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Continuous Modelling CellDesigner and COPASI

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Introduction

This training session is focused on reaction networks, a kind of networks used to model systems dynamical systems usually based on ordinary differential equations. Once again, remember that modelling often implies scaling down reality to a simpler representation. You should become able to translate ideas into formulas that represent the rate of change of certain entities. You will also learn that it is possible to fit experimental results and models automatically.

Introduction to Continuous Modelling

In this training session we will work with continuous models and, in particular, we will use CellDesigner to draw our model and we will use COPASI to analyse its behaviours. We will understand the complexity of making and analysing continuous models.

1. If you have CellDesigner correctly installed on your computer you should be able to start it either by double clicking on its icon or by typing this command in terminal: `./runCellDesigner4.4` (Note that the version number might be different). If you don't have it, download and install it.
2. Create a new model by clicking "File" → "New". Give it a name and click "OK".
3. Create a simple model where one protein *Protein A* has a simple transition to a *Modified Protein A*. Your model should look like the the following picture:

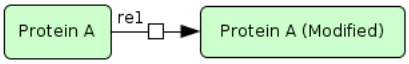

Figure 1:

4. By right clicking on the little square over the arrow you can select "Edit KineticLaw" to assign to a formula to this reaction. You should see the window in Figure 2.
5. Now you can add the Mass Action law to your reaction. The result of your reaction is the modified version of Protein A, whose identifier is s2. If you want to write a formula you want to write how s2 should be calculated. In our case we should write $s1 * k$, meaning that s2 is proportional to s1 by a constant k. In order to do this it is better to click

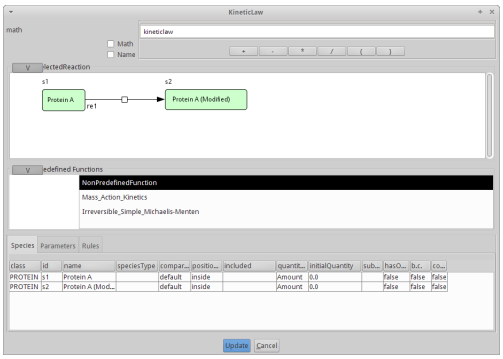

Figure 2:

on "Mass_Action_Kinetics" and fill in the given field. Leave s1 as is and assign an arbitrary value to k, for example 0.004. Once you set s1 and k close all open windows and go back to the main window.
Using predefined formulas will automatically create parameters in the environment which, in case you write your formulas by hand, need to be added separately in the "Parameters" tab.

6. Click on "Simulation" $\rightarrow$"Control Panel" and ignore the warning message.

7. Our reaction depends on the concentration of s1, which is transformed in s2. In order to see the rate of change we need to set an initial concentration. Click on the field "Initial Quantity" and set s1 to 10 units then hit "enter".

8. Set "End Time" to 500 and click the button "Execute". You should see a graph like the one shown in Figure 3. As you can see the concentration of one entity decreases as the concentration of the second one increases as expected. *Protein A* is consumed in favour of *Protein A (Modified)*

9. "Parameter sensitivity" tells us how much a system is affected by small alterations in variables and parameter. If you go to the "Parameter Scan" tab you can automatically vary one parameter and see how the system reacts. Check "Scan parameter" and toggle to "Parameter value", you will see "re1:k1" in the "Name" field. Set as "End time" 100 and click "Execute".

10. Click on "Results" tab, "Overlay Settings" and check both entities (Protein A and it's modified form). Check that all Overlays are checked and click "Show Graph". You will see a series of curves that depend on the different value of k1 in reaction 1. Clearly, a k of 0 doesn't change the concentration of the two species involved while with any other value of k you can see that the intersection of the two curves (The point where the concentration of the modified protein starts to become more than the non

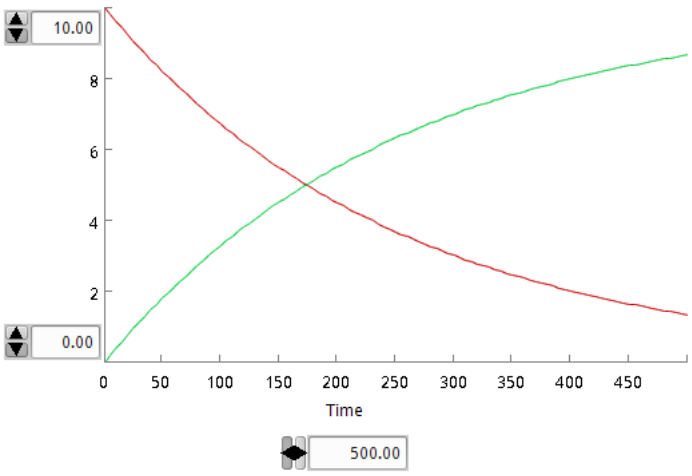

Figure 3:

modified protein) is delayed in time. This can tell us, for example, that a daises or a drug that alter this k can delay a "reaction" in the system.

11. Save this model with a name you remember, e.g.: "my_model.xml"

12. Suppose you did an experiment in lab and you had the following concentrations in time:

Time	Protein A	Protein A (Modified)
1	10	0
2	8	2
3	6	4
4	3	7
5	1	9

create a text file with these values separated by tabulation, include a header line.

13. Start COPASI and click "File" → "Import SBML" and select the file you saved during point 11. In this way you load the model we created in CellDesigner.

14. We now want to estimate the k of our reaction according to experimental results. Click on "Parameter Estimation" →. Click on the button "Experimental Data", then click on the little green plus sign in the middle of the window that shows up and open your experimental data from point 12.

15. Select "Time Course" ans set Time to type "Time", Protein A to "Dependent" (Depends on time chenges) and link it to "Transient Concentration"

for Protein A. Do the same for Modified Protein A and its rate. Click "OK".

16. The "Object" of our study is k, then click on the little 6 icon beside the "Object" field and select the "Reaction Parameter" k1. Click "Run".

17. In the "Results" subsection under "Parameter Estimation" you can find the "Parameters" tab that displays the estimated k "Value".

18. Go back to CellDesigner, set the estimated value for k in the simulator and run the simulation again. Under "Table" you can see that the estimated k can fit fairly well your experimental data. for example, our experiment at time 3 told us that we had 6 Protein A and 4 Protein A (Modified) while in the "Table", with the estimated k, we obtained 3.2 and 6.8 respectively. This final step tuned our model to our data, in this way, we can play with concentrations and see how the system reacts and, possibly, mimic the real behaviour of our experimental setting.

Conclusions

In this session you learn how to translate your idea into dynamical models using a common graphical standard and file format SBML. You know how to assign kinetic laws (laws that describe how things vary in time) to your reactions and how to simulate and perturb your model. Finally, you now know that it is possible to fit experimental data with dynamical models. CellDesigner is a powerful too to graphically model biological models based on reactions. COPASI offers a great variety of tools to do Stability Analysis, Parameter Estimation and other complex mathematical operations, if you have time, feel free to experiment other features of both software.