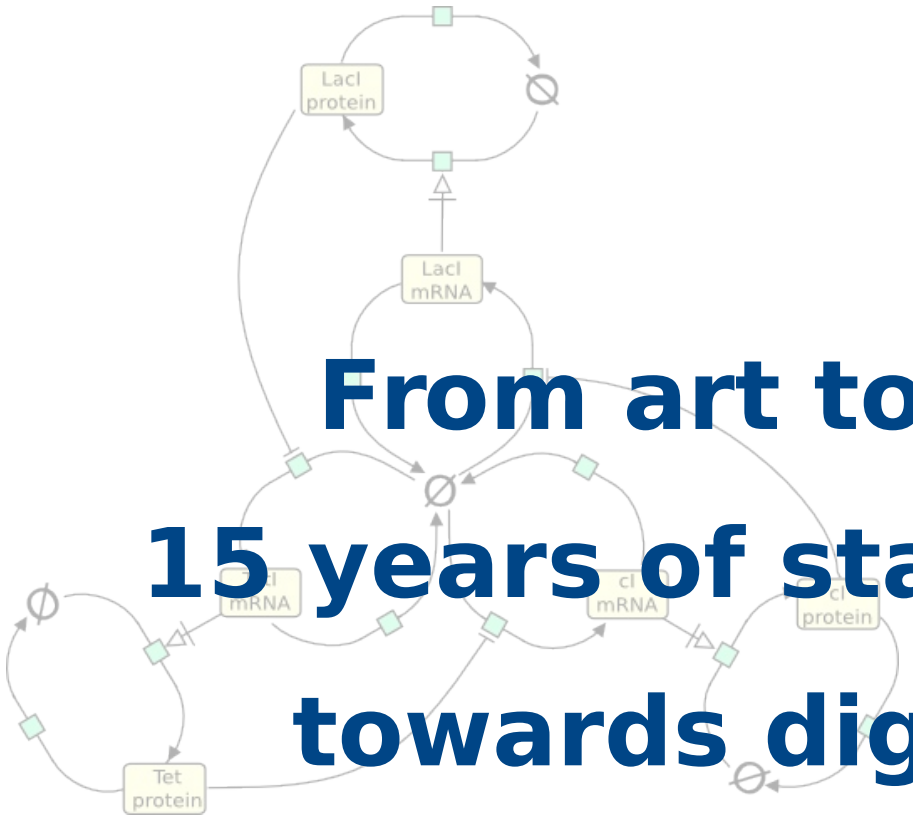
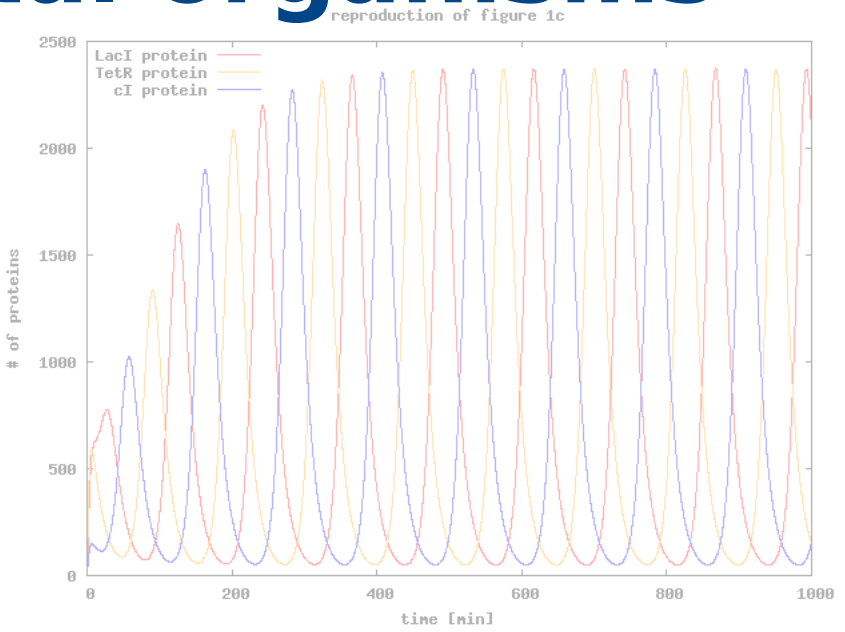


$$\frac{dm_i}{dt} = -m_i + \frac{\alpha}{(1+p_j^n)} + \alpha_0 \qquad \begin{pmatrix} i = lacI, tetR, cI \\ j = cI, lacI, tetR \end{pmatrix}$$

$$\frac{dp_i}{dt} = -\beta(p_i - m_i)$$

From art to engineering: 15 years of standards and tools towards digital organisms

Nicolas Le Novère
Babraham Institute,
Cambridge, UK
n.lenovere@gmail.com

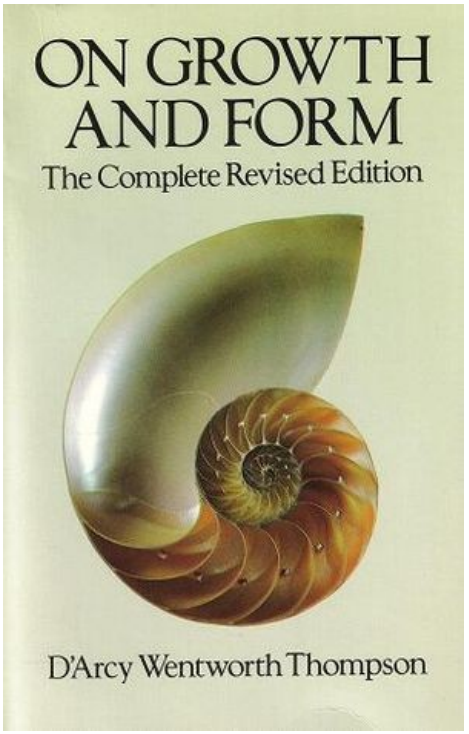


Babraham Institute

EMBL-EBI

Why using mathematical models?

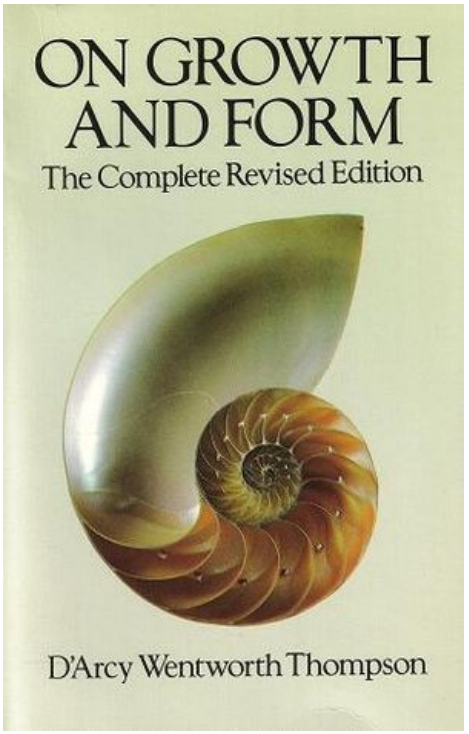
Describe



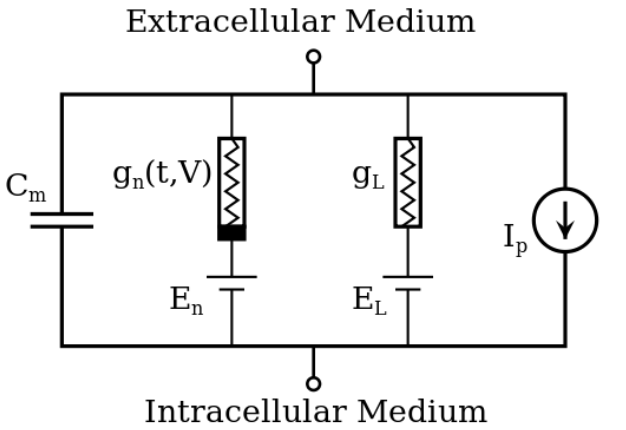
1917

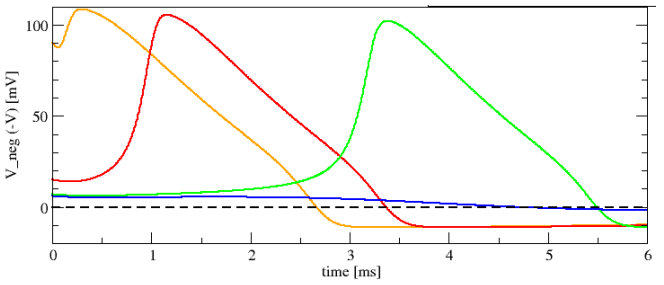
Why using mathematical models?

Describe	Explain



1917





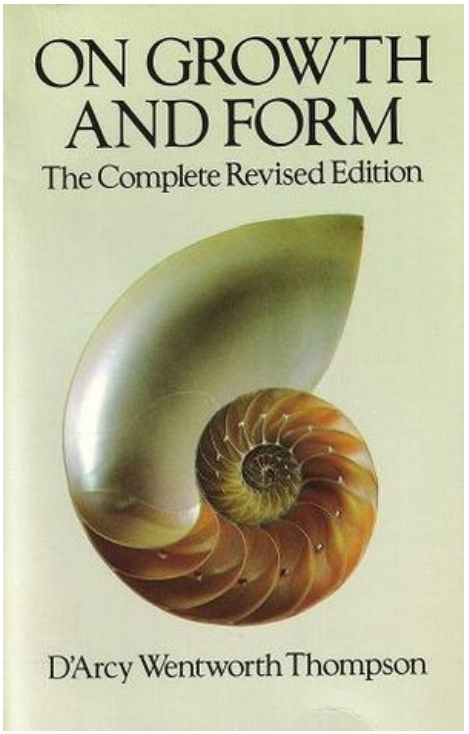
1952

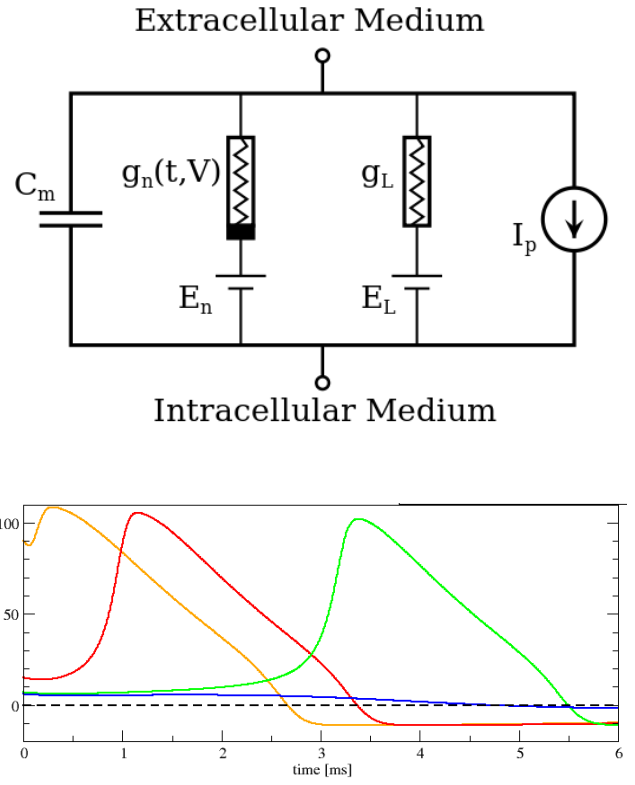
Babraham Institute

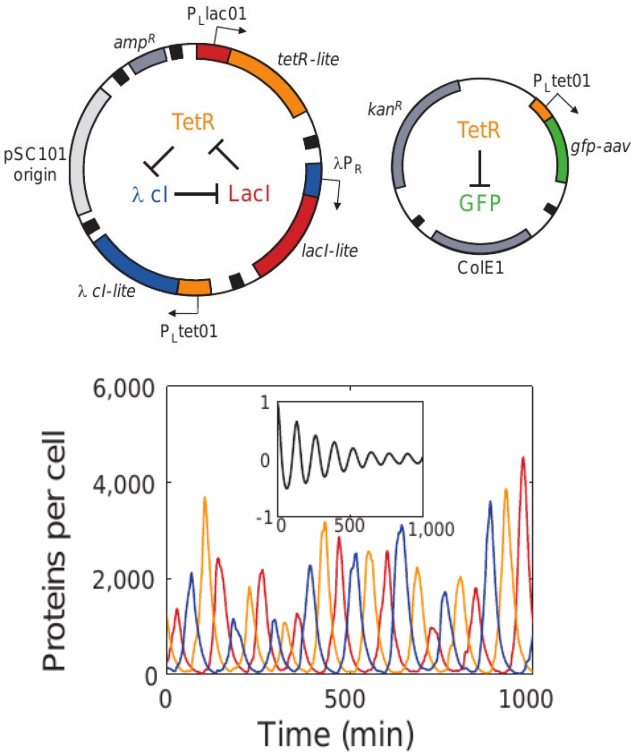
EMBL-EBI

Why using mathematical models?

Describe	Explain	Predict







1917 1952 2000

What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

variables
[x]
Vmax
Kd
EC_{50}
length
$t_{1/2}$

What we want to know or compare with experiments

What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

variables	relationships
[x]	$K_d = \frac{[A] \cdot [B]}{[AB]}$
Vmax	$d[X]/dt = k \cdot [Y]^2$
Kd	$\sum_i [X]_i - F(t) = 0$
EC_{50}	$k(t) \sim N(k, \sigma^2)$
length	If $\text{mass}_t > \text{threshold}$ then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$
$t_{1/2}$	

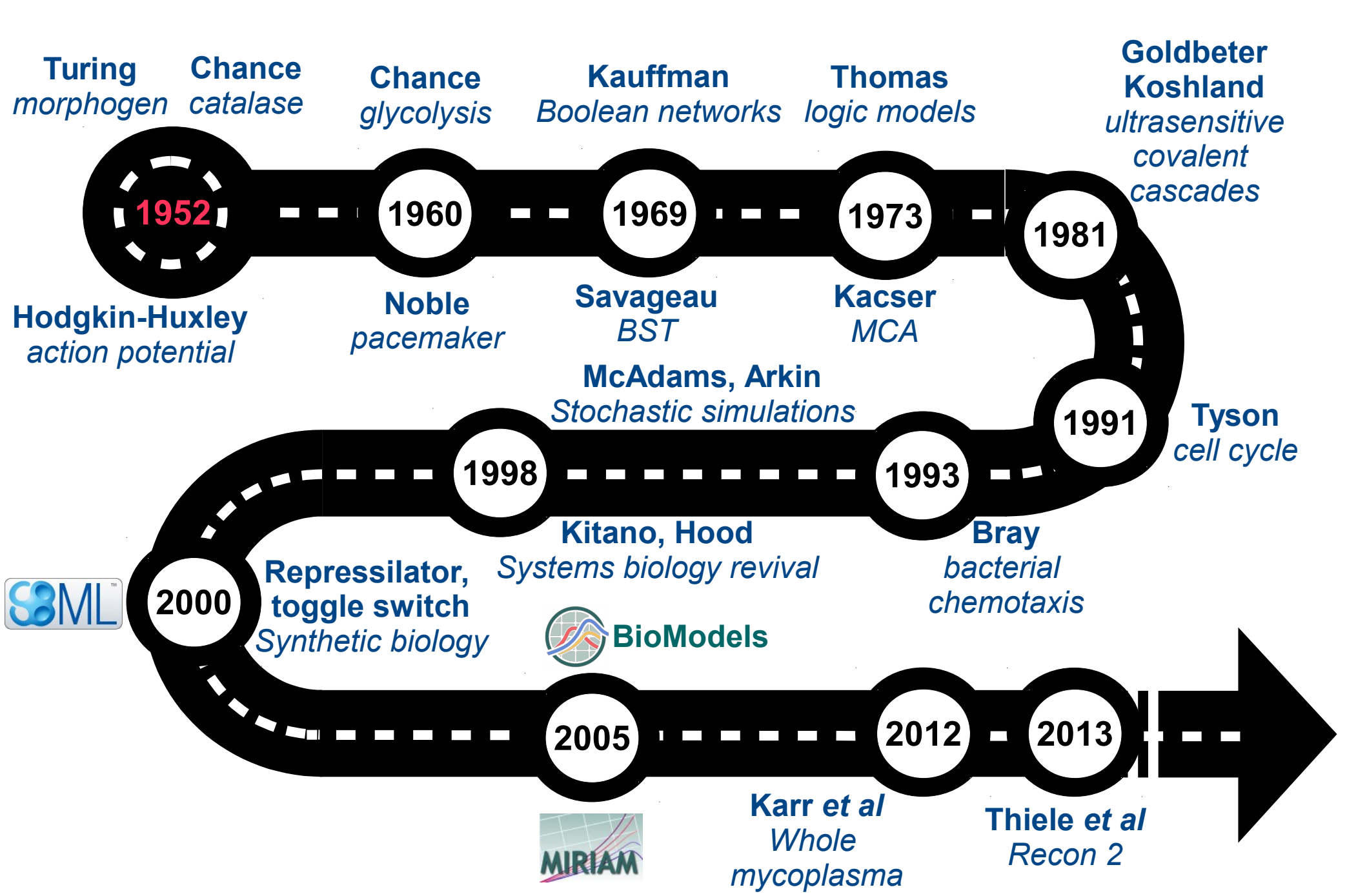
What we already know or want to test

What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

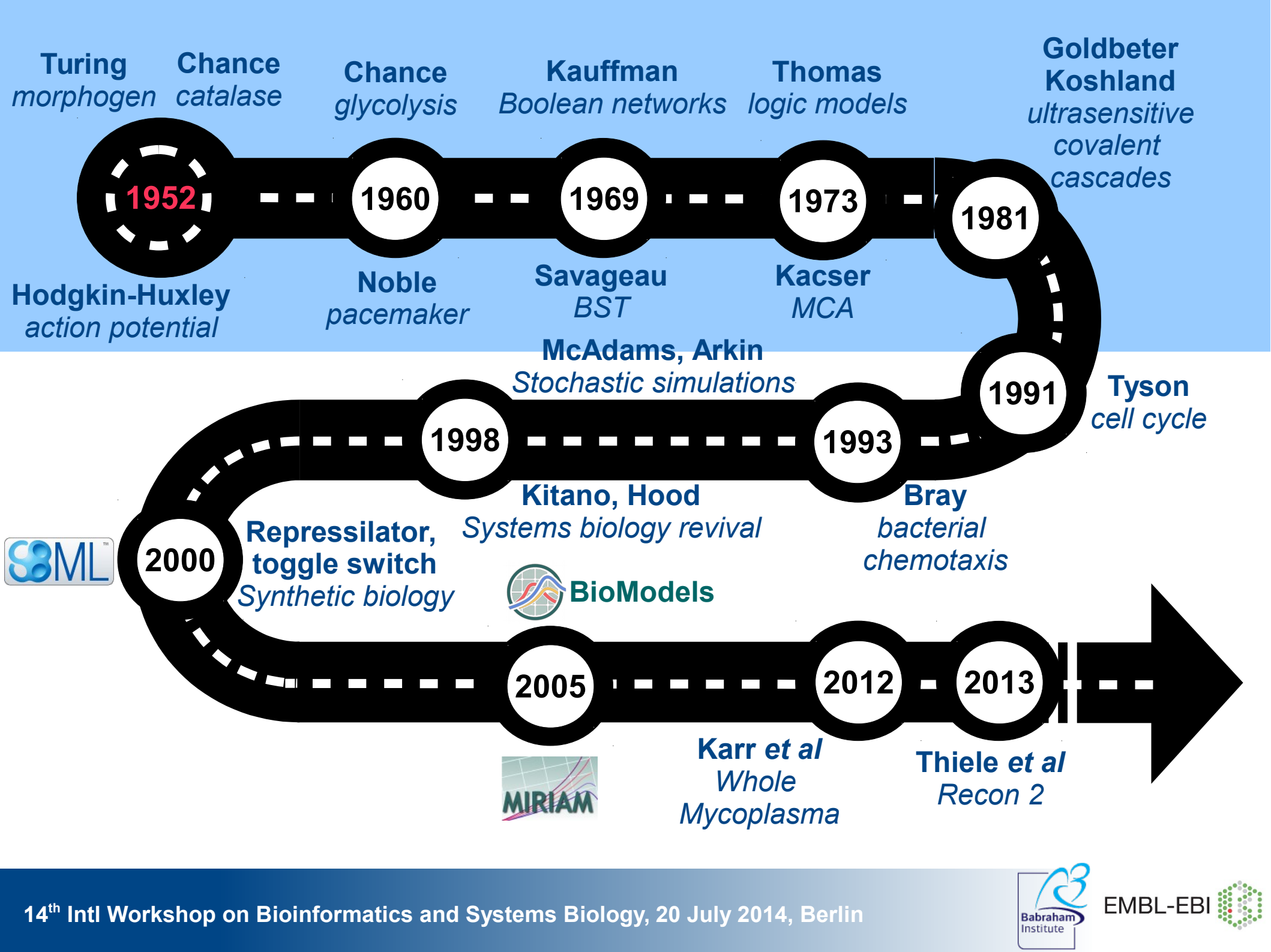
variables	relationships	constraints
[x]	$K_d = \frac{[A] \cdot [B]}{[AB]}$	[x]>0
Vmax	$d[X]/dt = k \cdot [Y]^2$	Energy conservation
Kd	$\sum_i [X]_i - F(t) = 0$	Boundary conditions (v < upper limit)
EC_{50}	$k(t) \sim N(k, \sigma^2)$	Objective functions (maximise ATP)
length	If $\text{mass}_t > \text{threshold}$ then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$	Initial conditions
$t_{1/2}$		

The context or what we want to ignore



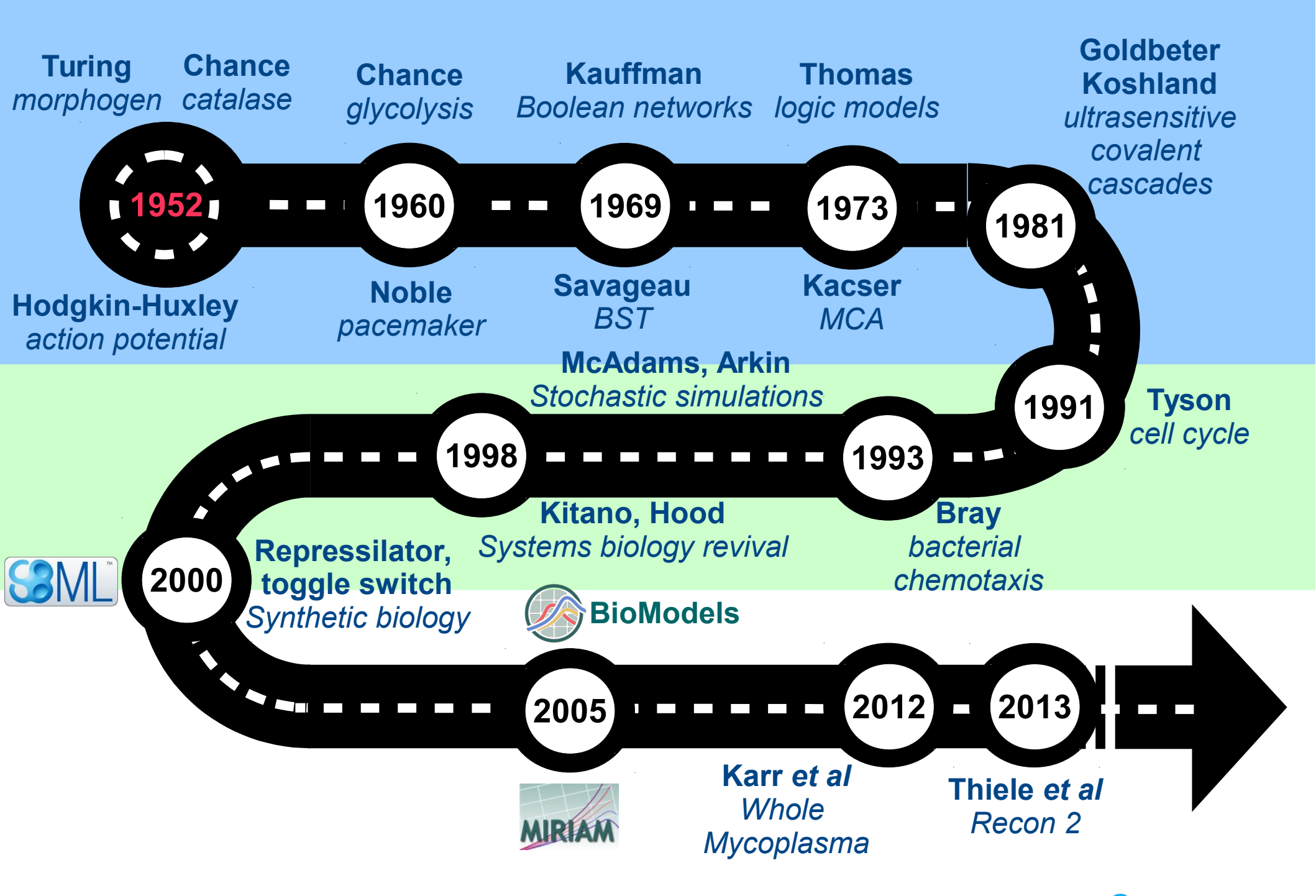
Babraham Institute

EMBL-EBI



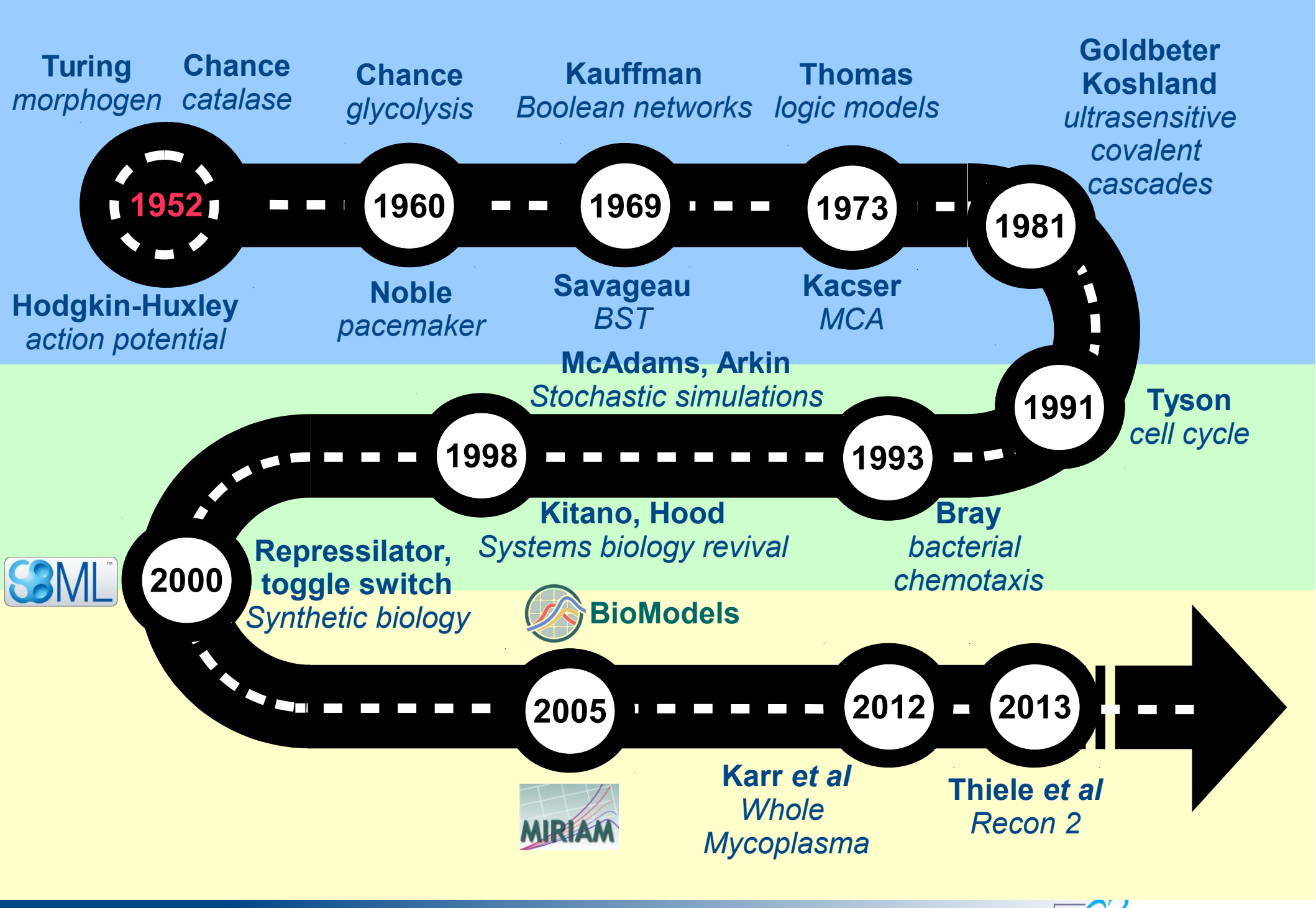
Babraham Institute

EMBL-EBI



Babraham Institute

EMBL-EBI



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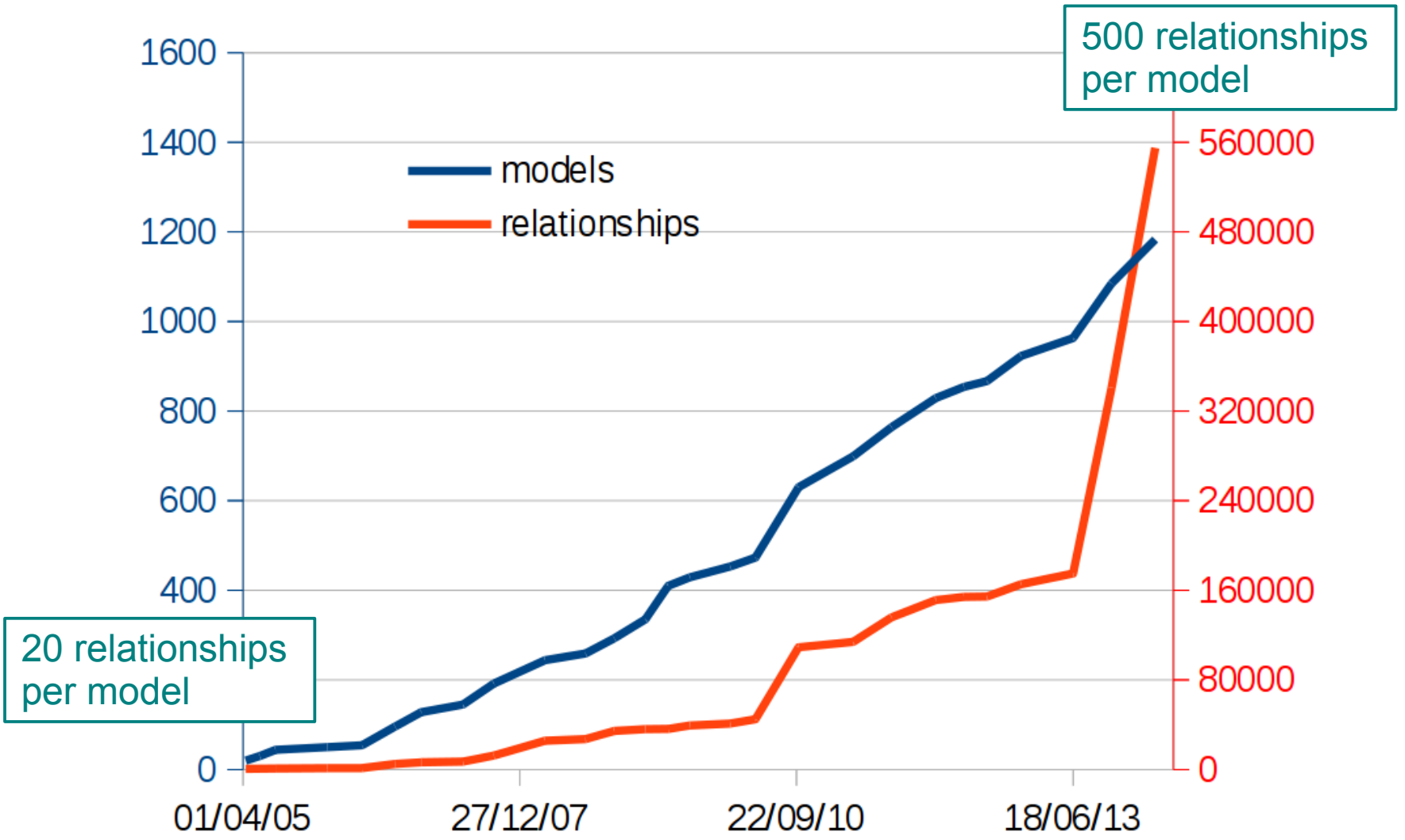
Computational models on the rise



BioModels Database growth (published models branch) since its creation

Improvised	Designed
One off	Many
Unique	Standard
Manually produced	Automated production
One or few artists	Collaboration
Produced in one go	Workflow
Fragile	Robust

Art.

Engineering

We need to

Verify

Re-use

Modify

Build upon

Integrate with

Therefore we need to share

Model descriptions

Simulation descriptions

Parametrisations

Biological meaning

Three types of standards

Minimal requirements **WHAT**	What to encode in order to share experiments and understand results MIBBI
Data-models **HOW**	How to encode the information defined above in a computer-readable manner combine
Terminologies	Structured representation of knowledge, with concept definitions and their relationships  OBO foundry

A language to describe computational models in biology

	Model descriptions
Data-models	SBML

Hucka et al. (2003)

Born in Caltech 2000

John Doyle

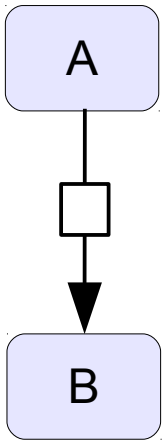
Hiroaki Kitano

Hamid Bolouri

Mike Hucka

Andrew Finney

Herbert Sauro



$$\frac{d[B]}{dt} = k \times [A]$$

```xml
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  <model name="Simple Model">
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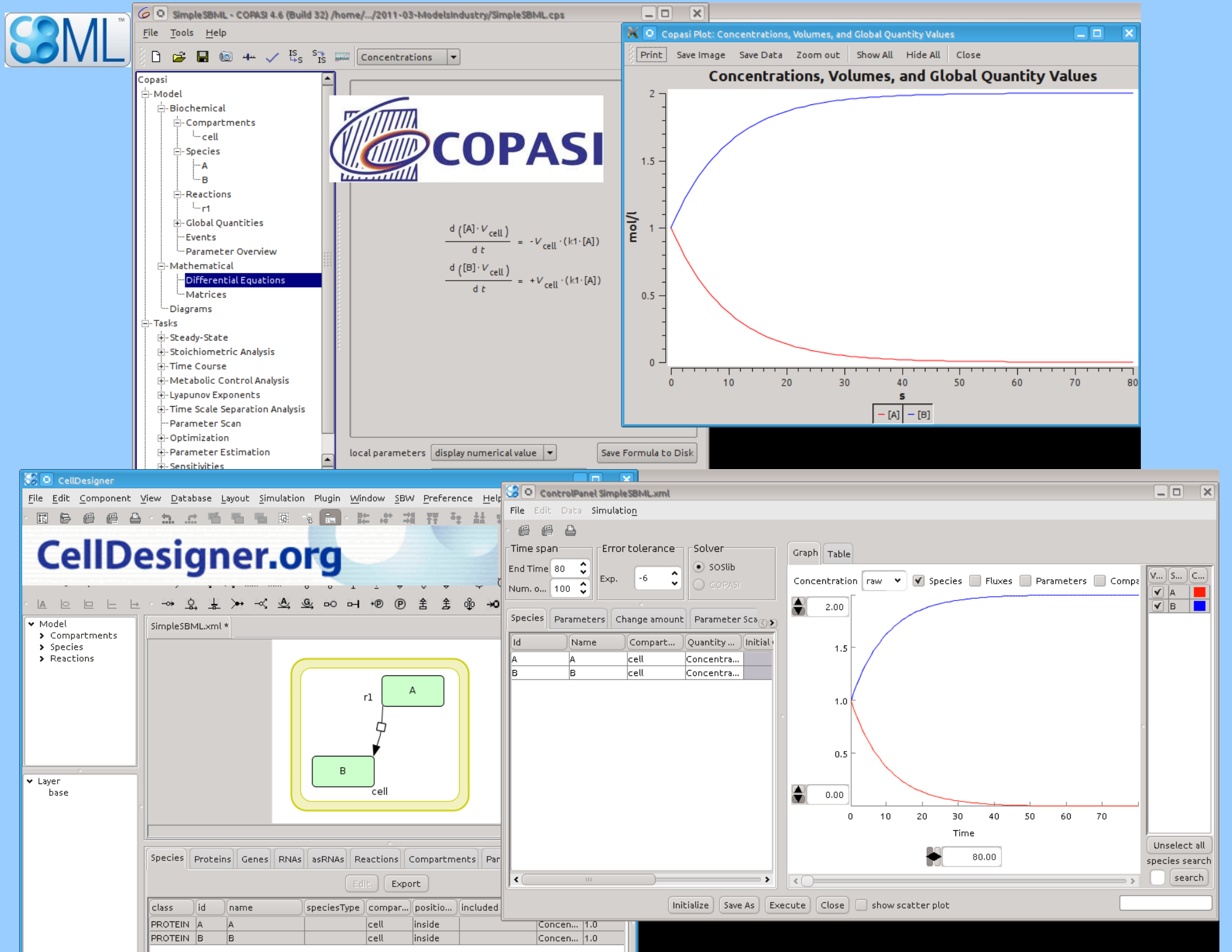
      <compartment id="cell" size="1" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="1"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="k1" value="0.1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction id="r1" reversible="false">
      <listOfReactants>
          <speciesReference species="A"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci> cell </ci>
              <ci> k1 </ci>
              <ci> A </ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

A very simple SBML file

http://sbml.org


SBML
SimpleSBML - COPASI 4.6 (Build 32) /home/.../2011-03-ModelsIndustry/SimpleSBML.cps
File Tools Help
Concentrations
Copasi
Model
Biochemical
Compartments
cell
Species
A
B
Reactions
r1
Global Quantities
Events
Parameter Overview
Mathematical
Differential Equations
Matrices
Diagrams
Tasks
Steady-State
Stoichiometric Analysis
Time Course
Metabolic Control Analysis
Lyapunov Exponents
Time Scale Separation Analysis
Parameter Scan
Optimization
Parameter Estimation
Sensitivities
COPASI
d([A]·V_cell)/dt = -V_cell·(k1·[A])
d([B]·V_cell)/dt = +V_cell·(k1·[A])
local parameters
display numerical value
Save Formula to Disk
Copasi Plot: Concentrations, Volumes, and Global Quantity Values
Print Save Image Save Data Zoom out Show All Hide All Close
Concentrations, Volumes, and Global Quantity Values
mol/l
s
[A] [B]
CellDesigner
File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help
CellDesigner.org
Model
Compartments
Species
Reactions
Layer
base
SimpleSBML.xml *
r1
A
B
cell
Species Proteins Genes RNAs asRNAs Reactions Compartments
Edit Export
class id name speciesType compar... positio... included
PROTEIN A A cell inside Concen... 1.0
PROTEIN B B cell inside Concen... 1.0
ControlPanel SimpleSBML.xml
File Edit Data Simulation
Time span
End Time 80
Num. o... 100
Error tolerance
Exp. -6
Solver
SOSlib
COPASI
Species Parameters Change amount Parameter Sca
Id Name Compart... Quantity ... Initial
A A cell Concentra...
B B cell Concentra...
Graph Table
Concentration raw
Species Fluxes Parameters Compa
2.00
0.00
Time
80.00
V... S... C...
A
B
Unselect all
species search
search
Initialize Save As Execute Close show scatter plot

_computational BIOLOGY

RESOURCE

A community-driven global reconstruction of human metabolism

Ines Thiele[1,2,37], Neil Swainston[3,4,37], Ronan M T Fleming[1,5], Andreas Hoppe[6], Swagatika Sahoo[1], Maike K Aurich[1], Hulda Haraldsdottir[1], Monica L Mo[7], Ottar Rolfsson[1], Miranda D Stobbe[8,9], Stefan G Thorleifsson[1], Rasmus Agren[10], Christian Bölling[6], Sergio Bordel[10], Arvind K Chavali[11], Paul Dobson[12], Warwick B Dunn[3,13], Lukas Endler[14], David Hala[15], Michael Hucka[16], Duncan Hull[4], Daniel Jameson[3,4], Neema Jamshidi[7], Jon J Jonsson[5], Nick Juty[17], Sarah Keating[17], Intawat Nookaew[10], Nicolas Le Novère[17,18], Naglis Malys[3,19,20], Alexander Mazein[21], Jason A Papin[11], Nathan D Price[22], Evgeni Selkov, Sr[23], Martin I Sigurdsson[1], Evangelos Simeonidis[22,24], Nikolaus Sonnenschein[25], Kieran Smallbone[3,26], Anatoly Sorokin[21,27], Johannes H G M van Beek[28–30], Dieter Weichart[3,31], Igor Goryanin[21,32], Jens Nielsen[10], Hans V Westerhoff[3,28,33,34], Douglas B Kell[3,35], Pedro Mendes[3,4,36] & Bernhard Ø Palsson[1,7]

Multiple models of human metabolism have been reconstructed, but each represents only a subset of our knowledge. Here we describe Recon 2, a community-driven, consensus 'metabolic reconstruction', which is the most comprehensive representation of human metabolism that is applicable to computational modeling. Compared with its predecessors, the reconstruction has improved topological and functional features, including ~2× more reactions and ~1.7× more unique metabolites. Using Recon 2 we predicted changes in metabolite biomarkers for 49 inborn errors of metabolism with 77% accuracy when compared to experimental data. Mapping metabolomic data and drug information onto Recon 2 demonstrates its potential for integrating and analyzing diverse data types. Using protein expression data, we automatically generated a compendium of 65 cell type–specific models, providing a basis for manual curation or investigation of cell-specific metabolic properties. Recon 2 will facilitate many future biomedical studies and is freely available at http://humanmetabolism.org/.

An understanding of metabolism is fundamental to comprehending the phenotypic behavior of all living organisms, including humans, where metabolism is integral to health and is involved in much of human disease. High quality, genome-scale 'metabolic reconstructions' are at the heart of bottom-up systems biology analyses and represent the entire network of metabolic reactions that a given organism is known to exhibit[1]. The metabolic-network reconstruction procedure is now well-established[2] and has been applied to a growing number of model organisms[3]. Metabolic reconstructions allow for the conversion of biological knowledge into a mathematical format and the subsequent computation of physiological states[1,4,5] to address a variety of scientific and applied questions[3,6]. Reconstructions enable network-wide mechanistic investigations of the genotype-phenotype relationship. A high-quality reconstruction of the metabolic network is thus

[1]Center for Systems Biology, University of Iceland, Reykjavik, Iceland. [2]Faculty of Industrial Engineering, Mechanical Engineering and Computer Science, University of Iceland, Reykjavik, Iceland. [3]Manchester Centre for Integrative Systems Biology, University of Manchester, Manchester Institute of Biotechnology, Manchester, UK. [4]School of Computer Science, University of Manchester, Manchester, UK. [5]Department of Biochemistry and Molecular Biology, University of Iceland, Reykjavik, Iceland. [6]Computational Systems Biochemistry Group, Charité– Universitätsmedizin Berlin, Berlin, Germany. [7]Department of Bioengineering, University of California, San Diego, La Jolla, California, USA. [8]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. [9]Netherlands Bioinformatics Centre, Nijmegen, the Netherlands. [10]Department of Chemical and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden. [11]Department of Biomedical Engineering, University of Virginia, Charlottesville, Virginia, USA. [12]Department of Chemical and Biological Engineering, University of Sheffield, Sheffield, UK. [13]Centre for Advanced Discovery and Experimental Therapeutics (CADET), Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, UK. [14]Institute for Theoretical Chemistry, University of Vienna, Vienna, Austria. [15]Department of Biology, University of North Texas, Denton, Texas, USA. [16]Computing and Mathematical Sciences Department, California Institute of Technology, Pasadena, California, USA. [17]European Molecular Biology Laboratory, European Bioinformatics Institute, Hinxton, UK. [18]Babraham Institute, Babraham Research Campus, Cambridge, UK. [19]Faculty of Life Sciences, University of Manchester, Manchester, UK. [20]School of Life Sciences, Gibbet Hill Campus, University of Warwick, Coventry, UK. [21]School of Informatics, University of Edinburgh, Edinburgh, UK. [22]Institute for Systems Biology, Seattle, Washington, USA. [23]Genome Designs, Inc., Walnut Creek, California, USA. [24]Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Campus Belval, Esch-sur-Alzette, Luxembourg. [25]School of Engineering and Science, Jacobs University Bremen, Bremen, Germany. [26]School of Mathematics, University of Manchester, Manchester, UK. [27]Institute of Cell Biophysics, Russian Academy of Sciences, Moscow region, Pushchino, Russia. [28]Department of Molecular Cell Physiology, Vrije Universiteit, Amsterdam, the Netherlands. [29]Section Medical Genomics, Department of Clinical Genetics, Vrije Universiteit University Medical Centre, Amsterdam, the Netherlands. [30]Netherlands Consortium for Systems Biology, Amsterdam, The Netherlands. [31]School of Dentistry, The University of Manchester, Manchester, UK. [32]Okinawa Institute Science and Technology, Okinawa, Japan. [33]School of Chemical Engineering and Analytical Science, University of Manchester, Manchester, UK. [34]Swammerdam Institute for Life Sciences, Faculty of Science, University of Amsterdam, Amsterdam, The Netherlands. [35]School of Chemistry, The University of Manchester, Manchester, UK. [36]Virginia Bioinformatics Institute, Virginia Tech, Blacksburg, Virginia, USA. [37]These authors contributed equally to this work. Correspondence should be addressed to I.T. (ines.thiele@gmail.com).

Received 7 September 2012; accepted 19 December 2012; published online 3 March 2013; doi:10.1038/nbt.2488

A not so simple SBML file (Recon2)

- 8 compartments
- 5 063 metabolites
- 2 194 proteins
- 7 440 reactions

MODEL1109130000

SBML Software Guide

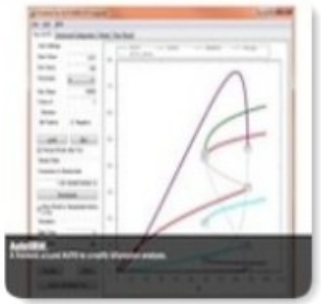
The following pages describe SBML-compatible software packages known to us. We offer different ways of viewing the information, all drawn from the same underlying data collected from the systems' developers via our **software survey**. The *Matrix* provides a table listing all known software and a variety of their features; the *Summary* provides general descriptions of most of the software; and the *Showcase* provides a sequential slideshow of a subset of the software.

Number of software packages listed in the matrix today: **263**.

Go to the SBML Software Matrix

Go to the SBML Software Summary

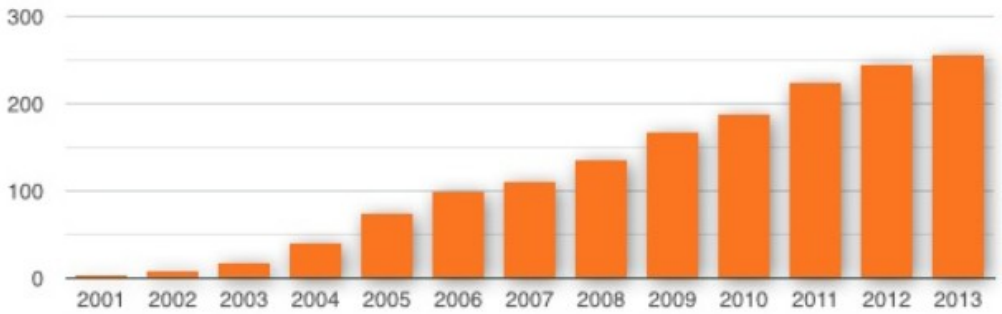
Go to the SBML Software Showcase



Please **tell us** about additions and updates.

Historical trend

The following graph shows the total number of known SBML-compatible software packages each year, as counted by the SBML Team. The counts shown are for approximately the middle of each year.



Adding the semantics to the syntax

	Model descriptions
Minimal requirements	MIRIAM
Data-models	SBML
Terminologies	SBO

Born in Heidelberg 2004

Le Novère *et al.* (2005), Courtot *et al.* (2011)

Minimal Information Required In the Annotation of Models

Reference correspondence

1. In a public, standardized, machine-readable format
2. Comply with the standard in which it is encoded
3. Clearly related to a single reference description
4. Reflect biological processes
5. Instantiable in a simulation all numbers provided
6. Able to reproduce results

Attribution

1. Has to be named
2. Citation must be provided
3. Model creators details
4. Date and time of creation and last modification
5. Link to precise statement about terms of distribution

External resources

1. Annotation unambiguously model constituent to data
2. Link to external information as a triplet {collection, identifier, qualifier}
3. Annotation written as a Uniform Resource Identifier
4. Identifier considered within framework of the collection.
5. Collection namespace and record identifier in one URI
6. Qualifiers to refine the link between model constituent and external knowledge
7. Standard set of valid URIs agreed upon by community

http://co.mbine.org/standards/miriam

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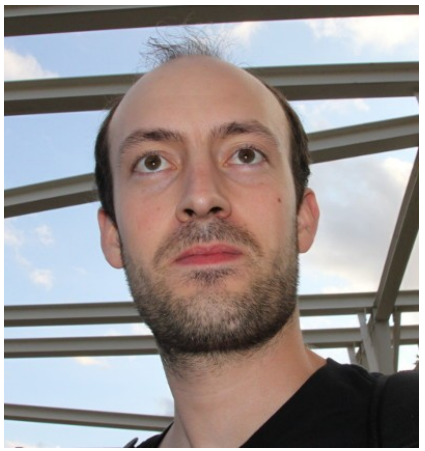
7. Standard set of valid URIs agreed upon by community

http://co.mbine.org/standards/miriam

identifiers.org (aka new MIRIAM URIs)

http://identifiers.org/namespace/identifier

protocol | type of URI | collection | record



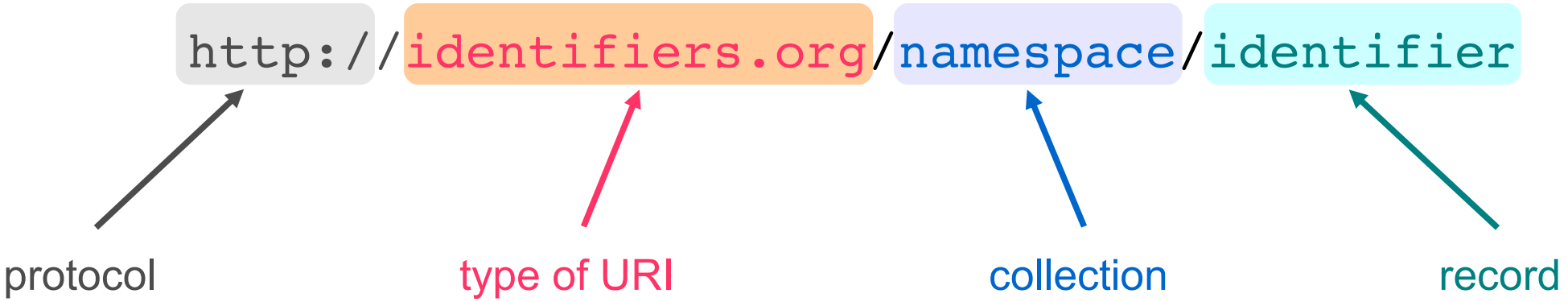
Camille Laibe

Nick Juty

Sarala Wimalaratne

Juty *et al.* (2012)

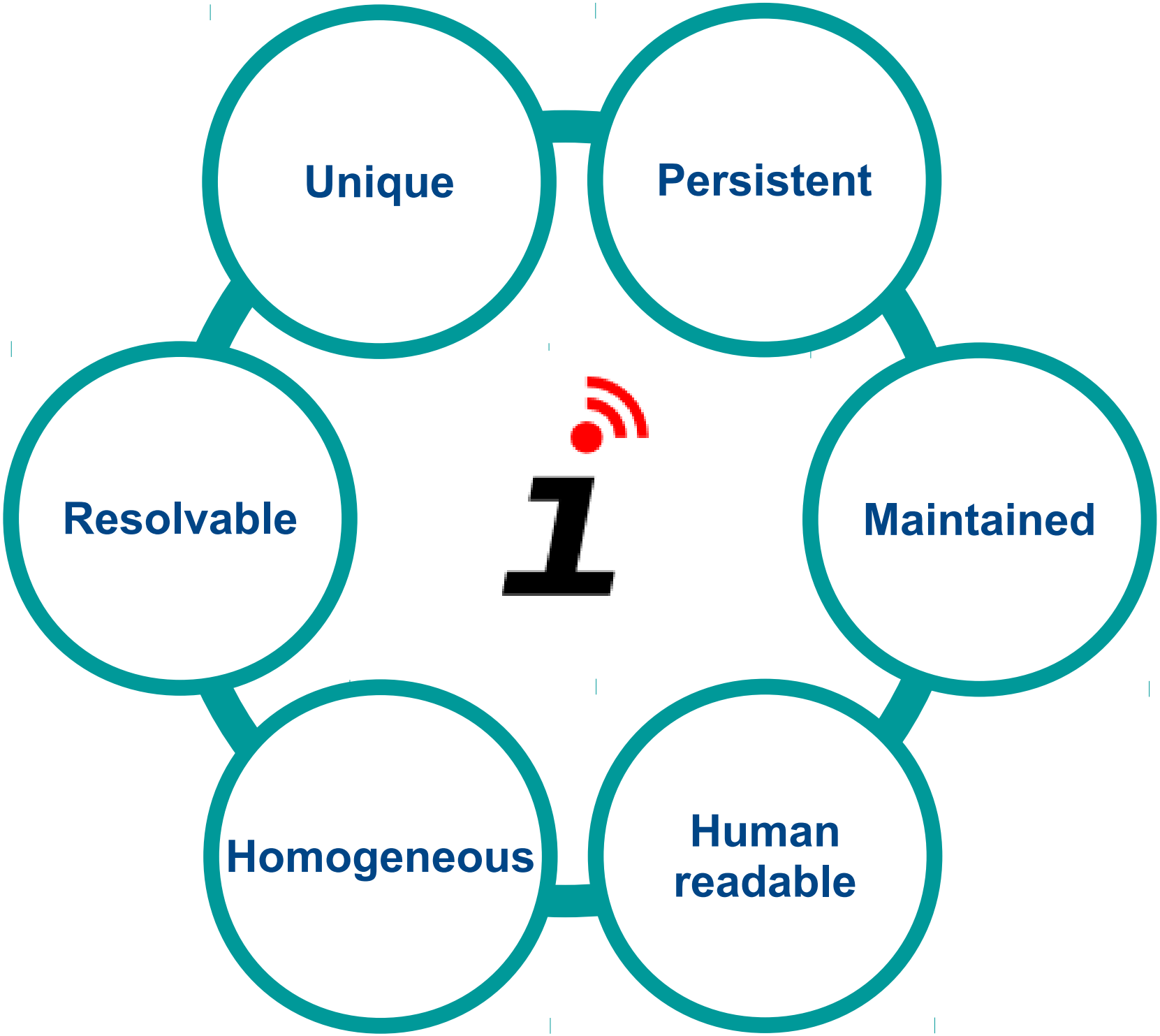
identifiers.org (aka new MIRIAM URIs)

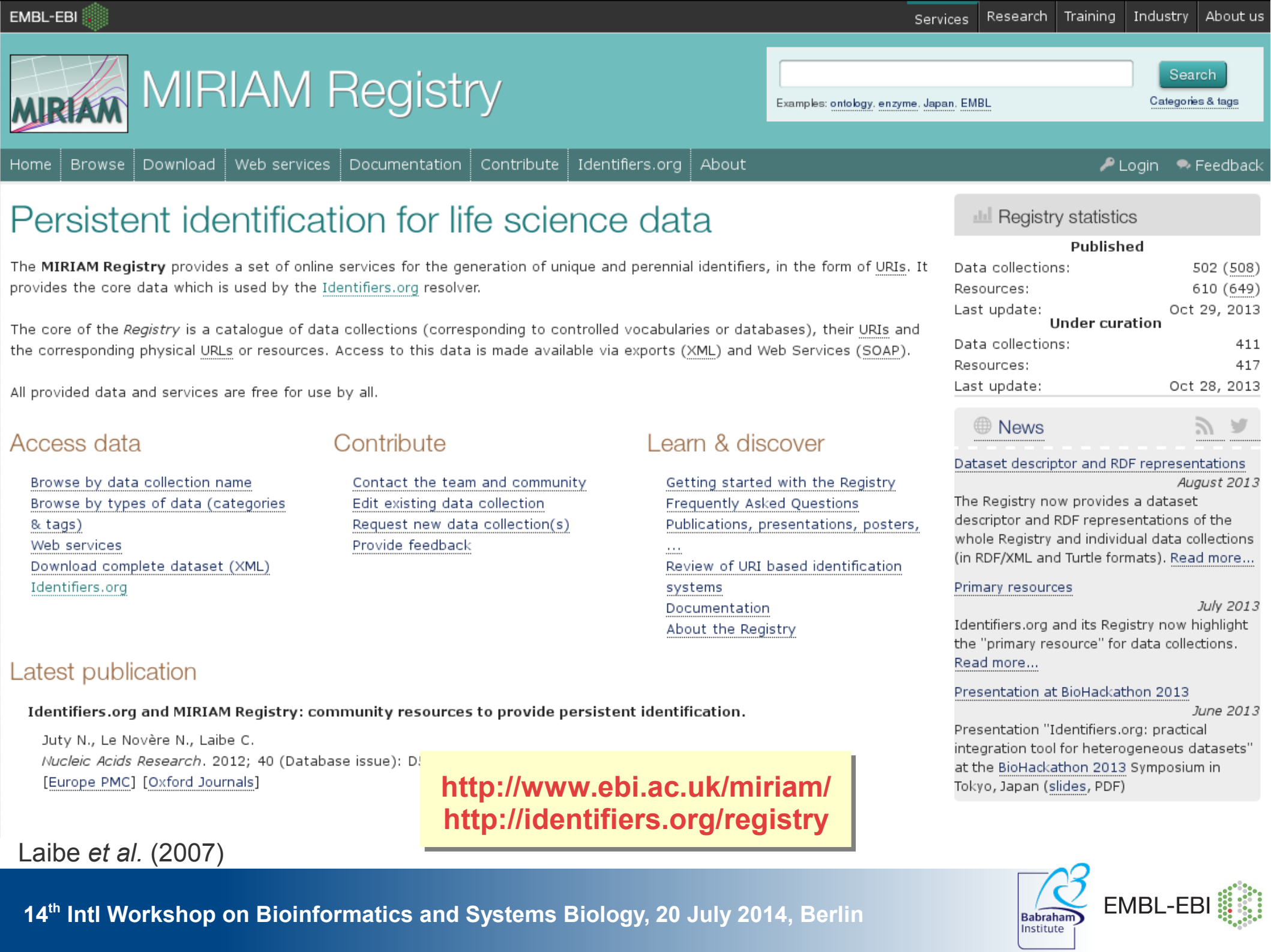


http://identifiers.org/pubmed/22140103

http://identifiers.org/ec-code/1.1.1.1

http://identifiers.org/go/GO:0000186


Unique
Persistent
Resolvable
Maintained
Homogeneous
Human readable



http://www.ebi.ac.uk/miriam/
http://identifiers.org/registry

Laibe *et al.* (2007)

SBML and Identifiers.org cross-references

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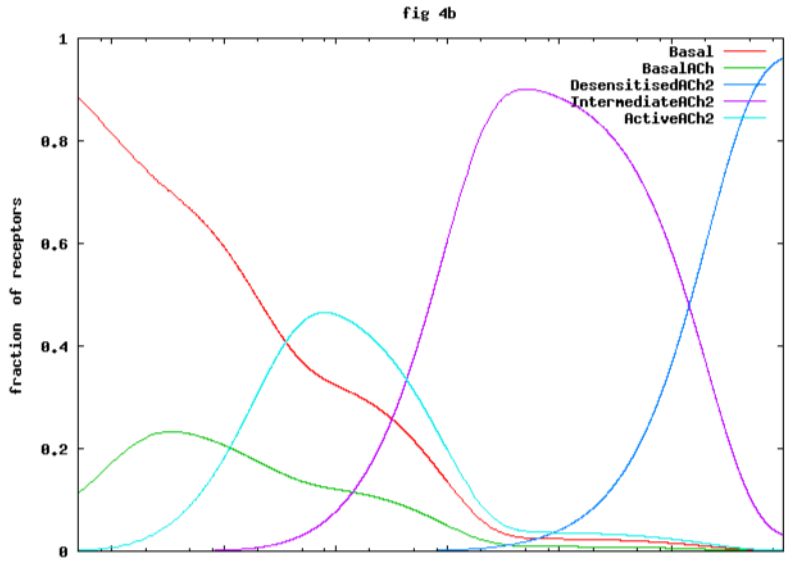
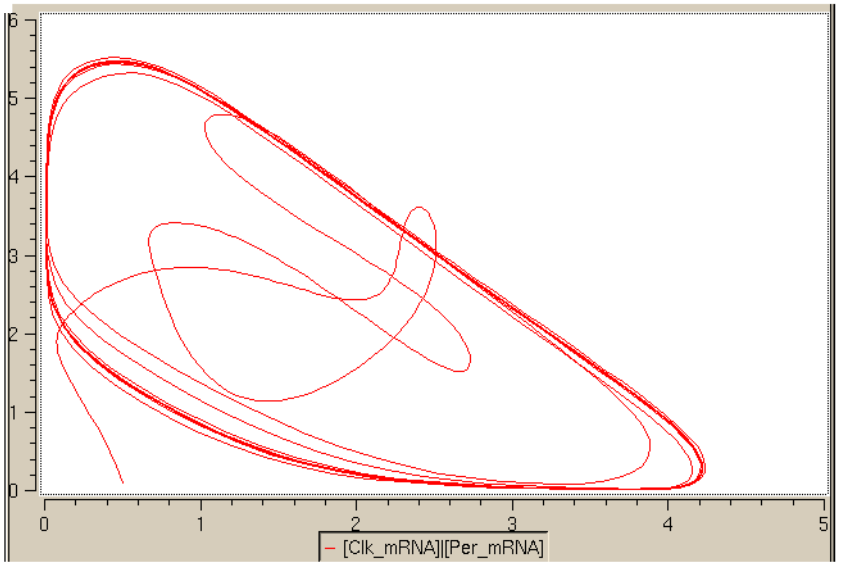
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/">
      <rdf:Description rdf:about="#cacam">
        <bqbiol:hadPart>
          <rdf:Bag>
            <rdf:li rdf:resource="http://identifiers.org/uniprot/62158"/>
            <rdf:li rdf:resource="http://identifiers.org/chebi/CHEBI:29108"/>
          </rdf:Bag>
        </bqbiol:hasPart>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

Surely, this is enough?

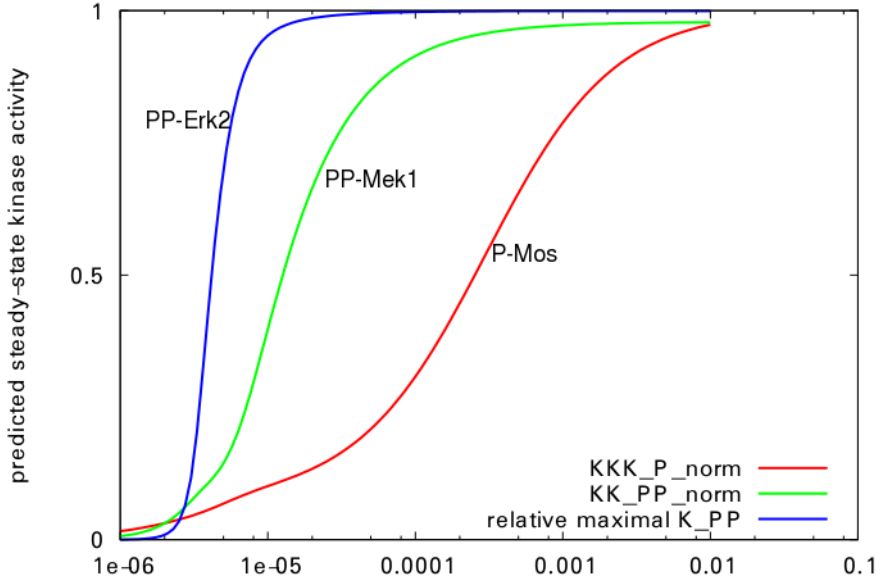
Simulation experiment = model + what to do with it



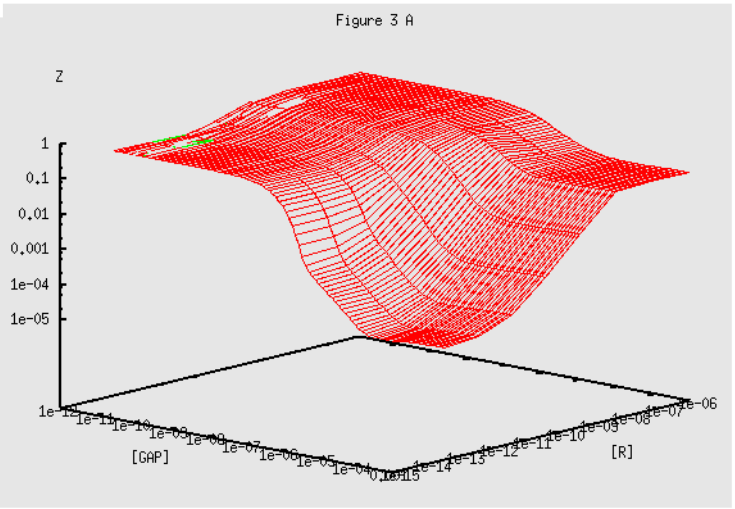
Edelstein et al 1996 (BIOMD0000000002)



Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)



Huang & Ferrell (BIOMD0000000009)

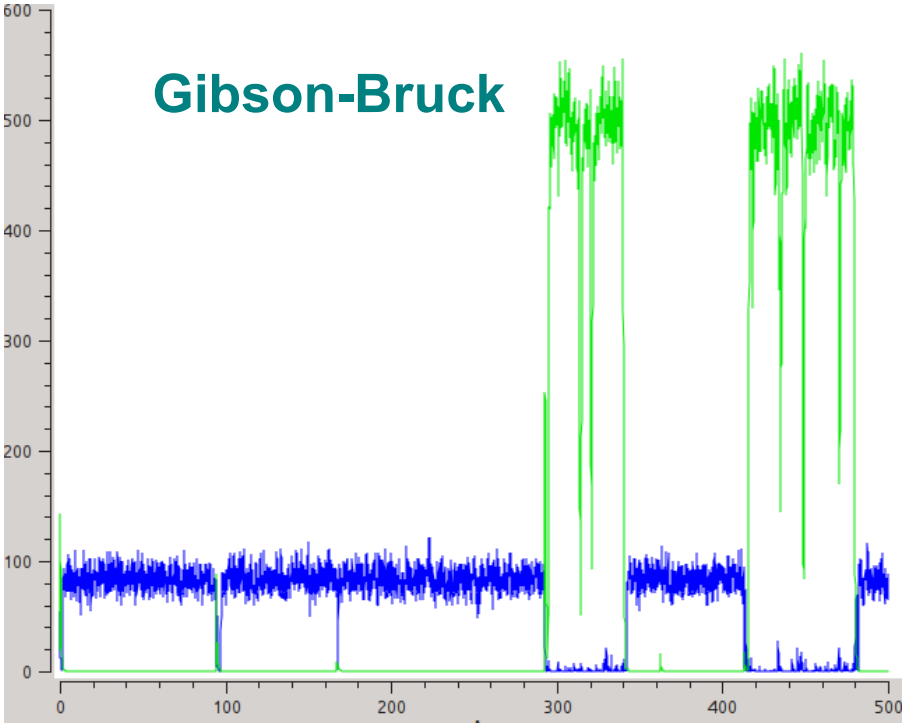


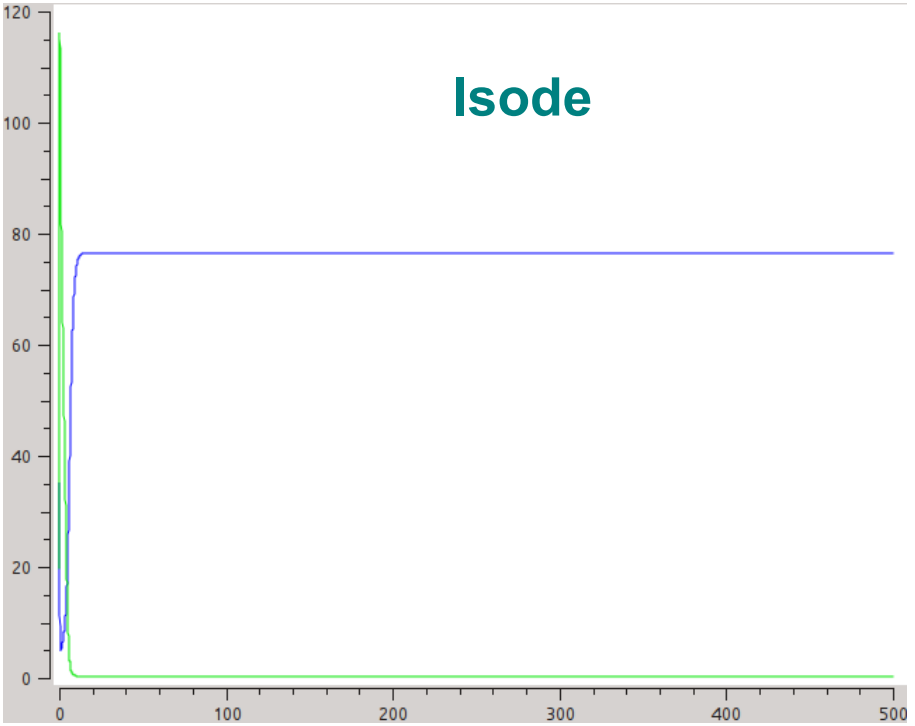
Bornheimer et al 2004 (BIOMD0000000086)

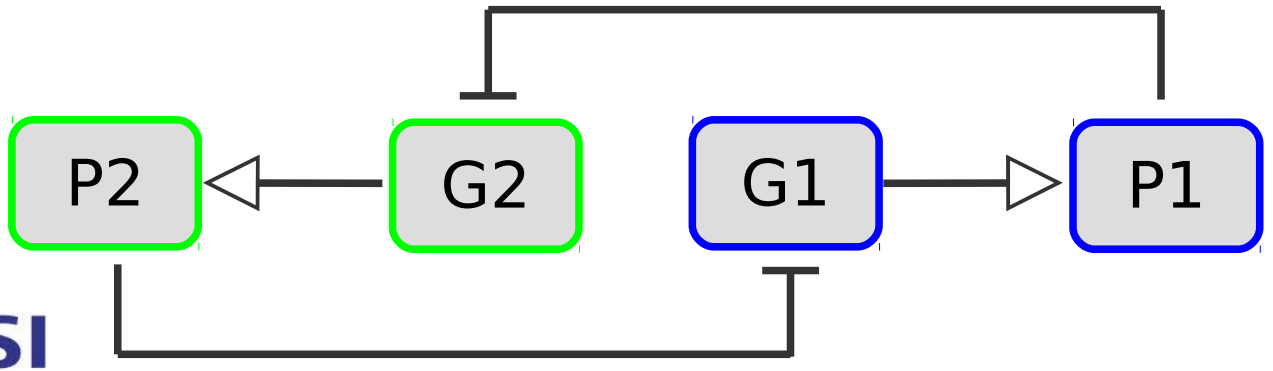
Babraham Institute

EMBL-EBI

Algorithm choice affects behaviour





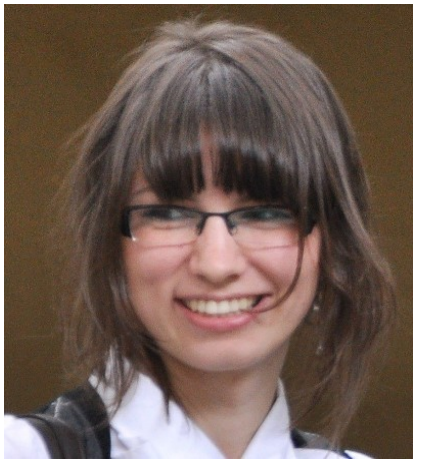


COPASI

Description of simulations and analyses

	Model descriptions	Simulations and analysis
Minimal requirements	MIRIAM	MIASE
Data-models	SBML, SBGN	SED-ML
Terminologies	SBO	KISAO

Dagmar Waltemath



Anna Zhukova

Born in Hinxton 2007

Waltemath *et al.* (2011, 2011), Courtot *et al* (2011)

Minimal Information About a Simulation Experiment

Models to use

1. Models provided, or precise mean of access
2. Model with all governing equations, parameter values and necessary conditions
3. Standard formats, otherwise code available. If not open code, full description provided
4. Description of modifications required before the execution of the simulation experiment

Simulation steps

1. Simulation steps described, with simulation algorithms, models, order of steps, data processing between steps
2. Information needed for correct implementation of necessary steps
3. If software source-code not available, information needed to reproduce the simulation, and not only repeat it, with algorithms and necessary info (e.g. discretization meth)
4. If divergence are known in different environments or platforms, explanation on how to be run with the specified environment/platform to achieve experiment's purpose

Output specification

1. Post-processing steps applied on the raw results to generate the final results, with identification of data to process, nature and order of changes to apply
2. If insights depend on relation between different results, (e.g. plot of one against another), the results to be compared must be specified.

http://co.mbine.org/standards/miase

Simulation Experiment Description Markup Language

```
<?xml version="1.0" encoding="utf-8"?>
<sedML xmlns="http://sed-ml.org/"
       xmlns:math="http://www.w3.org/1998/Math/MathML"
       level="1" version="1">
  <listOfSimulations><!-- --> </listOfSimulations>
  <listOfModels>
    <model id="" source="">
      <listOfChanges><!-- --></listOfChanges>
    </model>
  </listOfModels>
  <listOfTasks><!-- --></listOfTasks>
  <listOfDataGenerators><!-- --></listOfDataGenerators>
  <listOfOutputs>
    <plot2D />
    <plot3D />
    <report />
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```

http://sed-ml.org

Flexible model use in SED-ML

Any XML

```
<listOfModels>
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         language="http://identifiers.org/combine.specifications/sbml.level-2.version-4.release-1"
         source="http://identifiers.org/biomodels.db/BIOMD0000000127" />
  <model id="model2"
         name="chattering"
         source="model1">
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      </changeAttribute>
      <changeAttribute target=
           "/sbml/model/listOfParameters/parameter[@id='d']/@value" newValue="42">
      </changeAttribute>
    </listOfChanges>
  </model>
</listOfModels>
```

Remote access

Modif before simulations

That looks very useful. Where can I find those?

BioModels Database

Search

Advanced

BioModels Home | Models | Submit | Support | About BioModels | Contact us

BioModels Database serves as a reliable repository of computational models of biological processes. It hosts models described in peer-reviewed scientific literature and models generated automatically from pathway resources (Path2Models). A large number of models collected from literature are manually curated and semantically enriched with cross-references from external data resources. The resource allows scientific community to store, search and retrieve mathematical models of their interest. In addition, features such as generation of sub-models, online simulation, conversion of models into different representational formats, and programmatic access via web services, are provided.

Models published in the literature

- Browse curated models
- Browse curated models using GO
- Browse curated models using Taxonomy
- Browse non-curated models

Path2Models

Submit a model

Links

- Main instance at EMBL-EBI, UK
- Mirror at Caltech, USA
- Project on SourceForge
- Web Services
- Download archived models

Viji Chelliah

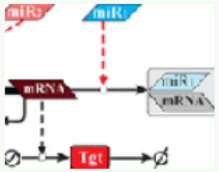
Marco Donizelli

Camille Laibe

http://www.ebi.ac.uk/biomodels

Model of the month

July, 2014



MicroRNAs (miRNAs) are an integral part of gene regulation at the post-transcriptional level. A pair of distinct miRNAs can mutually target a single mRNA, leading to the formation of RNA triplexes, which cooperatively regulates the target gene expression more effectively. Here, the mechanism of miRNA cooperativity has been studied using a mathematical model.

Please read more...

News

Follow us on Twitter

25 April 2014 **Our recent diabetes review most downloaded in April on CPT:PSP**

Our recent review "The impact of mathematical modeling on the understanding of diabetes and related complications" has been the most downloaded this month from the CPT: Pharmacometrics & Systems Pharmacology website!

24 April 2014 **Interview of Viji Chelliah, lead curator of BioModels Database, on PSPod**

The interview of Dr. Vijayalakshmi Chelliah, lead curator of BioModels Database, in the pharmacometrics and systems pharmacology podcast from the journal CPT: Pharmacometrics & Systems Pharmacology, produced in association with Nature Publishing Group (PSPod) is now online. Listen it.

11 April 2014 **27th release**

With the 27th release of BioModels Database, the resource now

>140 000 models

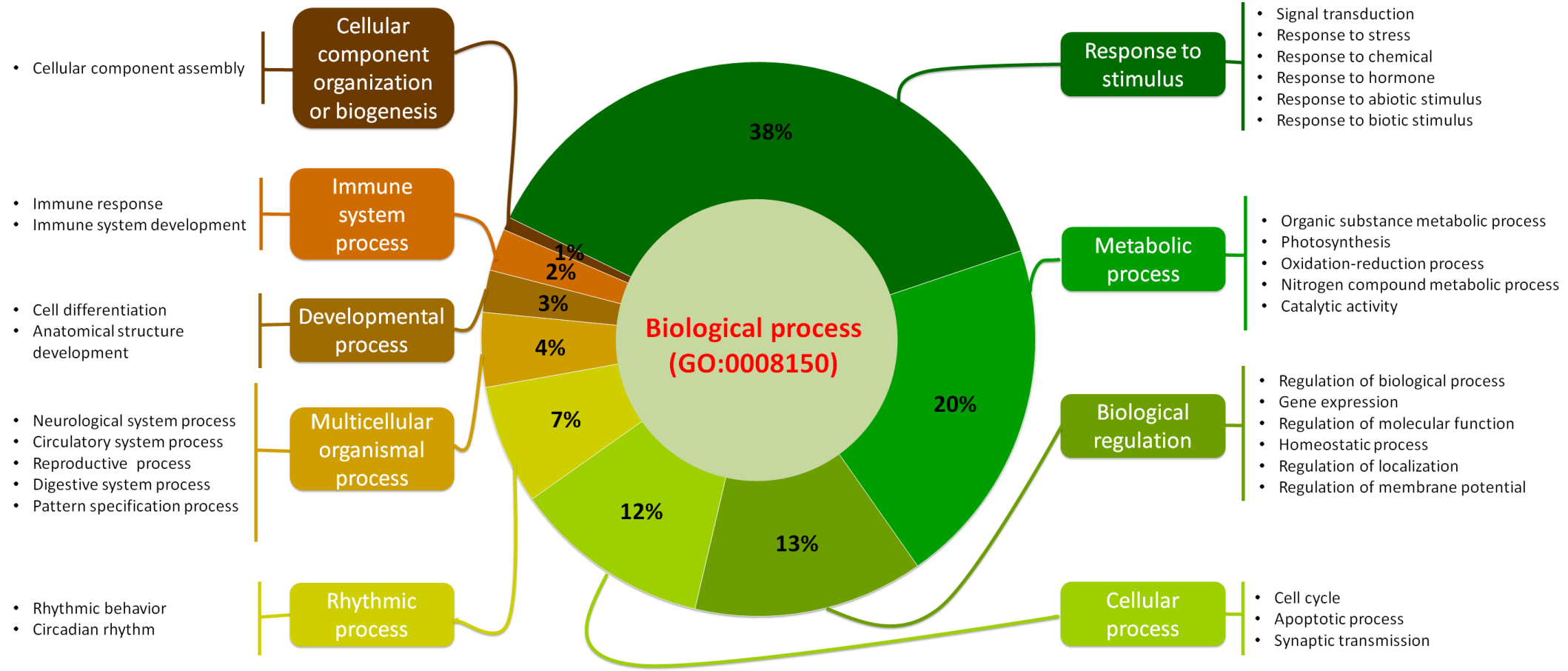
>10 millions math relations

~ 200 millions cross-refs

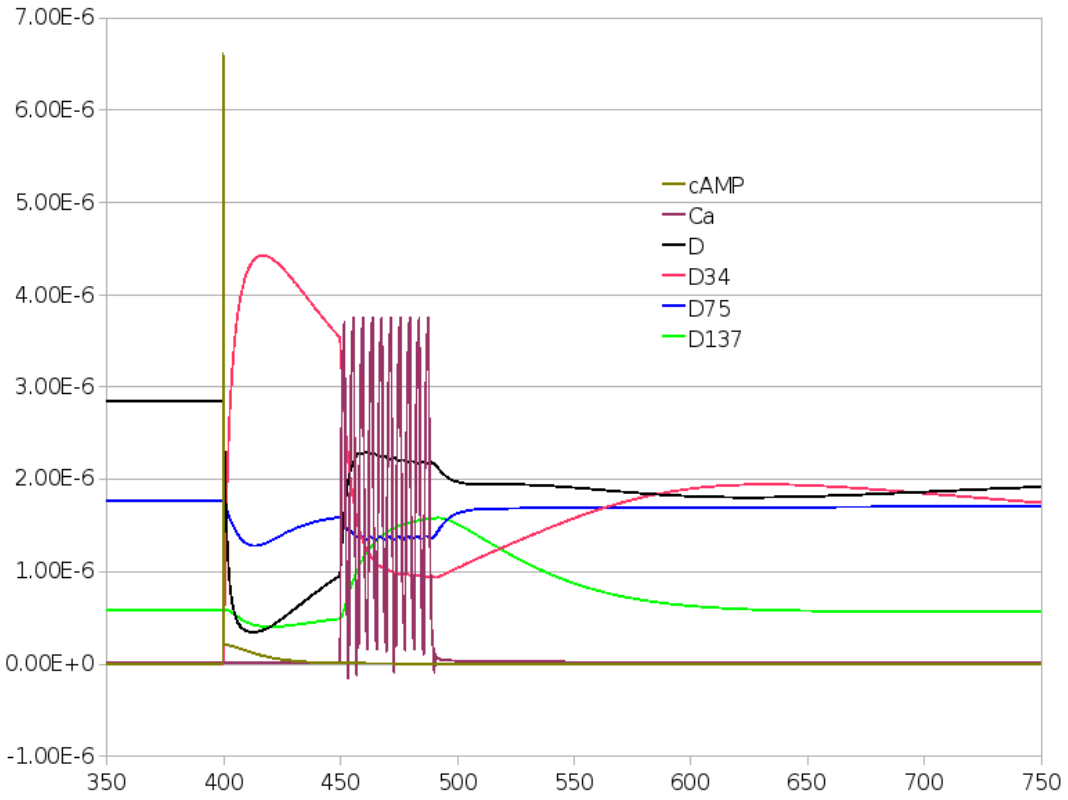
> 300 journals advise deposition

~ 1000 citations

1 million page requests per year

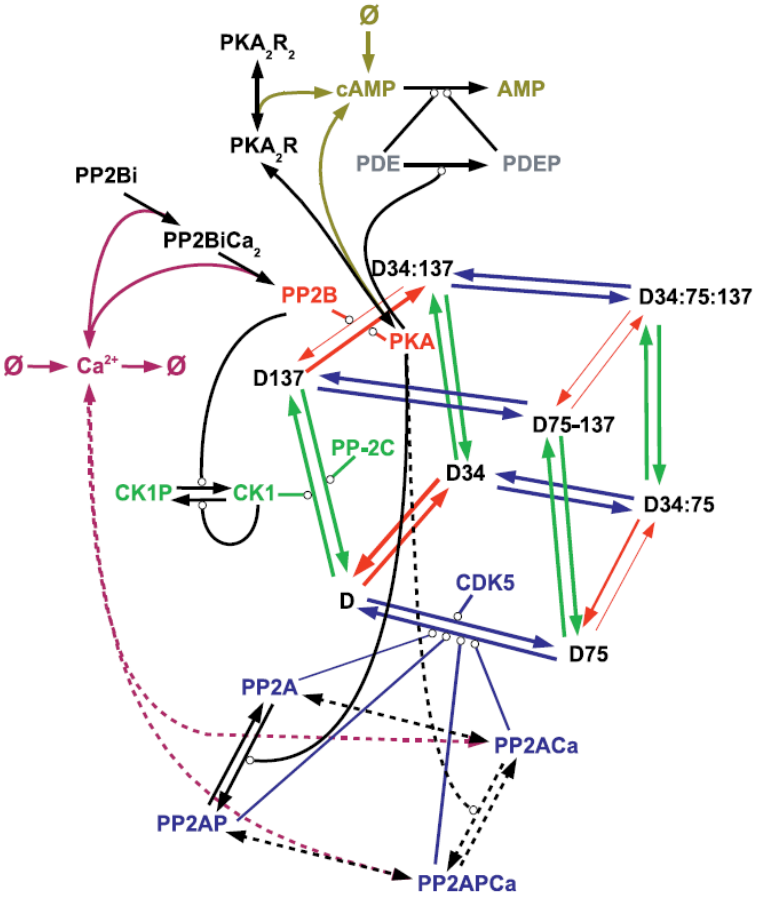

Cellular component organization or biogenesis
Cellular component assembly
Immune system process
Immune response
Immune system development
Developmental process
Cell differentiation
Anatomical structure development
Multicellular organismal process
Neurological system process
Circulatory system process
Reproductive process
Digestive system process
Pattern specification process
Rhythmic process
Rhythmic behavior
Circadian rhythm
Biological process (GO:0008150)
38%
20%
13%
12%
7%
4%
3%
2%
1%
Response to stimulus
Signal transduction
Response to stress
Response to chemical
Response to hormone
Response to abiotic stimulus
Response to biotic stimulus
Metabolic process
Organic substance metabolic process
Photosynthesis
Oxidation-reduction process
Nitrogen compound metabolic process
Catalytic activity
Biological regulation
Regulation of biological process
Gene expression
Regulation of molecular function
Homeostatic process
Regulation of localization
Regulation of membrane potential
Cellular process
Cell cycle
Apoptotic process
Synaptic transmission

Biochemical models



Fernandez et al. DARPP-32 is a robust integrator of dopamine and glutamate signals
PLoS Comput Biol (2006) 2: e176.

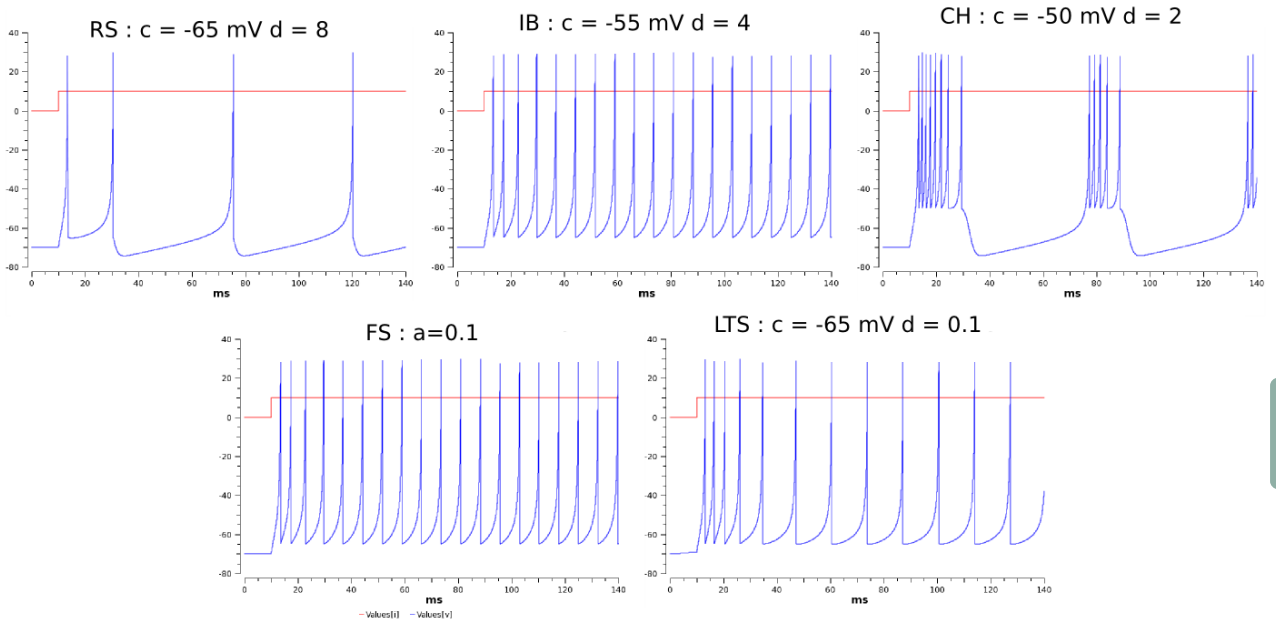
BIOMD0000000153



reaction:

$$v_{\text{on}} = k_{\text{on}} \times [\text{D}] \times [\text{CDK5}] \times \text{Vol}$$

Neuroscience models



Izhikevich EM. Simple model of spiking neurons. *IEEE Trans Neural Netw* (2003) 14(6):1569-1572.

BIOMD0000000127

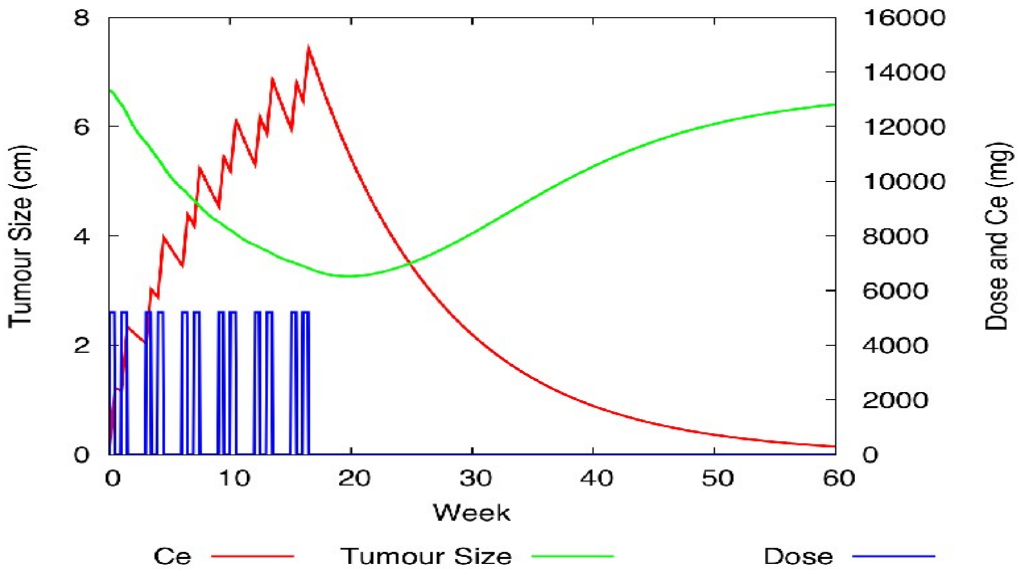
rate rule:

$$\frac{dv}{dt} = 0.04v^2 + 5v + 140 - U + i$$

event:

$$\text{when } v > V_{\text{thresh}} \begin{cases} v = c \\ U = U + d \end{cases}$$

Pharmacometrics models



Tham et al (2008) A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine + carboplatin in non-small cell lung cancer patients. *Clin Cancer Res*. 2008 14(13): 4213-8.

BIOMD0000000234

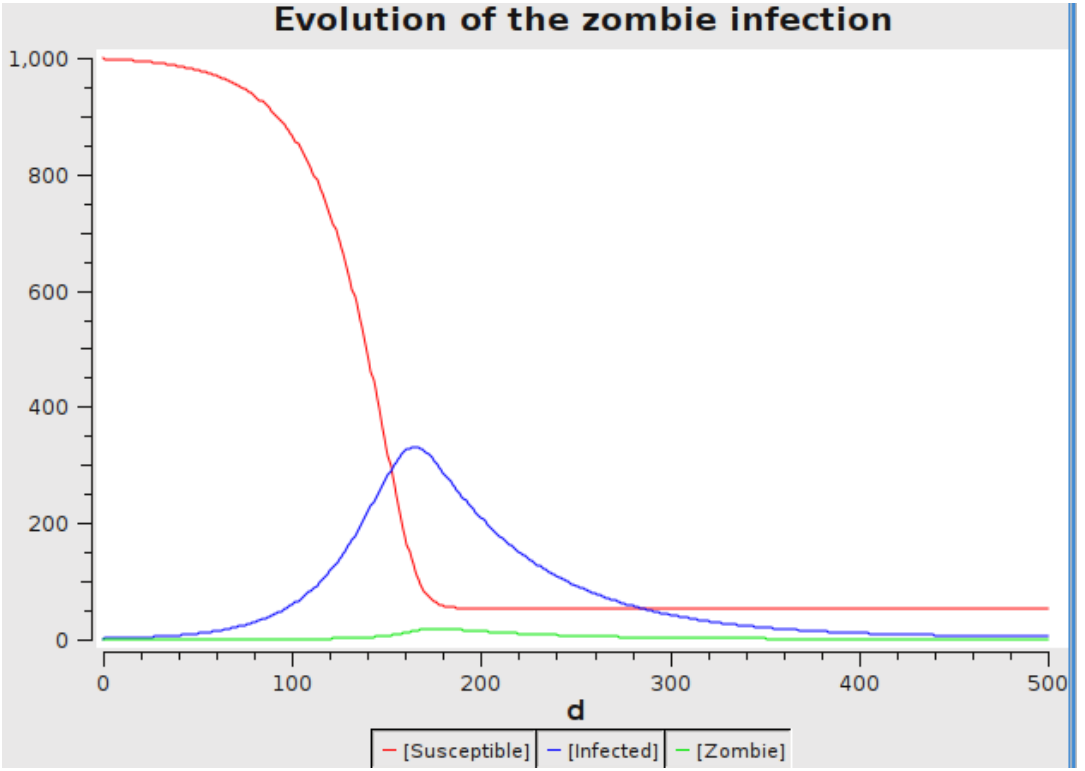
rate rule:

$$\frac{dSize}{dt} = (Rate_{in} \times Effect - K_{over} \times Size) \times Size$$

assignment rule:

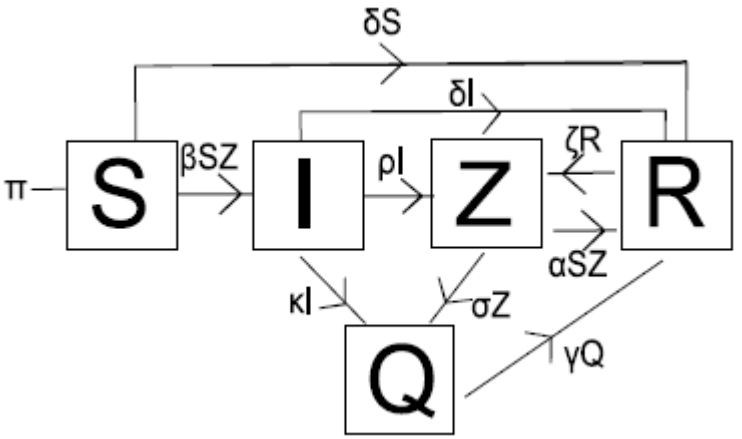
$$Effect = 1 - \frac{E_{max} \times Ce}{Amt_{50} + Ce}$$

Epidemiology models



Munz P et al. When zombies attack!: Mathematical modelling of an outbreak of zombie infection. in "Infectious Disease Modelling Research Progress", (2009)133-150

MODEL1008060001



Was it worth it?

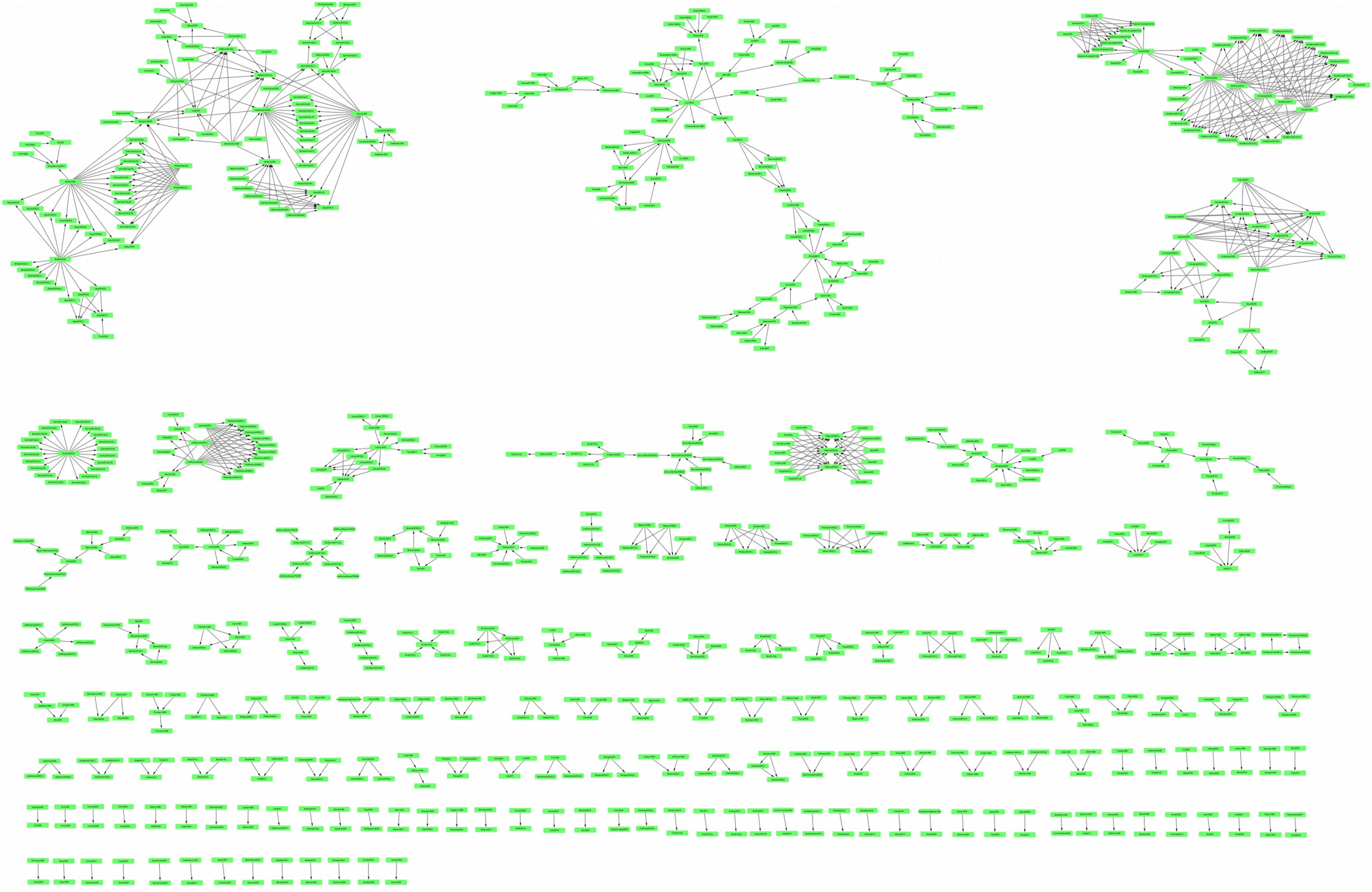
"You should not develop standards and easy to use modelling software. This allows biologists to write models, and they don't know how to do it properly."

Biomathematician, 2007

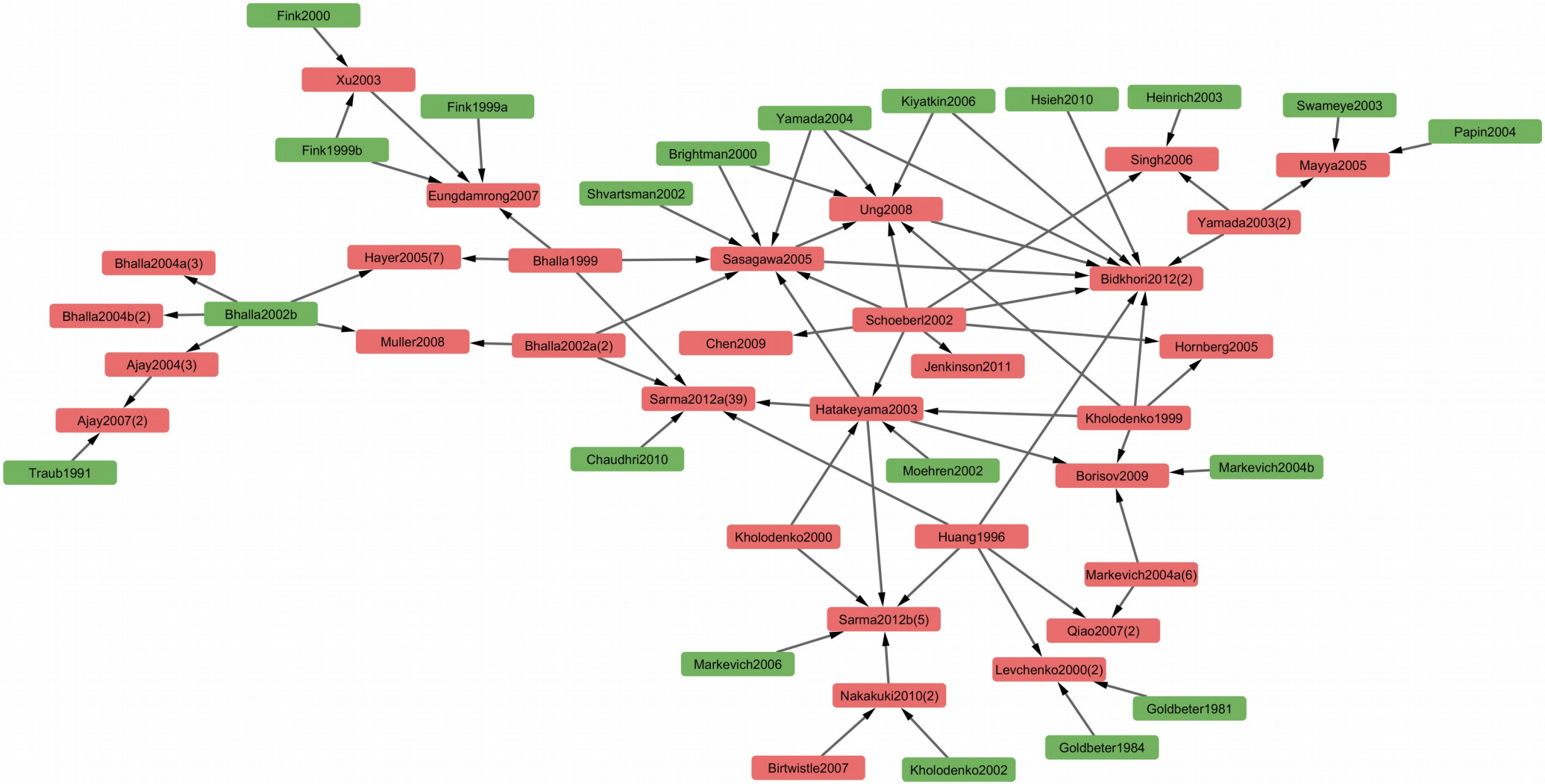
"By developing BioModels you harmed the cause of modelling in biology. My students do not learn how to make a model, they download it ready to use instead"

Theoretical biologist, 2006

REUSE

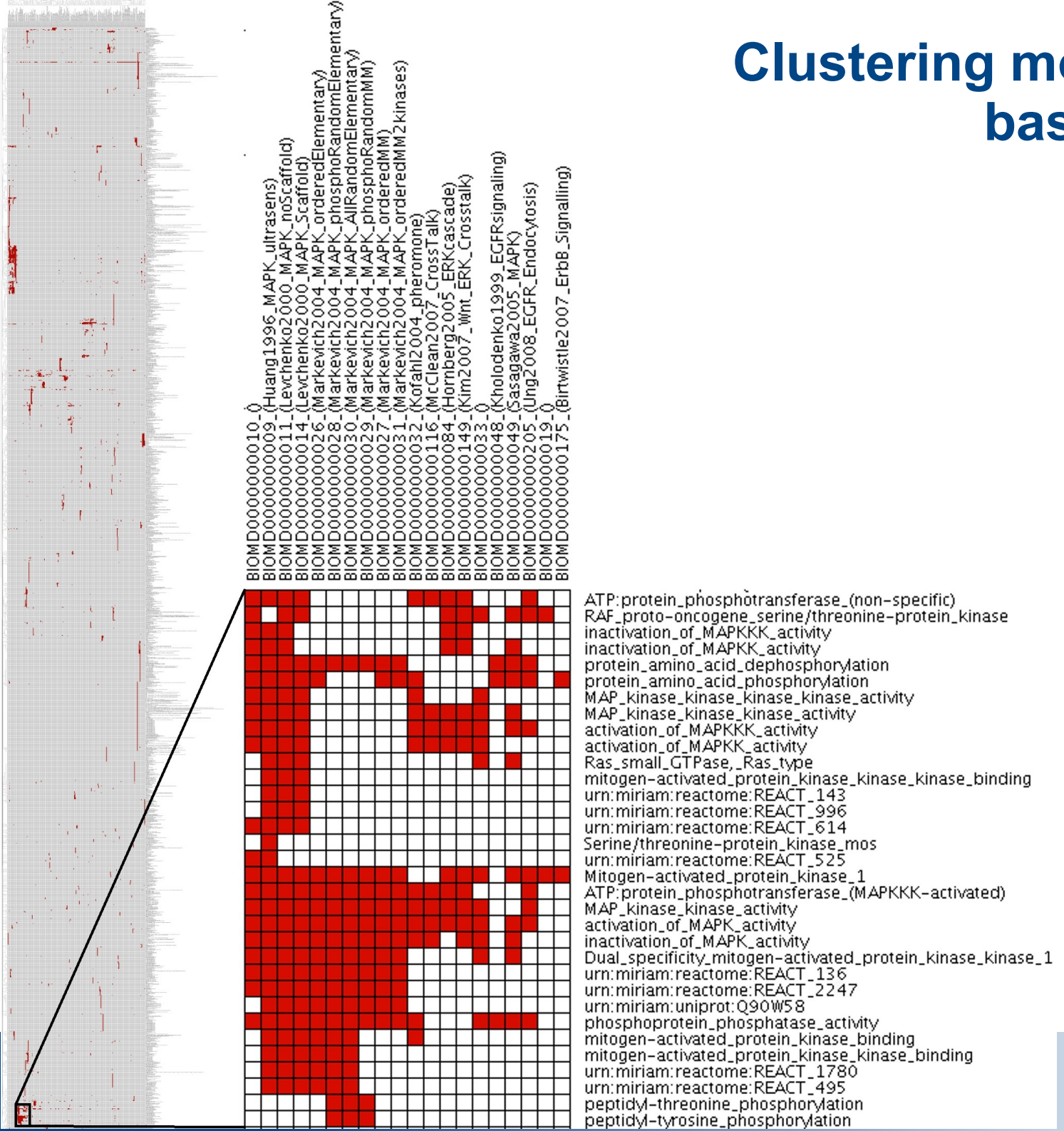


Erb receptor signalling



DISCOVER

Clustering models (and data) based on metadata



Schulz *et al.* (2011)

Babraham Institute

EMBL-EBI

Ranking and retrieval of models

Model	BioModel	Similarity	*P*-value	Overlap	*P*-value
Huang1996_MAPK_ultrasens	BIOMD0000000009	1.000	<=1e-3	30	0.0e+00
Levchenko2000_MAPK_noScaffold	BIOMD0000000011	0.930	<=1e-3	28	0.0e+00
Levchenko2000_MAPK_Scaffold	BIOMD0000000014	0.874	<=1e-3	26	0.0e+00
Kholodenko2000_MAPK_feedback	BIOMD0000000010	0.830	<=1e-3	20	0.0e+00
Markevich2004_MAPK_orderedElementary	BIOMD0000000026	0.749	<=1e-3	16	2.9e-15
Markevich2004_MAPK_phosphoRandomElementary	BIOMD0000000028	0.692	<=1e-3	15	9.1e-14
Markevich2004_MAPK_AllRandomElementary	BIOMD0000000030	0.692	<=1e-3	15	9.1e-14
Markevich2004_MAPK_orderedMM	BIOMD0000000027	0.691	<=1e-3	12	9.8e-10
Markevich2004_MAPK_orderedMM2kinases	BIOMD0000000031	0.691	<=1e-3	12	9.8e-10
Markevich2004_MAPK_phosphoRandomMM	BIOMD0000000029	0.626	<=1e-3	11	1.6e-08
Hornberg2005_ERKcascade	BIOMD0000000084	0.523	<=1e-3	9	2.7e-06
McClean2007_CrossTalk	BIOMD0000000116	0.453	<=1e-3	8	2.7e-05
Kofahl2004_pheromone	BIOMD0000000032	0.441	<=1e-3	12	9.8e-10
Goldbeter1991_MinMitOscil_ExplInact	BIOMD0000000004	0.389	<=1e-3	3	1.5e-01
Brown2004_NGF_EGF_signaling	BIOMD0000000033	0.371	<=1e-3	9	2.7e-06
Ung2008_EGFR_Endocytosis	BIOMD0000000205	0.363	<=1e-3	8	2.7e-05
Kim2007_Wnt_ERK_Crosstalk	BIOMD0000000149	0.355	<=1e-3	10	2.2e-07
Goldbeter1991_MinMitOscil	BIOMD0000000003	0.349	<=1e-3	3	1.5e-01
Sasagawa2005_MAPK	BIOMD0000000049	0.339	<=1e-3	9	2.7e-06
Swat2004_Mammalian_G1_S_Transition	BIOMD0000000228	0.317	<=1e-3	2	4.0e-01
Tyson1991_CellCycle_6var	BIOMD0000000005	0.304	<=1e-3	4	4.2e-02
Goldbeter1995_CircClock	BIOMD0000000016	0.274	<=1e-3	4	4.2e-02
Novak1997_CellCycle	BIOMD0000000007	0.259	<=1e-3	1	7.6e-01
Novak2001_FissionYeast_CellCycle	BIOMD0000000111	0.255	<=1e-3	2	4.0e-01
Leloup1999_CircClock	BIOMD0000000021	0.246	<=1e-3	4	4.2e-02
Birtwistle2007_ErbB_Signalling	BIOMD0000000175	0.236	<=1e-3	1	7.6e-01
Neves2008_Cell_Shape	BIOMD0000000182	0.222	<=1e-3	6	1.6e-03
Leloup1998_CircClock_LD	BIOMD0000000171	0.219	<=1e-3	4	4.2e-02
Veening2008_DegU_Regulation	BIOMD0000000240	0.211	4.0e-03	2	4.0e-01
Chen2004_CellCycle	BIOMD0000000056	0.209	4.0e-03	4	4.2e-02
Fernandez2006_ModelA	BIOMD0000000152	0.207	5.0e-03	2	4.0e-01
Fisher2006_NFAT_Activation	BIOMD0000000123	0.199	7.0e-03	2	4.0e-01
Hatakeyama2003_MAPK	BIOMD0000000146	0.198	7.0e-03	1	7.6e-01

MAPK

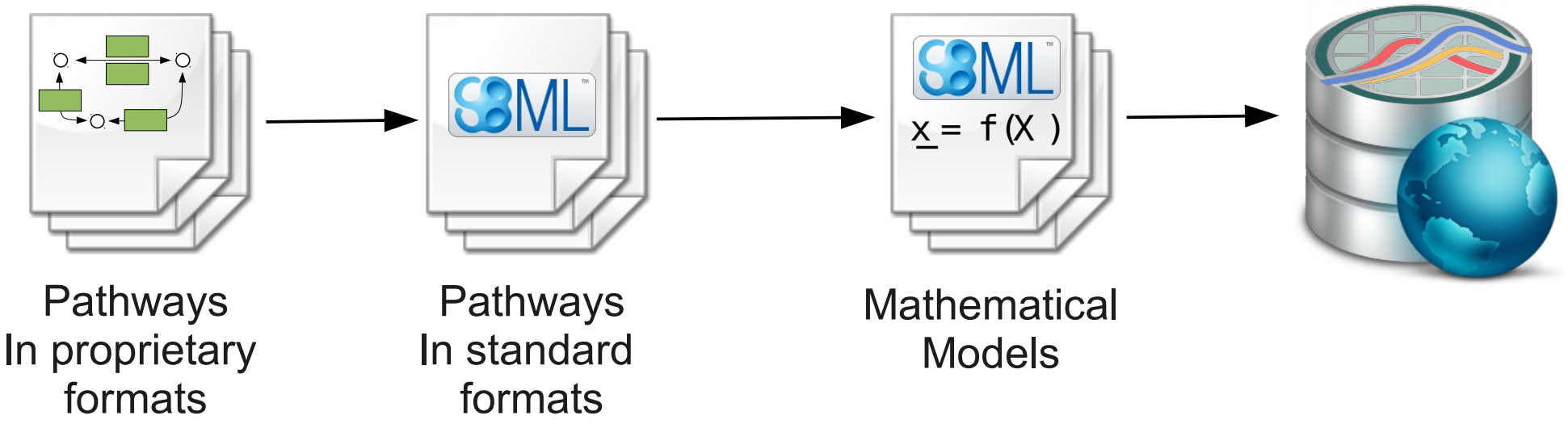
Retrieval of models using gene expression

Model	BioModel	Similarity	*P*-value	Overlap	*P*-value
Wolf2001 respiratory oscillations	BIOMD0000000090	0.207	<=1e-3	6	6.6e-09
Chassagnole2001_Threonine Synthesis	BIOMD0000000066	0.184	<=1e-3	4	1.5e-05
Curien2009_Aspartate_Metabolism	BIOMD0000000212	0.170	<=1e-3	5	3.6e-07
Curien2003_MetThr_synthesis	BIOMD0000000068	0.141	<=1e-3	2	1.0e-02
Proctor2007_ubiquitine	BIOMD0000000105	0.098	2.0e-03	1	1.4e-01
Curto1998_purineMetabol	BIOMD0000000015	0.063	1.1e-02	2	1.0e-02
Ibrahim2008_Spindle_Assembly_Checkpoint_dissociation	BIOMD0000000186	0.057	1.8e-02	0	1.0e+00
Ibrahim2008_Spindle_Assembly_Checkpoint_convey	BIOMD0000000187	0.057	1.8e-02	0	1.0e+00
Rodriguez-Caso2006_Polyamine_Metabolism	BIOMD0000000190	0.040	7.1e-02	1	1.4e-01
Nijhout2004_Folate_Cycle	BIOMD0000000213	0.032	1.1e-01	1	1.4e-01
Morrison1989_FolateCycle	BIOMD0000000018	0.030	1.3e-01	1	1.4e-01
Zatorsky2006_p53_Model3	BIOMD0000000154	0.023	2.5e-01	0	1.0e+00
Zatorsky2006_p53_Model6	BIOMD0000000155	0.023	2.5e-01	0	1.0e+00
Hunziker2010_p53_StressSpecificResponse	BIOMD0000000252	0.023	2.5e-01	0	1.0e+00
Zatorsky2006_p53_Model5	BIOMD0000000156	0.022	2.7e-01	0	1.0e+00
Zatorsky2006_p53_Model4	BIOMD0000000157	0.022	2.7e-01	0	1.0e+00
Zatorsky2006_p53_Model2	BIOMD0000000158	0.022	2.7e-01	0	1.0e+00
Zatorsky2006_p53_Model1	BIOMD0000000159	0.022	2.7e-01	0	1.0e+00
Proctor2008_p53_Mdm2_ATM	BIOMD0000000188	0.013	4.3e-01	0	1.0e+00
McClean2007_CrossTalk	BIOMD0000000116	0.012	4.7e-01	0	1.0e+00
Proctor2008_p53_Mdm2_ARF	BIOMD0000000189	0.012	4.9e-01	0	1.0e+00
Haberichter2007_cellcycle	BIOMD0000000109	0.011	5.0e-01	0	1.0e+00
Sasagawa2005_MAPK	BIOMD0000000049	0.006	5.5e-01	0	1.0e+00

BUILD

From pathways to models … path2models

- Provide pathways in a standard format
- Re-use existing pathway data to generate biochemically based models
- Provide starting points to build more quantitative models



Büchel *et al.* (2013)

Signalling Pathways

+

Logical models
of individual signalling pathways

Signalling Pathways

+

Logical models
of individual signalling pathways

Metabolic Networks

Chemical kinetics models
of individual metabolic pathways

Signalling Pathways

+

Logical models
of individual signalling pathways

Metabolic Networks

Chemical kinetics models
of individual metabolic pathways

Metabolic Networks

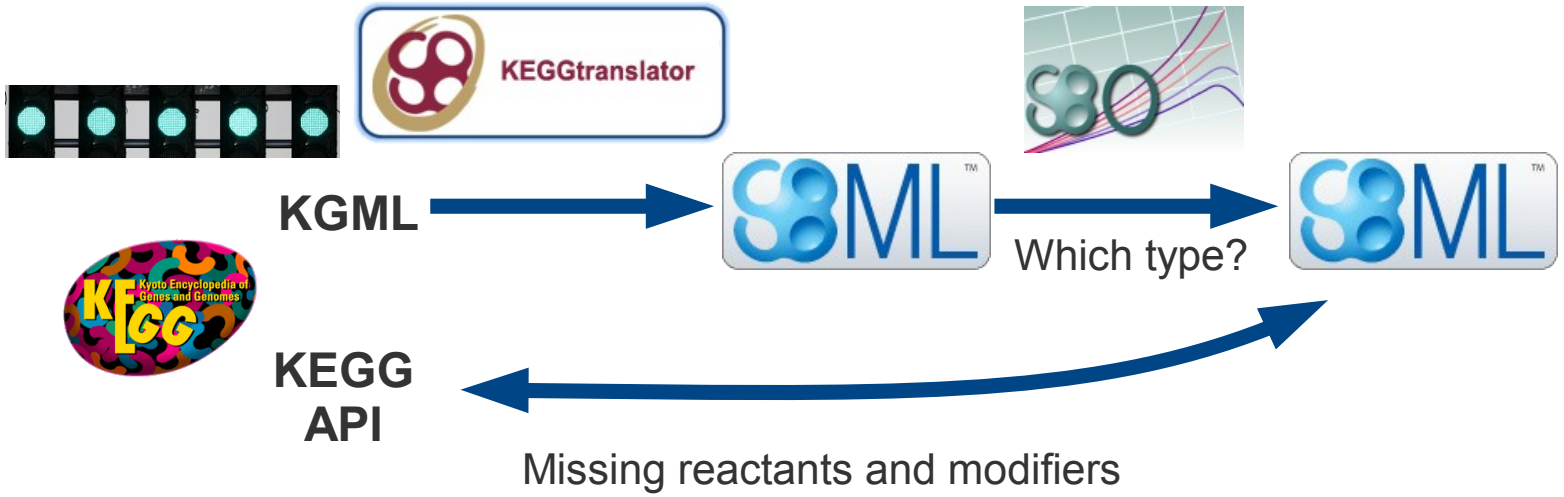
+

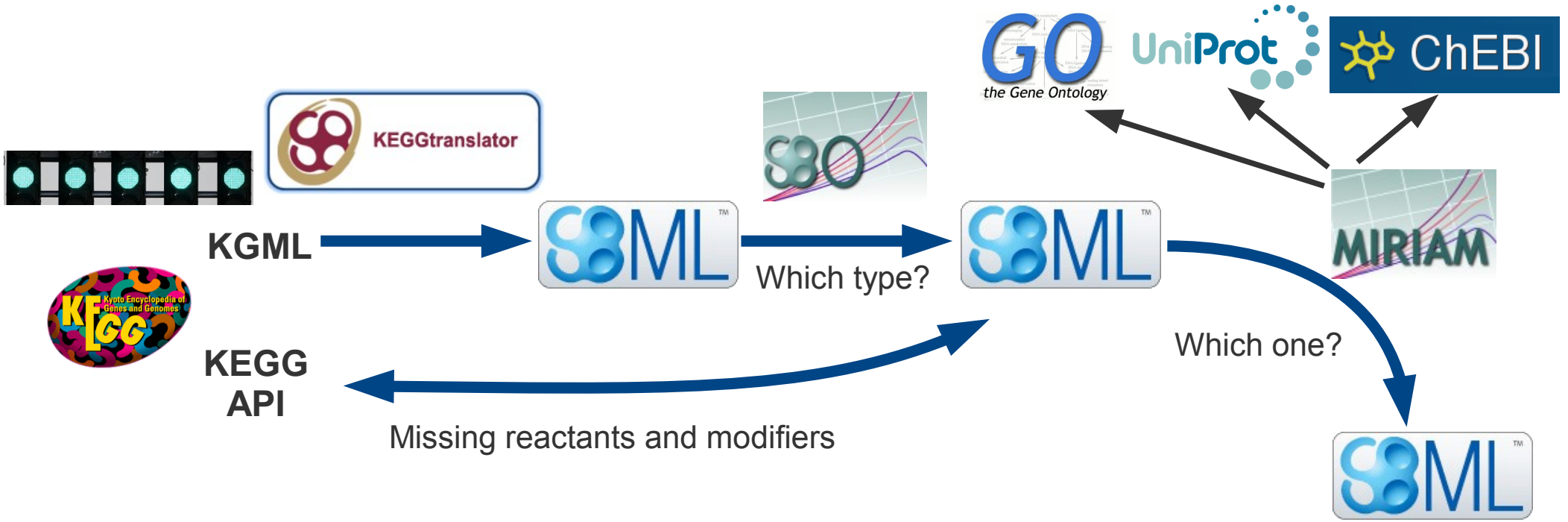
Flux Balance Analysis
of whole genome reconstructions

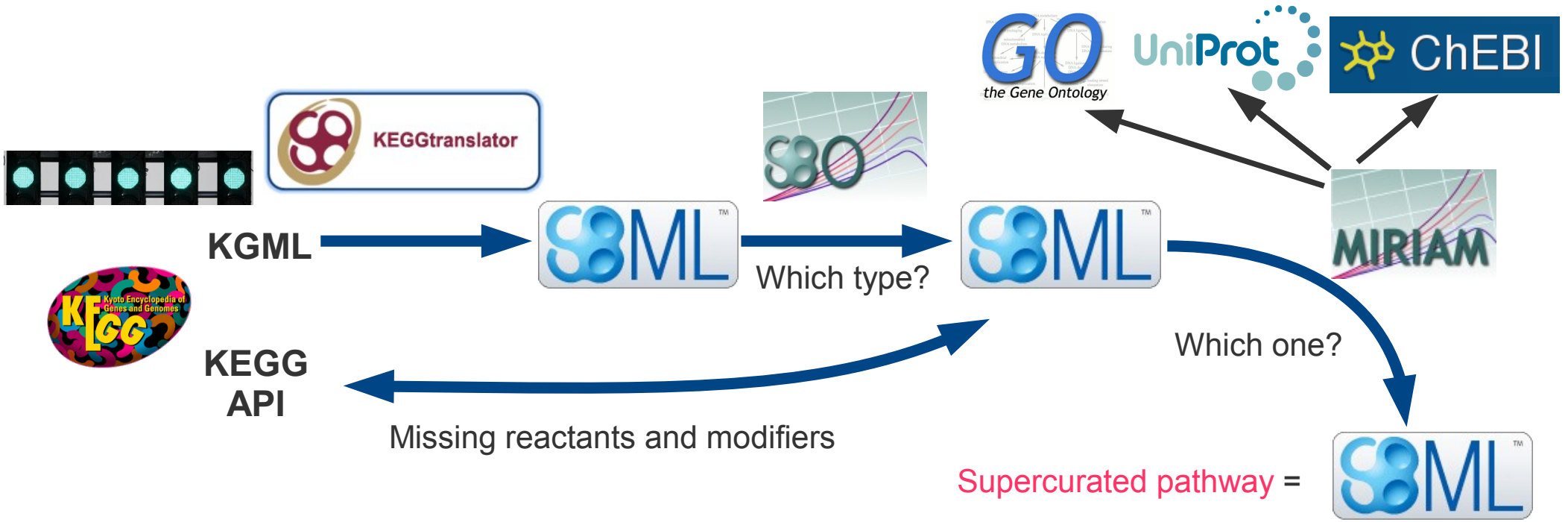
KEGGtranslator

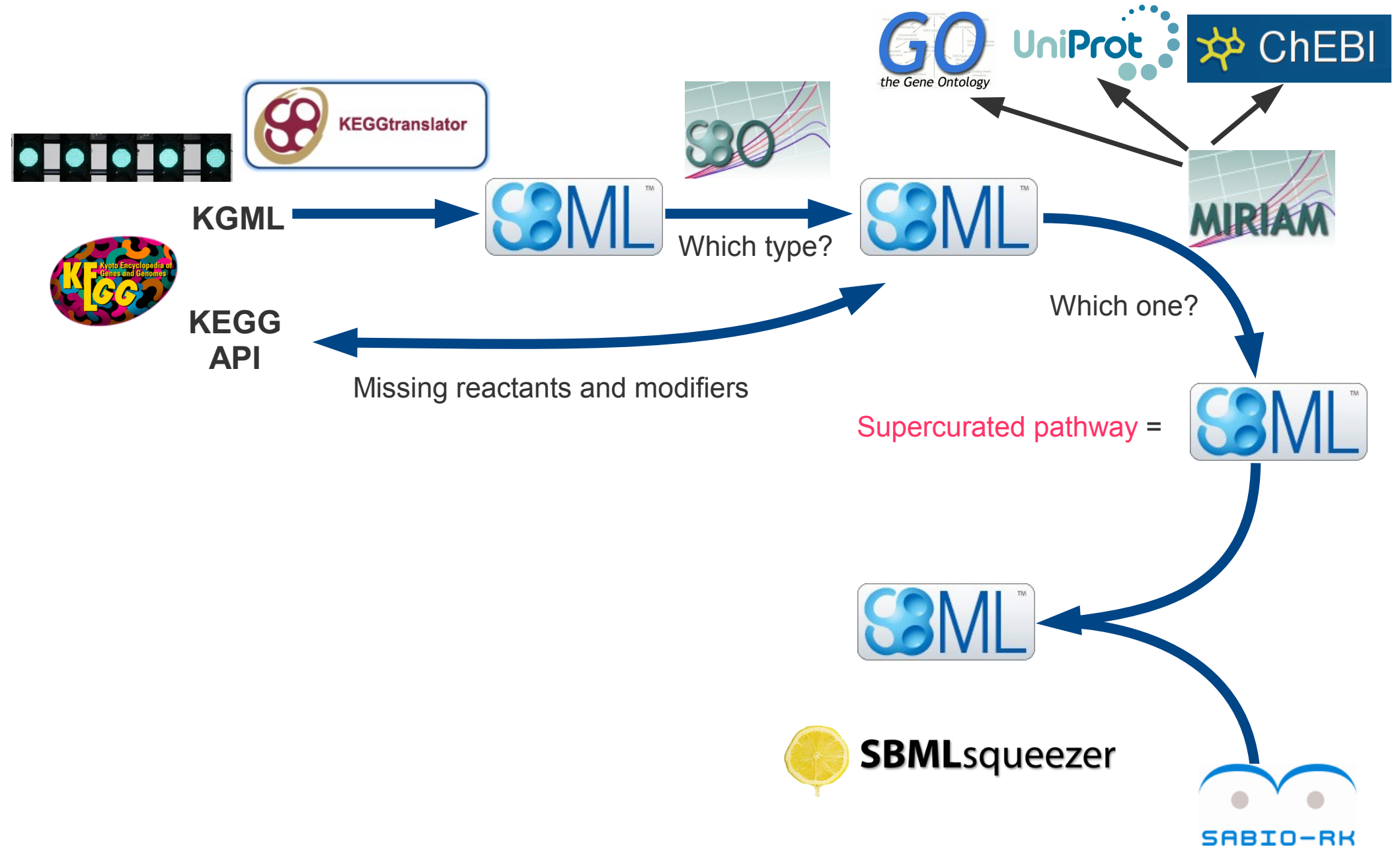
KGML → SBML™

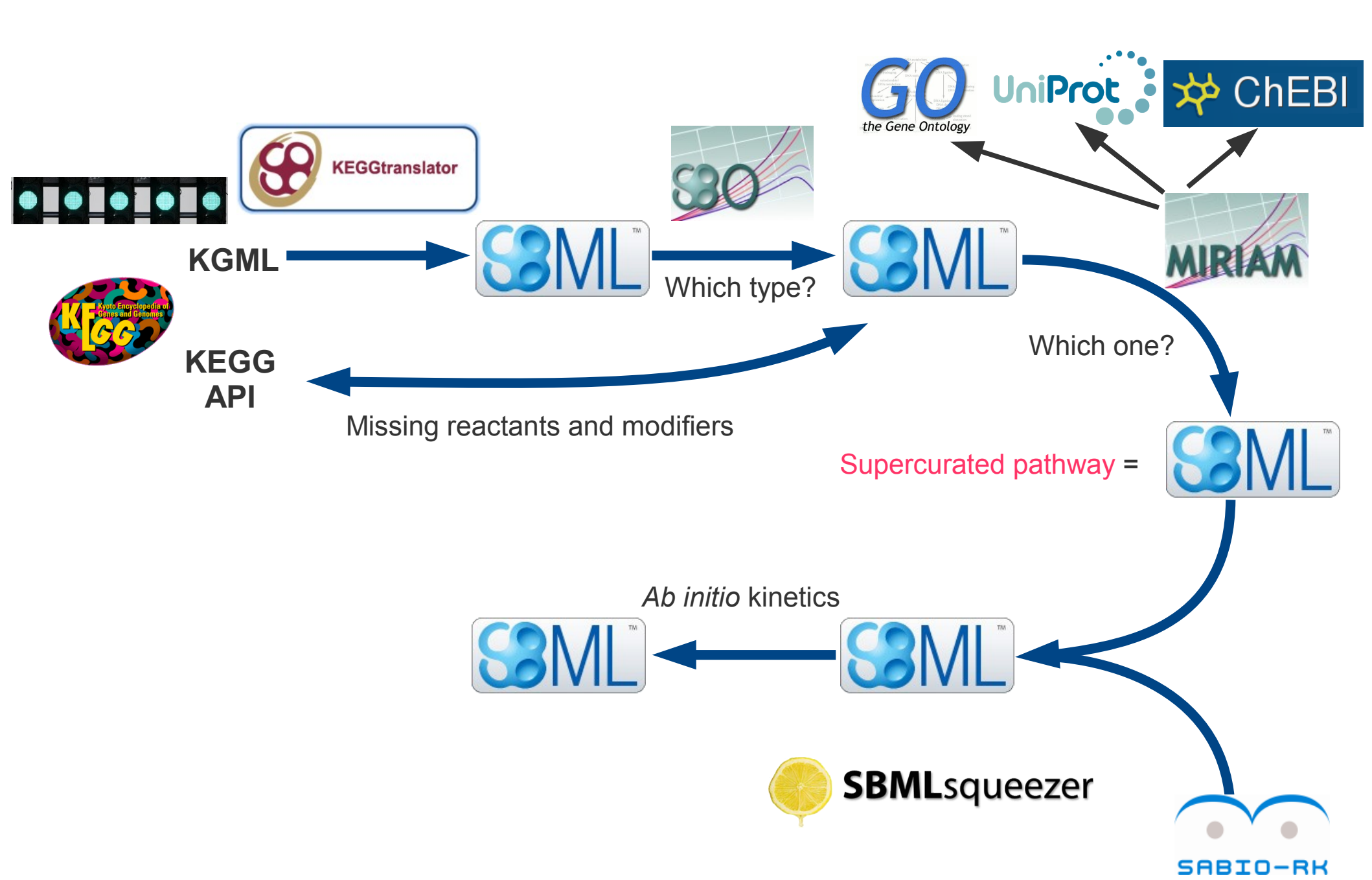

KEGGtranslator
KGML
Which type?


KEGGtranslator
KGML
Which type?
KEGG
API
Missing reactants and modifiers


GO
the Gene Ontology
UniProt
ChEBI
KEGGtranslator
SBO
MIRIAM
KGML
SBML
Which type?
SBML
Which one?
KEGG
API
Missing reactants and modifiers
SBML


GO
the Gene Ontology
UniProt
ChEBI
KEGGtranslator
SBO
KGML
SBML
Which type?
SBML
MIRIAM
KEGG
Kyoto Encyclopedia of Genes and Genomes
KEGG API
Which one?
Missing reactants and modifiers
Supercurated pathway =
SBML


GO
the Gene Ontology
UniProt
ChEBI
KEGGtranslator
SBO
KGML
SBML
Which type?
SBML
MIRIAM
Which one?
KEGG
API
Missing reactants and modifiers
Supercurated pathway =
SBML
SBML
SBMLsqueezer
SABIO-RK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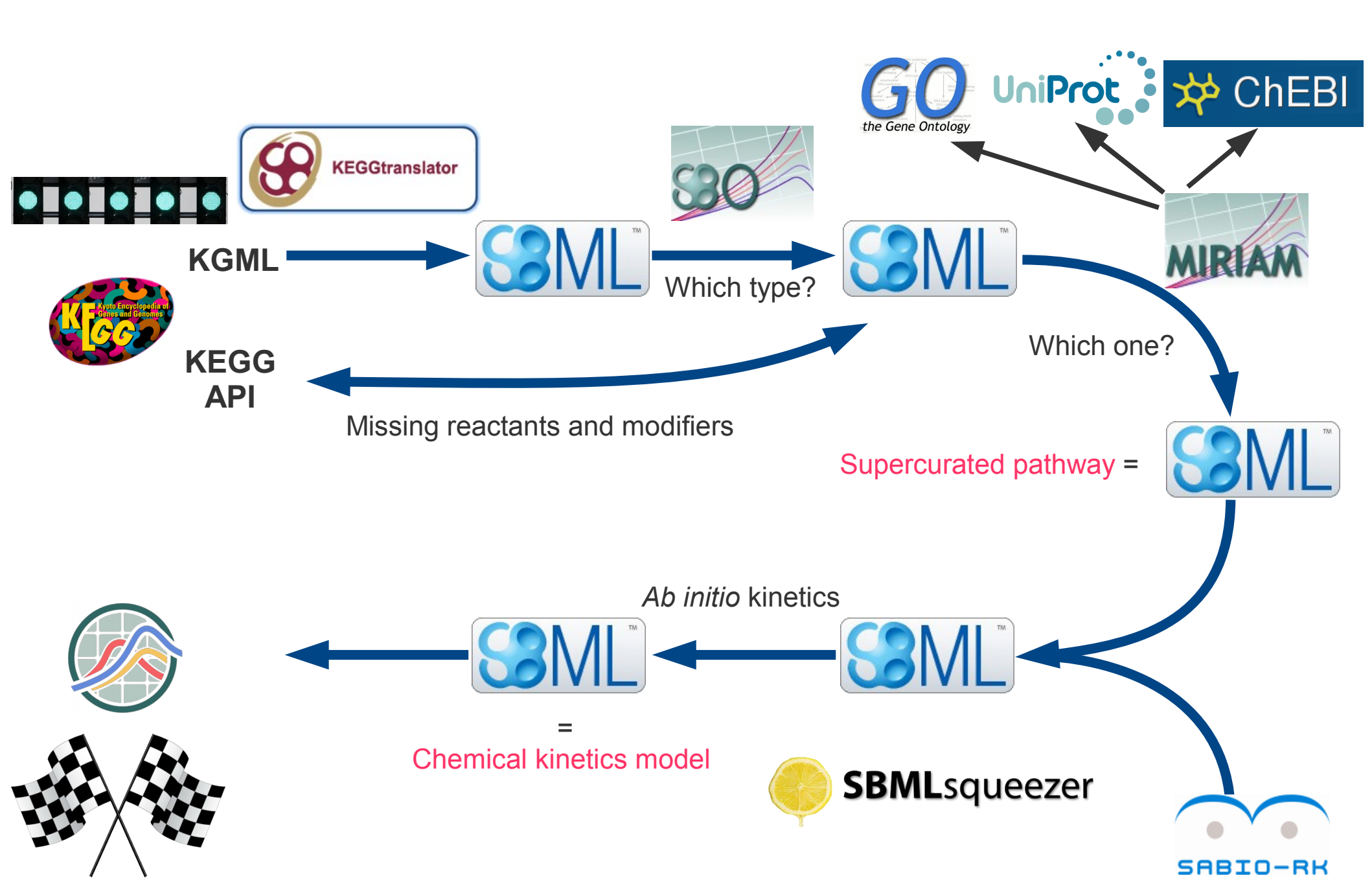
Supercurated pathway =
Ab initio kinetics
SBMLsqueezer
SABIO-RK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the Gene Ontology
UniProt
ChEBI
KEGGtranslator
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KGML
SBML
Which type?
SBML
MIRIAM
KEGG
API
Which one?
Missing reactants and modifiers
Supercurated pathway =
SBML
Ab initio kinetics
SBML
SBML
=
Chemical kinetics model
SBMLsqueezer
SABIO-RK

Are-we ready to develop comprehensive models of whole cells, organs and organisms?

Cell

A Whole-Cell Computational Model Predicts Phenotype from Genotype

Jonathan R. Karr,[1,4] Jayodita C. Sanghvi,[2,4] Derek N. Macklin,[2] Miriam V. Gutschow,[2] Jared M. Jacobs,[2] Benjamin Bolival, Jr.,[2] Nacyra Assad-Garcia,[3] John I. Glass,[3] and Markus W. Covert[2,*]

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[4]These authors contributed equally to this work
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http://dx.doi.org/10.1016/j.cell.2012.05.044

SUMMARY

Understanding how complex phenotypes arise from individual molecules and their interactions is a primary challenge in biology that computational approaches are poised to tackle. We report a whole-cell computational model of the life cycle of the human pathogen *Mycoplasma genitalium* that includes all of its molecular components and their interactions. An integrative approach to modeling that combines diverse mathematics enabled the simultaneous inclusion of fundamentally different cellular processes and experimental measurements. Our whole-cell model accounts for all annotated gene functions and was validated against a broad range of data. The model provides insights into many previously unobserved cellular behaviors, including in vivo rates of protein-DNA association

First, until recently, not enough has been known about the individual molecules and their interactions to completely model any one organism. The advent of genomics and other high-throughput measurement techniques has accelerated the characterization of some organisms to the extent that comprehensive modeling is now possible. For example, the mycoplasmas, a genus of bacteria with relatively small genomes that includes several pathogens, have recently been the subject of an exhaustive experimental effort by a European consortium to determine the transcriptome (Güell et al., 2009), proteome (Kühner et al., 2009), and metabolome (Yus et al., 2009) of these organisms.

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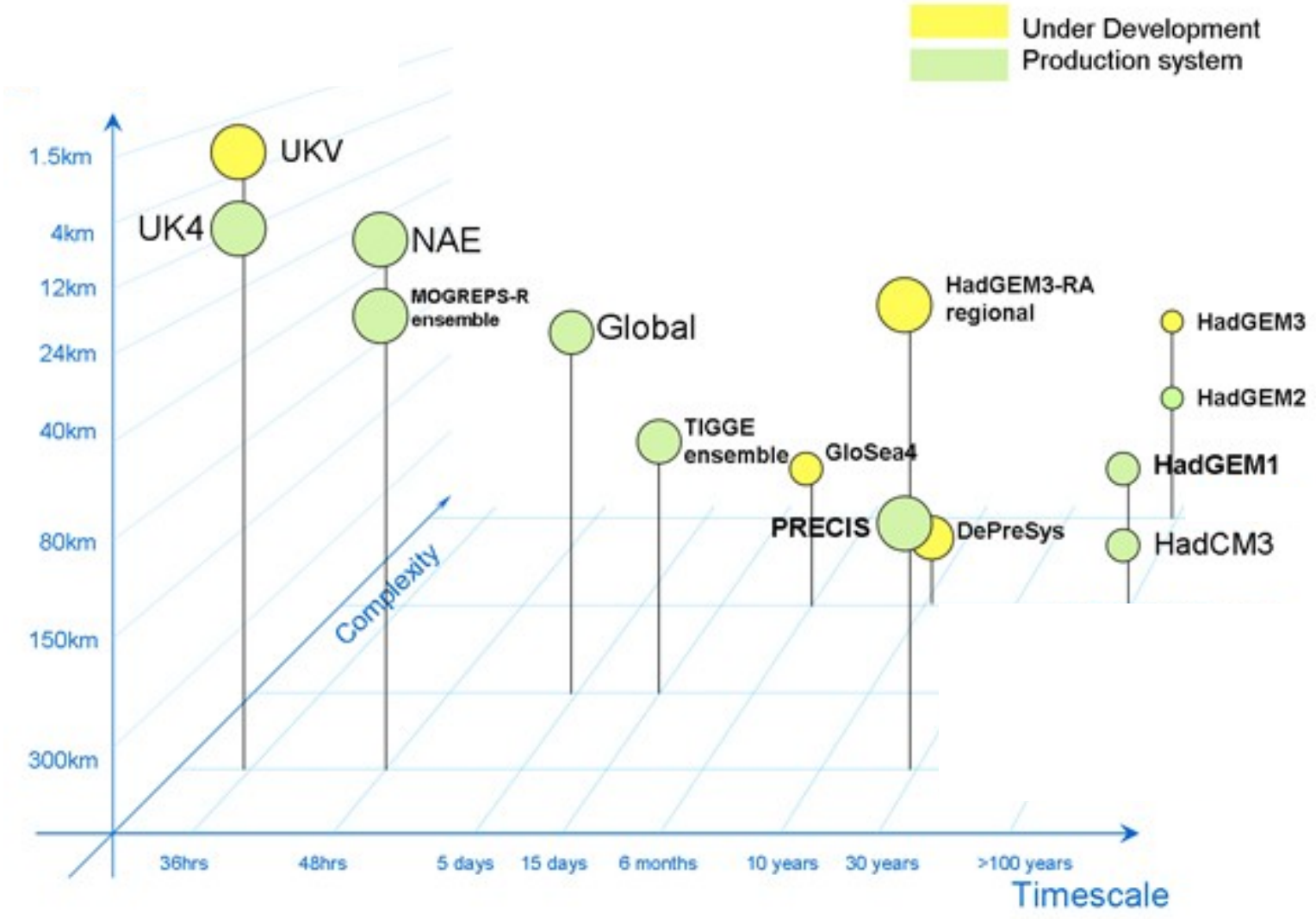
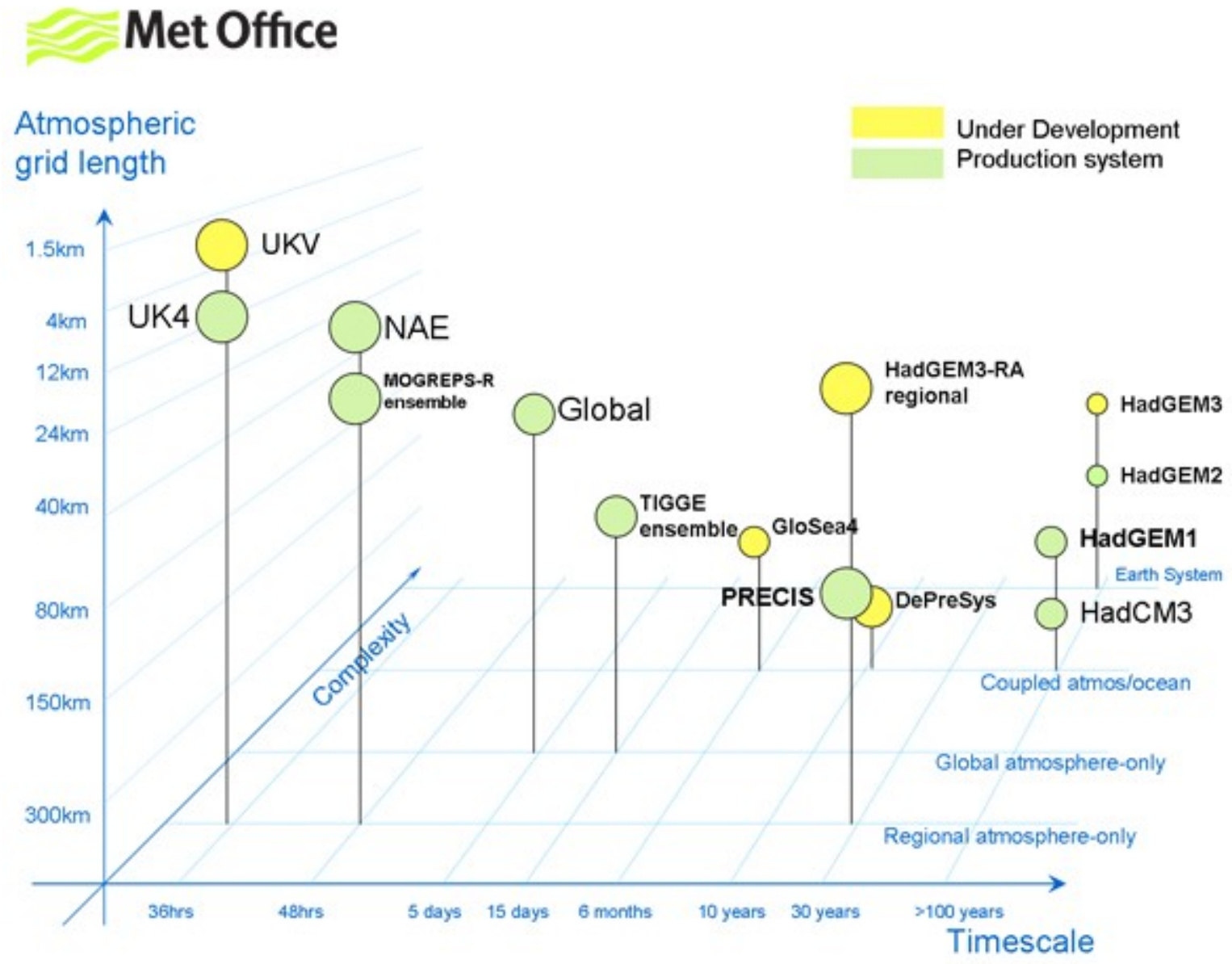
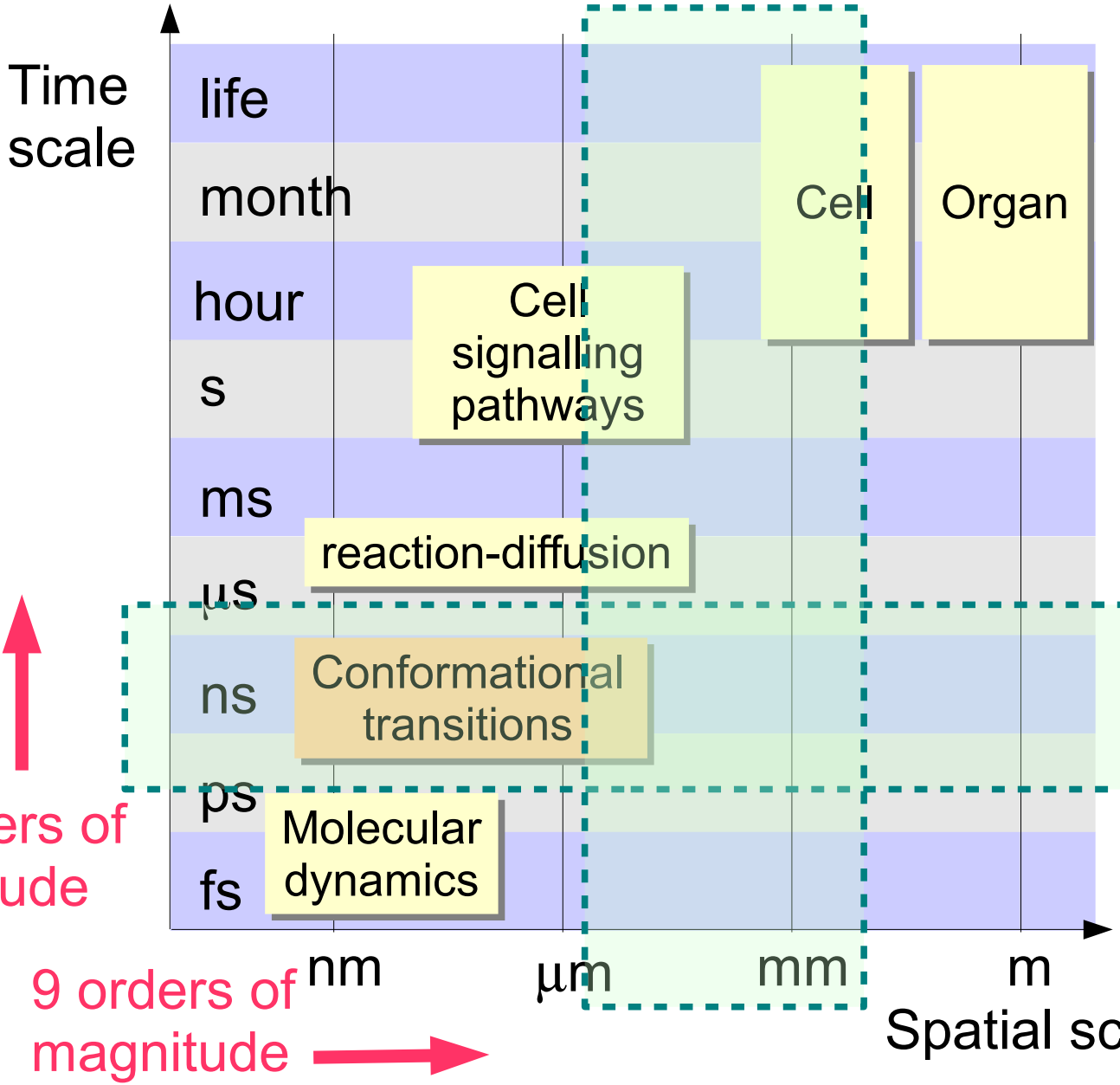

Under Development
Production system
1.5km
4km
12km
24km
40km
80km
150km
300km
UKV
UK4
NAE
MOGREPS-R ensemble
Global
TIGGE ensemble
GloSea4
HadGEM3-RA regional
PRECIS
DePreSys
HadGEM3
HadGEM2
HadGEM1
HadCM3
Complexity
36hrs
48hrs
5 days
15 days
6 months
10 years
30 years
>100 years
Timescale

Met Office Seamless Unified Model



Challenge 1: scales



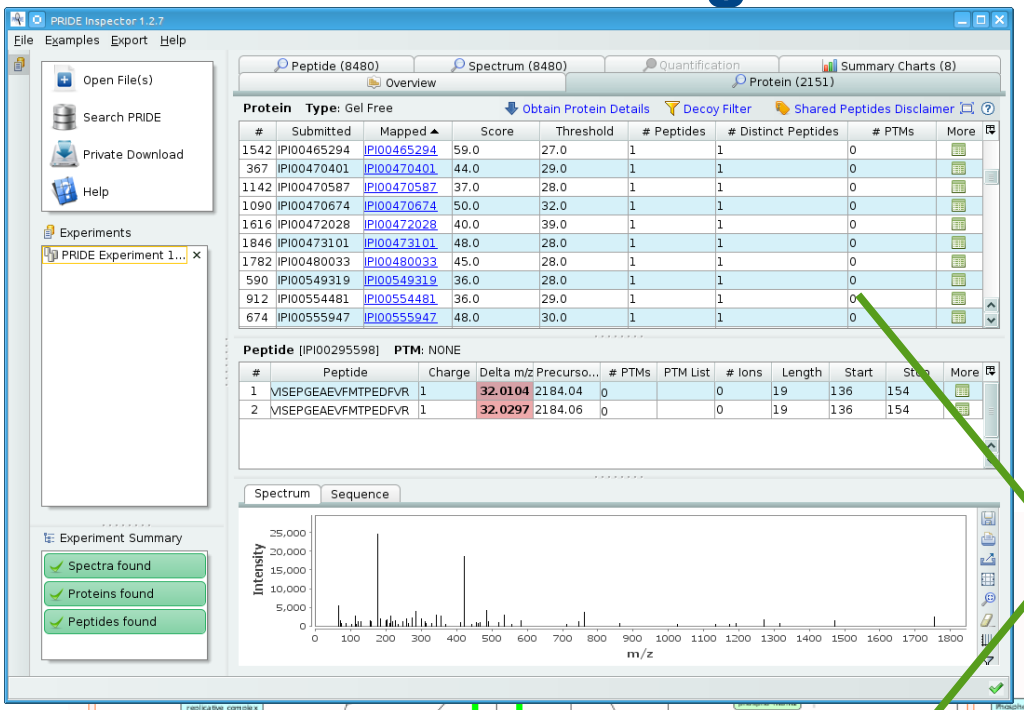
Coupled multi-scale models

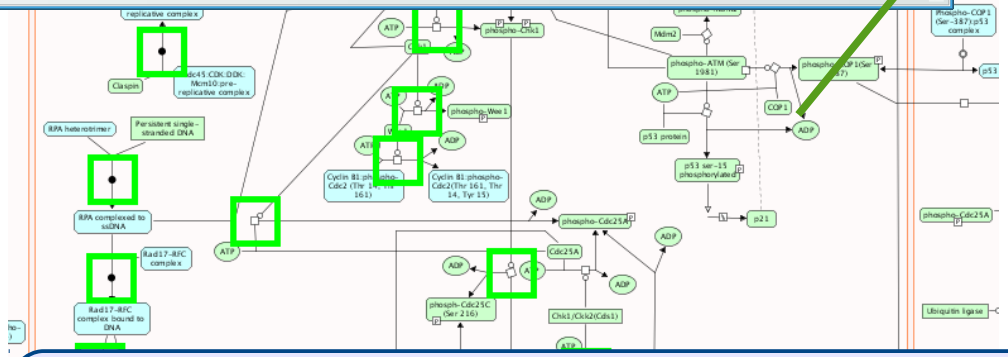
Theoretical and Computational roadblockers

24 orders of magnitude

9 orders of magnitude

Challenge 2: automatic generation





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$$
\begin{aligned}
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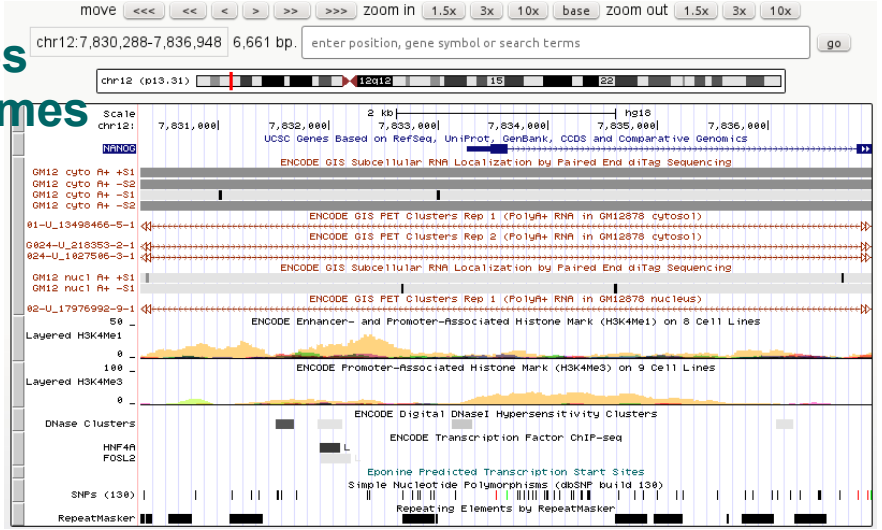
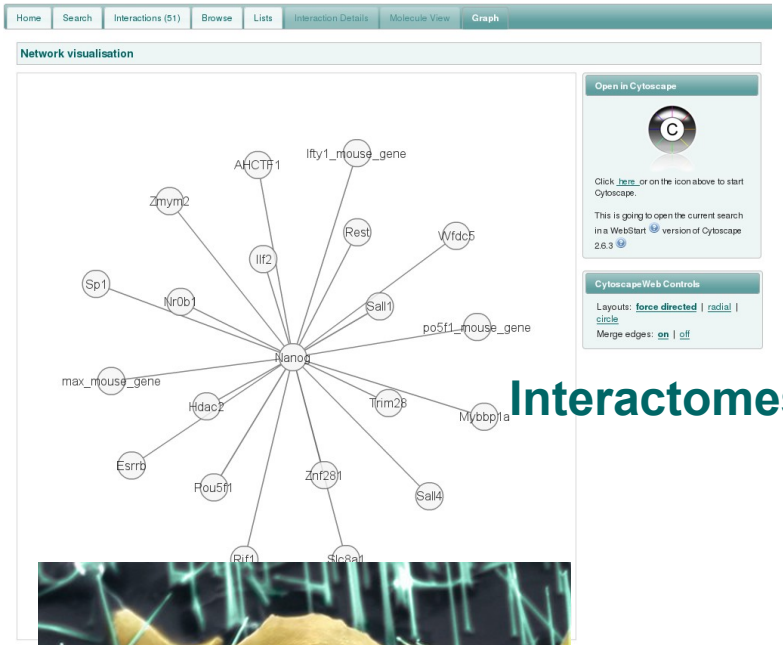
d[CP]/dt &= -k_3[CP][Y] + k_8[{\sim}P][C2] - k_9[CP] \\
d[pM]/dt &= k_3[CP][Y] - [pM]F([M]) + k_5[{\sim}P][M] \\
d[M]/dt &= [pM]F([M]) - k_5[{\sim}P][M] - k_6[M] \\
d[Y]/dt &= k_1[aa] - k_2[Y] - k_3[CP][Y] \\
d[YP]/dt &= k_6[M] - k_7[YP]
\end{aligned}
$$

Need to generate model automatically based on omics datasets. Known on small scale. The larger, the more human intervention needed.

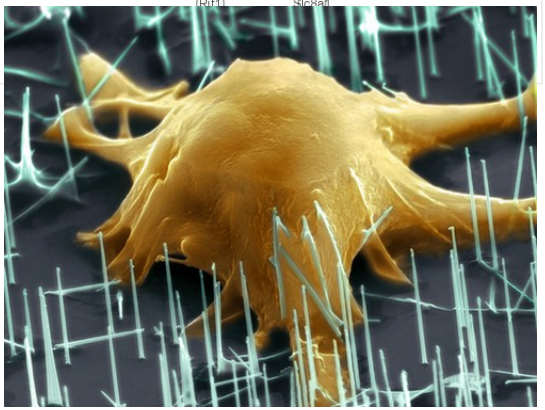
Challenge 3: data heterogeneity

Genomes epigenomes



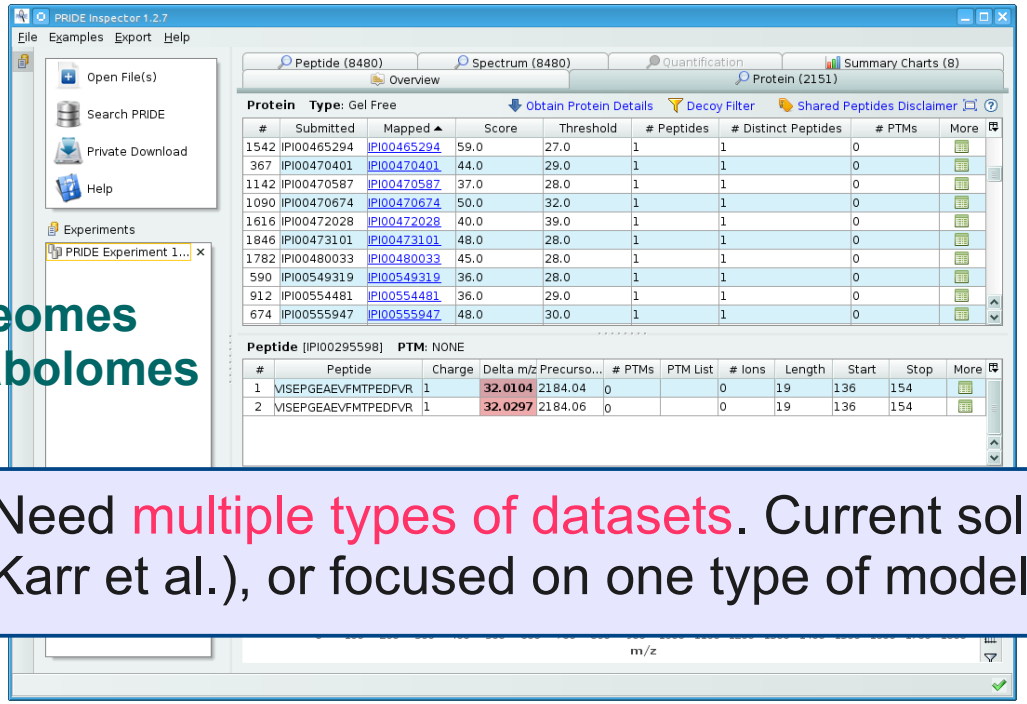


Interactomes



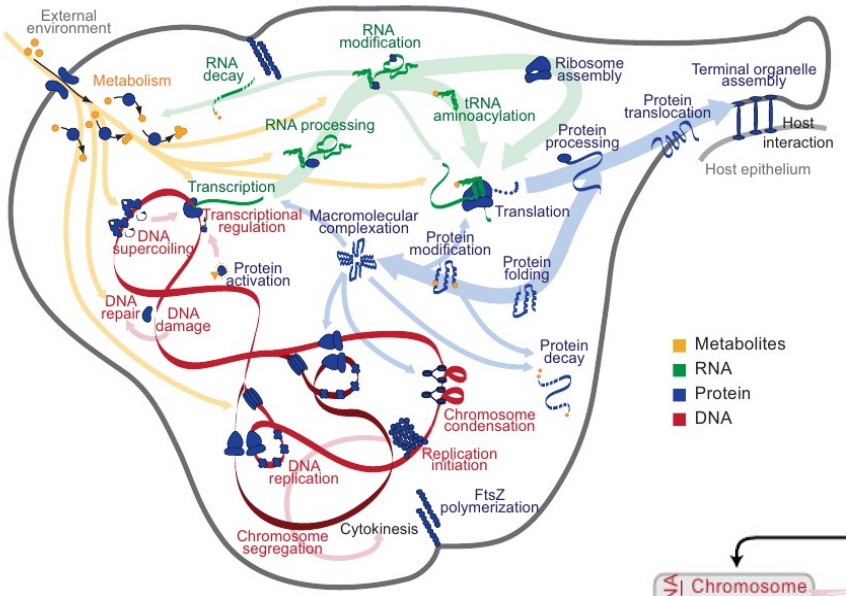
Imaging

Proteomes metabolomes



Need multiple types of datasets. Current solutions either for small models (e.g Karr et al.), or focused on one type of model and data (e.g. metabolic models)

Modularity is mandatory



Theory

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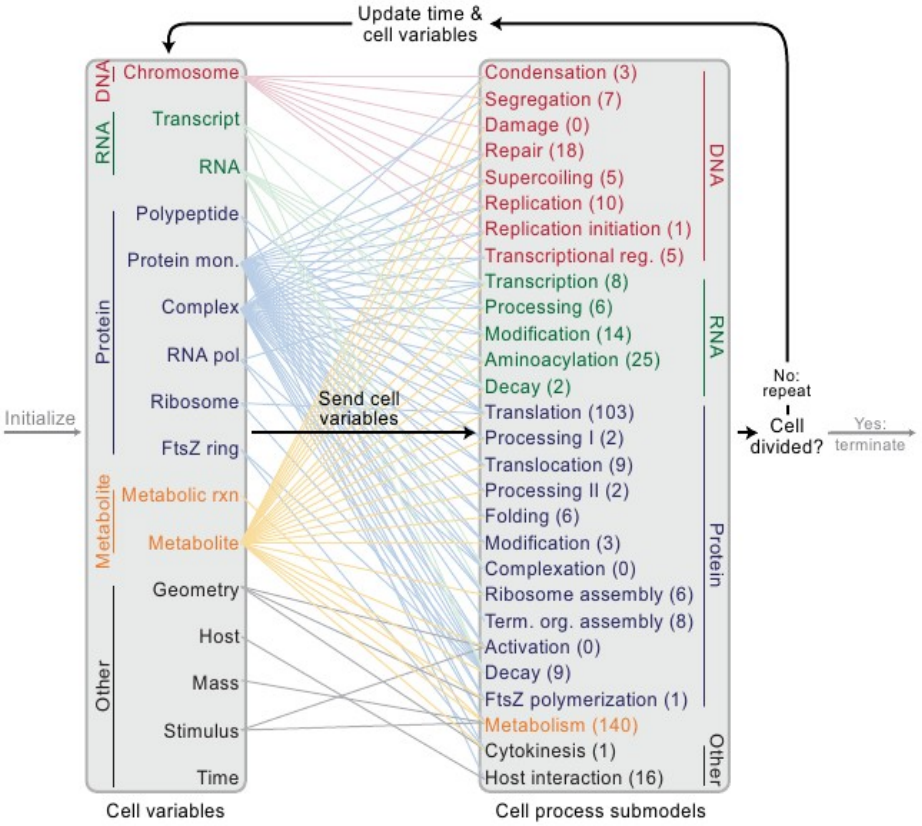

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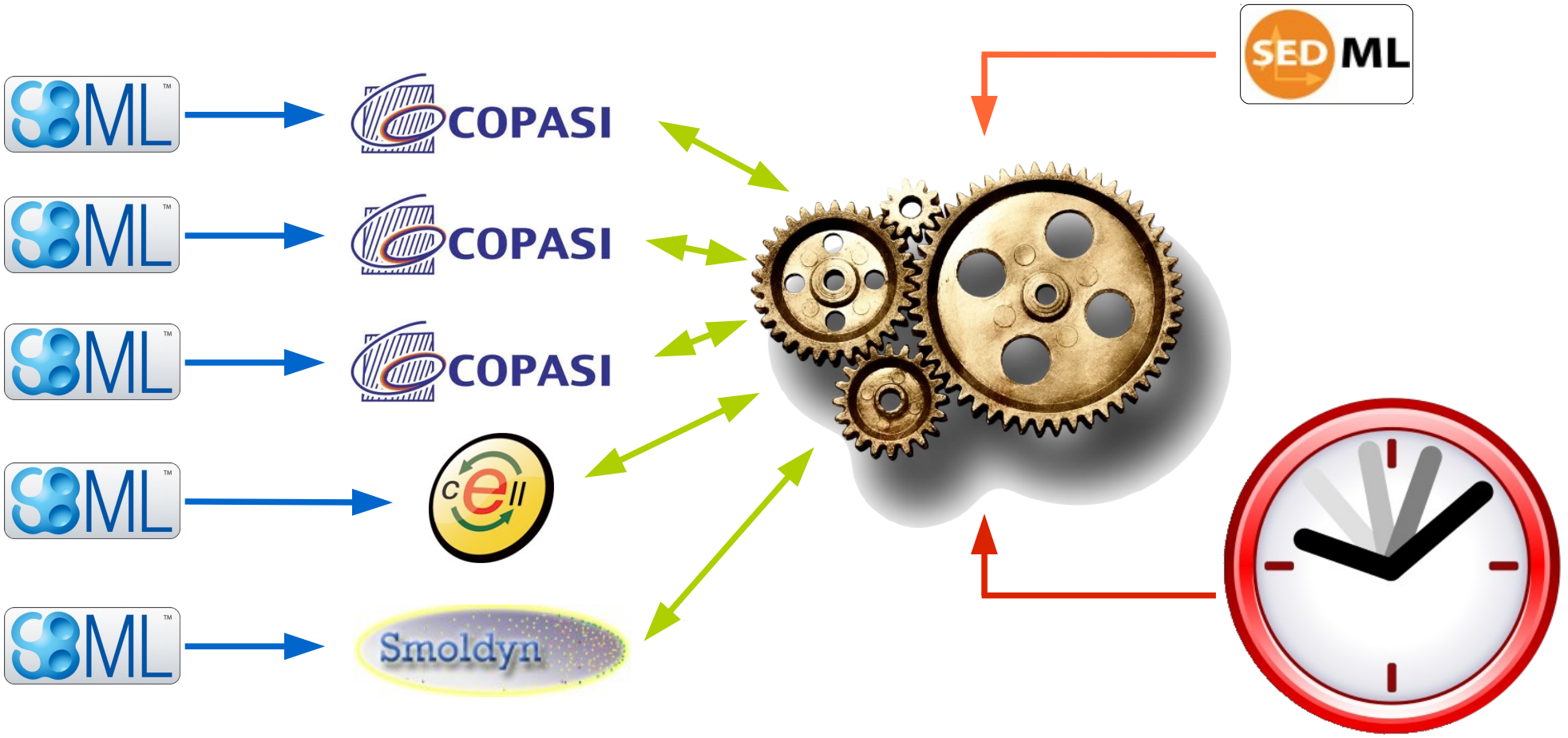
Challenge 4: Monolithic software not sufficient



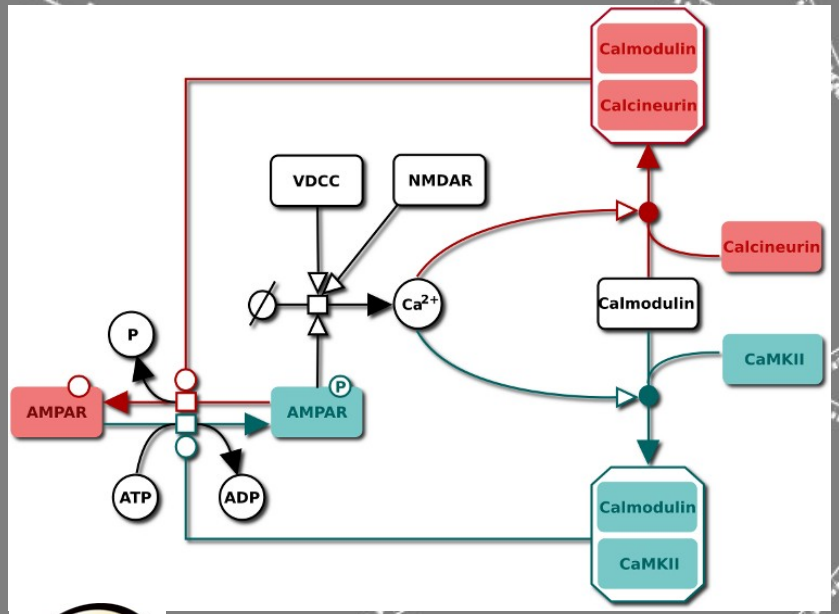
modular model

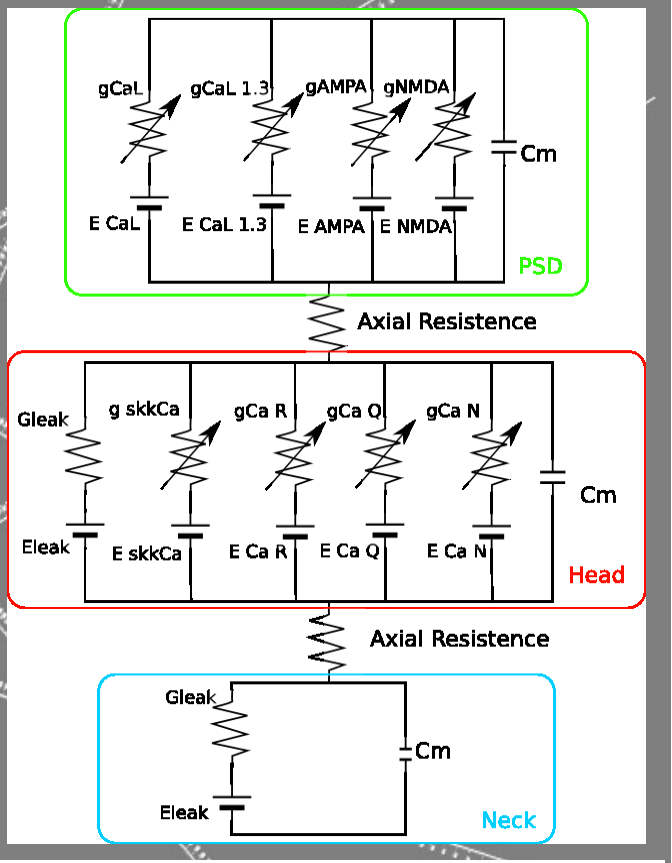
hybrid simulation system

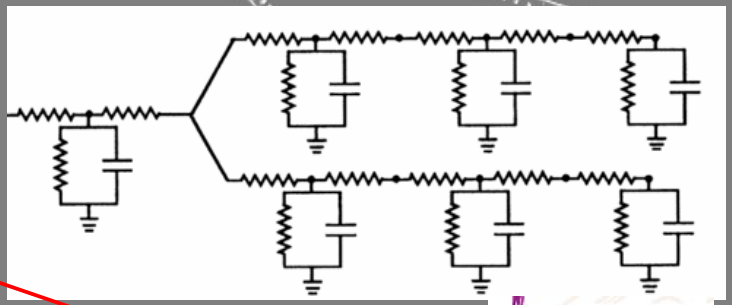
discrete event detection

adaptive synchronization

Whole cell: electro-biochemical models



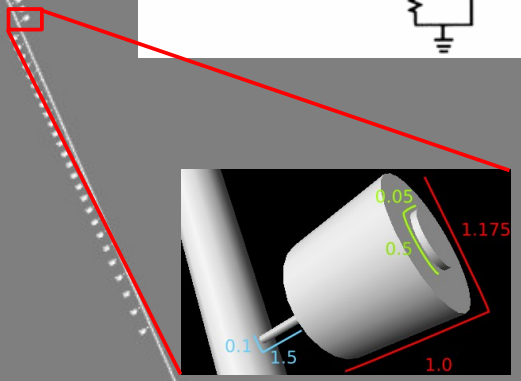




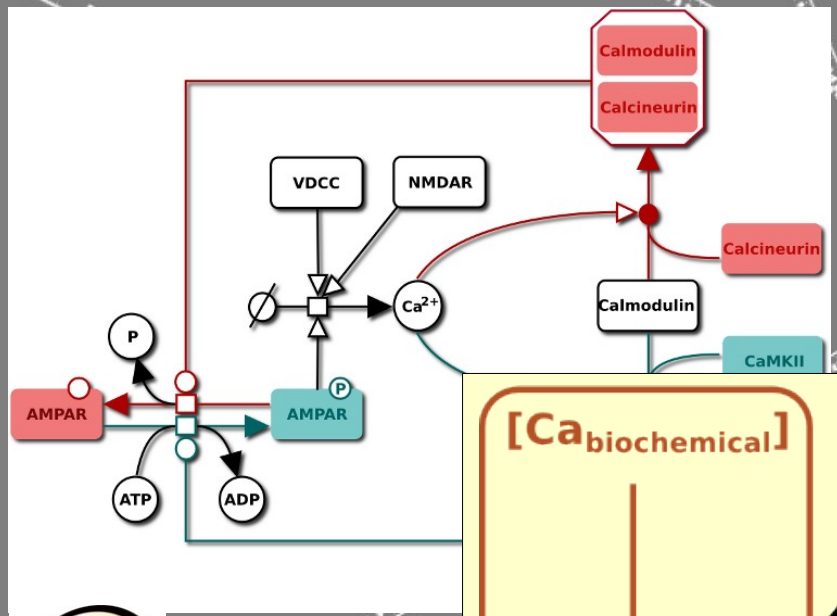
1504 spines

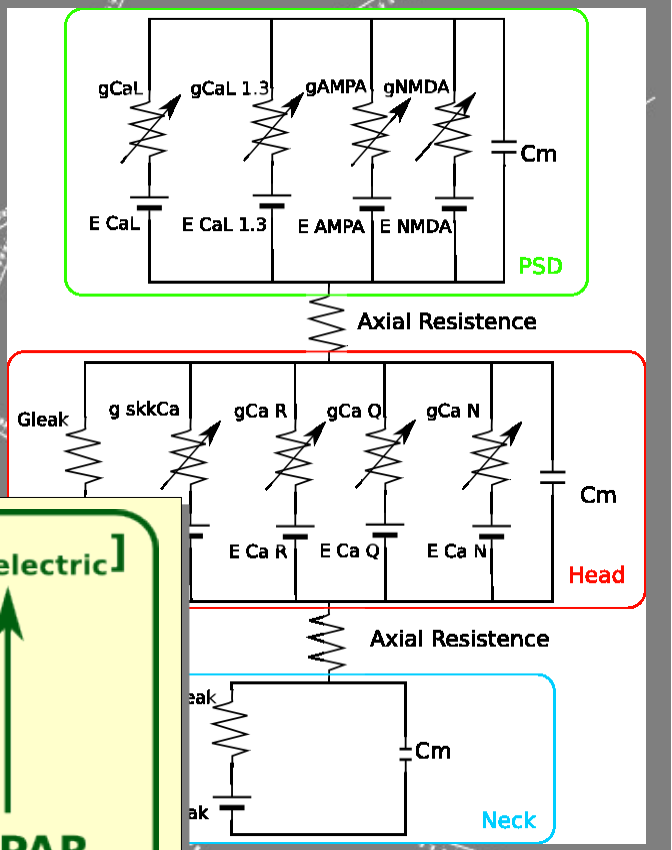
4761 compartments

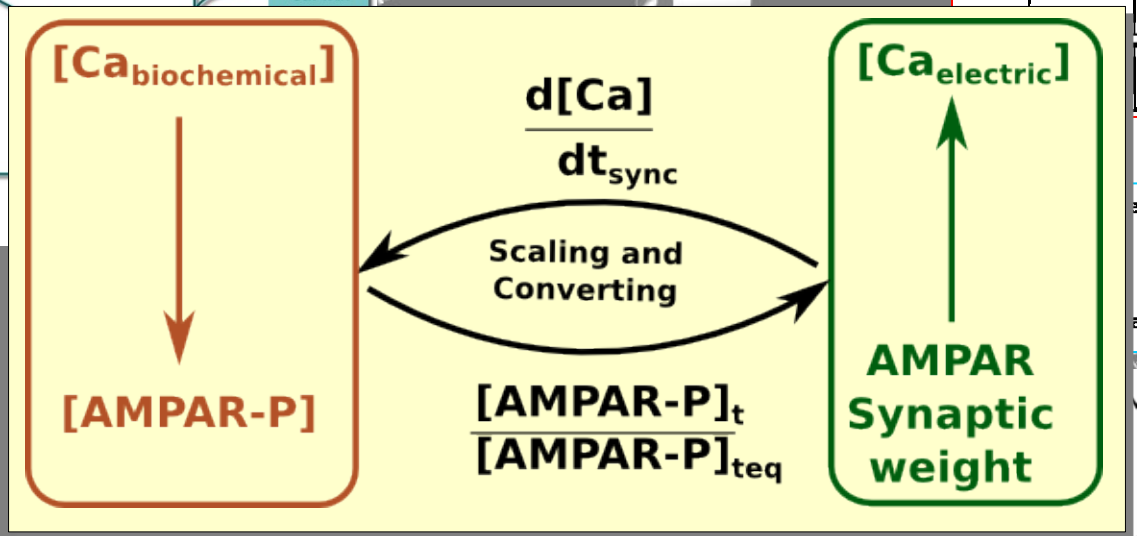
16362 channels

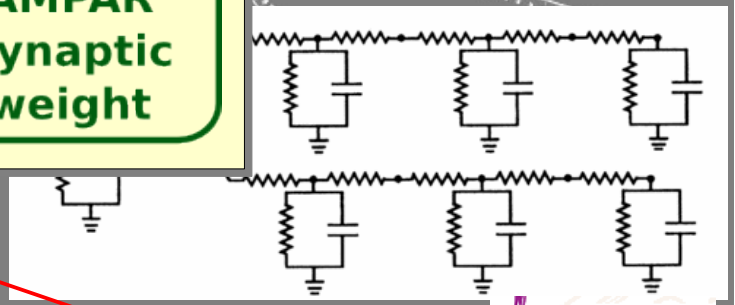


Mattioni et al (2012, 2013)









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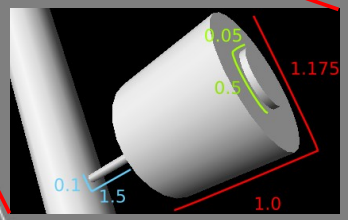
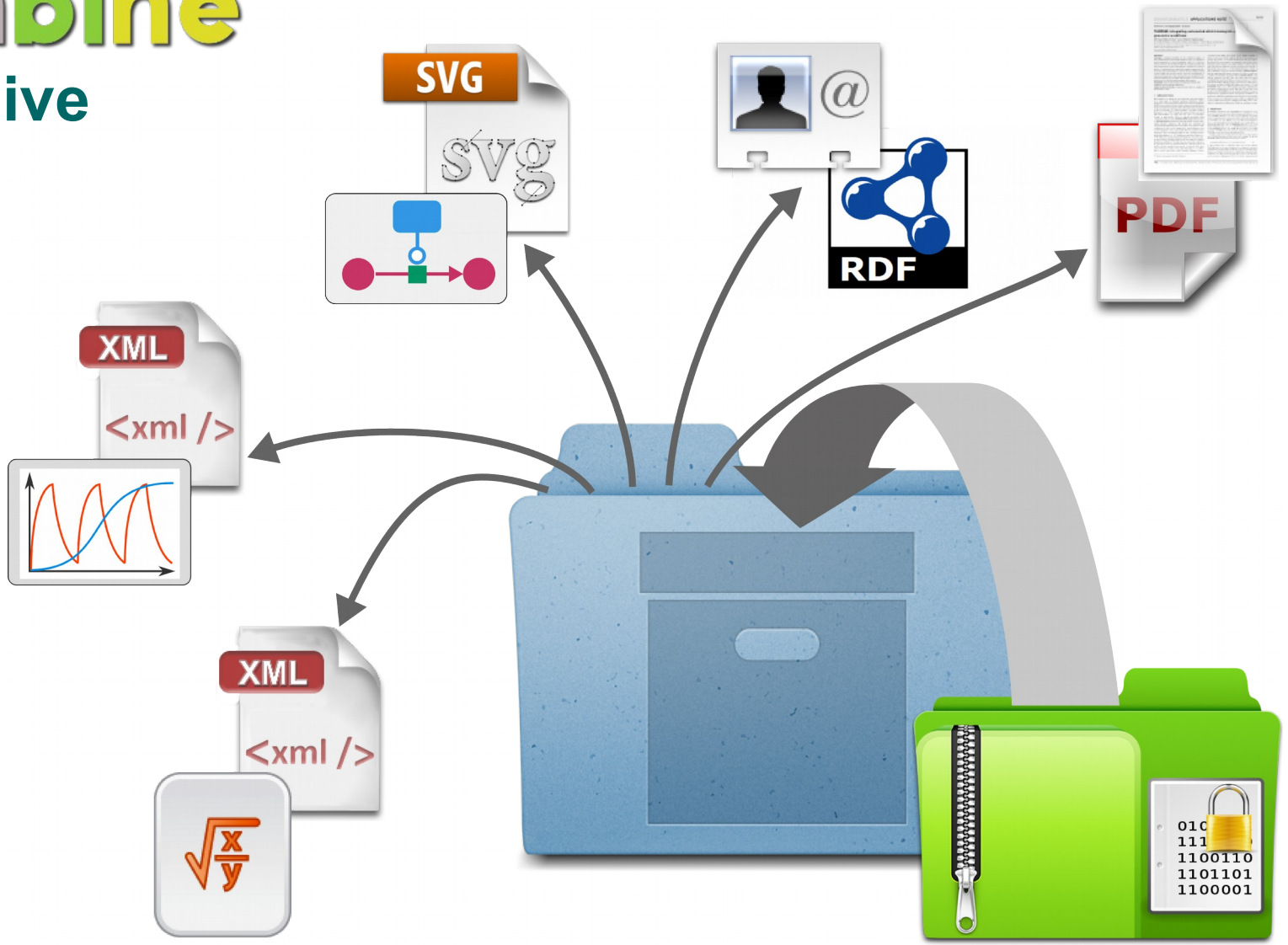


Mattioni et al (2012, 2013)

Challenge 5: virtualisation

Models must be self-contained and portable for everyone to reuse and customise → Virtual machines and modules (e.g. Rocks systems)

combine archive



http://co.mbine.org/standards/omex

Bergman *et al. submitted*

Combining standards for today‘s models

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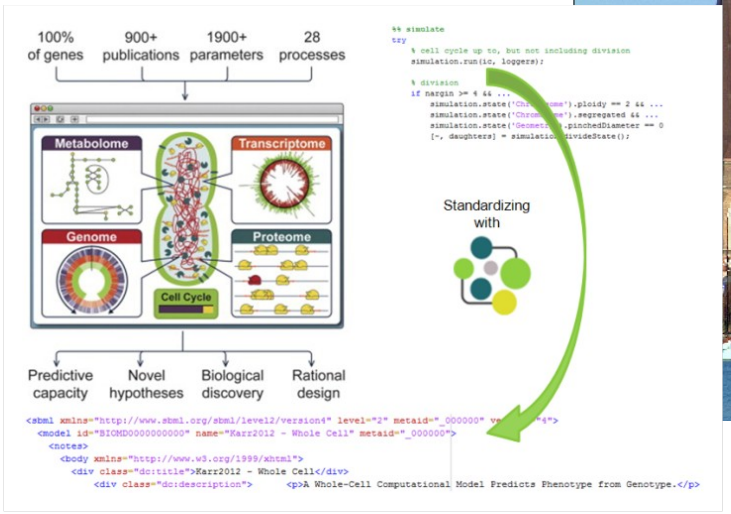
9th – 13th of March 2015, Rostock (Germany)
10 tutors & 50 students
fully funded

VolkswagenStiftung



@ITMZ Rostock

We need you to help us encode the whole-cell model in COMBINE standards!

Join us: http://bit.ly/wholecell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Laurence Calzone


Viji Chelliah


Jonathan Karr


Wolfram Liebermeister


Nicolas Le Novère


Pedro Mendes


Chris Myers


Falk Schreiber


Dagmar Waltemath

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Falk Schreiber
Neil Swainston
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Clemens Wrzodek
Andreas Zell

The numerous scientists who participated to discussions

The community of Computational Systems Biology

You!

Babraham Institute

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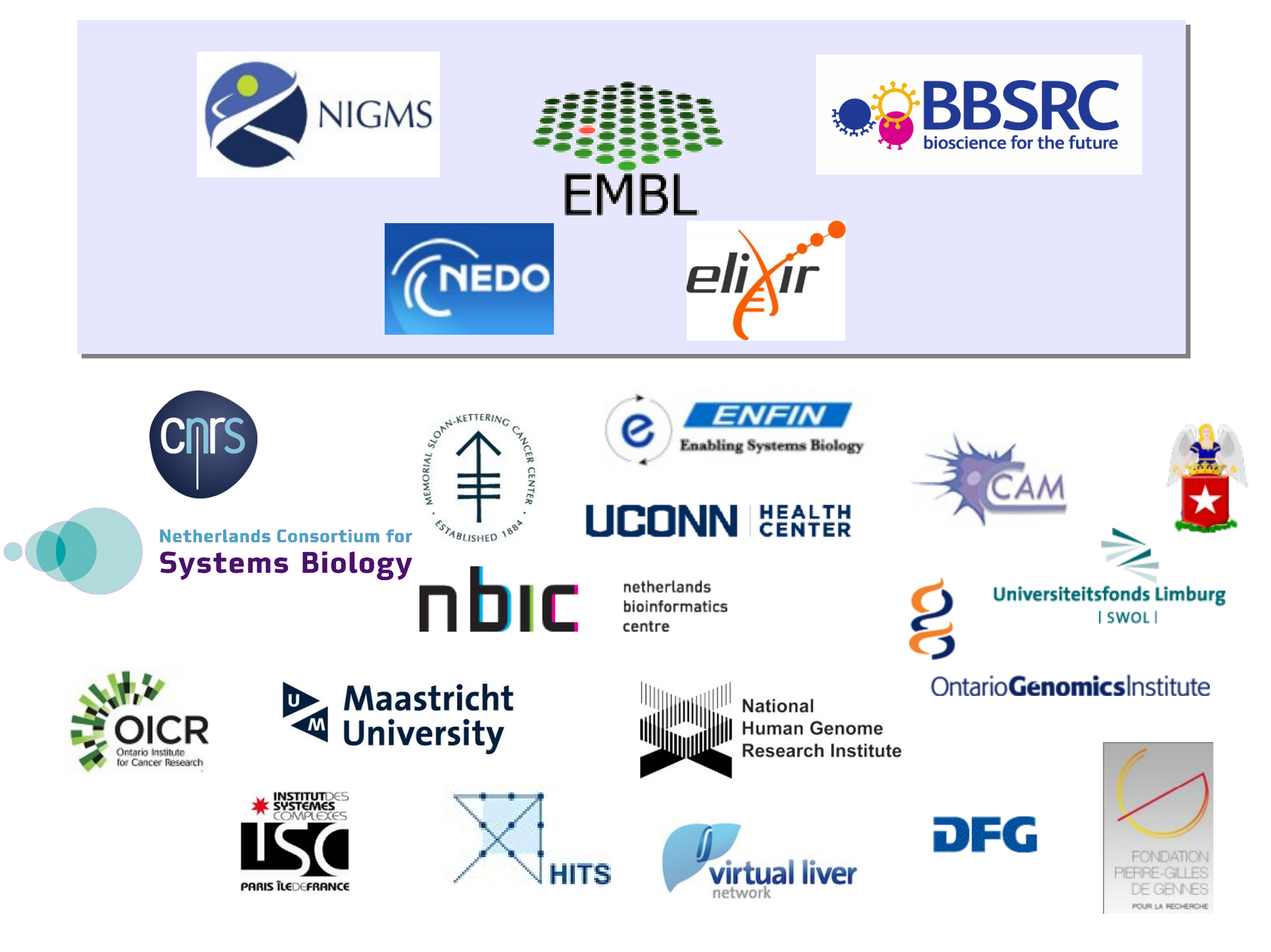
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HITS
virtual liver
network
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