

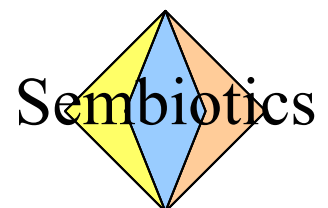


Sembiotics

Formal Semantics for BioModels

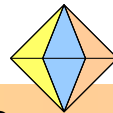
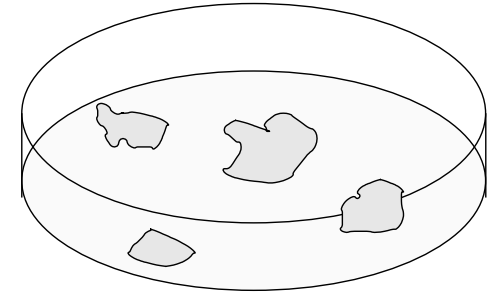
Christian Knüpper

Artificial Intelligence Group & Bio Systems Analysis Group
Friedrich Schiller University Jena
Jena Centre for Bioinformatics



Overview

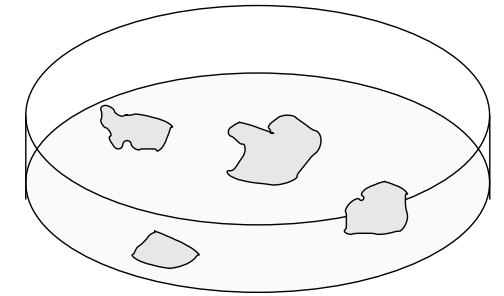
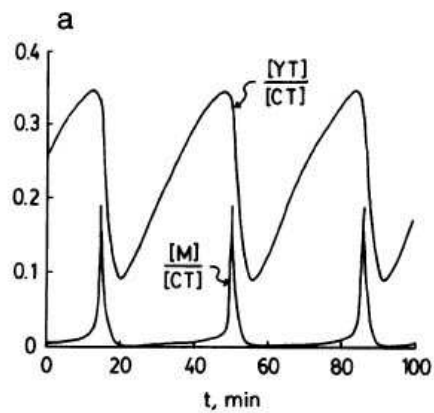
$$\begin{array}{l} \dot{x} = \dots \\ \dot{y} = \dots \end{array}$$



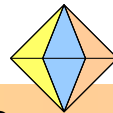
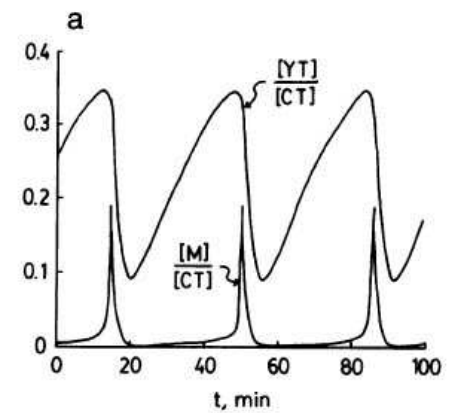
Overview

$$\begin{aligned}\dot{x} &= \dots \\ \dot{y} &= \dots\end{aligned}$$

Simulation
Analysis



Observation



Overview

$$\dot{x} = \dots$$

$$\dot{y} = \dots$$

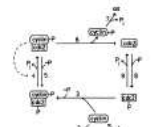
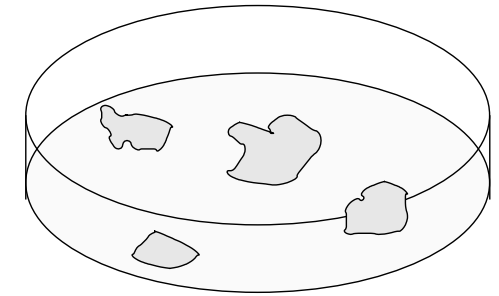
Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 7328-7333, August 1989
Cell Biology

Modeling the cell division cycle: cdc2 and cyclin interactions
(maturation promoting factor/metaphase arrest/yeast/cdk2)

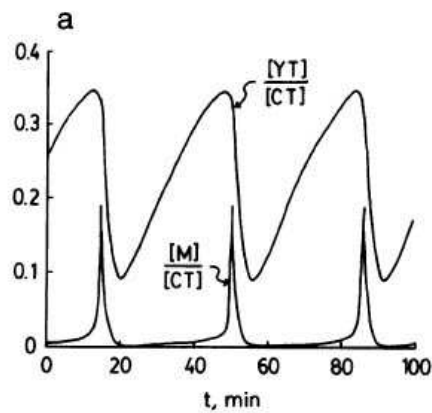
JOHN J. Tyson
Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061
Communicated by David M. Prescott, May 20, 1989 (received for review January 23, 1989)

ABSTRACT The proteins cdc2 and cyclin form a heterodimer (maturation promoting factor) that controls the major events of the cell cycle. A mathematical model for the interactions of cdc2 and cyclin is constructed. Simulation and analysis of the model show that the control system can operate in three modes: as a steady state with high maturation promoting factor activity, as a spontaneous oscillator, or as an excitable switch. We associate the steady state with metaphase arrest in unfertilized eggs, the spontaneous oscillations with rapid division cycles in early embryos, and the excitable switch with growth-controlled division cycles typical of mammalian cells.

Passage through the cell cycle is marked by a temporally organized sequence of events including DNA replication, ...

Scientific Paper



fertilized frog egg, the enucleated cell continues to undergo periodic cortical contractions at 10-min intervals, as if it were trying to divide (7). Enucleated sea urchin eggs even undergo cleavage and division into abnormal blastulae (8). As Madao (9) puts it, the cell cycle is really a cell "bicycle": the two wheels are the growth cycle and the division cycle, which normally turn in a 1:1 ratio but may turn independently.

The mitotic cycle in both embryonic and somatic cells appear to be controlled by the activity of an enzyme, maturation promoting factor (MPF), that peaks abruptly at metaphase (10-14). MPF is a heterodimer composed of cyclin (M₁ = 45,000) and a protein kinase (M₂ = 34,000) (15, 16). The protein kinase is sometimes called p34, in reference to its apparent molecular weight, and sometimes called cdc2, in reference to the gene (cdc2) that codes for the protein in fission yeast.

The interplay between cyclin and cdc2 in generating MPF activity is understood in some detail (see Fig. 1) (10-14). Newly synthesized cyclin subunits combine with preexisting cdc2 subunits to form an inactive MPF complex. The complex is then activated, in an autocatalytic fashion (17), by dephosphorylation at a specific tyrosine residue of the cdc2 subunit (24). Active MPF is known to stimulate a number of

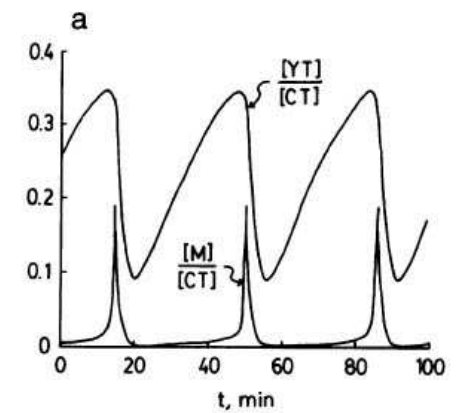
... partially reversed by cdc25, and the cycle repeats itself, as, with cdc25, -4, -437, 5, inorganic phosphate.

processes essential for nuclear and cell division (13, 14). At the transition from metaphase to anaphase, the MPF complex dissociates, and the cyclin subunit is rapidly degraded (15, 19-21). Then the cycle repeats itself.

MPF dissociation and cyclin proteolysis are necessary to complete the mitotic cycle; metaphase arrest of unfertilized eggs corresponds to steady high levels of active MPF, and fertilization releases the egg from metaphase by stimulating the breakdown of the active MPF complex (10). In early embryos, the cycle of MPF activation and inactivation seems to be controlled by the synthesis of cyclin (21, 22), although some evidence suggests that posttranslational events may be rate-limiting (13, 23). In any event, the cycle continues even in the absence of DNA synthesis (24). In somatic cells, by contrast, cyclin synthesis is not sufficient to activate MPF, and the MPF cycle is dependent on cell growth and periodic DNA synthesis (12). In fission yeast, activation of the MPF complex is controlled by at least two other gene products: wee1, an inhibitor of MPF, and cdc25, an activator (25, 26). These two proteins apparently maintain the mitochromatid ratio in the yeast cell and activate MPF at a critical value

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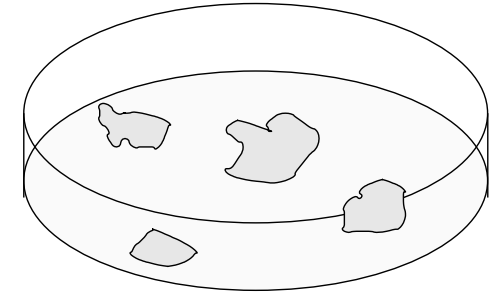
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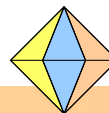
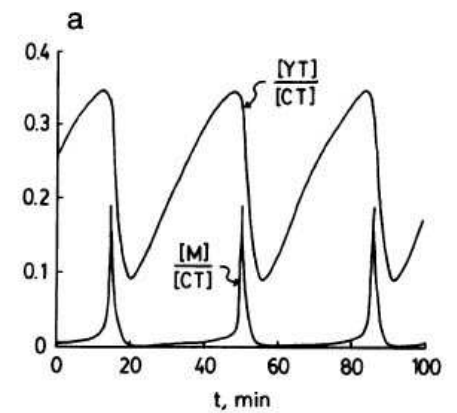
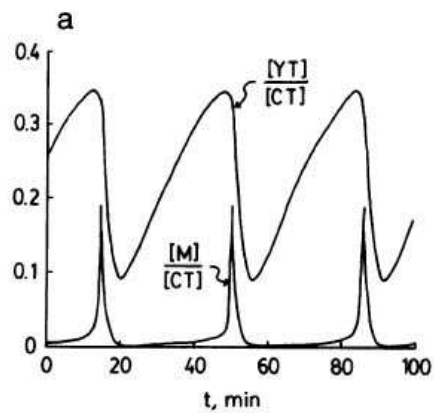
Overview

$$\begin{aligned} \dot{x} &= \dots \\ \dot{y} &= \dots \end{aligned}$$

BioModels Database



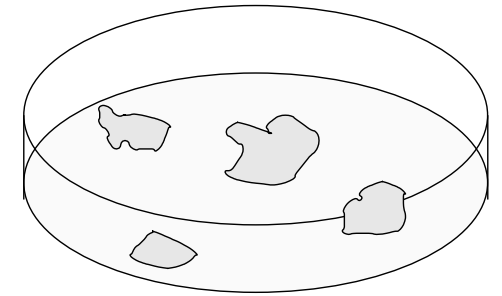
SBML



Overview

$$\begin{aligned}\dot{x} &= \dots \\ \dot{y} &= \dots\end{aligned}$$

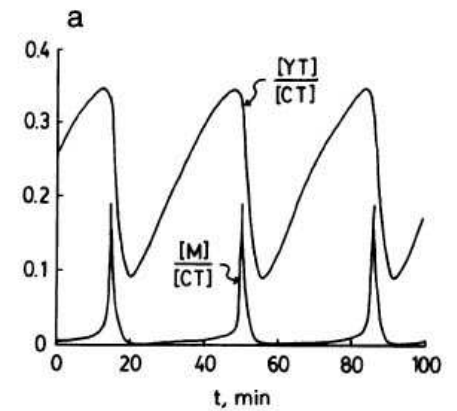
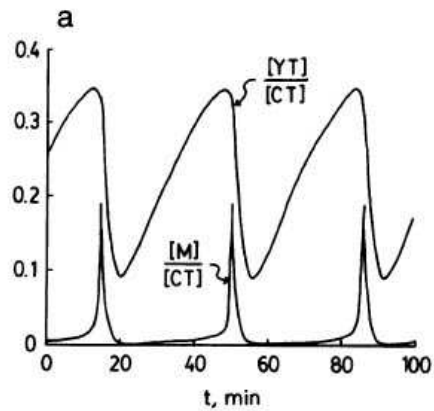
BioModels Database



SBML

BioModels Database

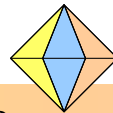
Sembiotics



Computer-Aided Modelling

- development
- curation
- retrieval
- composition
- integration
- usage
- modification

of bio-models



What do we Need?

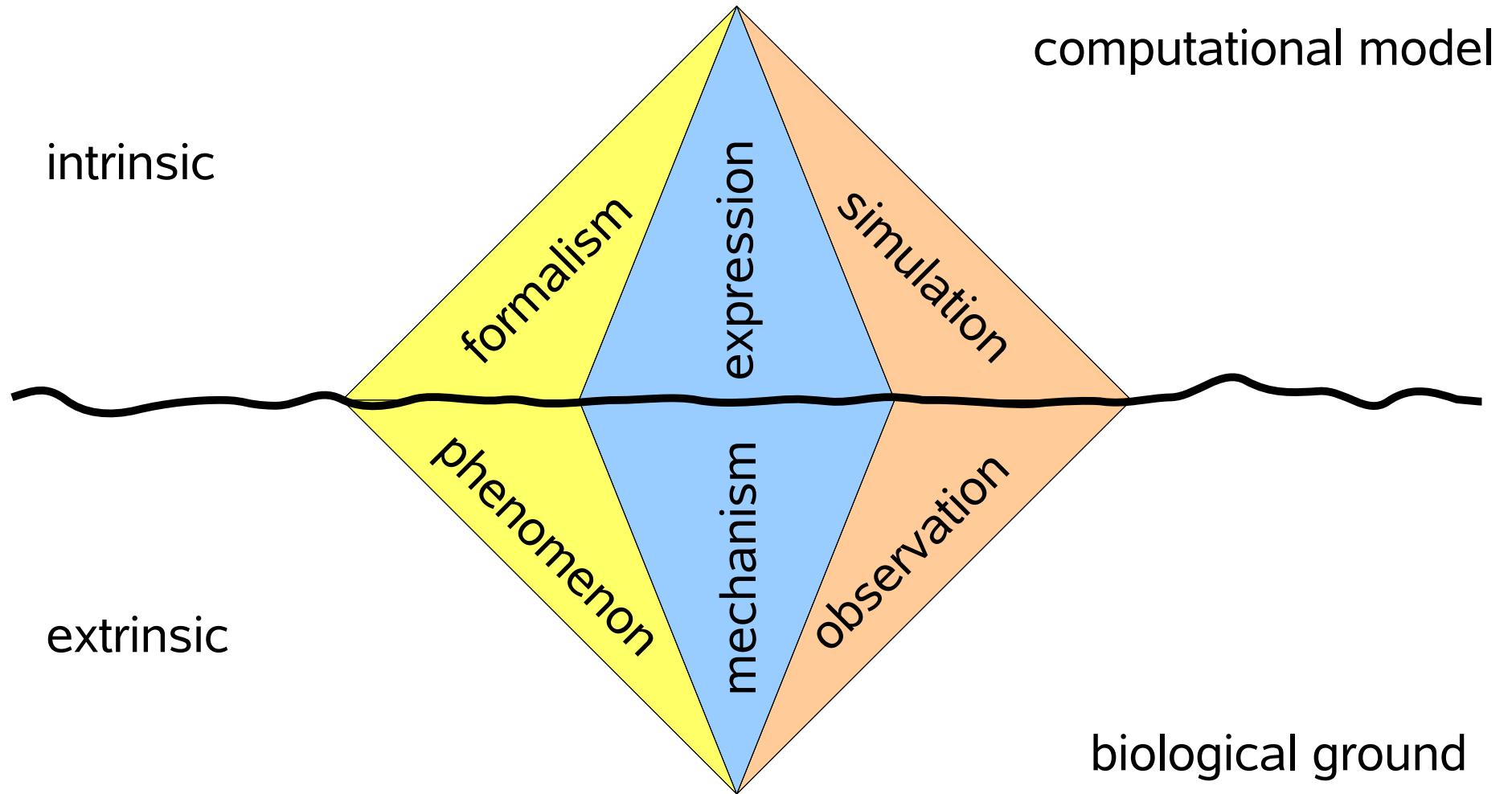
- computer-understanding
- reasoning

Formal Semantics

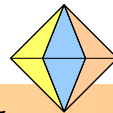
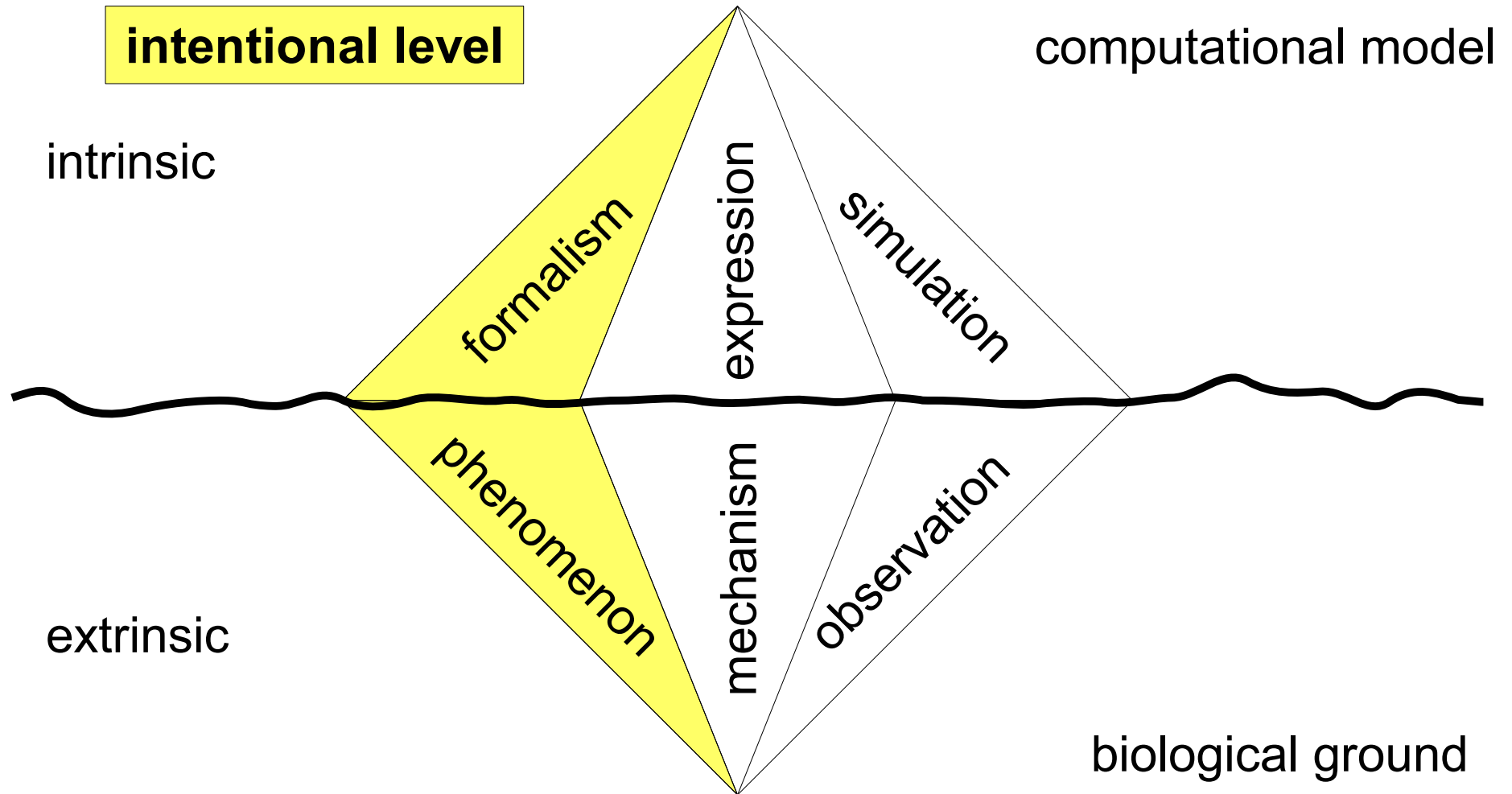
- all relevant aspects of the meaning
- relations between them
- rich model ontology



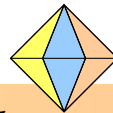
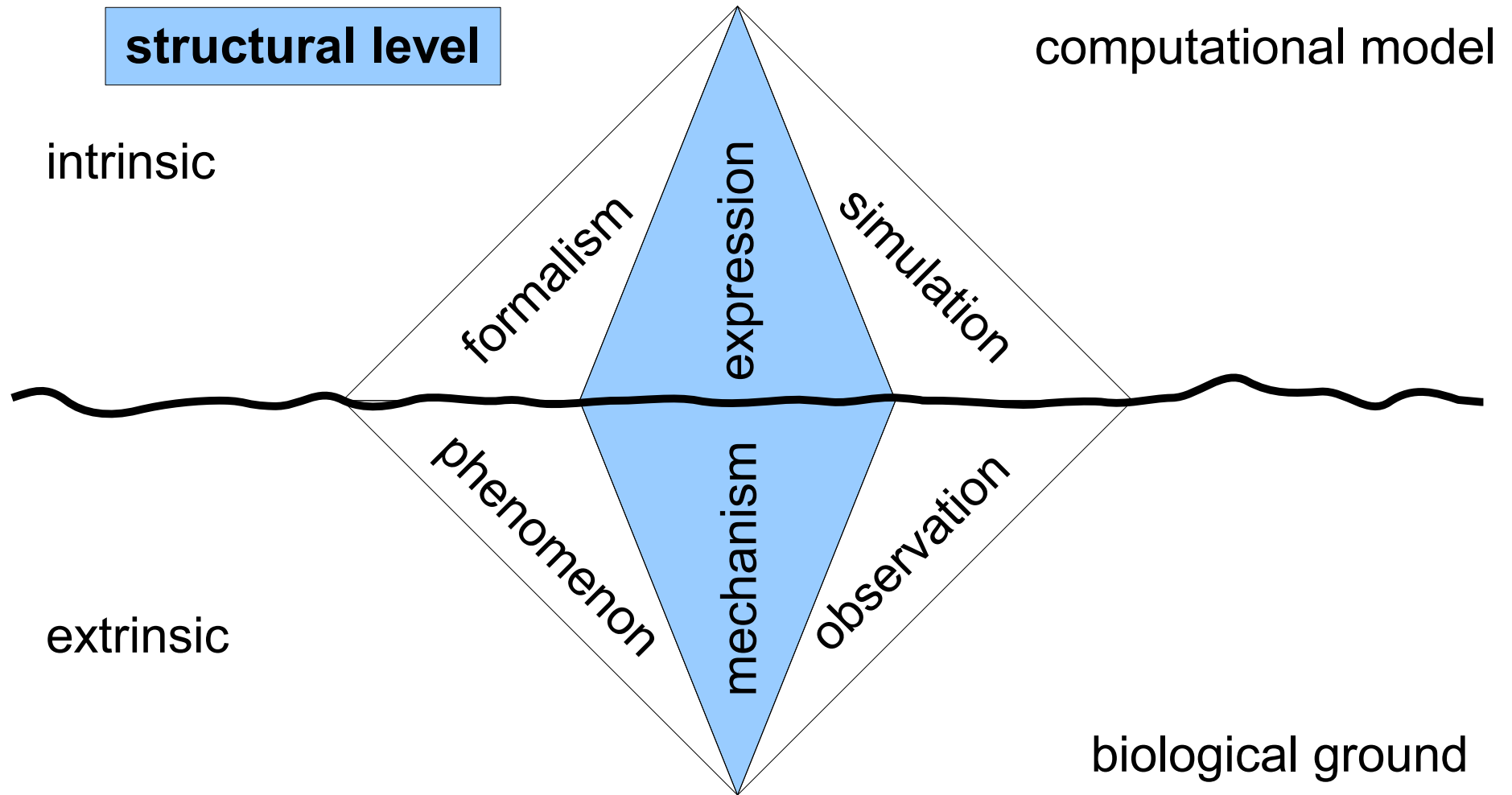
Meaning Facets



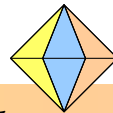
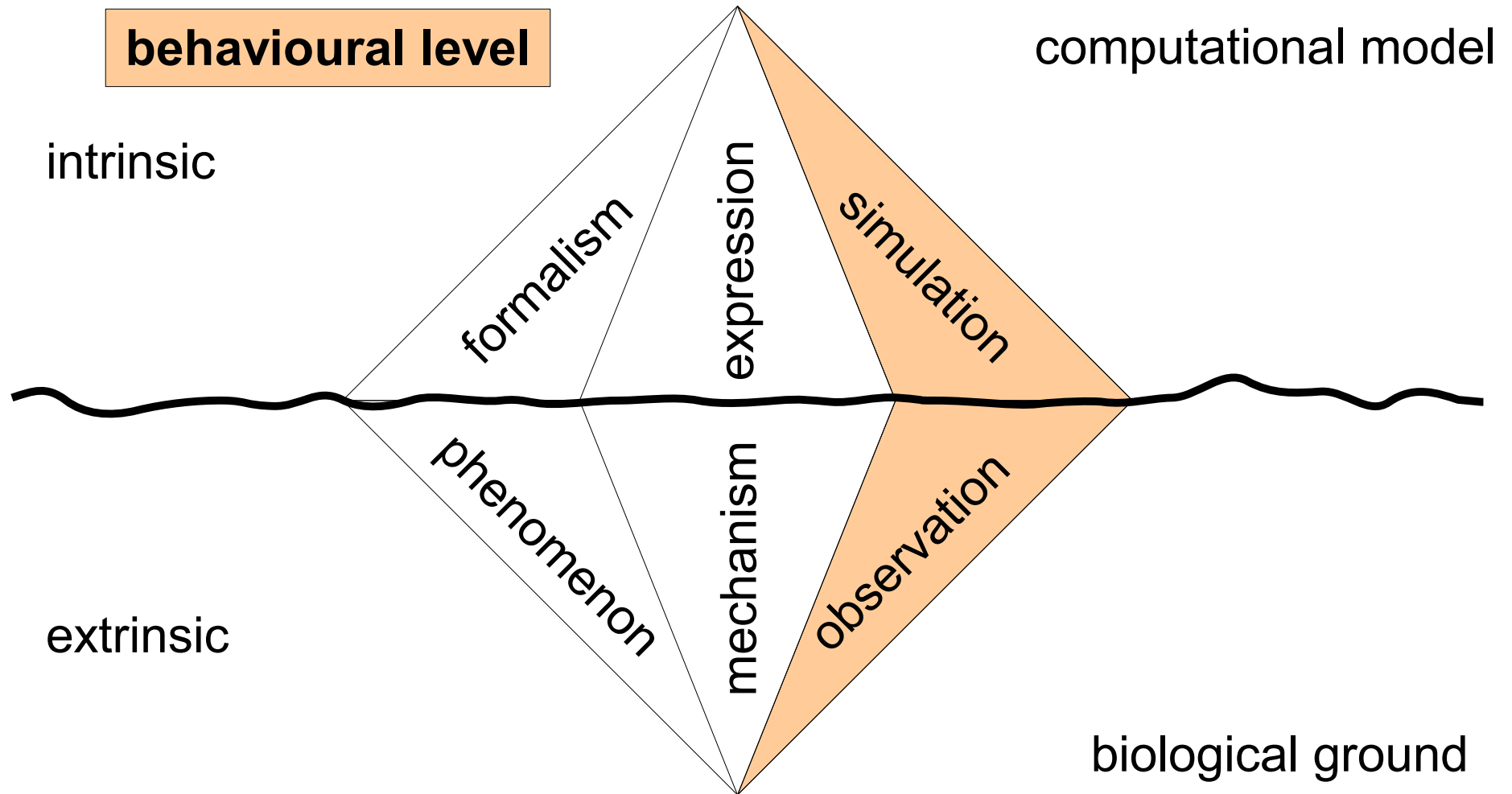
Meaning Facets



Meaning Facets



Meaning Facets



Sembiotics Framework

- formal specification of the meaning of bio-models
- commitment to meaning facets
- formal model ontology
- automated reasoning services



Sembiotics

*Bio-models as computational codes of
biological systems*



Sembiotics

*Bio-models as computational codes of
biological systems*



Sem**bio**tics

*Bio-models as computational codes of
biological systems*

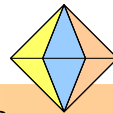


Common Goals

Improve

- access
- usage
- reuse
- exchange
- integration

of bio-models



Common Means

- precise
- explicit
- structured
- standardised
- concise

description of computational bio-models



Different Viewpoints

```
graph TD; A[Different Viewpoints] --> B[BioModels.net]; A --> C[Sembiotics];
```

BioModels.net

biologist viewpoint

model database for
modellers

Sembiotics

KR viewpoint

methodology for
formal model
descriptions



Case Study: Model 1

$$d[C2] / dt = k_6[M] - k_8[\sim P][C2] + k_9[CP] \quad (1)$$

$$d[CP] / dt = -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP] \quad (2)$$

$$d[pM] / dt = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M] \quad (3)$$

$$d[M] / dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M] \quad (4)$$

$$d[Y] / dt = k_1[aa] - k_2[Y] - k_3[CP][Y] \quad (5)$$

$$d[YP] / dt = k_6[M] - k_7[YP] \quad (6)$$

$$F([M]) = k'_4 + k_4([M]/[CT])^2 \quad (7)$$

$$[CT] = [C2] + [CP] + [pM] + [M] \quad (8)$$

Tyson1991_CellCycle_6var (BIOMD0000000005)



Case Study: Model 2

$$du/dt = k_4(\nu - u)(\alpha + u^2) - k_6u \quad (9)$$

$$d\nu/dt = (k_1[aa]/[CT]) - k_6u \quad (10)$$

$$u = [M]/[CT] \quad (11)$$

$$\nu = ([Y] + [pM] + [M])/[CT] \quad (12)$$

$$[CT] = [C2] + [CP] + [pM] + [M] \quad (13)$$

$$\alpha = k'_4/k_4 \quad (14)$$

Tyson1991_CellCycle_2var (BIOMD0000000006)



Mathematical Structure

$$\frac{du}{dt} = k_4(\nu - u)(\alpha + u^2) - k_6u$$
$$u = [M]/[CT]$$

ID	Description	Relation	Type	Subject
<i>u</i>	relative [M]	is_a	MO	Variable
M	YP_C2	is_a	MO	Substance
		has_part	THIS	C2, YP
CT	total cdc2k	is_a	MO	Substance
		has_prop	MO	\forall has_part.C2



Behavioural Modes

behavioural meaning facets of *Model 1*

ID	Description	Relation	Type	Subject
B1	steady state with high values of [M]	inst_of	MO	Attractor(Fixed_Point, PS1)
		has_prop	MO	Constraint(high([M]))
		represents	THIS	BP1
BP1	metaphase arrest	is_a	MO	Biological_Phenomenon
		part_of	GO	GO:0051323 (metaphase)
		is_a	GO	GO:0007050 (cell cycle arrest)
B2	spontaneous oscillation	inst_of	MO	Attractor(Limit_Cycle, PS2)
		represents	THIS	BP2
BP2	rapid division cycles in early embryos	is_a	MO	Biological_Phenomenon
		is_a	GO	GO:0040016 (embryonic cleavage)



Parameter Settings

ID	Description	Relation	Type	Subject
PS0	standard parameter setting	inst_of	MO	Constraint($[\sim P] = const., [aa] = const.,$ $k_1[aa]/[CT] = 0.015, k_2 = 0, k_3[CT] = 200,$ $10 \leq k_4 \leq 1000, k'_4 = 0.018, k_5[\sim P] = 0,$ $0.1 \leq k_6 \leq 10, k_7 = 0.6, k_8[\sim P] \gg k_9 \gg k_6$)
PS1	parameter setting for steady state	inst_of	MO	Constraint(PS0, $k_1[aa]/k_6[CT] > \sqrt{k_6/k_4}$)
PS2	parameter setting for spontaneous oscillation	inst_of	MO	Constraint(PS0, $\sqrt{k'_4/k_4} < k_1[aa]/k_6[CT] < \sqrt{k_6/k_4}$)
PS3	parameter setting for excitable switch	inst_of	MO	Constraint(PS0, $k_1[aa]/k_6[CT] < \sqrt{k'_4/k_4}$)



Relations between Models

intentional meaning facets of *Model 2*

ID	Description	Relation	Type	Subject
M2	Model 2	inst_of	MO	Model(SE2, BP0)
		inst_of	MO	Projection(Specialisation(M1,C1),{u,v})
SE2	ODE system of M2	inst_of	MO	ODE_System(equations (9)-(14) of <i>Model 2</i>)
BP0	interaction between C2 and Y forming M	is_a	MO	Biological_Phenomenon
		is_a	GO	GO:0051726 (regulation of cell cycle)
C1		inst_of	MO	Constraint(PS0, $\alpha = k'_4/k_4$, $0 < \nu < 1$)



Direct Benefits

Extensions of the BioModels Database:

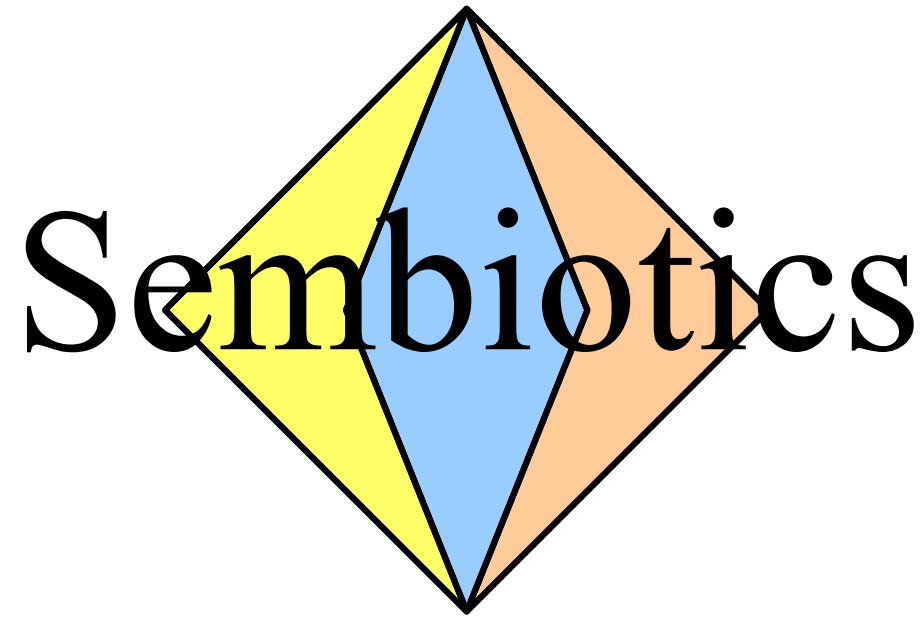
- behavioural level
- mathematical structure
- assumptions, parameter settings
- relations between models



Conclusion/Outlook

- BioModels.net and Sembiotics are complementary.
- They can benefit from each other.
- Computer-aided modelling needs formal semantics of bio-models.
- Sembiotics will provide the conceptual and methodological framework.





<http://www.informatik.uni-jena.de/csb/prj/symbiotics/>