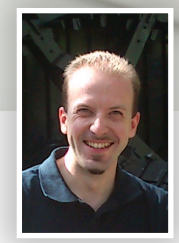
//Rondje Zilverling

Modeling biology with ANIMO

Using computer models to understand the communication system of living cells

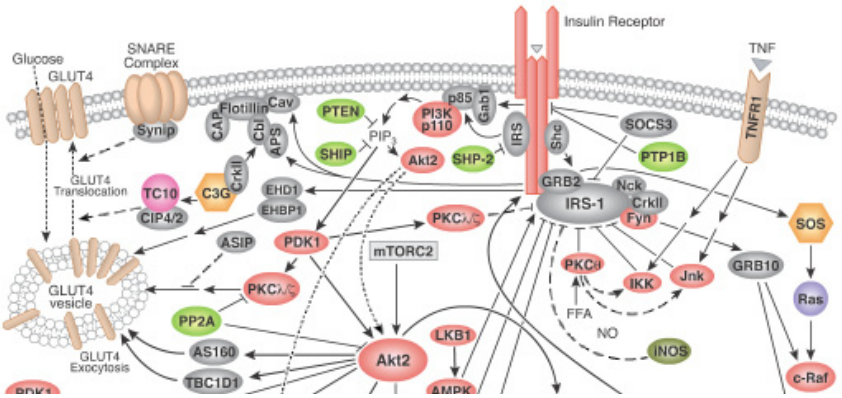


Door: Stefano Schivo
Formal Methods & Tools

When we fall sick, we take a medicine that (hopefully) makes us improve and feel better soon. But how does this medicine actually work '*under the hood*'? Why do we need exactly that amount of exactly those substances to get better? And what do computers have to do with this?

In the microscopic, our cells receive and process signals of many types: each type of molecule, such as the active principle of a medicine, is interpreted as a different signal. When a particular molecule comes in contact with a cell surface receptor (a sort of "detector" specific for that molecule), the receptor becomes '*activated*', and proceeds to activate other molecules on the inside of the cell. These in turn activate other molecules, in a cascade that allows the signal to travel inside the cell to the nucleus, where the DNA is kept. When a signal reaches the DNA, it is interpreted as an order to produce a particular type of protein: this is considered as the response to the signal. Every cell can produce and use a large variety of proteins, some of which are also involved in signaling tasks, thus the correct "understanding" of a signal is of the utmost importance for a cell to work properly.

Moreover, often a signal does not simply travel along a "relay race" to the nucleus: interferences from other signals or molecules drive and change the response of the cell, making the task of understanding how these mechanisms work very hard. As if this was not enough, performing the kind of biological experiments needed to obtain deeper insight into a particular signaling network requires considerable amounts of time (and money). It is thus very important to have a clear vision of how a signaling network is supposed to look like and behave, in order to organize existing knowledge and plan the laboratory experiments. And this is exactly what our software tool ANIMO (Analysis of Networks with Interactive MOdeling) does: thanks to an intuitive user interface, ANIMO allows to 'play' with a signaling network, seeing how it would evolve over time when certain signals are given. Moreover, as ANIMO is based on the formal language of Timed Automata, we can exploit the predictive power of a model by running '*in silico*' experiments, speeding up the process of understanding signaling networks. The cost, both in terms of time and money, of an in silico experiment is usually much lower than the corresponding '*wet lab*' experiment, and can be an asset in helping the development of medicines.



Signaling pathway of insuline (Cell Signaling Technology, Inc. www.cellsignal.com)

Models defined in the ANIMO user interface are automatically translated into Timed Automata systems, which are run "under the hood" thanks to the tool UPPAAL. The results are then shown to the user in the form of graphs plotting the activity intensity for each reactant in the modeled network. A slider under each graph, lets the user scroll through the time points in a simulation series: the nodes in the network model are colored according to the activity of the corresponding reactants at the selected instant. Experimental data series can be superposed to simulation results, allowing for a quick comparison between model prediction and experimental facts and accelerating model development.

We plan to apply ANIMO in a research on tissue generation, aimed at making life easier for people affected by osteoarthritis: computer science can be applied even to '*real science*'! ;-)

For more information, see http://fmt.cs.utwente.nl/tools/animo