CellDesigner Tutorial

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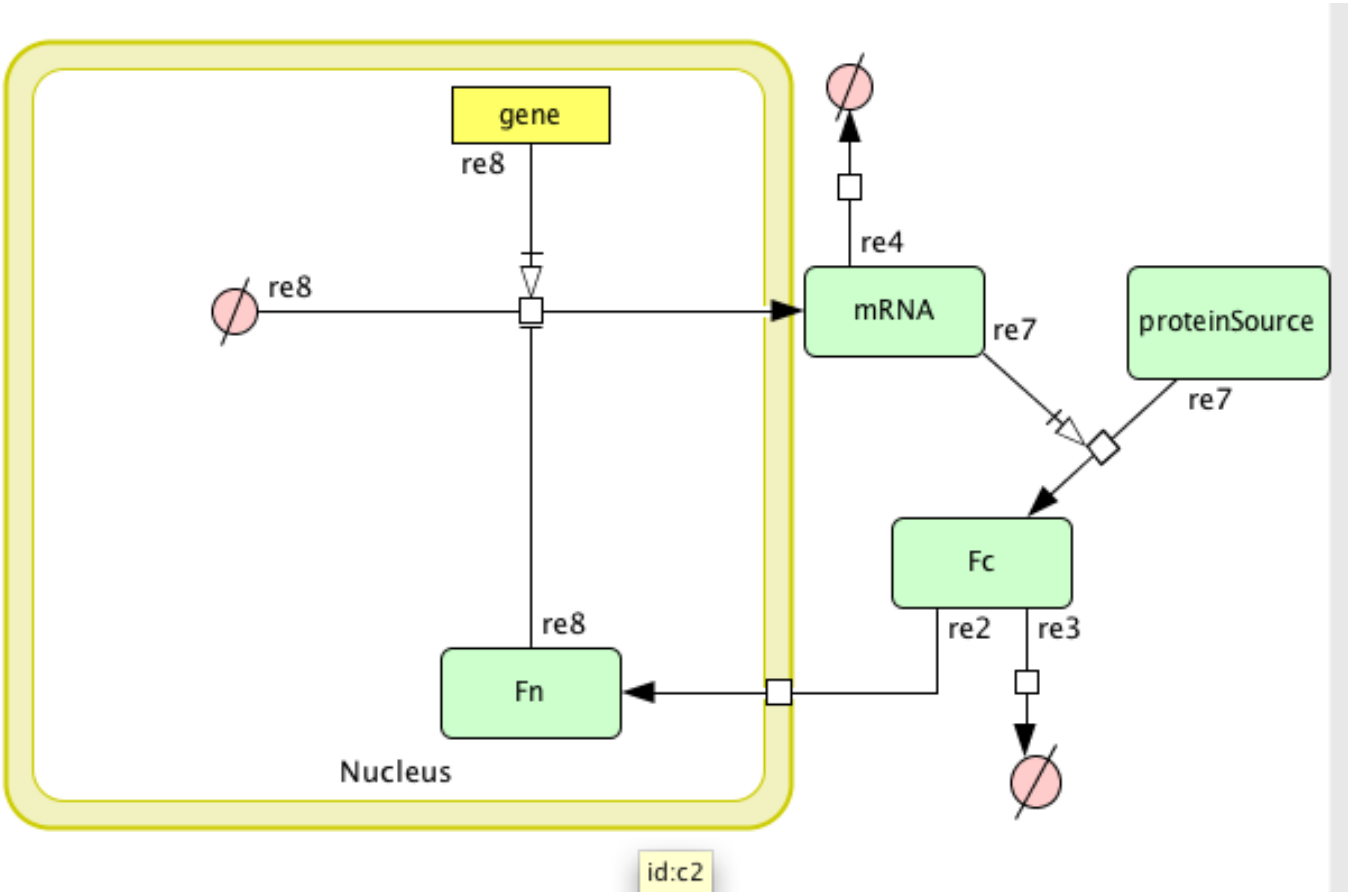
In this tutorial we will use Cell Designer to gain some practical experience with drawing SBGN diagrams. Once we have drawn the diagram we will add some rate equations to run a dynamic model from our static graphical model.

Installing CellDesigner

The version we will use in this tutorial is version 4.1, available from the CellDesigner web site, which includes installation instructions for Linux, Mac and Windows.

Example model 1

The example model we will be drawing is a simple series of reactions describing an early model of the Circadian Clock in *Neurospora* (Leloup et al., 1999). The article describing this is included with the tutorial resources.



In brief, these reactions provide an explanation for Circadian behaviour in *Neurospora* by the negative feedback loop of the gene *FRQ* and its encoded protein. Transcription of the *FRQ* gene is enhanced by light, and its translated product can re-enter the nucleus where it acts as a transcriptional repressor on its own gene.
Note that even though there is only one protein involved (FREQ), because its activities occur in two different compartments, it should be considered as two separate species, *Fc* and *Fn*.

Getting started with CellDesigner

CellDesigner provides copious Help Pages. In brief, though, to get started, create a new document by **File->New** and set the dimensions. For our example diagram, a size of 1200 × 800 pixels should be sufficient.

Creating species

A number of glyphs are available on the palette:

To add a protein, for example, click on the ‘Generic Protein’ icon and then click on the desired place on the map.

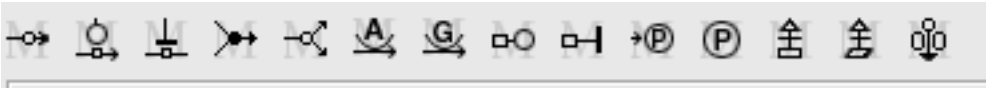
Creating reactions.

To create a reaction between two molecules, click on one of the **state transition** icons:

Now, click on the molecule you want to be the reactant, then on the product. The small blue squares on the border indicate where the connections will be anchored. The state transition, consumption arc and production arc will be generated automatically.

Macros

A number of canned templates are available for frequently used groups of entities – for example



provides a palette for phosphorylation, dimerization, complex formation, etc.

SBGN-PD view

The standard CellDesigner notation was developed before SBGN and therefore is not itself SBGN but also includes glyphs for other entities such as drugs, receptors, etc. To see a diagram in formal SBGN, click **View->Convert to SBGN viewer** which will display a read-only version of the diagram in SBGN, for export or printing. This view is not automatically refreshed, so after each edit this action needs to be repeated.

Identity

By default, each macromolecule created from the palette will be considered unique – i.e., it will have a unique ID. Copying and pasting an object will generate two identical (from a modelling perspective) objects, which, if viewed in the SBGN Viewer, will contain **clone marker** items. If you want to generate a unique item from the copied one, double-click the glyph, and, in the dialog ‘protein’ drop down list you can either assign it a new ID or mark it as a duplicate of an existing node.

Adding rate equations

Description of the rate equations

In the paper, Leloup et al describe the kinetics of the system using three rate equations, which describe the rates of change of the three species in the system – mRNA, cytoplasmic FREQ (F_c) and nuclear FREQ (F_n).

$$\frac{dM}{dt} = v_s \frac{K_I^n}{K_I^n + F_N^n} - v_m \frac{M}{K_m + M}$$

This first equation (above) describes the rate rules for mRNA (M), which are comprised of a synthesis term (green) and a degradation term (red). The parameters are as follows:

1. Vs, rate of transcription.

2. n, the Hill coefficient that describes the cooperativity of binding of the repressor F_n.
3. Ki, a threshold above which repression occurs.
4. Vm, the rate of decay of mRNA.
5. Km, the Michaelis constant for the decay reaction.

$$\frac{dF_C}{dt} = k_s M - v_d \frac{F_C}{K_d + F_C} - k_1 F_C + k_2 F_N$$

The second equation describes the rate of change of cytoplasmic FREQ (Fc) over time. Fc accumulates due to translation (green term), is degraded (red term), and can be shuttled in to the nucleus or accumulate back in the cytoplasm (blue term). The parameters are as follows:

1. Ks, the rate of translation.
2. Vd, rate of protein decay.
3. Kd, the Michealis constant for the decay reaction.
4. k1, the rate of accumulation of Fc into the nucleus.
5. k2, the rate of accumulation back into the cytoplasm.

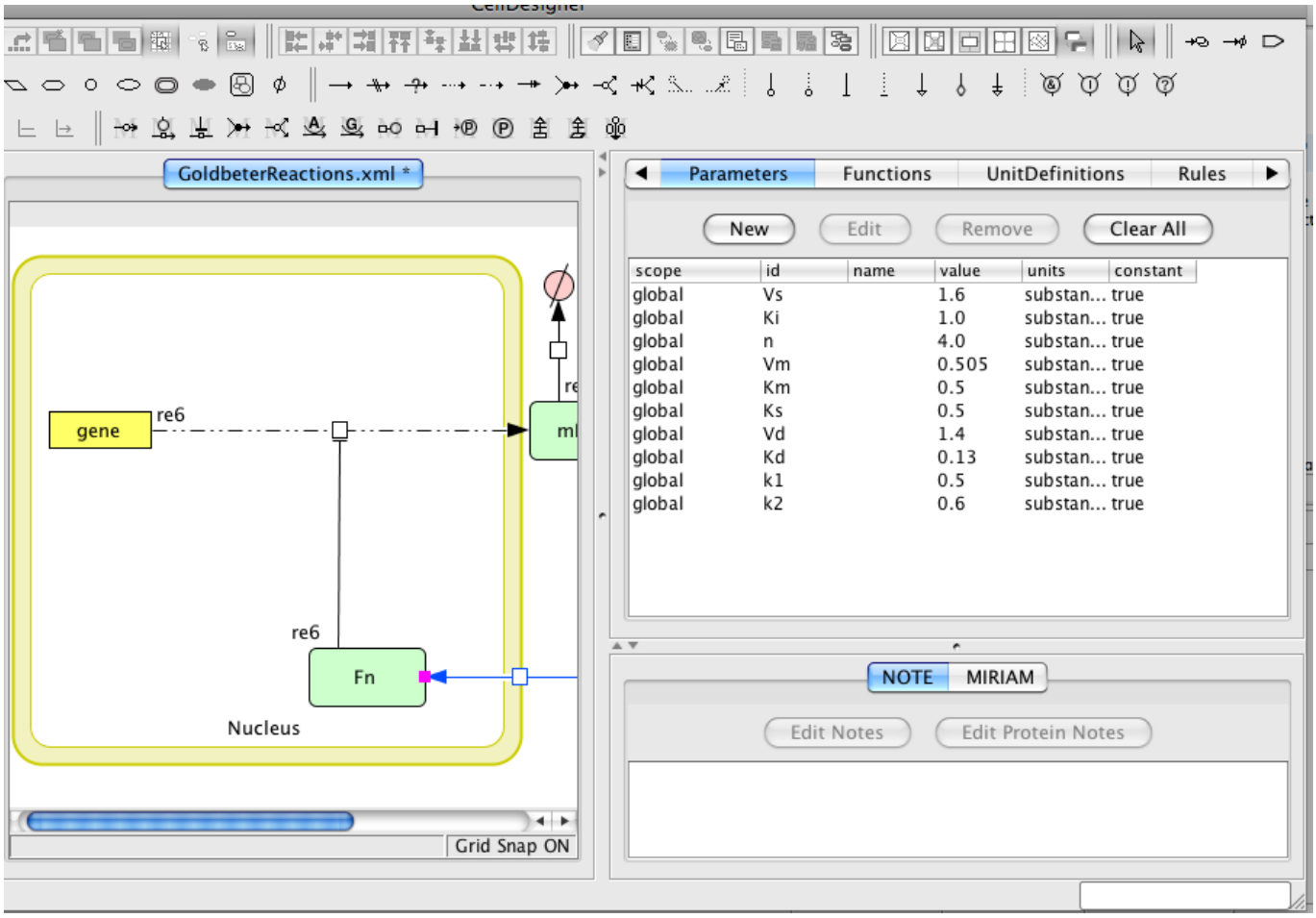
$$\frac{dF_N}{dt} = k_1 F_C - k_2 F_N.$$

The final equation describes the behaviour of Fn over time: this is governed by the rates of nuclear export and import (described by k1 and k2 parameters).

Adding the rate equations

We can add the equations easily in Cell Designer to our reaction diagram.

First of all we need to add the kinetic parameters into the system. Cycle through the tabs to get the parameters view.

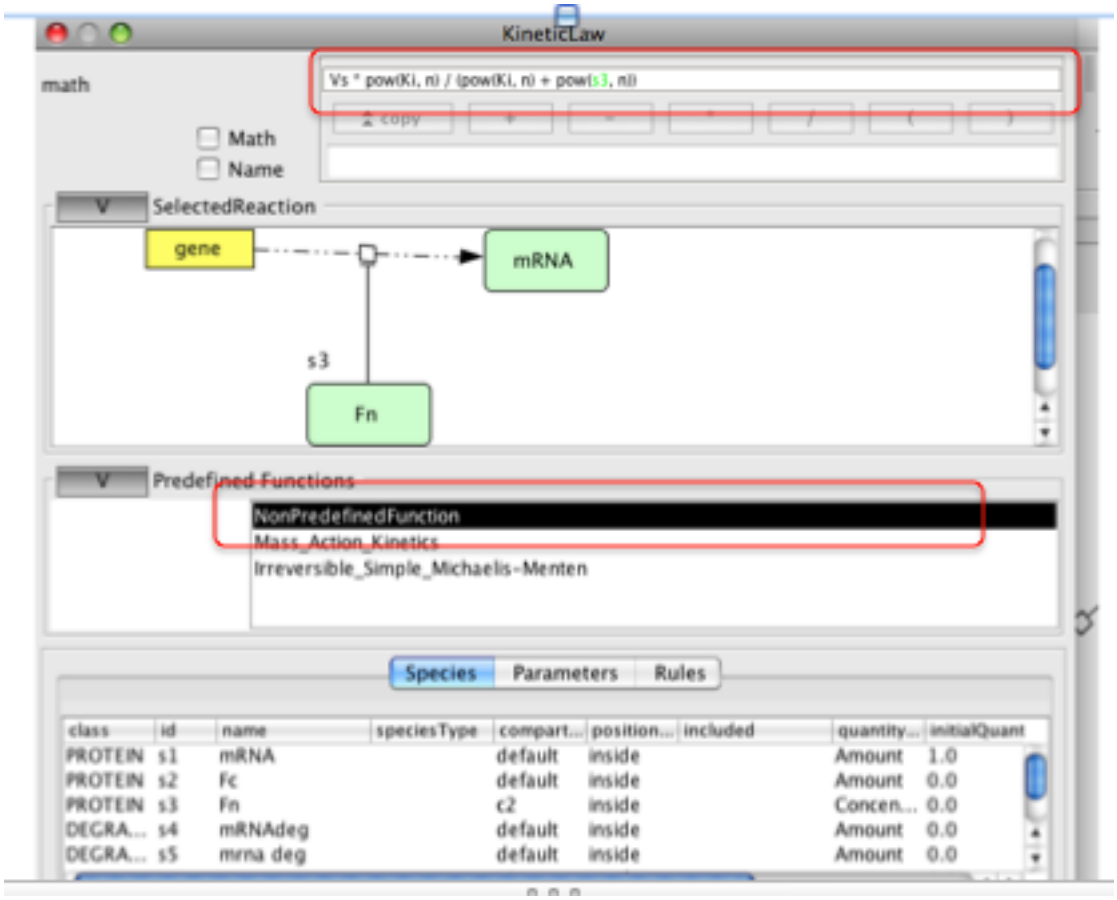


and add the following parameters:

Name	**Value**
Vs	1.6
Ki	1.0
n	4.0
Vm	0.505
Km	0.5
Ks	0.5
Vd	1.4
Kd	0.13
k1	0.5
k2	0.6

Secondly. we need to split the equations up so they can be added as **kinetic laws** in each reaction, adding terms for synthesis and degradation.

To add a kinetic law, select the reaction glyph (the square glyph connecting reactant and product), and from the context menu choose ‘Edit Kinetic law’. In the resulting dialog, add the kinetic law and choose ‘Non defined function’ as shown below:



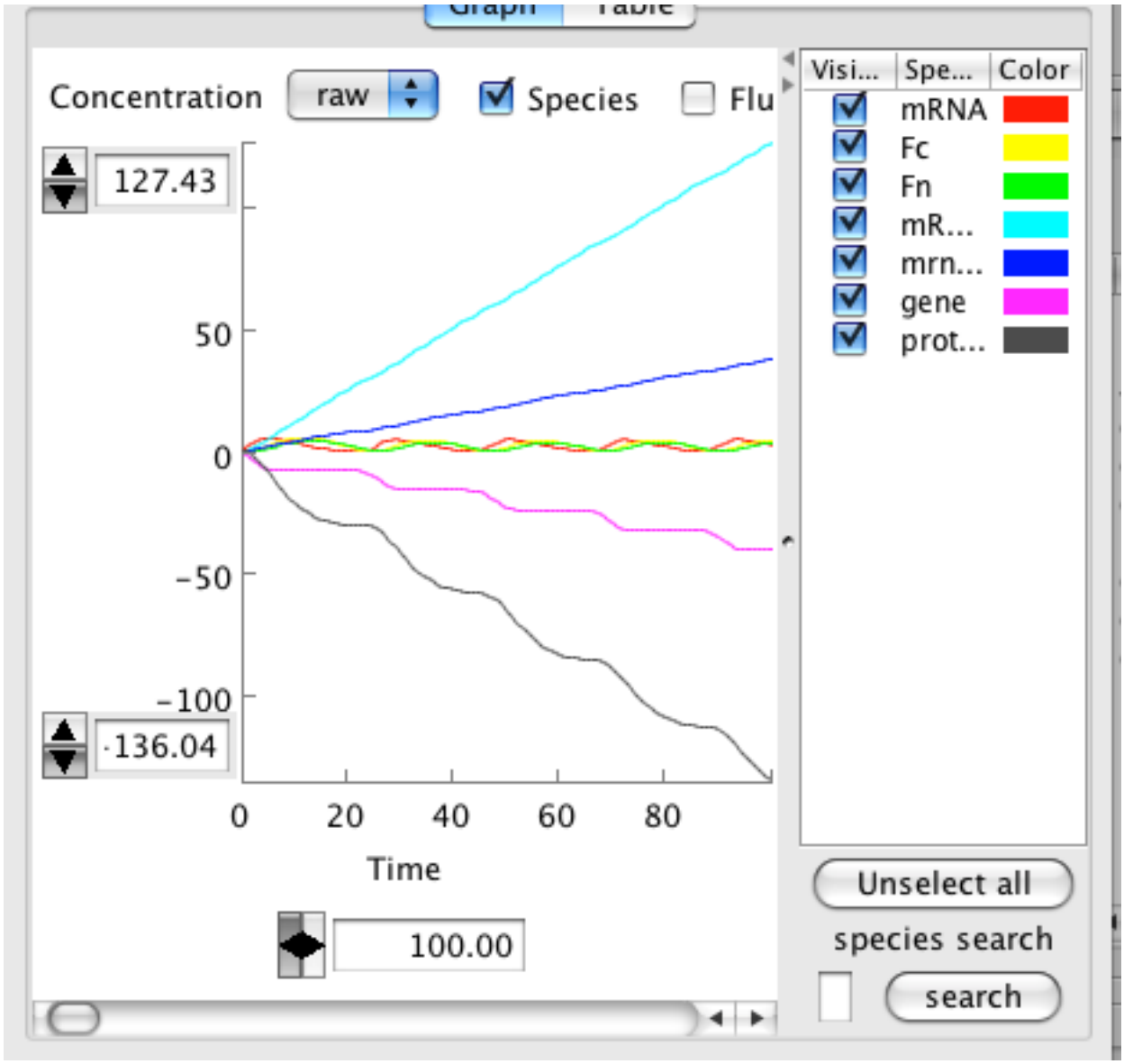
The equations needed for each reaction are as follows (you can copy and paste these into the dialogs).

- **gene -> RNA:** Vs * pow(Ki, n) / (pow(Ki, n) + pow(s3, n))
- **Degradation of RNA:** :Vm * s1 / (Km + s1)
- **Protein synthesis:** Ks * s1
- **Protein degradation:** Vd * s2 / (Kd + s2)
- **Protein import to nucleus:** k1 * s2 – k2 * s3

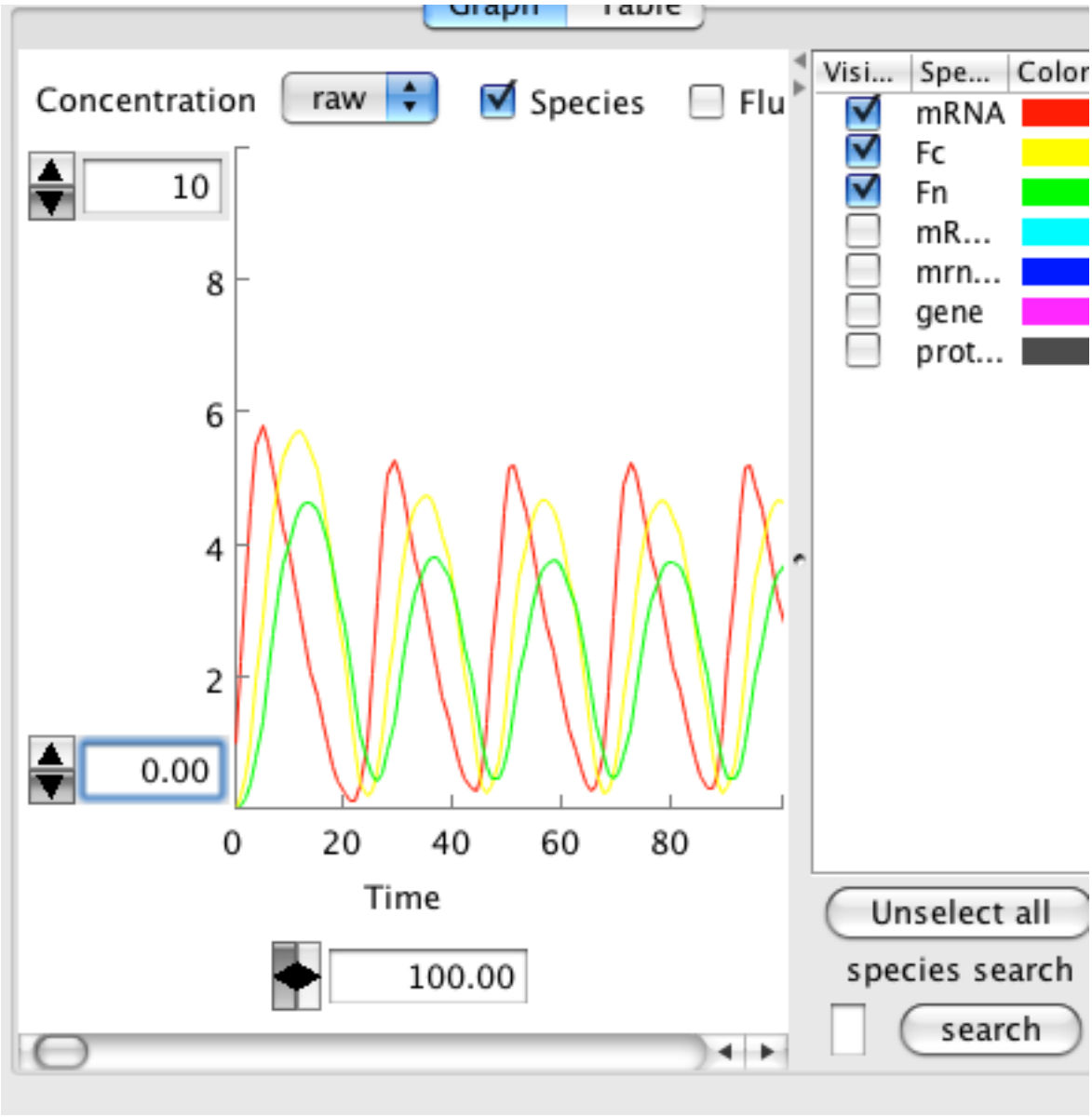
(In these reactions, s1 =RNA, s2 =Fc and s3 = Fn. Your names for the reactants may be different, as Cell Designer uses IDs rather than names to identify reaction participants.)

Running a simulation

Once you've added the kinetic laws then simulation is straightforward: Click **Simulation->Control panel**, set 'end time' to 100 and click **Execute**. You should see a graph like this:



This doesn't quite show what we want to see, as the graph is dominated by the synthesis and degradation terms. If we change the scales on the graph from 0-10, and only view mRNA. Fc and Fn (uncheck the other species), we can see nice oscillating cycles:
as seen below.



Further work a)- simulation and parameter scans

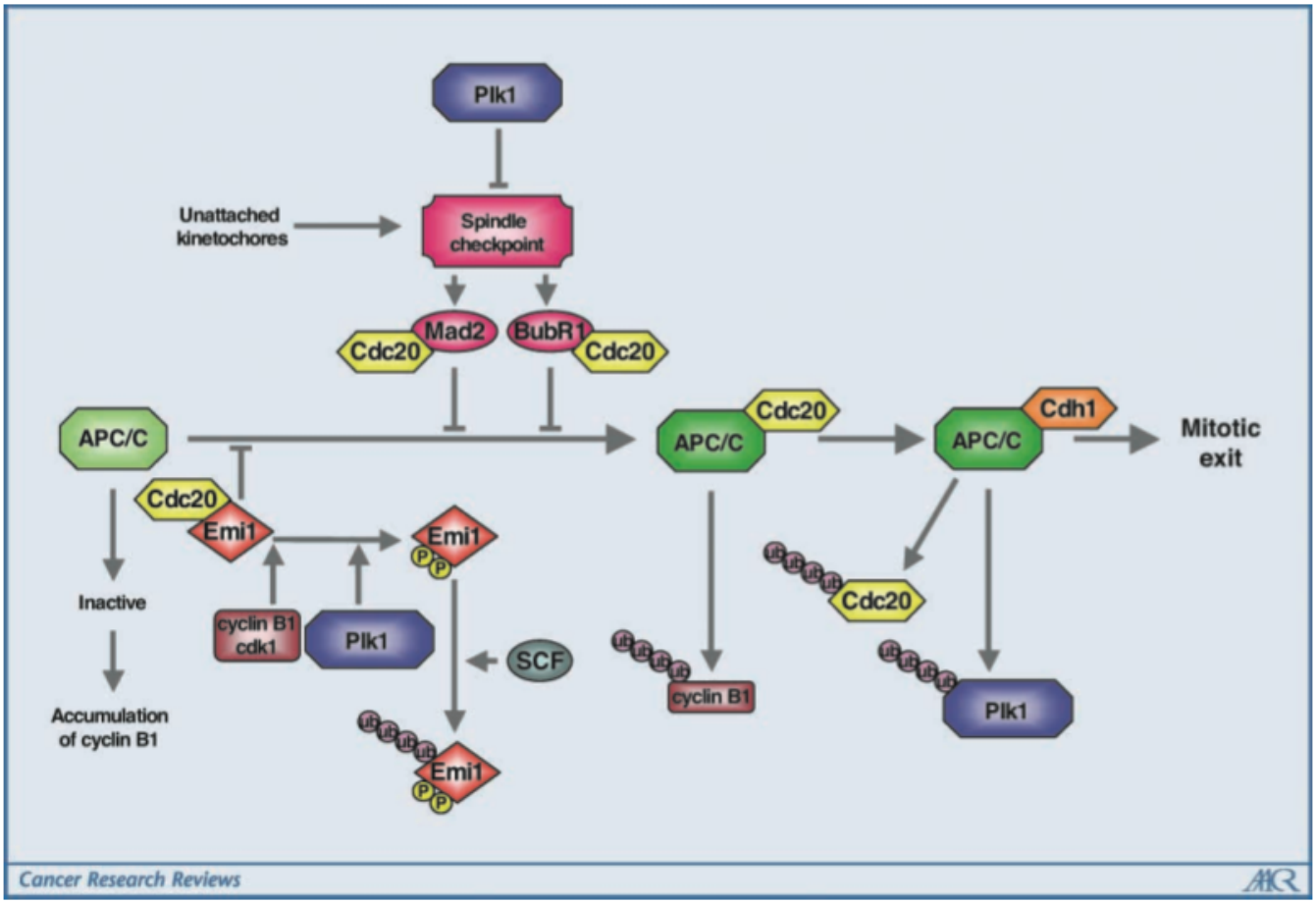
If time allows, you can investigate the consequences of changing parameter values on the simulation. CellDesigner has a parameter scan and an 'interactive simulation' facility which allows some automation of this procedure.

Using these tools it is possible to investigate some of these questions:

- What parameters affect the period of the oscillations?
- In what ways can oscillations be damped (I.e., oscillations die away over time)
- Does altering some parameter values have a greater effect on the system than altering others?

Further work b)- A more complex pathway.

This exercise is a more challenging pathway to convert to SBGN, as we don't have an underlying mathematical representation of the pathway available to provide unambiguous information.
Try converting the ambiguous cell cycle diagram below described into SBGN-PD notation using CellDesigner.



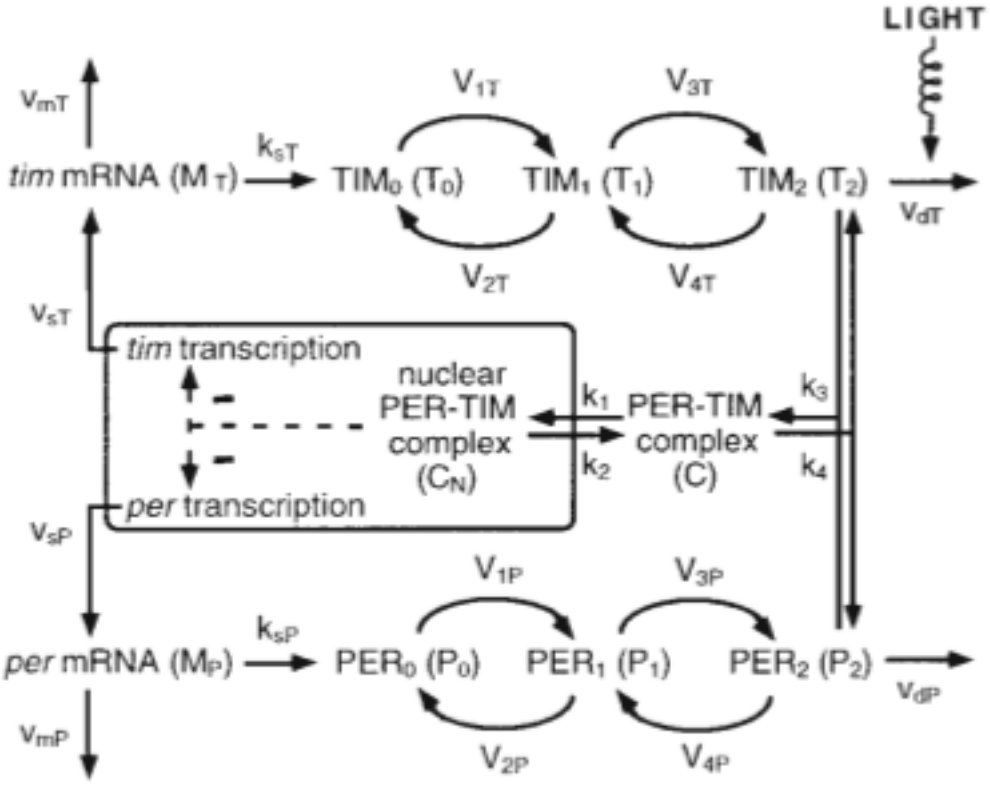
and think about the following questions for the discussion:

What challenges did you face drawing this diagram? For example

- Software support – is it easy to do what you want?
- Notational challenges – is the glyph selection appropriate?
- Interpreting the existing diagram – is it easy to convert to SBGN, what assumptions do you need to make?

Further work b)- Another more complex pathway.

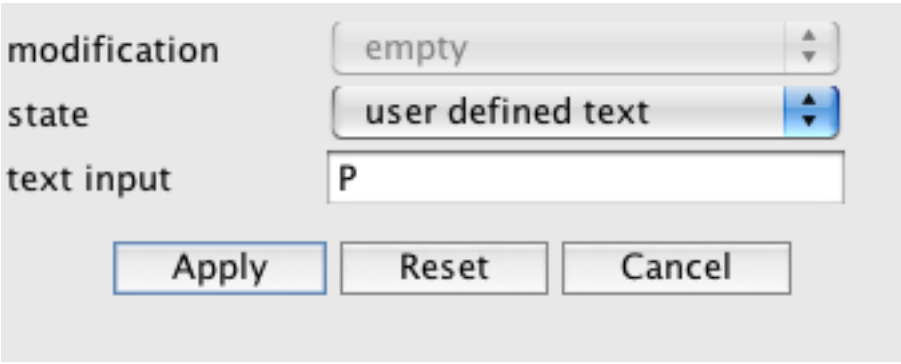
Try converting the *Drosophila* Circadian clock model (Fig 1A of the paper) to SBGN.



This pathway is a slightly more complicated version of the *Neurospora* model we drew earlier. Instead of a single protein, *Freq*, we have a transcriptional feedback loop regulated by a phosphorylated dimer of two proteins, *Per* and *Tim*. Therefore this pathway has additional steps of phosphorylation of each protein, and complex formation. In the diagram above, P(0) = unphosphorylated Per protein, P(1) = singly phosphorylated Per protein and P(2) is doubly phosphorylated Per protein. Tim protein is labelled in a similar way.

Cell Designer hints

To draw the *Drosophila* clock model, you will need to add *state variables* to the **Per** and **Tim** entities.
To do this, double-click on a protein, and edit the state variable as shown below:



CellDesigner recognizes that the same protein in different states are different species in a model – see how clone markers don't appear for proteins with the same name but different states.

Further work c) - Importing models from databases:

CellDesigner contains links to several databases, including BioModels, Panther Pathways and SabioRK. PantherPathways provides manually-drawn diagrams of many pathways which can serve as a starting point for your own project. You can spend some time investigating the available pathways.

Biomodels does not include layout information in its models, try using different layout algorithms. How usefule are they? If you don't know which model to choose, you can try importing some Circadian clock models such as Biomodels55, Biomodels 22 or Biomodels89.

Conclusion

In this tutorial we have drawn a model in Cell Designer in SBGN notation, and used this as a basis for modelling. In reality, we would probably not know the parameter values in advance but would need to fit the model to some experimental data or prior knowledge of the system to find suitable parameter values. That will be the topic of the next tutorial.