Worksheet: STOCHASTIC MODELLING (26. June 2012)
Lecture "Computational Systems Biology", Dr. Jürgen Pahle

1) Comprehension questions
a) What are the problems of deterministic modelling?
b) What are the problems of stochastic modelling and simulation?
c) How does Gillespie's Direct Method work?
d) Which random distributions are used in the Direct Method?
e) What are the reasons for hybrid modelling? What advantages and problems does it have?
f) Is the mean of the stochastic model always the same as the corresponding deterministic solution? If yes, prove it! If no, give a counter-example! Why is this important for models of populations?
g) Find out what is meant by "intrinsic" and "extrinsic fluctuations" in the literature.
h) Most models available must be adapted to be simulated stochastically. What are the main points here? See 2) for this.

2) Preparing models for stochastic simulation

Not all models are suitable for stochastic simulation directly. This has to be kept in mind particularly if biochemical models encoded in SBML are downloaded from online databases such as from the Biomodels.

Open COPASI and implement the Michaelis-Menten reaction scheme ($S + E \leftrightarrow ES$ and $ES \rightarrow E + P$). Set $[S](0) = 10$, $[E](0) = 1$, and $[ES](0) = [P](0) = 0$. Create an appropriate plot and simulate the system deterministically (LSODA) over 300 seconds (increase the number of intervals to 1000). Switch the simulation method to "Stochastic (Direct Method)" and press run. COPASI refuses to simulate the model. Instead it shows an error message saying that "At least one reaction is reversible. That means stochastic simulation is not possible." Why is that?

Use COPASI's "Convert to irreversible" tool to remedy that and have a look at the reactions and kinetic laws in the model afterwards. What has changed?

Try the stochastic simulation again. COPASI still refuses to simulate the model since it found out that the particle numbers in the system are too high for stochastic simulation. The reason for this is that the model has a

rather large volume and high concentration, leading to a very large number of particules. *E.g.* 6.02 x 10^{21} particles of *S* is a number that is clearly much too high for stochastic simulation. In fact, it cannot even be represented in the computer (not even in the 64 bit integer numbers that COPASI uses internally for particle numbers). This is a very common problem since the deterministic formalism (ODEs) is based on concentrations and uses floating point numbers (rather than integers) which allow representation of much larger numbers. In addition, the absolute volumes (cytoplasm, chemical reactor, etc.) are often not of interest to modellers. It is not uncommon to find models where the volumes are left at default values of the software tools which are totally unrealistic for cells (e.g. 1 l or 1 ml).

Even if the particle numbers can be represented in the computer they are very often so high that stochastic simulation does not make sense. Therefore, change the volume to 1e-19 l in your model; this adjusts the number of particles down (in order to keep the same concentrations) and the size of the system becomes manageable for the stochastic algorithm. Finally, run the stochastic simulation several times.

3) Stochastic effects

a) **Varying variances**

Implement a linear birth-death process ($S \rightarrow 2\ S$ and $S \rightarrow$) that represents, *e.g.*, the number of cells in a bacterial colony. Set the reaction constant of the first reaction to 0.1 and the one of the second reaction to 0.2. Create a plot with the particle number of *S* and simulate the system deterministically over 100 seconds. Now change the system's volume to 10^{-18} [ml] and run several stochastic simulations. How does the system's variance (in *S* particle number) change over time? COPASI's repeat tool in the Parameter Scan task helps here. Does it always increase? Change the two reaction rates, such that their difference stays the same, *e.g.* 2.1 and 2.2. How does this change the deterministic and stochastic solutions? Study the uncertainty about the system (variance) at time point $t = 20$ [s], say. Try to use COPASI's parameter scan (repeats) and histogram plot facilities to create a histogram of particle number of *S* at this time point.

b) **Bistability**

Download the model file Schloegl.cps from the course website and open it in COPASI. This model implements the Schlögl reaction system, a

classical example of a bistable system. Inspect the model and run several stochastic simulations. What can you say about the system's behaviour?

Switch back to deterministic simulation and simulate the system with different initial particle numbers of *X*. What happens?

Set the compartment volume to a value of 0.2 [l], go back to the time course task, change the simulation method back to one of the stochastic methods. Also, increase the simulation time ("Duration") to 1000, and the number of sampling intervals to 1000. Simulate the system a few times stochastically. What can you say about the systems behaviour?

Since the Schlögl system spends most of its time in the vicinity of its two stable states this leads to a bimodal system state probability distribution that displays two peaks at the two stable states. Try to generate a histogram plot for the particle number of *X* that lets you see this bimodal distribution and discuss it.

c) **Extinction of species**

Download the model file Lotka-Volterra.cps from the course website and open it in COPASI. This file contains a classical model of epidemiology. The Lotka-Volterra equations can be interpreted as a simple predator-prey system, where a predator species F ("foxes") feeds on a prey species R ("rabbits"). The rabbits reproduce with a constant rate (Reaction 1). When foxes and rabbits "meet" the rabbit is eaten and the fox can reproduce afterwards (Reaction 2). Also, the foxes eventually die with a constant rate (Reaction 3).

Run a deterministic simulation. How does the system behave? Now run a few stochastic simulations. What happens? And why?

4) Hybrid simulation

Download the file HybridModel.cps from the course webpage and open it in COPASI. Have a look at the reactions and settings, and try to understand the model. Run the simulation and then zoom into the timecourse to see what actually happens.

Read the section corresponding to hybrid simulation in

Hoops *et al.* (2006) COPASI - a COmplex PAthway SImulator. Bioinformatics 22(24):3067, doi:10.1093/bioinformatics/btl485

and the COPASI documentation and try to understand how the hybrid simulation works.