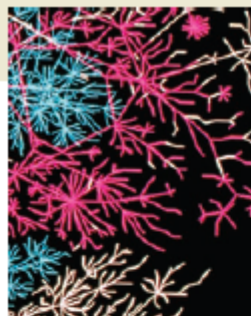


The Minimum Information About a Simulation Experiment

Nicolas Le Novère, EMBL-EBI



_computational
BIOLOGY

PERSPECTIVE

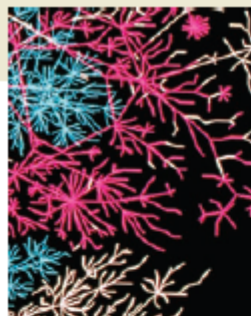
Minimum information requested in the annotation of biochemical models (MIRIAM)

Nicolas Le Novère^{1,15}, Andrew Finney^{2,15}, Michael Hucka³, Upinder S Bhalla⁴, Fabien Campagne⁵, Julio Collado-Vides⁶, Edmund J Crampin⁷, Matt Halstead⁷, Edda Klipp⁸, Pedro Mendes⁹, Poul Nielsen⁷, Herbert Sauro¹⁰, Bruce Shapiro¹¹, Jacky L Snoep¹², Hugh D Spence¹³ & Barry L Wanner¹⁴

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





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Minimum biochem

Nicolas Le Novère
Julio Collado-Vidal
Herbert Sauro^{10,11}

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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

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During the genome era we have witnessed a fast 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



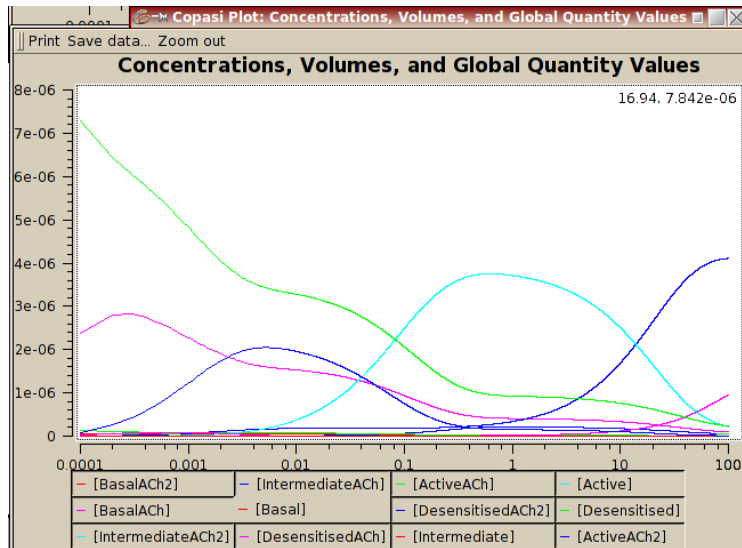
- A model is a mathematical description of the components of a system, their relationships, and the evolution of both.
 - ordinary differential equations (system evolution) $dX/dt = f(X)$
 - partial differential equation (system description) $\nabla X = g(X)$
 - algebraic equations (conservation laws) $h(X) = 0$
 - probability distributions $PX = i(X)$
 - master equation $dPX/dt = j(PX)$
 - cell automata/finite elements
 - ...



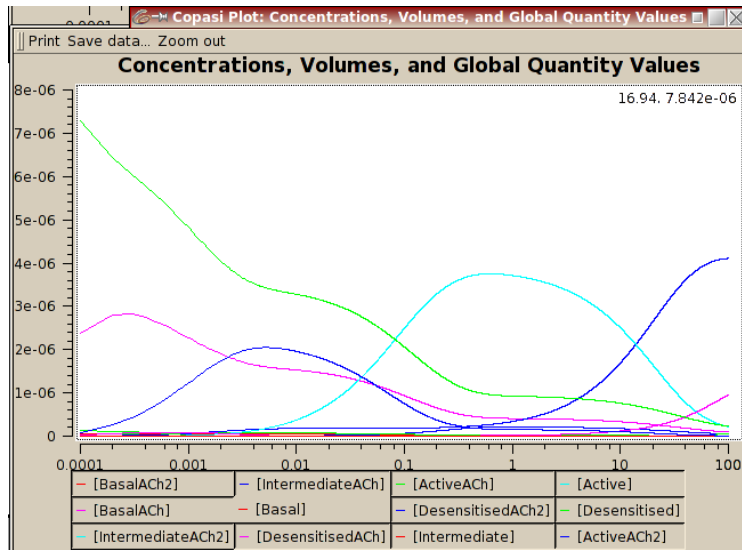
- A simulation is the instantiation of a model over time, using a given algorithmic approach, and a particular software: A model can beget simulations giving different results!
 - Logical (boolean or discrete) approach
 - Deterministic approach
 - Stochastic approach
 - Fixed timesteps
 - Adaptative timesteps
 - ...
- Plus ... range of simulations
 - parameter scan
 - parameter search/optimisation
 - phase-plane analysis
 - bifurcation analysis
 - ...



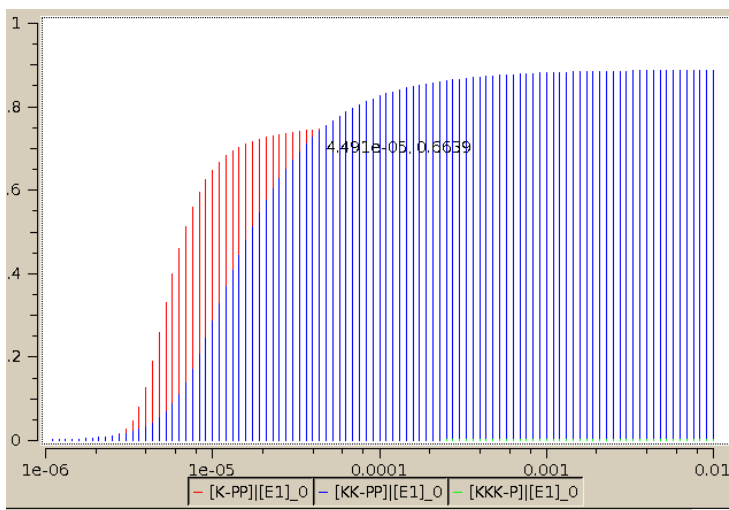
Edelstein et al 1996 (BIOMD0000000002)



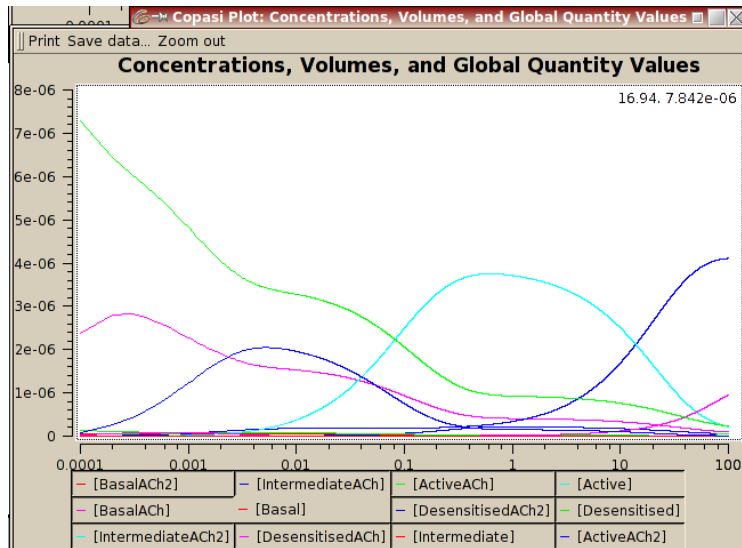
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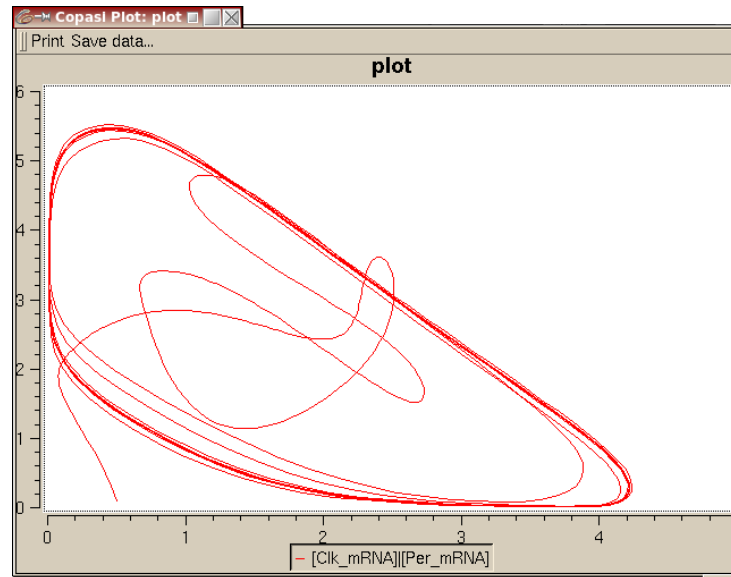
Huang & Ferrell (BIOMD0000000009)



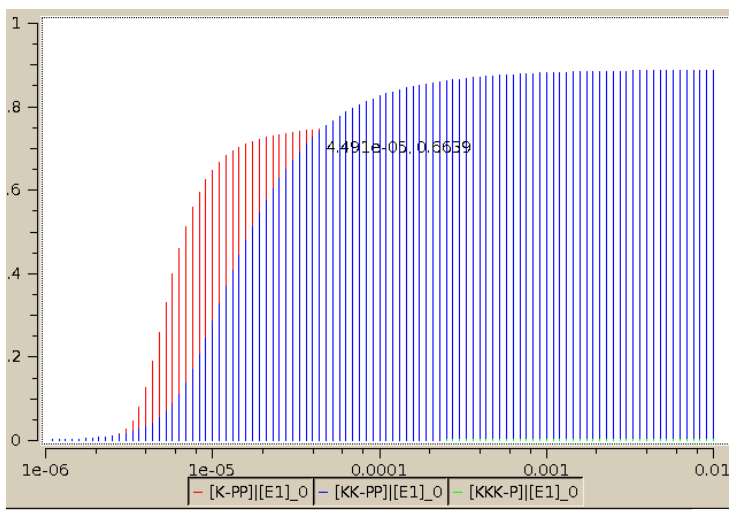
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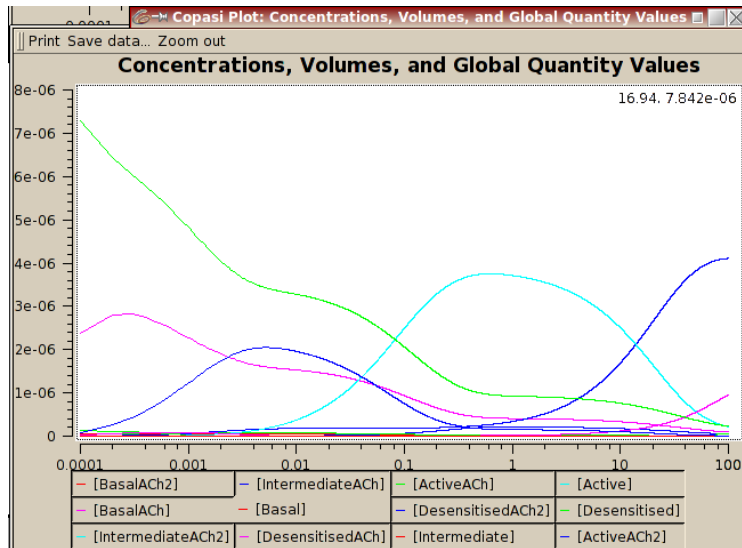
Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)



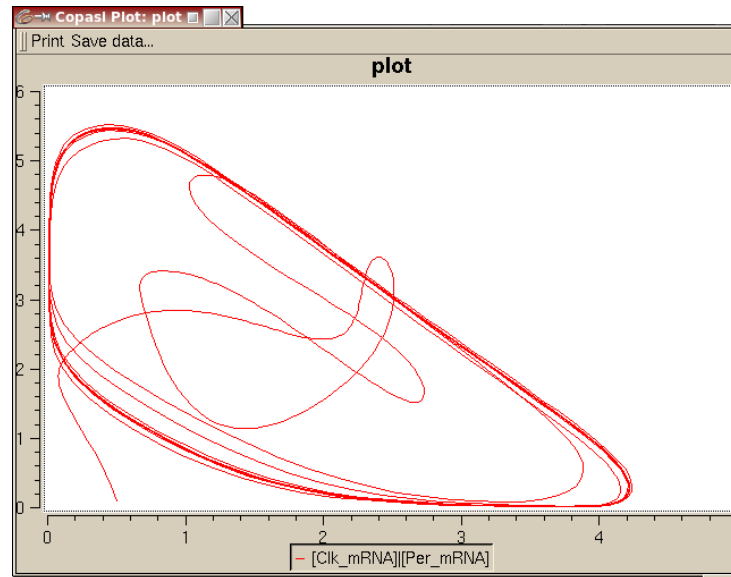
Huang & Ferrell (BIOMD0000000009)



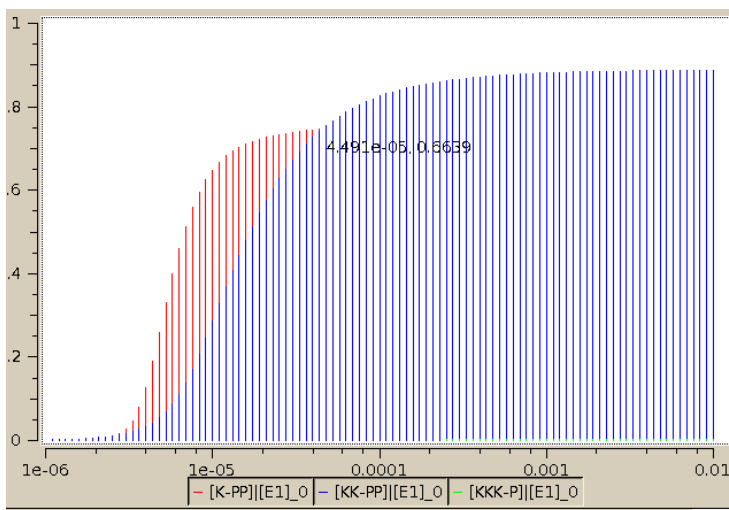
Edelstein et al 1996 (BIOMD0000000002)



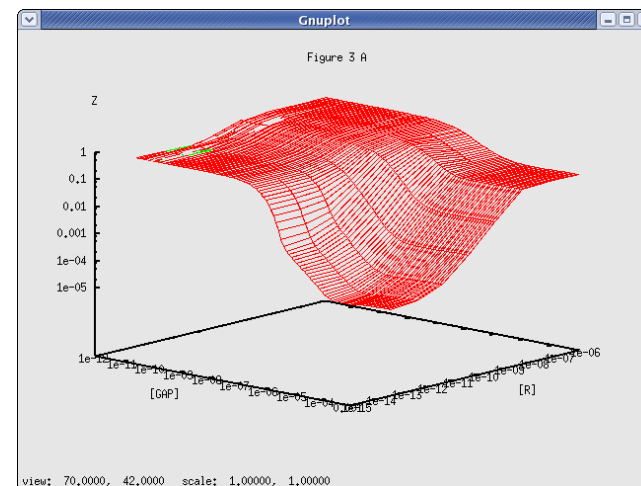
Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)



Huang & Ferrell (BIOMD0000000009)



Bornheimer et al 2004 (BIOMD0000000086)



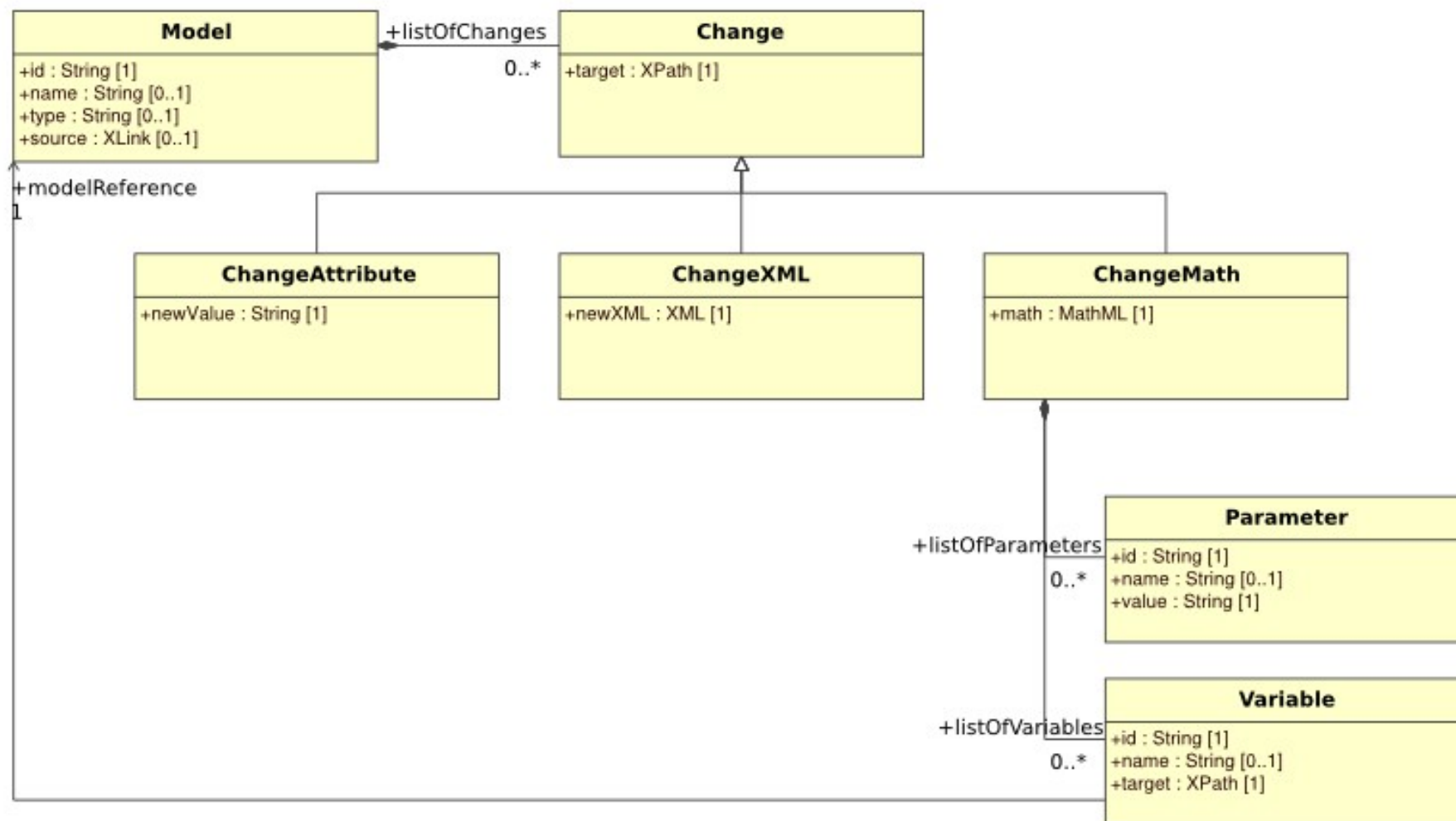
Minimum Information About a Simulation Experiment (MIASE)

<https://sourceforge.net/projects/miase>

MIASE aims at describing the information needed to run and repeat a numerical simulation experiment derived from a given quantitative model. The project is divided into three parts:

- MIASE - The list of requested information to repeat a simulation result
 - What base model to use & which modifications to apply
 - What simulation task to run on those models (algorithms, see KiSAO; simulation parameters)
 - How to post-process the numerical results and to present them
- KiSAO - Kinetic Simulation Algorithm Ontology
 - Classification of simulation algorithms & methods
 - Definition, literature references
 - Relations between different simulation algorithms & methods
- The Simulation Experiment Description Markup Language (SED-ML)
 - Formal encoding of a subset of MIASE guidelines





```
<?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">
        </changeAttribute>
      </listOfChanges>
    </model>
  </listOfModels>
```



```
<?xml version="1.0" encoding="utf-8"?>
<sedML version="1.0" xmlns="http://www.mhase.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">
        </changeAttribute>
      </listOfChanges>
    </model>
  </listOfModels>
```

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



```
<?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>
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        </changeAttribute>
      </listOfChanges>
    </model>
  </listOfModels>
```



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BIOMD0000000021 - Leloup1999_CircClock

<

SBML L2 V1

Other formats

Actions

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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 drosophila

Leloup JC, Goldbeter A.

Unite de Chronobiologie Theorique, Faculte des Sciences, Universite Libre de Bruxelles, Campus Plaine, C.P. 231, 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

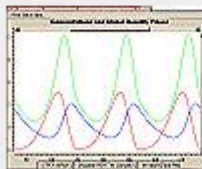
Creation Date: 2005-06-29T10:27:52+00:00

Creators: [Nicolas Le Novère](#)
[Bruce Shapiro](#)

set #1 bqbiol:is [Taxonomy Drosophila melanogaster](#)
[KEGG Pathway dme04710](#)

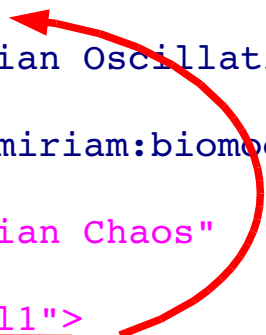
set #2 bqbiol:isVersionOf [Gene Ontology circadian rhythm](#)

Curation Result:



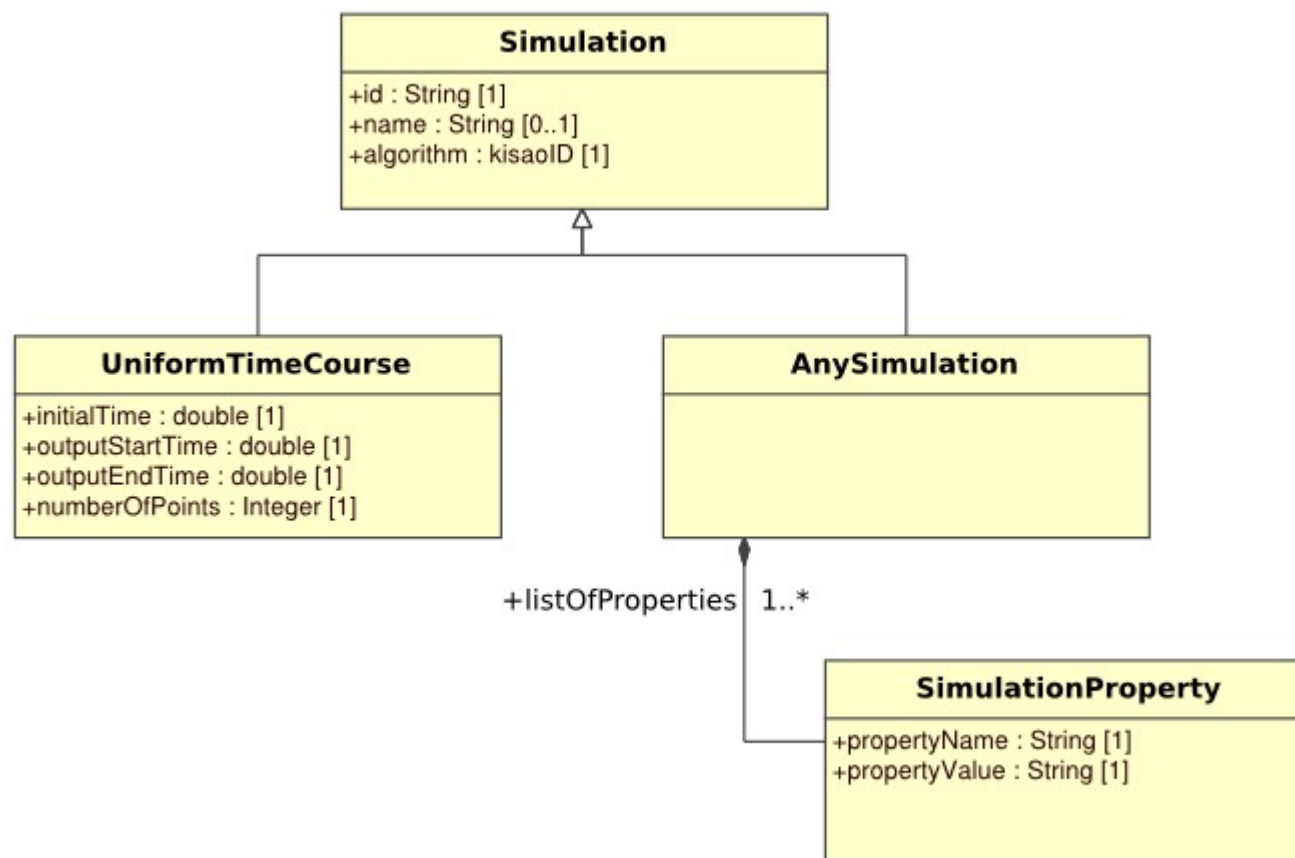
Notes

```
<?xml version="1.0" encoding="utf-8"?>
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  <notes>Changing a system from oscillation to chaos</notes>
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        </changeAttribute>
      </listOfChanges>
    </model>
  </listOfModels>
```





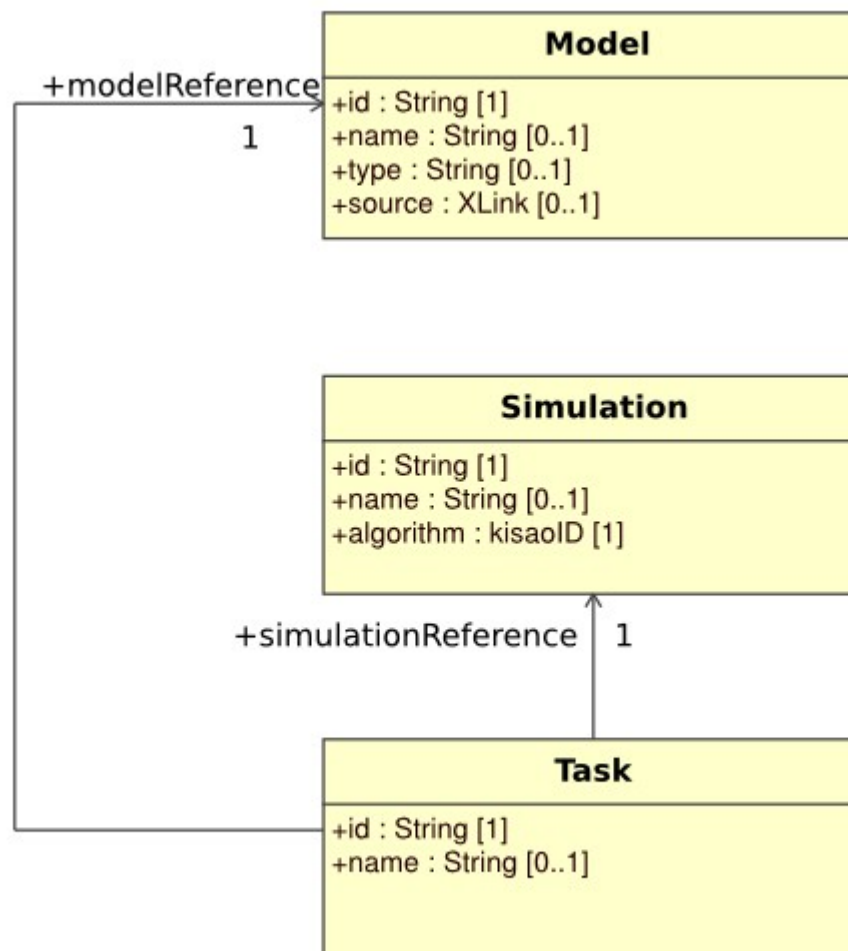
```
<listOfSimulations>  
  <uniformTimeCourse id="simulation1"  
    algorithm="KiSAO:0000071"  
    initialTime="0"  
    outputStartTime="50"  
    outputEndTime="1000"  
    numberOfPoints="1000" />  
</listOfSimulations>
```



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

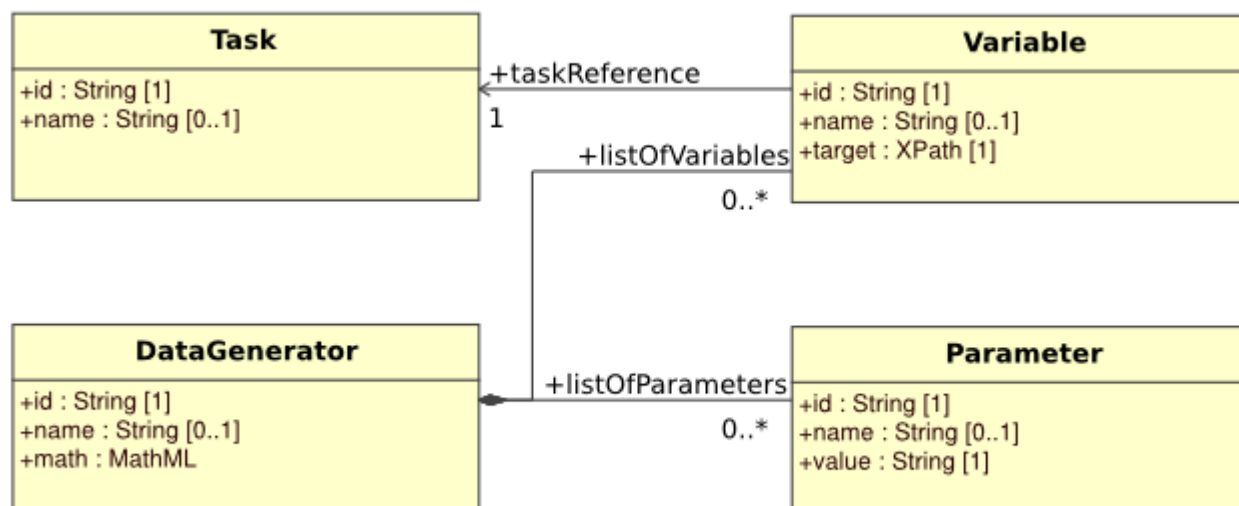
The screenshot displays the KiSAO web interface for the term 'Livermore solver for ordinary differential equations' (ID: KISA0:0000071). The interface is divided into several sections:

- Header:** Shows the ID 'KISA0:0000071' and the namespace 'KISA0'.
- Term name:** 'Livermore solver for ordinary differential equations'.
- Definition *:** Contains a text description of the LSODE solver and its references. The text describes LSODE as an explicit ODE solver based on the GEAR and GEARB packages, solving systems given explicitly as $dy/dt = f(t, y)$. It references Hindmarsh AC. LSODE and LSODI, two new initial value ordinary differential equation solvers. SIGNUM Newsletter, Volume 15 (4), pages 10-11 (1980). Radhakrishnan K, Hindmarsh AC. Description and Use of LSODE, the Livermore Solver for Ordinary Differential Equations. Lawrence Livermore National Laboratory Report, Vol. UCRL-ID-113855 (1993).
- Dbxrefs:** Lists database cross-references, including 'dk:16NOV2007' and 'doi:1218052.12180'.
- Synonyms *:** Shows a list of synonyms, including 'LSODE'. A message prompts the user to 'Select a synonym from the list to edit it, or press add to create a new synonym'. Buttons for 'Add' and 'Del' are present.
- DAG Viewer:** A hierarchical diagram showing the relationships between simulation algorithms. The hierarchy starts with 'kinetic simulation algorithm' and branches into various solvers, with 'Livermore solver for ordinary differential equations' highlighted.
- Commit:** A button at the bottom to save changes.



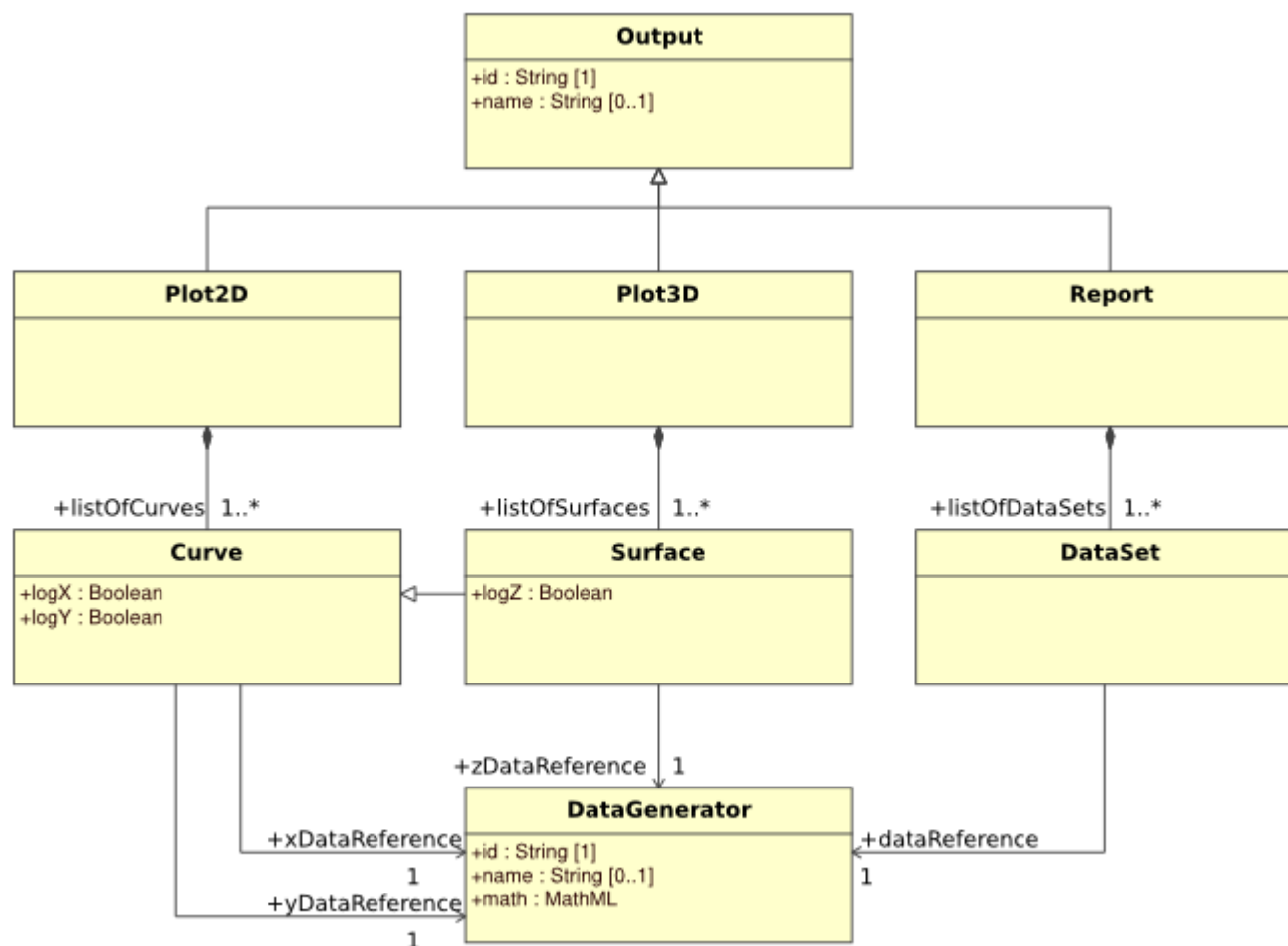
```
<listOfTasks>
  <task id="task1"
        name="Baseline"
        modelReference="model1"
        simulationReference="simulation1">
  </task>
  <task id="task2"
        name="Modified parameters"
        modelReference="model2"
        simulationReference="simulation1">
  </task>
</listOfTasks>
```





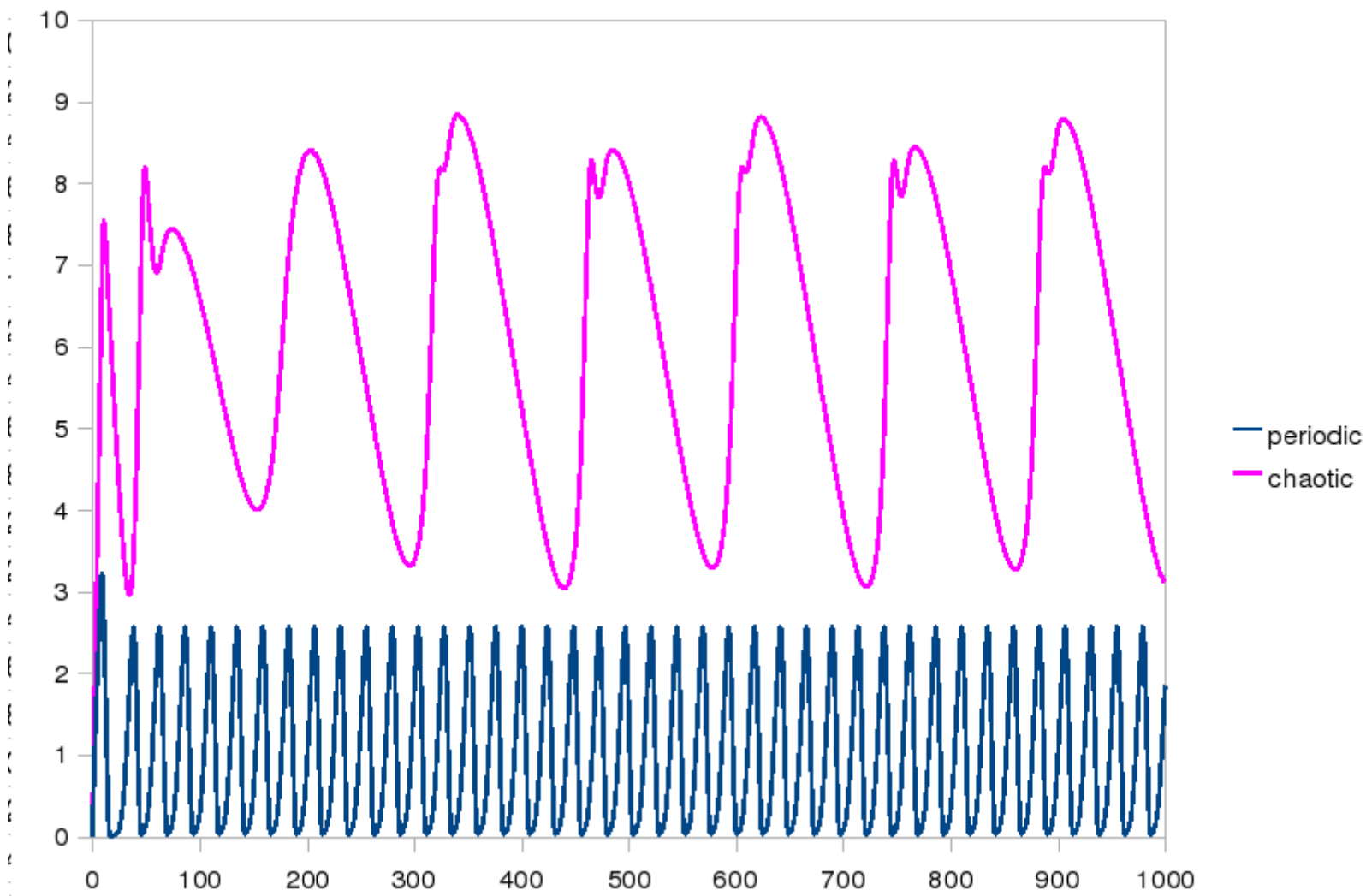
```
<listOfDataGenerators>
  <dataGenerator id="time" name="Time">
    <mathExpression>
      <math>
        <apply>
          <plus />
          <csymbol encoding="text"
            definitionURL="http://www.sbml.org/sbml/symbols/time">time
          </csymbol>
        </apply>
      </math>
    </mathExpression>
  </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>
```





```
<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>
```





Minimal
requirements



?

implements

Data-model



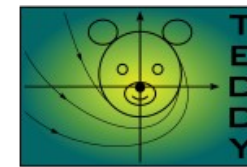
SED-ML

SBRML



Makes
sense of

Ontology





- Dagmar Köhn

- Frank Bergman (SBW)
- Ion Moraru (VCell)
- Henning Schmidt (SBToolbox)
- Sven Sahle (COPASI)
- Fedo Kolpakov (BioUML)
- ...

