Stochastic Modelling of Reaction, Diffusion and Taxis Processes in Biology

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Overview of the talk

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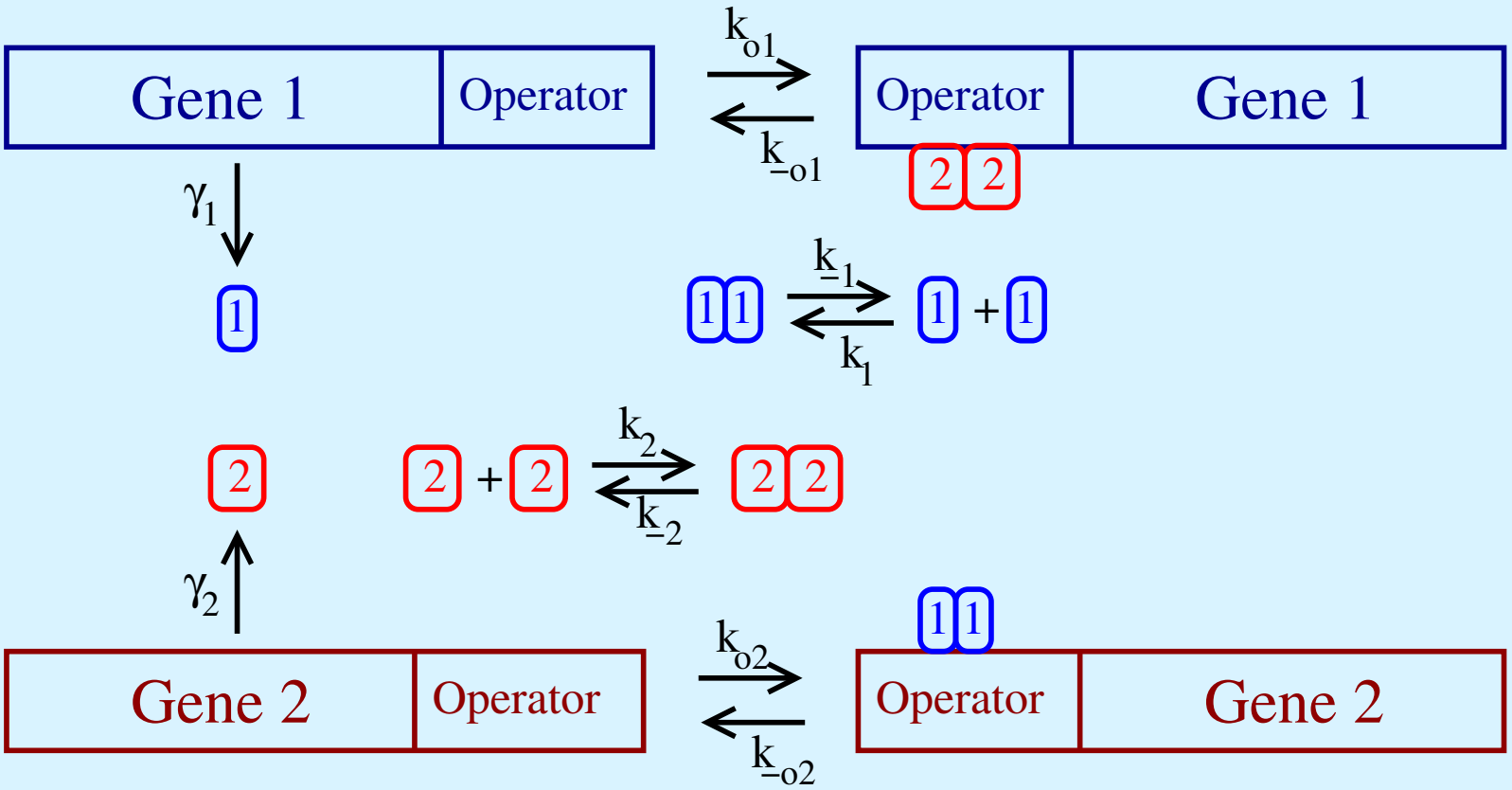
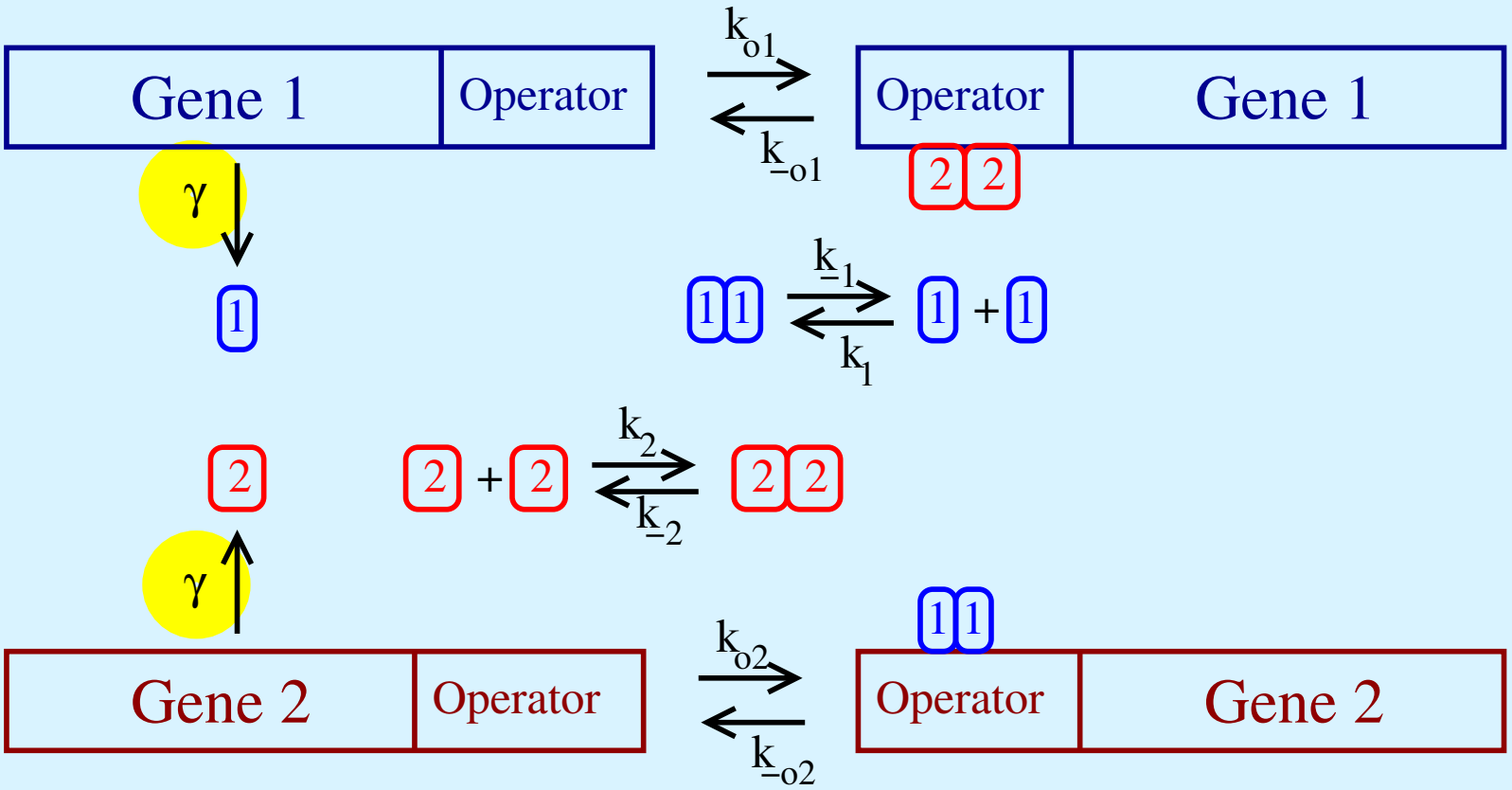
- stochastic modelling of chemical reactions, gene regulatory networks
- equation-free methods (effective free energy surfaces)
- selection of coarse variables (diffusion maps)
- stochastic modelling of spatially distributed problems, pattern formation
- derivation of reactive boundary conditions for stochastic models

Gene regulatory networks - mutual repressors



- system of mutually repressing genes

Gene regulatory networks - mutual repressors



- system of mutually repressing genes
- equation-free methods: we want to compute steady state distributions, effective potentials, first passage time of bistable systems and bifurcation diagrams

Evolution of the number of protein molecules

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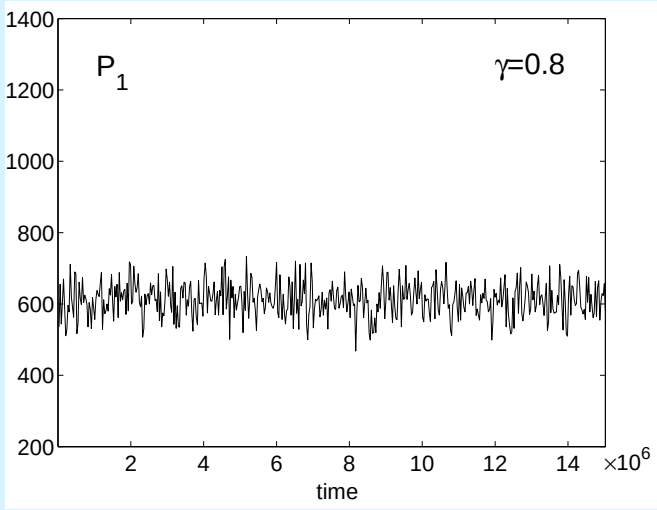
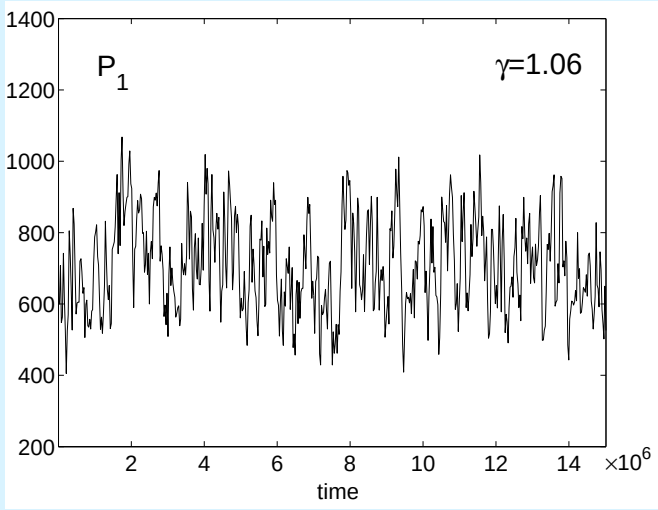
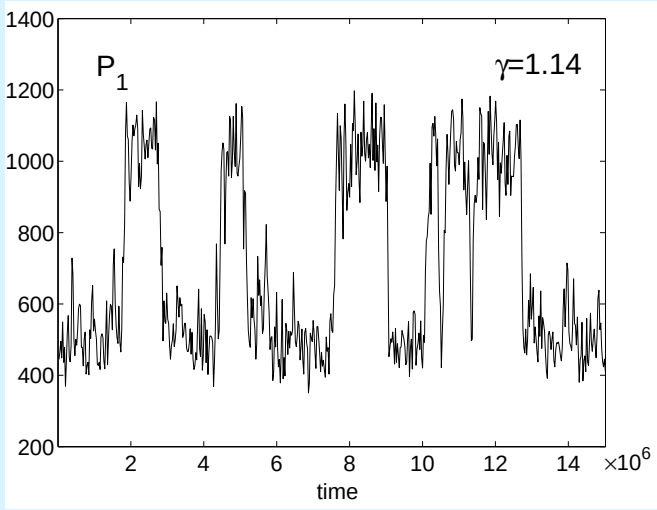
$\gamma = 0.8$ $\gamma = 1.06$ $\gamma = 1.14$

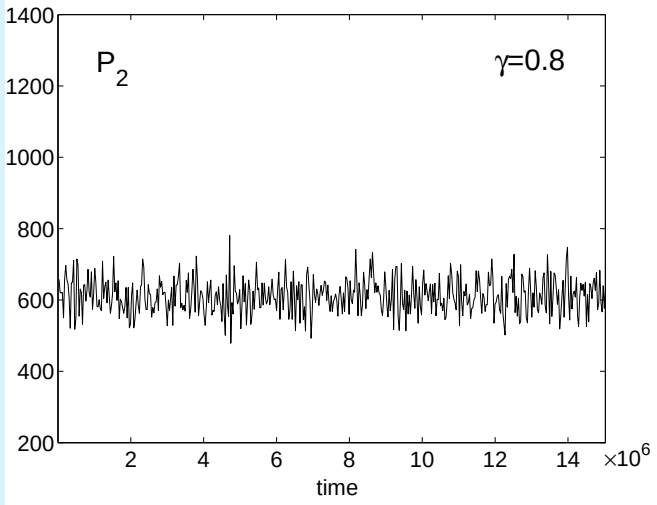
P_1

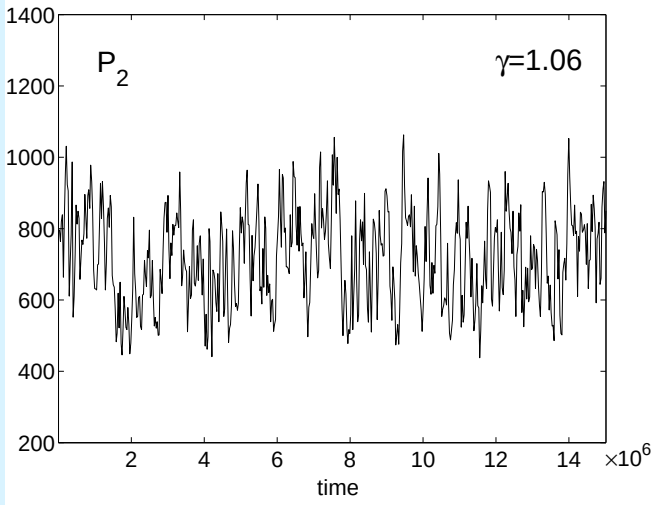


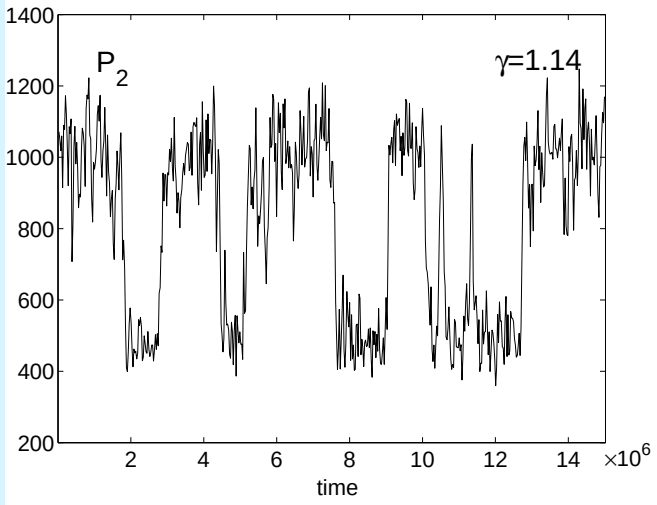




P_2







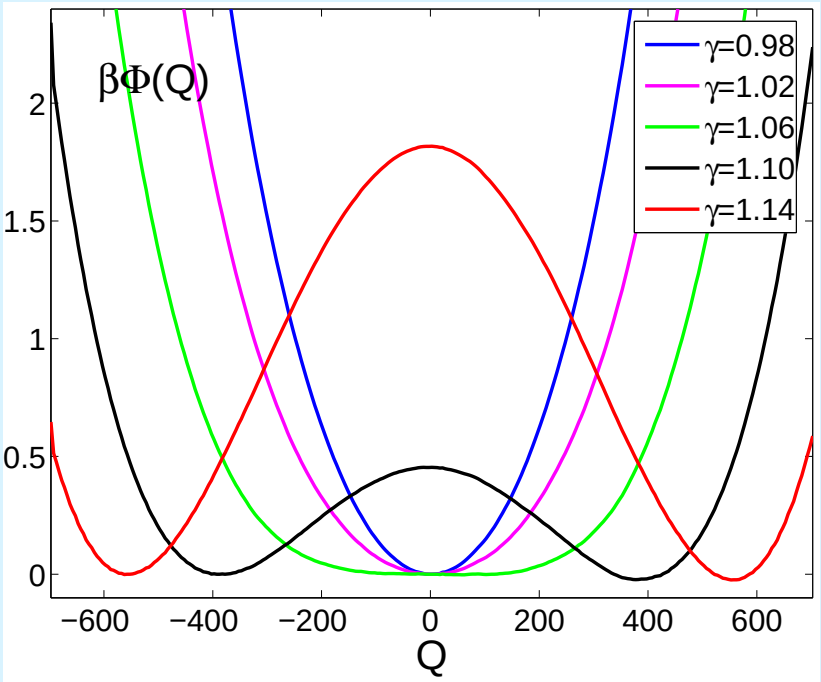
system is effectively one-dimensional (we later use macroscopic observable $Q = P_1 - P_2$), bistability for $\gamma > 1.06$

Effective potential and first passage time

$$\frac{\partial f}{\partial t} = \frac{\partial}{\partial Q}\left(\frac{\partial}{\partial Q}[D(Q)f(Q,t)] - V(Q)f(Q,t)\right)$$

$$V(Q) = \lim_{\Delta t \to 0} \frac{< Q(t+\Delta t) - Q(t) >}{\Delta t}$$

$$D(Q) = \frac{1}{2} \lim_{\Delta t \to 0} \frac{< [Q(t+\Delta t) - Q(t)]^2 >}{\Delta t}$$



mean exit time can be computed from the potential:

$$\tau_{e;p} = \int_{q_m}^{q_u} \exp\left[\beta\Phi(q)\right] \frac{1}{D(q)} \int_{-\infty}^{q} \exp\left[-\beta\Phi(\xi)\right] d\xi \, dq$$

or approximated by the Kramer's formula:

$$\tau_{e;k} \approx \frac{4\pi \exp\left[\beta\Phi(q_u) - \beta\Phi(q_m)\right]}{\beta[D(q_u) + D(q_m)]\sqrt{\Phi''(q_m)|\Phi''(q_u)|}}$$

Steady state distributions

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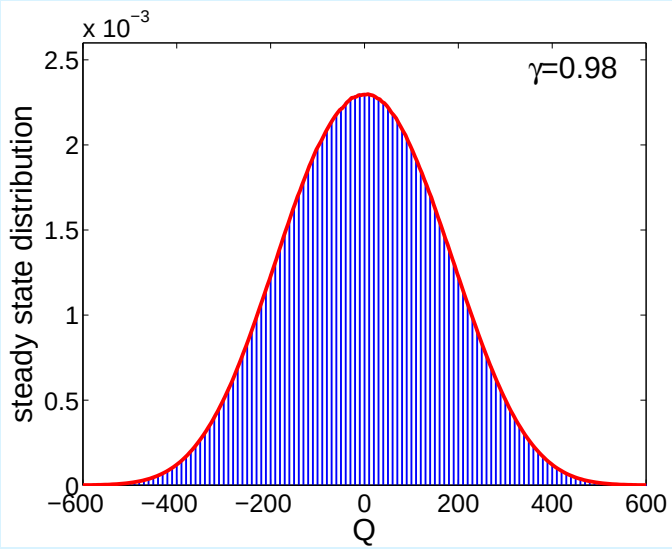
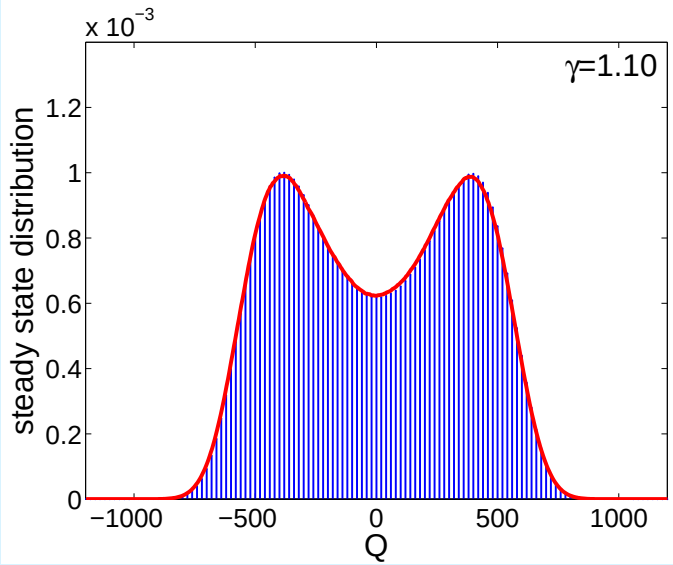
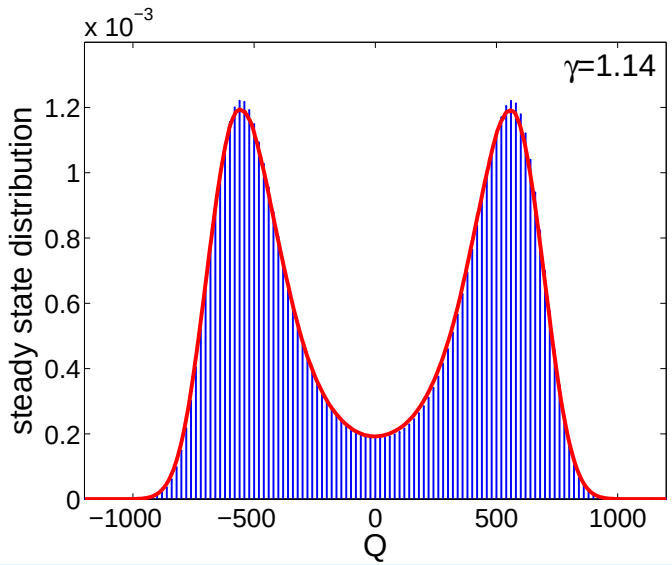
$\gamma = 0.98$



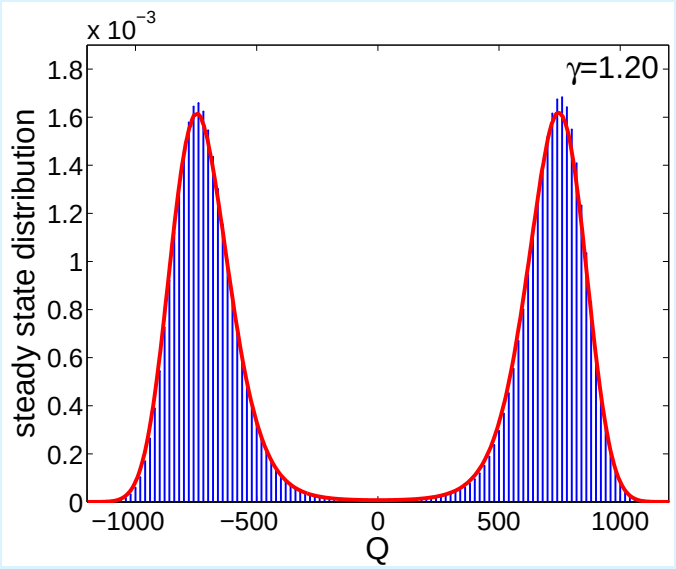
$\gamma = 1.10$



$\gamma = 1.14$



$\gamma = 1.20$

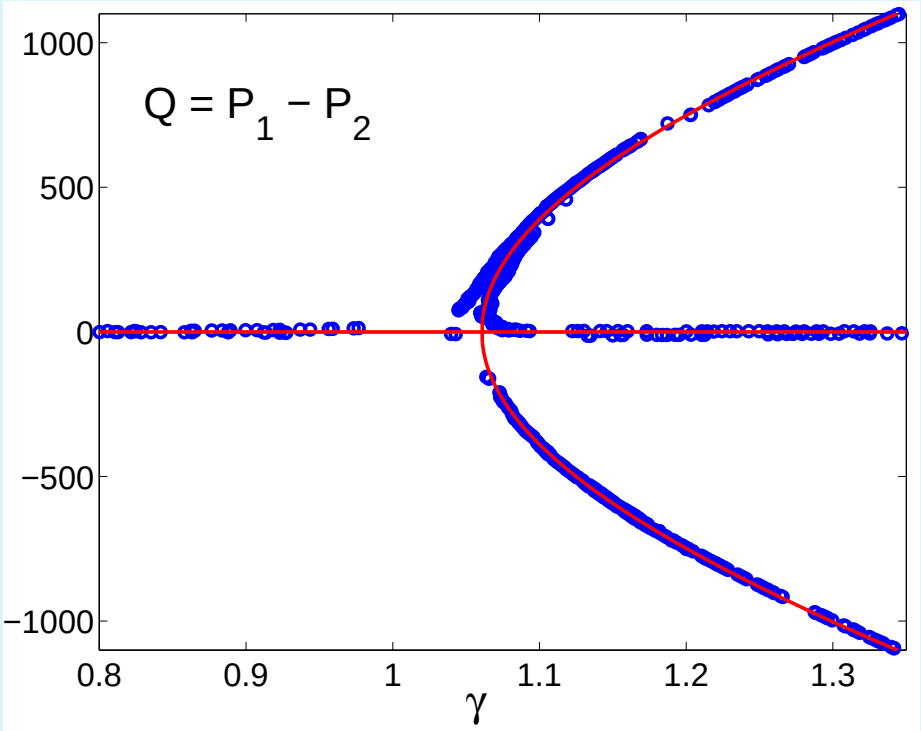


red line: steady state distributions obtained from potential $\Phi(Q)$ computed by the equation-free algorithm

blue histograms: obtained by direct long time simulations

R. Erban, I. Kevrekidis, D. Adalsteinsson and T. Elston, Journal of Chemical Physics, 2006

Equation-free bifurcation analysis

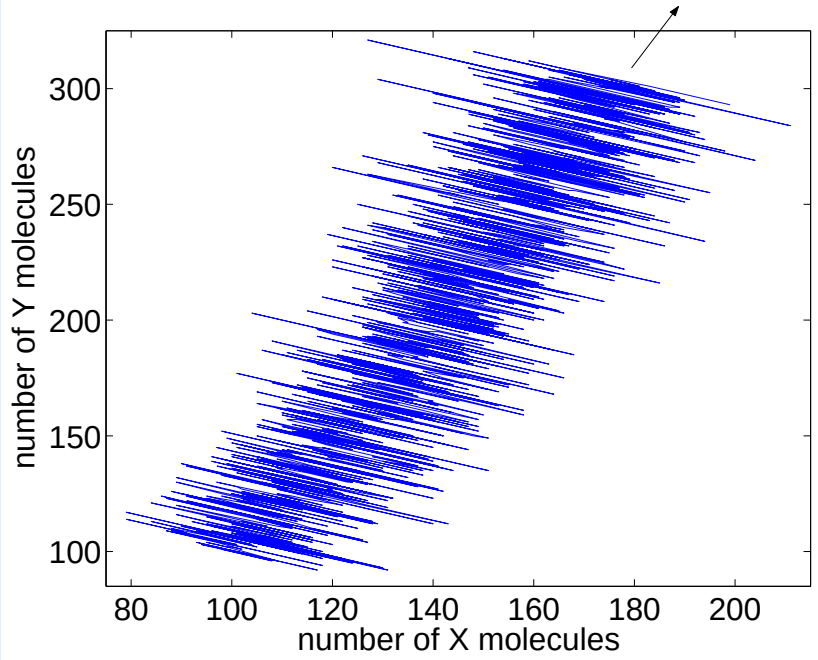


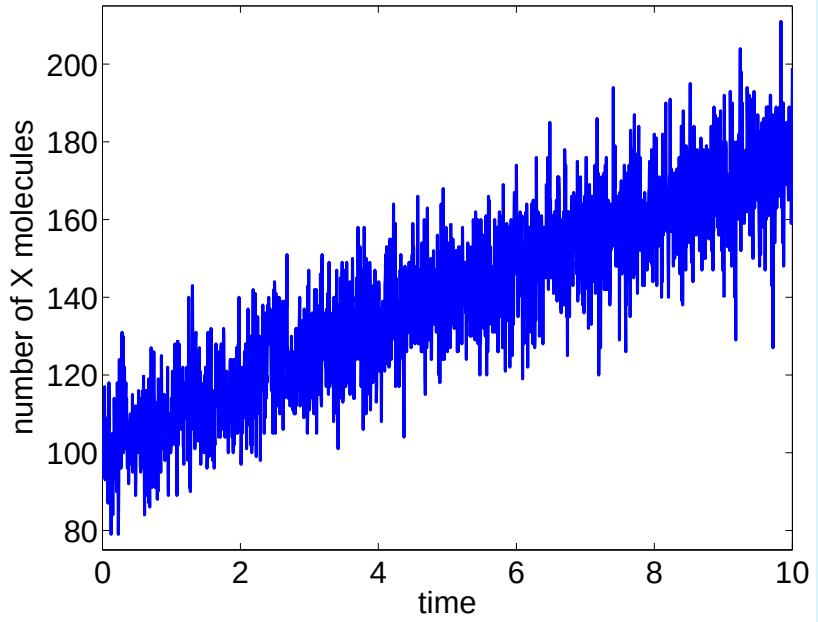
- continuation algorithm wrapped around the stochastic timestepper (blue circles)

$$\begin{cases} Q - F(Q,\gamma) & = & 0 \\ (Q-Q_2)(Q_2-Q_1) + (\gamma-\gamma_2)(\gamma_2-\gamma_1) - \delta & = & 0 \end{cases}$$

- deterministic steady states (red line)

Selection of coarse variables – diffusion maps

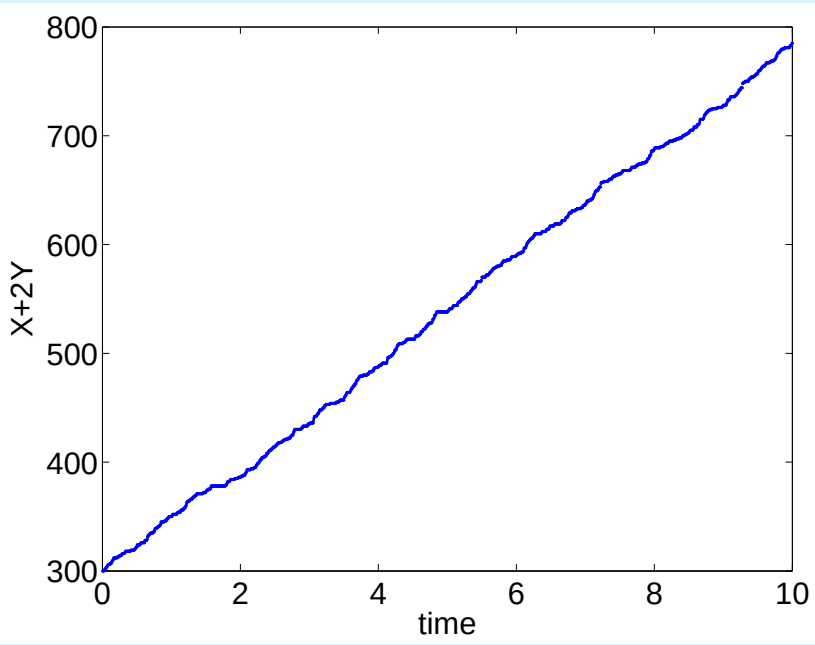




Model:

$$X + X \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Y \qquad \emptyset \xrightarrow{k_3} X$$

Slow variable? $X + 2Y$



Selection of coarse variables – diffusion maps

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Consider set of data points $\mathbf{X}^{(i)} = [X^{(i)}, Y^{(i)}]$, $i = 1, \ldots, M$.

For every data point $\mathbf{X}^{(i)} = [X^{(i)}, Y^{(i)}]$, compute:

$$\mathbf{A}^{(i)} = \frac{1}{\sigma_X^{(i)}\sigma_Y^{(i)} - (\sigma_{XY}^{(i)})^2} \begin{pmatrix} \sigma_Y^{(i)} & -\sigma_{XY}^{(i)} \\ -\sigma_{XY}^{(i)} & \sigma_X^{(i)} \end{pmatrix}$$

where

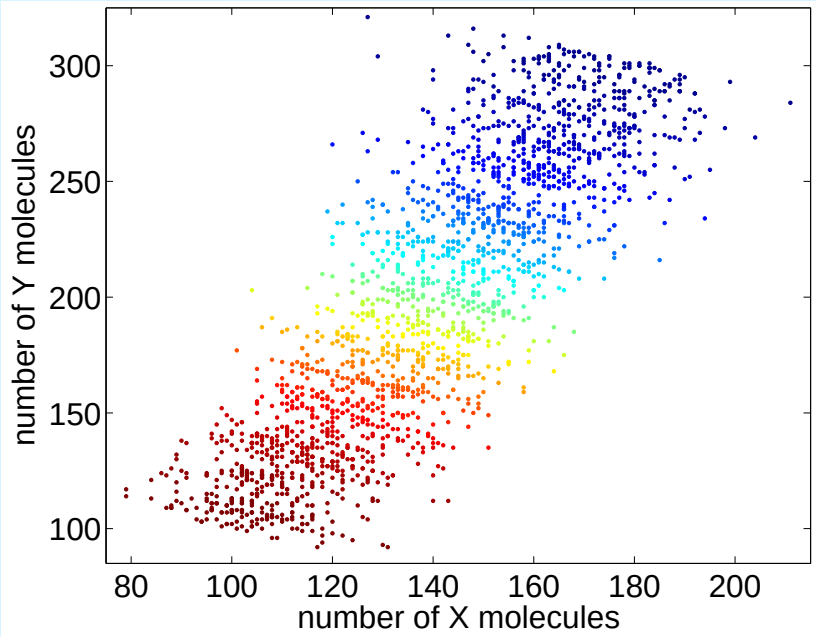
$$\begin{aligned} \sigma_X^{(i)} &= \left\langle X^2(\Delta t) \,|\, \mathbf{X}(0) = \mathbf{X}^{(i)} \right\rangle - (\mu_X^{(i)})^2 \\ \sigma_Y^{(i)} &= \left\langle Y^2(\Delta t) \,|\, \mathbf{X}(0) = \mathbf{X}^{(i)} \right\rangle - (\mu_Y^{(i)})^2 \\ \sigma_{XY}^{(i)} &= \left\langle X(\Delta t)Y(\Delta t) \,|\, \mathbf{X}(0) = \mathbf{X}^{(i)} \right\rangle - \mu_X^{(i)}\mu_Y^{(i)} \end{aligned}$$

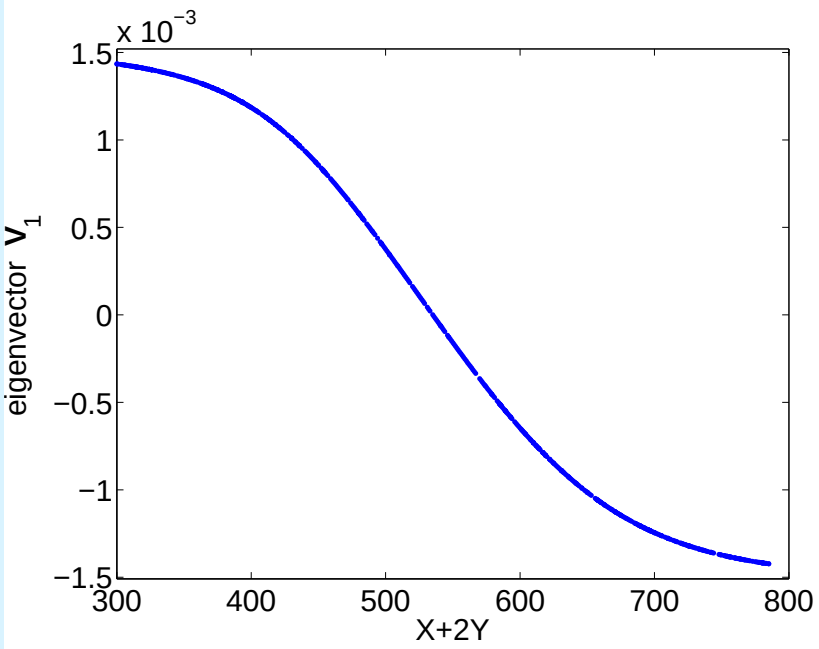
Distance of data points $\mathbf{X}^{(i)} = [X^{(i)}, Y^{(i)}]$ and $\mathbf{X}^{(j)} = [X^{(j)}, Y^{(j)}]$:

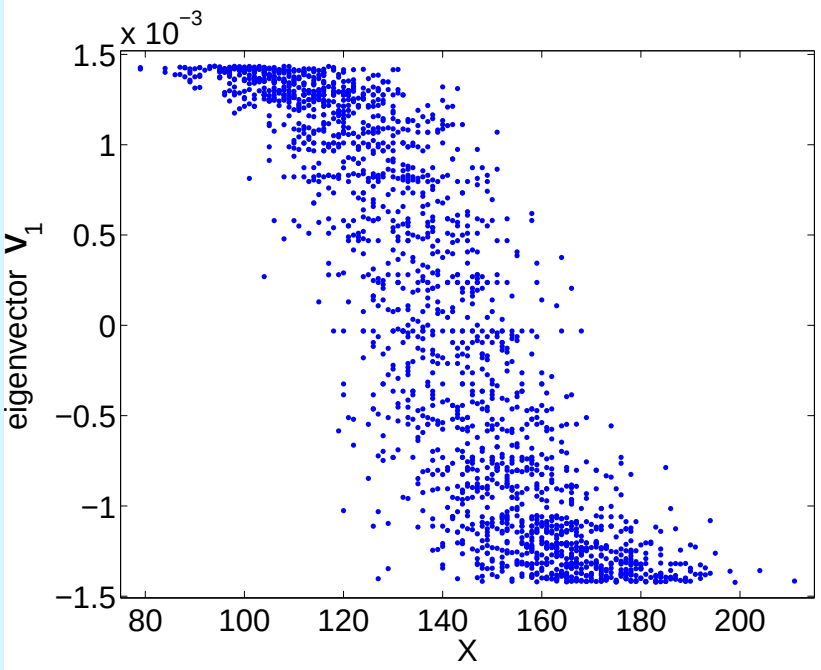
$$\text{dist}^2(\mathbf{X}^{(i)}, \mathbf{X}^{(j)}) = \frac{1}{2}(\mathbf{X}^{(i)} - \mathbf{X}^{(j)}) \left[\mathbf{A}^{(i)} + \mathbf{A}^{(j)}\right] (\mathbf{X}^{(i)} - \mathbf{X}^{(j)})^T$$

Apply diffusion maps (*Coifman et al, PNAS, 2005; Singer and Coifman, 2007*) using this local distance to find slow variable(s).

Selection of coarse variables – diffusion maps



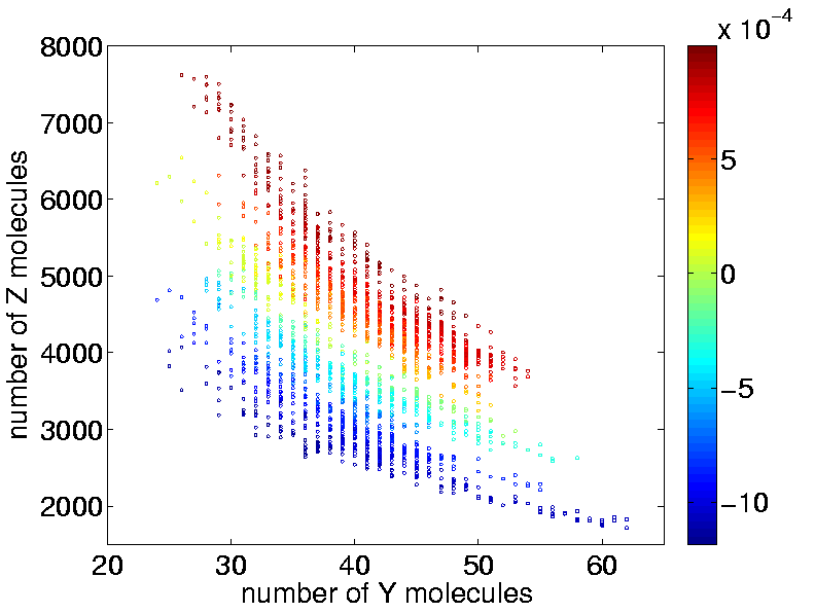


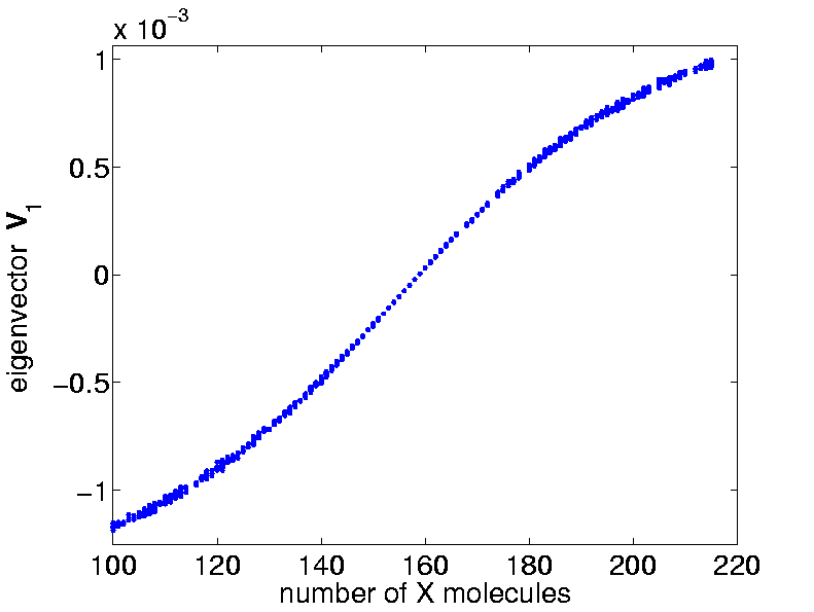


Diffusion maps (with the modified local distance) can be used to find the slow variable $X + 2Y$.

Next step - combine with equation-free approach (*R. Erban, T. Frewen, X. Wang, T. Elston, R. Coifman, B. Nadler and I. Kevrekidis, Journal of Chemical Physics, 2007*).

Selection of coarse variables – diffusion maps



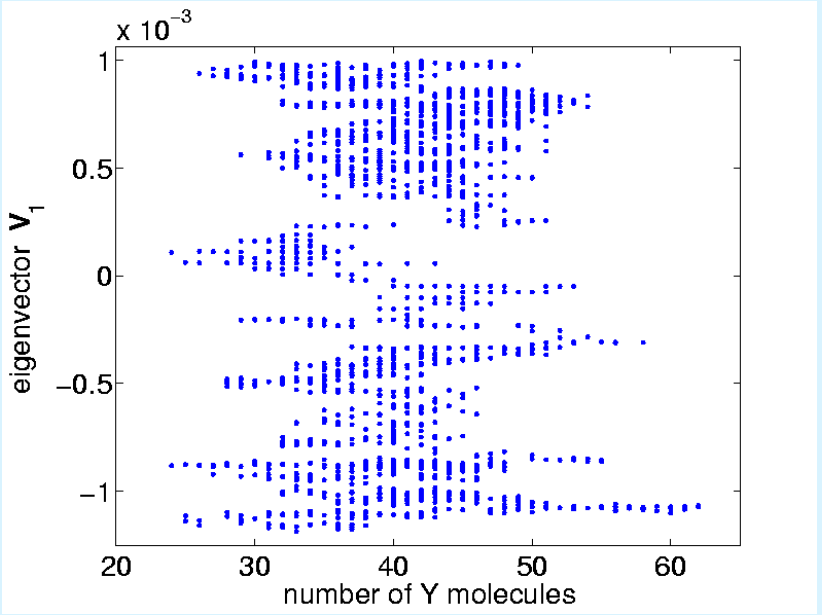


Model:

$$X \xrightarrow{k_1} X+Z, \qquad Y+Z \xrightarrow{k_2} Y \qquad \text{(fast)}$$

$$\emptyset \xrightarrow{k_3} Y, \qquad Y \xrightarrow{k_4} \emptyset \qquad \text{(medium)}$$

$$\emptyset \xrightarrow{k_5} X \qquad \text{(slow)}$$



Spatially Distributed Problems - Motivation

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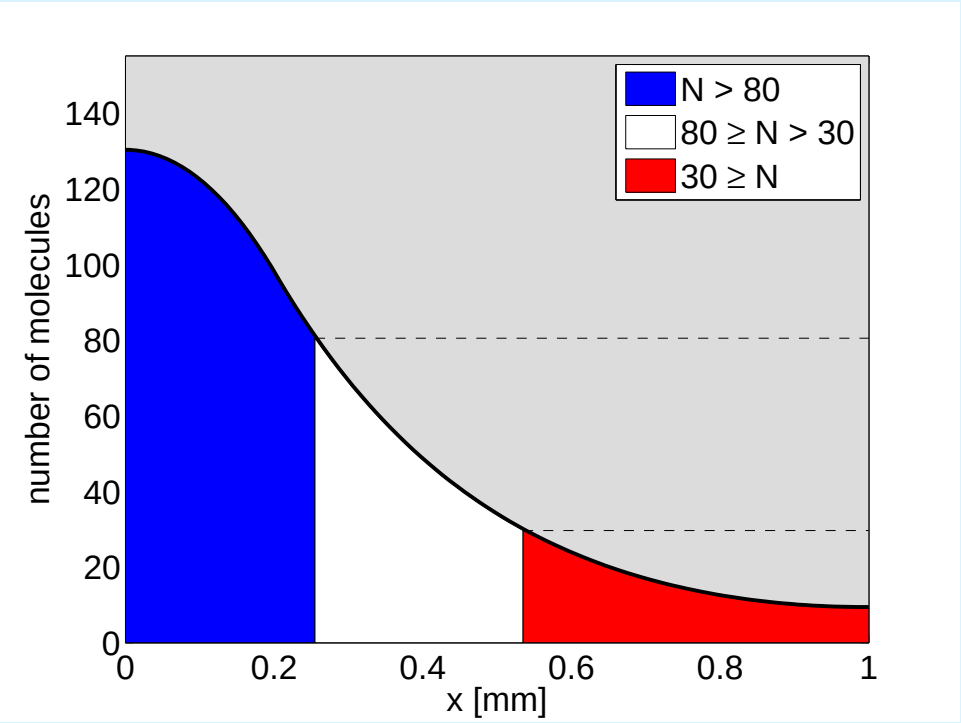
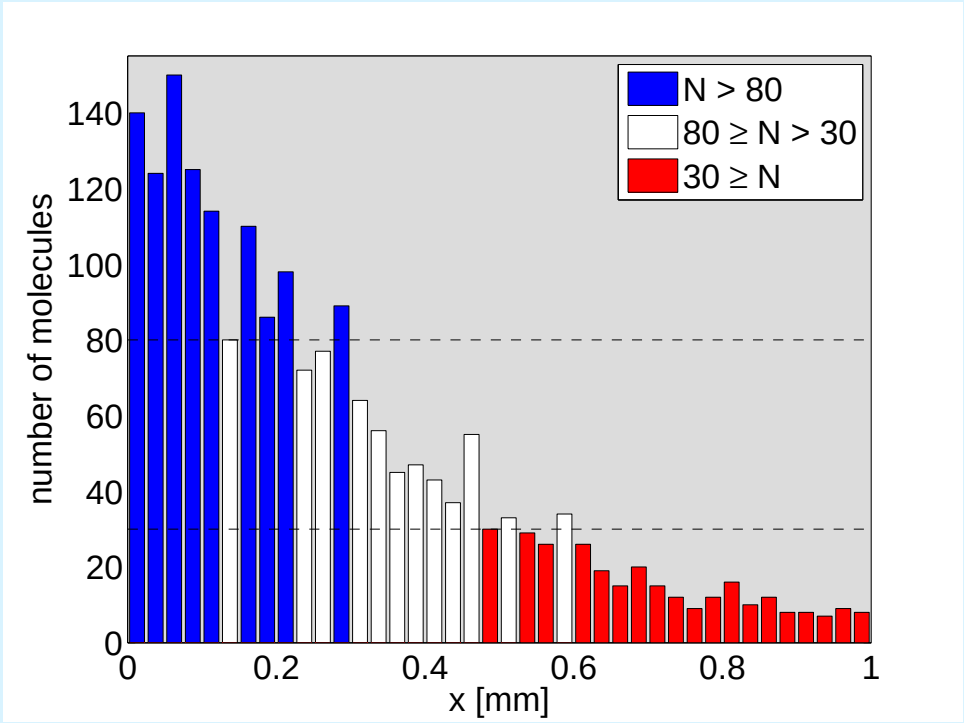
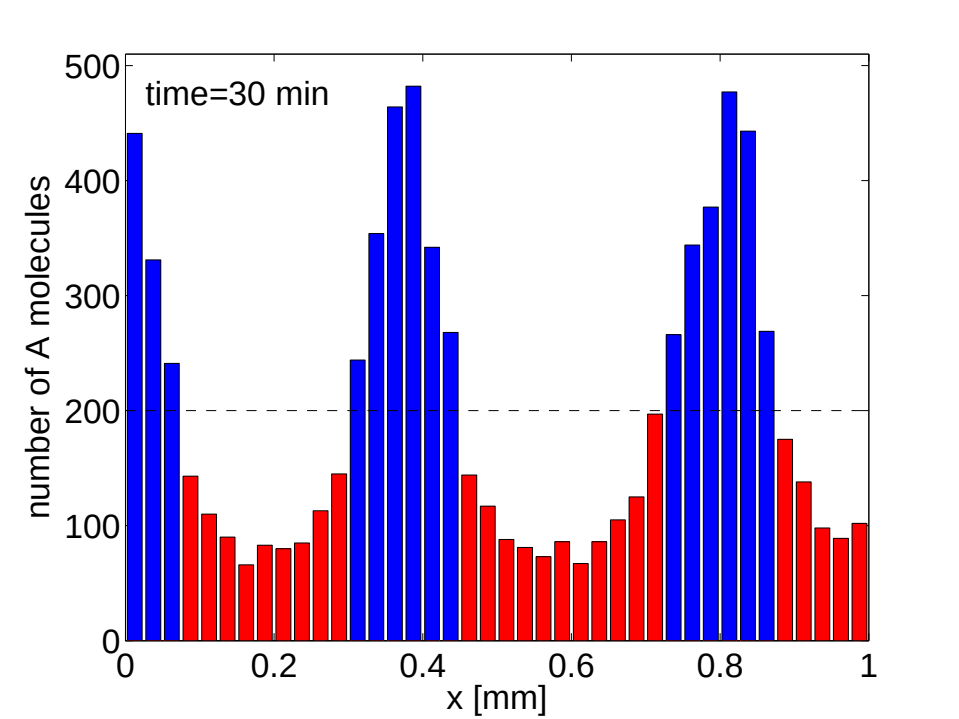


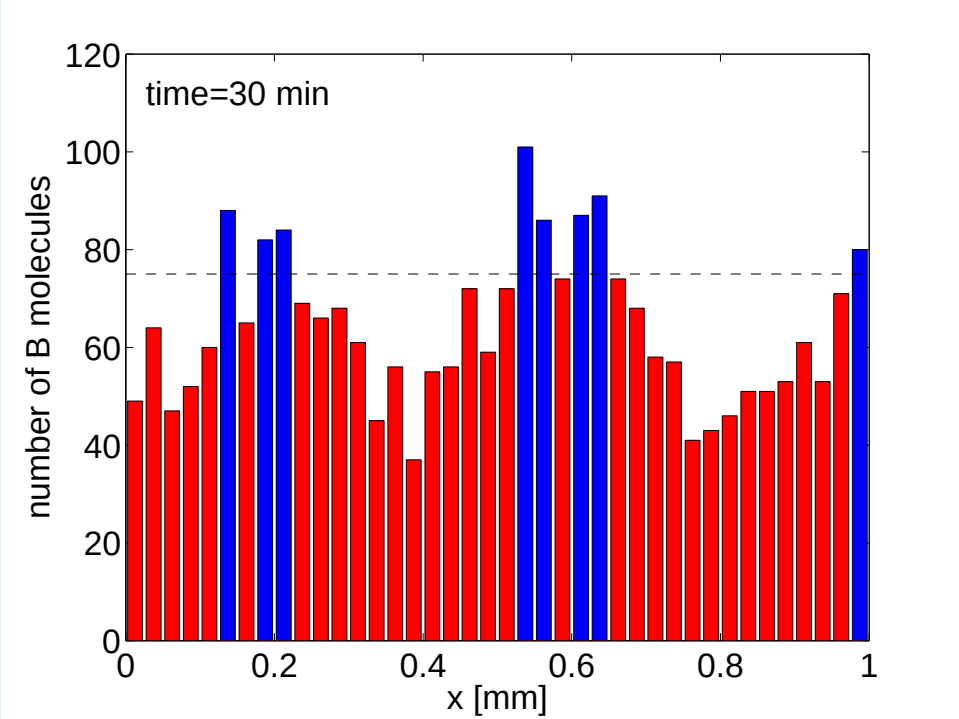


Model: diffusing morphogen which is produced in part of the domain and degraded everywhere

Morphogen gradient is interpreted by the layer of cells, utilizing thresholds, to produce different structures at different places – pattern formation.

Spatially Distributed Problems - Turing Patterns





Model: diffusion of A, B and $2A + B \xrightarrow{k_1} 3A$ $\emptyset \underset{k_3}{\overset{k_2}{\rightleftharpoons}} A$ $\emptyset \xrightarrow{k_4} B$

Turing patterns: homogeneous solution unstable, spatial patterns develop, number of blue peaks not unique (several favourable states)

Deterministic equations

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Reaction-diffusion partial differential equations:

$$\frac{\partial n_i}{\partial t} = D_i \triangle n_i + R_i(n_1, n_2, \ldots, n_k), \qquad i = 1, 2, \ldots, k$$

$n_i \equiv n_i(x,t)$ . . . concentration of the i-th chemical species at point x and time t

D_i . . . . . diffusion constant of the i-th chemical species

$R_i(n_1, n_2, \ldots, n_k)$ . . . changes of n_i because of chemical reactions

- equations considered in domain Ω (e.g. a cell bounded by its membrane)
- we need to introduce suitable boundary conditions

Stochastic simulation algorithms

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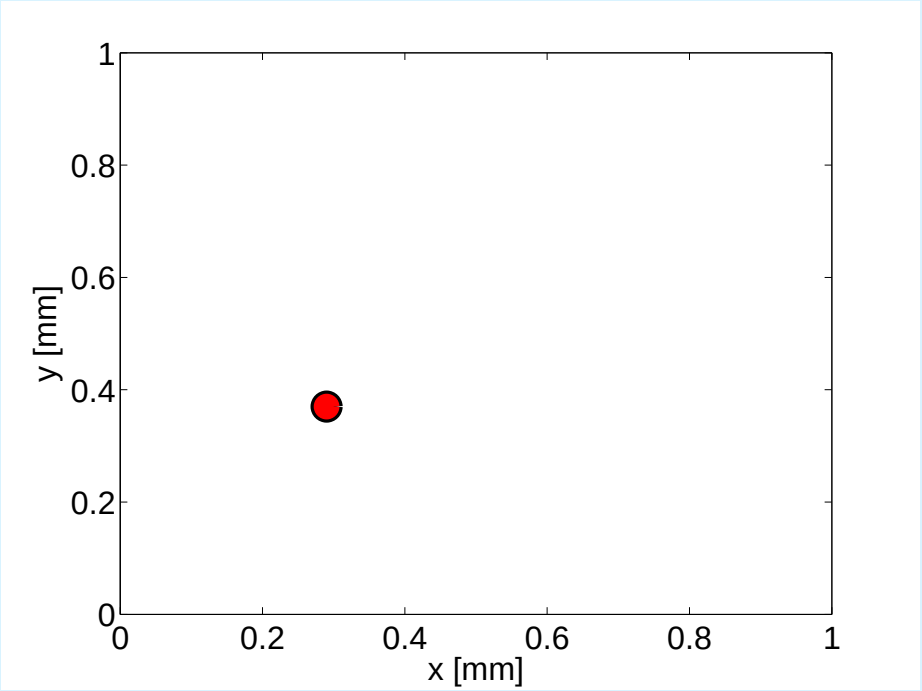
Diffusion:

$$X(t+\Delta t) = X(t) + \sqrt{2D\,\Delta t}\;\zeta_x$$
$$Y(t+\Delta t) = Y(t) + \sqrt{2D\,\Delta t}\;\zeta_y$$
$$Z(t+\Delta t) = Z(t) + \sqrt{2D\,\Delta t}\;\zeta_z$$

ζ_x, ζ_y, ζ_z ... normally distributed random variables with zero mean and unit variance

D ... diffusion constant



Stochastic simulation algorithms

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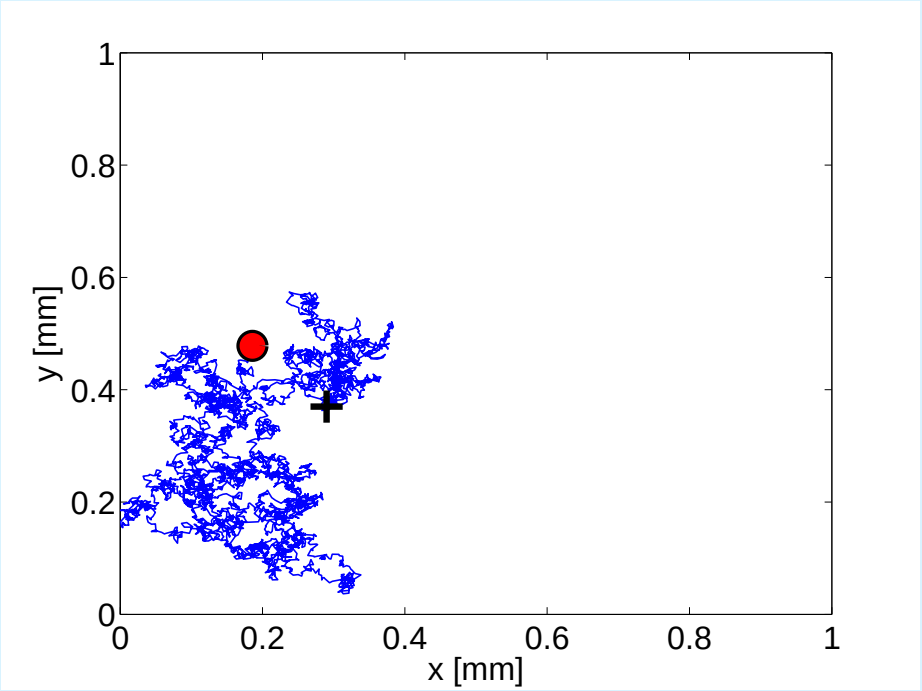

Stochastic simulation algorithms

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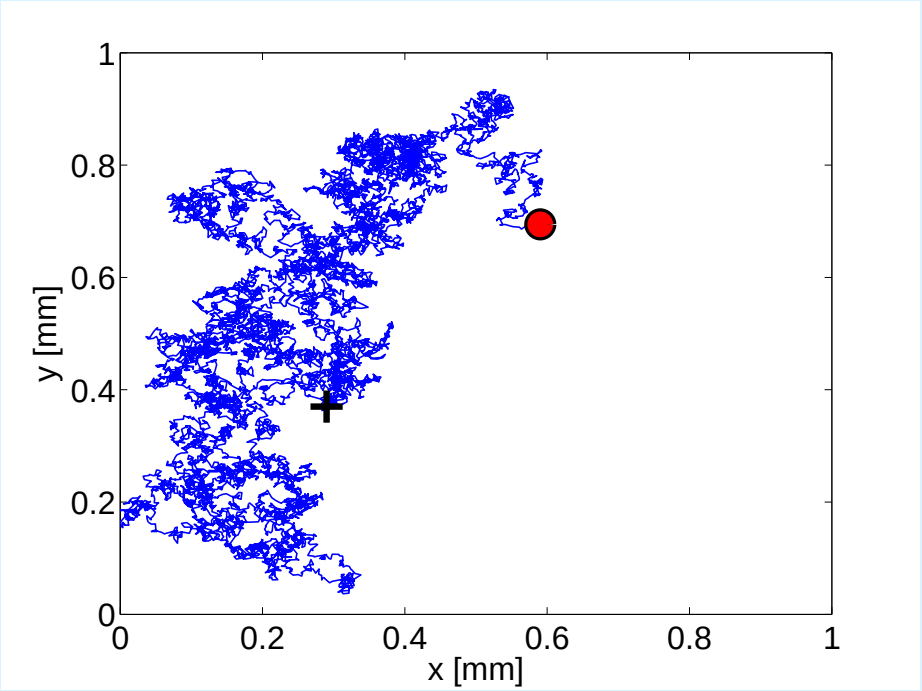

Stochastic simulation algorithms

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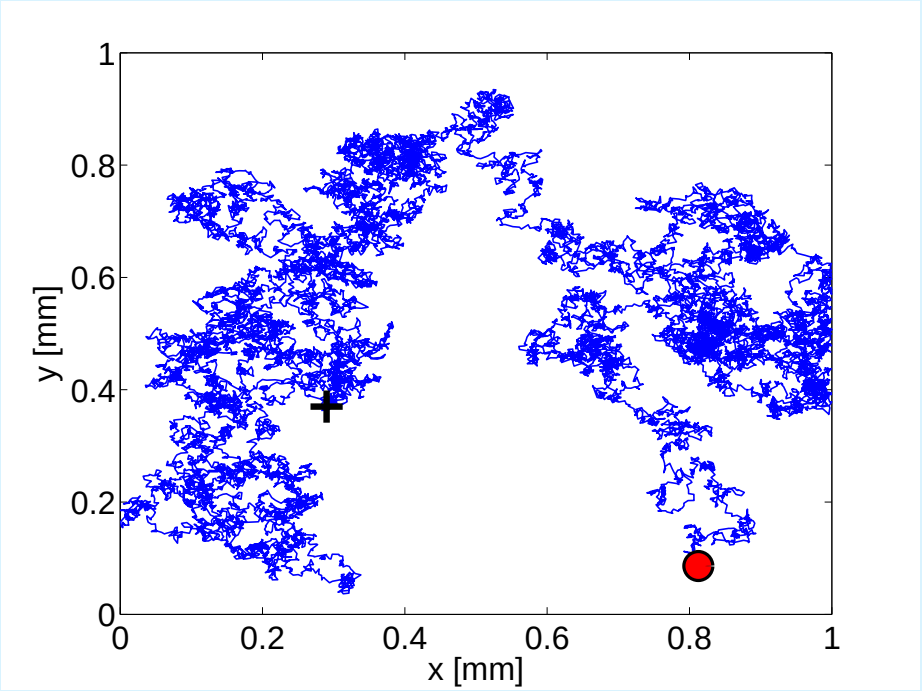

Several stochastic simulation algorithms for modelling diffusion, reaction and taxis: position jump processes, velocity jump processes

- stochastic simulation in domain Ω (e.g. a cell bounded by its membrane)
- we need to introduce suitable boundary conditions

Boundary condition – deterministic modelling

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One-dimensional diffusion equation in [0,L]: $\frac{\partial n}{\partial t} = D \frac{\partial^2 n}{\partial x^2}$

($n \equiv n(x,t)$ ... density of molecules at point x and time t; D ... diffusion constant)

Reactive (radiation, Robin) boundary condition at $x = 0$:

$$D \frac{\partial n}{\partial x}(0,t) = K\, n(0,t)$$

K ... reactivity of the boundary (e.g. rate constant of boundary chemical reaction)

- $K = 0$ ..... perfect reflection of molecules (zero-flux boundary condition)
- $K = \infty$ ... perfect adsorption of molecules (Dirichlet boundary condition)

Boundary conditions – stochastic modelling

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whenever a molecule hits the boundary, it is adsorbed with some probability, and reflected otherwise

P . . . probability that a molecule is adsorbed, rather than reflected

K . . . reactivity of the boundary (e.g. rate constant of boundary chemical reaction)

What is a relation between P and K?

Boundary conditions – stochastic modelling

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whenever a molecule hits the boundary, it is adsorbed with some probability, and reflected otherwise

P . . . probability that a molecule is adsorbed, rather than reflected

K . . . reactivity of the boundary (e.g. rate constant of boundary chemical reaction)

What is a relation between P and K?

- (zero-flux boundary) $K = 0 \Leftrightarrow P = 0$ (molecules always reflected)
- value of P depends on K and on the stochastic model for $K > 0$
- relations between P and K for four different stochastic simulation algorithms are derived in *R. Erban and J. Chapman, Physical Biology, 2007*

Same value $P = 5\,\%$ for different stochastic models

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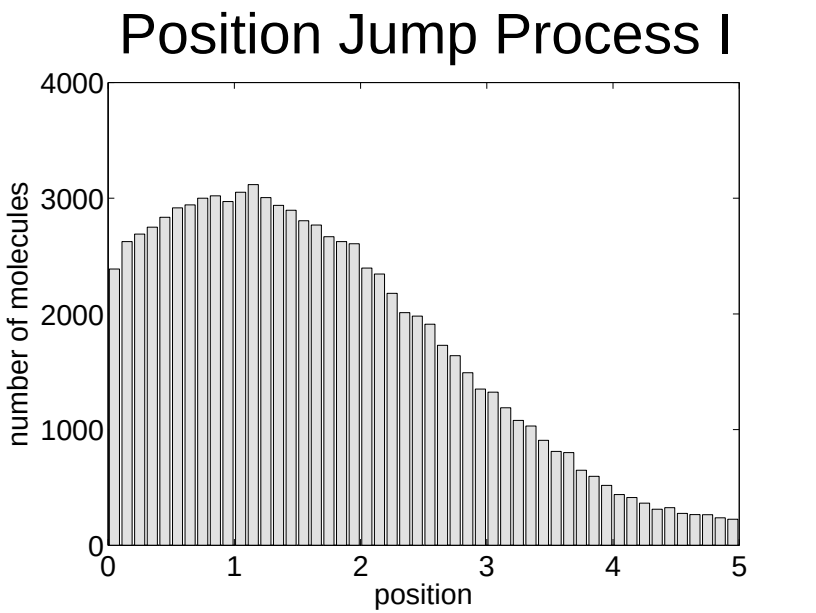

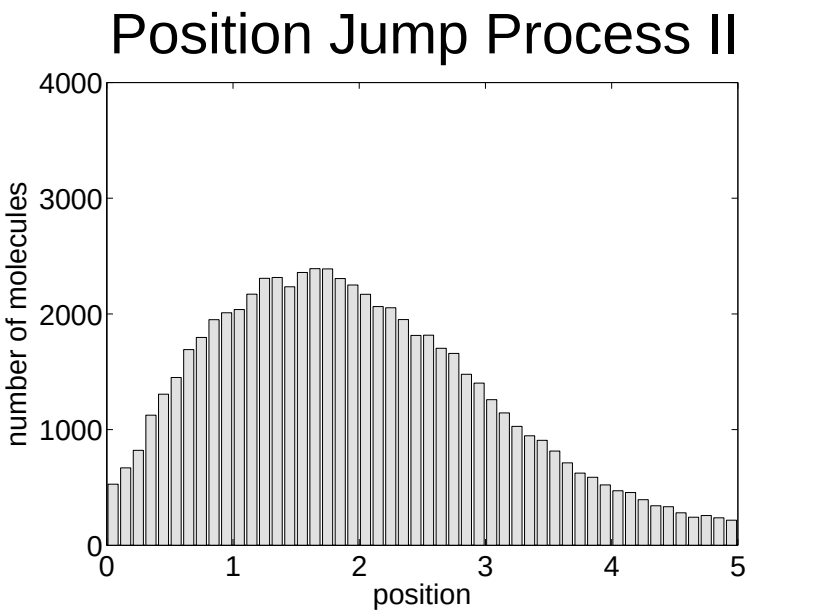

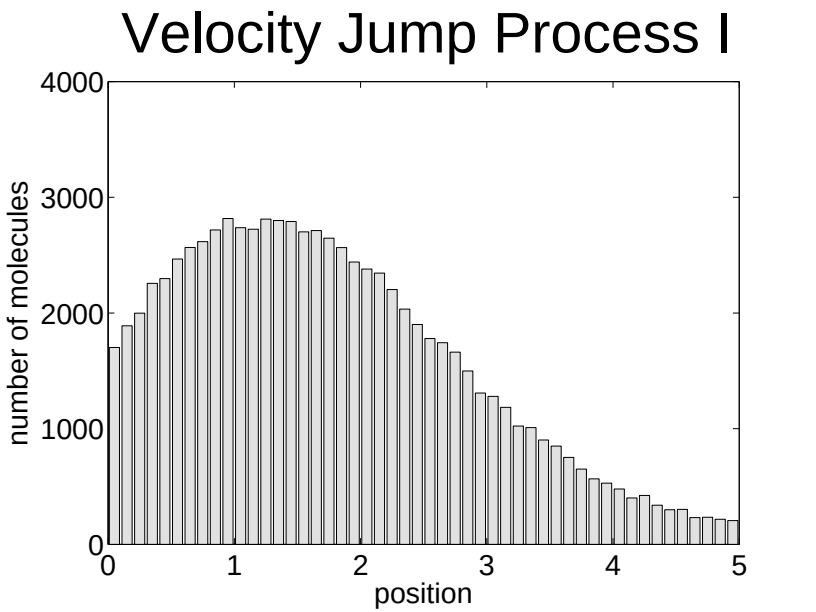

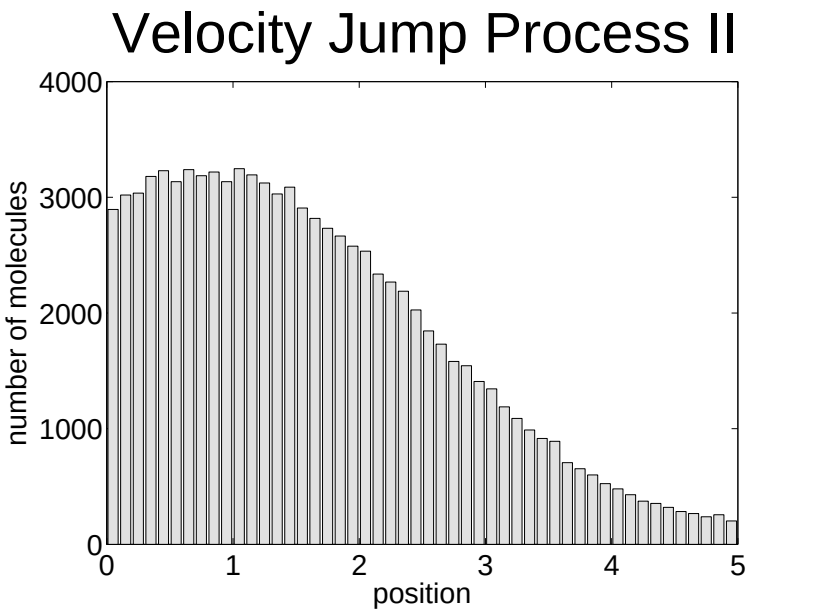

[whenever a molecule hits boundary $x = 0$, it is adsorbed with probability 5%, and reflected otherwise]

Boundary conditions – stochastic modelling

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Position Jump Process I: lattice points a distance h apart

$$X(t+\Delta t) = \begin{cases} X(t) & \text{with probability } 1 - 2D\Delta t/h^2 \\ X(t) - h & \text{with probability } D\Delta t/h^2 \\ X(t) + h & \text{with probability } D\Delta t/h^2 \end{cases}$$

Boundary condition: *whenever a molecule hits the boundary, it is adsorbed with probability* $P = P_1 h$*, and reflected otherwise*.

Position Jump Process 2: $X(t+\Delta t) = X(t) + \sqrt{2D\,\Delta t}\,\zeta_x$

Boundary condition: *whenever a molecule hits the boundary, it is adsorbed with probability* $P = P_2\sqrt{\Delta t}$*, and reflected otherwise*.

Relations between P and K:

$$P_1 = \frac{K}{D} \qquad\qquad P_2 = \frac{K\sqrt{\pi}}{2\sqrt{D}}$$

Correct choice of P for different stochastic models

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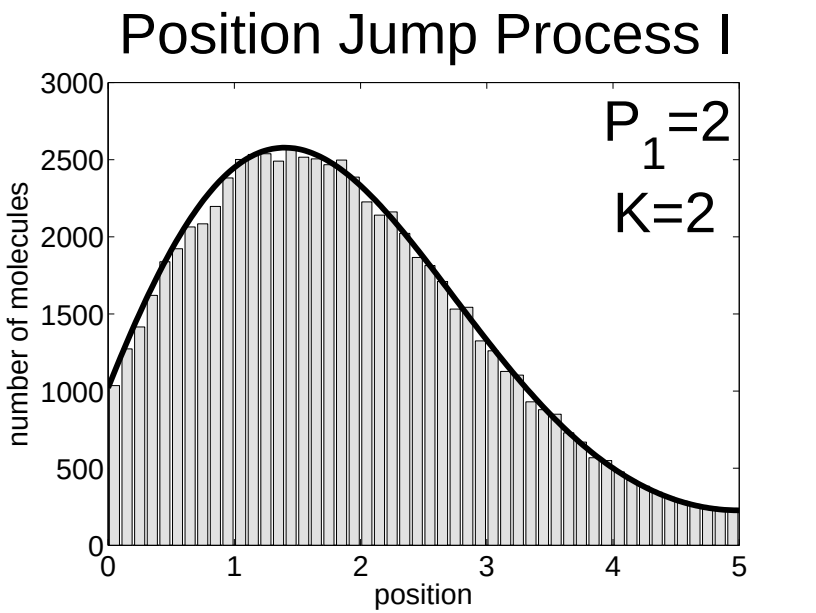

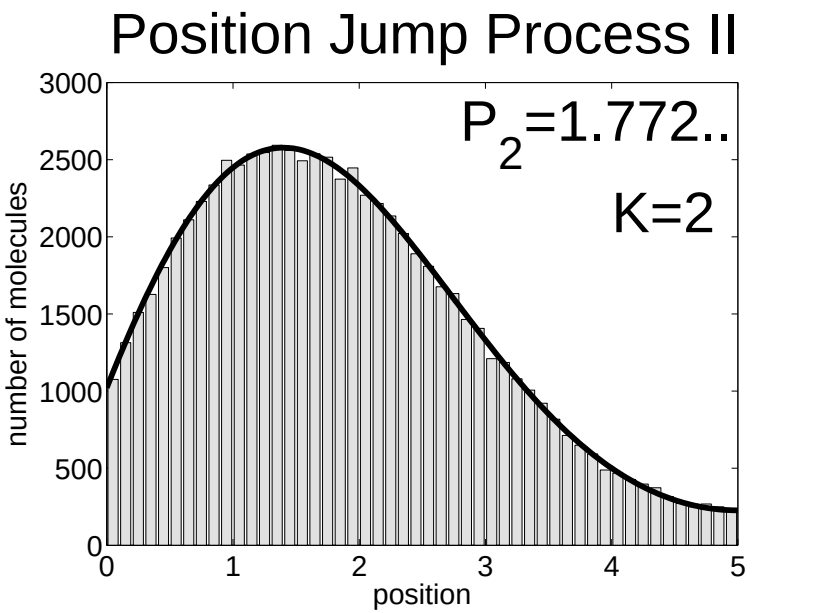

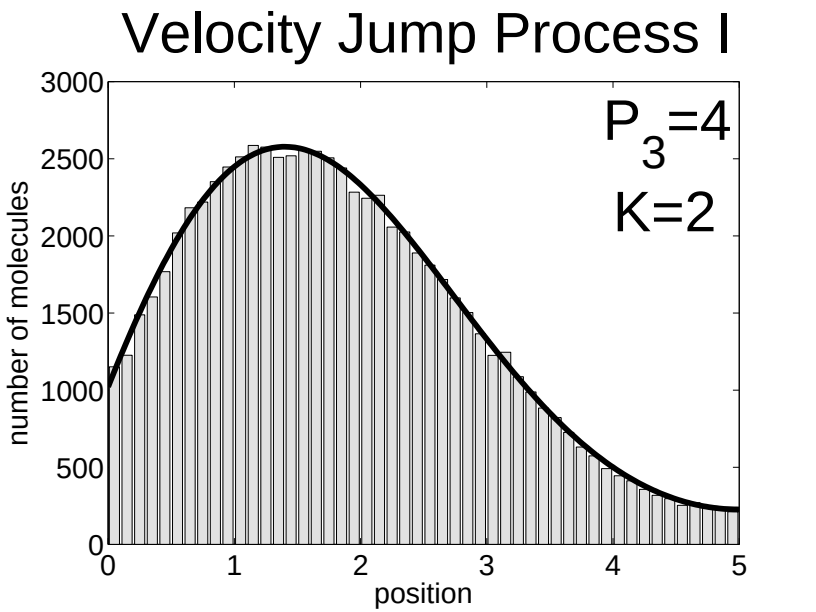

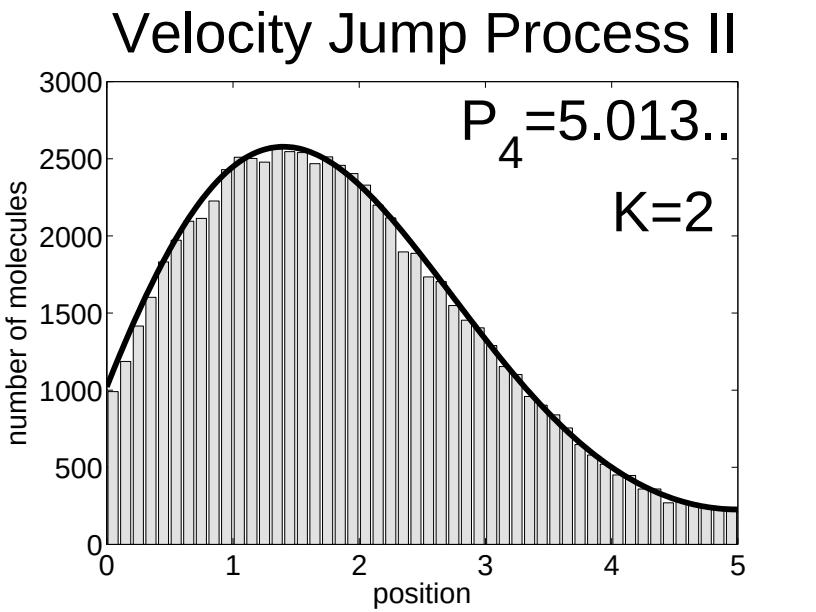

R. Erban and J. Chapman, Physical Biology, 2007

Reaction, diffusion and taxis processes in biology

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We considered only diffusion so far, but:

- the boundary conditions for stochastic models of reaction, diffusion and taxis depend on the corresponding model of the diffusion only
- chemical reactions (e.g. modelling gene regulatory networks) or taxis/advection (e.g. modelling ion channels) do not influence the boundary conditions

We considered behaviour of biomolecules (e.g. proteins) so far, but a stochastic description is also useful for modelling unicellular organisms (e.g. chemotaxis of bacteria or Dictyostelium):

RE, H. Othmer, SIAM Journal on Applied Mathematics, 2004
RE, H. Othmer, Multiscale Modeling and Simulation, 2005
RE, I. Kevrekidis and H. Othmer, Physica D, 2006
RE, H. Hwang, Discrete and Continuous Dynamical Systems Series B, 2006
RE, H. Othmer, Journal of Mathematical Biology, 2007

Summary

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- stochastic modelling of reaction, diffusion and taxis processes in biology
- equation-free methods (computation of steady state distributions, effective potentials, first passage time of bistable systems and bifurcation diagrams)
- selection of coarse variables (anisotropic diffusion maps)
- derivation of reactive boundary conditions for stochastic models

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- J. Chapman (University of Oxford)
- T. Elston, D. Adalsteinsson, C. Kelley, X. Wang (North Carolina)
- H. Othmer (University of Minnesota)

Preprints: **www.maths.ox.ac.uk/~erban**

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