SBML, where it's been, were it is going

Nicolas Le Novère, EMBL-EBI

A “complete” mosaic of standards

	Models	Simulation	Results
Minimal requirements	MIRIAM	MIASE	
Data-models	cellML biology. math. data. knowledge. SBML™ SBGN	SED-ML	SBRML
Ontologies	SBO	KISAO	TEDDY

SBML.org — The Systems Biology Markup Language

The **Systems Biology Markup Language** (**SBML**) is a computer-readable format for representing models of biological processes. It's applicable to simulations of metabolism, cell-signaling, and many other topics. SBML has been evolving since mid-2000 thanks to an international community of software developers and users. This website is the global portal for the SBML effort; here you can find information about all aspects of SBML.

For the curious

What *is* SBML? Read our **basic introduction** and then perhaps browse the **mailing lists** to get a sense for what's currently going on in the world of SBML.

For modelers

Are you looking for ready-to-run software that supports SBML? The **SBML Software Guide** lists over **175** systems today. Are you instead looking for ready-to-use models? Visit the **BioModels Database**, where you can find hundreds!

For software developers

Are you interested in developing SBML support for your software? Read our **basic introduction** and then the **SBML specifications** to understand how to use SBML. After that, you may want to look at **libSBML**, an API library supporting many programming languages.

No matter how you use SBML, we invite you to sign up for news updates either

SBML News

Review SBML on SourceForge!
(12 Nov.'09) SourceForge.net has a review system for projects. Please use it to **vote & comment** on the SBML project!

Call for SBML Editor nominations
(10 Nov.'09) The nomination phase for two new SBML Editors is **now open**.

LibSBML 4.0.0 released!
(26 Aug.'09) **LibSBML** is an API library for SBML. This release focuses on reducing opportunities for creating invalid SBML.

Older news ...

Community News

BioMet Toolbox
(29 Oct.'09) **BioMet Toolbox** is a web-based toolbox for analyzing genome-scale models.

modelMaGe v. 1.0beta
(27 Oct.'09) **modelMaGe** can generate models and fit models to data.

CycSim supports SBML
(27 Oct.'09) **CycSim** is a

What is SBML?

The Systems Biology Markup Language is a way to **exchange and reuse** (and hopefully **interface**) descriptions of quantitative models in “Systems Biology”, in fact mostly well-stirred chemical kinetics so far.

It is not a procedural language.

It is not a programming language.

It is not a format for specific software configuration files.

Tools are supposed to understand the whole of SBML but not obligatory make use of everything (will not be true for Level 3).

Development philosophy: Start small, get good support, extend.

A feature should only be included if at least two software tools can use it: It is an exchange language.

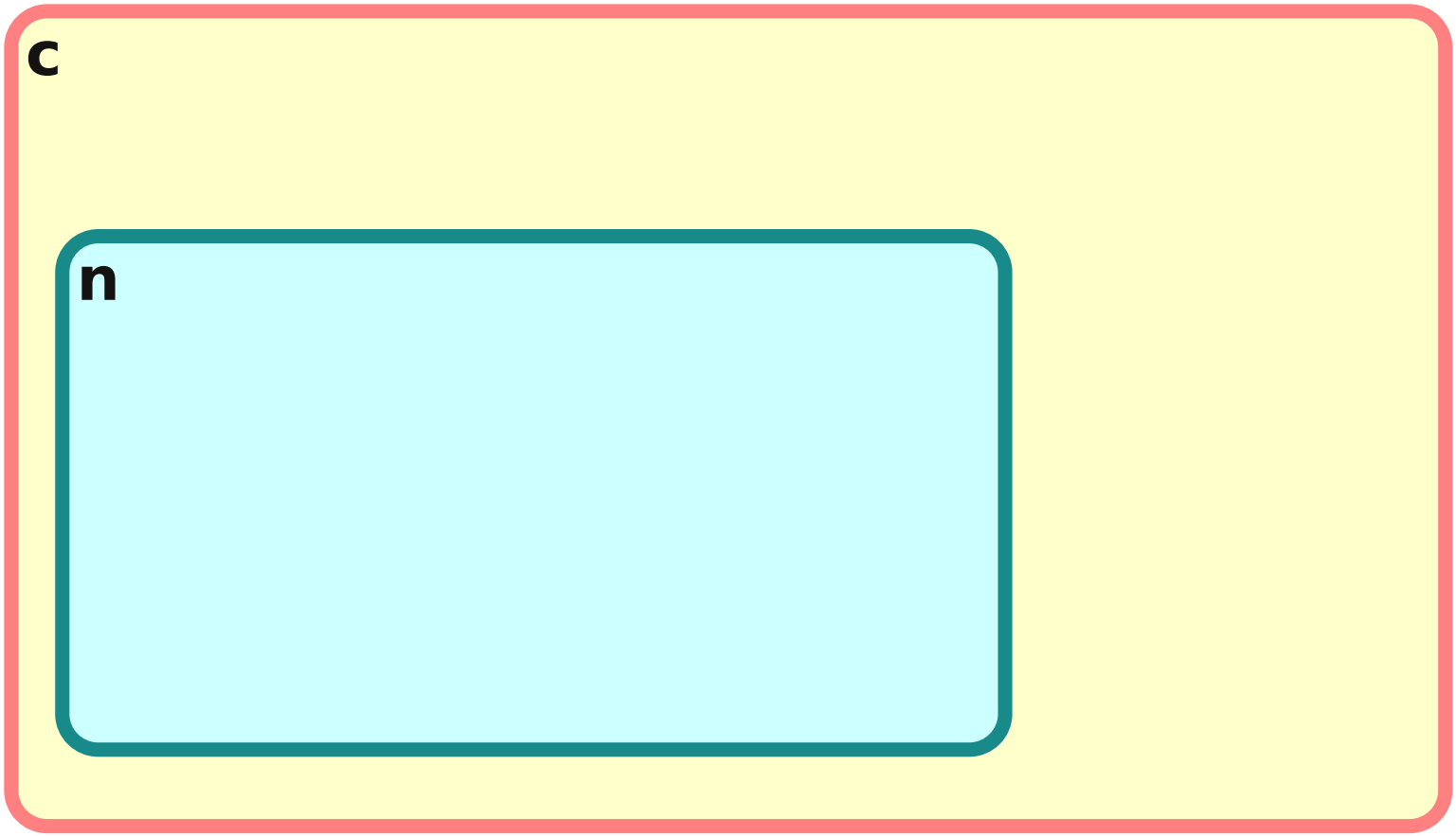
Basic tools are provided to read, validate, write and process SBML. No need to re-invent the wheel. Let's focus on science instead.

SBML itself re-uses other standards: MathML, XHTML, RDF, existing ontologies.

It is supported by a community large, diverse, active and **evolving.**

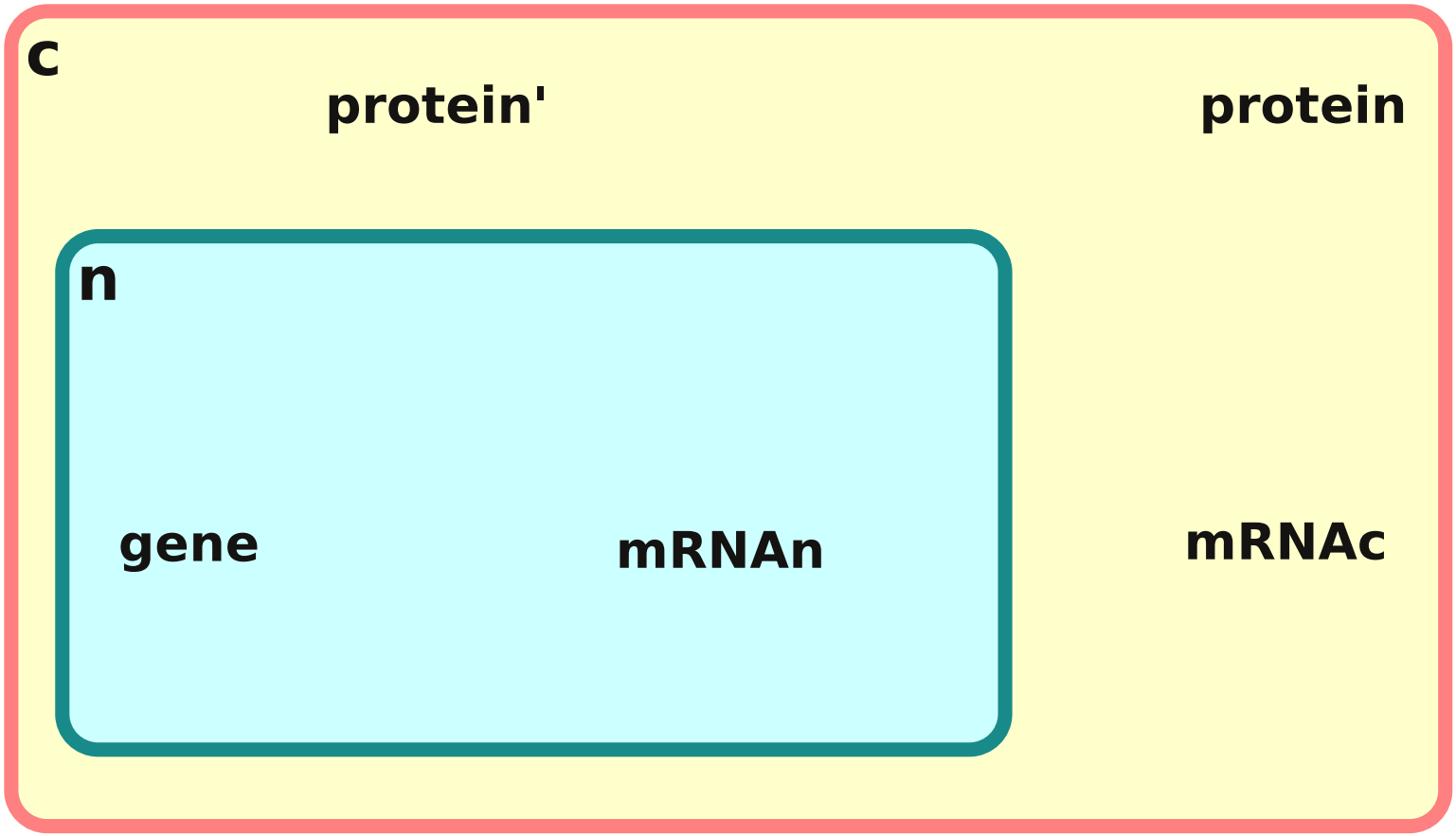
What can we encode in SBML Level 2?

containers (compartments)



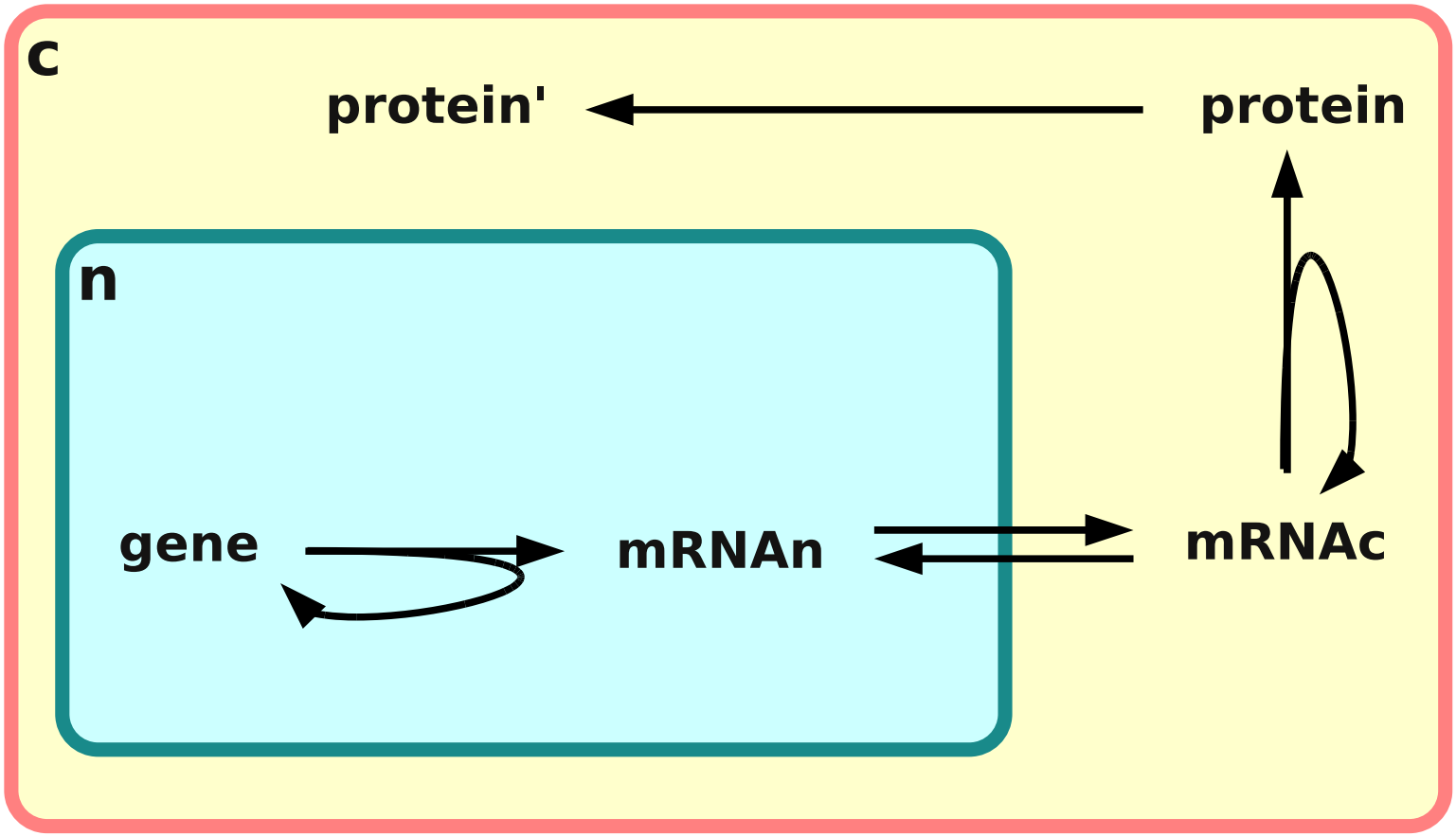
What can we encode in SBML Level 2?

species



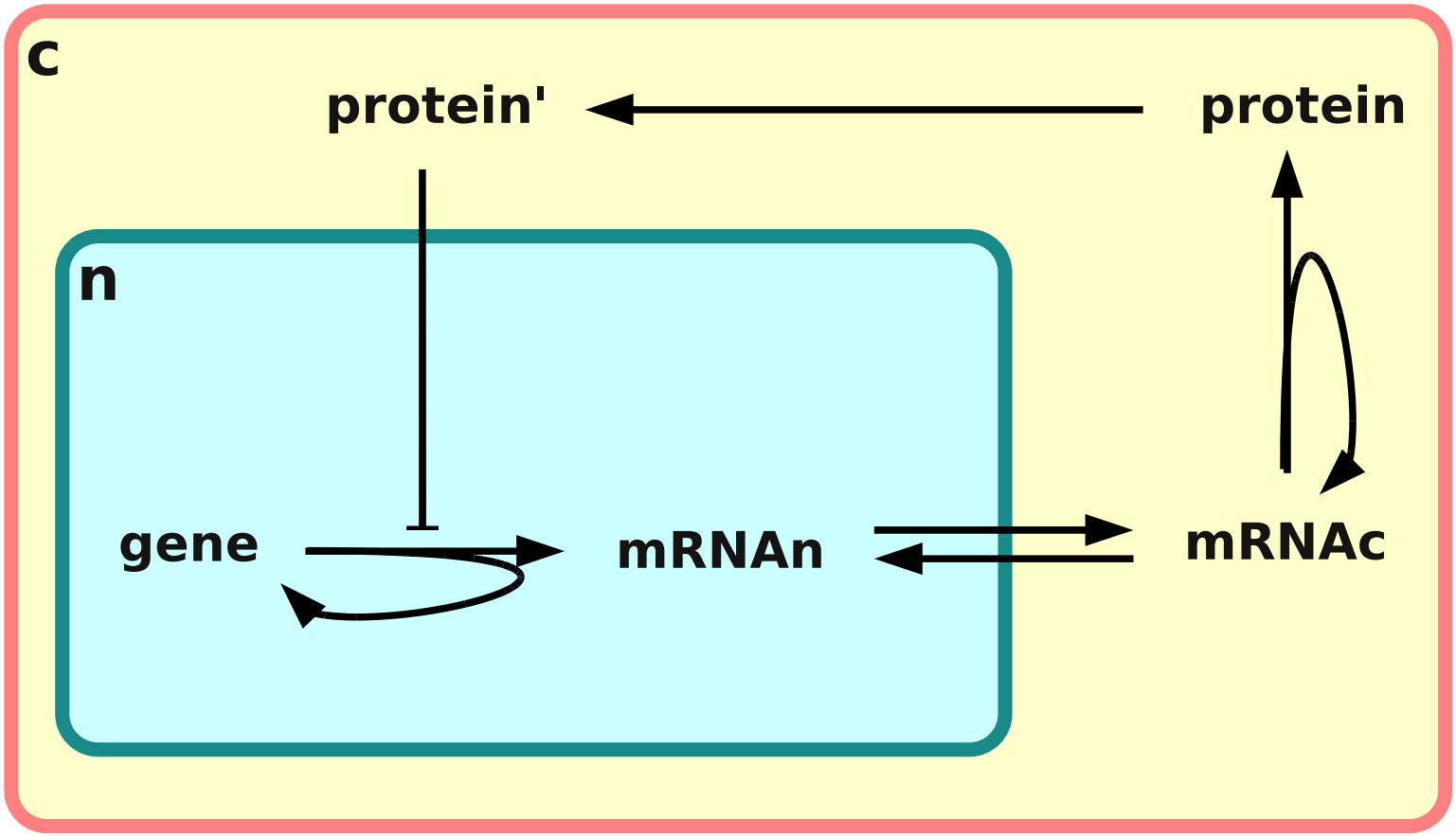
What can we encode in SBML Level 2?

reactions



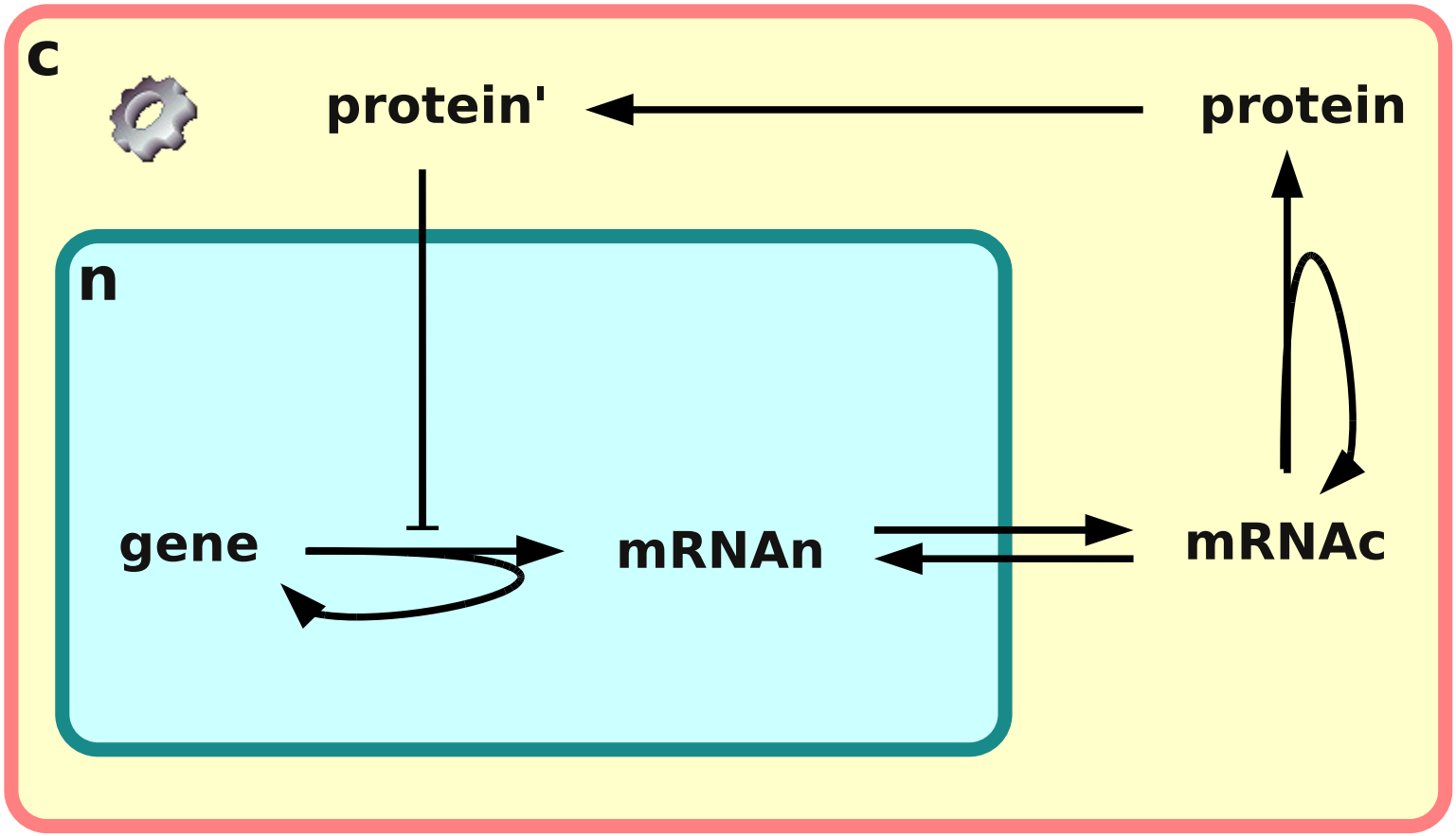
What can we encode in SBML Level 2?

modulations



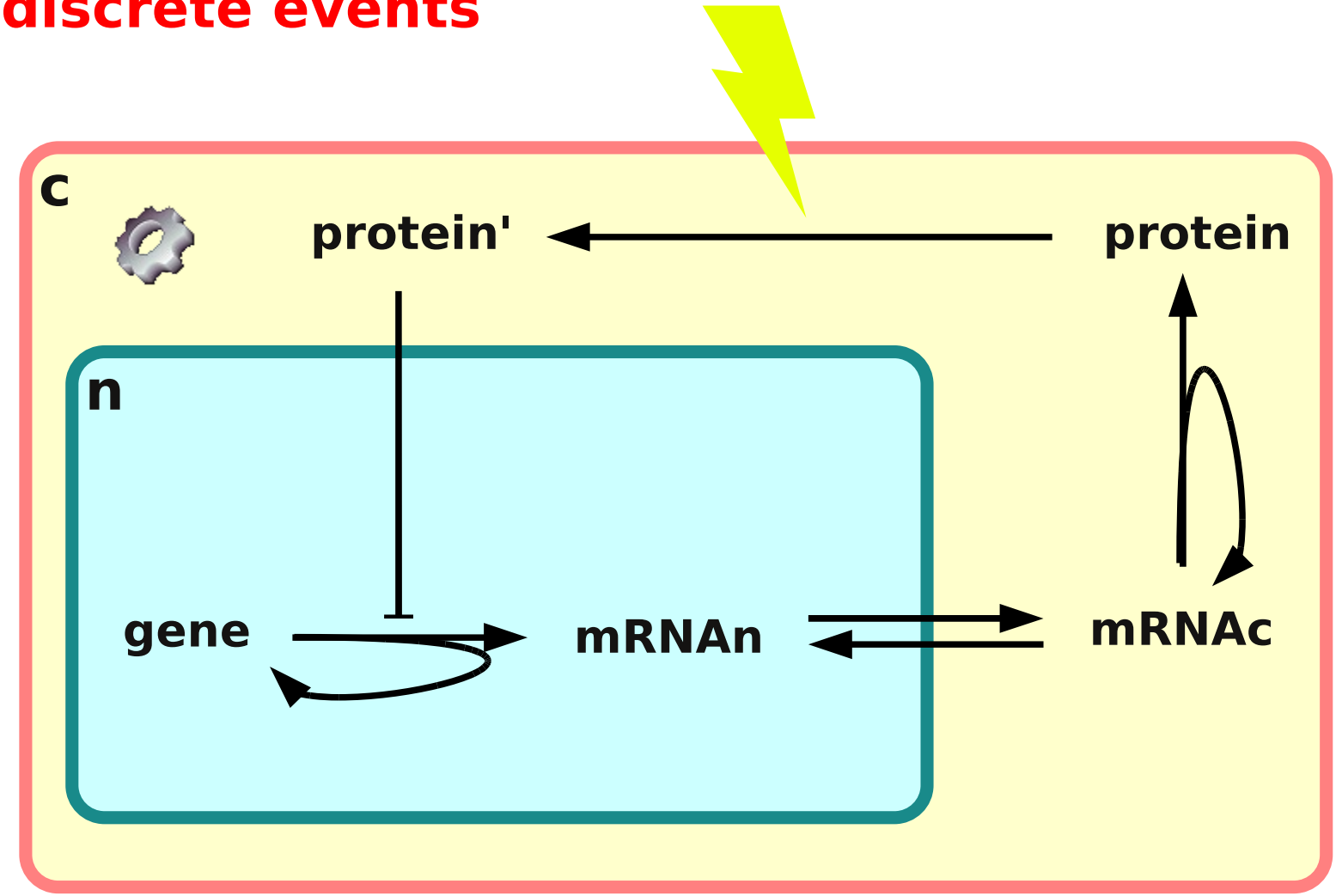
What can we encode in SBML Level 2?

arbitratry rules



What can we encode in SBML?

discrete events



SBML and XML

The Systems Biology Markup Language is defined as a set of classes represented in the Unified Modelling Language (UML)

In practise, it is used

A) as serialised in XML, using

- An XML schema 1) lists all the elements and attributes, 2) specifies the containment relationships between them, 3) precises the datatype of each
- An additional set of constraints is listed in the specification and implemented as a list of consistency checks, for instance in libSBML
- Strict system of unit consistency can be turned on

B) as an API (libSBML)

A → B

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```


No biological semantics in the language itself

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

Elements free of biological semantics: we do not know which type of species this is

Reusing existing standards

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

MathML

A more realistic example ...

```
<species
    id="A"
    name="α-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX"
    sboTerm="SBO:0000245" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of a microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
      <rdf:Description rdf:about="#PX">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P68370"/>
            <rdf:li rdf:resource="urn:miriam:obo.go:GO%3A0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

Externalisation of biological semantics

```
<species
    id="A"
    name="α-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX"
    sboTerm="SBO:0000245" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of a microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
      <rdf:Description rdf:about="#PX">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P68370"/>
            <rdf:li rdf:resource="urn:miriam:obo.go:GO%3A0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

macromolecule

Reusing existing standards again

```
<species
    id="A"
    name="α-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX"
    sboTerm="SBO:0000245" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of a microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
      <rdf:Description rdf:about="#PX">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P68370"/>
            <rdf:li rdf:resource="urn:miriam:obo.go:GO%3A0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

XHTML

RDF

SBML is not limited to biochemistry!

Rate Rules can describe the temporal evolution of any quantitative parameter, e.g. transmembrane voltage;

Events can describe any discontinuous change, e.g. neurotransmitter release or repolarisation;

A species is an entity participating to a reaction, **not always** a **chemical** entity:

- It can be a molecule
- It can be a cell
- It can be an organ
- It can be an organism

➔ Systems Biology is scale-free!

Hodgkin-Huxley

```
<rateRule metaid="metaid_0000048" variable="V">
  <notes><p xmlns="http://www.w3.org/1999/xhtml">dV/dt = (I - (i_Na + i_K + i_L))/Cm</p></notes>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <divide/>
      <apply>
        <minus/>
        <ci> I </ci>
        <apply>
          <plus/><ci> i_Na </ci><ci> i_K </ci><ci> i_L </ci>
        </apply>
      </apply>
      <ci> Cm </ci>
    </apply>
  </math>
</rateRule>
<assignmentRule metaid="metaid_0000042" variable="i_Na">
  <notes><p xmlns="http://www.w3.org/1999/xhtml">i_Na = g_Na * m^3.0 * h * (V - E_Na)</p></notes>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> g_Na </ci>
      <apply>
        <power/><ci> m </ci><cn> 3.0 </cn>
      </apply>
      <ci> h </ci>
      <apply>
        <minus/><ci> V </ci><ci> E_Na </ci>
      </apply>
    </apply>
  </math>
</assignmentRule>
```

rate rule:

dx/dt = f (x,y,z)

assignment rule:

x = f (y,z)

BioModels Home | Browse models | Submit | Sign in | Support | About BioModels | Search

BIOMD0000000020 - Hodgkin-Huxley1952 squid-axon

SBML L2 V1 | Other formats | Actions | Submit Model Comment/Bug

Model | Overview | Math | Physical entities | Parameters

Reference Publication

Publication ID: 12991237

J Physiol 1952 Aug;117(4):500-44.
A quantitative description of membrane current and its application to conduction and excitation in nerve.
HODGKIN AL, HUXLEY AF.
[more]

Model

Original Model: *Unspecified*

Submitter: Nicolas Le Novère

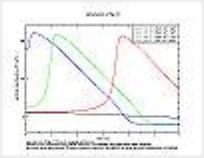
Submission Date: 2005-09-13T13:22:40+00:00

Last Modification Date: 2009-03-05T23:37:11+00:00

Creation Date: 2005-03-31T13:09:21+00:00

Creators: Maria Schilstra
Catherine Lloyd

Curation Result:

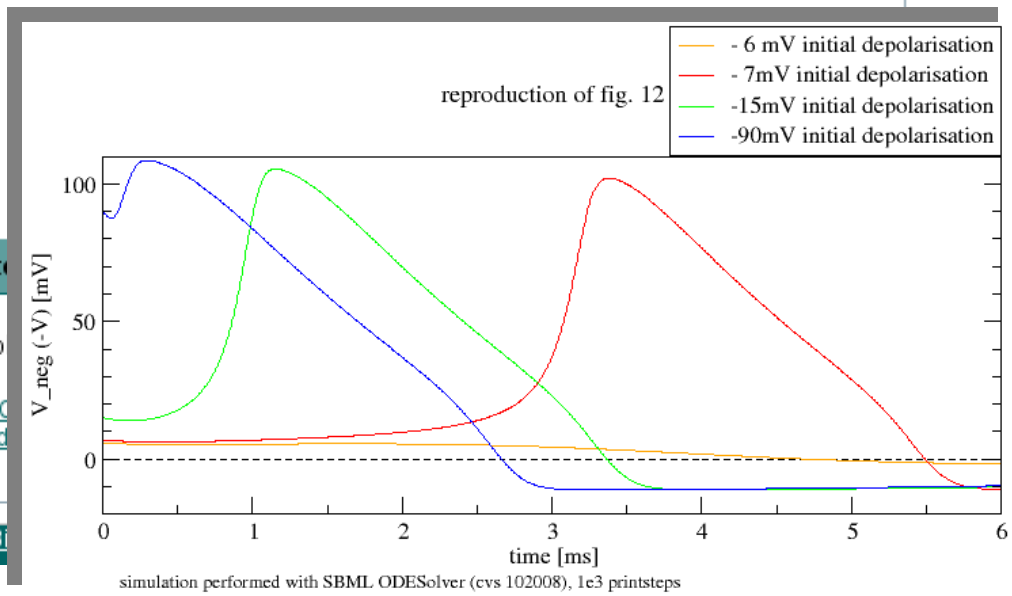


set #1	bqbiol:is	Taxonomy Loligo forbesi
set #2	bqbiol:isVersionOf	Gene Ontology voltage-gated potassium channel activity Gene Ontology voltage-gated sodium channel activity Gene Ontology action potential propagation

Not

This model originates from BioModels Database: A Database of Annotated Pub
For more information see the terms of use.
To cite BioModels Database, please use Le Novère N., Bornstein B., Broicher A., C
J.L., Hucka M. (2006) BioModels Database: A Free, Centralized Database of Curated
Nucleic Acids Res., 34: D689-D691.

Developed by BioModels Team of Computational Neurobiology Group in European Bi



An example of PD model

```
<rateRule metaid="metaid_0000031" variable="Size">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <apply>
        <minus/>
        <apply>
          <times/><ci> RateIn </ci><ci> Effect </ci>
        </apply>
        <apply>
          <times/><ci> Kover </ci><ci> Size </ci>
        </apply>
      </apply>
      <ci> Size </ci>
    </apply>
  </math>
</rateRule>
<assignmentRule metaid="metaid_0000027" variable="Effect">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <minus/>
      <cn> 1 </cn>
      <apply>
        <divide/>
        <ci> Ce </ci>
        <apply>
          <plus/><ci> AE50 </ci><ci> Ce </ci>
        </apply>
      </apply>
    </apply>
  </math>
</assignmentRule>
```

Tham et al (2008) A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine + carboplatin in non-small cell lung cancer patients. Clin Cancer Res. 2008 14(13): 4213-8.

$$\frac{Size}{dt} = (Rate_{in} \times Effect - K_{over} \times Size) \times Size$$

$$Effect = 1 - \frac{E_{max} - Ce}{Amt_{50} + Ce}$$

BIOMD0000000234 - Tham2008_PDmode_TumourShrinkage

SBML formats | Other formats | Actions | Curation Comment

Model | Overview | Math | Physical entities | Parameters | Curation

Reference Publication

Publication ID: 18594002

Clin Cancer Res 2008 Jul;14(13):4213-8.
A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine + carboplatin in non-small cell lung cancer patients.
Tham LS, Wang L, Soo RA, Lee SC, Lee HS, Yong WP, Goh BC, Holford NH.
Department of Hematology-Oncology, National University Hospital, Singapore. Tham_lai_san@lilly.com [more]

Model

Original Model: *BIOMD0000000234.xml.origin*

Submitter: Nick Holford

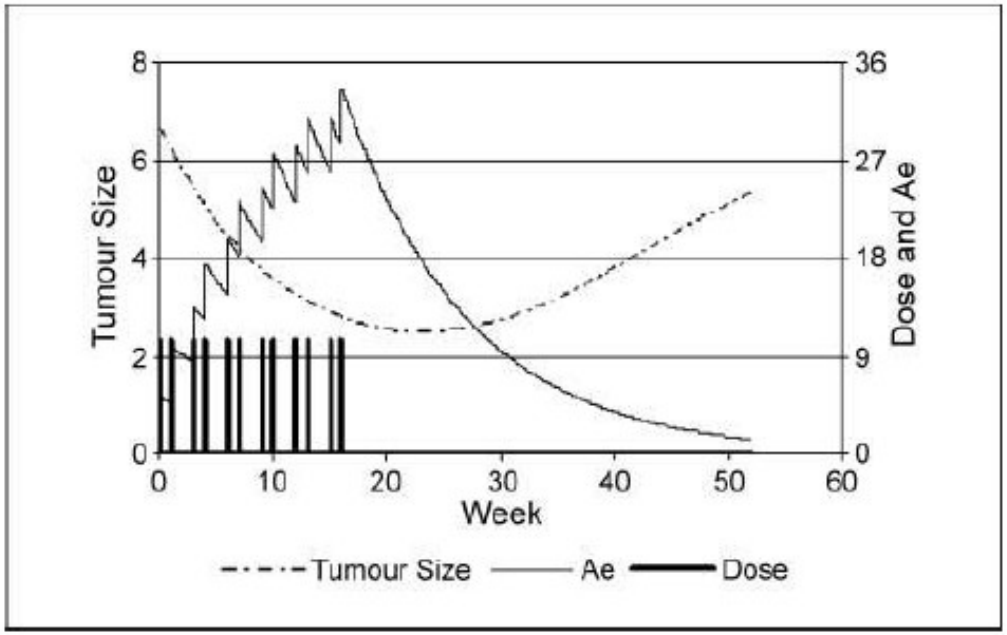
Submission ID: MODEL0911120001

Submission Date: 2009-11-16T19:41:59+00:00

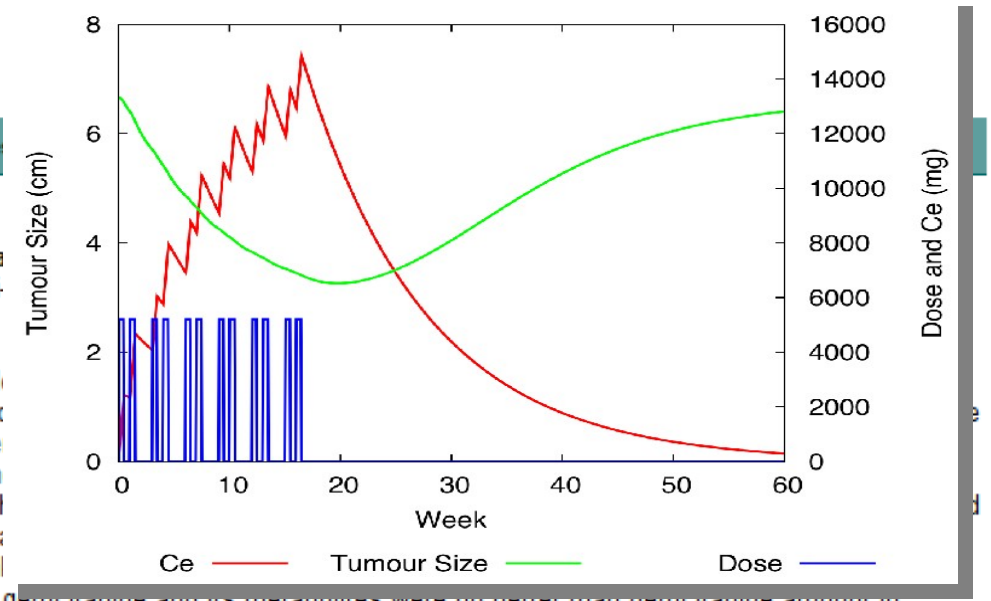
Last Modification Date: 2009-11-23T13:24:05+00:00

set #1	bqbiol:occursIn	Taxonomy Homo sapiens
set #2	bqbiol:isVersionOf	ICD C34 OMIM 211980

original article



reproduction with SBMLodeSolver



predicting tumor shrinkage in primary lung cancer lesions. Gemcitabine dose-based models did marginally better than treatment-based models that ignored doses of drug administered to patients. Modeling tumor shrinkage in primary lesions can be used to quantify individual sensitivity and response to antitumor effects of anticancer

SBML roadmap

- SBML Levels are supposed to co-exist, SBML Versions override previous ones
  - Level 1 Version 1: 2 March 2001
  - **Level 1 Version 2: 28 August 2003**
  - Level 2 Version 1: 28 July 2003
  - Level 2 Version 2: 26 September 2006
  - Level 2 Version 3 release 1: 16 June 2007
  - Level 2 Version 3 release 2: 26 September 2007
  - **Level 2 Version 4: 22 December 2008**
  - **Level 3 core draft: 22 August 2009**

conversion using libSBML

- Backward compatibility within Level at the level of the XML (but not 100% at the level of semantics)
- Unambiguous and bug-free specification requires heavy work ... 166 pages, single spacing, 10pt, small margin.

Difference between L1, L2 and L3

L1	L2	L3
predefined functions	function definitions	function definitions
proprietary infix math notation	all math in MathML	all math in MathML
reserved namespaces for annotation	no reserved namespaces for annotations	no reserved namespaces for annotations
no controlled annotation	controlled RDF annotation	controlled RDF annotation
no discrete events	discrete events	discrete events
monolithic	monolithic	modular
default values	default values	no default values

Progressive simplification, generalisation and externalisation

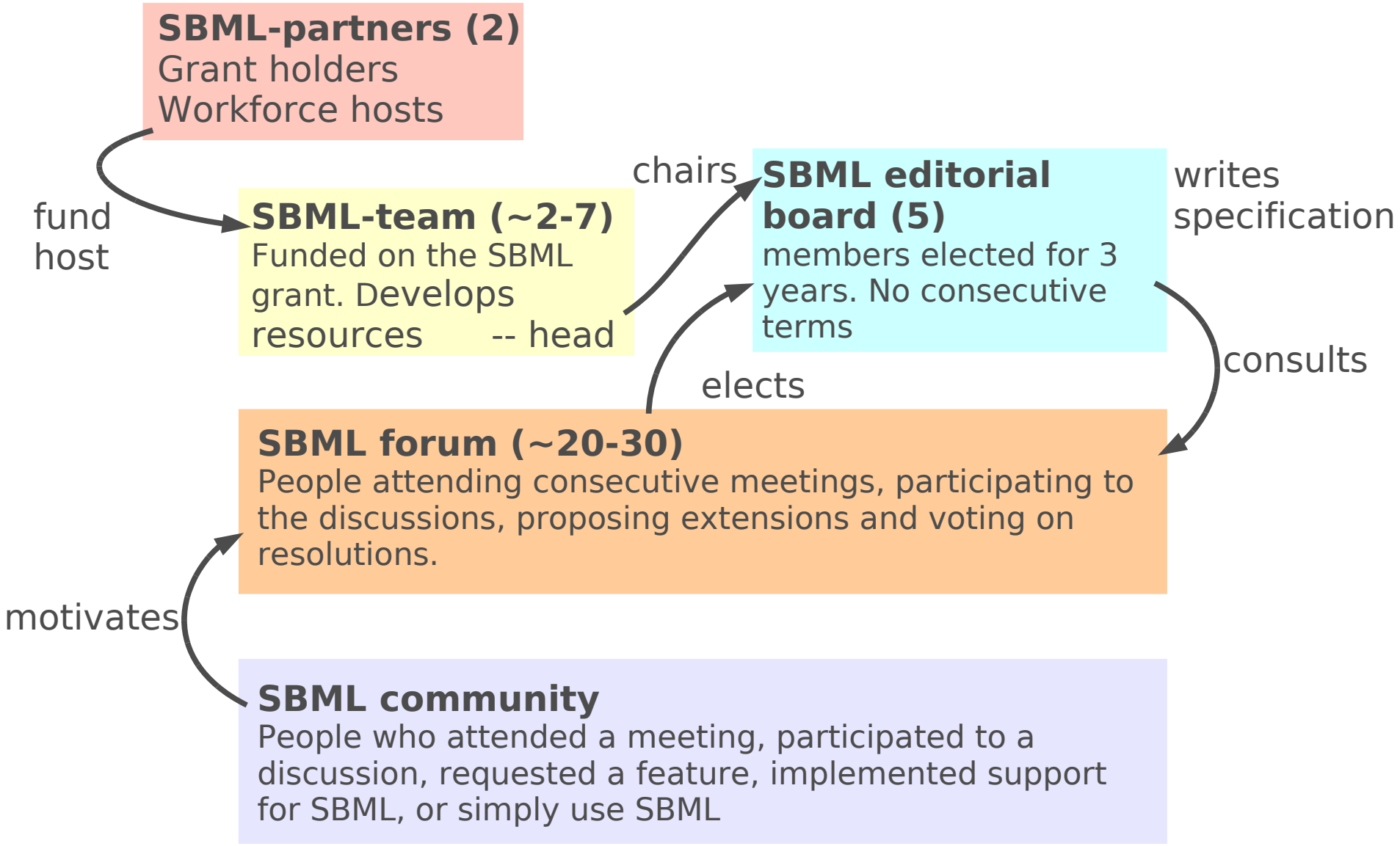
A glimpse of SBML Level 3

Modular SBML, with core + optional packages

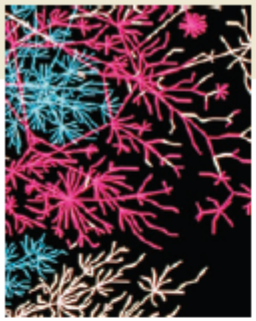
- Core package – draft specification available
- Graph Layout – specification finalised
- Complex species – specification finalised
- Groups - specification under discussion
- Model composition – specification under discussion
- Qualitative models – specification under discussion
- Graph rendering – specification proposed
- Distributions and ranges - specification proposed
- Arrays and sets – specifications proposed
- Geometry - specification proposed
- Spatial diffusion – needed
- Dynamic structures - needed

???

Current structure of the community



The Simulation Experiment Description Markup Language, the next step



_computational BIOLOGY

PERSPECTIVE

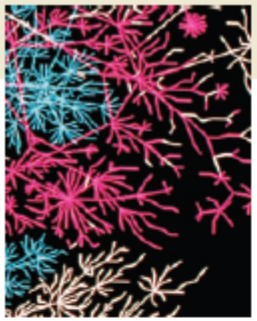
Publishing Group http://www.nature.com/naturebiotechnology

Minimum information requested in the annotation of biochemical models (MIRIAM)

Nicolas Le Novère[1,15], Andrew Finney[2,15], Michael Hucka[3], Upinder S Bhalla[4], Fabien Campagne[5], Julio Collado-Vides[6], Edmund J Crampin[7], Matt Halstead[7], Edda Klipp[8], Pedro Mendes[9], Poul Nielsen[7], Herbert Sauro[10], Bruce Shapiro[11], Jacky L Snoep[12], Hugh D Spence[13] & Barry L Wanner[14]

Most of the published quantitative models in biology are lost for the community because they are either not made available or they are insufficiently characterized to allow them to be reused. The lack of a standard description format, lack of stringent reviewing and authors' carelessness are the main causes for incomplete model descriptions. With today's increased interest in detailed biochemical models, it is necessary to define a minimum quality standard for the encoding of those models. We propose a set of rules for curating quantitative models of biological systems. These rules define procedures for encoding and annotating models represented in machine-readable form. We believe their

During the genomic era we have witnessed a vast increase in availability of large amounts of quantitative data. This is motivating a shift in the focus of molecular and cellular research from qualitative descriptions of biochemical interactions towards the quantification of such interactions and their dynamics. One of the tenets of systems biology is the use of quantitative models (see **Box 1** for definitions) as a mechanism for capturing precise hypotheses and making predictions[1,2]. Many specialized models exist that attempt to explain aspects of the cellular machinery. However, as has happened with other types of biological information, such as sequences, macromolecular structures or



_computational BIOLOGY

PERSPECTIVE

6. The model, when instantiated within a suitable simulation environment, must be able to reproduce all relevant results given in the reference description that can readily be simulated. Not only does the simulation have to provide results qualitatively similar to the reference description, such as oscillation, bistability, chaos, but the quantitative values of variables, and their relationships (e.g., the shape of the phase portrait) must be reproduced within some epsilon, the difference being attributable to the algorithms used to run the simulation, and the

Minimur tion of biochem

Nicolas Le Novère
Julio Collado-Vid en[7],
Herbert Sauro[10], I

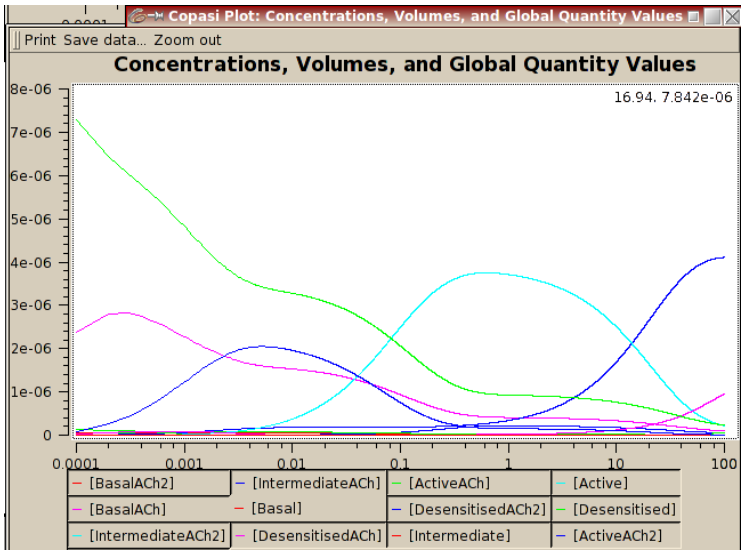
Most of the published quantitative models in biology are lost for the community because they are either not made available or they are insufficiently characterized to allow them to be reused. The lack of a standard description format, lack of stringent reviewing and authors' carelessness are the main causes for incomplete model descriptions. With today's increased interest in detailed biochemical models, it is necessary to define a minimum quality standard for the encoding of those models. We propose a set of rules for curating quantitative models of biological systems. These rules define procedures for encoding and annotating models represented in machine-readable form. We believe their

During the genomic era we have witnessed a rapid increase in availability of large amounts of quantitative data. This is motivating a shift in the focus of molecular and cellular research from qualitative descriptions of biochemical interactions towards the quantification of such interactions and their dynamics. One of the tenets of systems biology is the use of quantitative models (see **Box 1** for definitions) as a mechanism for capturing precise hypotheses and making predictions[1,2]. Many specialized models exist that attempt to explain aspects of the cellular machinery. However, as has happened with other types of biological information, such as sequences, macromolecular structures or

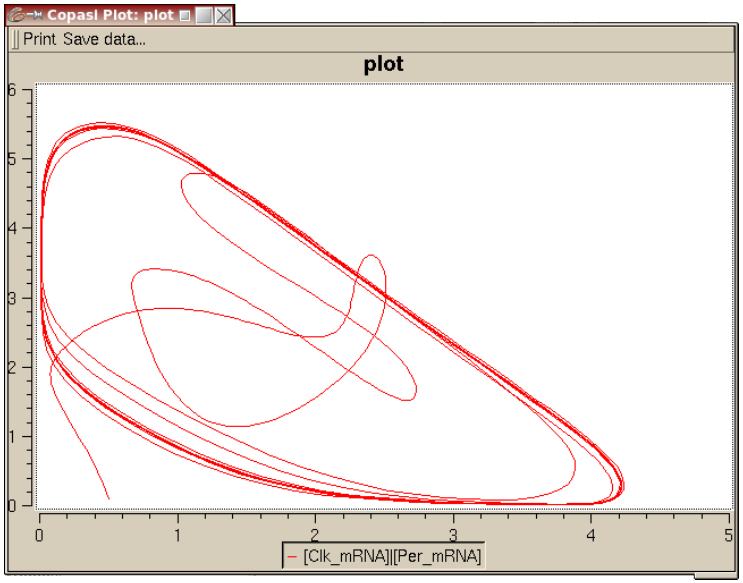
Publishing Group http://www.nature.com/naturebiotechnology

Examples from BioModels DB and COPASI

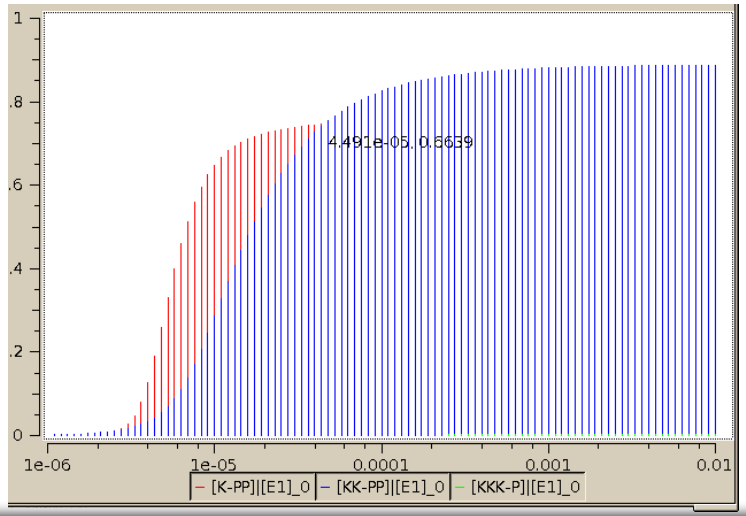
Edelstein et al 1996 (BIOMD0000000002)



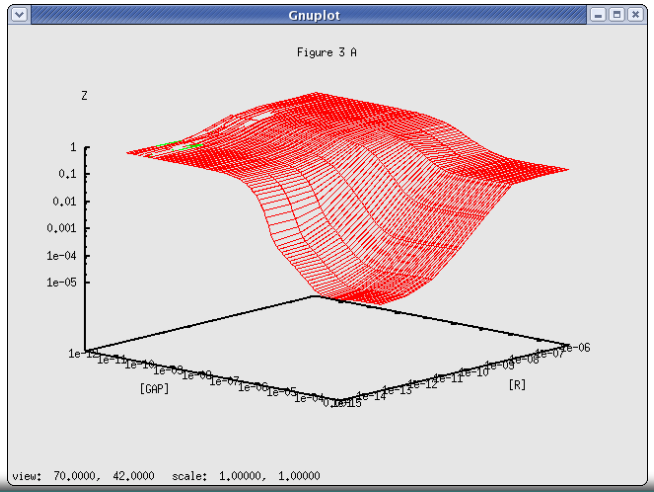
Ueda, Hagiwara, Kitanol 2001 (BIOMD0000000022)



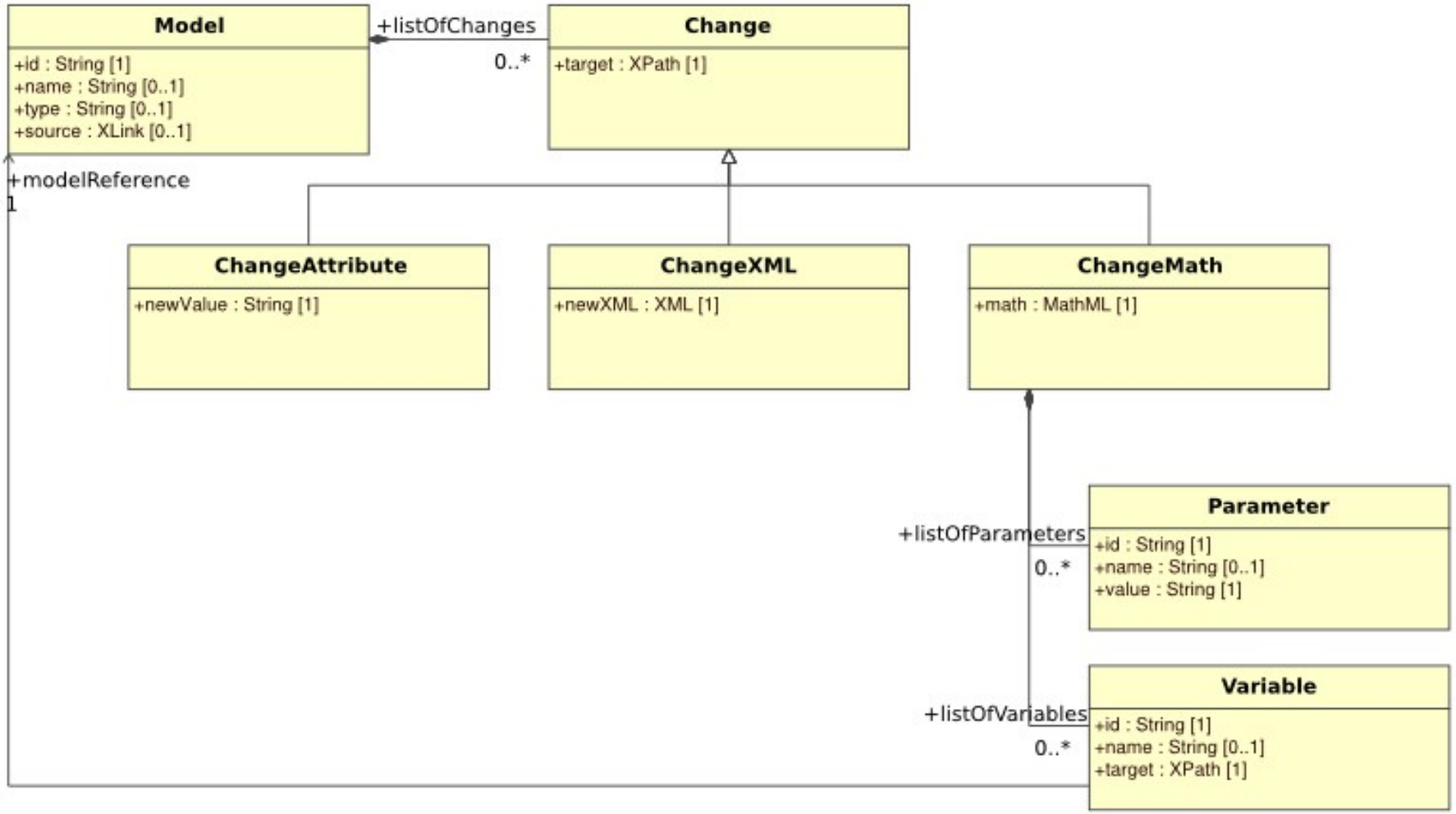
Huang & Ferrell (BIOMD0000000009)



Bornheimer et al 2004 (BIOMD0000000086)



Description of models



Description of models

```
<?xml version="1.0" encoding="utf-8"?>
<sedML version="1.0" xmlns="http://www.miase.org/">
  <notes>Changing a system from oscillation to chaos</notes>
  <listOfModels>
    <model id="model1"
           name="Circadian Oscillations"
           type="SBML"
           source="urn:miriam:biomodels.db:BIOMD0000000021" />
    <model id="model2"
           name="Circadian Chaos"
           type="SBML"
           source="model1">
      <listOfChanges>
        <changeAttribute target=
             "/sbml/model/listOfParameters/parameter[@id='V_mT']/@value" newValue="0.28">
        </changeAttribute>
        <changeAttribute target=
             "/sbml/model/listOfParameters/parameter[@id='V_dT']/@value" newValue="4.8">
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      </listOfChanges>
    </model>
  </listOfModels>
```

Description of models

```
<?xml version="1.0" encoding="utf-8"?>
<sedML version="1.0" xmlns="http://www.miase.org/">
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             "/sbml/model/listOfParameters/parameter[@id='V_dT']/@value" newValue="4.8">
        </changeAttribute>
      </listOfChanges>
    </model>
  </listOfModels>
```

Any model description
in XML such as SBML, CellML
VCML etc.

Description of models

```
<?xml version="1.0" encoding="utf-8"?>
<sedML version="1.0" xmlns="http://www.miase.org/">
  <notes>Changing a system from oscillation to chaos</notes>
  <listOfModels>
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        </changeAttribute>
        <changeAttribute target=
             "/sbml/model/listOfParameters/parameter[@id='V_dT']/@value" newValue="4.8">
        </changeAttribute>
      </listOfChanges>
    </model>
  </listOfModels>
```

Description of models

MIRIAM Resources

Data type: ***BioModels Database***

General | Tags | Annotation

General information about the data type

Name		
Identifier		MIR:00000007
Name		BioModels Database
Synonyms		BioModels
URIs		
Official URN		urn:miriam:biomodels.db
Deprecated		http://www.ebi.ac.uk/biomodels/
Information		
Definition		BioModels Database is a data resource that allows biologists to models of biological interests.
Identifier Pattern		^(BIOMD|MODEL)\d{10}$
Physical Locations		
Resource #1	**Data Entry**	http://www.ebi.ac.uk/biomodels-main/**$id** [Example: BIOMD000
	Data Resource	http://www.ebi.ac.uk/biomodels/
	Information	BioModels, a Database of Annotated Published Models
	Institution	European Bioinformatics Institute, United Kingdom
Resource #2	**Data Entry**	http://biomodels.caltech.edu/**$id** [Example: BIOMD0000000048
	Data Resource	http://biomodels.caltech.edu/
	Information	Mirror of BioModels Database
	Institution	California Institute of Technology, USA
Documentation		
URL(s)		⊞ http://srs.ebi.ac.uk/srsbin/cgi-bin/wgetz?-view+MedlineFull+[
Miscellaneous		
Date of creation		2006-08-14 19:38:06 GMT
Date of last modification		2009-06-05 17:43:08 GMT

Go back to the list of data types

BioModels Home | Browse Models | Submit | Sign In | Support | About

BIOMD0000000021 - Leloup1999_CircClock

SBML L2 V1 | Other formats | Actions | Submit Model Comment/Bug

Overview | **Model** | Math | Physical entities | Parameters

Reference Publication

Publication ID: 10366496

J Theor Biol 1999 Jun;198(3):445-59.
Chaos and birhythmicity in a model for circadian oscillations of the PER and TIM proteins in dr
Leloup JC, Goldbeter A.
Unite de Chronobiologie Theorique, Faculte des Sciences, Universite Libre de Bruxelles, Cam
B-1050 Brussels, Belgium. [more]

Model

Original Model: *Unspecified*

Submitter: Nicolas Le Novère

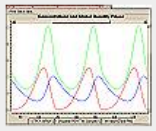
Submission Date: 2005-09-13T13:24:15+00:00

Last Modification Date: 2007-09-25T09:32:00+00:00

Creation Date: 2005-06-29T10:27:52+00:00

Creators: Nicolas Le Novère
Bruce Shapiro

Curation Result:



set #1	bqbiol:is	**Taxonomy** Drosophila melanogaster **KEGG Pathway** dme04710
set #2	bqbiol:isVersionOf	**Gene Ontology** circadian rhythm

Notes

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Description of models

```
<?xml version="1.0" encoding="utf-8"?>
<sedML version="1.0" xmlns="http://www.miase.org/">
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           source="urn:miriam:biomodels.db:BIOMD0000000021" />
    <model id="model2"
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           type="SBML"
           source="model1">
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        </changeAttribute>
        <changeAttribute target=
             "/sbml/model/listOfParameters/parameter[@id='V_dT']/@value" newValue="4.8">
        </changeAttribute>
      </listOfChanges>
    </model>
  </listOfModels>
```

Description of models

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<sedML version="1.0" xmlns="http://www.miase.org/">
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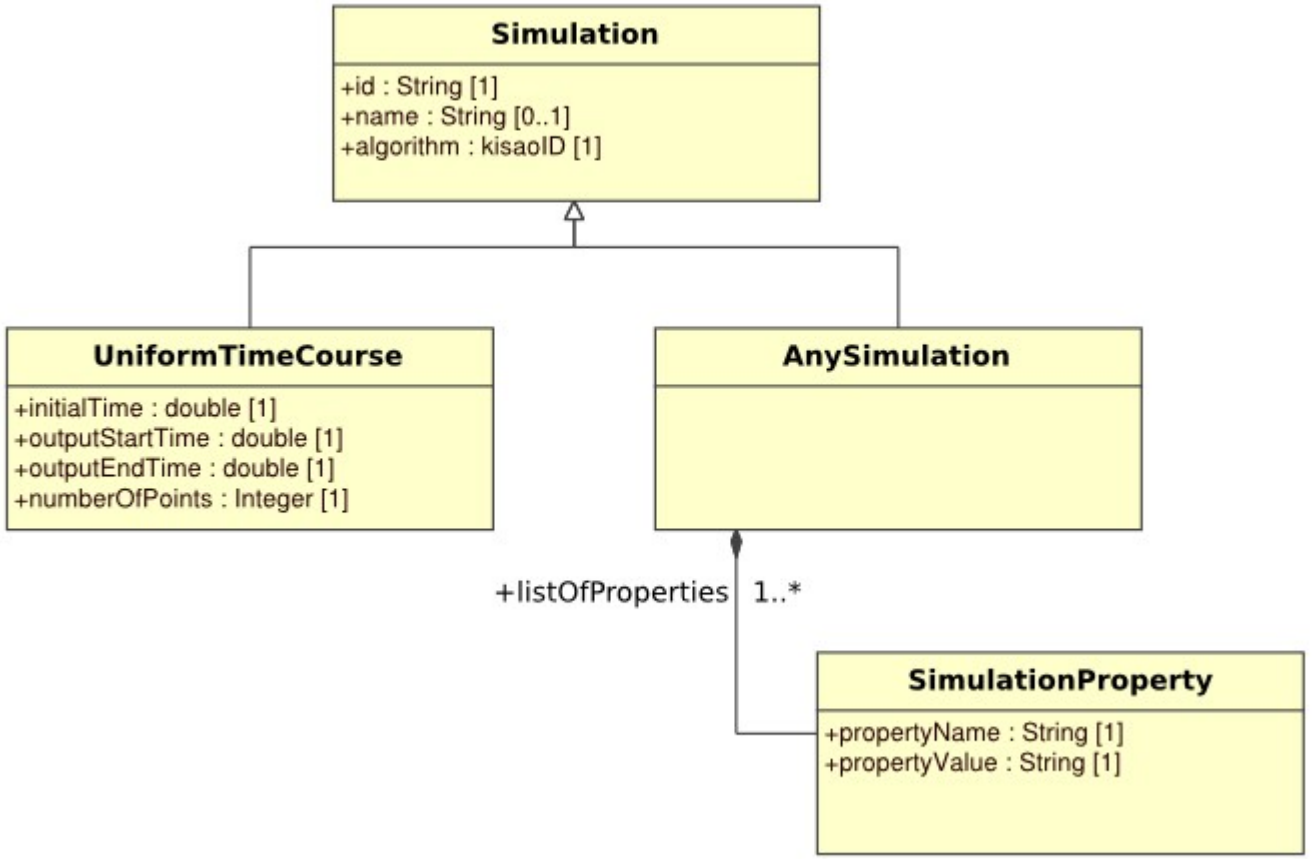
           source="urn:miriam:biomodels.db:BIOMD0000000021" />
    <model id="model2"
           name="Circadian Chaos"
           type="SBML"
           source="model1">
      <listOfChanges>
        <changeAttribute target=
             "/sbml/model/listOfParameters/parameter[@id='V_mT']/@value" newValue="0.28">
        </changeAttribute>
        <changeAttribute target=
             "/sbml/model/listOfParameters/parameter[@id='V_dT']/@value" newValue="4.8">
        </changeAttribute>
      </listOfChanges>
    </model>
  </listOfModels>
```

Simulation approach

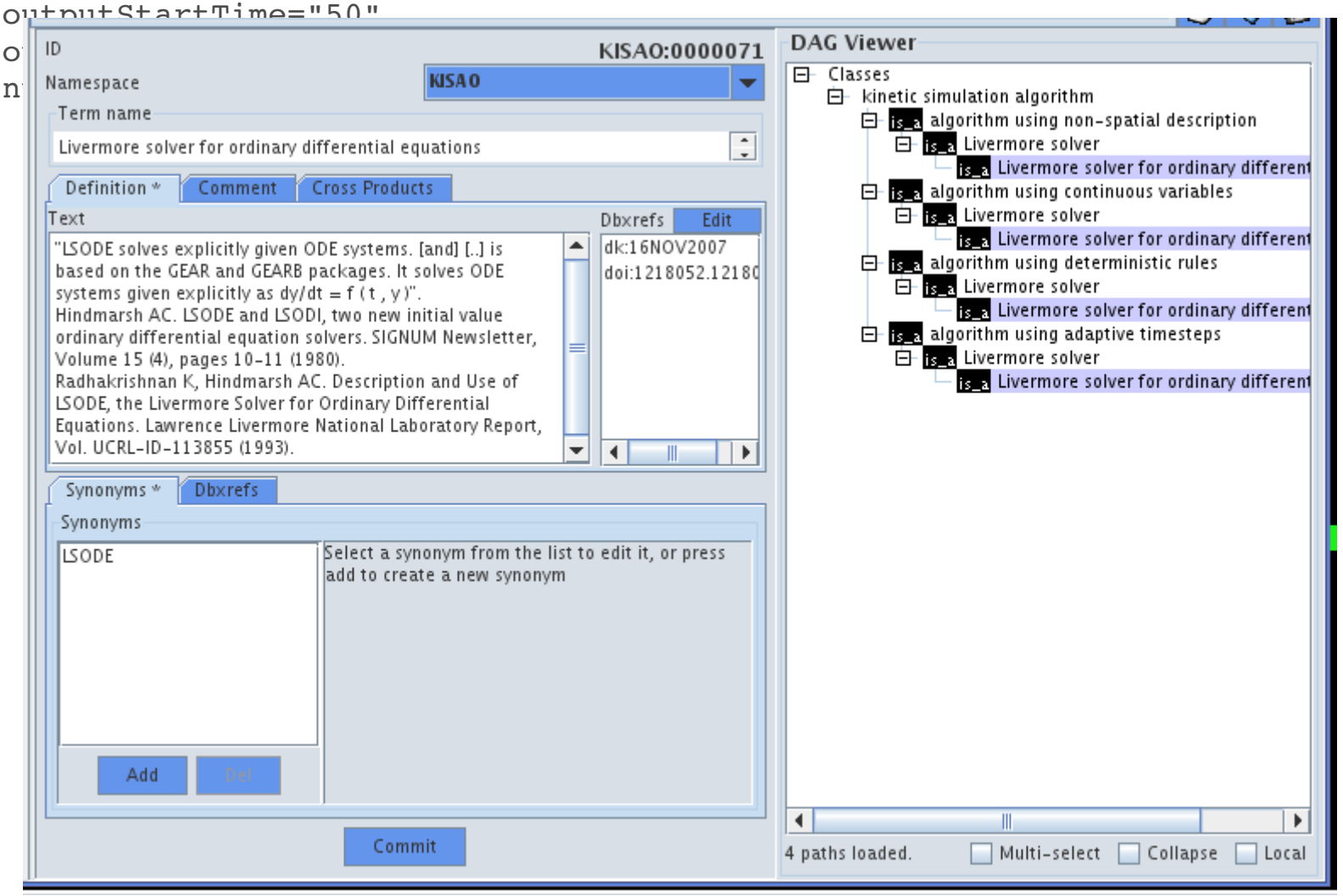


Simulation approach

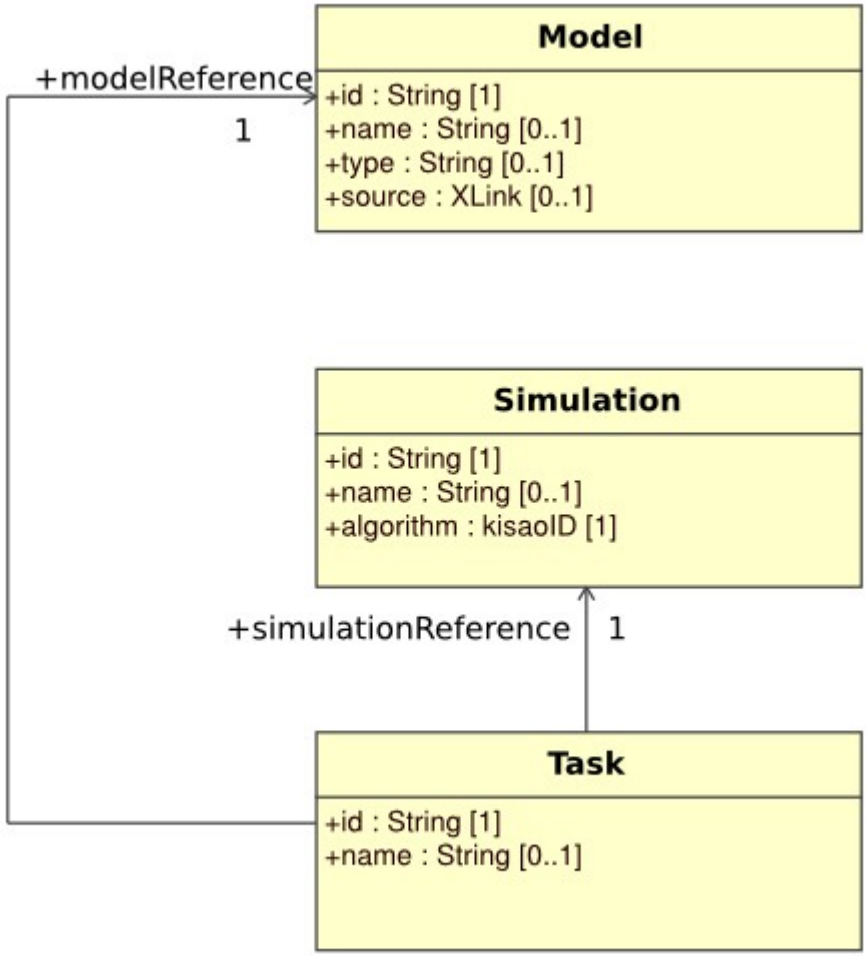
```
<listOfSimulations>
  <uniformTimeCourse id="simulation1"
                     algorithm="KiSAO:0000071"
                     initialTime="0"
                     outputStartTime="50"
                     outputEndTime="1000"
                     numberOfPoints="1000" />
</listOfSimulations>
```

Simulation approach

```
<listOfSimulations>
  <uniformTimeCourse id="simulation1"
                     algorithm="KiSAO:0000071"
                     initialTime="0"
                     outputStartTime="50"
                     o
                     n
</listOfSimulations>
```



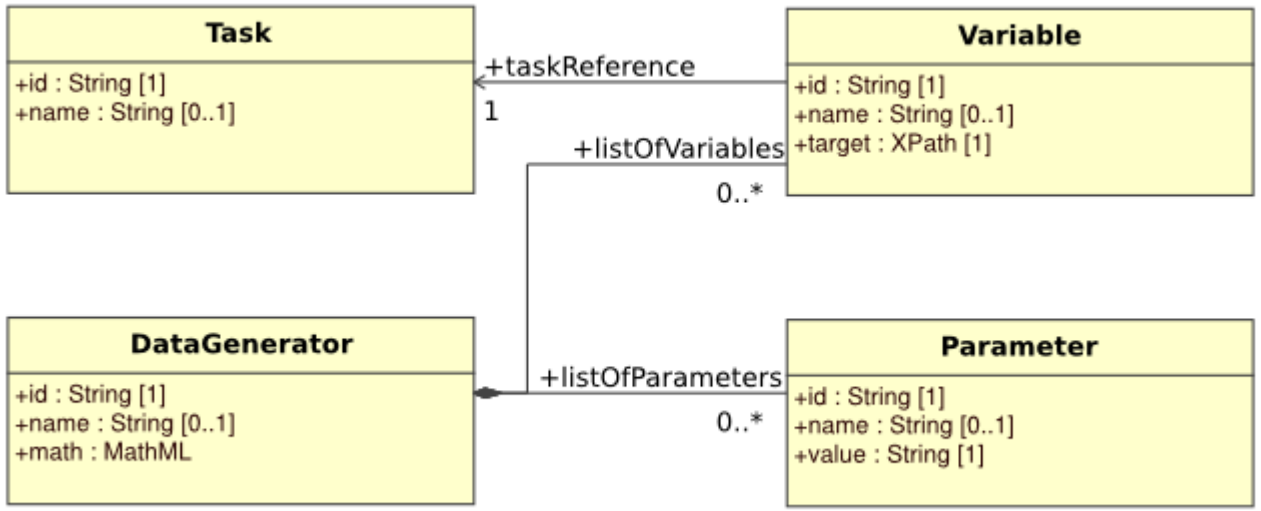
Simulation task



Simulation task

```
<listOfTasks>
  <task id="task1"
        name="Baseline"
        modelReference="model1"
        simulationReference="simulation1">
  </task>
  <task id="task2"
        name="Modified parameters"
        modelReference="model2"
        simulationReference="simulation1">
  </task>
</listOfTasks>
```

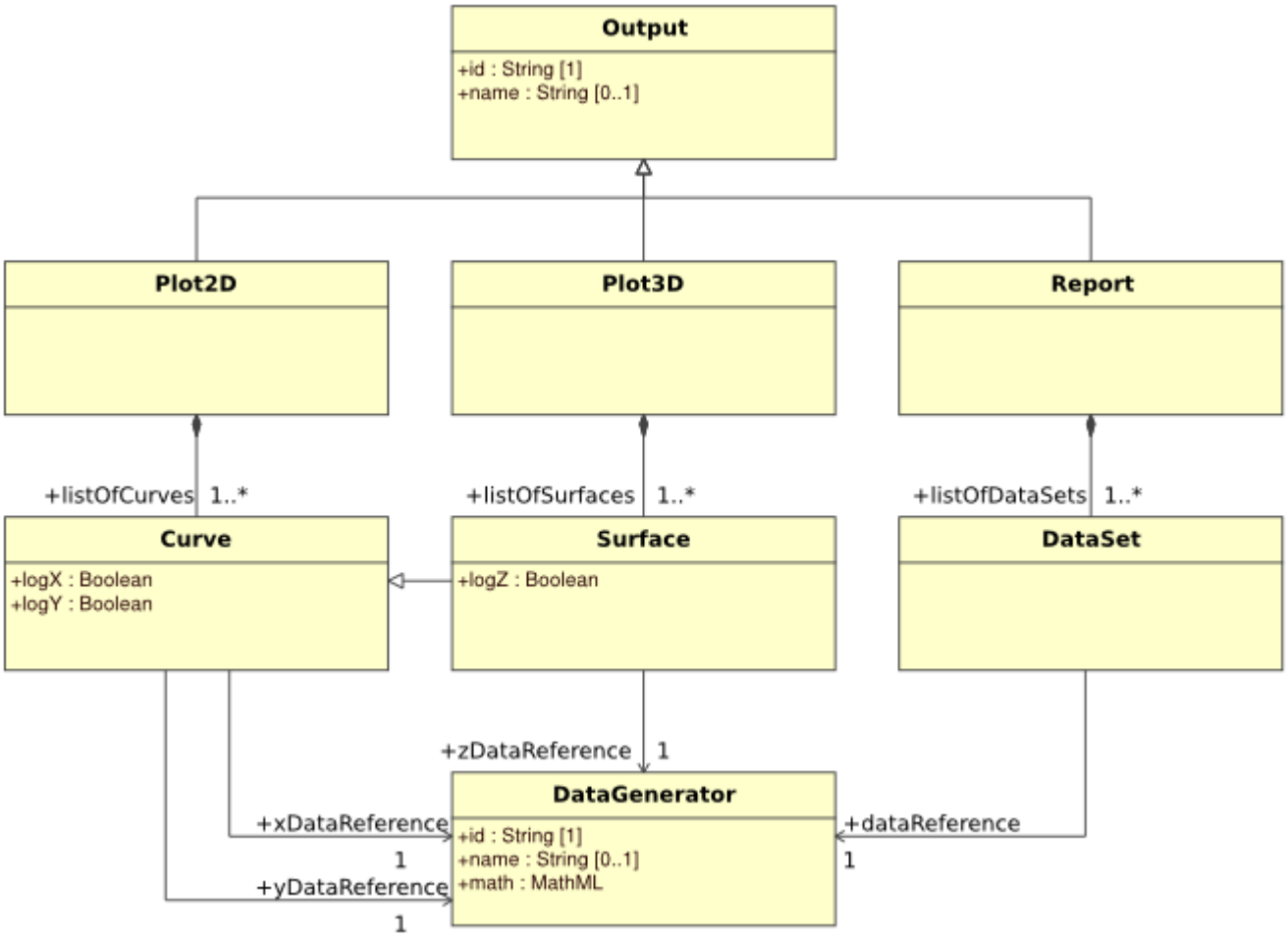
Data generation



Data generation

```
<listOfDataGenerators>
  <dataGenerator id="time" name="Time">
    <mathExpression>
      <math>
        <apply>
          <plus />
          <csymbol encoding="text"
          definitionURL="http://www.sbml.org/sbml/symbols/time">time
          </csymbol>
        </apply>
      </math>
    </mathExpression>
  </dataGenerator>
  <dataGenerator id="tim1" name="tim mRNA (total)">
    <listOfVariables>
      <variable id="v1" taskReference="task1"
      target="/sbml/model/listOfSpecies/species[@id='Mt']" />
    </listOfVariables>
    <mathExpression>
      <math>
        <apply>
          <plus />
          <ci>v1</ci>
        </apply>
      </math>
    </mathExpression>
  </dataGenerator>
 ...
</listOfDataGenerators>
```

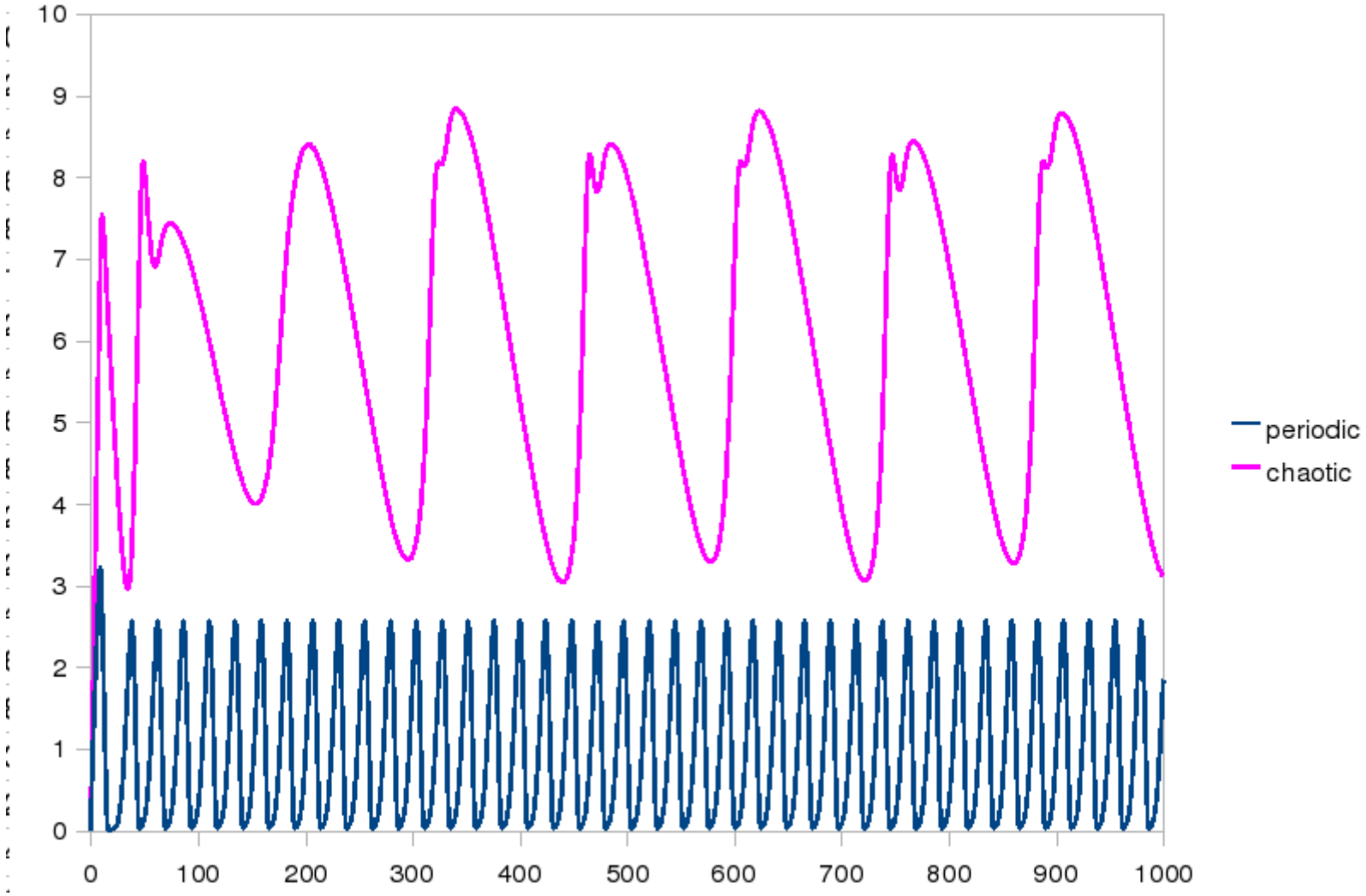
Production of results



Production of results

```
    <listOfOutputs>
    <plot2D id="plot1" name="tim mRNA with Oscillation and Chaos">
      <listOfCurves>
        <curve logX="false"
               logY="false"
               xDataReference="time"
               yDataReference="tim1" />
        <curve logX="false"
               logY="false"
               xDataReference="time"
               yDataReference="tim2" />
      </listOfCurves>
    </plot2D>
  </listOfOutputs>
</sedML>
```

Production of results



Where are-we?

+

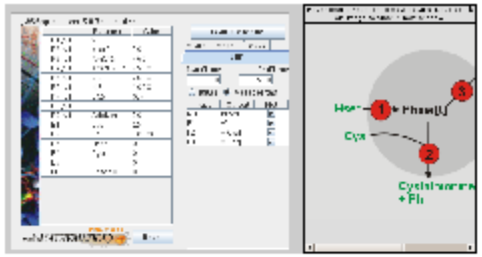
SED-ML

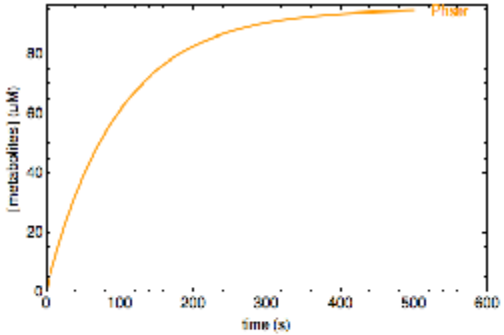
Model file

Simulator

Simulation result

Curien Model

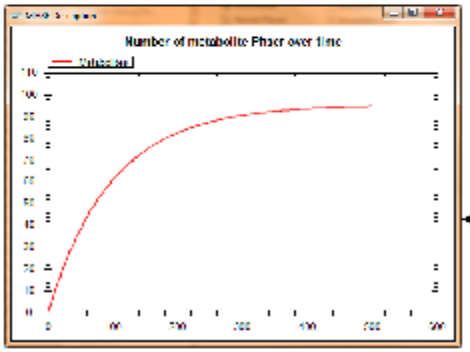


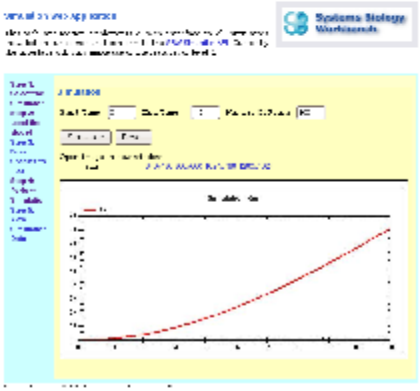


SBML (JWS online)

JWS Online

Simulation result





SED-ML

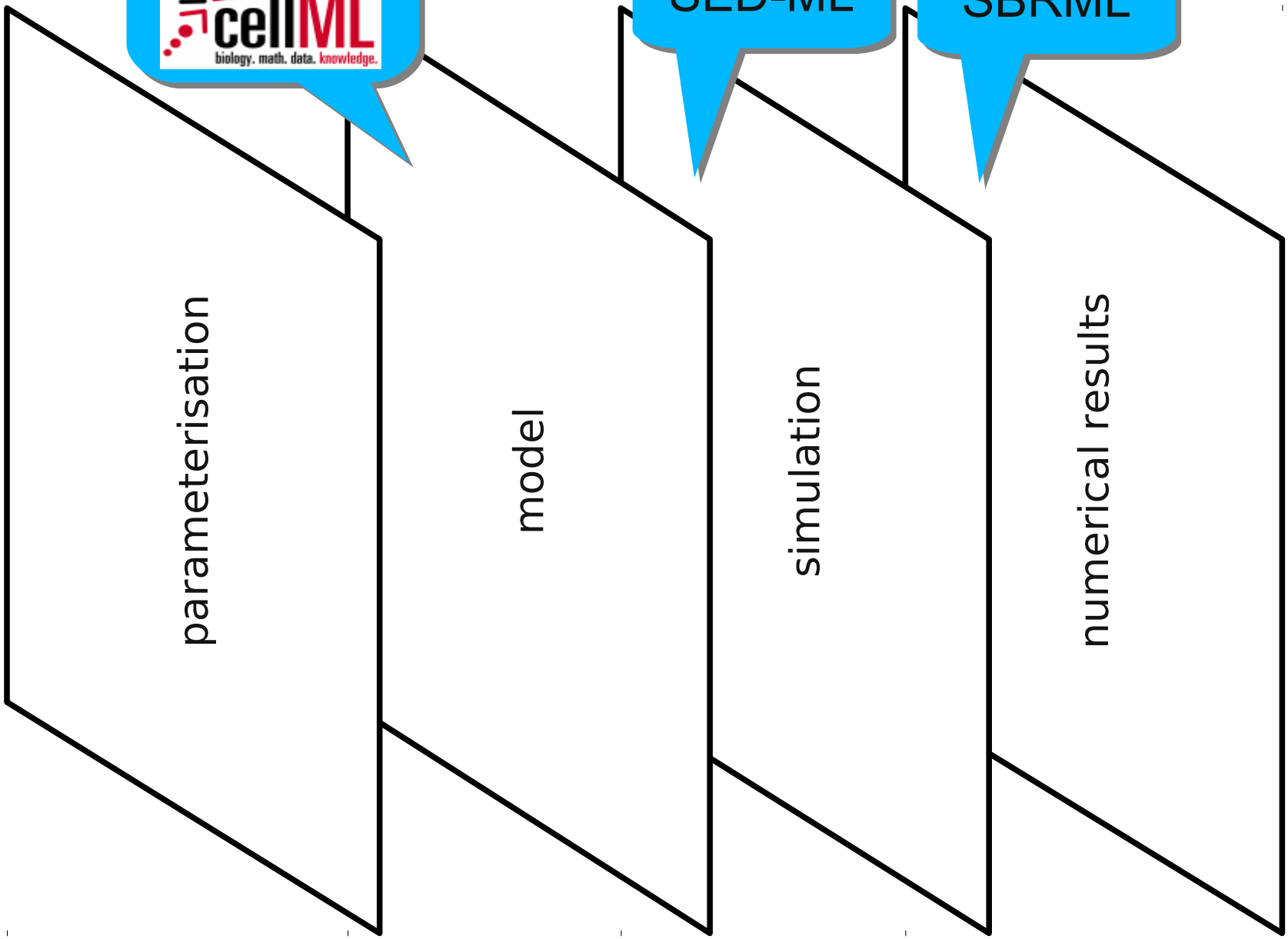
Simulation result

SBW Online

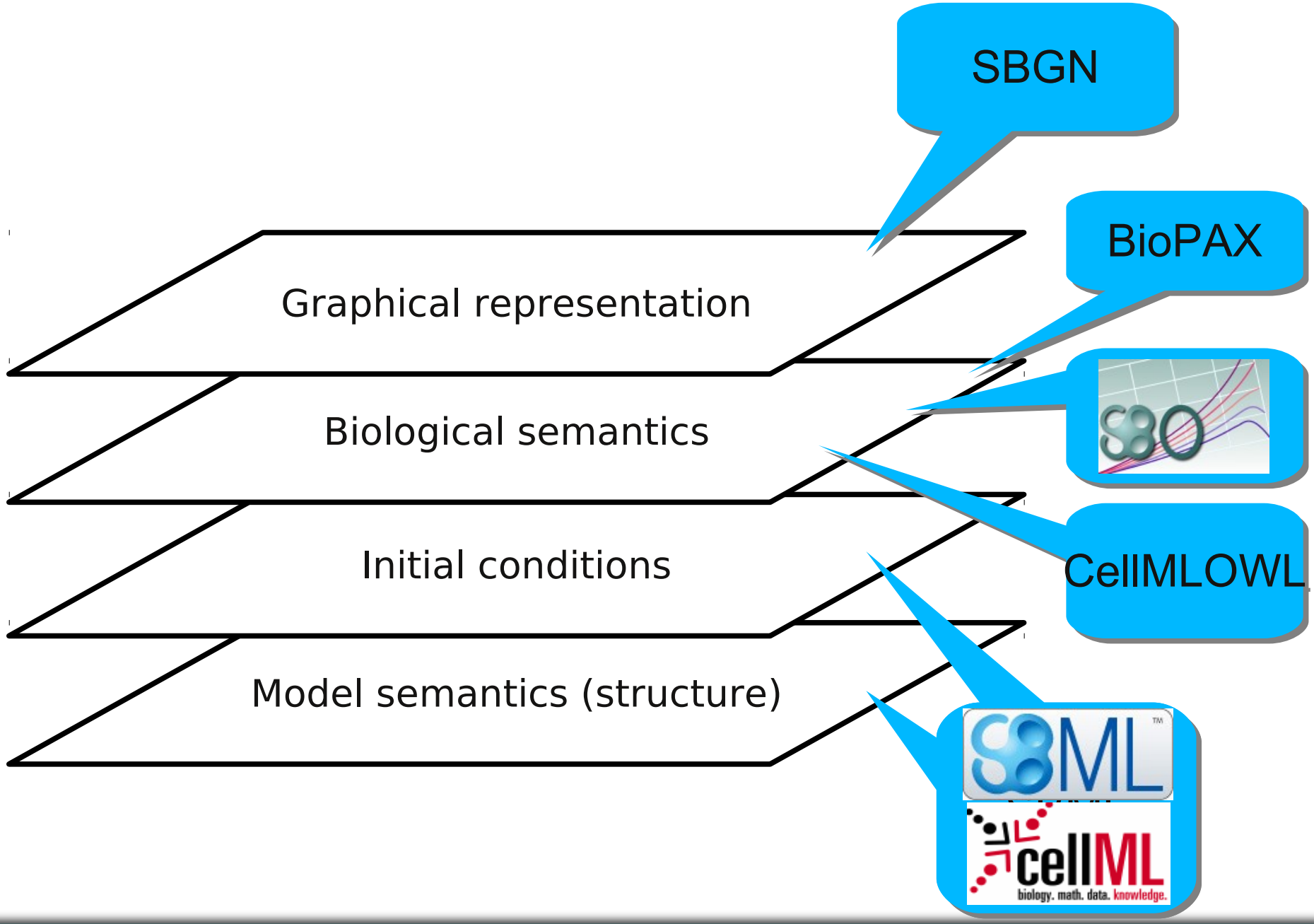
A “complete” mosaic of standards

	Models	Simulation	Results
Minimal requirements	MIRIAM	MIASE	
Data-models	SBML, SBGN	SED-ML	SBRML
Ontologies	SBO	KISAO	TEDDY

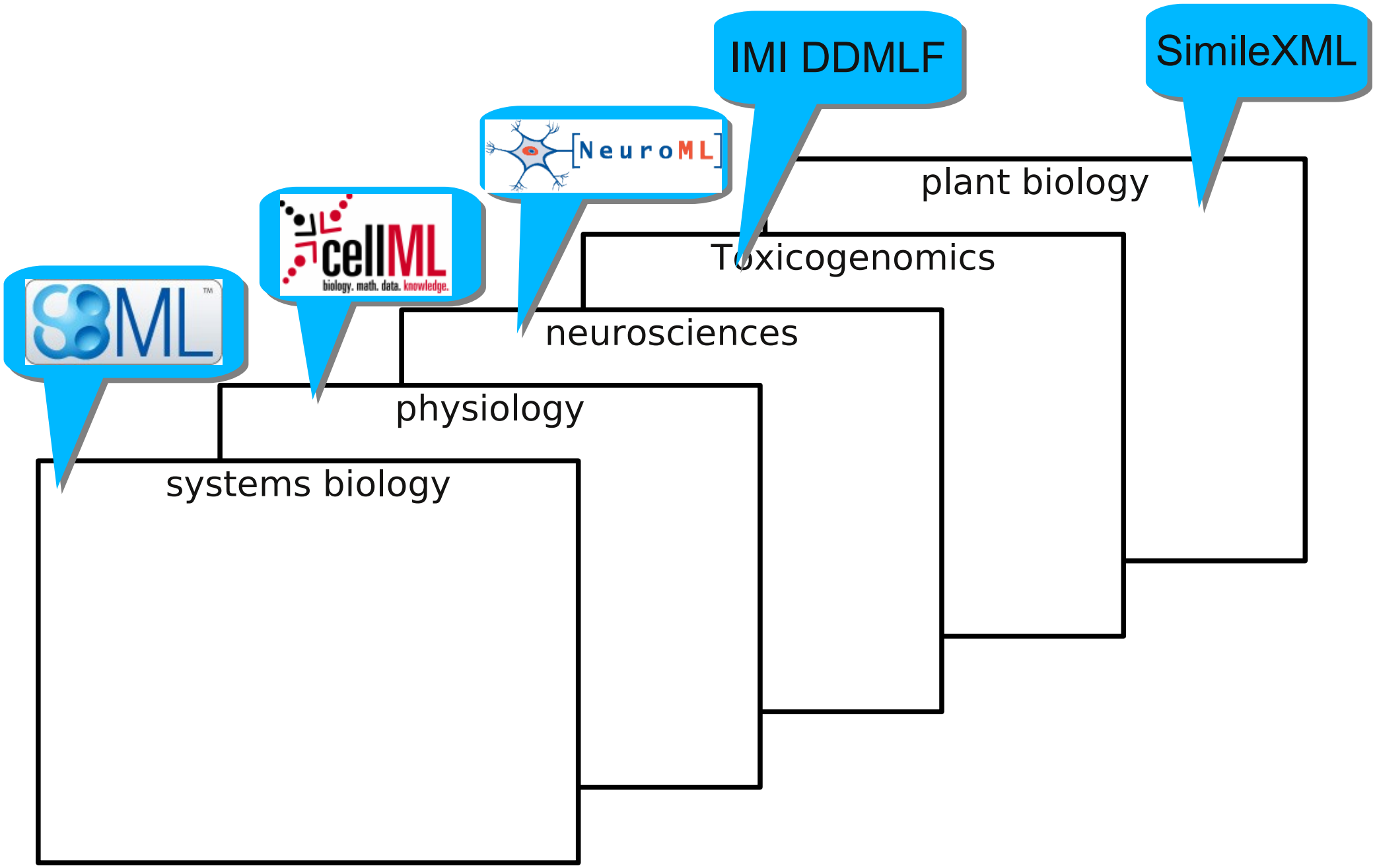
Disentangling the model life-cycle



Disentangling the level of discourse



Covering life-science



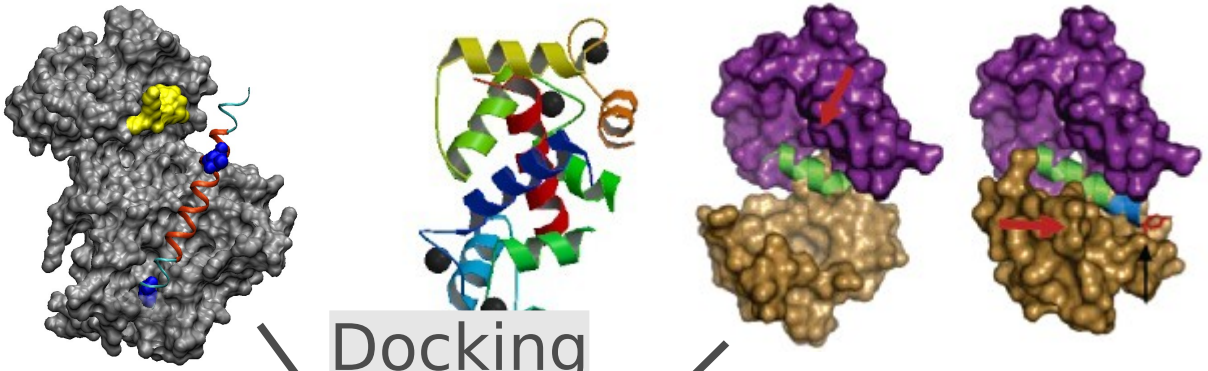
Interfacing standards in the three directions

- SBML to BioPAX: interface using annotations (MIRIAM annotations and SBO terms), e.g.
  - mapping between Species and PhysicalEntity
  - mapping between Reactions and PhysicalInteraction
- Usage of SBML descriptions (or CellML or VCML) in SED-ML: Identification of variables using XPath
- Descriptions using SBML and NeuroML: Interface based on shared namespaces

Separating scales and representations example of neurosciences

- Brain function is a multi-scale process
  - Molecular: Opening of ion channels
  - Subcellular: Signalling pathways
  - Cellular: Propagation of the action potentials
  - Multi-cellular: Computation by micro-circuits
  - Tissular: Consciousness and depolarization waves
- Modelling neuronal processes requires many approaches
  - Modelling biochemistry
  - Modelling electrical activity
  - Modelling mechanics
- Role of the International Neuroinformatics Coordinating Facility

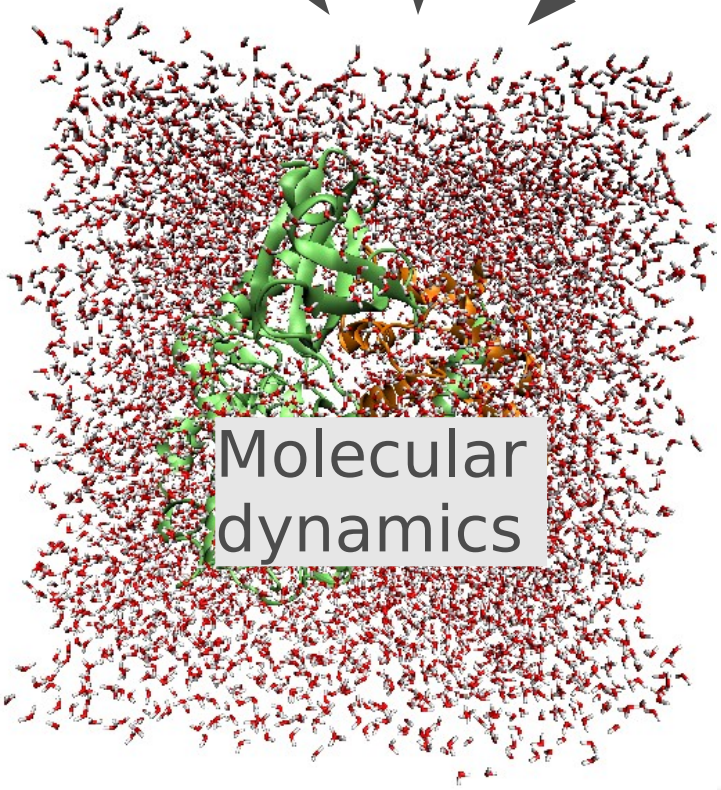
Molecule function: structural models



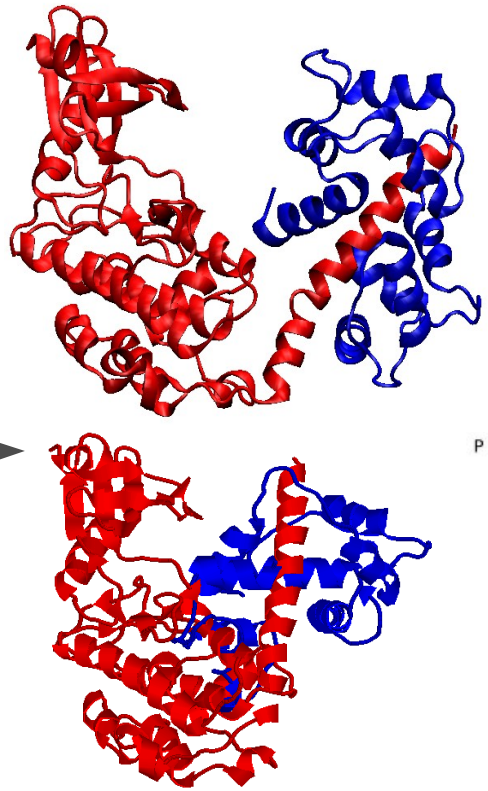
Docking

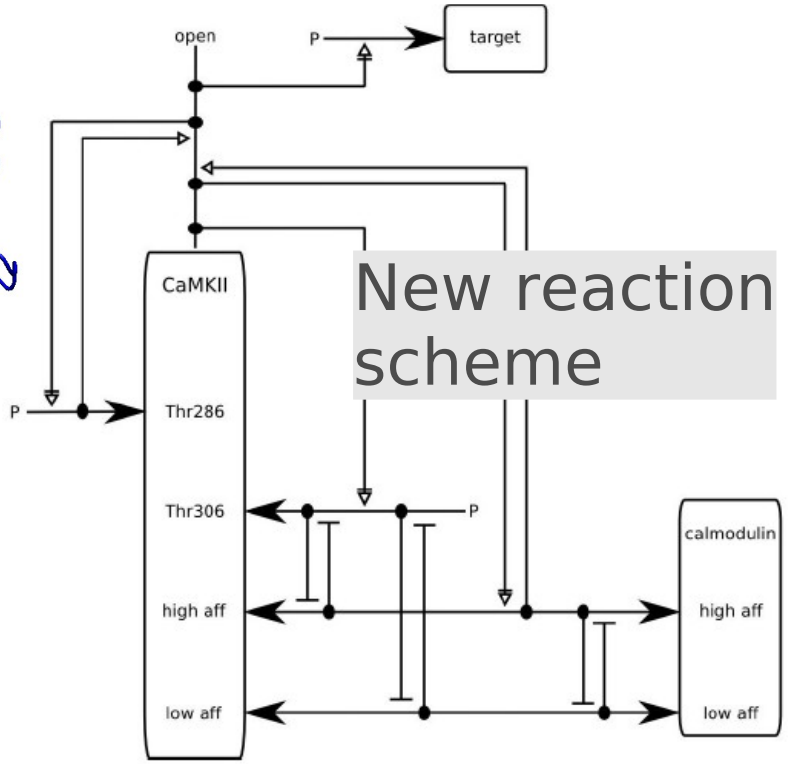
Melanie Stefan

David Marshall



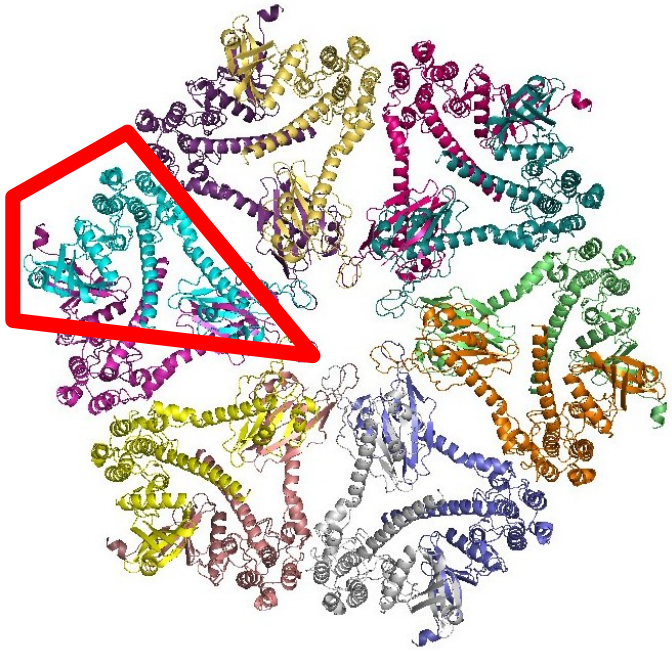
Molecular dynamics

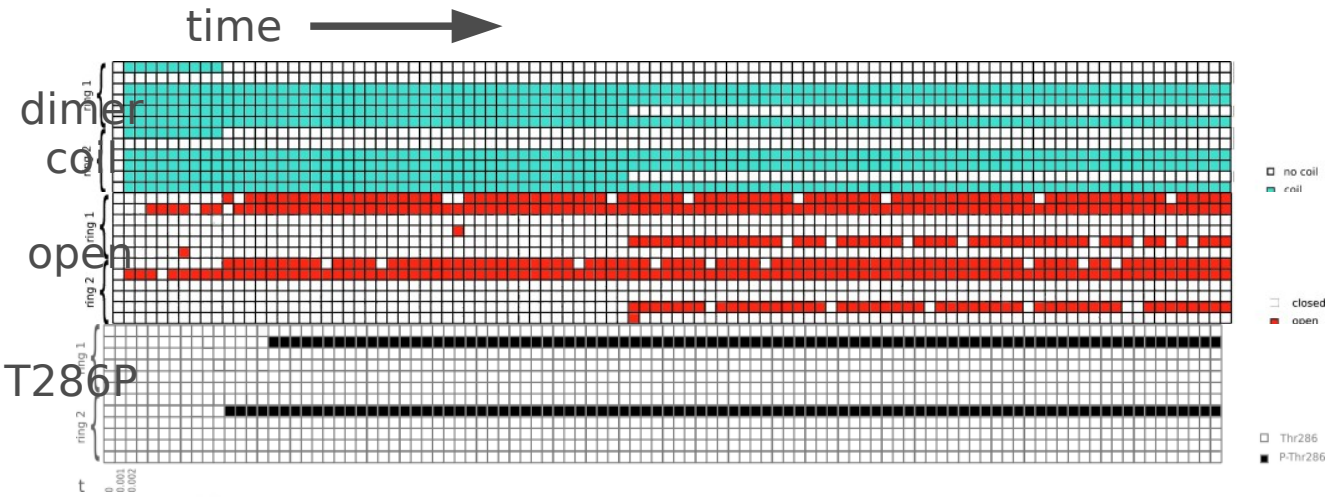


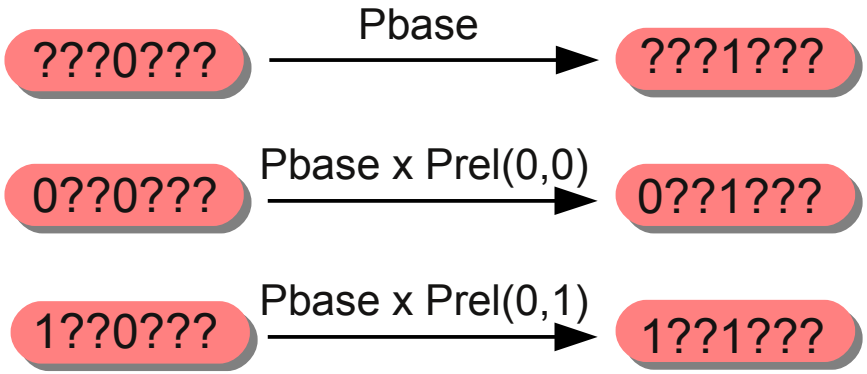


New reaction scheme

Stochastic multi-agent modeling with StochSim



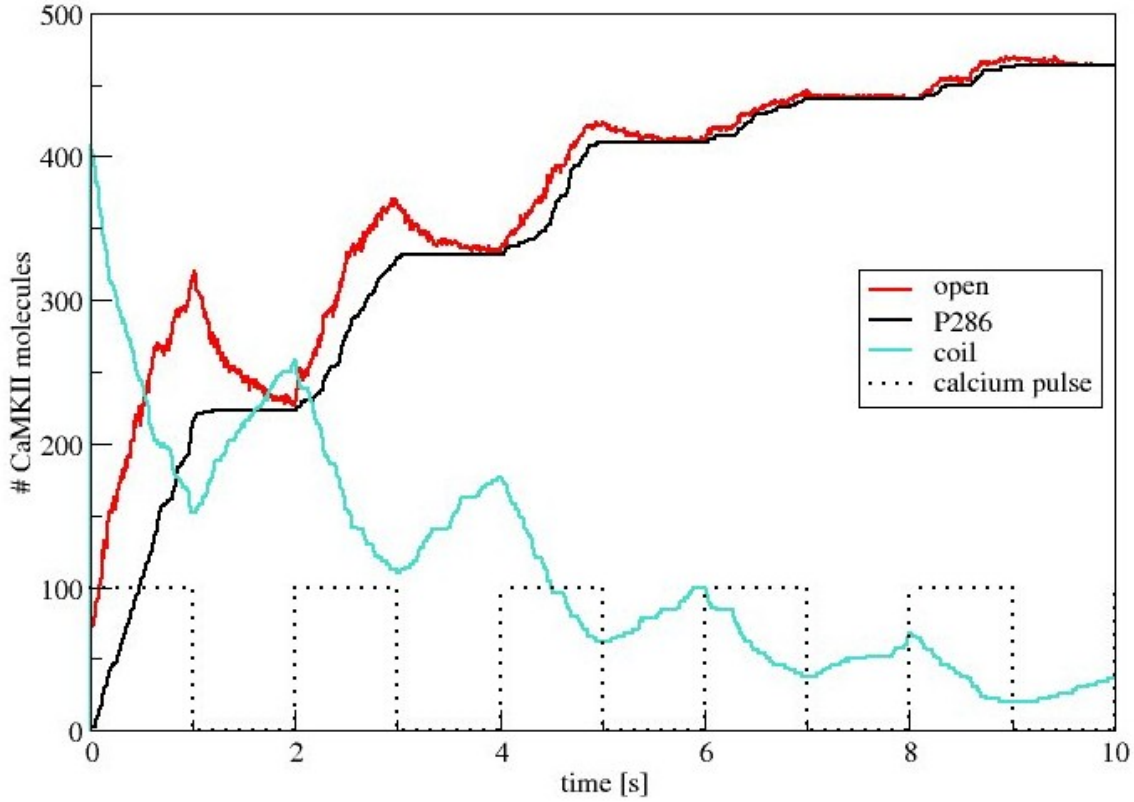




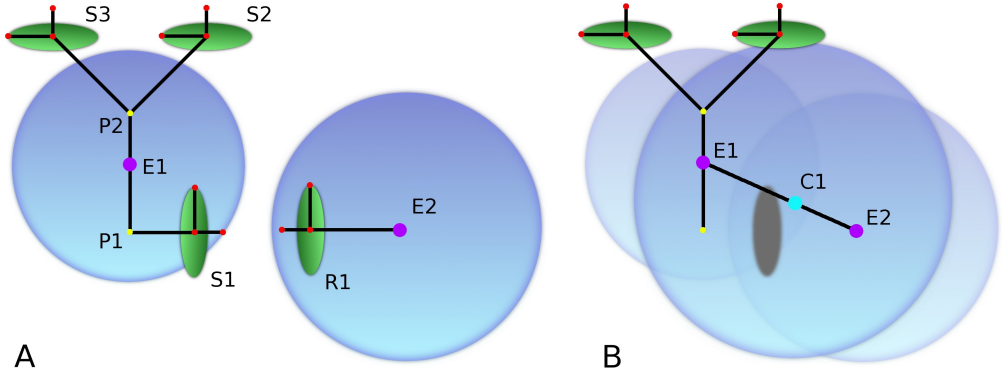
'?' Flags do not affect the reaction

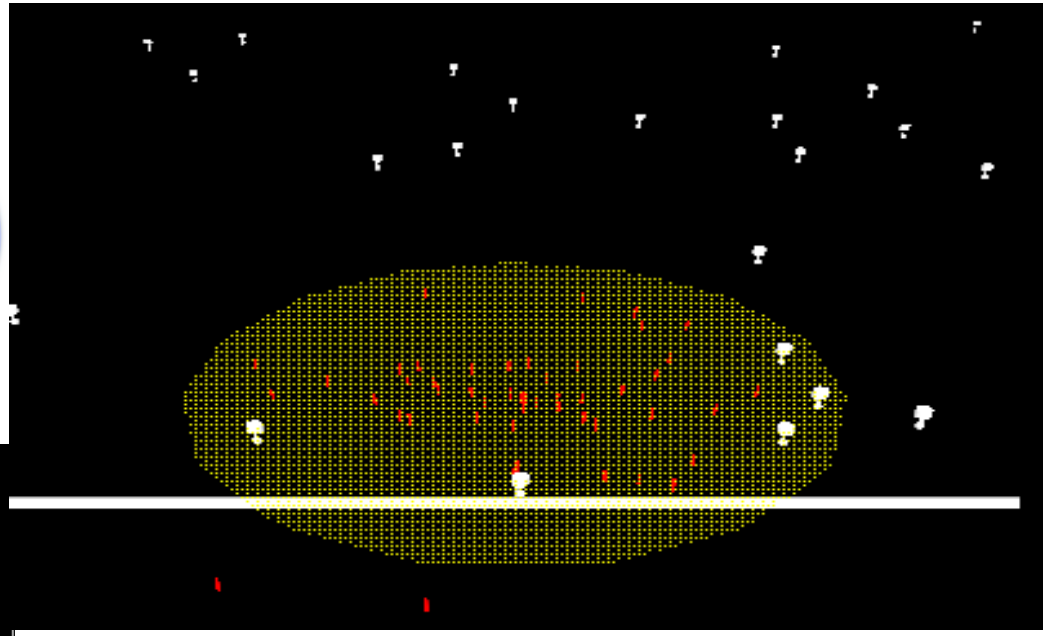
only 4 species are needed instead of 128

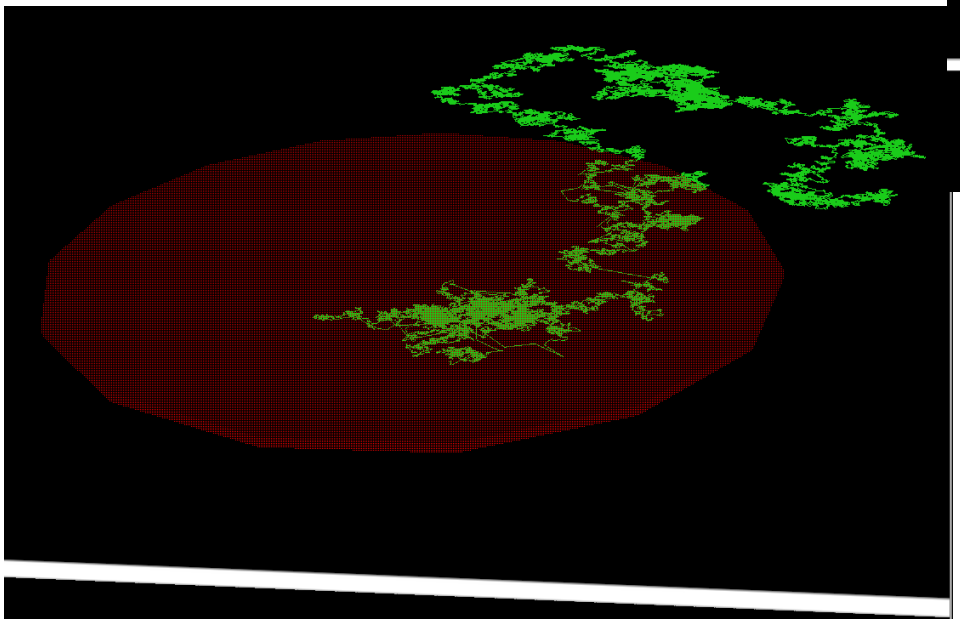
only 2 reactions are needed instead of 64



Post-synaptic density: single-particle models







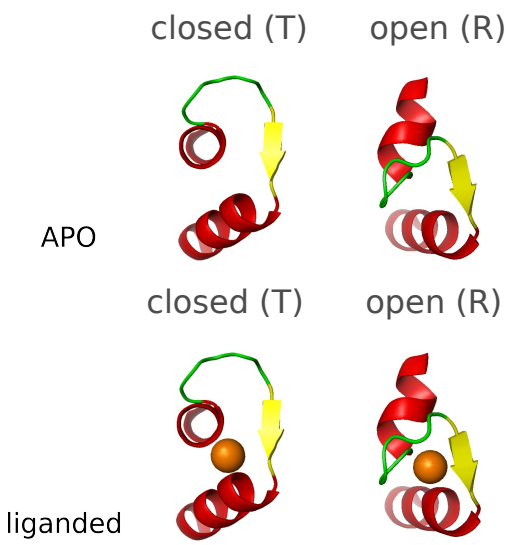
Dominic Tolle

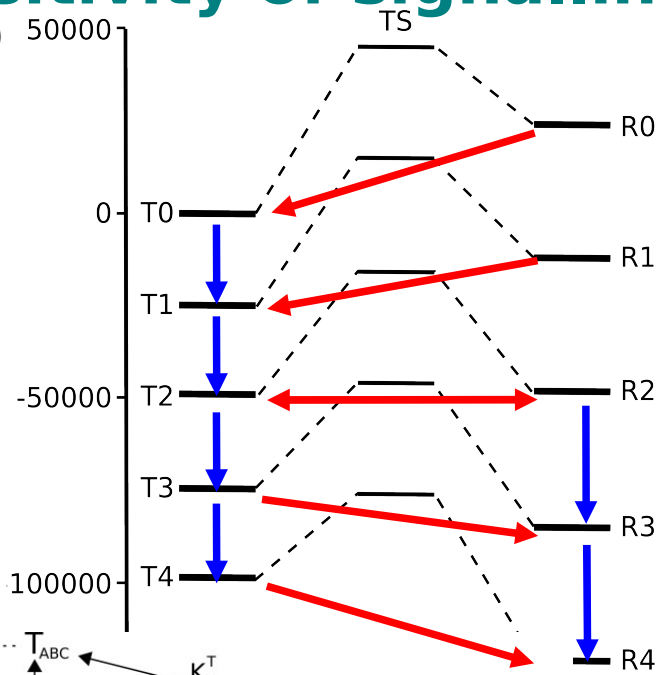
Each molecule is an object

Transient complex formation

Real space reaction-diffusion

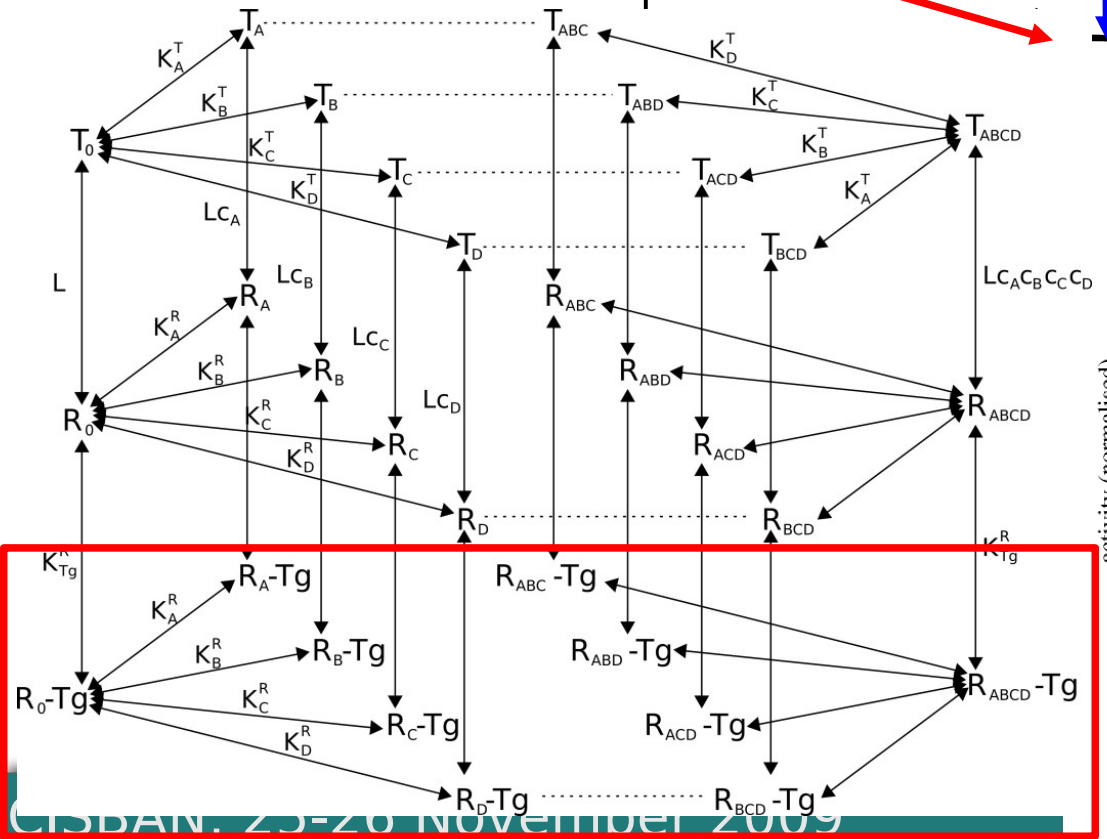
Sensitivity of signalling: thermodynamic models

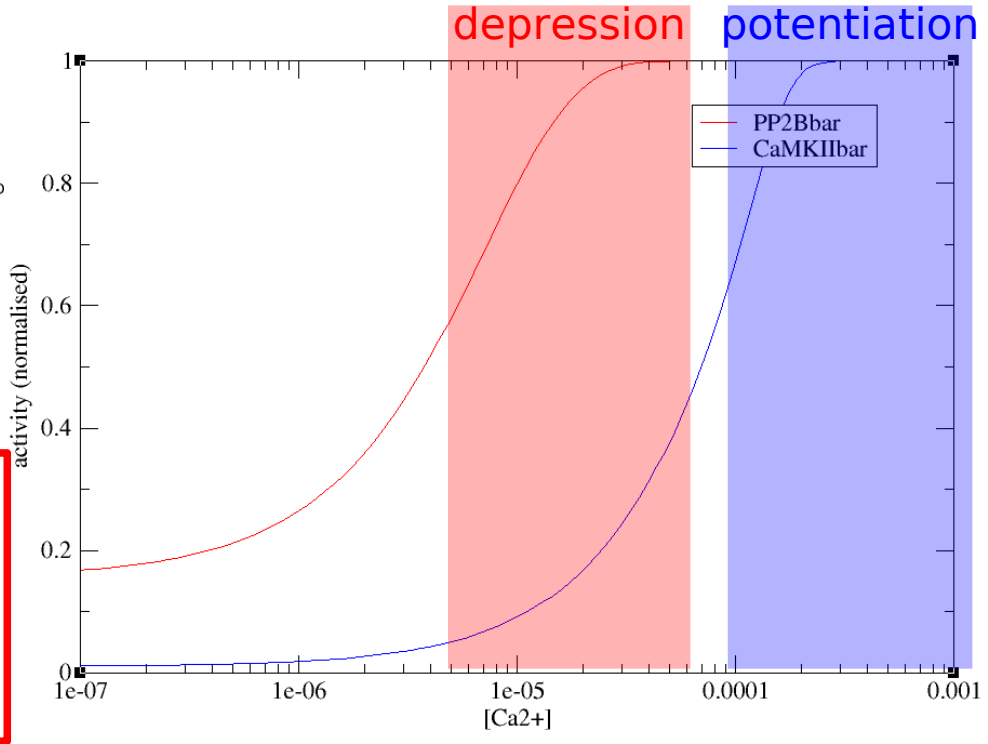




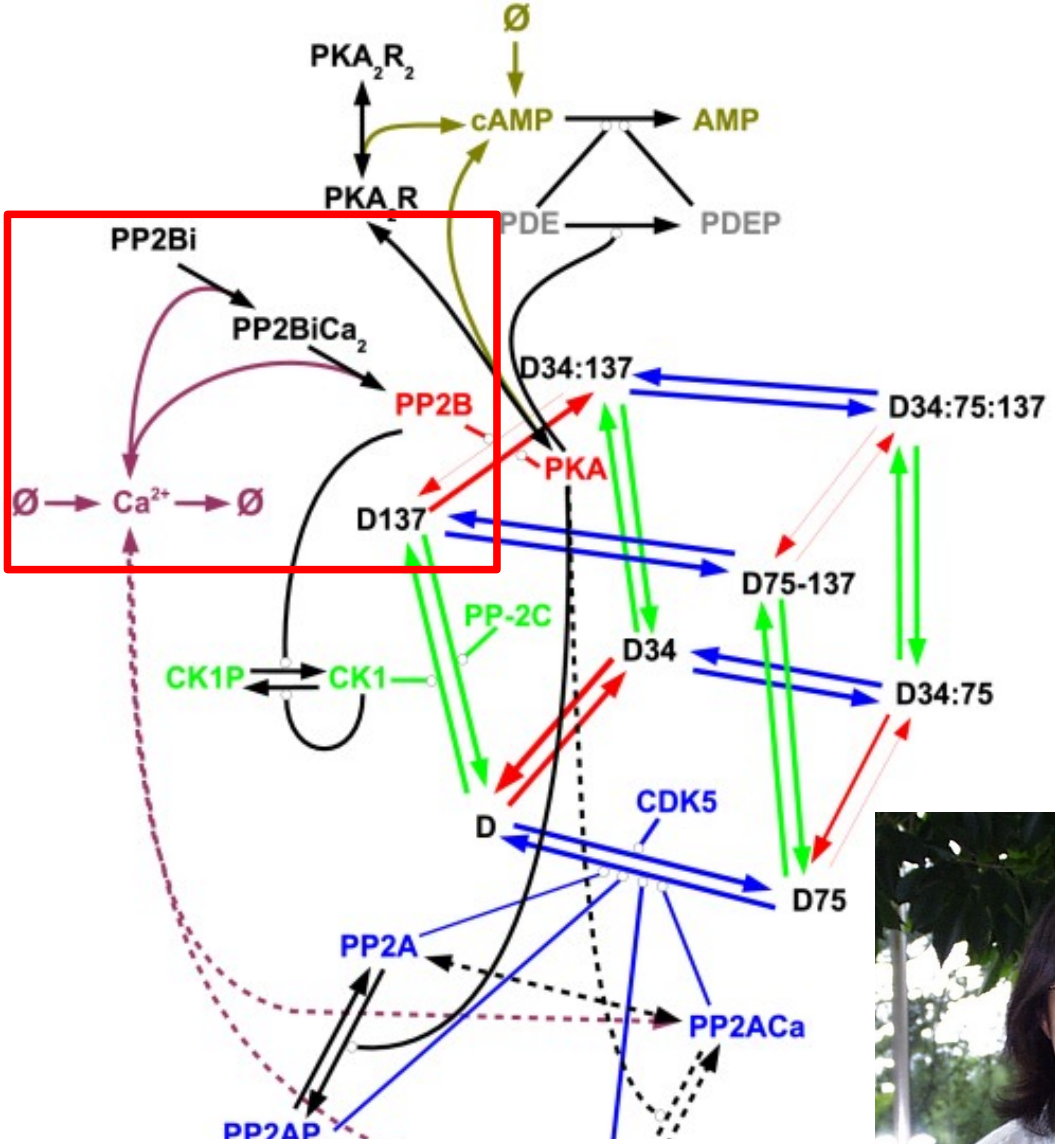
Melanie Stefan Stuart Edelstein

$$\bar{Y} = 0.25\frac{\sum_i\left(\alpha_i\prod_j(1+\alpha_j)\right)+L\sum_i\left(c_i\alpha_i\prod_j(1+c_j\alpha_j)\right)}{\prod_i(1+\alpha_i)+L\prod_i(1+c_i\alpha_i)}$$



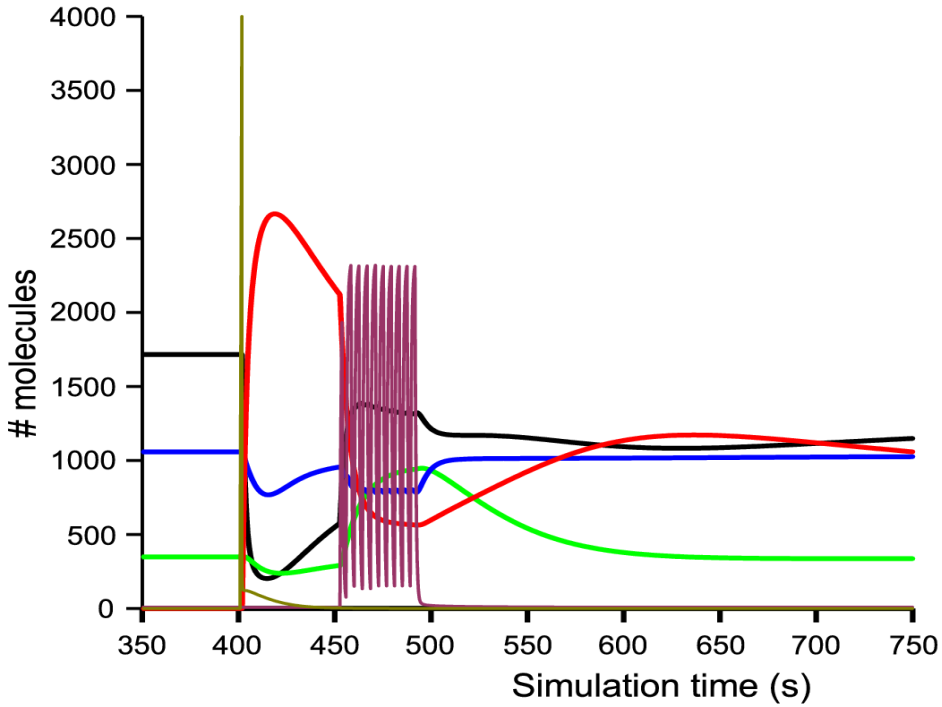


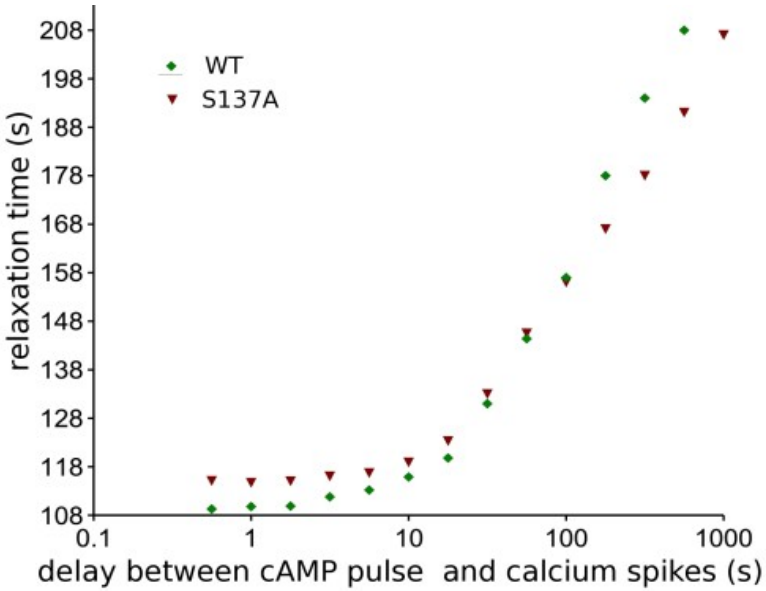
Signalling pathways: chemical kinetics models



$$\frac{dX_i}{dt} = \sum_j n_{ij} f(X_0, X_1, ..., X_n)$$

Lu Li



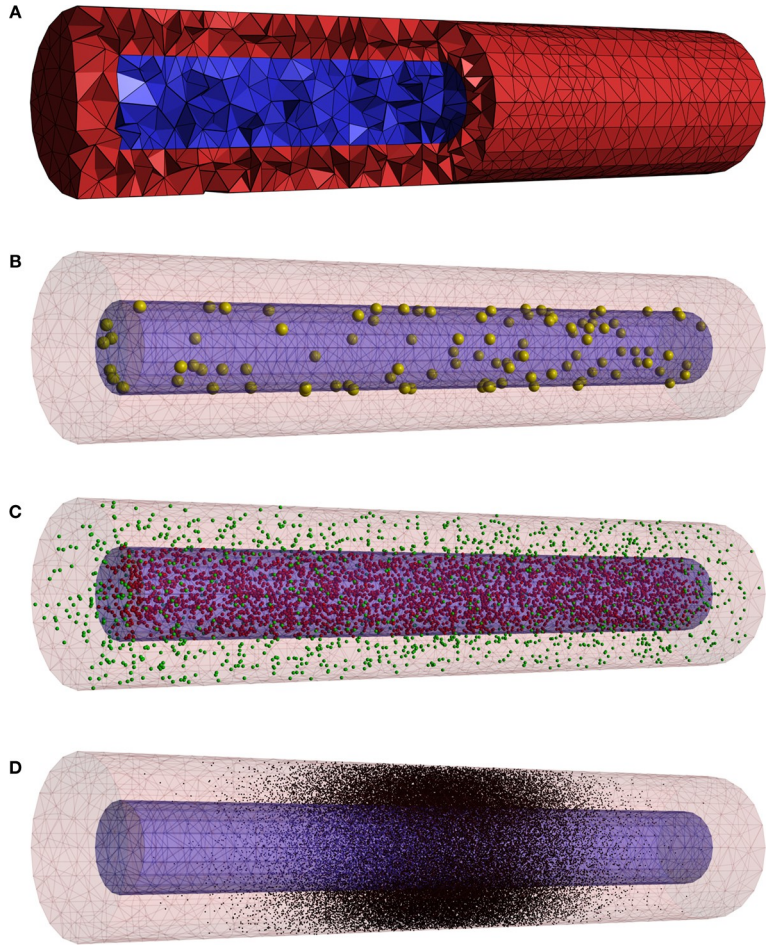


Spatial modelling and dendritic diffusion

Population of individual molecules.

Reaction-diffusion using “spatial Gillespie”.

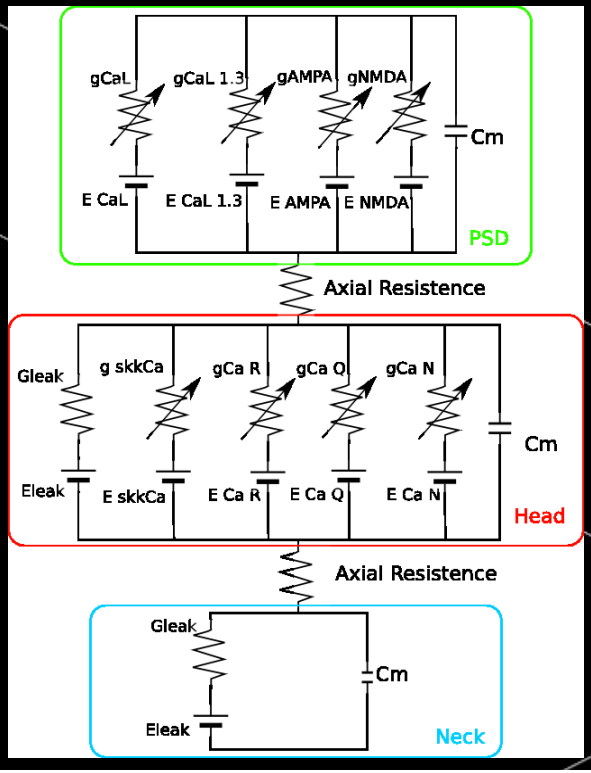
Wils S and De Schutter E (2009) STEPS: Modeling and simulating complex reaction-diffusion systems with Python. Front. Neuroinform. 3:15.

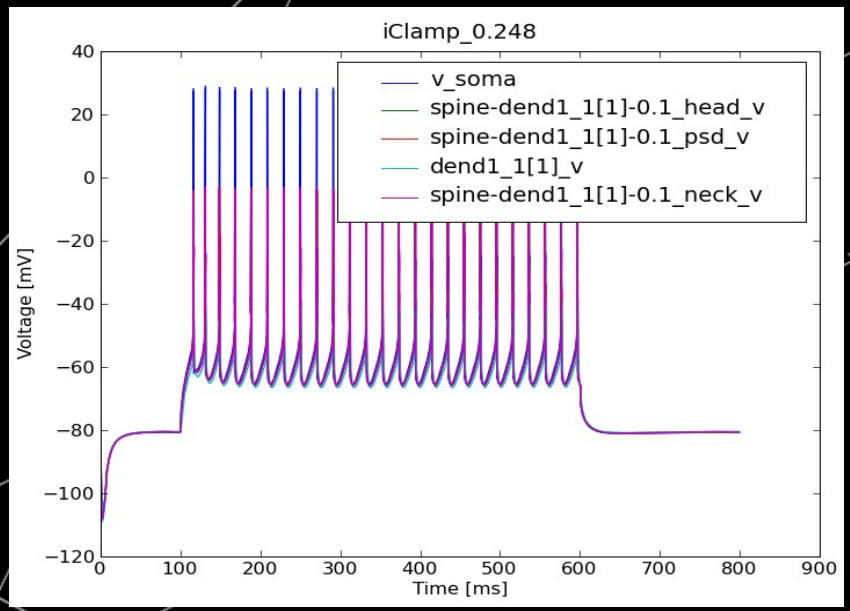


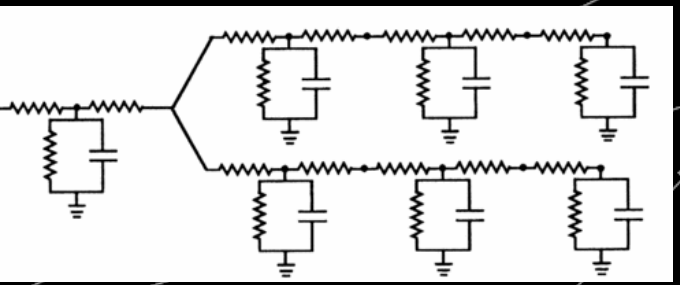
Cellular mechanics and neuronal growth

B. Rubinstein, K. Jacobson, A. Mogilner, Multiscale Two-Dimensional Modeling of a Motile Simple-Shaped Cell. SIAM J. MMS, 3 413-439 (2005)

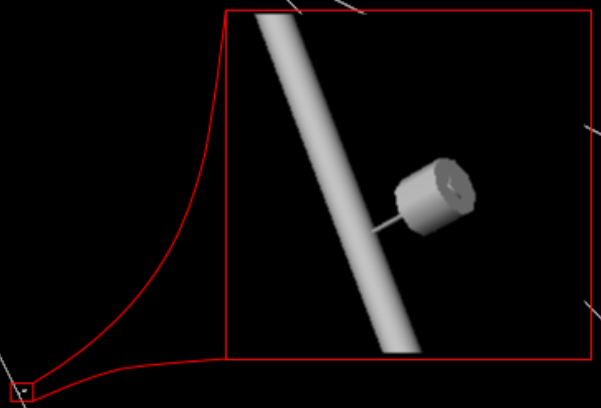
Whole-cell: electro-biochemical models







Michele Mattioni



1524 spines

4761 compartments

16362 channels

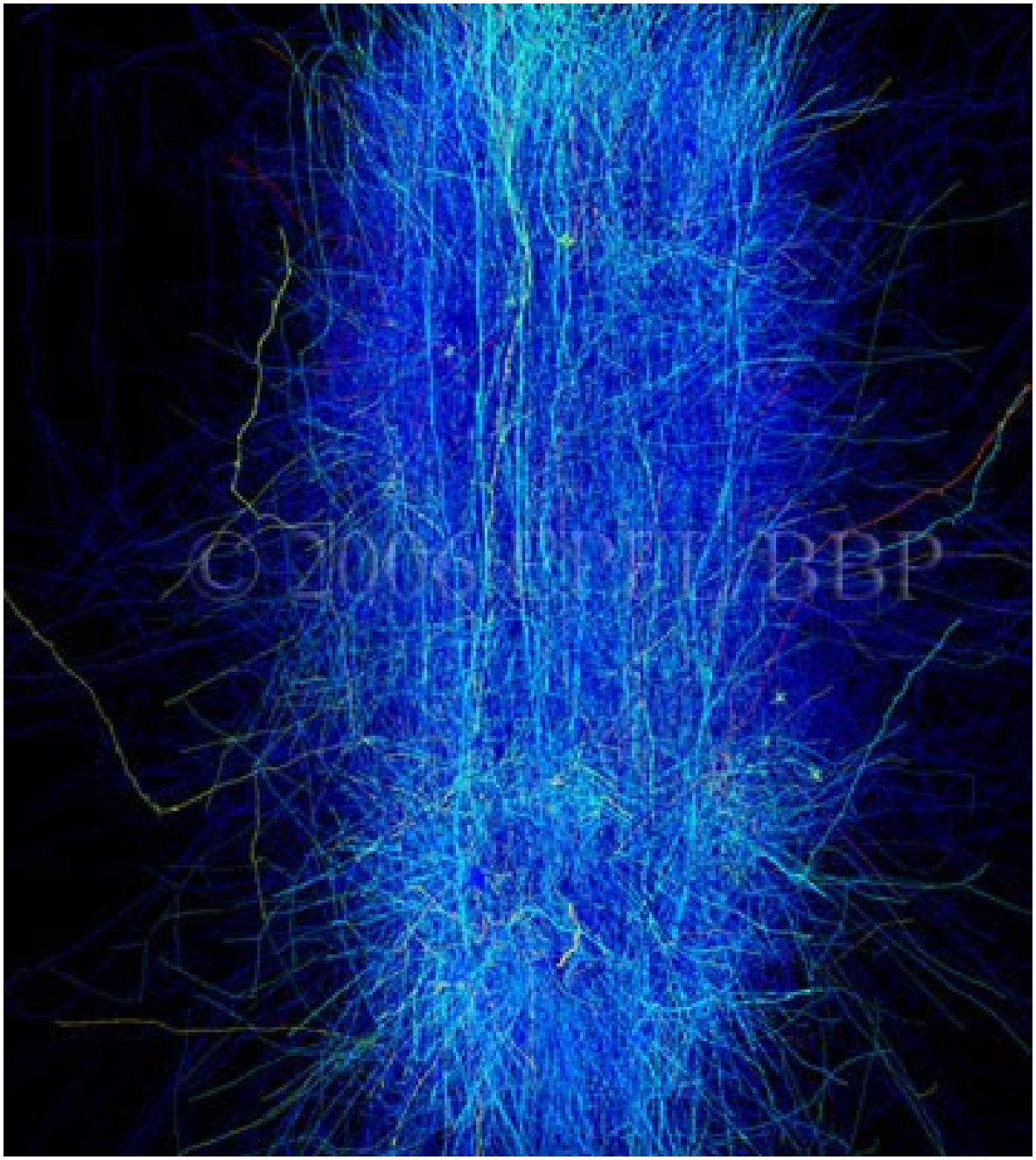
Network: multi-neuron model

The neocortical column of the blue-brain project

- 10 000 Neurons

~100 compartments

Next step: integrating electrophysiology and biochemistry



Markram (2006) *Nat Rev Neurosci* 7: 153-160.

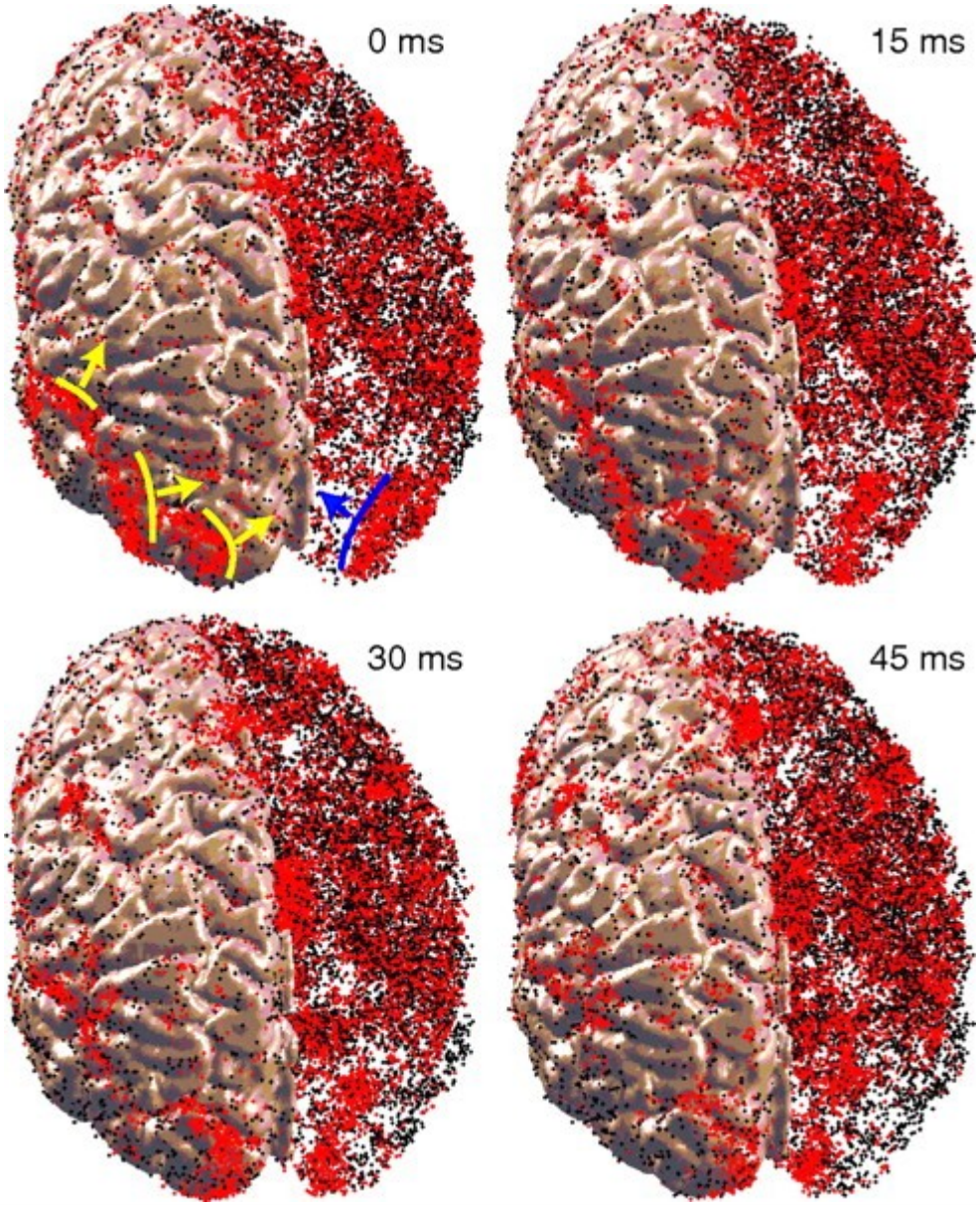
A whole organ

- 1 000 000 Neurons
- 10-50 compartments

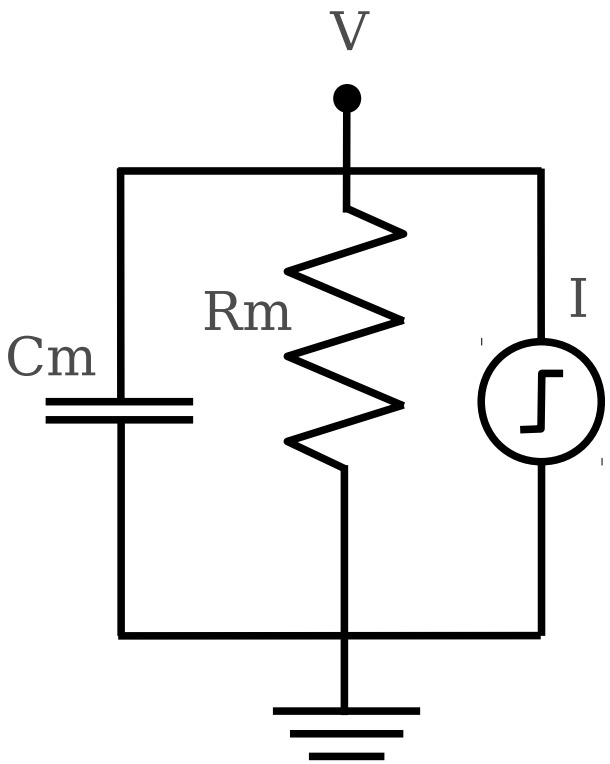
1 000 000 000 synapses

The thalamo-cortical system

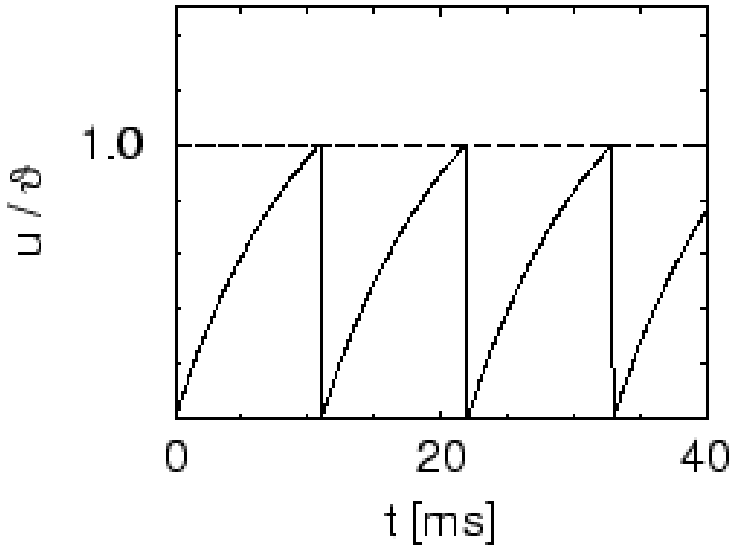
Izhikevich, Edelman (2008)
PNAS 105: 3593-3598



Leaky integrate and fire: phenomenological

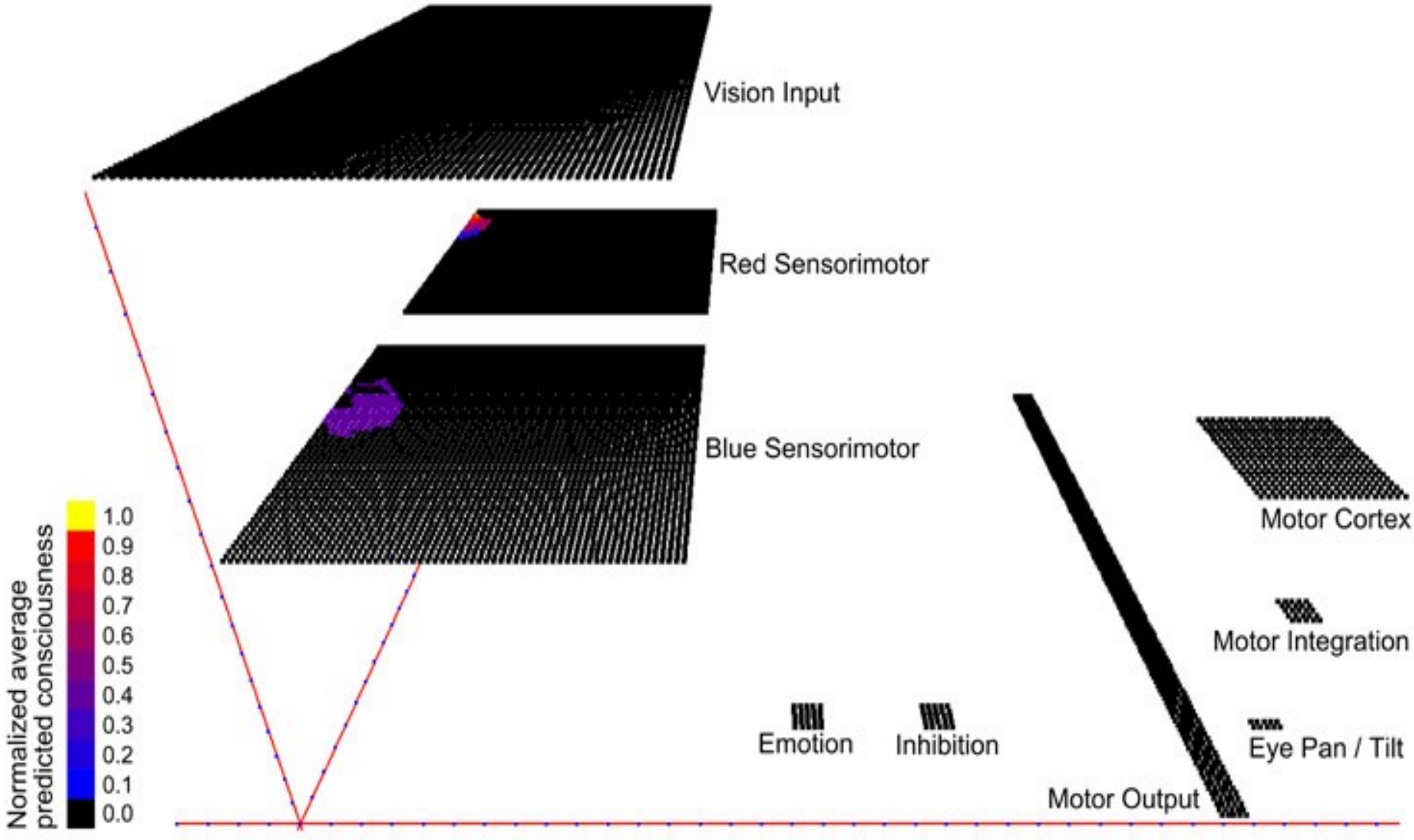


$$Cm\frac{dV}{dt} = -\frac{V}{Rm} + I$$



Lapicque (1907) *J Physiol Pathol Gen* 9: 620-635.

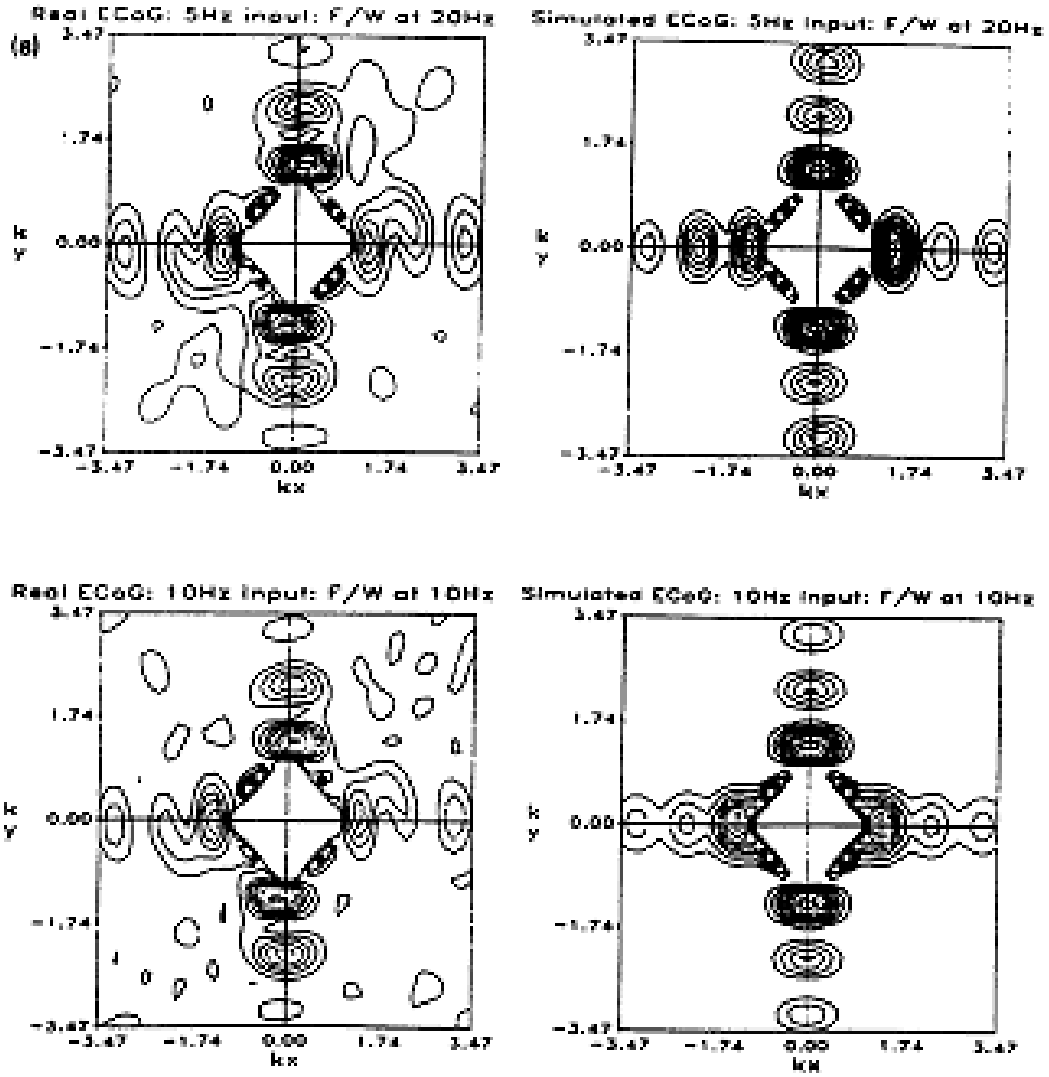
Circuits of single-compartment neurons and computation



David Gamez (2010).
Cons Cog, doi:10.1016/j.concog.2009.11.001

Mean-field approaches and global brain function

Wright, Liley (1996).
Behav Brain Sci 19: 285-320



The standardisation efforts

- ChannelML: state-based representation of molecule behaviour (part of NeuroML)
- SynapseML: (part of NeuroML)
- MorphML: cable representation of neurons (part of NeuroML)
- SBML: description of biochemical processes (interoperate with NeuroML)
- NeuML (temporary name): Effort started by the INCF to describe networks of single-compartment neurons
- Missing: Representation of mechanical processes
- Missing: Description of mean-field measurements

The standardisation efforts

electrical behaviours

- ChannelML: state-based representation of molecule behaviour (part of NeuroML)
- SynapseML: (part of NeuroML)
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- SBML: description of biochemical processes (interoperate with NeuroML)
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- Missing: Representation of tissus
- Missing: Description of mean-field measurements

The standardisation efforts

biochemical processes

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The standardisation efforts

mechanical processes

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- Missing: Description of mean-field measurements

The standardisation efforts

Networks of coupled cells

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- SynapseML: (part of NeuroML)
- MorphML: cable representation of neurons (part of NeuroML)
- SBML: description of biochemical processes (interoperate with NeuroML)
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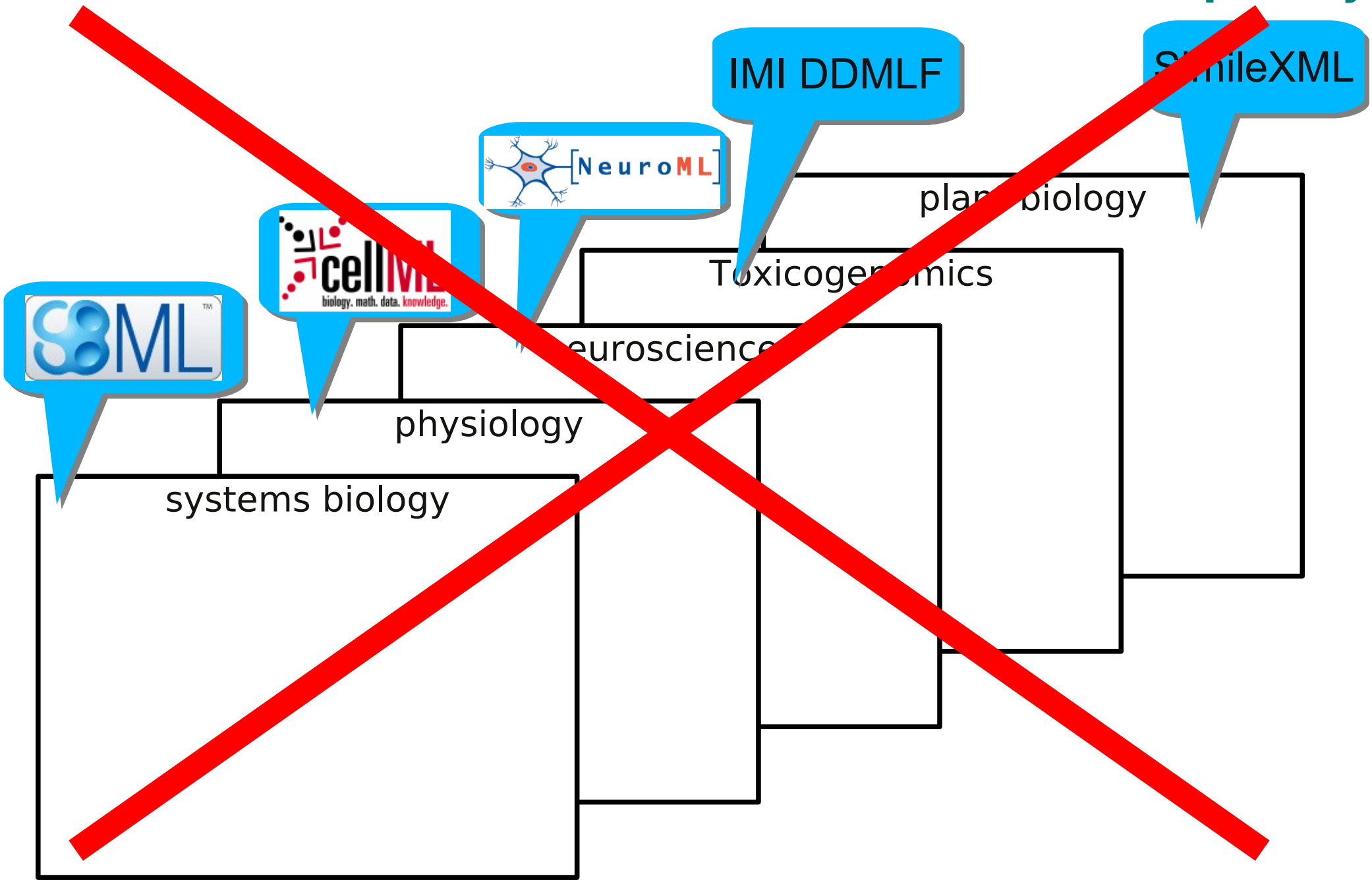
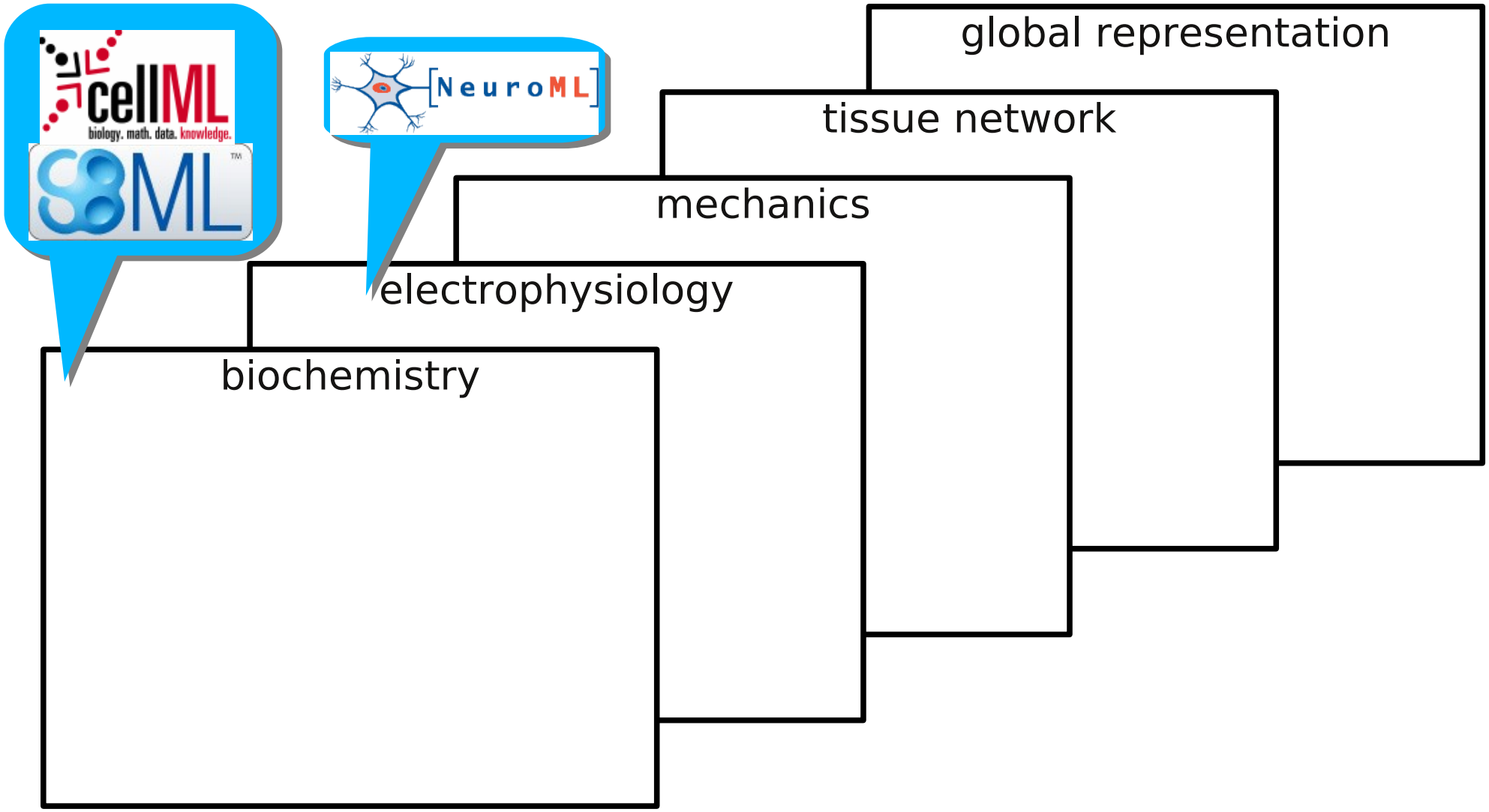
- Missing: Description of mean-field measurements

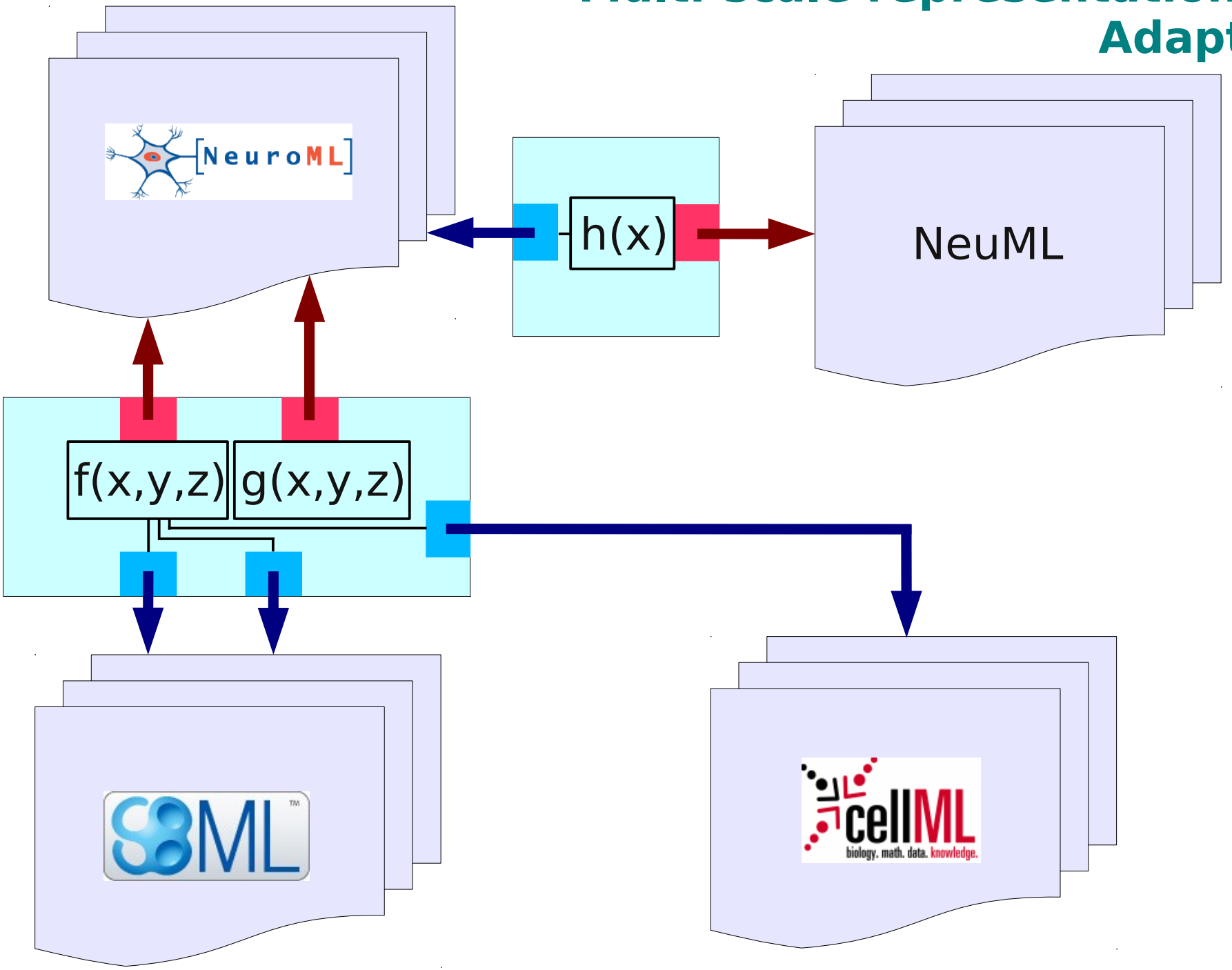
The issues to tackle are transdisciplinary



The issues to tackle are trans-disciplinary



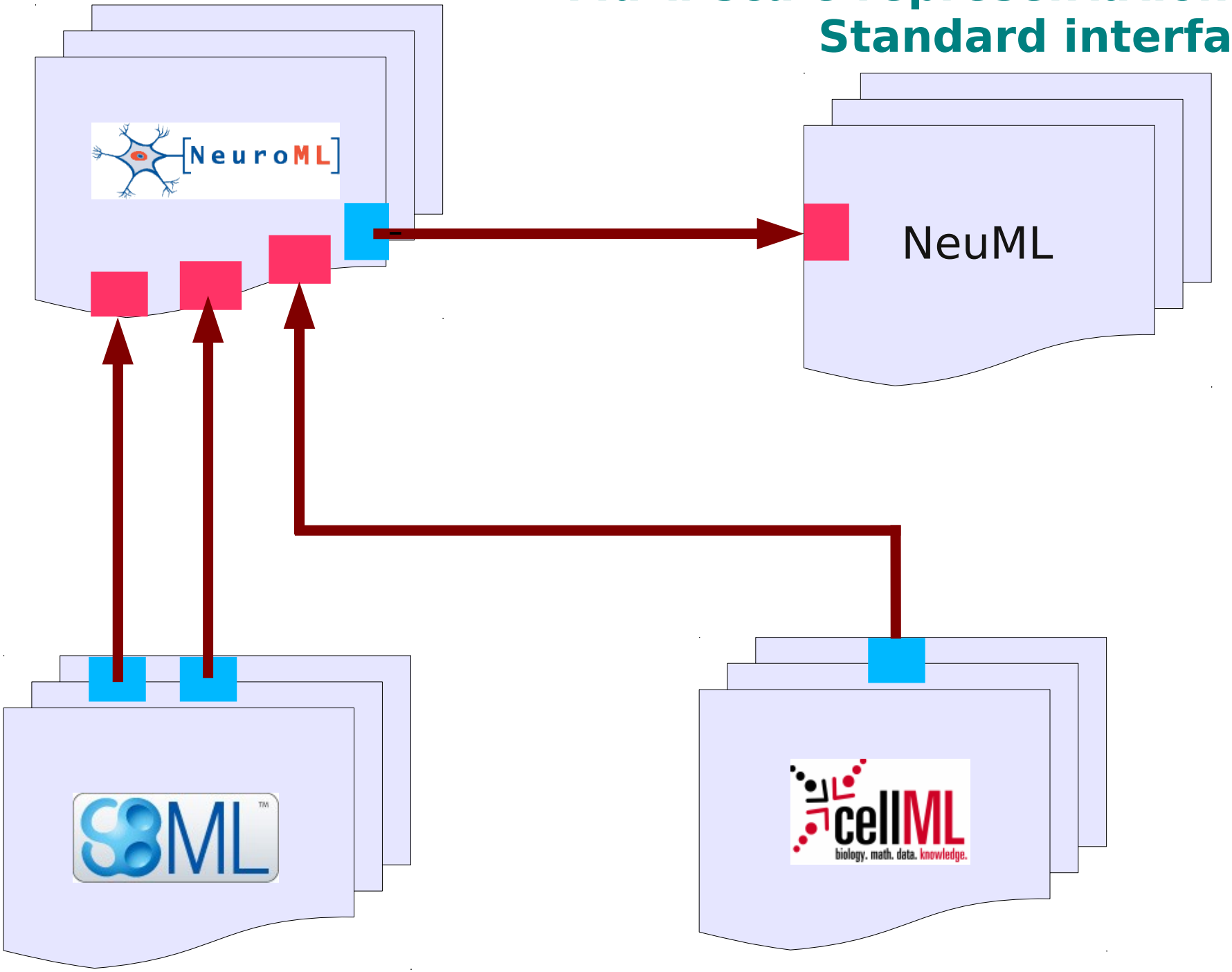
Multi-scale representation (1)
Adapters



Requirement for multi-scale representation (1)

- Able to connect any format as input and any format as output, as far as it is XML.
- Contains all the information necessary for building the model. The components do not know about it.
- The bridges cannot be reused. They are specific of a given set of components (because of the pointers).
- The components can be reused.

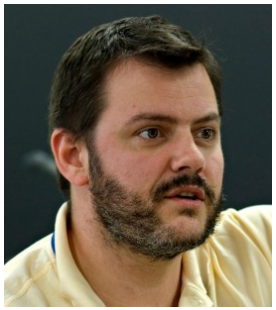
Multi-scale representation (2)
Standard interfaces



Requirement for multi-scale representation (2)

- Agreement on data-types and units
- The components contain the addressing
- The components with input terminals cannot be readily reused

CompNeur group



Nicolas Le Novère
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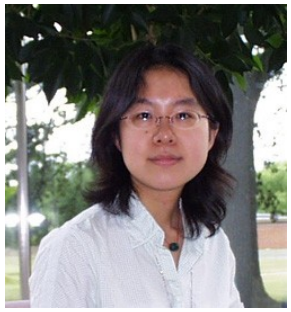
Camille Laibe,
project coordinator

BioModels.net team

Ron Henkel
visitor

Melanie Stefan, postdoc



Lu Li, predoc

Stuart Edelstein, visitor

Benedetta Baldi, predoc

Sarala Wimalaratne
ontologist

Lukas Endler
curator

Viji Chelliah,
curator

Sarah Keating
developer

Michele Mattioni, predoc

Christine Hoyer, predoc

Chen Li, developer

Nick Juty, curator

Nicolas Rodriguez
developer

Marine Dumousseau
developer