BIOMODEL ENGINEERING FOR SYSTEMS AND SYNTHETIC BIOLOGY

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SYSTEMS BIOLOGY

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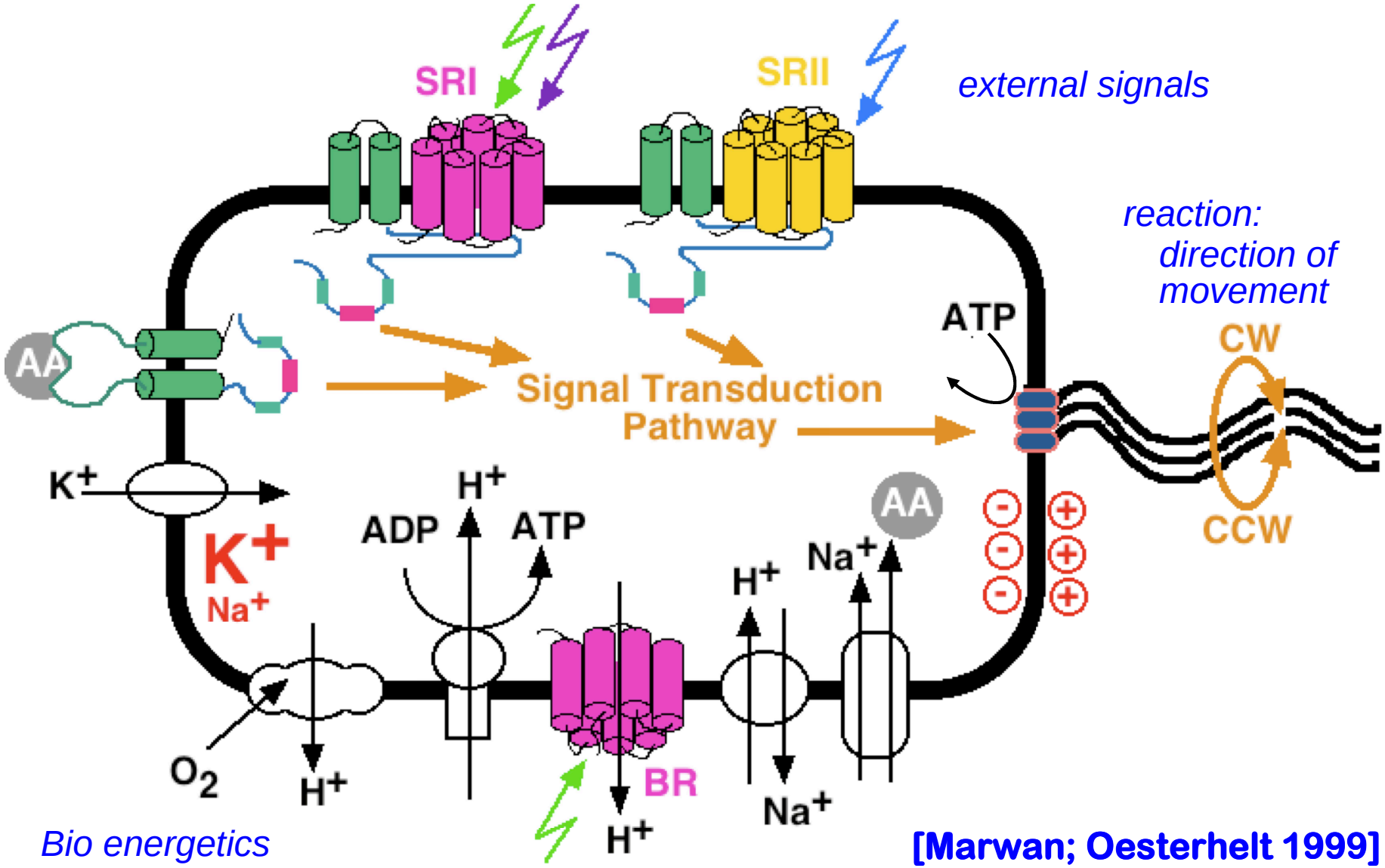
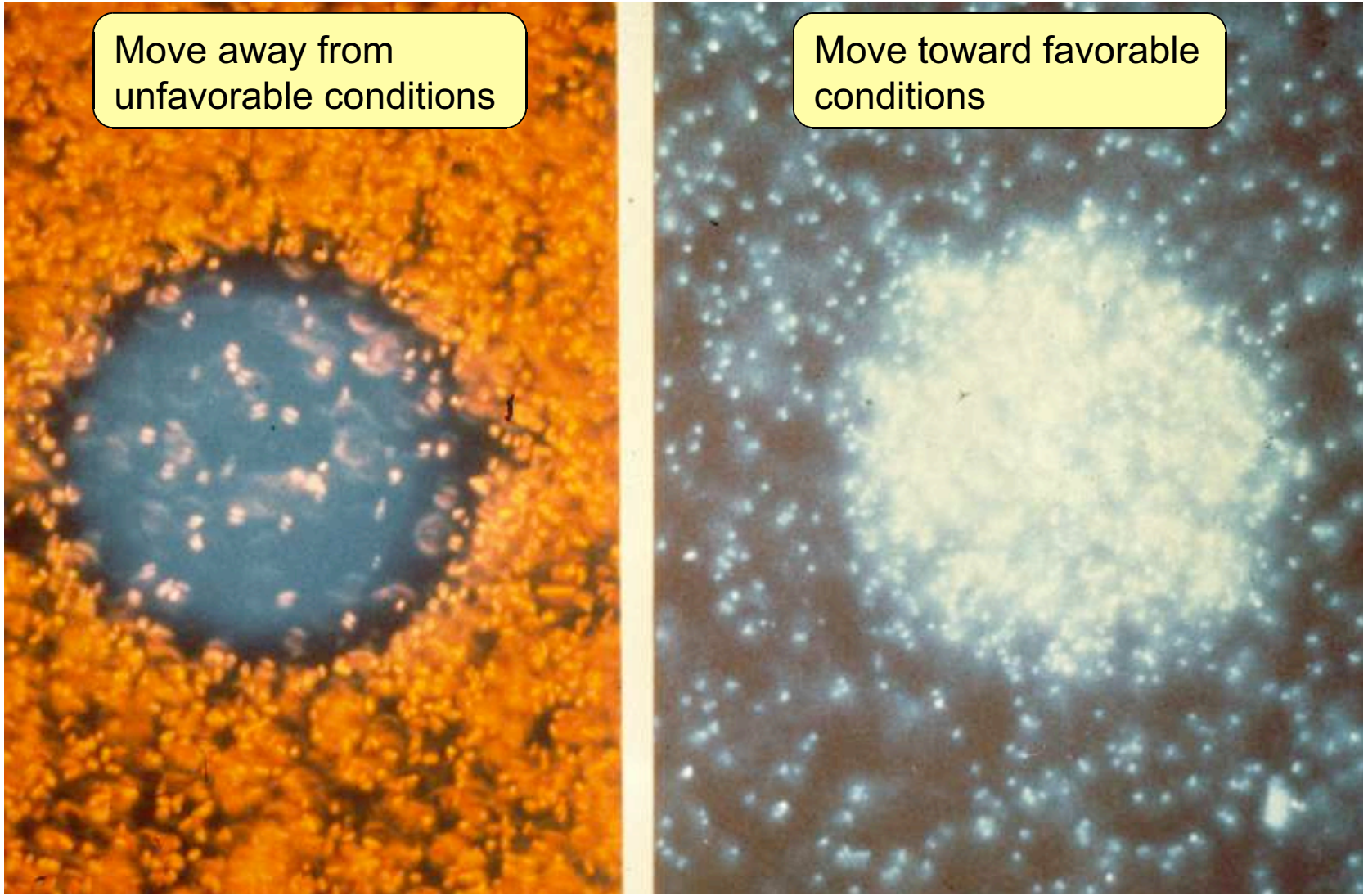
MODEL ORGANSIM - HALOBACTERIUM SALINARUM



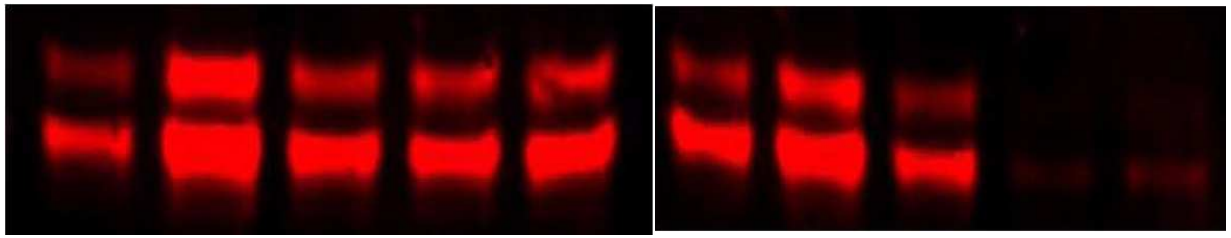
Bio energetics

[Marwan; Oesterhelt 1999]

HALO BACTERIUM - BEHAVIOUR



WETLAB EXPERIMENTS - OBSERVED BEHAVIOUR



colours distorted

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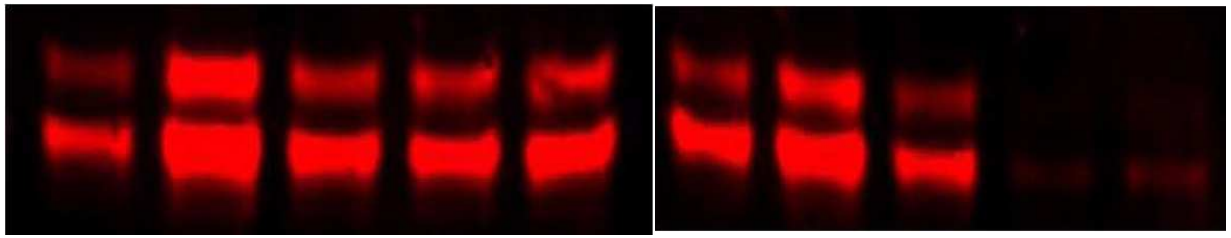

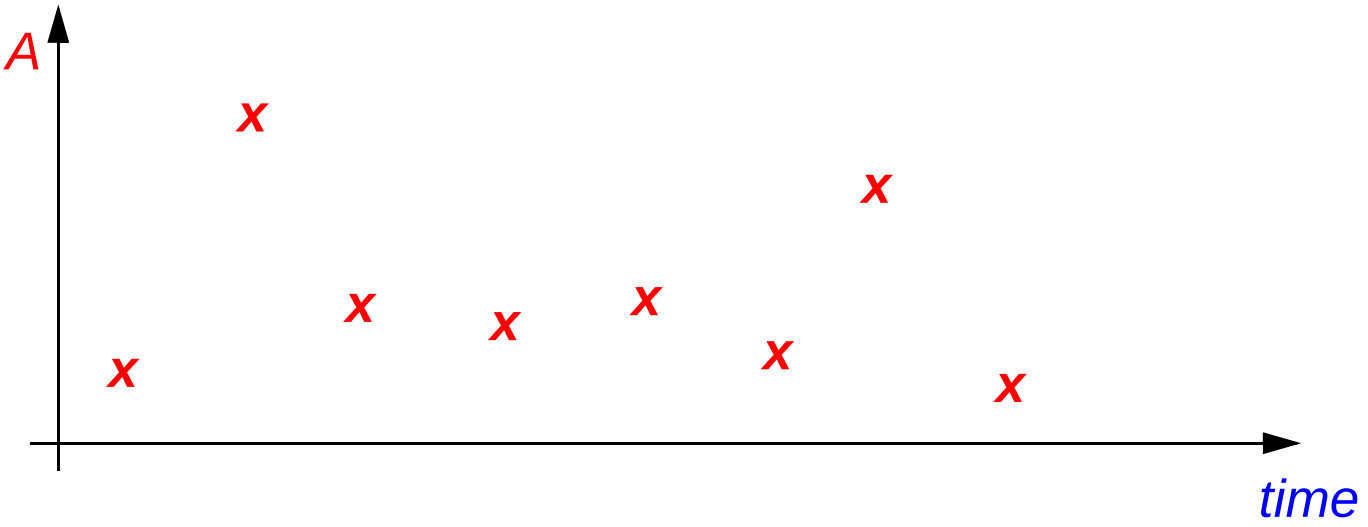

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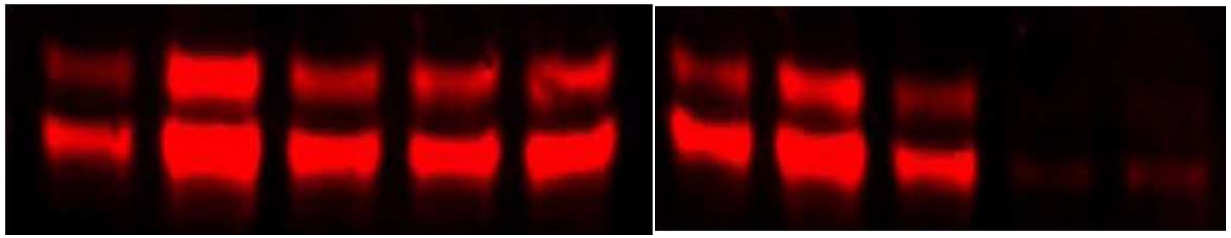

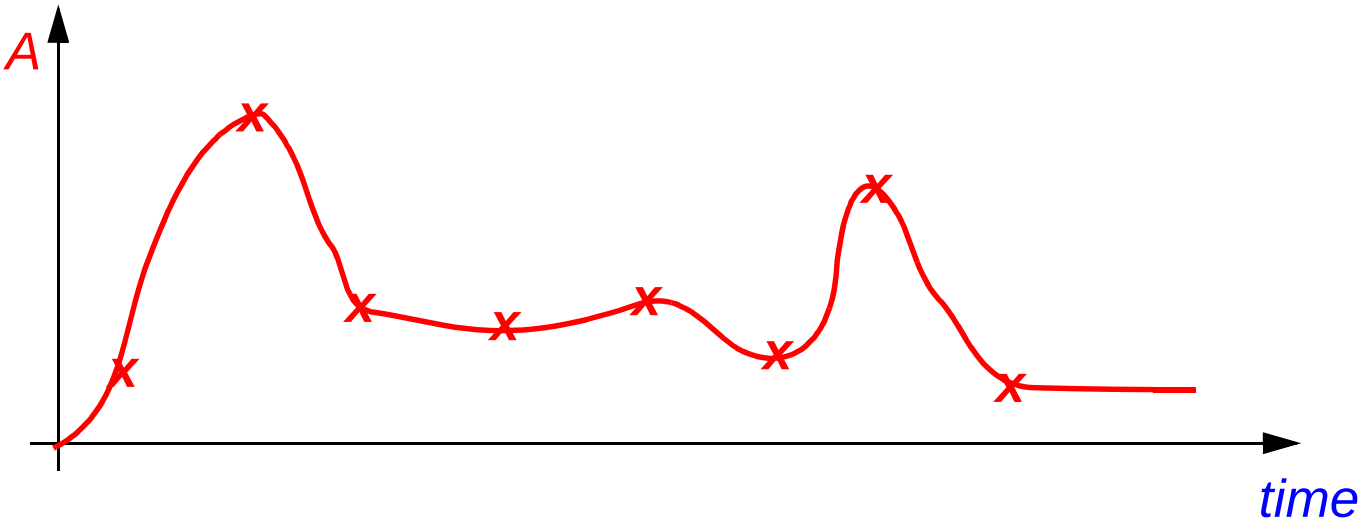

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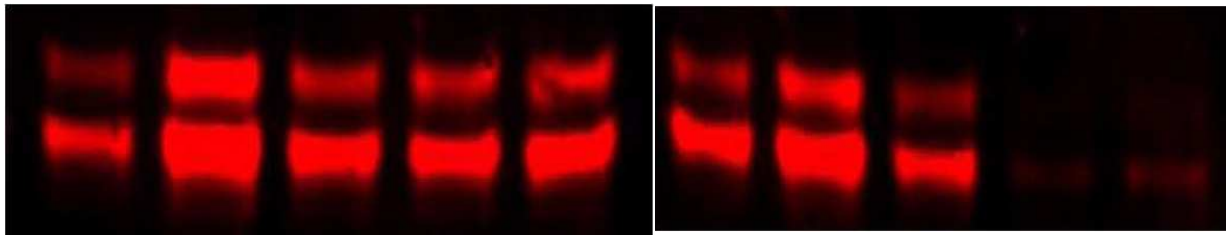

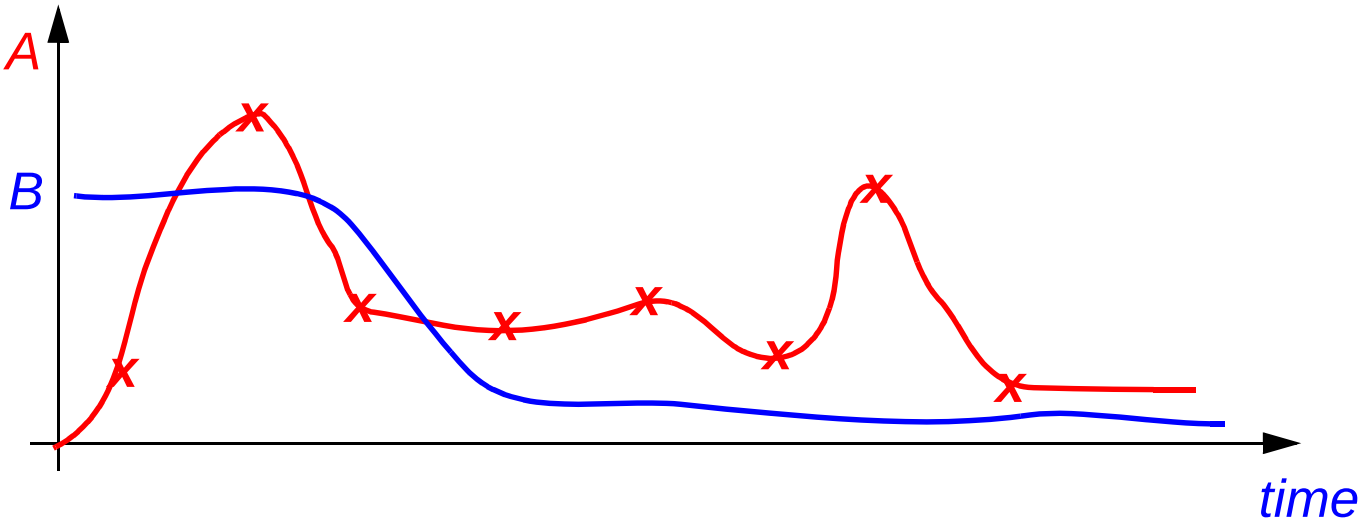

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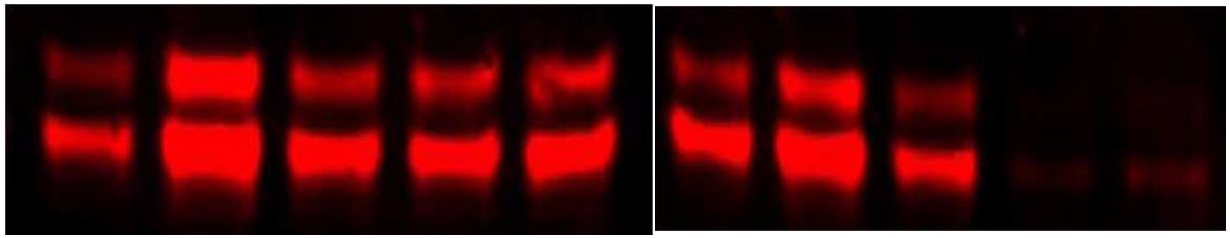

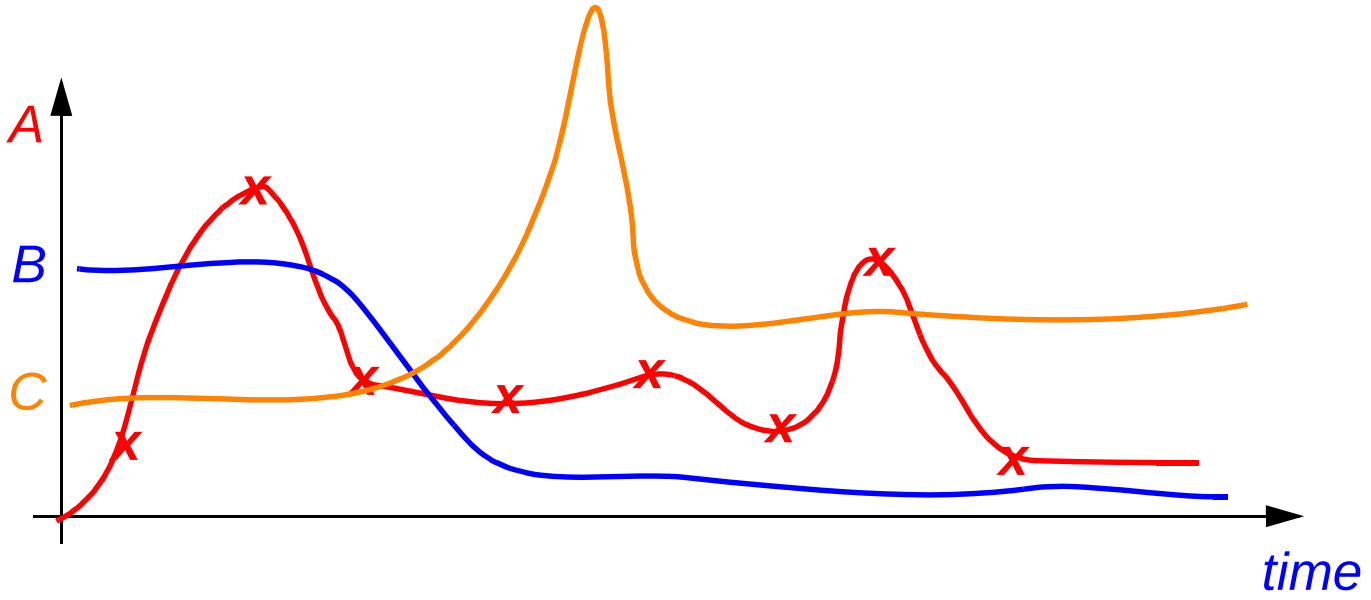

Qualitative

Protein A rises, then falls before rising again.

Protein B starts decreasing after the first peak of A until it reaches its steady state.

Protein C peaks between the two peaks of A.

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- **Semi-qualitative**

  Protein rises then falls to less than 50% of its peak concentration.

- **Qualitative**

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- **Semi-qualitative**

  Protein rises then falls to less than 50% of its peak concentration.

- **Semi-quantitative**

  Protein rises then falls to less than 50% of its peak concentration at 60 minutes.

WETLAB EXPERIMENTS - OBSERVED BEHAVIOUR

- **Qualitative**

  Protein A rises, then falls before rising again.

  Protein B starts decreasing after the first peak of A until it reaches its steady state.

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- **Semi-qualitative**

  Protein rises then falls to less than 50% of its peak concentration.

- **Semi-quantitative**

  Protein rises then falls to less than 50% of its peak concentration at 60 minutes.

- **Quantitative**

  Protein rises then falls to less than 100 microMol at 60 minutes.

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  Protein A rises, then falls before rising again.

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- **Quantitative**

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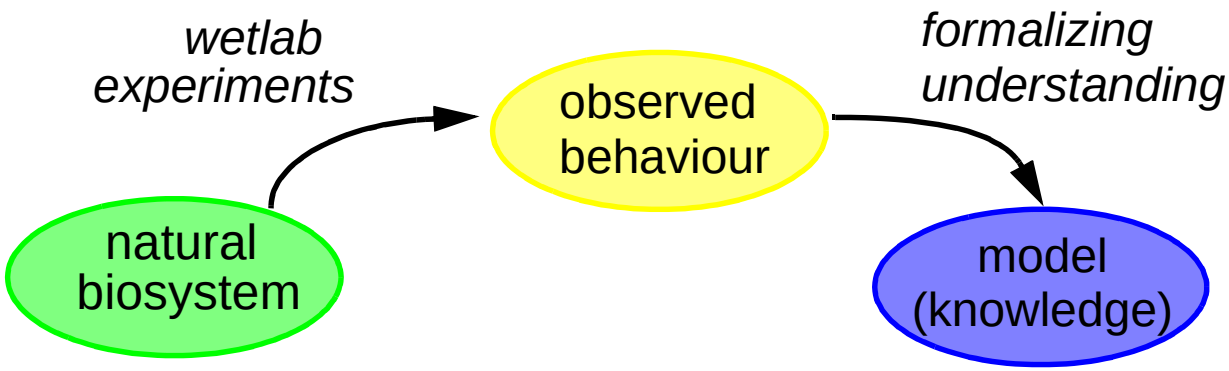
Models explaining these observations ?

MODELLING = FORMAL KNOWLEDGE REPRESENTATION



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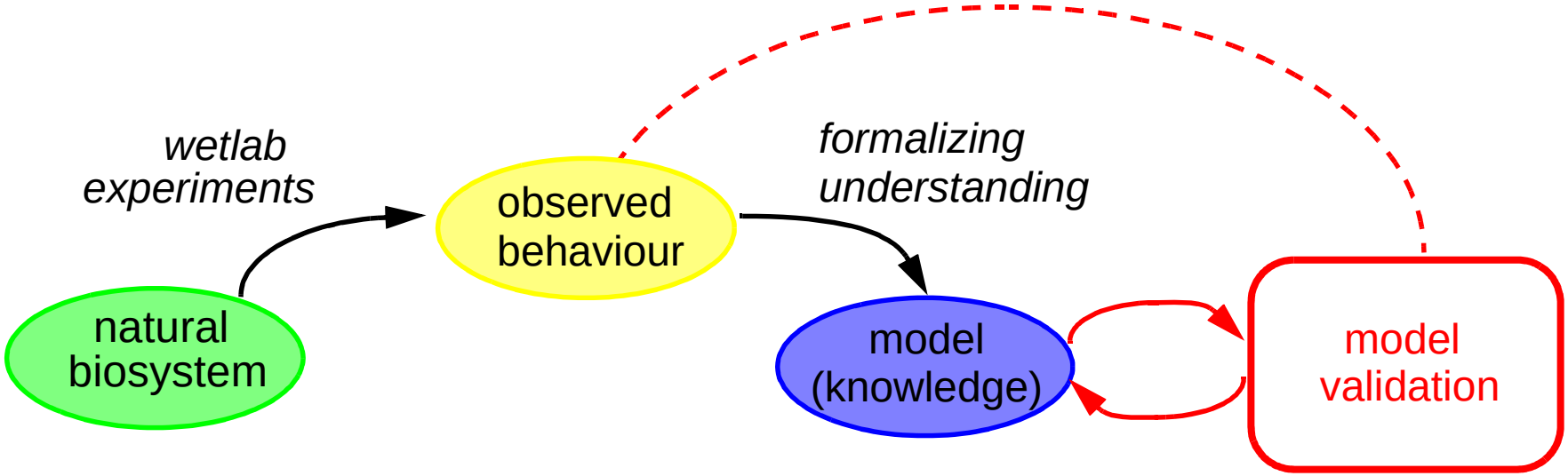
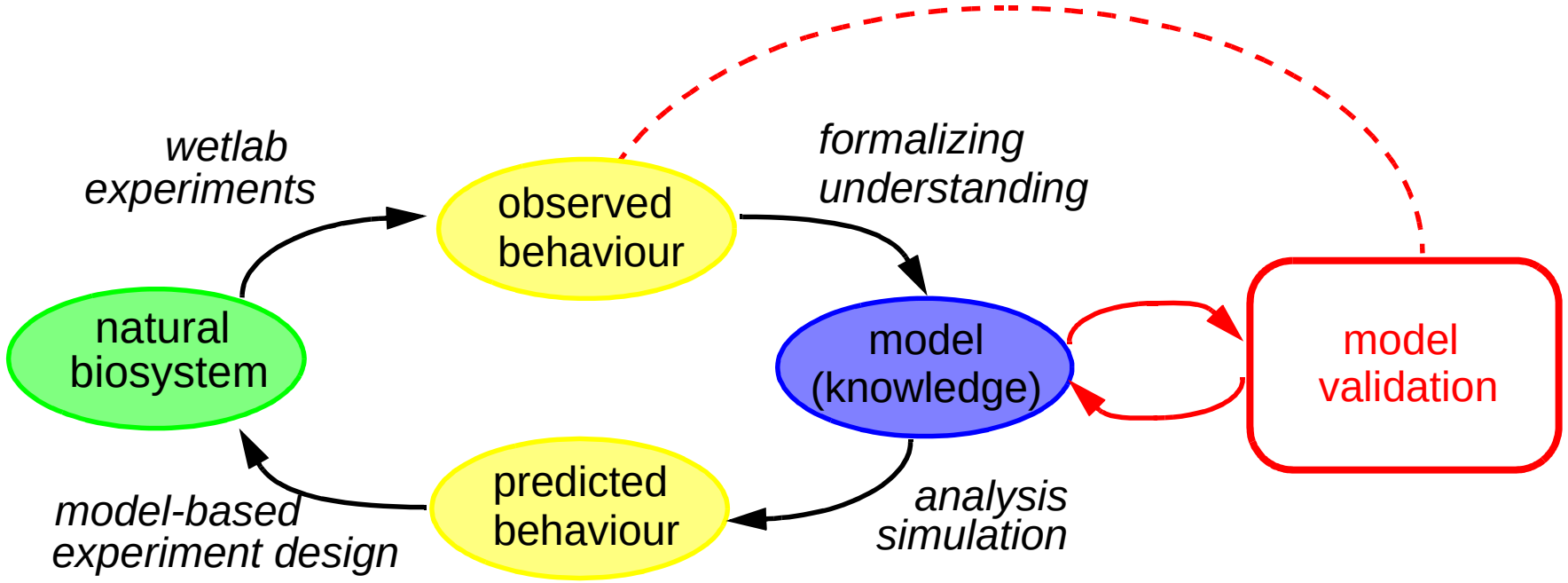


MODEL VALIDATION = CONFIDENCE INCREASE

MODELLING = FORMAL KNOWLEDGE REPRESENTATION



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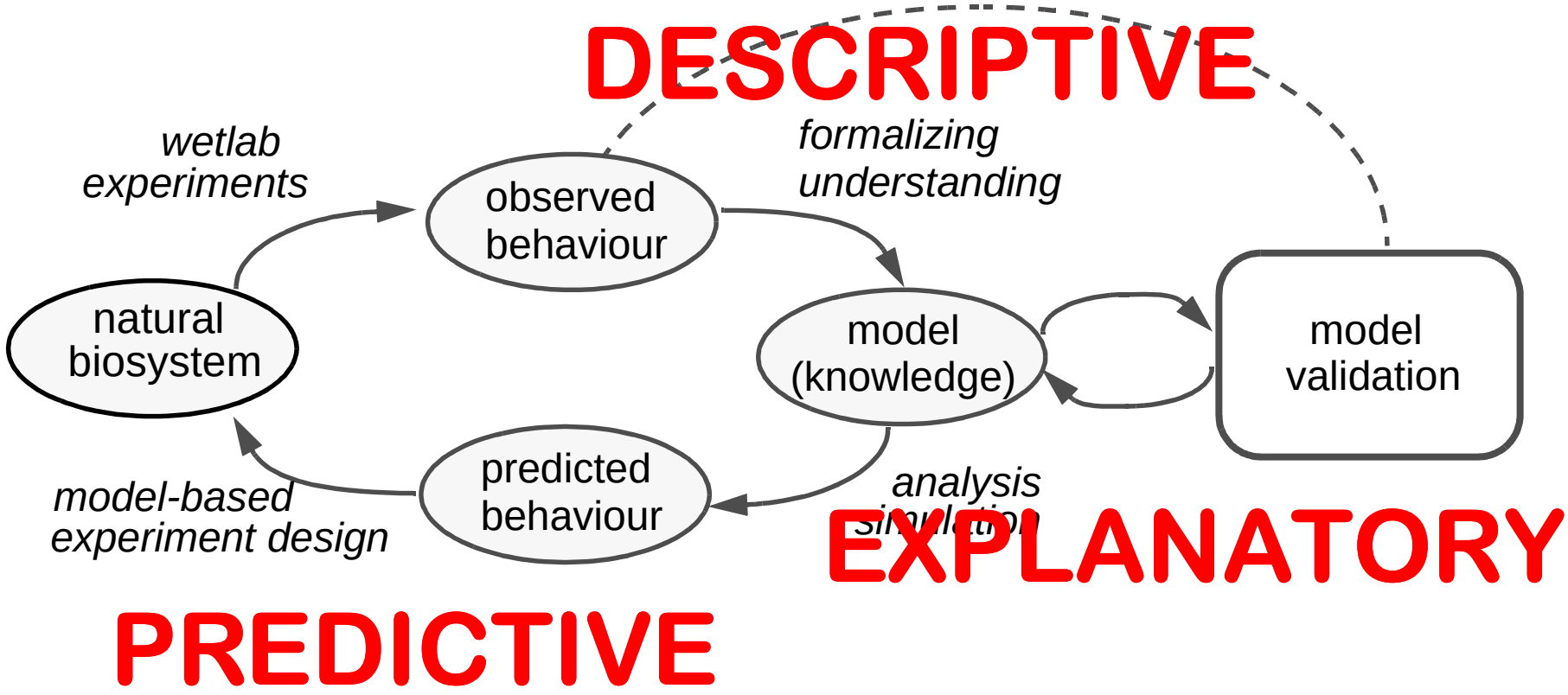
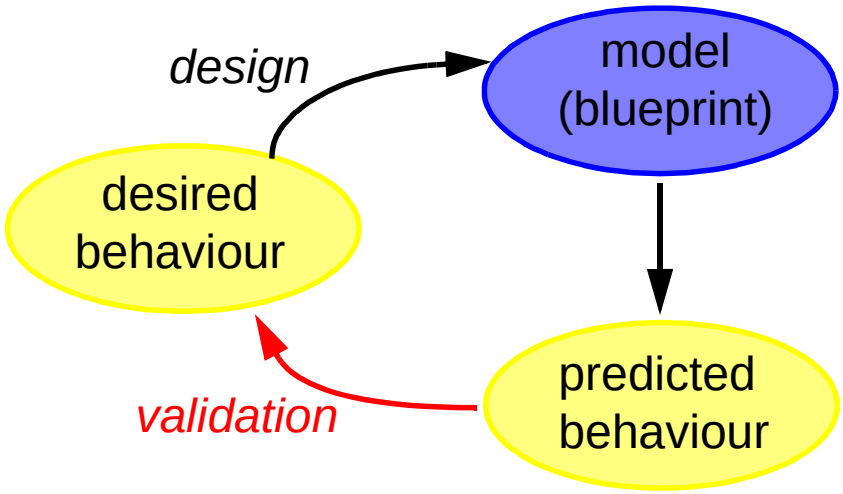


MODEL VALIDATION = CONFIDENCE INCREASE

MODELLING = BLUEPRINT FOR SYSTEM CONSTRUCTION



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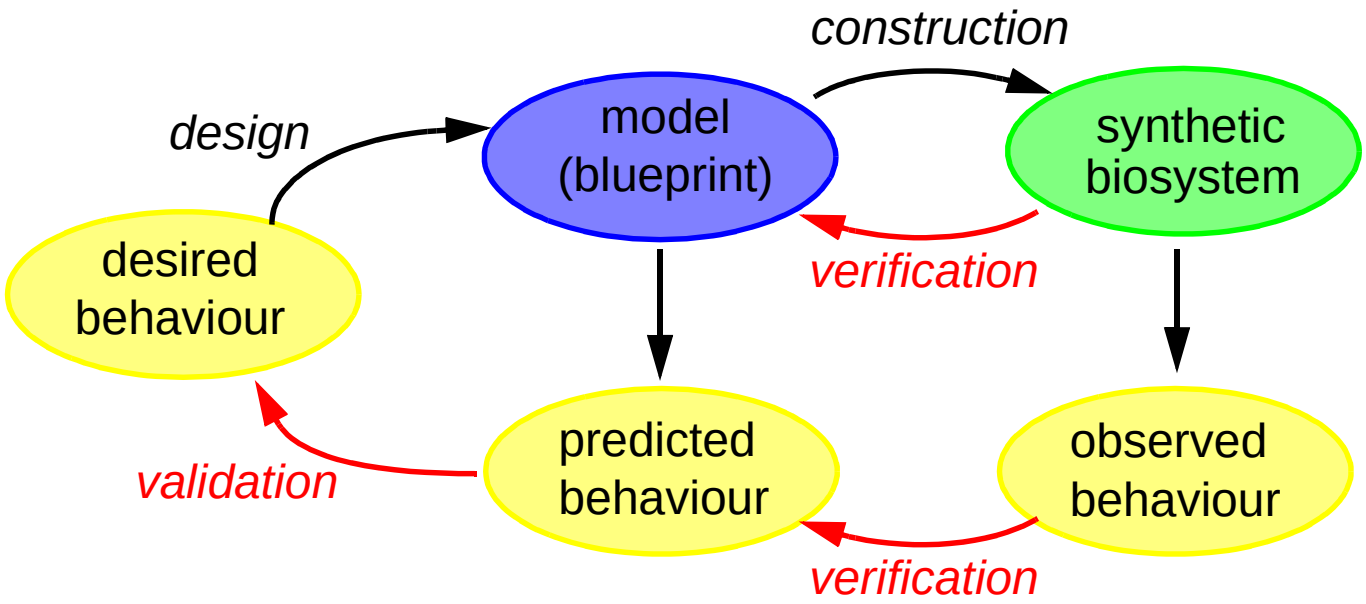

RELIABLE AND ROBUST ENGINEERING REQUIRES VERIFIED MODELS

WHAT KIND OF MODEL SHOULD BE USED?

(BIOCHEMICAL NETWORKS)

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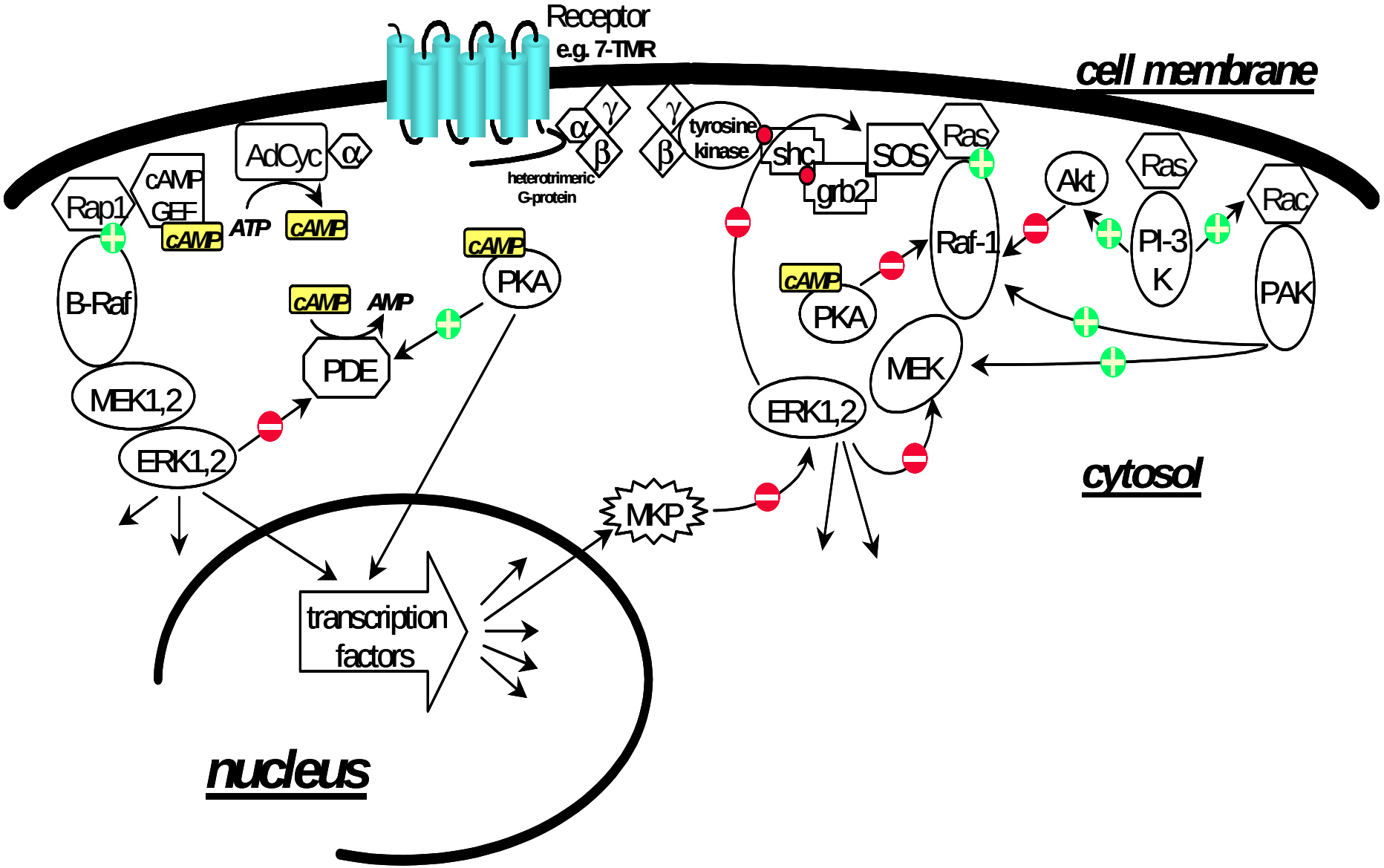
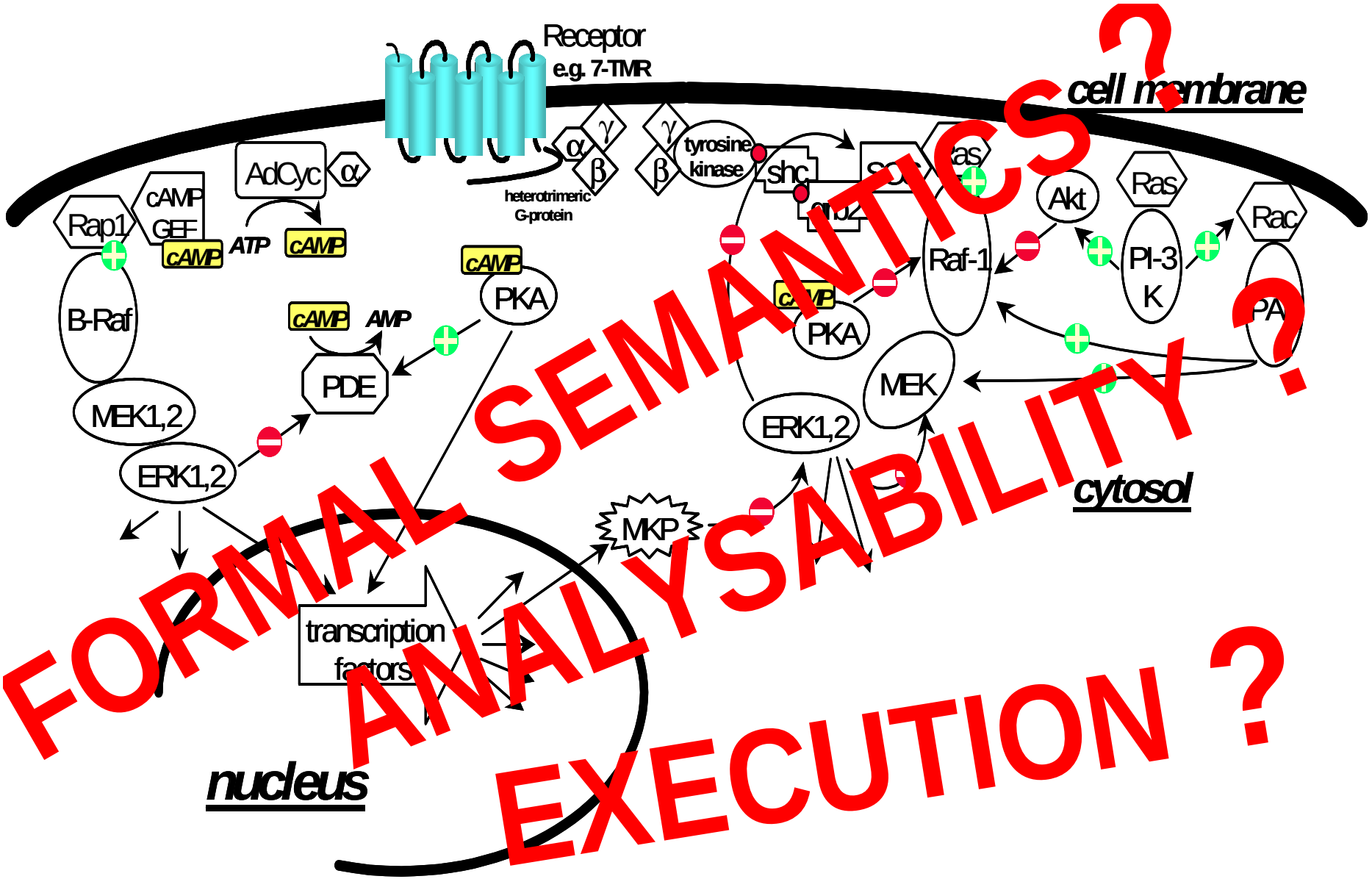
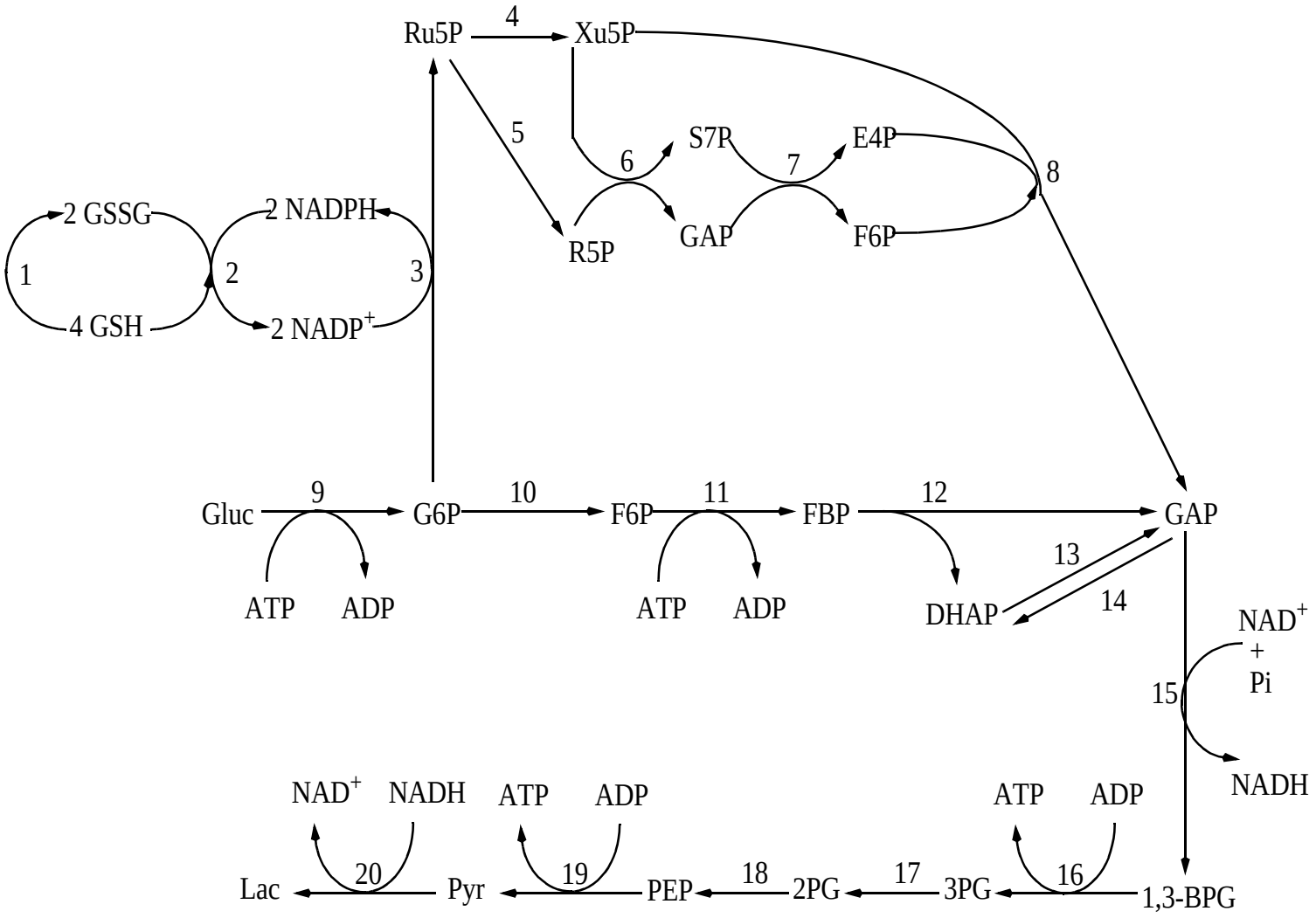
NETWORK REPRESENTATIONS, EX1

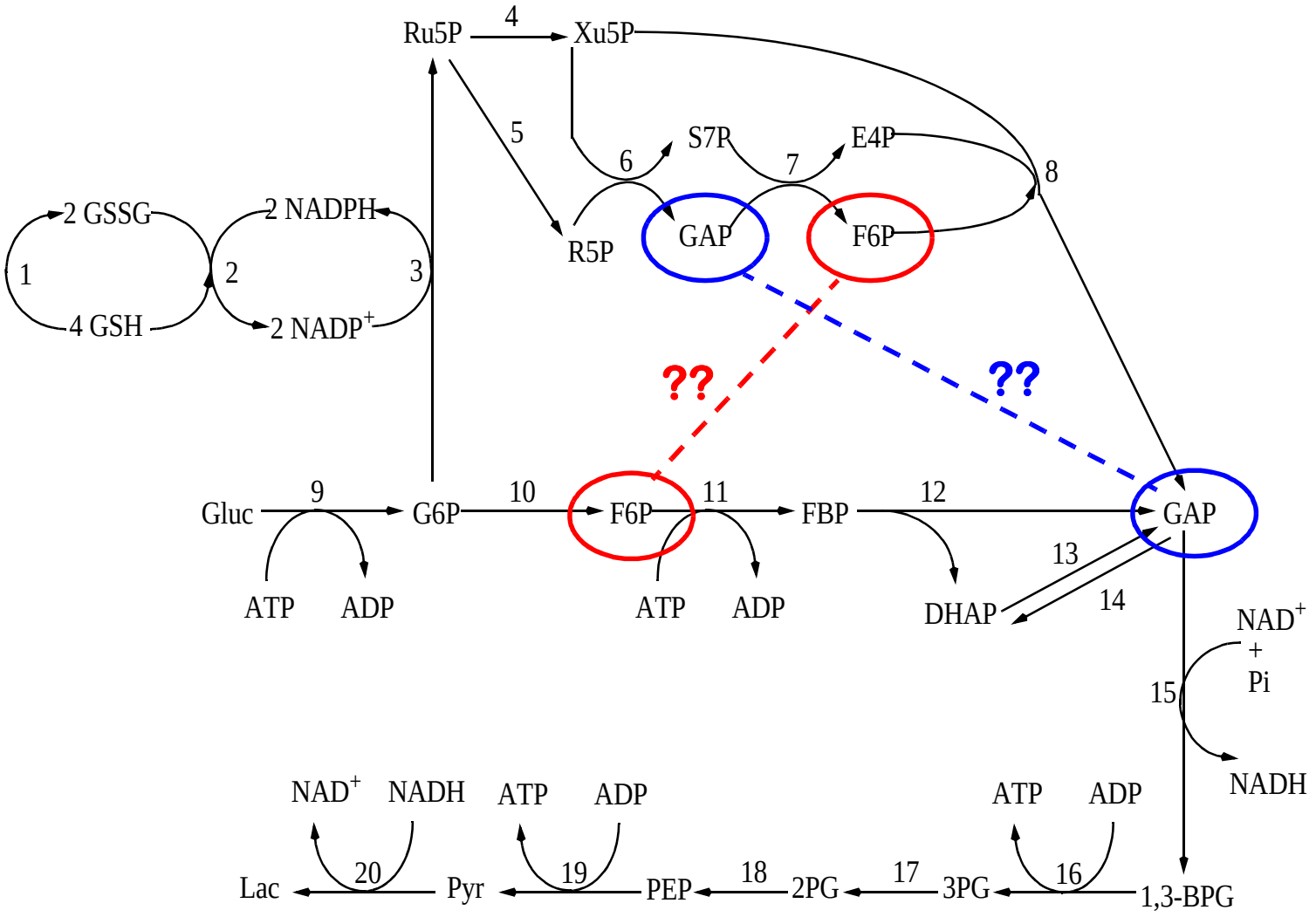



Receptor
e.g. 7-TMR
cell membrane
heterotrimeric
G-protein
tyrosine
kinase
shc
AdCyc
cAMP
GEF
ATP
Rap1
B-Raf
MEK1,2
ERK1,2
PDE
AMP
PKA
Raf-1
Akt
Ras
PI-3
K
Rac
MEK
MKP
transcription
factors
cytosol
nucleus
FORMAL SEMANTICS ?
ANALYSABILITY ?
EXECUTION ?

[Reddy 1993]

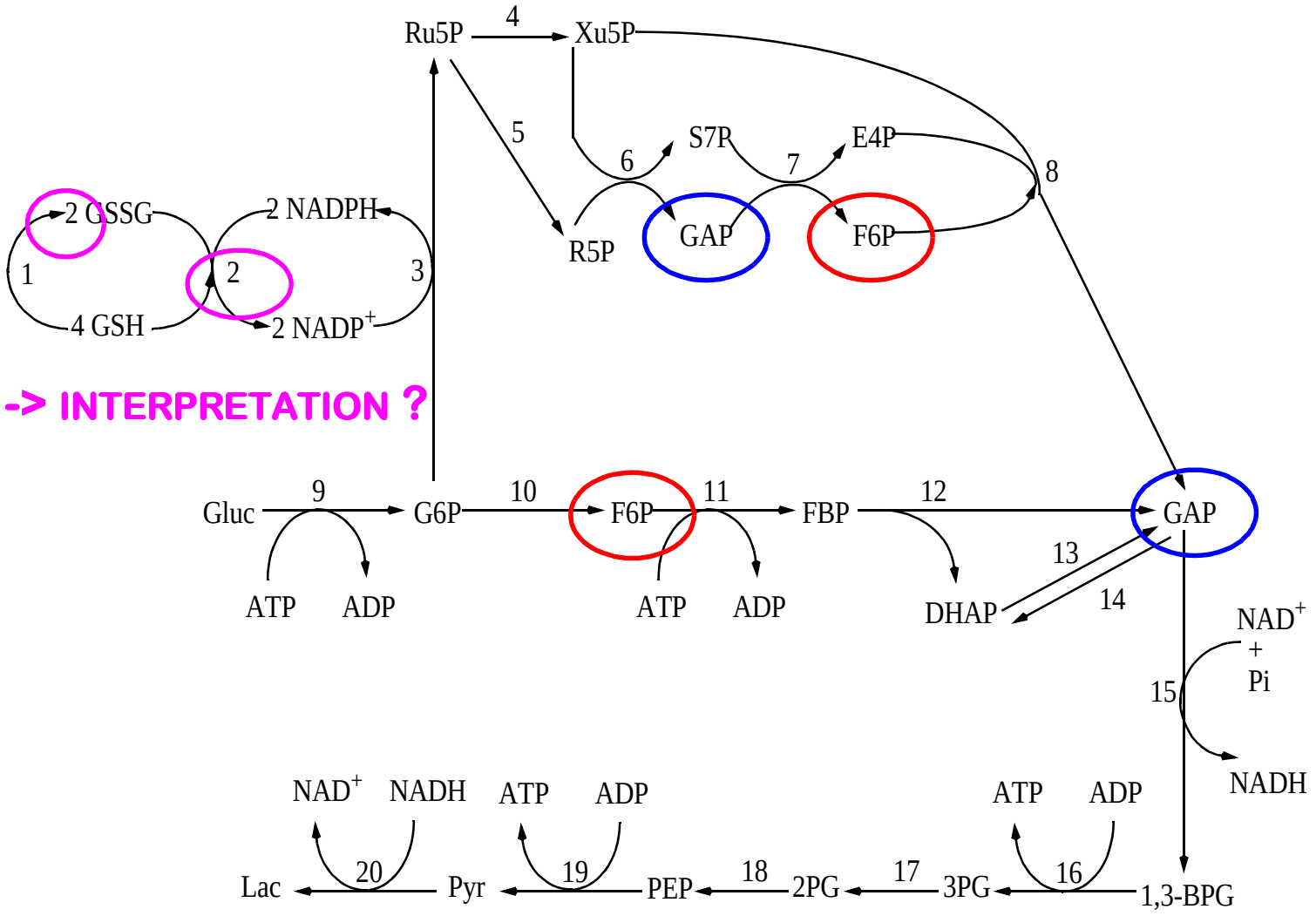

Ru5P
4
Xu5P
5
6
S7P
7
E4P
8
R5P
GAP
F6P
2 GSSG
2 NADPH
1
2
3
4 GSH
2 NADP+
Gluc
9
G6P
10
F6P
11
FBP
12
GAP
ATP
ADP
ATP
ADP
DHAP
13
14
NAD+
+
Pi
15
NADH
NAD+
NADH
ATP
ADP
ATP
ADP
Lac
20
Pyr
19
PEP
18
2PG
17
3PG
16
1,3-BPG

[Reddy 1993]


Ru5P
4
Xu5P
5
6
S7P
7
E4P
8
R5P
GAP
F6P
2 GSSG
2 NADPH
1
2
3
4 GSH
2 NADP+
??
??
Gluc
9
G6P
10
F6P
11
FBP
12
GAP
ATP
ADP
ATP
ADP
DHAP
13
14
NAD+
+
Pi
15
NADH
NAD+
NADH
ATP
ADP
ATP
ADP
Lac
20
Pyr
19
PEP
18
2PG
17
3PG
16
1,3-BPG

NETWORK REPRESENTATIONS, EX2

[Reddy 1993]



$$\frac{d\alpha}{dt} = -v_1$$
$$\frac{dSte2}{dt} = -v_2 + v_3 - v_5$$
$$\frac{dSte2_{active}}{dt} = v_2 - v_3 - v_4$$
$$\frac{dSst2_{active}}{dt} = v_{46} - v_{47}$$
$$\frac{dG\alpha\beta\gamma}{dt} = -v_6 + v_9$$
$$\frac{dG\alpha GTP}{dt} = v_6 - v_7 - v_8$$
$$\frac{dG\alpha GDP}{dt} = v_7 + v_8 - v_9$$
$$\frac{dG\beta\gamma}{dt} = v_6 - v_9 - v_{10} + v_{11} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} - v_{42} + v_{43}$$
$$\frac{dSte5}{dt} = -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$
$$\frac{dSte11}{dt} = -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$
$$\frac{dSte7}{dt} = -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$
$$\frac{dFus3}{dt} = -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} - v_{29} + v_{30} + v_{33}$$
$$\frac{dSte20}{dt} = -v_{18} + v_{19} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$

$$v_1 = \alpha[t] \cdot Bar1_{active}[t] \cdot k_1$$
$$v_2 = Ste2[t] \cdot \alpha[t] \cdot k_2$$
$$v_3 = Ste2_{active}[t] \cdot k_3$$
$$v_4 = Ste2_{active}[t] \cdot k_4$$
$$v_5 = Ste2[t] \cdot k_5$$
$$v_6 = Ste2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$
$$v_7 = G\alpha GTP[t] \cdot k_7$$
$$v_8 = G\alpha GTP[t] \cdot Sst2_{active}[t] \cdot k_8$$
$$v_9 = G\alpha GDP[t] \cdot G\beta\gamma[t] \cdot k_9$$
$$v_{10} = G\beta\gamma[t] \cdot C[t] \cdot k_{10}$$
$$v_{11} = D[t] \cdot k_{11}$$
$$v_{12} = Ste5[t] \cdot Ste11[t] \cdot k_{12}$$
$$v_{13} = A[t] \cdot k_{13}$$
$$v_{14} = Ste7[t] \cdot Fus3[t] \cdot k_{14}$$
$$v_{15} = B[t] \cdot k_{15}$$
$$v_{16} = A[t] \cdot B[t] \cdot k_{16}$$
$$v_{17} = C[t] \cdot k_{17}$$
$$v_{18} = D[t] \cdot Ste20[t] \cdot k_{18}$$

$$\frac{d\alpha}{dt} = -\nu_1$$

$$\frac{dSte2}{dt} = -\nu_2 + \nu_3 - \nu_5$$

$$\frac{dSte2_{active}}{dt} = \nu_2 - \nu_3 - \nu_4$$

$$\frac{dSst2_{active}}{dt} = \nu_{46} - \nu_{47}$$

$$\frac{dG\alpha\beta\gamma}{dt} = -\nu_6 + \nu_9$$

$$\frac{dG\alpha GTP}{dt} = \nu_6 - \nu_7 - \nu_8$$

$$\frac{dG\alpha GDP}{dt} = \nu_7 + \nu_8 - \nu_9$$

$$\frac{dG\beta\gamma}{dt} = \nu_6 - \nu_9 - \nu_{\cdot} + \nu_{\cdot} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32} - \nu_{42} + \nu_{43}$$

$$\frac{dSte5}{dt} = -\nu_{12} + \nu_{\cdot} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$

$$\frac{d\cdot}{dt} = -\nu_{\cdot} + \nu_{13} + \nu_{17} + \nu_{21} + \nu_{\cdot} + \nu_{25} + \nu_{27} + \nu_{32}$$

$$\frac{d\cdot}{dt} = -\nu_{14} + \nu_{15} + \nu_{17} + \nu_{\cdot} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$

$$\frac{dFus3}{dt} = -\nu_{14} + \nu_{15} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} - \nu_{29} + \nu_{30} + \nu_{33}$$

$$\frac{dSte\cdot}{dt} = -\nu_{\cdot} + \nu_{\cdot} - \nu_{\cdot} - \nu_{23} + \nu_{\cdot} - \nu_{\cdot} + \nu_{32}$$

$$\nu_1 = \alpha[t] \cdot Bar|_{active}[t] \cdot k_1$$

$$\nu_2 = Ste2[t] \cdot \alpha[t] \cdot k_2$$

$$\nu_3 = Ste2_{active}[t] \cdot k_3$$

$$\nu_4 = Ste2_{active}[t] \cdot k_4$$

$$\nu_5 = Ste2[t] \cdot k_5$$

$$\nu_6 = Ste2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$

$$\nu_7 = G\alpha GTP[t] \cdot k_7$$

$$\nu_8 = G\alpha GTP[t] \cdot \cdot st2_{active}[t] \cdot k_8$$

$$\nu_9 = \cdot\alpha GDP[t] \cdot G\beta\gamma[t] \cdot k_9$$

$$\nu_{10} = G\beta\gamma[t] \cdot C[t] \cdot k_{10}$$

$$\nu_{11} = D[t] \cdot k_{11}$$

$$\nu_{12} = Ste5[t] \cdot Ste11[t] \cdot k_{12}$$

$$\nu_{13} = A[t] \cdot k_{13}$$

$$\nu_{14} = Ste7[t] \cdot Fus3[t] \cdot k_{14}$$

$$\nu_{\cdot} = \cdot[t] \cdot k_{\cdot}$$

$$\nu_{16} = \cdot[t] \cdot [t] \cdot k_{16}$$

$$\nu_{17} = C[t] \cdot k_{17}$$

$$\nu_{18} = D[t] \cdot Ste20[t] \cdot k_{18}$$

READABILITY ?

CAUSALITY ?

UNIQUE STRUCTURE ?

- **knowledge** -> ***PROBLEM 1***
  - -> *uncertain*
  - -> *growing, changing*
  - -> *distributed over independent data bases, papers, journals, . . .*

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  - -> *verbose descriptions*
  - -> *diverse graphical representations*
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- **network structure** ***-> PROBLEM 3***
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  - -> *dense, apparently unstructured*
  - -> *hard to read*

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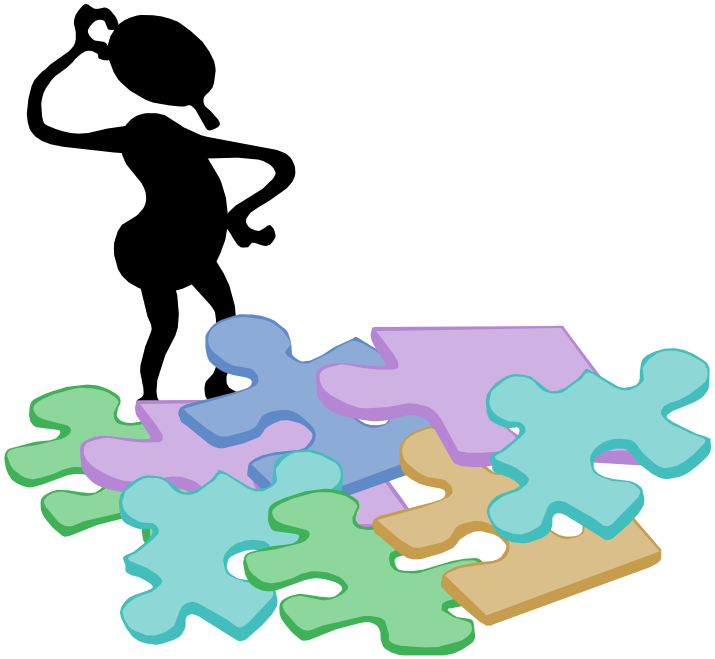
MODELS ARE PATCHWORKS FULL OF ASSUMPTIONS

BIO NETWORK REPRESENTATIONS SHOULD BE



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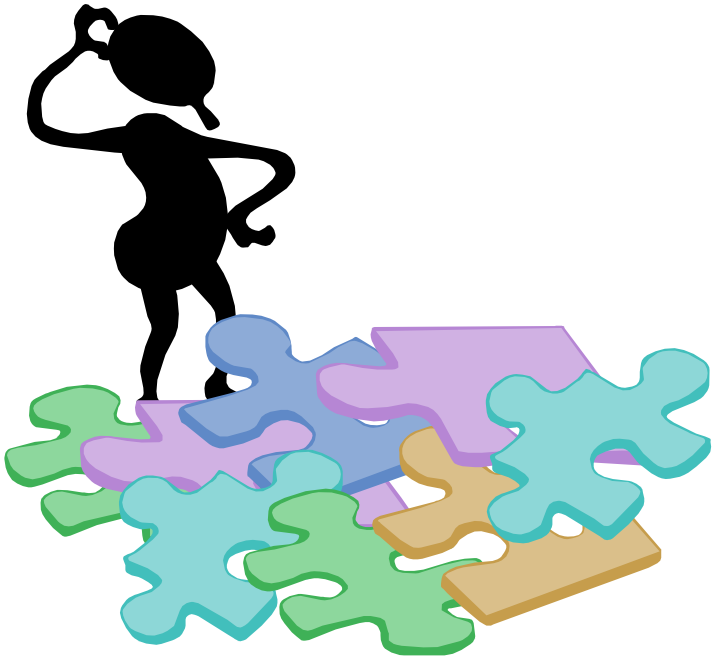

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  -> fault avoidant model construction
- **various abstraction levels**
- **locality - causality - concurrency**
- **compositional**

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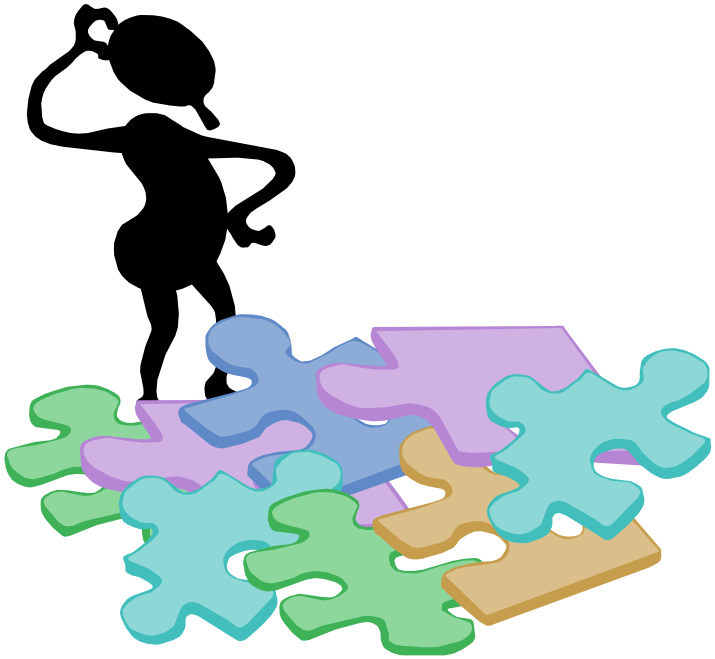

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  -> formal = mathematical representations
  -> high-level description for various analysis approaches

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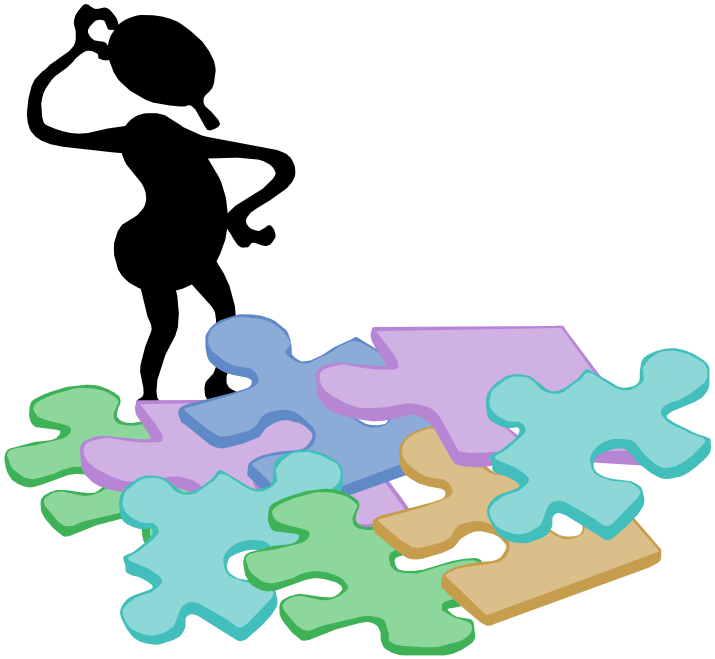

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- **AS SIMPLE AS POSSIBLE**
  -> how many model types do we need ?

MODELLING
=
ABSTRACTION

MODELLING = ABSTRACTION

- **hierarchical organisation of components -> model variables**

  genes, molecules, organelles, cells, tissues, organs, organisms

- **functionality of atomic events**

  chemical reactions with/out stoichiometry, conformational change, transport, . . .

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  qualitative versus quantitative models

- **individual vs population behaviour**

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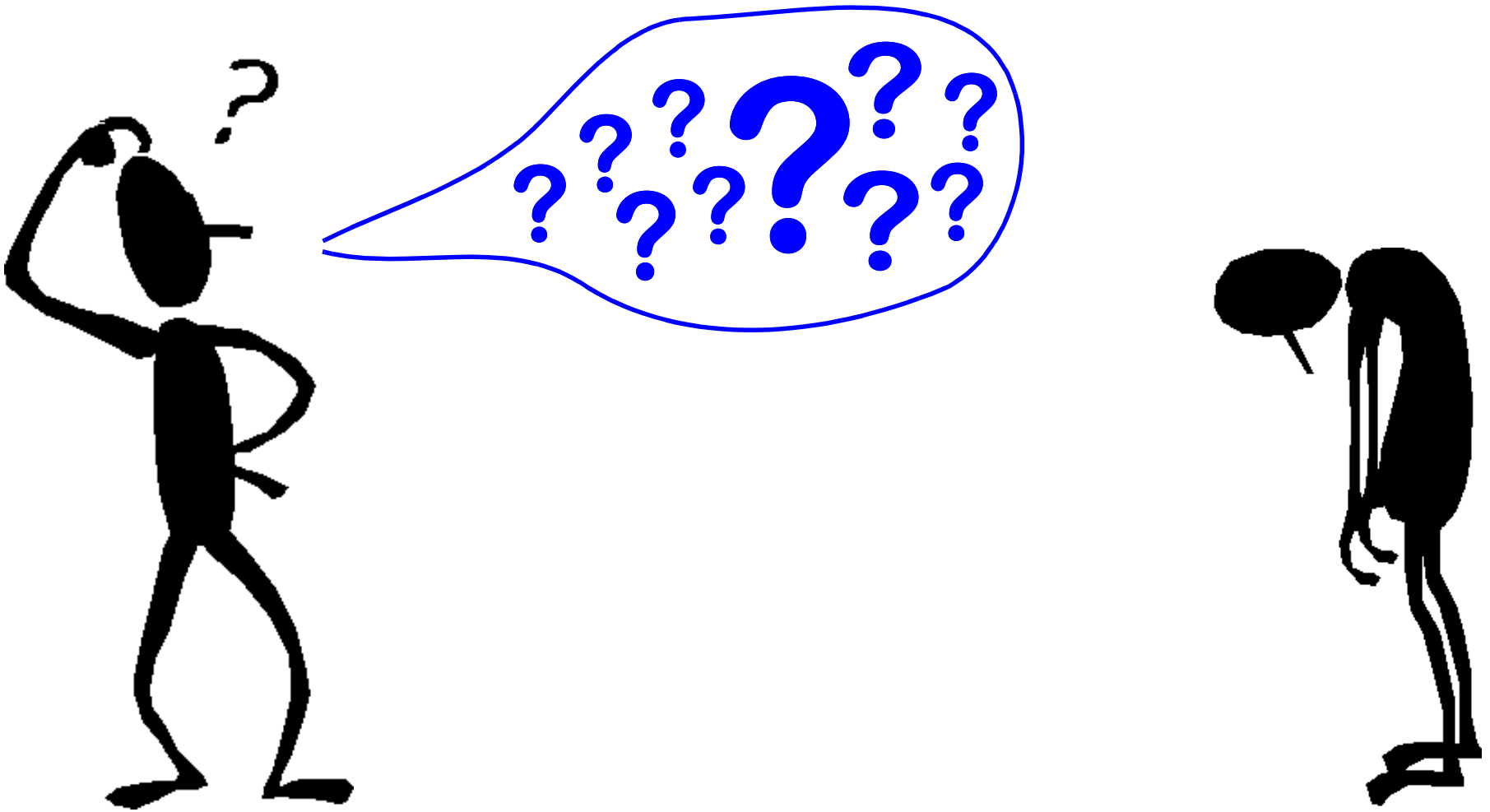
- **time**
  qualitative versus quantitative models
- **individual vs population behaviour**
- **(hierarchical) space**
- **shape and volume of components**
- **biosystem development**

A Use Case
(Let's Look in the Future)

MEDICAL TREATMENT

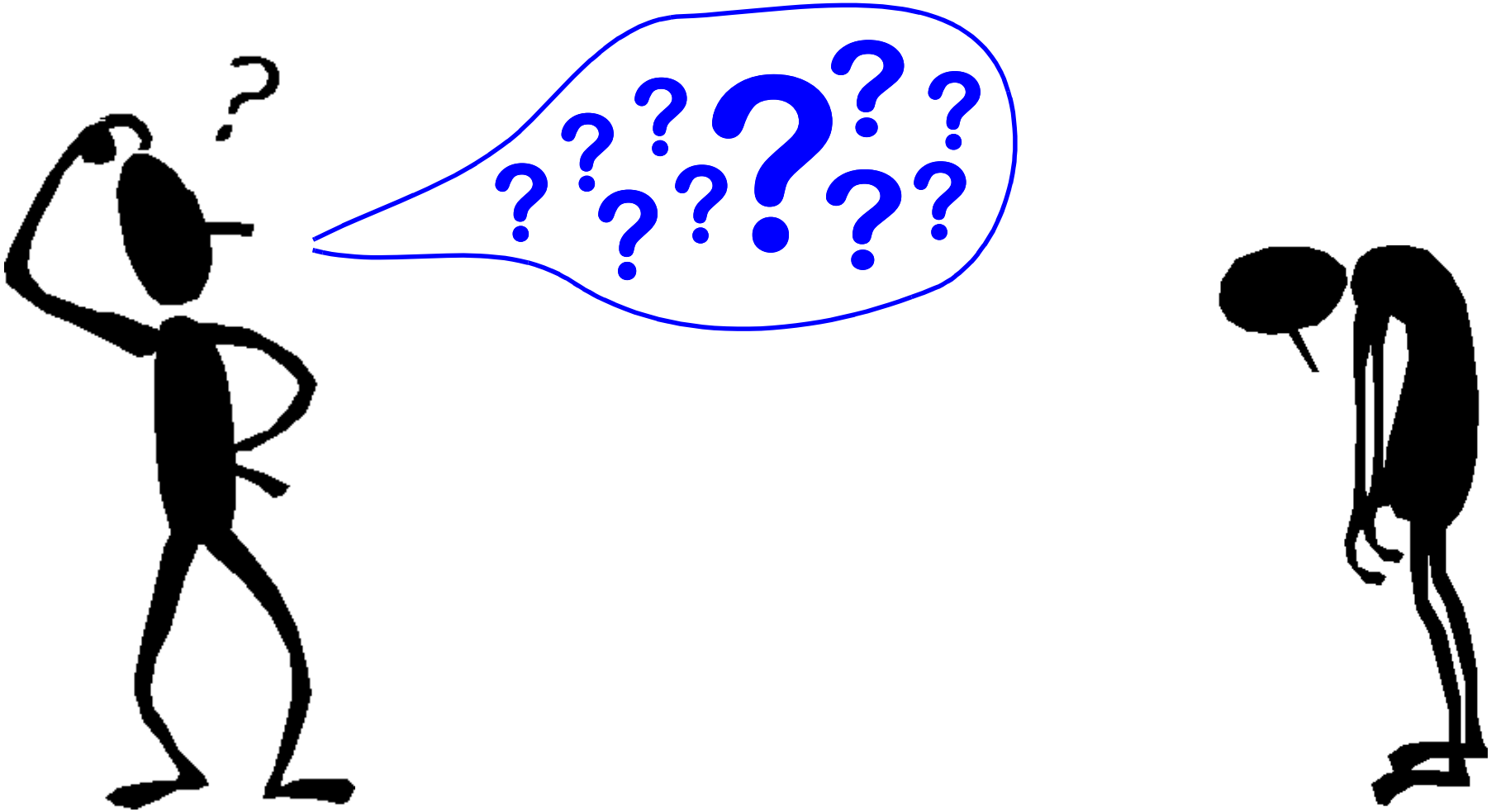
MEDICAL TREATMENT, APPROACH 1- TRIAL-AND-ERROR DRUG PRESCRIPTION



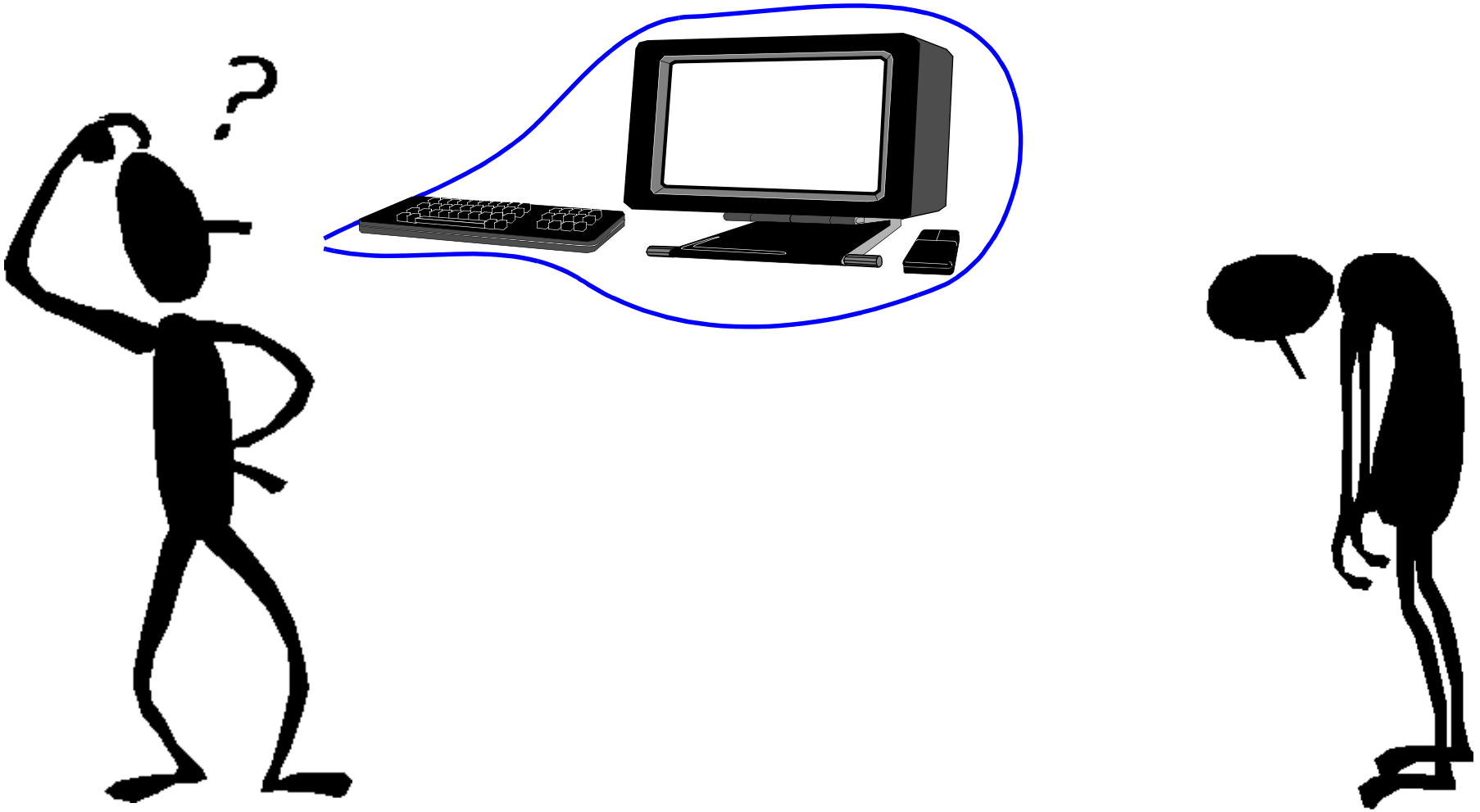
MEDICAL TREATMENT, APPROACH 1- TRIAL-AND-ERROR DRUG PRESCRIPTION

MEDICAL TREATMENT, APPROACH 1- TRIAL-AND-ERROR DRUG PRESCRIPTION

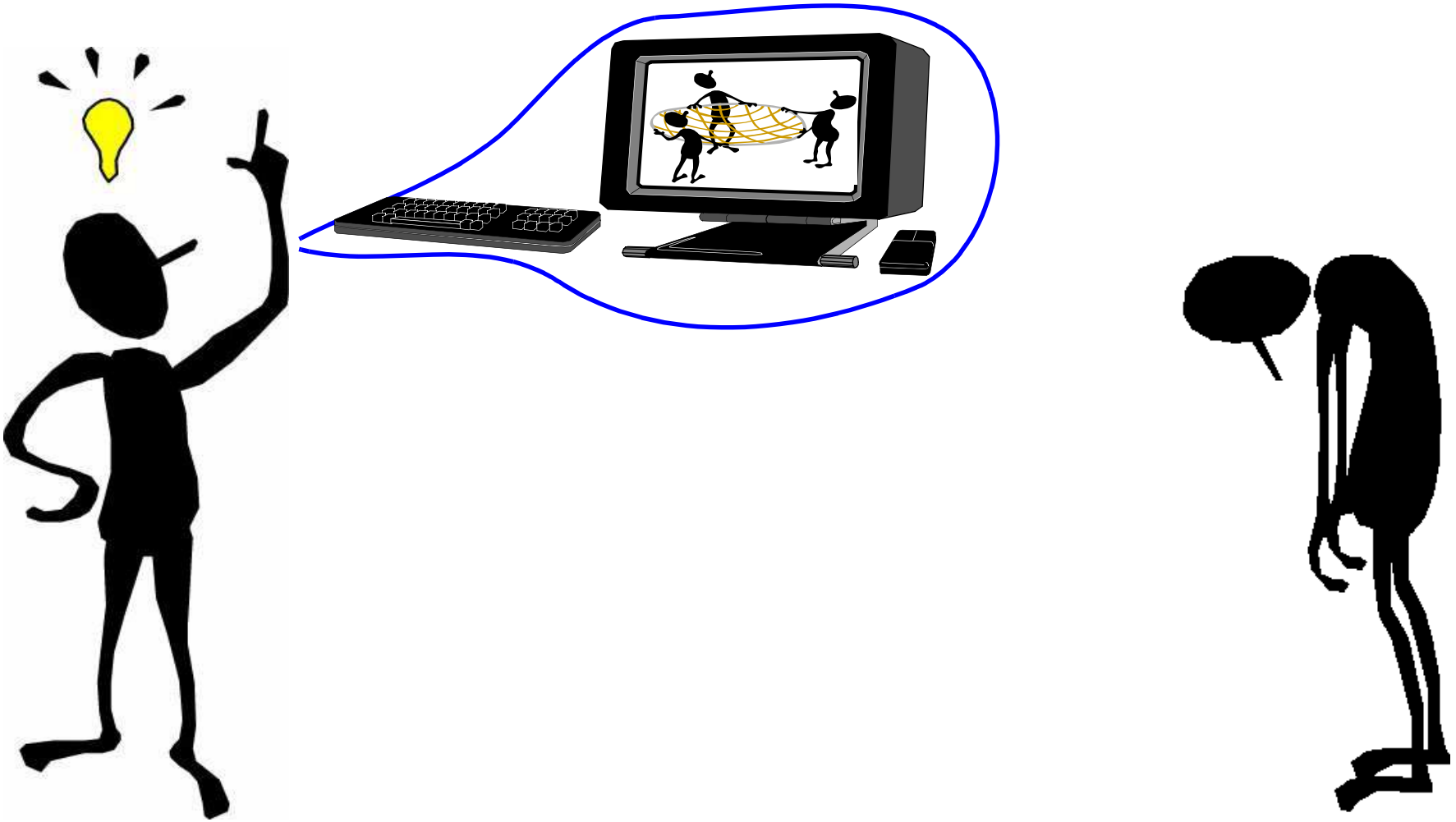
MEDICAL TREATMENT, APPROACH 2



MEDICAL TREATMENT, APPROACH 2 - MODEL-BASED DRUG PRESCRIPTION



MEDICAL TREATMENT, APPROACH 2 - MODEL-BASED DRUG PRESCRIPTION



MEDICAL TREATMENT, APPROACH 2 - MODEL-BASED DRUG PRESCRIPTION

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