Odefy - From discrete to continuous models in MATLAB

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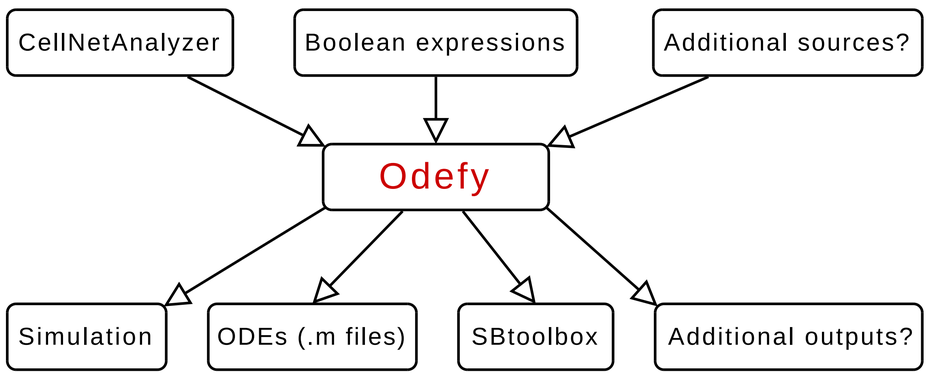
Motivation

The quantitative analysis of gene regulatory networks is a major goal in systems biology today. Often, however, only qualitative models of these regulatory networks are available which do not allow for a rich analysis and interpretation of the system. We developed a new technique called *HillCube* to convert any discrete boolean network into a continuous ODE model using multivariate polynomial interpolation. During this project we developed *Odefy*, a MATLAB toolbox which integrates model conversion and simulation methods into a single software package.

Implementation of Odefy

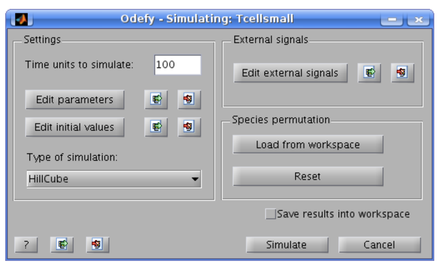


Sources of boolean regulatory networks for Odefy:

- **CellNetAnalyzer models** - Odefy can be directly integrated into the user interface of CellNetAnalyzer [2].
- **Boolean expressions** - The user can specify a set of boolean expressions to define the network, one for each species in the system.
- **Extensibility** - Further data sources can be easily integrated due to a straight forward internal model representation.

User interfaces

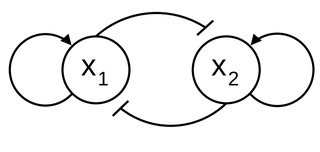
- Intuitive graphical user interface for exporting and simulation.
- Advanced working in the MATLAB environment with the exported .m ODE model files.

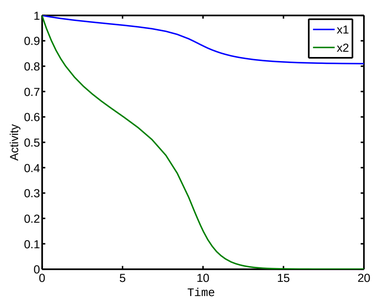


Toy example

$x_1 = x_1$ OR $\neg x_2$

$x_2 = x_2$ AND $\neg x_1$






```
d(x1) = (HillCube([0 1 ; 1 1], [x1 x2], params) - x1) / tau_x1;
d(x2) = (HillCube([0 0 ; 0 1], [x1 x2], params) - x1) / tau_x2;
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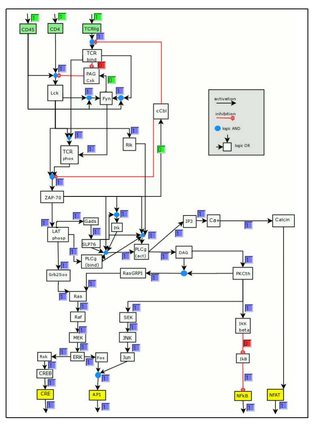
T-cell model

T-cells belong to the lymphocytes (white blood cells) and play a major role in the immune response of higher organisms (model by Klamt et al., 2006 [2]).

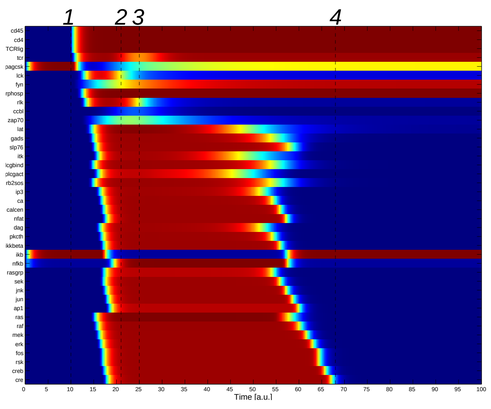


When activated by an antigen complex, a large signalling cascade is triggered resulting in the activation of specific transcription factors (CRE, AP1, NFAT, NFkB) and the proliferation of the T-cell.

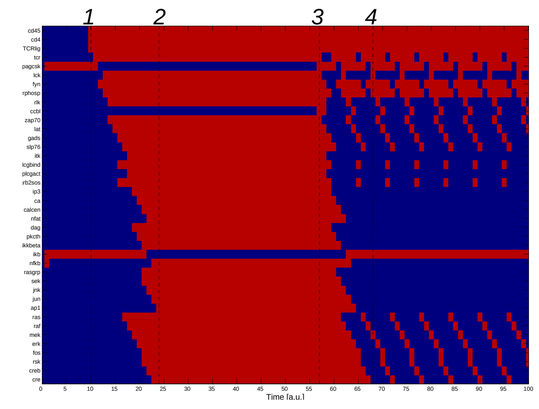
T-cell simulation

- We applied our HillCube continuous modeling approach to the T-cell signalling network.
- The feedback loops are activated slowly by adapting the corresponding reaction kinetics.

HillCube simulation



Boolean simulation



1. External activation of the three input species.
2. Full activation of the transcription factors.
3. Begin of deactivation due to activated negative feedback loops.
4. End of deactivation, cell is in resting state again.

This proof-of-concept shows (a) that real-world regulatory pathways can indeed be simulated using our method and (b) that the automatically generated continuous models show a rich dynamical behaviour.

Outlook

We are planning to

- integrate further data sources for boolean networks into Odefy.
- test the system on other regulatory pathways.
- perform parameter estimations based on experimental data.

References

[1] Wittmann *et al.* (2008) From Discrete To Continuous Modeling. *In preperation*

[2] Klamt *et al.* (2006) A methodology for the structural and functional analysis of signaling and regulatory networks. *BMC Bioinformatics*, 7, 56