LiSyM
Liver Systems Medicine

Bundesministerium
für Bildung
und Forschung

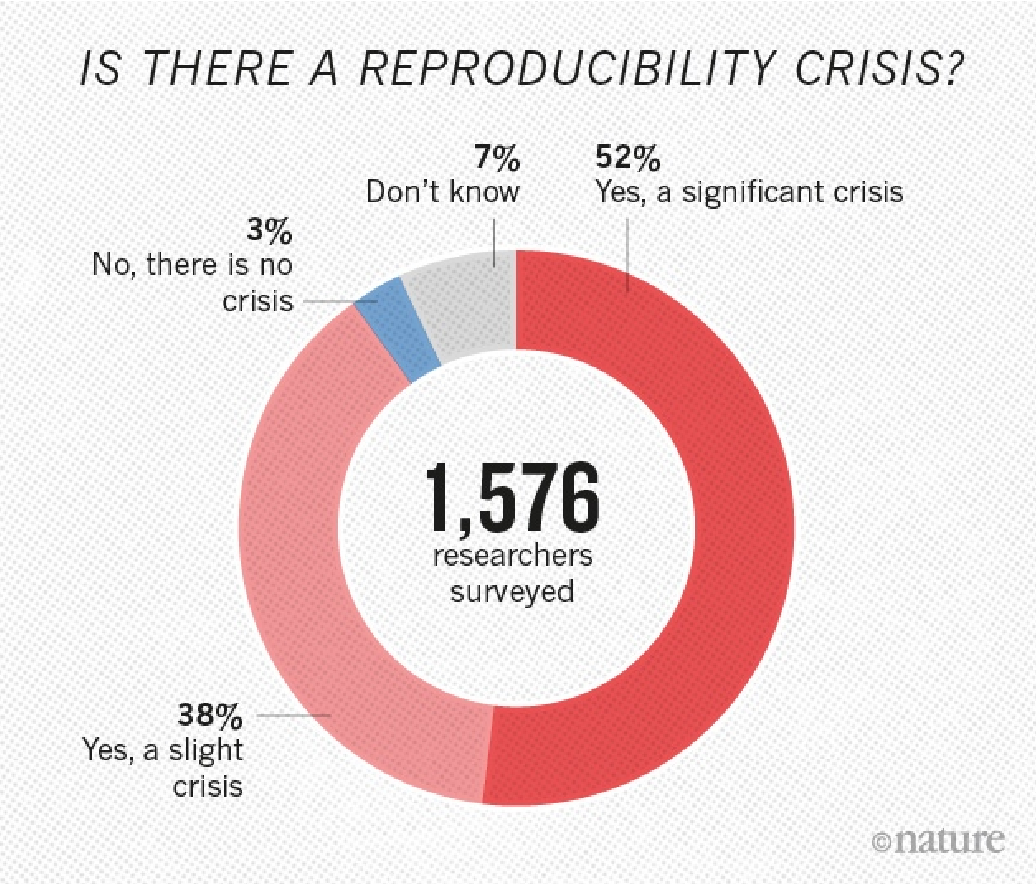
Pathway modeling with SBML

Matthias König, Junior Group, Systems Medicine of the Liver

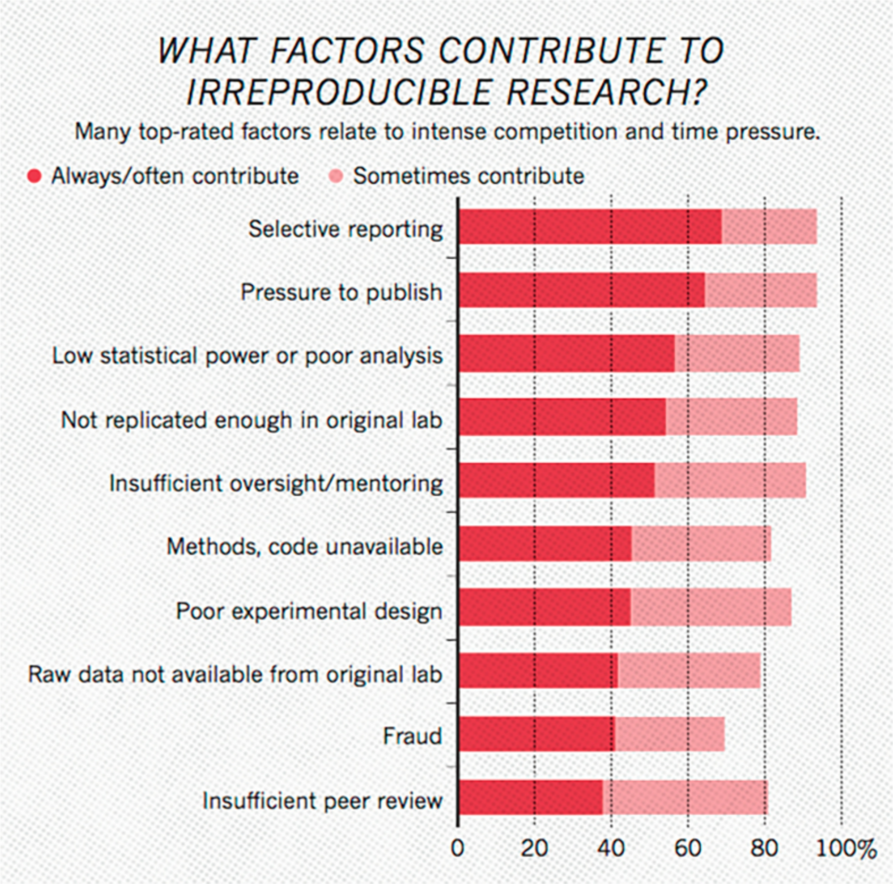
livermetabolism.com
konigmatt

de.NBI
GERMAN NETWORK FOR BIOINFORMATICS INFRASTRUCTURE

Reproducibility crisis


IS THERE A REPRODUCIBILITY CRISIS?

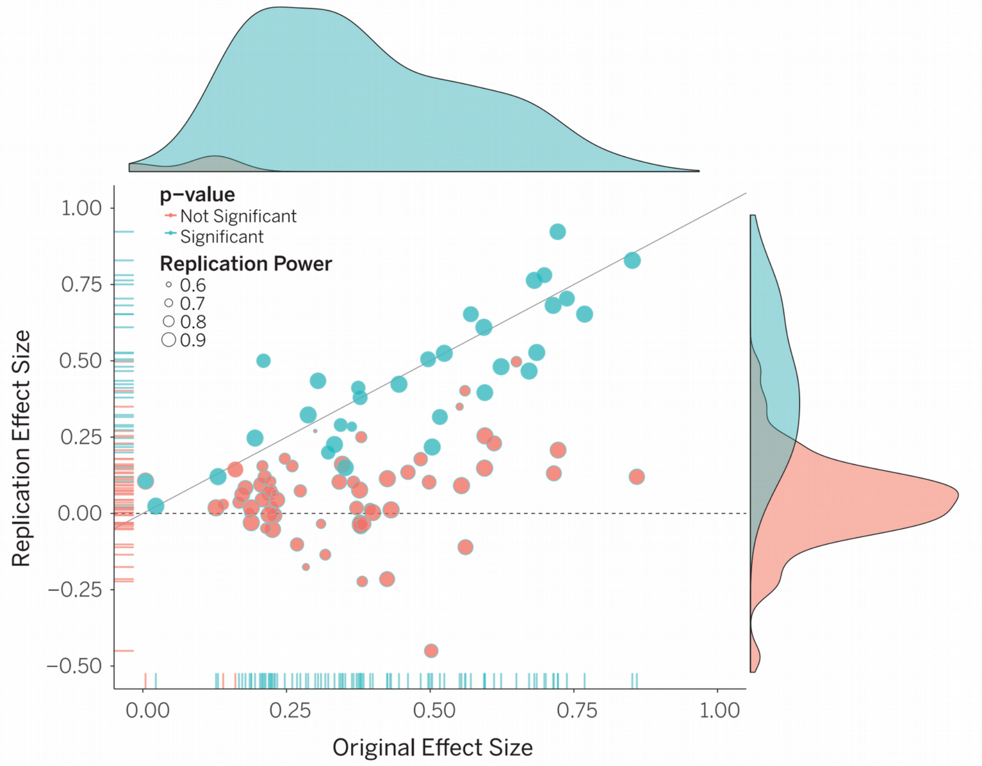
Baker, Nature May 2016, Vol 533, 453


WHAT FACTORS CONTRIBUTE TO IRREPRODUCIBLE RESEARCH?

Many top-rated factors relate to intense competition and time pressure.

FIGURE 5: Plot Representing What Researchers Believe are the Primary Causes of Reproducibility Failure in the Sciences.

Reproducibility efforts



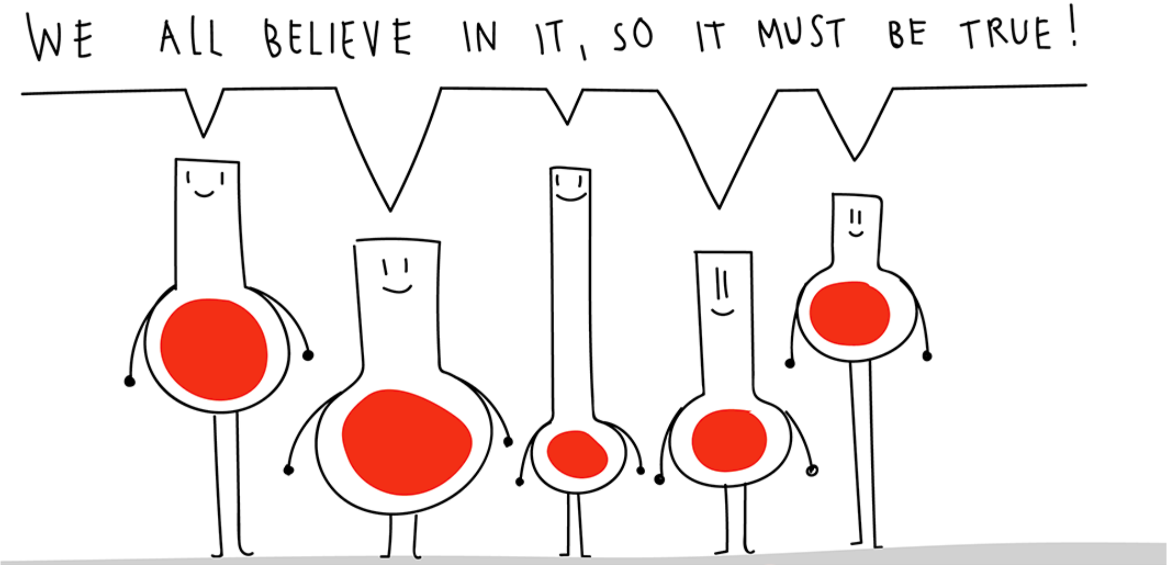
Original study effect size versus replication effect size (correlation coefficients). Diagonal line represents replication effect size equal to original effect size. Dotted line represents replication effect size of 0. Points below the dotted line were effects in the opposite direction of the original. Density plots are separated by significant (blue) and nonsignificant (red) effects.

Open Science Collaboration, Science, August 2015, Vol 349, Issue 6251

- Replication studies of 100 experimental and correlation studies (psychology studies)
- **97%** original statistically significant results, **37%** of replications
- Replication **effects half the magnitude of original**

> “it is impossible to believe most of the computational results shown in conferences and papers”

– Donoho, 2009



“An article about (computational) science in a scientific publication is not the scholarship itself, it is merely advertising of the scholarship.

The actual scholarship is the complete ... set of instructions and data which generated the figures.”

David Donoho, 1998

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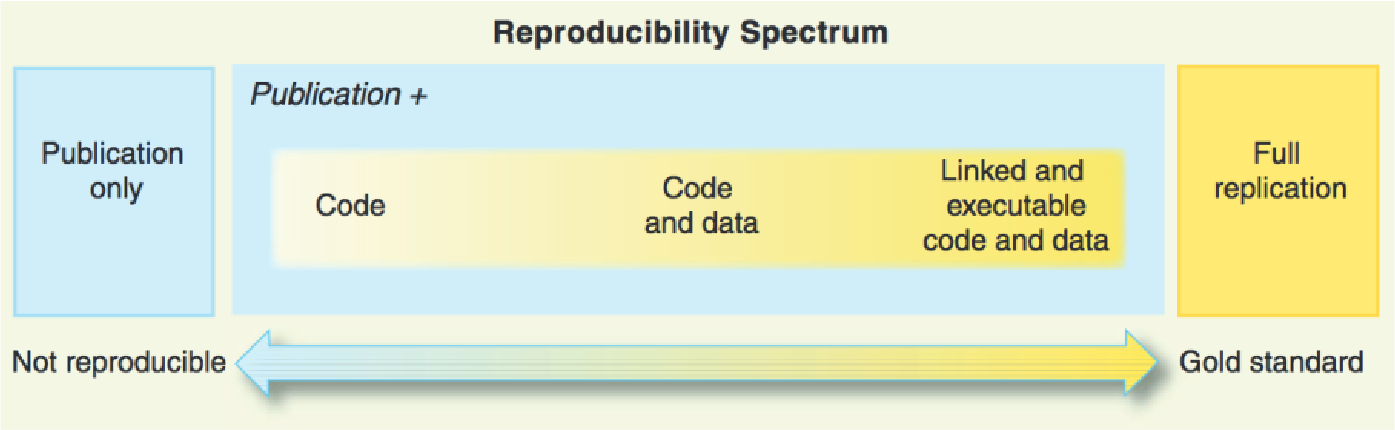


Reproducibility Spectrum

Publication only

Publication +

Code

Code and data

Linked and executable code and data

Full replication

Not reproducible

Gold standard

Full set of model instructions (ODE)

$$\dot{S}_1 = J_0 - v_1$$

$$\dot{S}_2 = v_1 - v_2$$

$$\dot{S}_3 = 2v_2 - v_3 - v_8$$

$$\dot{S}_4 = v_3 - v_4$$

$$\dot{S}_5 = v_4 - v_5$$

$$\dot{S}_6 = v_5 - v_6 - J$$

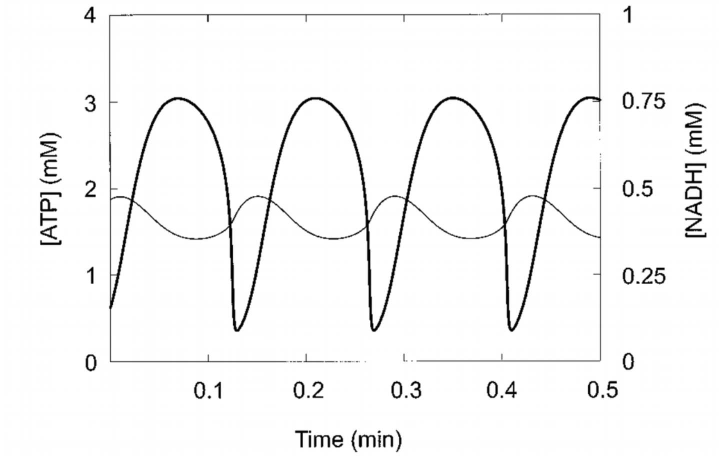
$$\dot{S}_6^{ex} = \varphi J - v_9$$

$$\dot{A}_3 = -2v_1 + v_3 + v_4 - v_7$$

$$\dot{N}_2 = v_3 - v_6 - v_8$$

TABLE 1 Parameter Values

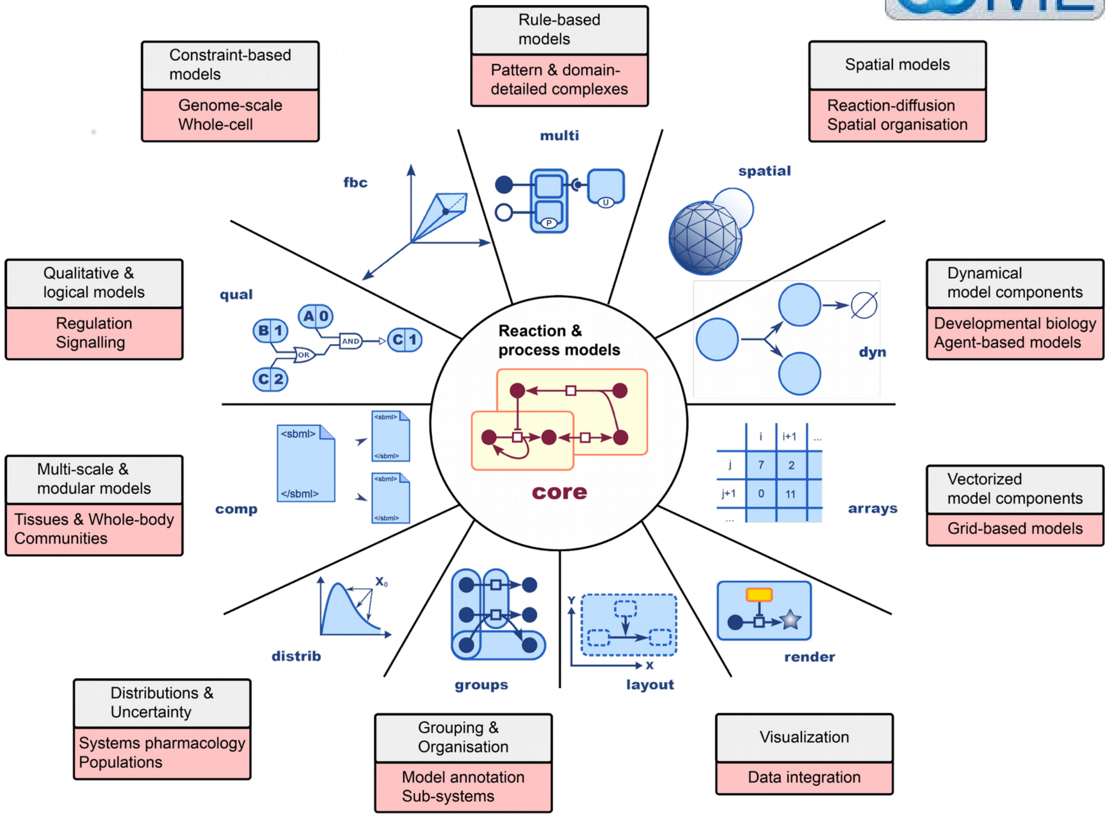
Parameter	Value
J_0	50.0 $\text{mM} \cdot \text{min}^{-1}$
k_1	550.0 $\text{mM}^{-1} \cdot \text{min}^{-1}$
K_i	1.0 mM
k_2	9.8 min^{-1}
k_{GAPDH+}	323.8 $\text{mM}^{-1} \cdot \text{min}^{-1}$
k_{GAPDH-}	57823.1 $\text{mM}^{-1} \cdot \text{min}^{-1}$
k_{PGK+}	76411.1 $\text{mM}^{-1} \cdot \text{min}^{-1}$
k_{PGK-}	23.7 $\text{mM}^{-1} \cdot \text{min}^{-1}$
k_4	80.0 $\text{mM}^{-1} \cdot \text{min}^{-1}$
k_5	9.7 min^{-1}
k_6	2000.0 $\text{mM}^{-1} \cdot \text{min}^{-1}$
k_7	28.0 min^{-1}
k_8	85.7 $\text{mM}^{-1} \cdot \text{min}^{-1}$
κ	375.0 min^{-1}
φ	0.1
A	4.0 mM
N	1.0 mM
n	4



$$v_3 = \frac{k_{GAPDH+}k_{PGK+}S_3N_1(A-A_3) - k_{GAPDH-}k_{PGK-}S_4A_3N_2}{k_{GAPDH-}N_2 + k_{PGK+}(A - A_3)}$$

Standardization

- Reproducible & exchangeable model encoding (**SBML**)
- Annotations to modelling, biological and medical ontologies (**SBML core**)
- Hierarchical models/multi-scale models (**SBML comp**)
- Model quality: validation, modeling practices, unit checking
- Distributions in models & uncertainty in data and parameters (**SBML distrib**)
- Mass- & charge balance (**SBML fbc**)
- **Use wide range of tool ecosystem** (visualization, parameter fitting, simulation, ...)



Constraint-based models
Genome-scale
Whole-cell

Rule-based models
Pattern & domain-detailed complexes

Spatial models
Reaction-diffusion
Spatial organisation

Qualitative & logical models
Regulation
Signalling

Dynamical model components
Developmental biology
Agent-based models

Multi-scale & modular models
Tissues & Whole-body
Communities

Vectorized model components
Grid-based models

Distributions & Uncertainty
Systems pharmacology
Populations

Grouping & Organisation
Model annotation
Sub-systems

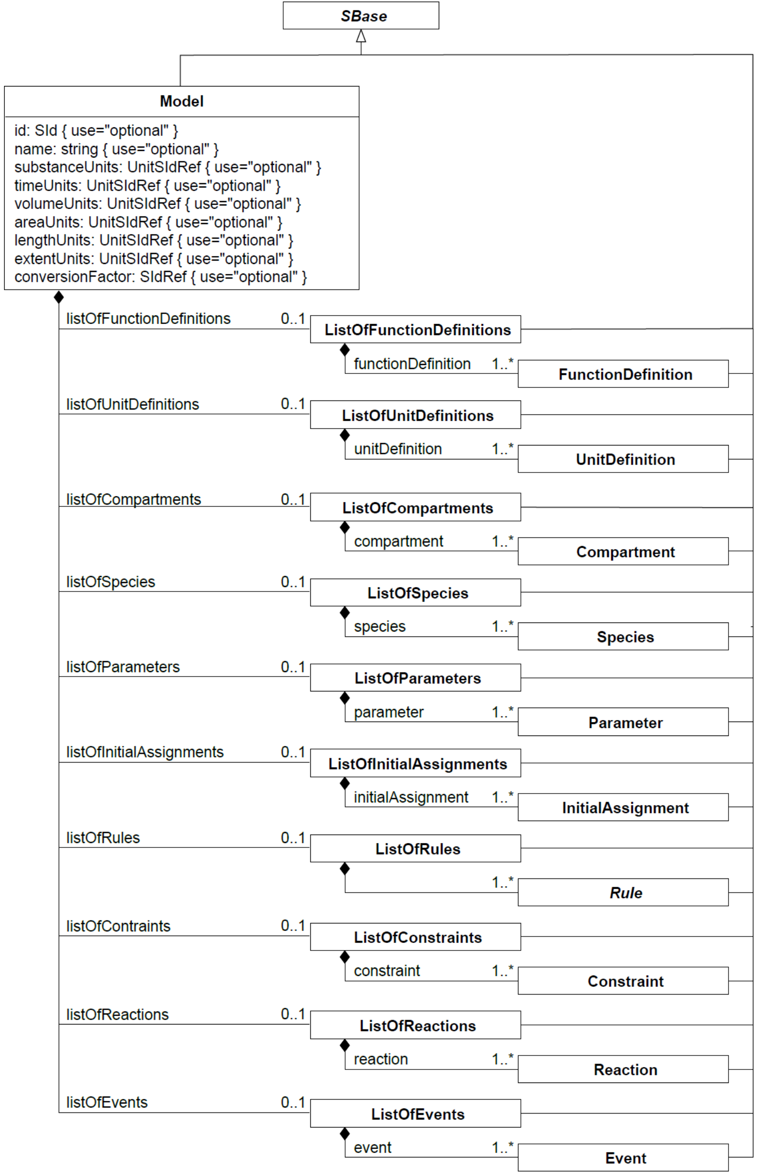
Visualization
Data integration

The Systems Biology Markup Language (SBML): Language Specification for Level 3 Version 2 Core
M. Hucka, F. Bergmann, C. Chaouiya, A. Dräger, S. Hoops, S. Keating, **M. König**, N Le Novere, C. Myers, B. Olivier, S. Sahle, J. Schaff, R. Sheriff, L. Smith, D. Waltemath, D. Wilkinson, F. Zhang, **J Integr Bioinform. 2019 [accepted]**

Simulation experiment description markup language (SED-ML) level 1 version 3 (L1V3).
Bergmann FT., Cooper J, **König M**, Ion Moraru I., Nickerson D., Le Novère N., Olivier BG., Sahle S, Smith L., and Waltemath D, **J Integr Bioinform 2018, 3**

Harmonizing semantic annotations for computational models in biology
Neal, **König**, Nickerson, Mısırlı, Kalbasi, Dräger, …, Waltemath
Brief Bioinform. 2018 Nov 21. doi: 10.1093/bib/bby087

- **De facto standard** for pathway models
- **Libraries**: libsbml (C++, python, R, JavaScript, ... & JSBML (Java)
- **TestSuite** and **Validators**
- Components
  - UnitDefinitions
  - FunctionDefinitions
  - Compartments
  - Species
  - Parameters
  - InitialAssignments
  - Rules
  - Reactions
  - Events



Full set of model instructions (ODE)

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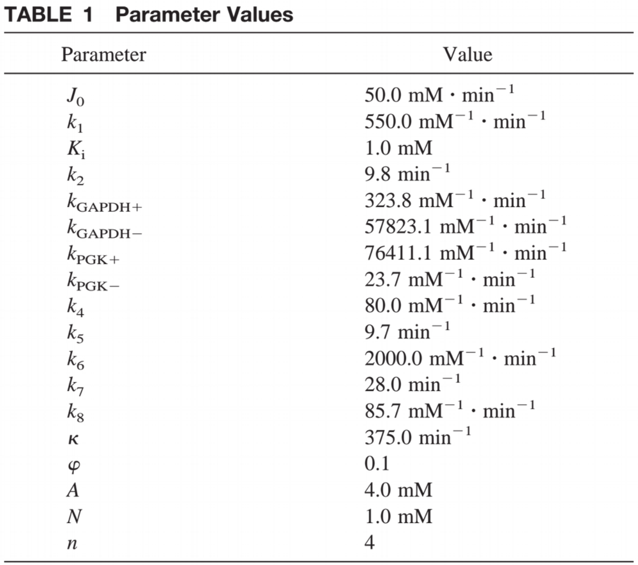
$$\dot{N}_2 = v_3 - v_6 - v_8$$



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κ	375.0 min^{-1}
φ	0.1
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N	1.0 mM
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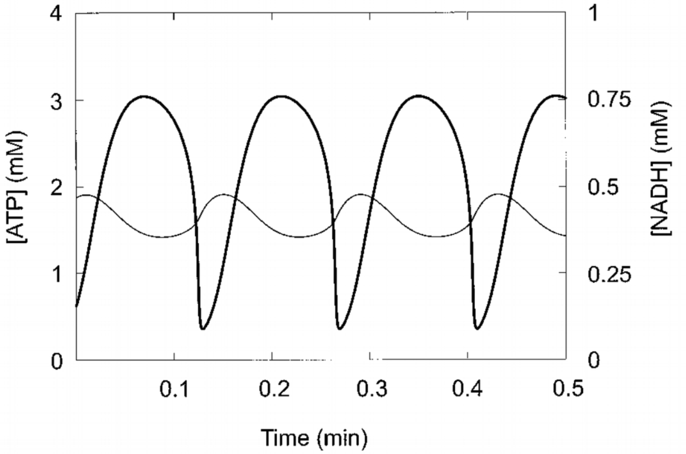
Parameters
& UnitDefinitions (SBML)

Simulations (SED-ML)



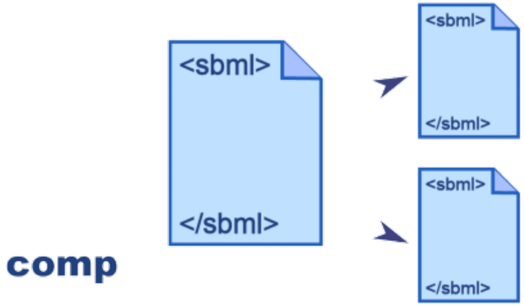
$$v_3 = \frac{k_{GAPDH+}k_{PGK+}S_3N_1(A-A_3) - k_{GAPDH-}k_{PGK-}S_4A_3N_2}{k_{GAPDH-}N_2 + k_{PGK+}(A - A_3)}$$

Species & Reactions (SBML)
(Defining Stoichiometric Matrix & KineticLaws)

Compartments (SBML)

SBML comp

- Hierarchical model composition
- Coupling of models



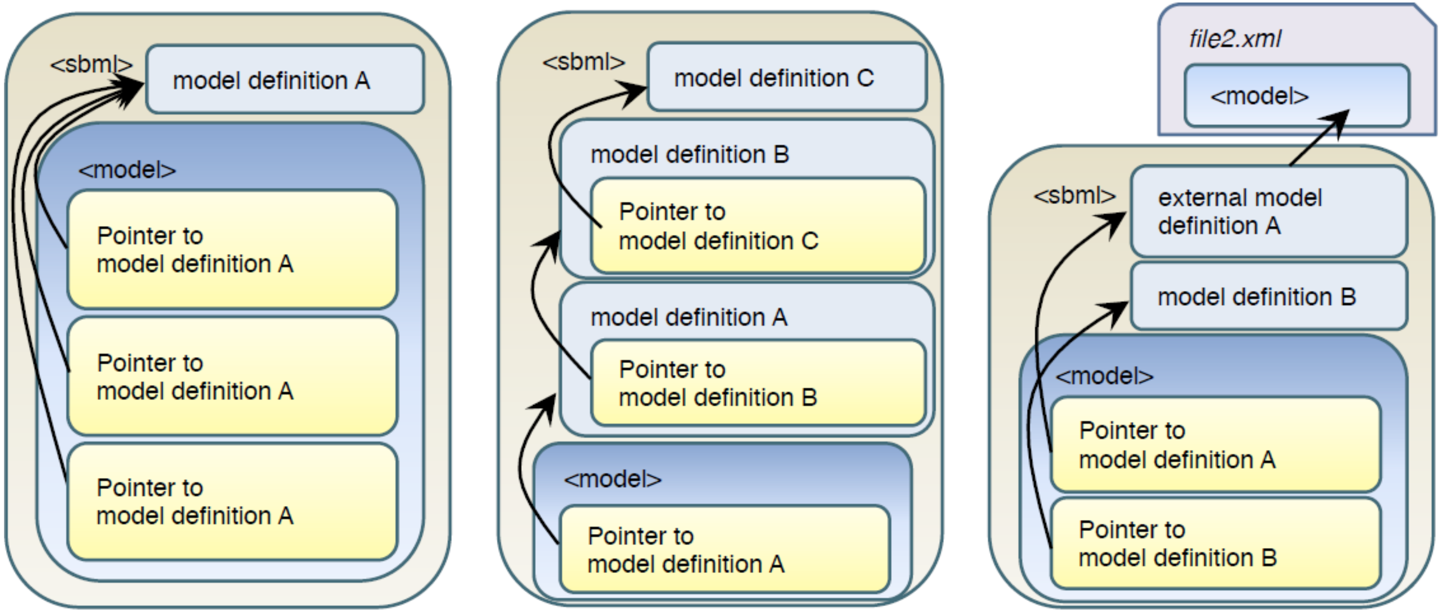
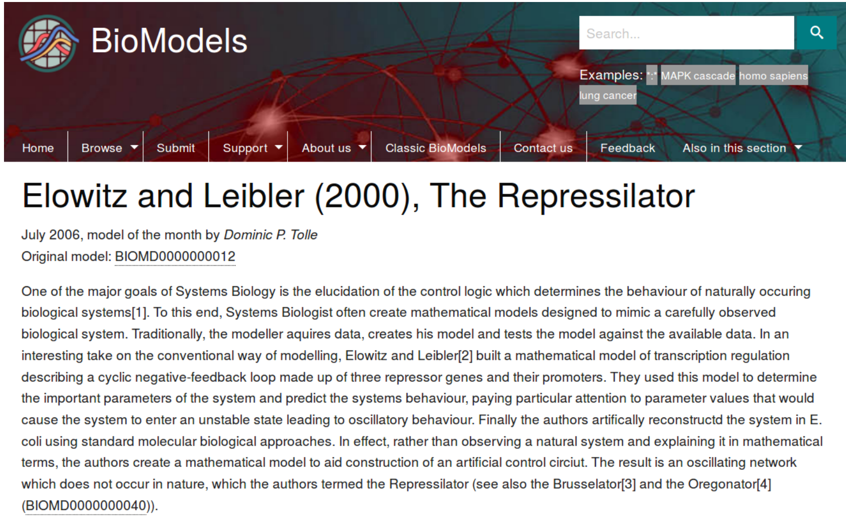


Figure 1: *Three different examples of model composition scenarios. From left to right: (1) a model composed of multiple instances of a single, internally-defined submodel definition; (2) a model composed of a submodel that is itself composed of submodels; and (3) a model composed of submodels, one of which is defined in an external file.*

SBML Model databases

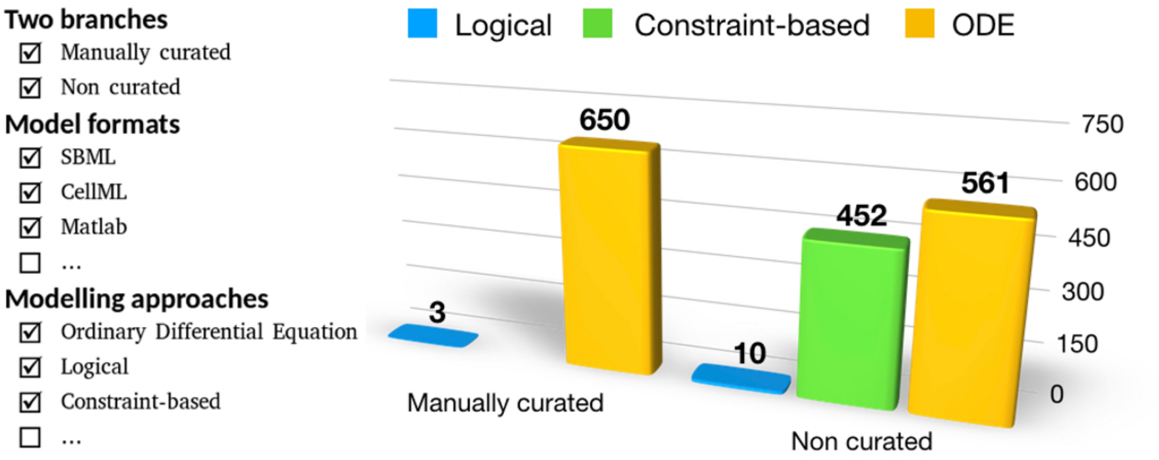
- Biomodels
  - large collection of freely available models https://biomodels.org



Elowitz and Leibler (2000), The Repressilator

July 2006, model of the month by *Dominic P. Tolle*
Original model: BIOMD0000000012

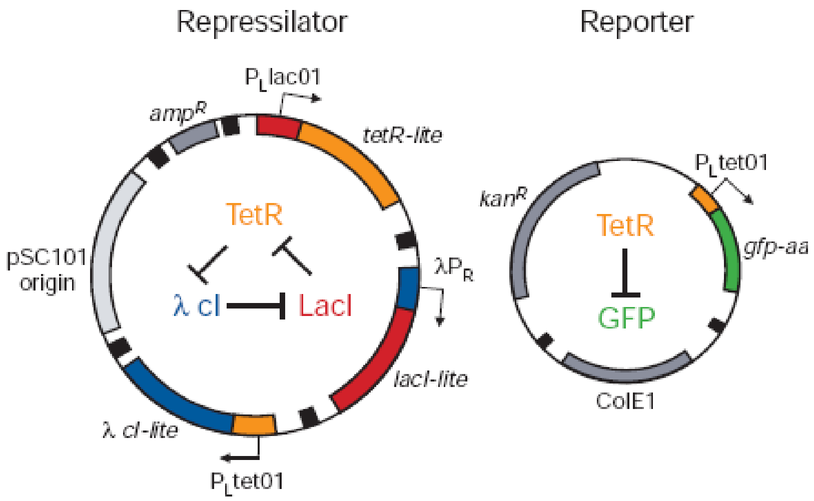
One of the major goals of Systems Biology is the elucidation of the control logic which determines the behaviour of naturally occuring biological systems[1]. To this end, Systems Biologist often create mathematical models designed to mimic a carefully observed biological system. Traditionally, the modeller aquires data, creates his model and tests the model against the available data. In an interesting take on the conventional way of modelling, Elowitz and Leibler[2] built a mathematical model of transcription regulation describing a cyclic negative-feedback loop made up of three repressor genes and their promoters. They used this model to determine the important parameters of the system and predict the systems behaviour, paying particular attention to parameter values that would cause the system to enter an unstable state leading to oscillatory behaviour. Finally the authors artifically reconstructd the system in E. coli using standard molecular biological approaches. In effect, rather than observing a natural system and explaining it in mathematical terms, the authors create a mathematical model to aid construction of an artificial control circiut. The result is an oscillating network which does not occur in nature, which the authors termed the Repressilator (see also the Brusselator[3] and the Oregonator[4] (BIOMD0000000040)).



Two branches
- ☑ Manually curated
- ☑ Non curated

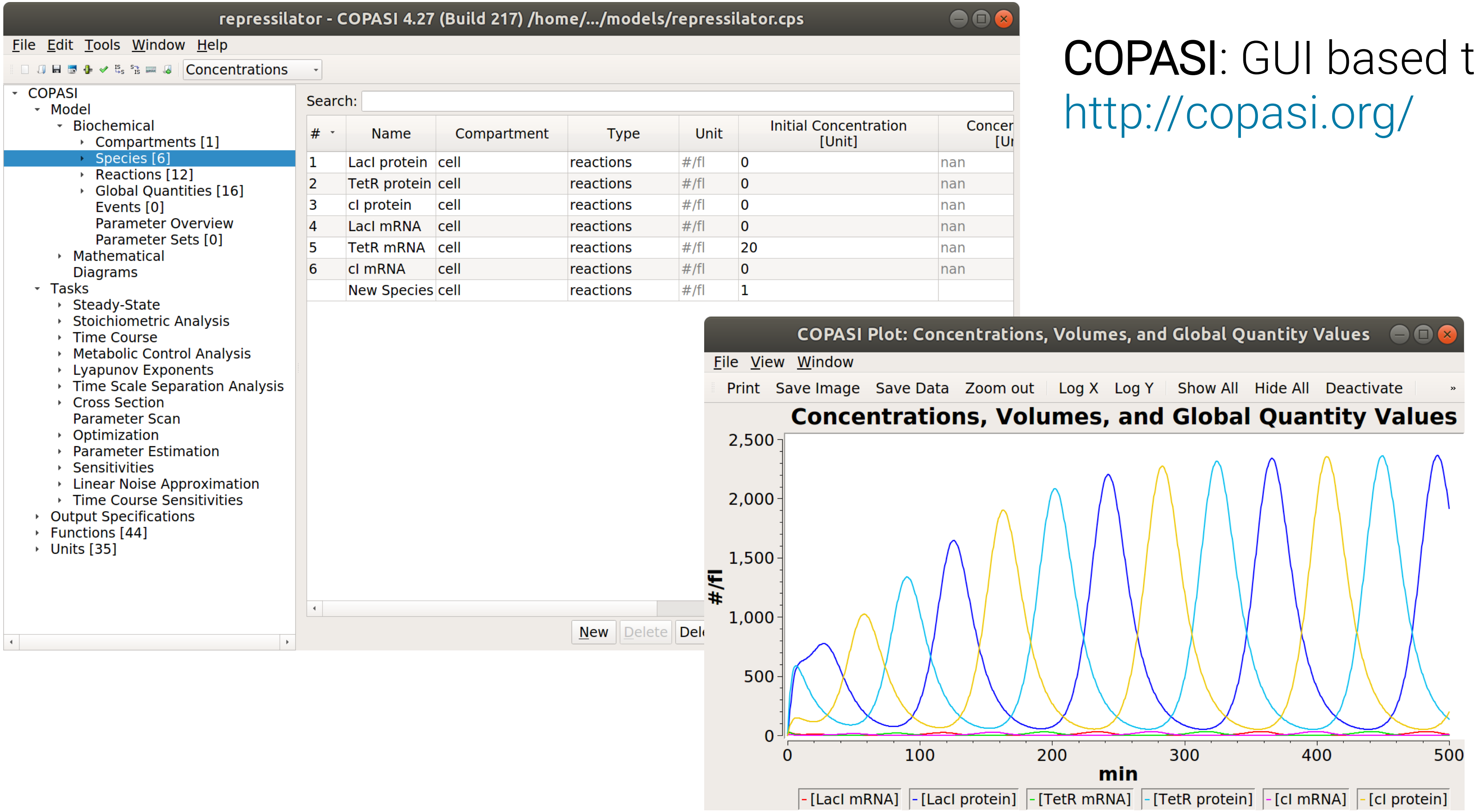
Model formats
- ☑ SBML
- ☑ CellML
- ☑ Matlab
- ☐ ...

Modelling approaches
- ☑ Ordinary Differential Equation
- ☑ Logical
- ☑ Constraint-based
- ☐ ...



GUI tools (analysis)

COPASI: GUI based tool, http://copasi.org/



repressilator - COPASI 4.27 (Build 217) /home/.../models/repressilator.cps

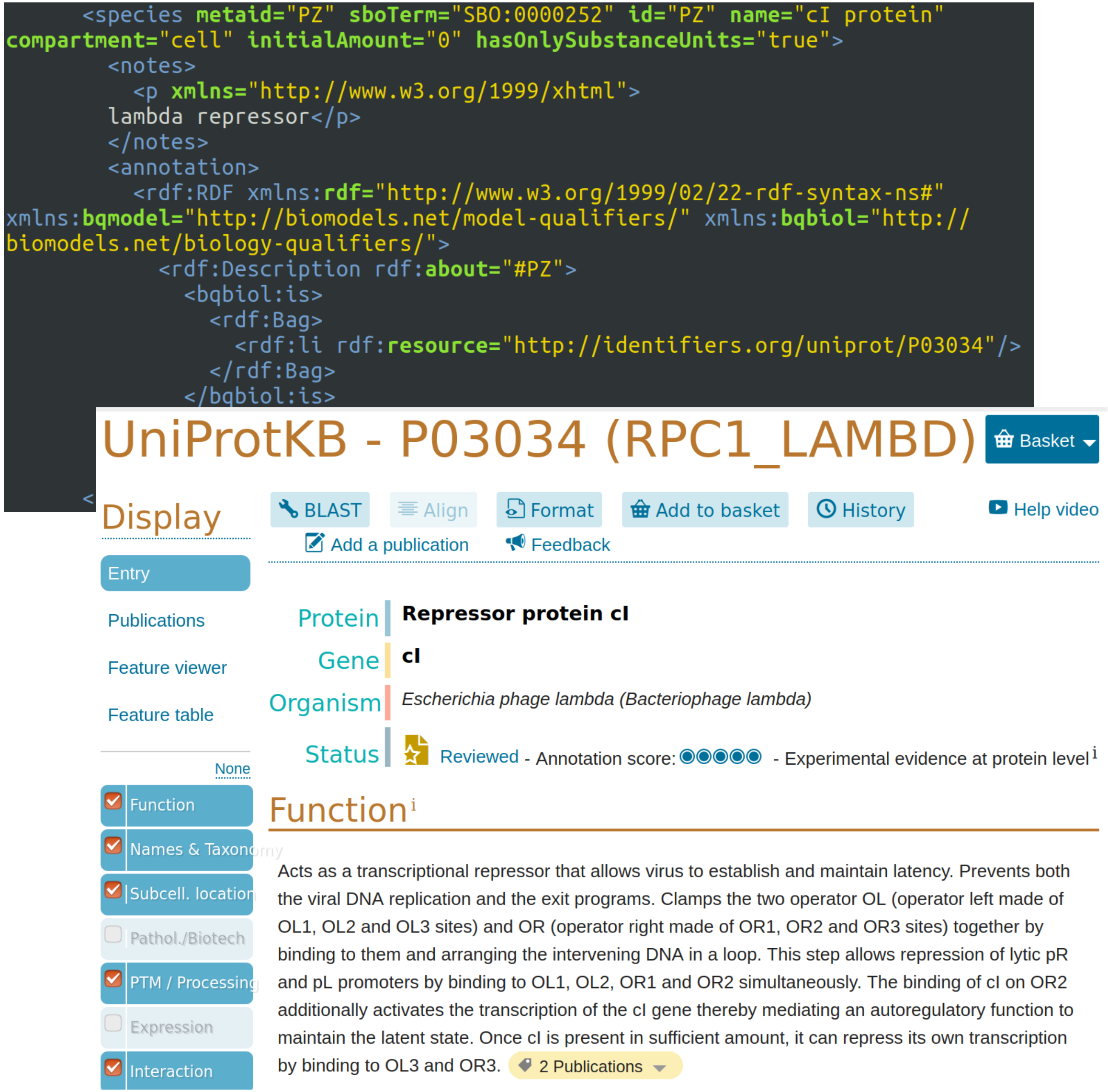
Search:

#	Name	Compartment	Type	Unit	Initial Concentration [Unit]	Concer [Ur
1	LacI protein	cell	reactions	#/fl	0	nan
2	TetR protein	cell	reactions	#/fl	0	nan
3	cI protein	cell	reactions	#/fl	0	nan
4	LacI mRNA	cell	reactions	#/fl	0	nan
5	TetR mRNA	cell	reactions	#/fl	20	nan
6	cI mRNA	cell	reactions	#/fl	0	nan
	New Species	cell	reactions	#/fl	1	

COPASI Plot: Concentrations, Volumes, and Global Quantity Values

Annotations

- Ontology
  - definition of controlled vocabulary with clear meaning and relationships
  - allows to precisely describe objects
- Annotation
  - process of attaching ontology terms to objects
  - important for mapping data onto models
  - important for automatic methods (model merging, reuse of components
- RDF triples
  - (subject, verb, object)
- Examples
  - CHEBI (chemical entities)
  - UniProt (proteins)
  - Ontology Lookup Service



```
      <species metaid="PZ" sboTerm="SBO:0000252" id="PZ" name="cI protein"
compartment="cell" initialAmount="0" hasOnlySubstanceUnits="true">
        <notes>
          <p xmlns="http://www.w3.org/1999/xhtml">
        lambda repressor</p>
        </notes>
        <annotation>
          <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
xmlns:bqmodel="http://biomodels.net/model-qualifiers/" xmlns:bqbiol="http://
biomodels.net/biology-qualifiers/">
            <rdf:Description rdf:about="#PZ">
              <bqbiol:is>
                <rdf:Bag>
                  <rdf:li rdf:resource="http://identifiers.org/uniprot/P03034"/>
                </rdf:Bag>
              </bqbiol:is>
```

UniProtKB - P03034 (RPC1_LAMBD)

Protein **Repressor protein cI**

Gene **cI**

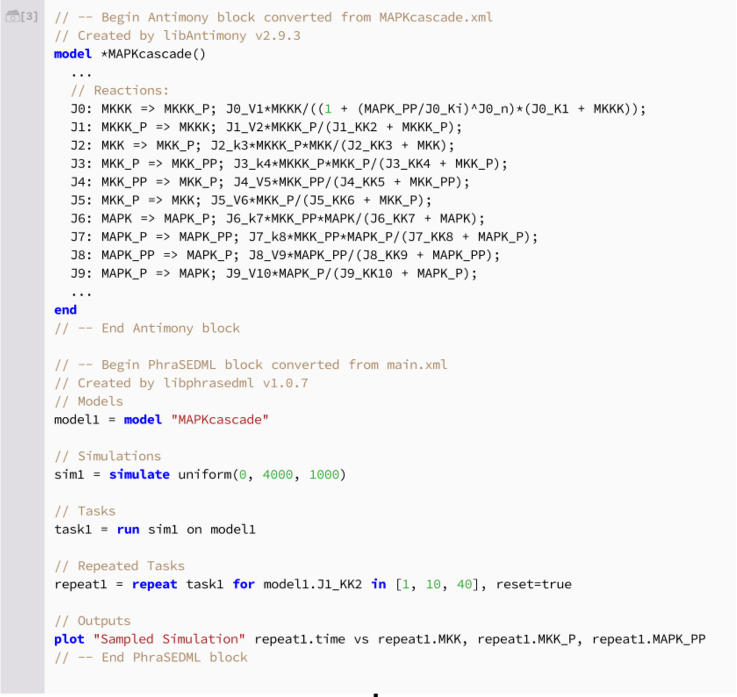
Organism *Escherichia phage lambda (Bacteriophage lambda)*

Status Reviewed - Annotation score: ●●●●● - Experimental evidence at protein level[i]

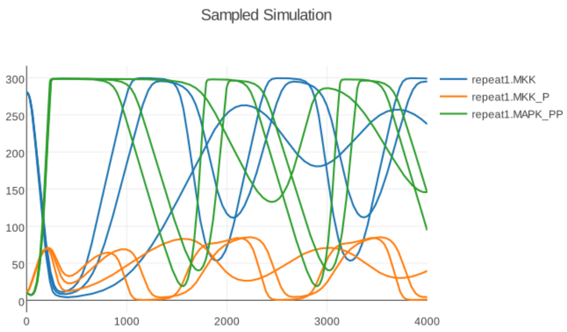
Function[i]

Acts as a transcriptional repressor that allows virus to establish and maintain latency. Prevents both the viral DNA replication and the exit programs. Clamps the two operator OL (operator left made of OL1, OL2 and OL3 sites) and OR (operator right made of OR1, OR2 and OR3 sites) together by binding to them and arranging the intervening DNA in a loop. This step allows repression of lytic pR and pL promoters by binding to OL1, OL2, OR1 and OR2 simultaneously. The binding of cI on OR2 additionally activates the transcription of the cI gene thereby mediating an autoregulatory function to maintain the latent state. Once cI is present in sufficient amount, it can repress its own transcription by binding to OL3 and OR3. 2 Publications

Libraries (analysis)



```
// -- Begin Antimony block converted from MAPKcascade.xml
// Created by libAntimony v2.9.3
model *MAPKcascade()
  ...
  // Reactions:
  J0: MKKK => MKKK_P; J0_V1*MKKK/((1 + (MAPK_PP/J0_Ki)^J0_n)*(J0_K1 + MKKK));
  J1: MKKK_P => MKKK; J1_V2*MKKK_P/(J1_KK2 + MKKK_P);
  J2: MKK => MKK_P; J2_k3*MKKK_P*MKK/(J2_KK3 + MKK);
  J3: MKK_P => MKK_PP; J3_k4*MKKK_P*MKK_P/(J3_KK4 + MKK_P);
  J4: MKK_PP => MKK_P; J4_V5*MKK_PP/(J4_KK5 + MKK_PP);
  J5: MKK_P => MKK; J5_V6*MKK_P/(J5_KK6 + MKK_P);
  J6: MAPK => MAPK_P; J6_k7*MKK_PP*MAPK/(J6_KK7 + MAPK);
  J7: MAPK_P => MAPK_PP; J7_k8*MKK_PP*MAPK_P/(J7_KK8 + MAPK_P);
  J8: MAPK_PP => MAPK_P; J8_V9*MAPK_PP/(J8_KK9 + MAPK_PP);
  J9: MAPK_P => MAPK; J9_V10*MAPK_P/(J9_KK10 + MAPK_P);
  ...
end
// -- End Antimony block

// -- Begin PhraSEDML block converted from main.xml
// Created by libphrasedml v1.0.7
// Models
model1 = model "MAPKcascade"

// Simulations
sim1 = simulate uniform(0, 4000, 1000)

// Tasks
task1 = run sim1 on model1

// Repeated Tasks
repeat1 = repeat task1 for model1.J1_KK2 in [1, 10, 40], reset=true

// Outputs
plot "Sampled Simulation" repeat1.time vs repeat1.MKK, repeat1.MKK_P, repeat1.MAPK_PP
// -- End PhraSEDML block
```



- **roadrunner**: high performance SBML simulator
- **tellurium**: python based modeling environment for SBML models http://tellurium.analogmachine.org/
- **antimony:** simple SBML script language
- **sbmlsim**:
  python library for simulation

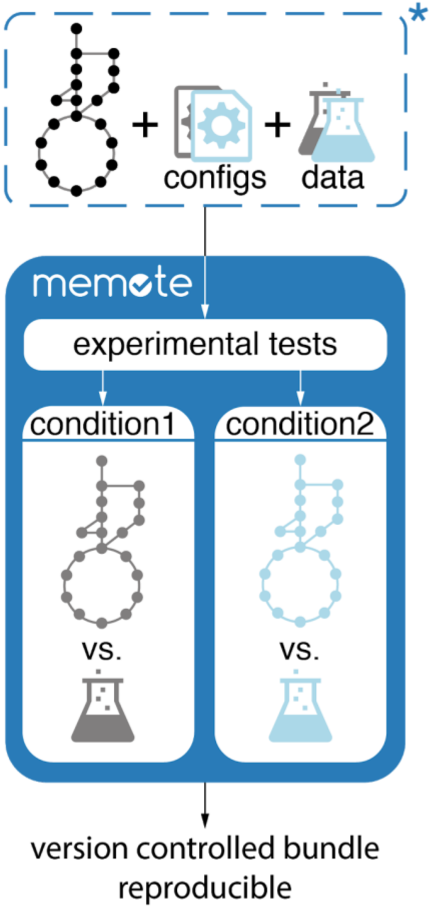
libRoadRunner: a high performance SBML simulation and analysis library.
Somogyi, Bouteiller, Glazier, **König**, Medley, Swat, Sauro.
Bioinformatics. 2015

Tellurium Notebooks - An Environment for Dynamical Model Development, Reproducibility, and Reuse
Medley K, Choi K, **König M**; Smith L, Gu S, Joseph Hellerstein, Sealfon S., Sauro HM.
PLoS, Comp. Bio. 2018

Tellurium: An Extensible Python-based Modeling
Environment for Systems and Synthetic Biology
K Choi, JK Medley, **M König**, K Stocking, L Smith, S Gua, HM Sauro
Biosystems. 2018 Jul 24. pii: S0303-2647(18)30125-4.

Model building, quality checks, visualization

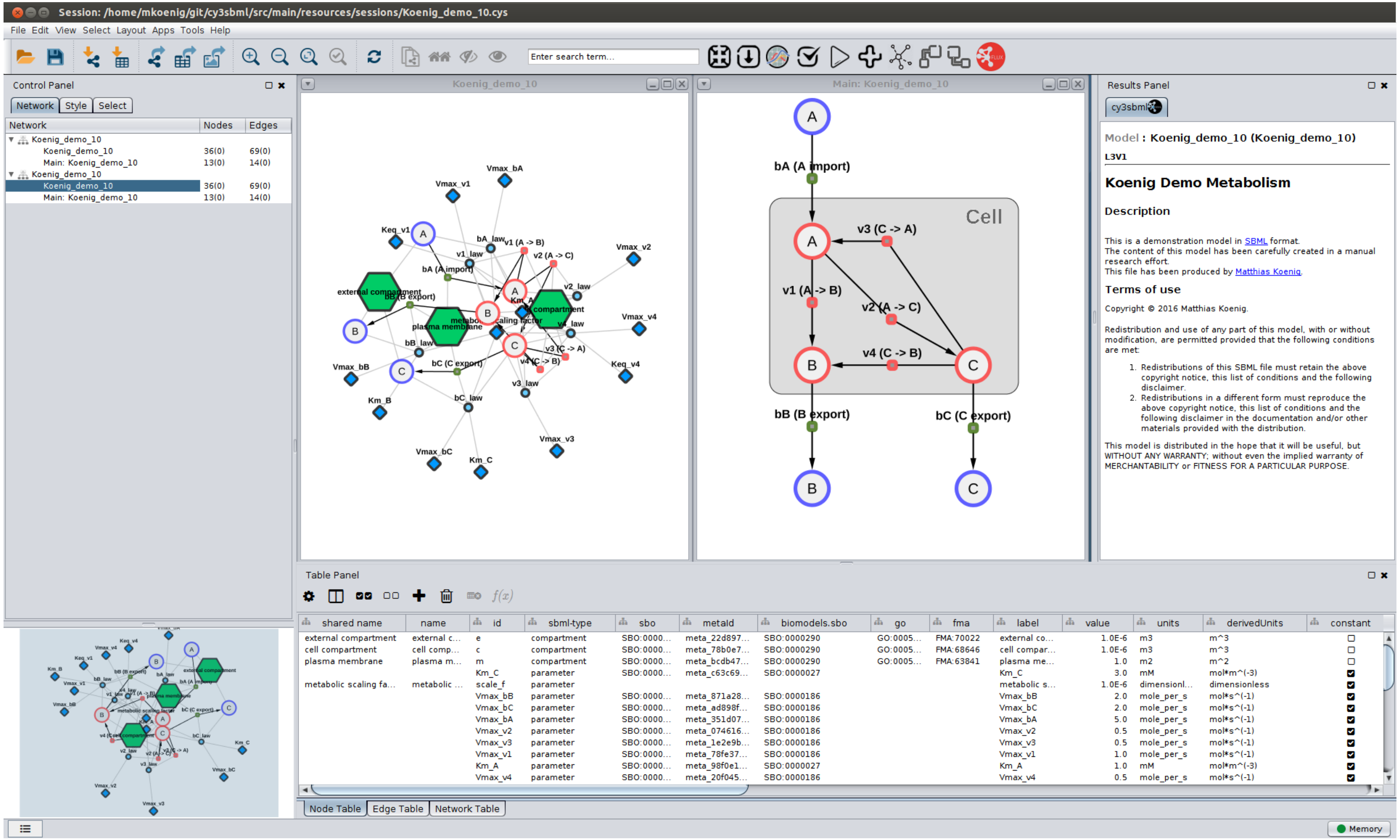
- **sbmlutils –** model building, annotation, reports
- **memote -** integrated testing for models and model checks



matthiaskoenig/sbmlutils: sbmlutils-v0.3.3 (Version v0.3.3)
M. König. (2019, April 29). Zenodo. http://doi.org/10.5281/zenodo.2653495

Memote: A community-driven effort towards a standardized genome-scale metabolic model test suite
C Lieven, M Beber, B Olivier, F Bergmann, M Ataman, P Babaei, J Bartell, L Blank, S Chauhan, K Correia, C Diener, A Dräger, B ..., **M König**, S Klamt, E Klipp, ..., J Wodke, J Xavier, Q Yuan, M Zakhartsev, C Zhang
bioRxiv 350991; doi: 10.1101/350991 Nature Biotechnology [in revision]

Visualization



Network	Nodes	Edges
Koenig_demo_10		
Koenig_demo_10	36(0)	69(0)
Main: Koenig_demo_10	13(0)	14(0)
Koenig_demo_10		
Koenig_demo_10	36(0)	69(0)
Main: Koenig_demo_10	13(0)	14(0)

Model : Koenig_demo_10 (Koenig_demo_10)

L3V1

Koenig Demo Metabolism

Description

This is a demonstration model in SBML format.
The content of this model has been carefully created in a manual research effort.
This file has been produced by Matthias Koenig.

Terms of use

Copyright © 2016 Matthias Koenig.

Redistribution and use of any part of this model, with or without modification, are permitted provided that the following conditions are met:

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2. Redistributions in a different form must reproduce the above copyright notice, this list of conditions and the following disclaimer in the documentation and/or other materials provided with the distribution.

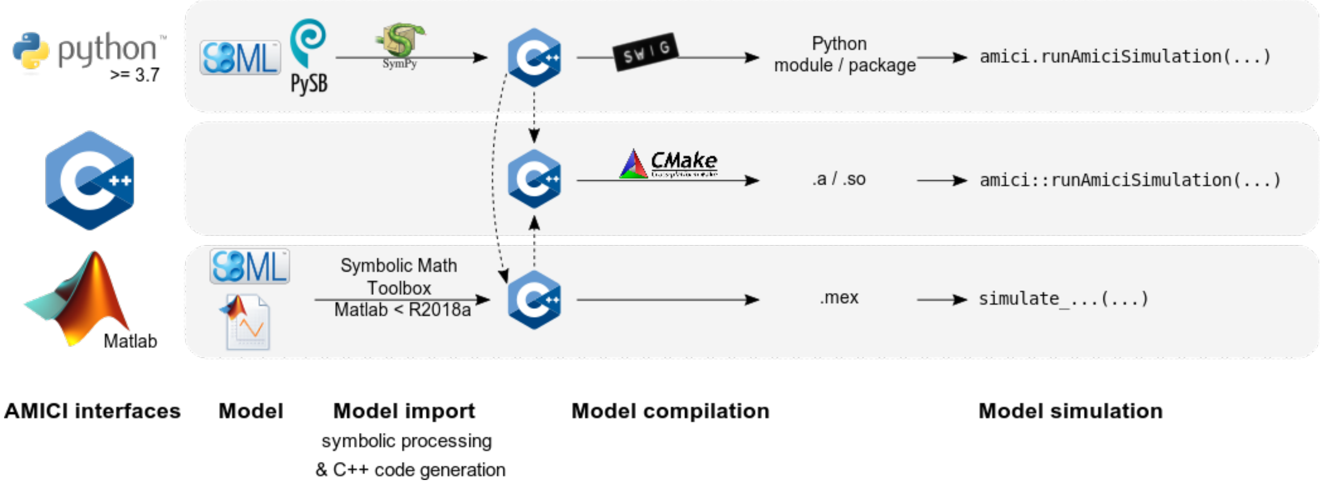
This model is distributed in the hope that it will be useful, but WITHOUT ANY WARRANTY; without even the implied warranty of MERCHANTABILITY or FITNESS FOR A PARTICULAR PURPOSE.

shared name	name	id	sbml-type	sbo	metaId	biomodels.sbo	go	fma	label	value	units	derivedUnits	constant
external compartment	external c...	e	compartment	SBO:0000...	meta_22d897...	SBO:0000290	GO:0005...	FMA:70022	external co...	1.0E-6	m3	m^3	☐
cell compartment	cell comp...	c	compartment	SBO:0000...	meta_78b0e7...	SBO:0000290	GO:0005...	FMA:68646	cell compar...	1.0E-6	m3	m^3	☐
plasma membrane	plasma m...	m	compartment	SBO:0000...	meta_bcdb47...	SBO:0000290	GO:0005...	FMA:63841	plasma me...	1.0	m2	m^2	☐
		Km_C	parameter	SBO:0000...	meta_c63c69...	SBO:0000027			Km_C	3.0	mM	mol*m^(-3)	☑
metabolic scaling fa...	metabolic ...	scale_f	parameter						metabolic s...	1.0E-6	dimensionl...	dimensionless	☑
		Vmax_bB	parameter	SBO:0000...	meta_871a28...	SBO:0000186			Vmax_bB	2.0	mole_per_s	mol*s^(-1)	☑
		Vmax_bC	parameter	SBO:0000...	meta_ad898f...	SBO:0000186			Vmax_bC	2.0	mole_per_s	mol*s^(-1)	☑
		Vmax_bA	parameter	SBO:0000...	meta_351d07...	SBO:0000186			Vmax_bA	5.0	mole_per_s	mol*s^(-1)	☑
		Vmax_v2	parameter	SBO:0000...	meta_074616...	SBO:0000186			Vmax_v2	0.5	mole_per_s	mol*s^(-1)	☑
		Vmax_v3	parameter	SBO:0000...	meta_1e2e9b...	SBO:0000186			Vmax_v3	0.5	mole_per_s	mol*s^(-1)	☑
		Vmax_v1	parameter	SBO:0000...	meta_78fe37...	SBO:0000186			Vmax_v1	1.0	mole_per_s	mol*s^(-1)	☑
		Km_A	parameter	SBO:0000...	meta_98f0e1...	SBO:0000027			Km_A	1.0	mM	mol*m^(-3)	☑
		Vmax_v4	parameter	SBO:0000...	meta_20f045...	SBO:0000186			Vmax_v4	0.5	mole_per_s	mol*s^(-1)	☑

matthiaskoenig/cy3sbml: cy3sbml-v0.2.7 (Version v0.2.7)
M. König, N. Rodriguez, A. Dräger (2017, November 12). Zenodo. http://doi.org/10.5281/zenodo.1045487

Parameter fitting

- Dmod (R)
- PyPESTO & AMICI (python)
  https://github.com/icb-dcm/pypesto
  https://icb-dcm.github.io/AMICI/index.html
- Data2dynamics (Matlab)
  https://github.com/Data2Dynamics/d2d



python >= 3.7

SBML

PySB

SymPy

SWIG

Python module / package

`amici.runAmiciSimulation(...)`

CMake

.a / .so

`amici::runAmiciSimulation(...)`

Matlab

SBML

Symbolic Math Toolbox

Matlab < R2018a

.mex

`simulate_...(...)`

AMICI interfaces **Model** **Model import** symbolic processing & C++ code generation **Model compilation** **Model simulation**

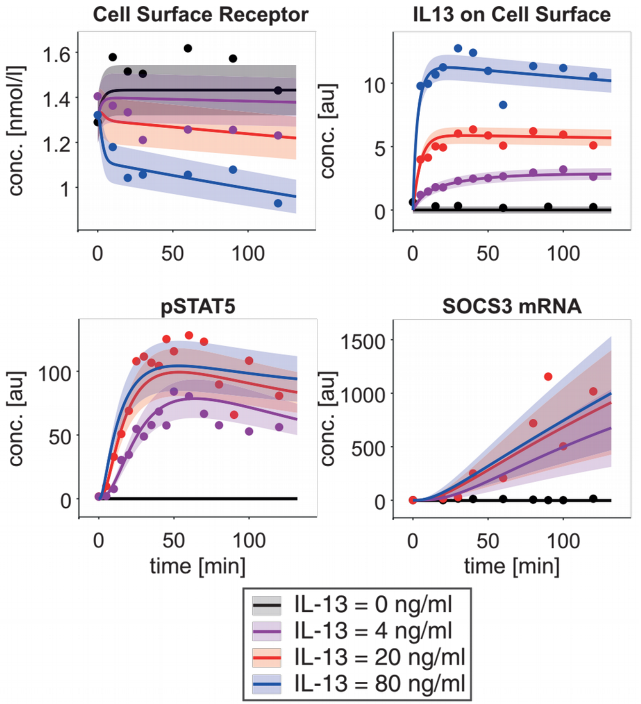
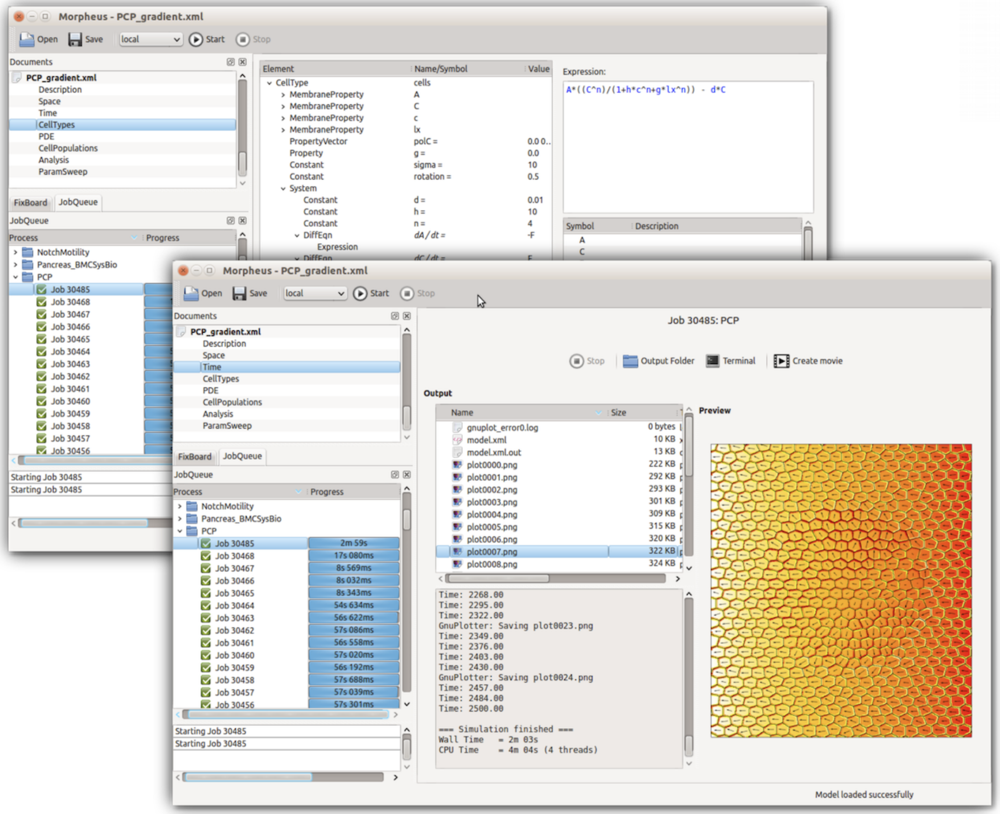


Fig. 1. Raia *et al.* (2011) model fitted to experimental data (dots) representing four different doses of IL-13. The solid lines are the fitted model trajectories and the shades the estimated experimental error of the data

Pathways as input for tissue models

- Morpheus
  https://morpheus.gitlab.io/



Element	Name/Symbol	Value
CellType	cells	
MembraneProperty	A	
MembraneProperty	C	
MembraneProperty	c	
MembraneProperty	lx	
PropertyVector	polC =	0.0 0..
Property	g =	0.0
Constant	sigma =	10
Constant	rotation =	0.5
System		
Constant	d =	0.01
Constant	h =	10
Constant	n =	4
DiffEqn	dA / dt =	-F
Expression		
DiffEqn	dC / dt =	F

Expression:

```
A*((C^n)/(1+h*c^n+g*lx^n)) - d*C
```

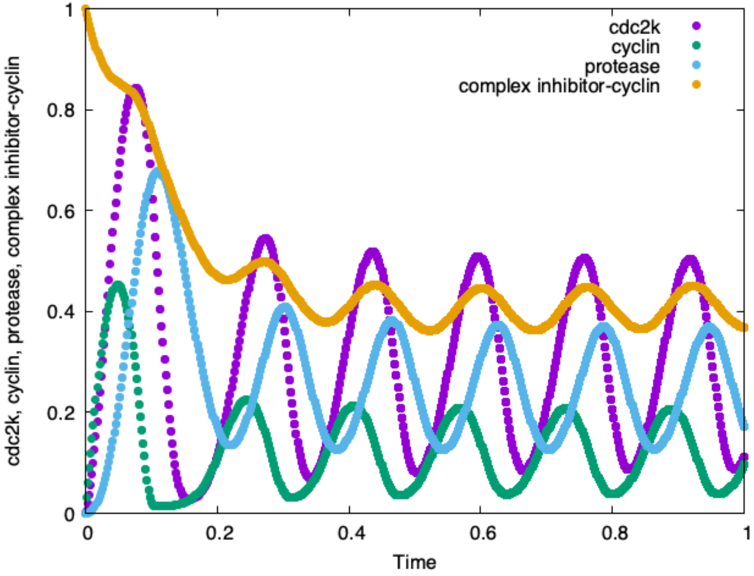
Process	Progress
Job 30485	2m 59s
Job 30468	17s 080ms
Job 30467	8s 569ms
Job 30466	8s 032ms
Job 30465	8s 343ms
Job 30464	54s 634ms
Job 30463	56s 622ms
Job 30462	57s 086ms
Job 30461	56s 558ms
Job 30460	57s 020ms
Job 30459	56s 192ms
Job 30458	57s 688ms
Job 30457	57s 039ms
Job 30456	57s 301ms

Starting Job 30485
Starting Job 30485

Name	Size
gnuplot_error0.log	0 bytes
model.xml	10 KB
model.xml.out	13 KB
plot0000.png	222 KB
plot0001.png	292 KB
plot0002.png	293 KB
plot0003.png	301 KB
plot0004.png	309 KB
plot0005.png	315 KB
plot0006.png	320 KB
plot0007.png	322 KB
plot0008.png	324 KB

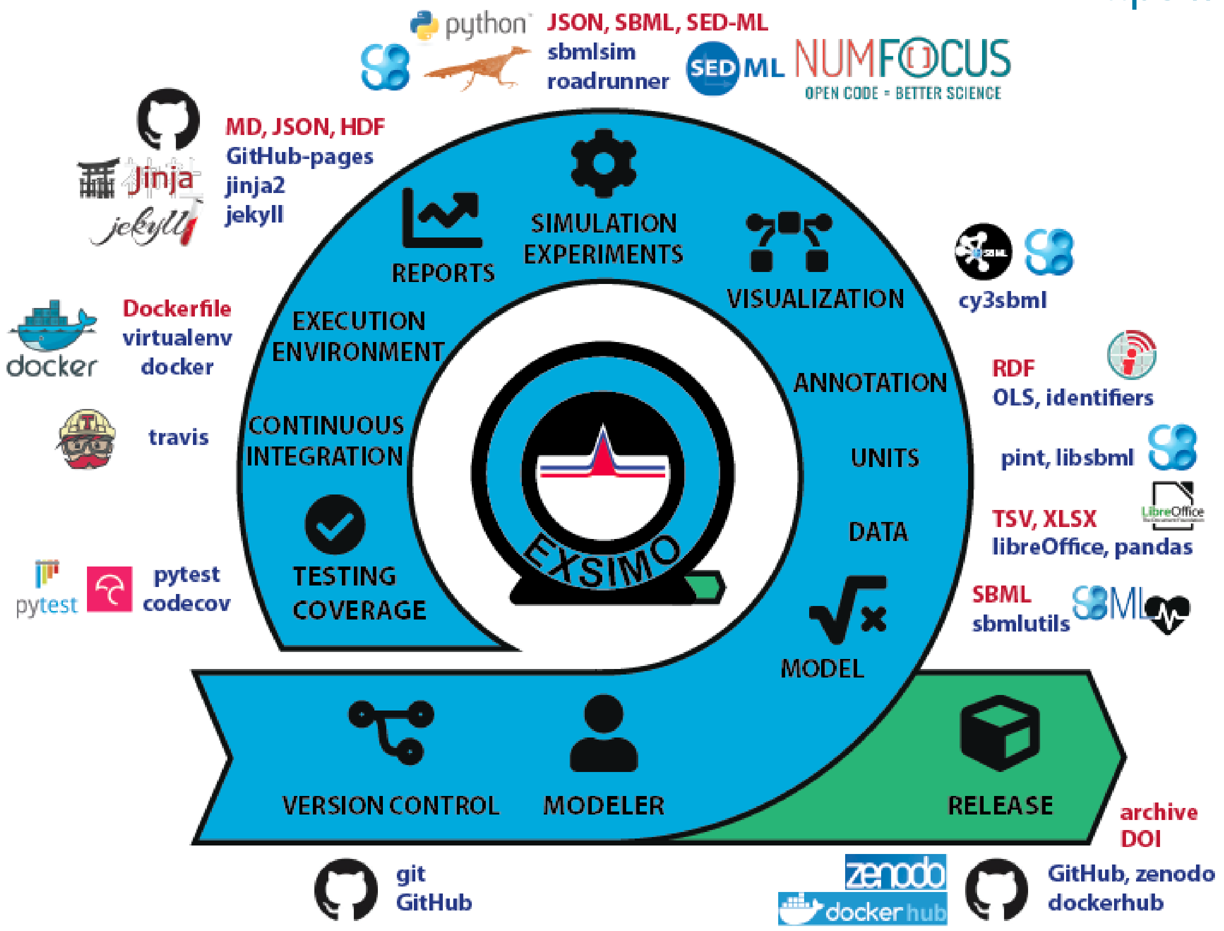
```
Time: 2268.00
Time: 2295.00
Time: 2322.00
GnuPlotter: Saving plot0023.png
Time: 2349.00
Time: 2376.00
Time: 2403.00
Time: 2430.00
GnuPlotter: Saving plot0024.png
Time: 2457.00
Time: 2484.00
Time: 2500.00

=== Simulation finished ===
Wall Time   = 2m 03s
CPU Time    = 4m 04s (4 threads)
```

SBML™ →

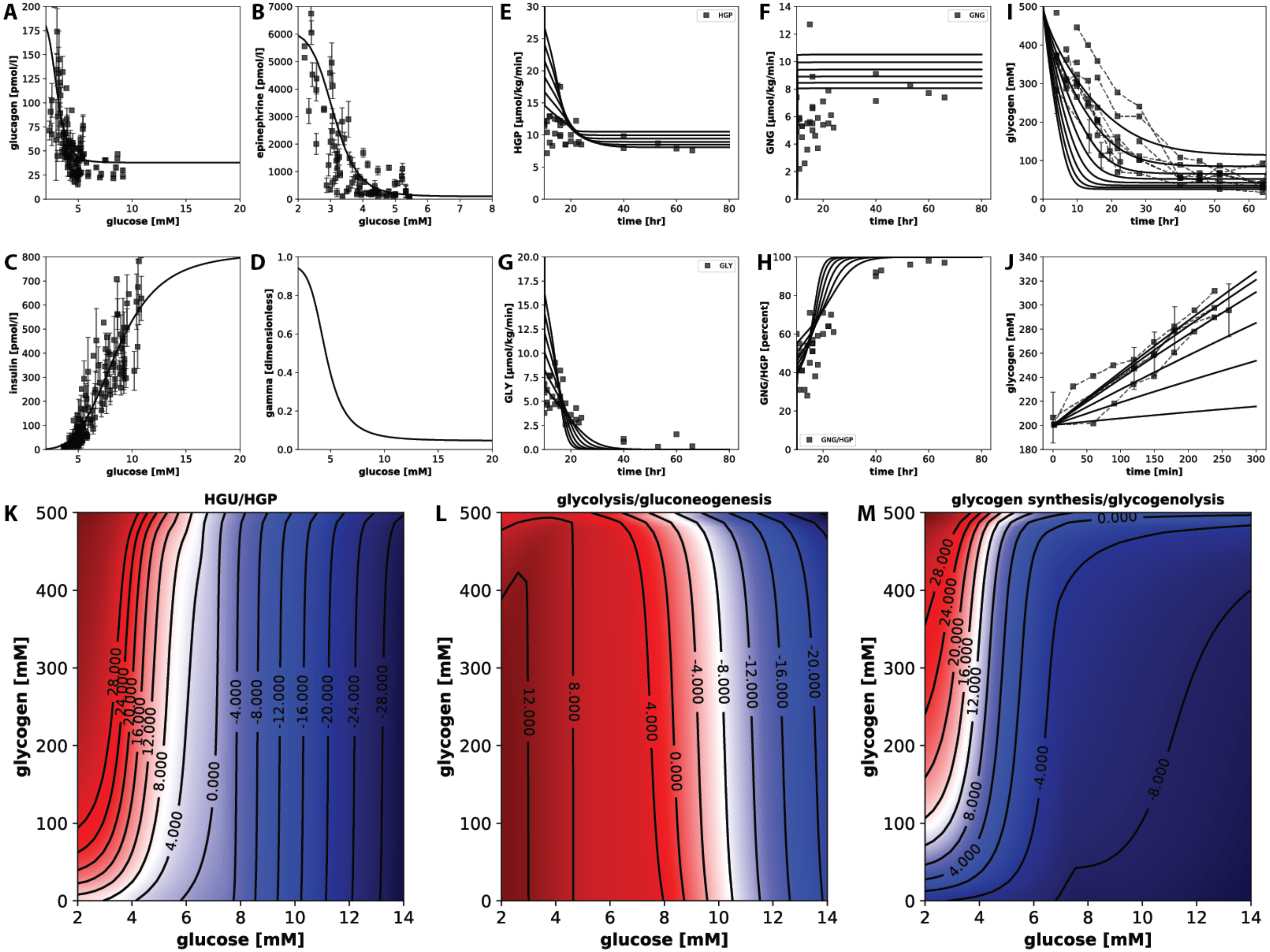


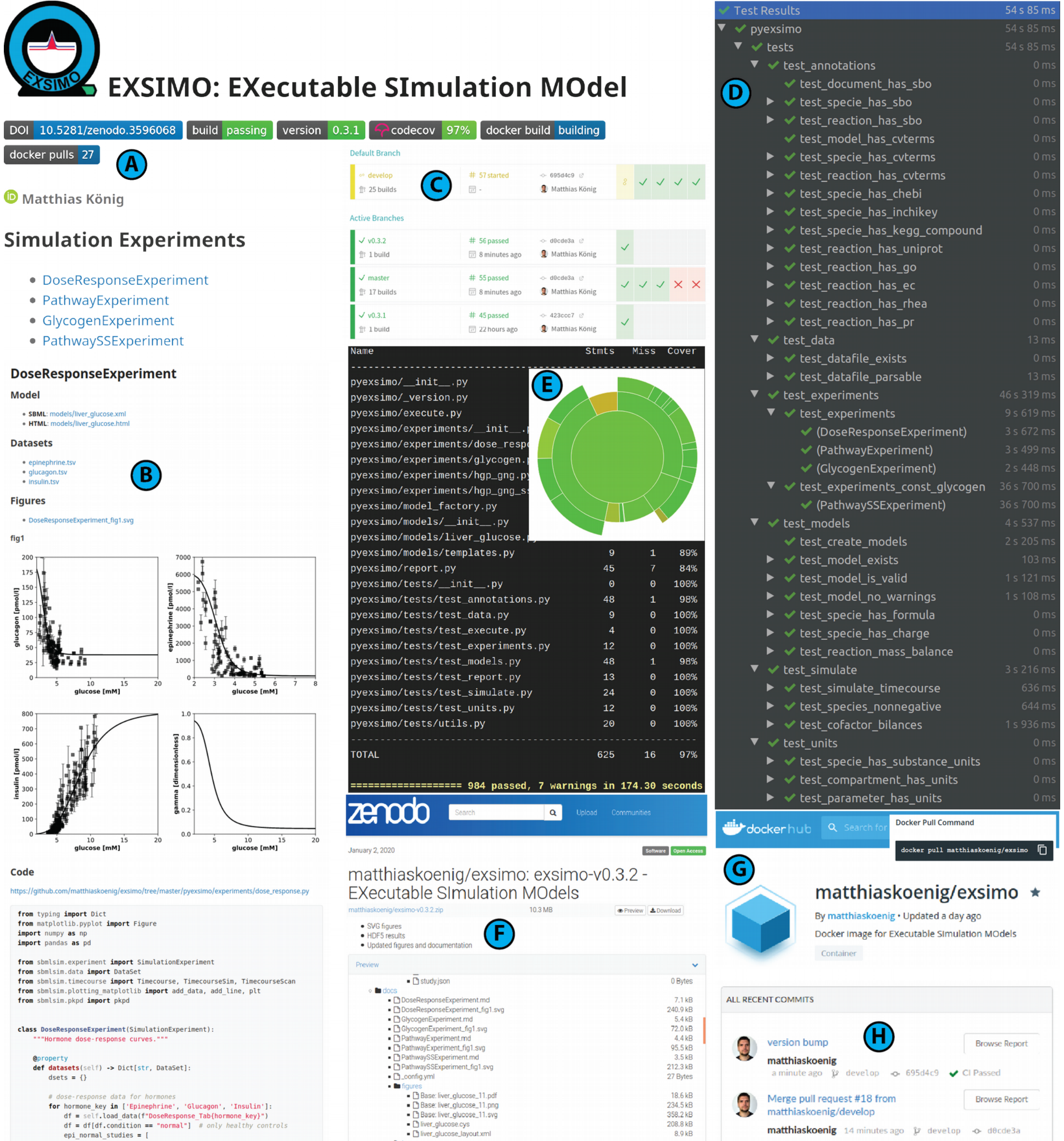
Executable simulation model

https://matthiaskoenig.github.io/exsimo/



...the complete ... set of instructions and data which generated the figures.


A
glucagon [pmol/l]
glucose [mM]
B
epinephrine [pmol/l]
glucose [mM]
E
HGP [µmol/kg/min]
HGP
time [hr]
F
GNG [µmol/kg/min]
GNG
time [hr]
I
glycogen [mM]
time [hr]
C
insulin [pmol/l]
glucose [mM]
D
gamma [dimensionless]
glucose [mM]
G
GLY [µmol/kg/min]
GLY
time [hr]
H
GNG/HGP [percent]
GNG/HGP
time [hr]
J
glycogen [mM]
time [min]
K
HGU/HGP
glycogen [mM]
glucose [mM]
28.000
24.000
20.000
16.000
12.000
8.000
4.000
0.000
-4.000
-8.000
-12.000
-16.000
-20.000
-24.000
-28.000
L
glycolysis/gluconeogenesis
glycogen [mM]
glucose [mM]
12.000
8.000
4.000
0.000
-4.000
-8.000
-12.000
-16.000
-20.000
M
glycogen synthesis/glycogenolysis
glycogen [mM]
glucose [mM]
0.000
28.000
24.000
20.000
16.000
12.000
8.000
4.000
-4.000
-8.000



EXSIMO: EXecutable SImulation MOdel

Matthias König

Simulation Experiments

- DoseResponseExperiment
- PathwayExperiment
- GlycogenExperiment
- PathwaySSExperiment

DoseResponseExperiment

Model

- **SBML**: models/liver_glucose.xml
- **HTML**: models/liver_glucose.html

Datasets

- epinephrine.tsv
- glucagon.tsv
- insulin.tsv

Figures

- DoseResponseExperiment_fig1.svg

fig1

Code

https://github.com/matthiaskoenig/exsimo/tree/master/pyexsimo/experiments/dose_response.py

```python
from typing import Dict
from matplotlib.pyplot import Figure
import numpy as np
import pandas as pd

from sbmlsim.experiment import SimulationExperiment
from sbmlsim.data import DataSet
from sbmlsim.timecourse import Timecourse, TimecourseSim, TimecourseScan
from sbmlsim.plotting_matplotlib import add_data, add_line, plt
from sbmlsim.pkpd import pkpd


class DoseResponseExperiment(SimulationExperiment):
    """Hormone dose-response curves."""

    @property
    def datasets(self) -> Dict[str, DataSet]:
        dsets = {}

        # dose-response data for hormones
        for hormone_key in ['Epinephrine', 'Glucagon', 'Insulin']:
            df = self.load_data(f"DoseResponse_Tab{hormone_key}")
            df = df[df.condition == "normal"]  # only healthy controls
            epi_normal_studies = [
```

Default Branch

develop 25 builds	# 57 started -	695d4c9 Matthias König	✓ ✓ ✓ ✓

Active Branches

✓ v0.3.2 1 build	# 56 passed 8 minutes ago	d0cde3a Matthias König	✓
✓ master 17 builds	# 55 passed 8 minutes ago	d0cde3a Matthias König	✓ ✓ ✓ ✗ ✗
✓ v0.3.1 1 build	# 45 passed 22 hours ago	423ccc7 Matthias König	✓

```
Name                                           Stmts   Miss  Cover
------------------------------------------------------------------
pyexsimo/__init__.py
pyexsimo/_version.py
pyexsimo/execute.py
pyexsimo/experiments/__init__.
pyexsimo/experiments/dose_resp
pyexsimo/experiments/glycogen.
pyexsimo/experiments/hgp_gng.p
pyexsimo/experiments/hgp_gng_s
pyexsimo/model_factory.py
pyexsimo/models/__init__.py
pyexsimo/models/liver_glucose.
pyexsimo/models/templates.py                       9      1    89%
pyexsimo/report.py                                45      7    84%
pyexsimo/tests/__init__.py                         0      0   100%
pyexsimo/tests/test_annotations.py                48      1    98%
pyexsimo/tests/test_data.py                        9      0   100%
pyexsimo/tests/test_execute.py                     4      0   100%
pyexsimo/tests/test_experiments.py                12      0   100%
pyexsimo/tests/test_models.py                     48      1    98%
pyexsimo/tests/test_report.py                     13      0   100%
pyexsimo/tests/test_simulate.py                   24      0   100%
pyexsimo/tests/test_units.py                      12      0   100%
pyexsimo/tests/utils.py                           20      0   100%
------------------------------------------------------------------
TOTAL                                            625     16    97%

==================== 984 passed, 7 warnings in 174.30 seconds
```

January 2, 2020

matthiaskoenig/exsimo: exsimo-v0.3.2 - EXecutable SImulation MOdels

matthiaskoenig/exsimo-v0.3.2.zip 10.3 MB

- SVG figures
- HDF5 results
- Updated figures and documentation

Preview

study.json	0 Bytes
docs	
DoseResponseExperiment.md	7.1 kB
DoseResponseExperiment_fig1.svg	240.9 kB
GlycogenExperiment.md	5.4 kB
GlycogenExperiment_fig1.svg	72.0 kB
PathwayExperiment.md	4.4 kB
PathwayExperiment_fig1.svg	95.5 kB
PathwaySSExperiment.md	3.5 kB
PathwaySSExperiment_fig1.svg	212.3 kB
_config.yml	27 Bytes
figures	
Base: liver_glucose_11.pdf	18.6 kB
Base: liver_glucose_11.png	234.5 kB
Base: liver_glucose_11.svg	358.2 kB
liver_glucose.cys	208.8 kB
liver_glucose_layout.xml	8.9 kB

```
✓ Test Results                                     54 s 85 ms
  ✓ pyexsimo                                       54 s 85 ms
    ✓ tests                                        54 s 85 ms
      ✓ test_annotations                                0 ms
        ✓ test_document_has_sbo                         0 ms
        ✓ test_specie_has_sbo                           0 ms
        ✓ test_reaction_has_sbo                         0 ms
        ✓ test_model_has_cvterms                        0 ms
        ✓ test_specie_has_cvterms                       0 ms
        ✓ test_reaction_has_cvterms                     0 ms
        ✓ test_specie_has_chebi                         0 ms
        ✓ test_specie_has_inchikey                      0 ms
        ✓ test_specie_has_kegg_compound                 0 ms
        ✓ test_reaction_has_uniprot                     0 ms
        ✓ test_reaction_has_go                          0 ms
        ✓ test_reaction_has_ec                          0 ms
        ✓ test_reaction_has_rhea                        0 ms
        ✓ test_reaction_has_pr                          0 ms
      ✓ test_data                                      13 ms
        ✓ test_datafile_exists                          0 ms
        ✓ test_datafile_parsable                       13 ms
      ✓ test_experiments                          46 s 319 ms
        ✓ test_experiments                         9 s 619 ms
          ✓ (DoseResponseExperiment)               3 s 672 ms
          ✓ (PathwayExperiment)                    3 s 499 ms
          ✓ (GlycogenExperiment)                   2 s 448 ms
        ✓ test_experiments_const_glycogen         36 s 700 ms
          ✓ (PathwaySSExperiment)                 36 s 700 ms
      ✓ test_models                                4 s 537 ms
        ✓ test_create_models                       2 s 205 ms
        ✓ test_model_exists                            103 ms
        ✓ test_model_is_valid                      1 s 121 ms
        ✓ test_model_no_warnings                   1 s 108 ms
        ✓ test_specie_has_formula                       0 ms
        ✓ test_specie_has_charge                        0 ms
        ✓ test_reaction_mass_balance                    0 ms
      ✓ test_simulate                              3 s 216 ms
        ✓ test_simulate_timecourse                     636 ms
        ✓ test_species_nonnegative                     644 ms
        ✓ test_cofactor_balances                   1 s 936 ms
      ✓ test_units                                      0 ms
        ✓ test_specie_has_substance_units               0 ms
        ✓ test_compartment_has_units                    0 ms
        ✓ test_parameter_has_units                      0 ms
```

Docker Pull Command

```
docker pull matthiaskoenig/exsimo
```

matthiaskoenig/exsimo ★

By matthiaskoenig • Updated a day ago

Docker image for EXecutable SImulation MOdels

ALL RECENT COMMITS

version bump
matthiaskoenig a minute ago develop 695d4c9 ✓ CI Passed

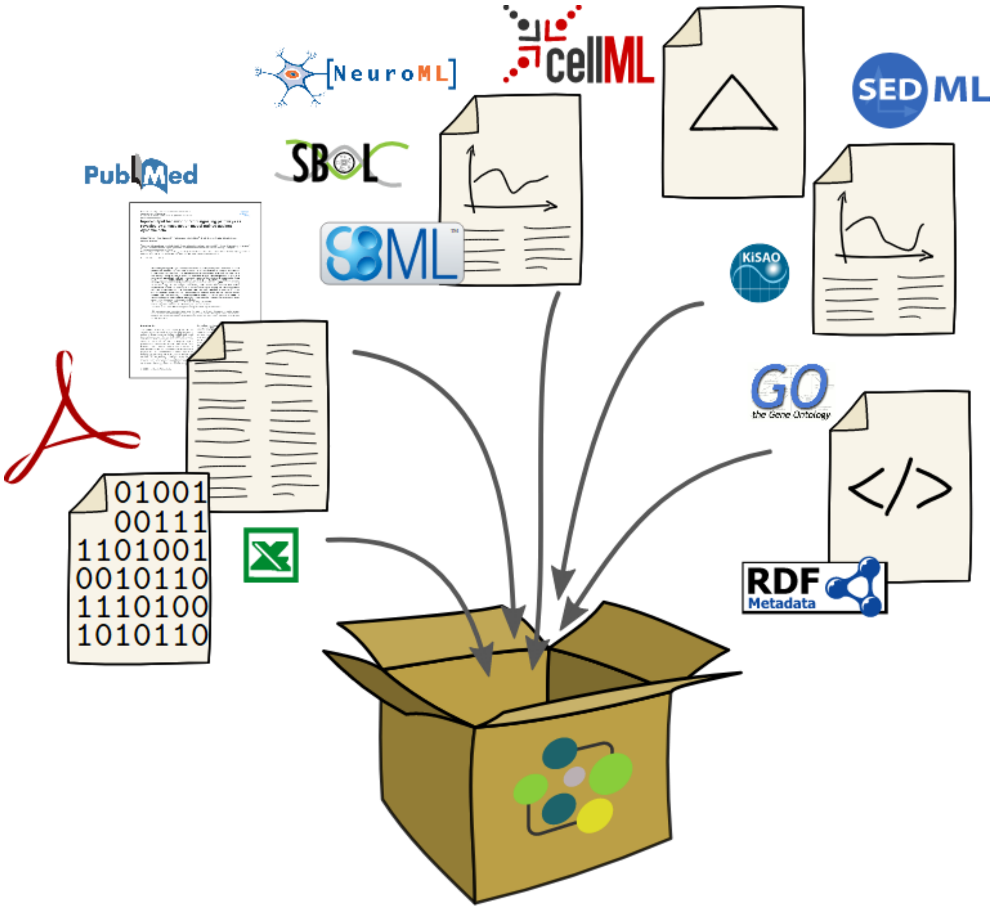
Merge pull request #18 from matthiaskoenig/develop
matthiaskoenig 14 minutes ago develop d0cde3a

combine the computational modeling in biology network

- initiative to coordinate the development of the various community standards and formats for computational models
- COMBINE meeting & HARMONY hackathon
- Core standards
  http://co.mbine.org/Standards#Core_COMBINE_standards
  - **SBML** Systems Biology Markup Language
  - **SED-ML** Simulation Experiment Description Language (SED-ML)
  - **SBGN** Systems Biology Graphical Notation
  - **CellML**
  - **SBOL** Synthetic Biology Open Language Data
  - **NeuroML**

COMBINE archive

- A COMBINE archive is a single file bundling the various documents necessary for a modeling and simulation project.
- The archive is encoded using the **Open Modeling EXchange format (OMEX).**



Tools not accessible

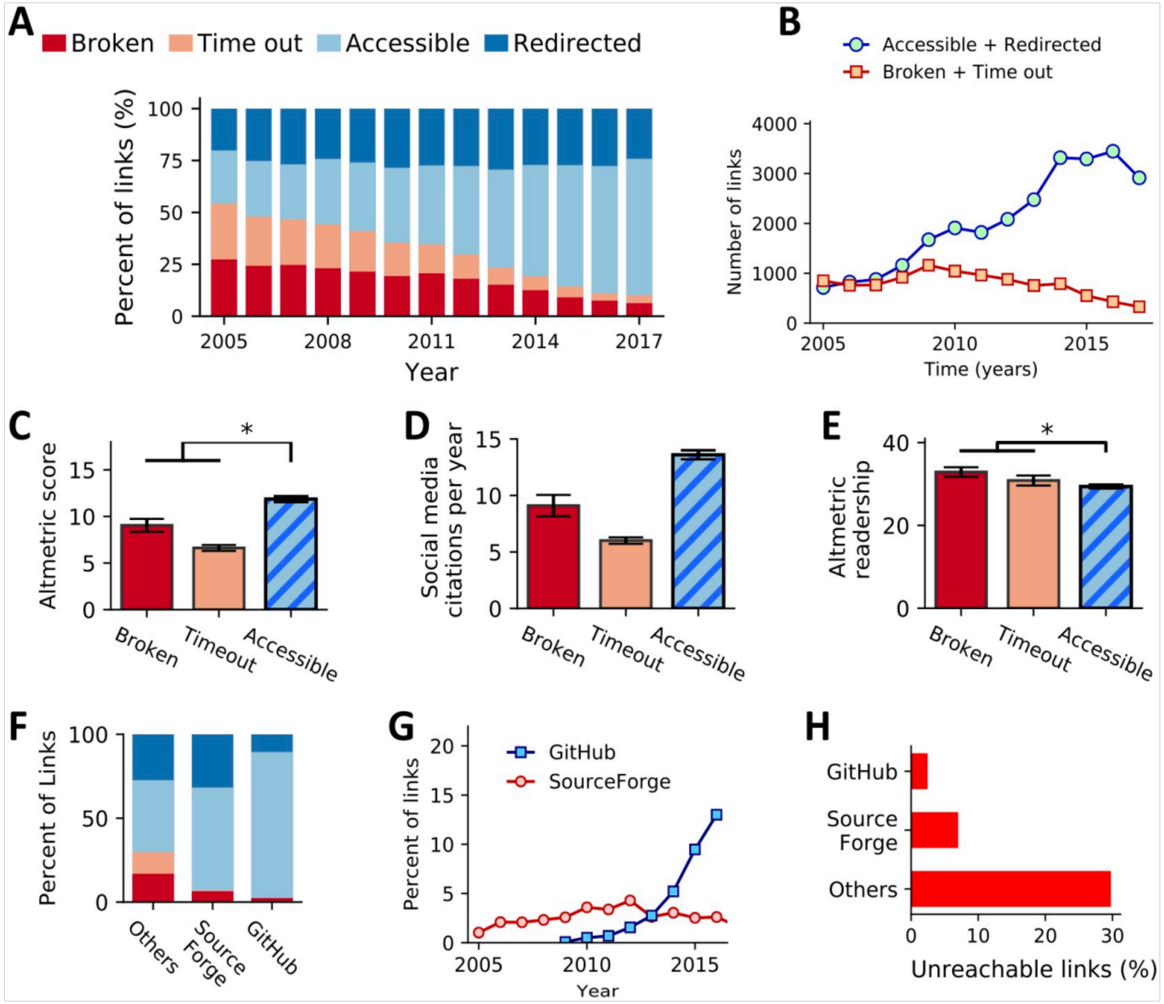
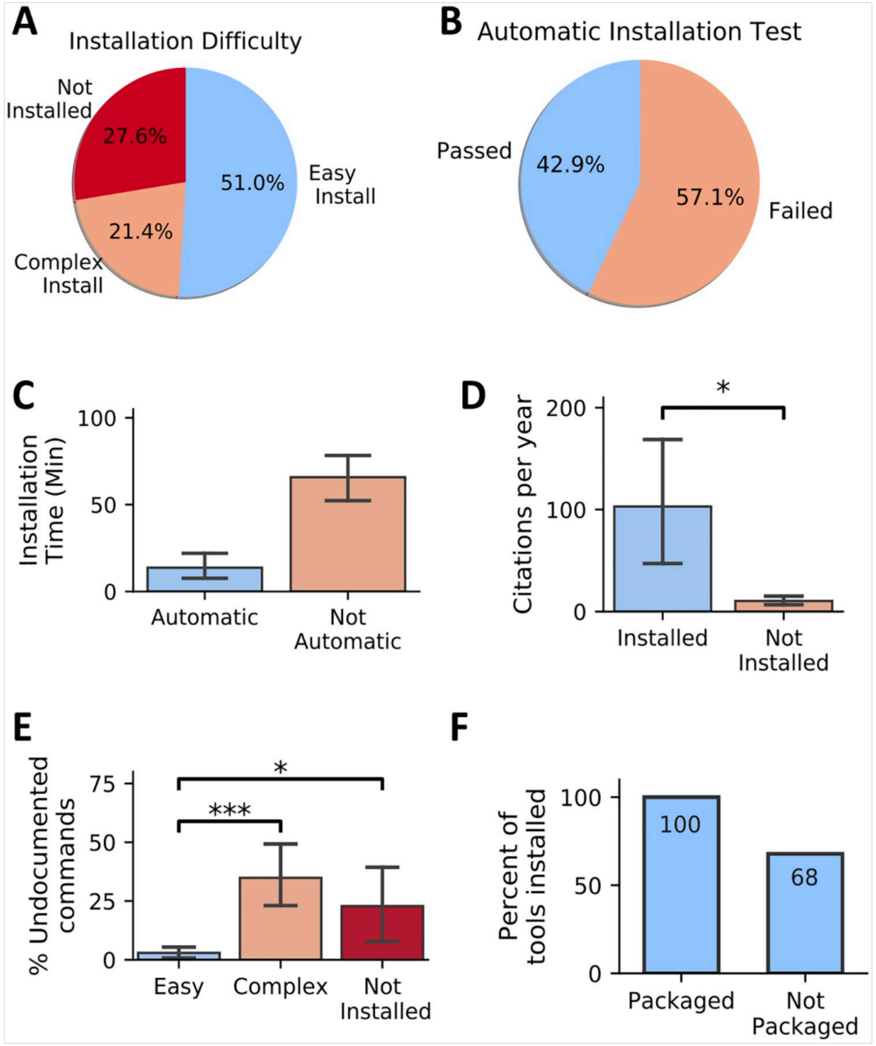


Fig 1. Archival stability of 36,702 published URLs across 10 systems and computational biology journals over the span of 13 years. An asterisk (*) denotes categories that have a difference that is statistically significant. Error bars, where present, indicate SEM. (A) Archival stability status of all links evaluated from papers published between 2005 and 2017. Percentages of each category (y-axis) are reported over a 13-year span (x-axis). (B) A line graph comparing the overall numbers (y-axis) of functional (green circles) and nonfunctional (orange squares) links observed in papers published over time (x-axis). (C) A bar chart showing the mean Altmetric "attention score" (y-axis) for papers, separated by the status of the URL (x-axis) observed in that paper. (D) A bar chart showing the mean number of mentions of papers in social media (blog posts, Twitter feeds, etc.) according to Altmetric, divided by the age of the paper in years (y-axis). Papers are separated by the status of the URL (x-axis) found in the paper. (E) A bar chart illustrating the mean Altmetric readership count per year of papers (y-axis) containing URLs in each of the categories (x-axis). (F) The proportion of unreachable links (due to connection time-out or due to error) stored on web services designed to host source code (e.g., GitHub and SourceForge) and "Other" web services. (G) A line plot illustrating the proportion (y-axis) of the total links observed in each year (x-axis) that point to GitHub or SourceForge. (H) A bar chart illustrating the proportion of links hosted on GitHub or SourceForge (vertical axis) that are no longer functional (horizontal axis) compared with links hosted elsewhere. SEM, standard error of the mean; URL, uniform resource locators.

Mangul, Serghei, et al. "Challenges and recommendations to improve the installability and archival stability of omics computational tools." PLoS biology 17.6 (2019): e3000333.

Tools not installable



Mangul, Serghei, et al. "Challenges and recommendations to improve the installability and archival stability of omics computational tools." PLoS biology 17.6 (2019): e3000333.