

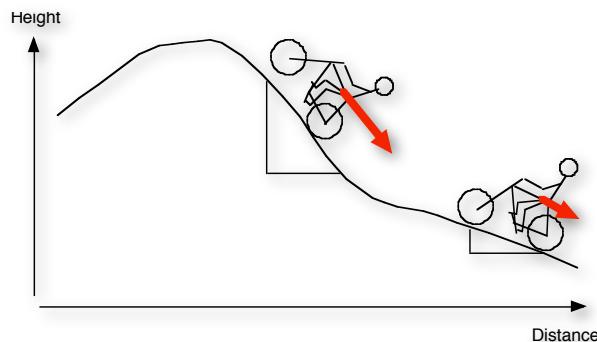
Bioinformatics 3

# V22 – Dynamic Modelling: Rate Equations + Stochastic Propagation

Fri, Jan 20, 2012

# Differential Equations

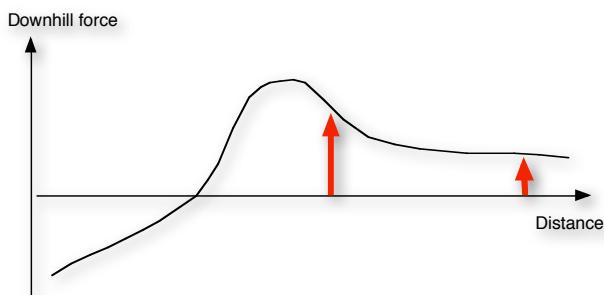
## Energy and Force



Energy increases when you go up the hill

$$E(x) = mgh(x)$$

**Energy:** describes the altitude of the landscape



You need more force for a steeper ascent

$$F(x) = -\frac{dE(x)}{dx}$$

**Force:** describes the change of the altitude, pointing downwards

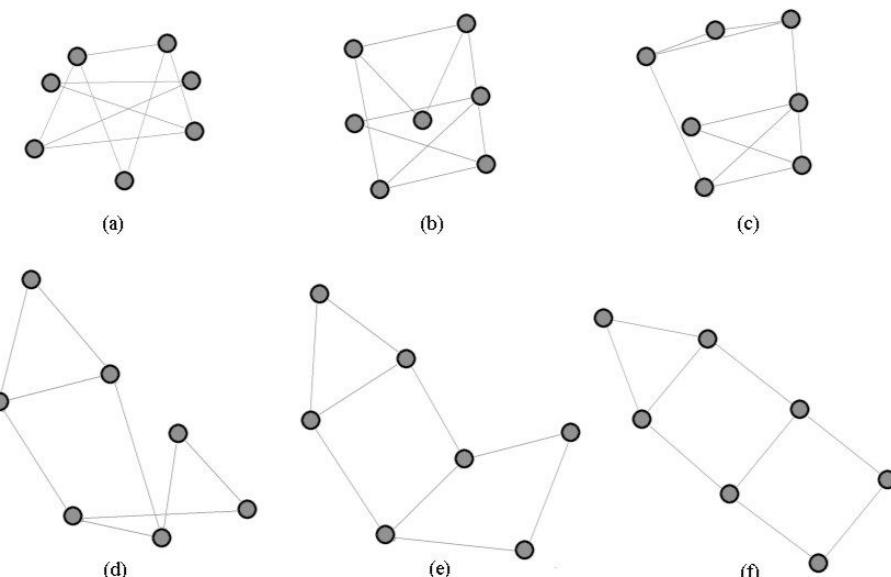
# Force-Directed Graph Layout

**Move** the edges according  
to **local** information  
(=forces) over the **global**  
energy landscape towards  
the steady state  
**(=minimum)**

For a chemical system:  
=> **evolution** of fluxes/  
concentrations from  
**actual** (non-equilibrium)  
concentrations

Also: reactions to perturbations

$$\vec{F}(\vec{x}) = -\nabla E(\vec{x}) = - \begin{pmatrix} \frac{\partial E}{\partial x} \\ \frac{\partial E}{\partial y} \\ \frac{\partial E}{\partial z} \end{pmatrix}$$



# Mass Action Kinetics

Most simple dynamic system: anorganic chemistry

Consider reaction     $A + B \rightleftharpoons AB$

Interesting quantities:

(changes of) densities of A, B, and AB

$$\text{density} = \frac{\text{number of particles}}{\text{unit volume}}$$

$$[A] = \frac{N_A}{V}, \quad \frac{d}{dt}[A](t)$$

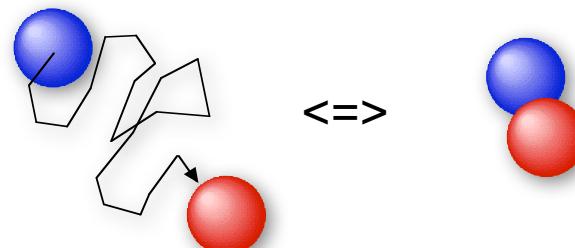
$$1 \text{ mol} = 1 \text{ Mol / Liter} = 6.022 \times 10^{23} \times (0.1 \text{ m})^{-3} = 0.6 \text{ nm}^{-3}$$

**Association:** probability that A finds and reacts with B

=> changes proportional to densities of A and of B

**Dissociation:** probability for AB to break up

=> changes proportional to density of AB



How to put that  
into formulas?

# Mass Action II

Again:



Objective: mathematical description of (= formulas for)  
the changes of  $[A]$ ,  $[B]$ , and  $[AB]$

Consider  $[A]$ :

**Gain** from dissociation  $\mathbf{AB} \Rightarrow \mathbf{A} + \mathbf{B}$

**Loss** from association  $\mathbf{A} + \mathbf{B} \Rightarrow \mathbf{AB}$

$$\frac{d}{dt}[A] = G_A - L_A$$

$\mathbf{AB}$  falls apart

$\Rightarrow G_A$  depends only on  $[AB]$

$\mathbf{A}$  has to find  $\mathbf{B}$

$\Rightarrow L_A$  depends on  $[A]$  and  $[B]$

$$G_A = k_r [AB]$$

phenomenological  
proportionality constant

$$L_A = k_f [A] [B]$$

$$\frac{d}{dt}[A] = k_r [AB] - k_f [A] [B]$$

# Mass Action !!!



For [A]: from above we had

$$\frac{d}{dt}[A] = k_r[AB] - k_f[A][B]$$

For [B]: for symmetry reasons

$$\frac{d}{dt}[B] = \frac{d}{dt}[A]$$

For [AB]: exchange gain and loss

$$\frac{d}{dt}[AB] = -\frac{d}{dt}[A] = k_f[A][B] - k_r[AB]$$

With  $[A](t_0)$ ,  $[B](t_0)$ , and  $[AB](t_0) \Rightarrow$  complete description of the system

time course = initial conditions + dynamics

# A Second Example

Slightly more complex:  $A + 2B \rightleftharpoons AB_2$

Association:

- one A and two B have to come together
- one  $AB_2$  requires two B

$$L_A = k_f [A] [B] [B] = k_f [A] [B]^2 \quad L_B = 2k_f [A] [B]^2$$

Dissociation: one  $AB_2$  decays into one A and two B

$$G_A = k_r [AB_2] \quad G_B = 2k_r [AB_2]$$

Put everything together

$$\frac{d}{dt}[A] = k_r [AB_2] - k_f [A] [B]^2 \quad \frac{d}{dt}[B] = 2\frac{d}{dt}[A] \quad \frac{d}{dt}[AB_2] = -\frac{d}{dt}[A]$$

# Some Rules of Thumb

$A + 2B \rightleftharpoons AB_2$      "A is produced when  $AB_2$  falls apart or  
is consumed when  $AB_2$  is built from one A and two B"

Sign matters: Gains with "+", losses with "-"

Logical conditions: "...from A and B"  
and = "x"    or = "+"

Stoichiometries:    one factor for each educt ( $\Rightarrow [B]^2$ )  
prefactors survive

Mass conservation: terms with "-" have to show up with "+", too

$$\frac{d}{dt}[A] = k_r [AB_2] - k_f [A] [B]^2 \quad \frac{d}{dt}[B] = 2 \frac{d}{dt}[A] \quad \frac{d}{dt}[AB_2] = -\frac{d}{dt}[A]$$

# A Worked Example

Lotka-Volterra population model



prey X lives on A



predator Y lives on prey X



predator Y dies

Rates for the reactions

$$\frac{dR_1}{dt} = k_1 A X$$

$$\frac{dR_2}{dt} = k_2 X Y$$

$$\frac{dR_3}{dt} = k_3 Y$$

=> Change of X:

$$\frac{dX}{dt} = +k_1 A X - k_2 X Y + 0$$

	R1	R2	R3
A	-1		
X	1	-1	
Y		1	-1
B			1

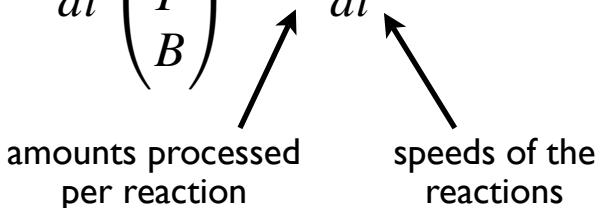
Changes of the metabolites

stoichiometric  
matrix S

# Setting up the Equations

With  $\vec{v} = \frac{d\vec{R}}{dt} = \begin{pmatrix} dR_1/dt \\ dR_2/dt \\ dR_3/dt \end{pmatrix}$  and  $S = \begin{pmatrix} -1 & 0 & 0 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \\ 0 & 0 & 1 \end{pmatrix}$

we get:  $\frac{d\vec{X}}{dt} = \frac{d}{dt} \begin{pmatrix} A \\ X \\ Y \\ B \end{pmatrix} = S \frac{d\vec{R}}{dt}$  or  $\frac{dX_i}{dt} = \sum_j S_{ij} \frac{dR_j}{dt}$



Plug in to get:

$$\frac{dA}{dt} = -\frac{dR_1}{dt} = -k_1 A X$$

$$\frac{dX}{dt} = +\frac{dR_1}{dt} - \frac{dR_2}{dt} = k_1 A X - k_2 X Y$$

$$\frac{dB}{dt} = +\frac{dR_3}{dt} = k_3 Y$$

$$\frac{dY}{dt} = +\frac{dR_2}{dt} - \frac{dR_3}{dt} = k_2 X Y - k_3 Y$$

# How Does It Look Like?

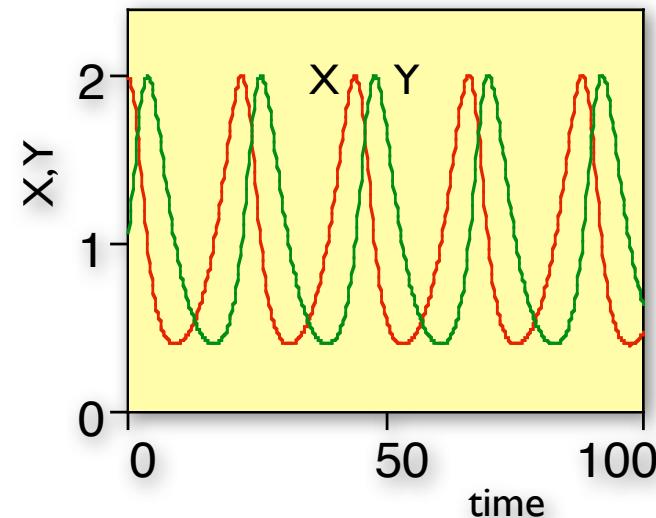
Lotka–Volterra: assume  $A = \text{const}$ ,  $B$  ignored

=> cyclic population changes

$$\frac{dX}{dt} = k_1 AX - k_2 XY$$

$$\frac{dY}{dt} = k_2 XY - k_3 Y$$

$$k_1 = k_2 = k_3 = 0.3$$



**Steady State:** when do the populations **not** change?

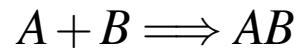
$$\frac{dX}{dt} = \frac{dY}{dt} = 0 \quad => \quad Y = \frac{k_1}{k_2} A \quad X = \frac{k_3}{k_2}$$

Steady state =  
fluxes balanced

With  $k_1 = k_2 = k_3 = 0.3$  and  $A = 1$     =>  $X = Y = 1$

# From rates to differences

Reaction:



Rate equation:

$$\frac{dA}{dt} = -k \cdot A \cdot B = f(A(t), B(t))$$

derivative of  $A(t)$  = some function

Taylor expansion:

$$A(t) = A(0) + t \cdot \frac{dA}{dt}(0) + \frac{t^2}{2} \cdot \frac{d^2A}{dt^2}(0) + \dots = \sum_{k=0} \frac{t^k}{k!} \cdot \frac{d^kA}{dt^k}(0)$$

Linear approximation:

$$\begin{aligned} A(t) &\approx A(0) + t \cdot \frac{dA}{dt}(0) + O(t^2) \\ &\approx A(0) + t \cdot f(A(0), B(0)) + O(t^2) \end{aligned}$$

# From rates to differences II

Linear approximation to (true)  $A(t)$ :

$$\begin{aligned} A(t) &\approx A(0) + t \cdot \frac{dA}{dt}(0) + O(t^2) \\ &\approx A(0) + t \cdot f(A(0), B(0)) + O(t^2) \end{aligned}$$



initial condition      increment      error

For  $t \rightarrow 0$ :

$$t \cdot \frac{dA}{dt}(0) \gg \frac{t^2}{2} \cdot \frac{d^2A}{dt^2}(0) \gg \dots$$

Use linear approximation for small time step  $\Delta t$ :

$$A(t + \Delta t) = A(t) + \Delta t \cdot \frac{dA}{dt}(t)$$

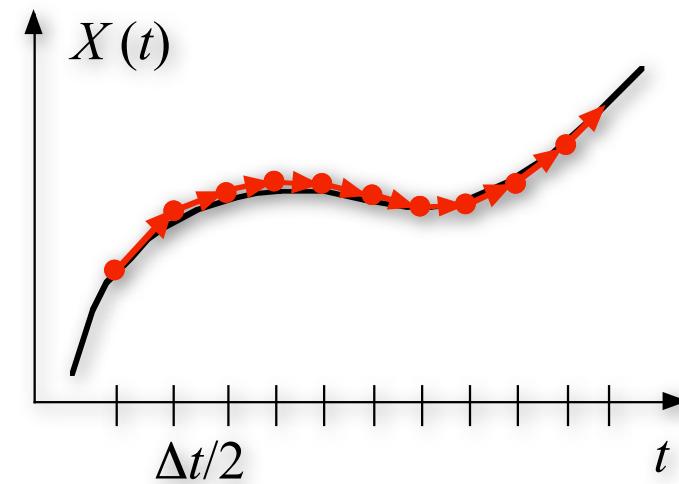
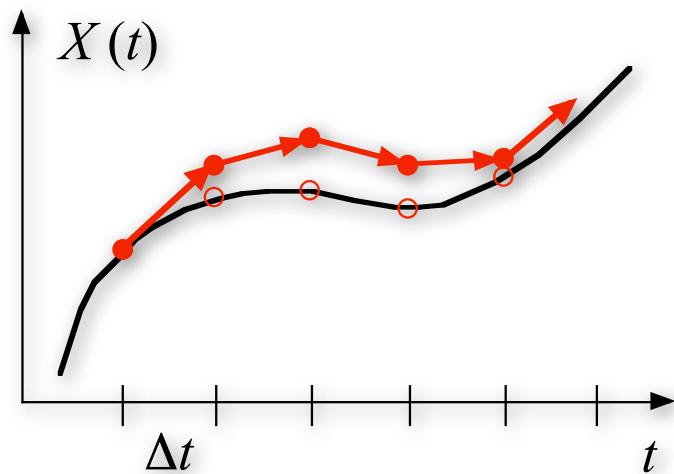
"forward Euler" algorithm

# “Forward Euler” algorithm

General form:  $\vec{X}_i(t + \Delta t) = \vec{X}_i(t) + \Delta t \cdot \vec{f}(\vec{X}_j(t)) + O(\Delta t^2)$

relative error:  $\varepsilon = \frac{\Delta t^2 / 2 \cdot X''}{\Delta t X'} \propto \Delta t$       1st order algorithm

relative error decreases with 1st power of step size  $\Delta t$



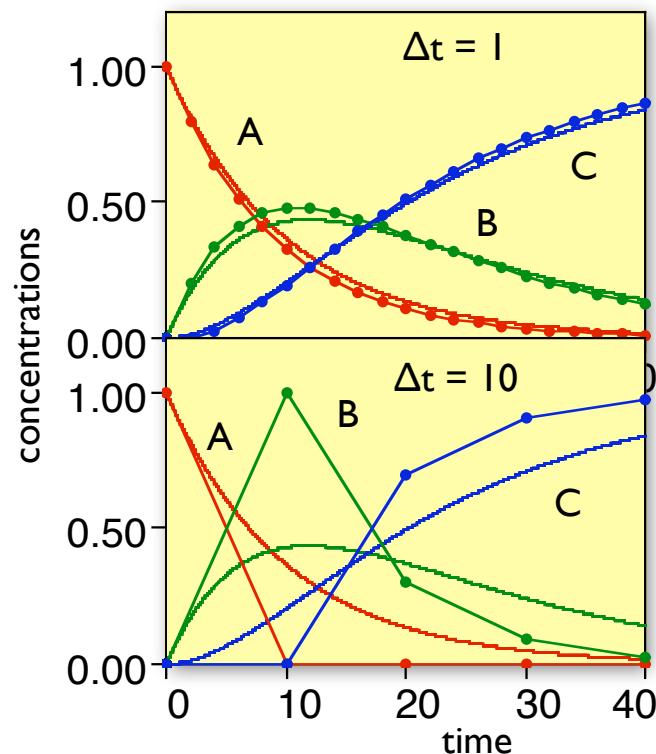
# Example: chained reactions

Reaction:

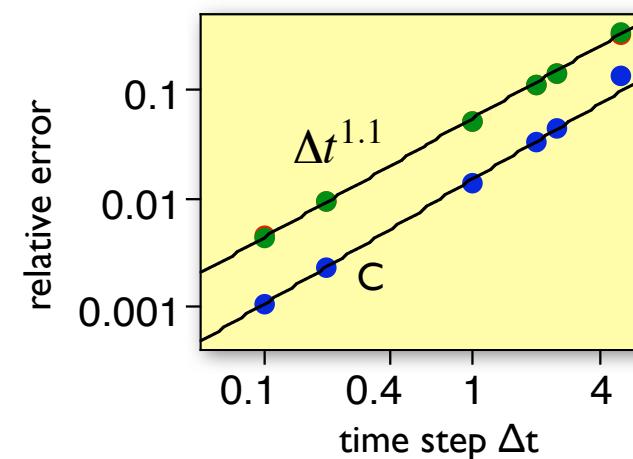


$$k_{AB} = 0.1, \quad k_{BC} = 0.07$$

Time evolution:



Relative error vs.  $\Delta t$   
at  $t = 10$ :



$$\text{runtime} \propto (\Delta t)^{-1}$$

# Example Code: Forward Euler

```
# Initial values
A = 1.0
B = 0.0
C = 0.0

# Rate constants
k1 = 0.1
k2 = 0.07

dt = 0.1
t = 0

# main loop
while(t < 20.0):
    # derivatives
    dR1 = k1 * A
    dR2 = k2 * B

    # add up changes
    A += dt * (-dR1)
    B += dt * (dR1 - dR2)
    C += dt * dR2

    # increment t
    t += dt

    # output
    print t, A, B, C
```

A => B => C

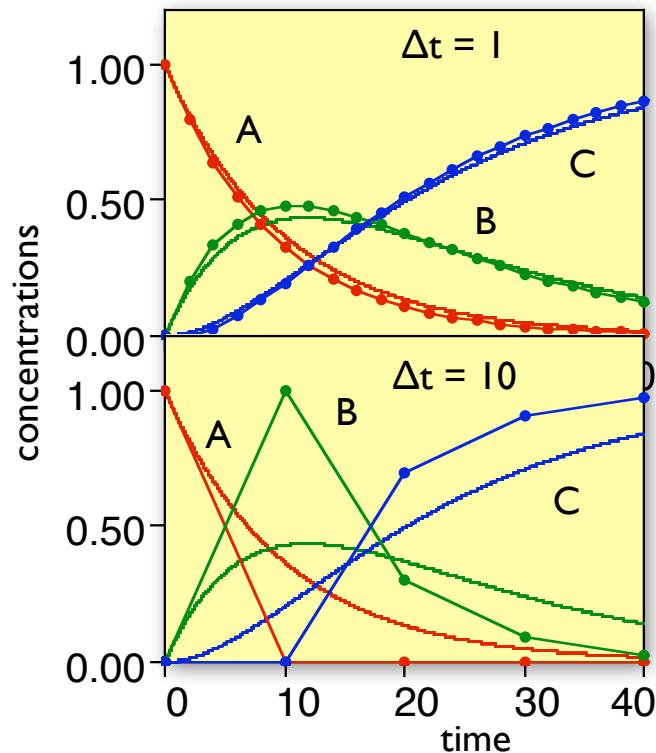
## Iterate:

$$A(t + \Delta t) = A(t) + \Delta t \cdot \frac{dA}{dt}(t)$$

## Important:

first calculate all derivatives,  
then update densities!

# The “correct” time step?



Approximation works for:

$$|\Delta A| = \left| \Delta t \frac{dA}{dt} \right| = |-k_{AB} \cdot A \cdot \Delta t| \ll A$$

$$\Rightarrow \Delta t \ll \frac{1}{\max(k)}$$

Here:  $k_{AB} = 0.1$ ,  $k_{BC} = 0.07$

$$\Rightarrow \Delta t \ll 0.1^{-1} = 10$$

## Note 1:

read “ $\ll$ ” as “a few percent”

## Note 2:

for  $A + B \Rightarrow AB$

consider  $\Delta t \ll (\max(kA, kB))^{-1}$

# From Test Tubes to Cells

Rate equations  $\Leftrightarrow$  description via densities

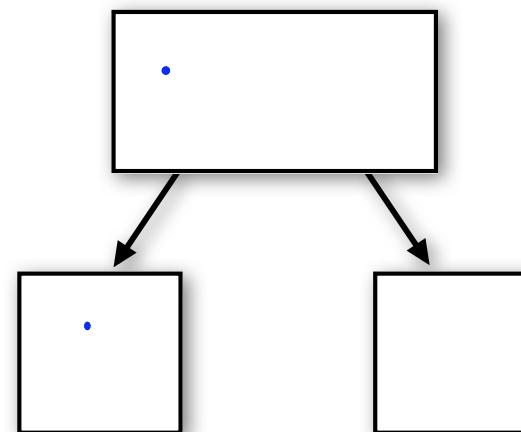
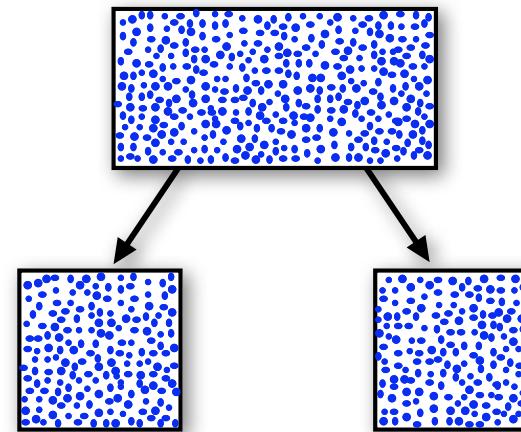
$$\text{density} = \frac{\text{indistinguishable particles}}{\text{volume element}}$$

=> density is a continuum measure,  
independent of the volume element

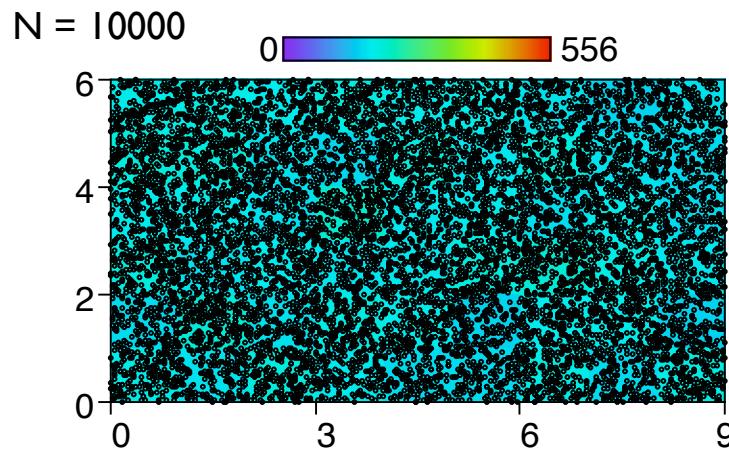
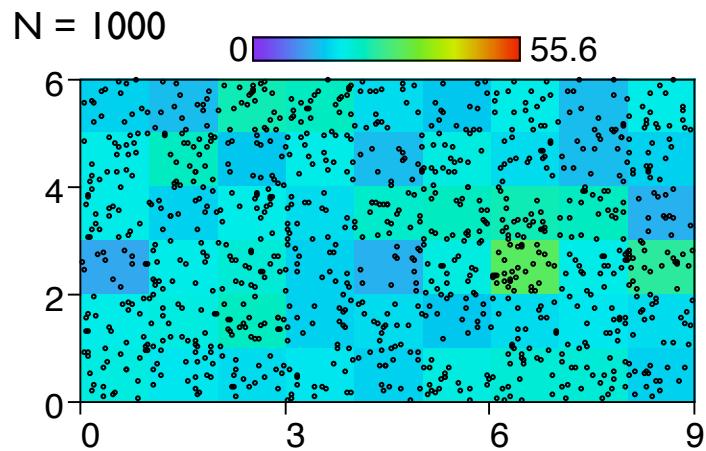
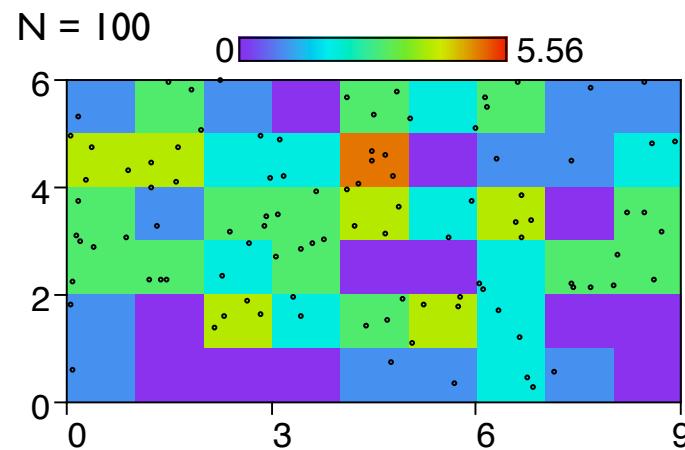
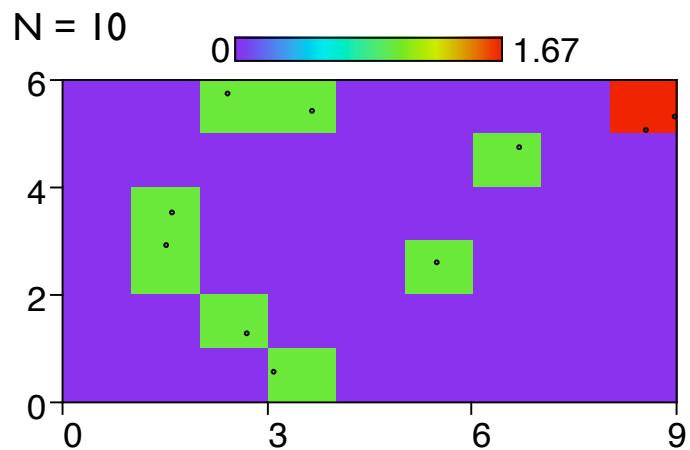
"half of the volume => half of the particles"

When density gets very low  
=> each particle matters

Examples:  
~10 Lac repressors per cell, chemotaxis,  
transcription from a single gene, ...



# Density Fluctuations



# Spread: Poisson Distribution

Probability that  $k$  events occur (event = "a particle is present"):

$$p_k = \frac{\lambda^k}{k!} e^{-\lambda} \quad k = 0, 1, 2, \dots$$

Average:  $\langle k \rangle = \sum k p_k = \lambda$       Variance:  $\sigma^2 = \sum p_k (k - \langle k \rangle)^2 = \lambda$   
 $\sigma = \sqrt{\lambda}$

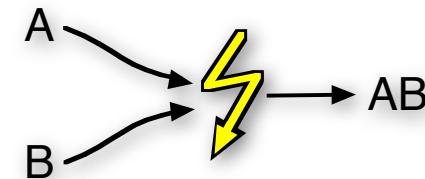
Relative spread (error):  $\frac{\Delta k}{k} = \frac{\sigma}{\langle k \rangle} = \frac{1}{\sqrt{\lambda}}$

Avg. number of particles per unit volume	100	1000	1 Mol
relative uncertainty	10%	3%	1e-12

=> Fluctuations negligible for "chemical" test tube situations

# Reactions in the Particle View

Consider association:



Continuous rate equation:  $\frac{d[AB]}{dt} = k[A][B]$

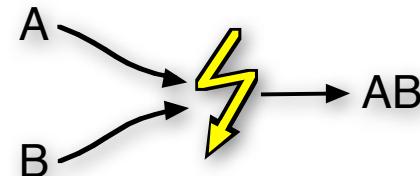
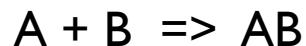
Number of new AB in volume V during  $\Delta t$ :

$$\begin{aligned}\Delta N_{AB} &= \frac{d[AB]}{dt} V \Delta t \\ &= k_{AB} \frac{N_A}{V} \frac{N_B}{V} V \Delta t \\ &= \frac{k_{AB} \Delta t}{V} N_A N_B \\ &= P_{AB} N_A N_B\end{aligned}$$

reaction rate  $k_{AB} \Rightarrow$  reaction probability  $P_{AB}$

# Units!

Consider:



Change in the number of AB:

$$\Delta N_{AB} = P_{AB} N_A N_B$$

Association probability:

$$P_{AB} = \frac{k_{AB} \Delta t}{V}$$

Units: **continuous**

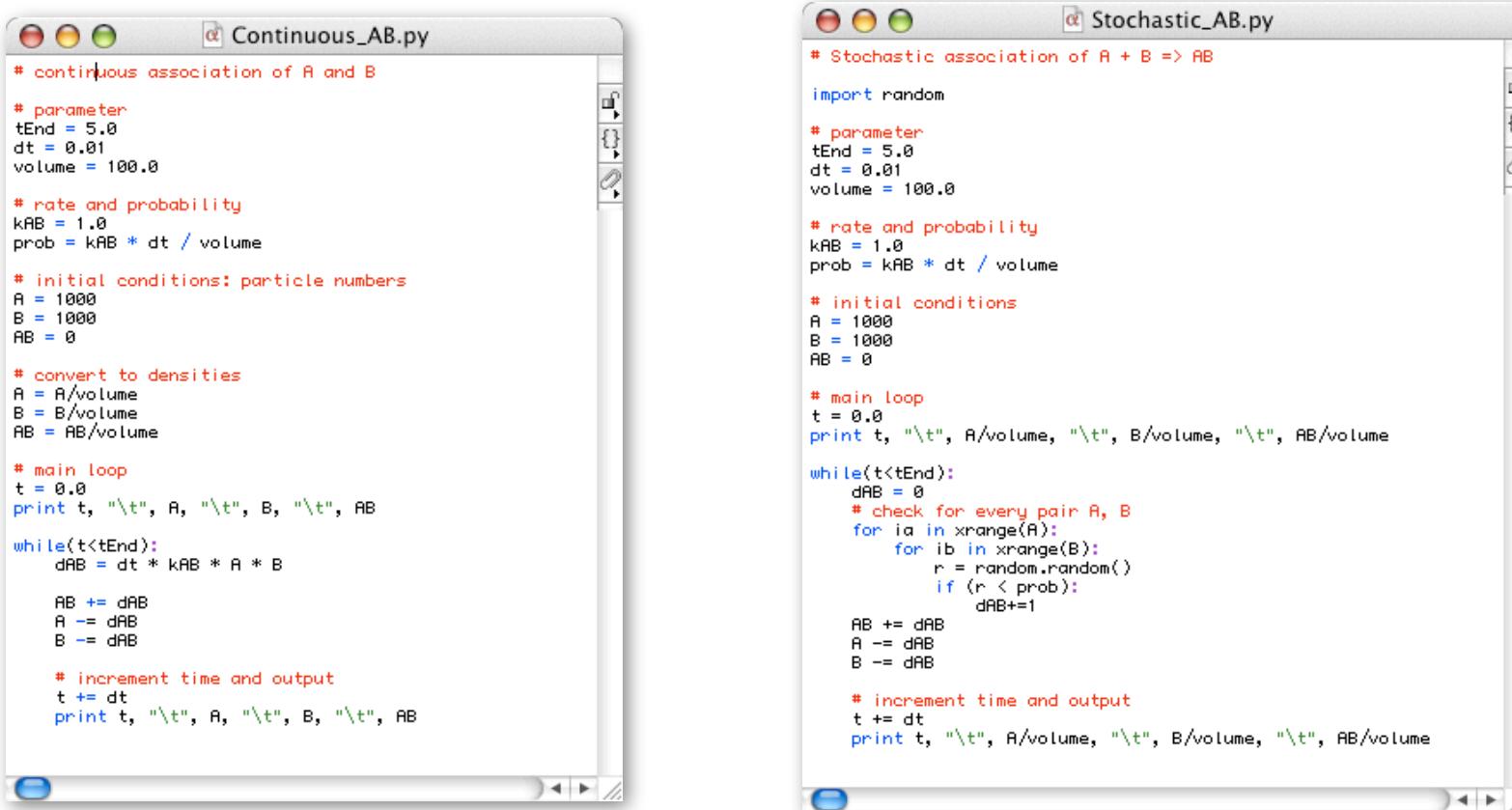
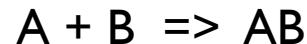
$$\frac{dAB}{dt} = k_{AB} A B$$

$$\left[ \frac{dAB}{dt} \right] = \frac{\text{Mol}}{\text{l s}} \quad [A] = [B] = \frac{\text{Mol}}{\text{l}} \quad \Leftrightarrow \quad [k_{AB}] = \frac{\text{l}}{\text{Mol s}}$$

**stochastic**

$$[N_{AB}] = [N_A] = [N_B] = 1 \quad \Leftrightarrow \quad [P_{AB}] = 1$$

# Direct Implementation



The image shows two side-by-side code editors. The left editor is titled "Continuous\_AB.py" and the right one is titled "Stochastic\_AB.py". Both files contain Python code for simulating the reaction  $A + B \Rightarrow AB$ .

```
# Continuous_AB.py
# continuous association of A and B
# parameter
tEnd = 5.0
dt = 0.01
volume = 100.0

# rate and probability
kAB = 1.0
prob = kAB * dt / volume

# initial conditions: particle numbers
A = 1000
B = 1000
AB = 0

# convert to densities
A = A/volume
B = B/volume
AB = AB/volume

# main loop
t = 0.0
print t, "\t", A, "\t", B, "\t", AB

while(t<tEnd):
    dAB = dt * kAB * A * B

    AB += dAB
    A -= dAB
    B -= dAB

    # increment time and output
    t += dt
    print t, "\t", A, "\t", B, "\t", AB
```

```
# Stochastic_AB.py
# Stochastic association of A + B => AB
import random

# parameter
tEnd = 5.0
dt = 0.01
volume = 100.0

# rate and probability
kAB = 1.0
prob = kAB * dt / volume

# initial conditions
A = 1000
B = 1000
AB = 0

# main loop
t = 0.0
print t, "\t", A/volume, "\t", B/volume, "\t", AB/volume

while(t<tEnd):
    dAB = 0
    # check for every pair A, B
    for ia in xrange(A):
        for ib in xrange(B):
            r = random.random()
            if (r < prob):
                dAB+=1

    AB += dAB
    A -= dAB
    B -= dAB

    # increment time and output
    t += dt
    print t, "\t", A/volume, "\t", B/volume, "\t", AB/volume
```

Note: both versions are didactic implementations

# Example: Chained Reactions



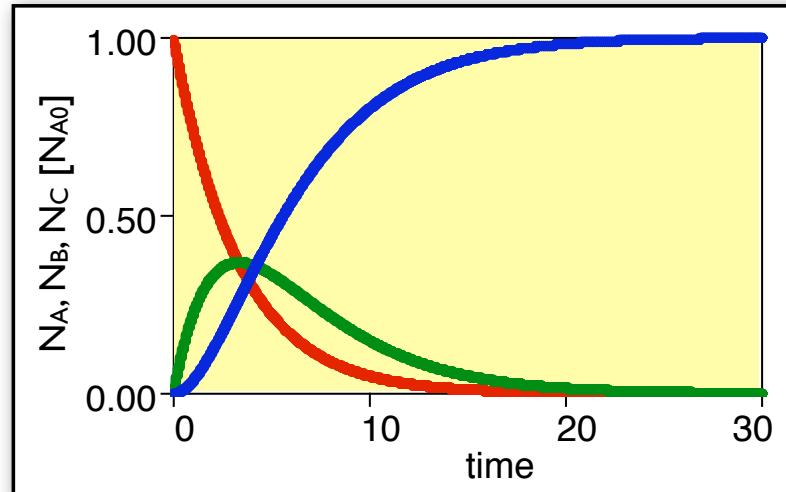
Rates:

$$\frac{dA}{dt} = -k_1 A$$

$$\frac{dB}{dt} = k_1 A - k_2 B$$

$$\frac{dC}{dt} = k_2 B$$

Time course from continuous rate equations (benchmark):



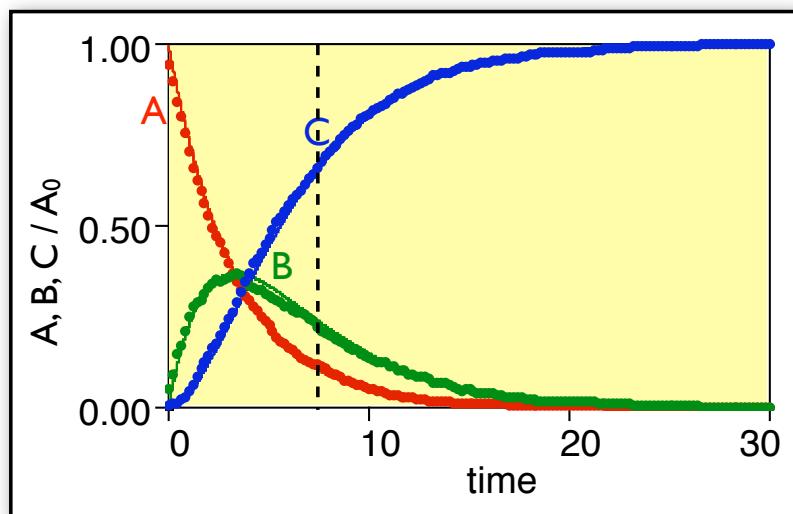
$$k_1 = k_2 = 0.3 \text{ (units?)}$$

# Stochastic Implementation

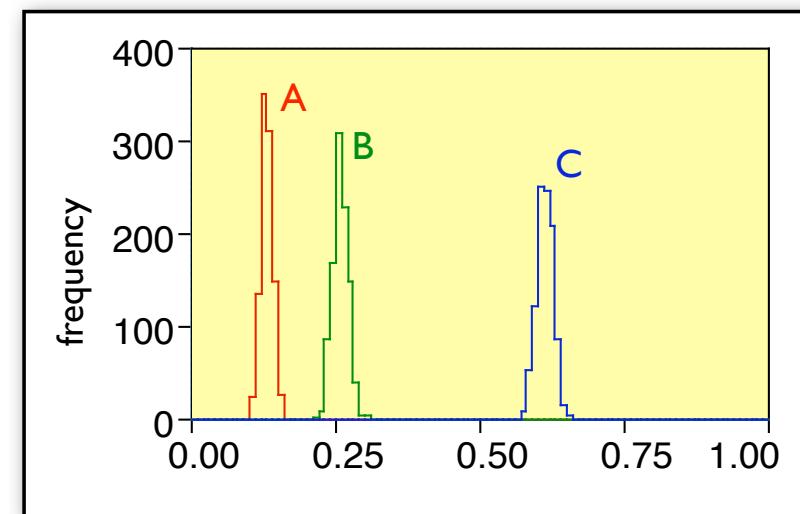
$A \Rightarrow B \Rightarrow C$

$A_0 = 1000$  particles initially

$t = 7$



$k_1 = k_2 = 0.3$

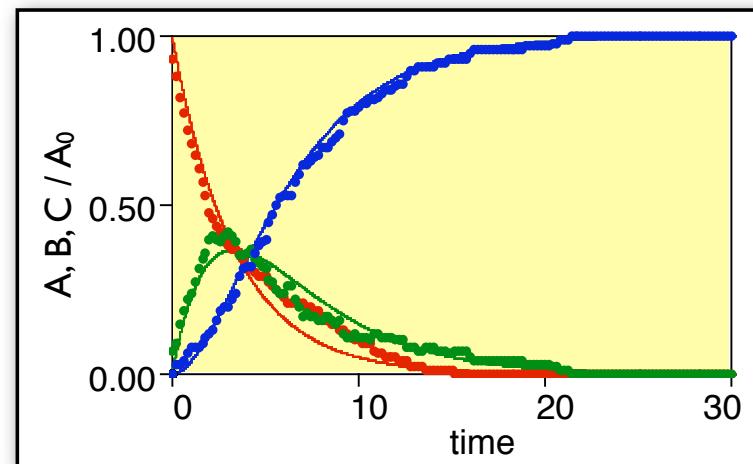
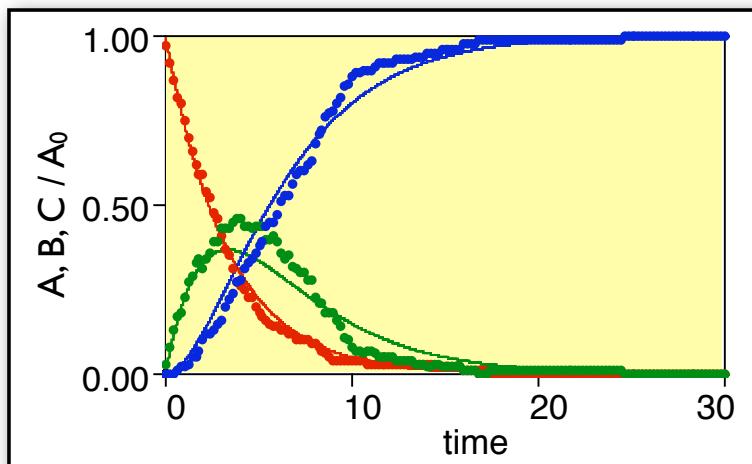
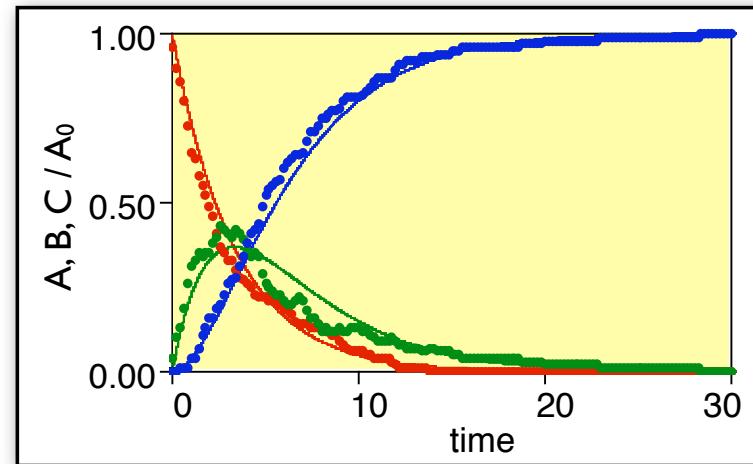
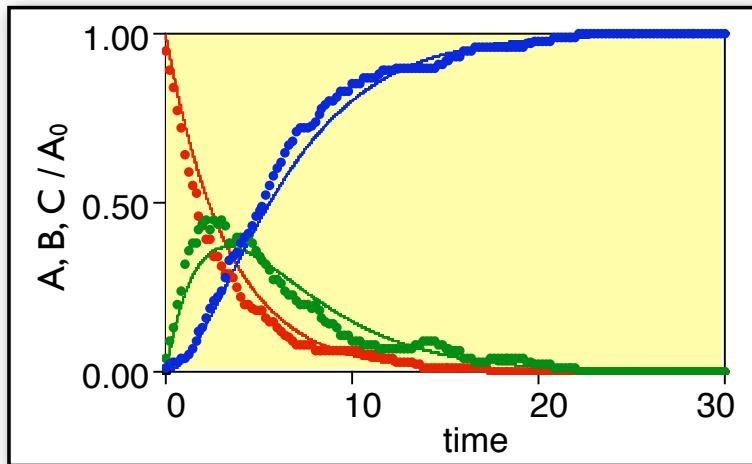


Values at  $t = 7$  (1000 tries)

=> Stochastic version exhibits fluctuations

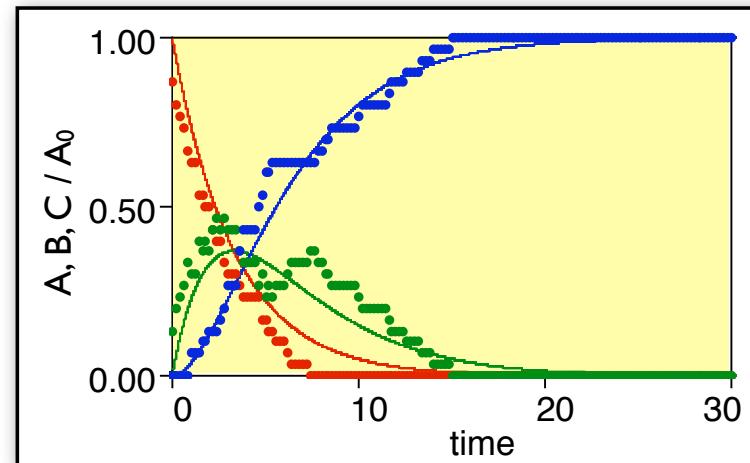
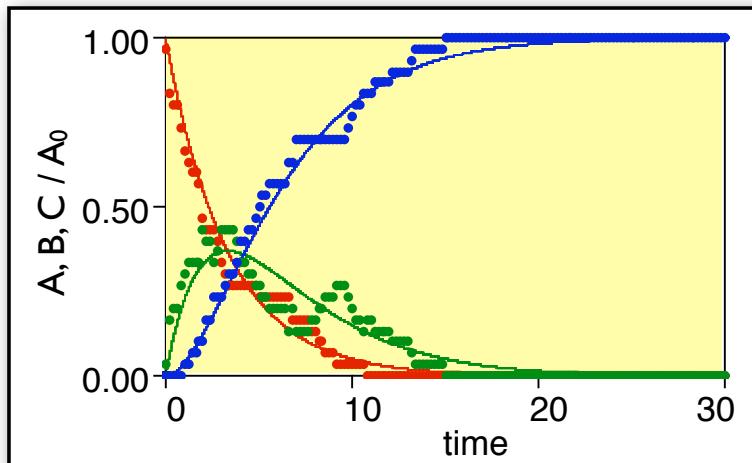
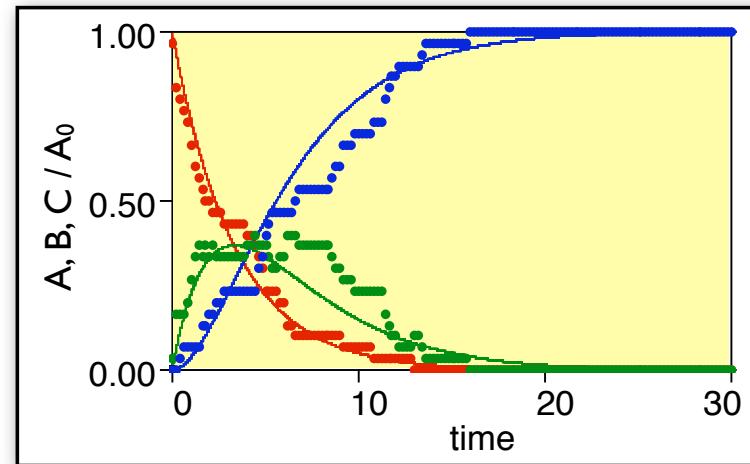
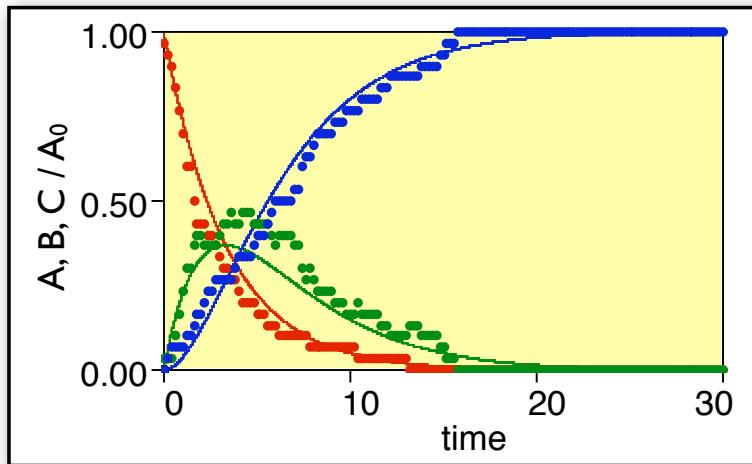
# Less Particles => Larger Fluctuations

$A_0 = 100$



# Even Less Particles

$A_0 = 30$



# Spread vs. Particle Number

Poisson:

$$\text{relative fluctuations} \propto 1/\sqrt{N}$$

Repeat calculation 1000 times  
and record values at  $t = 7$ .

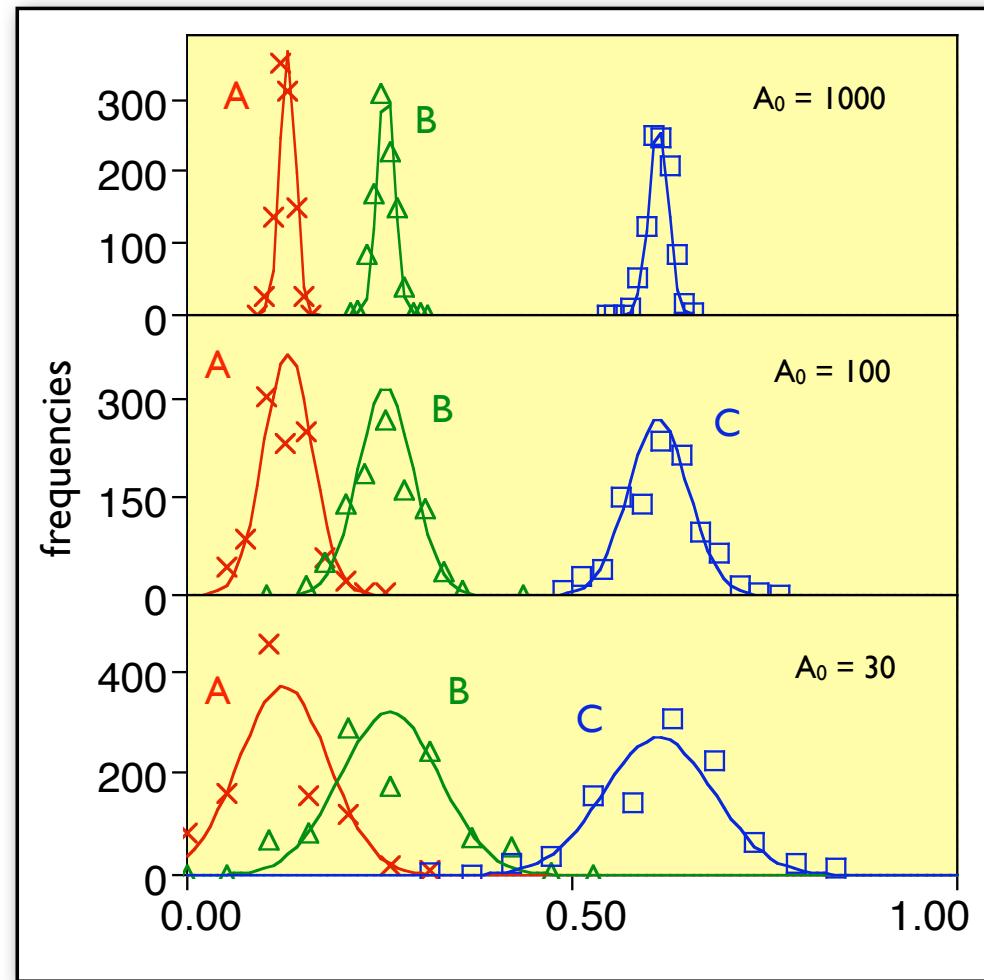
Fit distributions with Gaussian  
(Normal distribution)

$$g(x) = \exp \left[ -\frac{(x - \langle x \rangle)^2}{w/\sqrt{A_0}} \right]$$

$$\langle A \rangle = 0.13, w_A = 0.45$$

$$\langle B \rangle = 0.26, w_B = 0.55$$

$$\langle C \rangle = 0.61, w_C = 0.45$$



# Stochastic Propagation

## Naive implementation:

```
For every timestep:  
events = 0  
For every possible pair of A, B:  
    get random number r ∈ [0, 1)  
    if r ≤ PAB:  
        events++  
    AB += events  
    A, B -= events
```

## Problems?

- + very simple
- + direct implementation of the underlying process
- runtime  $O(N^2)$
- first order approximation
- one trajectory at a time

=> how to do **better**???

Determine complete probability distribution  
=> Master equation

More efficient propagation  
=> Gillespie algorithm

# A Fast Algorithm

2340

Daniel T. Gillespie

## Exact Stochastic Simulation of Coupled Chemical Reactions

Daniel T. Gillespie\*

Research Department, Naval Weapons Center, China Lake, California 93555 (Received May 12, 1977)

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There are two formalisms for mathematically describing the time behavior of a spatially homogeneous chemical system: The *deterministic approach* regards the time evolution as a continuous, wholly predictable process which is governed by a set of coupled, ordinary differential equations (the "reaction-rate equations"); the *stochastic approach* regards the time evolution as a kind of random-walk process which is governed by a single differential-difference equation (the "master equation"). Fairly simple kinetic theory arguments show that the stochastic formulation of chemical kinetics has a firmer physical basis than the deterministic formulation, but unfortunately the stochastic master equation is often mathematically intractable. There is, however, a way to make exact numerical calculations within the framework of the stochastic formulation without having to deal with the master equation directly. It is a relatively simple digital computer algorithm which uses a rigorously derived Monte Carlo procedure to *numerically simulate* the time evolution of the given chemical system. Like the master equation, this "stochastic simulation algorithm" correctly accounts for the inherent fluctuations and correlations that are necessarily ignored in the deterministic formulation. In addition, unlike most procedures for numerically solving the deterministic reaction-rate equations, this algorithm never approximates infinitesimal time increments  $dt$  by finite time steps  $\Delta t$ . The feasibility and utility of the simulation algorithm are demonstrated by applying it to several well-known model chemical systems, including the Lotka model, the Brusselator, and the Oregonator.

D. Gillespie, J. Phys. Chem. **81** (1977) 2340–2361

# Gillespie – Step 0

Decay reaction:  $A \Rightarrow \emptyset$

Probability for one reaction in  $(t, t+\Delta t)$  with  $A(t)$  molecules =  $A(t) k \Delta t$

Naive Algorithm:

```
A = A0
For every timestep:
    get random number r ∈ [0, 1)
    if r ≤ A*k*dt:
        A = A-1
```

It works, but:  $A*k*dt \ll 1$  for accuracy  
=> many many steps where nothing happens  
=> adaptive stepsize method?

# Gillespie – Step I

**Idea:** Figure out **when** the **next reaction** will take place!

(Inbetween the discrete events nothing happens anyway ... :-)

Suppose  $A(t)$  molecules of in the system at  $t$

$f(A(t), s) = \text{prob. that with } A(t) \text{ molecules the next reaction takes place in } (t+s, t+s+ds) \text{ with } ds \Rightarrow 0$

$g(A(t), s) = \text{prob. that with } A(t) \text{ molecules no reaction occurs in } (t, t+s)$

Then:  $f(A(t), s) ds = g(A(t), s) A(t + s) k ds$

No reaction during  $(t, t+s)$ :

$$f(A(t), s) ds = g(A(t), s) \underbrace{A(t) k ds}_{\text{prob. for reaction in } (t+s, t+s+ds)}$$

# Probability for (No Reaction)

Now we need  $g(A(t), s)$

Extend  $g(A(t), s)$  a little more:

$$g(A(t), s + ds) = g(A(t), s) [1 - A(t + s) k ds]$$

Again  $A(t+s) = A(t)$  and resorting:

$$\lim_{ds \rightarrow 0} \frac{g(A(t), s + ds) - g(A(t), s)}{ds} = \frac{dg(A(t), s)}{ds} = -A(t)k g((A(t), s))$$

With  $g(A, 0) = 1$  ("no reaction during no time")

=> Distribution of waiting times between discrete reaction events:

$$g(A(t), s) = \exp[-A(t)ks]$$

Life time = avg. waiting time:  $s_0 = \frac{1}{kA(t)}$

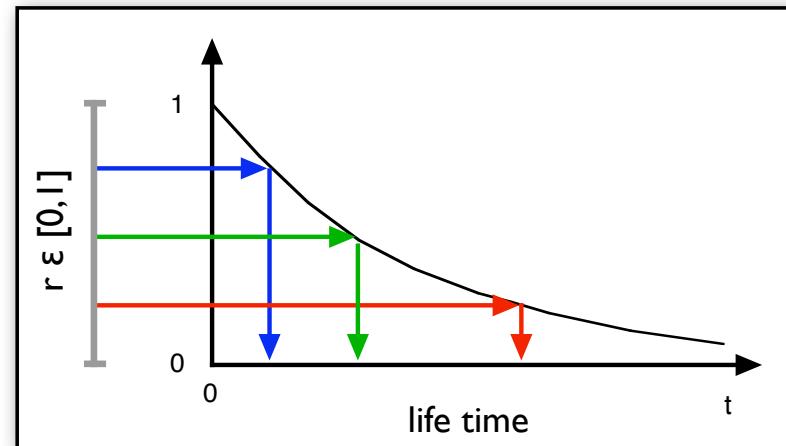
# Exponentially Distributed Random Nrs.

Exponential probability distribution:

$$g(A(t), s) = \exp[-A(t)ks]$$

Solve  $r = \exp[-A(t)ks]$  for s:

$$s = \frac{1}{kA(t)} \ln \left[ \frac{1}{r} \right] = \frac{1}{\alpha_0} \ln \left[ \frac{1}{r} \right]$$



Simple Gillespie algorithm:

```
A = A0
While(A > 0):
    get random number r ∈ [0, 1]
    t = t + s(r)
    A = A-1
```

# Gillespie vs. Naive Algorithm

## Naive:

"What is the probability that an event will occur during the next  $\Delta t$ ?"

=> small fixed timesteps

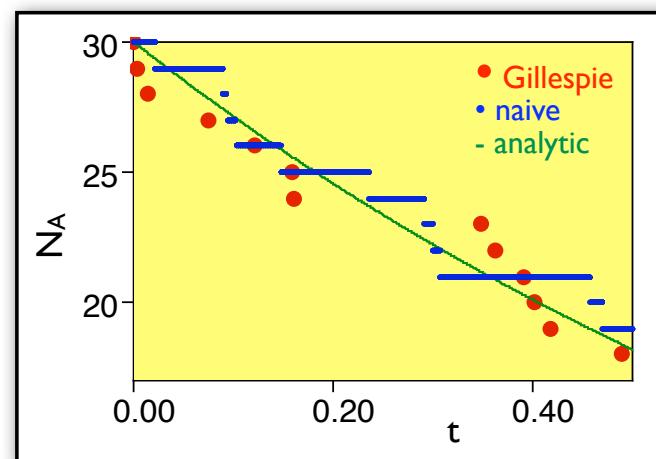
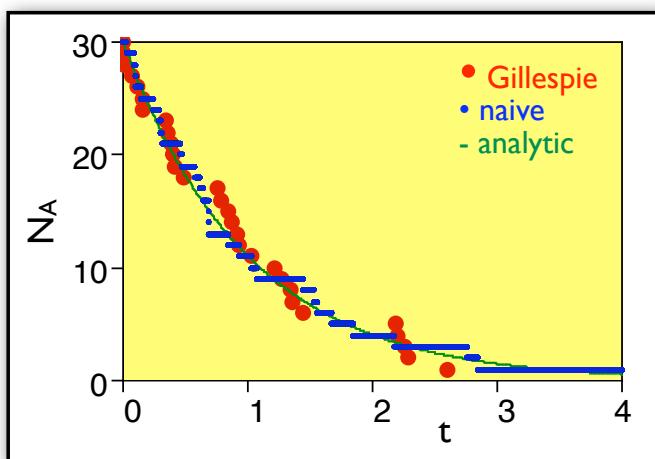
=> 1st order approximation

## Gillespie:

"How long will it take until the next event?"

=> variable timesteps

=> exact



# Gillespie – Complete

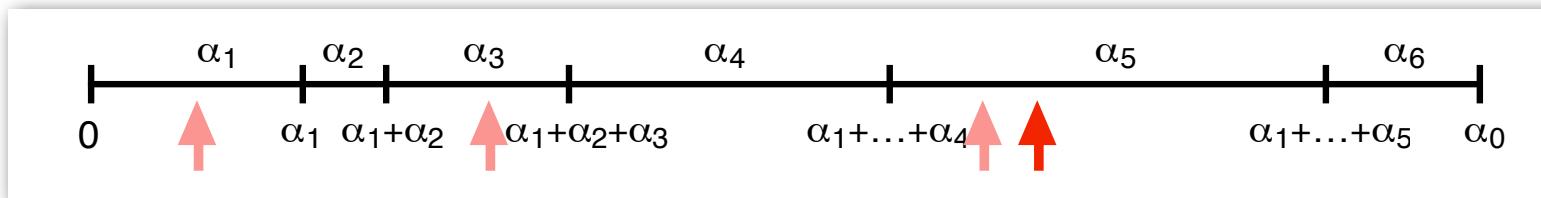
For an arbitrary number of reactions (events):

(i) determine probabilities for the individual reactions:  $\alpha_i \quad i = 1, \dots, N$

$$\text{total probability } \alpha_0 = \sum \alpha_i$$

(ii) get time  $s$  until next event in any of the reactions:  $s = \frac{1}{\alpha_0} \ln \left[ \frac{1}{r_1} \right]$

(iii) Choose the next reaction  $j$  from:  $\sum_{i=1}^{j-1} \alpha_i \leq \alpha_0 r_2 < \sum_{i=1}^j \alpha_i$



(iv) update time and particle numbers

# An Example with Two Species

Reactions:  $A + A \xrightleftharpoons{k_1} \emptyset$      $A + B \xrightleftharpoons{k_2} \emptyset$      $\emptyset \xrightleftharpoons{k_3} A$      $\emptyset \xrightleftharpoons{k_4} B$

Continuous rate equations:  $\frac{dA}{dt} = k_3 - 2A^2k_1 - ABk_2$      $\frac{dB}{dt} = k_4 - ABk_2$

Stationary state:  $A_{ss} = \sqrt{\frac{k_3 - k_4}{2k_1}}$      $B_{ss} = \frac{k_4}{k_2 A}$

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

$$\Rightarrow A_{ss} = 10, \quad B_{ss} = 10$$

Chemical master equation:

$$\begin{aligned}\frac{dp_{n,m}}{dt} = & k_1(n+2)(n+1)p_{n+2,m} - k_1n(n-1)p_{n,m} \\ & + k_2(n+1)(m+1)p_{n+1,m+1} - k_2nm p_{n,m} \\ & + k_3 p_{n-1,m} - k_3 p_{n,m} + k_4 p_{n,m-1} - k_4 p_{n,m}\end{aligned}$$

# Gillespie Algorithm

- (a4) Generate two random numbers  $r_1, r_2$  uniformly distributed in  $(0, 1)$ .
- (b4) Compute the propensity functions of each reaction by  $\alpha_1 = A(t)(A(t)-1)k_1$ ,  
 $\alpha_2 = A(t)B(t)k_2$ ,  $\alpha_3 = k_3$  and  $\alpha_4 = k_4$ . Compute  $\alpha_0 = \alpha_1 + \alpha_2 + \alpha_3 + \alpha_4$ .
- (c4) Compute the time when the next chemical reaction takes place as  $t + \tau$  where

$$\tau = \frac{1}{\alpha_0} \ln \left[ \frac{1}{r_1} \right]. \quad (2.29)$$

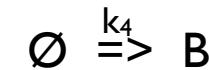
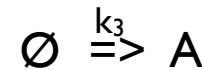
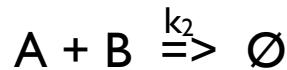
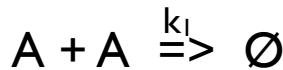
- (d4) Compute the number of molecules at time  $t + \tau$  by

$$A(t + \tau) = \begin{cases} A(t) - 2 & \text{if } 0 \leq r_2 < \alpha_1/\alpha_0; \\ A(t) - 1 & \text{if } \alpha_1/\alpha_0 \leq r_2 < (\alpha_1 + \alpha_2)/\alpha_0; \\ A(t) + 1 & \text{if } (\alpha_1 + \alpha_2)/\alpha_0 \leq r_2 < (\alpha_1 + \alpha_2 + \alpha_3)/\alpha_0; \\ A(t) & \text{if } (\alpha_1 + \alpha_2 + \alpha_3)/\alpha_0 \leq r_2 < 1; \end{cases} \quad (2.30)$$

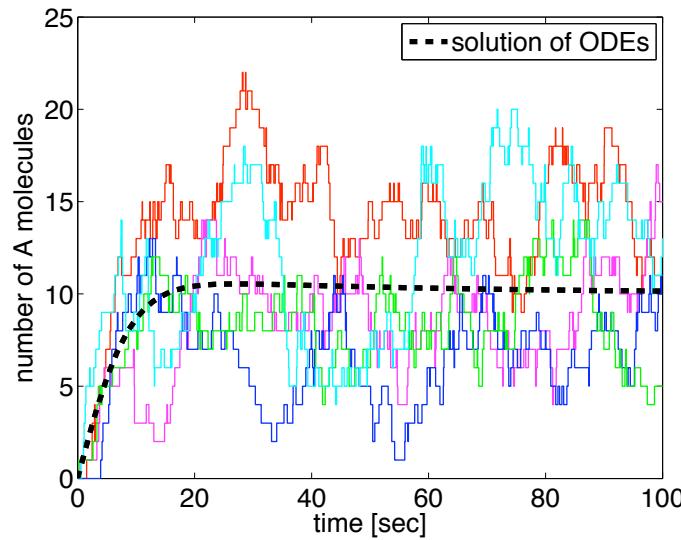
$$B(t + \tau) = \begin{cases} B(t) & \text{if } 0 \leq r_2 < \alpha_1/\alpha_0; \\ B(t) - 1 & \text{if } \alpha_1/\alpha_0 \leq r_2 < (\alpha_1 + \alpha_2)/\alpha_0; \\ B(t) & \text{if } (\alpha_1 + \alpha_2)/\alpha_0 \leq r_2 < (\alpha_1 + \alpha_2 + \alpha_3)/\alpha_0; \\ B(t) + 1 & \text{if } (\alpha_1 + \alpha_2 + \alpha_3)/\alpha_0 \leq r_2 < 1; \end{cases} \quad (2.31)$$

Then continue with step (a4) for time  $t + \tau$ .

# Stochastic Simulation



(a)



(b)

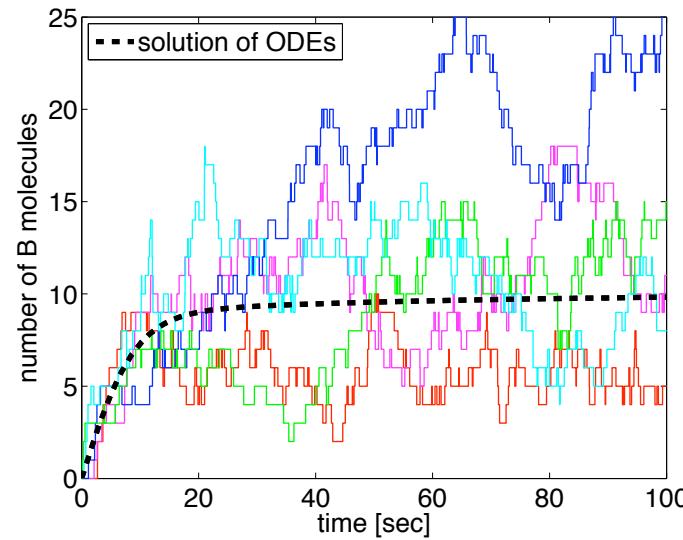
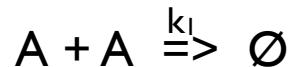
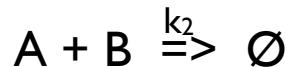


FIG. 2.3. Five realizations of SSA (a4)–(d4). Number of molecules of chemical species A (left panel) and B (right panel) are plotted as functions of time as solid lines. Different colours correspond to different realizations. The solution of (2.33)–(2.34) is given by the dashed line. We use  $A(0) = 0$ ,  $B(0) = 0$ ,  $k_1 = 10^{-3} \text{ sec}^{-1}$ ,  $k_2 = 10^{-2} \text{ sec}^{-1}$ ,  $k_3 = 1.2 \text{ sec}^{-1}$  and  $k_4 = 1 \text{ sec}^{-1}$ .

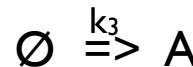
# Distribution of Stationary States



$$k_1 = 10^{-3} \text{ s}^{-1}$$



$$k_2 = 10^{-2} \text{ s}^{-1}$$



$$k_3 = 1.2 \text{ s}^{-1}$$

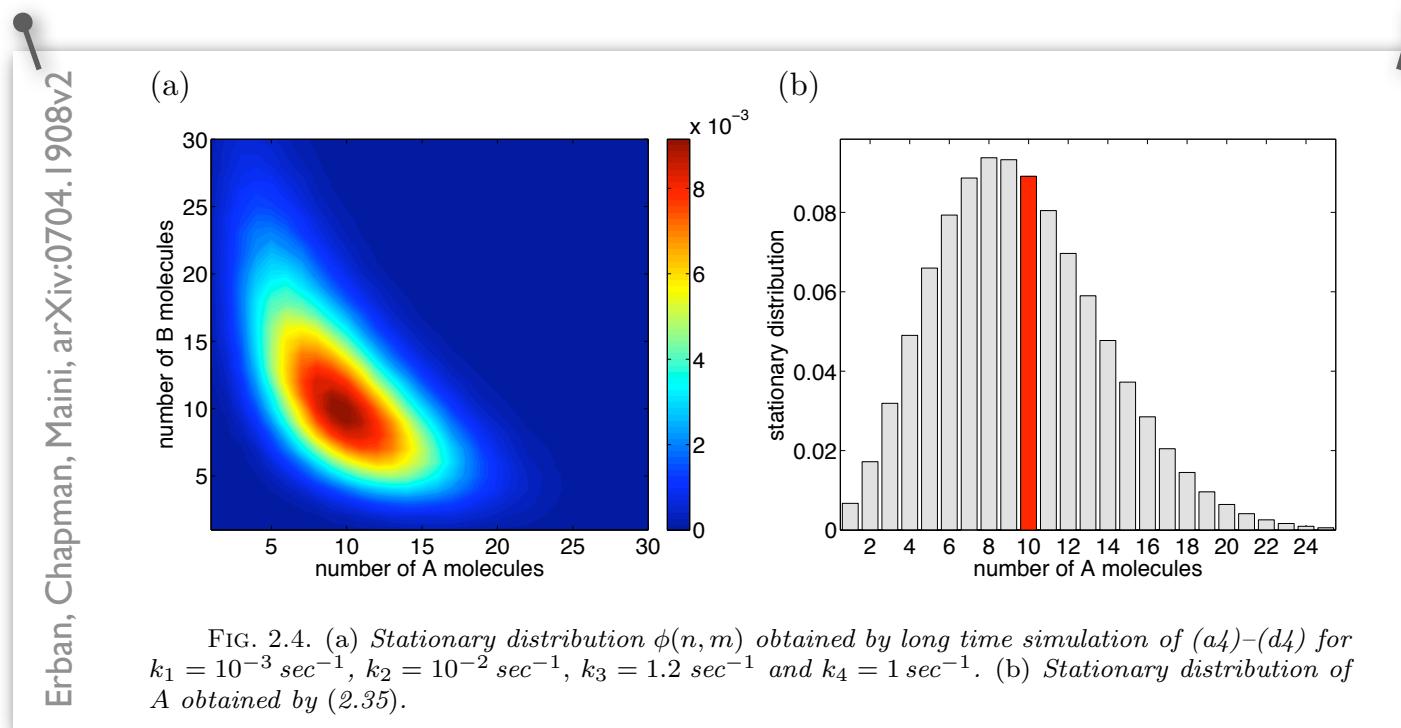


$$k_4 = 1 \text{ s}^{-1}$$

Continuous model:  
 $A_{ss} = 10, B_{ss} = 10$

$\Leftrightarrow$

From long-time Gillespie runs:  
 $\langle A \rangle = 9.6, \langle B \rangle = 12.2$



# Stochastic vs. Continuous

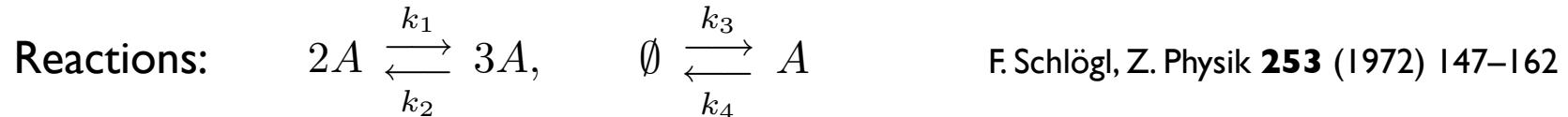
For **many** simple systems:

**stochastic** solution looks like **noisy deterministic** solution

Some more examples, where stochastic description gives **qualitatively different results**

- swapping between two stationary states
- noise-induced oscillations
- Lotka-Volterra with small populations
- sensitivity in signalling

# Two Stationary States



Rate equation:  $\frac{dA}{dt} = k_1 A^2 - k_2 A^3 + k_3 - k_4 A$

With:  $k_1 = 0.18 \text{ min}^{-1}$      $k_2 = 2.5 \times 10^{-4} \text{ min}^{-1}$      $k_3 = 2200 \text{ min}^{-1}$      $k_4 = 37.5 \text{ min}^{-1}$

Stationary states:  $A_{s1} = 100$ ,  $A_{s2} = 400$  (stable)     $A_u = 220$  (unstable)

=> Depending on initial conditions ( $A(0) <> 220$ ),  
the deterministic system goes into  $A_{s1}$  or  $A_{s2}$  (and stays there).

# Two States – Stochastic

Erban, Chapman, Maini, arXiv:0704.1908v2

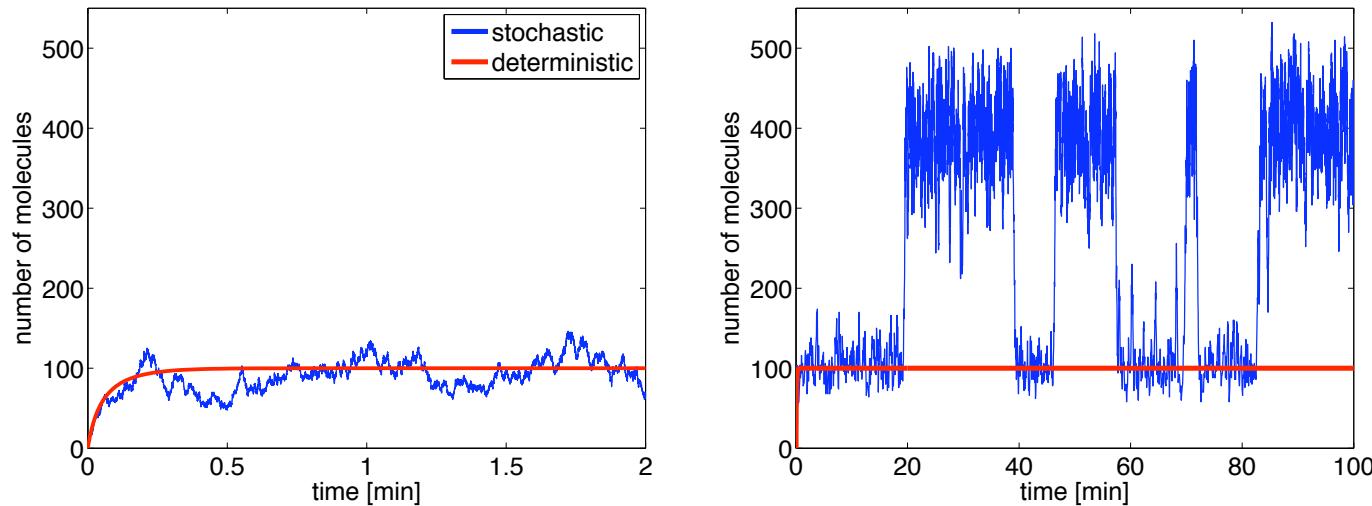
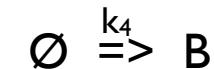
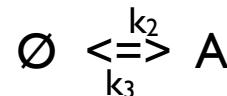
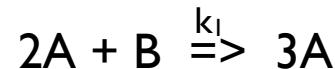


FIG. 5.1. Simulation of (5.1). One realization of SSA (a5)–(d5) for the system of chemical reactions (5.1) (blue line) and the solution of the deterministic ODE (5.2) (red line). (a) The number of molecules of A as a function of time over the first two minutes of simulation. (b) Time evolution over 100 minutes.

=> Fluctuations can drive the system from one stable state into another

# Self-Induced Stochastic Resonance

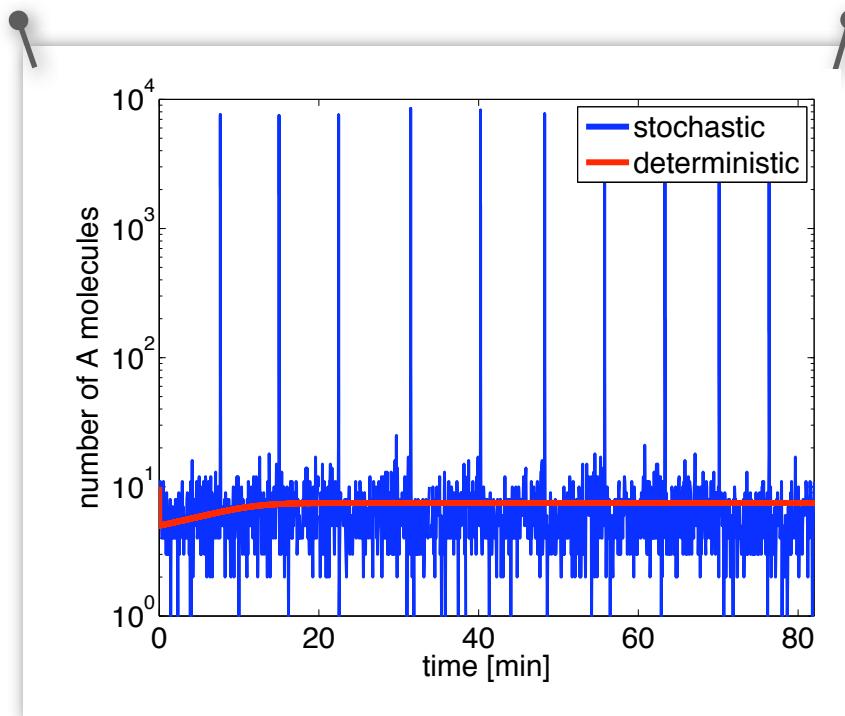
System



Compare the time evolution from initial state  $(A, B) = (10, 10)$  in deterministic and stochastic simulations.

=> **deterministic** simulation converges to and **stays** at fixed point  $(A, B) = (10, 1.1e4)$

=> periodic **oszillations** in the **stochastic** model



=> **DIY in Assignment 10**

# Summary

## Today:

- Mass action kinetics
  - => solving (integrating) differential equations for time-dependent behavior
  - => Forward-Euler: extrapolation, time steps
- Stochastic Description
  - => why stochastic?
  - => Gillespie algorithm
  - => different dynamic behavior

## Next lecture:

- higher order integrators
- stochastic Master equation
- More examples