



***What it is***  
***What it could be***

# What happened to Biology at the end of XX<sup>th</sup> century?

Annu. Rev. Genomics Hum. Genet. 2001. 2:343-72  
Copyright © 2001 by Annual Reviews. All rights reserved

## A NEW APPROACH TO DECODING LIFE: Systems Biology

Trey Ideker<sup>1,2</sup>, Timothy Galitski<sup>1</sup>, and Leroy Hood<sup>1,2,3,4,5</sup>  
*Institute for Systems Biology<sup>1</sup>, Seattle, Washington 98105; Departments of*

New Generation Computing, 18(2000)199-216  
Ohmsha, Ltd. and Springer-Verlag

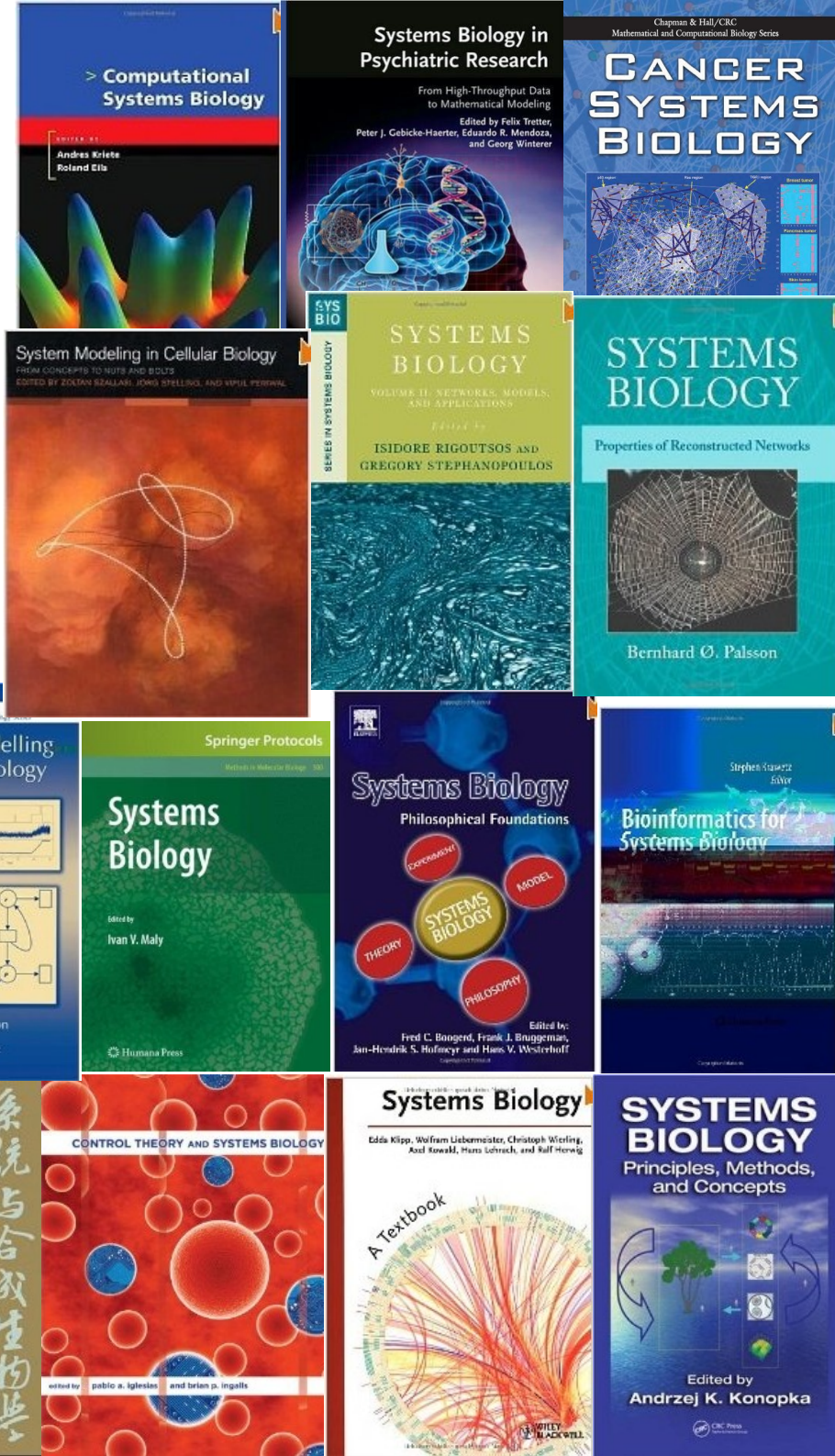
invited paper

## Perspectives on Systems Biology

Hiroaki KITANO  
*Sony Computer Science Laboratories, Inc.*

NEW  
GENERATION  
COMPUTING

©Ohmsha, Ltd.





# What happened to biology at the end of XX<sup>th</sup> century?

## RESEARCH ARTICLE

### Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome

Daniel G. Gibson,<sup>1</sup> John I. Glass,<sup>1</sup> Carole Lartigue,<sup>1</sup> Vladimir N. Noskov,<sup>1</sup> Ray-Yuan Chuang,<sup>1</sup> Mikkel A. Algire,<sup>1</sup> Gwynedd A. Benders,<sup>2</sup> Michael G. Montague,<sup>1</sup> Li Ma,<sup>1</sup> Monzia M. Moodie,<sup>1</sup> Chuck Merryman,<sup>1</sup> Sanjay Vashee,<sup>1</sup> Radha Krishnakumar,<sup>1</sup> Nacyra Assad-Garcia,<sup>1</sup> Cynthia Andrews-Pfannkoch,<sup>1</sup> Evgeniya A. Denisova,<sup>1</sup> Lei Young,<sup>1</sup> Zhi-Qing Qi,<sup>1</sup> Thomas H. Segall-Shapiro,<sup>1</sup> Christopher H. Calvey,<sup>1</sup> Prashanth P. Parmar,<sup>1</sup> Clyde A. Hutchison III,<sup>2</sup> Hamilton O. Smith,<sup>2</sup> J. Craig Venter<sup>1,2\*</sup>

2 JULY 2010 VOL 329 SCIENCE www.sciencemag.org

### Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Cell

Kazutoshi Takahashi<sup>1</sup> and Shinya Yamanaka<sup>1,2,\*</sup>

<sup>1</sup>Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan

<sup>2</sup>CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan

\*Contact: yamanaka@frontier.kyoto-u.ac.jp

DOI 10.1016/j.cell.2006.07.024

Cell 126, 663–676, August 25, 2006 ©2006 Elsevier Inc. 663



## EXTREME GENETIC ENGINEERING

*An Introduction to Synthetic Biology*

January 2007



### A synthetic oscillatory network of transcriptional regulators

Michael B. Elowitz & Stanislas Leibler

Departments of Molecular Biology and Physics, Princeton University, Princeton, New Jersey 08544, USA

NATURE | VOL 403 | 20 JANUARY 2000 | www.nature.com



page discussion view source history teams

#### About

The **International Genetically Engineered Machine competition (iGEM)** is a Biology competition. Student teams are given a kit of biological parts at the beginning of the year. Working at their own schools over the summer, they use t

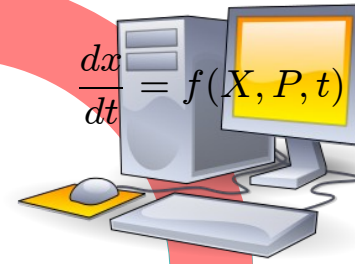
# New way of doing biomedical research

Needs for interplay between models and reality tests

Experiment

model

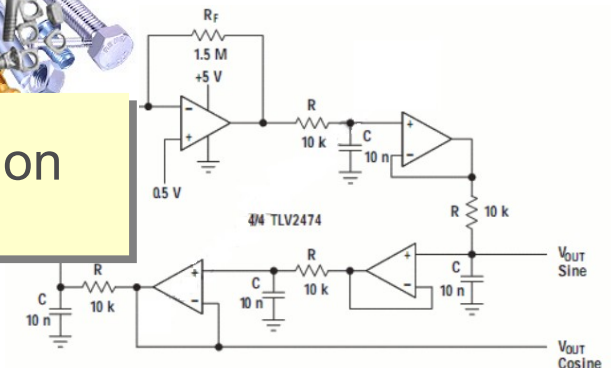
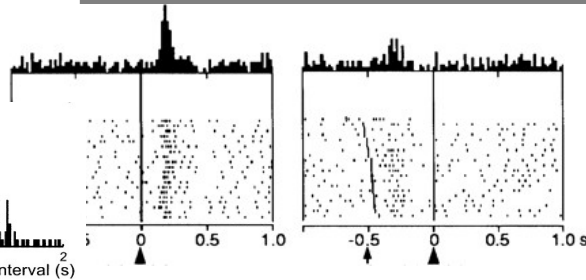
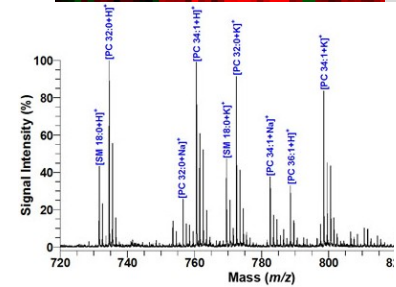
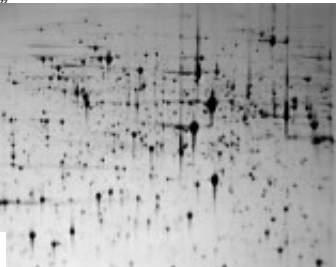
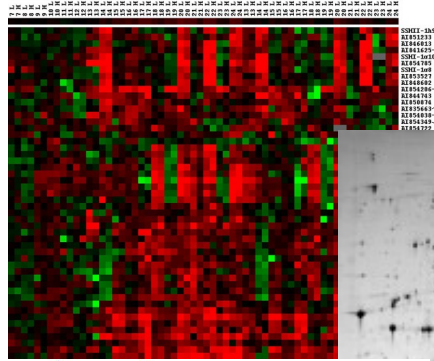
$$\frac{dx}{dt} = f(X, P, t)$$



hypothesis

Needs for systems thinking and integration of heterogeneous knowledge

Needs for cooperation and standardisation

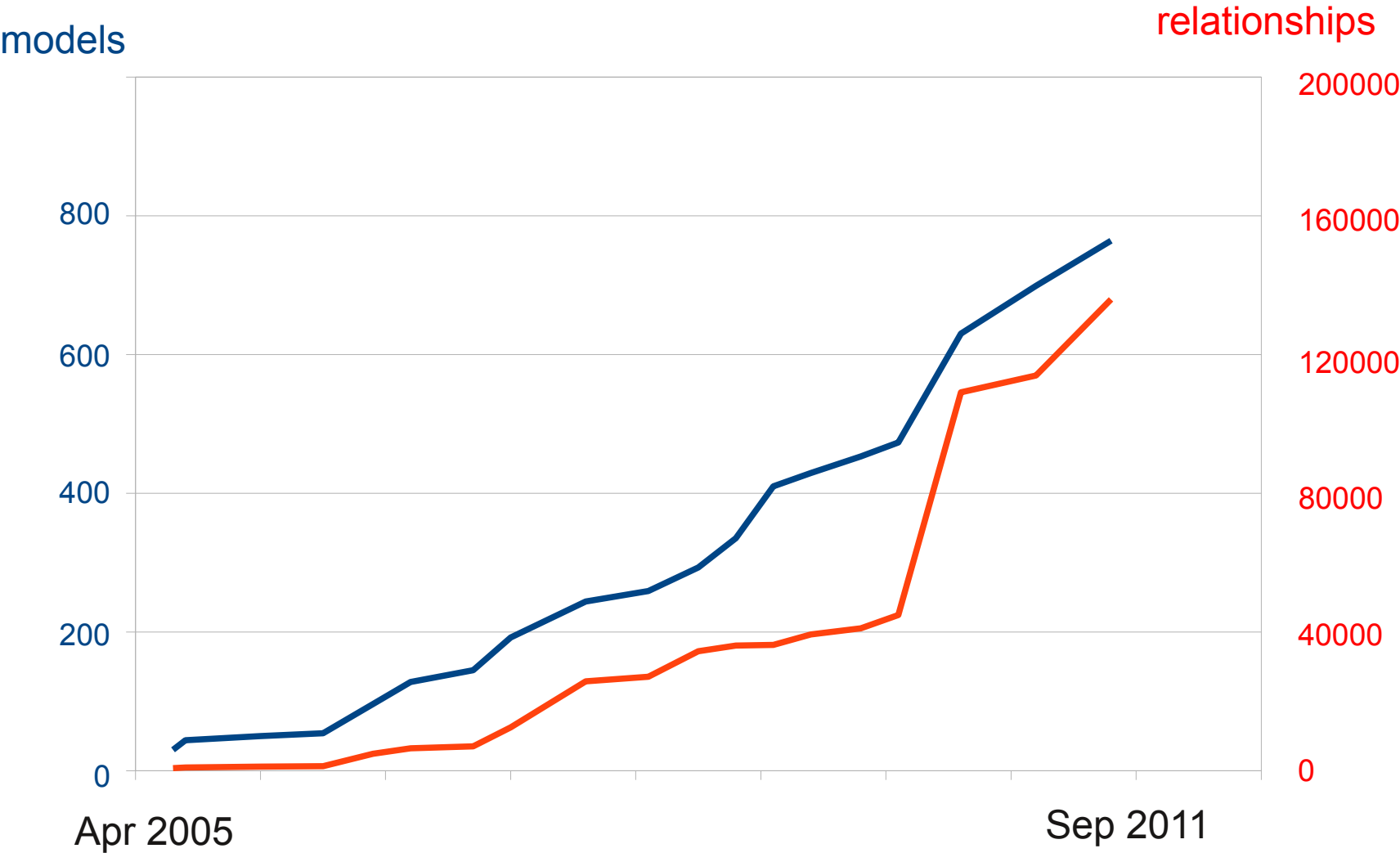


# Computational modelling left the niches

- **Metabolic networks** Fung et al. A synthetic gene-metabolic oscillator. *Nature* 2005; Herrgård et al. A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology. *Nat Biotechnol* 2008
- **Signalling pathways** Bray et al. Receptor clustering as a cellular mechanism to control sensitivity. *Nature* 1998; Bhalla and Iyengar. Emergent properties of signaling pathways. *Science* 1998; Schoeberl et al. Computational modeling of the dynamics of the MAP kinase cascade activated by surface and internalized EGF receptors. *Nat Biotechnol* 2002; Hoffmann et al. The I $\kappa$ B-NF- $\kappa$ B signaling module: temporal control and selective gene activation. *Science* 2002; Smith et al. Systems analysis of Ran transport. *Science* 2002; Bhalla et al. MAP kinase phosphatase as a locus of flexibility in a mitogen-activated protein kinase signaling network. *Science* 2002; Nelson et al. Oscillations in NF- $\kappa$ B Signaling Control the Dynamics of Gene Expression. *Science* 2004; Werner et al. Stimulus specificity of gene expression programs determined by temporal control of IKK activity. *Science* 2005; Sasagawa et al. Prediction and validation of the distinct dynamics of transient and sustained ERK activation. *Nat Cell Biol* 2005; Basak et al. A fourth I $\kappa$ B protein within the NF- $\kappa$ B signaling module. *Cell* 2007; McLean et al. Cross-talk and decision making in MAP kinase pathways. *Nat Genet* 2007; Ashall et al. Pulsatile Stimulation Determines Timing and Specificity of NF- $\kappa$ B-Dependent Transcription. *Science* 2009; Becker et al. Covering a broad dynamic range: information processing at the erythropoietin receptor. *Science* 2010
- **Gene regulatory networks** McAdams and Shapiro. Circuit simulation of genetic networks. *Science* 1995; Yue et al. Genomic cis-regulatory logic: Experimental and computational analysis of a sea urchin gene. *Science* 1998; Von Dassow et al. The segment polarity network is a robust developmental module. *Nature* 2000; Elowitz and Leibler. A synthetic oscillatory network of transcriptional regulators. *Nature* 2000; Shen-Orr et al. Network motifs in the transcriptional regulation network of Escherichia coli. *Nat Genet* 2002; Yao et al. A bistable Rb-E2F switch underlies the restriction point. *Nat Cell Biol* 2008; Friedland. Synthetic gene networks that count. *Science* 2009
- **Pharmacometrics models** Labrijn et al. Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo. *Nat Biotechnol* 2009
- **Physiological models** Noble. Modeling the heart from genes to cells to the whole organ. *Science* 2002; Izhikevich and Edelman. Large-scale model of mammalian thalamocortical systems. *PNAS* 2008
- **Infectious diseases** Perelson et al. HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time. *Science* 1996; Nowak. Population dynamics of immune responses to persistent viruses. *Science* 1996; Neumann et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. *Science* 1998



# Computational models on the rise



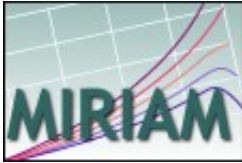
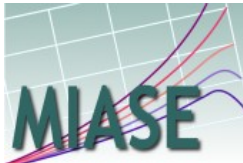


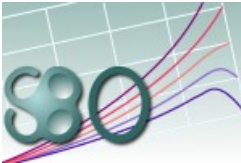


BioModels Database growth since its creation



# Interest from new stakeholders

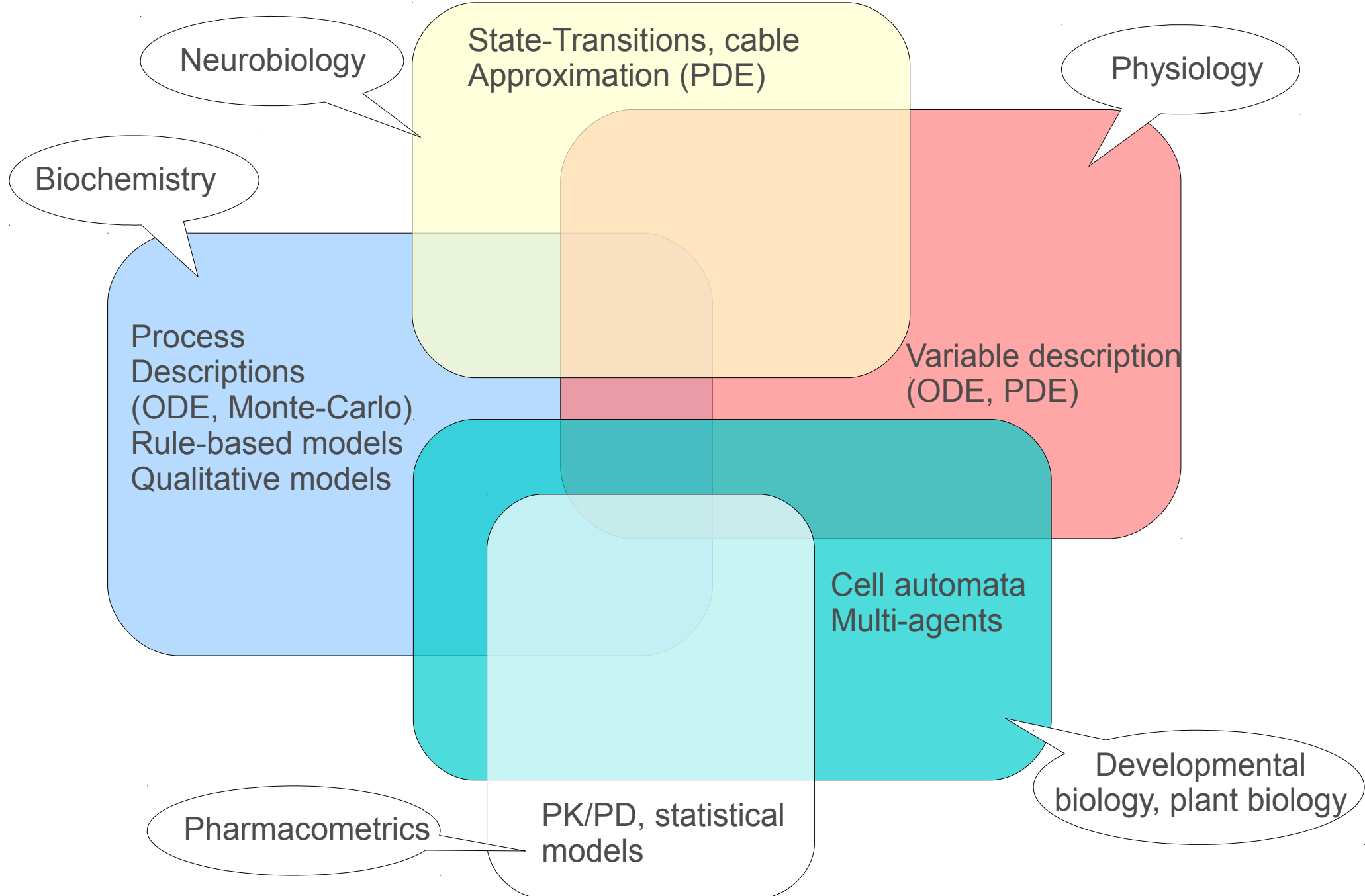
- “Biologists”: computational models look “useful”, “serious”
- Publishers: computational are respectable, and can be published in high profile journals
- Funding agencies: Models could help with the major challenges (read “science that can be sold to citizen/electors”): Health, Food, Energy...
- Industries: Models could help with the major challenges (read “new opportunities to make money”): Pharmas, crops, biofuels ...

# The matrix of standards for M&S in Sys Bio

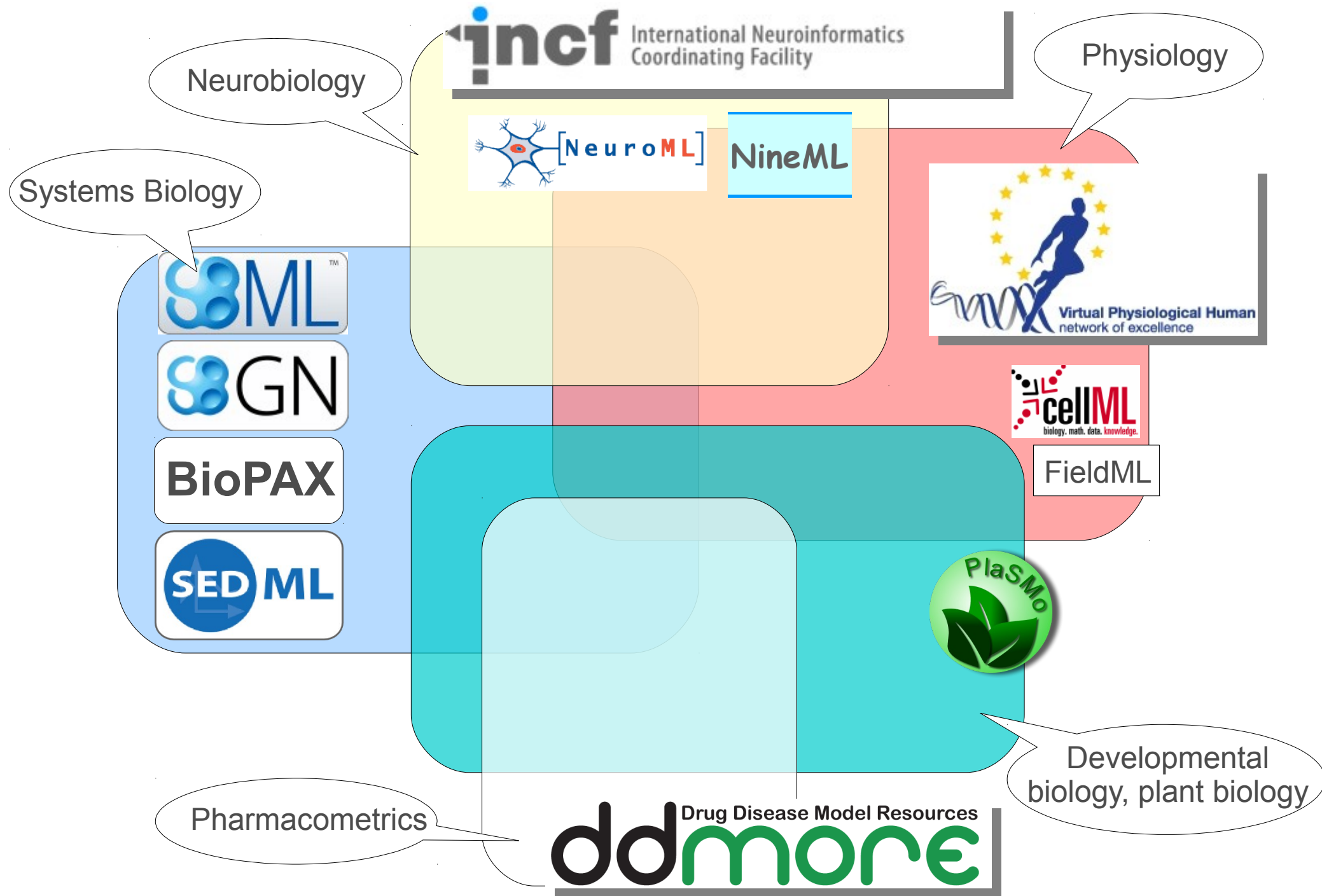
	Model descriptions	Simulations and analysis	Numerical results
Minimal requirements			
Data-models			NuML?
Terminologies			



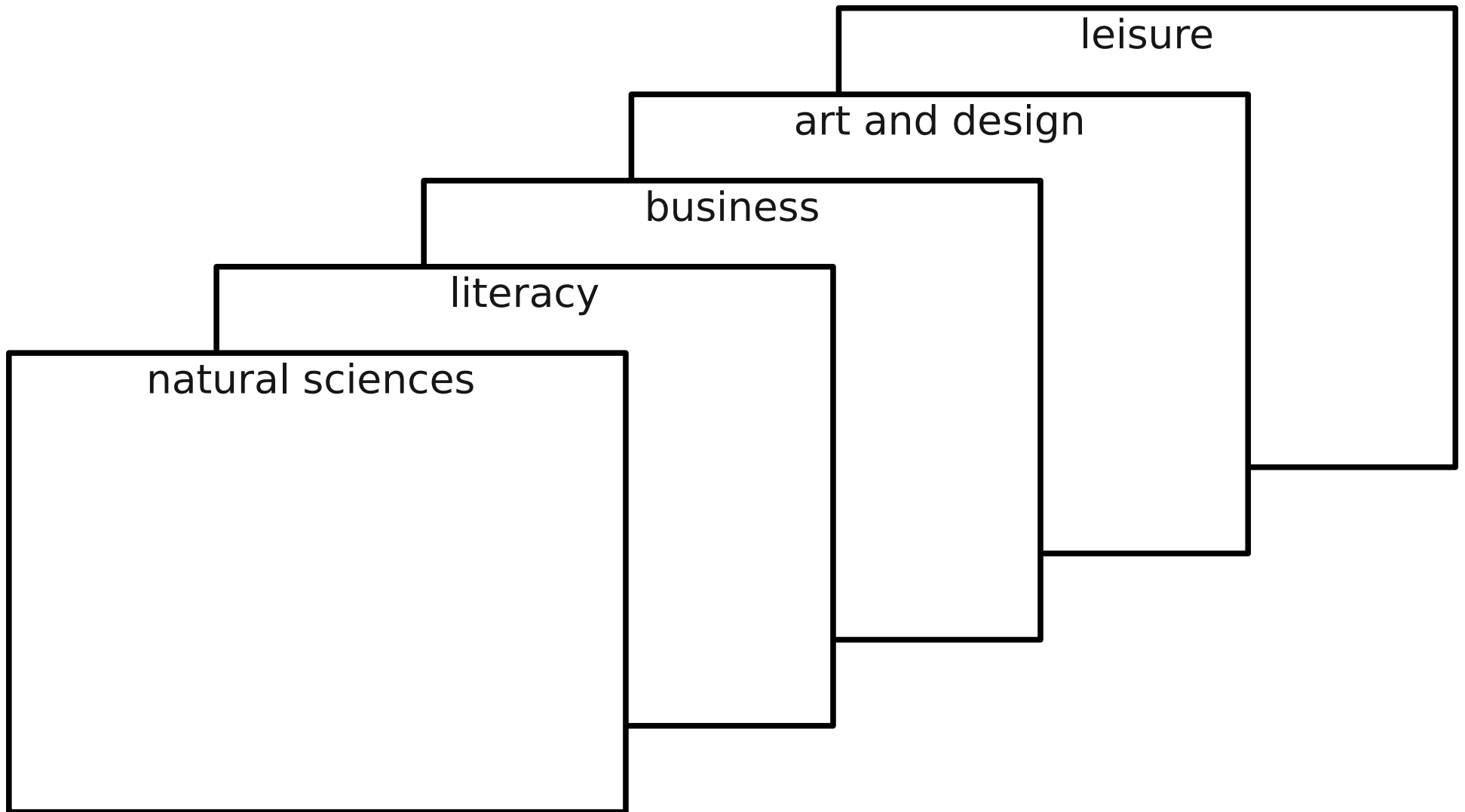
# Dimension 3: Covering alternative modelling approaches



# Parallel and redundant efforts

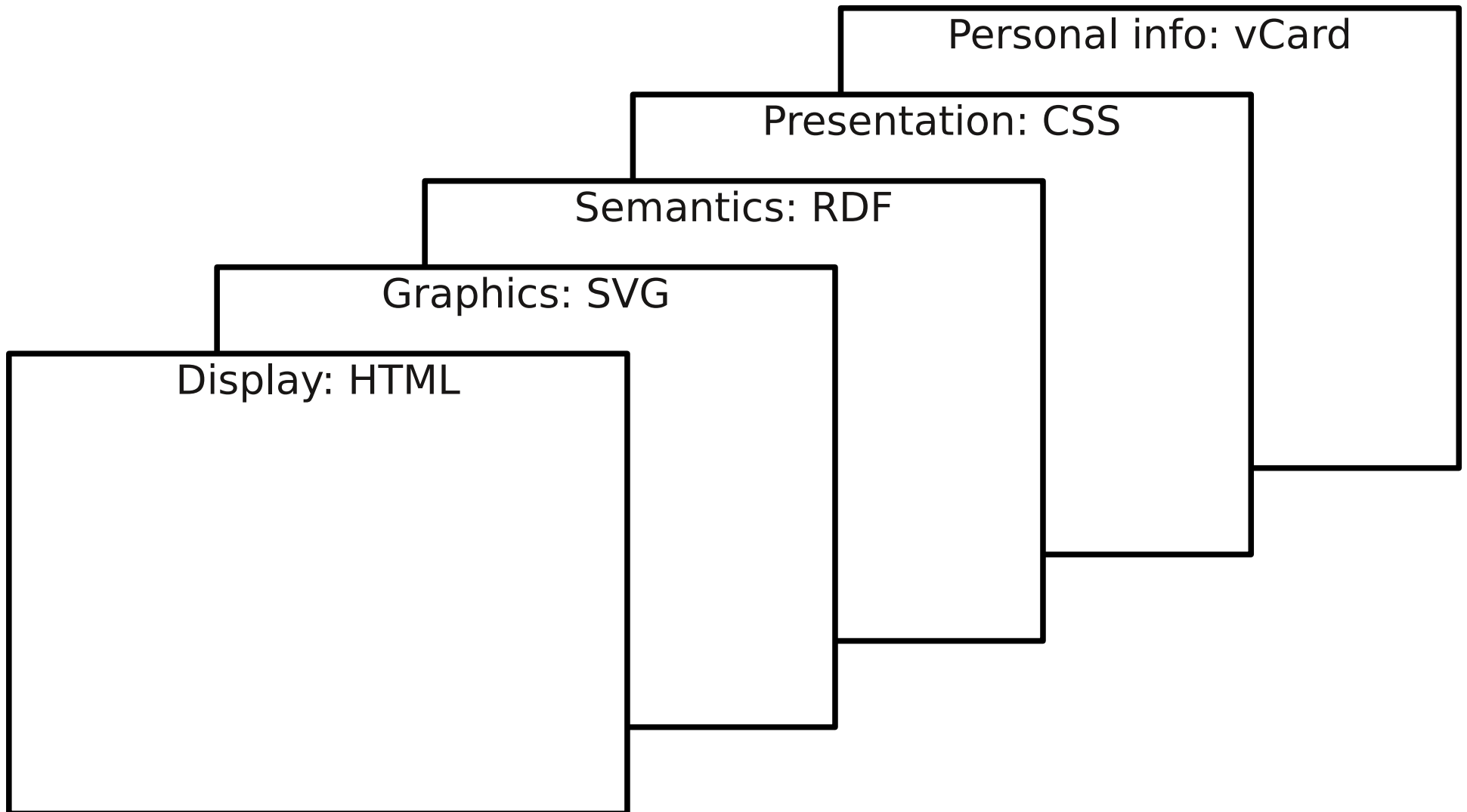


# What if the world-wide web was built like this?

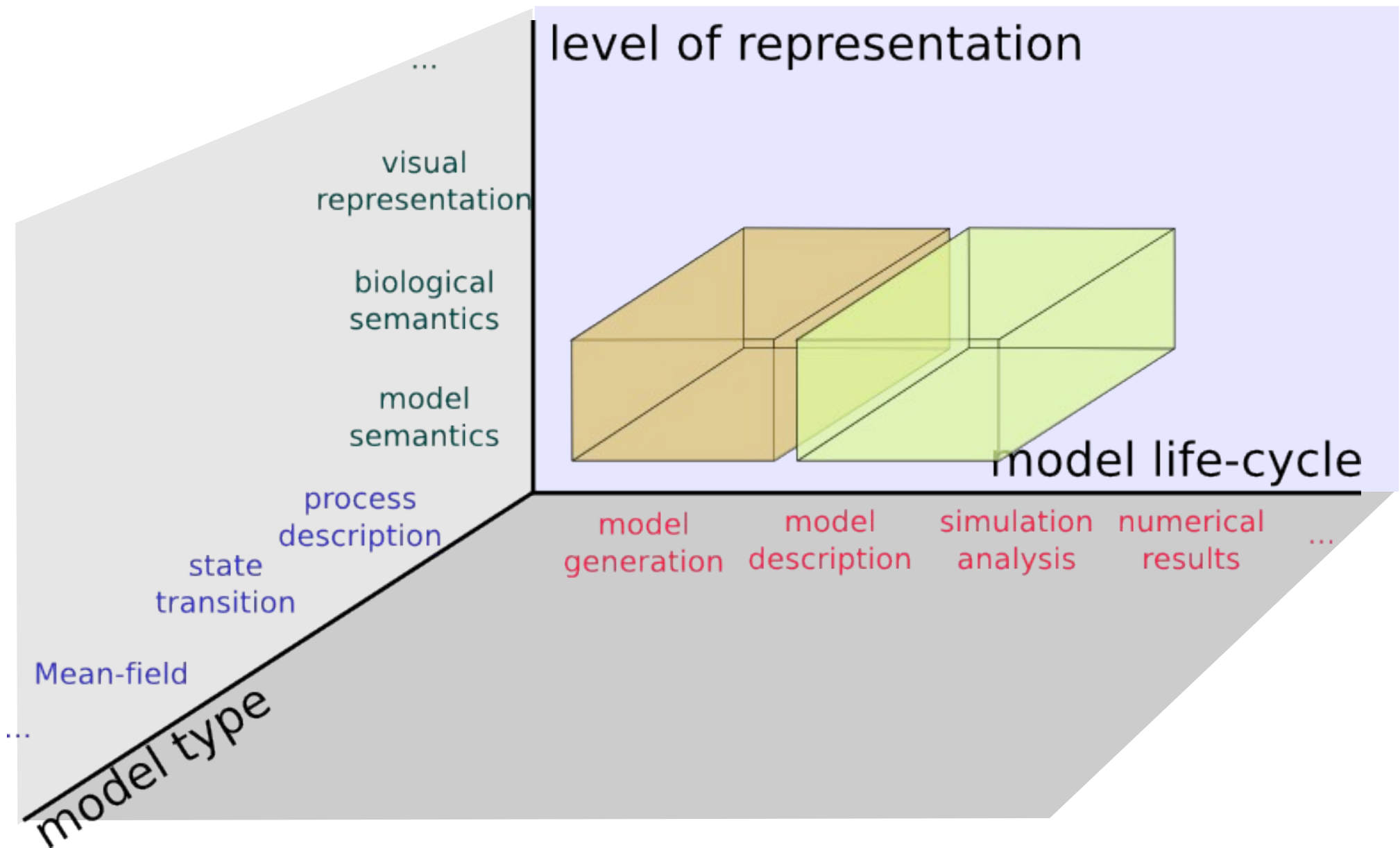




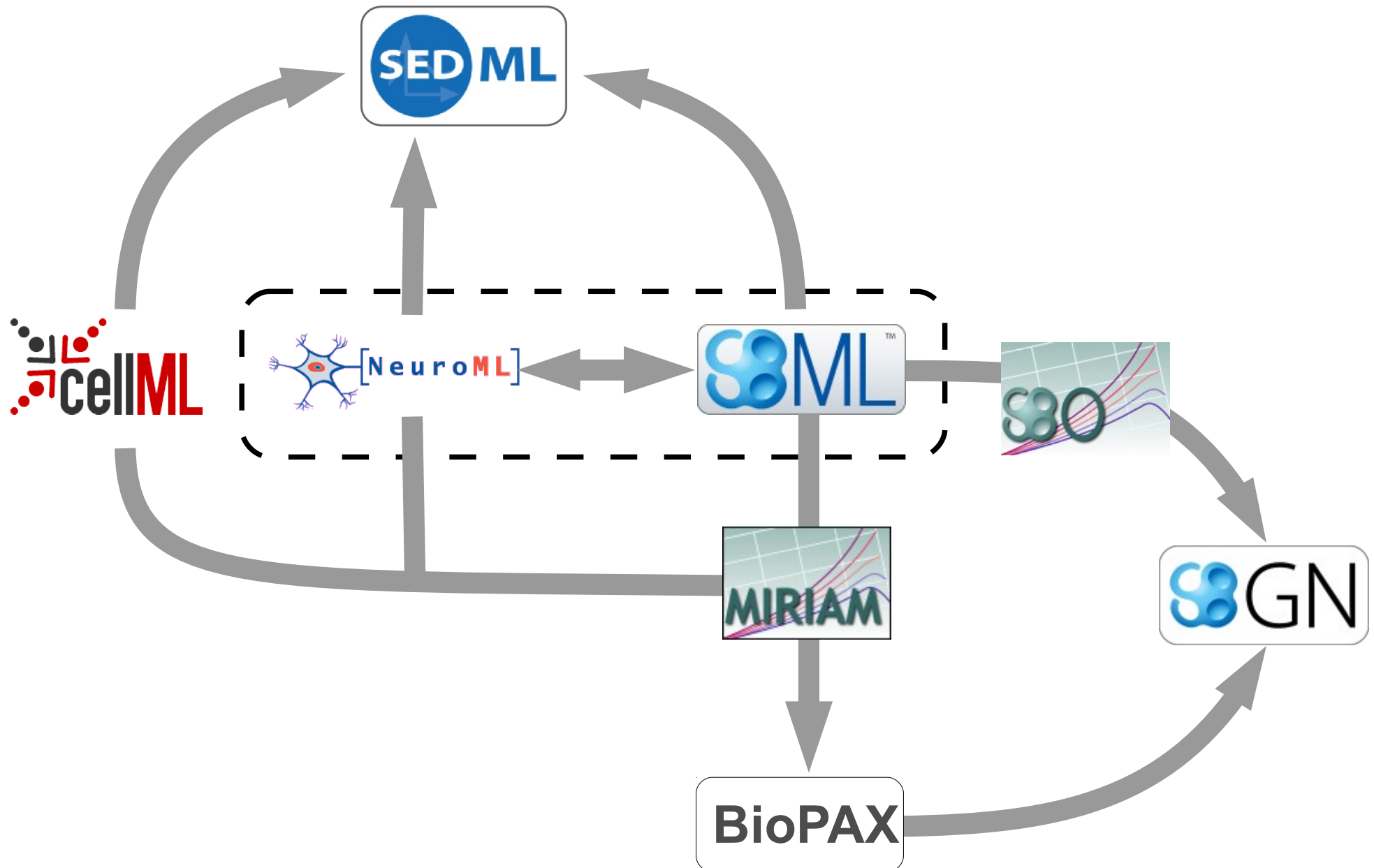
# The correct way to do it



# Covering the entire modeling in the life-sciences



# Existing standards interoperability





# Threats to the whole enterprise

- Current efforts are largely dependent on key people. Their disengagement means stalling or disaggregation.
- Current funding structure is fragile. Many different grants, sometimes only supporting meetings, none of them infrastructure rolling funding, often tied to individuals.
- Current efforts, being developed under the umbrellas of specific institutions are not immune against intellectual property claims that would harm the community.
- Existing standards are developed with very different approaches, quality checks, and are based on completely different assumptions (e.g. implicit knowledge versus explicit mathematics).
- APIs, converters etc. need industry-grade support, incompatible with standard academic usages and possibilities

# Overarching standardisation structure



The “WorldWide Web consortium” of modelling in biology

<http://co.mbine.org/>

# Mission 1: Coordinating the standards

- **CORE STANDARDS:** Efforts fulfilling COMBINE criteria and aiming at following COMBINE rules and interoperate with other COMBINE standards
- **ASSOCIATED EFFORTS:** Standards that are not representation formats, but aiming at enrich or bridge the core standards
- **RELATED EFFORTS:** Formats developed by other communities, that complement or interoperate with COMBINE formats, and that we would like to see joining COMBINE or collaborating closely to COMBINE



# Current core COMBINE standards

- Model semantics, Model structure, Process description:



- Models semantics, Simulation and Analysis:



- Biological semantics, Model structure, Process description, Entity relationships:

BioPAX

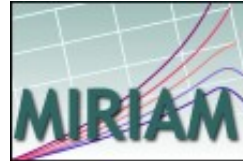
- Visual representation, Model structure, Process description, Entity Relationships, Activity flow:



# Current associated standardization efforts

- Concept and data reference:

- MIRIAM Registry



- Identifiers.org URIs



- Terminologies:

- Modeling

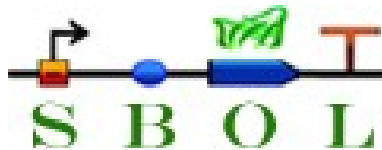


- Simulation



:

# Related standardization efforts



**PSI-MI**



**FieldML**

**NuML?**



COMBINE does NOT aim to take over the development of the standard formats, but help coordinating and supporting this process

## Mission 2: Coordinating meetings

- Annual COMBINE meetings
  - COMBINE 2010: October 6–9, Edinburgh, **81 attendees**
  - COMBINE 2011: September 3-7, Heidelberg, 82 registrations
  - COMBINE 2012: End of summer, beginning autumn , Toronto
  - COMBINE 2013: Date unknown, location unknown  
<http://www.surveymonkey.com/s/combine-harmony-hosting-interest>
- The Hackathons on Resources for Modeling in Biology
  - HARMONY 2011: April 18-22, New-York City, **59 attendees**
  - HARMONY 2012; Date unknown, location unknown  
<http://www.surveymonkey.com/s/combine-harmony-hosting-interest>

# Mission 3: Developing Standard Operating Procedures

- Technical requirements
  - Who format covers what portion of the modeling space
  - Which technical solutions exist and must be used by the formats
  - How do formats interface
  - How to specify and document formats
  - ...
- Governance
  - How to initiate and maintain standardisation efforts
  - How to communicate with users and developers
  - How to develop a democratic and robust governance
  - ...

# First tentative SOP: guidelines to develop a core COMBINE standard

- List the new development as a related standardization effort
- Join COMBINE community and attend meetings
- Comply with COMBINE criteria
  - Must cover aspects of modeling significantly different from the existing set of COMBINE standards
  - Must be described in precise technical specification documents and formal specification languages
  - Specifications and other materials must be publicly available free of charge to everyone and be unencumbered by licensing restrictions
  - Development must be open. The entire COMBINE community must be able to participate without exclusion
  - Must be developed and used by more than a single team or organisation.
  - Development process must be led by democratically elected editorial boards
  - Mature software support must exist, including standard API implementations, and possibly validation tools
  - Development must be stable and active
- Decision by the coordinators (alt: vote of the community?)

## Mission 4: Recognised voice

- COMBINE aims to become a “standardisation” body
  - This means a quality label. A “COMBINE standard” is a guarantee of stability, community endorsement, support etc.
  - COMBINE production can be used in SOPs at other organisations
  - COMBINE must be an actor on par with FGED, PSI, INCF etc.
- Single point of contact with user organisations including Industry
  - Tool developers (General platforms or specific tools)
  - Publishers
  - Pharmaceutical industry
- A point of contact for funding bodies
- A point of contact for legal entities, e.g. government and regulatory bodies

# Where to find more information?

## Communities

## Semantics

## Coordination

<http://co.mbine.org/>

<http://biopax.org/>

<http://sbgn.org/>

<http://sbml.org/>

<http://sed-ml.org/>

<http://biomodels.net/>

<http://biomodels.net/biomodels/>

<http://biomodels.net/kisao>

<http://biomodels.net/sbo>

<http://biomodels.net/teddy>

<http://biomodels.net/miase>

<http://biomodels.net/miriam>



# Acknowledgements

SBML editors: Frank Bergmann, *Andrew Finney*, *Stefan Hoops*, Michael Hucka, *Nicolas Le Novère*, Sarah Keating, Chris Myers, *Sven Sahle*, *Herbert Sauro*, Jim Schaff, Lucian Smith, *Darren Wilkinson*

SBGN editors: Emek Demir, Nicolas Le Novère, Huaiyu Mi, Stuart Moodie, *Falk Schreiber*, *Anatoly Sorokin*, Alice Villéger

BioPAX editors: Peter D'Eustachio, Oliver Ruebenacker, Andrea Splendiani

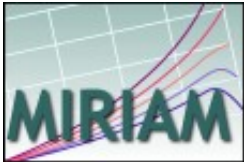
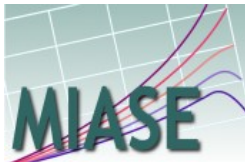




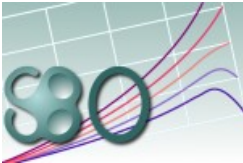


SED-ML editors: Richard Adams, Franck Bergmann, Nicolas Le Novère, Andrew Miller, David Nickerson, Dagmar Waltemath

Metadata: Mélanie Courtot, Nick Juty, Camille Laibe, Anna Zhukova

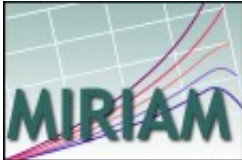
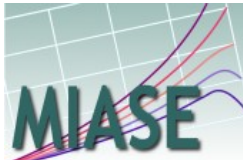






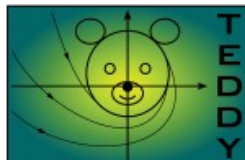
The whole community of Computational Systems Biology





# Is the matrix of standards complete?

	Model descriptions	Simulations and analysis	Numerical results
Minimal requirements			
Data-models	  		NuML?
Terminologies			

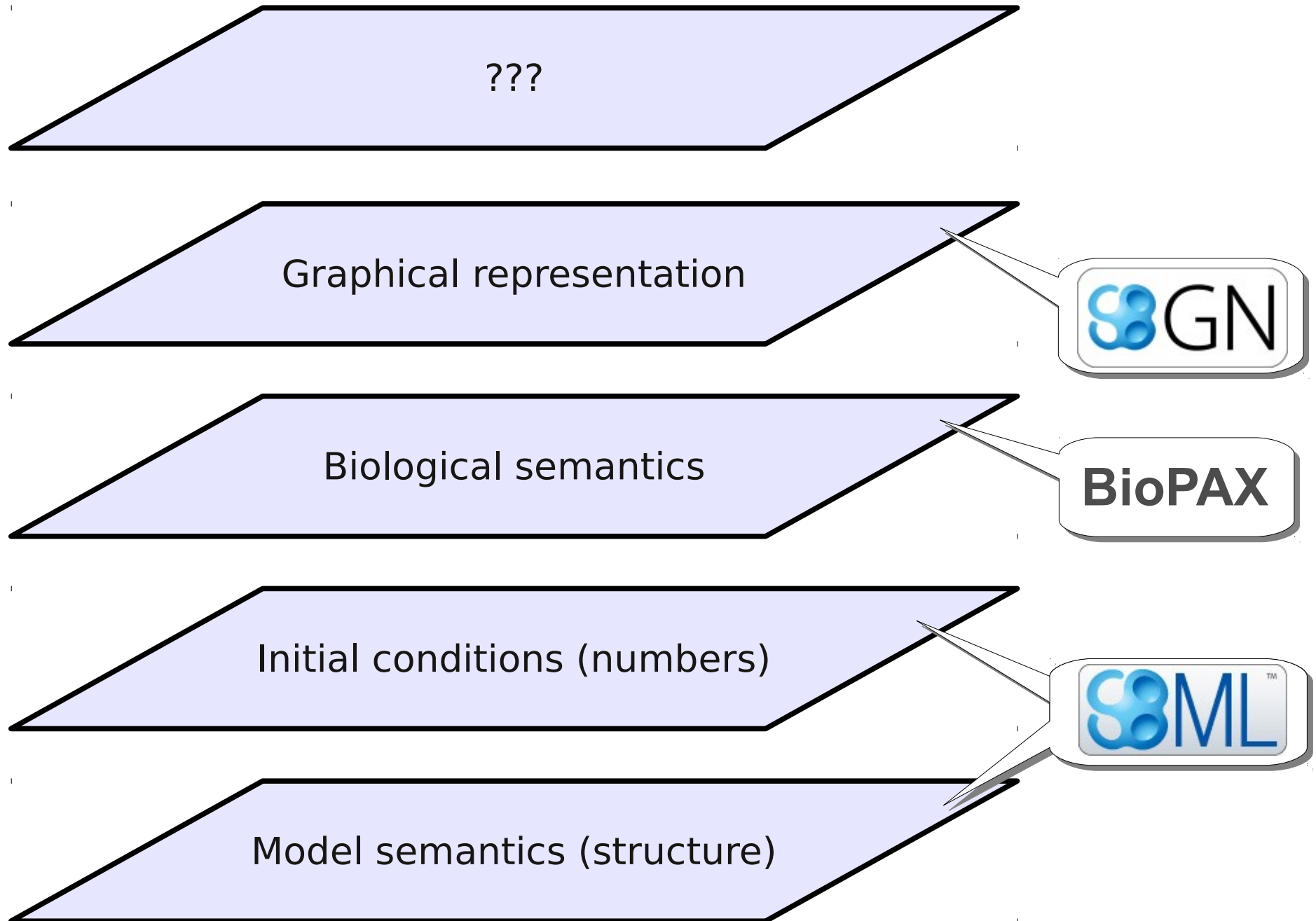
# Is the matrix of standards complete?

	Model descriptions	Simulations and analysis	Numerical results
Minimal requirements			
Data-models	  		NuML?
Terminologies			

# Dimension 1: Covering the entire model life-cycle

Model generation	Model structure	Parametrisation	Simulations and analysis	Numerical results
?		?		NUML?

## Dimension 2: Representing the levels of discourse



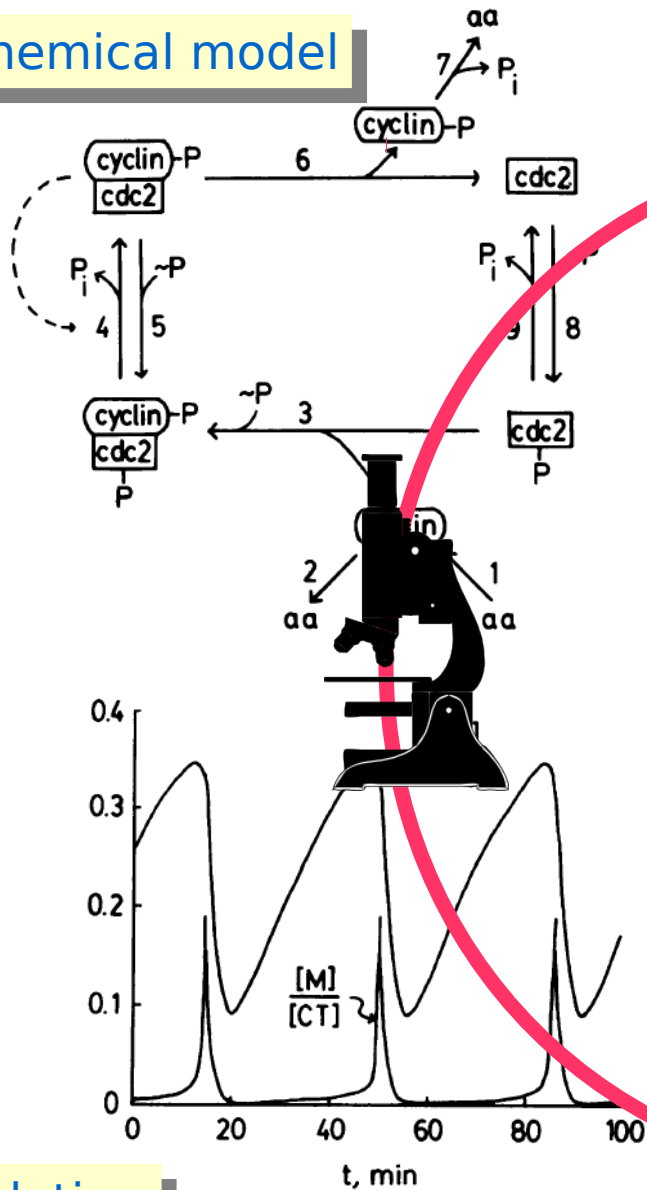




# The models I am talking about

biochemical model

mathematical model



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

Parameter	Value	Notes
$k_1[aa]/[CT]$	$0.015 \text{ min}^{-1}$	*
$k_2$	0	†
$k_3[CT]$	$200 \text{ min}^{-1}$	*
$k_4$	$10\text{--}1000 \text{ min}^{-1}$ (adjustable)	
$k_4'$	$0.018 \text{ min}^{-1}$	
$k_5[\sim P]$	0	‡
$k_6$	$0.1\text{--}10 \text{ min}^{-1}$ (adjustable)	
$k_7$	$0.6 \text{ min}^{-1}$	†
$k_8[\sim P]$	$\gg k_9$	§
$k_9$	$\gg k_6$	§

simulation

Tyson et al (1991) PNAS 88(1):7328-32

computational model