

<MulticellML/>

**FAIR data exchange in the life sciences
by standardization of heterogenous
data and multicellular models**

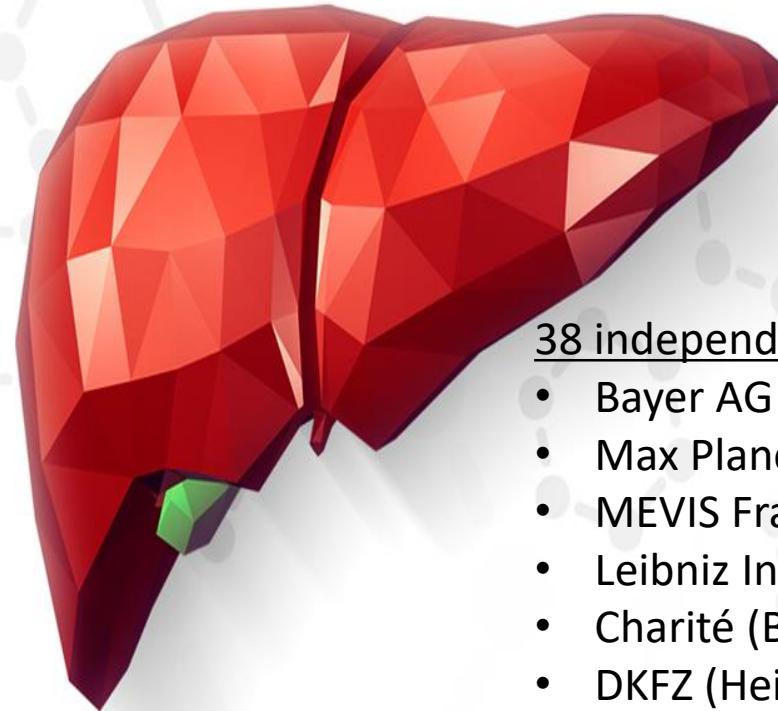
Martin Golebiewski

HITS gGmbH (Heidelberg, Germany)

COMBINE 2018, Boston, MA (USA), October 8th-12th, 2018

LiSyM

Research Network on Systems Medicine for Liver Disease



Multiple disciplines

- Medicine
- Biology, Biochemistry
- Pharmacology
- Physics
- Bioinformatics
- Data management
- Industry

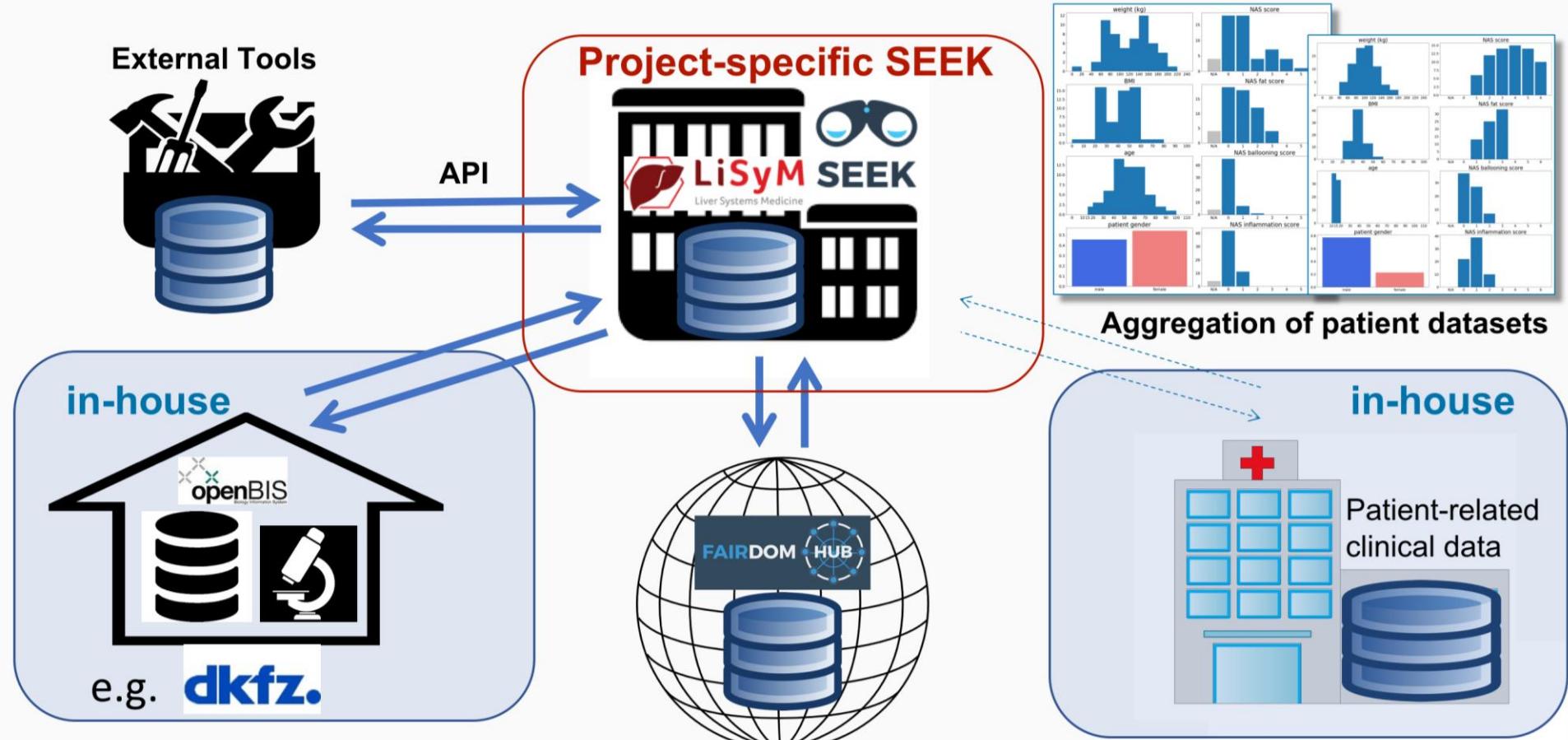
38 independent research groups

- Bayer AG
- Max Planck (Dresden and Berlin)
- MEVIS Fraunhofer (Bremen)
- Leibniz Institute IfaDo (Dortmund)
- Charité (Berlin)
- DKFZ (Heidelberg)
- Hospitals: Dresden, Kiel, Aachen, Homburg, Berlin, Heidelberg, Munich
- + 18 Universities

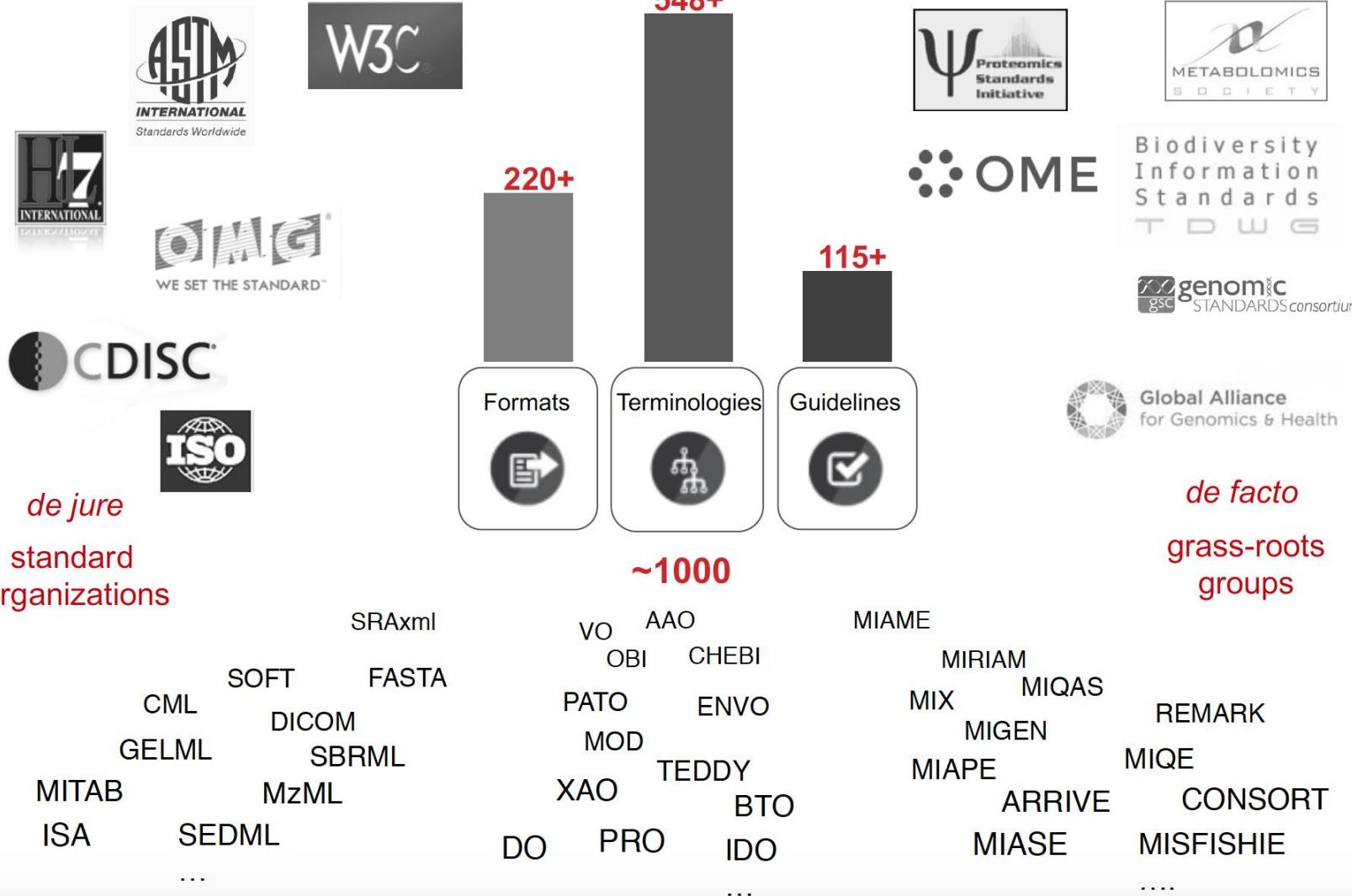
Supported by

The German Federal Ministry of Education and Research 2016-2020

Project-Specific Data Management Support: German Liver Systems Medicine Network (LiSyM)



Community (de-facto) Standards in Life Sciences



The NormSys Registry for Modeling Standards

This registry aims at surveying standard formats for computational modeling in biology. It not only lists the standards, but also compares their major features, their possible fields of biological application and use cases (including model examples), as well as their relationships, commonalities and differences. This registry provides a common entry point for modelers and software developers who plan to apply the standards for their respective case of application, and serves them with detailed information and links to the standards, their specifications and APIs.

The information provided in this system does not claim to be complete or all-encompassing, nor can we guarantee any absence of defectiveness. However, we collect and assemble the information to the best of our knowledge and belief to assist in selecting the appropriate standard format for your specific requirements. Please note that the system is work in progress and is constantly revised and extended. Any feedback and suggestions for corrections or improvements, as well as for new fields of applications to be included (with example models) are highly welcome.

<http://normsys.h-its.org/>

Format Classes

Systems Biology Markup Language (SBML)

[Formats](#)[Details](#)

CellML

[Formats](#)[Details](#)

Systems Biology Graphical Notation (SBGN)

[Formats](#)[Details](#)

Simulation Experiment Description Markup Language (SED-ML)

[Formats](#)[Details](#)

Pharmacometrics Markup Language (pharmML)

[Formats](#)[Details](#)

NeuroML

[Formats](#)[Details](#)

FieldML

[Formats](#)[Details](#)

Synthetic Biology Open Language (SBOL)

[Formats](#)[Details](#)

Supported by:



Federal Ministry
for Economic Affairs
and Energy

NORMSYS



Show results for:

Select

Format

or filter by

Format class

 Systems Biology Markup Language (S)

Biological application

Modeling formalism

Software

Api language

Supported biological scale

- molecular
- cellular
- tissue
- organ
- organism
- ecosystem

Spatial representation

- Compartment
- Dimensions

Standard Formats

Displaying: 1 Found: 1 Total: 16

SBML L3V1 Core

Systems Biology Markup Language Level 3 Version 1 Core

Synopsis

Representation of biological processes as a set of processes, that are converting pools of entities into other pools entities.

Description

Systems Biology Markup Language (SBML), a free, open, XML-based format for representing biochemical reaction networks. SBML is a software-independent language for describing models common to research in many areas of computational biology, including cell signaling pathways, metabolic pathways, gene regulation, and others.*

*(M. Hucka et al. Bioinformatics (2003) 19 (4): 524-531)

[Biological Applications](#) [Class](#) [Details](#) [License](#) [Links](#) [Transformations](#) [APIs](#) [Validator](#)

Publication Date

© 10/2010

Authors

 Hucka, Michael
 Sahle, Sven

 Bergmann, Frank
 Schaff, James

 Hoops, Stefan
 Smith, Lucian

 Keating, Sarah
 Wilkinson, Darren

Organizations

- combine

Biological Scales

Scale	molecular	cellular	tissue	organ	organism	ecosystem
Support	intrinsic	potential	potential	unknown	unknown	potential



Show results for:

Select

Format

or filter by

Format class

 Systems Biology Markup Language (f)

Biological application

Modeling formalism

Software

Api language

Supported biological scale

molecular

Standard Formats

Displaying: 1 Found: 1 Total: 16

SBML L3V1 Core

Systems Biology Markup Language Level 3 Version 1 Core

Synopsis

Representation of biological processes as a set of processes, that are converting pools of entities into other pools entities.

Description

Systems Biology Markup Language (SBML), a free, open, XML-based format for representing biochemical reaction networks. SBML is a software-independent language for describing models common to research in many areas of computational biology, including cell signaling pathways, metabolic pathways, gene regulation, and others.*

*(M. Hucka et al. Bioinformatics (2003) 19 (4): 524-531)

Biological Applications	Class	Details	License	Links	Transformations	APIs	Validator
Webpage	Specification			Publication			
	<ul style="list-style-type: none">• SBML			<ul style="list-style-type: none">• The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models.			
Model repository	Software Repository			<ul style="list-style-type: none">• SBML Software Guide			



Show results for:

Select

Format

or filter by

Format class

Systems Biology Markup Language (!)

Biological application

Modeling formalism

Software

Api language

Supported biological scale

- molecular
- cellular
- tissue
- organ
- organism
- ecosystem

Spatial representation

- Compartment

Standard Formats

Displaying: 1 Found: 1 Total: 16

SBML L3V1 Core

Systems Biology Markup Language Level 3 Version 1 Core

Synopsis

Representation of biological processes as a set of processes, that are converting pools of entities into other pools entities.

Description

Systems Biology Markup Language (SBML), a free, open, XML-based format for representing biochemical reaction networks. SBML is a software-independent language for describing models common to research in many areas of computational biology, including cell signaling pathways, metabolic pathways, gene regulation, and others.*

*(M. Hucka et al. Bioinformatics (2003) 19 (4): 524-531)

Biological Applications	Class	Details	License	Links	Transformations	APIs	Validator
					Output		
					SBML L3V1 Core		
					CellML 1.1		
					SBGN PD L1 V1.3		
					NeuroML 2 beta 3		
					SBOL v2.0		
					SBGN-ML 0.2		
SBML L3V1 Core	—	libAntimony	CellDesigner Arcadia		SBML2SBGNML		
CellML 1.1	libAntimony	—	—	—	—	—	—
SBGN PD L1 V1.3	—	—	—	—	—	—	—
NeuroML 2 beta 3	jNeuroML	—	—	—	—	—	—
SBOL v2.0	iBioSim	—	—	—	—	—	—
SBGN-ML 0.2	—	—	—	—	—	—	—

Supported by:



Federal Ministry
for Economic Affairs
and Energy

NORMSYS



Biological Application	Format												Biological Applications		Format Transformation	
	SBML L3 V1 Core	CellML 1.1	SBGN ER L1 V1.2	SBGN PD L1 V1.3	SBGN AF L1 V1.0	MorphML v1.8.1	NeuroML 2 beta 3	PharmML v0.6	SBOL v2.0	SBOL Visual v1.0.0	ChannelML v1.8.1	Biophysics v1.8.1	NetworkML v1.8.1			
<u>Multi-organism Process</u>	✓	✓	—	—	—	—	—	—	—	—	—	—	—	—	—	
<u>Cell Cycle</u>	✓	✓	✓	—	—	—	—	—	—	—	—	—	—	—	—	
<u>Signaling</u>	✓	✓	✓	✓	✓	—	—	—	—	—	—	—	—	—	—	
<u>Single Cell Morphology</u>	—	—	—	—	—	✓	✓	—	—	—	—	—	—	—	—	
<u>Pharmacokinetic</u>	✓	✓	—	—	—	—	—	✓	—	—	—	—	—	—	—	
<u>Pharmacodynamics</u>	✓	✓	—	—	—	—	—	✓	—	—	—	—	—	—	—	
<u>Izhikevich-based Neuron Models</u>	✓	—	—	—	—	—	✓	—	—	—	—	—	—	—	—	
<u>Synthetic Gene Regulatory Network</u>	✓	—	✓	✓	✓	—	—	—	✓	✓	—	—	—	—	—	
<u>Metabolic Process</u>	✓	✓	—	✓	—	—	—	✓	—	—	—	—	—	—	—	
<u>Immune Response</u>	✓	✓	—	—	✓	—	—	—	—	—	—	—	—	—	—	
<u>Circadian Rhythm</u>	✓	✓	✓	—	—	—	✓	—	—	—	—	—	—	—	—	
<u>Regulation of Gene Expression</u>	✓	✓	✓	✓	✓	—	—	—	✓	✓	—	—	—	—	—	
<u>Electrophysiology</u>	✓	✓	—	—	—	—	✓	—	—	✓	✓	✓	—	—	—	

Given the FullXSD schema, the given model has 1 errors!



Given the FullXSD schema, the given model has 1 errors!



Validation

You can validate your xml model file against a selected format.

This validation is using libxml2 (<http://xmlsoft.org/>) to process the xml file using the Format's xsd schema (and dependencies).

After you select the Format your model is for, and upload a model file (*.xml), the file will be validated on this server. Upon completion you should see on top, if it was successful.

The two tabs below show the model file (with annotated errors if there are such). Alternatively, all errors can be inspected as a table.

Format

Systems Biology Markup Language Level 2 Version 5

Model file as xml

Datei auswählen Keine Datei...ausgewählt

Validate Model File

Model File

XML Errors 1

External resource annotation 2

RDF Graphs 37

Alternative Validators

XML Errors; jump to: 7

External Resource Problems; jump to:

```
1 <?xml version='1.0' encoding='UTF-8' standalone='no'?>
2
3 <!-- This model was downloaded from BioModels Database -->
4 <!-- Mon Oct 10 15:40:40 BST 2016 -->
5 <!-- http://www.ebi.ac.uk/biomodels/ -->
```



NormSys Registry for Modelling Standards

- **Information** resource for community standards
- **Comparison** of their main characteristics and features
- **Classification** by fields of application (with examples)
- **Transformation** options between the standards
- **Bundled links** to corresponding web resources: specifications, websites, publications, repositories, APIs...
- **Faceted browsing** and search by different criteria
- **Validation** of models for several standards
- COMBINE standards and related efforts (for a start)



<http://normsys.h-its.org/>

Supported by:



Federal Ministry
for Economic Affairs
and Energy

Lessons learned from 10 years of declarative multicellular modeling

- MorpheusML
 - xml-language of open-source framework Morpheus [3,4], Specs in [5] by Jörn Starruß and Walter de Back
 - similar to combination of SBML L3 packages dyn(CBO)+spatial+comp
- Model repository [1] and 30+ scientific applications [2]
 - Separation of bio/physics from spatial model-formalisms
 - Entity-changing operations (birth/death of submodels)
 - Lexical and spatial scoping (using cell-cell neighbor relations)
 - Symbol dependency network to automatically schedule order of updates and generate sequential scheme

[1] <https://imc.zih.tu-dresden.de/wiki/morpheus/doku.php?id=examples:examples>

[2] <https://academic.oup.com/bioinformatics/CrossRef-CitedBy/234757>

[3] <https://morpheus.gitlab.io>

[4] Starruß et al., J. Stat. Phys. 128, 269 (2007). DOI: 10.1007/s10955-007-9298-9

[5] Starruß et al., Bioinformatics 30, 1331 (2014). DOI:

<http://dx.doi.org/10.1093/bioinformatics/btt772>

Structure: separating bio/physics from spatial model formalisms

```
<?xml version='1.0' encoding='UTF-8'?>
<MultiCellML version="0.2" xmlns="...">
  <Model name="...">
    <Description> (optional) </Description>
    <Space symbol="space"> (required) ...physical, boundary conditions... </Space>
    <Time symbol="time"> (optional) </Time>
    <ListOfSpatialCompartmentTypes> (required)
      <GlobalType> (required) ...properties, dynamics, nesting of comp. </GlobalType>
      <SolidType> (optional, one or multiple) </SolidType>
      <LiquidType> (optional, one or multiple) </LiquidType>
      <CellType> (optional, one or multiple) ...incl. SBML-defined dynamics... </CellType>
    </ListOfSpatialCompartmentTypes>
    <ListOfInteractions> (opt.) inter-entity processes and neighborhoods </ListOfInteractions>
  </Model>
  <Simulation>
    ...parametrization of various spatial model formalisms (vertex, CPM, CBM...)
  </Simulation>
</MultiCellML>
```



Nesting of spatial compartments

```
<ListOfSpatialCompartmentTypes>
    <GlobalType>
        ...dynamical system definition from referenced SBML...
        <SpatialSubCompartmentTypes space-tiling="true">
            <CompartimeType ref="ct1" />
            <CompartimeType ref="ct2" />
            <CompartimeType ref="medium" />
        </SpatialSubCompartmentTypes>
        <BoundaryValues default="medium">
            <BoundaryValue axis= "x" value="solid1" />
        </BoundaryValues>
    </GlobalType>
```

-> Nesting tree of arbitrary depth incl. all spatial compartment types

Cell type declaration

```
<CellType name="..." id="...">
    <Volume value="...">
        <cpm::VolumeConstraint strength="..."/>
        <vertex::VolumeConstraint strength="..."/>      (optional framework-specific
                                                    parameters)
    </Volume>
    <Surface value="..." mode="absolute/asphericity">
        <cpm::SurfaceConstraint strength="..."/>
        <vertex::SurfaceConstraint strength="..."/>
    </Surface>
    <SurfaceCompartment>
        ... optional, dynamical system definition for states along object shape...
    </SurfaceCompartment>

    ...optional, dynamical system definition from referenced SBML...

    <ListOfEntityProcesses>
        ...processes changing number of entities of given CellType, following CBO...
    </ListOfEntityProcesses>
</CellType>
```

Parametrization of model formalisms

```
<Simulation>
  <StopTime value="1.0"/>
  <RandomSeed value="0"/>
  <DefaultTemporalSolver solver="..." time-step="1.0">
    <SpatialFramework>
      <Vertex>
        ...
      </Vertex>
      <CPM>
        <Lattice class="square/hexagonal/cubic">
          <NodeLength value="1.0"/>
        </Lattice>
        <MonteCarloSampler stepper="edgelist">
          <MCSDuration value="1.0"/>
          <Neighborhood>
            <Order>2</Order>
          </Neighborhood>
          <MetropolisKinetics temperature="10.0"/>
        </MonteCarloSampler>
      </CPM>
      ...
    </SpatialFramework>
```

Model example in MultiCellML and derived simulator-specific codes

Multicellular model in MultiCellML

Cell_Sorting_MultiCellML.xml – Datei

Dokumente Projekte

```
<ListofSpatialCompartmentTypes>
  <CellType name="Cell Type 1" id="ct1">
    <Volume value="50">
      <cpr::VolumeConstraint strength="0.1"/>
      <vertex::VolumeConstraint strength="0.1"/>
    </Volume>
    <Surface value="1.0" mode="asphericity">
      <cpr::SurfaceConstraint strength="0.01"/>
      <vertex::SurfaceConstraint strength="0.01"/>
    </Surface>
  </CellType>
  <CellType name="Cell Type 2" id="ct2">
    <Volume value="50">
      <cpr::VolumeConstraint strength="0.1"/>
      <vertex::VolumeConstraint strength="0.1"/>
    </Volume>
    <Surface value="1.0" mode="asphericity">
      <cpr::SurfaceConstraint strength="0.01"/>
      <vertex::SurfaceConstraint strength="0.01"/>
    </Surface>
  </CellType>
  <LiquidType name="Medium" id="medium">
  </LiquidType>
</ListofSpatialCompartmentTypes>
<ListofInteractions>
  <SurfaceInteraction default="0.0">
    <Contact type1="ct1" type2="ct2" value="0.5"/>
    <Contact type1="ct1" type2="medium" value="0.2"/>
    <Contact type1="ct2" type2="medium" value="1.0"/>
    <Contact type1="ct2" type2="ct2" value="0.1"/>
    <Contact type1="ct1" type2="ct1" value="0.1"/>
  </SurfaceInteraction>
</ListofInteractions>
```

Rückgängig Wiederherstellen

Zeile: 59 von 131 Spalte: 25 Zeichen: 3 694 ZEILE EINF Cell_Sorting_MultiCellML.xml UTF-8

Translation for Morpheus simulator

```
<CellTypes>
  <CellType class="spatial" name="ct1">
    <VolumeConstraint target="50" strength="0.1"/>
    <SurfaceConstraint target="1.0" mode="asphericity" strength="0.01"/>
    <Chemotaxis field="chem" strength="0.05" retraction="false"/>
    <NeighborhoodReporter>
      <Input scaling="length" value="cell.type == celltype.ct2.id"/>
      <Output symbol-ref="fl" mapping="sum"/>
    </NeighborhoodReporter>
  </CellType>
  <CellType class="biological" name="ct2">
    <VolumeConstraint target="50" strength="0.1"/>
    <SurfaceConstraint target="1.0" mode="asphericity" strength="0.01"/>
  </CellType>
  <CellType class="medium" name="medium"/>
</CellTypes>
<CP>
  <Interaction default="0.0">
    <Contact type1="ct1" type2="ct2" value="0.5"/>
    <Contact type1="ct1" type2="medium" value="0.2"/>
    <Contact type1="ct2" type2="medium" value="1.0"/>
    <Contact type1="ct2" type2="ct2" value="0.1"/>
    <Contact type1="ct1" type2="ct1" value="0.1"/>
  </Interaction>
  <MonteCarloSampler stepper="edgelist">
    <MetropolisKinetics temperature="0.2"/>
    <Neighborhood>
      <Order></Order>
    </Neighborhood>
    <MCSDuration value="0.01"/>
  </MonteCarloSampler>
  <ShapeSurface scaling="norm">
    <Neighborhood>
```

Zeile: 50 von 131 Spalte: 59 Zeichen: 3 751 ZEILE EINF Cell_Sorting_MorpheusML.xml UTF-8

Code generation for Chaste, M3 and other simulators

```
// Create PottsUpdateRule
MAKE_PTR(VolumeConstraintPottsUpdateRule<2>, p_volume_constraint_update_rule);
p_volume_constraint_update_rule->SetMatureCellTargetVolume(16);
p_volume_constraint_update_rule->SetFormationEnergyParameter(0.1);
simulator.AddUpdateRule(p_volume_constraint_update_rule);

// Create SurfaceAreaConstraintPottsUpdateRule
MAKE_PTR(SurfaceAreaConstraintPottsUpdateRule<2>, p_surface_constraint_update_rule);
p_surface_constraint_update_rule->SetMatureCellTargetSurfaceArea(16);
p_surface_constraint_update_rule->SetFormationEnergyParameter(0.01);
simulator.AddUpdateRule(p_surface_constraint_update_rule);

// Create DifferentialAdhesionPottsUpdateRule
MAKE_PTR(DifferentialAdhesionPottsUpdateRule<2>, p_differential_adhesion_update_rule);
p_differential_adhesion_update_rule->SetLabelledCellLabelledCellAdhesionEnergyParameter(0.1);
p_differential_adhesion_update_rule->SetLabelledCellCellAdhesionEnergyParameter(0.5);
p_differential_adhesion_update_rule->SetCellCellAdhesionEnergyParameter(0.1);
p_differential_adhesion_update_rule->SetCellBoundaryAdhesionEnergyParameter(0.2);
p_differential_adhesion_update_rule->SetLabelledCellBoundaryAdhesionEnergyParameter(1.0);
simulator.AddUpdateRule(p_differential_adhesion_update_rule);

// Run simulation

```

Aktuelles Projekt

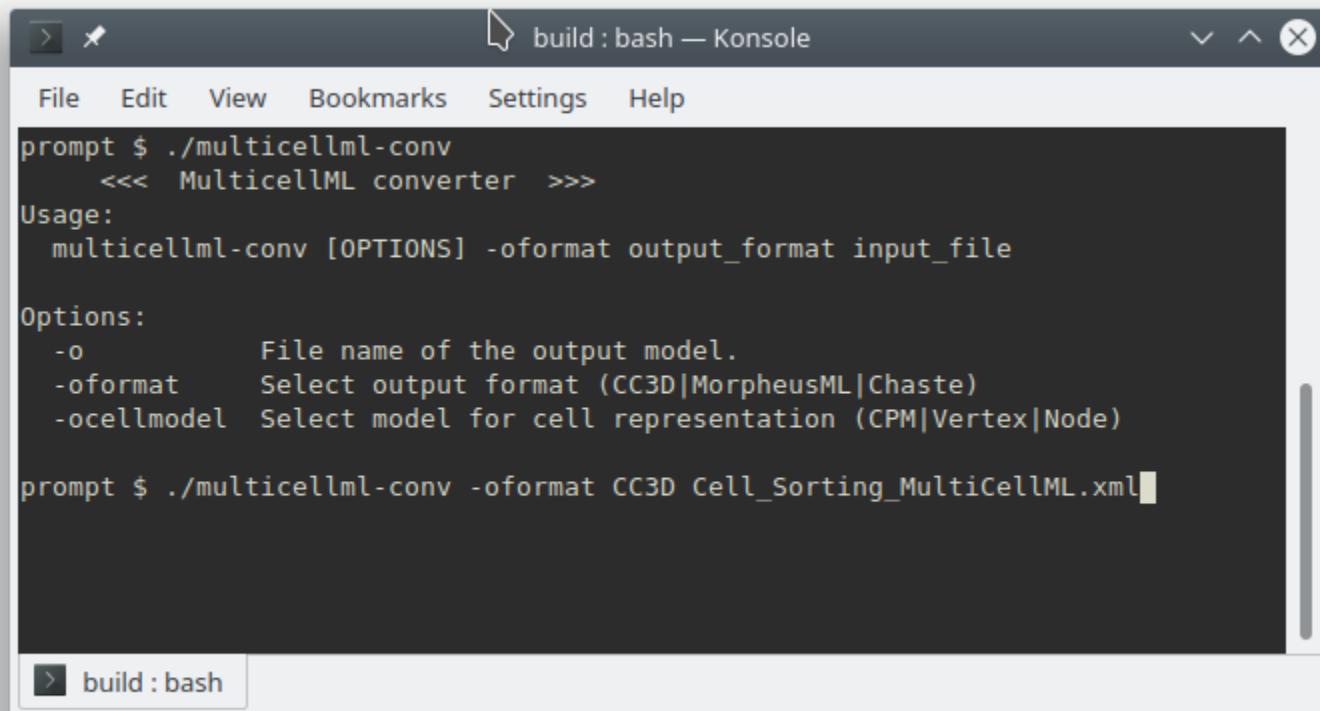
Zeile: 220 von 502 Spalte: 1 Zeichen: 20 588 BLOCK EINF Cell_Sorting_Chaste.hpp UTF-8 Zeile: 33 von 50 Spalte: 47 Zeichen: 1 705 ZEILE EINF Cell_Sorting_CC3DML.xml UTF-8

Conversion for CompuCell3D simulator

```
<Plugin Name="CellType">
  <CellType Id="1" TypeName="ct1"/>
  <CellType Id="2" TypeName="ct2"/>
  <CellType Id="0" TypeName="Medium"/>
</Plugin>
<Plugin Name="Volume">
  <VolumeEnergyParameters TargetVolume="50" LambdaVolume="0.1" CellType="ct1"/>
  <VolumeEnergyParameters TargetVolume="50" LambdaVolume="0.1" CellType="ct2"/>
</Plugin>
<Plugin Name="Surface">
  <SurfaceEnergyParameters CellType="ct1" TargetSurface="25.0663" LambdaSurface="0.01"/>
  <SurfaceEnergyParameters CellType="ct2" TargetSurface="25.0663" LambdaSurface="0.01"/>
</Plugin>
<Plugin Name="Contact">
  <Energy Type1="ct1" Type2="ct2">0.166667</Energy>
  <Energy Type1="ct1" Type2="Medium">>0.066667</Energy>
  <Energy Type1="ct2" Type2="Medium">>0.333333</Energy>
  <Energy Type1="ct2" Type2="ct1">0.0333333</Energy>
  <Energy Type1="ct1" Type2="ct1">0.0333333</Energy>
  <NeighborOrder>2</NeighborOrder>
</Plugin>
```

Zeile: 19 von 39 Spalte: 59 Zeichen: 3 751 ZEILE EINF Cell_Sorting_CC3DML.xml UTF-8

Converter using libMultiCellML as testbed for specification



The screenshot shows a terminal window titled "build : bash — Konsole". The window contains the following text:

```
prompt $ ./multicellml-conv
    <<< MulticellML converter  >>>
Usage:
    multicellml-conv [OPTIONS] -oformat output_format input_file

Options:
    -o          File name of the output model.
    -oformat     Select output format (CC3D|MorpheusML|Chaste)
    -ocellmodel Select model for cell representation (CPM|Vertex|Node)

prompt $ ./multicellml-conv -oformat CC3D Cell_Sorting_MultiCellML.xml
```

The terminal window has a dark background and light-colored text. The title bar says "build : bash — Konsole". The bottom left corner of the window frame also displays the text "build : bash".

Simulation in CompuCell3D

Cell_Sorting_CC3DML.cc3d - CompuCell3D Player

File View Simulation Visualization Tools Window Help

Model Editor

Property	Value
> Potts	Potts
> Steppable	FlexibleDiffusionSolverFE
Plugin	CellType
CellType	TypId 1 TypeName ct1
CellType	TypId 2 TypeName ct2
CellType	TypId 0 TypeName Medium
> Plugin	Volume
> Plugin	Surface
> Plugin	Chemotaxis
> Plugin	Contact
> Steppable	BlobInitializer

xy 0 Cell_Field

Y

X

MC Step: 1510 Min: 0 Max: 0

Simulation in Morpheus

Morpheus - Cell Sorting_MorpheusML.xml

File Examples About
Open Save local Start Stop

Documents
Cell_Sorting_Morpheus...
Description Space Time Global CellTypes CPM CellPopulations Analysis ParamSweep

FixBoard

JobQueue
Process Prc
Job 21 Job 20 Job 19
Starting Job 19 Starting Job 20 Starting Job 21

Element Name/Symbol
CellType ct1
VolumeConstraint SurfaceConstraint
CellType ct2
VolumeConstraint SurfaceConstraint
CellType medium

Attributes:
mode asphericity
strength 0.01
target 1.0
 name ...

Symbols
Symbol Description
> cell
> celtype
chem Chemical fractional_length
> fl
> size
> space
time

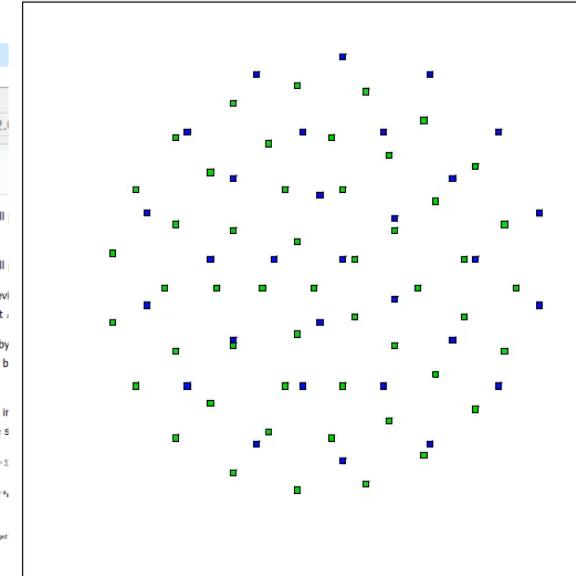
Plugins
Plugin Category

Documentation
NeighborhoodVectorReporter
PersistentMotion
Property
PropertyVector
Protrusion
SurfaceConstraint
System

CellType ID

SurfaceConstraint
Penalizes deviations from target cell
More...
Penalizes deviations from target cell
The surface constraint penalizes deviation of surface area ϵ_{surf} from a given target ϵ_{target} . This models the cell cortex rigidity by surface area to its volume (or ratio b 2D). The target can be defined explicitly in asphericity mode as a multiple of the surface area. The Hamiltonian is given by $E_{Surface} = \frac{1}{2} \int \epsilon_{surf}^2$. For each proposed copy attempt $\epsilon_{before} \rightarrow \epsilon_{after}$, energy is computed as:
$$\Delta E = \lambda \cdot ((\epsilon_{before} - \epsilon_{target})^2 - (\epsilon_{after} - \epsilon_{target})^2)$$
 where

- λ is strength of the constraint
- ϵ_{before} is the current surface area
- ϵ_{after} is the projected (if updated would be accepted) surface area of cell at time t



Model loaded successfully

MultiCellML Roadmap

- Oct. 2018 v0.3 – Jörn's talk and live demo at ICSB, Lyon
- Mid 2019 v0.7
 - benchmark models from [1] declarable
 - libMultiCellML -> Morpheus, CC3D, Chaste
 - exploration of SBML L3 ext. compatibility
 - draft specs (incl. CPM namespace package)
 - hackathon in Dresden/Heidelberg, Germany for MultiCellML support by simulators
- End 2019 v1.0
 - consolidated specs (incl. CPM, Vertex, CBM)
 - repository for multicellular models
- End 2020 v2.0
 - support for Units, MathML, annotations
 - language bindings to libMultiCellML

[1] Osborne et al., Comparing individual-based approaches to modelling the self-organization of multicellular tissues. PLoS Comput Biol 13(2): e1005387. DOI: 10.1371/journal.pcbi.1005387

ISO/IEC 23092 - MPEG-G (Genomic Information Representation)

MPEG-G at a Glance

ISO/IEC 23092

Developed by ISO/IEC JTC 1/SC 29/WG 11
a.k.a. Moving Picture Experts Group (MPEG)

Part 1 DIS

Transport and Storage of
Genomic Information

The technology to
transport and access
data

Part 2 DIS

Coding of Genomic
Information

The compressed
representation

Part 3 CD

APIs

The standard interfaces
with genomic data
applications and formats

Part 4 CD

Reference Software

The standard support to
the implementation of
applications

Part 5 WD

Conformance

The methodology to test
compliance with the
standard

Standardization Workplan

October 2017

Committee Draft

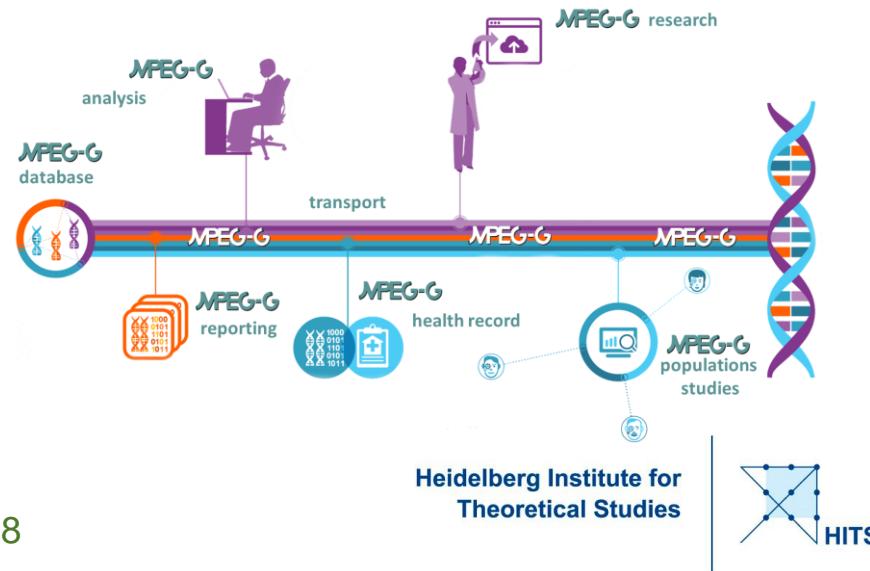
July 2018

Draft International Standard (DIS)

January 2019

Final Draft International Standard (FDIS)

International Standard (IS)



Requirements for data formatting and description in the life sciences for downstream data processing and integration workflows

ISO/TC 276 Biotechnology WG 5 (Data Processing and Integration) works on a draft for a new ISO standard in the life sciences:

Reference framework („hub“) standard for (non-ISO) community standards:

- Rules and application guidelines for community standards for the formatting and documentation of life science data and computer models
- Recommended workflows for the structured processing, storing and integration of data and corresponding computer models
- Catalogue of criteria and requirements for life science data formats and model formats as prerequisites for a framework of interoperable standards

Towards MultiCellML

Jörn Starruß, Walter de Back, Lutz Brsuch

Center for Information Services and High
Performance Computing, TU Dresden, Germany





Heidelberg Institute for
Theoretical Studies



<http://normsys.h-its.org/>

Concept & project lead: Martin Golebiewski

Design: Jill Zander

Implementation: Nils Wötzl

Content: Martin Golebiewski, Alexander Nikolaew

Collaboration partners:

Susanne Hollmann & Bernd Müller-Röber (University of Potsdam)

Babette Regierer (SB ScienceManagement UG, Berlin)

Vitor Martins dos Santos (LifeGlimmer GmbH, Berlin)



Supported by:

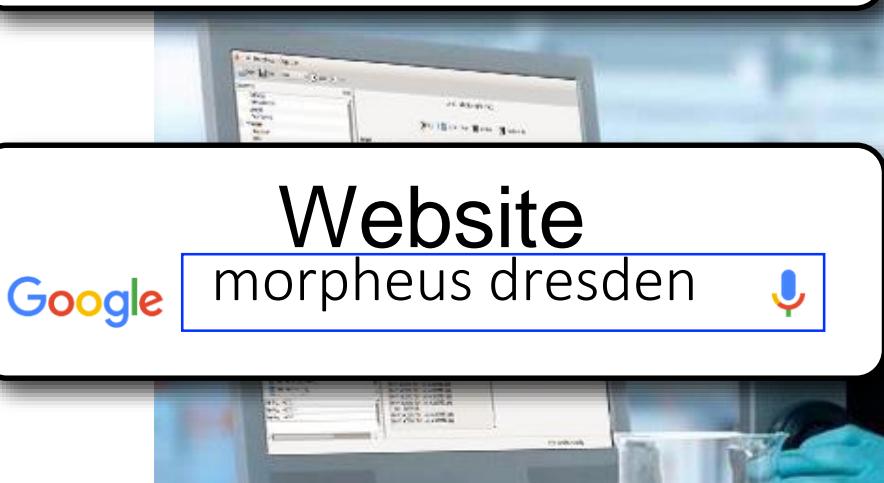
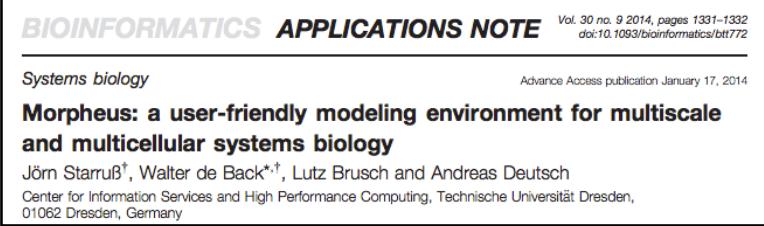


Appendix

Overview of Morpheus

Publication

Starruß et al., *Bioinformatics*, 2014



Website



morpheus dresden

Morpheus 2.0



Open source GPL license
Plugin development
GitLab repository

Available for



Developers

Jörn Starruß (core)
Walter de Back (co)

References

de Back et al., *J RS Interface*, 2012
de Back et al., *BMC Sys Biol*, 2013
Starruß et al., *Bioinformatics*, 2014
Herberg et al., *Cytometry A*, 2015

Funding



Bundesministerium
für Bildung
und Forschung



Models

Job archive

Messages

Start / Stop

Editor

Attributes

Symbols

Docs

Plugins

The screenshot displays the Morpheus software interface with several windows and panels:

- Models:** A sidebar showing project files: CellCycle.xml, CPM, CellPopulations, Analysis, Activatable_2D.xml, and CellSorting_2D.xml.
- Job archive:** A sidebar showing a list of jobs, with "Job 2761" selected.
- Messages:** A panel at the bottom showing log messages related to starting and saving jobs.
- Start / Stop:** A central window showing the state of a model named "Morpheus - CellCycle.xml". It has buttons for Start, Stop, and Step. The status bar indicates "Model loaded successfully".
- Editor:** A window showing the XML structure of the model. It highlights the "System" section under "CellType" and shows properties like "cells", "CDK1", "Plk1", and "APC". It also lists "DiffEqn" and "Constant" expressions.
- Attributes:** A window showing attributes for a system. It includes fields for "solver" (runge-kutta), "time-step" (4e-2), and "time-scaling" (20).
- Symbols:** A window showing a list of symbols and their descriptions. Examples include APC (Anaphase-promoting complex), c (division timeout), cc (cellcount), CDK1 (Cyclin-dependent kinase 1), d (divisions), dPlk1 (Polo-like kinase 1), K (Michaelis constant), n (Hill coefficient), p (portion), and Plk1 (Polo-like kinase 1).
- Documentation:** A sidebar with a tree view of documentation categories: Continuous Process Plugins, Instantaneous Process Plugins, ModelStructure, Symbols, MathExpressions, Plugins, Concepts, and ContactLogger.
- System:** A panel showing the environment for tightly coupled Rule and DiffEqn. It states that expressions with a System are synchronously updated and may contain recurrence relations.
- Plugins:** A table showing the available plugins and their categories.

Models

Job archive

Messages

Morpheus - CellCycle.xml

local Start Stop

Documents

CellCycle.xml
Description
Global
Space
Time
CellTypes
CPM
CellPopulations
Analysis
ParamSweep
ActivatorInhibitor_2D.xml
Description
Global
Space
Time
Analysis
ParamSweep
CellSorter_2D.xml
Documentation JobQueue FixBoard

BIOMD0000000...
Example-Activat...
Example-Activat...
Example-Activat...
Example-Autocri...
Example-CellCyc...
Job 276
Job 2760
Job 2759
Job 2758
Job 2757
Job 2756
Job 2755
Job 2686
Job 2685
Job 2684

Starting job 2758
Saving job 2758
Starting job 2758

Job 2761: Example-CellCycle

Tools

Output file browser

Preview

Simulation output

TIME Schedule Performance Table

```
+ 82.42% = 21230.92[ms] | CPM [Vt] -> [cell.center]
+ 6.32% = 1627.84[ms] | CellDivision [CDK1,c] -> [Vt,c,cell.center,d]
+ 6.01% = 1546.87[ms] | Gnuplotter [CDK1] -> []
+ 4.70% = 1211.54[ms] | DependencyGraph [] -> []
+ 0.37% = 95.89[ms] | Logger [APC,CDK1,Plk1] -> []
+ 0.18% = 24.48[ms] | Server [K,n,α,β,γ,β̂,β̃,β̄,β̅] -> [APC,CDK1,Plk1]
+ 0.01% = 1.80[ms] | Event [CDK1] -> [c]
```

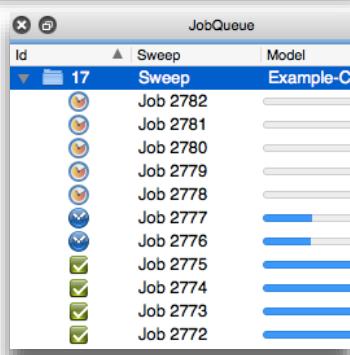
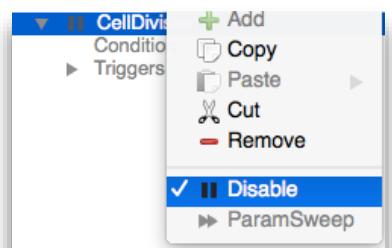
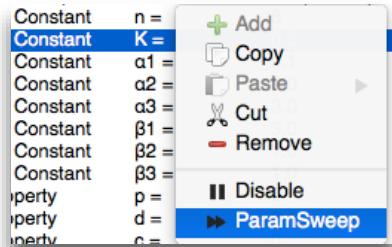
```
==== Simulation finished ====
Init Time      = 0s 102ms
Wall Time     = 25s 758ms
CPU Time      = 22s 210ms (4 threads)

Memory peak = 29.5703 Mb
Deleting scope root
Deleting scope CellType[cells]
```

Model loaded successfully

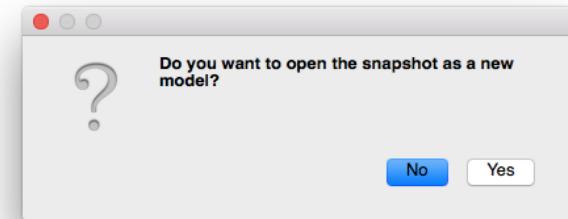
Graphical user interface

Features



Mathematical expressions

In familiar in-fix notation

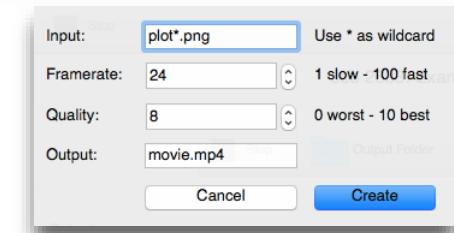


Re-use models

Stored in job archive

Parameter exploration

Batch simulation within GUI

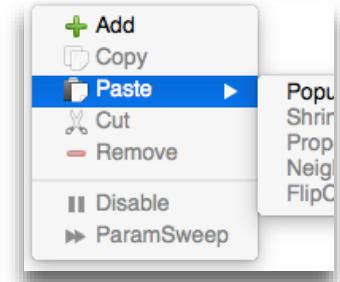


Create movies

From image sequences

Temporarily disable elements

Testing and debugging



Copy-paste elements

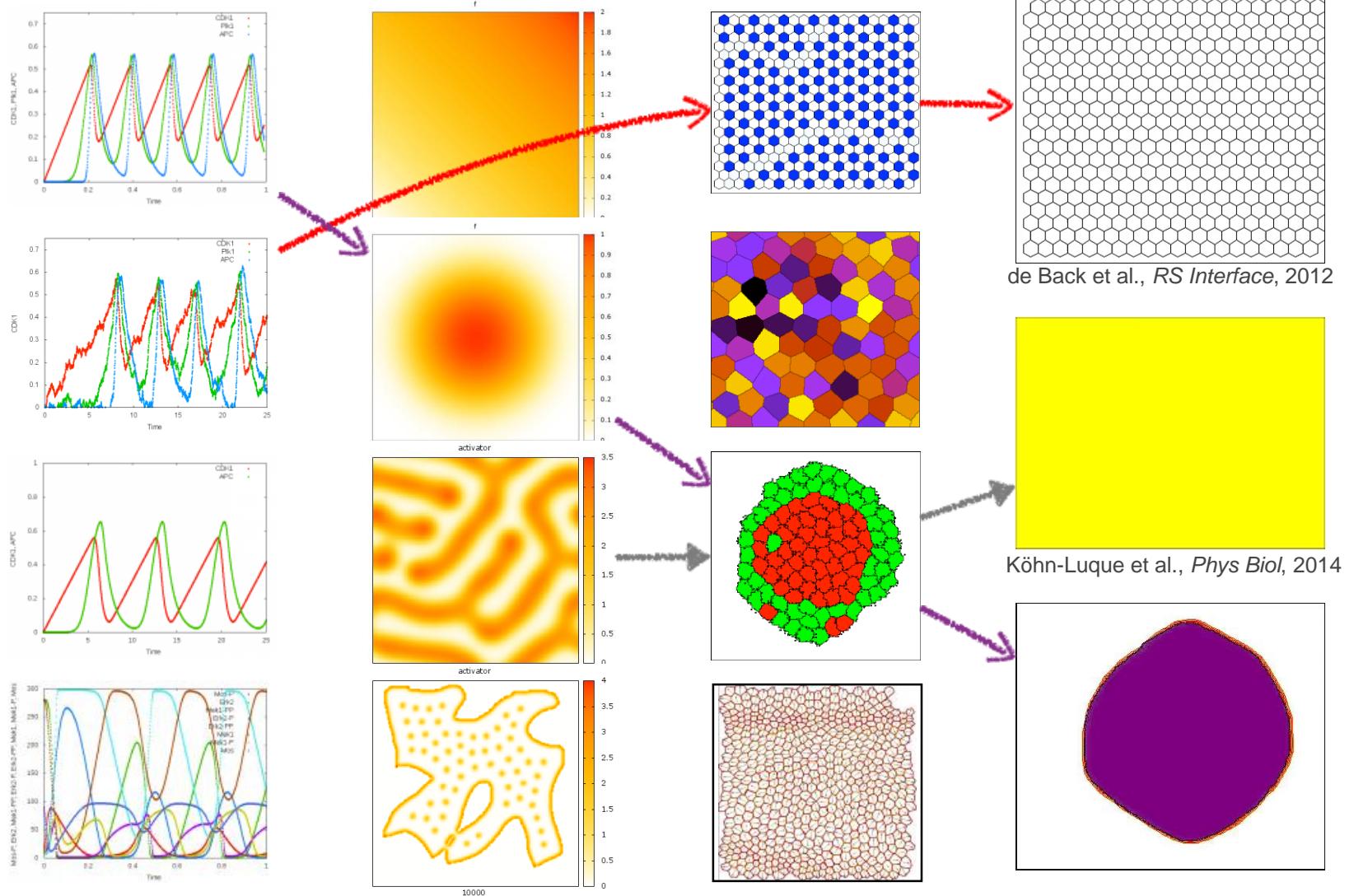
Between different models

Job scheduling

Multithreading and parallel simulation

Multi-scale models

Coupling model formalisms



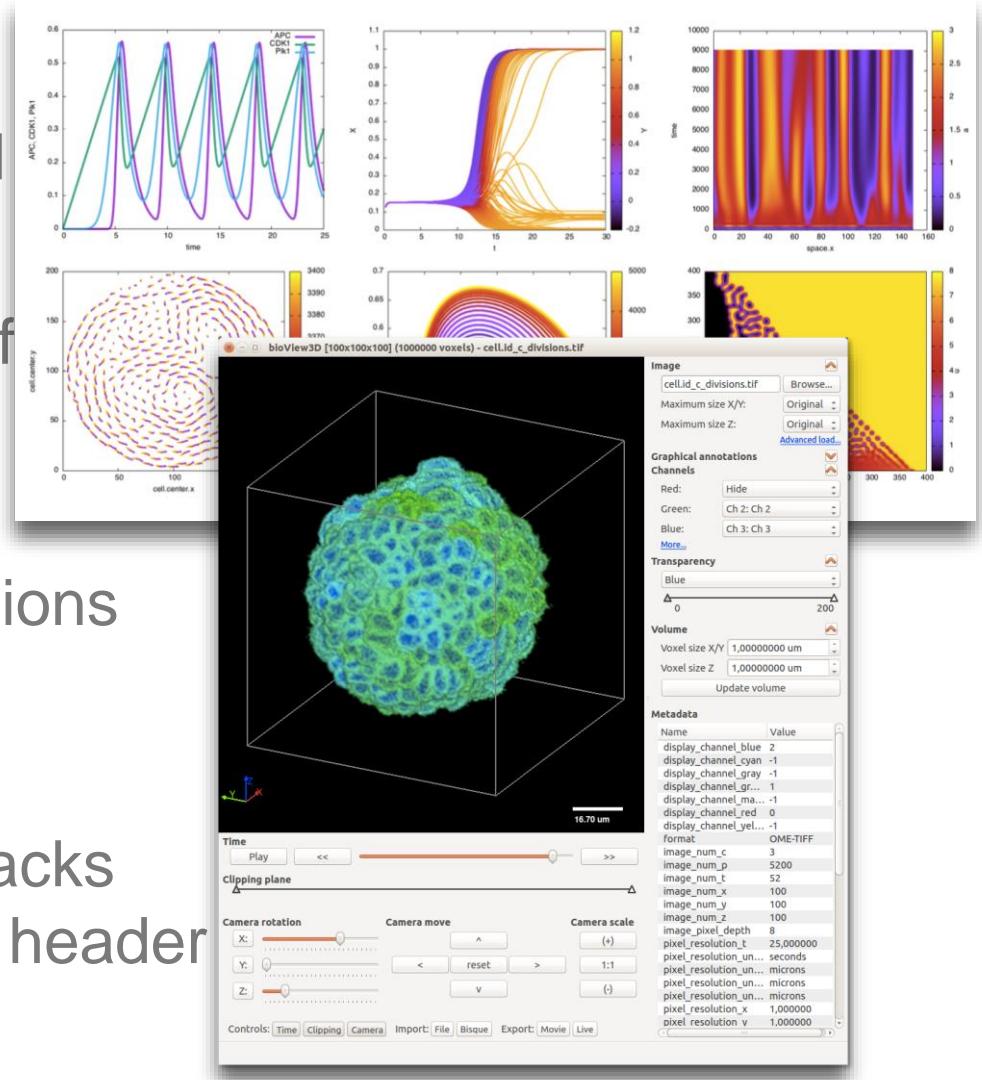
Graphical user interface

Data export and visualization

Gnuplotter
Visualize cell Properties and
Logger
Data export in csv or matrix f
and versatile tool for plotting

HistogramLogger
Compute frequency distributions
and visualization

TIFFPlotter
Export multichannel TIFF stacks
with OME (open microscopy) header



Morpheus in education

Teaching mathematical and computational modeling

Lecture course

Introduction to mathematical biology

TU Dresden

Practical course

Pattern formation in tissues

DIGS-BB (biomedicine and bioengineering)

Summer schools

Math. modeling of tissue mechanics

Euro. Mathematical Society (EMS) and ESMTB

Multiscale Biology

UK Multi-scale biology network, Nottingham

OpenMultiMed Training School in Erlangen

Friedrich Alexander University Erlangen-Nürnberg

Workshops

Computational stem cell biology

German Stem Cell Network (GSCN), and at Helmholtz Centres in Munich, Braunschweig

Multi-scale modeling of biological systems

National University La Plata, Buenos Aires



Code Repository

gitlab.com/morpheus.lab

Git repository
distributed version control

BSD License
permissive open-source

Issue tracker
bugs and features

Documentation
plugin development

Community
distributed development

The screenshot shows a Mac OS X desktop environment with a GitLab project page open in a browser window. The URL in the address bar is <https://gitlab.com/morpheus.lab/morpheus>. The browser window has a title bar with the GitLab logo and the project name. The left sidebar contains links for Project, Activity, Files, Commits, Builds (with 0 builds), Graphs, Milestones, Issues (with 7 issues), Merge Requests (with 2 merge requests), Members, Labels, Wiki, Forks, and a user profile for 'wdeback'. The main content area displays the project's logo, which is a hexagon divided into six triangles colored red, yellow, and blue. Below the logo, the project name 'morpheus' is shown with a gear icon. A brief description states: 'Morpheus is a modeling and simulation environment for multiscale and multicellular systems biology. It is developed by Jörn Starruß and Walter de Back at the TU Dresden, Germany.' To the right of the description is a terminal-like code block containing the following command:

```
git clone git@gitlab.com:morpheus.lab/morpheus.git morpheus
cd morpheus
mkdir build
cd build
cmake ..
make && sudo make install
```

At the bottom of the page, there is a section titled 'Morpheus' with a brief description: 'Morpheus is a modeling and simulation environment for the study of multiscale and multicellular systems. For further information look at <https://imc.zih.tu-dresden.de/wiki/morpheus>'. There is also a note: 'Morpheus has been developed by Jörn Starruß and Walter de Back at the Center for High Performance Computing at the Technische Universität Dresden, Germany.'