



David Nickerson  
CellML Workshop 2012

# Reproducible simulation experiments with SED-ML

13.03.2012

Dagmar Waltemath



SYSTEMS BIOLOGY  
BIOINFORMATICS  
ROSTOCK

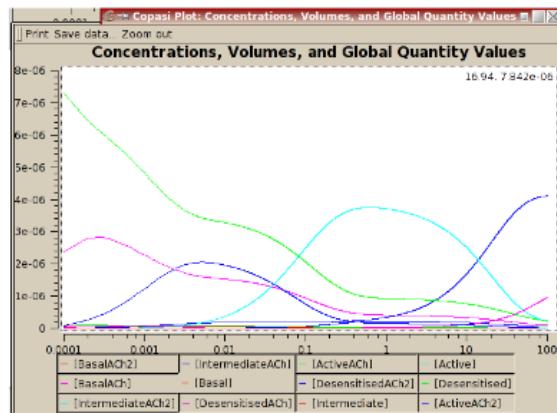
Universität  
Rostock



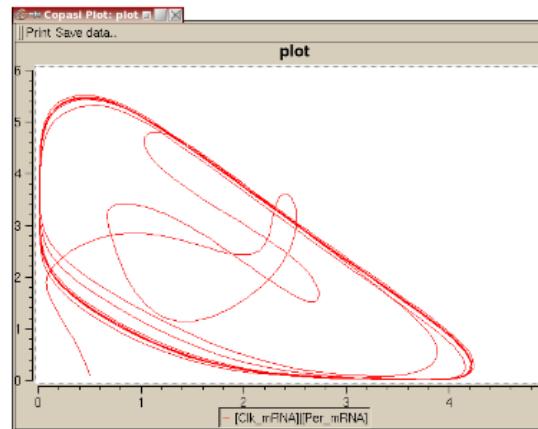
Traditio et Innovatio

# The necessity for reproducible science

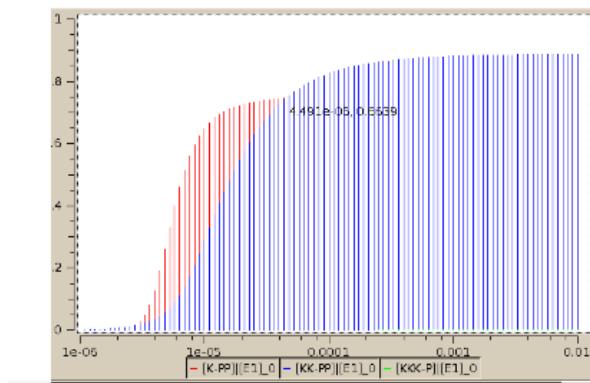
Edelstein et al 1996 (BIOMD0000000002)



Ueda, Hagiwara, Kitanol 2001 (BIOMD0000000022)



Huang & Ferrell (BIOMD0000000009)



Bornheimer et al 2004 (BIOMD0000000086)

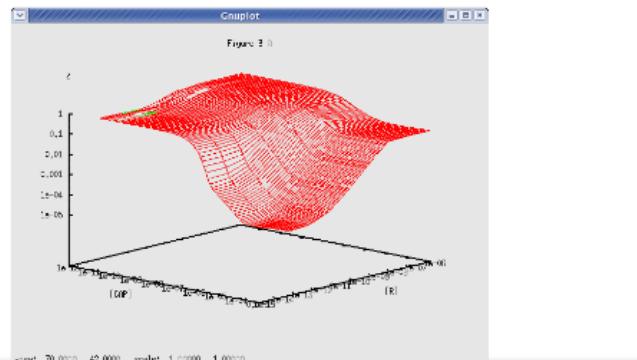
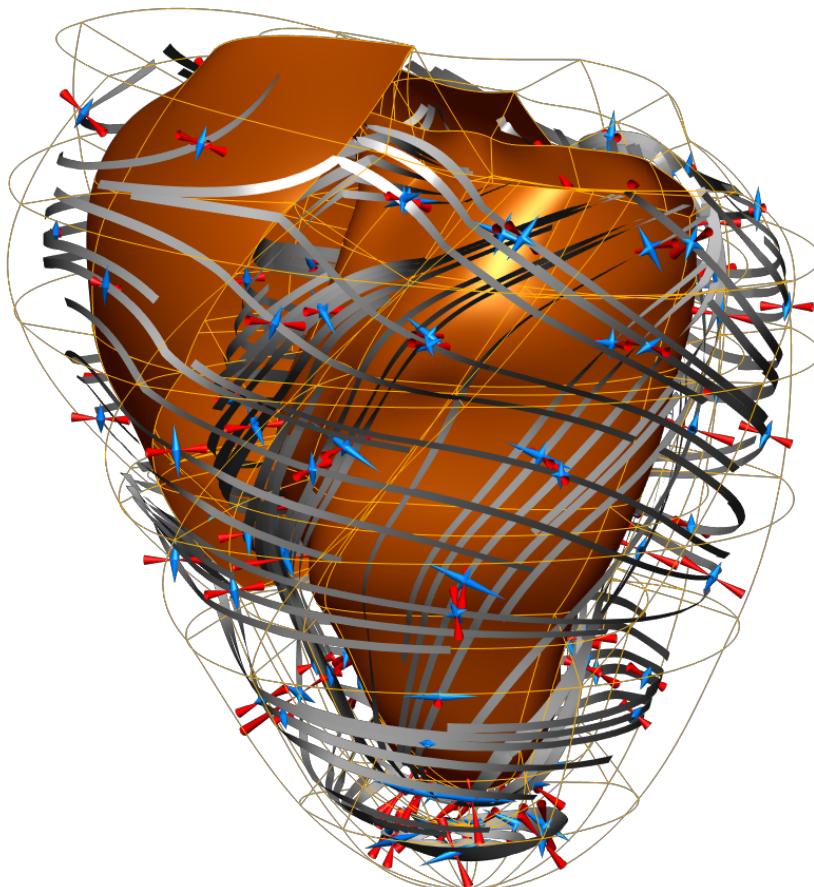


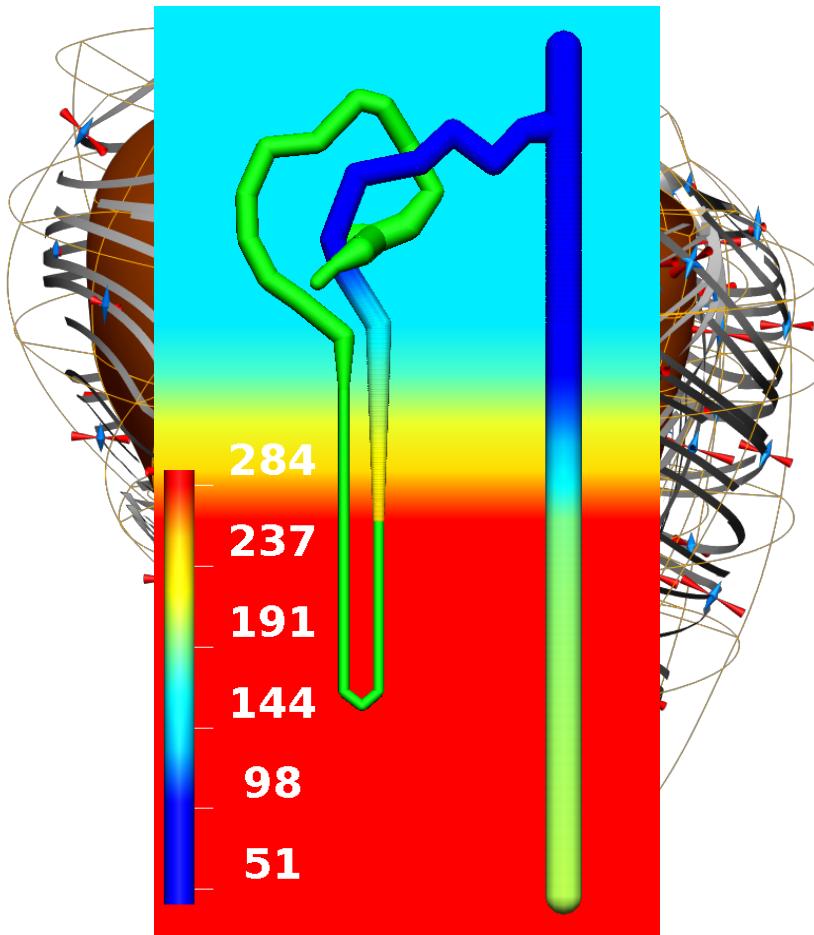
Fig.: Example simulation results (Le Novère, *Neuroinformatics* (2010))

# Similarly for complex models!

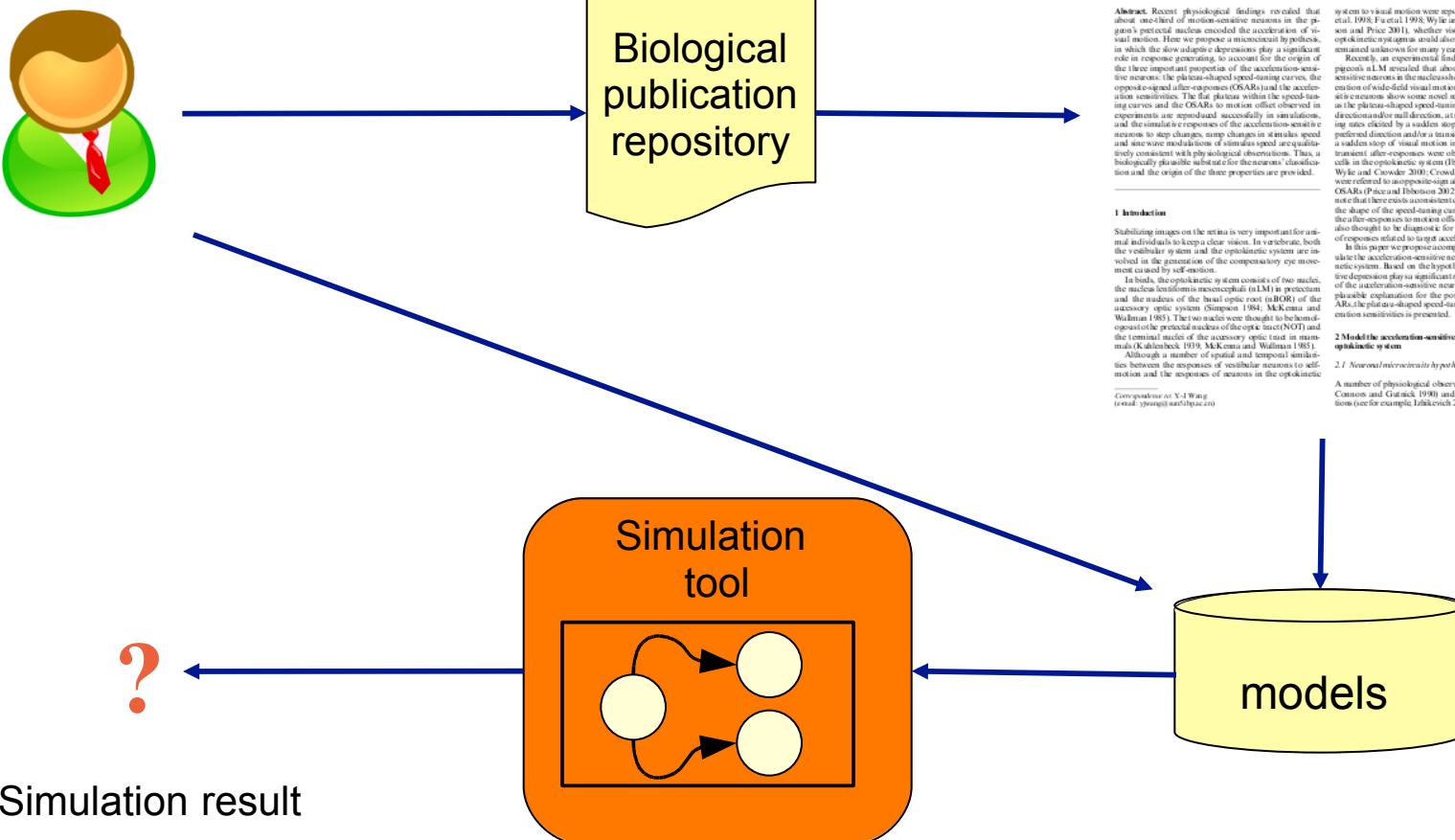


- × time
- × patient
- × drug dose
- × ...

# Similarly for complex models!



- × time
- × patient
- × drug dose
- × ...



## Modeling the acceleration sensitive neurons in the pigeon optokinetic system

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Received: 12 October 2004 / Accepted: 24 January 2005 / Published online: 24 March 2005

**Abstract.** Recent physiological findings revealed that about one-third of motion-sensitive neurons in the pigeons' optic nerve responded to the acceleration of visual motion. Here we propose a microcircuit hypothesis, in which the slow adapting depressions play a significant role in response generation, to explain the origin of the three typical properties of the acceleration-sensitive neurons: the plateau-shaped speed-tuning curves, the opposite-sign after-exposures (OsARs) and the acceleration-sensitivity. The speed-tuning curves, similar to the tuning curves and OsARs to motion offset observed in experiments are reproduced successfully in simulations, and the properties of the neurons are explained. The neurons respond to step changes, ramp changes in stimulus speed and sine-wave modulations of stimulus speed are qualitatively consistent with physiological data. As a biologically plausible substrate for the neurons' classification and the origin of the three properties are provided.

### 1 Introduction

Stabilizing images on the retina is very important for animal individuals to keep a clear vision. In vertebrates, both the vestibular system and the optokinetic system are involved in the regulation of the compensatory eye movement caused by self-motion.

In birds, the optokinetic system consists of two nuclei, the nucleus prepositus (nucleus prepositus nucleus) and fibers of the nucleus rotulus (nucleus rotulus) of the accessory optic system (Simpson 1984; McKenna and Wolfman 1985). The two nuclei were thought to be homologous to the terminal nuclei of the accessory optic tract in mammals (Kühnlebeck 1939; McKenna and Wolfman 1985). The optokinetic system has been shown to have similarities between the responses of vestibular neurons to self-motion and the responses of neurons in the optokinetic system to visual motion were reported (Miles 1984; Wylie et al. 1984; Miles 1998; Wylie and Crowder 2000; Blehm and Price 2001). The responses of the neurons in the optokinetic system appear to also respond to acceleration information unknown for many years.

Recently, a report of finding (Guo et al. 2004) in pigeons (Columba livia) revealed that about one-third of motion-sensitive neurons in the nucleus rotulus sensitively to acceleration of wide-field visual motion. The acceleration-sensitive neurons have three typical properties, such as the plateau-shaped speed-tuning curves in the preferred direction and/or null direction, a transient inhibition in the preferred direction and/or a transient excitation evoked by a sudden stop of visual motion in the null direction. The transient after-exposures were observed (Wylie and Miles 1984; Wylie and Crowder 2000; Crowder and Wylie 2001) and were referred to as opposite-sign after-exposures, for short, OsARs. The authors of the report (Guo et al. 2004) also note that there exists a consistent correspondence between the shape of the speed-tuning curves and the presence of the OsARs. The authors of the report (Guo et al. 2004) also thought to be diagnostic for the presence or absence of responses related to target acceleration or deceleration.

In this paper, we propose a microcircuit hypothesis to explain the acceleration-sensitive neurons in pigeon optokinetic system. Based on the hypothesis that the slow adapting depressions play a significant role in shaping responses of the neurons to visual motion, we present a model. A plausible explanation for the possible origin of the OsARs, the plateau-shaped speed-tuning curve and the acceleration sensitivities is presented.

### 2 Model of the acceleration-sensitive neurons in pigeon optokinetic system

#### 2.1 Neural microcircuit hypothesis

A number of physiological observations (see for example Cannon and Gottlieb 1980) and computational simulations (see for example Lohkamp 2003) have demonstrated

Correspondence to: Yuan Wu  
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# SED-ML Motivation

“[..] in Biomodels database the model *BIOMD0000000139* and *BIOMD0000000140* are **two different models** and they are **supposed to show different results**. Unfortunately simulating them in Copasi gives **same result** for both the models. [...]”  
 (arvin mer on sbml-discuss)

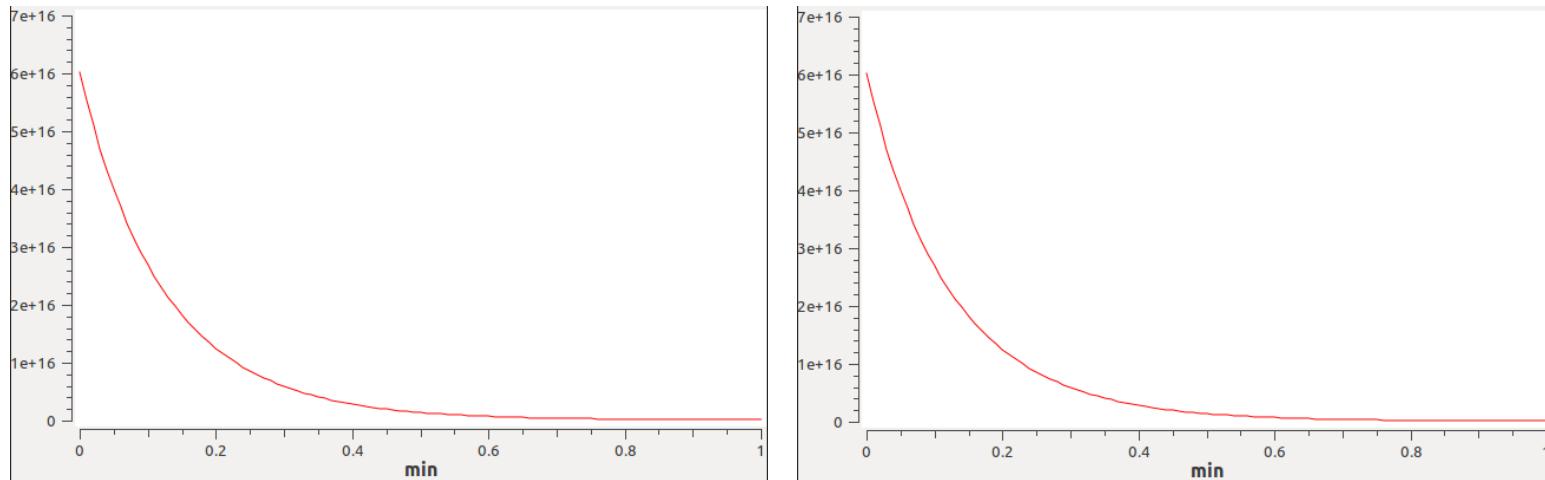


Fig.: running model files (COPASI simulation tool)

“[..] in Biomodels database the model *BIOMD0000000139* and *BIOMD0000000140* are **two different models** and they are **supposed to show different results**. Unfortunately simulating them in Copasi gives **same result** for both the models. [...]”  
(arvin mer on sbml-discuss)

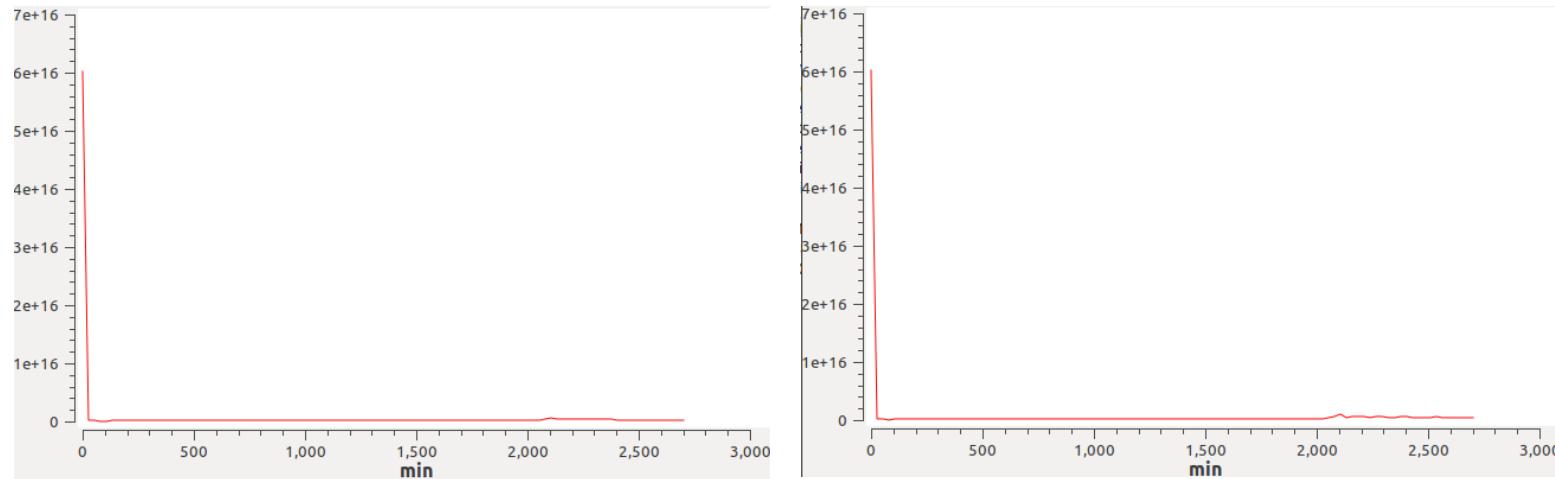
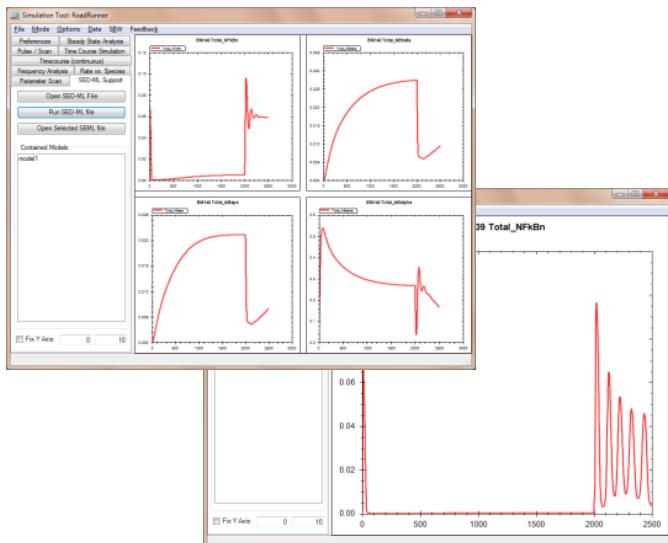


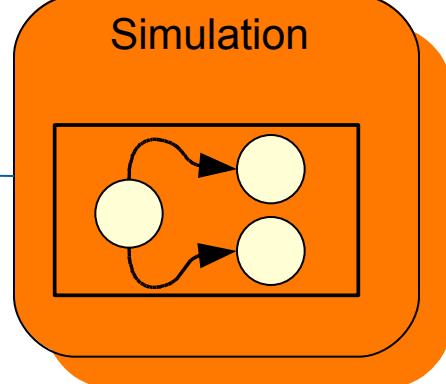
Fig.: running model files (COPASI simulation tool)



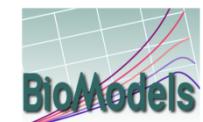
BIOMD0000000139 , BIOMD0000000140



Simulation results (SBW Workbench)



 Systems Biology  
Workbench



Levels: major revisions containing substantial changes

Simulation Experiment Description Markup  
Language (SED-ML) :  
Level 1 Version 1

March 25, 2011

Versions: minor revisions containing corrections and refinements

Dagmar Waltemath  
Frank T. Bergmann  
Richard Adams  
Nicolas Le Novère

Editors  
*University of Rostock, Germany*  
*University of Washington, Seattle, USA*  
*University of Edinburgh, UK*  
*European Bioinformatics Institute, UK*

Editorial board: coordinates SED-ML development  
(elected by sed-ml-discuss members)

The latest release of the Level 1 Version 1 specification is available at  
<http://sed-ml.org/>

To discuss any aspect of the current SED-ML specification as well as language details, please send your messages to the mailing list  
[sed-ml-discuss@lists.sourceforge.net](mailto:sed-ml-discuss@lists.sourceforge.net).

To get subscribed to the mailing list, please write to the same address  
[sed-ml-discuss@lists.sourceforge.net](mailto:sed-ml-discuss@lists.sourceforge.net).

To contact the authors of the SED-ML specification, please write to  
[sed-ml-editors@lists.sourceforge.net](mailto:sed-ml-editors@lists.sourceforge.net)



SED-ML Level 1 Version 1:

- multiple models
- multiple simulation setups
- time course simulations
- no “nested simulation”
- only explicit model entities can be addressed (XPath)

The SED-ML specification is written by an editorial board consisting of five editors. They are elected by the SED-ML community (members of the sed-ml-discuss mailing list) and serve for 3-year terms as volunteers.

The screenshot shows a web browser window with the URL [sed-ml.org/about.html](http://sed-ml.org/about.html). The page displays five editorial board members with their portraits and brief bios:

- Frank Bergmann (editor, elected 2011-2014)**  
Frank T. Bergmann (PhD in Computational and Systems Biology) is a researcher at the [California Institute of Technology](#) where his primary interest is in standardization efforts around [SBML](#). He is also the lead developer of the [Systems Biology Workbench](#) along with the [LibSEDML library](#).
- Dagmar Waltemath (editor, elected 2011-2014)**  
Dagmar Waltemath (Diploma degree in Computer Science) is guest researcher at the [Systems Biology and Bioinformatics group, Rostock](#). She works on the standardisation of simulation experiment descriptions in Computational Biology ([MIASE](#)).
- Richard Adams (editor, elected 2011-2013)**  
Richard Adams (PhD in Cell Biology) is software project manager at the [Centre for Systems Biology, Edinburgh](#). He works on the [SBSI systems biology software framework](#), SED-ML tools and the [jlibsedml](#) Java library for SED-ML.
- David Nickerson (editor, elected 2011-2013)**  
David Nickerson is a Research Fellow in the Auckland Bioengineering Institute where he leads the Auckland Kidney Physiome project. David is also involved in many aspects of the CellML project as well as various cardiac modeling projects. He also develops several CellML-related software tools.
- Andrew Miller (editor, elected 2011-2012)**  
Andrew Miller is a researcher at the [Auckland Bioengineering Institute](#). His research interests focus around the representation of mathematical models; he is involved in the development of tools for processing [CellML](#) models, including SProS, a SED-ML processing service that forms part of the CellML API.
- Nicolas Le Novère (editorial advisor)**  
Nicolas Le Novère is a group leader at the [EMBL-European Bioinformatics Institute](#). His research unfolds along two axis: 1) modelling neuronal signalling, at the molecular, sub-cellular and cellular levels, and 2) developing tools and resources for systems biology, in particular including standards.

# Main building blocks

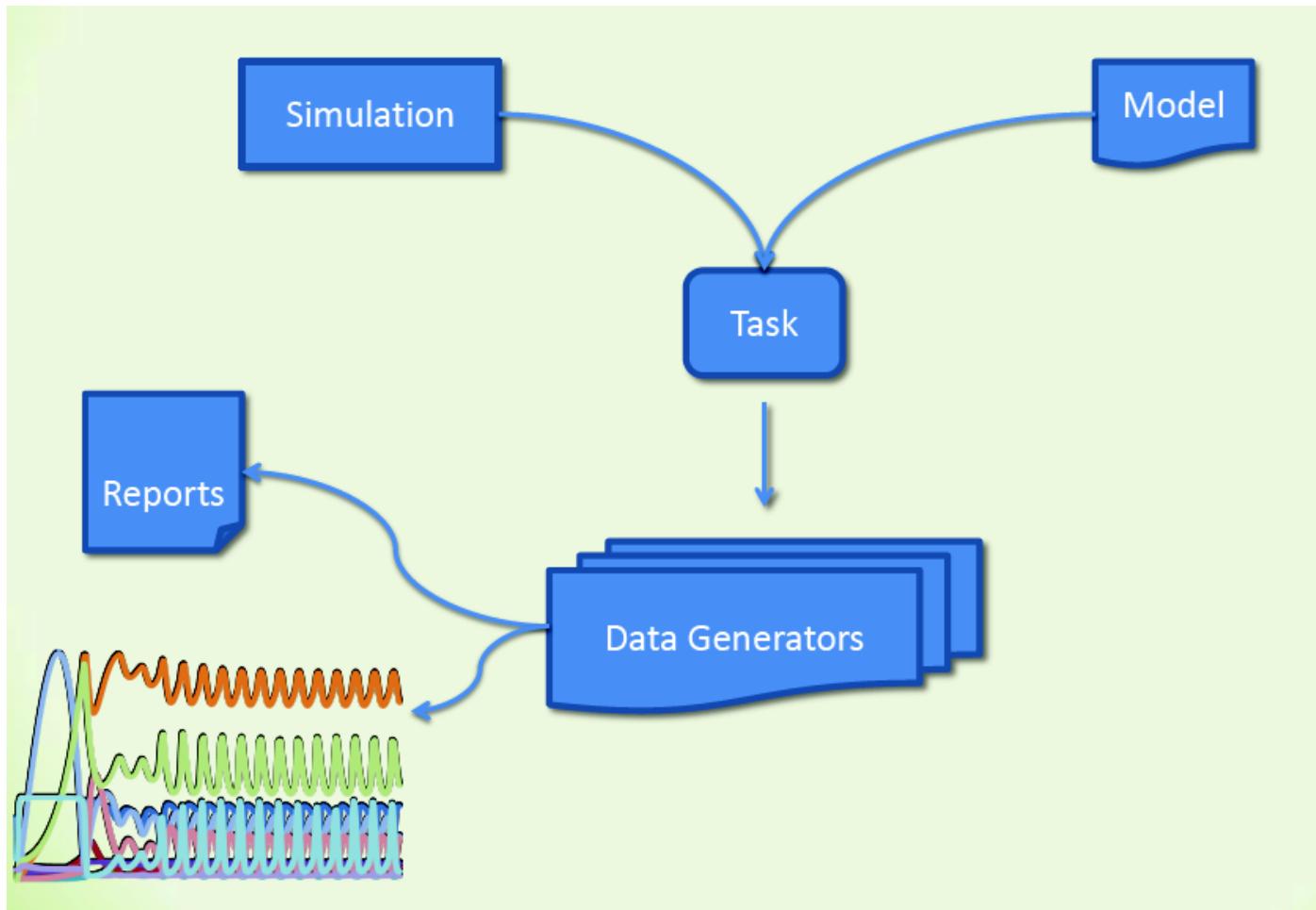


Figure: SED-ML structure (*Waltemath et al., 2011*)

# SED-ML – What does it look like?

```
<listOfSimulations>
    <uniformTimeCourse id="simulation1" initialTime="0"
        outputStartTime="0" outputEndTime="1000" numberOfPoints="1000">
        <algorithm kisaoID="KISA0:0000088" />
    </uniformTimeCourse>
    <uniformTimeCourse id="simulation2" initialTime="0"
        outputStartTime="0" outputEndTime="1000" numberOfPoints="1000">
        <algorithm kisaoID="KISA0:0000027" />
    </uniformTimeCourse>
</listOfSimulations>
<listOfModels>

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        language="urn:sedml:language:	sbml.level-2.version-3" source="urn:miriam:biomodels.db:BIOMD00000000012" >
        <notes>
            <p xmlns="http://www.w3.org/1999/xhtml">
                This is the unmodified model.
            </p>
        </notes>
    </model>
    <model id="model2" name="Damped oscillations"
        language="urn:sedml:language:	sbml.level-2.version-3" source="modell">
        <notes>
            <p xmlns="http://www.w3.org/1999/xhtml">
                This variant produces damped oscillations.
            </p>
        </notes>
    </model>
</listOfModels>
```

# SED-ML – What does it look like?

```
<listOfSimulations>
    <uniformTimeCourse id="simulation1" initialTime="0"
        outputStartTime="0" outputEndTime="1000" numberOfPoints="1000">
        <algorithm kisaoID="KISAO:0000088" />
    </uniformTimeCourse>
    <uniformTimeCourse id="simulation2" initialTime="0"
        outputStartTime="0" outputEndTime="1000" numberOfPoints="1000">
        <algorithm kisaoID="KISAO:0000027" /> ← next reaction method
    </uniformTimeCourse>
</listOfSimulations>
<listOfModels>

    <model id="model1" name="Repressilator-regular oscillations"
        language="urn:sedml:language:sbml.level-2.version-3" source="urn:miriam:biomodels.db:BIOMD0000000012" >
        <notes>
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                This is the unmodified model.
            </p>
        </notes>
    </model>
    <model id="model2" name="Repressilator-damped oscillations"
        language="urn:sedml:language:sbml.level-2.version-3" source="urn:miriam:biomodels.db:BIOMD0000000012" >
        <notes>
            <p xmlns="http://www.w3.org/1999/xhtml">
                This variant produces damped oscillations.
            </p>
        </notes>
    </model>

```



The image shows a screenshot of a web browser displaying a SBML model page. The URL in the address bar is "https://www.miriam.org/BIOMD0000000012". The page title is "BIOMD0000000012 - Elowitz2000\_Repressilator". Below the title, there are tabs for "Download SBML", "Other formats (auto-generated)", and "Actions". A red arrow points from the "source" attribute in the XML code above to the "source" field in the Biomodels database entry. The Biomodels entry includes fields for "Publication ID" (10659856), "Reference Publication" (Elowitz MB, Leibler S. A synthetic oscillatory network of transcriptional positive and negative feedback. Nature 2000 Jan;403(6767):335-8.), and "Email" (melowitz@princeton.edu). There is also a "[more]" link.

# Example: Running a simple model of spiking neurons

IEEE TRANSACTIONS ON NEURAL NETWORKS, VOL. 14, NO. 6, NOVEMBER 2003

## Simple Model of Spiking Neurons

Eugene M. Izhikevich

**Abstract**—A model is presented that reproduces spiking and bursting behavior of known types of cortical neurons. The model combines the biologically plausibility of Hodgkin–Huxley-type dynamics and the computational efficiency of integrate-and-fire neurons. Using this model, one can simulate tens of thousands of spiking cortical neurons in real time (1 ms resolution) using a desktop PC.

**Index Terms**—Bursting, cortex, Hodgkin–Huxley, PCNN, quadratic integrate-and-fire, spiking, thalamus.

**BIOMD0000000127 - Izhikevich2003\_SpikingNeuron**

SBML formats | Other formats | Actions | Submit Model Comment

Model | Overview | Math | Physical entities | Parameters

Reference Publication

Publication ID: [18244602](#)

IEEE Trans Neural Netw 2003;14(6):1569-72.  
Simple model of spiking neurons.  
Izhikevich EM.  
The Neurosciences Inst., San Diego, CA, USA. [more]

Model

Original Model: [BIOMD0000000127.xml.origin](#)

Submitter: [Enuo He](#)

Submission ID: MODEL4880479792

Submission Date: 28 Jul 2007 04:22:14 UTC

Last Modification Date: 22 Apr 2009 00:46:12 UTC

Creation Date: 16 Jul 2007 17:41:14 UTC

Encoders: [Enuo He](#)

Gene Ontology regulation of action potential  
Gene Ontology regulation of membrane potential  
Gene Ontology regulation of action potential

set #1 bqbiol:isVersionOf DOI 10.1109/TNN.2003.820440

set #2 bqmodel:isDescribedBy DOI 10.1109/TNN.2003.820440

set #3 bqbiol:is Taxonomy Mammalia

Notes

The model is according to the paper *Simple Model of Spiking Neurons*. In this paper, a simple spiking model is presented yet as computationally efficient as the integrate-and-fire model. Known types of neurons correspond to different values. Figure 2 RS, IB, CH, FS, LTS have been simulated by MathSBML.

RS: a=0.02, b=-0.2, c=-65, d=8.

IB: a=0.02, b=0.2, c=-55, d=4

CH: a=0.02, b=0.2, c=-50, d=2

FS: a=0.1, b=0.2, c=-65, d=2

LTS: a=0.02, b=0.25, c=-65, d=2

## Example: What is encoded in the model

- 1 compartment
- 1 standard species
- No reactions
- 8 global quantities (parameters)
- 2 rate rules
- 2 events

# Example: What is encoded in the model

Model available from **BioModels DB**:

[urn:miriam:biomodels.db:BIOMD0000000127](#)

Representing the **Simple model of spiking neurons** published by **Izhikevich (2003)** in

[urn:miriam:pubmed:18244602](#)

Model is for organism **mammals** [urn:miriam:taxonomy:40674](#)

**1 compartment** is version of

a **cellular compartment** [urn:miriam:obo.go:GO%3A0005623](#)

**1 standard species**

**No reactions**

**8 global quantities (parameters)**

**2 rate rules** encoded: the **regulation of membrane potential** (variable **v**)  
[urn:miriam:obo.go:GO%3A0042391](#), the **positive regulation of potassium ion transport** (variable **U**)

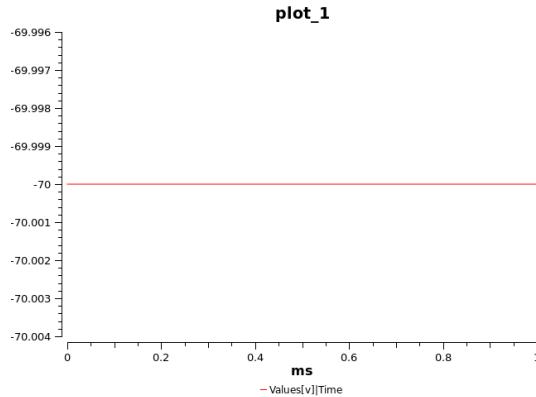
[urn:miriam:obo.go:GO%3A0043268](#)

**2 events** encoded: a version of the **stabilization of membrane potential** (event **event\_0000001**) [urn:miriam:obo.go:GO%3A0030322](#), and the **detection of electrical stimulus** (event **Stimulus**) [urn:miriam:obo.go:GO%3A0050981](#)

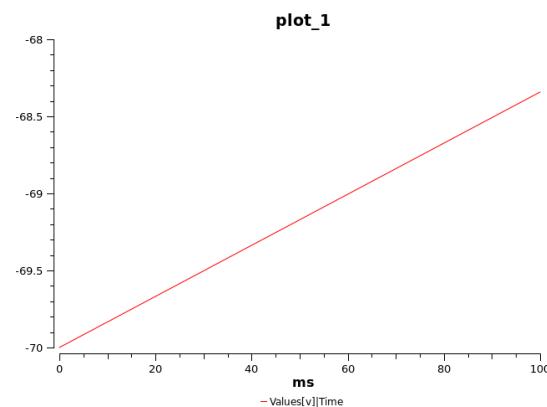
# Example: What happens if I just simulate?

First attempt to run the model, measuring the spiking rate  $v$  over time

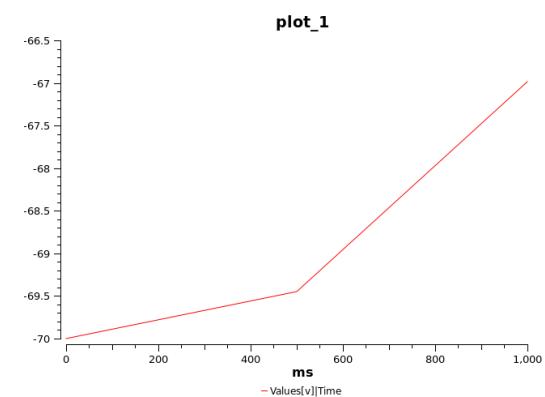
- load SBML into the simulation tool COPASI
- use parametrisation as given in the SBML file
- define output variables ( $v$ )
- run the time course



1 ms (standard)



100ms



1000ms

## Example: What happens if I just simulate?

Second attempt to run the model, adjusting simulation step size and duration

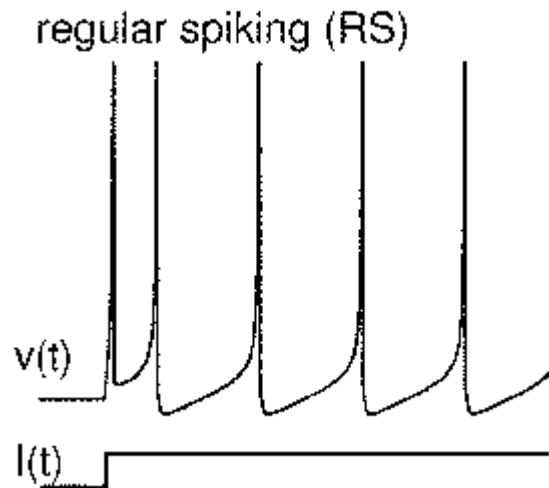


Fig: reference publication

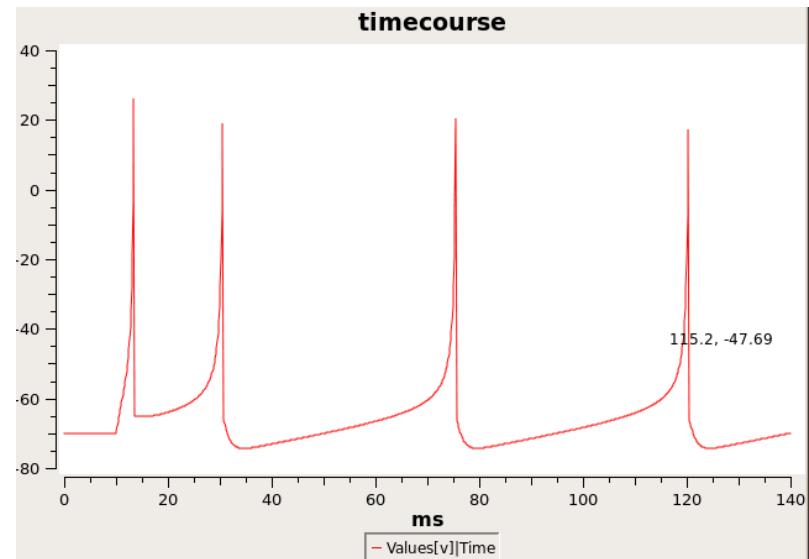


Fig.: COPASI simulation, duration: 140ms, step size: 0.14

## Example: What happens if I just simulate?

Third attempt to run the model, updating initial model parameters

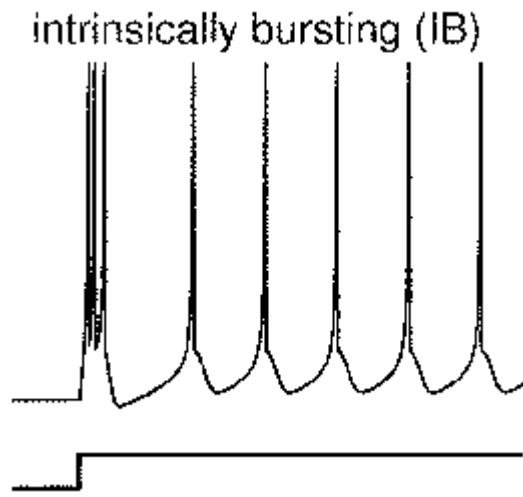


Fig.: reference publication

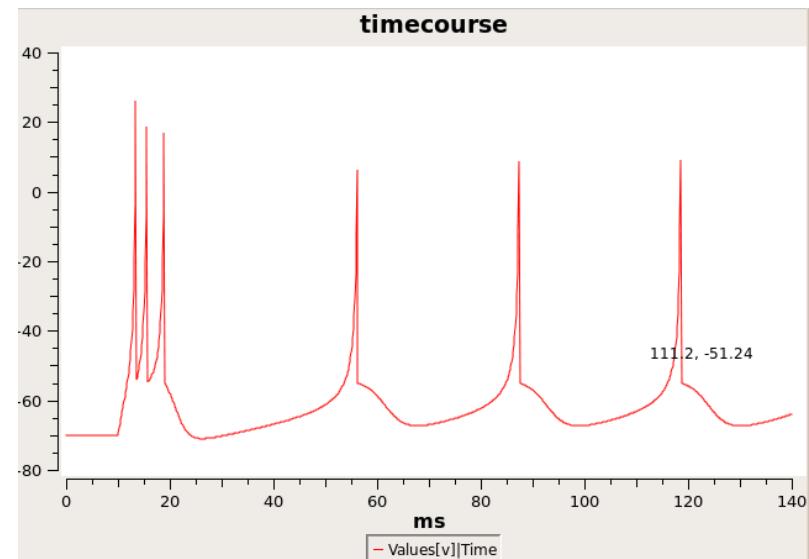


Fig.: COPASI, adjusted parameter values  
**( $a=0.02$ ,  $b=0.2$   $c=-55$ ,  $d=4$ )**

www.cellml.org/community/ Workshop Programme -- Cel The Lorenz Attractor, a class The ORd human ventricular The CellML project team

models.cellml.org/e/71/view

# cellML

Models Home Exposures Documentation

You are here: Home > Exposures > The ORd human ventricular action potential model

Log In | Register

## The ORd human ventricular action potential model

This workspace houses a CellML 1.0 encoding of the 2011 O'Hara, Virág, Varró, & Rudy 2011 human cardiac ventricular action potential model (ORd). The original article is available at: <http://www.ncbi.nlm.nih.gov/pubmed/21637795>. This model was encoded based on the Matlab version of the code available from: <http://rudylab.wustl.edu/research/cell/>.

The CellML 1.0 encoding of the ORd model was contributed by Steven Niederer. While the units in the CellML encoding are not yet perfect, it is a match for the Matlab code and matches the simulation output for a single beat perfectly. The figure below shows the output of the simulation experiment [action-potential.xml](#) encoded in SED-ML using the original version of the model from Steve. This output is generated by running the simulation experiment using the SED-ML Web Tools.

The screenshot shows the SED-ML Web Tools interface. The main window displays a graph titled "Action Potential" with a red line representing the membrane potential. The y-axis ranges from -120 to 80, and the x-axis ranges from 0 to 1000. The potential starts at approximately 40 mV, drops sharply to about -90 mV around time 300, and remains constant. A legend indicates "Membrane Potential". To the right of the graph, there is a "Simulate" button and two upload buttons for SED-ML documents. The top navigation bar includes links for Home, Create, Edit, Details, Stimulate, Validate, and About. The left sidebar has sections for Simulate, Action Potential, and a feedback link.

### Model Curation

Curation Status:

### Source

Derived from workspace [An encoding of the human ORd model by Steve Niederer](#) at changeset [a96ef0c61614](#).

### Downloads

Complete Archive as .tgz

### Navigation

Ohara\_Rudy\_2011.cellml  
 action-potential.xml

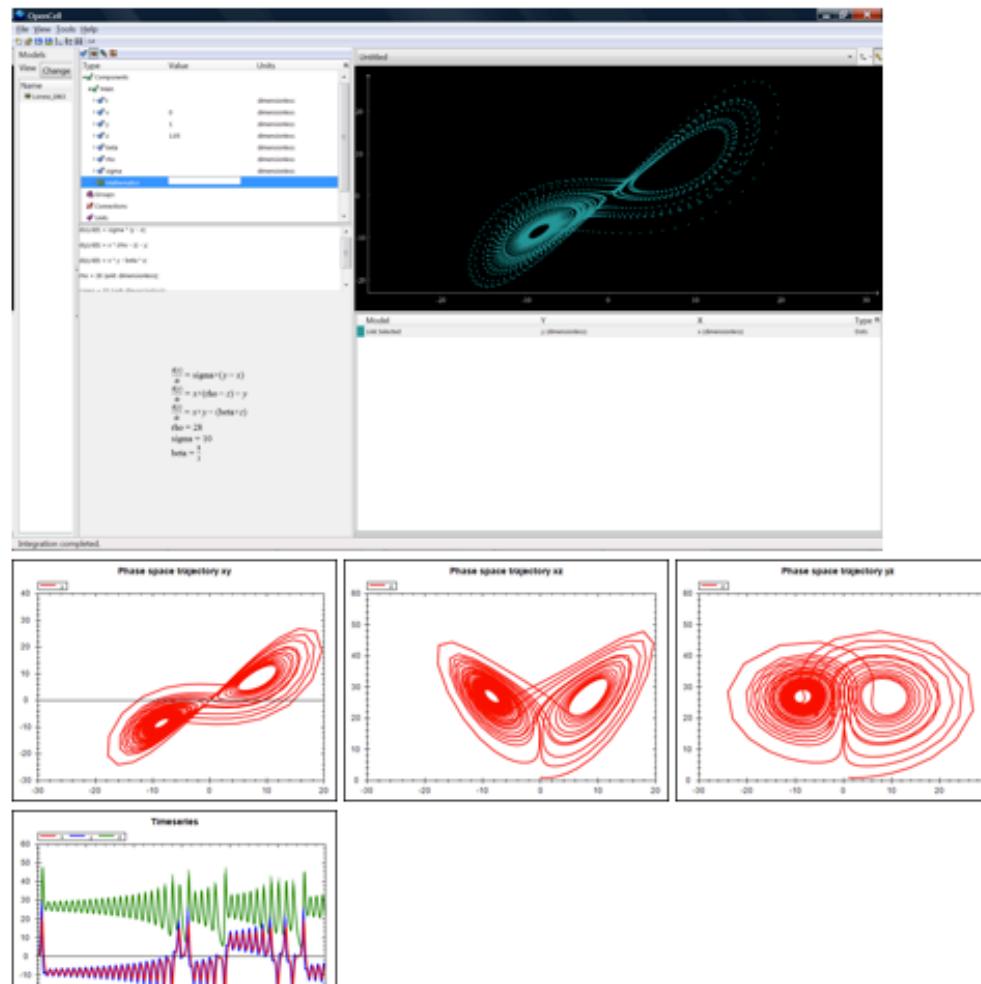


You are here: [Home](#) > [Exposures](#) > The Lorenz Attractor, a classical mathematical model

## The Lorenz Attractor, a classical mathematical model

This workspace houses a CellML encoding of the 1963 Lorenz model which became a well-known demonstration of deterministic chaos. The original article DOI is [10.1175/1520-0469\(1963\)020<0130:DNF>2.0.CO;2](https://doi.org/10.1175/1520-0469(1963)020<0130:DNF>2.0.CO;2). This model was encoded based on the Octave code available in the related [Wikipedia article](#).

An [OpenCell 0.8 session file](#) is available. [SED-ML](#) can also be used to simulate this model, the simulation description is in [Lorenz\\_1963\\_sedml.xml](#), and the simulation experiment can be run using the [SED-ML Web Tools](#). The figures below show the results from using [SED-ML](#).



### Model Curation

Curation Status:



OpenCell:



### Source

Derived from workspace

Deterministic Nonperiodic Flow at changeset [1cdf5c612924](#).

### Downloads

Complete Archive as .tgz

### Navigation

[The Lorenz Attractor, a classical mathematical model](#)

1. Have a look at the current SED-ML Specification document on <http://sed-ml.org>
  
2. Try out some of the existing examples  
<http://sed-ml.org> and <http://sourceforge.net/projects/libsedml>
  
3. Identify what is missing for you to encode your simulation experimental setups - What can you not express?
  
4. Submit a feature request & post it on the list  
feature request tracker: <http://sourceforge.net/projects/sed-ml>  
mailing list: [sed-ml-discuss@lists.sourceforge.net](mailto:sed-ml-discuss@lists.sourceforge.net)
  
1. ... submit a proposal with example files and prototype  
proposal tracker: <http://sourceforge.net/projects/sed-ml>