Models For All

Standards for Describing the Whole Life-Cycle of Modeling in Life Sciences

Nicolas Le Novère, EMBL-EBI
New way of doing biomedical research

Needs for cooperation and standardisation

Needs for interplay between models and reality tests

Needs for systems thinking and integration of heterogeneous knowledge
Many complementary modelling approaches

- Biochemistry
- Neurobiology
- Physiology
- Developmental biology, plant biology
- Process Descriptions (ODE, Monte-Carlo)
- State-Transitions, cable Approximation (PDE)
- Variable description (ODE, PDE)
- Cell automata
- Multi-agents
- PK/PD, statistical models
- Pharmacometrics
Computational modelling left the niches


- **Pharmacometrics models** Labrijn et al. Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo. *Nat Biotechnol* 2009

- **Physiological models** Noble. Modeling the heart from genes to cells to the whole organ. *Science* 2002; Izhikevich and Edelman. Large-scale model of mammalian thalamocortical systems. *PNAS* 2008

BioModels Database - A Database of Annotated Published Models

BioModels Database is a repository of peer-reviewed, published, computational models. These mathematical models are primarily from the field of systems biology, but more generally are those of biological interest. This resource allows biologists to store, search and retrieve published mathematical models. In addition, models in the database can be used to generate sub-models, can be simulated online, and can be converted between different representational formats. This resource also features programmatic access via Web Services.

All unmodified models in the database are available freely for use and distribution, to all users. This resource is developed and maintained by the BioModels.net initiative. More information about BioModels Database can be found in the Frequently Asked Questions.

Browse models

- Curated models (326)
- Browse models
- Non-curated models (373)

Simulate in JWS Online

Submit a model

Links

- Main instance at EMBL-EBI, UK
- Mirror at Caltech, USA
- Project on SourceForge
- Web Services

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

June, 2011
Two complementary synthetic genetic counters in E.coli that can count up to three induction events: the first, a riboregulated transcriptional cascade, and the second, a recombinase-based cascade of memory units, has been reported. Read more...

15 April 2011 Nineteenth Release!
Download All Models Under SBML Format

4 February 2011 JUMMP: JUst a Model Management Platform
To provide the worldwide community with a modern tool for the collaborative creation and sharing of models in an efficient and secured way, the Jurgen Eils and Nicolas Le Novère groups are announcing the JUMMP project. It is planned that JUMMP will be used as the software infrastructure running BioModels Database. Read more...

17 November 2010 New availability of the Models of the Month
Models of the Month are now linked from BioMed Central's Systems Biology Gateway

BioModels Database growth since its creation

Computational models on the rise

models

relationships

Apr 2005

Jun 2011

BioModels Database growth since its creation
A language to describe computational models in biology

<table>
<thead>
<tr>
<th>Data-models</th>
<th>Model descriptions</th>
</tr>
</thead>
</table>

[Caltech 2000]
What can we encode in SBML (core)?

Why the Extensible Markup Language (XML)?

- **HTML**
  A `<strong>`strong word`</strong>` and an `<a href="http://www.w3.org/">hyperlink</a>`

- **SVG**
  `<circle r="100" fill="red" stroke="blue" stroke-width="10" />`

- **MathML**
  `<apply>`
    `<int/>`
    `<bvar><ci> x </ci></bvar>`
    `<lowlimit><cn> 0 </cn></lowlimit>`
    `<uplimit><ci> a </ci></uplimit>`
    `<apply><ci> f </ci><ci> x </ci></apply>`
  `</apply>`

- **Excel**
  `<row r="1">
    <c r="A1"><v>1</v></c>
    <c r="B1">C11*E11</c>
    <v>102</v>
  </row>`

A strong word and an hyperlink

\[
\int_0^a f(x) \, dx
\]
Why the Extensible Markup Language (XML)?

- Easy to define and validate
  - Rapid prototyping, processing tools can be generated and thrown away
- Existence of a very large toolkit
  - Libraries in every programming languages
  - A very large number of description formats in life sciences are in XML
- Associated technologies
  - Definition: XML Schema, Schematron (themselves XML)
  - Conversion: XSLT (using XSL in XML)
  - Linking: XPath and XQuery
Global structure of a SBML file

```xml
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="3" version="1">
  <xmlns="http://www.sbml.org/sbml/level3/version1/core">
    <model>
      <listOfFunctionDefinitions/>
      <listOfUnitDefinitions/>
      <listOfCompartments/>
      <listOfSpecies/>
      <listOfParameters/>
      <listOfInitialAssignments/>
      <listOfRules/>
      <listOfConstraints/>
      <listOfReactions/>
      <listOfEvents/>
    </model>
  </sbml>
```
A very simple SBML file (A → B)

```xml
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4" level="2" version="4">
  <model name="Simple Model">
    <listOfCompartments>
      <compartment id="cell" size="1" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="1"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="k1" value="0.1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction id="r1" reversible="false">
        <listOfReactants>
          <speciesReference species="A"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci> cell </ci>
              <ci> k1 </ci>
              <ci> A </ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```
A very simple SBML file (A → B)

```xml
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4" level="2" version="4">
  <model name="Simple Model">
    <listOfCompartments>
      <compartment id="cell" size="1" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="1"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="k1" value="0.1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction id="r1" reversible="false">
        <listOfReactants>
          <speciesReference species="A"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci> cell </ci>
              <ci> k1 </ci>
              <ci> A </ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```
A more realistic example ...

```xml
<species id="A" name="a-tubulin" compartment="cell" initialAmount="1000" substanceUnits="item" hasOnlySubstanceUnits="true" boundaryCondition="true" constant="false" charge="0" metaid="PX" sboTerm="SB0:0000245">
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of a microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF
      xmlns:bqi="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">
        <bqi:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P68370"/>
            <rdf:li rdf:resource="urn:miriam:obo.go:G0%3A0045298"/>
          </rdf:Bag>
        </bqi:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```
A more realistic example ...

```xml
<species
  id="A"
  name="a-tubulin"
  compartment="cell"
  initialAmount="1000"
  substanceUnits="item"
  hasOnlySubstanceUnits="true"
  boundaryCondition="true"
  constant="false"
  charge="0"
  metaid="PX"
  sboTerm="SBO:0000245"> biological semantics: macromolecule
</species>
```

**XHTML**

```xml
<body xmlns="http://www.w3.org/1999/xhtml">
  <p>One of the components of a microtubule</p>
</body>
```

**RDF**

```xml
<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:G0%3A0045298"/>
      </rdf:Bag>
    </bqbiol:is>
  </rdf:Description>
</rdf:RDF>
```
### Difference between SBML L1, L2 and L3

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>- predefined functions</td>
<td>- function definitions</td>
<td>- function definitions</td>
</tr>
<tr>
<td>- proprietary infix</td>
<td>- all math in MathML</td>
<td>- all math in MathML</td>
</tr>
<tr>
<td>math notation</td>
<td>- no reserved namespaces for annotations</td>
<td>- no reserved namespaces for annotations</td>
</tr>
<tr>
<td>- reserved namespaces</td>
<td>- controlled RDF annotation</td>
<td>- controlled RDF annotation</td>
</tr>
<tr>
<td>for annotation</td>
<td>- discrete events</td>
<td>- discrete events</td>
</tr>
<tr>
<td>- no controlled</td>
<td>- monolithic</td>
<td>- modular</td>
</tr>
<tr>
<td>annotation</td>
<td>- default values</td>
<td>- no default values</td>
</tr>
<tr>
<td>- no discrete events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- monolithic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- default values</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Progressive simplification, generalisation and externalisation

~15 software  ~135 software  >220 software
SBML definition and API

- SBML syntax and semantics are very precisely defined
  - SBML specification document: Level 3 Version 1 = 167 pages, small margins
  - XML schema (L1 and L2) and Schematron (forthcoming for L3)
  - Hundreds of validation rules to check compliance
- A standard Application Programming Interface with two implementations
  - LibSBML in C and C++, with binding to C#, Java, Python, Perl, MatLab, Octave, Ruby
  - JSBML, native Java version
- Test suite of 5514 models either testing a feature or a documented error
SBML Software Guide

The following summarize all SBML-compatible systems known to us. The matrix provides an at-a-glance summary, whereas the summary provides longer descriptions of each software or project grouped by themes.

Number of software packages listed in the matrix today: 225.

Please use the survey form to notify us about additions and suggestions.

Historical trend

The following graph shows the total number of known SBML-compatible software packages each year, as counted by the SBML Team. The counts shown are for approximately the middle of each year.

(Note: the flat period in 2007 is an artifact of inadequate record keeping rather than a lull in SBML software development.)
SBML supporting tools

- Simulators
  - Discrete stochastic (25)
  - Continuous deterministic (42)
  - Spatial (4)
- Modelling and simulation environments (29)
  - Based on Mathematica (3)
  - Based on Matlab (12)
  - Based on Python/SciPy (9)
  - Based on R (3)
- Flux/metabolic analysis (16)
- Integrated framework (3)
- Libraries (3)
- Model Management, Data Integration, and Analysis (12)
- Model development tools (18)
- Model visualisation (7)
- Model Repositories, Test Suites, and Databases (16)
- Converters (7)
- Analysis and utility (12)
SBML Level 3 packages

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

???
SBML is not limited to biochemistry!

- A **species** is a pool of entities participating to a reaction, **not always** a **chemical** entity
  - It can be a pool of molecules
  - It can be a pool of cells
  - It can be a pool of organs
  - It can be a population of organisms
- **Rate Rules** can describe the temporal evolution of **any quantitative parameter**, e.g. transmembrane voltage, tumour size etc.
- **Events** can describe any discontinuous change, e.g. neurotransmitter release, repolarisation, cell division etc.

→ SBML is about process descriptions
Fernandez et al. DARPP-32 is a robust integrator of dopamine and glutamate signals


**reaction:**

\[ v_{on1} = k_{on1} \times [D] \times [CDK5] \times Vol \]
Pharmacometrics models


rate rule:
\[
\frac{dSize}{dt} = (Rate_{in} \times Effect - K_{over} \times Size) \times Size
\]

assignment rule:
\[
Effect = 1 - \frac{E_{max} - Ce}{Amt_{50} + Ce}
\]
Single-compartment neurons


rate rule:
\[ \frac{dv}{dt} = 0.04v^2 + 5 \times V + 140 - U + i \]

event:
when \( v > V_{\text{thresh}} \) then
\[ \begin{cases} v = c \\ U = U + d \end{cases} \]
Munz P et al. When zombies attack!: Mathematical modelling of an outbreak of zombie infection. in "Infectious Disease Modelling Research Progress", (2009) 133-150
### Adding the semantics to the syntax

<table>
<thead>
<tr>
<th>Model descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal requirements</td>
</tr>
<tr>
<td>Data-models</td>
</tr>
<tr>
<td>Terminologies</td>
</tr>
</tbody>
</table>

- Born in Heidelberg 2004
Models must:

- be encoded in a public machine-readable format
- be clearly linked to a single reference description
- reflect the structure of the biological processes described in the reference paper (list of reactions etc.)
- be instantiable in a simulation (possess initial conditions etc.)
- be able to reproduce the results given in the reference paper
- contain creator’s contact details
- annotation to unambiguously identify each model constituent

Why are annotations important?

Annotation of model components are essential to:

- allow efficient search strategies
- unambiguously identify model components
  - improve understanding the structure of the model
  - allow easier comparison of different models
  - ease the integration of models
- add a semantic layer to the model
  - improve understanding of the biology behind the model
  - allow conversion and reuse of the model
  - ease the integration of model and biological knowledge
MIRIAM identifiers

Data-type identifier (required)

URI

Not a URL, not a “location”!

Data-set Identifier (required)

text string

Format depends on the resource identified by the data-type

UniProt and P62158 (human calmodulin) → urn:miriam:uniprot:P62158

EC code and 1.1.1.1 (alcohol dehydrogenase) → urn:miriam:ec-code:1.1.1.1

Gene Ontology and GO:0000186 (activation of MAPKK activity) → urn:miriam:obo.go:GO%3A0000186
Qualification of annotation

model element \(\xrightarrow{\text{qualifier}}\) annotation

represents

\(\xrightarrow{\text{relationship}}\)

biological entity A \(\xrightarrow{\text{represents}}\) biological entity B
Qualification of annotation

- species MPF
  - represents
  - M-phase promoting factor
    - bqbiol:hasPart
  - represents
    - UniProt P04551
      - has a part
      - CDC2
SBML and MIRIAM cross-references

<species id="Ca_calmodulin" metaid="cacam">
  <annotation>
    <rdf:RDF
      xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
      xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
    >
      <rdf:Description rdf:about="#cacam">
        <bqbiol:hasPart>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P62158"/>
          </rdf:Bag>
        </bqbiol:hasPart>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
MIRIAM Registry are a set of online services created in support of MIRIAM, a set of guidelines for the annotation and curation of computational models.

The core of MIRIAM Registry is a catalogue of data types (namespaces corresponding to controlled vocabularies or databases), their URIs and the corresponding physical URLs or resources. Access to this data is made available via exports (XML) and Web Services (SOAP).

MIRIAM Registry is developed and maintained under the BioModels.net initiative, and are free for use by all.

Quick links

<table>
<thead>
<tr>
<th>Browse</th>
<th>Web Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>by data type name</td>
<td>services available</td>
</tr>
<tr>
<td>by tags</td>
<td>usage of the services</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Search</th>
<th>Exports</th>
</tr>
</thead>
<tbody>
<tr>
<td>generic search</td>
<td>XML</td>
</tr>
</tbody>
</table>

Registure

MIRIAM Registry is composed of four components: a database, some Web Services, a Java library and this web application.

Database

The core of the system is a MySQL database. It allows us to store the data types (which can be controlled vocabularies or databases), their URIs and the corresponding physical URLs, and other details such as documentation and resource identifier patterns.

Each entry contains a diverse set of details about the data type: official name and synonyms, root URI, pattern of identifiers, documentation, etc. Moreover, each data type can be associated with several resources (or physical locations).

Web Services

Web Services (based on Apache Axis and SOAP messages). In addition, REST-based services are currently solve model annotations, but also to generate appropriate URIs, based upon the provision of a resource name and accession number. A list of available web services, and a WSDL are provided. A browser-based online demonstration of the Web Services is also provided.
## Data type: Enzyme Nomenclature

### General Information about the data type

<table>
<thead>
<tr>
<th>Identifier</th>
<th>MIR:00000004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Enzyme Nomenclature</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Enzyme Classification</td>
</tr>
</tbody>
</table>

### URLs

<table>
<thead>
<tr>
<th>Official URN</th>
<th>urn:miriam:ec-code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deprecated</td>
<td><a href="http://www.ec-code.org/">http://www.ec-code.org/</a></td>
</tr>
<tr>
<td></td>
<td><a href="http://urn.isctec-code.org/">http://urn.isctec-code.org/</a></td>
</tr>
<tr>
<td></td>
<td><a href="http://www.ebi.ac.uk/IntEnz/">http://www.ebi.ac.uk/IntEnz/</a></td>
</tr>
</tbody>
</table>

### Information

**Definition**
The Enzyme Classification contains the recommendations of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology on the nomenclature and classification of enzyme-catalysed reactions.

**Identifier Pattern**
`^[a-zA-Z]+[\-]+[a-zA-Z]+$`

### Physical Locations

<table>
<thead>
<tr>
<th>Resource #1</th>
<th>Data Entry</th>
<th><a href="http://www.ebi.ac.uk/intenz/query?cmd=SearchEC&amp;ec=$id">http://www.ebi.ac.uk/intenz/query?cmd=SearchEC&amp;ec=$id</a> <a href="http://www.ebi.ac.uk/intenz/query?cmd=SearchEC&amp;ec=1.1.1.1">Example: 1.1.1.1</a></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Data Resource</td>
<td><a href="http://www.ebi.ac.uk/intenz/">http://www.ebi.ac.uk/intenz/</a></td>
</tr>
<tr>
<td></td>
<td>Information</td>
<td>IntEnZ (Integrated relational Enzyme database)</td>
</tr>
<tr>
<td></td>
<td>Institution</td>
<td>European Bioinformatics Institute, United Kingdom</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Information</td>
<td>KEGG Ligand Database for Enzyme Nomenclature</td>
</tr>
<tr>
<td></td>
<td>Institution</td>
<td>Kyoto University Bioinformatics Center, Japan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resource #3</th>
<th>Data Entry</th>
<th><a href="http://us.expasy.org/cgi-bin/nicezyme.pl?$id">http://us.expasy.org/cgi-bin/nicezyme.pl?$id</a> <a href="http://us.expasy.org/cgi-bin/nicezyme.pl?1.1.1.1">Example: 1.1.1.1</a></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Data Resource</td>
<td><a href="http://us.expasy.org/enzyme/">http://us.expasy.org/enzyme/</a></td>
</tr>
<tr>
<td></td>
<td>Information</td>
<td>Enzyme nomenclature database, ExPASy (Expert Protein Analysis System)</td>
</tr>
<tr>
<td></td>
<td>Institution</td>
<td>Swiss Institute of Bioinformatics, Switzerland</td>
</tr>
</tbody>
</table>

### Documentation

- [http://www.chem.gmu.ac.uk/tumb/enzyme/](http://www.chem.gmu.ac.uk/tumb/enzyme/)
- [http://ssr.ebi.ac.uk/ssrbin/cgi-bin/wgetz?-view+MedlineFull+[medline-PMD:10812475](http://ssr.ebi.ac.uk/ssrbin/cgi-bin/wgetz?-view+MedlineFull+[medline-PMD:10812475)]

### Miscellaneous

- **Date of creation**: 2006-08-14 19:38:06 GMT
- **Date of last modification**: 2009-05-08 14:59:31 GMT
General information about the resource: **Enzyme nomenclature database, ExPASy (Expert Protein Analysis System)**

(associated with the data type: **Enzyme Nomenclature**)

### Health statistics

<table>
<thead>
<tr>
<th>Last known state</th>
<th>up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last check</td>
<td>2010-12-09 06:31:32</td>
</tr>
<tr>
<td>Uptime ratio</td>
<td>99% (651 checks)</td>
</tr>
<tr>
<td>Downtime ratio</td>
<td>0% (4 checks)</td>
</tr>
<tr>
<td>Unknown ratio</td>
<td>0% (0 checks)</td>
</tr>
<tr>
<td>URL used</td>
<td><a href="http://us.expasy.org/cgi-bin/nicezyme.pl?1.1.1">http://us.expasy.org/cgi-bin/nicezyme.pl?1.1.1</a></td>
</tr>
</tbody>
</table>

### Health history

Full record of the health checks performed on this resource.

#### 2010

- **January**
- **February**
- **March**
- **April**
- **May**
- **June**
- **July**
- **August**
- **September**
- **October**
- **November**
- **December**

#### 2009

- **January**
- **February**
- **March**
- **April**
- **May**
- **June**
- **July**
- **August**
- **September**
Essential activator

<listOfModifiers>
  <modifierSpeciesReference sboTerm="SBO:0000461" species="Y"/>
</listOfModifiers>

http://www.ebi.ac.uk/sbo/
Direct model re-use: e.g. EGFR signalling and glycolysis

- Schoeberl et al. 2002 (BIOMD0000000019)
- Singh et al. 2006 (BIOMD0000000151)
- Ung et al. 2008 (BIOMD0000000205)
- Hornberg et al. 2005 (MODEL0848279215)
- Huang et al. 2010
- Teusink et al. 2000 (BIOMD0000000064)
- Pritchard et al. 2002 (BIOMD0000000172)
- Conant et al. 2007 (BIOMD0000000176, BIOMD0000000177)
Standard formats generate new research

  - MODEL0072364382: 2152 species, 1857 reactions
    - stoichiometric map, no concentrations, no kinetics

  - MODEL1001200000: 1748 species, 1059 reactions
    - Concentrations and flux from BioModels Database
    - Constraint-based model and simplified linlog kinetics

  - MODEL1012110000: 2657 species, 1865 reactions

  - MODEL1012110001
    - Workflows using experimental kinetic information database (SABIO-RK) plus metabolomics and proteomics database
    - Full quantitative chemical kinetics descriptions
Clustering models (and data) based on metadata

Schulz et al. Mol Syst Biol, in the press
## Ranking and retrieval of models

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Schulz et al. *Mol Syst Biol, in the press*
The interface with all biologists

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<th>Model descriptions</th>
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Born in Tokyo 2005
What is SBGN?

- An unambiguous way of graphically describing and interpreting biochemical and cellular events
- Limited amount of symbols
  Re-use existing symbols
  - Smooth learning curve
- Can represent logical or mechanistic models, biochemical pathways, at different levels of granularity
- Detailed technical specification, precise data-models and growing software support
- Developed over four years by a diverse community, including biologists, modellers, computer scientists etc.

Graph trinity: three languages in one notation

- Process Descriptions
  - Unambiguous
  - Mechanistic
  - Sequential
  - Combinatorial explosion

- Entity Relationships
  - Unambiguous
  - Mechanistic
  - Non-sequential
  - Independence of relationships

- Activity Flows
  - Ambiguous
  - Conceptual
  - Sequential
Process Descriptions are bipartite graphs

- **PN** (process node)
- **EPN** (entity pool node)

Connectors:
- "continuants", what is
- "occurants", what happens
Metabolic network in Process Description Language
If A exists, the assignment of the value P to the state variable T of B is increased.

(A stimulates the phosphorylation of B on the threonine)
If A exists, the assignment of the value P to the state variable T of B is increased.

If P is assigned to the state variable T of B, the assignment of the value P to the state variable S of B is decreased.
ER map of calcium-regulated synaptic plasticity

increases synaptic weight

decreases synaptic weight
Example of Activity Flow map
Linking SBGN maps to external information

catalytic processes
transport processes
contractile proteins
Linking SBGN maps to external information
Linking SBGN maps to external information
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

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\(^1\). 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
Reproduction of published simulation results

Edelstein et al 1996 (BIOMD0000000002)

Huang & Ferrell (BIOMD0000000009)

Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)

Bornheimer et al 2004 (BIOMD0000000086)
## Description of simulations and analyses

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<td><img src="image6" alt="KISAO" /></td>
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Description of model simulation and analysis

Minimum Information About a Simulation Experiment (MIASE) common set of information a modeller needs to provide in order to enable the execution and reproduction of a numerical simulation experiment, derived from a given set of quantitative models


Simulation Experiment Description Markup Language (SED-ML) XML-based format for encoding simulation experiments, following the requirements defined in the MIASE guidelines


Kinetic Simulation Algorithm Ontology (KiSAO) covers the most important simulation algorithms and simulation methods used to simulate biological kinetic models and puts those algorithms and methods into relation

Courtot et al submitted
General structure of SED-ML

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Description of models

Any model description in XML such as SBML, CellML, NeuroML, VCML, NineML etc.
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Retrieving models

MIRIAM Resources

Data type: BioModels Database

General Information about the data type

Identifier
 Name
 Synonym

Information

Definition
 BioModels Database is a data repository of models of biological interests.

Identifier Pattern

Retrieving models

BIOMD0000000127 - Izhikevich2003_SpikingNeuron

SBML formats Other formats (auto-generated) Actions

Submit Model Community

Model

Overview

Math

Physical entities

Parameters

Curation

Reference Publication

Publication ID: 18244892


Simple model of spiking neurons.

Izhikevich EM

The Neurosciences Inst., San Diego, CA, USA

Notes

This model is according to the paper Simple Model of Spiking Neurons in this paper, a simple spiking model is presented that is as biologically plausible as the Hodgkin-Huxley model yet as computationally efficient as the Morris-Lecar model. Figure3R1H.CM.F1. The LTS have been simulated by MathSBML.

-4.8-10

-4

-65-3

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-50-6.42

-0.1b=0.26

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0.8

This model originates from BioModels Database: A Database of Annotated Published Models. It is copyright (c) 2005-2010 The BioModels Team.

For more information see the terms of use.
Modifying models

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    source="urn:miriam:biomodels.db:BIOMD0000000127" />
  <model id="model2"
    name="chattering"
    source="model1">
    <listOfChanges>
      <changeAttribute target="/sbml/model/listOfParameters/parameter[@id='c']/@value" newValue="-50"/>
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    </listOfChanges>
  </model>
</listOfModels>
```
Simulation approach

<listOfSimulations>
  <uniformTimeCourse id="simulation1"
    initialTime="0"
    outputStartTime="0"
    outputEndTime="140"
    numberOfPoints="1000">
    <algorithm kisaoID="KiSAO:0000030"/>
  </uniformTimeCourse>
</listOfSimulations>
Simulation approach

```xml
<listOfSimulations>
  <uniformTimeCourse id="simulation1"
    initialTime="0"
    outputStartTime="0"
    outputEndTime="140"
    number_of_points="1000"
  >
    <algorithm kisaoID="KiSAO:0000030"/>
  </uniformTimeCourse>
</listOfSimulations>
```
## Characterising dynamical behaviours

<table>
<thead>
<tr>
<th></th>
<th>Model descriptions</th>
<th>Simulations and analysis</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimal requirements</strong></td>
<td><img src="MIRIAM.png" alt="MIRIAM" /></td>
<td><img src="MIASE.png" alt="MIASE" /></td>
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<tr>
<td><strong>Data-models</strong></td>
<td><img src="SBML.png" alt="SBML" /></td>
<td><img src="SEDML.png" alt="SEDML" /></td>
<td>SBRML</td>
</tr>
<tr>
<td><strong>Terminologies</strong></td>
<td><img src="SSO.png" alt="SSO" /></td>
<td><img src="KISAO.png" alt="KISAO" /></td>
<td></td>
</tr>
<tr>
<td>Is the matrix of standards complete?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
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<tr>
<td>Terminologies</td>
<td><img src="image" alt="SBGN" /></td>
<td><img src="image" alt="KISAO" /></td>
<td><img src="image" alt="TEDDY" /></td>
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<tr>
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<td>Model descriptions</td>
<td>Simulations and analysis</td>
<td>Numerical results</td>
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<tr>
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<td>![S80]</td>
<td>![KISAO]</td>
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</table>

Is the matrix of standards complete?
Covering the entire model life-cycle

<table>
<thead>
<tr>
<th>Model generation</th>
<th>Model structure</th>
<th>Parametrisation</th>
<th>Simulations and analysis</th>
<th>Numerical results</th>
</tr>
</thead>
<tbody>
<tr>
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<td>SBRML</td>
<td>?</td>
<td>SEDML</td>
<td>SBRML</td>
</tr>
</tbody>
</table>
Disentangling the level of discourse

Graphical representation

Biological semantics

Initial conditions (numbers)

Model semantics (structure)
Parallel and redundant efforts

- Neurobiology
- Systems Biology
- Pharmacometrics
- Physiology
- Developmental biology, plant biology
- BioPAX
- NeuroML
- NineML
- FieldML
- ddmore
- Drug Disease Model Resources
What if the world-wide web was built like this?

- leisure
- art and design
- business
- literacy
- natural sciences
The correct way to do it

Personal info: vCard
Presentation: CSS
Semantics: RDF
Graphics: SVG
Display: HTML
Existing standards interoperability

- SEDML
- NeuroML
- SBML
- MIRIAM
- BioPAX
- SBO
- SGN
Overarching standardisation structure

The “WorldWide Web consortium” of modelling in biology
http://co.mbine.org/

- **HARMONY 2011**
  - 18 to 22 April 2011, New-York
- **COMBINE 2011**
  - 3 to 7 September 2011, Heidelberg
  - http://co.mbine.org/events/COMBINE_2011
- **Standard Operating Procedures**
  - Technical requirements
  - Governance
- **Single voice**
  - Discussions with Industry
  - Financial support
Where to find more information?

Communities

http://biopax.org/
http://sbgn.org/
http://sbml.org/
http://sed-ml.org/
http://biomodels.net/
http://biomodels.net/kisao
http://biomodels.net/sbo
http://biomodels.net/teddy
http://biomodels.net/miase
http://biomodels.net/miriam

Coordination

http://combine.org/
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Visionary: Hiroaki Kitano

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SBGN editors: Emek Demir, Nicolas Le Novère, Huaiyu Mi, Stuart Moodie, Falk Schreiber, Anatoly Sorokin, Alice Villeger

SED-ML editors: Richard Adams, Franck Bergmann, Nicolas Le Novère, Andrew Miller, David Nickerson, Dagmar Waltemath

Metadata: Mélanie Courtot, Nick Juty, Camille Laibe, Anna Zhukova

The whole community of Computational Systems Biology

The EBI group Computational Systems Neurobiology

NIGMS  BBSRC  EMBL  ELIXIR