CellML, PMR, OpenCOR, CRBM, ...

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• XML format for encoding mathematical models
• Reproducibility
  – Unambiguous description of the mathematical model
• Reusability
  – Modular, composable
• Comprehensible
  – Metadata to describe the biological semantics

• Tool support
  – CellML API library and service
  – Most tools don’t support model composition
CellML 2.0

- Reactions are gone!
- Only CellML allowed in the XML document
  - No metadata, annotations, cmeta:id
  - No extension elements
- XML syntax simplifications
  - Grouping replaced with only encapsulation
  - No more map_components
- Improved reusability
  - Connections no longer have direction
  - Single interface attribute controlling scope: public, private, public_and_private, none
cellML 2.0

- Units clarifications
  - No need to specify base_units explicitly
  - Units with offsets removed
  - “celsius” removed from built-in units
  - Component-scope unit definitions removed
- Reset rules
  - Arbitrary rules to “reset” variables
- New and compulsory MathML subset
  - No more “recommended” subset to support
  - Well defined, no confusion
• New C++ library to meet the needs of users
• Supporting CellML 2.0 and beyond
• Much more streamlined and maintainable
• Better suited for testing out new features and extensions to the specification
  – Allowing rapid prototyping
  – Exploring alternatives
  – Testing model exchange and reproducibility
The Physiome Model Repository – PMR

https://models.physiomeproject.org/

- Over 800 publicly available workspaces
  - Version control repositories (git)
  - Historically mostly CellML models from the literature
  - Gradually getting more non-CellML data contributed (SED-ML, FE models, code)
- Many more exposures
  - "releases" of workspaces
  - A specific version processed for display and interaction
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](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/](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.

Component: intracellular_ions

\[
\frac{d}{dt} \left( \text{CaMKt} \right) = a_{\text{CaMK}} \space \text{CaMKb} \left( \text{CaMKb} + \text{CaMKt} \right) - \left( b_{\text{CaMK}} \space \text{CaMKt} \right)
\]

\[
\frac{d}{dt} (\text{cmax}) = \begin{cases} 
\text{cmax}_\text{b1.3 if celltype} = 1 \\
\text{cmax}_\text{b} \text{ otherwise}
\end{cases}
\]

\[
\frac{d}{dt} (\text{nai}) = \frac{-\left( [(\text{Na}+1)\text{NaL}+3(\text{NaCa}_{\text{i}})+3(\text{NaCa}_{\text{ra}})] \right) \text{Acap}}{F \text{ vmyo}} + \text{Bcna}
\]

\[
\frac{d}{dt} (\text{nass}) = \frac{-\left( \text{CaNa}_{\text{si}} \right) \text{Acap}}{F \text{ vss}} - \text{JdiffNa}
\]

\[
\frac{d}{dt} (\text{ki}) = \frac{-\left( \text{Kb}+3\text{Kb}+3\text{Kb}+1\text{Kb}+1\text{Kb} \right) \text{Acap}}{F \text{ vss}} + \text{Bcass}
\]

\[
\frac{d}{dt} (\text{cass}) = \frac{-\left( \text{CaCa}_{\text{si}} \right) \text{Acap}}{F \text{ vss}} + \text{Jut}_{\text{vss}}
\]

\[
\frac{d}{dt} (\text{cajsr}) = \frac{\text{Bcajsr} (Jut - Jrel)}{1 + \left( \frac{Jut}{Jrel} \right) \text{ Acap}}
\]
Generated Code

The following is the MATLAB code generated by the CellML API from this CellML file. (Back to language selection)

The raw code is available.

function [RATES, ALGEBRAIC] = computeRates(V0, STATES, CONSTANTS)
    global algebraicVariableCount;
    statesSize = size(STATES);
    statesColumnCount = statesSize(2);
    if (statesColumnCount == 1)
        STATES = STATES';
    end
    ALGEBRAIC = zeros(1, algebraicVariableCount);
    ALGEBRAIC = zeros(statesRowCount, algebraicVariableCount);
    RATES = zeros(statesRowCount, statesColumnCount);
    end

    ALGEBRAIC(:,1) = 1.000000/.(1.000000+exp((STATES(:,1)-0.876100)/7.488000));
    RATES(:,18) = (ALGEBRAIC(:,1) - STATES(:,18))./CONSTANTS(1,44);
    ALGEBRAIC(:,1) = 1.000000/.(1.000000+exp((STATES(:,1)-0.938100)/7.488000));
    RATES(:,19) = (ALGEBRAIC(:,1) - STATES(:,19))./CONSTANTS(1,96);
    ALGEBRAIC(:,1) = 1.000000/.(1.000000+exp((STATES(:,1)-0.876100)/7.488000));
    RATES(:,14) = (ALGEBRAIC(:,1) - STATES(:,14))./CONSTANTS(1,33);
    ALGEBRAIC(:,1) = 1.000000/.(1.000000+exp((STATES(:,1)-0.876100)/7.488000));
    RATES(:,37) = (ALGEBRAIC(:,1) - STATES(:,37))./CONSTANTS(1,39);
    RATES(:,11) = (ALGEBRAIC(:,1) - STATES(:,11))./CONSTANTS(1,14);
    ALGEBRAIC(:,1) = 1.000000/.(1.000000+exp((STATES(:,1)-0.876100)/7.488000));
    RATES(:,15) = (ALGEBRAIC(:,1) - STATES(:,15))./CONSTANTS(1,41);
    ALGEBRAIC(:,1) = 1.000000/.(1.000000+exp((STATES(:,1)-0.876100)/7.488000));
    RATES(:,22) = (ALGEBRAIC(:,2) - STATES(:,22))./ALGEBRAIC(:,15);
    ALGEBRAIC(:,16) = 1.000000/.(0.001000+exp((STATES(:,2)+17.55000)/28.05000)+0.3343000.*exp((STATES(:,1)-5.73000)/56.66000));
    RATES(:,13) = (ALGEBRAIC(:,2) - STATES(:,13))./ALGEBRAIC(:,16);
    ALGEBRAIC(:,5) = 1.000000/.(1.000000+exp((STATES(:,1)-14.34000)/14.82000));
    ALGEBRAIC(:,18) = 1.051500/.(1.000000+exp((STATES(:,1)-18.40000)/29.3814)+3.500000/.(1.000000+exp((STATES(:,1)+100.000)/29.3814)));
    RATES(:,20) = (ALGEBRAIC(:,5) - STATES(:,20))./ALGEBRAIC(:,18);
    ALGEBRAIC(:,7) = 1.000000/.(1.000000+exp((STATES(:,1)+3.94000)/4.23000));
The Physiome Model Repository – PMR

- Consistent browser and tool integration
  - Content type negotiation
  - Same URL
  - REST
- RDF triplestore
  - Indexing versioned annotations
  - Supporting (semantic) querying
- Tools for model composition, parameter estimation, etc.
A modelling environment for reproducible science

https://opencor.ws
Hands on tutorial

• Using OpenCOR to explore modularity and reuse with CellML models (including SED-ML)
• Making use of PMR as a version controlled workspace to archive and share your work FAIRly
• Python-enabled OpenCOR
• Starting to explore what is possible with machine learning using TensorFlow, CellML, OpenCOR, and Python.

Alan Garny
Gonzalo Maso Talou
CENTER FOR REPRODUCIBLE BIOMEDICAL MODELING

https://reproduciblebiomodels.org/
Goals

**Long-term**
- Enable more comprehensive and more predictive models that advance precision medicine and synthetic biology

**Short-term**
- Make modeling more reproducible, comprehensible, reusable, composable, collaborative, and scalable
- Develop technological solutions to the barriers to modeling
- Integrate the technology into user-friendly solutions
- Push researchers to use these tools
- Partner with journals
TR&Ds

Models

Informatics

Data

Simulation results

TR&D1

TR&D3

TR&D2
Training and dissemination

- Center Workshops
- Other domains
- Model Curation Service
- Newsletter/Online Courses
- YouTube
- DREAM Challenges

powered by Sage Bionetworks
Manuscripts received by journals will be curated to make sure that any author supplied code will faithfully reproduce the results presented in the manuscript.
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SPARC

Center for Reproducible Biomedical Modeling

https://doi.org/10.17608/k6.auckland.10080263
ModelXchange
SED-ML Motivation

Simulation result

Biological publication repository

Simulation tool

models
Example

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

Fig.: COPASI simulation, duration: 140ms, step size: 0.14
Third attempt to run the model, updating initial model parameters

Fig.: COPASI, adjusted parameter values
(a=0.02, b=0.2 c=\textbf{-55}, d=4)
Core Standards

- Standards for Knowledge Representation
  - BioPAX
  - SBOL

- Standards for Visual Representation
  - SBGN
  - SBOL VISUAL

- Standards for Models and their Analyses
  - SBML
  - CellML
  - NeuroML
  - SED-ML

Associated Standards

- BIoModels.net qualifiers

Projects

Infrastructure

Controlled Vocabularies
- Coordination board
- Coordinating new efforts, meetings, etc.
  - COMBINE Archive
  - Harmonizing annotation
  - Uncertainty?
- Publications
- Forums/mailing lists
- FAIR and FAIRsharing
Enabling technologies  Representation formats

1999

March 2001
SBML Level 1

August 2001
CellML 1.0, NeuroML

2003
libSBML

June 2003
SBML Level 2

July 2004
BioPAX Level 1

December 2005
BioPAX Level 2

2005
MIRIAM, SBO, BioModels qualifiers

2006
PaxTools

2007
MIASE, KiSAO

August 2008
SBGN PD L1

September 2009
SBGN ER L1, SBGN AF L1

March 2010
SED-ML Level 1

July 2010
BioPAX Level 3

October 2010
SBML Level 3

October 2011
SBOL v1

March 2013
SBOLvisual v1

2011
Identifiers.org

September 2014
COMBINE Archive

2010

Influential meetings

April 1999
NATO workshop, proposing to create a language to encode metabolic models

April 2000
Start of SBML at the 1st "ERATO Kitano" workshop,

August 2002
Start of BioPAX project at the 4th Biopathway consortium meeting

July 2003
1st SBML hackathon

October 2005
Start of SBGN project at the BioPAX face 2 face meeting

2006
Decision to create a language for synth biol designs

January 2008
Okinawa superhackathon

SBGN, BioPAX, SBO, MIRIAM

April 2008
1st SBOL meeting

April 2009
Waiheke combined meeting

CellML, SBGN, BioPAX, SBO, MIASE

Creation of COMBINE

October 2010
1st COMBINE forum

April 2011
1st HARMONY hackathon

https://doi.org/10.1109/WSC.2017.8247840
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<td>COMBINE news</td>
<td>@combine_coord</td>
<td>General announcement about COMBINE and its activities</td>
</tr>
<tr>
<td>COMBINE discuss</td>
<td><a href="mailto:combine-discuss@googlegroups.com">combine-discuss@googlegroups.com</a></td>
<td>Main discussion forum of the COMBINE community, Feel free to use it to any aspect of the project, meetings, technology etc.</td>
</tr>
<tr>
<td>COMBINE archive</td>
<td><a href="mailto:combine-archive@googlegroups.com">combine-archive@googlegroups.com</a></td>
<td>Forum to discuss the OMEX format, the structure of the COMBINE archive, implementation issues, and all related questions. For more information about the COMBINE archive, please see the OMEX page.</td>
</tr>
<tr>
<td>COMBINE annotation</td>
<td><a href="mailto:combine-annot@googlegroups.com">combine-annot@googlegroups.com</a></td>
<td>Forum and working group for policies and technologies for improved annotation of biosimulation models.</td>
</tr>
<tr>
<td>COMBINE multicell</td>
<td><a href="mailto:combine-multicell@googlegroups.com">combine-multicell@googlegroups.com</a></td>
<td>Forum and working group for the specification, implementation and further developments of a standard format for multi-cellular, agent-based models.</td>
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<td>COMBINE metadata</td>
<td><a href="mailto:combine-meta@googlegroups.com">combine-meta@googlegroups.com</a></td>
<td>Forum to discuss the structure and content of metadata to use together with COMBINE formats.</td>
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<td>COMBINE site support</td>
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<td>Use this address to report problems with the website.</td>
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<tr>
<td>COMBINE coordinators</td>
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<td>Use this address to contact COMBINE coordinators.</td>
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10th COMBINE Anniversary
July 15-19 in Heidelberg
Registration now open!
Abstract submission deadline extended to June 15!
http://co.mbine.org/events/COMBINE_2019