

4th International Hands-on Tutorial on Logical Modeling

Background

The motivation of this tutorial is to provide hands-on experience with several logical modeling software tools. This tutorial will be made accessible to participants with no modeling experience as well as to those who are seasoned modelers.

Logical modeling provides a computational approach to the visualization and analysis of the dynamics of biochemical and biological systems complementary to others such as reaction-based or rule-based modeling. One of the main advantages of logical models is their scalability and the relatively easy method of construction. In part due to these attributes, logical models have become increasingly more popular among the computational biology community. This has, in turn, led to the development of different techniques and software tools that enable the construction, simulation, and analysis of logical models and their variants (Boolean, multilevel, deterministic, stochastic, etc.) to address various biological questions.

This workshop aims at extending the outreach of the logical modeling community (namely, the Consortium for Logical Modelling and Tools, CoLoMoTo, colomoto.org), and providing an overview of recent achievements in tool development that render possible the modeling and the analysis of large cellular networks, covering intricate signaling pathways, sophisticated transcriptional networks, as well as novel regulatory mechanisms.

Specifically, two hands-on tutorials will cover the Cell Collective (www.cellcollective.org) and CellNOpt (www.cellnopt.org) software tools.

Schedule

Afternoon Session

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| 12:30-13:00 | Welcome and Introduction to logical modeling frameworks |
| 13:00-15:30 | CellNOpt: Julio Saez-Rodriguez |
| 15:30-16:00 | Coffee break |
| 16:00-18:30 | Cell Collective: Tomas Helikar |

A description of the workshop/tutorial format

The tutorial will begin with an overview presentation of logical modeling. Each subsequent tool tutorials will also provide introduction to the respective software, as well as any additional logical modeling “nuggets” that are specific and relevant to the software. In addition, each tool presenter will also first present an example of a previous application of the software. This brief introduction of each tool tutorial will be followed by an interactive hands-on session, teaching the participants how to use the software, and how to interpret its output. The objective of the tutorial is that the participants can begin using the software tools for their own research after the tutorial. To help facilitate this objective, we will encourage participants to come prepared with their own research questions and/or biological systems they would like to begin modeling/analyzing. The logical modeling software tools to be covered in the tutorial include Cell Collective and CellNOpt (overview is provided below).

Cell Collective (www.cellcollective.org)

Cell Collective is an on-line platform for construction, simulations, and analyses of large-scale computational models in a collaborative fashion. Its user interface enables scientists to build and simulate models without manually creating complex mathematical equations (logical functions) or computer code, enabling those with diverse backgrounds to contribute to the construction of these models. Cell Collective allows users to simulate and analyze the models in real-time on the web, including the ability to simulate loss/gain of function and test various what-if scenarios.

Cell Collective currently contains hundreds of user-created models, and 65 published peer-reviewed models. These seed models represent biological and biochemical networks in organisms ranging from bacteria and viruses to yeast, flies, plants, and humans. Models in the Cell Collective are fully annotated within its wiki-like system, enabling researchers to track and discuss the biological evidence and assumptions used to construct each model. Finally, Cell Collective models are accessible and share-able not only within the platform, but they are also available for download in a number of open formats, including SBML.

During this tutorial, you will learn about some of the major features of Cell Collective, and you will construct and simulate a new model. If you have a biological system of your interest, that you would like to model, please bring your own ideas and any materials that will help you construct a model for your research. You can create a model of almost any network biological process (gene regulation, signal transduction, cell-cell interaction, metabolism, etc.) Examples of useful materials to help get started include:

- A network diagram of a biological process,
- A review paper describing a biological process,
- An existing computational model developed in another software tool, etc. (Cell Collective contains over 60 peer-reviewed logical models so you can choose to build on top of one of those)

CellNOpt (www.cellnopt.org)

CellNOpt (Terfve et al. 2012) is a software used for creating logic-based models of signal transduction networks using different logic formalisms, including Boolean, Fuzzy, or differential equations (MacNamara et al. 2012). CellNOpt uses information on signaling pathways encoded as a Prior Knowledge Network, and trains it against high-throughput biochemical data to create cell-specific models. CellNOpt is freely available under GPL license in R and Matlab languages. It can be also accessed through a python wrapper, and a Cytoscape plugin called CytoCopter provides a graphical user interface. CellNOpt is compatible with the SBML-qual format (Chaouiya et al. 2013), facilitating exchange with other tools such as Cell Collective.

CellNOpt uses pathway information, normally from literature, that can be retrieved systematically with the tool OmniPath (Türei et al. 2016). It can also find missing links in literature curated pathways (Eduati et al. 2012). Training is performed with the complementary tool MEIGO (Egea et al. 2014).

CellNOpt typically uses phosphoproteomic data obtained from antibody-based technologies, but it has been extended to process mass spectrometry data with the related tool PHONEMeS (Terfve et al. 2015).

During the tutorial, we will discuss the process of building logic models with CellNOpt:

- Obtain the relevant pathway information,

- Choose the right mathematical logic formalism
- Fit models to data
- Interpret model results

The use of CellNOpt will be illustrated with a recent example where it was used to find biomarkers and novel therapies in colorectal cancer (Eduati et al. 2017)

Names and affiliations of main organizers

Tomas Helikar, PhD.

Department of Biochemistry

University of Nebraska, USA

thelikar2@unl.edu

www.helikarlab.org | @helikarlab | @tomashelikar

Julio Saez-Rodriguez

Joint Research Center for Computational Biomedicine (JRC-COMBINE)

RWTH Aachen University, Faculty of Medicine

www.saezlab.org - @sysbiomed

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