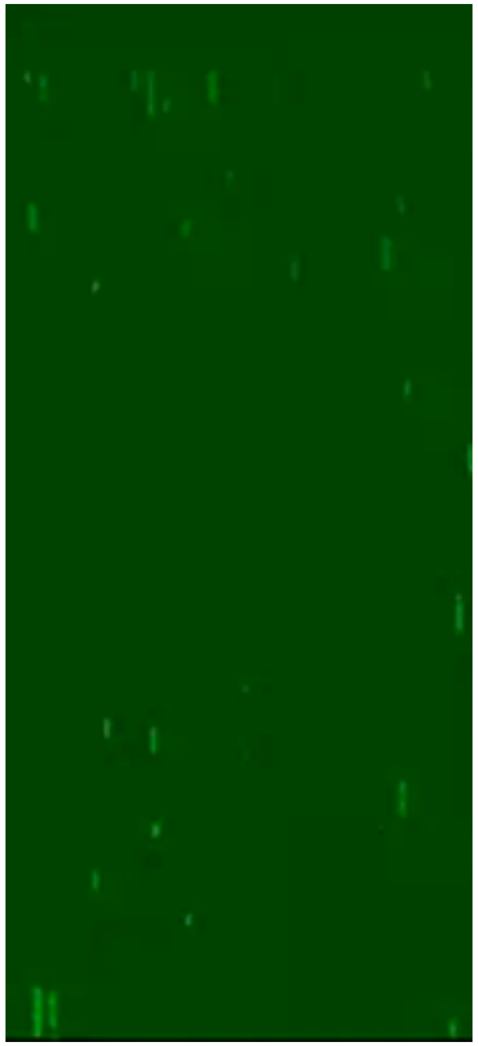
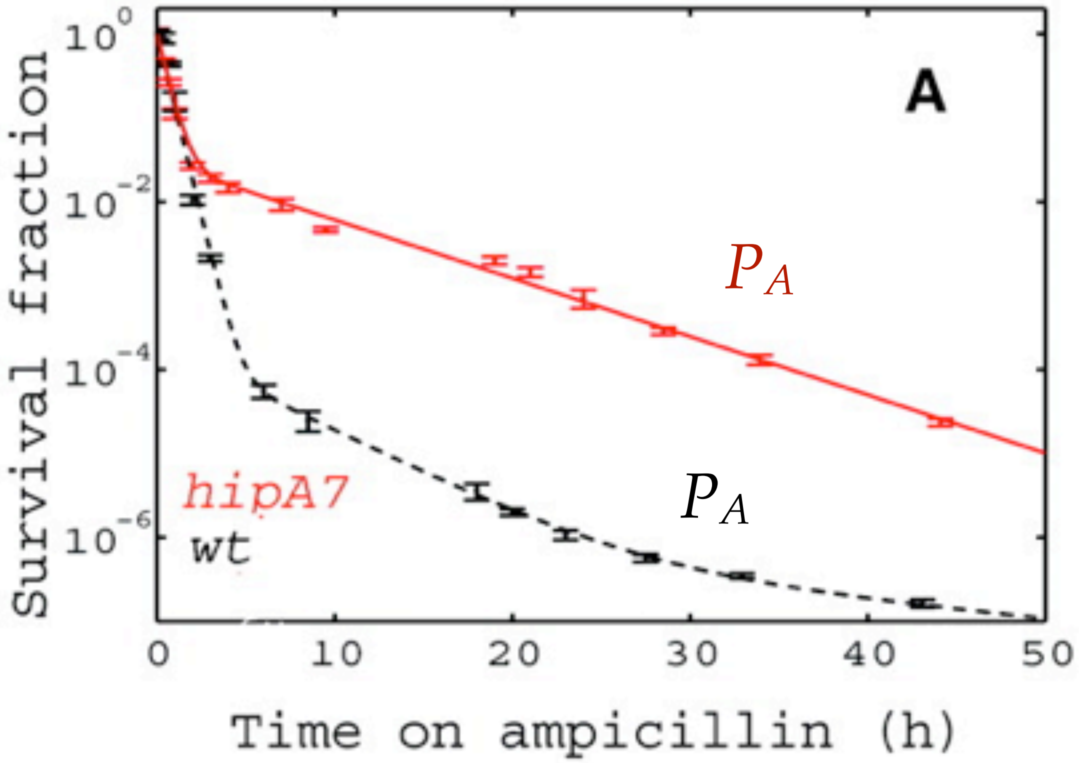
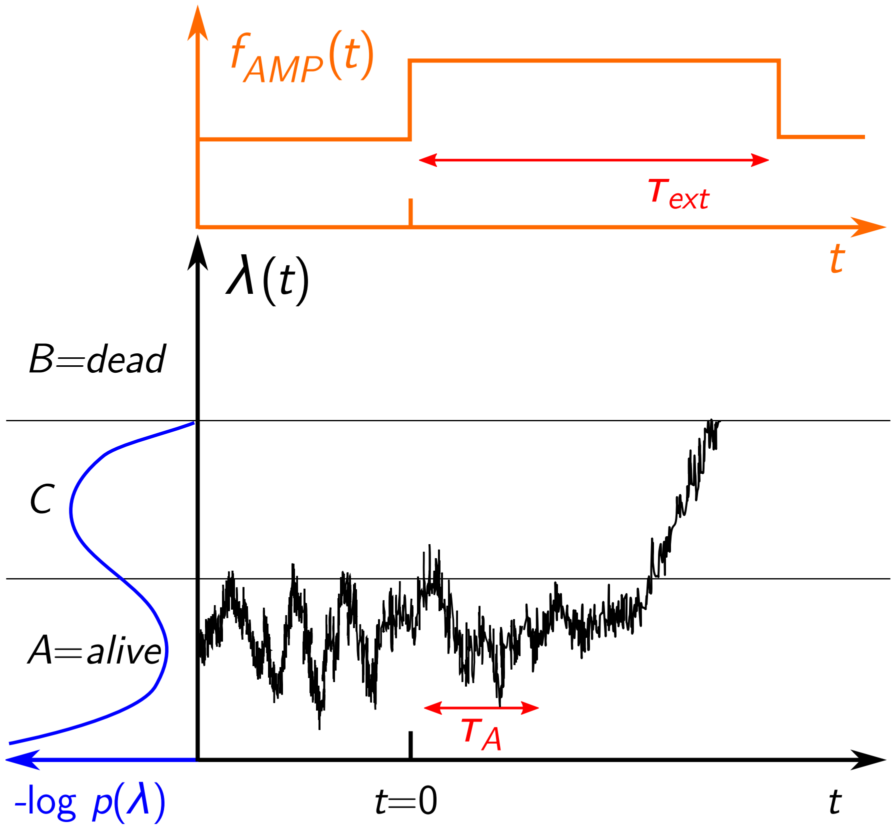
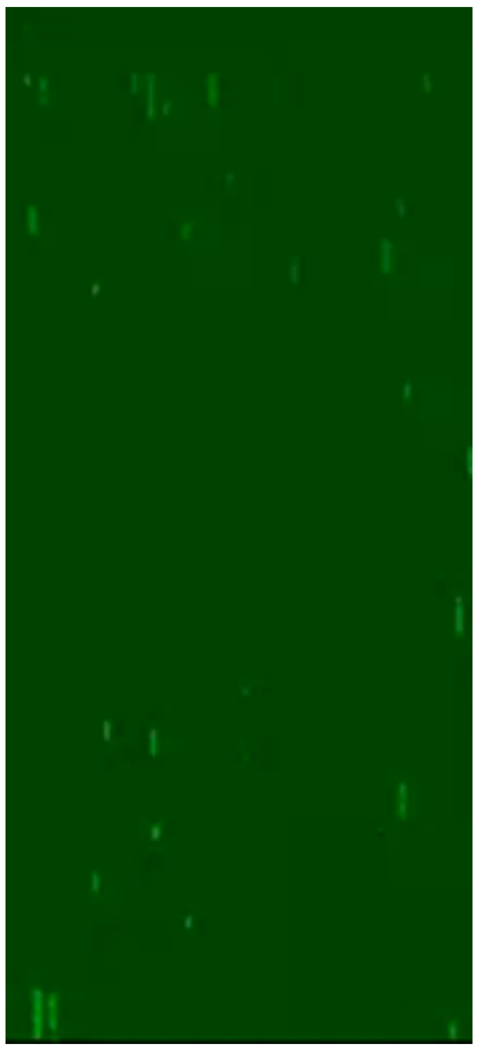


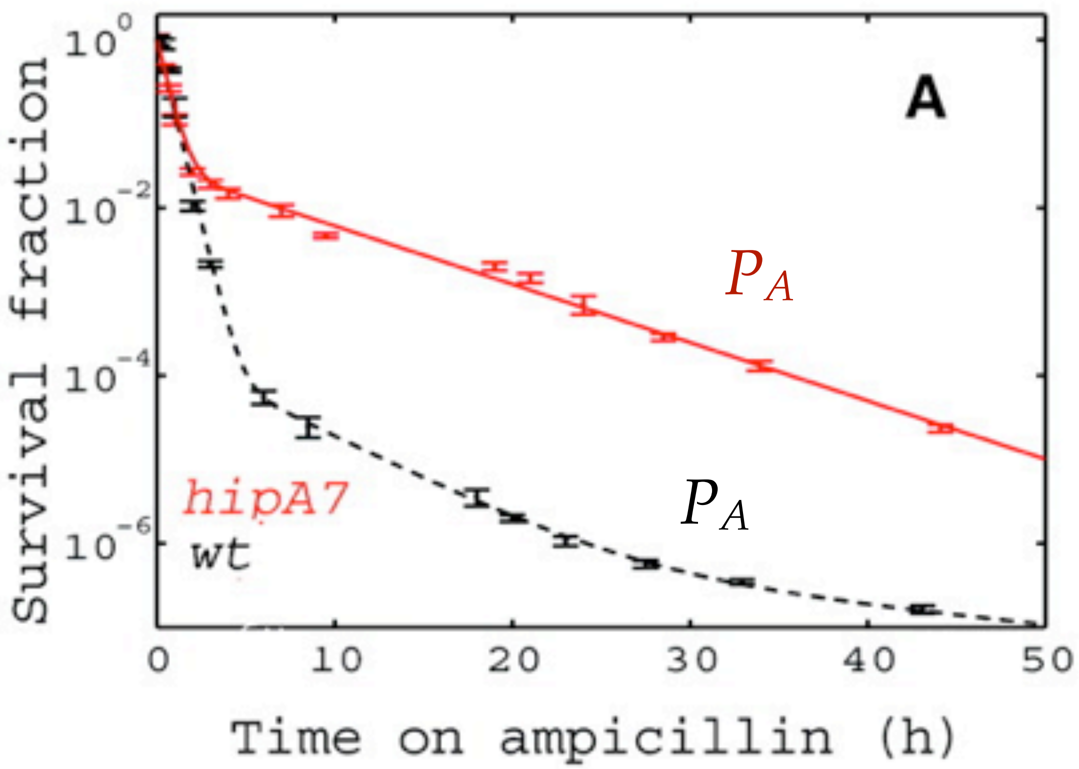


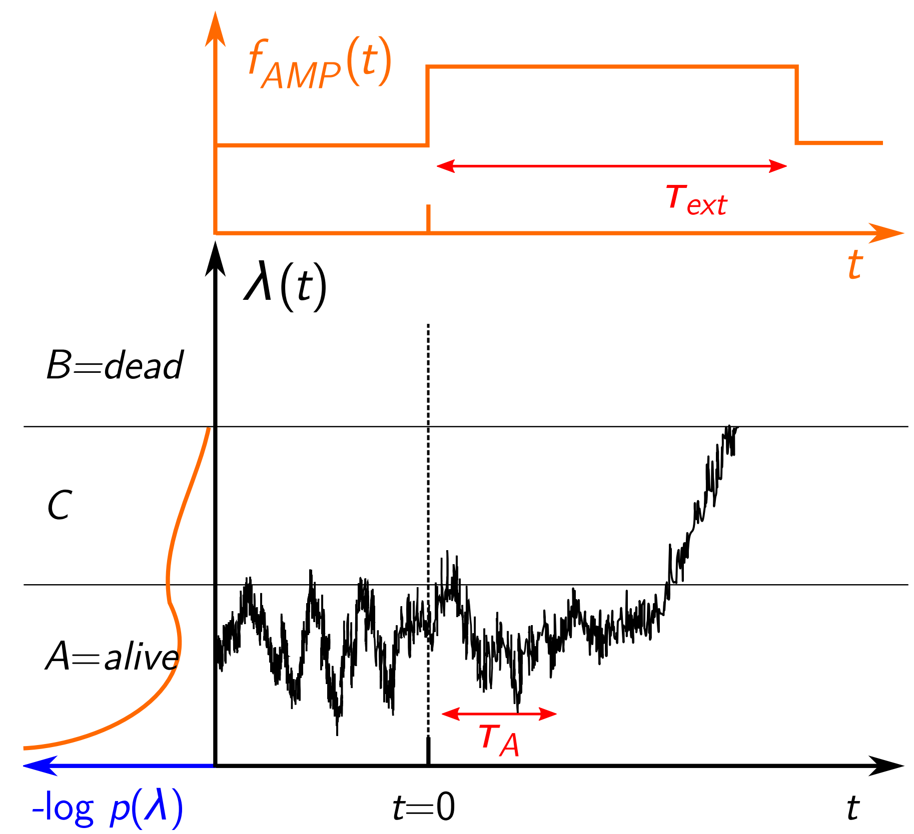


Balaban et al., Science, 2004

Resistance against antibiotics: A non-stationary rare event

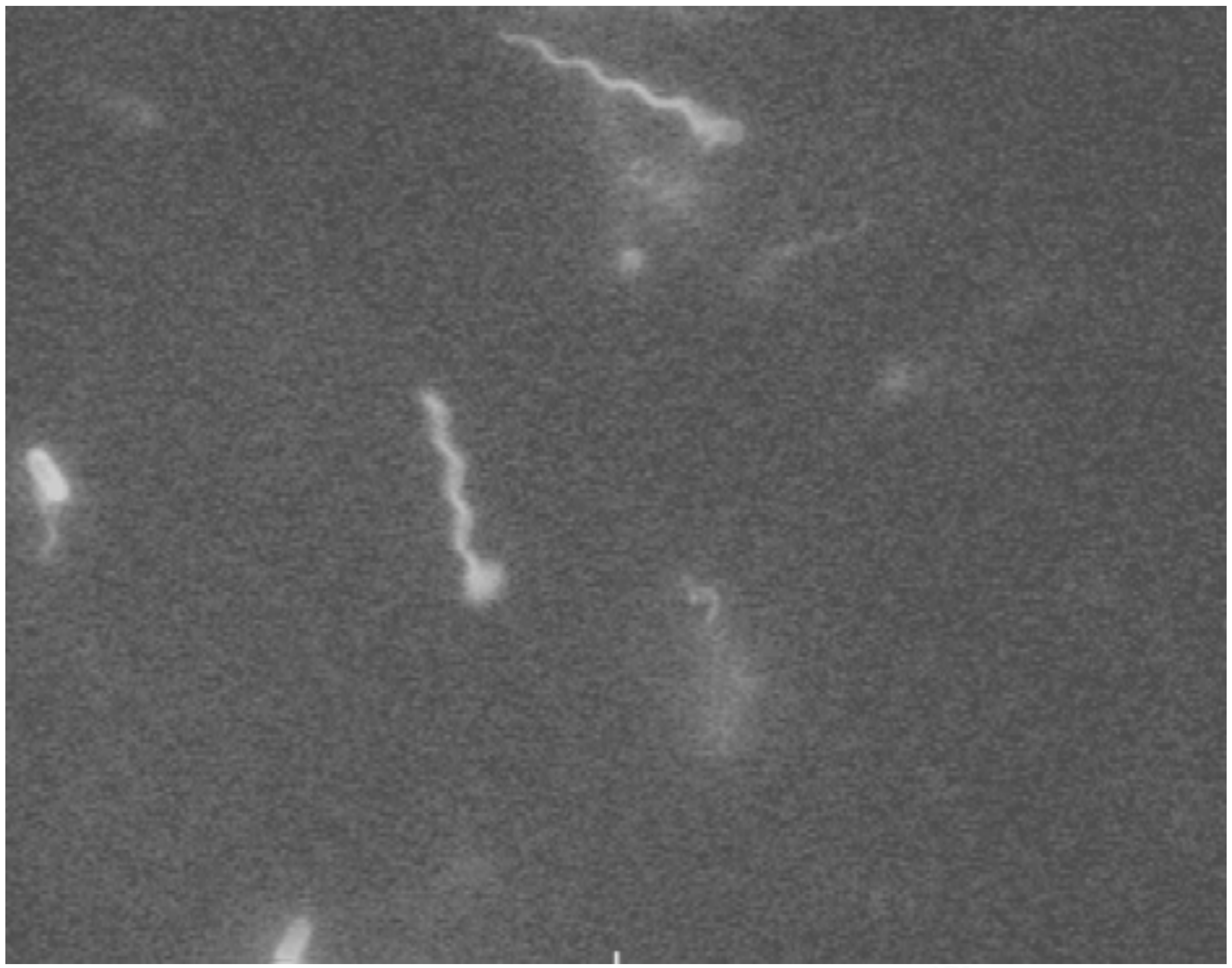


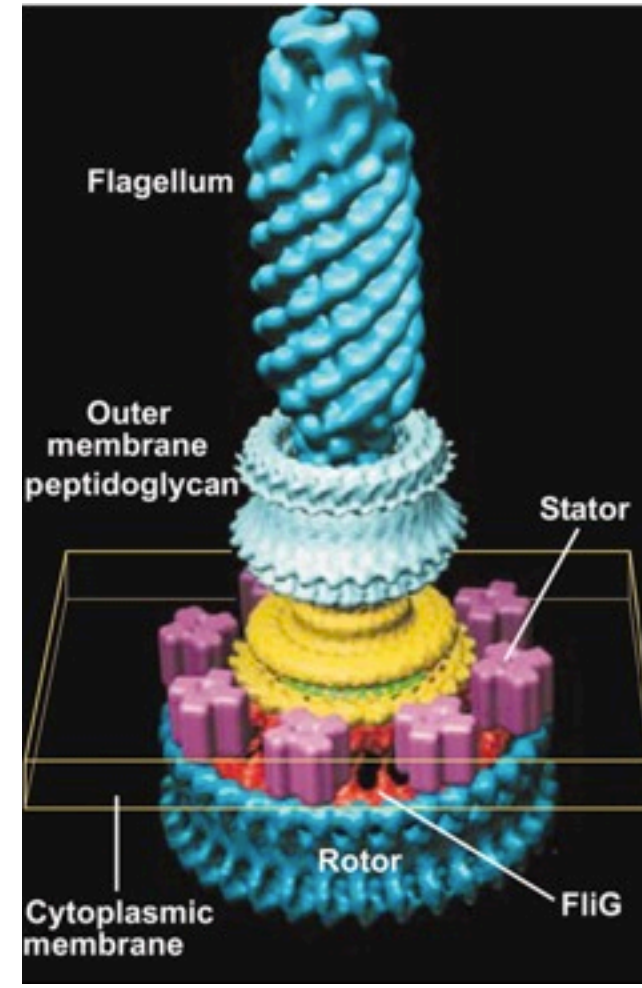




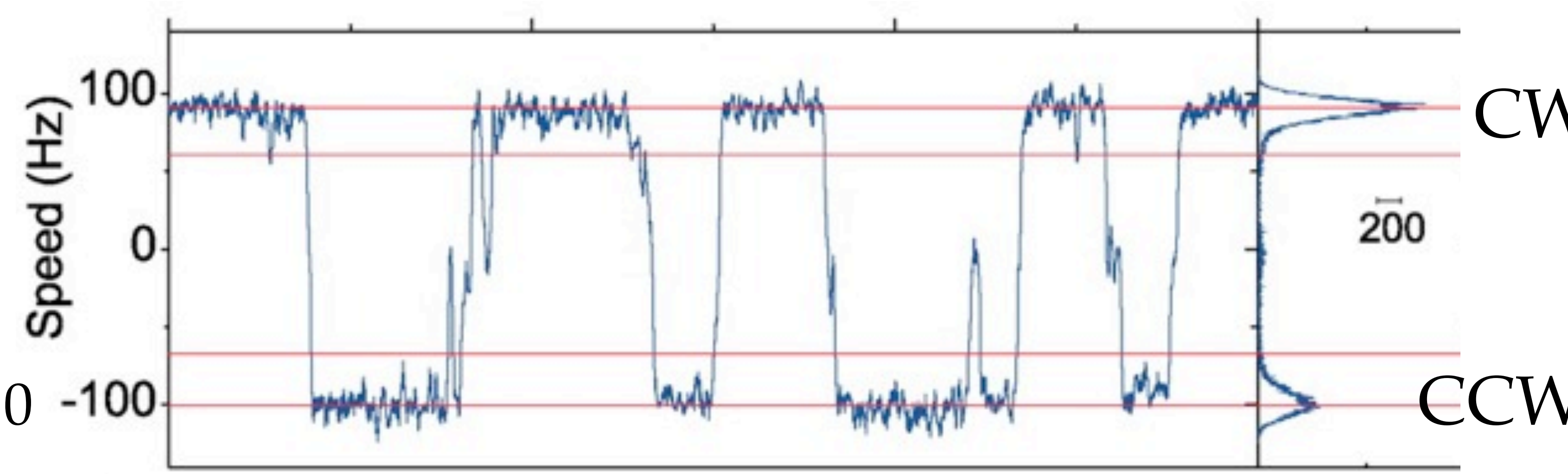
Balaban et al., Science, 2004

Switching of the bacterial flagellar motor: Non-Markovian dynamics





Howard Berg lab



Berry et al., Science 2010

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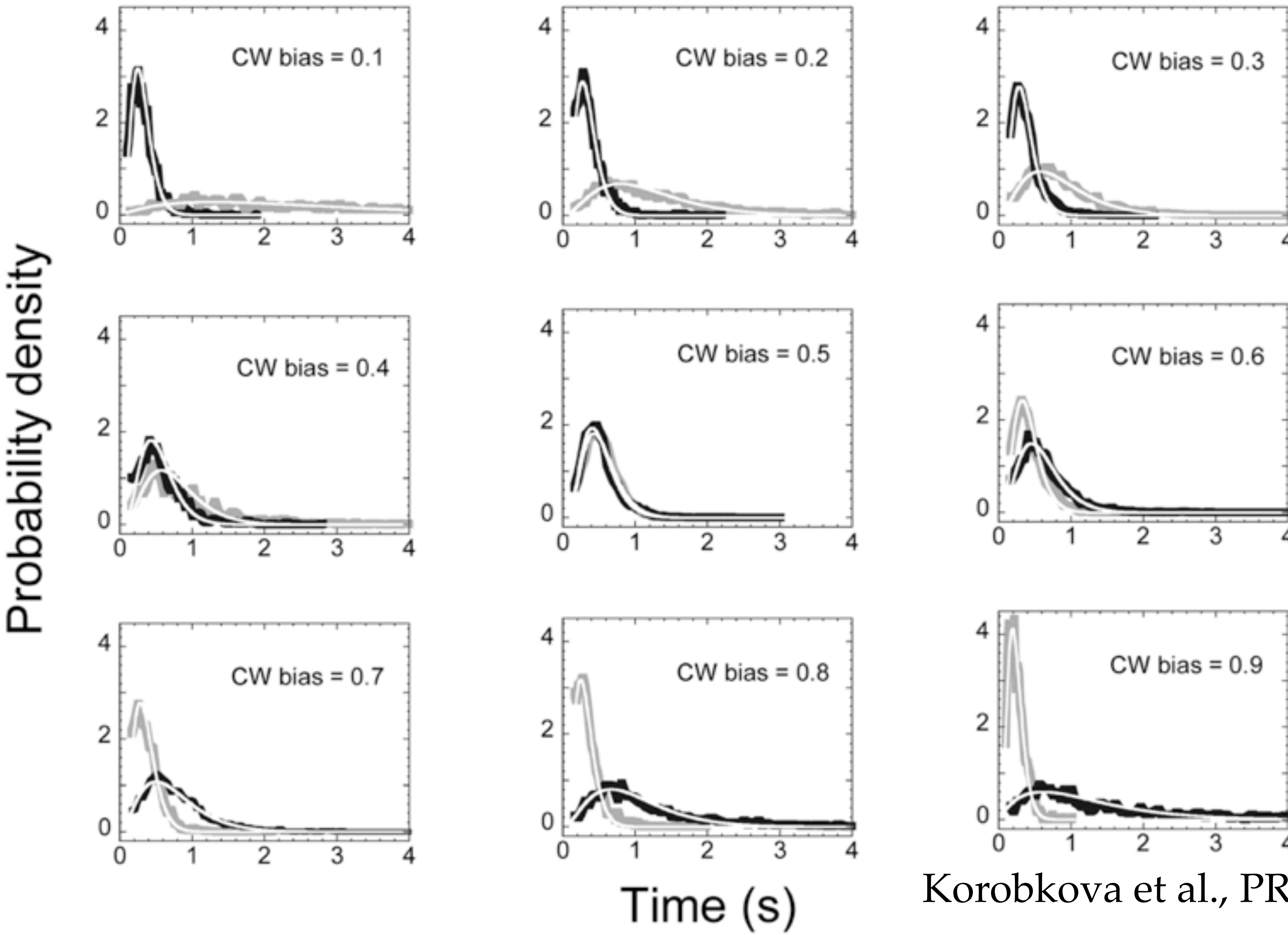


Korobkova et al., PRL, 2006

Questions

- How do we describe these systems?
- Can we derive microscopic expressions in terms of correlation functions for the macroscopic rate constants and rate kernels?
- Can we simulate these non-stationary and non-Markovian systems efficiently?

Macroscopic description of two-state system

- Waiting time longer than transition time: two-state description

$$\frac{\partial}{\partial t} P_B(t; t', t'', \dots) = \delta(t - t') k_{AB}(t' | t'', \dots) P_A(t'; t'', \dots) - k_{BA}(t | t', t'', \dots) P_B(t; t', t'', \dots)$$

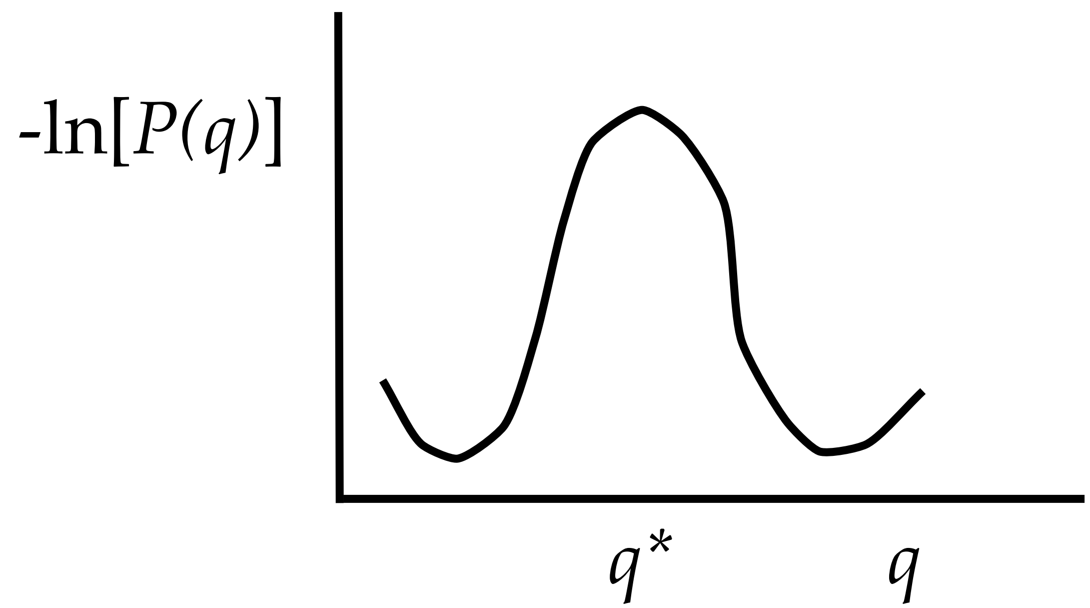
$$\frac{d}{dt} P_B(t) = \int_{t \leq t' \leq t'' \leq \dots} \frac{\partial}{\partial t} P_B(t; t', t'', \dots) dt' dt'' \dots .$$

- Eqs. cannot be solved in general — Chandler, JCP (1978)
- Experiment has to inform us about most meaningful model

Microscopic description

- Define macroscopic states in terms of microscopic indicator functions:

$$h_A(x_t) = \theta[q^* - q(x_t)],$$
$$h_B(x_t) = \theta[q(x_t) - q^*].$$



- Macroscopic rate constants are related to time derivative of:

$$C(t) = \int dx_0 dx_t \rho(x_0) p(x_t|x_0) h_B(x_t)$$
$$= \langle h_B(x_t) \rangle_0$$

Markov systems

- Experiment reveals that there exists a macroscopic time resolution Δt on which the propensity to switch is independent of the history:

$$k_{AB}(t|t', t'', \ldots) = k_{AB}(t)$$

- Rate equation:

$$\frac{d}{dt} P_B(t) = k_{AB}(t) P_A(t) - k_{BA}(t) P_B(t)$$

Markov systems

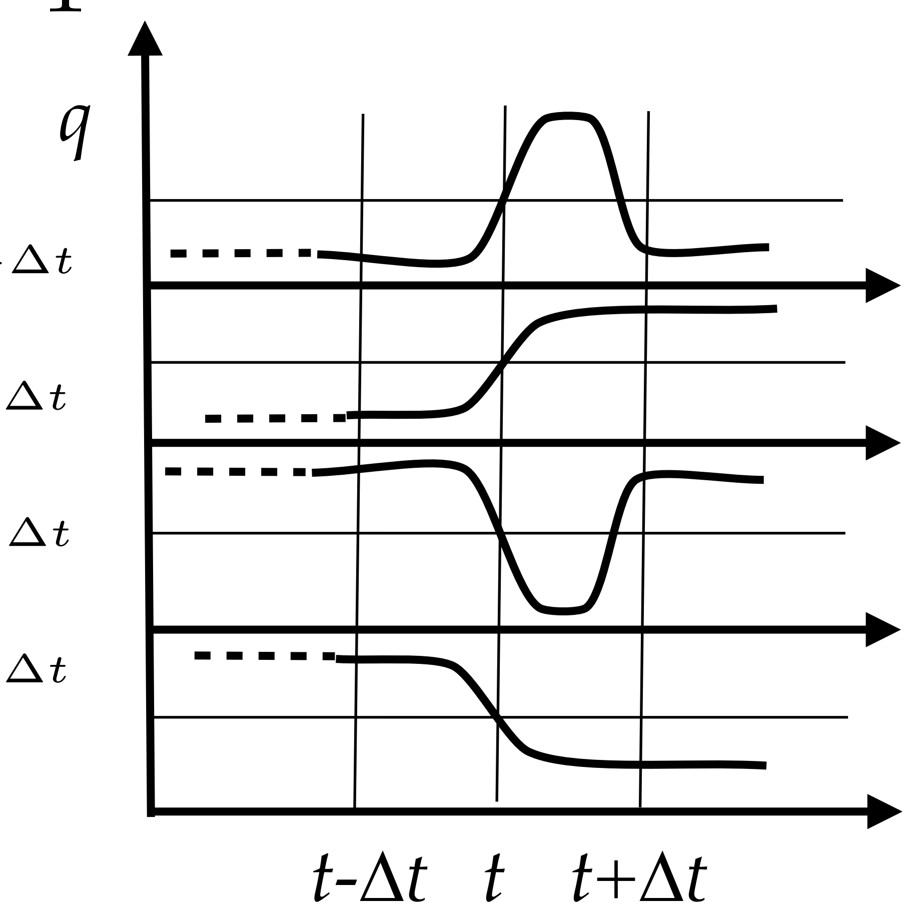
- Consider:

$$\dot{C}(t) = \langle \dot{h}_B(t) \rangle_{A_0}$$

- Insert:

$$h_A(t-\Delta t) + h_B(t-\Delta t) = 1$$
$$h_A(t+\Delta t) + h_B(t+\Delta t) = 1$$

$$\begin{aligned}
\dot{C}(t) &= \langle h_A(t-\Delta t)\rangle_{A_0} \langle \dot{h}_B(t) h_A(t+\Delta t)\rangle_{A_{t-\Delta t}} \\
&+ \langle h_A(t-\Delta t)\rangle_{A_0} \langle \dot{h}_B(t) h_B(t+\Delta t)\rangle_{A_{t-\Delta t}} \\
&+ \langle h_B(t-\Delta t)\rangle_{A_0} \langle \dot{h}_B(t) h_B(t+\Delta t)\rangle_{B_{t-\Delta t}} \\
&+ \langle h_B(t-\Delta t)\rangle_{A_0} \langle \dot{h}_B(t) h_A(t+\Delta t)\rangle_{B_{t-\Delta t}} \\
&\equiv j_{AA}(t) + j_{AB}(t) + j_{BB}(t) + j_{BA}(t)
\end{aligned}$$



Markov systems

- If system is time reversible or time-homogeneous or memoryless on time scale Δt, then $j_{AA}(t)$ and $j_{BB}(t)$ are zero:

$$
\begin{aligned}
\dot{C}(t) &= \langle h_A(t-\Delta t)\rangle_{A_0} \langle \dot{h}_B(t) h_A(t+\Delta t)\rangle_{A_{t-\Delta t}} \\
&+ \langle h_B(t-\Delta t)\rangle_{A_0} \langle \dot{h}_B(t) h_A(t+\Delta t)\rangle_{B_{t-\Delta t}} \\
&\simeq P_A(t)\langle \dot{h}_B(t) h_B(t+\Delta t)\rangle_{A_{t-\Delta t}} + P_B(t)\langle \dot{h}_B(t) h_A(t+\Delta t)\rangle_{B_{t-\Delta t}} \\
&= dP_B(t)/dt
\end{aligned}
$$

- Hence, time-dependent rate constants are given by:

$$
\begin{aligned}
k_{AB}(t) &= \langle \dot{h}_B(t) h_B(t+\Delta t)\rangle_{A_{t-\Delta t}}, \\
k_{BA}(t) &= -\langle \dot{h}_B(t) h_A(t+\Delta t)\rangle_{B_{t-\Delta t}}.
\end{aligned}
$$

Bennett, Chandler

Markov system with external driving

- Two-state system with driving force that varies on time scale τ_ϕ
- Markov description requires that $\tau_{\mathrm{trans}} < \Delta t << \tau_{\mathrm{rxn}}$
- Two simple scenarios:
  - quasi-static case:

    $$\tau_{\mathrm{trans}} < \Delta t < \tau_\phi << \tau_{\mathrm{rxn}} : k(t) = k(\phi(t))$$

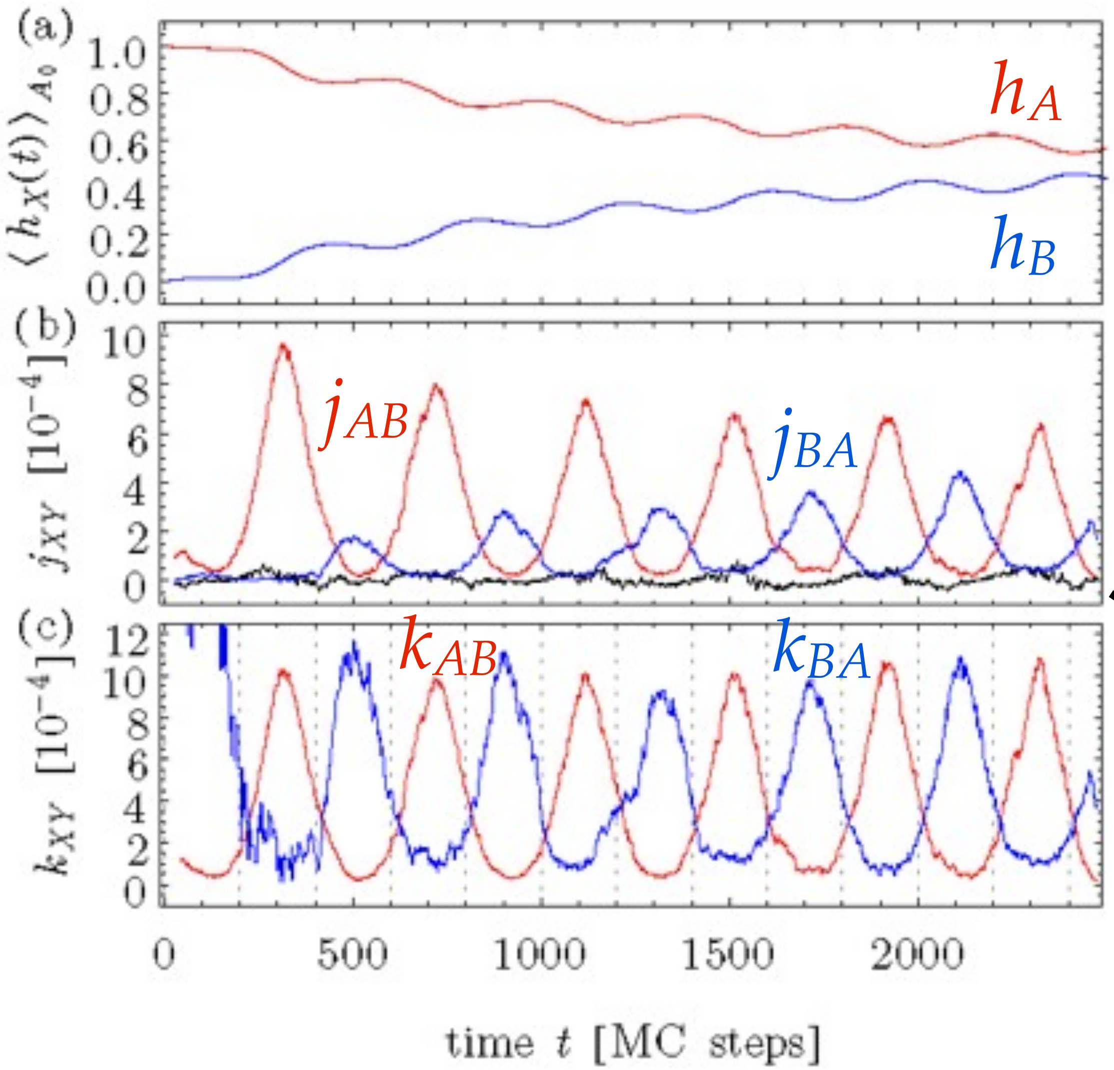
  - rapidly varying force:

    $$\tau_{\mathrm{trans}}, \tau_\phi < \Delta t << \tau_{\mathrm{rxn}}$$

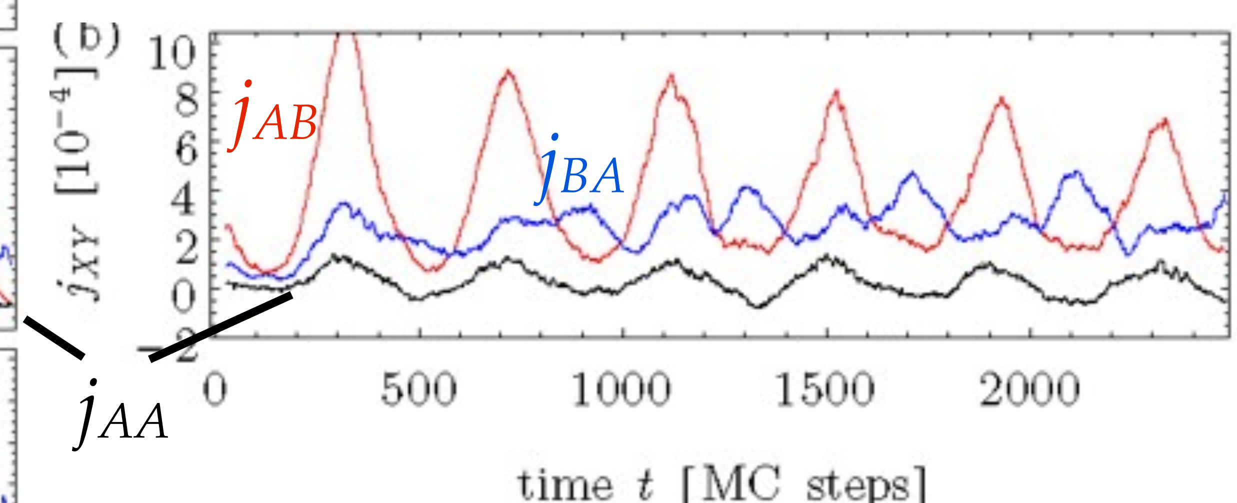
Markov system with external driving

- One-dimensional barrier with oscillatory force
- Quasi-static case:

$$\tau_{\text{trans}} < \Delta t < \tau_\phi << \tau_{\text{rxn}} : k(t) = k(\phi(t))$$



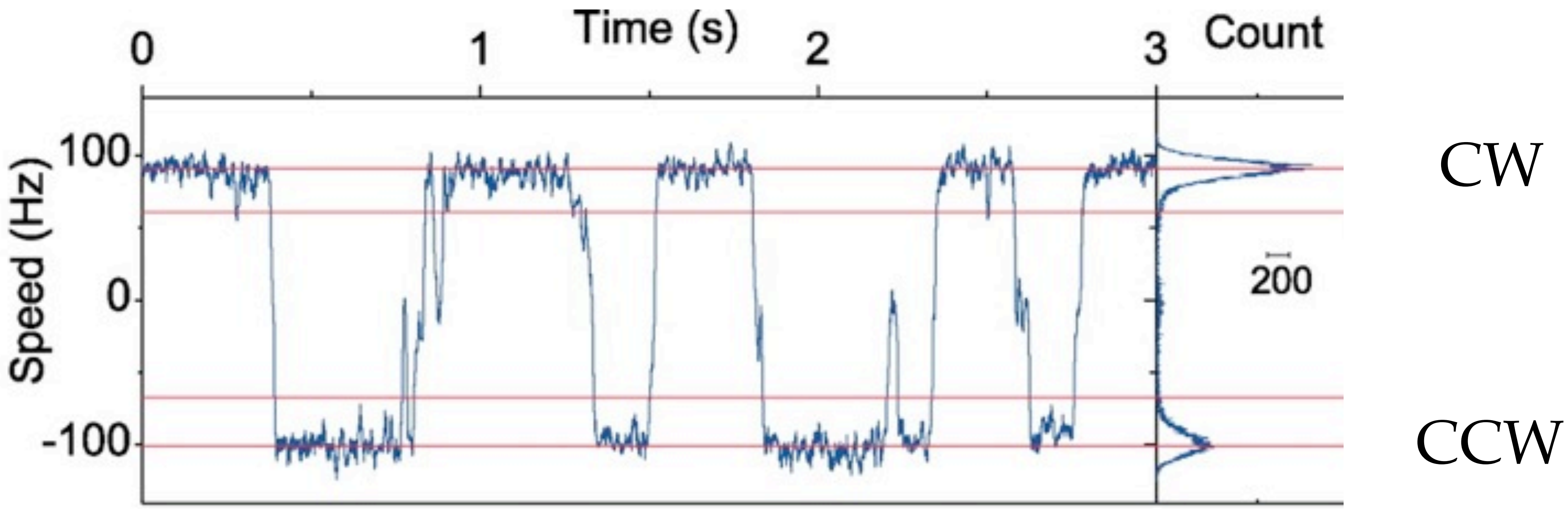
$\Delta t = 20$



$\Delta t = 2$

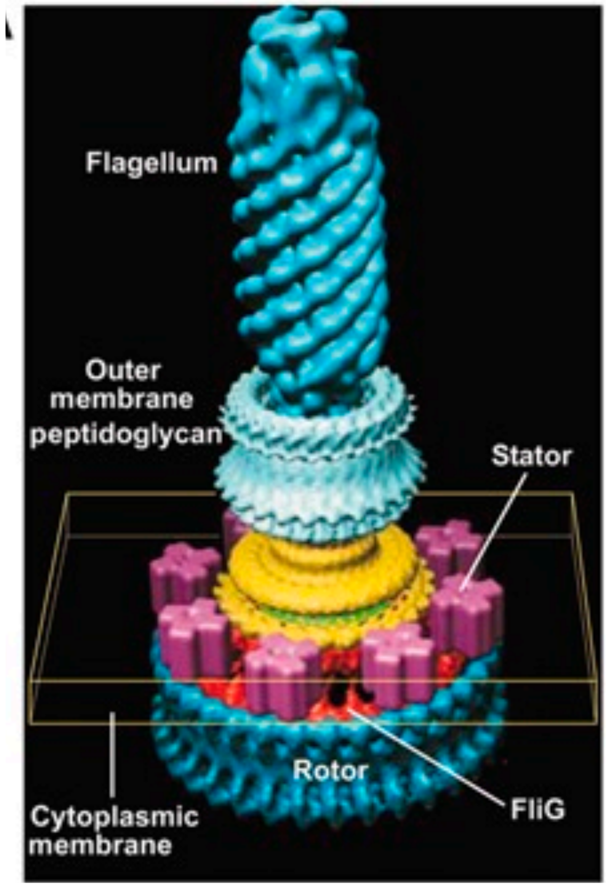
correlations persist and recrossing fluxes are non-zero

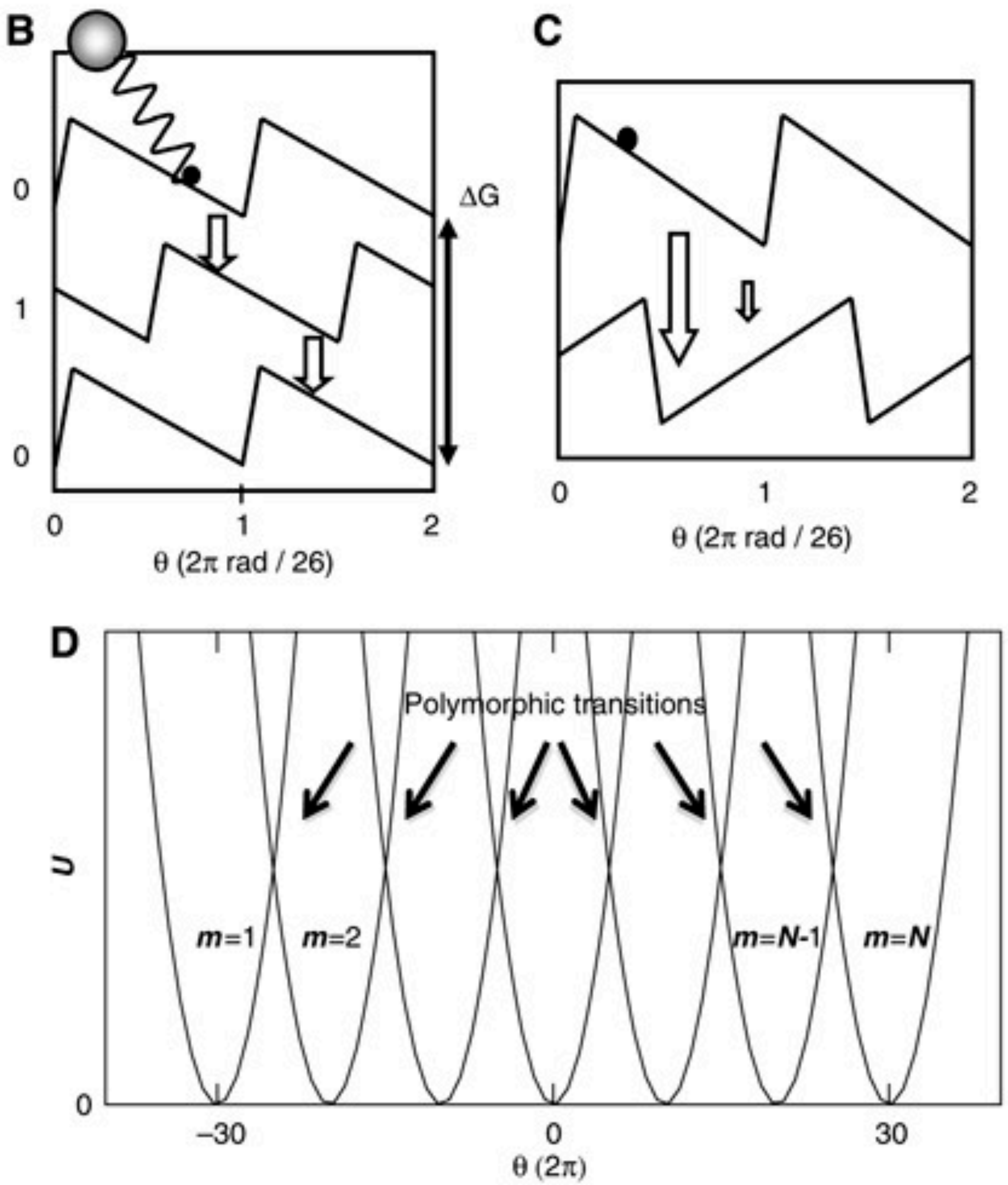
Non-Markov system: flagellar motor

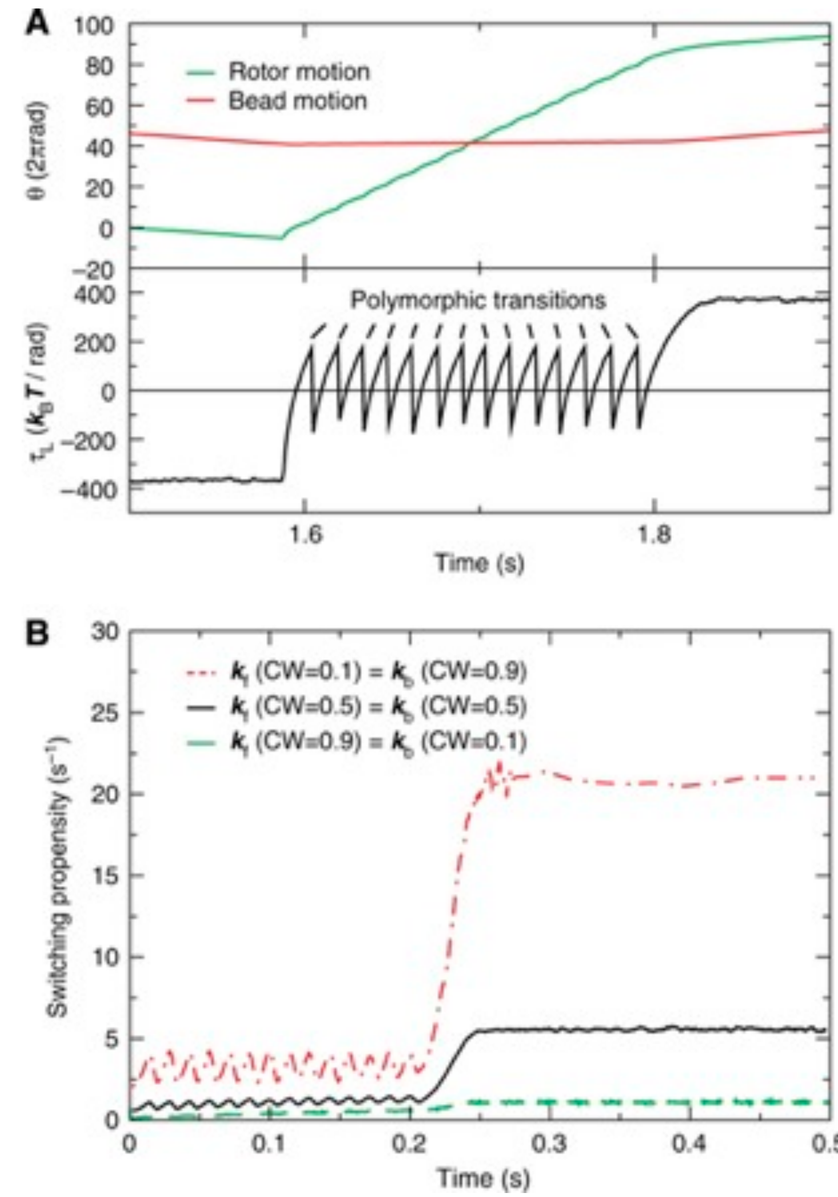


- Randomly shuffling clockwise and counterclockwise intervals does not change power spectrum; moreover, power spectrum can be reproduced from waiting-time distributions only
- System is a time-homogeneous non-Markovian system: transitions are independent and the different intervals are temporally uncorrelated, but they are *not* exponentially distributed.
- Switching propensity depends only upon the time that has passed since the last switching event.

The flagellar motor







Albada, Tanase-Nicola, PRtW, Nat MSB (2009)

Non-Markov systems
Macroscopic description

- Clock resetting:

$$\frac{d}{dt}P_B(t) = \int_{t \le t'} [k_{AB}(t|t')P_A(t;t') - k_{BA}(t|t')P_B(t;t')]dt'$$

- $P_A(t;t')$: Probability that the system is in A at time t and has switched into that state for the last time within an earlier time interval $(t',t'+dt)$

- $k_{AB}(t|t')$: The propensity that the system switches from A to B at time t given that it has switched into A at time $t' < t$ and is still in A at time t

Non-Markov systems
microscopic description

- Need indicator function that measures time since last switching event:

$$H_X(t,t') \equiv \prod_{t \geq t'' > t'} h_X(t''); \; H_X(t,t) = 1$$

- Relate macroscopic rate equation to:

$$\dot{h}_B(t) = \dot{h}_B(t) \sum_{X=A,B} H_X(t,t)$$

$$= \partial_t H_B(t,t_0) - \partial_t H_A(t,t_0)$$

$$+ \int_{t_0}^{t} [\partial_t \partial_{t'} H_B(t,t') - \partial_t \partial_{t'} H_A(t,t')] dt'$$

Non-Markov system
microscopic description

- Microscopic expressions for P_B(t,t′) and k_{AB}(t,t′):

$$\partial_{t'}\langle H_B(t,t')\rangle dt' = \langle H_B(t,t')\dot{h}_B(t')\rangle dt' = P_B(t;t')dt',$$

$$\frac{\partial_t\partial_{t'}\langle H_B(t,t')\rangle}{\partial_{t'}\langle H_B(t,t')\rangle} = \frac{\langle \dot{h}_B(t)H_B(t,t')\dot{h}_B(t')\rangle}{\langle H_B(t,t')\dot{h}_B(t')\rangle} = -k_{AB}(t|t')$$

Non-Markov system
microscopic description

- Integrate over transient crossings over the dividing surface:

$$h_B(t;\Delta t) = \theta\big[\int_{t-\Delta t}^{t} h_B(t')dt' - \Delta t/2\big]$$

glasses, Chandler et al.

- Microscopic expressions for P_B(t,t′) and k_{AB}(t,t′) depend on Δt :

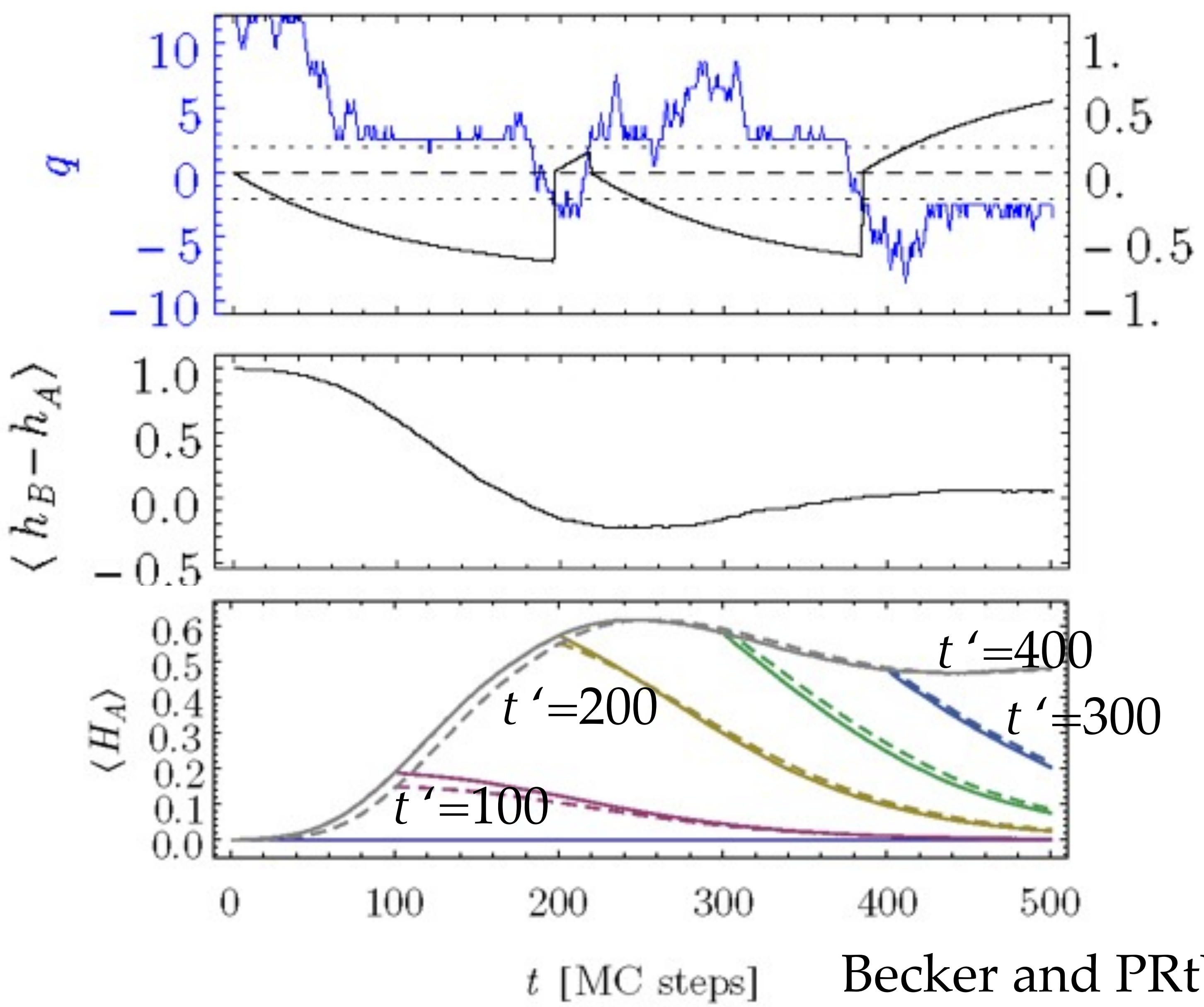
$$P_B(t;t';\Delta t)dt' = \partial_{t'}\langle H_B(t,t';\Delta t)\rangle dt',$$

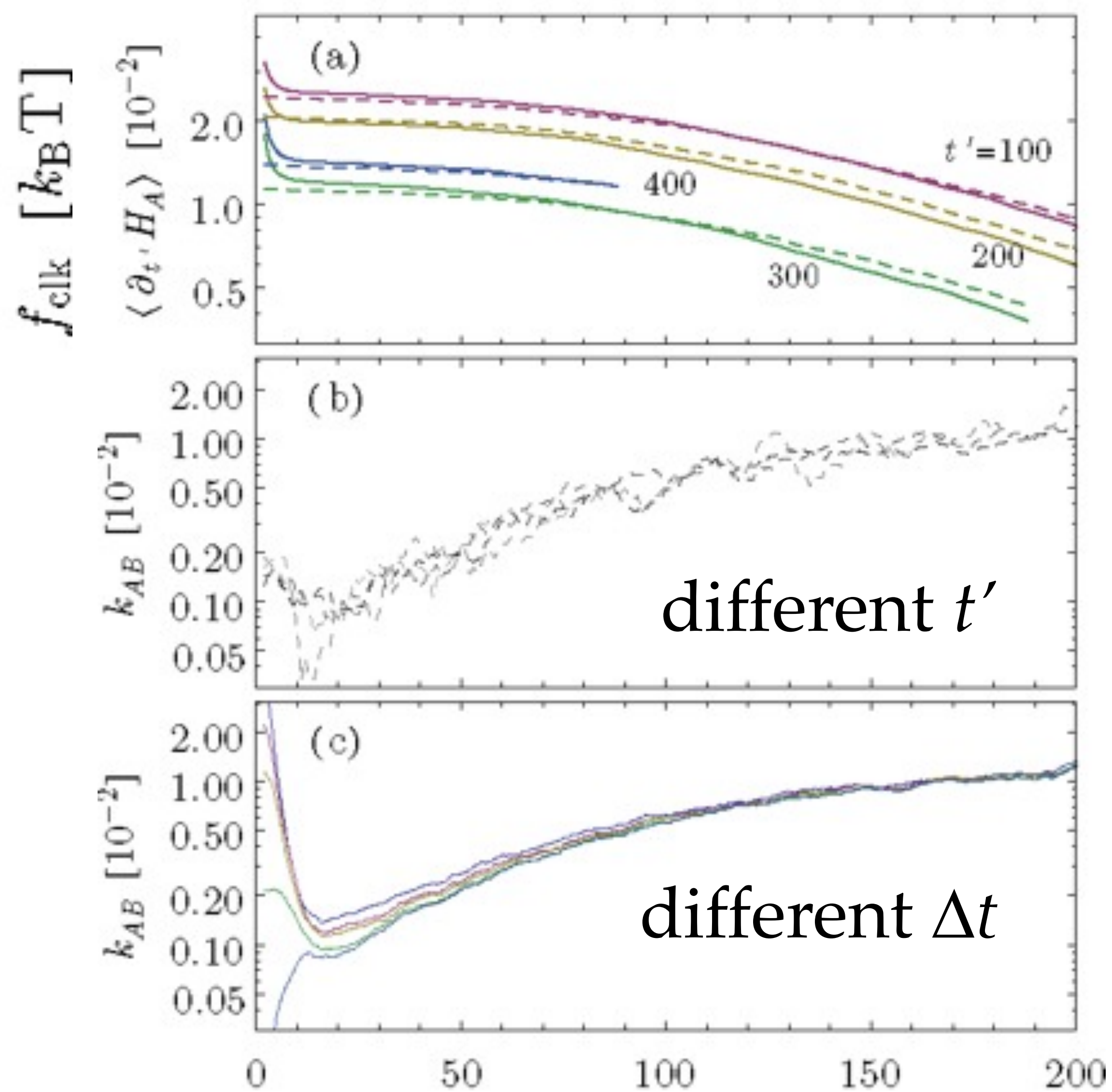
$$k_{AB}(t|t';\Delta t) = -\frac{\partial_t \partial_{t'}\langle H_B(t,t';\Delta t)\rangle}{\partial_{t'}\langle H_B(t,t';\Delta t)\rangle}$$

Non-Markov system

microscopic description

- One-dimensional barrier problem where after a barrier-crossing event the other state becomes progressively more stable





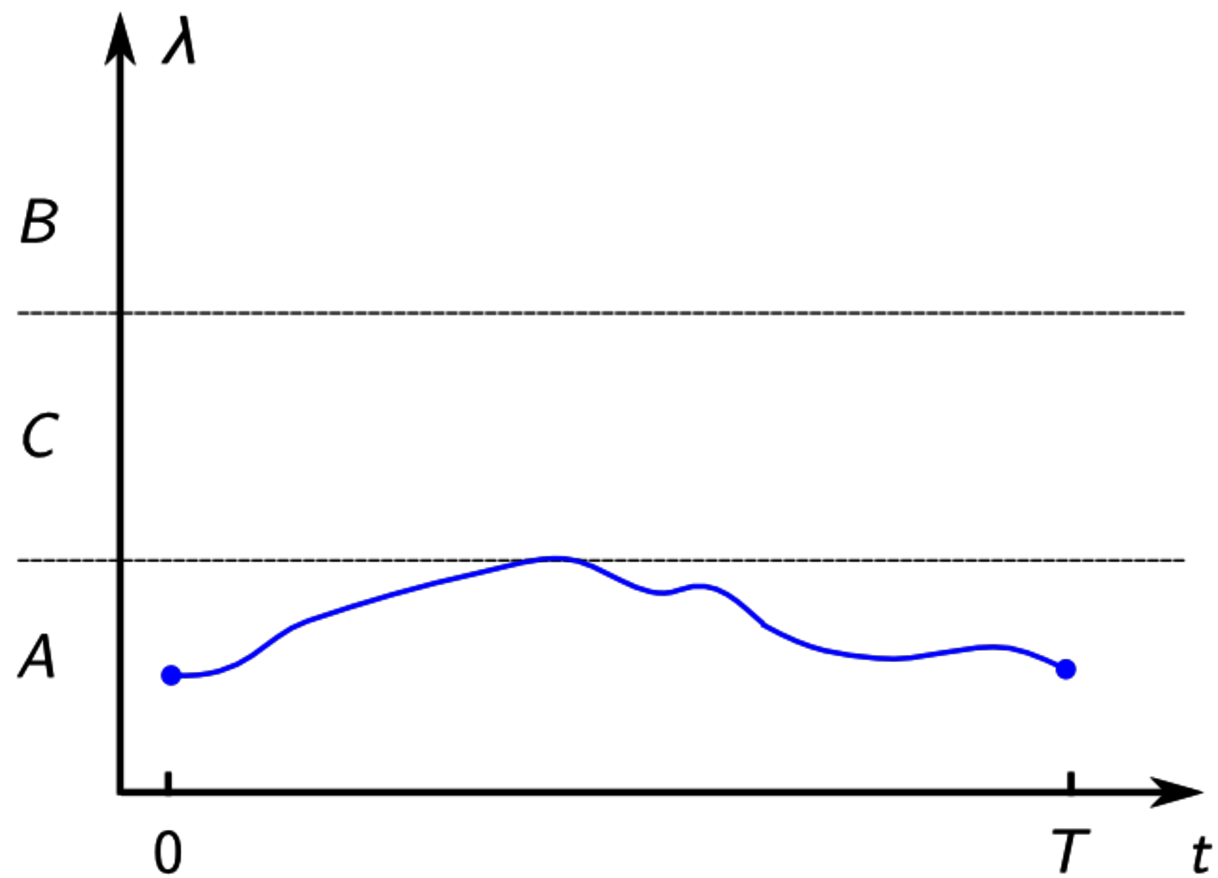
Becker and PRtW, JCP (2012)

Monday, July 2, 12

How to simulate non-stationary and non-Markovian rare events?

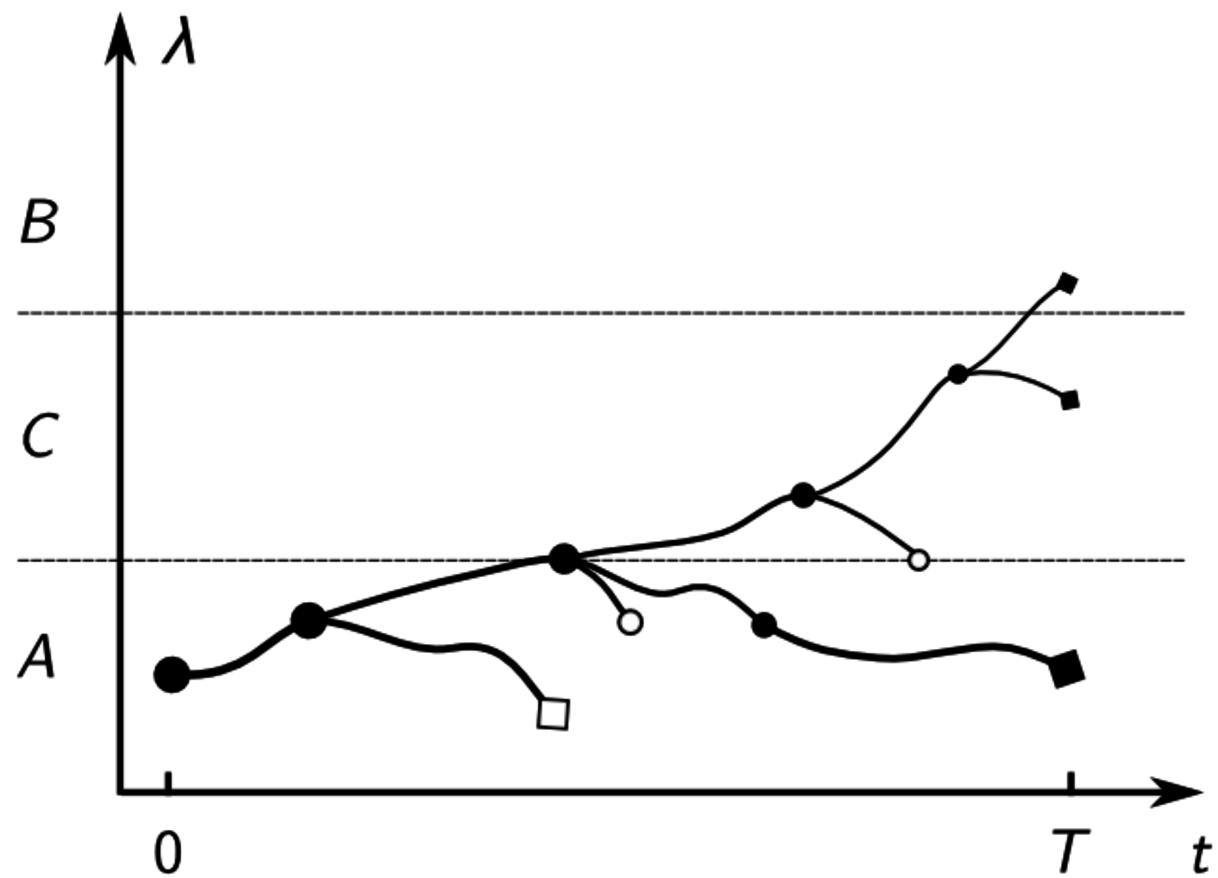
Non-Stationary Forward Flux Sampling

Non-Stationary FFS



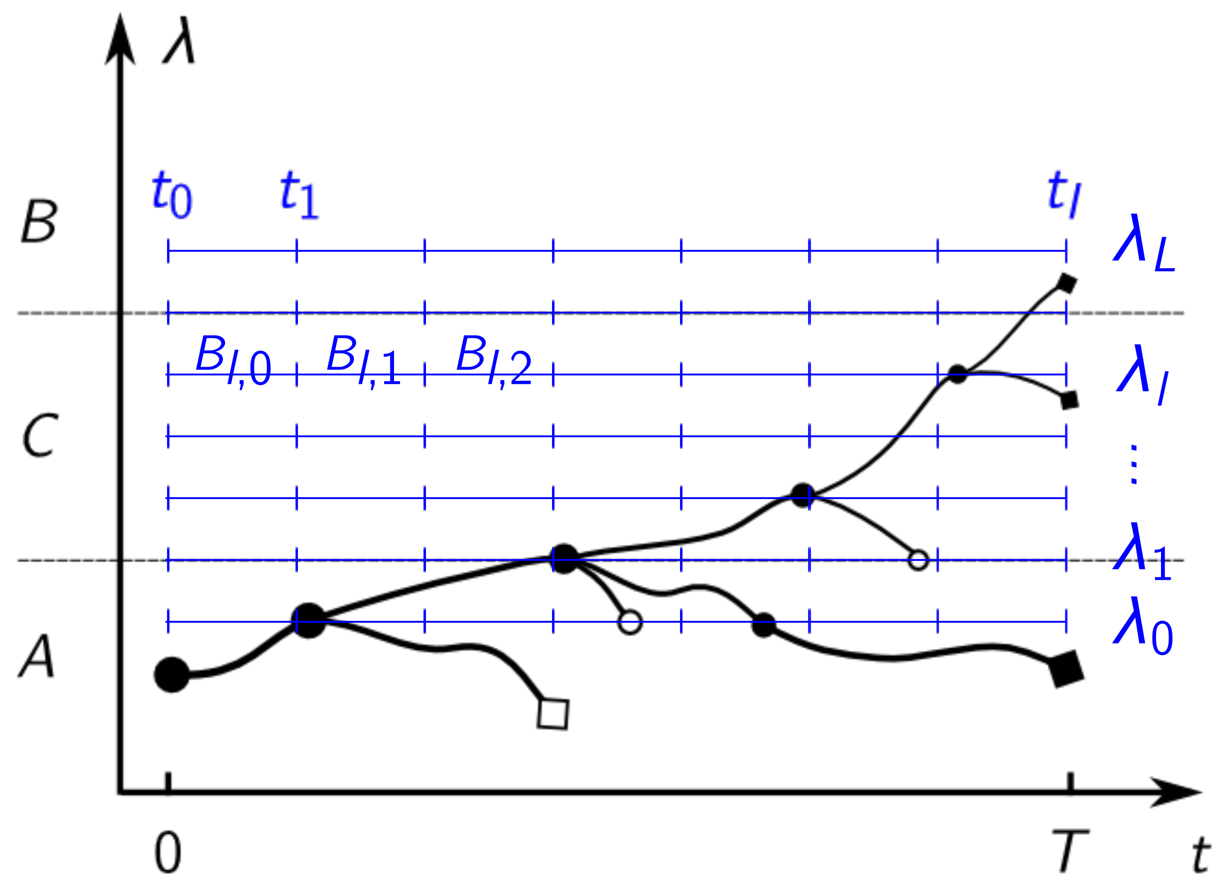
- Approach the saddle by ratcheting (FFS)
- Trigger branching/pruning on crossing

Non-Stationary FFS



- Approach the saddle by ratcheting (FFS)
- Trigger branching/pruning on crossing

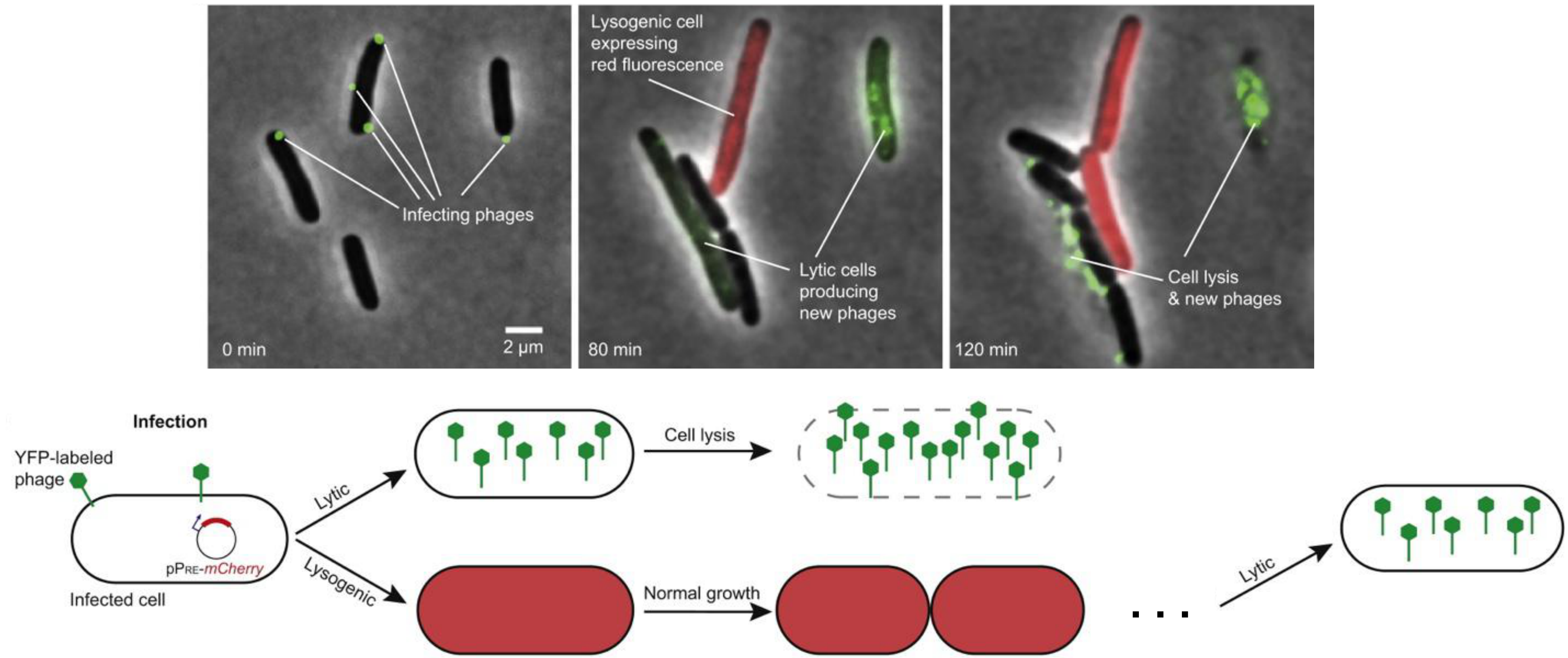
NS-FFS: flatPERM branching rule



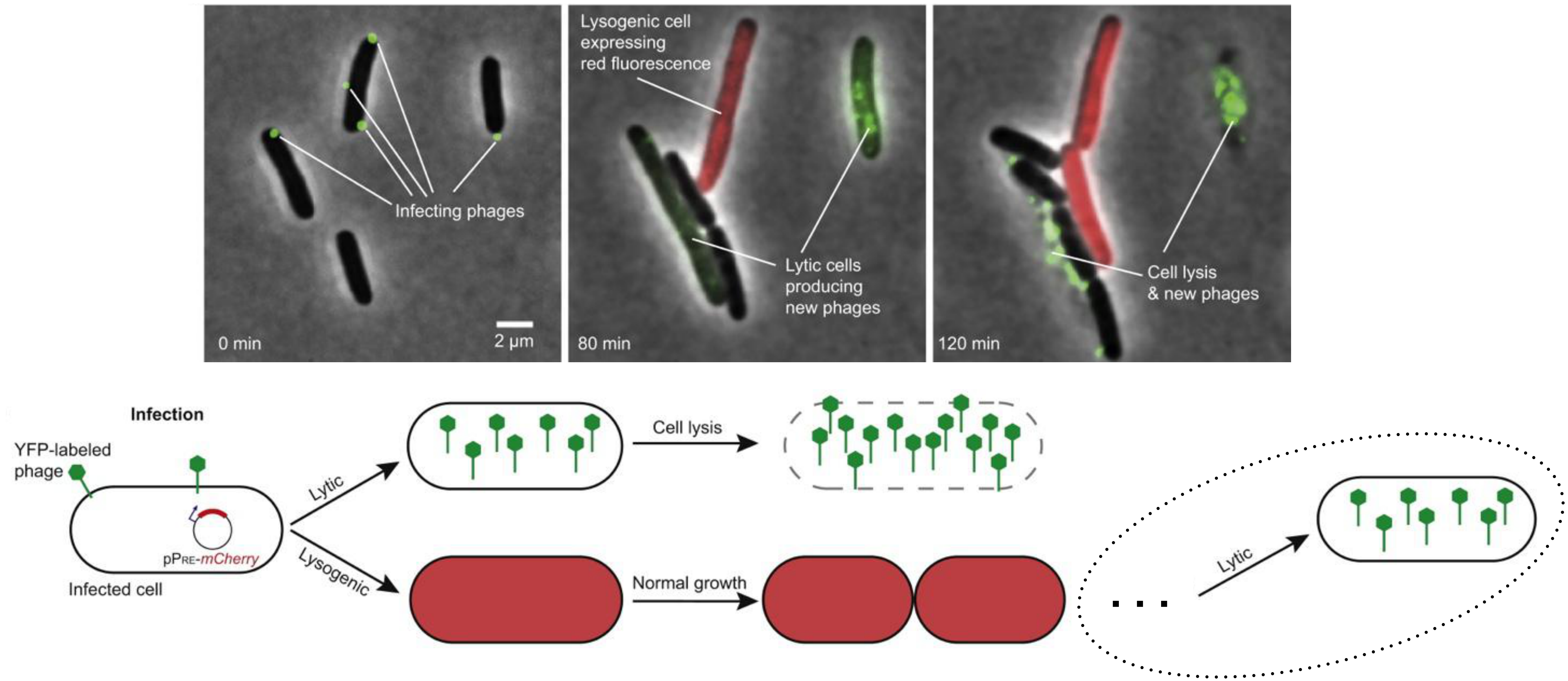
- 'Branch uphill, prune downhill'
- Sampling uniformly by branching/pruning (flatPERM)

  Prellberg, T. & Krawczyk, J. PRL (2004); Grassberger, P. PRE (1997)
- Flat sampling of trajectory space Becker, Allen, PRtW, JCP (2012)

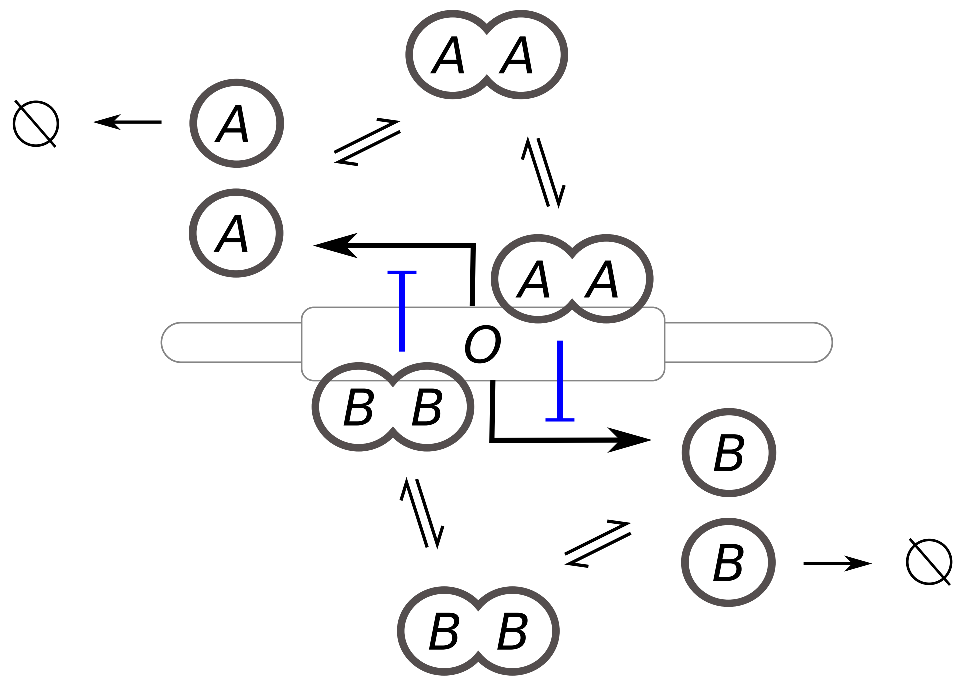
Bacteriophage-λ infection



Bacteriophage-λ infection



The toggle switch



$$A + A \rightleftharpoons A_2$$
$$O + A_2 \rightleftharpoons OA_2$$
$$O \to O + A$$
$$OA_2 \to OA_2 + A$$
$$A \to \varnothing$$

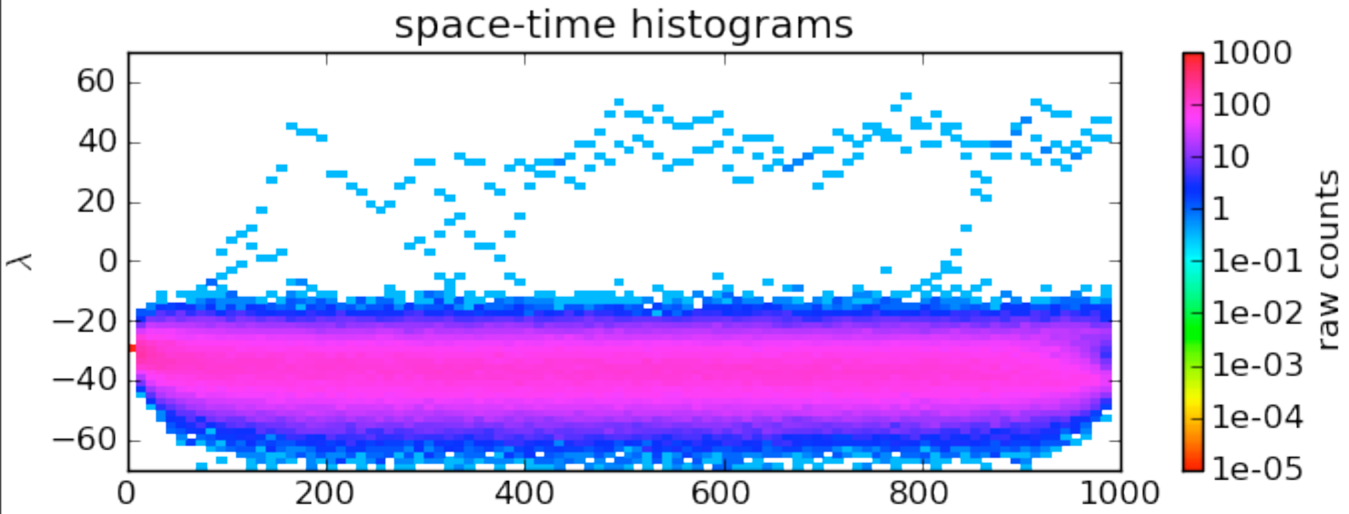
- Toy model of the phage-λ genetic switch.
- Progress coordinate: total B monomers - total A monomers

$$\lambda = [B] + 2[B_2] + 2[OB_2] - ([A] + 2[A_2] + 2[OA_2])$$

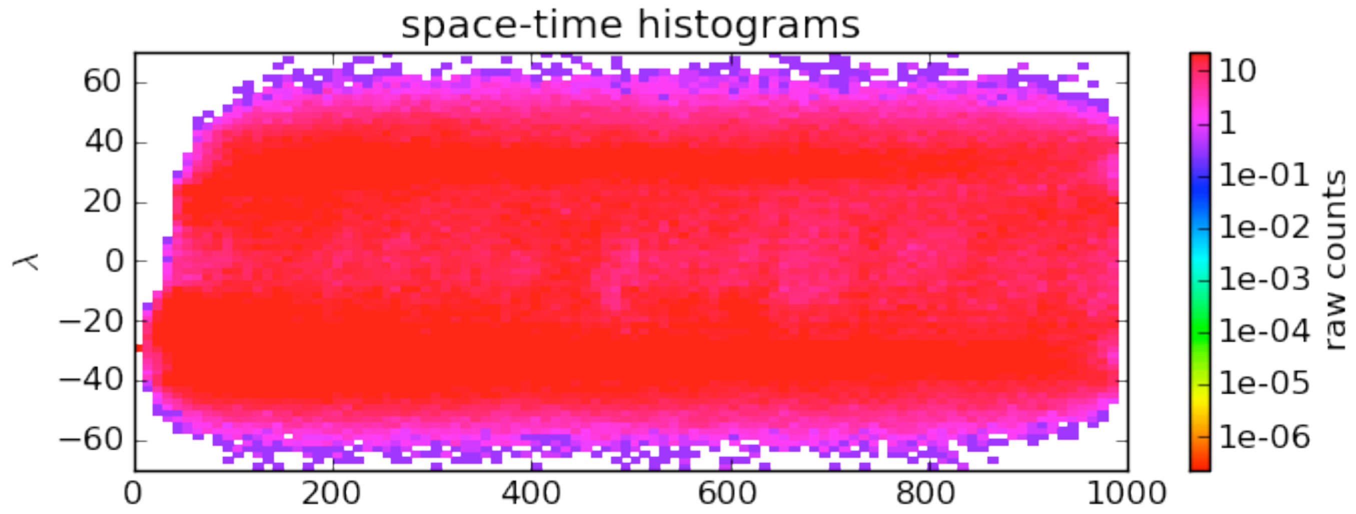
e.g. Allen et al, JCP 2006

Spontaneous transitions

brute force



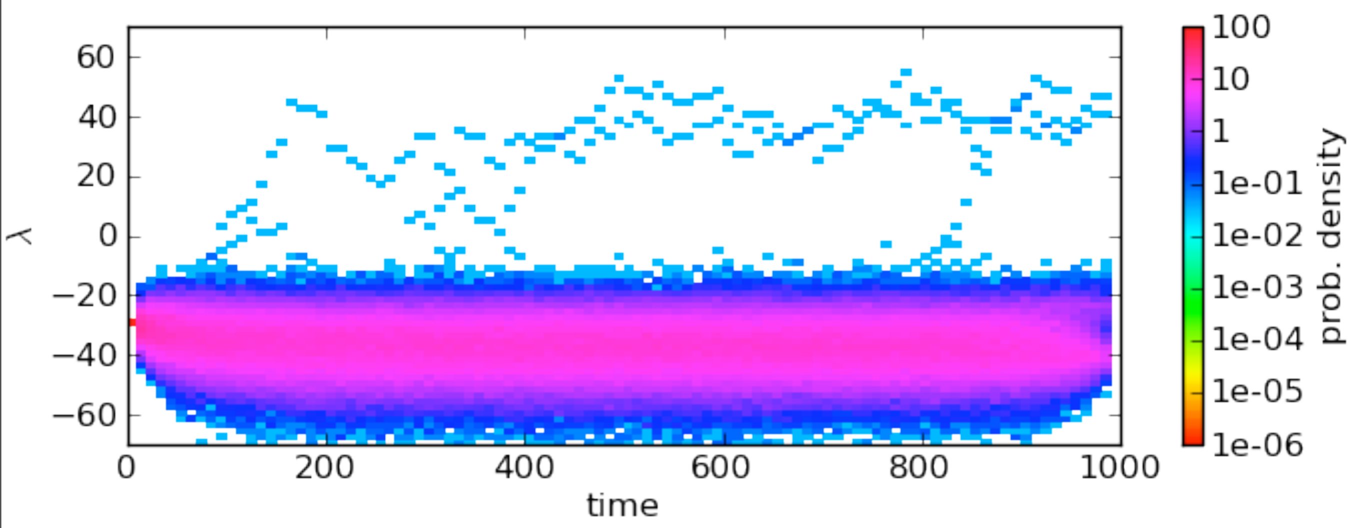
NS-FFS



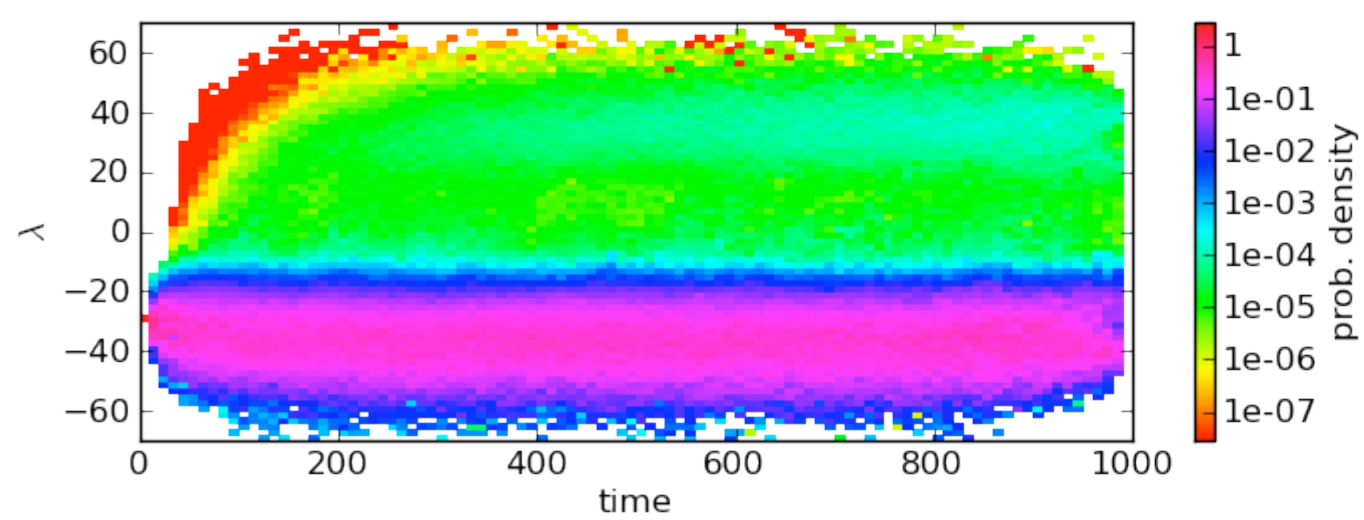
Prob(flipped until $t = 800$) = .07%

Spontaneous transitions

brute force

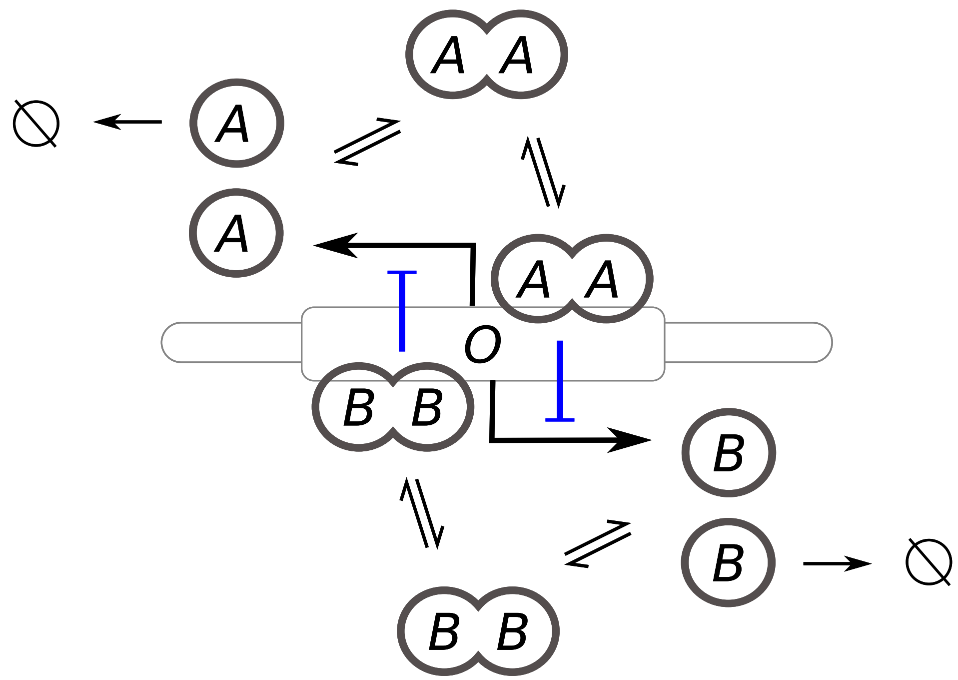


NS-FFS



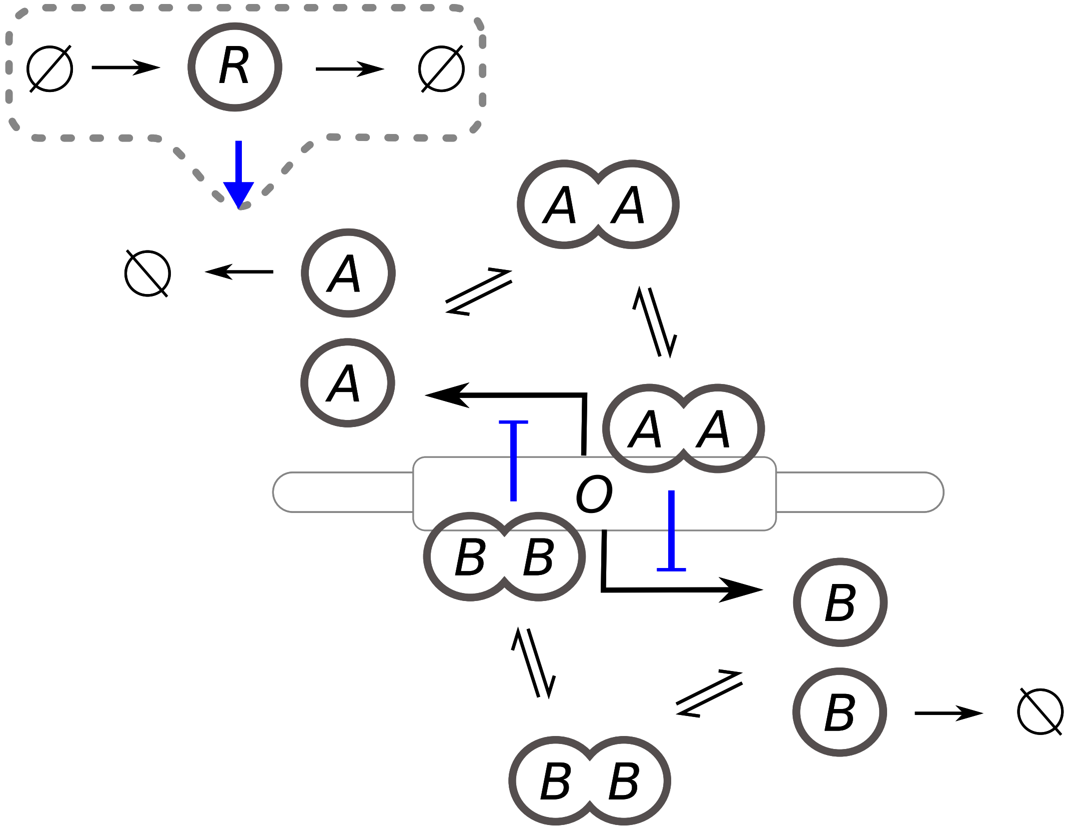
Prob(flipped until $t = 800$) = .07%

Flipping the switch



mean-field forcing: $\gamma n_R^\infty = \mathit{fixed}$

Flipping the switch



$$\varnothing \xrightarrow{k_R} R \xrightarrow{\mu_R} \varnothing$$

$$R + A \xrightarrow{\gamma} R$$

mean-field forcing: $\gamma n_R^\infty = fixed$

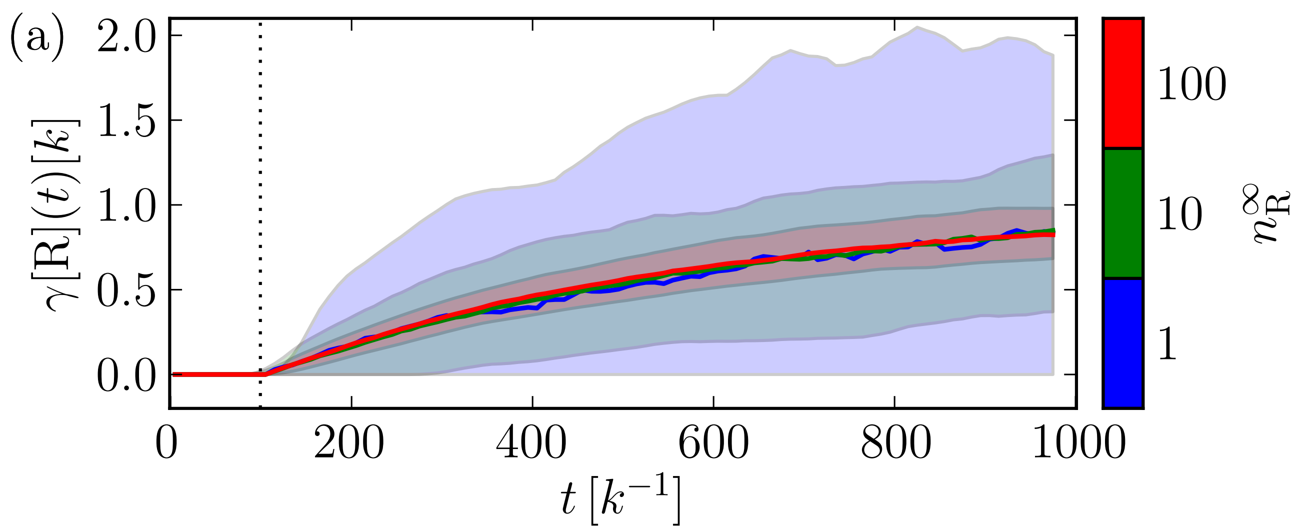
- New chemical species: R (~ RecA in phage λ)
- R degrades A monomers $\rightarrow$ flips the switch from A to B

Flipping the switch with a ramp

- accumulation of R :

  $\langle R(t) \rangle = n_R^\infty (1 - e^{-\mu_R t})$
- steady-state: $n_R^\infty = k_R / \mu_R$
- mean-field forcing: $\gamma n_R^\infty = fixed$
- increasing fluctuations:

  $n_R^\infty = 100, 10, 1$



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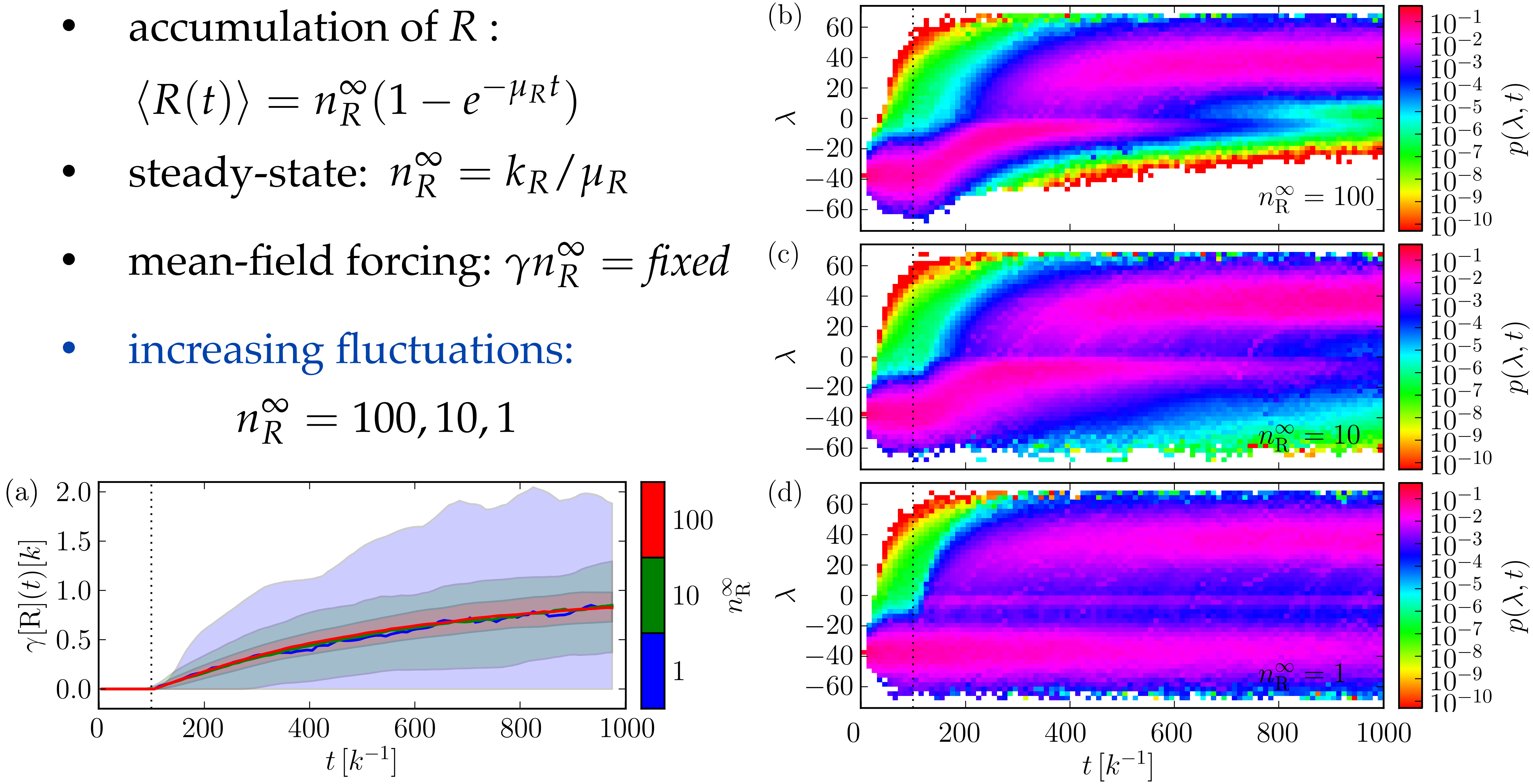


Flipping the switch with a pulse

- decaying R pulse:

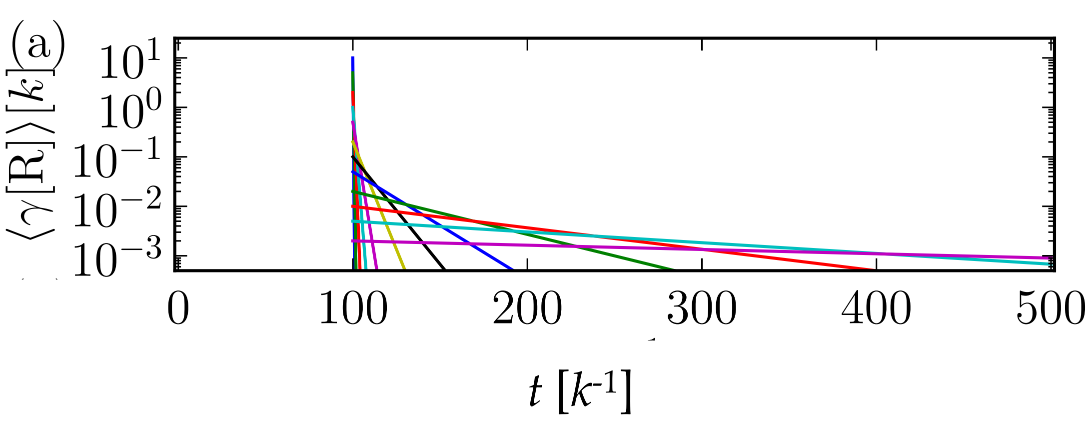
$$\langle R(t)\rangle = R_0 e^{-\mu_R(t-t_0)}\Theta(t-t_0)$$

- time-integrated bias:

$$\gamma\int_0^\infty \langle R(t)\rangle\, dt = \mathit{fixed}$$

- decreasing pulse duration:

$$\mu_R^{-1} = 100, 1, 0.1$$



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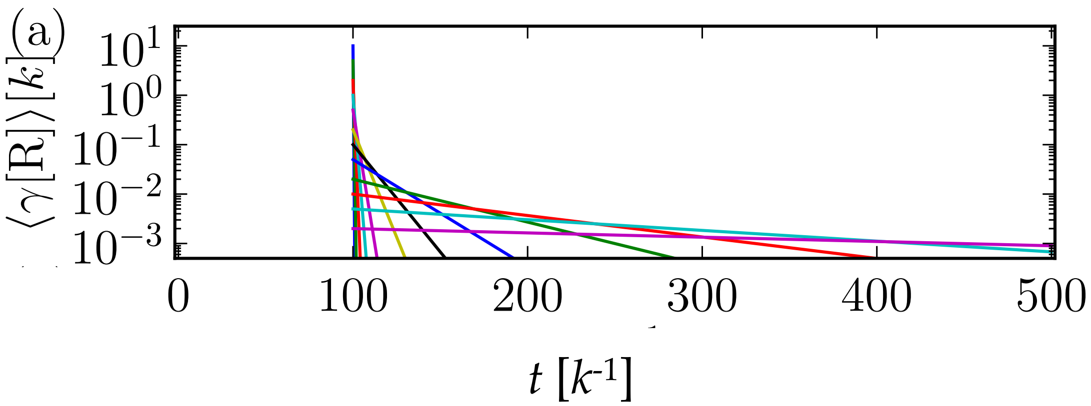
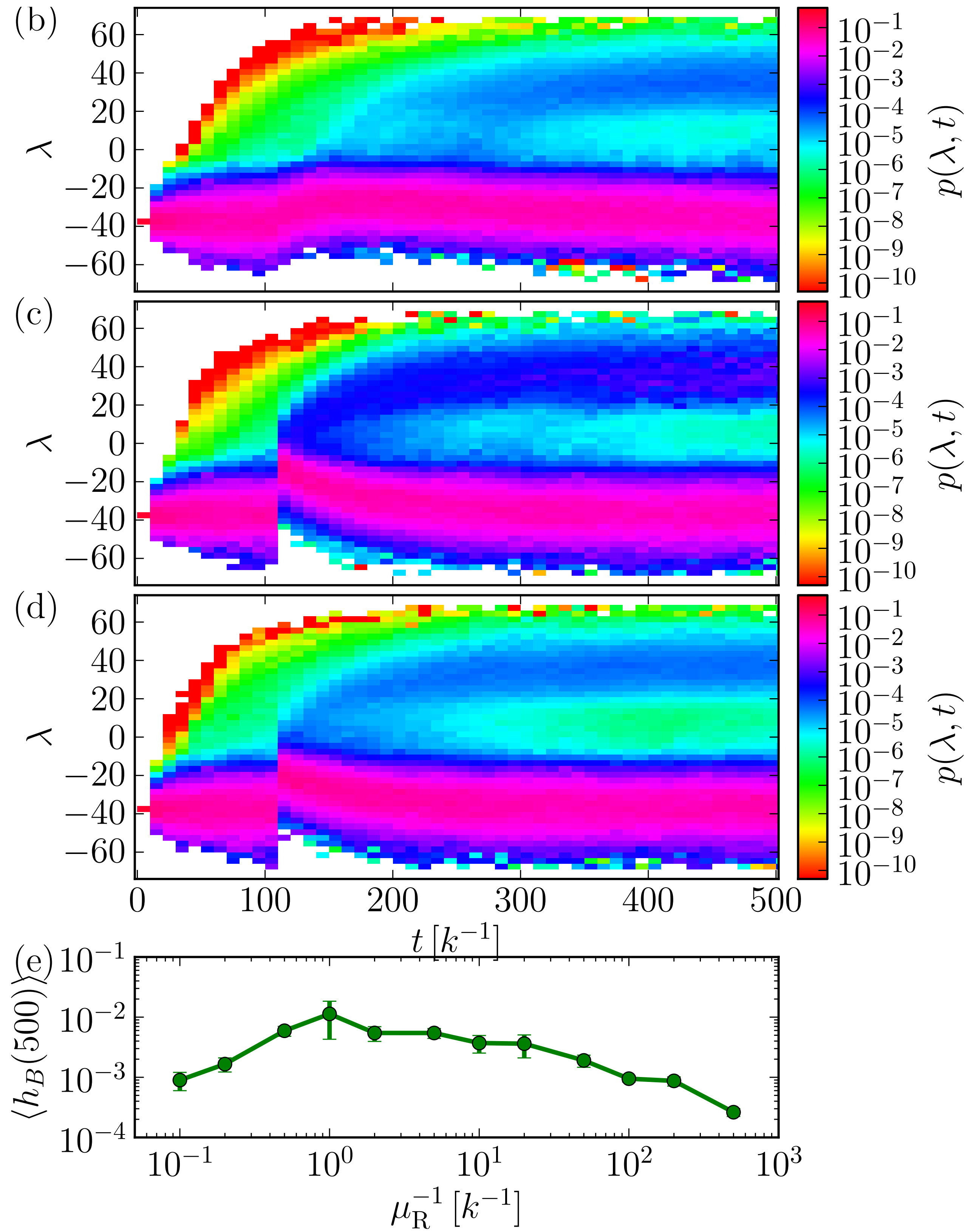
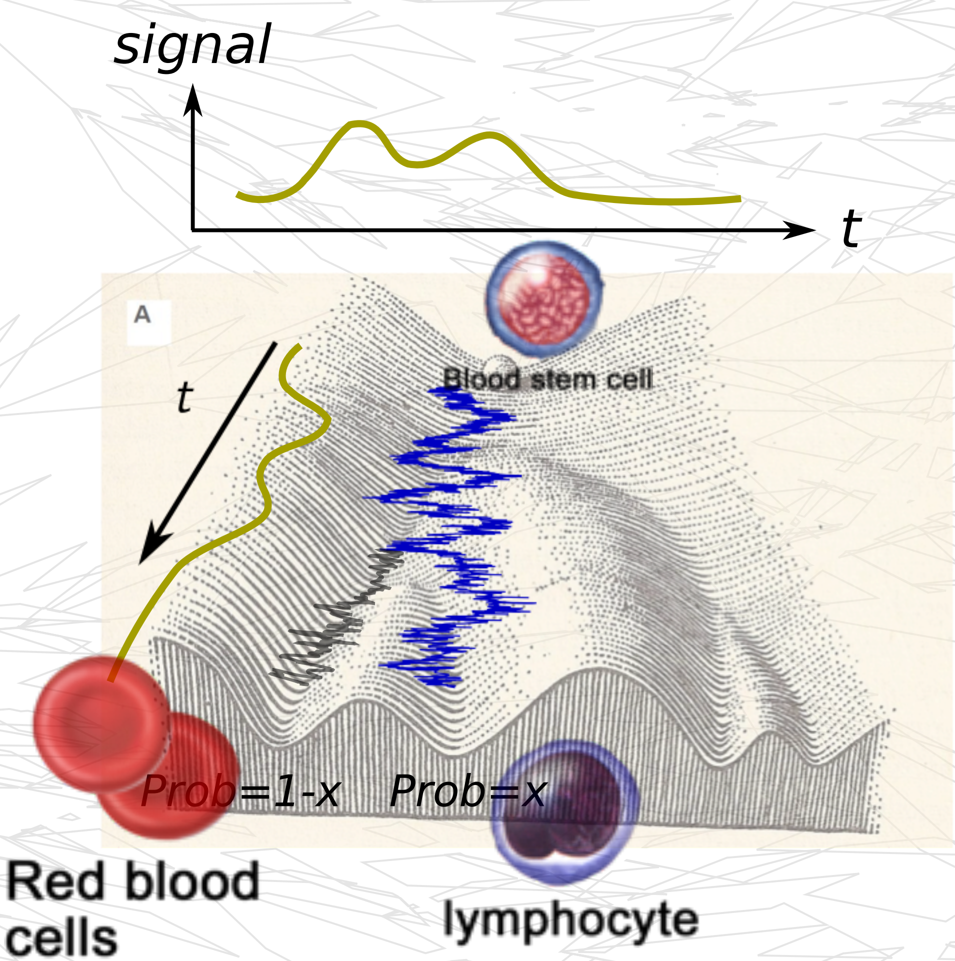




Summary

- Non-stationary rare events are omnipresent, interesting and relevant
- A non-Markovian state model can be a useful coarse-grained description
- NS-FFS is a novel method for enhanced sampling of non-stationary rare events.
- *Outlook*: Cell differentiation occurs via induced switching and is stable afterwards. *How*?



Becker, Allen, PRtW, JCP (2012)
Becker, PRtW, JCP (2012)

Extra slides

Microscopic expressions for rate functions

time-inhomogeneous Markov case:

$$k_{AB}(t) = \langle \dot{h}_B(t) h_B(t+\Delta t) | h_A(t-\Delta t) \rangle$$

non-Markovian case:

$$h_A(t;\Delta t) = \theta[\int_{t-\Delta t}^{t} h_A(t')\, dt' - \Delta t/2]$$

$$H_A(t;t';\Delta t) = \prod_{t \geq t'' > t'} h_A(t'';\Delta t)$$

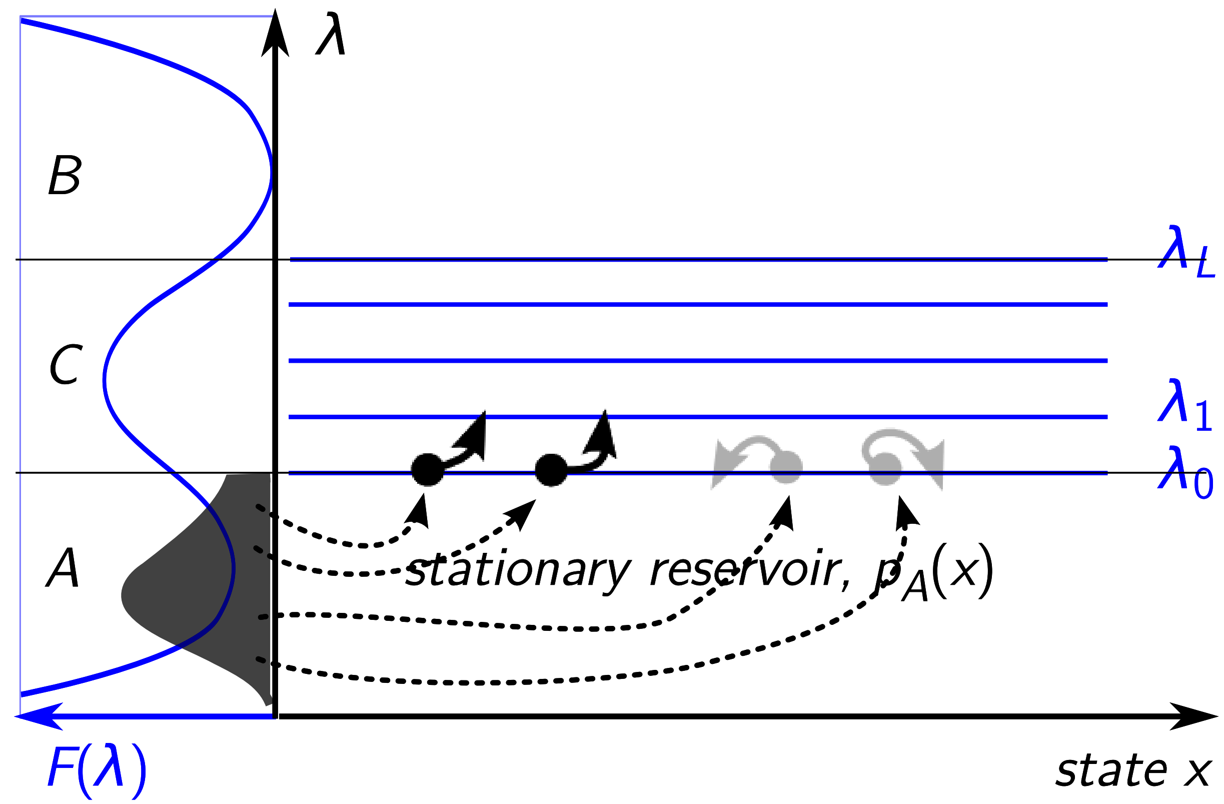
$$k_{AB}(t|t') = -\frac{\langle \partial_t \partial_{t'} H_A(t;t';\Delta t) \rangle}{\langle \partial_{t'} H_A(t;t';\Delta t) \rangle}$$

NS-FFS algorithm

- *Init*. Weight histogram $H_{li} = 0$, tree count $S = 0$, growing branch list $G = \{\}$
- *Run*. Iterate until convergence:
  - If G is empty, start a new trajectory with weight $w = 1$ at $t = 0$ and add it to G
  - Pick and remove a trajectory from G
  - Propagate to $t = T$, *unless* an interface is crossed; then:
    - increase H_{li} by the current weight w
    - draw a child number $n(S, H_{li}) = 0, 1, \ldots$
    - add n children with weight $wr(n)$ to G.

back

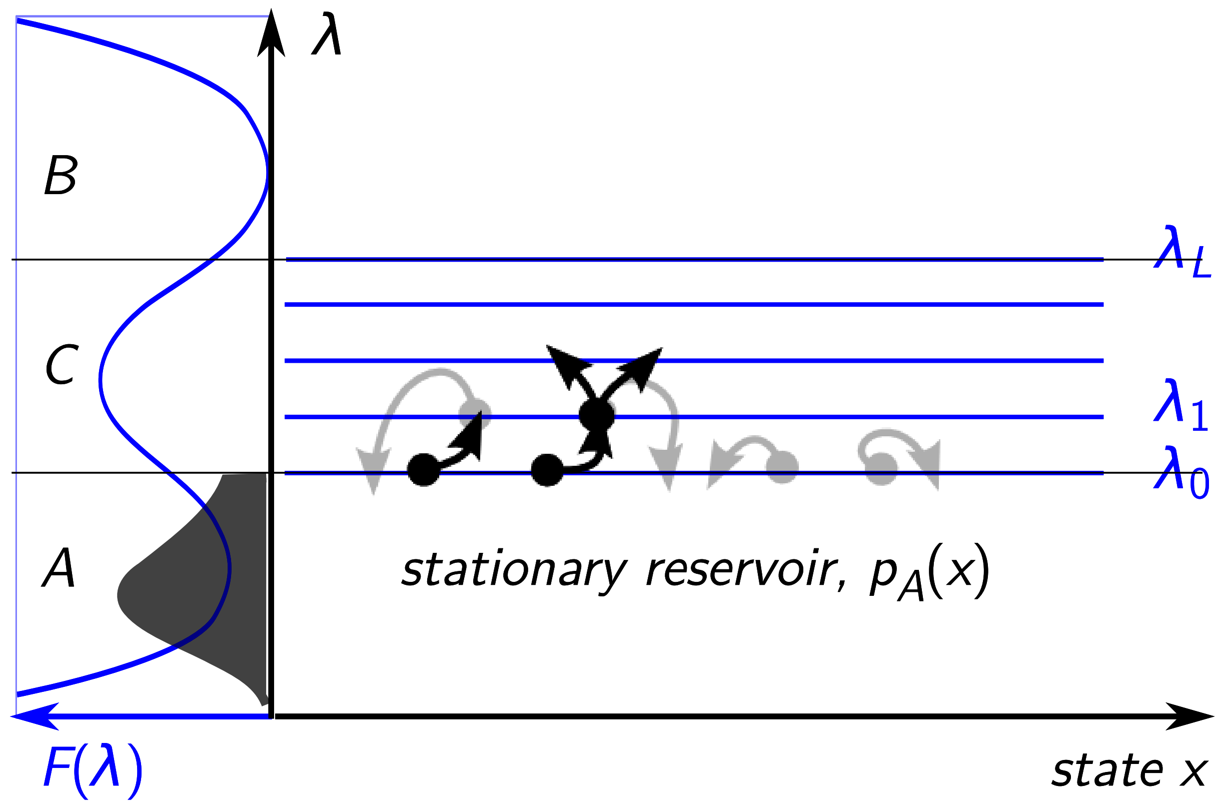
Enhanced sampling in stationary state (FFS)



1. Simulate stationary distribution in A once and for all
2. Shoot short trajectories from each interface to the next

Allen et al, JCP 2006

Enhanced sampling in stationary state (FFS)



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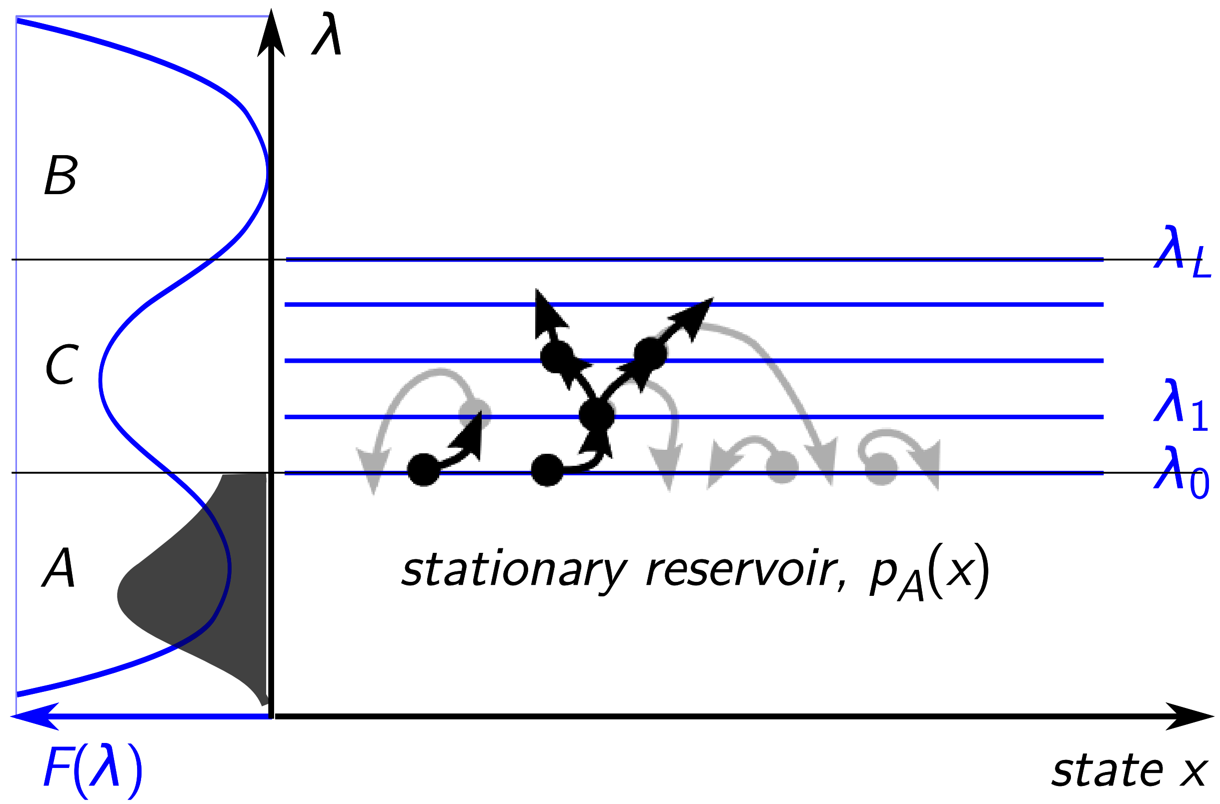
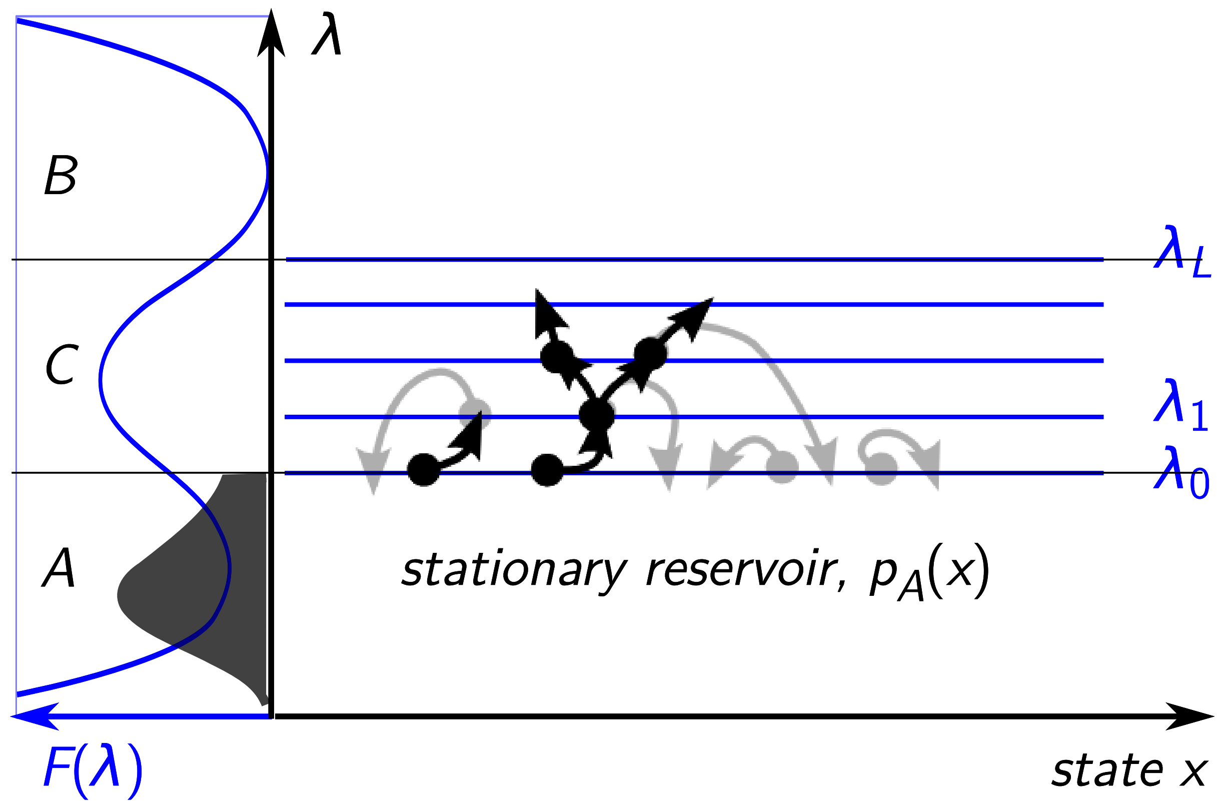


1. Simulate stationary distribution in *A* once and for all
2. Shoot short trajectories from each interface to the next

Allen et al, JCP 2006

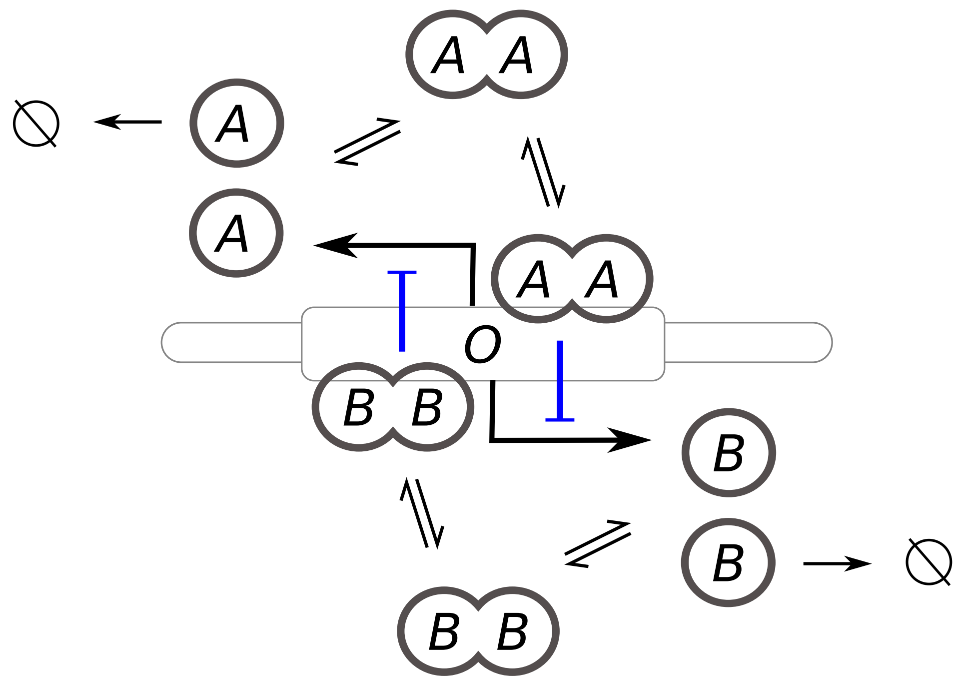
Enhanced sampling in stationary state (FFS)



1. Simulate stationary distribution in A once and for all ✔
2. Shoot short trajectories from each interface to the next

Allen et al, JCP 2006

The toggle switch



$$A + A \rightleftharpoons A_2$$
$$O + A_2 \rightleftharpoons OA_2$$
$$O \to O + A$$
$$OA_2 \to OA_2 + A$$
$$A \to \emptyset$$

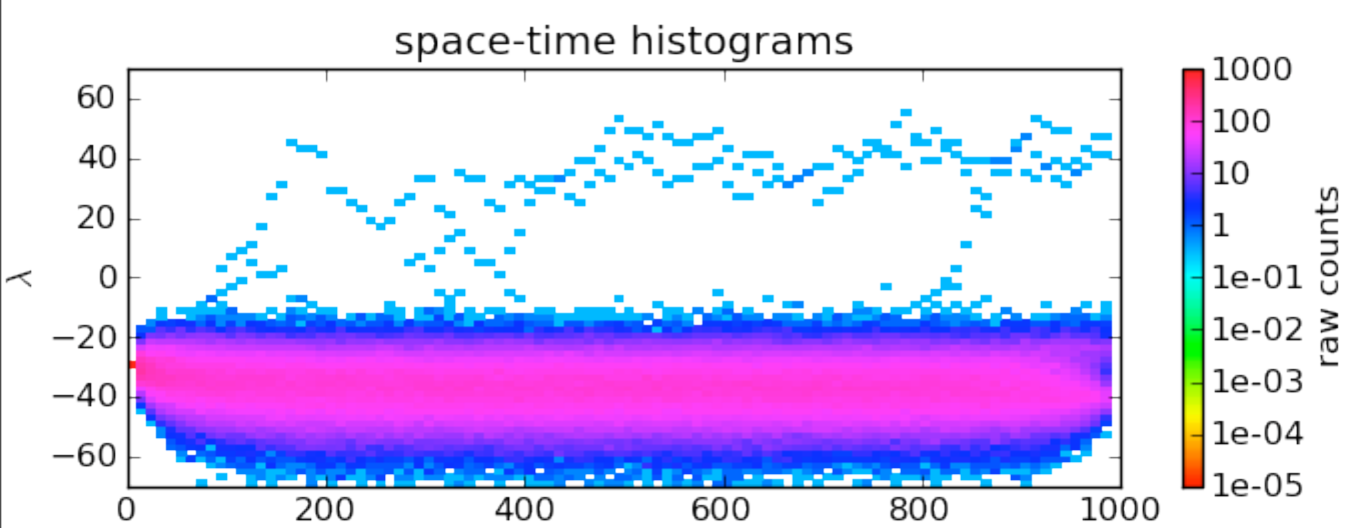
- Toy model of the phage-λ genetic switch.
- Progress coordinate: total B monomers - total A monomers

$$\lambda = [B] + 2[B_2] + 2[OB_2] - ([A] + 2[A_2] + 2[OA_2])$$

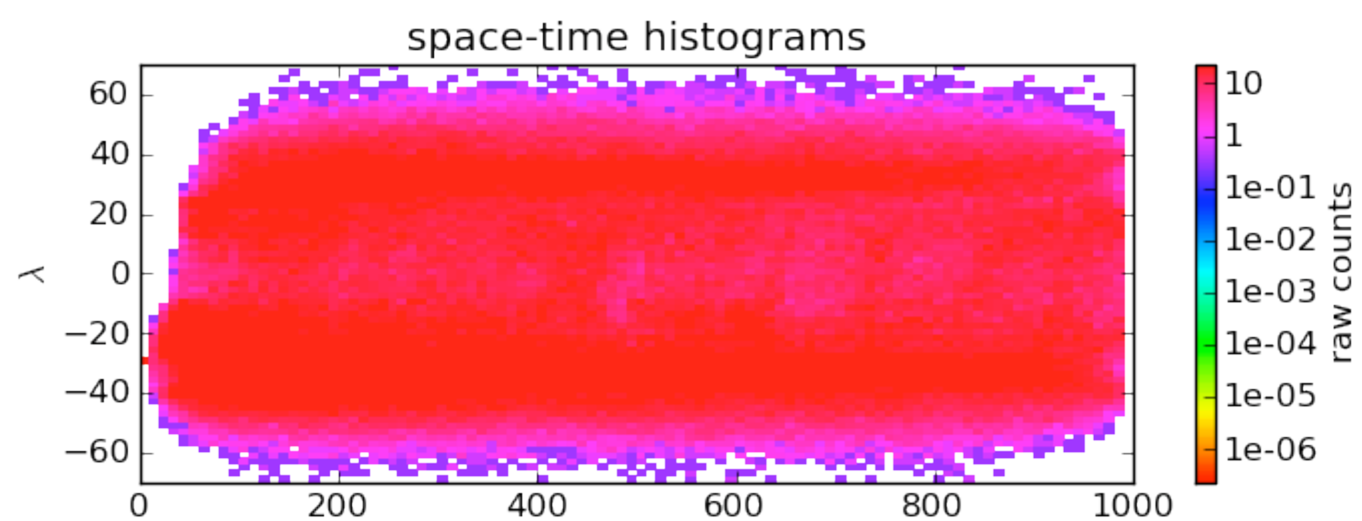
e.g. Allen et al, JCP 2006

Spontaneous transitions

brute force



NS-FFS



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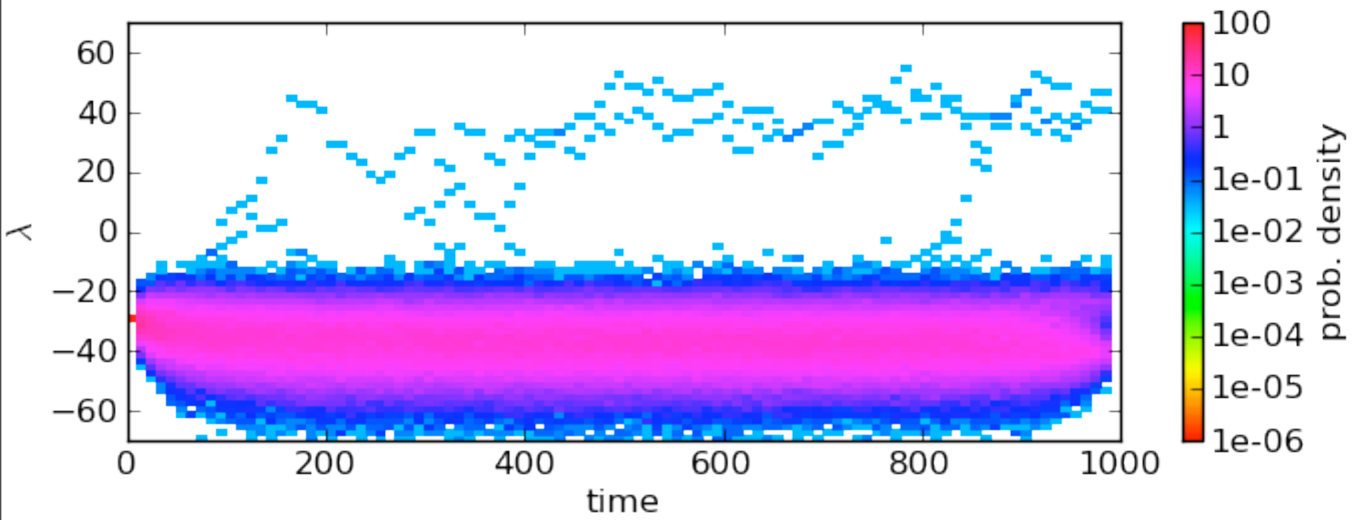
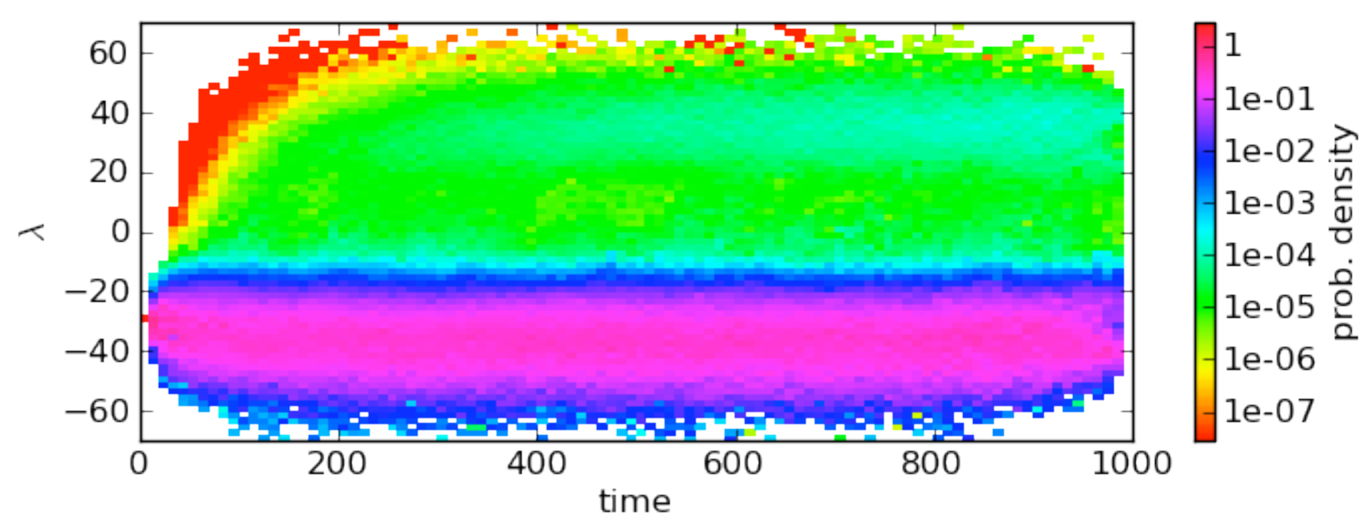


NS-FFS



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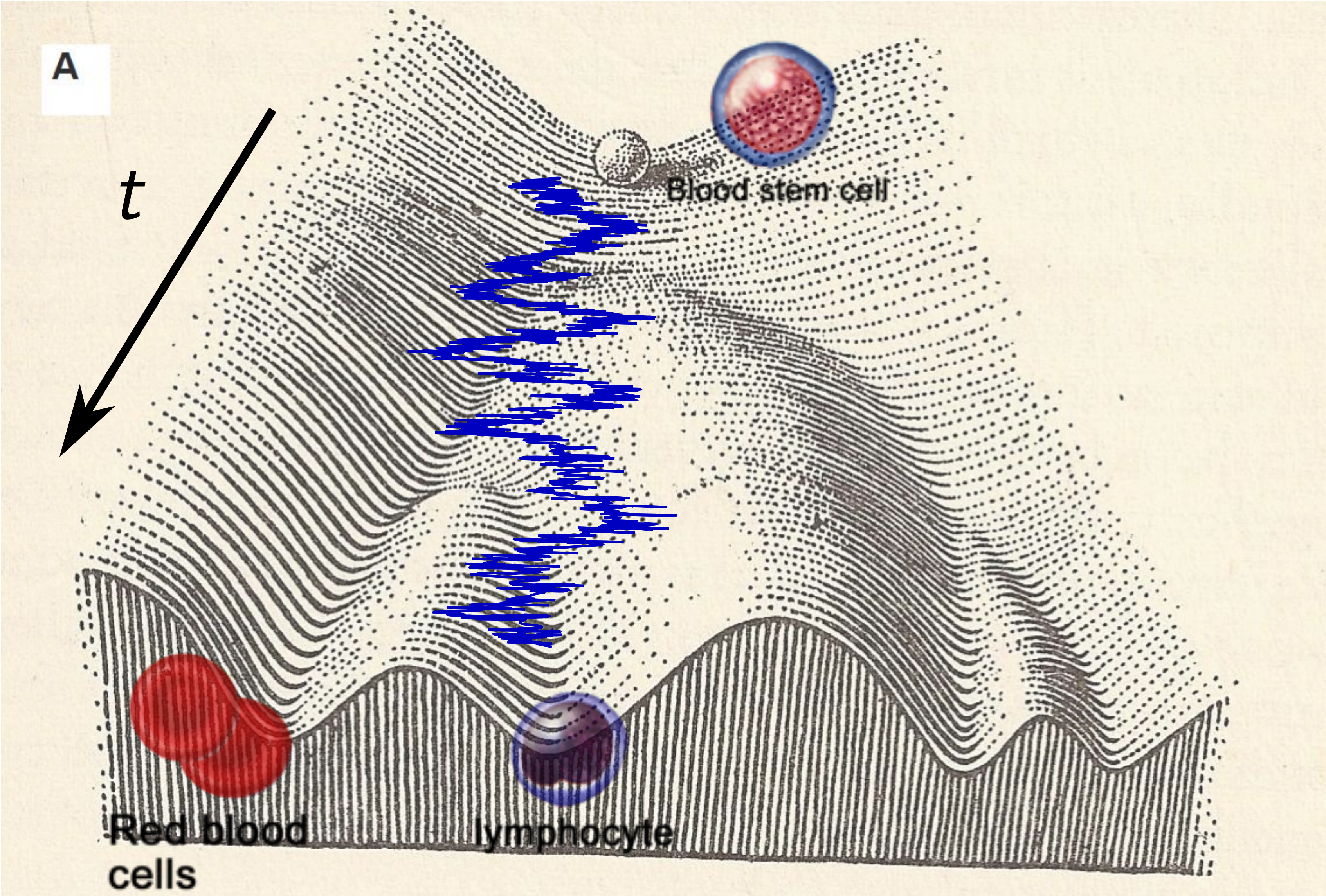
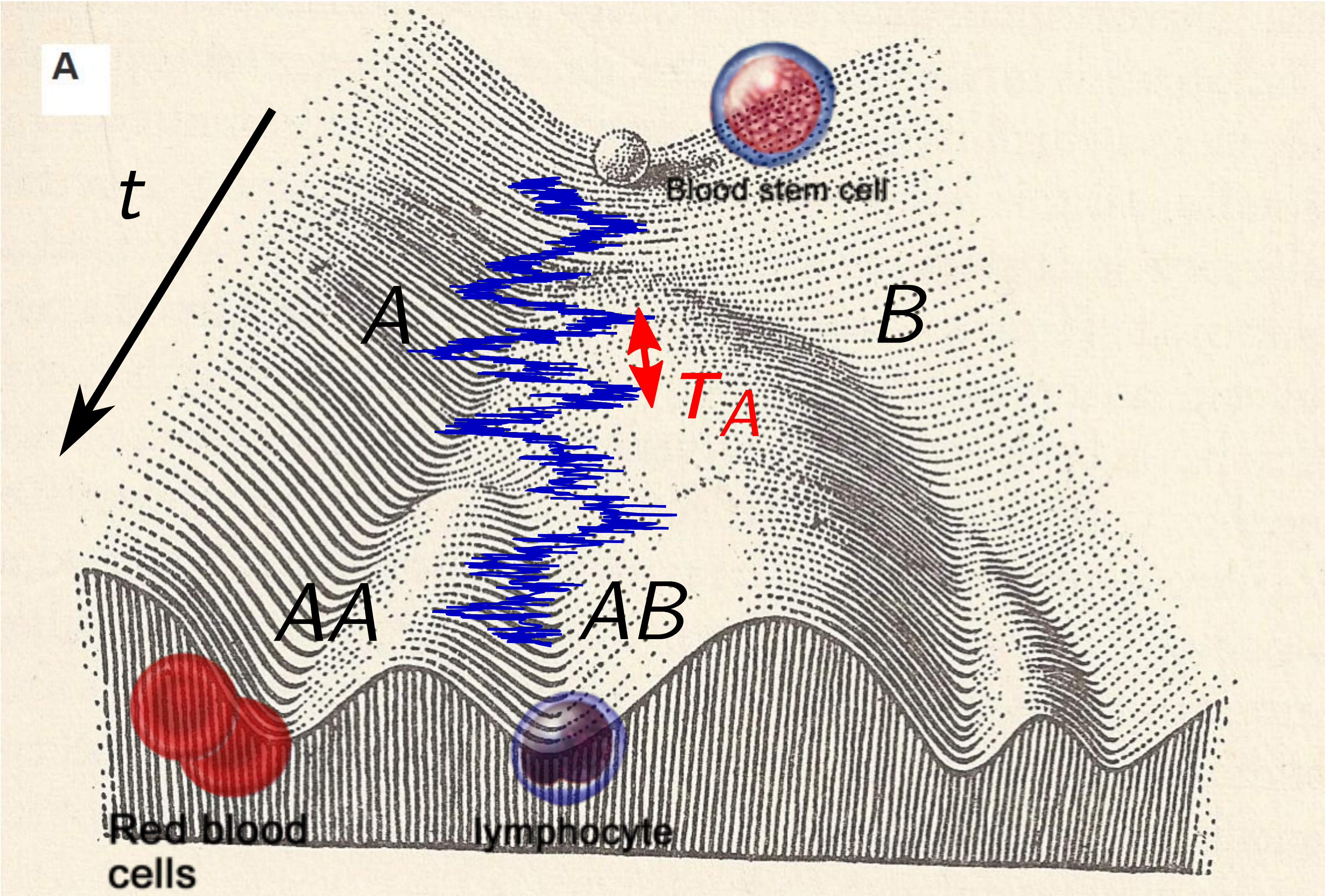
Outlook



Waddington (1940s), e.g. S. Huang, Cell & Molecular Biology (2011)

Outlook



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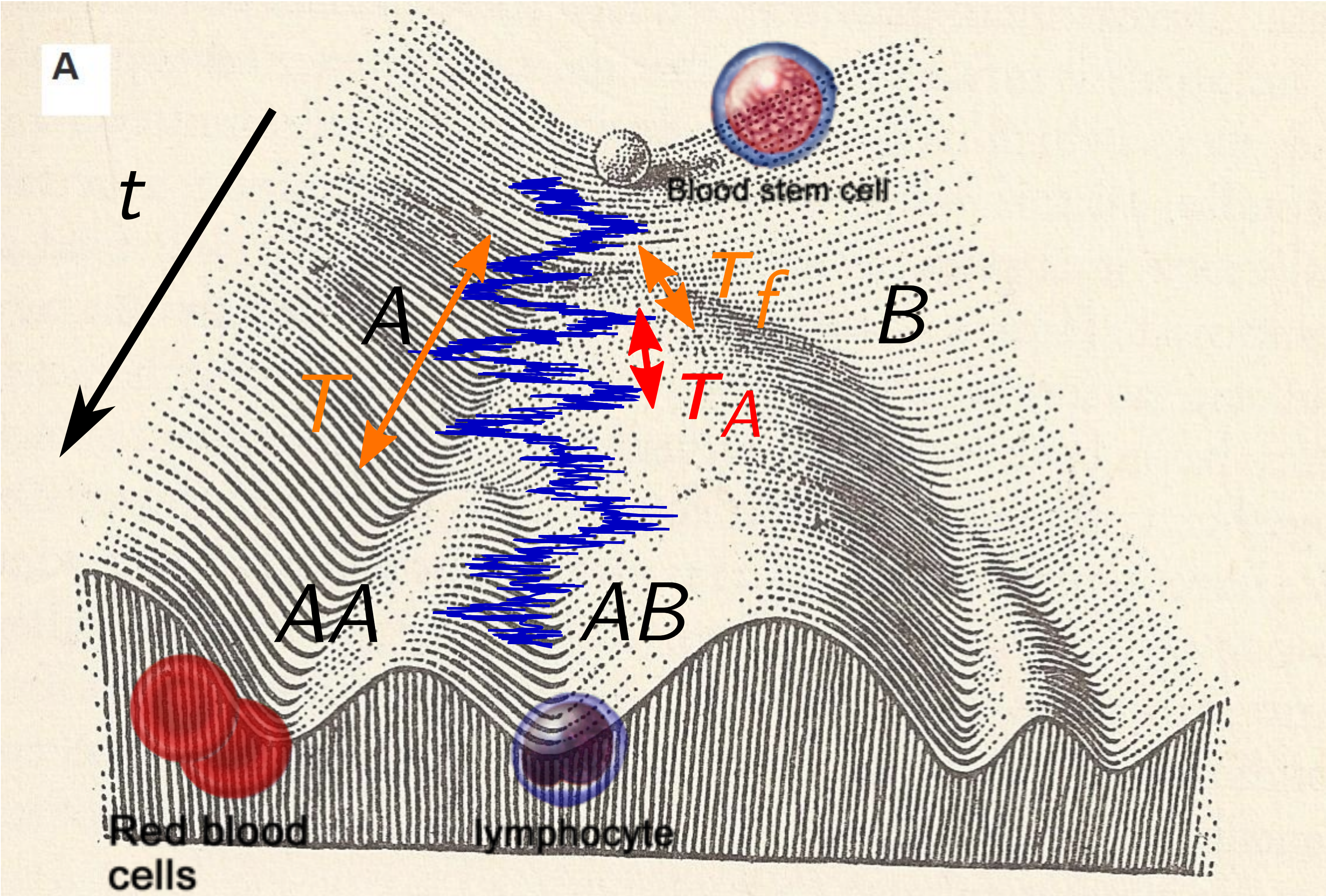

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