Modelling with Petri Nets: Case Studies

Network Medicine

https://www.ibisc.univ-evry.fr/~sivanov/en/pn-biomodelling.html

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1 Playing Around with Petri Nets

1.1 Software Tools

The software tool I recommend for this section is Tina: <u>Ti</u>me Petri <u>N</u>et <u>A</u>nalyser. It can be downloaded here:

http://projects.laas.fr/tina//download.php

Once you have downloaded the archive, unpack it, go under the directory `bin` and launch the file called `nd`. You should be presented with a window having a workspace, a toolbar, and a menu bar. To create a place, click on the button with a circle on it. To create a transition, click on the button with a square on it. To add an arc, click on the button with a black horizontal arrow, then click on a place and drag the mouse to the transition you want to connect it to. To add tokens to a place, right-click on it and, in the popup window, modify the number in the field "marking".
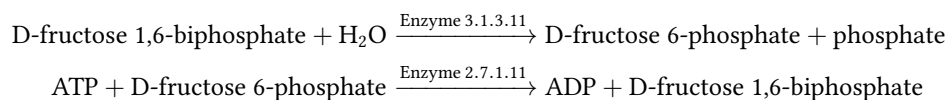
To run the Petri net, go to the "Tools" menu and choose "stepper simulator". This will show you a window in which the enabled transitions will be highlighted in red. Click on one of the enabled transitions to run it once. Be sure to click on the space between the transition label and the square border: TINA seems to not capture clicks on the label itself.

If you are feeling curious (and lucky), you may also check out the rather long list of different Petri net-related software tools:

https://www.informatik.uni-hamburg.de/TGI/PetriNets/tools/quick.html

1.2 Glycolysis Pathway

Glycolysis is the metabolic pathway that converts glucose $C_6H_{12}O_6$ into pyruvate CH_3COCOO^- + H^+. The free energy released in this process is used to form the high-energy molecules ATP and NADH [4]. This pathway includes the following two reactions [5]:

$$\text{D-fructose 1,6-biphosphate} + H_2O \xrightarrow{\text{Enzyme 3.1.3.11}} \text{D-fructose 6-phosphate} + \text{phosphate}$$

$$\text{ATP} + \text{D-fructose 6-phosphate} \xrightarrow{\text{Enzyme 2.7.1.11}} \text{ADP} + \text{D-fructose 1,6-biphosphate}$$

1. Represent the interactions induced by these equations in a Petri net.

2. Draw the Petri net using the suggested software tool (see above) and explore its dynamic behaviour under the asynchronous mode.

3. Check some dynamic properties (e.g., reachability of a particular marking) of the resulting Petri net.

For more details on this example, see [1, Section 4.1.1].

1.3 Kinase (MAPK) Cascade

The mitogen-activated protein kinase cascade is the core of the ubiquitous ERK/MAPK pathway that can transmit various signals (cell division, differentiation, etc. [2, Section 3]) from the cell membrane to the nucleus. Figure 1 describes the typical modular structure of this pathway. In each layer, forward reactions are catalysed by kinases and reverse reactions by phosphatases. RasGTP is considered to be the input signal and ERKPP the output signal.
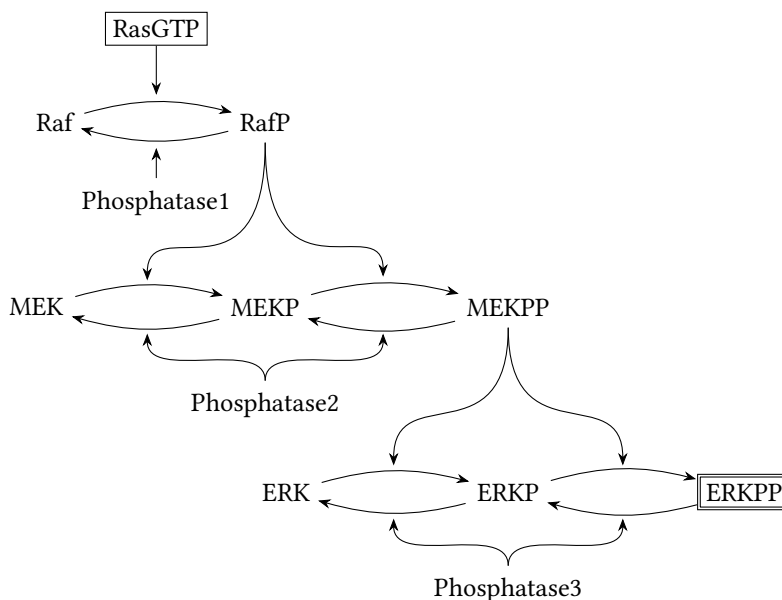

Figure 1: The general scheme of the MAPK cascade. Redrawn from [2, Fig. 3].

1. Represent the interactions induced by these equations in a Petri net.

2. Draw the Petri net using the suggested software tool (see above) and explore its dynamic behaviour under the asynchronous mode.

3. Check some dynamic properties (e.g., reachability of a particular marking) of the resulting Petri net.

2 Programming Petri Nets

While software tools allowing to graphically design and analyse Petri nets are quite practical, sometimes more flexibility is required. For example, one may need to automatically incorporate the results of a data analysis routine into the structure of a Petri net or into its initial marking. Achieving this task by hand is often tedious and sometimes impossible due to the sheer amount of information which has to be transferred between the two stages of the workflow. In such situations, using a software library allowing to integrate Petri nets into a larger application is more appropriate.

For this assignment I recommend using the Python library SNAKES (SNAKES is the net algebra kit for editors and simulators) developed by Franck Pommereau, a researcher at the IBISC lab in Évry [3]. SNAKES implements the powerful concepts of high-level Petri nets. In such Petri nets, places are allowed to contain arbitrary values (strings, lists, etc.), and transitions can be assigned guards verifying arbitrary properties on their preplaces.

1. Follow this tutorial to install and start using SNAKES:

   `https://snakes.ibisc.univ-evry.fr/tutorial/first-steps-with-snakes.html`

2. Follow this second tutorial to better understand how arc annotations work in SNAKES:

   `https://snakes.ibisc.univ-evry.fr/tutorial/arc-annotations.html`

3. Implement the case studies from the previous section in SNAKES.

4. Draw the resulting Petri nets using the `gv` plugin of SNAKES.

5. Run the resulting Petri nets for several steps (say, 10) and output a log of what is happening.

References

[1] Paolo Baldan, Nicoletta Cocco, Andrea Marin, and Marta Simeoni. Petri nets for modelling metabolic pathways: a survey. Natural Computing, 9(4):955–989, Dec 2010. Draft available at `http://www.math.unipd.it/~baldan/Papers/Soft-copy-pdf/BioPN.pdf`.

[2] Monika Heiner, David Gilbert, and Robin Donaldson. Petri nets for systems and synthetic biology. In Marco Bernardo, Pierpaolo Degano, and Gianluigi Zavattaro, editors, Formal Methods for Computational Systems Biology: 8th International School on Formal Methods for the Design of Computer, Communication, and Software Systems, SFM 2008 Bertinoro, Italy, June 2-7, 2008 Advanced Lectures, pages 215–264. Springer Berlin Heidelberg, Berlin, Heidelberg, 2008. Available on Research Gate.

[3] Franck Pommereau. SNAKES: a flexible high-level Petri nets library. In Proceedings of PETRI NETS'15, volume 9115 of LNCS, pages 254–265. Springer, 06 2015.

[4] Wikipedia. Glycolysis — Wikipedia, The Free Encyclopedia, 2017. [Online; accessed 4-November-2017].

[5] The KEGG pathway database. `http://www.genome.jp/kegg/pathway.html`.