

Stochastic Modelling

www.sbi.uni-rostock.de

Law of Mass Action (LMA):

$$\Delta(\#S) \propto \#S \cdot \Delta t$$

"Averaging" molecule populations: Assume $\#S$ large and Δt small...

$$\frac{dS(t)}{dt} = (k^+ - k^-)S(t) \quad \text{with solution} \quad S(t) = S(0) \cdot e^{(k^+ - k^-)t} \quad (1)$$

This is *not* a deterministic model ... in the position-momentum phase space

For a stochastic model, we are aiming for an expression

$$P(\#S(t + \Delta t) = n) = \sum_m P(\#S(t + \Delta t) = n, \#S(t) = m) \quad (2)$$

From the definition of conditional probability we have

$$P(\#S(t + \Delta t) = n, \#S(t) = m) = P(\#S(t) = m) \cdot P(\#S(t + \Delta t) = n | \#S(t) = m)$$

Substituting this in (2), we get

$$P(\#S(t + \Delta t) = n) = \sum_m P(\#S(t + \Delta t) = n | \#S(t) = m) \cdot P(\#S(t) = m)$$

www.sbi.uni-rostock.de

The cell a soup of molecules?

...choosing an appropriate modelling formalism.

Olaf Wolkenhauer

www.sbi.uni-rostock.de

Markov Modelling

www.sbi.uni-rostock.de

Let $p_{m,n}$ be the transition probability from m to n molecules: (homogenous Markov process):

$$p_{m,n}(t + \Delta t) = \sum_{m=1}^{\infty} p_{m,n} P_m(t)$$

Considering single-step changes, i.e., assuming Δt sufficiently small

$$p_{n,n} = 1 - p_{n,n+1} - p_{n,n-1},$$

the stochastic equivalent of (1) is

$$P_n(t + \Delta t) = p_{n-1,n} \cdot P_{n-1}(t) + p_{n+1,n} \cdot P_{n+1}(t) + (1 - p_{n,n+1} - p_{n,n-1}) \cdot P_n(t)$$

Let

$$p_{n-1,n} = k^+(n-1)\Delta t, \quad p_{n+1,n} = k^-(n+1)\Delta t,$$

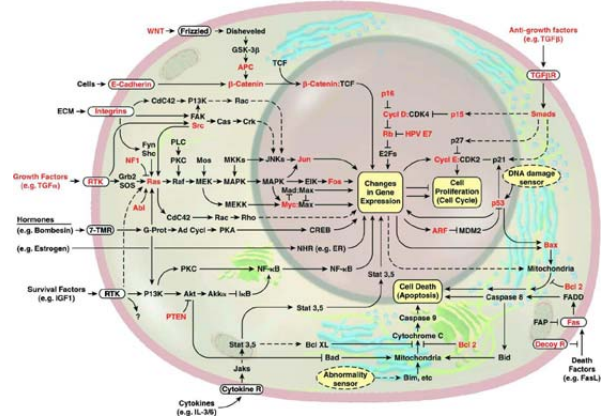
$$p_{n,n-1} = k^-n\Delta t, \quad p_{n,n+1} = k^+n\Delta t.$$

... hence $p_{n,n+1} + p_{n,n-1} \leq 1$ and thus

$$\Delta t \leq \frac{1}{(k^- - k^+)n}$$

Pathways: Networks of Biochemical Reactions

www.sbi.uni-rostock.de



Picture from D.Harshan and R.A.Weinberg "The hallmarks of cancer", Cell, 11(2000): 57-70

Chemical Master Equation Approach

www.sbi.uni-rostock.de

Substituting this above, we get

$$P_n(t + \Delta t) = k^+(n-1)\Delta t P_{n-1}(t) + k^-(n+1)\Delta t P_{n+1}(t) + (1 - k^+n\Delta t - k^-n\Delta t)P_n(t) - (k^+ - k^-)n\Delta t P_n(t) + P_n(t)$$

Taking $P_n(t)$ to the left-hand side and dividing by Δt ,

$$\frac{P_n(t + \Delta t) - P_n(t)}{\Delta t} = k^+(n-1)P_{n-1}(t) + k^-(n+1)P_{n+1}(t) - (k^+ + k^-)nP_n(t)$$

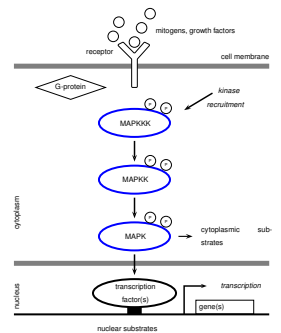
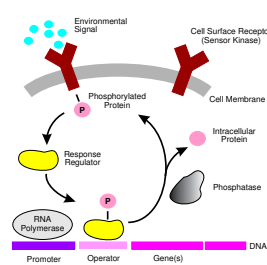
... as $\Delta t \rightarrow 0$, gives the **chemical master equation**.

We are looking for solution of these n ODEs, i.e., $P_n(t)$

Cell Signalling

www.sbi.uni-rostock.de

The Textbook Idea:



... translocation introduces transport delays.

... there are no linear cascades!

ODE model = mean of the master equation model?

www.sbi.uni-rostock.de

$$\begin{aligned}\dot{E}[S_1] &= \sum_{S_1, S_2=0}^{\infty} S_1 \dot{P}(S_1, S_2, t) \\ &= \sum_{S_1, S_2=0}^{\infty} S_1 \left[k_1 A(S_1 - 1)P(S_1 - 1, S_2, t) + k_2(S_1 + 1)(S_2 - 1)P(S_1 + 1, S_2 - 1, t) \right. \\ &\quad \left. + k_3(S_2 + 1)P(S_1, S_2 + 1, t) - (k_1 A S_1 + k_2 S_1 S_2 + k_3 S_2)P(S_1, S_2, t) \right].\end{aligned}$$

Changing the sum indices to get every term to contain $P(S_1, S_2, t)$ we find,

$$\dot{E}[S_1] = \sum_{S_1, S_2=0}^{\infty} k_1 A S_1 - k_2 S_1 S_2 = k_1 A E[S_1] - k_2 E[S_1 S_2].$$

To make this an equation about expectations only, the next step would require

$$E[S_1(t)S_2(t)] = E[S_1(t)] \cdot E[S_2(t)].$$

... at present it is an equation about cross-correlations between the variables.

Chemical Master Equations are not suitable for modelling average processes

LMA-ODE model = E[CME model] ?

www.sbi.uni-rostock.de

Take the expectation of the stochastic, master equation model:

$$\langle S(t) \rangle = \sum_{n=1}^{\infty} n \cdot P_n(t)$$

Insert the eq. for $P_n(t + \Delta t)$ in the equation above

$$\begin{aligned}\langle S(t) \rangle &= \sum_{n=1}^{\infty} n \left[p_{n-1, n} \cdot P_{n-1}(t) + p_{n+1, n} \cdot P_{n+1}(t) + (1 - p_{n, n+1} - p_{n, n-1}) \cdot P_n(t) \right] \\ &= \sum_{n=1}^{\infty} (n+1) p_{n, n+1} P_n(t) + (n-1) p_{n, n-1} P_n(t) + n(1 - p_{n, n+1} - p_{n, n-1}) P_n(t) \\ &= \sum_{n=1}^{\infty} (n + p_{n, n+1} - p_{n, n-1}) P_n(t)\end{aligned}$$

Let $p_{n, n-1} = k^- n \Delta t$ and $p_{n, n+1} = k^+ n \Delta t$, we recover the LMA-ODE model:

$$S(t + \Delta t) = (1 + k^+ - k^-) S(t)$$

... but does this hold for multi-molecular systems ?

Summary: All models are wrong, some useful

www.sbi.uni-rostock.de

▷ LMA-ODE Modelling:

- ✗ continuity in time and magnitude.
- ✗ population model.
- ✗ #S large.

▷ Chemical Master Equation (CME) Approach:

- ✗ Chapman-Kolmogorov Equations
- ✗ Basis e.g.: Poisson-, Birth-Death Processes.
- ✗ population model.
- ✗ LMA-ODE model \neq E[CME model]
- ✗ $\Delta t \leq \frac{1}{(k^- - k^+)n}$

▷ Open Questions:

- ✗ How to simulate a stochastic model?
- ✗ What happens if we deal with few molecules?

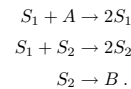
LMA-ODE model = mean of master equation model?

www.sbi.uni-rostock.de

Example: LV coupled differential equations:

$$\begin{aligned}\frac{dS_1}{dt} &= k_1 A S_1 - k_2 S_1 S_2 \\ \frac{dS_2}{dt} &= k_2 S_1 S_2 - k_3 S_2.\end{aligned}$$

Reaction diagram:



Probabilistic model:

$$\begin{aligned}P(\Delta S_1 = 1 \mid \Delta S_2 = 0) &= k_1 A S_1 \Delta t \\ P(\Delta S_1 = -1 \mid \Delta S_2 = 1) &= k_2 S_1 S_2 \Delta t \\ P(\Delta S_1 = 0 \mid \Delta S_2 = -1) &= k_3 S_2 \Delta t \\ P(\Delta S_1 = 0 \mid \Delta S_2 = 0) &= 1 - (k_1 A S_1 + k_2 S_1 S_2 + k_3 S_2) \Delta t\end{aligned}$$

An ODE to ODEs

www.sbi.uni-rostock.de

"The assumptions made by the **deterministic method** do not hold true for many intracellular processes which are sensitive to the behavior of a relatively **small number of molecules**." [LNS01]

"In many situations of interest within cells, the concentration of some or all of the reactants involved in the model is low, and consequently the populations of these may be of the order of less than a **few thousand**. In these cases one can no longer assume that these concentrations vary continuously and the **differential equation approach breaks down**." [vGK01]

"There is also a problem of interpretation by users. Systems of differential equations have a number of parameters that must be fitted from experimental data. However, the **parameters may have no meaning** to the biologists, who are therefore unable to gauge whether the values are appropriate." [XW03]

ODE model = mean of the master equation model?

www.sbi.uni-rostock.de

Notation alert: use S for #S.

As before, using Chapman-Kolmogorov equations, we have the CME-model:

$$\begin{aligned}\frac{P(S_1, S_2, t + \Delta t) - P(S_1, S_2, t)}{\Delta t} &= k_1 A(S_1 - 1)P(S_1 - 1, S_2, t) \\ &\quad + k_2(S_1 + 1)(S_2 - 1)P(S_1 + 1, S_2 - 1, t) \\ &\quad + k_3(S_2 + 1)P(S_1, S_2 + 1, t) \\ &\quad - (k_1 A S_1 + k_2 S_1 S_2 + k_3 S_2)P(S_1, S_2, t).\end{aligned}$$

Suppose we now wish to get the equation for the expectation of S_1 :

$$E[S_1] = \sum_{S_1, S_2=0}^{\infty} S_1 \cdot P(S_1, S_2, t).$$

Inserting the CME in this...

Rate constant k vs. stochastic reaction constant c_μ

www.sbi.uni-rostock.de

... cont'd:

$$\frac{d}{dt} \langle \#X_i \rangle = \sum_{\mu=1}^M \frac{\delta_{i\mu} k_\mu}{(NAV)^{K_\mu-1}} \prod_{j=1}^N \langle \#X_j \rangle^{l_{j\mu}} \quad (6)$$

Assert for the temporal evolution of $\langle \#X_i \rangle$ a "particle-ODE":

$$\frac{d}{dt} \langle \#X_i \rangle = \sum_{\mu=1}^M \delta_{i\mu} k'_\mu \prod_{i=1}^N \langle \#X_i \rangle^{l_{i\mu}} \quad (7)$$

Comparing (7) with (6), we find

$$k'_\mu = \frac{k_\mu}{(NAV)^{K_\mu-1}} \quad (8)$$

From (7) it follows that

$$\langle \#R_\mu \rangle = k'_\mu \cdot \prod_{j=1}^N \langle \#X_j \rangle^{l_{j\mu}} dt \quad (9)$$

... the average number of R_μ reactions in $(t, t + dt)$.

Stochastic Modelling

www.sbi.uni-rostock.de

Objective:

$$\text{Prob}\{\#X(t) = n\} = P_n(t)$$

... where $n \in \mathbb{Z}_+^N, \delta_\mu \in \mathbb{Z}^N$.

Possible state-transitions:

$$n - \delta_\mu \xrightarrow{a_\mu(n - \delta_\mu)} n \quad \dots \text{ from other states to state } n$$

... with propensity $a_\mu(n - \delta_\mu)$.

$$n \xrightarrow{a_\mu(n)} n + \delta_\mu \quad \dots \text{ moving away from state } n$$

... with propensity $a_\mu(n)$.

Chemical Master Equation (CME):

$$\frac{\partial P_n(t)}{\partial t} = \sum_{\mu=1}^M [a_\mu(n - \delta_\mu) P_{(n - \delta_\mu)}(t) - a_\mu(n) P_n(t)] \quad (3)$$

Rate constant k vs. stochastic reaction constant c_μ

www.sbi.uni-rostock.de

$\#R_\mu$: no. of R_μ reactions, is a rv with pmf $p_{r_\mu} = \text{Prob}\{\#R_\mu = r_\mu\}$ and

$$\langle \#R_\mu \rangle = \sum_{r_\mu} r_\mu p_{r_\mu} \quad r_\mu = 0, 1, 2, \dots \quad (10)$$

where

$$p_{r_\mu} = \begin{cases} a_\mu dt + o(dt) & : r_\mu = 1 \\ 1 - a_\mu dt + o(dt) & : r_\mu = 0 \\ o(dt) & : r_\mu > 1 \end{cases} \quad (11)$$

Equation (10) thus becomes

$$\langle \#R_\mu \rangle = 0 \cdot p_0 + 1 \cdot p_1 + \sum_{r_\mu > 1} r_\mu p_{r_\mu}$$

... and from (10) and (11) we therefore have

$$\langle \#R_\mu \rangle = \langle a_\mu dt \rangle + o(dt) \quad (12)$$

Gillespie Modelling

www.sbi.uni-rostock.de

Probability that an R_μ reaction will occur in $(t, t + dt)$:

$$P_\mu(dt) = a_\mu dt$$

... where the propensity of R_μ :

$$a_\mu = h_\mu \cdot c_\mu \quad (4)$$

where $h_\mu = 1$ if $l_{i\mu} = 0$, or if $n_i > l_{i\mu}$

$$h_\mu = \prod_{i=1}^N \binom{n_i}{l_{i\mu}} \quad \dots \text{ for large } n_i \dots \quad h_\mu \cong \frac{\prod_{i=1}^N n_i^{l_{i\mu}}}{\prod_{i=1}^N l_{i\mu}!} \quad (5)$$

... the distinct combinations of R_μ reactant molecules.

... $c_\mu dt$ is the probability that a particular selected combination of R_μ reactant molecules will react in $(t, t + dt)$.

c_μ ... is called the stochastic rate constant

Rate constant k vs. stochastic reaction c_μ

www.sbi.uni-rostock.de

Compare

$$\langle \#R_\mu \rangle = \langle a_\mu dt \rangle + o(dt) \quad (12)$$

with

$$\langle \#R_\mu \rangle = k'_\mu \cdot \prod_{j=1}^N \langle \#X_j \rangle^{l_{j\mu}} dt \quad (9)$$

... gives us an expression for the propensity of R_μ to occur in dt :

$$\langle a_\mu \rangle = k'_\mu \prod_{j=1}^N \langle \#X_j \rangle^{l_{j\mu}} \quad (13)$$

Substitute approximate (5) for h_μ into $a_\mu = h_\mu c_\mu$, and average to get a second equation for a_μ :

$$\langle a_\mu \rangle = c_\mu \cdot \left\langle \frac{\prod_{j=1}^N \langle \#X_j \rangle^{l_{j\mu}}}{\prod_{j=1}^N (l_{j\mu}!)} \right\rangle \quad (14)$$

Rate constant k vs. stochastic reaction constant c_μ

www.sbi.uni-rostock.de

Differential Equation Model (ODE):

$$\frac{d}{dt} x_i = \sum_{\mu=1}^M \delta_{i\mu} k_\mu \prod_{j=1}^N x_j^{l_{j\mu}} \quad (??)$$

... substituting $[X] = X/V = \langle \#X \rangle / (NAV)$ gives

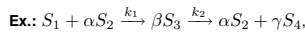
$$\frac{d}{dt} \left(\frac{\langle \#X_i \rangle}{NAV} \right) = \sum_{\mu=1}^M \delta_{i\mu} k_\mu \prod_{j=1}^N \left(\frac{\langle \#X_j \rangle}{NAV} \right)^{l_{j\mu}}$$

... rewrite ...

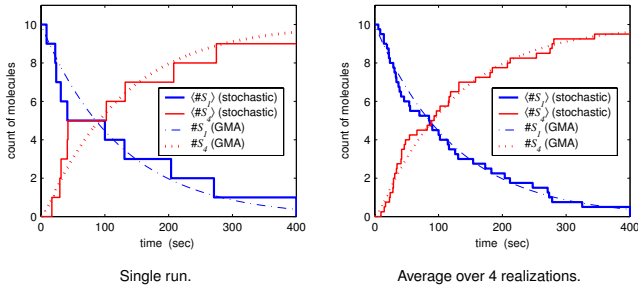
$$\frac{d}{dt} \langle \#X_i \rangle = \sum_{\mu=1}^M \frac{\delta_{i\mu} k_\mu}{(NAV)^{K_\mu-1}} \prod_{j=1}^N \langle \#X_j \rangle^{l_{j\mu}} \quad (6)$$

Stochastic Simulation

www.sbi.uni-rostock.de



$V = 1 \text{ pL}, k_1 = 0.5 \text{ (nM} \cdot \text{sec)}^{-1}, k_2 = 0.2 \text{ sec}^{-1}, \alpha = 1, \beta = 1, \gamma = 1,$
 $\#S_2(0) = \#S_3(0) = 0$



O.Wolkenhauer, Dynamic Pathway Modelling

22

Deriving propensity a_μ of R_μ

www.sbi.uni-rostock.de

Comparing the last two expressions, (14) and (13)

$$k'_\mu \prod_{j=1}^N \langle \#X_j \rangle^{l_{j\mu}} = \frac{c_\mu \left\langle \prod_{j=1}^N (\#X_j)^{l_{j\mu}} \right\rangle}{\prod_{j=1}^N \langle l_{j\mu}! \rangle}$$

Assuming $\langle \#X_i \#X_j \rangle = \langle \#X_i \rangle \langle \#X_j \rangle$,

$$k'_\mu = \frac{c_\mu}{\prod_{j=1}^N \langle l_{j\mu}! \rangle}, \quad \therefore c_\mu = k'_\mu \cdot \prod_{j=1}^N \langle l_{j\mu}! \rangle \quad (15)$$

Inserting (8) for k'_μ , we arrive at an expression for the stochastic rate constant:

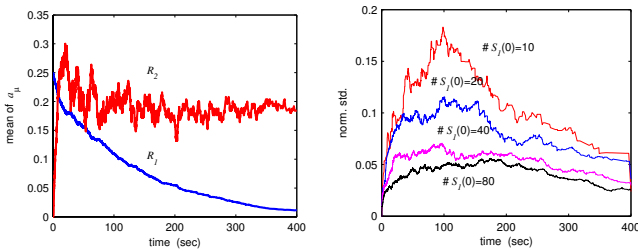
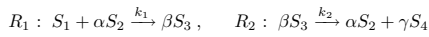
$$c_\mu = \left(\frac{k_\mu}{(N_A V)^{K_\mu - 1}} \right) \cdot \prod_{j=1}^N \langle l_{j\mu}! \rangle \quad (16)$$

O.Wolkenhauer, Dynamic Pathway Modelling

19

Stochastic Simulation

www.sbi.uni-rostock.de



O.Wolkenhauer, Dynamic Pathway Modelling

23

Gillespie Stochastic Simulation

www.sbi.uni-rostock.de

$P(\mu, \tau) d\tau$, the probability that reaction R_μ will occur in $(t + \tau, t + \tau + d\tau)$, given the system is in state $n(t)$.

Gillespie's algorithm answers the following questions:

- Which reaction will occur next?
- When does it occur?

Probability that any of the M reactions occurs in $(t, t + \tau)$

$$\sum_{\nu=1}^M a_\nu d\tau \quad \text{denote} \quad a^* = \sum_{\nu=1}^M a_\nu$$

When?

$$P^{(1)}(\tau) d\tau = \sum_{\nu=1}^M P(\mu, \tau) d\tau = a^* e^{-a^* \tau} d\tau$$

Which?

$$P^{(2)}(\mu|\tau) = \frac{P(\mu, \tau)}{P(\tau)} = \frac{a_\mu e^{-a^* \tau}}{a^* e^{-a^* \tau}} = \frac{a_\mu}{a^*}$$

O.Wolkenhauer, Dynamic Pathway Modelling

20

Summary: Spot the Randomness!

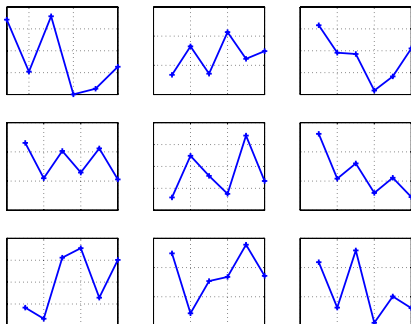
www.sbi.uni-rostock.de

Gillespie simulation:

... realisations of chemical master equations.

... requires repeated simulations for model validation if $\#S$ is low.

Don't forget WYSIWYM!



O.Wolkenhauer, Dynamic Pathway Modelling

24

Gillespie's Direct Method [Gil77]

www.sbi.uni-rostock.de

Step 1. Initialization:

- Set $t = 0$. Fix initial numbers of molecules $\#X_i(0)$.
- Initialize random number generator.

Step 2. Calculate the propensity functions

- $a_\nu = h_\nu \cdot c_\nu$ for $\nu = 1, \dots, M$.
- Calculate $a^* = \sum_{\nu=1}^M a_\nu$

Step 3. Generate two uniformly distributed random numbers r_1, r_2 from the unit interval.

- Determine $\tau = (1/a^*) \ln(1/r_1)$.
- Determine μ such that $\sum_{\nu=1}^{\mu-1} a_\nu \leq r_2 \cdot a^* < \sum_{\nu=1}^{\mu} a_\nu$.

Step 4. Update

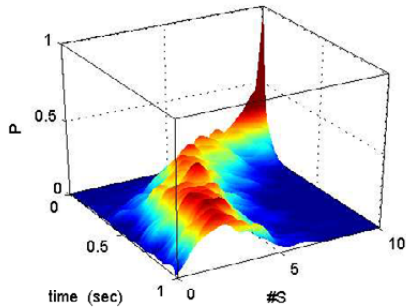
- the number of molecules $\#X_i$ according to the reaction schema of R_μ .
- Put $t = t + \tau$.
- Go to Step 2.

O.Wolkenhauer, Dynamic Pathway Modelling

21

What if?

For $k_1 = 3, k_2 = 1$, focussing on transient changes:



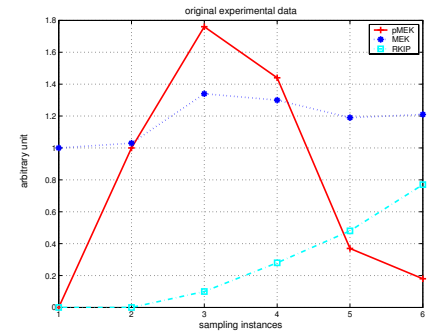
WYSIWYM: What you see is what you model!

Random variable: $\delta_{i\mu}$

$$\Delta(\#X_i) = \sum_{\mu}^M \delta_{i\mu}$$

... δ is $\sim \mathcal{N}(\cdot, \sigma_{\delta}^2)$.

For any further averaging process with m elements (e.g. using 10^7 cells in immunoblotting), the variance is of the order σ^2/m .



Isomerization Reaction

Using *cumulant generating functions* for the general birth-death Markov process:

$$\frac{d\kappa_1(t)}{dt} = \left(\sum_{\mu} c_{\mu 0} \nu_{\mu} \right) + \left(\sum_{\mu} c_{\mu 1} \nu_{\mu} \right) \kappa_1$$

$$\frac{d\kappa_2(t)}{dt} = 2 \left(\sum_{\mu} c_{\mu 1} \nu_{\mu} \right) \kappa_2 + \left(\sum_{\mu} c_{\mu 1} \nu_{\mu}^2 \right) \kappa_1 + \sum_{\mu} c_{\mu 0} \nu_{\mu}^2$$

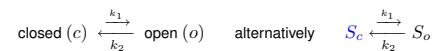
$$\frac{d\kappa_3(t)}{dt} = 3 \left(\sum_{\mu} c_{\mu 1} \nu_{\mu} \right) \kappa_3 + 3 \left(\sum_{\mu} c_{\mu 1} \nu_{\mu}^2 \right) \kappa_2 + \left(\sum_{\mu} c_{\mu 1} \nu_{\mu}^3 \right) \kappa_1 + \sum_{\mu} c_{\mu 0} \nu_{\mu}^3$$

Applied to S_c of the isomerization reaction:

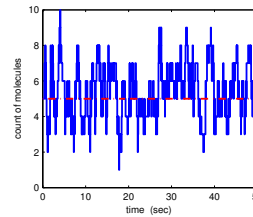
$$\begin{bmatrix} \dot{\kappa}_1 \\ \dot{\kappa}_2 \end{bmatrix} = \begin{bmatrix} -(k_1 + k_2) & 0 \\ k_1 - k_2 & -2(k_1 + k_2) \end{bmatrix} \begin{bmatrix} \kappa_1 \\ \kappa_2 \end{bmatrix} + \begin{bmatrix} k_2 n_T \\ k_2 n_T \end{bmatrix} \quad (17)$$

Isomerization Reaction

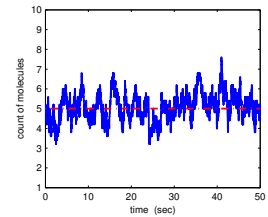
Ex.: Isomerization or gating [RWA02]:



$$\frac{d}{dt} P_c(t) = k_2(n_T - c + 1)P_{c-1}(t) - k_2(n_T - c)P_c(t) + k_1(c + 1)P_{c+1}(t) - k_1cP_c(t)$$

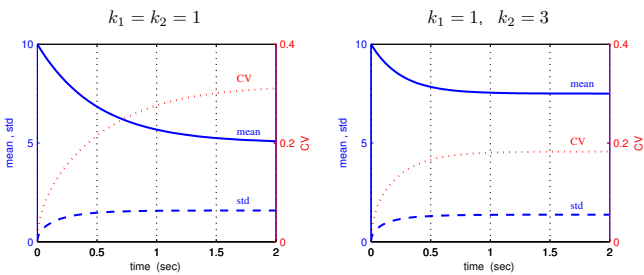


single run



average over 5 runs

Isomerization Reaction

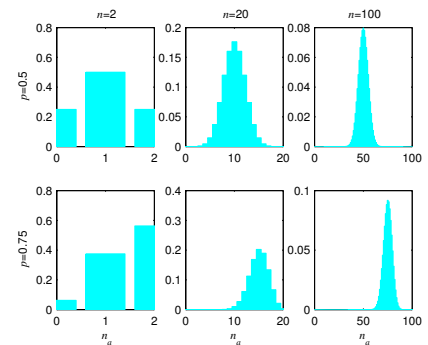


$$\kappa_1(t) = \frac{n_T}{k_1 + k_2} \left(k_2 + k_1 e^{-(k_1 + k_2)t} \right), \quad \kappa_2(t) = \frac{k_1}{k_1 + k_2} \left(1 - e^{-(k_1 + k_2)t} \right) \kappa_1(t)$$

$$CV[S_c(t)] = \sqrt{\frac{k_1}{k_1 + k_2} \left(1 - e^{-(k_1 + k_2)t} \right)} \cdot \frac{1}{\sqrt{\kappa_1(t)}}$$

Isomerization Reaction

Steady-state probability distribution for S_c :



The key issue for modelling intracellular dynamics:

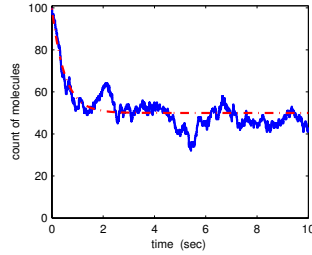
We have to distinguish, physical realism, modelling principles and laws, and modelling relationships we can observe and validate with given experimental data.

Why do ODEs appear to be a 'natural' choice?

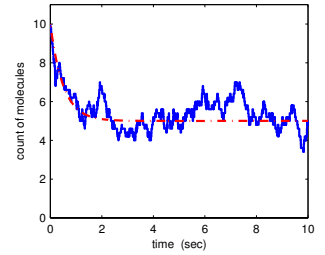
Causation is the principle of explanation of *change* in the realm of matter.

For anything to be different from anything else, either *space* or *time*, or both have to be presupposed.

Causation is a relationship, not between things, but between changes of *states* of things.



single run ($k_1 = k_2 = 1$)



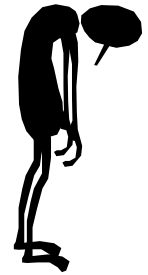
average over 5 runs ($k_1 = k_2 = 1$)

```
new KKK1<> new KKKat1<> new E1<> new E2<>
new KK1<> new KK_P1<> new KK_PP1<> new KFPse1<>
new R1<> new R_P1<> new R_PP1<> new RFPse1<>
new a11.0<> new k11.0<> new a21.0<> new k21.0<>
new a31.0<> new k31.0<> new a41.0<> new k41.0<>
new a51.0<> new k51.0<> new a61.0<> new k61.0<>
new a71.0<> new k71.0<> new a81.0<> new k81.0<>
new a91.0<> new k91.0<> new a101.0<> new k101.0<>
new spike1<>int* (* a spike #2 high of #1 molecules *)
| !spike(a,n); if n=0 then () else (a<> | spikeca,n-1)
| !KKK1();
new d11.0<>
(a1<d1> (d1<>KKK1<> + k1<>KKK1<>))
| !KKK1();
new d21.0<>
(a2<d2> (d2<>KKK1<> + k2<>KKK1<>) +
a3<d3> (d3<>KKK1<> + k3<>KKK1<>) +
a5<d5> (d5<>KKK1<> + k5<>KKK1<>))
| !E1();
a1<d1> (d1<>E1<> + k1<>E1<>)
| !E2();
a2<d2> (d2<>E2<> + k2<>E2<>)
| !R1();
new d31.0<>
(a3<d3> (d3<>KK_P1<> + k3<>KK_P1<>))
| !KK_P1();
new d41.0<>
(a4<d4> (d4<>KK_PP1<> + k4<>KK_PP1<>) +
a5<d5> (d5<>KK_PP1<> + k5<>KK_PP1<>))
| !KK_PP1();
new d61.0<>
(a6<d6> (d6<>KK_PP1<> + k6<>KK_PP1<>) +
a7<d7> (d7<>KK_PP1<> + k7<>KK_PP1<>) +
a9<d9> (d9<>KK_PP1<> + k9<>KK_PP1<>))
| !KFPse1();
a4<d4> (d4<>KFPse1<> + k4<>KFPse1<>) +
a6<d6> (d6<>KFPse1<> + k6<>KFPse1<>)
| !R1();
new d71.0<>
(a7<d7> (d7<>R_P1<> + k7<>R_P1<>))
| !R_P1();
new d81.0<>
(a8<d8> (d8<>R_PP1<> + k8<>R_PP1<>) +
a9<d9> (d9<>R_PP1<> + k9<>R_PP1<>))
| !R_PP1();
new a101.0<>
(a10<d10> (d10<>R_PP1<> + k10<>R_PP1<>))
| !RFPse1();
a8<d8> (d8<>RFPse1<> + k8<>RFPse1<>) +
a10<d10> (d10<>RFPse1<> + k10<>RFPse1<>)
| E1<> (* input signal *) | E2<> | KFPse1<> | RFPse1<>
| spike<KKK,100> | spike<KK,100> | spike<K,100>
```

```
(a6<d6> (d6<>KK_PP1<> + k6<>KK_PP1<>) +
a7<d7> (d7<>KK_PP1<> + k7<>KK_PP1<>) +
a9<d9> (d9<>KK_PP1<> + k9<>KK_PP1<>))
| !KFPse1();
a4<d4> (d4<>KFPse1<> + k4<>KFPse1<>) +
a6<d6> (d6<>KFPse1<> + k6<>KFPse1<>)
| !R1();
new d71.0<>
(a7<d7> (d7<>R_P1<> + k7<>R_P1<>))
| !R_P1();
new d81.0<>
(a8<d8> (d8<>R_PP1<> + k8<>R_PP1<>) +
a9<d9> (d9<>R_PP1<> + k9<>R_PP1<>))
| !R_PP1();
new a101.0<>
(a10<d10> (d10<>R_PP1<> + k10<>R_PP1<>))
| !RFPse1();
a8<d8> (d8<>RFPse1<> + k8<>RFPse1<>) +
a10<d10> (d10<>RFPse1<> + k10<>RFPse1<>)
| E1<> (* input signal *) | E2<> | KFPse1<> | RFPse1<>
| spike<KKK,100> | spike<KK,100> | spike<K,100>
```

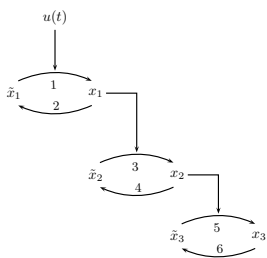
Assumptions made:

- ✗ ... constant volume
- ✗ ... constant temperature
- ✗ ... gas-phase
- ✗ ... well mixed
- ✗ ... rapid diffusion



Markov assumption justified for hard spheres colliding, i.e., collision time is minimal such that collisions are independent.

... all models are wrong, some are useful!



$$\frac{d}{dt}x_1 = \underbrace{\frac{k_1 u(t)(\bar{x}_1 - x_1(t))}{K_{m1} + (\bar{x}_1 - x_1(t))}}_{\text{phosphorylation}} - \underbrace{\frac{k_2 x_1(t)}{K_{m2} + x_1(t)}}_{\text{dephosphorylation}}$$

$$\frac{d}{dt}x_2 = \frac{k_3 x_1(t)(\bar{x}_2 - x_2(t))}{K_{m3} + (\bar{x}_2 - x_2(t))} - \frac{k_4 x_2(t)}{K_{m4} + x_2(t)}$$

$$\frac{d}{dt}x_3 = \frac{k_5 x_2(t)(\bar{x}_3 - x_3(t))}{K_{m5} + (\bar{x}_3 - x_3(t))} - \frac{k_6 x_3(t)}{K_{m6} + x_3(t)}$$

- ✗ ODE model not really "deterministic"
- ✗ ODE models \neq mean of CME
- ✗ CME almost certainly more complex than ODE
- ✗ Stochastic simulation exact realization of CME
- ✗ In implementations c_μ of CME 'relies' on k 's of ODE
- ✗ Derivation of c_μ relied on large $\#X$
- ✗ We were looking at pools of molecules (which is fine!)
- ✗ Stochastic simulation allows for changes in temperature, volume
- ✗ For small populations, multiple realizations, replicate time series required
- ✗ Dynamic or transient vs. steady state modelling
- ✗ Single cell vs. culture/tissue modelling
- ✗ WYSIWYM: What you see - is what you (should) model.



Systems biology is the art of making the right assumptions!

References

- [Gil77] D.T. Gillespie. Exact stochastic simulation of coupled chemical reactions. *The Journal of Physical Chemistry*, 81(25):2340–2361, 1977.
- [LNS01] N. Le Novère and T.S. Shimizu. STOCHSIM: modelling of stochastic biomolecular processes. *Bioinformatics*, 17:575, 2001.
- [RWA02] C.V. Rao, D.M. Wolf, and A.P. Arkin. Control, exploitation and tolerance of intracellular noise. *Nature*, 420:231–237, 2002.
- [vGK01] C. van Gend and U. Kummer. STODE - automatic stochastic simulation of systems described by differential equations. In Yi and Hucka, editors, *Proceedings of the 2nd International Conference on Systems Biology*, pages 326–333, Pasadena, 2001. Omnipress.
- [XW03] X.-Q. Xia and M.J. Wise. DIMSim: A discrete-event simulator of metabolic networks. *J. Chem. Inf. Comput. Sci.*, 43:1011–1019, 2003.

... only one more slide!

Other Formalisms:

- ✗ Cells as Computation: π -Calculus
- ✗ Molecules as Agents: Discrete Event System Specifications (DEVS)

Their Critique of Differential Equation Modelling:

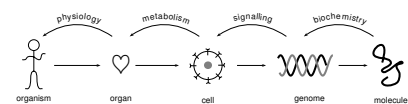
- ▷ Molecule model with higher resolution
- ▷ Changes discrete not continuous
- ▷ Events time-driven not state-driven
- ▷ Spatial simulation easy

The Purpose of Modelling and Simulation:

- ▷ DEVS/ π -calculus people employ Gillespie algorithm for simulation
- ▷ Simulation vs. Modelling
- ▷ Monte-Carlo vs. Stability- and Bifurcation Analysis

Control, Regulation, Feedback

Choosing the right level and resolution:



Dynamic interactions of system variables give rise to *cell functions*.

Systems- and Control Theory:

1. To *control, regulate* or *coordinate* whatever, means to adapt, maintain, optimize.
2. There must exist a *goal* or *objective*.
3. To induce a change, information must be *fed back*.
4. Feedback implies a *before* and *after* – in a *dynamic system*.
5. Therefore: **Feedback loops are the basis for control and regulation in dynamic systems.**

It is feedback that gives rise to *dynamic motifs*, including oscillations, switching, adaption, tracking etc.

Thank you for your attention!

**A cell is built up of molecules, as a house is with stones.
But a soup of molecules is no more a cell
than a heap of stones is a house.**