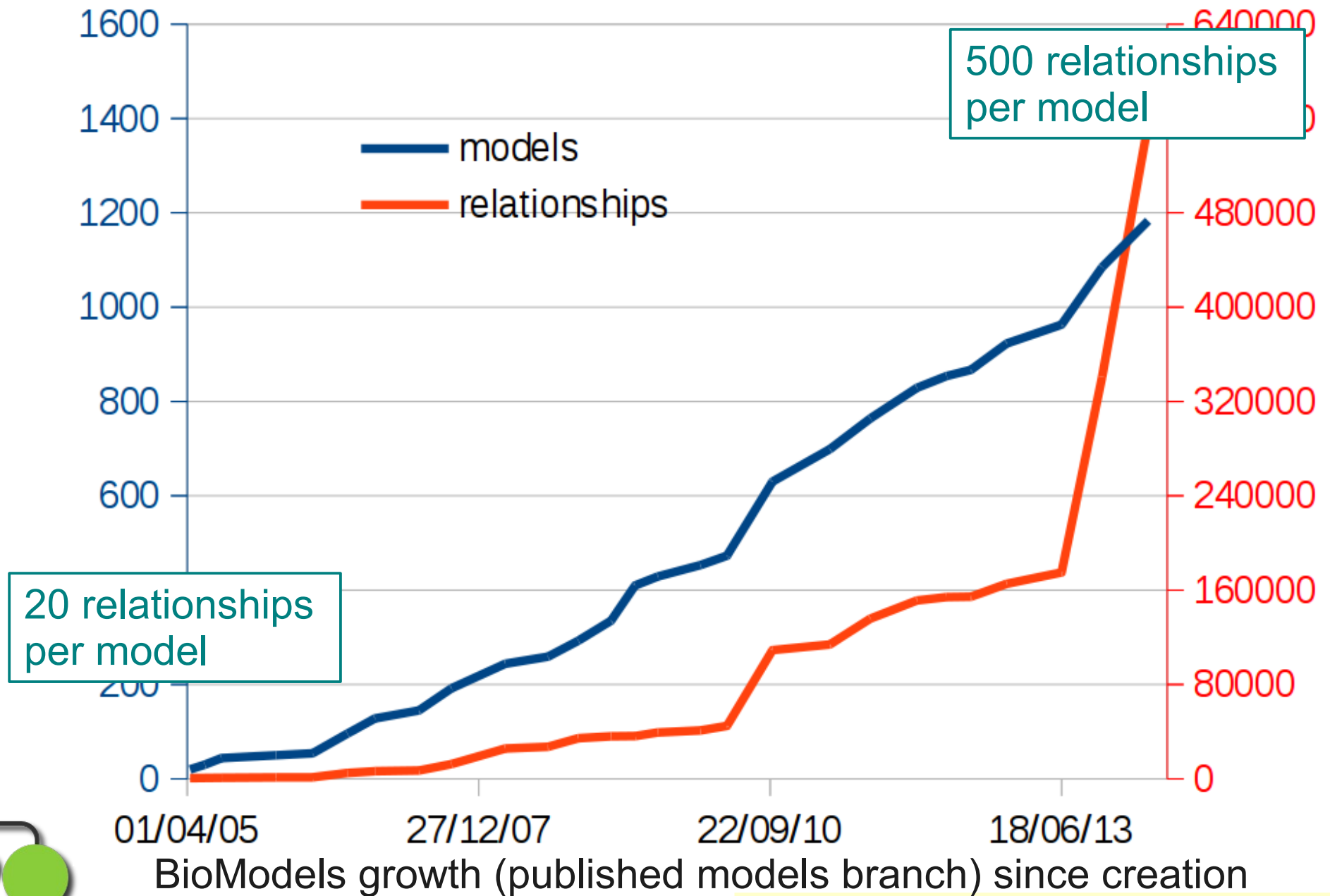




***Interoperable Standards
For modelling in biology***

Computational models on the rise



<http://www.ebi.ac.uk/biomodels/>



We need to

Verify

Re-use

Modify

Build upon

Integrate with

Therefore we need to share

Model descriptions

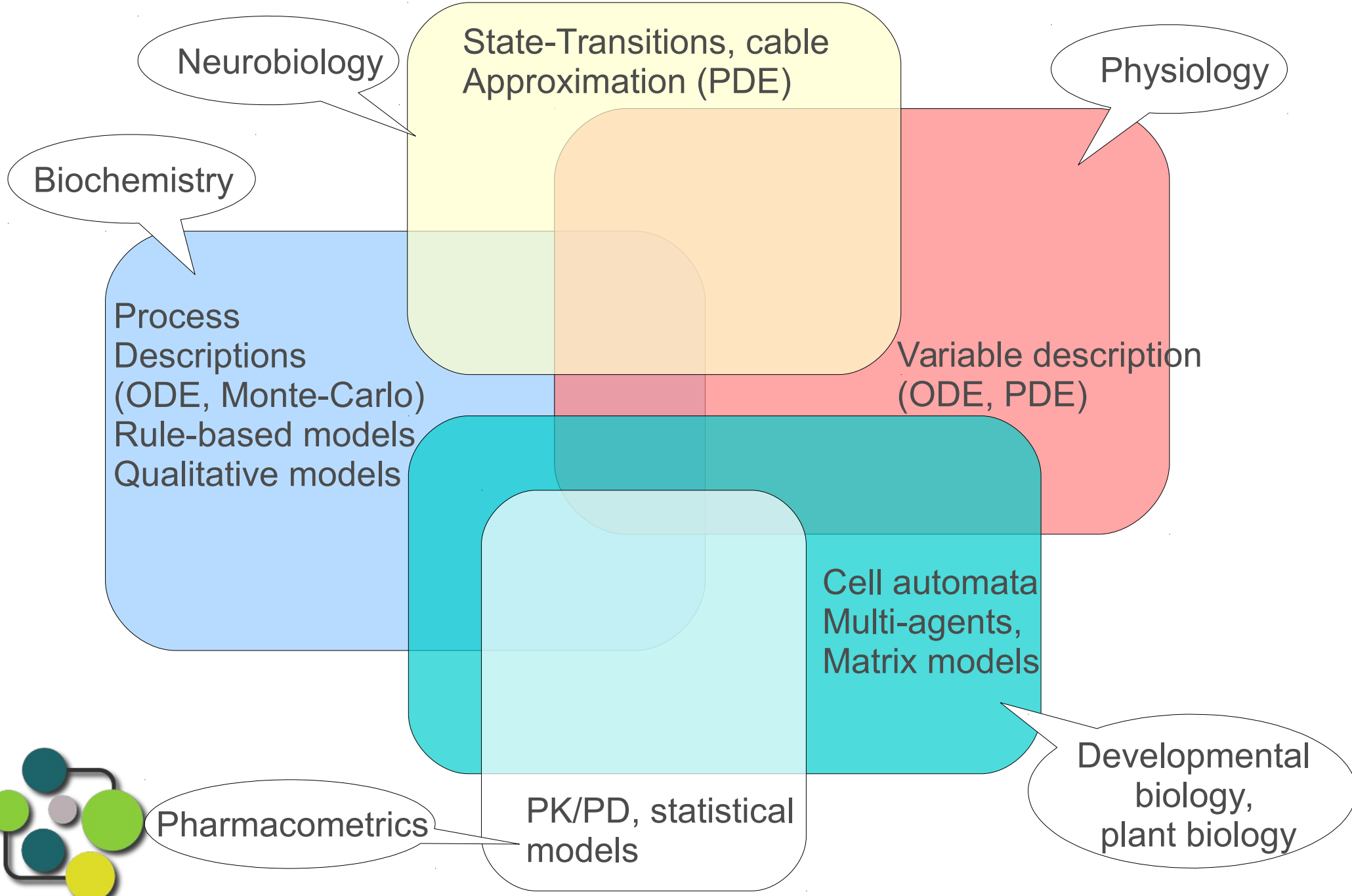
Simulation descriptions

Parametrisations

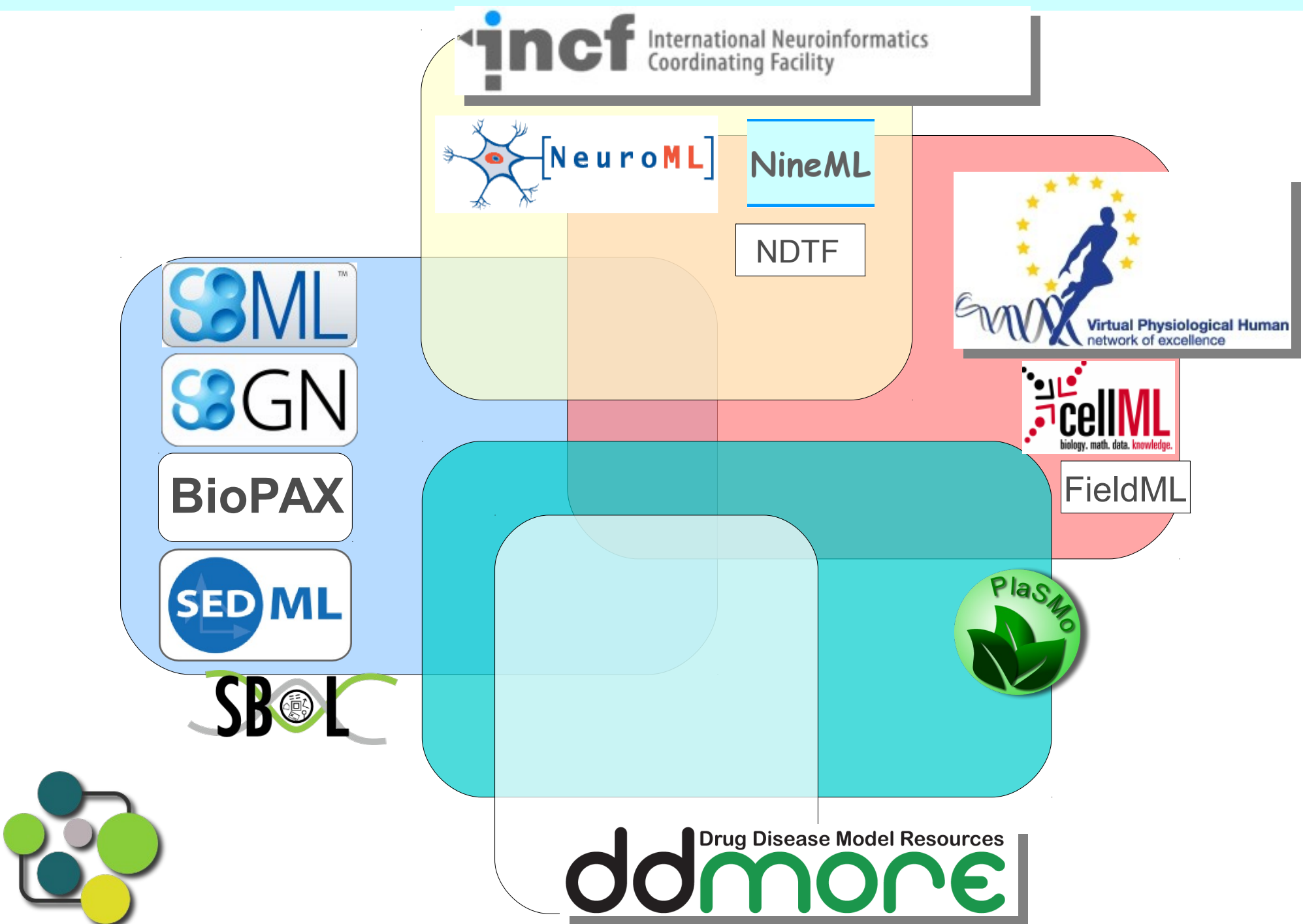
Biological meaning



Many alternative modelling approaches



Parallel and redundant efforts





Overarching standardisation structure



<http://co.mbine.org/>



Mission 1: Coordinating development of standards



ASSOCIATED
TOOLS



CORE STANDARDS

NuML

FieldML

PharmML



RELATED EFFORTS



Format specification infrastructure

- Each format comes with many different flavors, described in **many different specification documents**.
- Format specifications are distributed in different ways, through **different websites**.
- The means of distribution for format specifications evolve over time, making **hard to consistently refer to them**.
- Trying to find **reliable third parties proved difficult** (e.g. Nature Precedings).
- We need a **consistent way of naming** specification documents



COMBINE specifications

[View](#)
[Edit](#)
[Revisions](#)
[Access control](#)

Name of the specification	Identifier	Location	node
Biological Pathway Exchange format	biopax	standards/biopax	86
BioPAX Level 1	biopax.level-1	standards/biopax/level-1	89
BioPAX Level 2	biopax.level-2	standards/biopax/level-2	88
BioPAX Level 3	biopax.level-3	standards/biopax/level-3	87
CellML 1.0	cellml.1.0	standards/cellml/1/0	93
CellML 1.1	cellml.1.1	standards/cellml/1/1	94
Systems Biology Graphical Notation	sbgn	standards/sbgn	52
SBGN Activity Flow language	sbgn.af	standards/sbgn/af	66
SBGN AF Level 1	sbgn.af.level-1	standards/sbgn/af/level-1/version-1/0	67
SBGN AF Level 1 Version 1	sbgn.af.level-1.version-1	standards/sbgn/af/level-1/version-1/0	67
SBGN AF Level 1 Version 1.0	sbgn.af.level-1.version-1.0	standards/sbgn/af/level-1/version-1/0	67
SBGN ER	sbgn.er	standards/sbgn/er	57
SBGN ER Level 1	sbgn.er.level-1	standards/sbgn/er/level-1/version-1/2	56
SBGN ER Level 1 Version 1	sbgn.er.level-1.version-1	standards/sbgn/er/level-1/version-1/2	56
SBGN ER Level 1 Version 1.0	sbgn.er.level-1.version-1.0	standards/sbgn/er/level-1/version-1/0	60
SBGN ER Level 1 Version 1.1	sbgn.er.level-1.version-1.1	standards/sbgn/er/level-1/version-1/1	59
SBGN ER Level 1 Version 1.2	sbgn.er.level-1.version-1.2	standards/sbgn/er/level-1/version-1/2	56
SBGN PD	sbgn.pd	standards/sbgn/pd	61
SBGN PD Level 1	sbgn.pd.level-1	standards/sbgn/pd/level-1/version-1/3	62
SBGN PD Level 1 Version 1.0	sbgn.pd.level-1.version-1.0	standards/sbgn/pd/level-1/version-1/3	62
SBGN PD Level 1 Version 1.1	sbgn.pd.level-1.version-1.1	standards/sbgn/pd/level-1/version-1/2	65
SBGN PD Level 1 Version 1.2	sbgn.pd.level-1.version-1.2	standards/sbgn/pd/level-1/version-1/2	64
SBGN PD Level 1 Version 1.3	sbgn.pd.level-1.version-1.3	standards/sbgn/pd/level-1/version-1/3	63
SBGN PD Level 1 Version 1.4	sbgn.pd.level-1.version-1.4	standards/sbgn/pd/level-1/version-1/3	62
Systems Biology Markup Language	sbml	standards/sbml	55
SBML Level 1	sbml.level-1	standards/sbml/level-1/version-2	78
SBML Level 1 Version 1	sbml.level-1.version-1	standards/sbml/level-1/version-1	79

<http://co.mbine.org/standards/specifications/>

SBGN ER Level 1 Version 1.2

View

Edit

Revisions

Access control

Version 1.2 of Level 1 of the SBGN Entity Relationship Language was published on 14 April 2011.

The specification can be found at:

- <http://co.mbine.org/specifications/sbgn.er.level-1.version-1.2.pdf>
- <http://dx.doi.org/10.1038/npre.2011.5902.1>
- http://sbgn.svn.sourceforge.net/viewvc/sbgn/EntityRelationship/tags/Level1-Version1.2/sbgn_ER-level1.pdf

Identifier for this specification is: <http://identifiers.org/combine.specifications/sbgn.er.level-1.version-1.2>

To cite this document, please use:

Nicolas Le Novère, Emek Demir, Huaiyu Mi, Stuart Moodie, Alice Villéger. Systems Biology Graphical Notation: Entity Relationship language Level 1, Version 1.2. Available from COMBINE <<http://identifiers.org/combine.specifications/sbgn.er.level-1.version-1.2>> (2011)

<http://identifiers.org/combine.specifications/sbgn.er.level-1.version-1.2>



COMBINE standards at this tutorial

Model encoding



Mike Hucka 9:35
Session 1a 14:00



David Nickerson 9:55
Session 1b 14:00

Model representation



Falk Schreiber 10:15
Session 2b 16:15

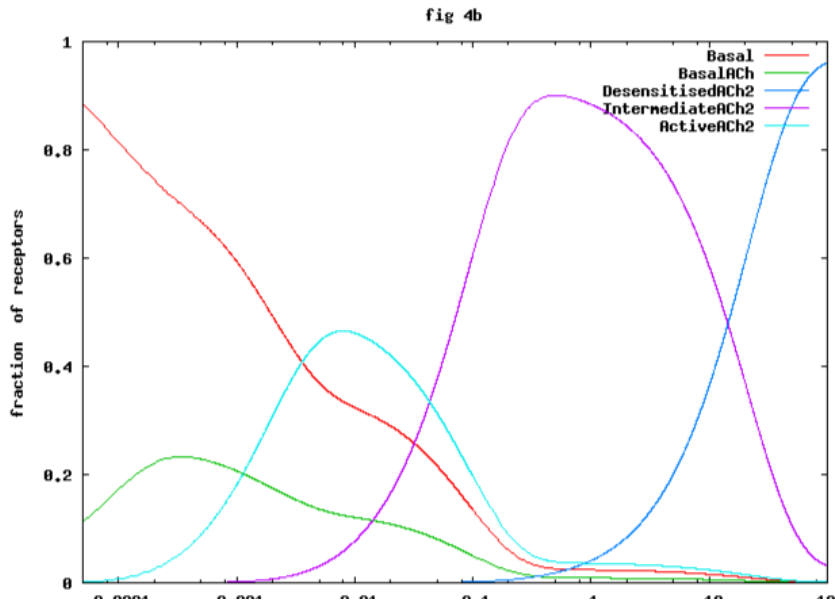
Synthetic biology



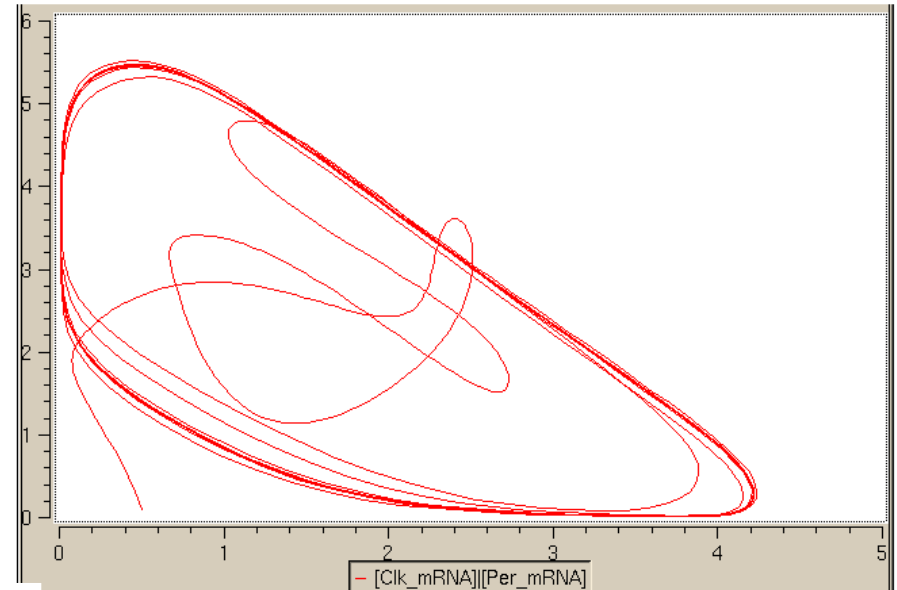
Chris Myers 10:35



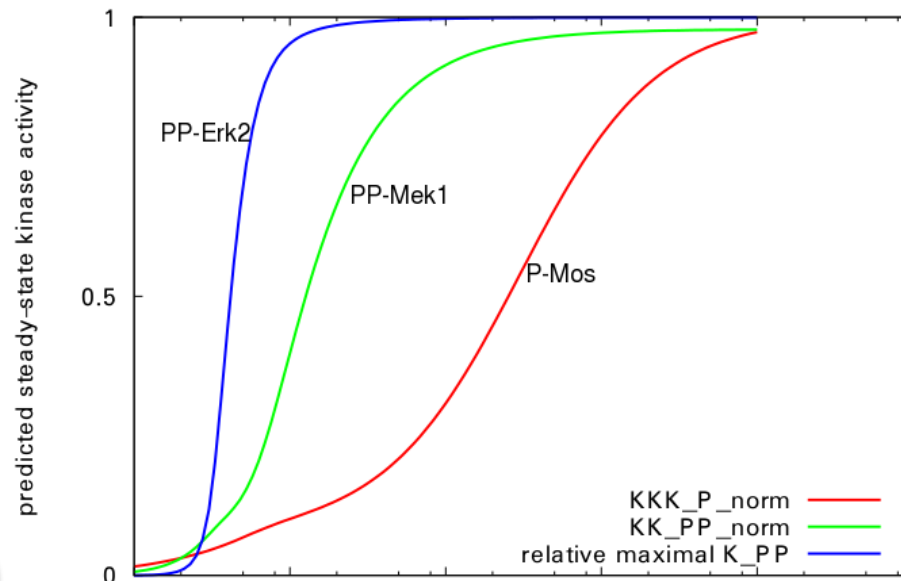
Reproduction of published simulation results



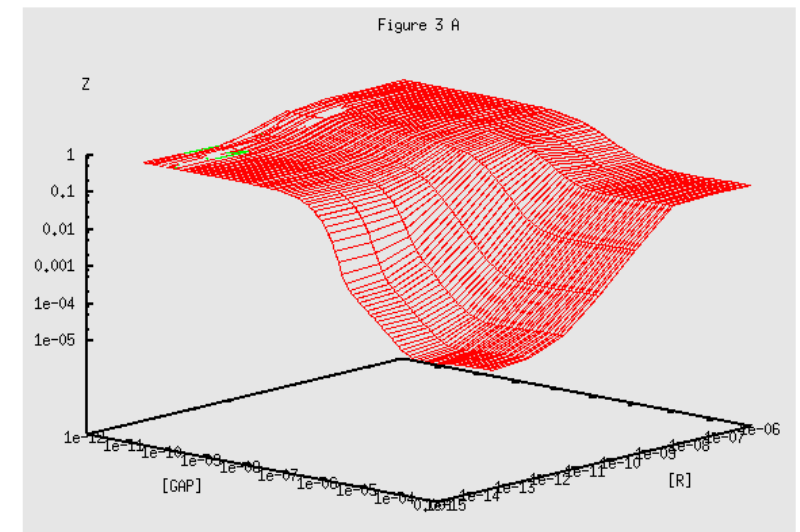
Eidelstein et al 1996 (BIOMD0000000002)



Ueda, et al 2001 (BIOMD0000000022)



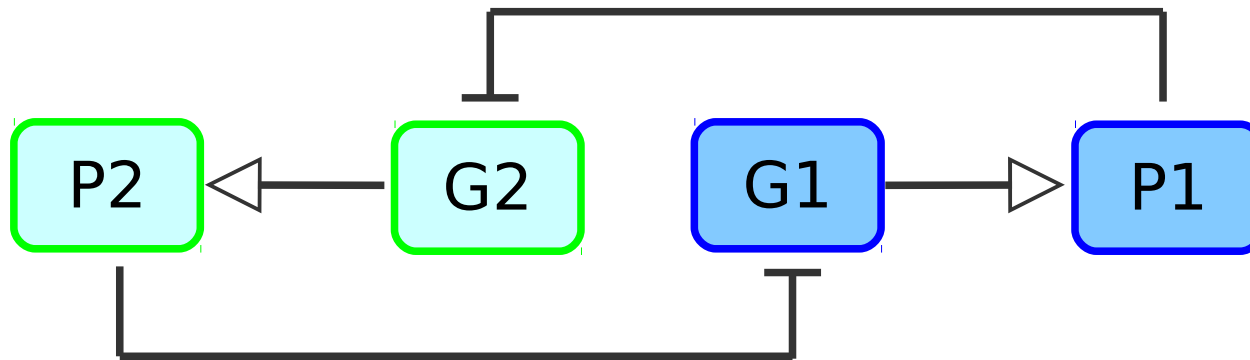
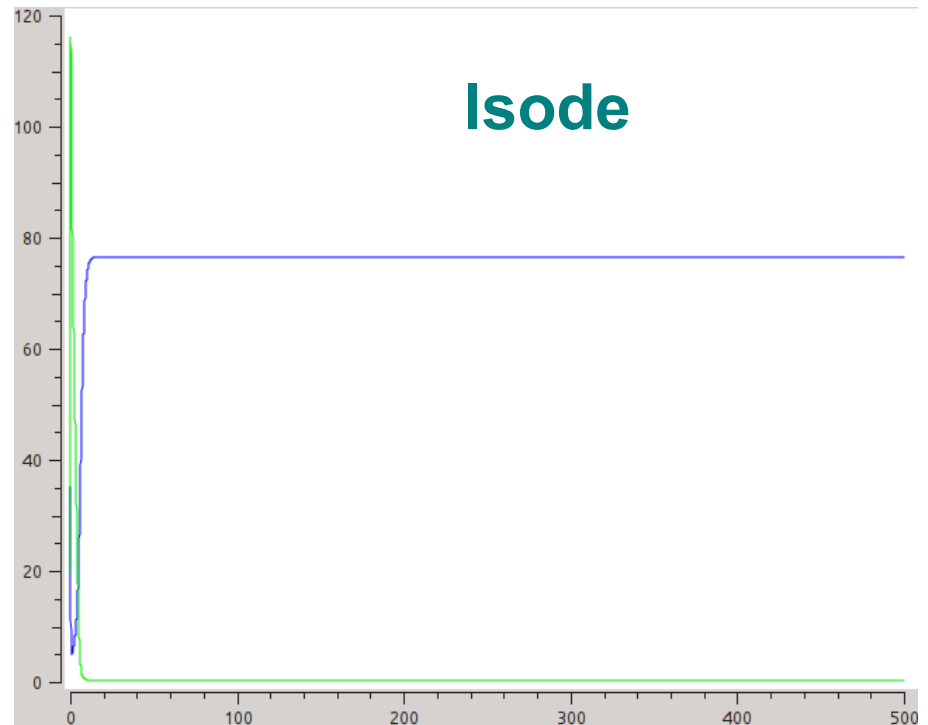
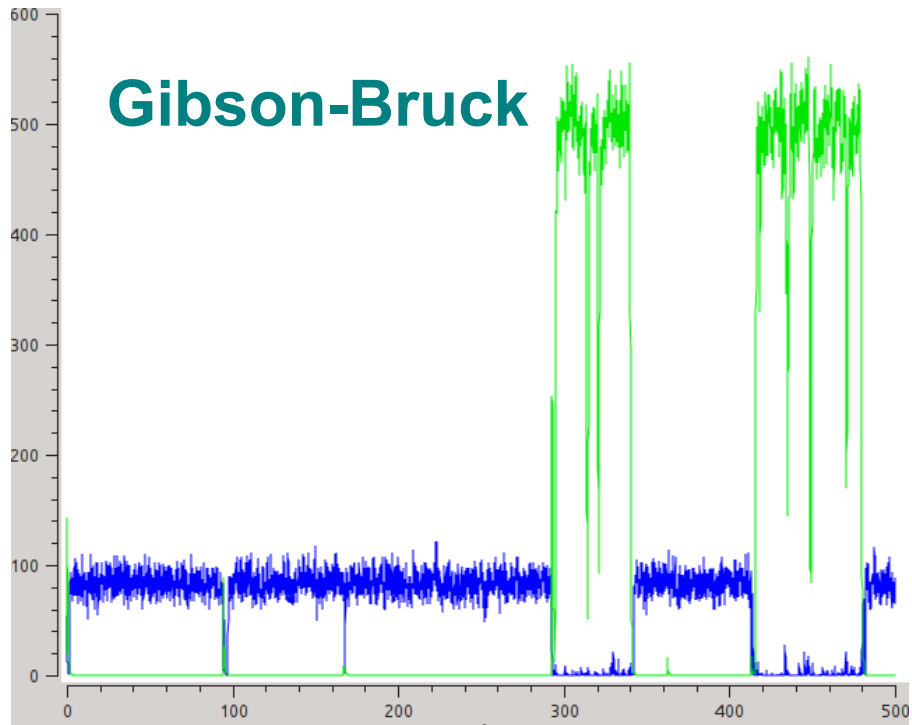
Huang & Ferrell (BIOMD0000000009)



Bornheimer et al 2004 (BIOMD0000000086)



Algorithm choice and multistability



Simulation Experiment Description Markup Language

```
<?xml version="1.0" encoding="utf-8"?>
<sedML xmlns:math="http://www.w3.org/1998/Math/MathML"
  xmlns="http://sed-ml.org/"
  level="1" version="1">
  <listOfModels>
    <model id="model1" name="Repressilator-regular oscillations">
      <listOfChanges><!-- --></listOfChanges>
    </model>
  </listOfModels>
  <listOfSimulations><!-- --></listOfSimulations>
  <listOfTasks><!-- --></listOfTasks>
  <listOfDataGenerators><!-- --></listOfDataGenerators>
  <listOfOutputs><!-- --></listOfOutputs>
</sedML>
```



<http://sed-ml.org>

Flexible model use in SED-ML

```
<listOfModels>
  <model id="model1" name="Repressilator-regular oscillations"
    language="urn:sedml:language:sbml.level-2.version-3"
    source="http://identifiers.org/biomodels.db/BIOMD0000000012" >
  </model>
  <model id="model2" name="Damped oscillations"
    language="urn:sedml:language:sbml.level-2.version-3"
    source="model1">
    <listOfChanges>
      <changeAttribute
        target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@name='tps']"
        newValue="1.3e-5">
      </changeAttribute>
      <changeAttribute
        target="/sbml:sbml/sbml:model/sbml:listOfParameters/sbml:parameter[@name='tps']"
        newValue="0.013">
      </changeAttribute>
    </listOfChanges>
  </model>
</listOfModels>
```

Any XML

Remote access

Modifications before simulations

Access to internal entities via XPath



Multiple simulations algorithms

```
<listOfSimulations>
```

```
  <uniformTimeCourse id="simulation1" initialTime="0"  
    outputStartTime="0" outputEndTime="1000" number  
    <algorithm kisaoID="KISA0:0000088" />  
  </uniformTimeCourse>
```

LSODA

```
  <uniformTimeCourse id="simulation2" initialTime="0"  
    outputStartTime="0" outputEndTime="1000" number  
    <algorithm kisaoID="KISA0:0000027" />  
  </uniformTimeCourse>
```

Gibson-Bruck method



Tasks: simulating models

```
<listOfTasks>
```

```
  <task id="task1" name="Oscillations using a deterministic simulator"  
        modelReference="model1" simulationReference="simulation1" />
```

```
  <task id="task2" name="Damped oscillations using a deterministic simulator"  
        modelReference="model2" simulationReference="simulation1" />
```

```
  <task id="task3" name="Oscillations using a stochastic simulator"  
        modelReference="model1" simulationReference="simulation2" />
```

```
</listOfTasks>
```



Generating numerical results

```
<listOfDataGenerators>
```

```
  <dataGenerator id="timeDG" name="Time">
```

```
    <listOfVariables>
```

```
      <variable id="Time" taskReference="task1" symbol="urn:sedml:symbol:time" />
```

```
    </listOfVariables>
```

```
    <math:math>
```

```
      <math:ci> Time </math:ci>
```

```
    </math:math>
```

```
  </dataGenerator>
```

```
  <dataGenerator id="LacINormalizedDG" name=" NormalizedLaCI repressor">
```

```
    <listOfVariables>
```

```
      <variable id="LacI" taskReference="task1"
```

```
        target="/sbml:sbml/sbml:model/sbml:listOfSpecies/sbml:species[@id='PX']" />
```

```
    </listOfVariables>
```

```
    <math:math>
```

```
      <math:apply>
```

```
        <math:divide />
```

```
        <math:ci>LacI</math:ci>
```

```
        <math:apply>
```

```
          <math:max />
```

```
          <math:ci>LacI</math:ci>
```

```
        </math:apply>
```

```
      </math:apply>
```

```
    </math>
```

```
  </dataGenerator>
```

```
</listOfDataGenerators>
```

$$LacINormalizedDG(t) = \frac{LacI(t)}{\max(LacI)}$$



Presenting results

```
<listOfOutputs>
```

```
<plot2D id="plot_normalized" name="Normalized protein levels">
```

```
<listOfCurves>
```

```
<curve id="c7" logX="false" logY="false"  
  xDataReference="timeDG"  
  yDataReference="TetRNormalizedDG" />
```

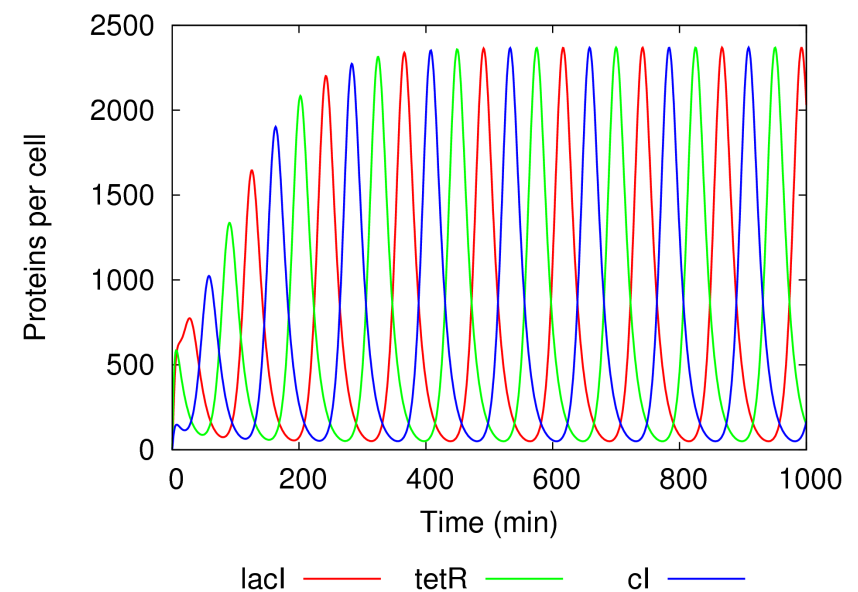
```
<curve id="c8" logX="false" logY="false"  
  xDataReference="timeDG"  
  yDataReference="CIb_normalizedDG" />
```

```
<curve id="c9" logX="false" logY="false"  
  xDataReference="timeDG"  
  yDataReference="LacIbNormalizedDG" />
```

```
</listOfCurves>
```

```
</plot2D>
```

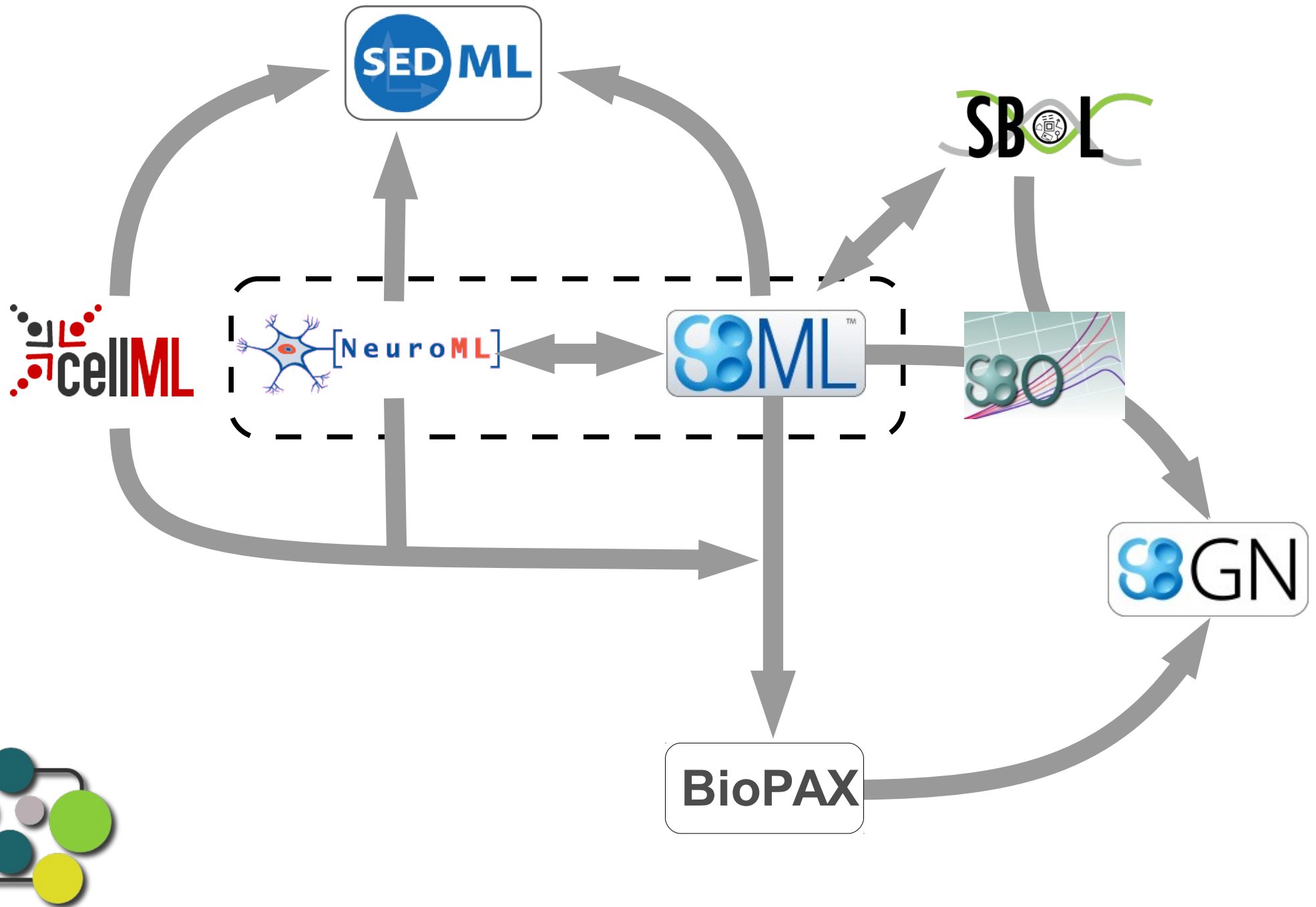
```
</listOfOutputs>
```

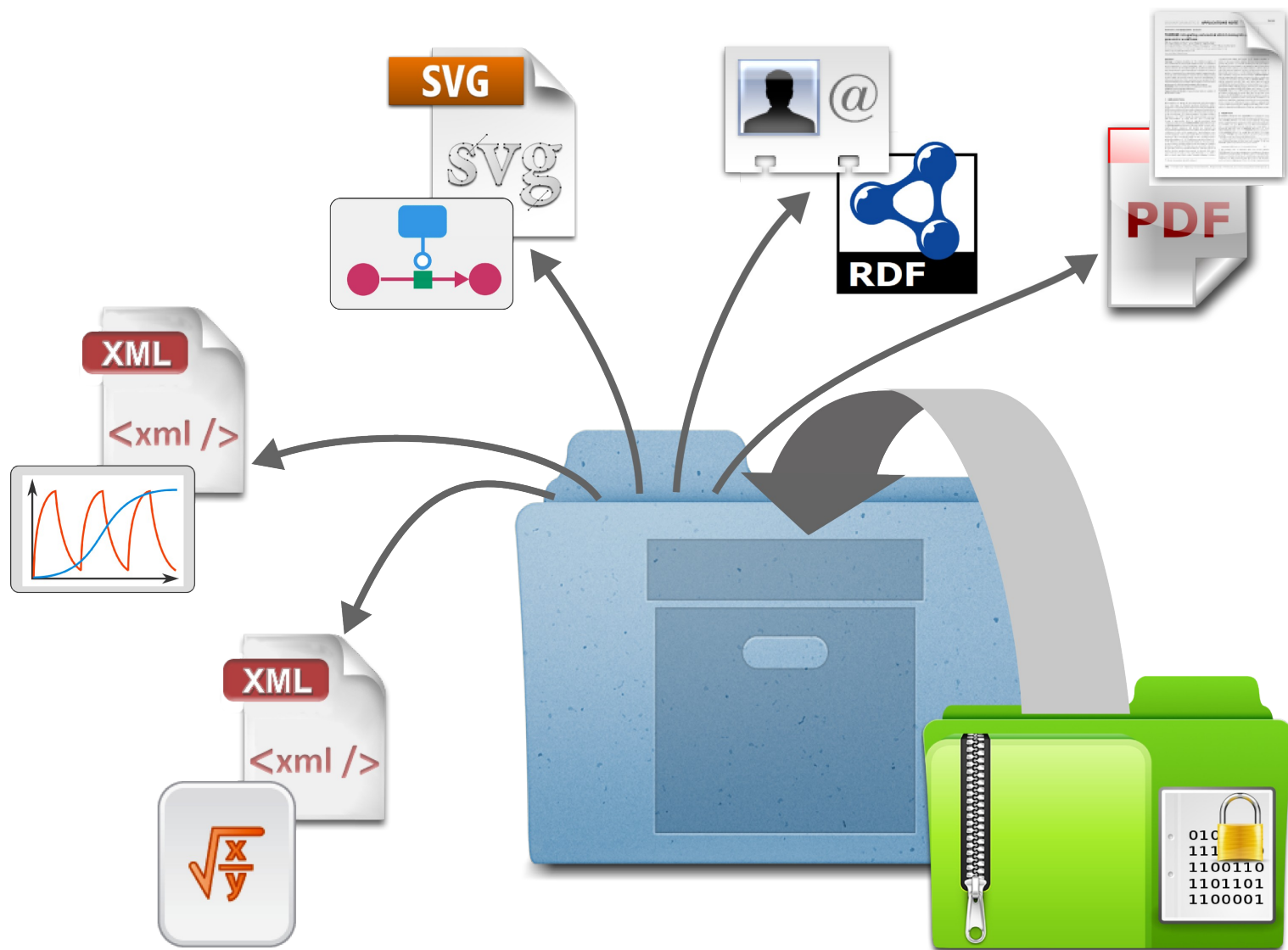


COMBINE does NOT aim to take over the development of the standard formats, but to help coordinating and supporting this process



Interoperable standards = coupled development





<http://co.mbine.org/standards/omex>

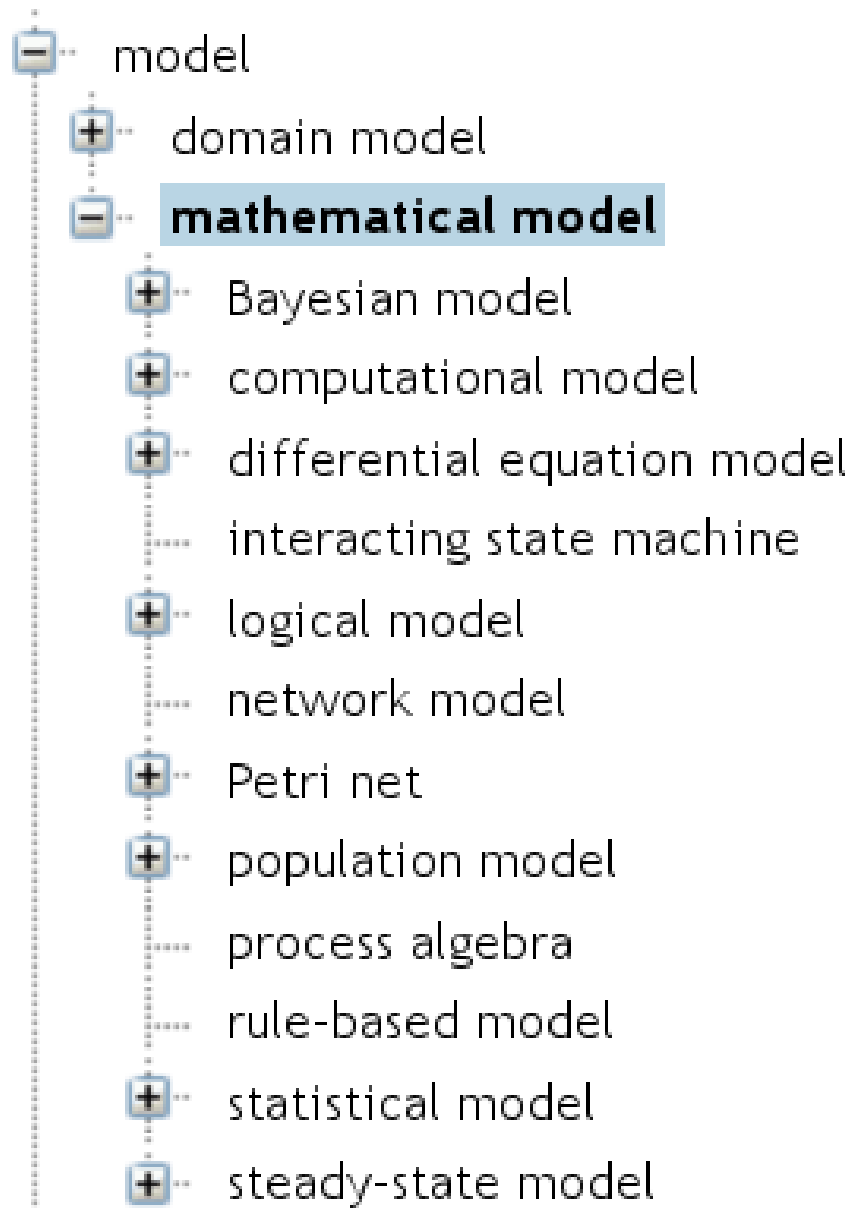


Open Modeling EXchange format

- The COMBINE archive is encoded in OMEX
- Zip file
- Extensions: *.omex*, *.sbex*, *.sedx*, *.cmex*, *.sbox*, *.neux.*, *.phex*
- Mandatory *manifest.xml*: list of all files and their format (as Identifiers.org URIs or Internet Media Type), plus indication of the “master” file
- Optional *metadata.rdf*



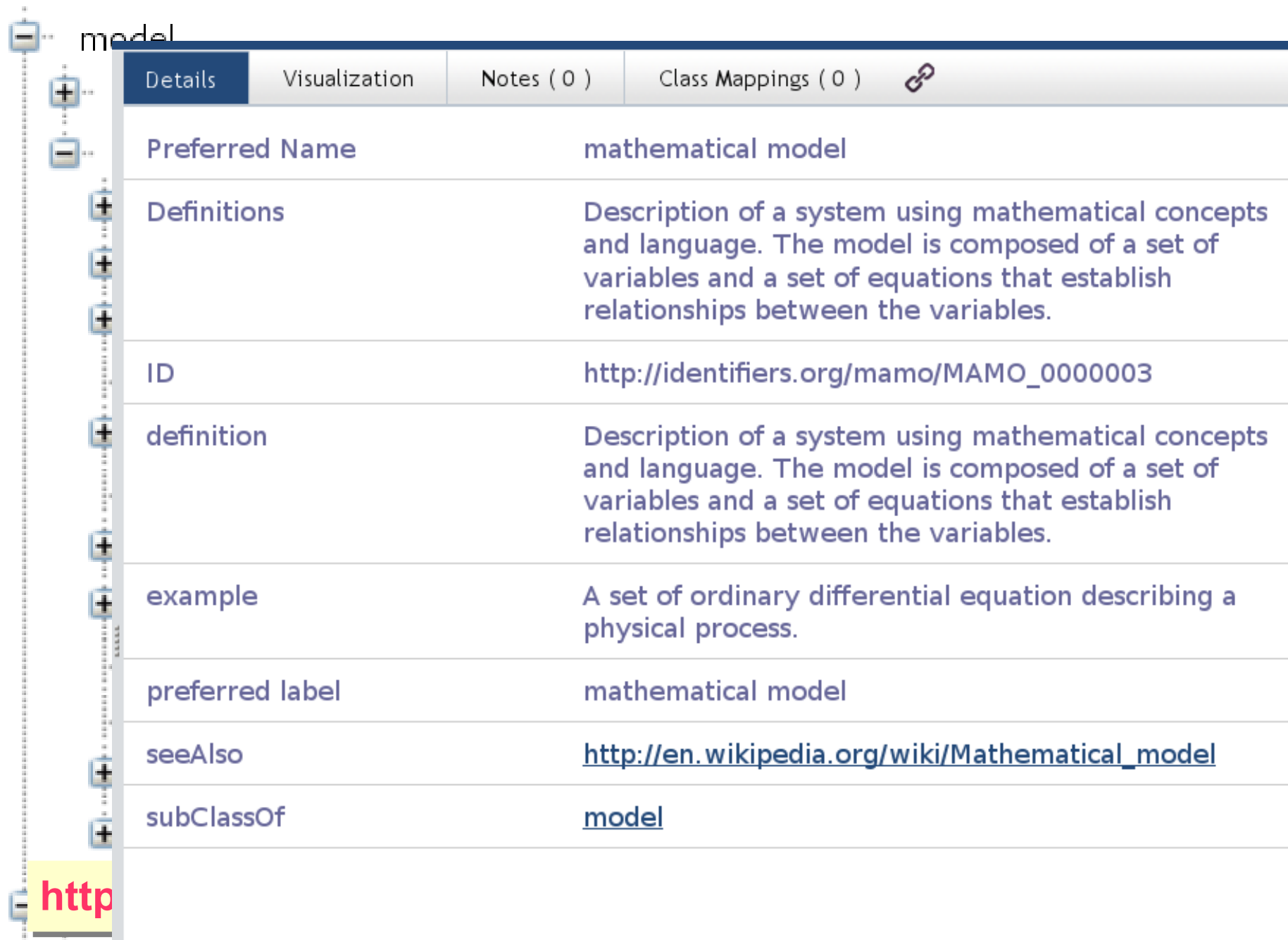
Mathematical Modeling Ontology (MAMO)



<http://sourceforge.net/projects/mamo-ontology/>



Mathematical Modeling Ontology (MAMO)



model

Details Visualization Notes (0) Class Mappings (0)

Preferred Name	mathematical model
Definitions	Description of a system using mathematical concepts and language. The model is composed of a set of variables and a set of equations that establish relationships between the variables.
ID	http://identifiers.org/mamo/MAMO_0000003
definition	Description of a system using mathematical concepts and language. The model is composed of a set of variables and a set of equations that establish relationships between the variables.
example	A set of ordinary differential equation describing a physical process.
preferred label	mathematical model
seeAlso	http://en.wikipedia.org/wiki/Mathematical_model
subClassOf	model

http

So many meetings ...

BioPAX face 2 face

SBML forum

SBGN meeting

SBML hackathon

BioModels training camp

SuperHackathon

CellML workshop

NeuroML workshop



Mission 2: Coordinating meetings

COMBINE coordinate the organisation of common meetings, where developers of all standards and related tools can gather together:

- Efficient collaboration and synergy
- Money saving
- Time saving

<http://co.mbine.org/events>

<http://co.mbine.org/events/calendar>



COMBINE Annual forum

Workshop-style event with oral presentations plus discussion, poster and breakout sessions. It is aimed at [further developing the standards](#). The meetings cover the COMBINE standards and associated or related standardization efforts. The participants are everyone wishing to participate to the development of the standards.

- COMBINE 2010: October 6–9, Edinburgh, UK
- COMBINE 2011: September 3-7, Heidelberg, DE
- COMBINE 2012: August 15-19, Toronto, CA
- COMBINE 2013: September 16-20, Paris, FR
- COMBINE 2014: August 18-22, Los Angeles, USA



HARMONY hackathons

Hackathon-type meetings, with a focus on development of the **support for standards, their interoperability and software infrastructure**. Focus is not on general discussions or oral presentations but hands-on hacking and interaction between people focused on practical development of standards and supporting software. The participants are generally developers.

- HARMONY 2011: April 18-22, New-York City, USA
- HARMONY 2012; May 21-25, Maastricht, NL
- HARMONY 2013: May 20-23, Farmington, USA
- HARMONY 2014: April 20-15, Manchester, UK
- **HARMONY 2015: April 20-24, Wittenberg, DE**



End-user meetings

Attached to major scientific events such as the ICSB, COMBINE meetings are organised to **communicate with scientists who benefit from our standards**, primarily through their software tools. Those meetings are made up of tutorials, demo and non-technical presentations.

- Satellite of ICSB 2012: Toronto
- Satellite of ICSB 2013: Copenhagen
- Satellite of ICSB 2014: Melbourne = you!



HARMONY hackaton 2015



- April 20 to 24, 2015
- Leucorea, Wittenberg
- http://co.mbine.org/events/HARMONY_2015
- Local organisers:

Tobias Czauderna



Falk Schreiber



Dagmar Waltemath



Want to join the conversation?

<http://co.mbine.org/>



@combine_coord

list name	post address	aim
COMBINE announce	combine-announce @ ebi.ac.uk	Very low flux diffusion list for COMBINE news. To receive COMBINE news, you can also follow @combine_coord
COMBINE discuss	combine-discuss @ googlegroups.com	Main discussion forum of the COMBINE community. Topics include the project, meetings, technology etc.
COMBINE archive	combine-archive @ googlegroups.com	Forum to discuss the OMEX format, the structure and content of the COMBINE archive, and all related questions. For more information on the COMBINE archive, please see the OMEX page
COMBINE metadata	combine-meta @ googlegroups.com	Forum to discuss the structure and content of metadata [e.g. COMBINE formatters].
COMBINE site support	combine-support @ googlegroups.com	Use this address to report problems with the website
COMBINE coordinators	combine-coord @ googlegroups.com	



Thank-you

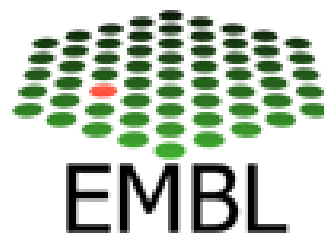
BioPAX, CellML, SBML, SED-ML editors

Developers of related ontologies and software

Organisers of meetings and efforts to support our standards

The community of Computational Systems Biology





Netherlands Consortium for
Systems Biology



UConn HEALTH
CENTER



Universitätsfonds Limburg
| SWOL |

nbic

netherlands
bioinformatics
centre



Maastricht
University



National
Human Genome
Research Institute



Ontario Genomics Institute



DFG



