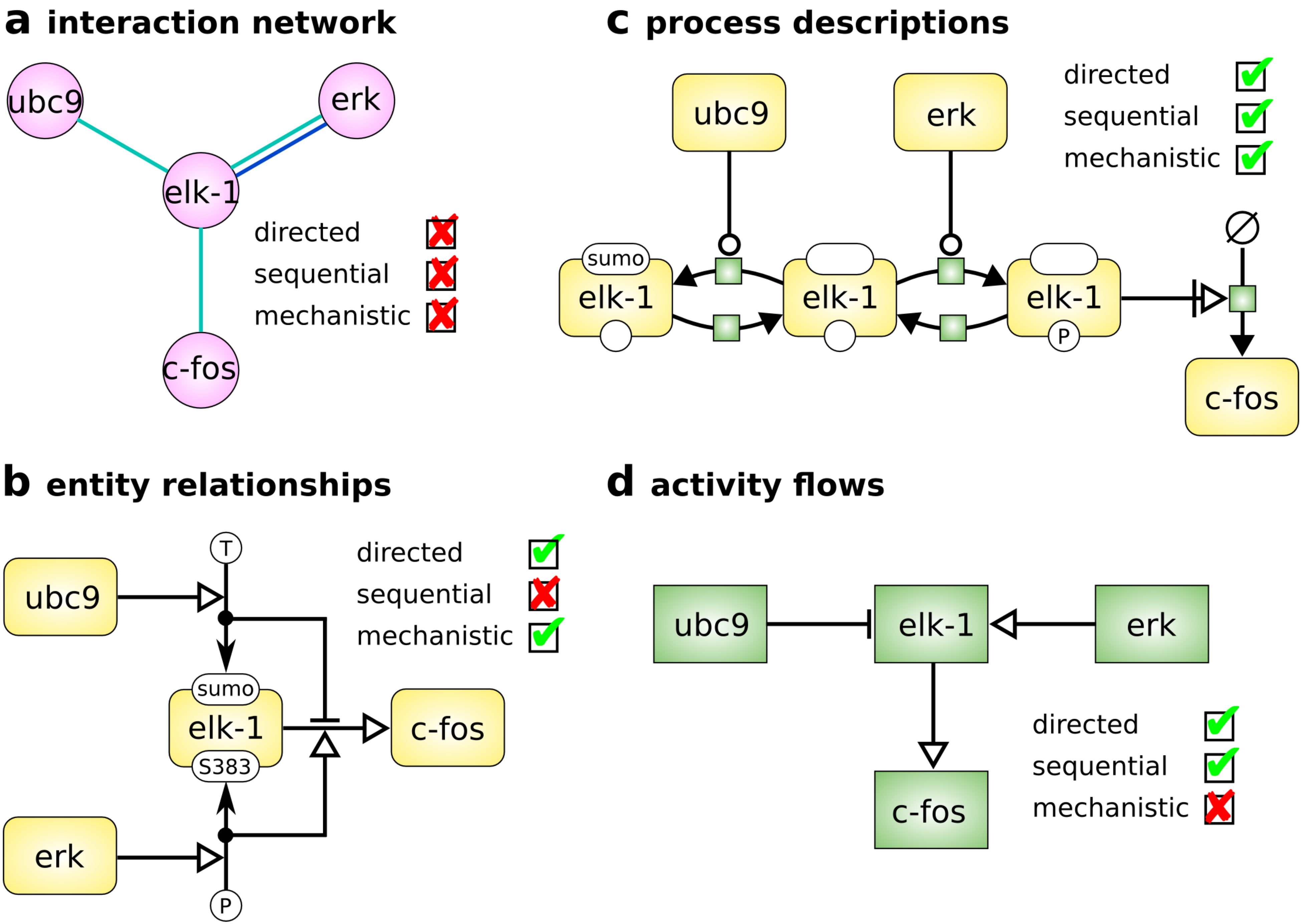
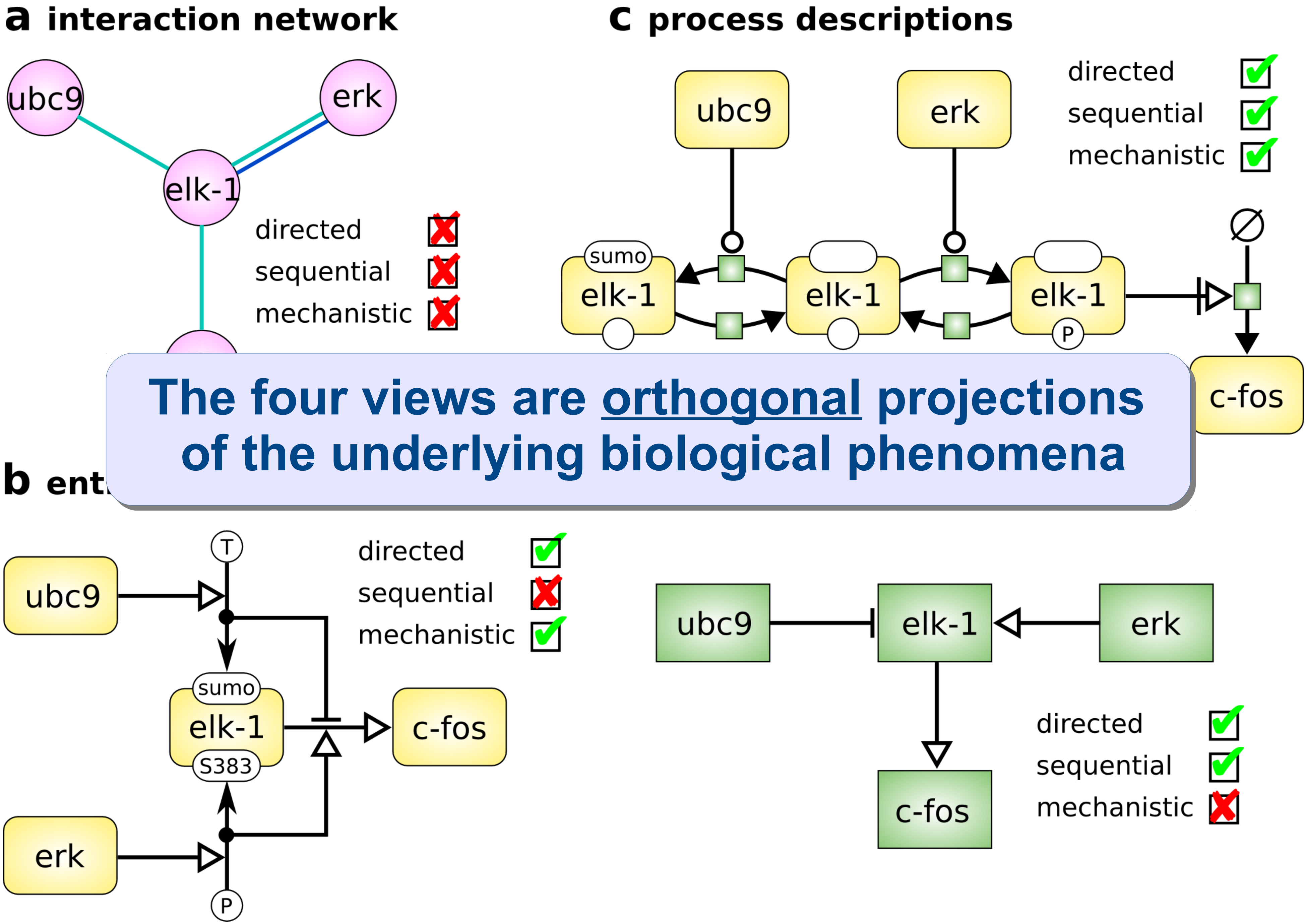
Modelling in Systems Biology,
A few challenges

The four views of molecular systems biology

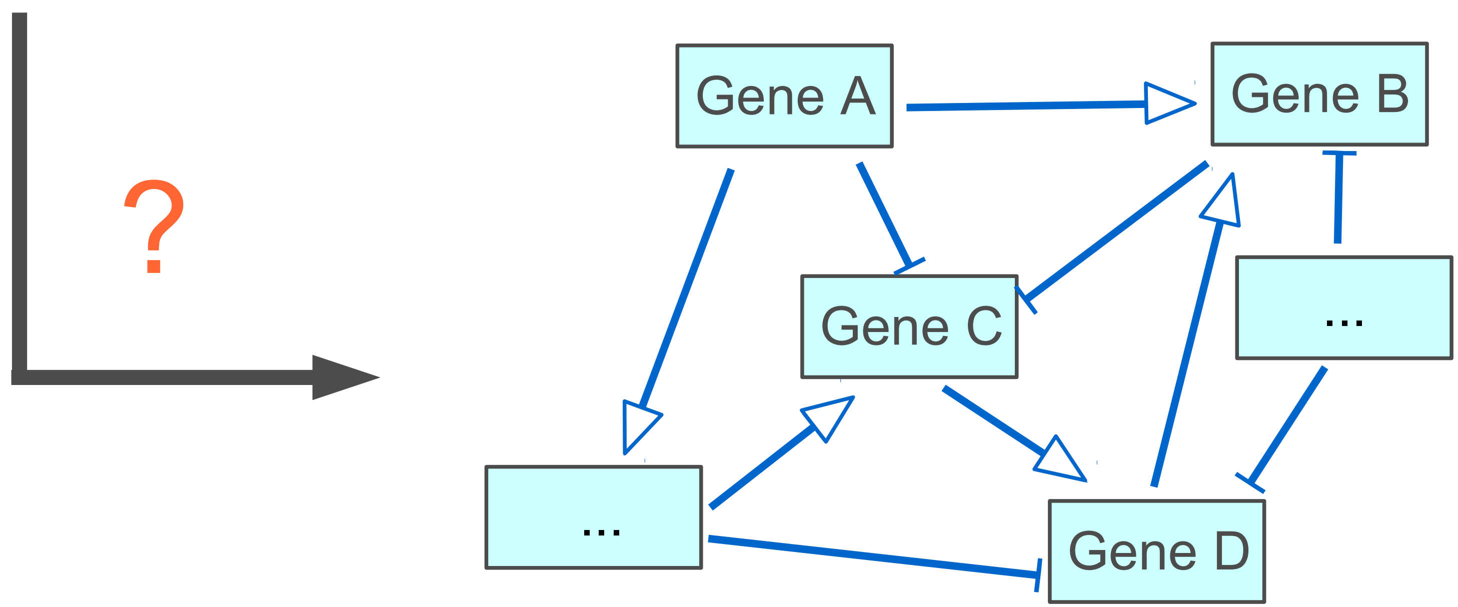


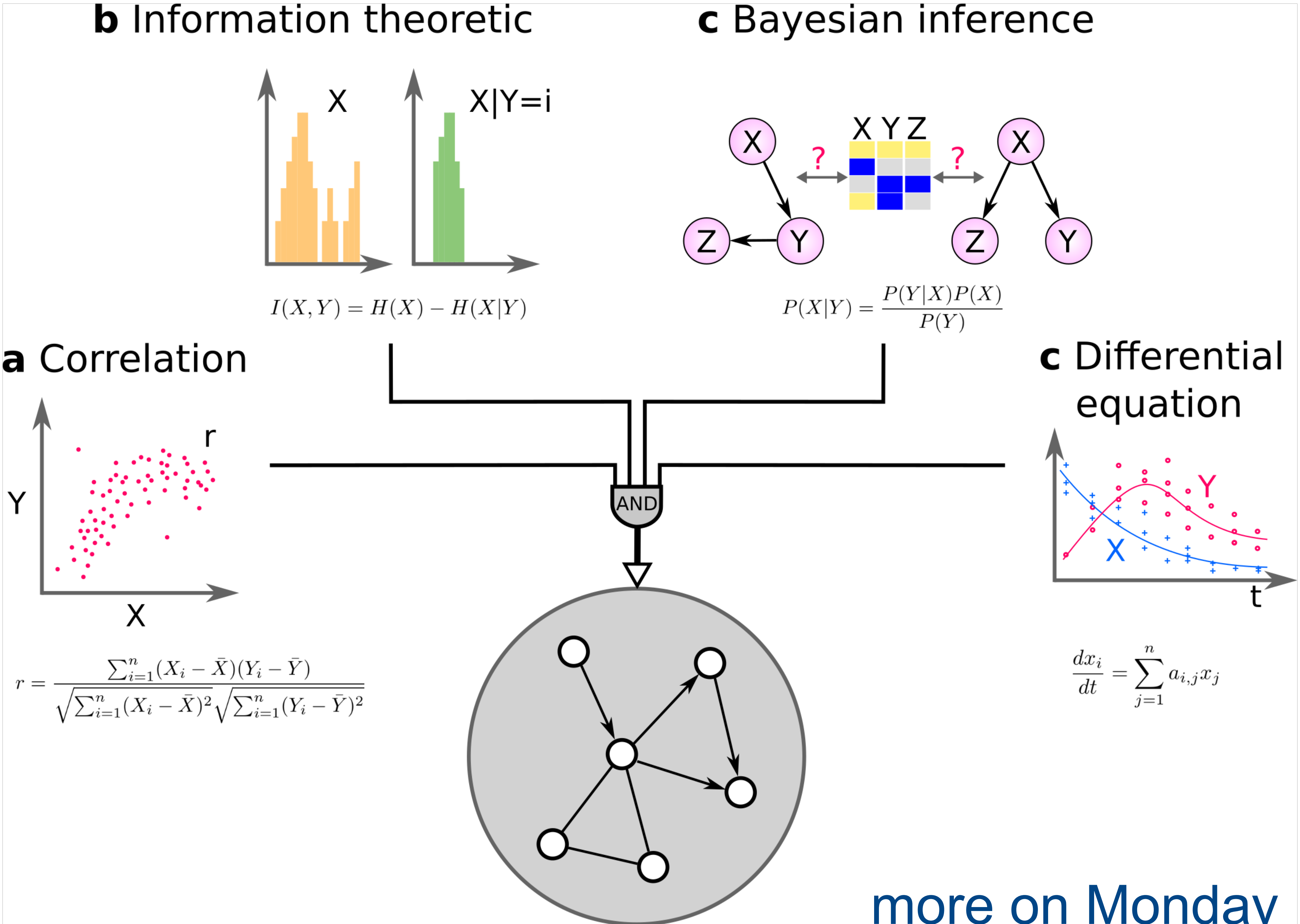


a interaction network
ubc9
erk
elk-1
directed
sequential
mechanistic
c process descriptions
ubc9
erk
directed
sequential
mechanistic
sumo
elk-1
elk-1
elk-1
P
∅
c-fos
The four views are orthogonal projections
of the underlying biological phenomena
b ent
T
ubc9
directed
sequential
mechanistic
sumo
elk-1
S383
c-fos
erk
P
ubc9
elk-1
erk
c-fos
directed
sequential
mechanistic

Reverse engineering is hard ...

	Gene A	Gene B	Gene C	Gene D	...
Phenotype X	✔	✘	✔	✘	
Phenotype Y	✔	✘	✘	✔	
Phenotype Z	✘	✔	✔	✘	
...					





b Information theoretic
X
X|Y=i
$I(X,Y) = H(X) - H(X|Y)$
c Bayesian inference
X Y Z
?
?
X
Y
Z
$P(X|Y) = \frac{P(Y|X)P(X)}{P(Y)}$
a Correlation
r
Y
X
$r = \frac{\sum_{i=1}^{n}(X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^{n}(X_i - \bar{X})^2}\sqrt{\sum_{i=1}^{n}(Y_i - \bar{Y})^2}}$
c Differential equation
Y
X
t
$\frac{dx_i}{dt} = \sum_{j=1}^{n} a_{i,j}x_j$
AND
more on Monday

Bridging Bioinformatics and Systems Biology

Big historical divide: Origin of scientists (math/bio Vs eng/physics), journals, conferences, scientific societies etc.

Frontiers tend to blur: Network inference from omics data, parametrisation of models, optimisation (e.g. whole-genome metabolic models), precision medicine (perturbations and drugs explained in mechanistic context)

SysMod attempts to bring back systems modelling to ISCB (society) and ISMB (conference)

Improve the conversation between communities of bioinformatics/genomics and modelling

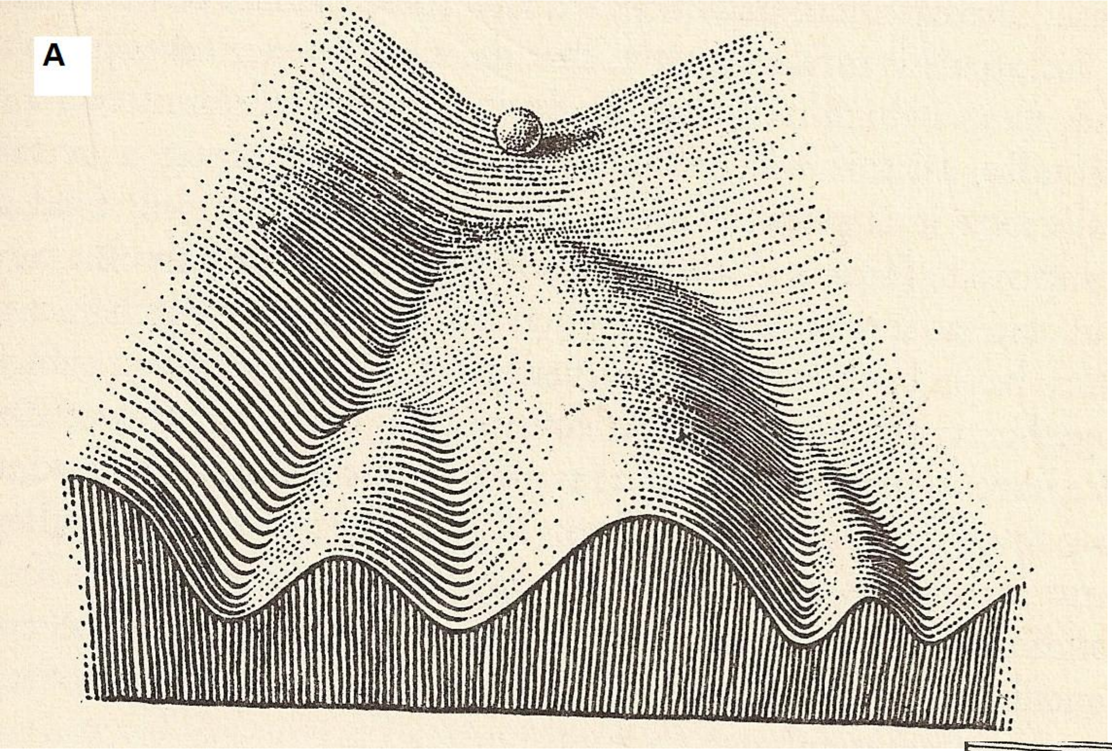
Annual meeting (Prague, 23 July 2017)

Mailing list (sysmod@googlegroups.com)

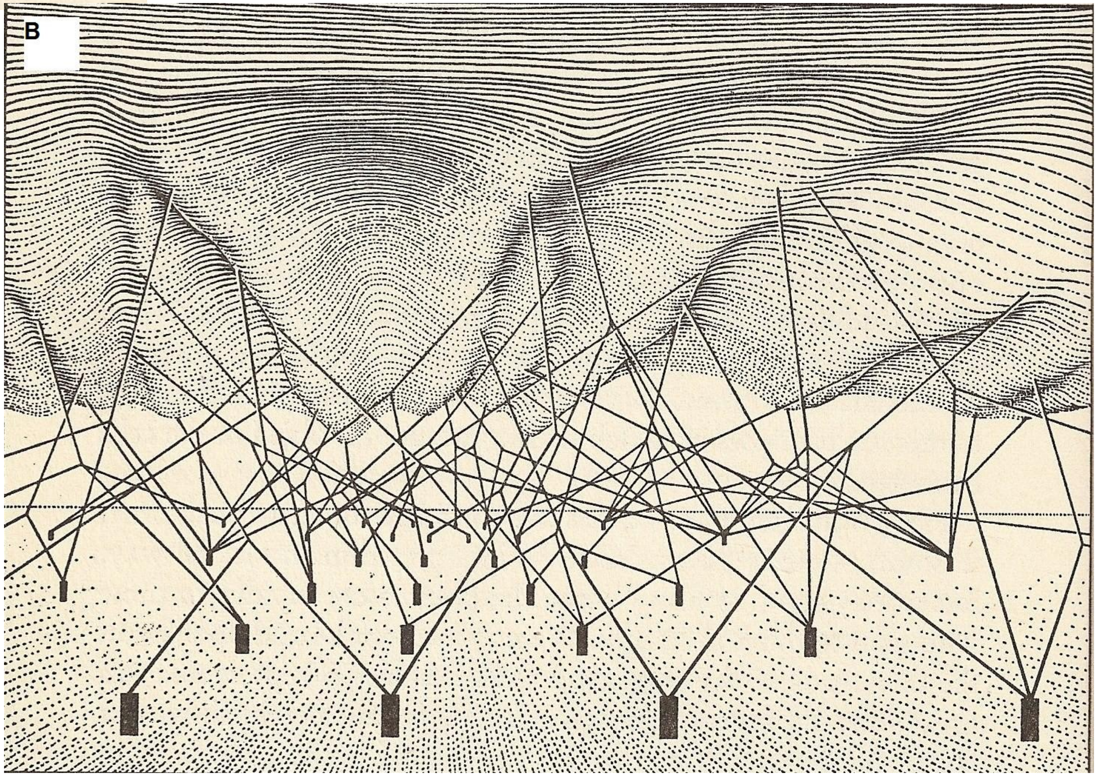
? (your idea)

http://sysmod.info

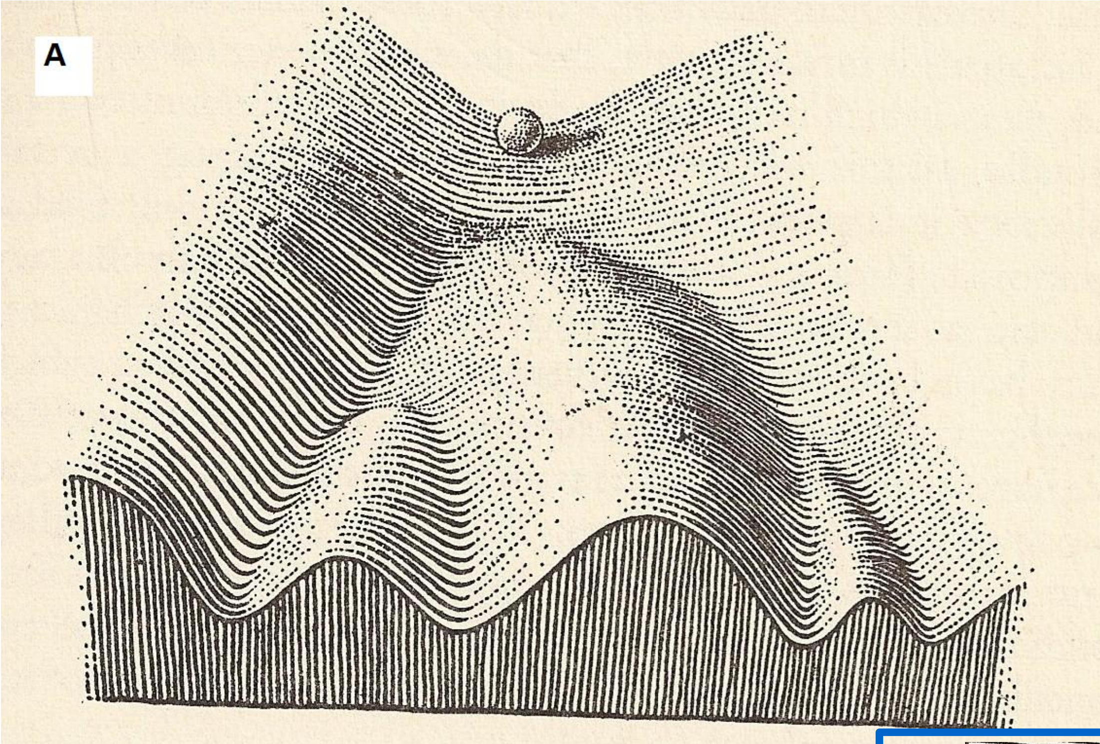
Emergent properties and the gene-system-phenotype puzzle



Waddington C.H., Kacser H (1957)
The Strategy of the Genes:
A Discussion of Some Aspects of
Theoretical Biology.
George Allen & Unwin



Emergent properties and the gene-system-phenotype puzzle



Waddington C.H., Kacser H (1957)
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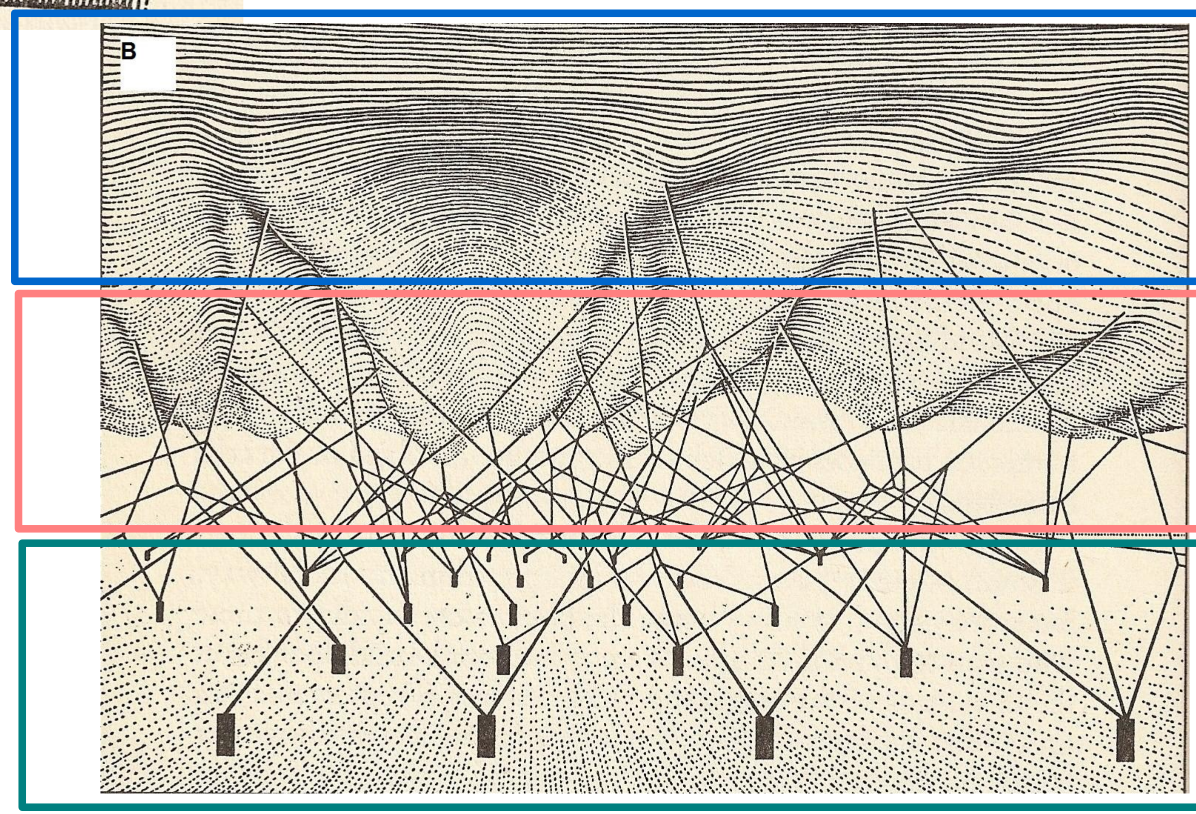
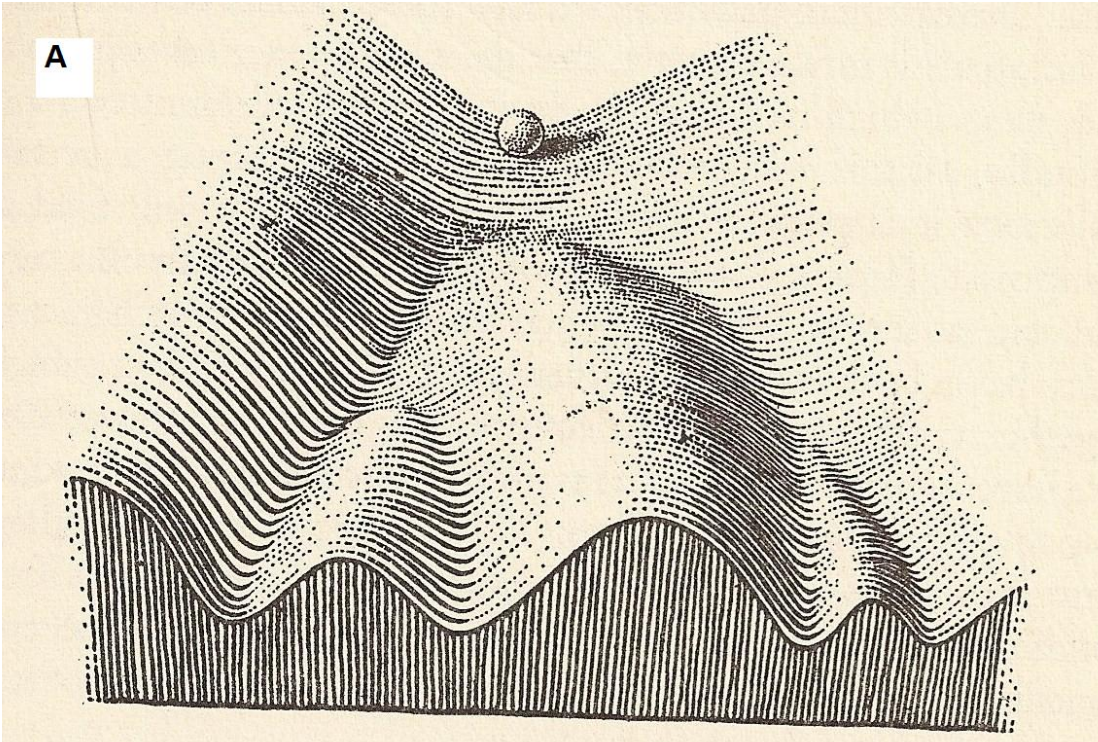
physiology ← phenotype

systems biology ← system

genetics ← genotype



Emergent properties and the gene-system-phenotype puzzle



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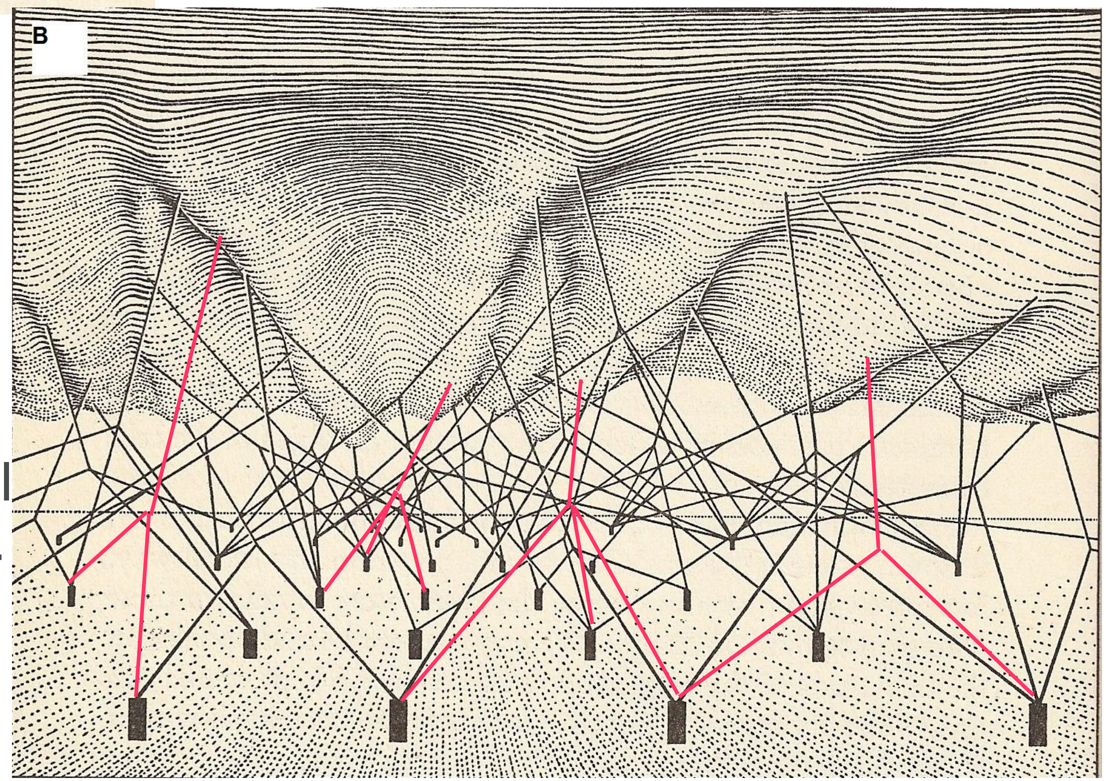
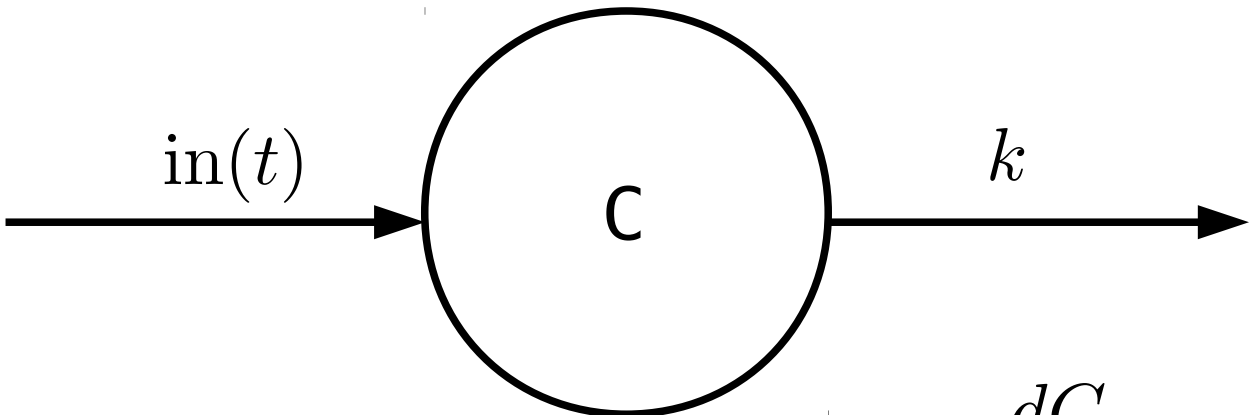
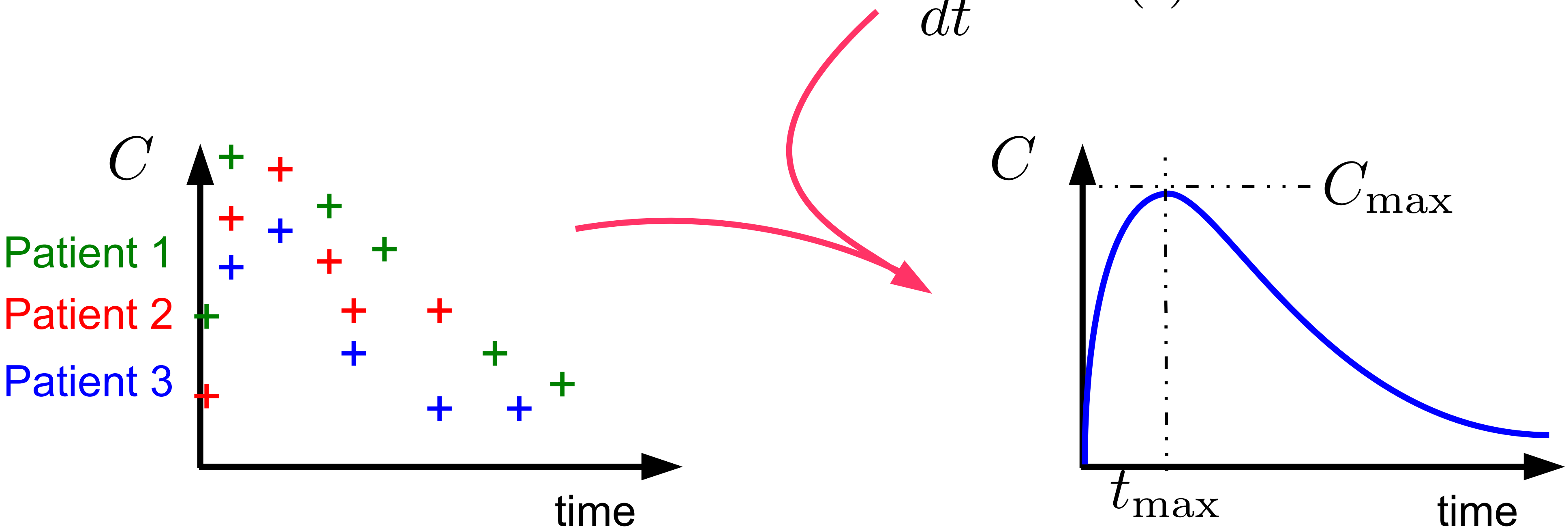


Many networks can theoretically generate the same phenotype, and this happens, in a <u>synchronous</u> (sister cells with same phenotype but different transcript/prote/metabol/omes) and <u>diachronous</u> manner (*omes of a cell changes over time but same phenotype).

Drug discovery modelling: pharmacometrics

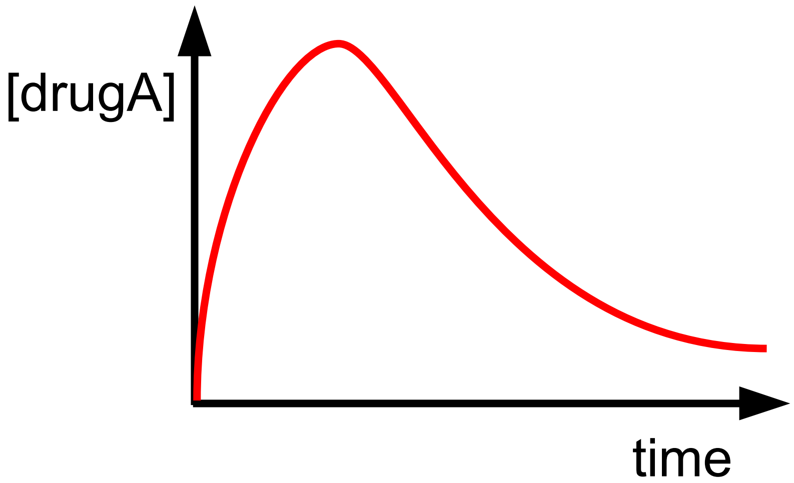


$$\frac{dC}{dt} = \mathrm{in}(t) - k \times C$$

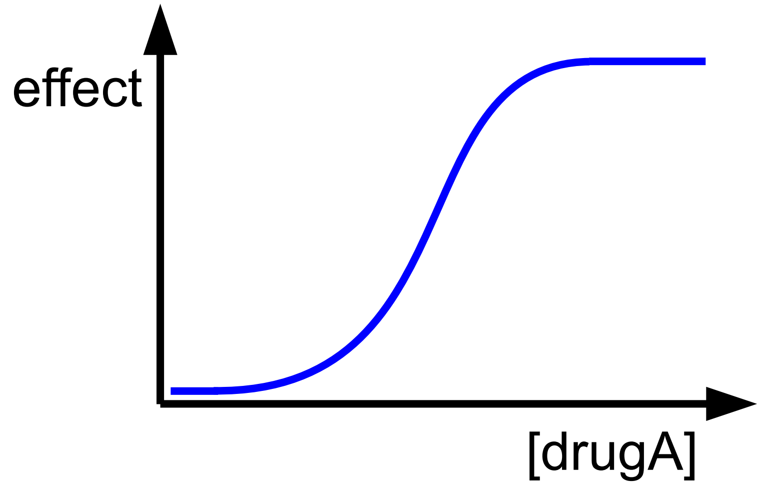


Drug discovery modelling: pharmacometrics

PK

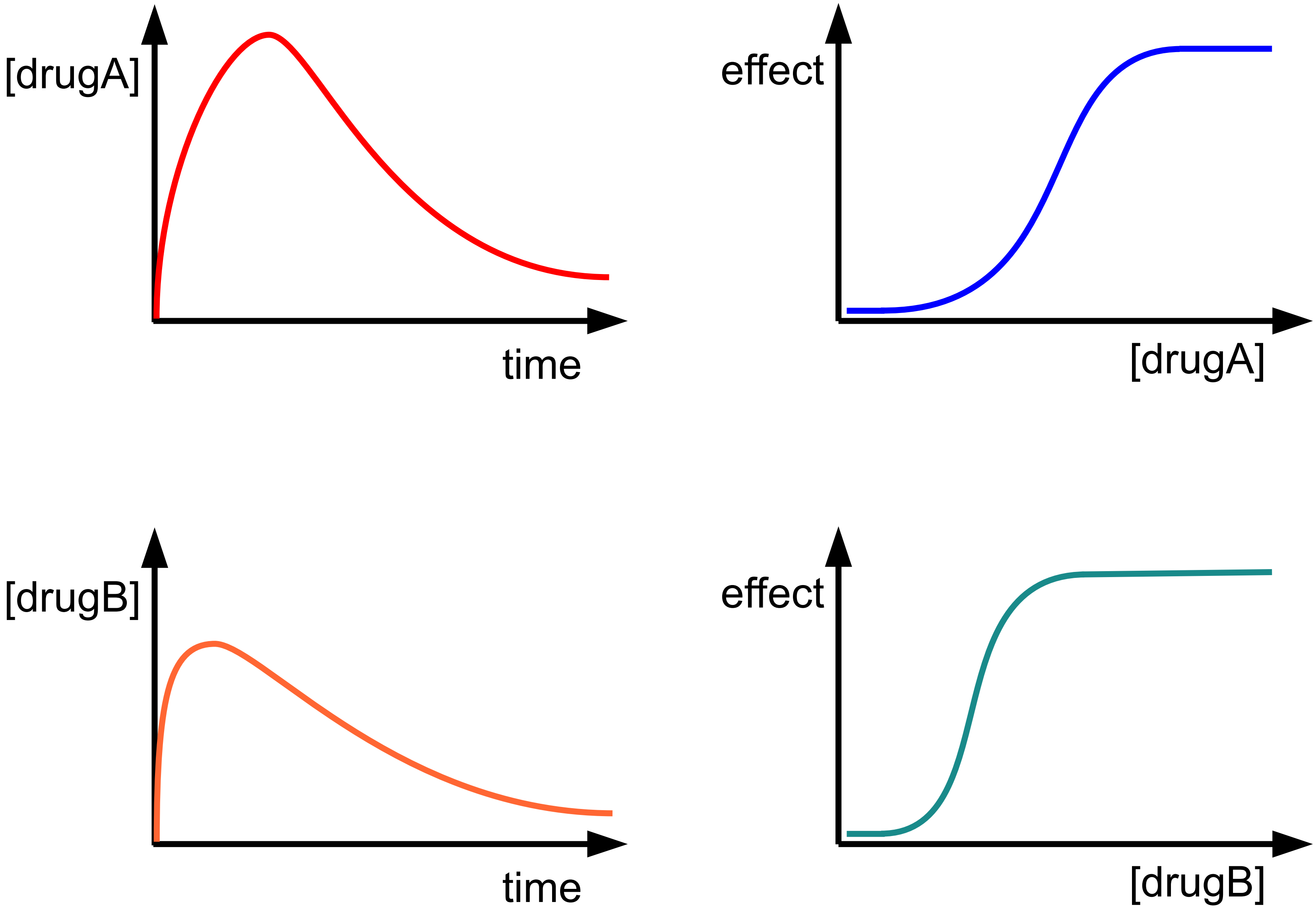


PD

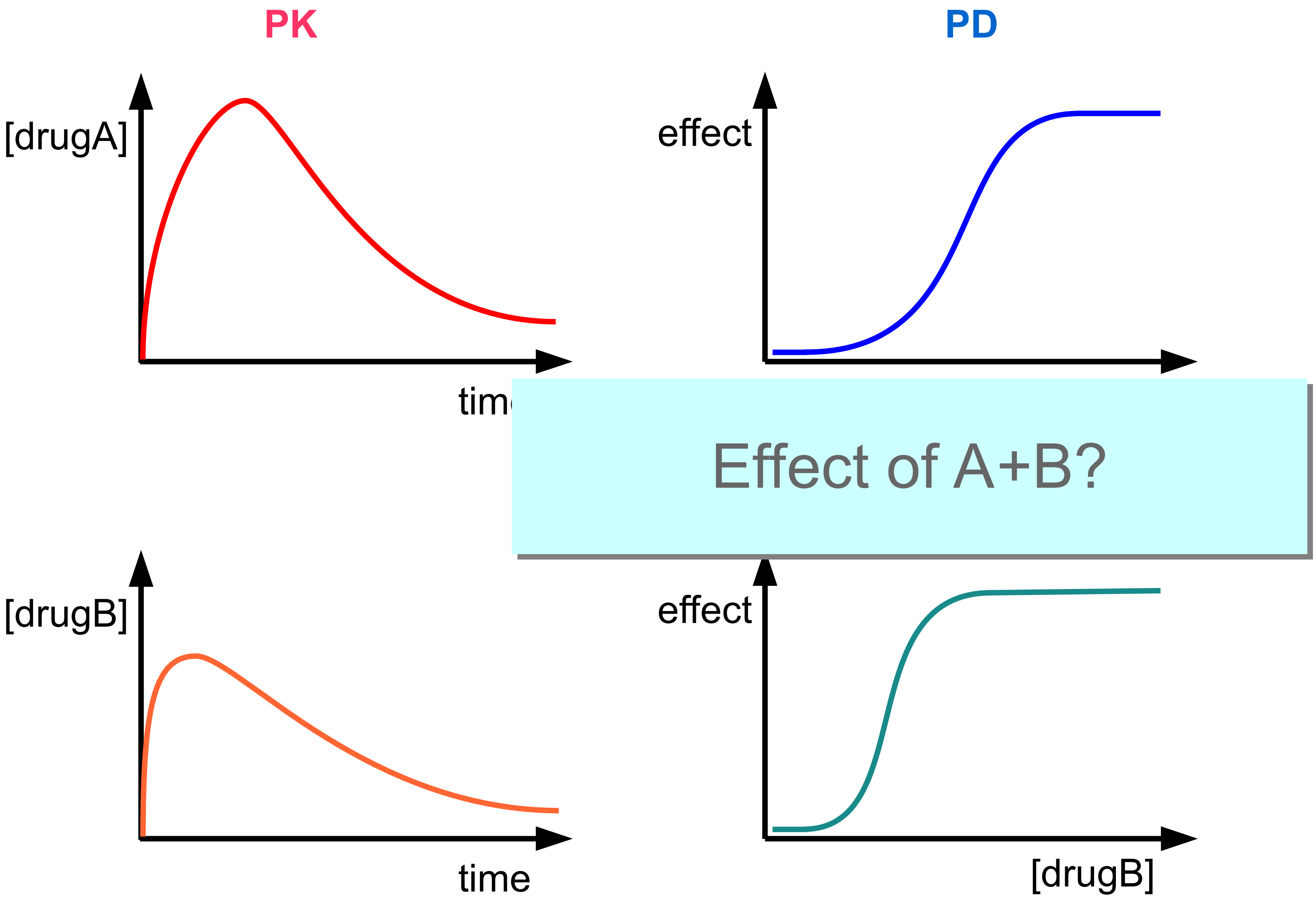


Drug discovery modelling: pharmacometrics

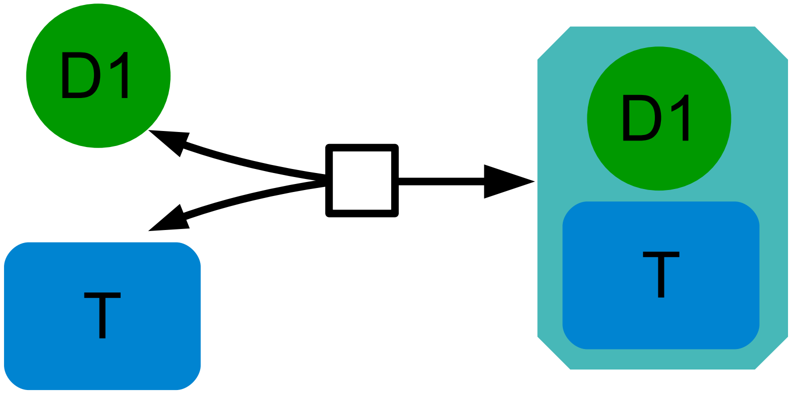
PK **PD**



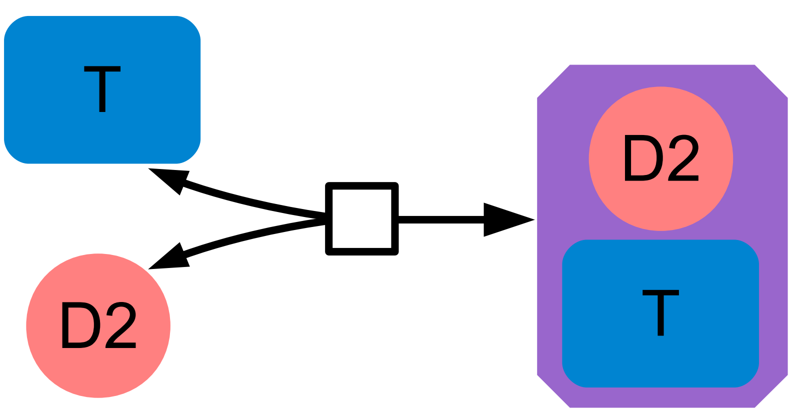
Drug discovery modelling: pharmacometrics



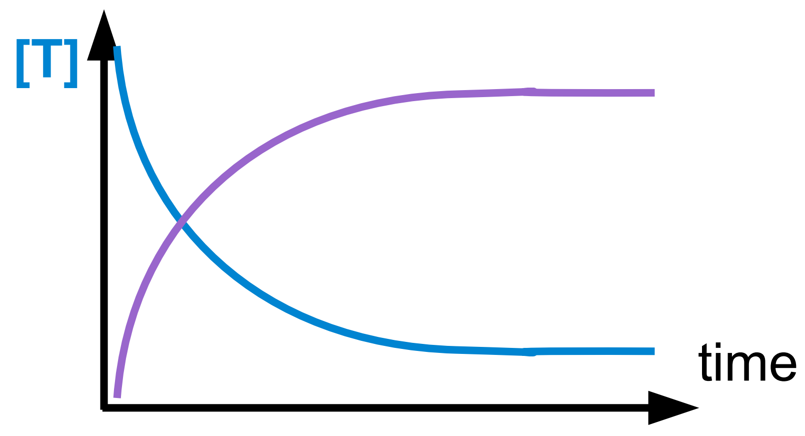
Systems modelling



$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1]$$

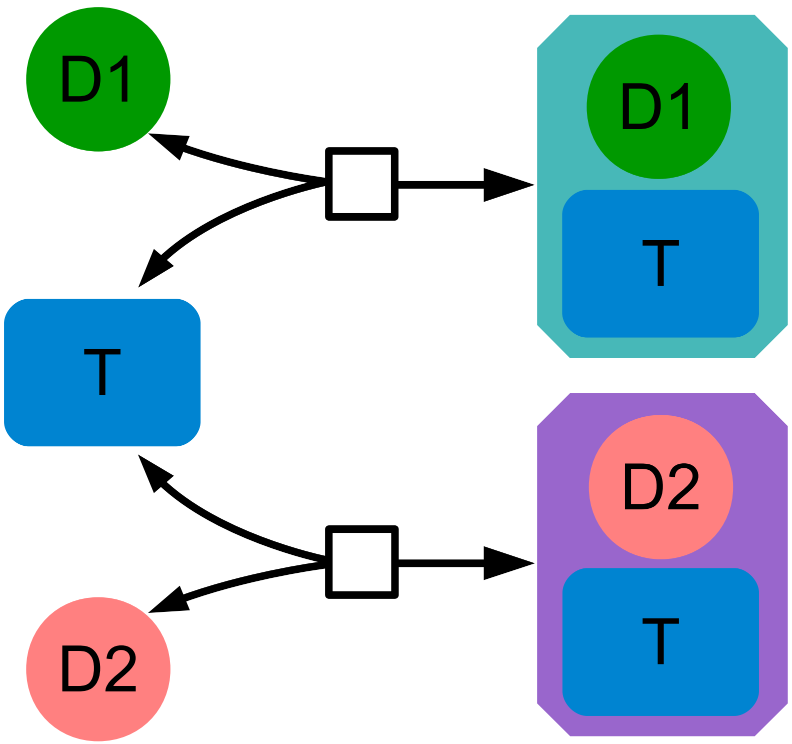


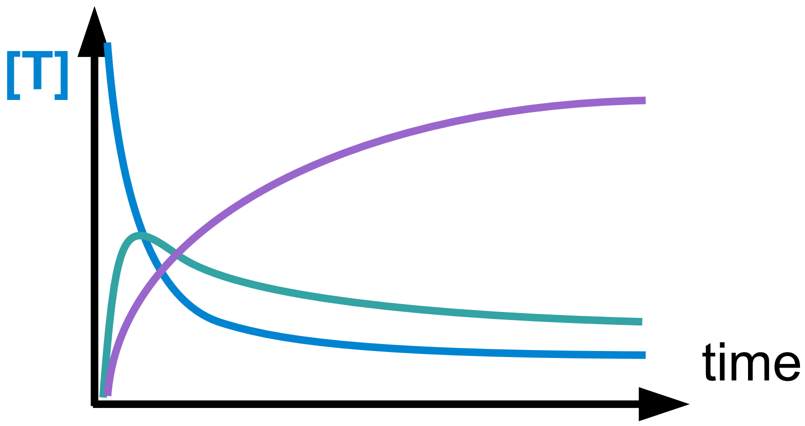
$$\frac{d[T]}{dt} = -k2 \times [T] \times [D2]$$

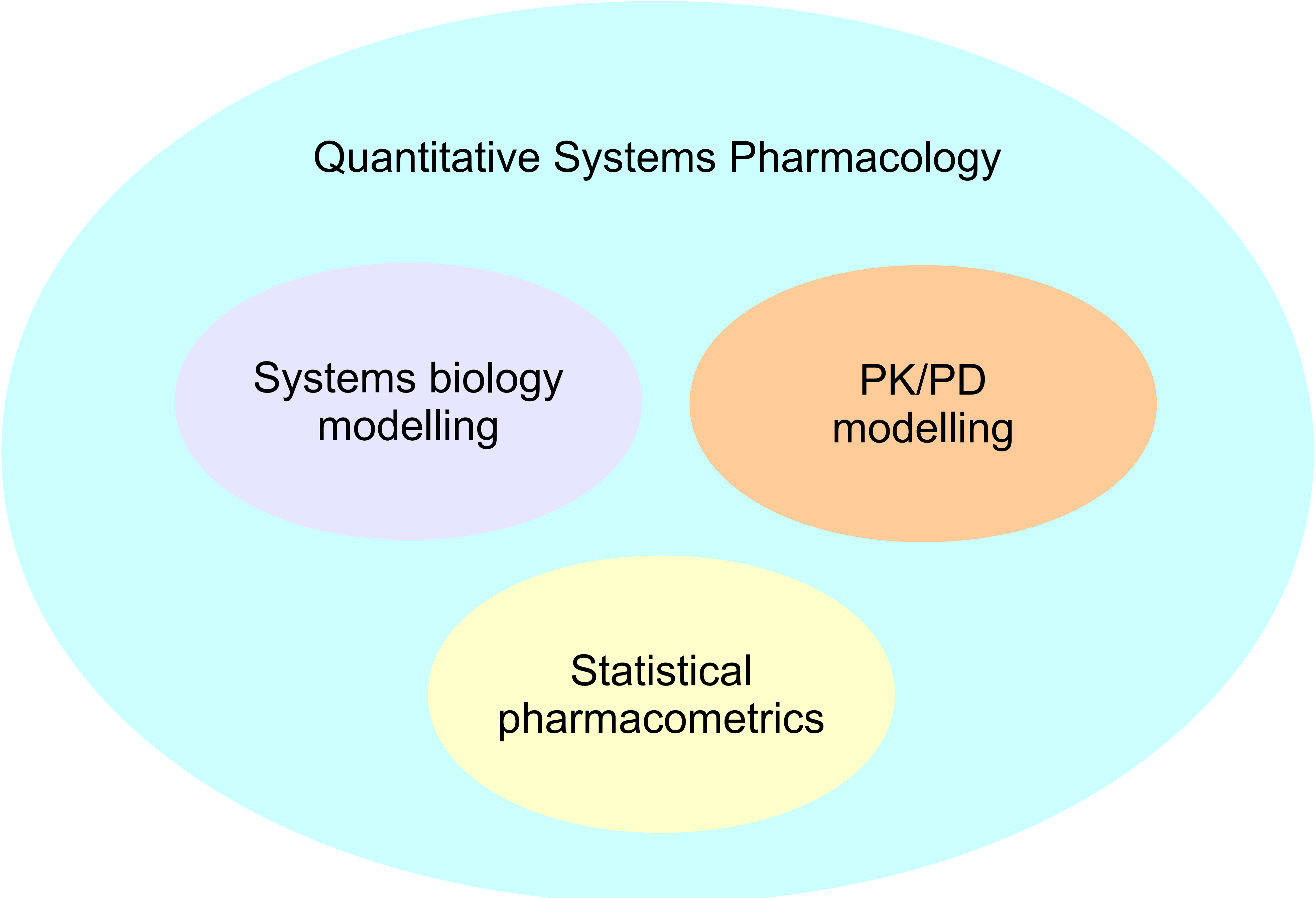


Systems modelling

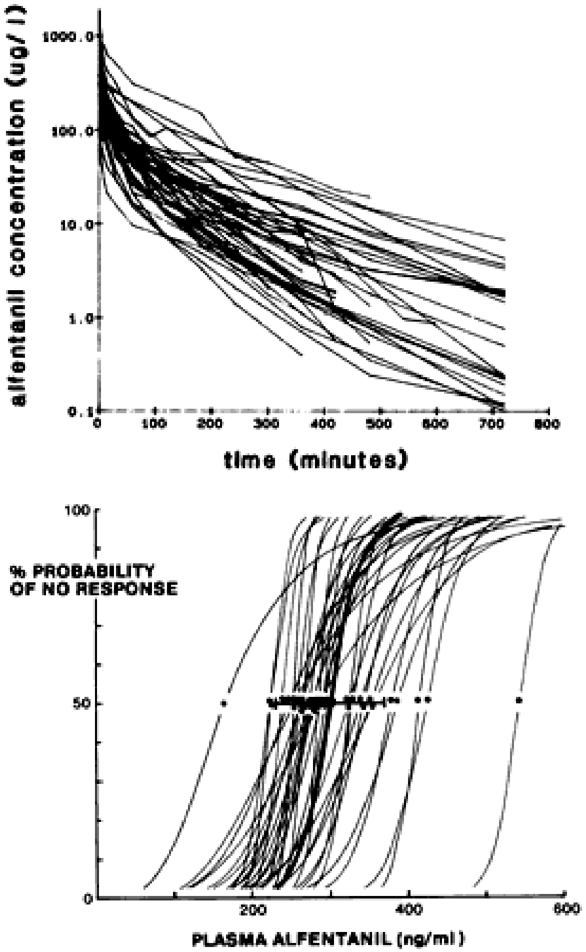
$$\frac{d[T]}{dt} = -k1 \times [T] \times [D1] - k2 \times [T] \times [D2]$$

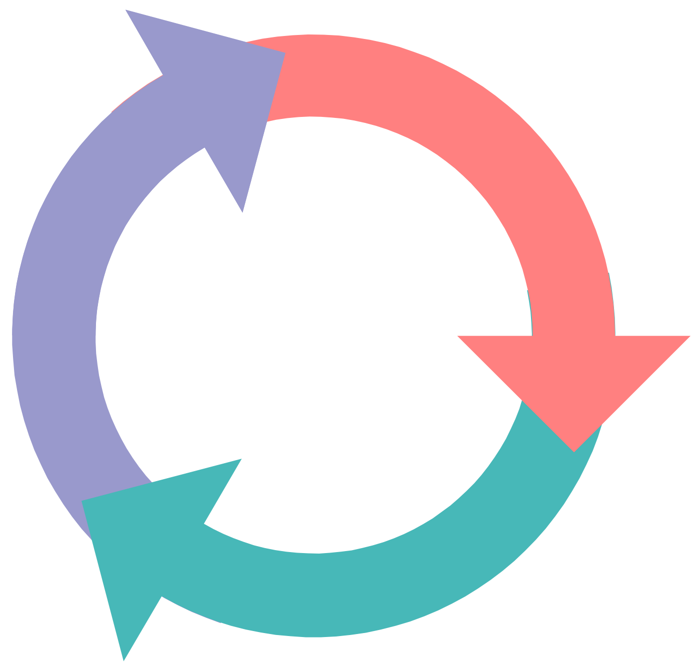


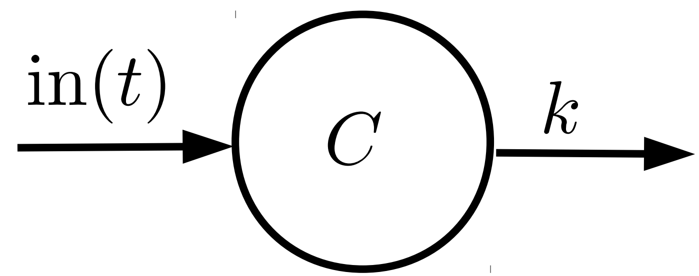


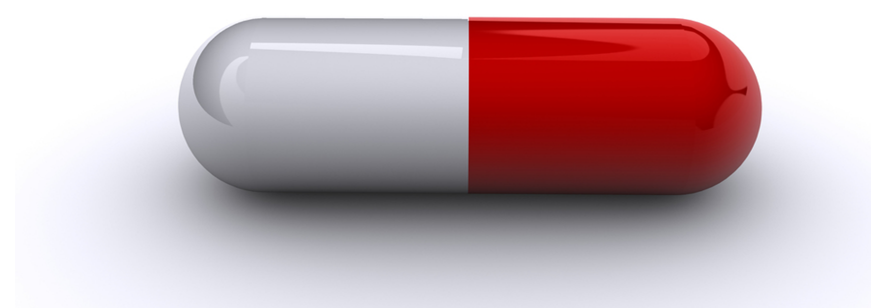

Quantitative Systems Pharmacology
Systems biology modelling
PK/PD modelling
Statistical pharmacometrics

Drug discovery and pharmacometrics models

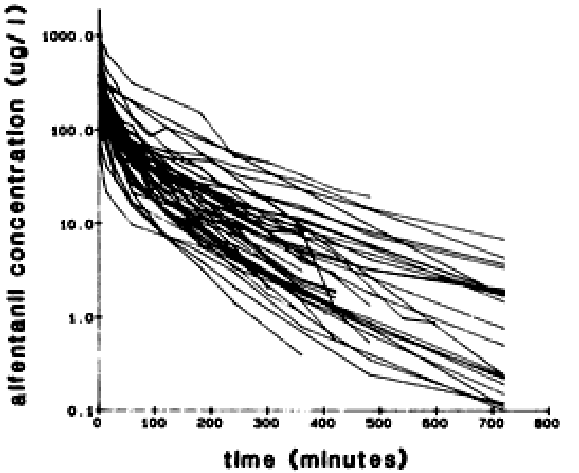


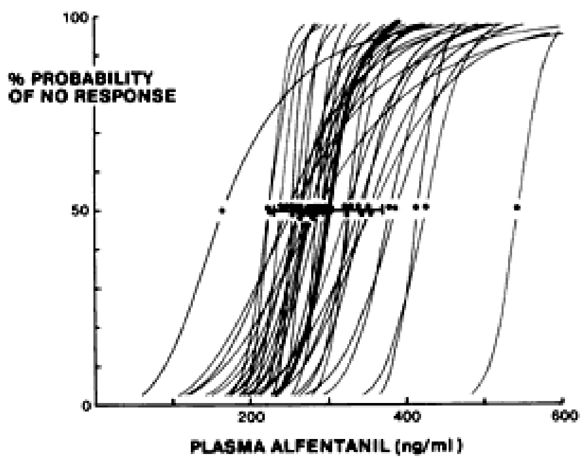


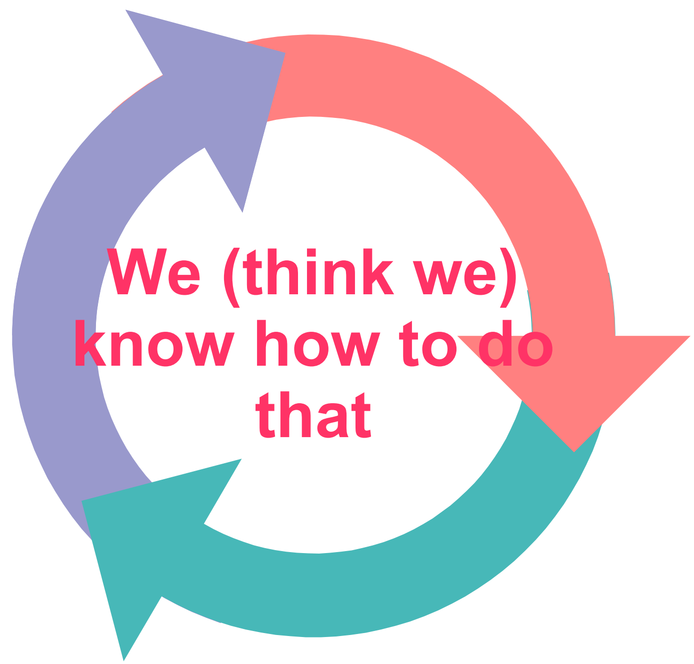


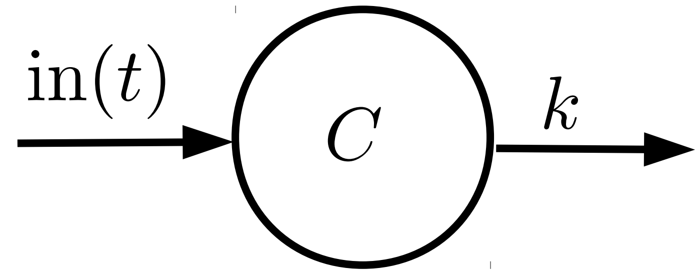


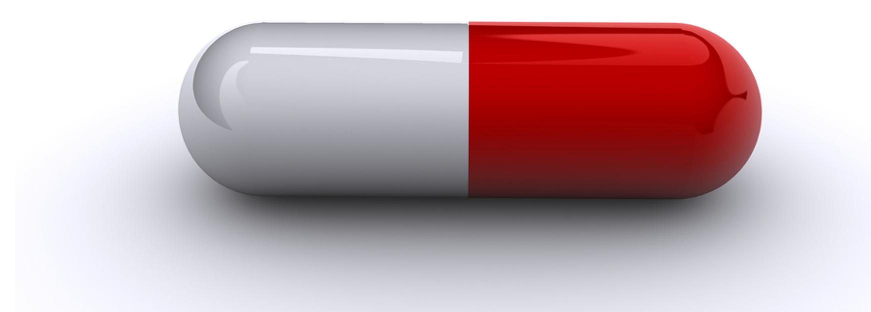
Drug discovery and pharmacometrics models



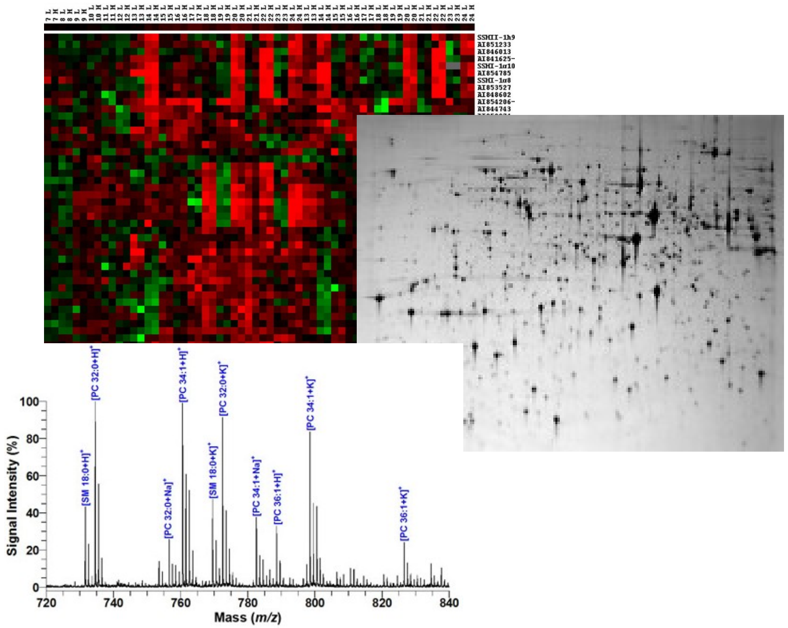


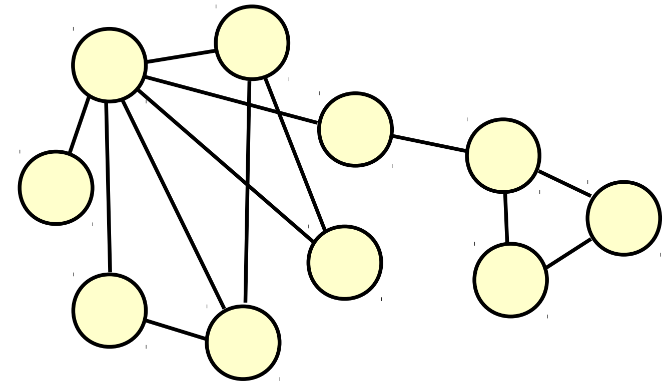


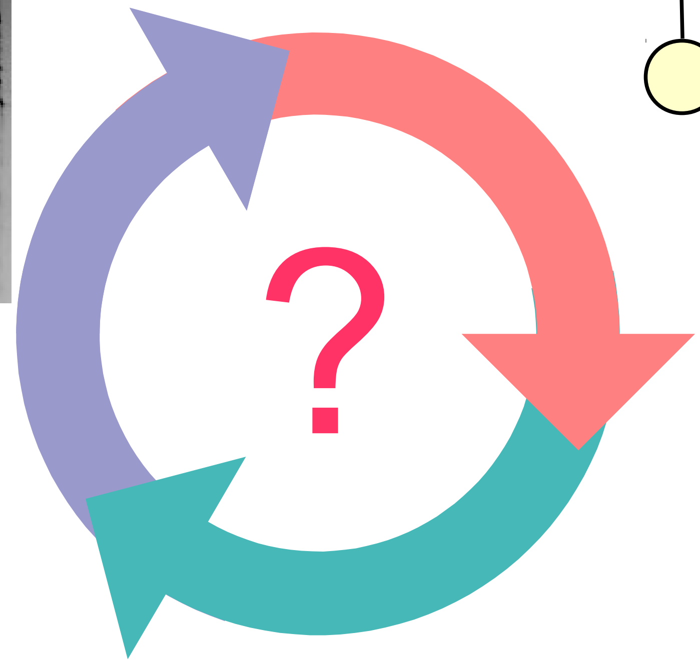


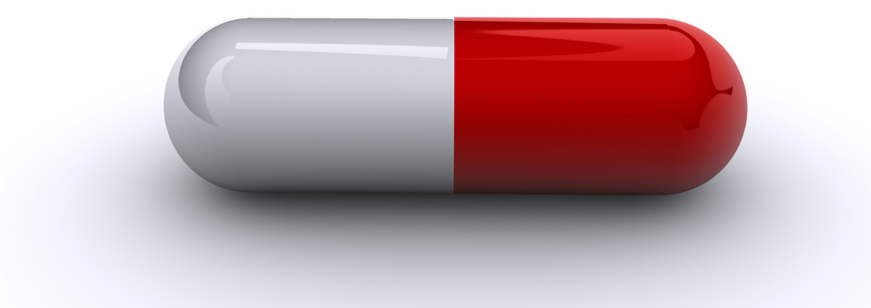


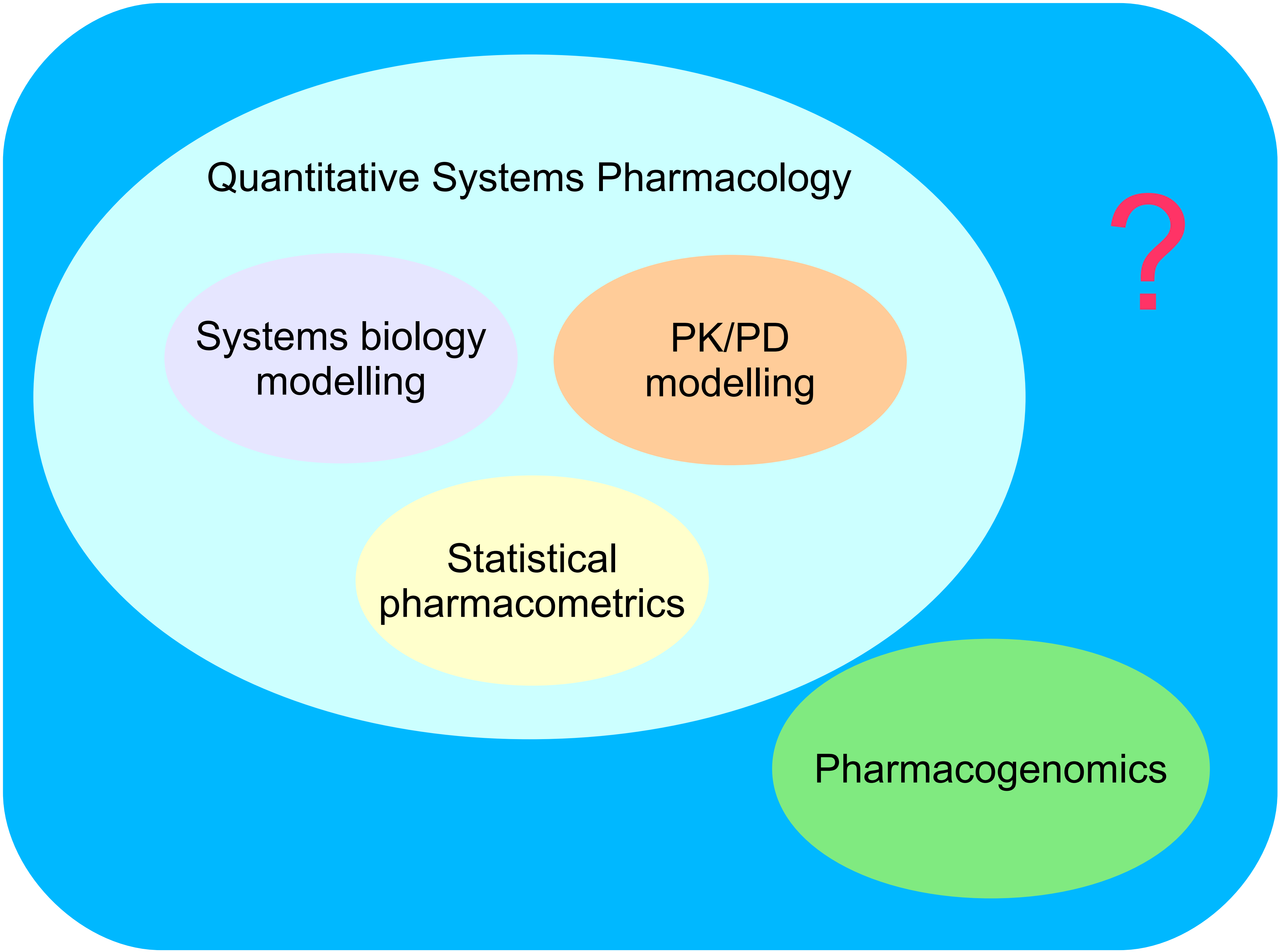
Drug discovery and omics



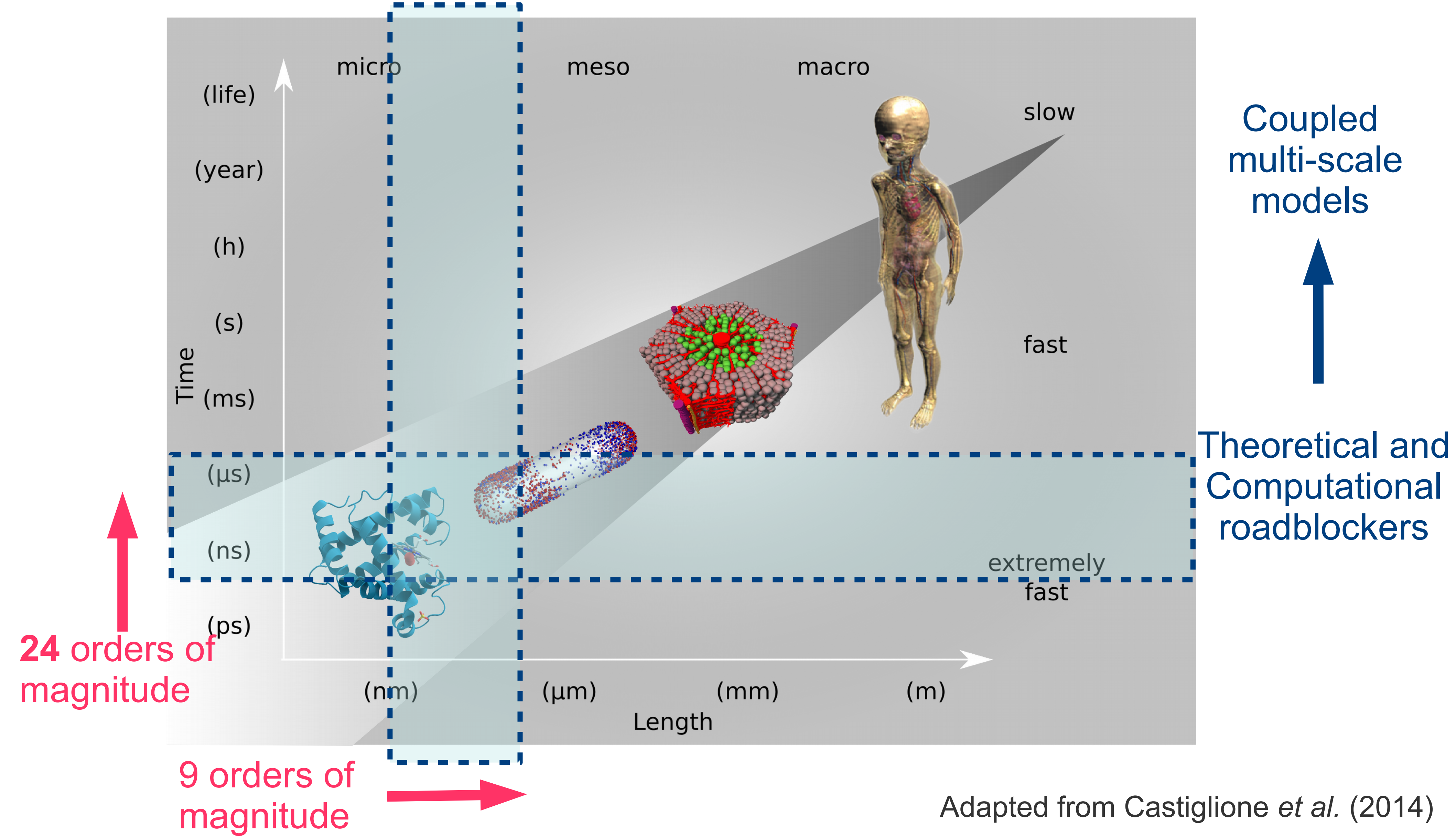




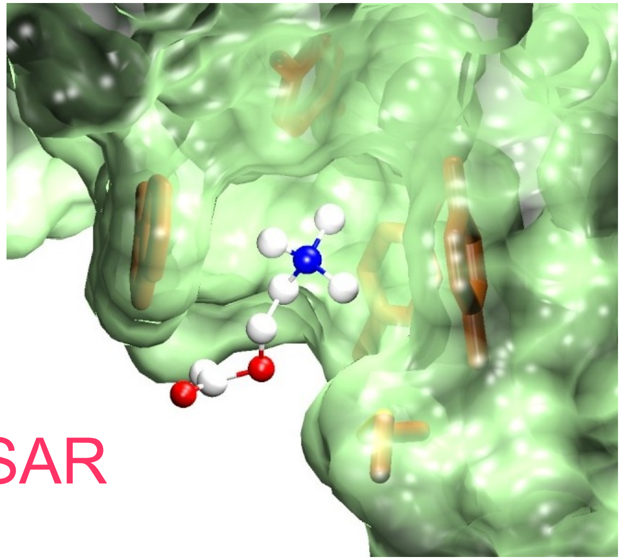



Quantitative Systems Pharmacology
Systems biology modelling
PK/PD modelling
Statistical pharmacometrics
Pharmacogenomics
?

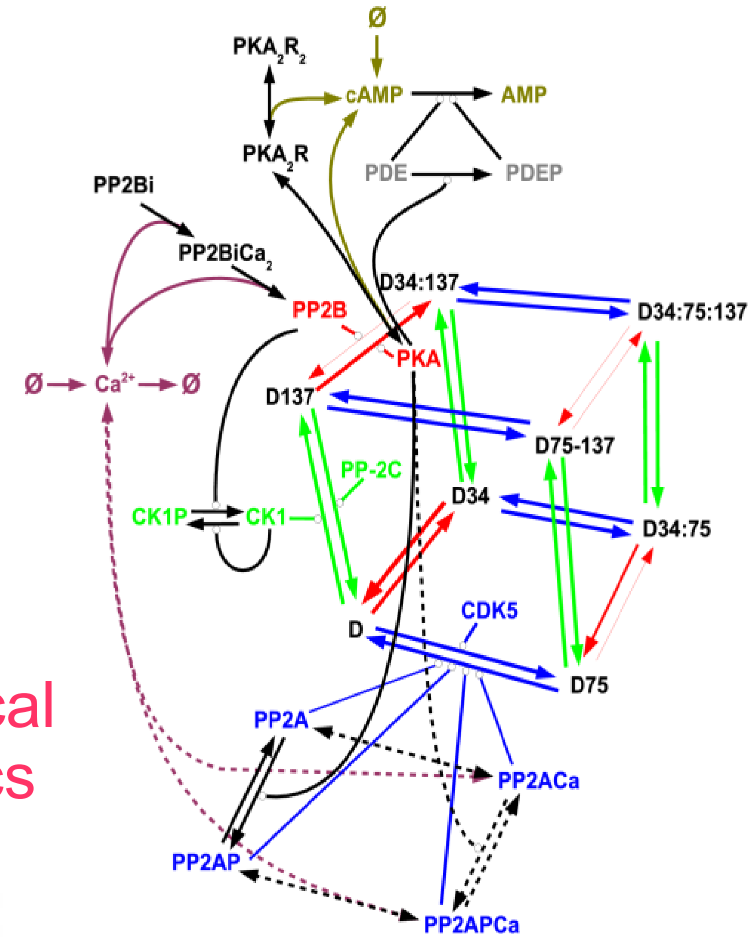
The problem of scales



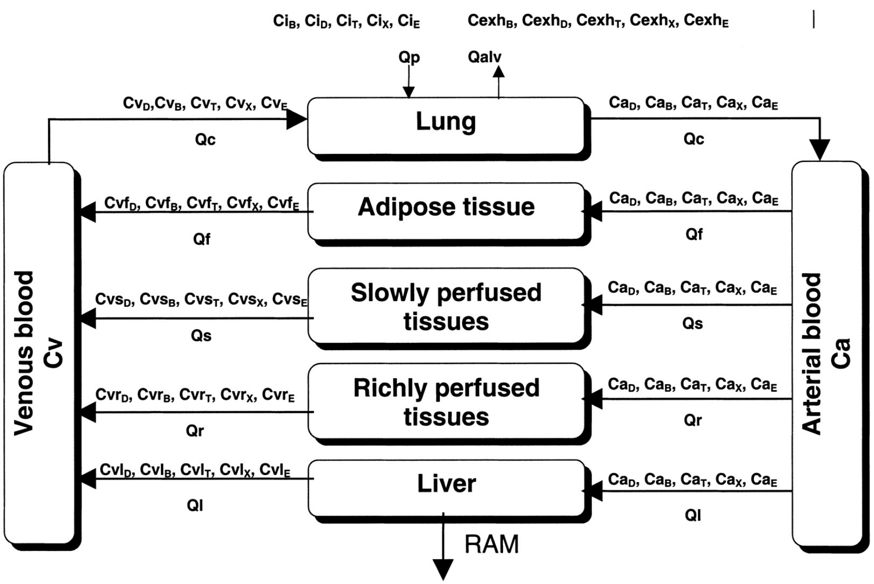
Adapted from Castiglione *et al.* (2014)



QSAR



chemical kinetics



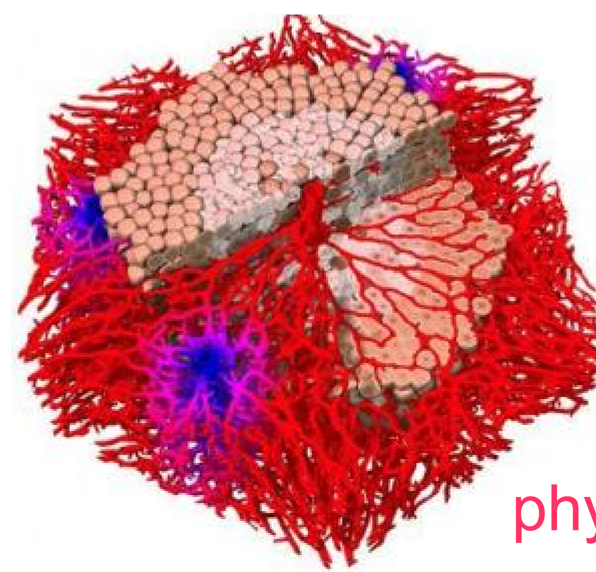
$$RAM_D = \frac{Vmax_D \; Cvl_D}{Km_D\left(1+\frac{Cvl_B}{Ki_{BD}}+\frac{Cvl_T}{Ki_{TD}}+\frac{Cvl_X}{Ki_{XD}}+\frac{Cvl_E}{Ki_{ED}}\right)+Cvl_D}$$

$$RAM_B = \frac{Vmax_B \; Cvl_B}{Km_B\left(1+\frac{Cvl_D}{Ki_{DB}}+\frac{Cvl_T}{Ki_{TB}}+\frac{Cvl_E}{Ki_{EB}}+\frac{Cvl_X}{Ki_{XB}}\right)+Cvl_B}$$

$$RAM_T = \frac{Vmax_T \; Cvl_T}{Km_T\left(1+\frac{Cvl_D}{Ki_{DT}}+\frac{Cvl_B}{Ki_{BT}}+\frac{Cvl_E}{Ki_{ET}}+\frac{Cvl_X}{Ki_{XT}}\right)+Cvl_T}$$

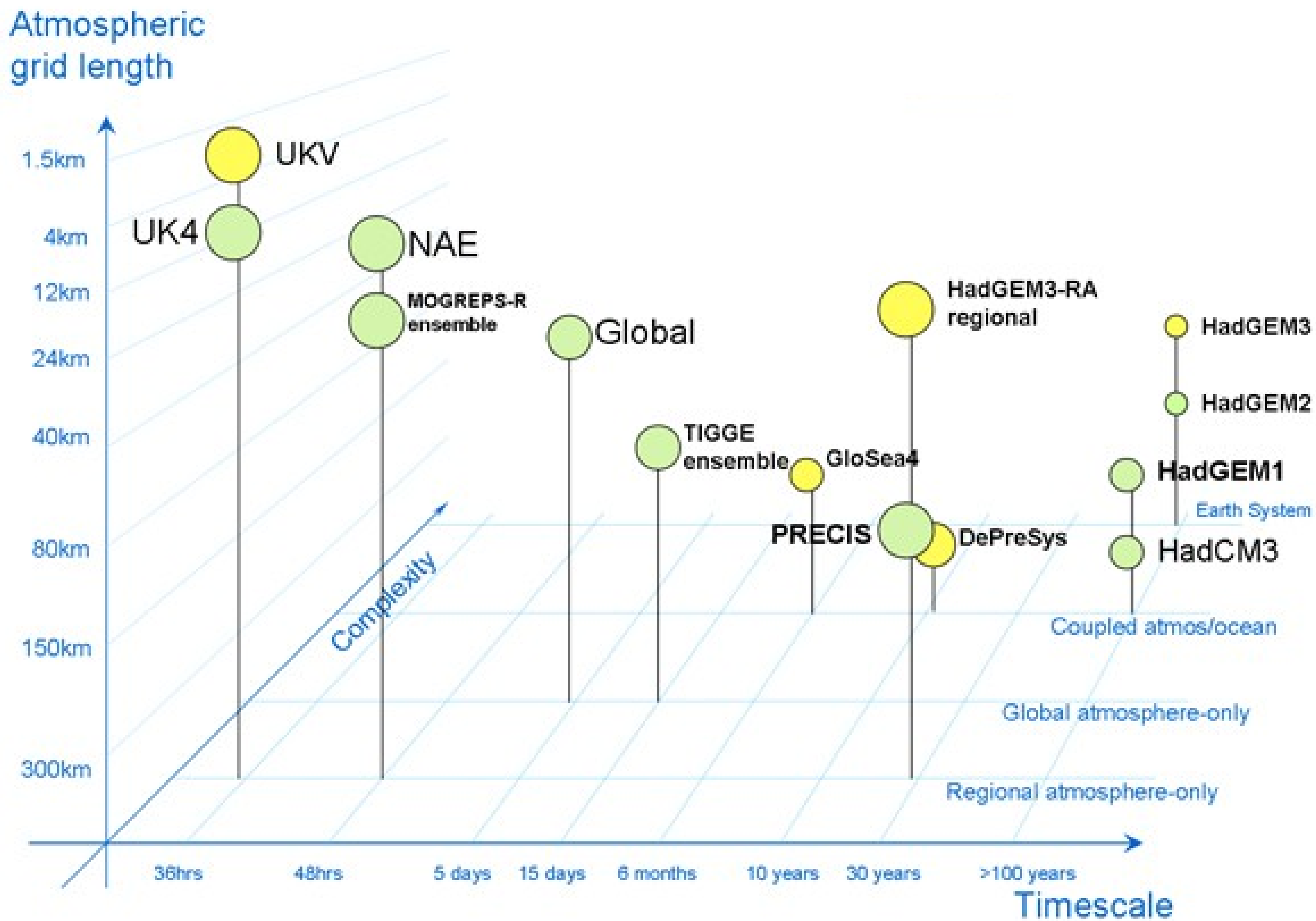
$$RAM_E = \frac{Vmax_E \; Cvl_E}{}$$

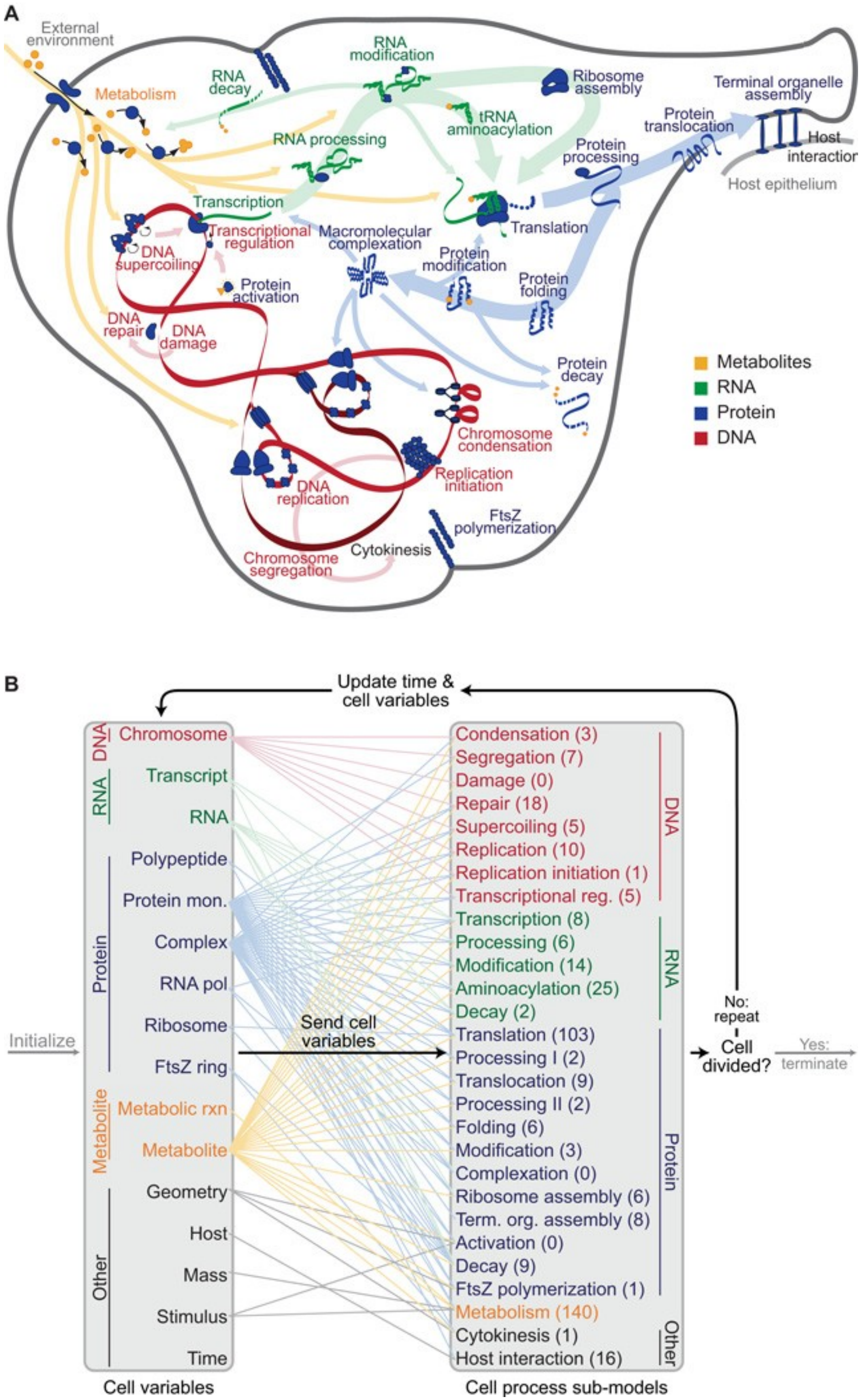
pharmacometrics



physiology

Met Office Seamless Unified Model





Theory

2012 Jul 20

Cell

A Whole-Cell Computational Model Predicts Phenotype from Genotype

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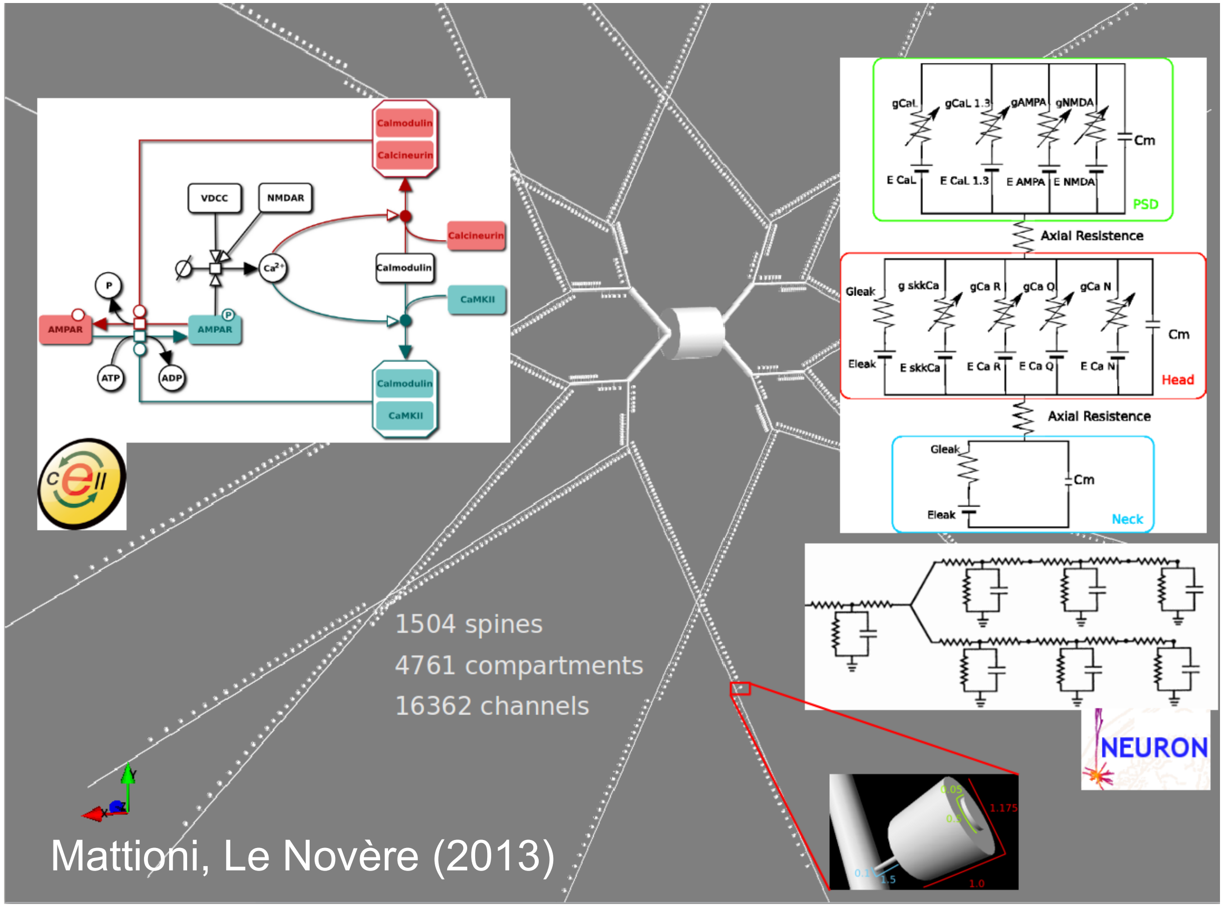
http://dx.doi.org/10.1016/j.cell.2012.05.044

SUMMARY

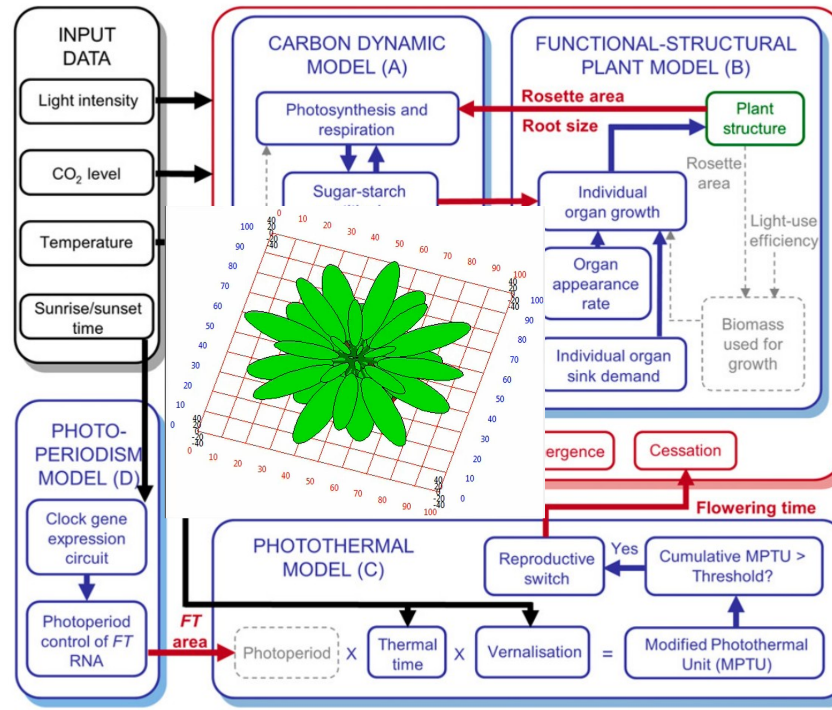
Understanding how complex phenotypes arise from individual molecules and their interactions is a primary challenge in biology that computational approaches are poised to tackle. We report a whole-cell computational model of the life cycle of the human pathogen *Mycoplasma genitalium* that includes all 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.

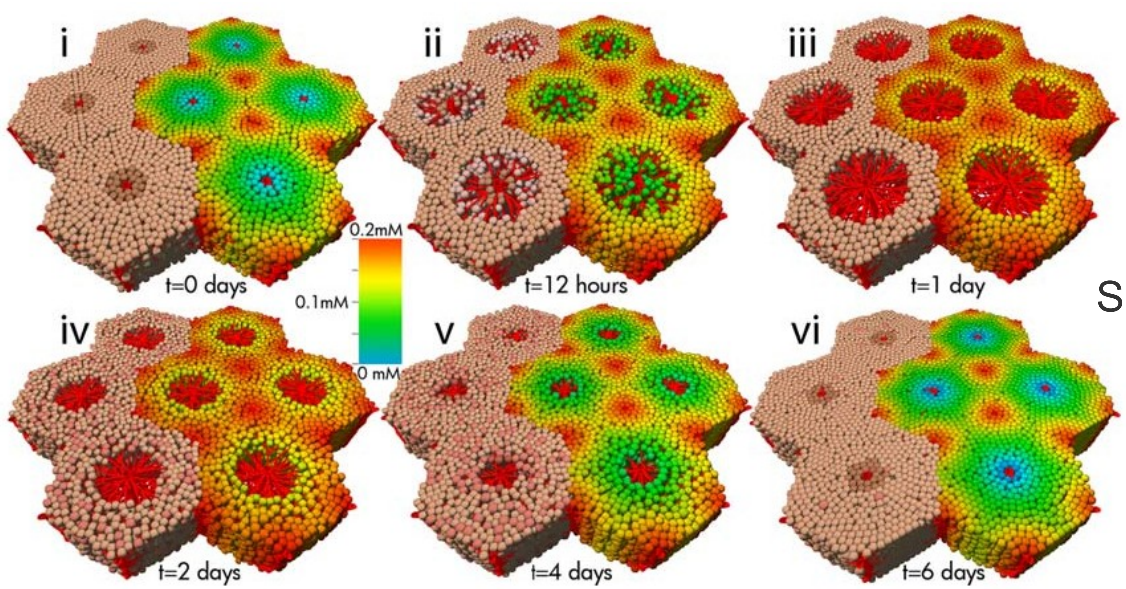
The second limiting factor has been that no single computational method is sufficient to explain complex phenotypes in terms of molecular components and their interactions. The first approaches to modeling cellular physiology, based on ordinary differential equations (ODEs) (Atlas et al., 2008; Browning et al., 2004; Castellanos et al., 2004, 2007; Domach et al., 1984; Tomita et al., 1999), were limited by the difficulty in obtaining the necessary model parameters. Subsequently, alternative



Mattioni, Le Novère (2013)



Chew *et al.* (2014)



Schliess *et al.* (2014)

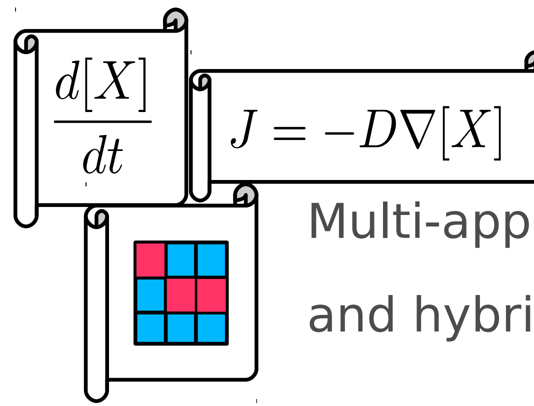
Models need to be developed differently

Modular

Collaborative

Built on

knowledge-bases



Multi-approach

and hybrid models

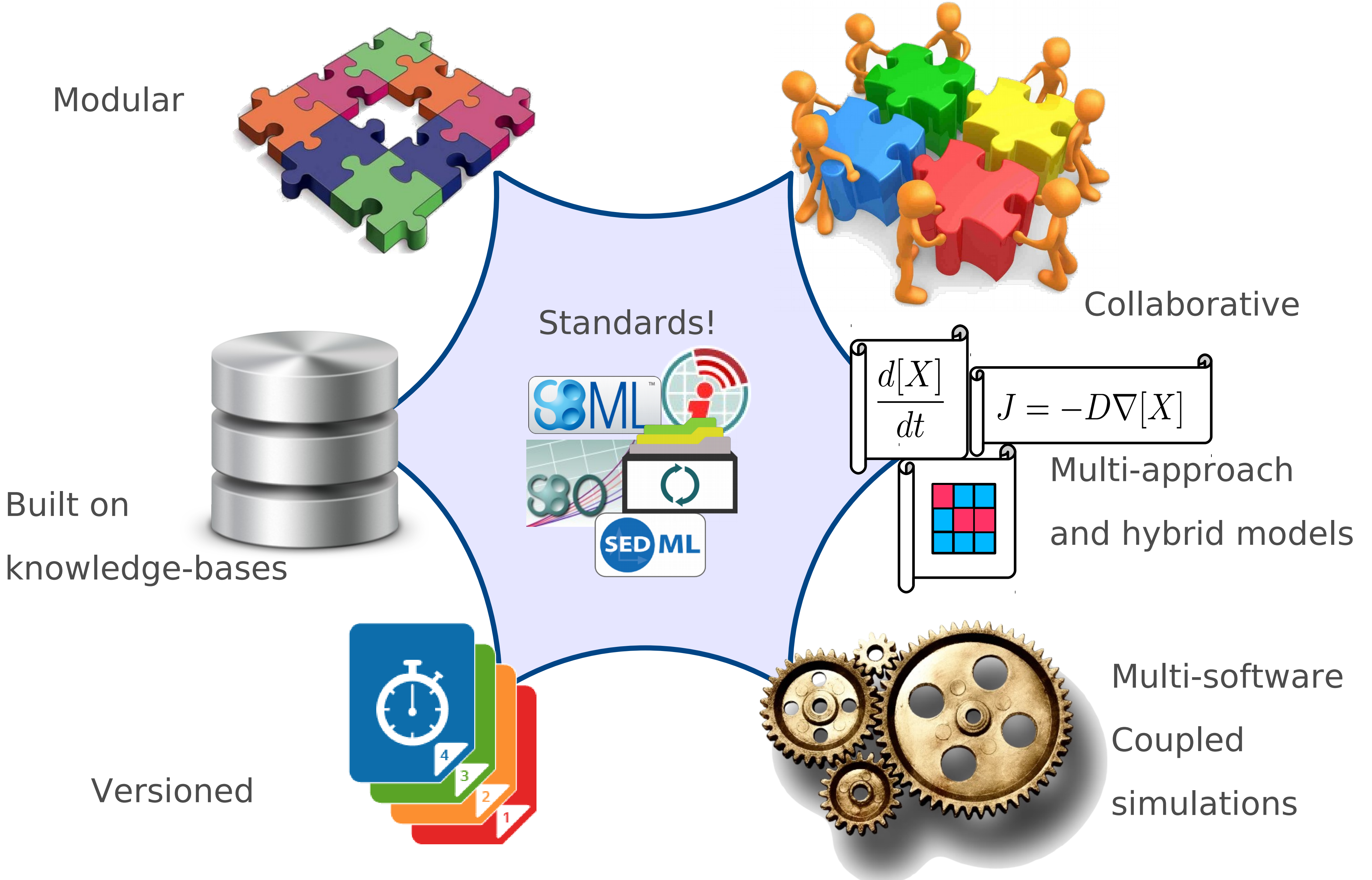
Versioned

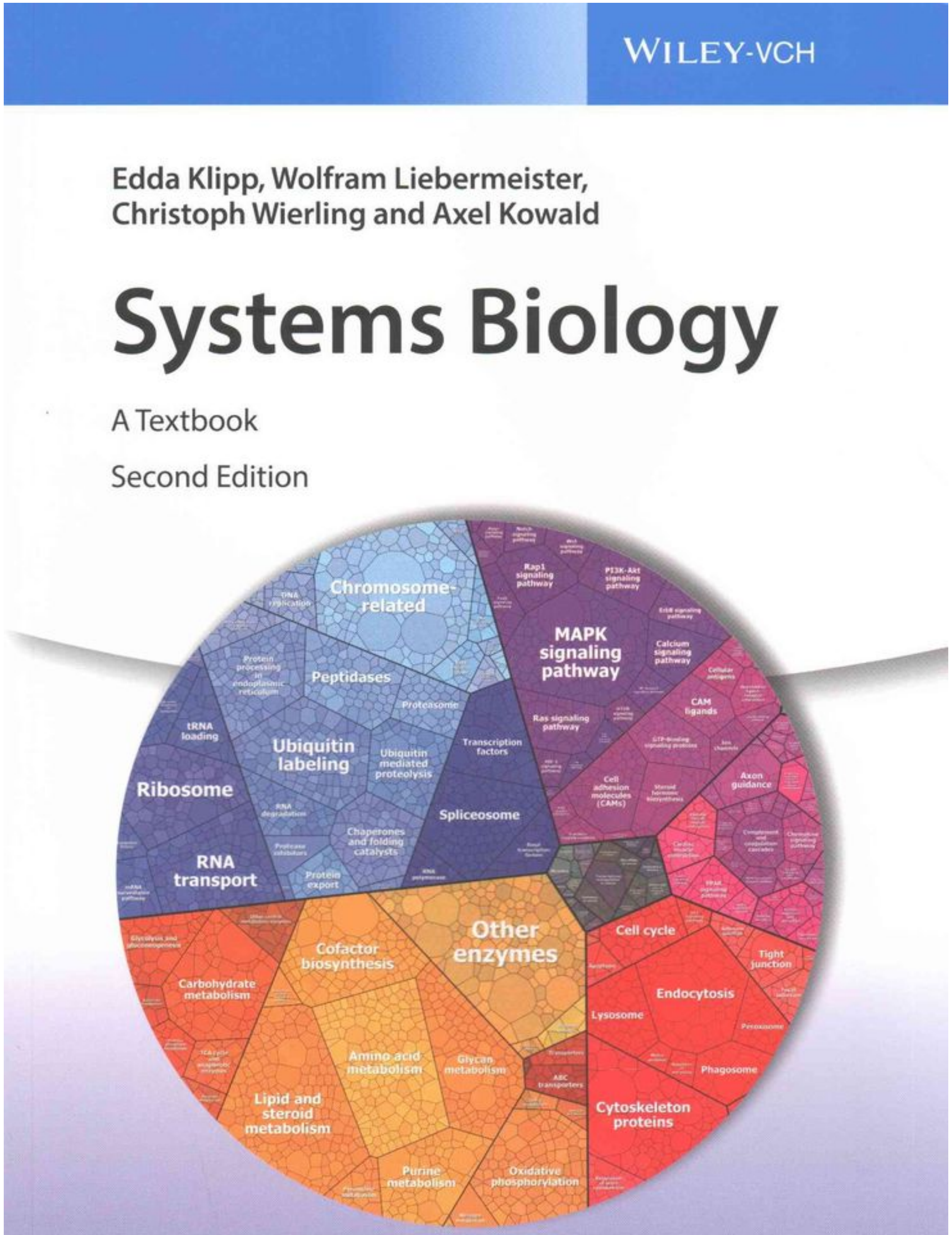
Multi-software

Coupled

simulations

Models need to be developed differently




WILEY-VCH
Edda Klipp, Wolfram Liebermeister,
Christoph Wierling and Axel Kowald
Systems Biology
A Textbook
Second Edition
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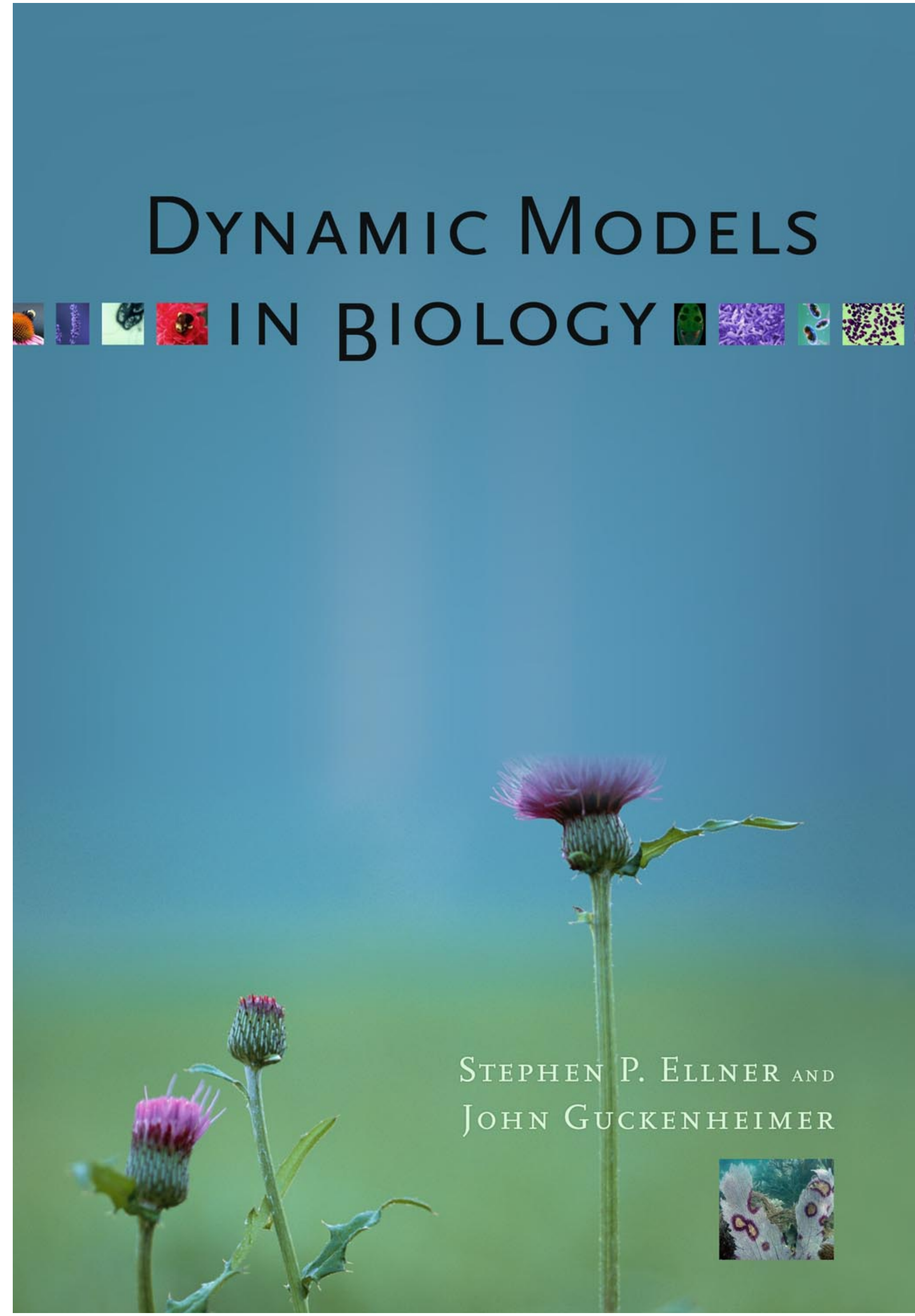
MAPK signaling pathway
Peptidases
Ubiquitin labeling
Ribosome
RNA transport
Spliceosome
Other enzymes
Cofactor biosynthesis
Carbohydrate metabolism
Cell cycle
Endocytosis
Amino acid metabolism
Lipid and steroid metabolism
Cytoskeleton proteins


DYNAMIC MODELS
IN BIOLOGY
STEPHEN P. ELLNER AND
JOHN GUCKENHEIMER