Mathematical modelling:
Choosing the right simulation method

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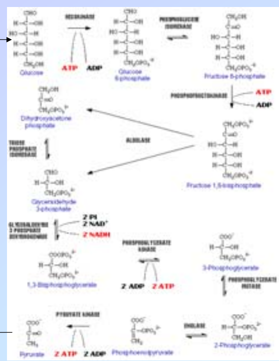
Overview

- Introduction
- Numerical Integration
- Stochastic simulation (e.g. Gillespie)
- Deciding on the right method
- Conclusion

You have a model e.g. for glycolysis:

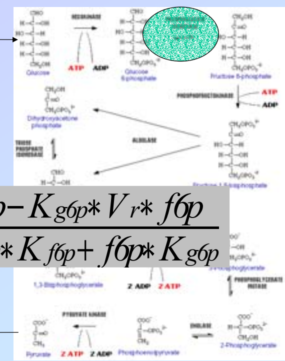
$glc' = v_{trans} - v_{hk}$
$g6p' = v_{hk} - v_{pgi}$
$f6p' = v_{pgi} - v_{pfk}$
$f16p' = v_{pfk} - v_{ald}$
$dhap' = v_{ald} - v_{ti}$
$gap' = v_{ald} + v_{ti} - v_{gpdh}$
$bpg' = v_{gpdh} - v_{pgk}$
$p3g' = v_{pgk} - v_{pgm}$
$p2g' = v_{pgm} - v_{eno}$
$pp' = v_{eno} - v_{pyk}$
$py' = v_{pyk} - v_{py}$



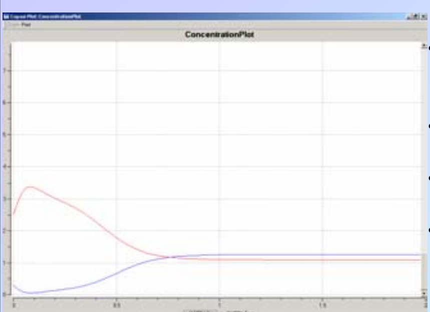
where all terms v_i stand for reaction, transport or diffusion kinetics, e.g. V_{pgi}

- Reversible MM

$$v_{pgi} = \frac{K_{f6p} * V_{hin} * g6p - K_{g6p} * V_r * f6p}{K_{g6p} * K_{f6p} + g6p * K_{f6p} + f6p * K_{g6p}}$$



Bringing a model to life - Simulation

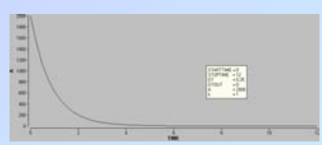


- Numerical Integration of ODEs
- Stochastic methods
- (Petri-Nets)
- (Process algebra)

Solving the ODE analytically?

- Only possible for linear systems and a few simple nonlinear ones

Example:
$dA/dt = - k*A$



Separation of variables:
-> $\int_{A0}^{A} \frac{dA}{A} = \int_{0}^{t} -k * dt$

Integration:
-> $\ln \frac{A}{A_0} = -k * t$

$A(t) = A_0 * e^{-k*t}$

Numerics: e.g. Euler:

Problem:

$dx/dt = f(x)$

and $x = (x_1, \ldots\ldots. x_n)$

Approach:

Discretize time in intervals Δt.

Initial value:

$x(t_0) = x_0$

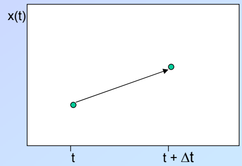
look for $x(t_0 + \Delta t) = ???$

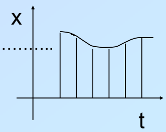
Taylor expansion:

$x(t_0 + \Delta t) = x(t_0) + (dx/dt)_{t0} {*} \Delta t + 1/2(d^2x/dt^2)_{t0} {*} \Delta t^2 + \ldots\ldots\ldots\ldots$

For small Δt : $x(t_0 + \Delta t) = x(t_0) + (dx/dt)_{t0} {*} \Delta t$
$x(t_0 + \Delta t) = x(t_0) + f(x) {*} \Delta t$

Error is proportional to (d^2x/dt^2)





Other numerical methods

- Euler and Runge-Kutta of low order are not suitable in our context
- Advanced Runge-Kutta-Methods with variable time steps and other features (e.g.: Rosenbrock)
- Predictor-Corrector-Methods:
  Control of the integration by backwards differentiation.
  (e.g.: Gear, LSODE (Hindmarsh et al.), LSODA)

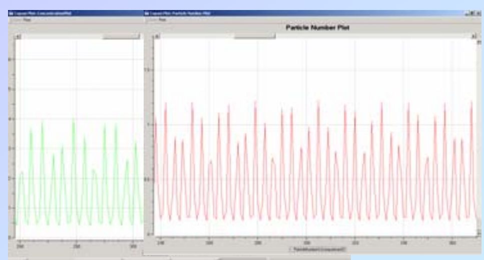
Details s. Numerical Recipes

Software

- Practical all mathematics software like MAPLE, Matlab Mathematica, Octave etc.
- Linux: gnuode
- More comfortable:
  Madonna, SBW,
  Copasi (collaboration with Pedro Mendes) etc.

When ODEs fail.....

- low number of particles -> no continous concentrations
  -> high stochasticity



Monte Carlo Simulations

- $w_j {*} dt$ gives the average probability that a SINGLE reaction of type j will occur in the time interval dt
- E.g.: $X \longrightarrow B$
  w for the transition $n \longrightarrow n-1$: $w_{(n-1){*}n} \sim n$
  or $w_{(n-1){*}n} = k{*}V{*}c_x$
- E.g.: $A + 2X \longrightarrow 3X$
  w for the transition $n \longrightarrow n+1$: $w_{(n+1)n} \sim n{*}(n-1){*}c_A$

Simulation of a trajectory using the Gillespie algorithm

(1) Calculate total reaction probability:

$$u_0(n) = \sum_j w_j$$

(2) Determine a stochastic time step:

$$\Delta t = -\frac{\ln(\xi_1)}{u_0(n)}$$

(3) Determine the reaction that takes place:

$$\sum_{j=1}^{\alpha-1} \frac{w_j}{u_0(n)} \le \xi_2 \le \sum_{j=1}^{\alpha} \frac{w_j}{u_0(n)}$$

(4) Realize the reaction -> (1)

Advanced stochastic methods

• Gibson and Bruck:
In principle, no different from Gillespie, but faster since reactions are sorted in a priority-queue according to their individual “tau”

• Tau-leap-Method by Gillespie:
Tries to do several steps at once

• Hybrid-Methods (e.g. Haseltine, Pahle, Kierzek etc.)

Software

• STODE

• StochSim

• Stochastirator

• Copasi

• etc.

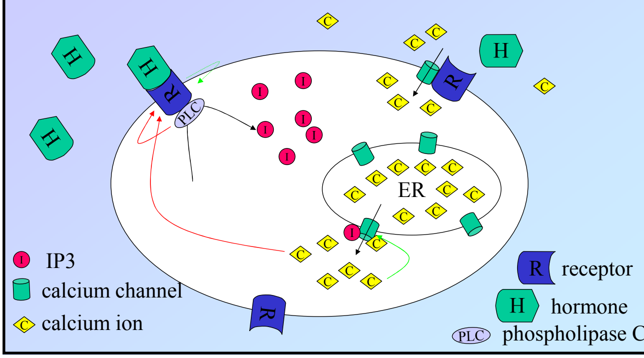
How do you decide?

• Passively (never thought about it)

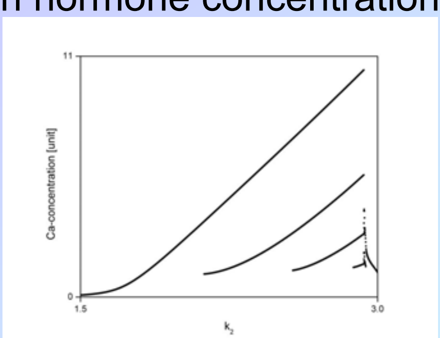
• A little bit actively (following some heuristics)

• Very actively (trying it out)

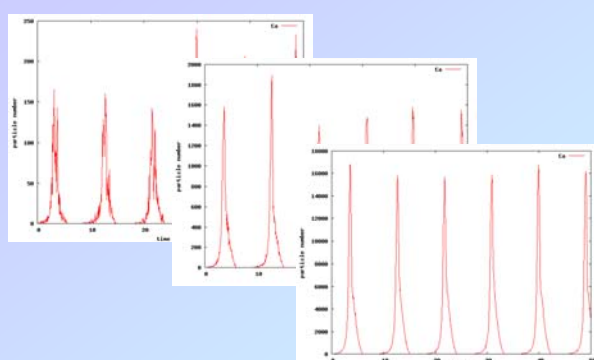
Example: Calcium signal transduction



Different dynamics depending on hormone concentration



Transition stochastic/deterministic



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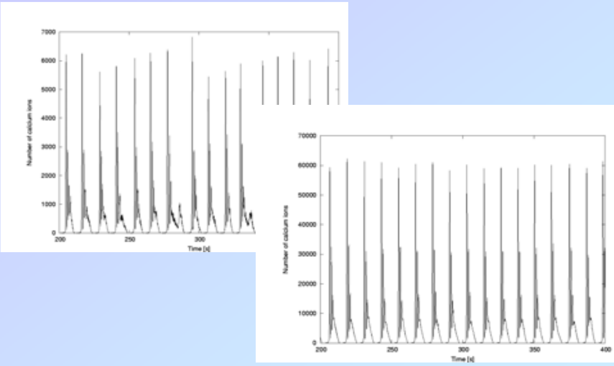
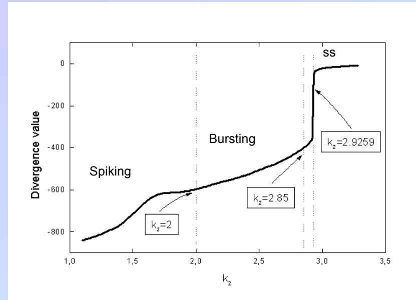
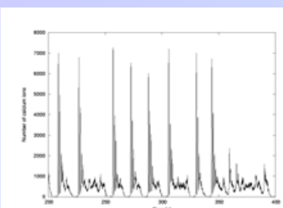
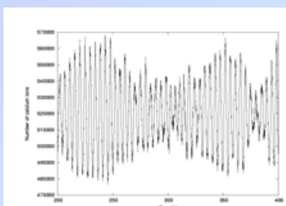


Correlation with divergence



Stochastics does not only add noise....





Approaching a steady state!

Conclusion

- Decision between simulation methods has to be done with care
- No general decision w.r.t. a specific model possible
- Calculating the divergence can help

Acknowledgments

Funding:
Klaus Tschira Foundation
BMBF