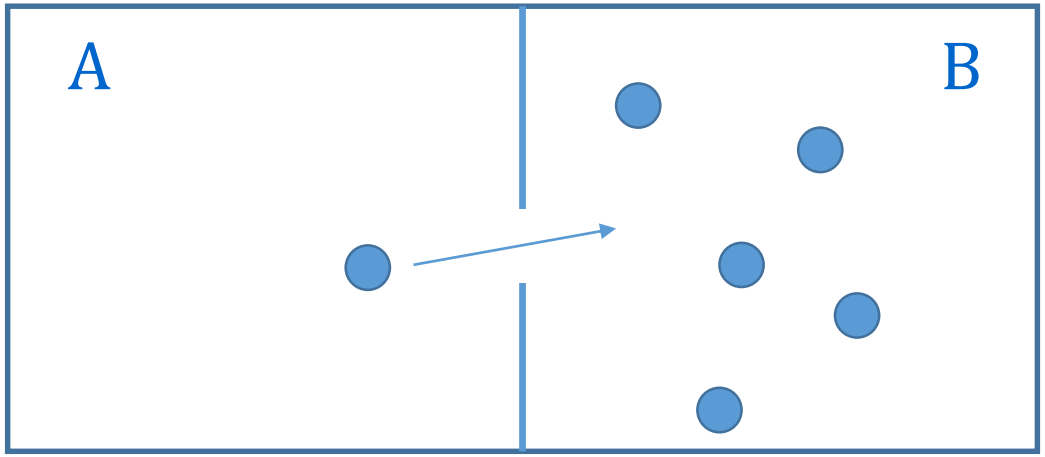
Systems with low numbers and noise

- Usually we work with average properties
- averages require large numbers

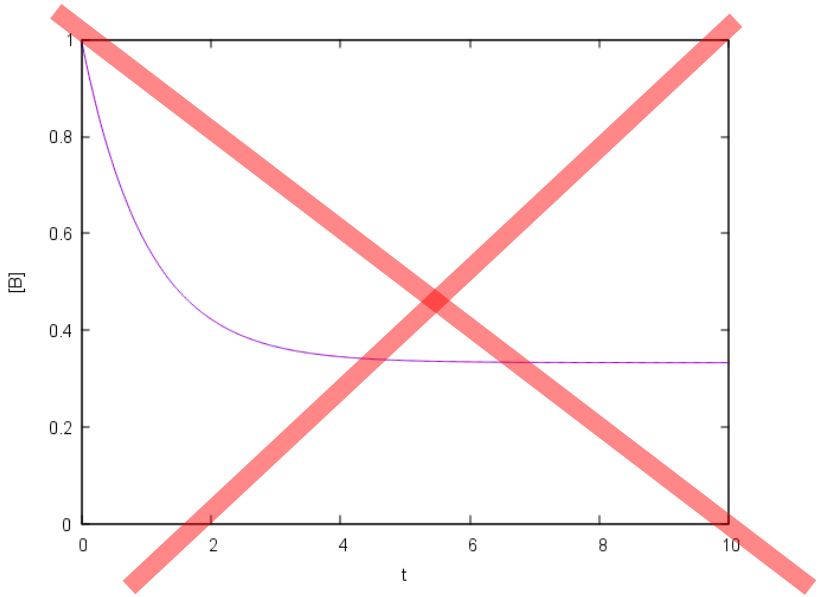
- when are they definitely wrong ?

- I would say there is $\frac{1}{6}$ chance of going backwards (away from equilibrium)



Stock market

- yesterday trade at € 10
- buy offer at € 9, sell at € 11
- widow decides to sell husbands shares at € 9
- report of 10% share price drop
- you are asked to judge the significance
  - simulate how often it happens by chance



Queuing simulations

- shops, transport

more low copy dynamic systems

Lotka-Volterra

- foxes and hares $\frac{dn_h}{dt} = \alpha n_h - \beta n_h n_f$ and $\frac{dn_f}{dt} = \gamma n_h n_f - \delta n_f$
  n_h, n_f number of hares and foxes
- but what if fox/hare meetings are not so common ?

Dilute chemistry ? exotic

- lac repressor - < 40 copies per cell – well studied, classic DNA regulator
- what are chances of a protein repressor drifting through a cell and finding exactly the right piece of DNA ?

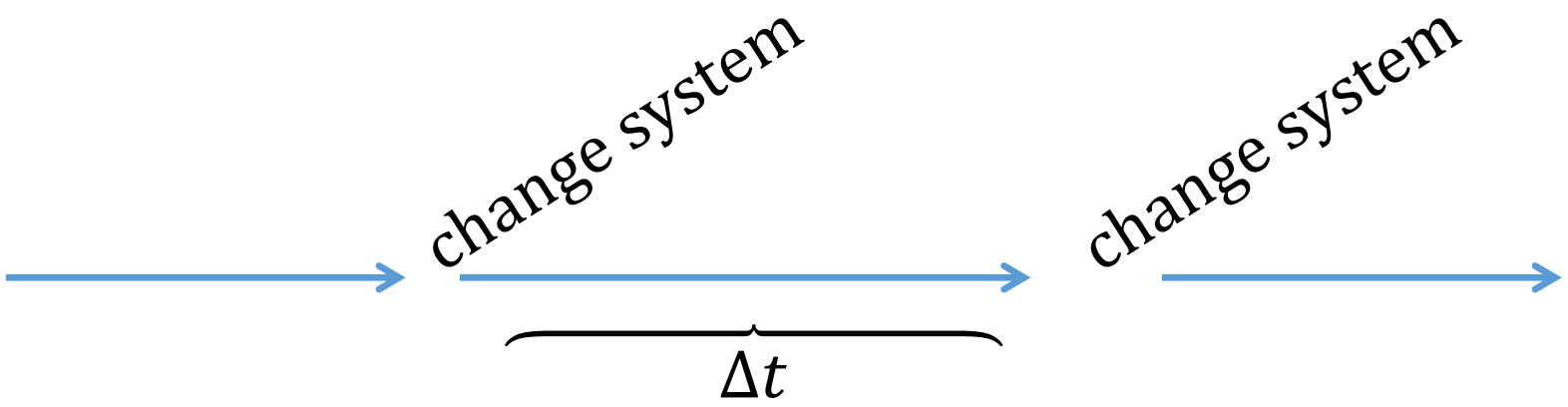
Epidemiology

- states – healthy, sick, immune

Simulating rare events

Two aspects

- when do events occur ?
- what to do ?



Frequencies of rare events

Event are not correlated

- this particle is independent of that one
- calls into help line are independent
- flood in this time not correlated with some other time

Average μ is known – number of events in a time period in time t

- average number of calls in day, Geiger counter counts / s, ..

- later use rate λ so in time t, $\mu = \lambda t$
- average time between events ? $\tau = \lambda^{-1}$ (check dimensions here)

Two names will keep coming up

- poisson distribution - think of μ
- exponential distribution - think of τ

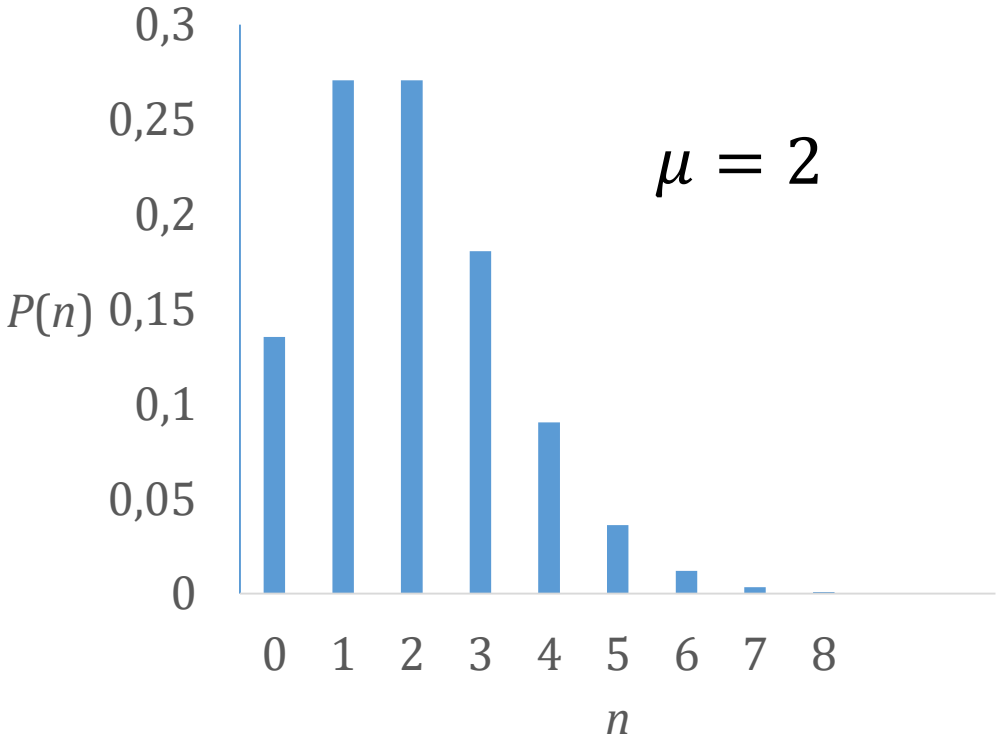
Poisson

Used for next step

What is the probability of n events in time t ?

$$P(x = n) = e^{-\mu}\frac{\mu^n}{n!}$$

$\mu = 2$ but probability of seeing 2 events is only $\approx {}^1/_4$



how to derive ? Do derivation of binomial and take limit

time between events

We have $P(x = n) = e^{-\mu}\frac{\mu^n}{n!} = e^{-\lambda t}\frac{\mu^n}{n!}$

- something does not happen for τ, then happens
- zero events over some t ? $P(x = 0) = e^{-\lambda t}\frac{\mu^0}{0!} = e^{-\lambda t}$

- This means the first event happened at τ and $\tau > t$ so
- $P(\tau > t) = P(x = 0) = e^{-\lambda t}$ but then probability of an event is
- $P(\tau \leq t) = 1 - P(x = 0) = 1 - e^{-\lambda t}$

- Cumulative probability over all τ is $1 - e^{-\lambda t}$
- instantaneous probability for some t will be the derivative

time between events

- Cumulative probability over all τ is $1 - e^{-\lambda t}$
- instantaneous probability for some t will be the derivative

$$\frac{d}{dt} P(T \leq t) = \frac{d}{dt} 1 - e^{-\lambda t} = \lambda e^{-\lambda t}$$

- distribution of gaps between events τ is $\lambda e^{-\lambda t}$ or exponential distribution

Formally, τ is a random variable drawn from $f(\tau, t) = \lambda e^{-\lambda t}$

- back to simulation question

simulating with rare events

- λ 10 events a second or 20 calls an hour
- define our time step as τ

  because τ is the time between events

- simulate

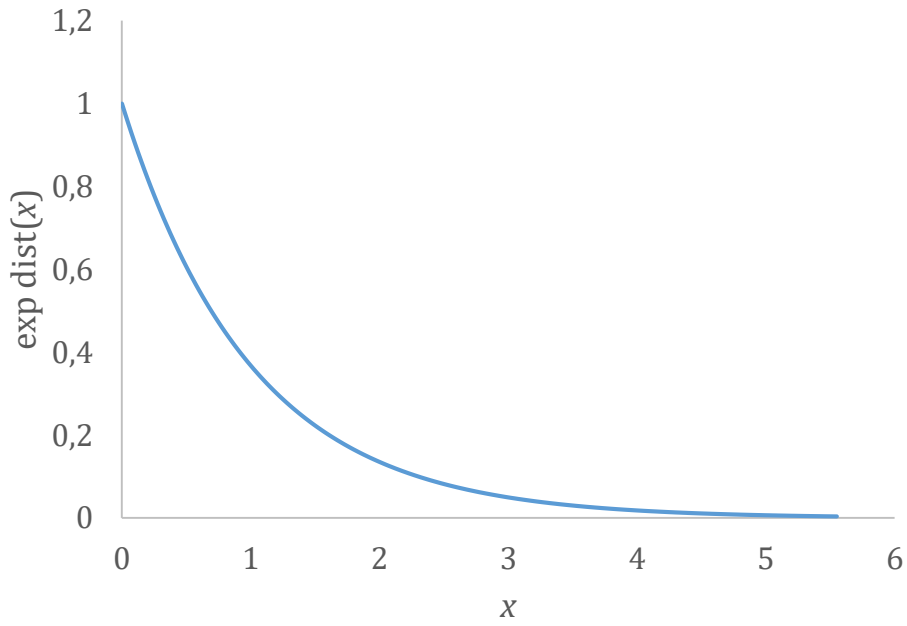
while $(t < t_{max})$

  pick τ from $P(\tau = t) = \lambda e^{-\lambda t}$

  $t := t + \tau$

  do something

- bit more complicated



more than one event type

$$\mathrm{E+S} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_3} \mathrm{E+P}$$

- three reactions – each is a poisson process
- total poisson process
  - I have A's and B's happening independently
  - I see μ_A events and μ_B events
    - total μ_0 is just $\mu_A + \mu_B$ so I can just add up λ's

- $P(x = n) = e^{-\mu} \frac{\mu^n}{n!}$ μ is the average number of times something happens
- add up the rates, say $\lambda_0 = \sum_{i=1}^{N_{rates}} \lambda_i$
- $P(x = n) = e^{\lambda_o t} \frac{\mu^n}{n!}$ or maybe you prefer $P(x = n) = e^{-\mu_0} \frac{\mu^n}{n!}$
- we can draw timestep from this distribution, but what happens there ?

$\mu_0 = \lambda_0 t$ total events per time

- simulate

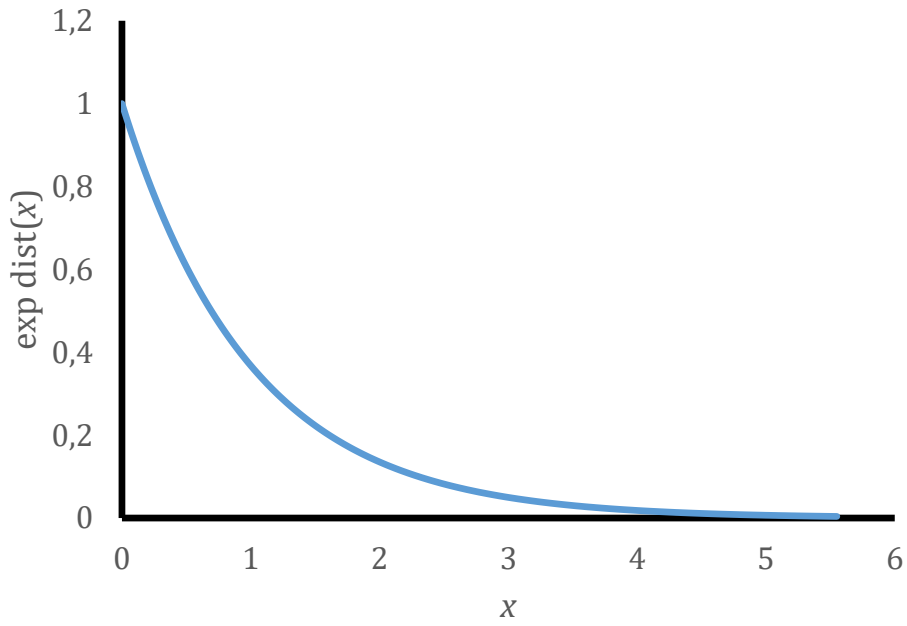
while $(t < t_{max})$

pick Δt from $P(\tau = t) = \lambda_0 e^{-\lambda_0 t}$

$t := t + \tau$

pick a reaction

- choosing a reaction…



choosing a reaction

N_λ rates each λ_i (three in previous example)

- probability of reaction i

$$p_i = \frac{\lambda_i}{\sum_j^{N_\lambda} \lambda_j}$$

implementation to choose which reaction happens

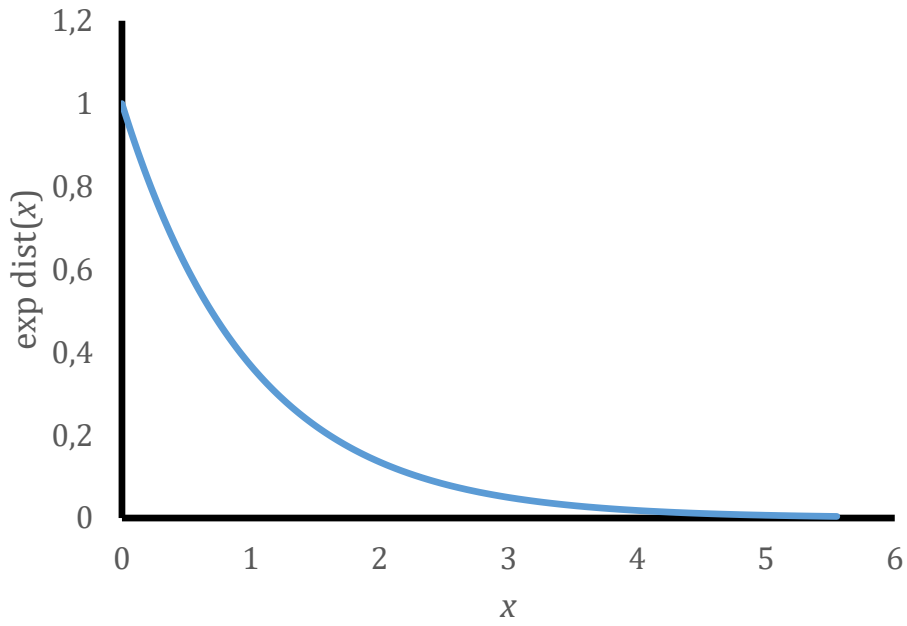
- make a table of $q_i = \sum_{j=1}^{i} p_j$

```
r = rand(0..1)
for (i = 0; i < n; i++) {
    if r< q_i { return i}}
```

p_i	q_i
0.2	0.2
0.3	0.5
0.5	1.0

The Gillespie algorithm

- $\mu_0 = \lambda_0 t$ total events per time
- calculate rate λ_0



- simulate

while $(t < t_{max})$

pick τ from $P(\tau = t) = \lambda_0 e^{-\lambda_0 t}$

$t := t + \tau$

pick a reaction from recipe on previous slide

update rates (λ's) since quantities have changed

What did Mr Gillespie find ?

1977 computer graphics..

$\overline{\mathrm{X}} + \mathrm{Y} \xrightarrow{c_1} 2\mathrm{Y}$ and $\overline{\mathrm{X}}$ means a large pool of X

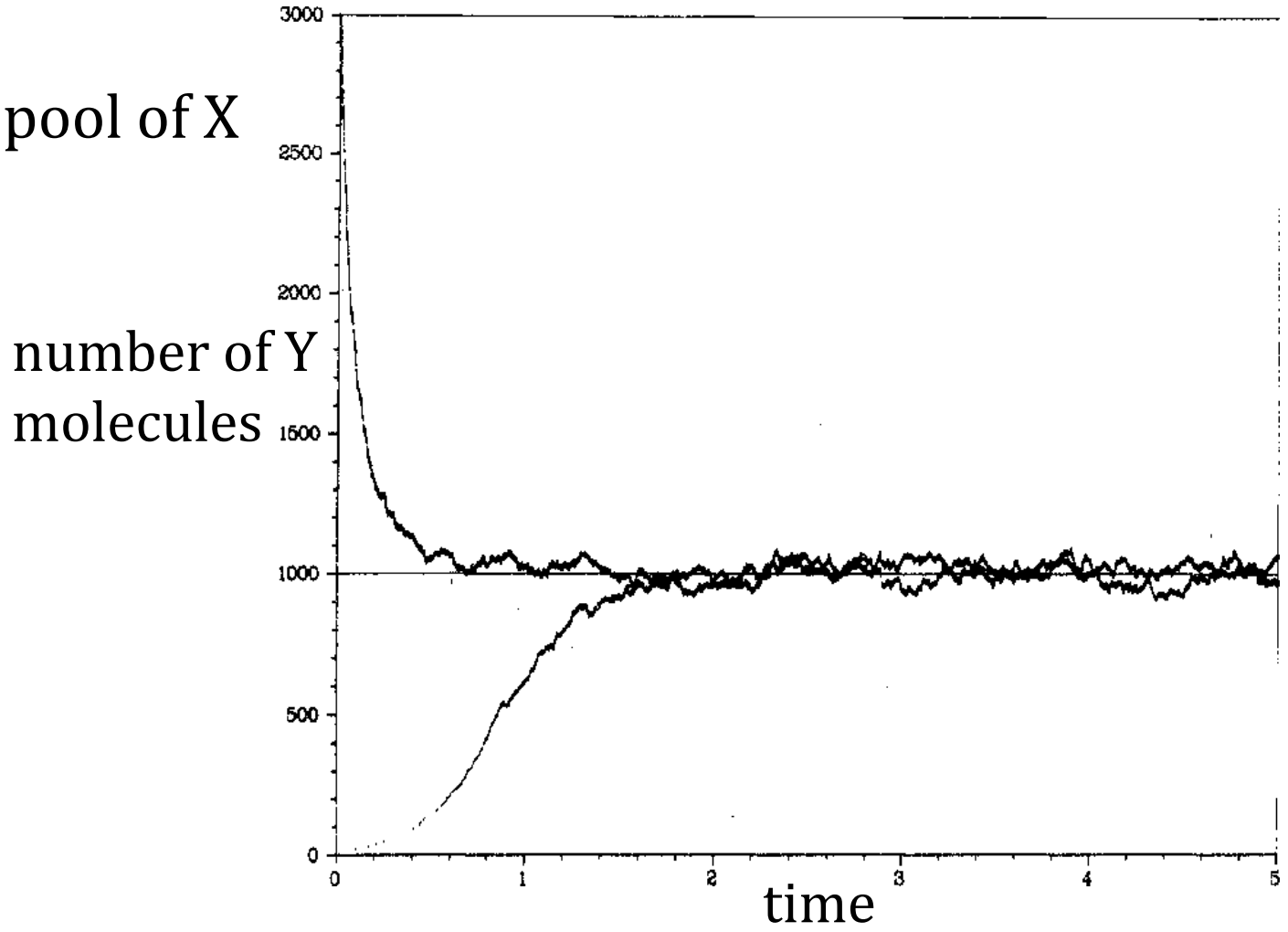
$2\mathrm{Y} \xrightarrow{c_2} \mathrm{Z}$

Two starting conditions

- n_{Y} =10 or 1000

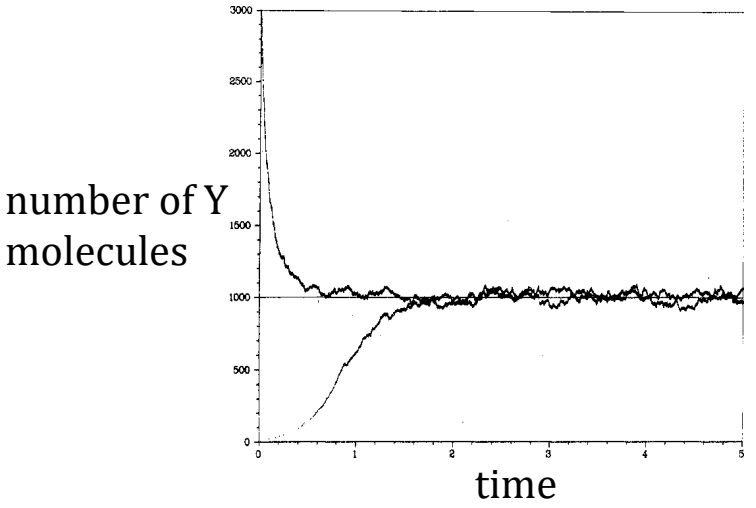
  some values for c_1, c_2 and n_{X}

  Have you learnt much ?



Gillespie, D.T. J. Phys. Chem. 81, 2340-2361 (1977)

Why do Gillespie simulations ?



You already know average behaviour from classic kinetics

- You can predict $[Y]_t$ but it is an average

Run simulation 1000 times

- gives you $[Y]_t \pm \sigma_Y$
- can predict fluctuation around equilibrium values

Back to cell with one DNA + 40 copies of repressor

- from some estimates of kinetics, can predict
  - average occupancy
  - lifetime of bound state
  - fraction of time DNA site is occupied, confidence intervals

Extensions / Applications of Gillespie method

Fuchsen + blue hares and red hares

- move randomly, meet randomly fox + hare → fox
  - widely used in eco-system modelling

Spatial diffusion problem in cells

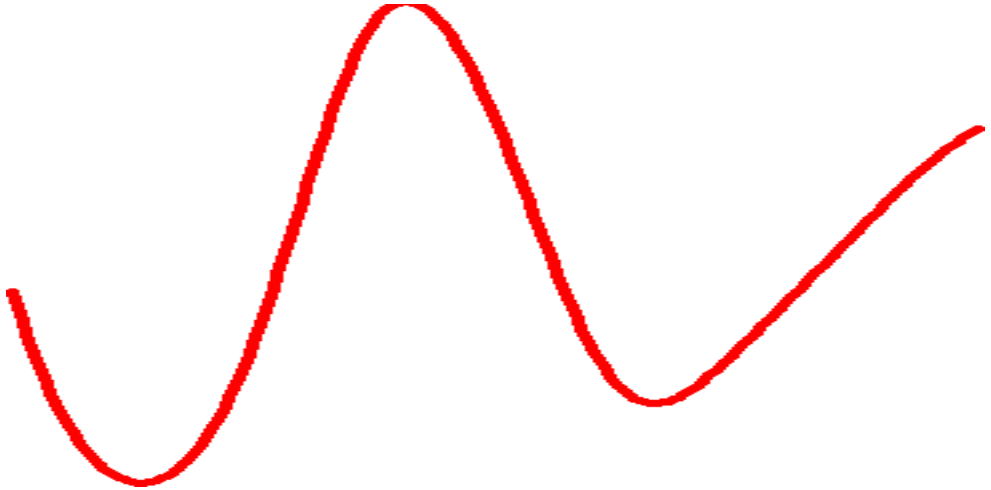
- for a particle in box_1, $\text{box}_1 \xrightarrow{k} \text{box}_2$
  - diffusive simulations + chemistry – states are mixture of chemistry and location

Finance

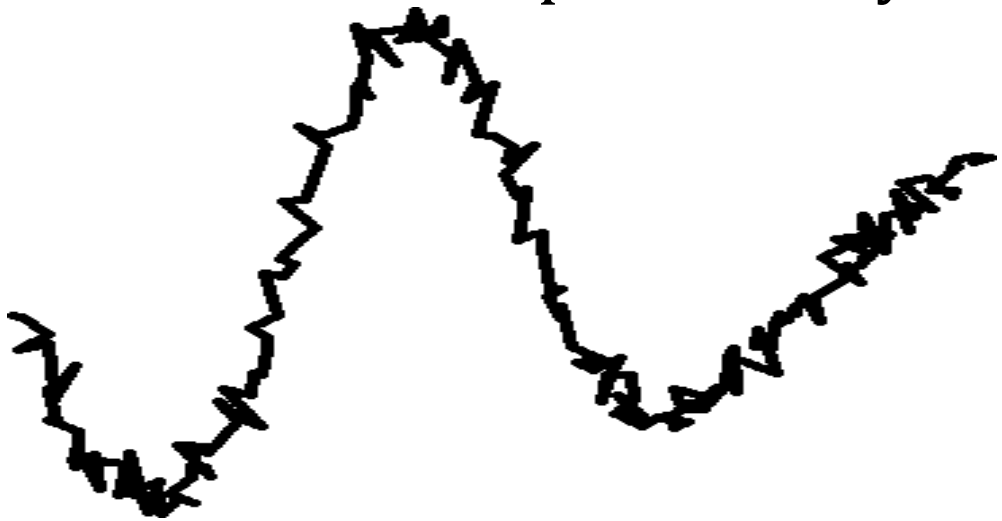
- buyers and sellers do not often meet – not the Börse

Alternative philosophy

- Follow a trajectory in some field



but path is noisy



A particle moves is hit by other particles

- you do not want to model the particles explicitly
- a chemical trajectory with side reactions

Adding noise to systems

Examples here

- Gaussian (normal) noise
  - mean $\mu = 0$
  - call my noise $W(t)$ means $\mu = 0$ and variance $(\sigma^2) = t$
  - not obvious – Brownian processes – you move randomly

Want to build noise into normal simulations

- Normally (Newtonian dynamics, chemical kinetics) – simple integrator

$\frac{dx}{dt} = f(x)$ where f comes from a force or chemistry rate of change

and we have just said $x_{n+1} = x_n + \Delta t\ f(x)$

use $W(x)$ – Wiener process

$x_{n+1} = x_n + \Delta t\ f(x)$ can also write

$x_{n+1} = x_n + dx$

if I have a random process W
$x_{n+1} = x_n + dW$

- Meaning of dW ?
- $W(t)$ is the fluctuation over t – random variable from Gaussian (0,t)
- dW also a random variable - $\sqrt{\Delta t} \cdot \text{gaussian}(0, t)$ more concisely $\sqrt{t}N(0, t)$
  usually use $N()$ to represent Gaussian random number

integrate over random variable

$\frac{dx}{dt} = f(x)$ so $dx = f\big(x(t)\big)dt$

$x = \int f\big(x(t)\big)dt$

for random variable

$dx = dW$

$x = \int dW$ define $X(T) = \int_0^T x(t)dW(t)$ make it discrete

$$\lim_{\Delta t \to 0} \sum_{j=0}^{N_{step}} x(j\Delta t) \cdot \big(W\big((j+1)\Delta t\big) - W(j\Delta t)\big) = \sum_{j=0}^{N\_step} x(j\Delta t)\left(\sqrt{\Delta t}N(0,1)\right)$$

- so a recipe for the diffusive / Brownian motion
- more interesting to combine it

combining classic with noisy methods

A variable X feels a deterministic force $f(X)$ and random $g(X)$

$$dX(t) = f\big(X(t)\big)dt + g\big(X(t)\big)dW(t)$$

$$X(t) = X_0 + \int_0^t f\big(X(x)\big)ds + \int_0^t g\big(X(s)\big)dW(s)$$

- think of a protein *in vacuo* with Newtonian dynamics from $f(X)$ and random effects of solvent from $g(X)$

- connect back to last week and this week chemistry

stochastic chemistry – not Gillespie

- $\mathrm{A} + \mathrm{B} \xrightarrow{k} \mathrm{C}$

$dA = -kAB\ dt \qquad dB = -kAB\ dt \qquad dC = kAB\ dt$

- then add noise

$dA = -kAB\ dt + \kappa A\ dW_1(t) \quad dB = -kAB\ dt + \kappa B\ dW_2(t)$ and

$dC = kAB\ dt + \kappa C\ dW_3(t)$

- simulating ? easy

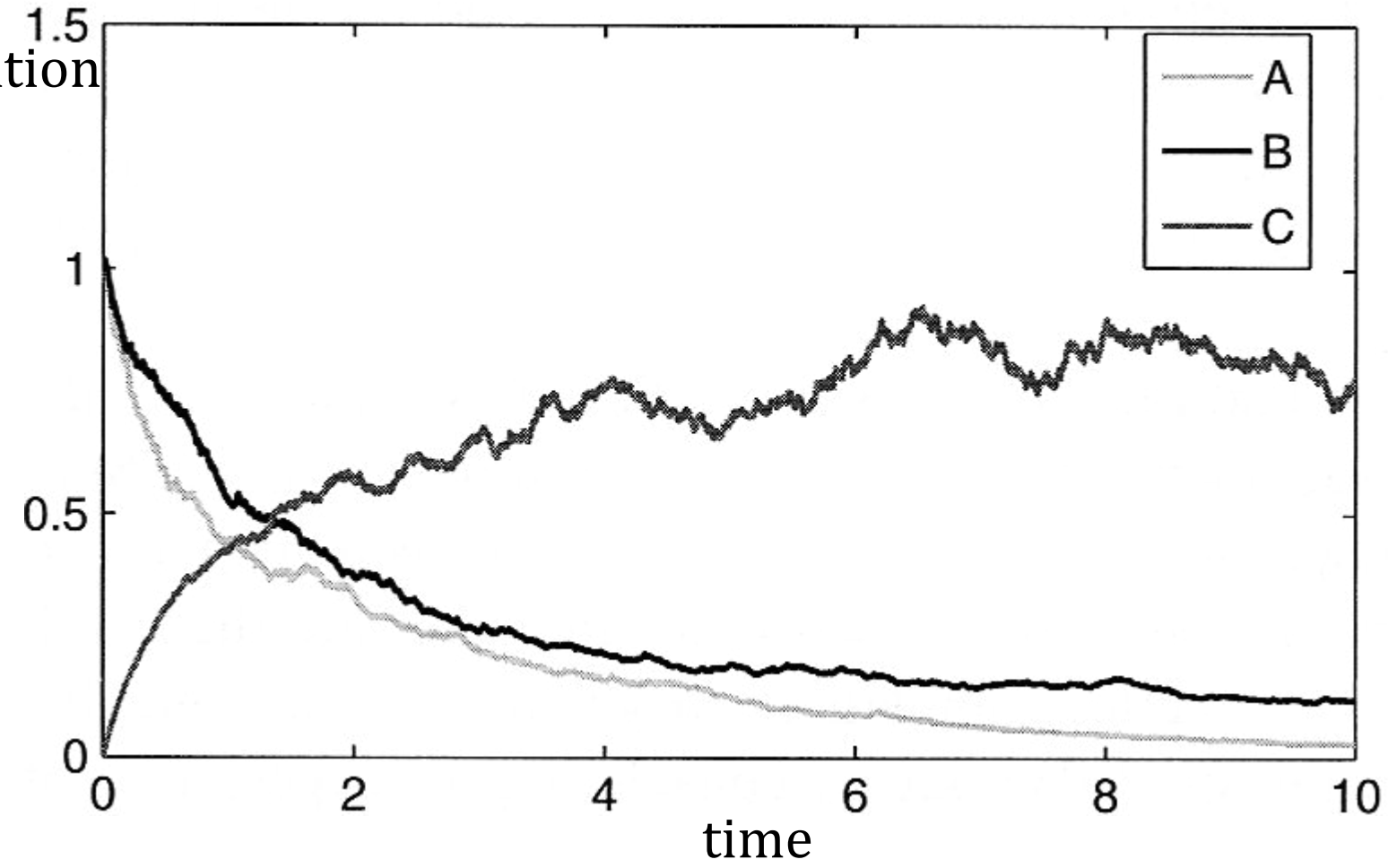
$A_{i+1} = A_i - kA_iB_i\Delta t + \kappa A_0\ \sqrt{\Delta t}\ N(0,1)$

and similar for B and C

$$A + B \xrightarrow{k} C$$

$k = 1 \quad \kappa = 0.01$

$A(0) = 1,\ B(0) = 1,\ C(0) = 0$



Schwartz, R, "Biological modelling and simulation, MIT Press, Massachussets (2008)

Who uses this ?

- Chemistry – reactions with random side reactions
- epidemiology
- ecosystems
- finance – first google hit with maple .. finance [wienerprocess]

Ende Des Semesters

Last week

- simulations and processes using just a transition matrix
- from chemistry to mutations (also works for epidemiology, finance)

Gillespie

- very rigorous
- rather slow

Stochastic differential methods

- general noise
- Brownian dynamics, markets, epidemiology, chemical kinetics
- requires a model for noise - occasionally rigorous