Reaction-diffusion systems

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Based on lecture notes of Radek Erban
http://www.maths.ox.ac.uk/courses/course/19651/material
http://www.maths.ox.ac.uk/cmb/education

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Summer school, Prague, 6–8 August, 2013

Outline

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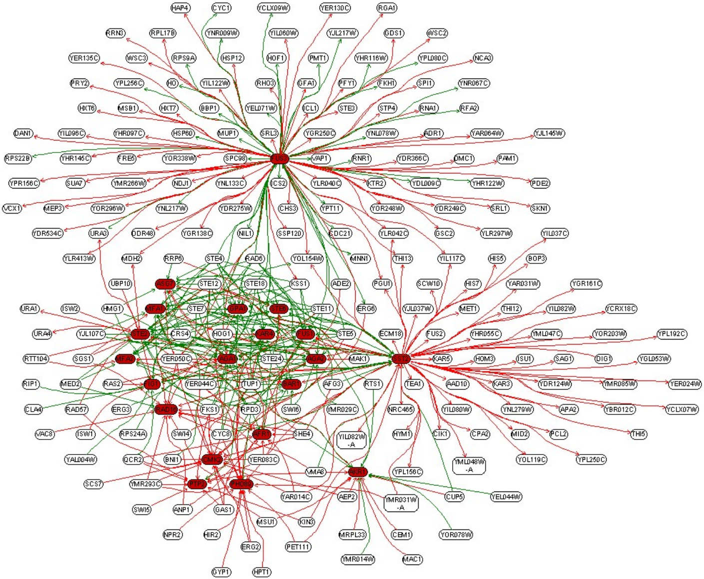
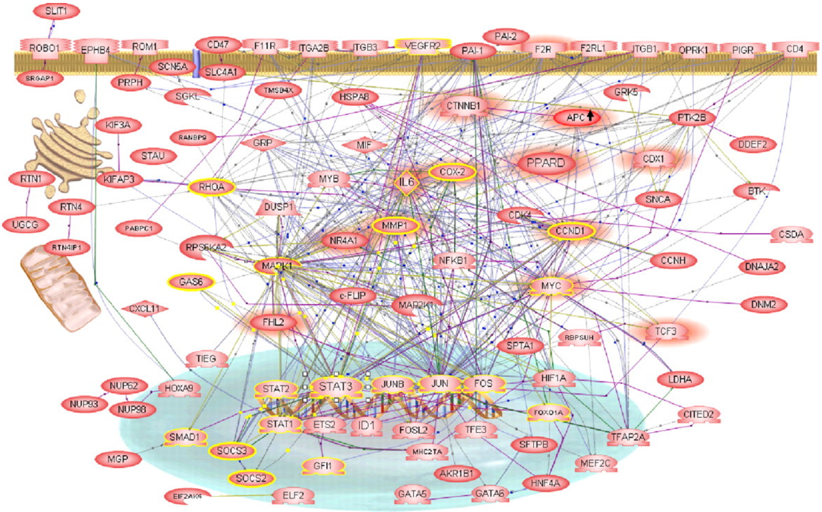
- Motivation
- Reaction kinetics: deterministic and stochastic models
- Models of diffusion
- Application to circadian rhythms
- Application to pattern formation

Motivation – gene regulatory networks



Neighbourhood of mating response genes [Rung, Schlitt, et al, 2002]

Motivation – gene regulatory networks



Angiogenic signaling network. [Abdollahi et al, PNAS 2007]

Degradation

$$A \xrightarrow{k} \emptyset$$

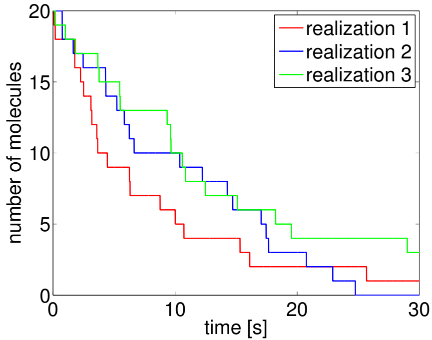
Naive stochastic simulation algorithm (SSA):

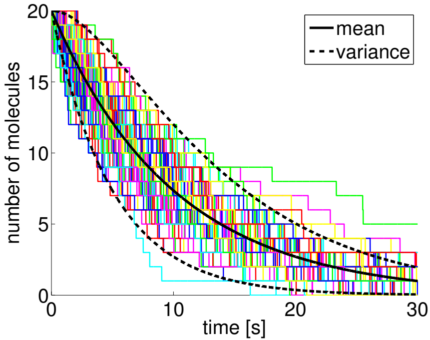
Initialization: $\Delta t > 0$ small, for $t = 0$ set $A(0) = n_0$.

(a1) Generate a random number r uniformly distributed in $(0, 1)$

(b1) If $r < A(t)k\Delta t$ then $A(t + \Delta t) = A(t) - 1$;
else $A(t + \Delta t) = A(t)$

Naive SSA: degradation





$k = 0.1, \; A(0) = 20, \; \Delta t = 0.005$

naivessa_mean_anim.m

Gillespie SSA for degradation

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$$A \xrightarrow{k} \emptyset$$

Initialization: set $A(0) = n_0$.

(a2) Generate a random number r uniformly distributed in $(0, 1)$

(b2) Compute the next reaction time $\tau = \frac{1}{A(t)k} \ln \left[\frac{1}{r} \right]$

(c2) Update the number of molecules: $A(t + \tau) = A(t) - 1$
Set $t := t + \tau$ and go to (a2)

Chemical reactions of higher-order

order	reaction	propensity	units of k
0	$\emptyset \xrightarrow{k} A$	$k\nu$	$\mathrm{m}^{-3}\mathrm{sec}^{-1}$
1	$A \xrightarrow{k} \emptyset$	$A(t)k$	sec^{-1}
2	$A + B \xrightarrow{k} \emptyset$	$A(t)B(t)k/\nu$	$\mathrm{m}^{3}\mathrm{sec}^{-1}$
2	$2A \xrightarrow{k} \emptyset$	$A(t)(A(t)-1)k/\nu$	$\mathrm{m}^{3}\mathrm{sec}^{-1}$
3	$A + B + C \xrightarrow{k} \emptyset$	$A(t)B(t)C(t)k/\nu^2$	$\mathrm{m}^{6}\mathrm{sec}^{-1}$
3	$2A + B \xrightarrow{k} \emptyset$	$A(t)(A(t)-1)B(t)k/\nu^2$	$\mathrm{m}^{6}\mathrm{sec}^{-1}$
3	$3A \xrightarrow{k} \emptyset$	$A(t)(A(t)-1)(A(t)-2)k/\nu^2$	$\mathrm{m}^{6}\mathrm{sec}^{-1}$

System with two species

$$2A \xrightarrow{k_1} \emptyset, \quad A + B \xrightarrow{k_2} \emptyset, \quad \emptyset \xrightarrow{k_3} A, \quad \emptyset \xrightarrow{k_4} B,$$

Gillespie SSA:

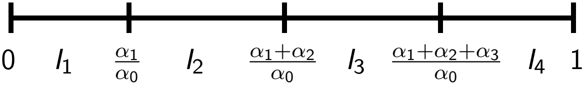
(a4) Generate two random numbers: $r_1, r_2 \sim U(0,1)$

(b4) Compute propensities:
$\alpha_1(t) = k_1 A(t)(A(t)-1)$, $\alpha_2(t) = k_2 A(t) B(t)$,
$\alpha_3 = k_3$, $\alpha_4 = k_4$, and $\alpha_0 = \alpha_1(t) + \alpha_2(t) + \alpha_3 + \alpha_4$

(c4) Next reaction time $\tau = \frac{1}{\alpha_0} \ln \left[\frac{1}{r_1} \right]$

(d4) Update the numbers of molecules:

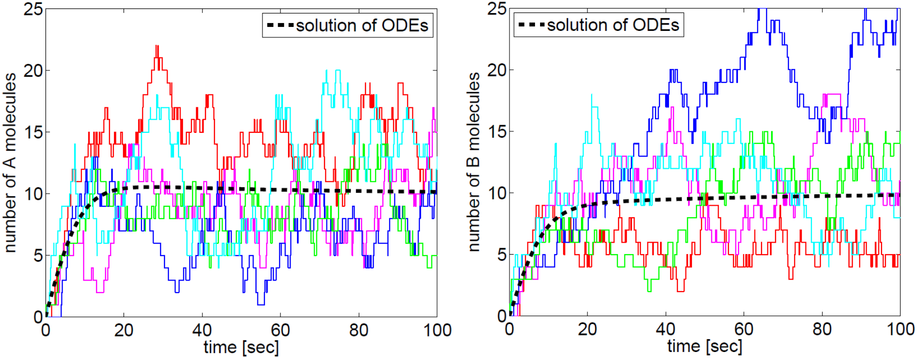
	$r_2 \in I_1$	$r_2 \in I_2$	$r_2 \in I_3$	$r_2 \in I_4$
$A(t+\tau)$	$A(t)-2$	$A(t)-1$	$A(t)+1$	$A(t)$
$B(t+\tau)$	$B(t)$	$B(t)-1$	$B(t)$	$B(t)+1$



Set $t := t + \tau$ and go to (a4)

System with two species

Trajectories



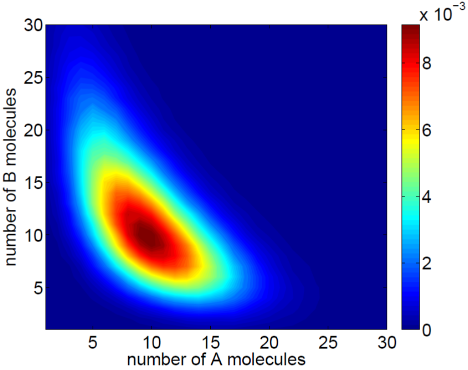
$A(0) = B(0) = 0,\ k_1 = 10^{-3},\ k_2 = 10^{-2},\ k_3 = 1.2,\ k_4 = 1\ \mathrm{sec}^{-1}$

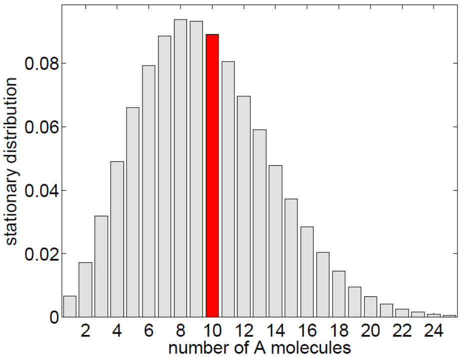
$A_s = 9.6,\ B_s = 12.2$

$a_s = 10,\ b_s = 10$

System with two species

Stationary distribution





$k_1 = 10^{-3},\ k_2 = 10^{-2},\ k_3 = 1.2,\ k_4 = 1\ \text{sec}^{-1}$

$A_s = 9.6,\ B_s = 12.2$

$a_s = 10,\ b_s = 10$

General Gillespie SSA

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Notation

q ... number of chemical reactions

$\alpha_j(t)$ ... propensity function of j-th reaction, $j = 1, 2, \ldots, q$

$\alpha_j(t)\,\mathrm{d}t$ = probability that j-th reaction occurs in $[t, t + \mathrm{d}t)$

Algorithm

(a5) Generate random numbers r_1, r_2 uniformly distributed in $(0, 1)$

(b5) Compute propensity $\alpha_j(t)$ of each reaction and $\alpha_0 = \sum_{j=1}^{q} \alpha_j$

(c5) Next reaction time $\tau = \dfrac{1}{\alpha_0} \ln \left[\dfrac{1}{r_1}\right]$

(d5) Compute which reaction occurs at time $t + \tau$. Find j such that

$$r_2 \geq \frac{1}{\alpha_0} \sum_{i=1}^{j-1} \alpha_i(t) \quad \text{and} \quad r_2 < \frac{1}{\alpha_0} \sum_{i=1}^{j} \alpha_i(t)$$

(e5) The j-th reaction takes place. Update numbers of molecules. Set $t := t + \tau$ and go to (a5)

System with multiple favourable states

Schlögl system

$$3A \underset{}{\overset{k_1,k_2}{\rightleftharpoons}} 2A \qquad A \underset{}{\overset{k_3,k_4}{\rightleftharpoons}} \emptyset$$

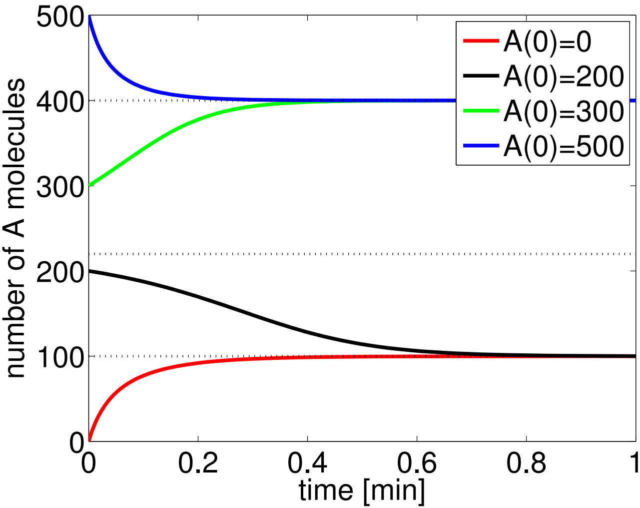
Concentration: $a(t) = A(t)/\nu$

$$\frac{da}{dt} = -k_1 a^3 + k_2 a^2 - k_3 a + k_4$$

Average number of molecules: $\overline{A}(t) = a(t)\nu$

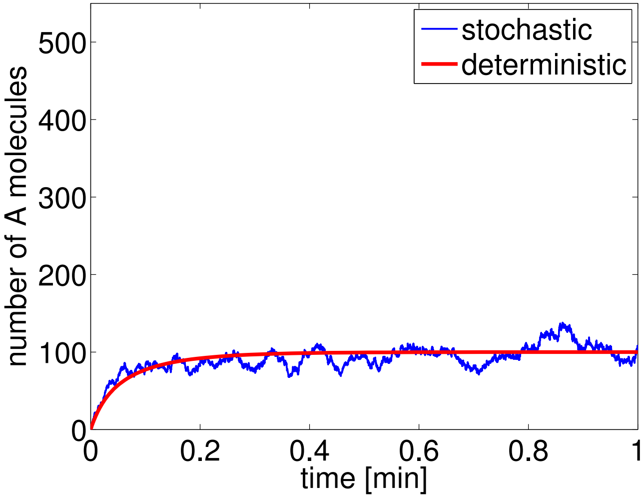
$$\frac{d\overline{A}}{dt} = -\frac{k_1}{\nu^2}\overline{A}^3 + \frac{k_2}{\nu}\overline{A}^2 - k_3\overline{A} + k_4\nu$$

Schlögl system



$$\frac{k_1}{\nu^2} = 2.5 \times 10^{-4}, \quad \frac{k_2}{\nu} = 0.18, \; k_3 = 37.5, \; k_4 \nu = 2200 \quad [\text{min}^{-1}]$$

Schlögl system



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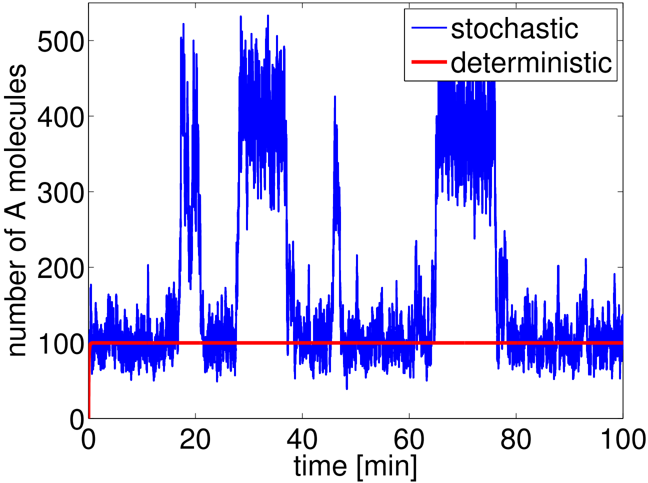

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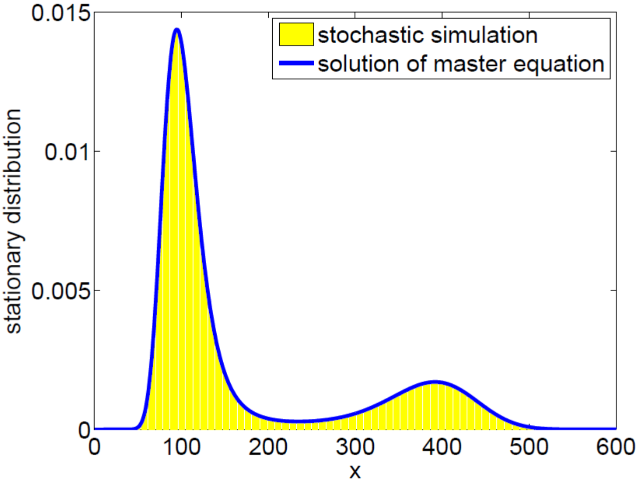
Schlögl system



$$\frac{k_1}{\nu^2} = 2.5 \times 10^{-4}, \quad \frac{k_2}{\nu} = 0.18, \quad k_3 = 37.5, \quad k_4 \nu = 2200 \quad [\text{min}^{-1}]$$

Self-induced stochastic resonance

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Schnakenberg system

$$2A + B \xrightarrow{k_1} 3A \qquad \emptyset \underset{}{\overset{k_2,k_3}{\rightleftharpoons}} A \qquad \emptyset \xrightarrow{k_4} B$$

Concentration:

$$\frac{da}{dt} = k_1 a^2 b + k_2 - k_3 a$$

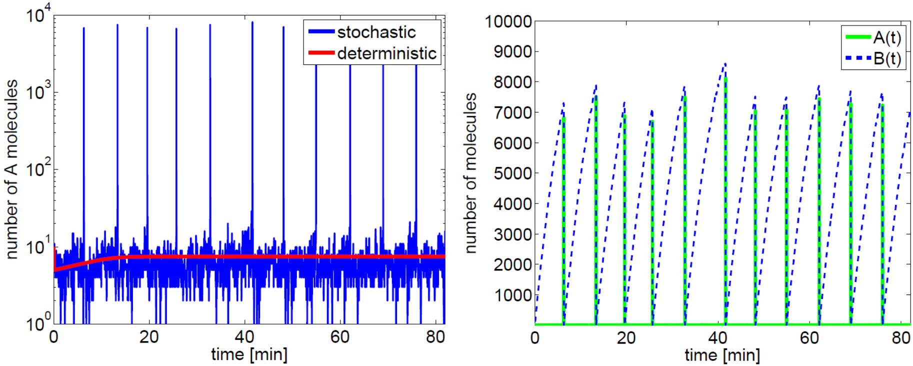
$$\frac{db}{dt} = -k_1 a^2 b + k_4$$

Average numbers of molecules:

$$\frac{d\overline{A}}{dt} = \frac{k_1}{\nu^2}\overline{A}^2\overline{B} + k_2\nu - k_3\overline{A}$$

$$\frac{d\overline{B}}{dt} = -\frac{k_1}{\nu^2}\overline{A}^2\overline{B} + k_4$$

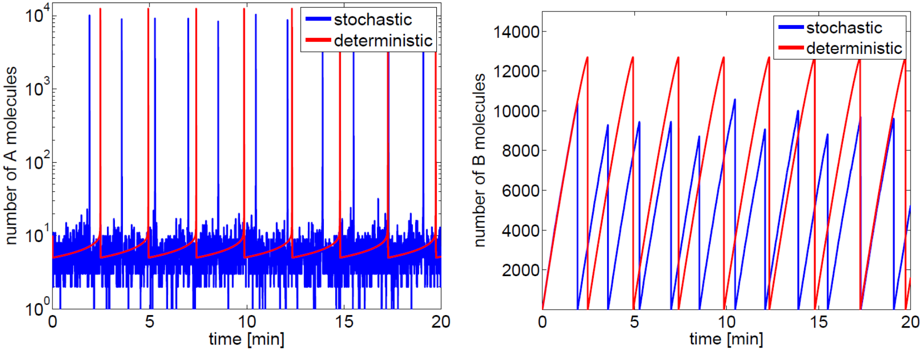
Schnakenberg system



$$\frac{k_1}{\nu^2} = 4 \times 10^{-5}, \;\; k_2\nu = 50, \;\; k_3 = 10, \;\; k_4\nu = 25 \quad [\text{sec}^{-1}]$$

$$A(0) = 10, \quad B(0) = 10$$

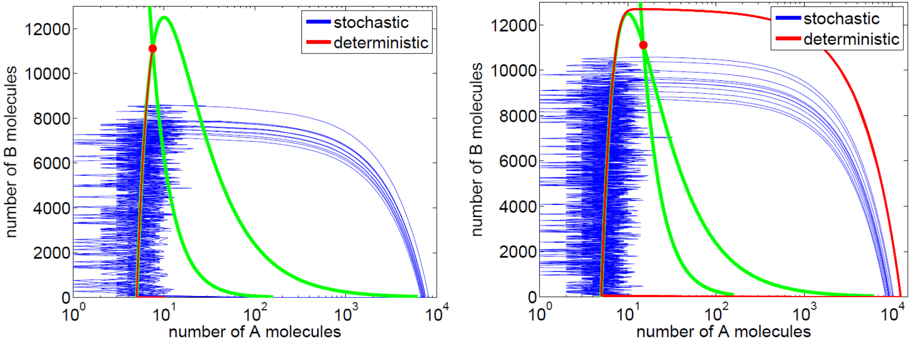
Schnakenberg system



$$\frac{k_1}{\nu^2} = 4 \times 10^{-5}, \; k_2\nu = 50, \; k_3 = 10, \; k_4\nu = 100 \quad [\text{sec}^{-1}]$$

$$A(0) = 10, \quad B(0) = 10$$

Schnakenberg system



$k_4\nu = 25\ \text{sec}^{-1}$ $\qquad$ $k_4\nu = 100\ \text{sec}^{-1}$

Stochastic differential equations (SDE)

$$X(t + \mathrm{d}t) = X(t) + f(X(t), t)\,\mathrm{d}t + g(X(t), t)\,\mathrm{d}W$$

$\mathrm{d}W$ ... white noise, $\mathrm{d}W \approx \sqrt{\Delta t}\xi$, with $\xi \sim N(0, 1)$

Simulation algorithm

$X(0) = x_0$, $\Delta t > 0$ small

(a6) $\xi \sim N(0, 1)$

(b6) $X(t + \Delta t) = X(t) + f(X(t), t)\Delta t + g(X(t), t)\sqrt{\Delta t}\xi$

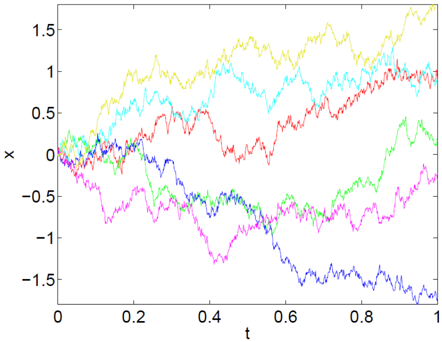
Set $t := t + \Delta t$ and go to (a6)

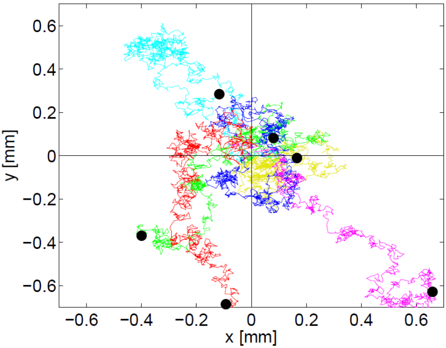
Example 1: $f(x,t) = 0$, $g(x,t) = 1$

Trajectories:

$$X(t + \mathrm{d}t) = X(t) + \mathrm{d}W$$

$$X(t + \mathrm{d}t) = X(t) + \mathrm{d}W_1$$
$$Y(t + \mathrm{d}t) = Y(t) + \mathrm{d}W_2$$

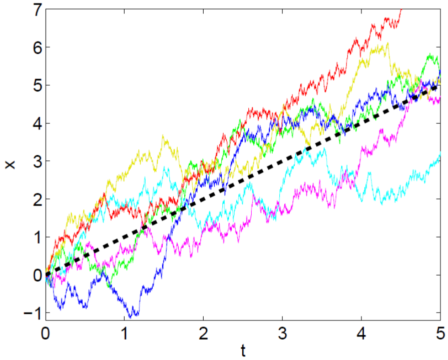




Example 2: $f(x,t) = 1$, $g(x,t) = 1$

Trajectories:

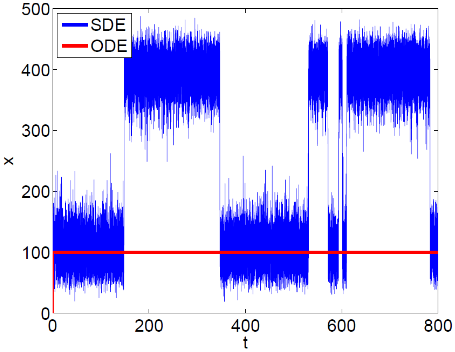
$$X(t + \mathrm{d}t) = X(t) + \mathrm{d}t + \mathrm{d}W$$



Example 3: two favourable states

Trajectories:

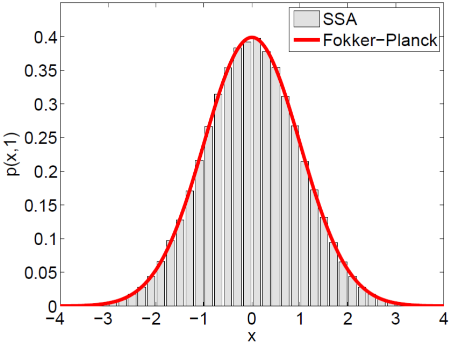
$$f(x,t) = -k_1 x^3 + k_2 x^2 - k_3 x + k_4, \quad g(x,t) = k_5$$
$$k_1 = 10^{-3},\ k_2 = 0.75,\ k_3 = 165,\ k_4 = 10^4,\ k_5 = 200,$$
$$X(t + \mathrm{d}t) = X(t) + f(X(t),t)\,\mathrm{d}t + g(X(t),t)\,\mathrm{d}W$$



Example 1: $f = 0$, $g = 1$ (revisited)

Stationary probability distribution:

$X(t + \mathrm{d}t) = X(t) + \mathrm{d}W$



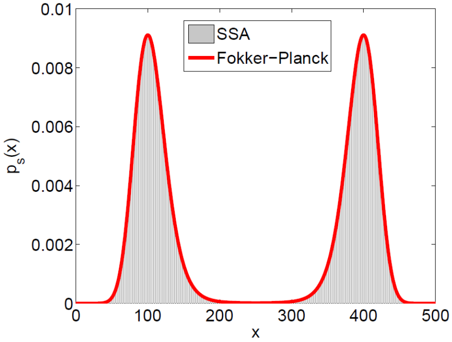
Example 3: two favourable states (revisited)

Stationary probability distribution:

$$f(x,t) = -k_1 x^3 + k_2 x^2 - k_3 x + k_4, \quad g(x,t) = k_5$$

$$k_1 = 10^{-3},\ k_2 = 0.75,\ k_3 = 165,\ k_4 = 10^4,\ k_5 = 200,$$

$$X(t + \mathrm{d}t) = X(t) + f(X(t),t)\,\mathrm{d}t + g(X(t),t)\,\mathrm{d}W$$



Example 3: two favourable states (revisited)

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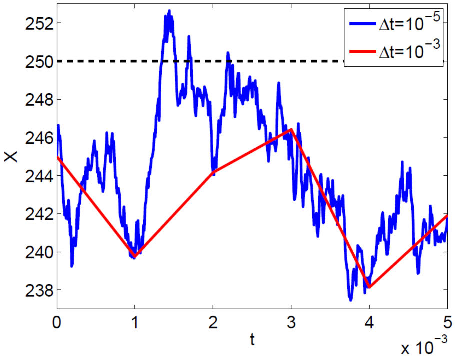
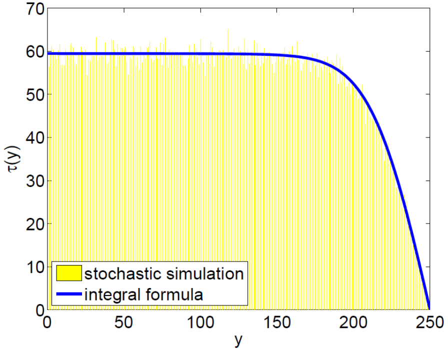
Mean exit time:

$\tau_{\mathrm{sim}} = 64.7$

$\tau_{x_{s_1}} = 59.45$





Stochastic equations for chemical kinetics

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$$\sum_{i=1}^{N} \nu_{ji}^{\mathrm{r}} X_i \xrightarrow{k_j} \sum_{i=1}^{N} \nu_{ji}^{\mathrm{p}} X_i, \qquad j = 1, 2, \ldots, q$$

Notation:

- Well mixed reactor: N chemical species, q reactions $(R_1, \ldots, R_q)$
- $\mathbf{X} = [X_1, \ldots, X_N]$, $X_i(t)$ = number of molecules, $i = 1, \ldots, N$
- $\alpha_j(x)$ is propensity function of reaction R_j, $j = 1, \ldots, q$ ($\alpha_j(\mathbf{x})\,\mathrm{d}t$ = probability that one reaction R_j occurs in $[t, t + \mathrm{d}t)$, given $\mathbf{X}(t) = \mathbf{x}$)
- $\nu_{ji} = \nu_{ji}^{\mathrm{p}} - \nu_{ji}^{\mathrm{r}}$, change of X_i during reaction R_j,
- $\boldsymbol{\nu}_j = [\nu_{j1}, \ldots, \nu_{jN}]$
- $p(\mathbf{x}, t)$ = probability that $\mathbf{X}(t) = \mathbf{x}$

Stochastic equations for chemical kinetics

Chemical master equation (CME) – exact

$$\frac{\partial}{\partial t} p(\mathbf{x}, t) = \sum_{j=1}^{q} \left[\alpha_j(\mathbf{x} - \boldsymbol{\nu}_j) p(\mathbf{x} - \boldsymbol{\nu}_j, t) - \alpha_j(\mathbf{x}) p(\mathbf{x}, t) \right]$$

Chemical Langevin equation (CLE) – approximate

$$\mathrm{d}X_i = f_i(\mathbf{X}(t))\,\mathrm{d}t + \sum_{j=1}^{q} d_{ji}(\mathbf{X}(t))\,\mathrm{d}W_j$$

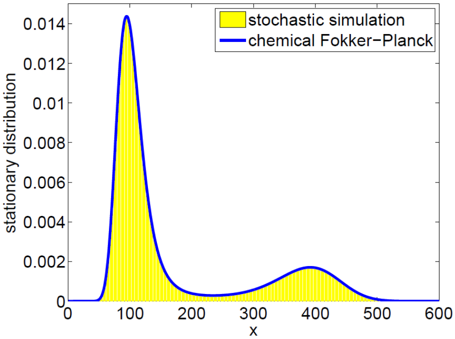
where $f_i(\mathbf{X}(t)) = \sum_{j=1}^{q} \nu_{ji} \alpha_j(\mathbf{X}(t)), \quad d_{ji}(\mathbf{X}(t)) = \nu_{ji} \sqrt{\alpha_j(\mathbf{X}(t))}$

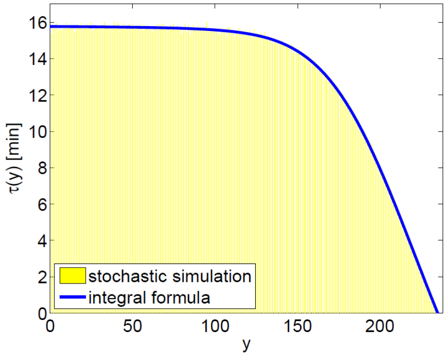
Chemical Fokker-Planck equation (CFP) $\Leftrightarrow$ CLE

$$\frac{\partial}{\partial t} p(\mathbf{x}, t) = \frac{1}{2} \sum_{i=1}^{N} \sum_{k=1}^{N} \frac{\partial^2}{\partial x_i \partial x_k} \left[\left(\sum_{j=1}^{q} d_{ji}(\mathbf{x}) d_{jk}(\mathbf{x}) \right) p(\mathbf{x}, t) \right] - \sum_{i=1}^{N} \frac{\partial}{\partial x_i} \left[f_i(\mathbf{x}) p(\mathbf{x}, t) \right]$$

Schlögl system (revisited)

$$3A \underset{}{\overset{k_1,k_2}{\rightleftharpoons}} 2A \qquad A \overset{k_3,k_4}{\rightleftharpoons} \emptyset$$



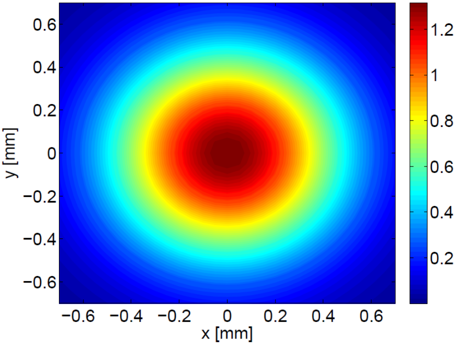


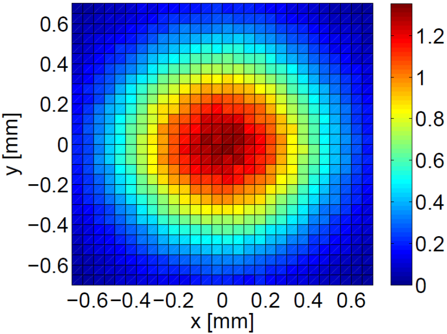
$$\frac{k_1}{\nu^2} = 2.5 \times 10^{-4}, \quad \frac{k_2}{\nu} = 0.18, \quad k_3 = 37.5, \quad k_4\nu = 2200 \quad [\text{min}^{-1}]$$

$$x_{s_1} = 95, \; x_u = 235, \; x_{s_2} = 392, \; \tau(x_{s_1}) = 15.6$$

Diffusion – position jump process

$$X(t + \mathrm{d}t) = X(t) + \sqrt{2D}\,\mathrm{d}W_x$$
$$Y(t + \mathrm{d}t) = Y(t) + \sqrt{2D}\,\mathrm{d}W_y$$
$$Z(t + \mathrm{d}t) = Z(t) + \sqrt{2D}\,\mathrm{d}W_z$$





$D = 10^{-4}$ mm^{2}sec^{-1}, $t = 10$ min

10^6 realizations

Reflecting boundary condition

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Simulation algorithm

$X(0) = x_0$, $\Delta t > 0$ small

(a7) $\xi \sim N(0,1)$

(b7) $X(t+\Delta t) = X(t) + \sqrt{2D\Delta t}\xi$

(c7) If $X(t+\Delta t) < 0$ then $X(t+\Delta t) = -X(t) - \sqrt{2D\Delta t}\xi$
If $X(t+\Delta t) > L$ then $X(t+\Delta t) = 2L - X(t) - \sqrt{2D\Delta t}\xi$
Set $t := t + \Delta t$ and go to (a7)

Reflecting boundary condition

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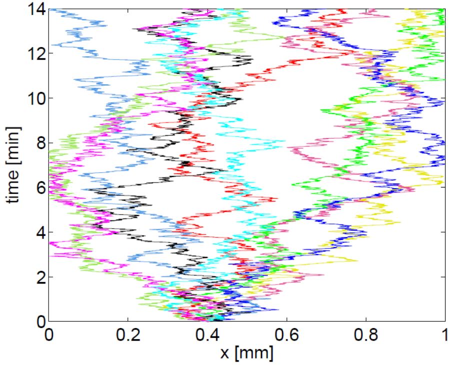
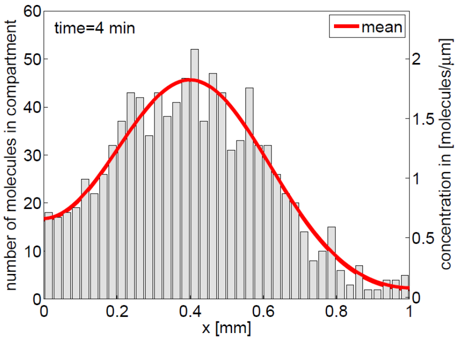
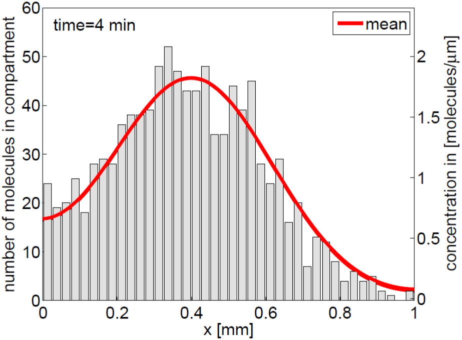


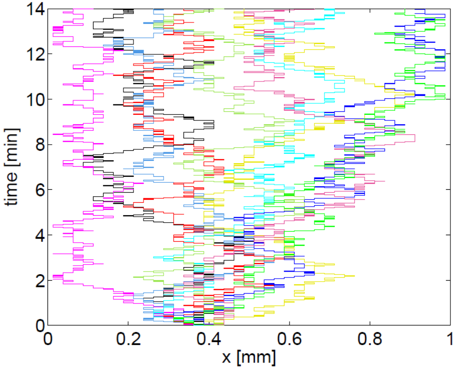


$D = 10^{-4}$ mm^{2}sec^{-1}, $\quad L = 1$ mm, $\quad\quad t = 4$ min, $\quad h = 25\ \mu$m

$X(0) = 0.4$ mm, $\quad \Delta t = 0.1$ sec

Compartment based model





$t = 4$ min

$K = 40,\ h = 1/K,\ d = D/h^2 = 0.16\ \text{sec}^{-1}$

$N_{\rm mol} = 1000,\ A_{16}(0) = A_{17}(0) = 500$

$a(0) = \delta_{0.4}(x)$

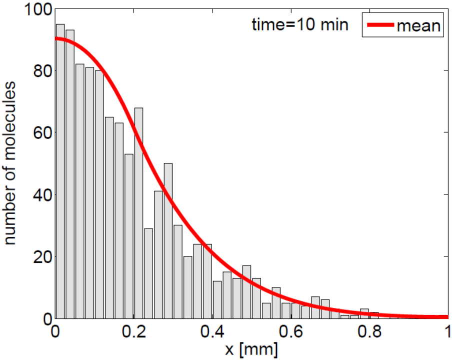
10 realizations

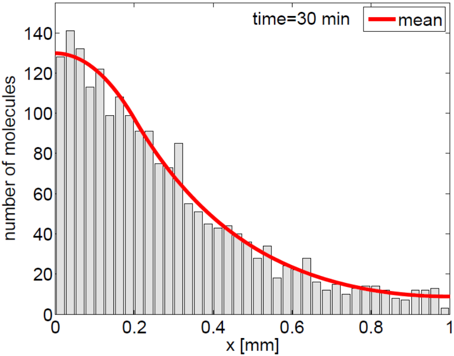
1 molecule

`comp_diff.m`

Compartment based reaction-diffusion

$$A \xrightarrow{k_1} \emptyset \text{ in } [0, L], \qquad \emptyset \xrightarrow{k_p} A \text{ in } [0, L/5],$$





$t = 10$ min $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad$ $t = 30$ min

$K = 40,\ h = 1/K,\ d = D/h^2 = 0.16 \text{ sec}^{-1}$

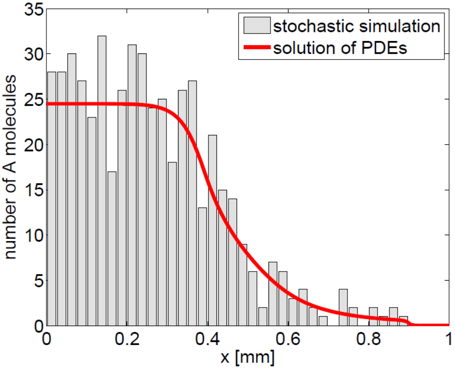
$k_1 = 10^{-3} \text{ sec}^{-1},\ k_p = 0.012\ \mu\text{m}^{-1}\text{sec}^{-1},\ k_2 = k_p h$

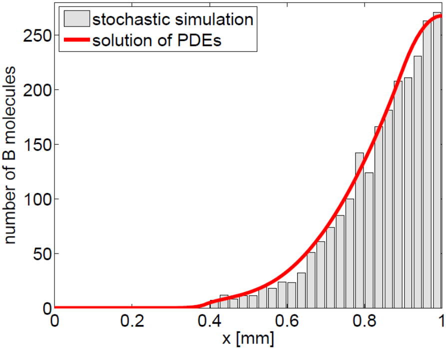
$A_i(0) = 0, \quad a(0) = 0$ `compRD_lin.m`

Compartment based reaction-diffusion

$$2A \xrightarrow{k_1} \emptyset, \quad A + B \xrightarrow{k_2} \emptyset \quad \text{in } [0, L],$$

$$\emptyset \xrightarrow{k_3} A \text{ in } [0, 9L/10], \qquad \emptyset \xrightarrow{k_4} B \text{ in } [2L/5, K],$$





$t = 30$ min

compRD_nonlin.m

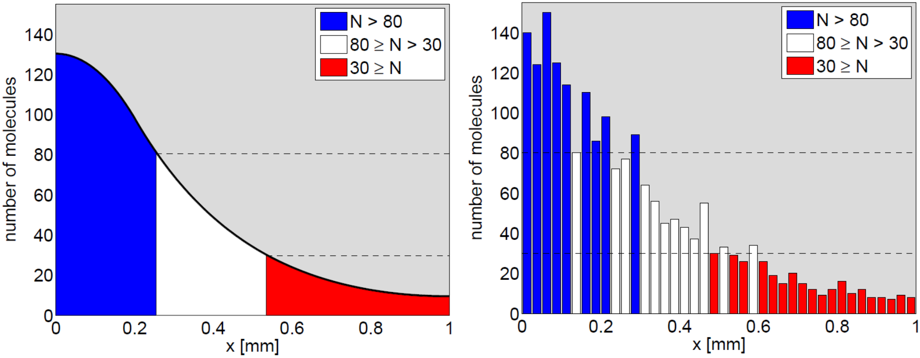
$K = 40,\ h = 1/K,\ d = D/h^2 = 0.16\ \text{sec}^{-1}$

$k_1 = 10^{-3},\ k_2 = 10^{-2},\ k_3 = 1.2,\ k_4 = 1\ \text{sec}^{-1}$ per one compartment

$A(0) = B(0) = 0, \quad a(0) = b(0) = 0$

Pattern formation – French flag

$$A \xrightarrow{k_1} \emptyset \text{ in } [0, L], \qquad \emptyset \xrightarrow{k_p} A \text{ in } [0, L/5], \qquad +\text{diffusion}$$



deterministic

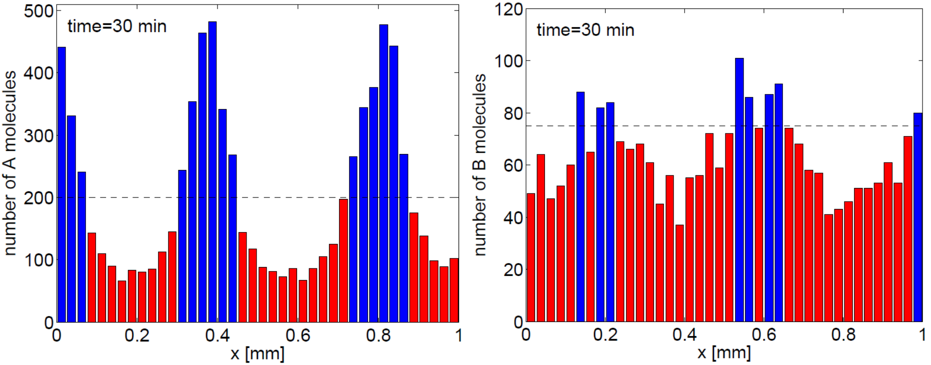
stochastic

Pattern formation – Turing instability

Schnakenberg system

$$2A + B \xrightarrow{k_1} 3A \qquad \emptyset \underset{}{\overset{k_2,k_3}{\rightleftharpoons}} A \qquad \emptyset \xrightarrow{k_4} B$$

$$+ \text{ diffusion } D_A = 10^{-5},\ D_B = 10^{-3}\ [\text{mm}^2\text{sec}^{-1}]$$



$$L = 1 \text{ mm},\ K = 40,\ h = \frac{L}{K} = 25\ \mu\text{m}$$

$$A_i(0) = a_s = 200,\ B_i(0) = b_s = 75$$

Acknowledgement

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This presentation is based on "A practical guide to stochastic simulations of reaction-diffusion processes" written by R. Erban, S.J. Chapman, and P.K. Maini and on lecture notes "Stochastic modelling of biological processes" by R. Erban.

I am thankful to Radek Erban and Philip K. Maini for their support and fruitful discussions about the topics presented during this summer school.

Marie Curie Fellowship, StochDetBioModel

EUROPEAN COMMISSION

The research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013) under REA grant agreement no. 328008.

Thank you for your attention

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Based on lecture notes of Radek Erban
http://www.maths.ox.ac.uk/courses/course/19651/material
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