Install Copasi

Download files and installation instructions can be found at `http://www.copasi.org/tiki-view_articles.php`

1 In-class exercise: Drug binding

This is a deliberately long and difficult exercise. We do not expect you to finish it all in class. Just go through the steps and do what you can in the allocated time. If you get bored, feel free to jump to the "Mystery Model" exercise in section 2.

1.1 Drug-receptor binding

A drug binds to a receptor with a 1:1 stochiometry to form a drug-receptor complex. Encode this model in Copasi and run a time course simulation. Go through the following steps:

1. Start CopasiUI (UI stands for User Interface)

2. Specify the chemical species of your model first (i.e. the drug, the receptor and the complex). You can do so by going to Model → Biochemical → Species. Double click on the first species in the species table. You will see a little interface that allows you to name the species and to give it an initial concentration (in mmol/ml). You do not have to worry about the other fields for now. Hit "Commit" when you are done.

3. Save your model (now and frequently in the future) by clicking on File → Save. The model will be saved in Copasi's native .cps format. It is also possible to export a model to SBML, which is a standard format that can be read by a range of other tools.

4. Specify the reaction rates in Model → Biochemical → Global Quantities. Again, you can name your quantities (since we are specifying binding rates, something like kf and kb would be good names for the forward and backward reaction) and give them an initial value. (Units will depend on the reactions the rates are used in, and will be assigned by Copasi automatically). Don't forget to hit "Commit" when you are done.

5. Specify the reaction by going to Model → Biochemical → Reactions. Give the reaction a name. Reactions are specified by using a "chemical" type of notation. For instance, if A binds to B to produce C, we would write

   ```
   A + B -> C
   ```
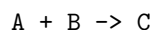
   You can choose whether or not to make the reaction reversible. Note that if you make the reaction reversible, the little arrow changes into an equal sign (=). You will also notice, that as you type the colour of the reaction

window changes between pink and blue. Blue means that the reaction syntax is OK, pink means that something is wrong.

Once you have specified the reaction, choose the rate law from the drop-down menu. In this workshop, we will use Mass Action for everything. You can now assign a parameter to your reaction in the "Symbol Definition" table: The drop-down menu under "Mapping" will allow you to specify one of the parameters you have previously defined in "Global Quantities".

6. Before you can run a simulation, you have to specify what it is you want to see. To do this, go to Output Specifications → Plots and create a new plot. In your plot, clicking on "New Curve" allows you to specify what you want to plot. In our case, we want Model time on the x axis (Time → Model Time) and transient concentrations of our species of interest on the y axis (Species → Transient Concentrations). Several species can be selected at once by using Ctrl-click.

7. Now you are ready to run the simulation. Go to Tasks → Time Course, and select the duration (in seconds), and the number of intervals (100 is usually not bad). Clicking "Run" should start the simulation and bring up the plot you have specified previously.

Answer the following questions:

- Does your system reach a steady-state? What happens if you increase or decrease the simulation time?

- What changes if you make your reaction irreversible (i.e. drug binds to receptor, but never dissociates)

- What changes if the reaction is reversible, but you change one of the reaction rates?

- What happens if you change the concentration of receptor?

1.2 Drug delivery and clearance

Now, we extend the model. Instead of starting with a fixed amount of drug which is being used in the reaction, we will add a constant flow of drug delivery (imagine an IV drip), and a constant rate of clearance (imagine excess drug being cleared from the blood).

1. Define two additional rates (delivery and clearance).

2. Define two new reactions. In Copasi, one side of a reaction can be left empty in order to model creation (or destruction) of a chemical species.

Answer the following questions

- How does the behaviour of this system change from the one in the previous exercise?

- What happens if you increase the rate of drug clearance? What happens if you decrease the rate of drug clearance?

1.3 Two binding sites

So far, one molecule of the drug has been binding to one molecule of the receptor. But what if the receptor has two binding sites for the drug?

There are several ways to encode this, so think about it, and choose a way that makes sense for you.

- How do forms of the receptor (unbound, bound to one molecule of your drug, bound to two molecules of your drug) change over time?

- Can you make ligand binding cooperative?

1.4 Competition

What if your drug competes with an internal ligand for the same receptor that can bind to the same binding sites? How much drug do you need to outcompete the internal ligand, and how does this depend on reaction rates?

2 Mystery Model

- The following model contains four non-reversible reactions. Here are the reactions and their rates:

Reaction	rate
A + B -> 2 * A + B	$0.02 \frac{\text{ml}}{\text{mmol}*\text{s}}$
A ->	$0.4\ s^{-1}$
B -> 2 * B	$0.1\ s^{-1}$
A + B -> A	$0.02 \frac{\text{ml}}{\text{mmol}*\text{s}}$

- Draw a diagram of what happens in this model.

- Encode the model in Copasi. Choose initial concentrations of $1 \frac{\text{mmol}}{\text{ml}}$ for A and $100 \frac{\text{mmol}}{\text{ml}}$ for B.

- How do you think the concentrations of A and B will change over time?

- Plot concentrations of A and B, and run a time course for $20\,$s. What do you see?

- Run a time course for $200\,$s. What do you see?

- What is the maximum value of B?

- If you increased A from 1 to 100, how would you expect your results to change?

- Increase A from 1 to 100. What happens?

- The county of Utopia has a rabbit problem. In order to control the rabbit population, the local government decides to increase the number of foxes by a factor of 100. Is this a winning strategy? Why or why not?

- If you wanted to model actual foxes and rabbits in the wild, what changes would you need to make to your model? How does this affect what happens?

3 BioModels Database

- Go to the "Model of the Month" pages on BioModels database: `https://www.ebi.ac.uk/biomodels-main/modelmonth` They contain nicely written descriptions of selected models, their biological context and their main results with a link to the model itself.

- Look for a model that seems interesting to you. Read the "Model of the Month" article about it.

- Follow the link to the model itself. Explore the description of the model on BioModels database. What information can you find?

- Download the paper describing the model.

- Click on "Download SBML" to get the model. (SBML stands for Systems Biology Markup Language, a standard format for encoding biological models). If you have a choice, download the version marked "curated" (in bold)

- In Copasi, use File $\rightarrow$ Import SBML to import the SBML file. (If you see a warning message, you can probably ignore it). Explore the model. How many chemical species does it have? How many reactions? How many parameters? Can you relate all the parts of the model to what you read in the "Model of the Month" feature?

- Can you run a simulation and reproduce some of the figures in the paper?