

Qualitative modelling of biological networks current developments

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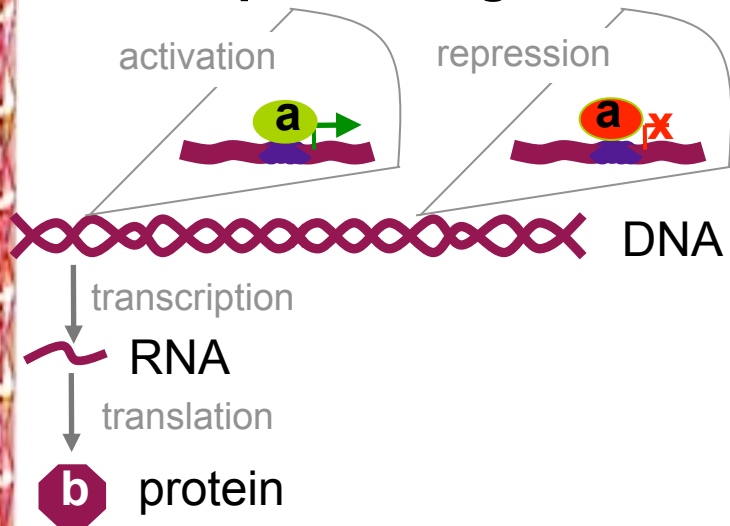
Outline

- Introduction
- **GINsim** & other tools dedicated to the **logical modelling** of regulatory networks
- **QUAL** SBML Level 3 Package proposal
- Conclusion



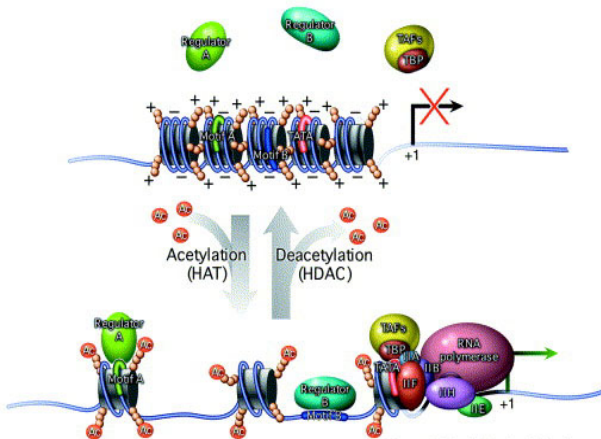
Regulatory & signalling networks

Transcriptional regulation



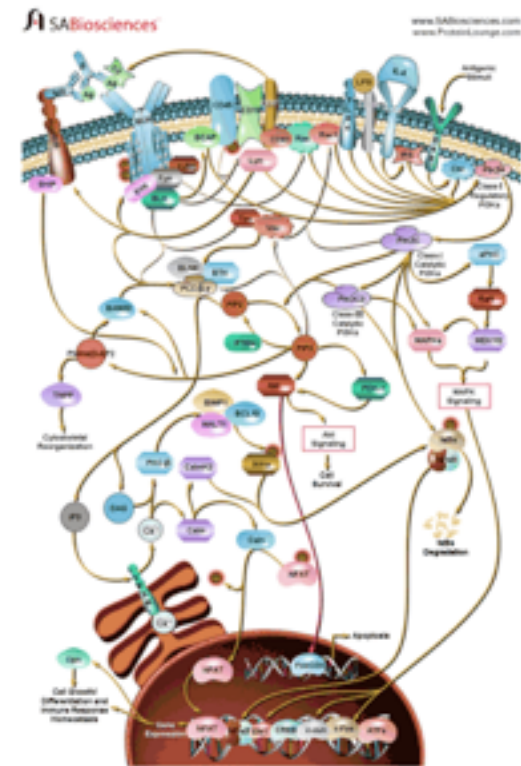
Other regulatory mechanisms

Phosphorylation, Complex formation, Splicing, Chromatine structure, ...



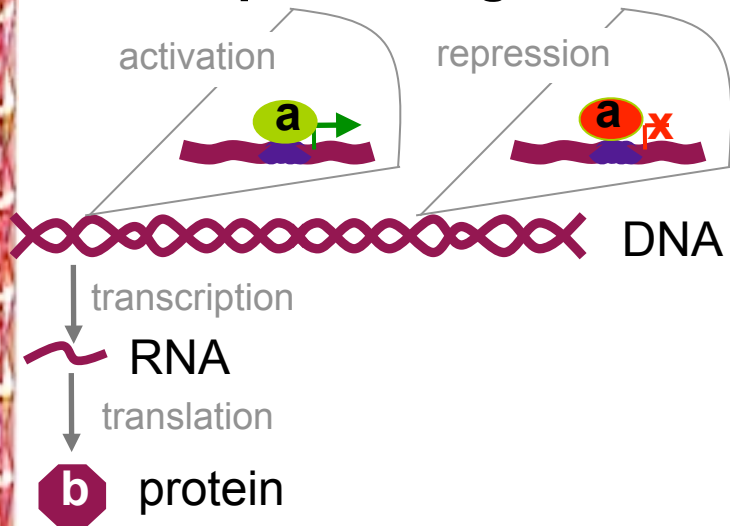
Current Opinion in Genetics & Development

Signalling pathways



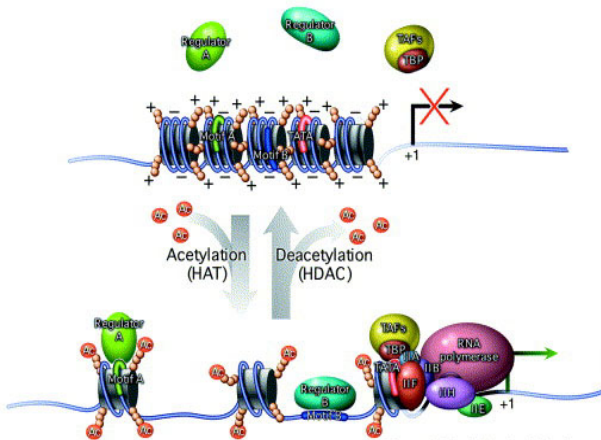
Regulatory & signalling networks

Transcriptional regulation



Other regulatory mechanisms

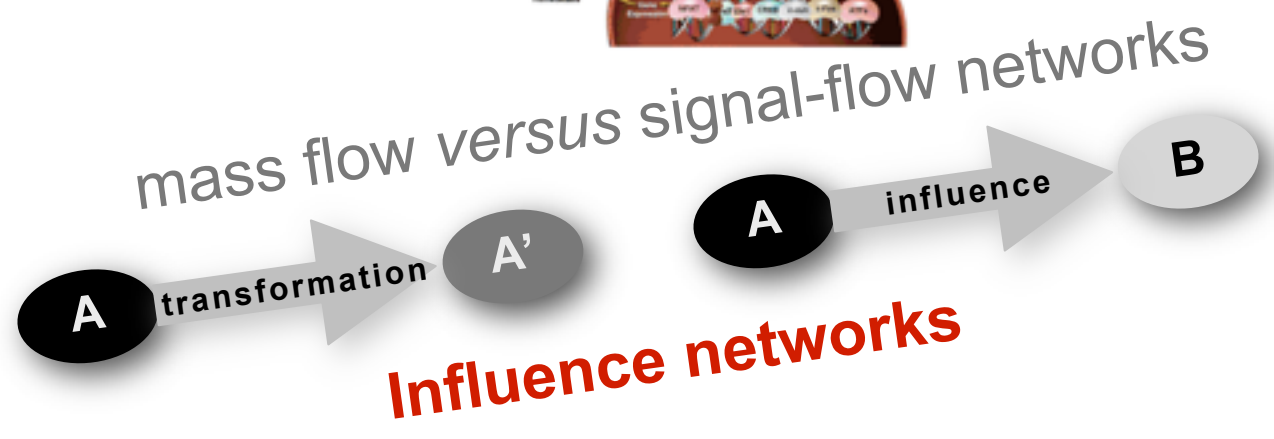
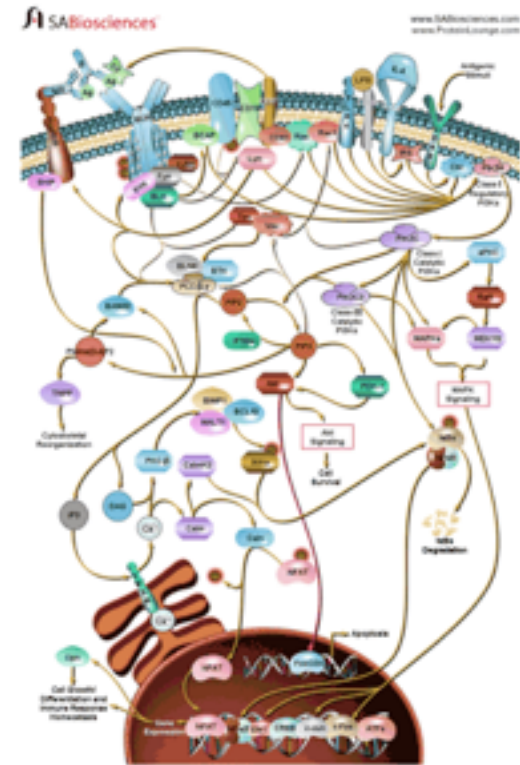
Phosphorylation, Complex formation, Splicing, Chromatine structure, ...



Current Opinion in Genetics & Development

COMBINE Heidelberg, Sept 2011

Signalling pathways



Influence networks

Qualitative frameworks

Qualitative formalisms: discrete state space, (implicit) discrete time ➡ dynamics represented by **state transition graphs**

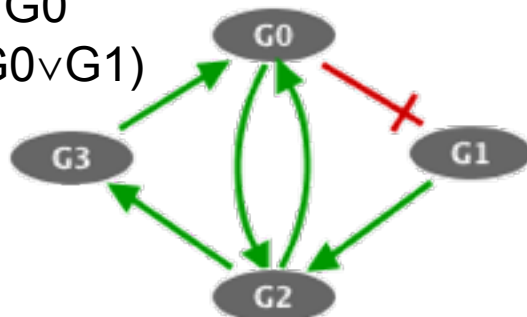
- **Boolean and multi-valued networks**
- Petri nets
- PLDE models
- ...

Model (logical equations)

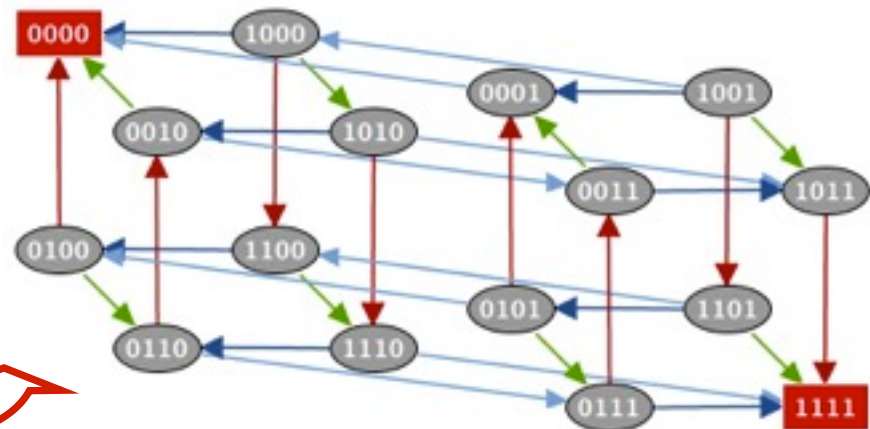
$G0 \text{ if } (G2 \wedge G3)$

$G1 \text{ if } \neg G0$

$G2 \text{ if } (G0 \vee G1)$



State transition graph



Qualitative frameworks

- Regulatory components associated to
 - ✓ discrete functional levels
 - ✓ logical rules defining their behaviours (effects of combinations of incoming interactions)
- Properties on state transition graphs refer to
 - ✓ attractors (stable states or complex cycles)
 - ✓ properties along trajectories (eg reachability)
- Analysis of perturbations
- Development of efficient methods to analyse large models
 - STG reduction: eg priority classes
 - Circuit analysis
 - Model reduction
 - Model-checking technics

...



Softwares



Softwares



S. Klamt (MPI Magdeburg)



CellNetOptimizer

J. Saez-Rodrigues (EBI, UK)

Odefy

F. Theis (CMB, Helmholtz Zentrum
München, DE)



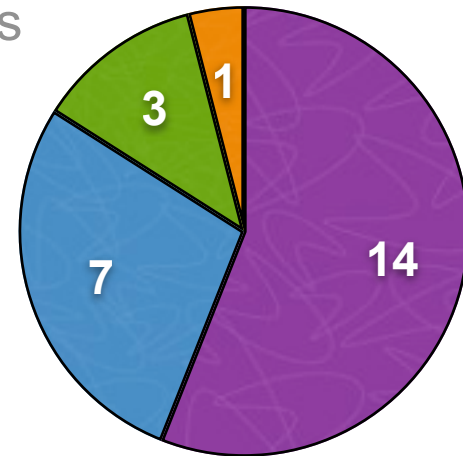
Ioannis Xenarios (ENFIN / Vital-IT, CH)

ChemChains

T. Helikar (Univ Nebraska, USA)



> 25 groups working with Boolean/multi-valued logical models



- Europe
- USA, Canada
- Brasil, Chile, Mexico
- Japan

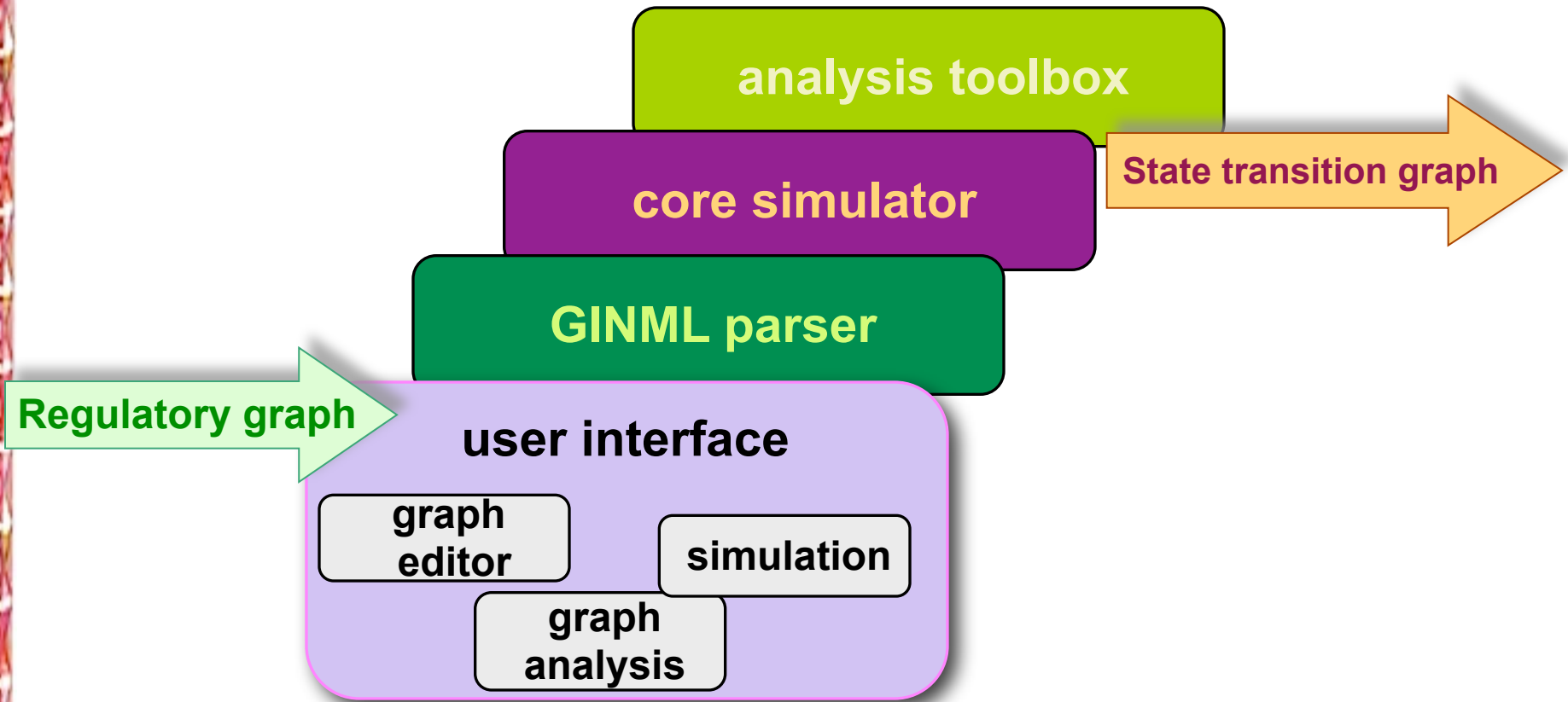
Increasing number of published
models of ever larger networks

CoLoMoTo (Common Logical Modelling Toolbox)

- Gather the community involved in the development of computational tools
- Provide a common toolbox for qualitative (discrete) modelling of biological (regulatory) networks
- Take advantage of existing softwares
- First meeting in November 2010
 - ✓ SBML QUAL Package
 - ✓ a model editor, relying on the common, modular core of Cytoscape
 - ✓ use of MIRIAM



GINsim (Gene Interaction Networks simulation)

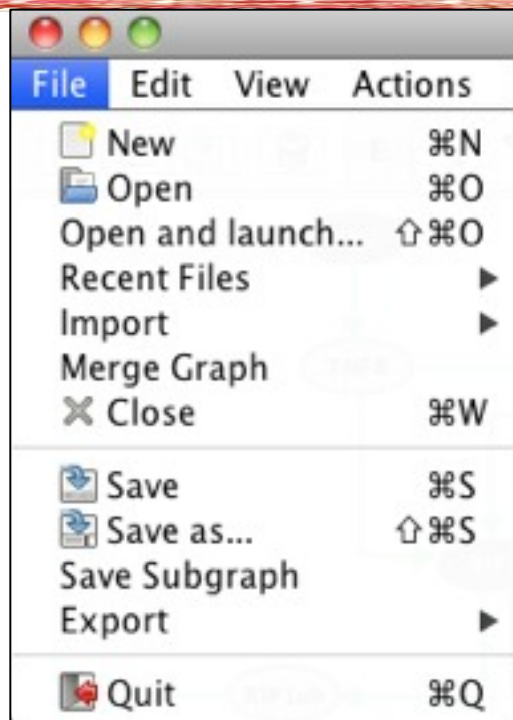


Available at <http://gin.univ-mrs.fr/GINsim>

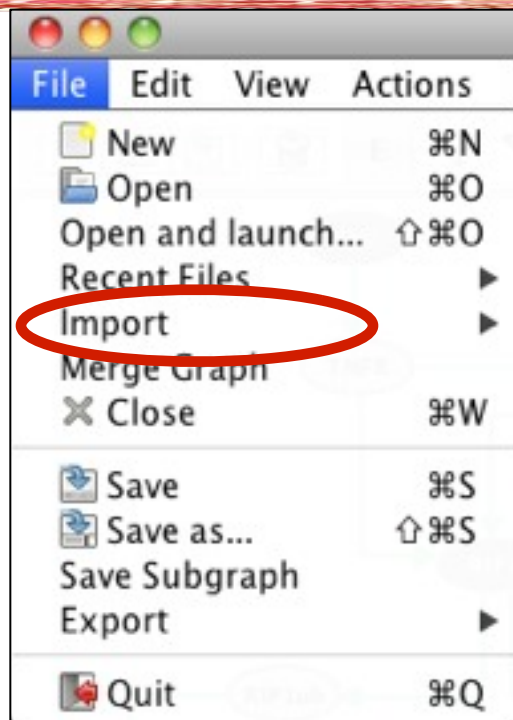
Naldi A *et al* 2009 Biosystems 97(2):134-9



GINsim (Gene Interaction Networks simulation)



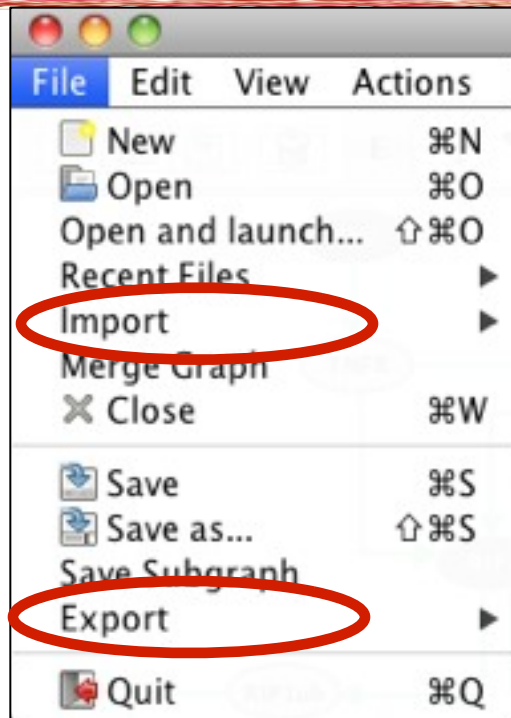
GINsim (Gene Interaction Networks simulation)



SBML qual



GINsim (Gene Interaction Networks simulation)



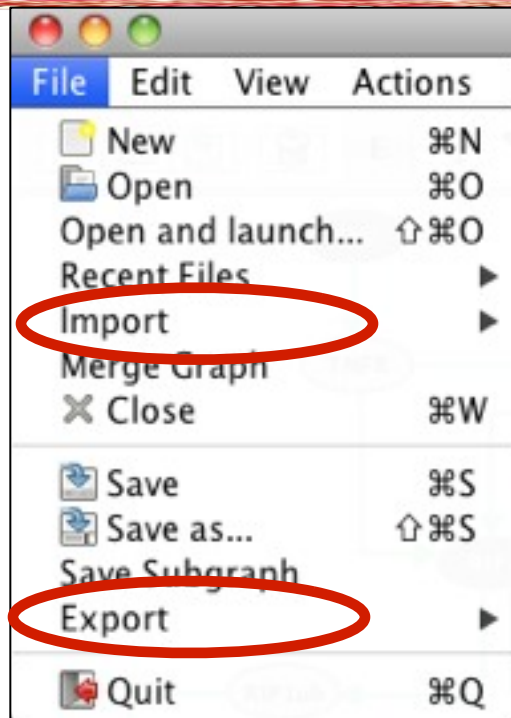
SBML qual

Graphviz, BioLayout
SVG, Image
Documentation
Cytoscape
Petri net

SBML qual
NuSMV



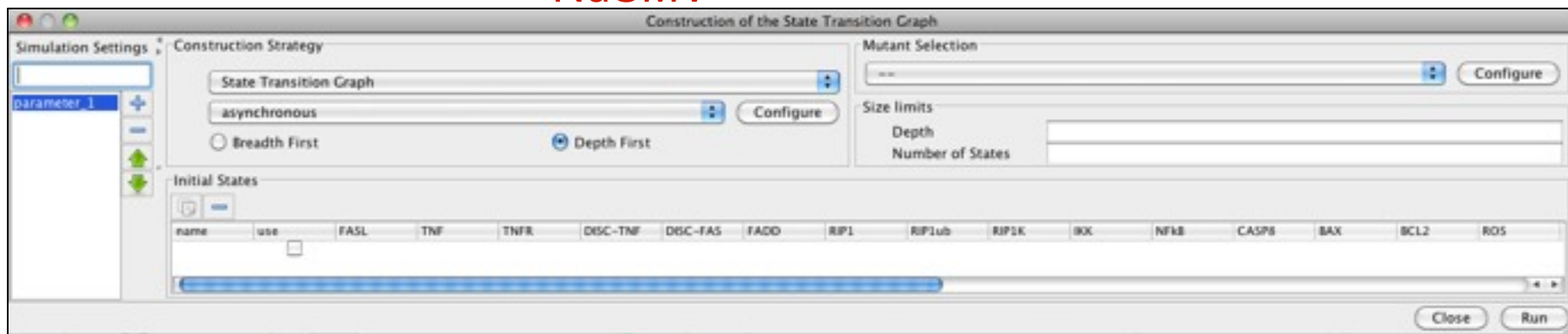
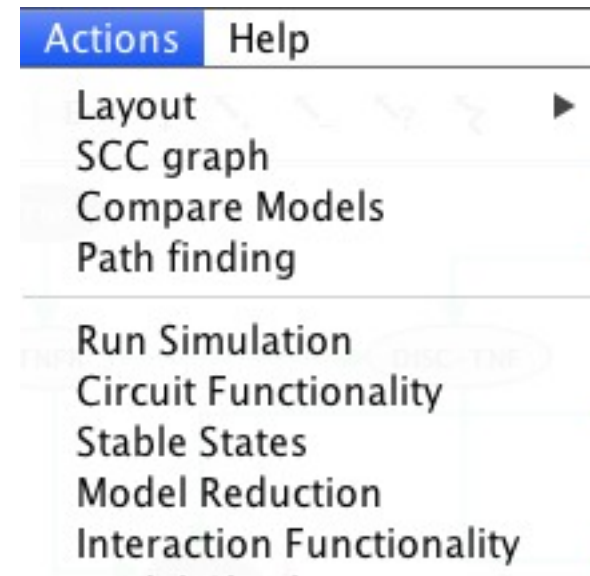
GINsim (Gene Interaction Networks simulation)



SBML qual

Graphviz, BioLayout
SVG, Image
Documentation
Cytoscape
Petri net

SBML qual
NuSMV



GINML: the GINsim format

XML format, based on GXL (graph exchange format)

GINML.2.* → GINML.3

```
gxl
  graph
    node id, maxvalue
      parameter idActiveInteractions, value
        value val           ← logical terms
          expr str
        annotation ← model documentation
      comment
    ...
    edge id, from, to, minvalue, maxvalue, sign
    ...
```



SBML package proposal: Qualitative Models (qual)

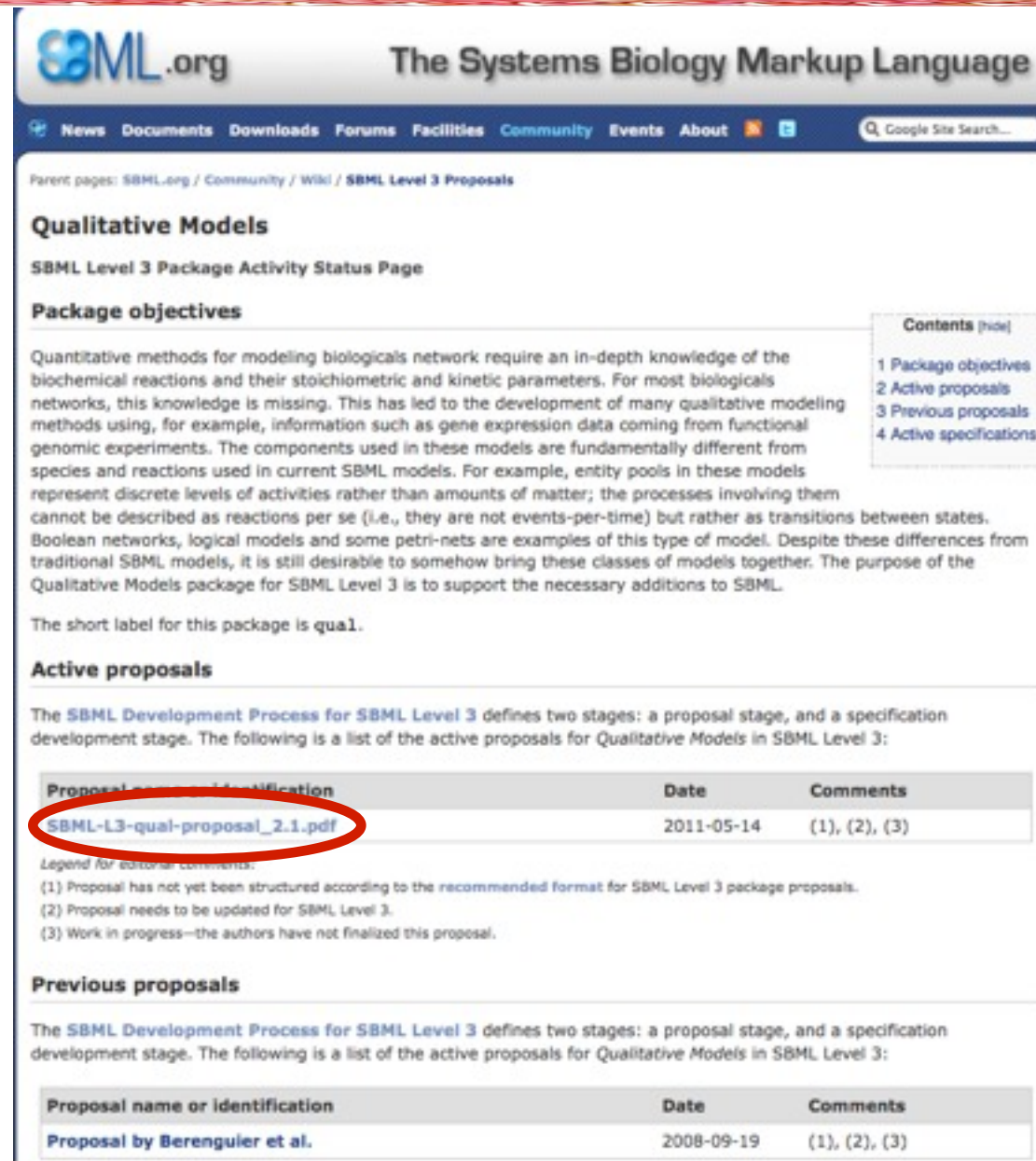
Logical models in SBML

Early proposal at ICSB'06
Attempt to fit it in SBML L2 →
ambiguous use of existing tags

2008 1st SBML L3 qual proposal

2009 SBML L3 core release

2010 2nd SBML L3 qual proposal



The screenshot shows the SBML.org website with the following structure:

- Header:** SBML.org logo and "The Systems Biology Markup Language".
- Navigation:** News, Documents, Downloads, Forums, Facilities, Community, Events, About. A search bar is also present.
- Breadcrumbs:** Parent pages: SBML.org / Community / Wiki / SBML Level 3 Proposals.
- Section:** Qualitative Models.
- Sub-section:** SBML Level 3 Package Activity Status Page.
- Package objectives:** A paragraph explaining the need for qualitative models in SBML, contrasting them with quantitative models.
- Active proposals:** A table listing active proposals for Qualitative Models in SBML Level 3. The first proposal, "SBML-L3-qual-proposal_2.1.pdf", is circled in red.
- Previous proposals:** A table listing previous proposals for Qualitative Models in SBML Level 3.

Contents (hide)

- 1 Package objectives
- 2 Active proposals
- 3 Previous proposals
- 4 Active specifications

Package objectives

Quantitative methods for modeling biologicals network require an in-depth knowledge of the biochemical reactions and their stoichiometric and kinetic parameters. For most biologicals networks, this knowledge is missing. This has led to the development of many qualitative modeling methods using, for example, information such as gene expression data coming from functional genomic experiments. The components used in these models are fundamentally different from species and reactions used in current SBML models. For example, entity pools in these models represent discrete levels of activities rather than amounts of matter; the processes involving them cannot be described as reactions per se (i.e., they are not events-per-time) but rather as transitions between states. Boolean networks, logical models and some petri-nets are examples of this type of model. Despite these differences from traditional SBML models, it is still desirable to somehow bring these classes of models together. The purpose of the Qualitative Models package for SBML Level 3 is to support the necessary additions to SBML.

The short label for this package is `qual`.

Active proposals

The SBML Development Process for SBML Level 3 defines two stages: a proposal stage, and a specification development stage. The following is a list of the active proposals for Qualitative Models in SBML Level 3:

Proposal name or identification	Date	Comments
SBML-L3-qual-proposal_2.1.pdf	2011-05-14	(1), (2), (3)

Legend for editorial comments:

- (1) Proposal has not yet been structured according to the recommended format for SBML Level 3 package proposals.
- (2) Proposal needs to be updated for SBML Level 3.
- (3) Work in progress—the authors have not finalized this proposal.

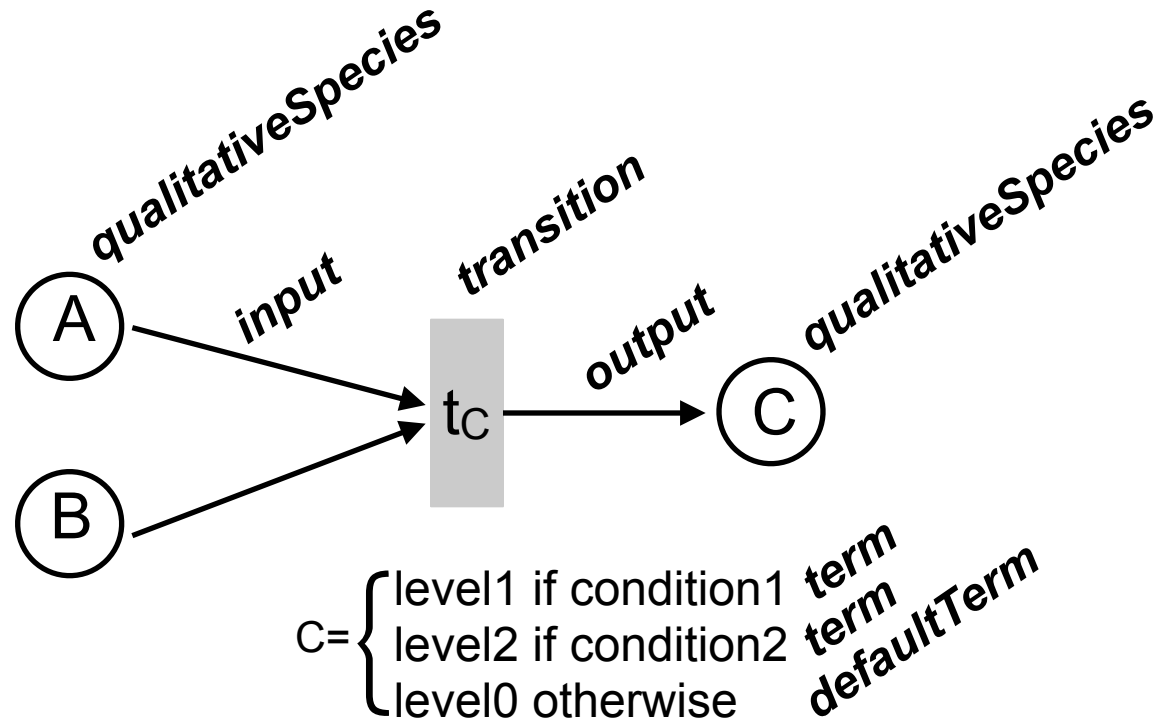
Previous proposals

The SBML Development Process for SBML Level 3 defines two stages: a proposal stage, and a specification development stage. The following is a list of the active proposals for Qualitative Models in SBML Level 3:

Proposal name or identification	Date	Comments
Proposal by Berenguier et al.	2008-09-19	(1), (2), (3)



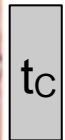
SBML package proposal: Qualitative Models (qual)



SBML package proposal: Qualitative Models (qual)

(A) <qualitativeSpecies id="A" maxLevel="1">

(B) <qualitativeSpecies id="B" maxLevel="2">

 <transition id="tr_C" sign="SBO:0000459">

(A) $\xrightarrow{\theta_A=1}$

<input qualitativeSpecies="A" id="theta_A" thresholdLevel="1" transitionEffect="none" />

\longrightarrow (C)

<output qualitativeSpecies="C" transitionEffect="assignmentLevel" />

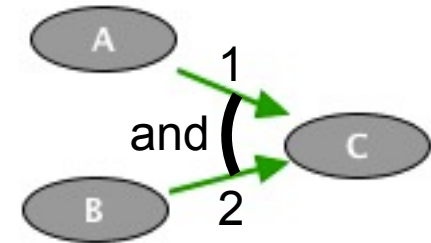
$$C = \begin{cases} 1 & \text{if } A \geq \theta_A \text{ and } B \geq \theta_B \\ 0 & \text{otherwise} \end{cases}$$

```
<listOfFunctionTerms>
  <functionTerm resultLevel="1">
    <math>
      A \geq \text{theta\_A} \text{ and } B \geq \text{theta\_B}
    </math>
  </functionTerm>
  <defaultTerm resultLevel="0" />
</listOfFunctionTerms>
```



SBML package proposal: Qualitative Models (qual)

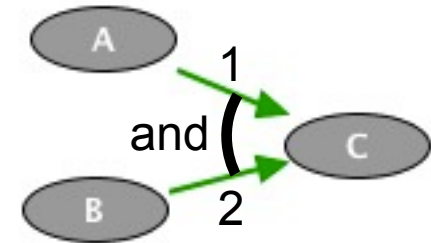
```
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xmlns:qual="http://sbml.org/Community/Wiki/SBML_Level_3_Proposals/Qualitative_Models" qual:required="true">
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    <listOfCompartments>
      <compartment id="c_default_name"/>
    </listOfCompartments>
    <listOfQualitativeSpecies xmlns="http://sbml.org/Community/Wiki/SBML_Level_3_Proposals/Qualitative_Models">
      <qualitativeSpecies id="A" name="" compartment="c_default_name" maxLevel="1" initialLevel="0"/>
      <qualitativeSpecies id="B" name="" compartment="c_default_name" maxLevel="2" initialLevel="0"/>
      <qualitativeSpecies id="C" name="" compartment="c_default_name" maxLevel="1" initialLevel="0"/>
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                    <geq/>
                    <ci>B</ci>
                    <cn>2</cn>
                  </apply>
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      </listOfTransitions>
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  </sbml>
```



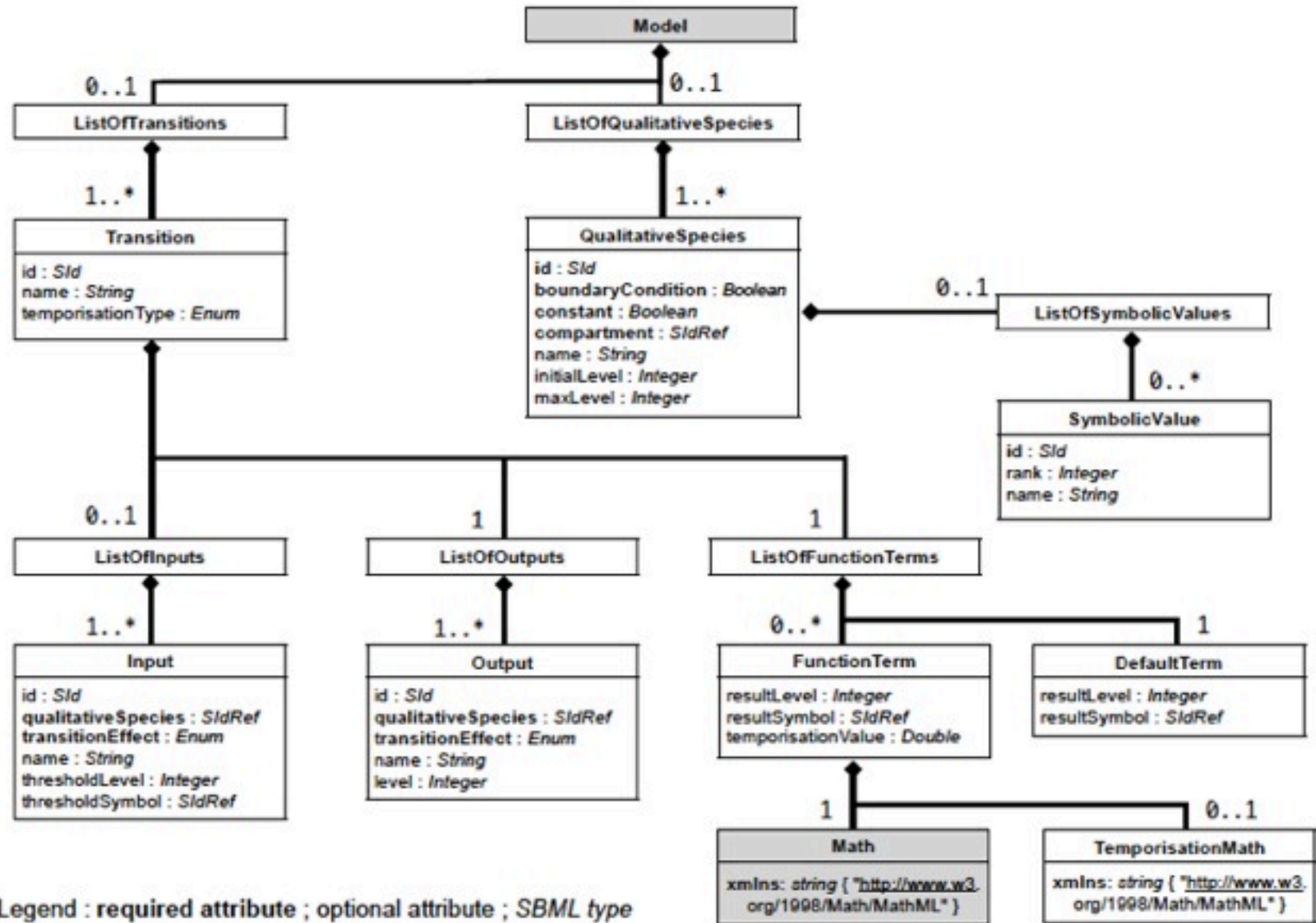
```
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<gxl xmlns:xlink="http://www.w3.org/1999/xlink">
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    <node id="B" maxvalue="2">
    </node>
    <node id="A" maxvalue="1">
    </node>
    <node id="C" maxvalue="1">
      <parameter idActiveInteractions=" A:C B:C" val="1"/>
    </node>
    <edge id="B:C" from="B" to="C" minvalue="2" sign="positive">
    </edge>
    <edge id="A:C" from="A" to="C" minvalue="1" sign="positive">
    </edge>
  </graph>
</gxl>
```

SBML package proposal: Qualitative Models (qual)

```
<transition id="tr_C">
  <listOfInputs>
    <input qualitativeSpecies="A" transitionEffect="none" sign="SB0:0000459"/>
    <input qualitativeSpecies="B" transitionEffect="none" sign="SB0:0000459"/>
  </listOfInputs>
  <listOfOutputs>
    <output qualitativeSpecies="C" transitionEffect="assignmentLevel"/>
  </listOfOutputs>
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    <functionTerm resultLevel="1">
      <math xmlns="http://www.w3.org/1998/Math/MathML">
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          <apply>
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              <cn>1</cn>
            </apply>
            <apply>
              <geq/>
              <ci>B</ci>
              <cn>2</cn>
            </apply>
          </and>
        </or>
      </math>
    </functionTerm>
  </listOfFunctionTerms>
</transition>
```



SBML package proposal: Qualitative Models (qual)



Conclusion

- Implementation of export/import facilities into
GINsim
ChemChains
CellNetOptimizer
- Include annotations
- Support for Petri nets, other qualitative frameworks?
- Different views of models
- Hybrid / hierarchical models?
- Towards a shared platform for logical modelling, the CoLoMoTo project...



Acknowledgements

Thank you!

GINsim@France

- ★ D. Thieffry (ENS Paris)
- ★ D. Berenguier (IML, TAGC, Marseille)
- G-R. Assoumou (TAGC, Marseille)

GINsim@Switzerland

- ★ A. Naldi (CIG Lausanne)

- ★ N. Le Novère (EMBL-EBI, Hinxton, UK)
- ★ S. Klamt & A. Von Kamp MPI Magdeburg, DE
- ★ T. Helikar (University of Nebraska, USA)
- ★ I. Xenarios (ISB-SIB Lausanne, CH)

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- P. Monteiro (IGC, Oeiras)
- J. Alexander (IGC, Oeiras)
- ITT Team (IGC, Oeiras)

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