

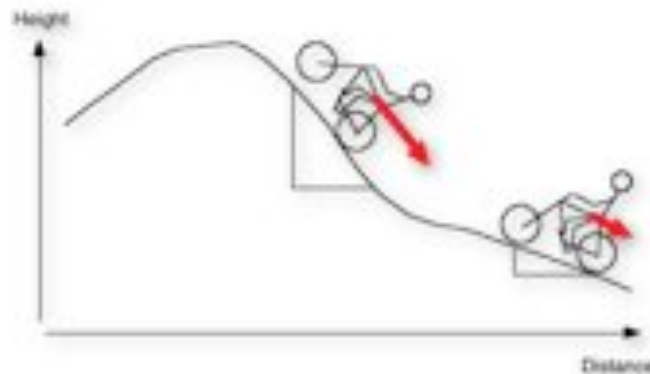
Bioinformatics 3

V21 – Dynamic Modelling: Rate Equations + Stochastic Propagation

Fri, Jan 17, 2014

Differential Equations

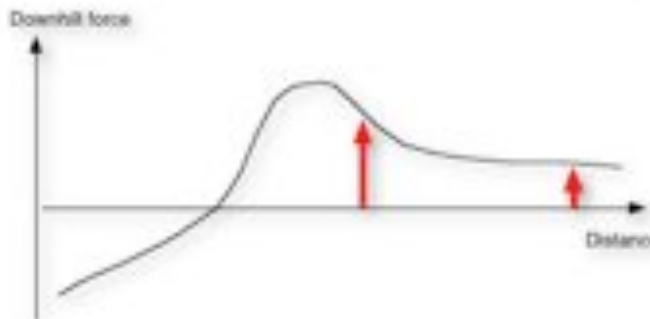
Energy and Force



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

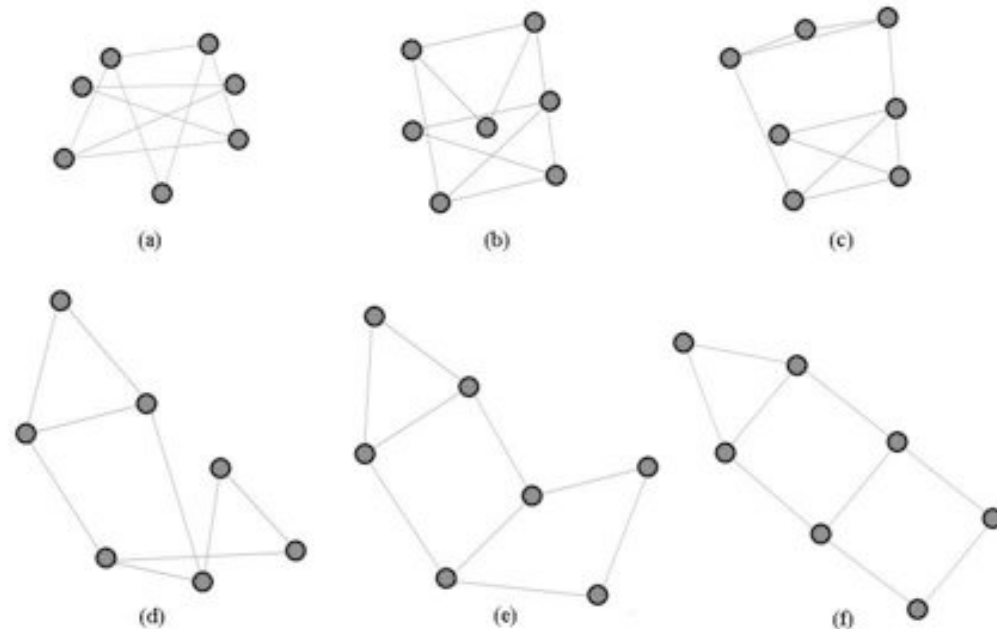
Force-Directed Graph Layout

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

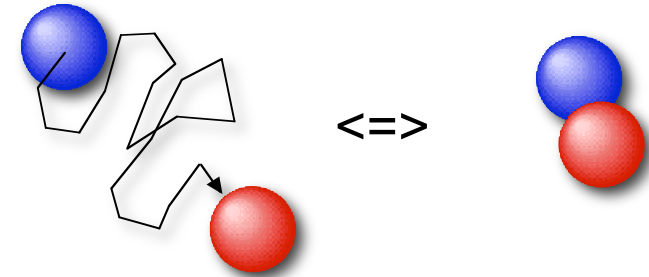
$$\vec{F}(\vec{x}) = -\nabla E(\vec{x}) = - \begin{pmatrix} \frac{\partial E}{\partial x} \\ \frac{\partial E}{\partial y} \\ \frac{\partial E}{\partial z} \end{pmatrix}$$



Mass Action Kinetics

Most simple dynamic system: inorganic chemistry

Consider reaction $A + B \rightleftharpoons AB$



Interesting quantities:

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

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

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

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

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 for the changes of
[A], [B], and [AB]

Consider [A]:

Gain from dissociation $AB \Rightarrow A + B$

Loss from association $A + B \Rightarrow AB$

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

AB falls apart

$\Rightarrow G_A$ depends only on [AB]


A has to find B

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

$$G_A = k_r [AB]$$

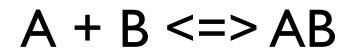
$$L_A = k_f [A] [B]$$

phenomenological
proportionality constant



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

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 = "+"

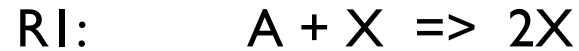
Stoichiometries: one factor for each educt ($\Rightarrow [B]^2$)
prefactors survive

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:

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

Changes of the metabolites

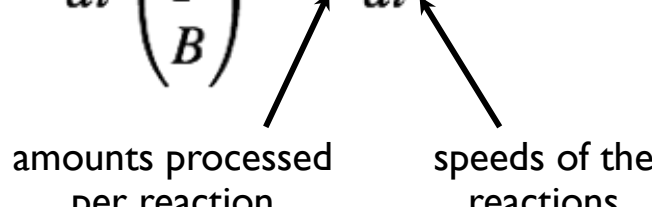
	R1	R2	R3
A	-1		
X	1	-1	
Y		1	-1
B			1

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



 amounts processed per reaction speeds of the reactions

Plug in to get:

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

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

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

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

How Does It Look Like?

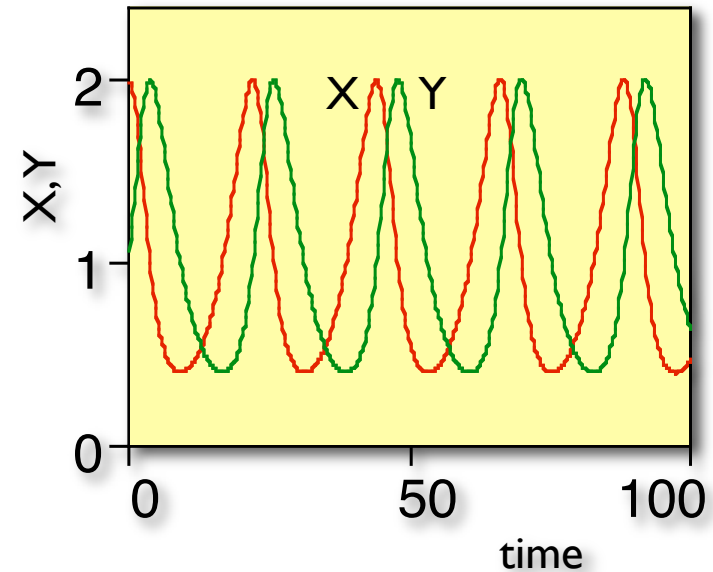
Lotka–Volterra: assume $A = \text{const}$, B ignored

=> 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?

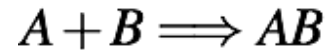
$$\frac{dX}{dt} = \frac{dY}{dt} = 0 \quad \Rightarrow \quad Y = \frac{k_1}{k_2} A \quad X = \frac{k_3}{k_2}$$

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:

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

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 Δt :

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

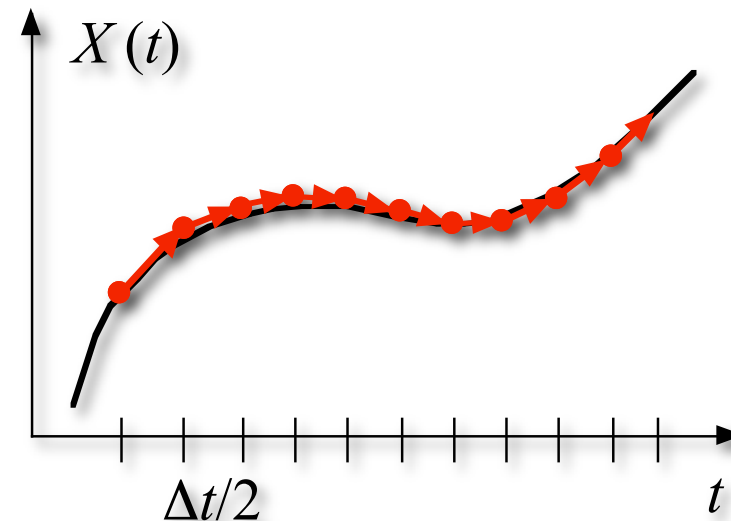
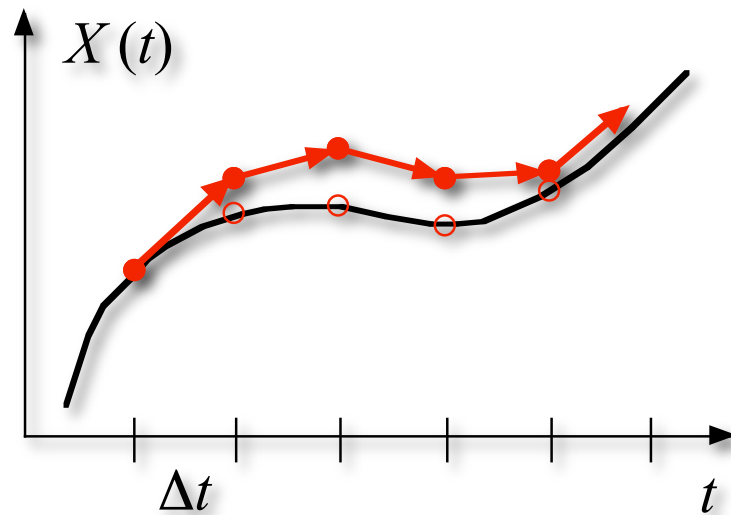
"forward Euler" algorithm

“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

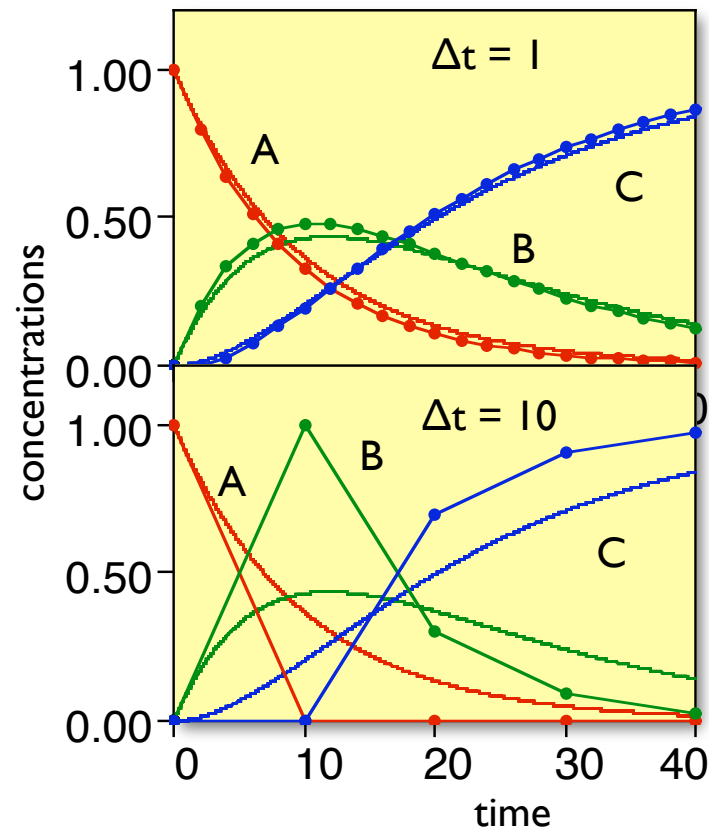
relative error decreases with 1st power of step size Δt



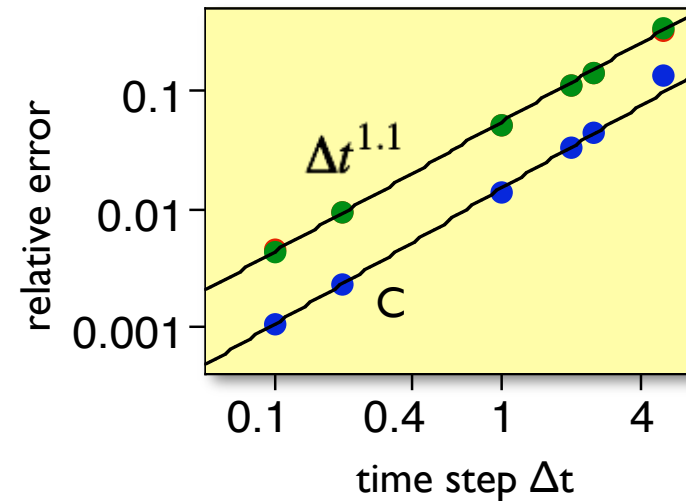
Example: chained reactions

Reaction: $A \Rightarrow B \Rightarrow C$ $k_{AB} = 0.1$, $k_{BC} = 0.07$

Time evolution:



Relative error vs. Δt
at $t = 10$:



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

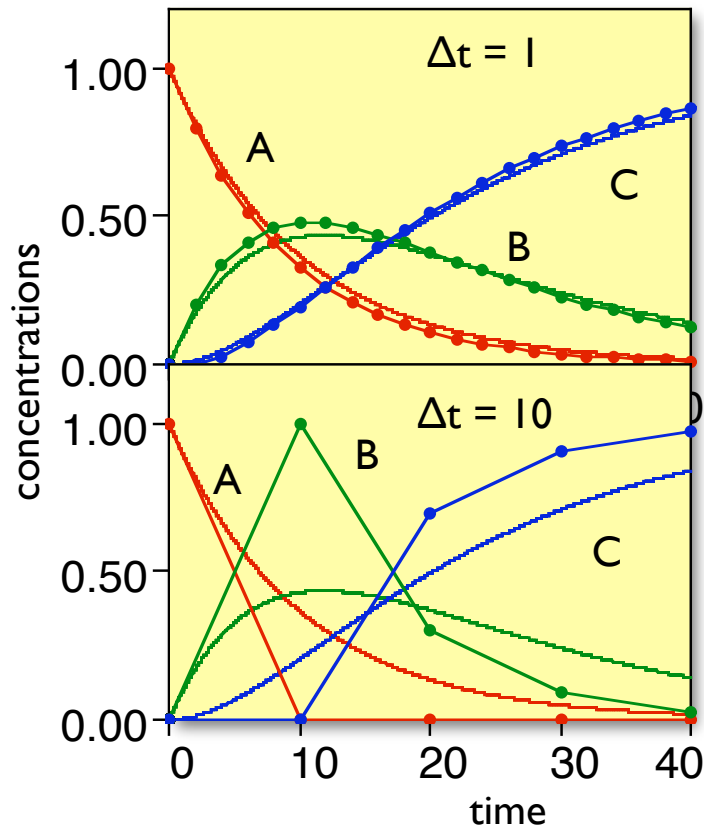
Iterate:

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

Important:

first calculate all derivatives,
then update densities!

The “correct” time step?



Note 1:

read “ \ll ” as “a few percent”



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 2:

for $A + B \Longrightarrow AB$

consider $\Delta t \ll (\max(k_A, k_B))^{-1}$

From Test Tubes to Cells

Rate equations \Leftrightarrow description via densities

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

\Rightarrow density is a continuum measure,
independent of the volume element

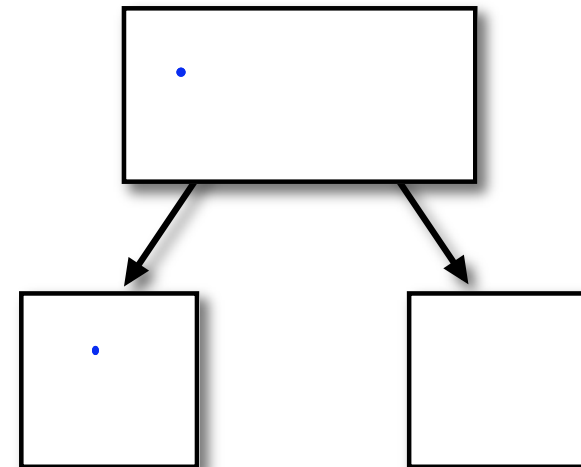
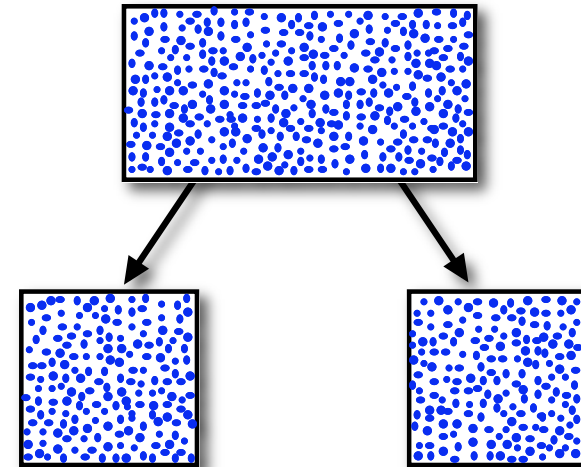
"half of the volume \Rightarrow half of the particles"

When density gets very low

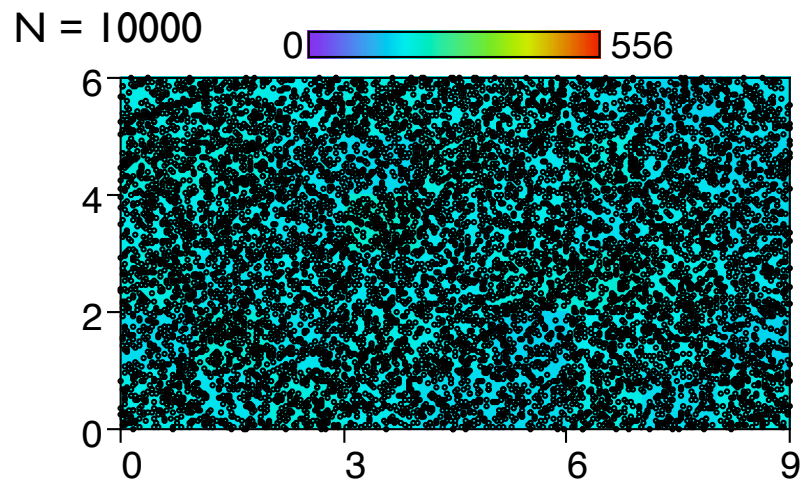
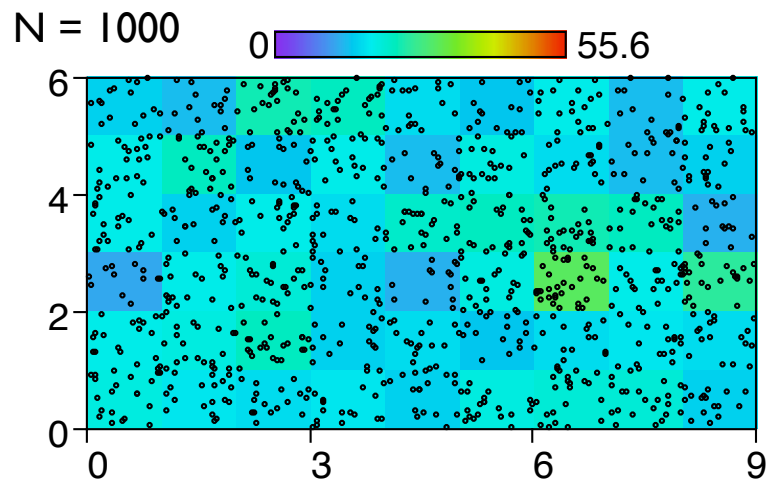
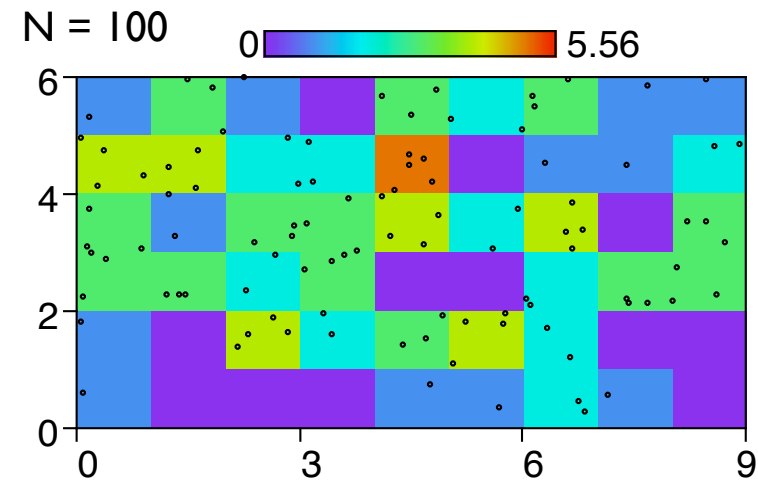
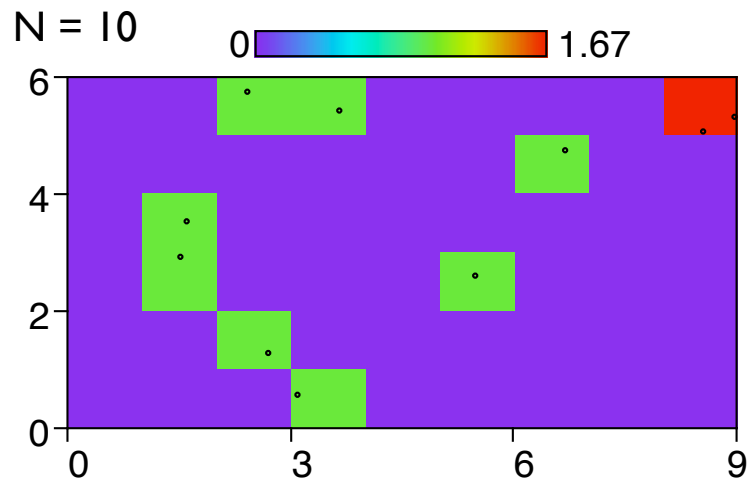
\Rightarrow each particle matters

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

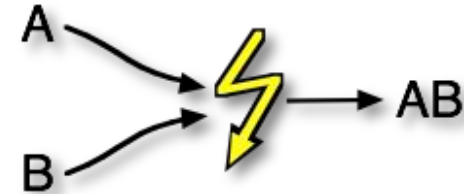
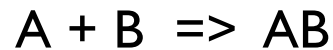
Relative spread (error): $\frac{\Delta k}{k} = \frac{\sigma}{\langle k \rangle} = \frac{1}{\sqrt{\lambda}}$

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

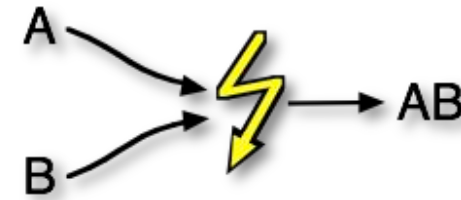
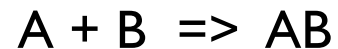
Number of new AB in volume V during Δt :

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

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**

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

$$\left[\frac{dAB}{dt} \right] = \frac{\text{Mol}}{l s}$$

$$[A] = [B] = \frac{\text{Mol}}{l}$$

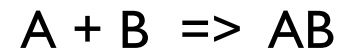
$$\Leftrightarrow [k_{AB}] = \frac{l}{\text{Mol } s}$$

stochastic

$$[N_{AB}] = [N_A] = [N_B] = 1$$

$$\Leftrightarrow [P_{AB}] = 1$$

Direct Implementation



```
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
```

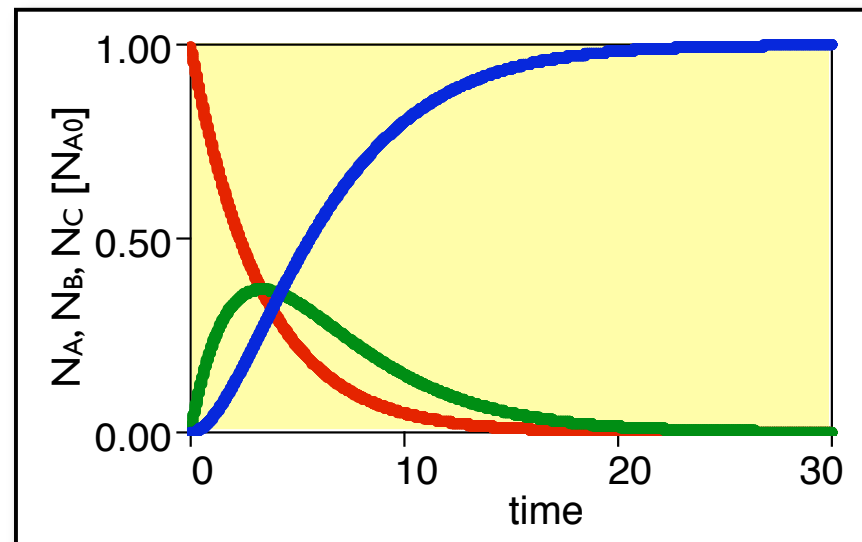
Note: both versions are didactic implementations

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):



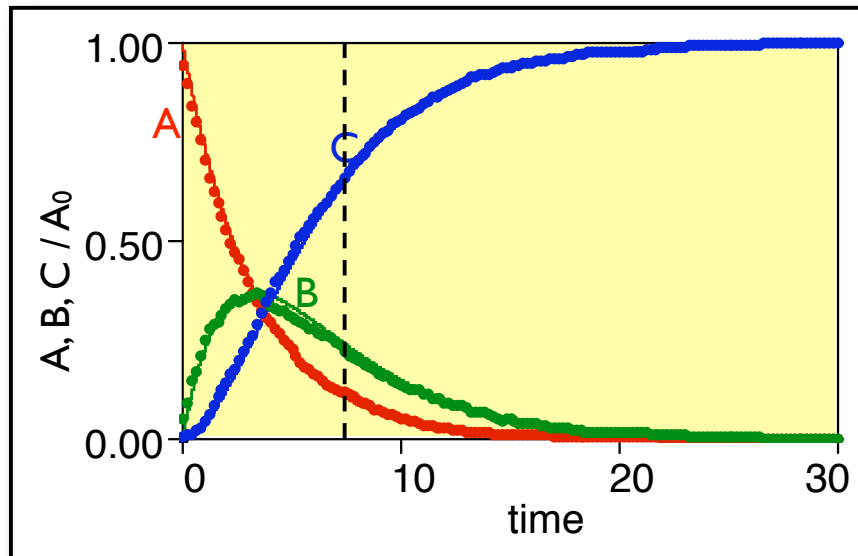
$$k_1 = k_2 = 0.3 \quad (\text{units?})$$

Stochastic Implementation

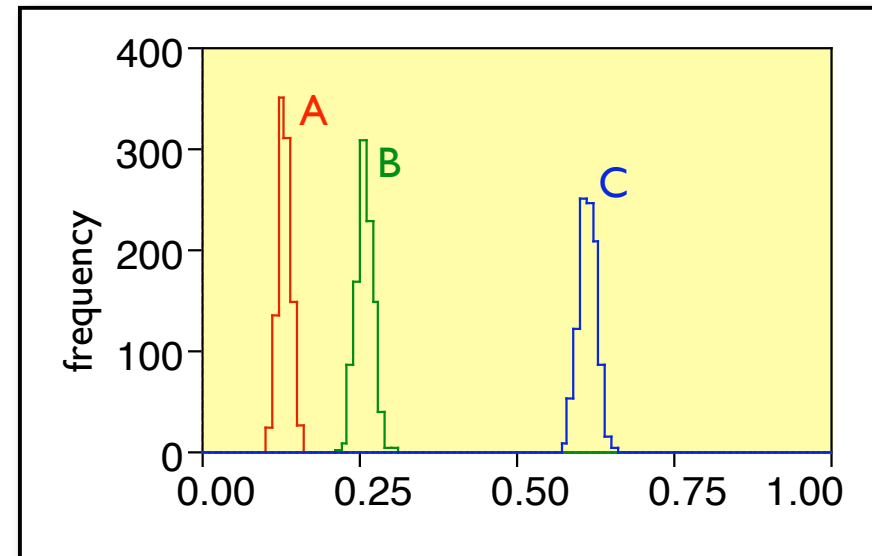


$A_0 = 1000$ particles initially

$t = 7$



$k_1 = k_2 = 0.3$

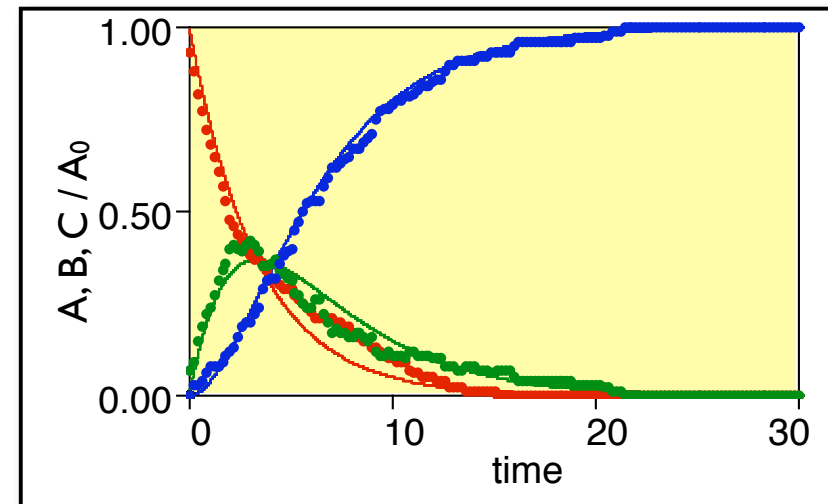
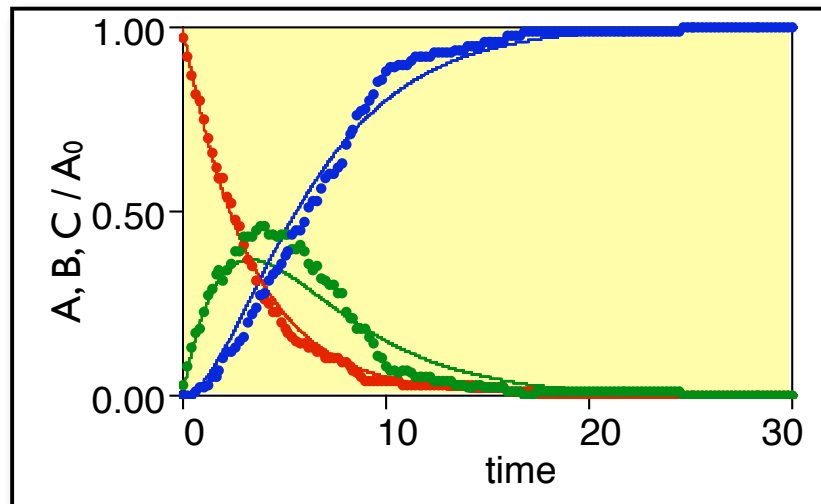
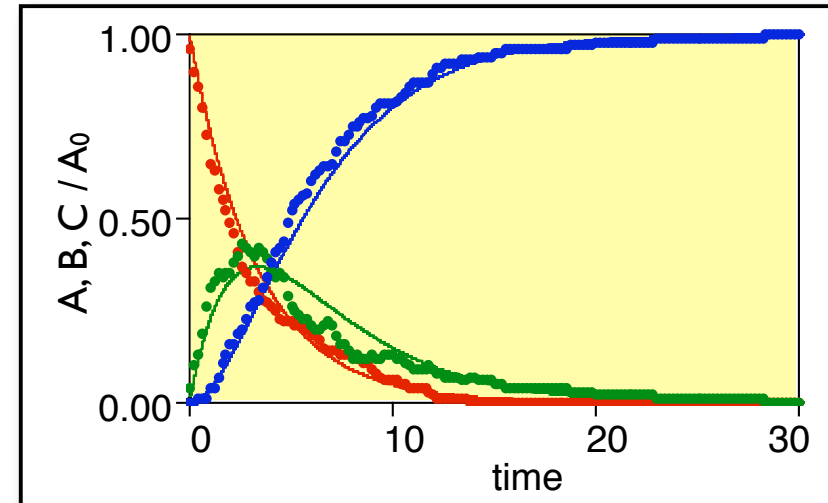
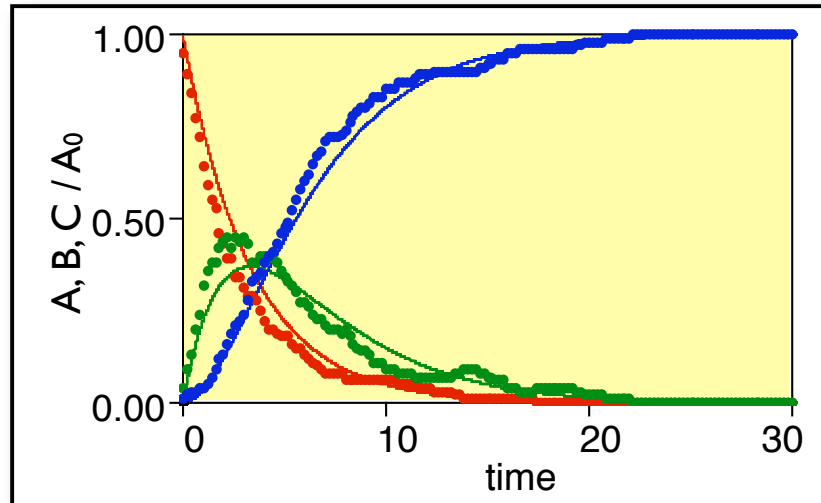


Values at $t = 7$ (1000 tries)

\Rightarrow Stochastic version exhibits fluctuations

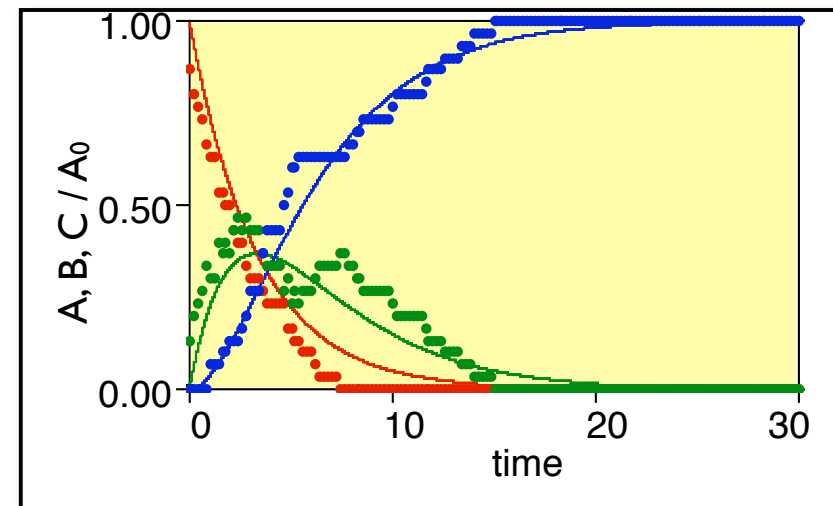
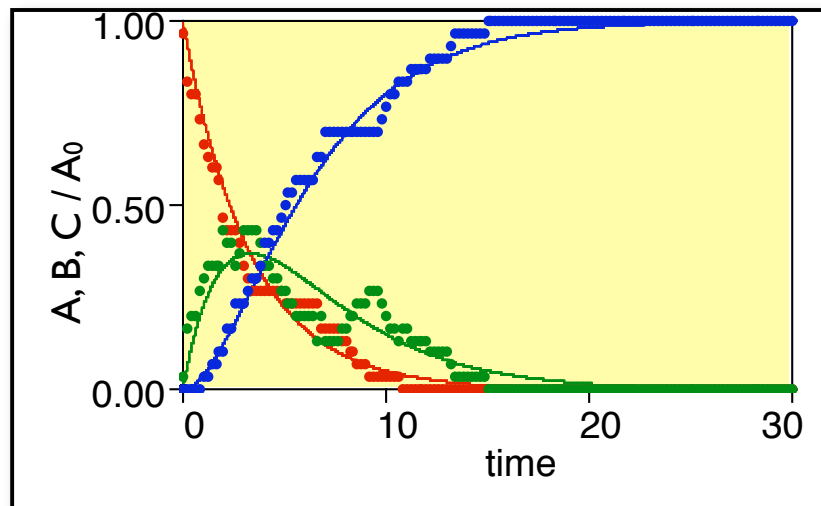
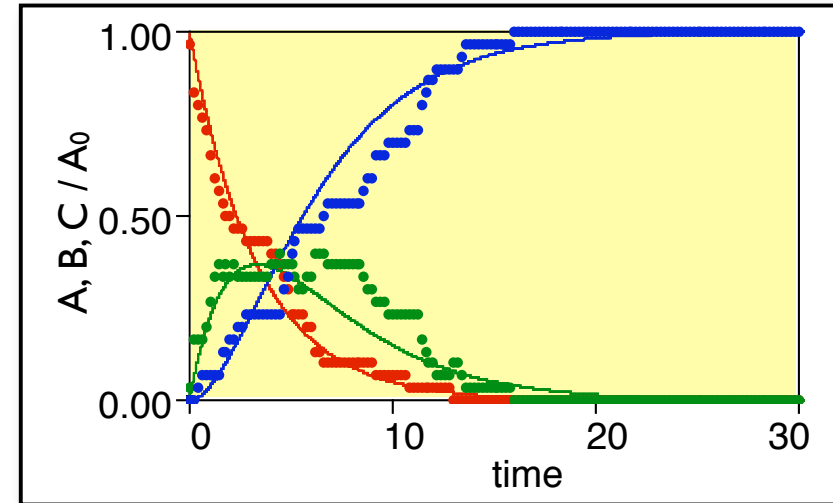
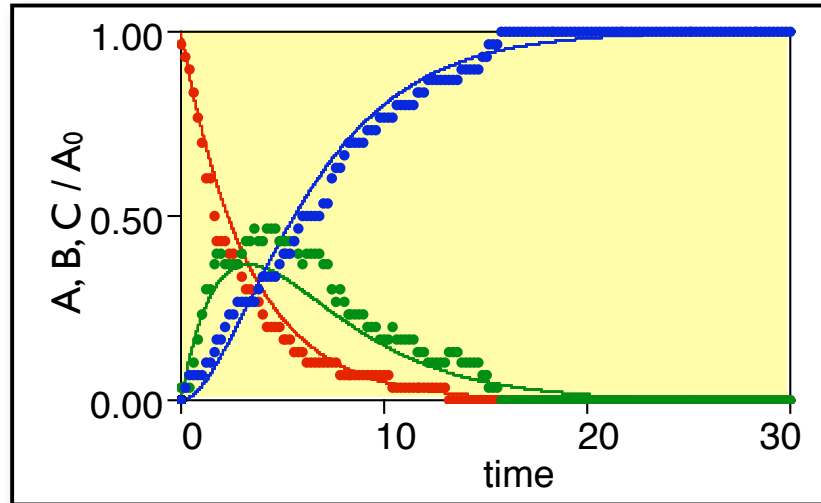
Less Particles => Larger Fluctuations

$A_0 = 100$



Even Less Particles

$$A_0 = 30$$



Spread vs. Particle Number

Poisson:

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

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

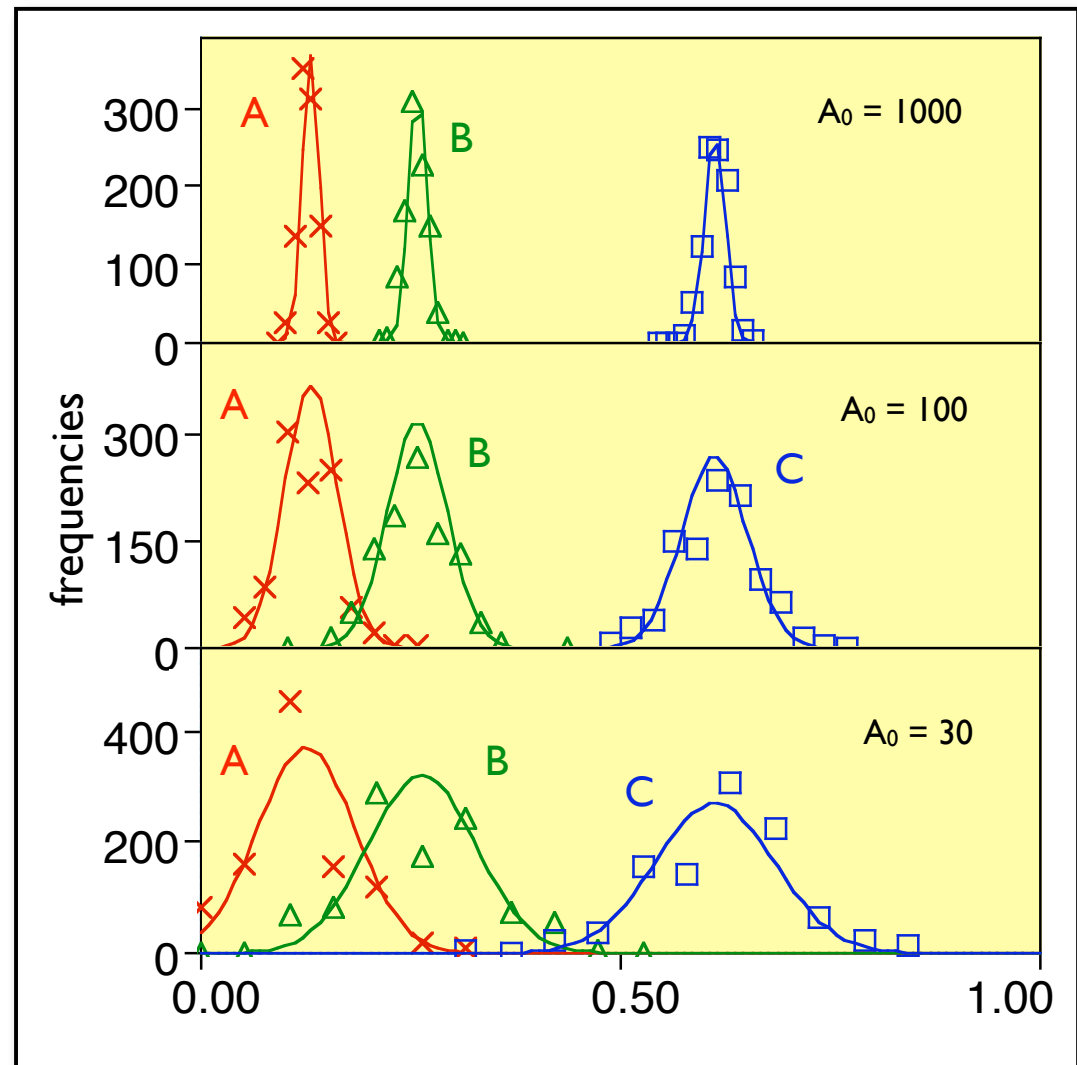
Fit distributions with Gaussian
(Normal distribution)

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

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

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

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



Stochastic Propagation

Naive implementation:

```
For every timestep:  
  events = 0  
  For every possible pair of A, B:  
    get random number  $r \in [0, 1)$   
    if  $r \leq P_{AB}$ :  
      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)

Publication costs assisted by the Naval Weapons Center

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 Δt . 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  $r \in [0, 1)$ 
  if  $r \leq A*k*dt$ :
    A = A-1
```

It works, but: $A*k*dt \ll 1$ for accuracy

\Rightarrow many many steps where nothings happens

\Rightarrow adaptive stepsize method?

Gillespie – Step I

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

(In between the discrete events nothing happens anyway ... :-)

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

$f(A(t), s)$ = probability that with $A(t)$ molecules the next reaction takes place in $(t+s, t+s+ds)$ with $ds \Rightarrow 0$

$g(A(t), s)$ = probability that with $A(t)$ 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 $(t, t+s)$:

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

Probability for (No Reaction)

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

Extend $g(A(t), s)$ a bit:

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

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 = average waiting time: $s_0 = \frac{1}{kA(t)}$

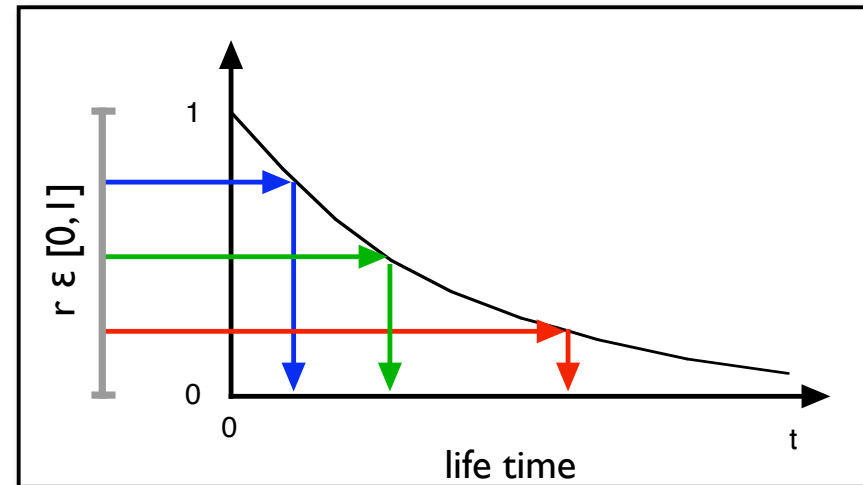
Exponentially Distributed Random Numbers

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  $r \in [0, 1)$ 
     $t = t + s(r)$ 
     $A = A - 1$ 
```

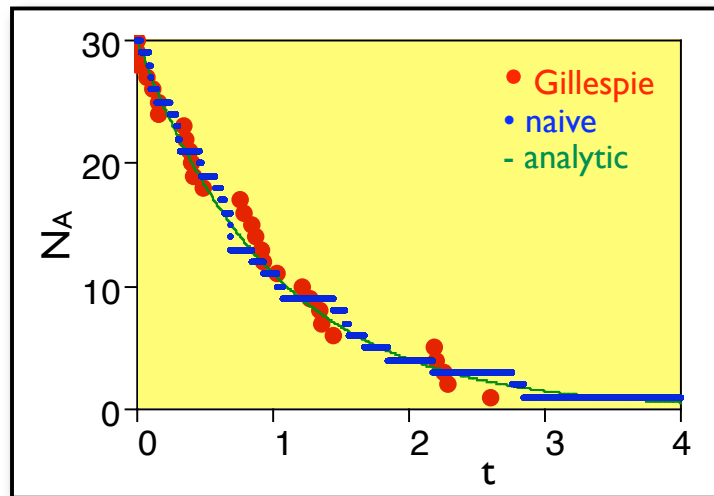
Gillespie vs. Naive Algorithm

Naive:

"What is the probability that an event will occur during the next Δt ?"

=> small fixed timesteps

=> 1st order approximation

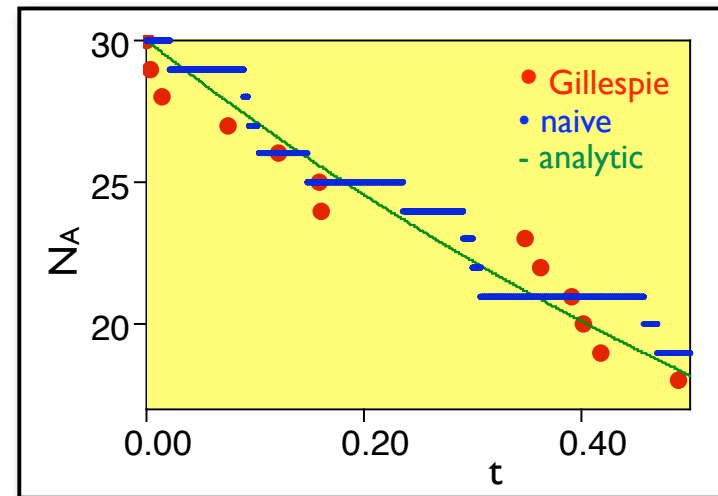


Gillespie:

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

=> variable timesteps

=> exact



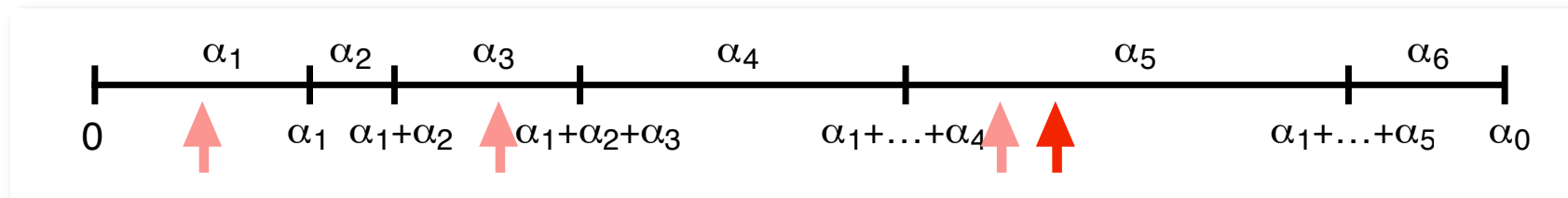
Gillespie – Complete

For an arbitrary number of reactions (events):

(i) determine probabilities for the individual reactions: α_i $i = 1, \dots, N$
 total probability $\alpha_0 = \sum \alpha_i$

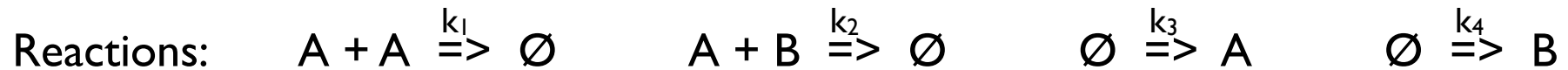
(ii) get time s until next event in any of the reactions: $s = \frac{1}{\alpha_0} \ln \left[\frac{1}{r_1} \right]$

(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



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

Erban, Chapman, Maini, arXiv:0704.1908v2 [q-bio.SC]

- (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

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

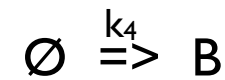
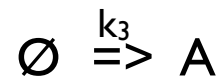
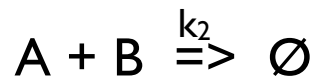
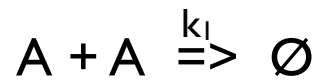
- (d4) Compute the number of molecules at time $t + \tau$ by

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

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

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

Stochastic Simulation



Erban, Chapman, Maini, arXiv:0704.1908v2 [q-bio.SC]

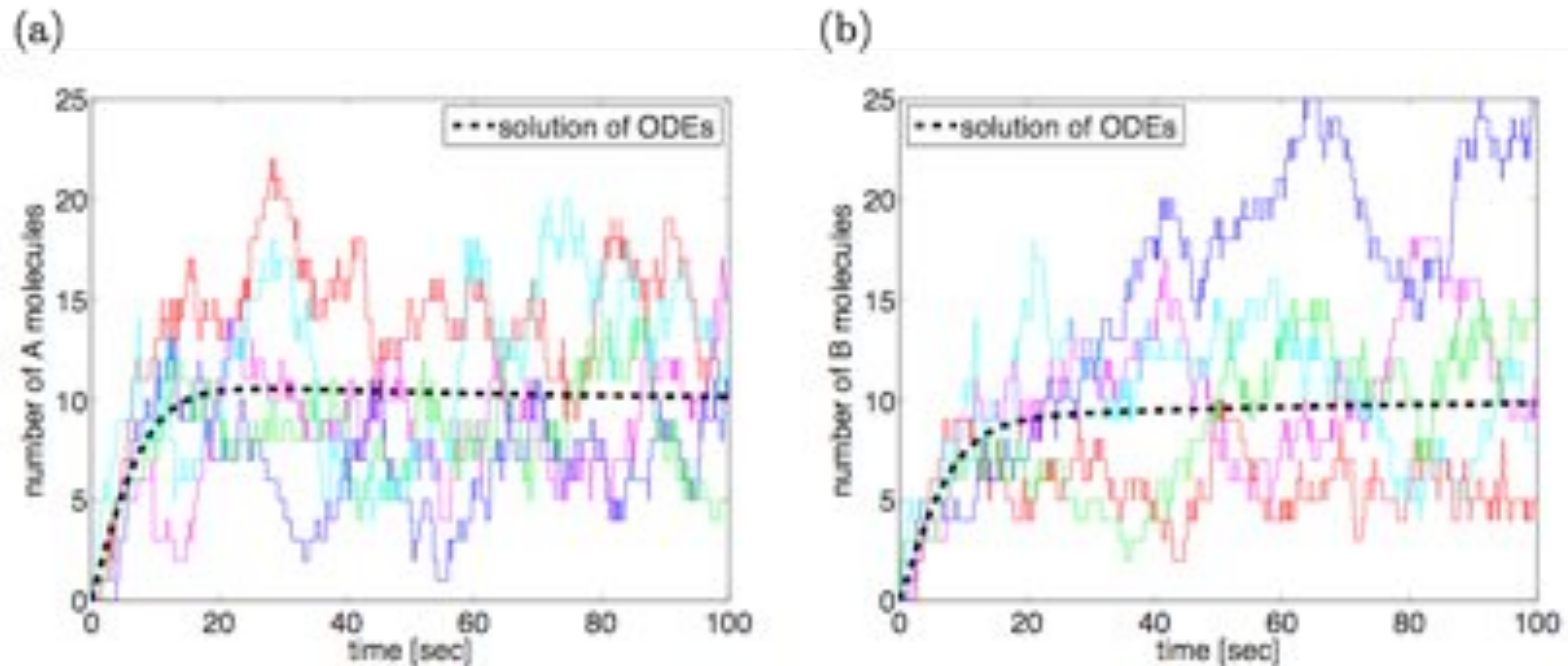
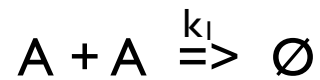
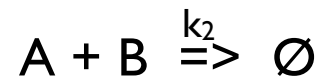


FIG. 2.3. Five realizations of SSA (a4)–(d4). Number of molecules of chemical species *A* (left panel) and *B* (right panel) are plotted as functions of time as solid lines. Different colours correspond to different realizations. The solution of (2.33)–(2.34) is given by the dashed line. We use $A(0)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

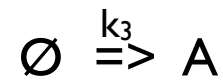
Distribution of Stationary States



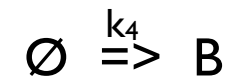
$$k_1 = 10^{-3} \text{ s}^{-1}$$



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



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



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

Continuous model:

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

\Leftrightarrow

From long-time Gillespie runs:

$$\langle A \rangle = 9.6, \quad \langle B \rangle = 12.2$$

Erban, Chapman, Maini, arXiv:0704.1908v2

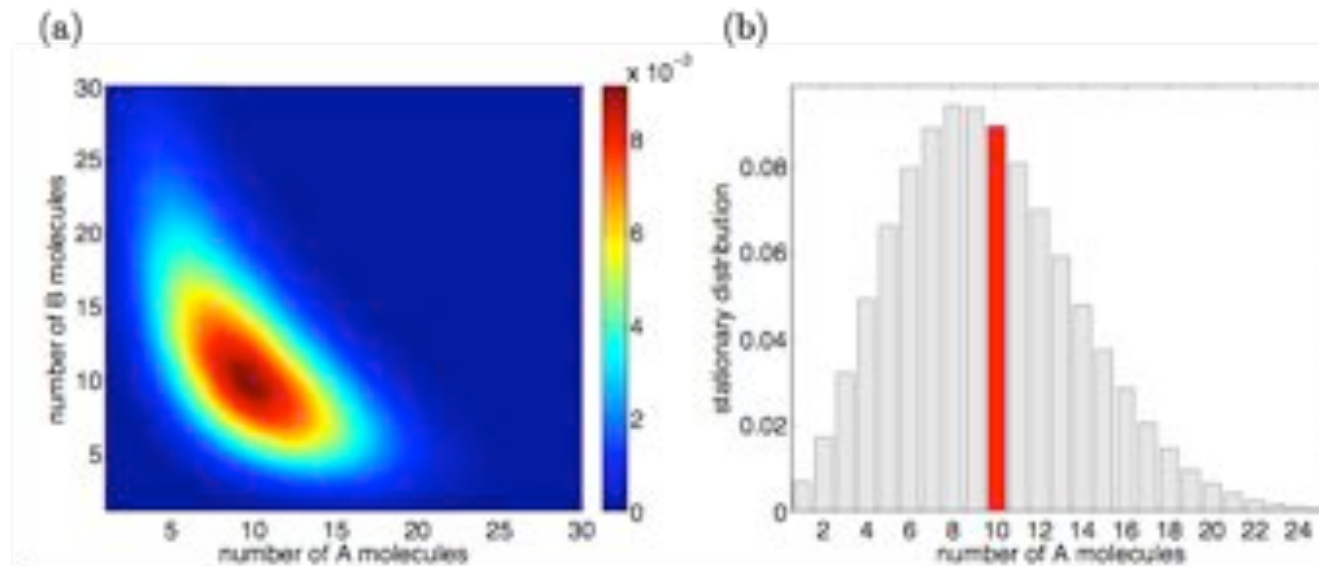


FIG. 2.4. (a) Stationary distribution $\phi(n, m)$ obtained by long time simulation of (a4)–(d4) for $k_1 = 10^{-3} \text{ sec}^{-1}$, $k_2 = 10^{-2} \text{ sec}^{-1}$, $k_3 = 1.2 \text{ sec}^{-1}$ and $k_4 = 1 \text{ sec}^{-1}$. (b) Stationary distribution of A obtained by (2.35).

Stochastic vs. Continuous

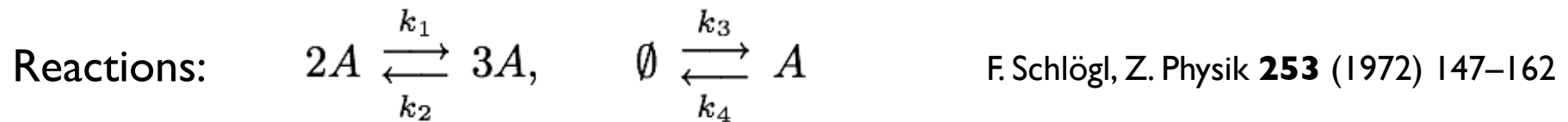
For **many** simple systems:

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 ($A(0) \neq 220$),
the deterministic system goes into A_{s1} or A_{s2} (and stays there).

Two States – Stochastic

Erban, Chapman, Maini, arXiv:0704.1908v2

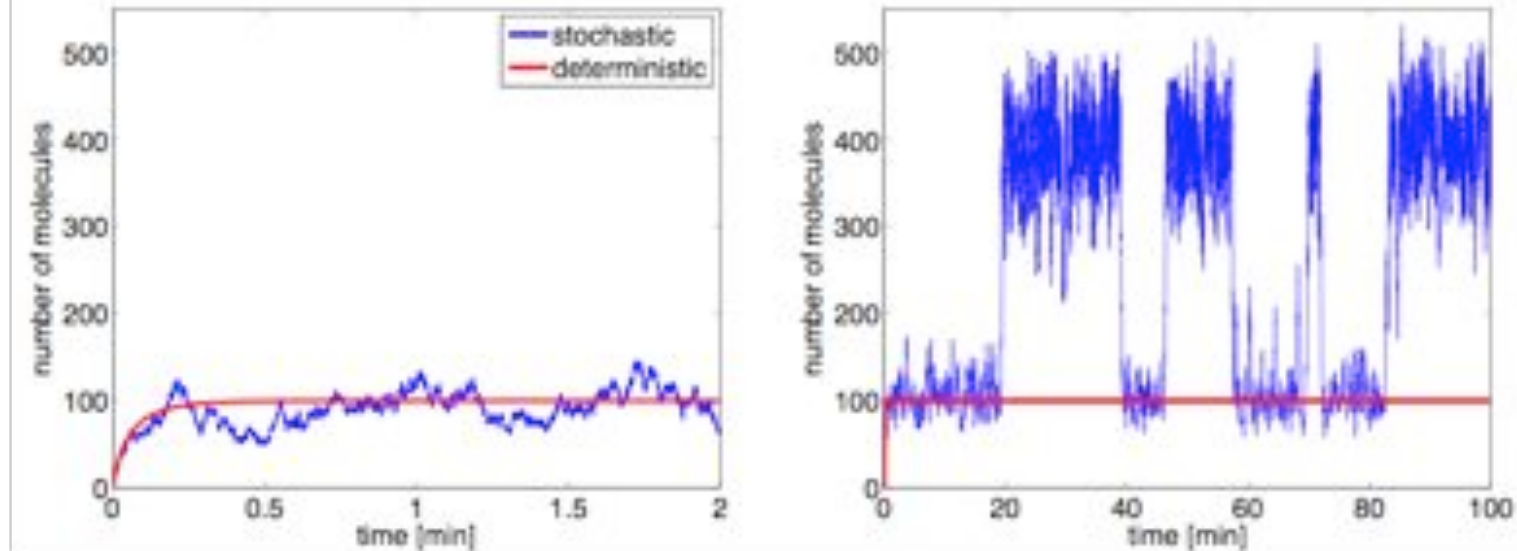


FIG. 5.1. Simulation of (5.1). One realization of SSA (a5)–(d5) for the system of chemical reactions (5.1) (blue line) and the solution of the deterministic ODE (5.2) (red line). (a) The number of molecules of A as a function of time over the first two minutes of simulation. (b) Time evolution over 100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

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

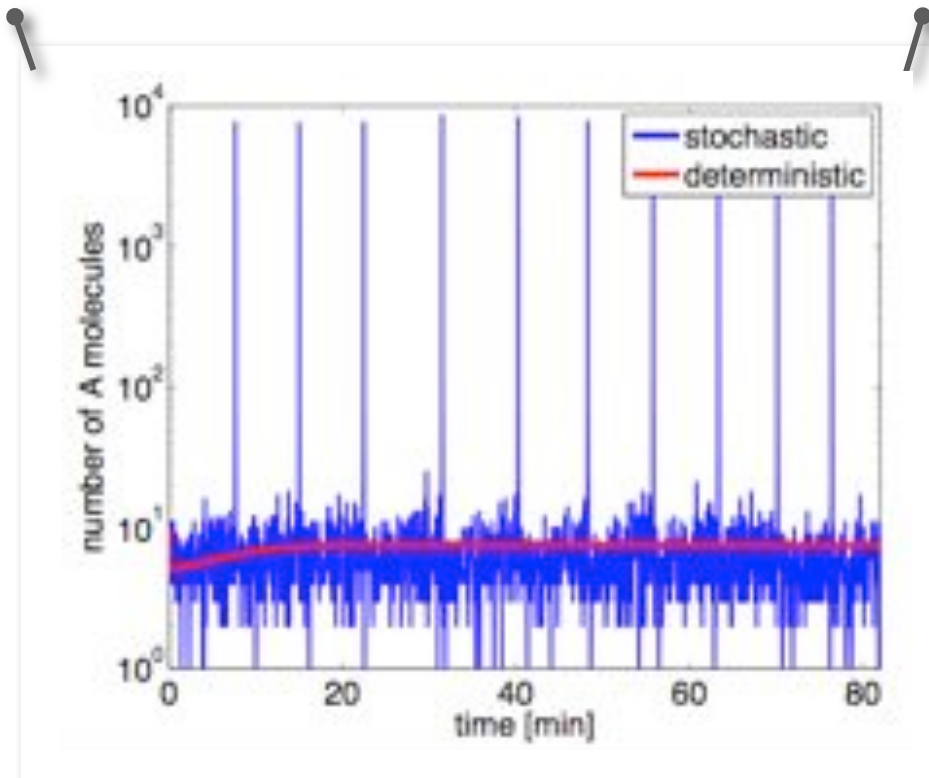
Self-Induced Stochastic Resonance



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 **oscillations** in the **stochastic** model



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