5th International Hands-on tutorial on logical modeling

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Schedule

9:00-9:15 Welcome and Introduction to logical modeling frameworks

9:15-10:30 CellNOpt: Julio Saez-Rodriguez

10:30-11:00 **Coffee break**

11:00-12:30 Cell Collective: Tomas Helikar

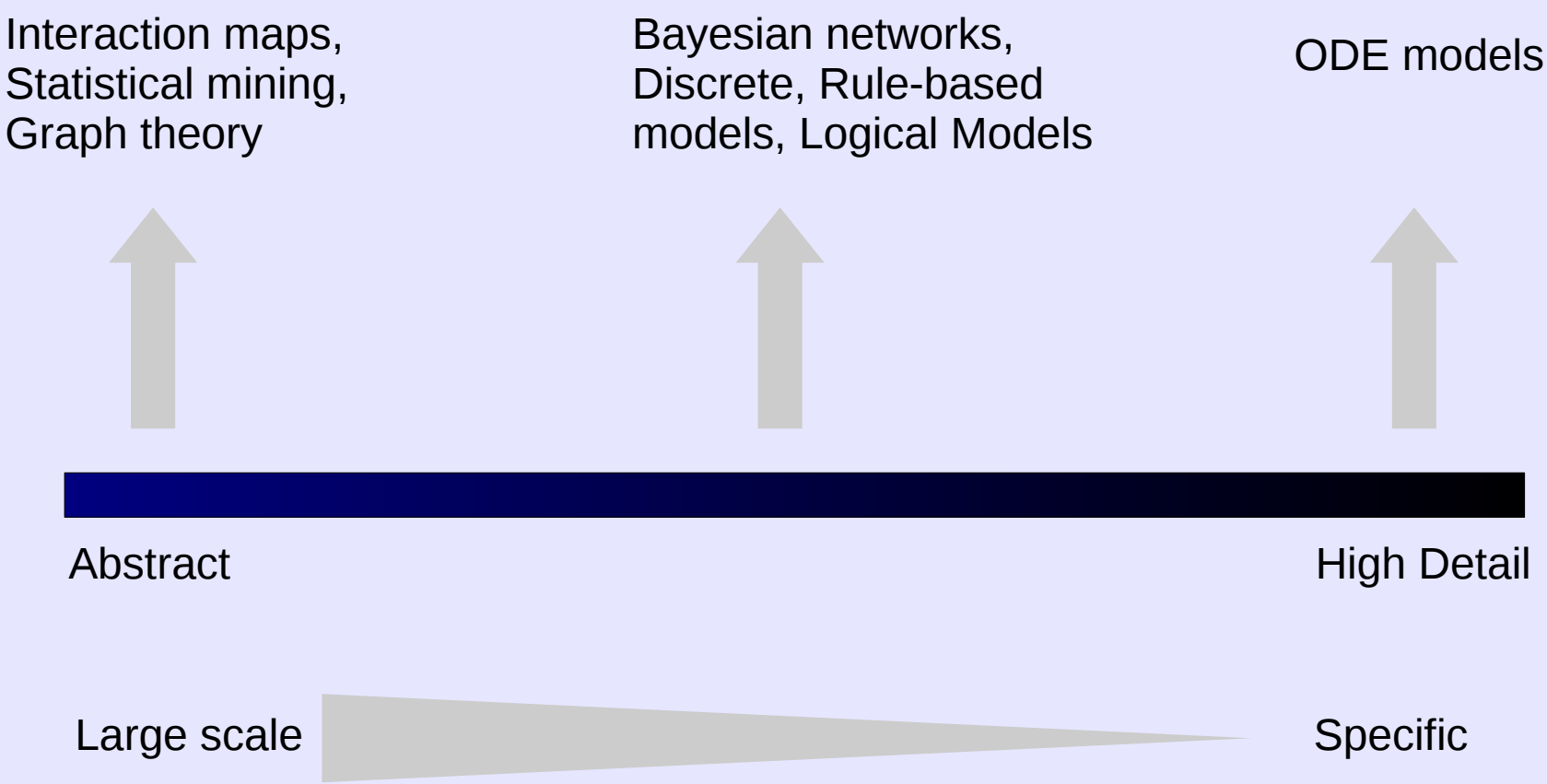
12:30-13:30 **Lunch break**

13:30-15:00 GINsim: Aurelien Naldi & Denis Thieffry

15:00-15:30 **Coffee break**

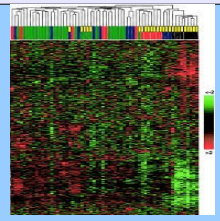
15:30-17:00 CoLoMoTo Interactive Notebook: Loïc Pauleve

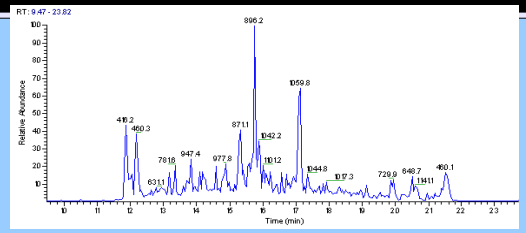
Network Modeling Methods



Bottom up vs top down modeling

Top-down

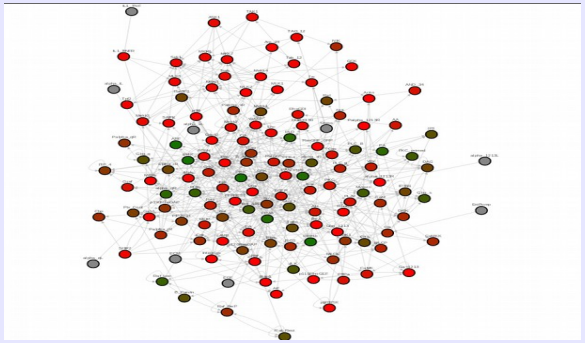




Global profiling (omics)

Data analysis

Model inference

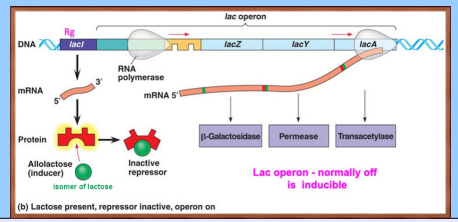


Mechanism description

Interaction identification

Literature curation

Bottom-up

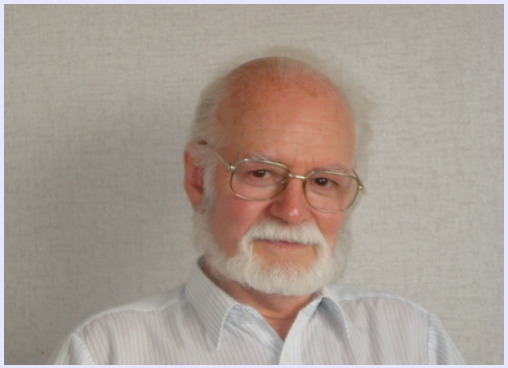


Logical (Boolean) Modeling

Stuart Kauffman (1969)

- Generic model of gene regulatory network with nodes with predefined in-degree, random connections
- Deterministic behavior defined by a Boolean function

Rene Thomas (1973)

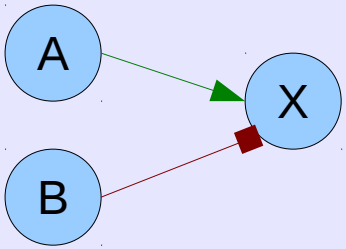


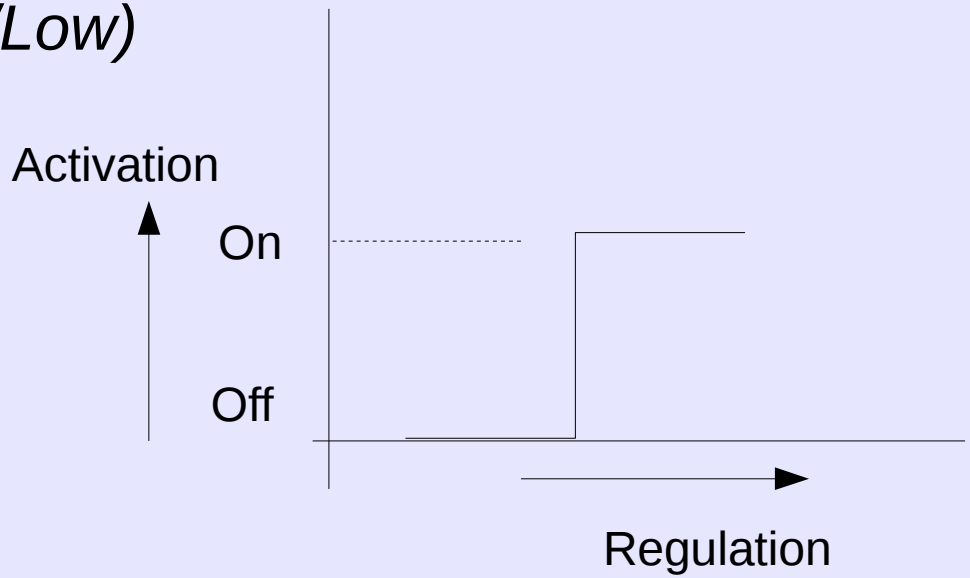
- Specific gene regulatory networks

Modeling Method

Logical Model Network

Active (On/High) or Inactive (*Off/Low)*





(Kinetic) Parameter independent

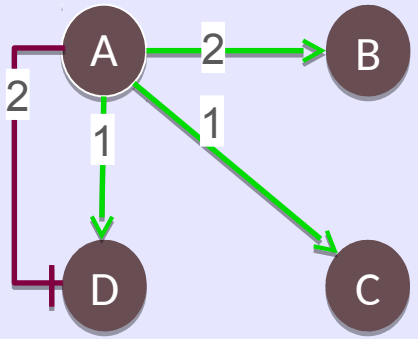
Qualitative logic, i.e. “Protein *A* activates protein *X*”
- straight forward to retrieve from biochemical literature

Efficient simulations

Variants of the formalism

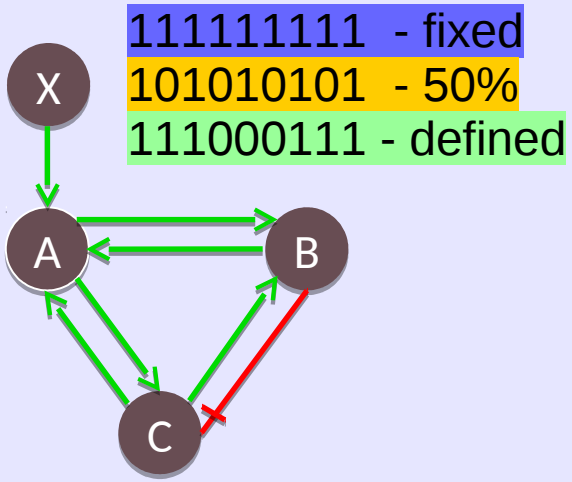
- Multivalued variables {0,1,2}
- Time delays (multiple time scales)
- Semi-continuous input/output
- Specific classes of logical functions, e.g.

  threshold function (sum of regulatory effects relative to a threshold)



Control networks

variable set to a fixed value,
sampled, specific signal sequence



Examples of investigations of logical models

What are the attractors (long term behaviors)?

Stable states (all components are stable)

Cyclical attractors (oscillations)

What are their reachability properties? e.g.

- Is a given attractor reachable from a given initial state?
- What are the properties along the trajectories leading to an attractor?

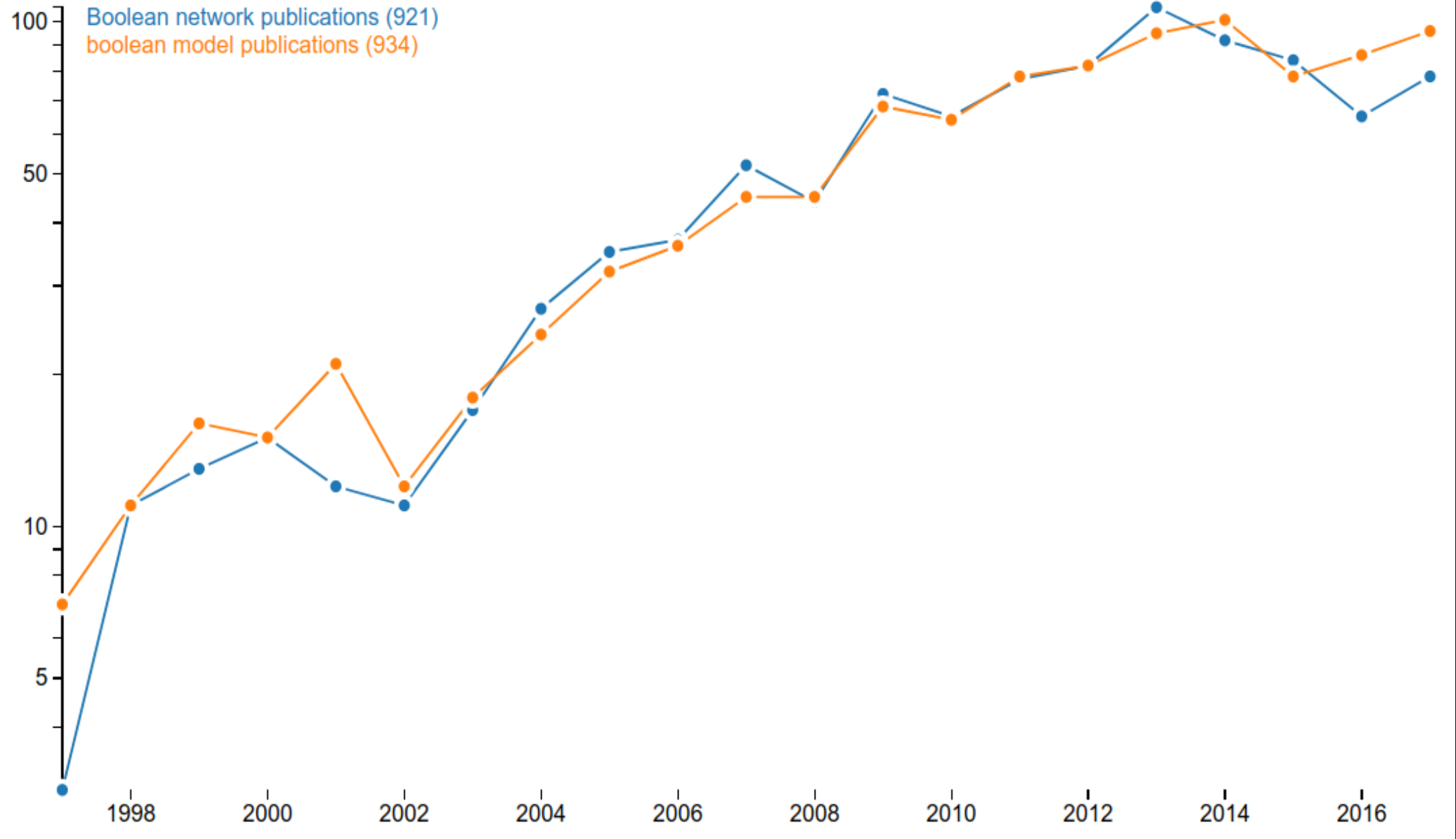
What are the properties upon model perturbations? e.g.

- Knock-out → variable maintained to 0
- Gain-of-function → variable maintained to 1

How does the environment effect the dynamics? (control networks)

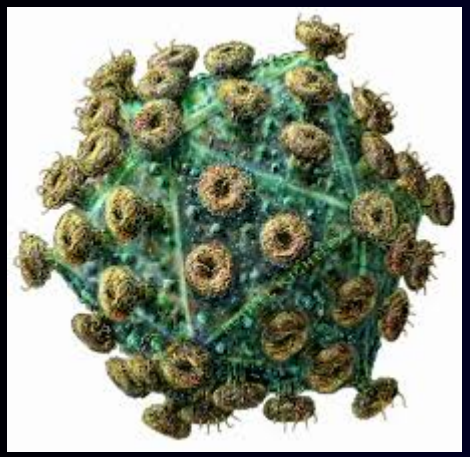
Challenges

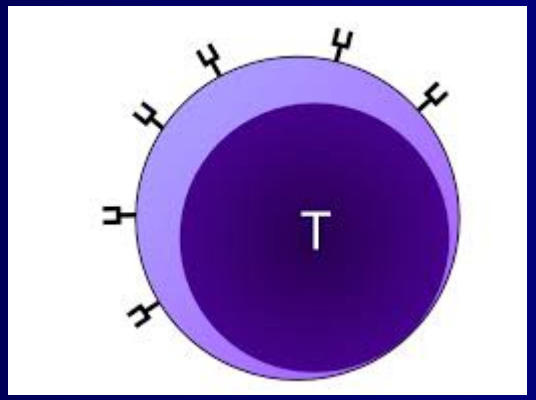
- Combinatorial explosion of the number of states with the number of components (2^n states for n network components)
- Scalability of creating large-scale and accurate models
- Model transparency (can I believe the model?)
- Model (re-)usability and sharing

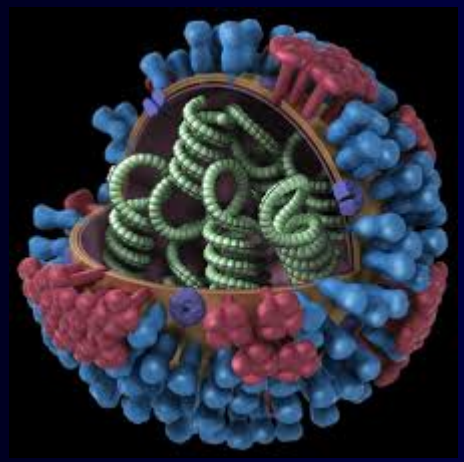

Boolean network publications (921)
boolean model publications (934)
100
50
10
5
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016

Models and Model repositories

Cell Collective (www.cellcollective.org)
http://ginsim.org/models_repository
Biomodels.net







Tools (not exhaustive!)

Tool	Range	Updating	Feature	Syst. Req.
Adam	Multi-val	Seq/Sync	SS & CA	Web serv
BooleanNet	Bool	A/Sync, Time sync, Stoch async	Switch to PLDE Attractors (reduc.)	Python
BoolNet	Bool	A/Synch, Stoch async	RBN generation	R
Cell Collective	Bool	A/Sync, Time Delay, Thresholds	Stochastic, Real-time	Online
CoLoMoTo Interactive Notebook	Mixed	A/Sync, Time sync, Stoch async	Integrative	Docker
CellNetAnalyzer	Bool	-	Structural analysis (Mini. Int. Sets)	Matlab
CellNOpt	Bool	Sync	Model training, Fuzzy Logic, ODE	R / Cytoscape plugin
GINsim	Multi-val	A/Sync, priorities	Stable states, functionality, HTG	Java
MaBoss	Bool	continuous/discrete time Markov processes		C++
PyBoolNet	Bool	A/Sync	Attractors, Model Checking	Python

Community Efforts

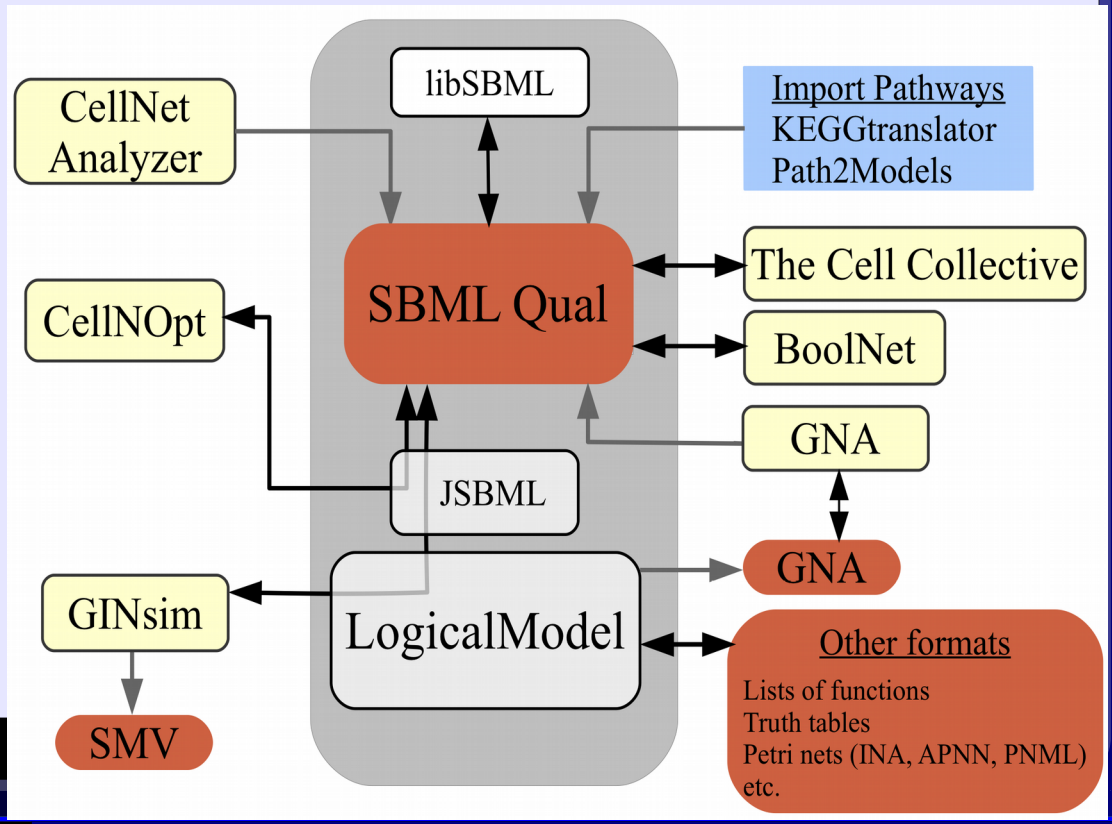
A community effort for standardization has been launched (CoLoMoTo) http://colomoto.org

- SBML Level 3 Qualitative Model Package Version 1

A standard format to store logical models

- *LogicalModel* library

github.com/colomoto



Community Efforts

METHODOLOGY ARTICLE Open Access

SBML qualitative models: a model representation format and infrastructure to foster interactions between qualitative modelling formalisms and tools http://www.biomedcentral.com/1752-0509/7/135

BMC Systems Biology

Systems biology

Bioinformatics

Cooperative development of logical modelling standards and tools with CoLoMoTo

Aurélien Naldi[1], Pedro T. Monteiro[2,3], Christoph Müssel[4], the Consortium for Logical Models and Tools*,†, Hans A. Kestler[4,5,6], Denis Thieffry[7], Ioannis Xenarios[1,8], Julio Saez-Rodriguez[9], Tomas Helikar[10] and Claudine Chaouiya[3]

http://dx.doi.org/10.1093/bioinformatics/btv013

Journal of Integrative Bioinformatics, 12(2):270, 2015 http://journal.imbio.de/

SBML Level 3 package: Qualitative Models, Version 1, Release 1

Claudine Chaouiya[1*], Sarah M Keating[2], Duncan Berenguier[3], Aurélien Naldi[4], Denis Thieffry[5], Martijn P. van Iersel[2], Nicolas Le Novère[6] and Tomáš Helikar[7]

frontiers in Genetics

REVIEW
published: 31 May 2016
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CrossMark

Logical Modeling and Dynamical Analysis of Cellular Networks

*Wassim Abou-Jaoudé[1], Pauline Traynard[1], Pedro T. Monteiro[2,3], Julio Saez-Rodriguez[4], Tomáš Helikar[5], Denis Thieffry[1] and Claudine Chaouiya[3]**

Outreach – Meetings, workshops and tutorials

Lisbon, PT, 2010 (meeting)
Hinxton, UK, 2012 (meeting)
Paris, FR, 2013 (COMBINE – SBML qual)
Lausanne, SUI, 2014 (meeting)
Copanhagen, DK, 2014 (ECCB – workshop)
Basel, SUI, 2015 (BC2 – tutorial)
Singapore, 2015 (ICSB – tutorial + workshop)
Barcelona, SP, 2016 (ICSB – tutorial)
Blacksburg, Virginia, 2017 (ICSB – tutorial)

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IMPACT July 2015 FACTOR

Systems Biology

Matteo Barberis and Tomáš Helikar (Eds.)

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Logical Modeling of Cellular Processes:

From Software Development to Network Dynamics

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