

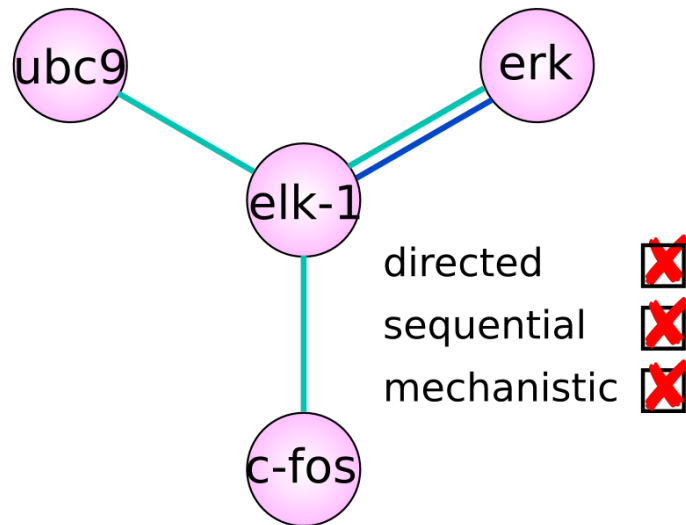
Modelling in systems biology, a few challenges

Nicolas Le Novère, The Babraham Institute

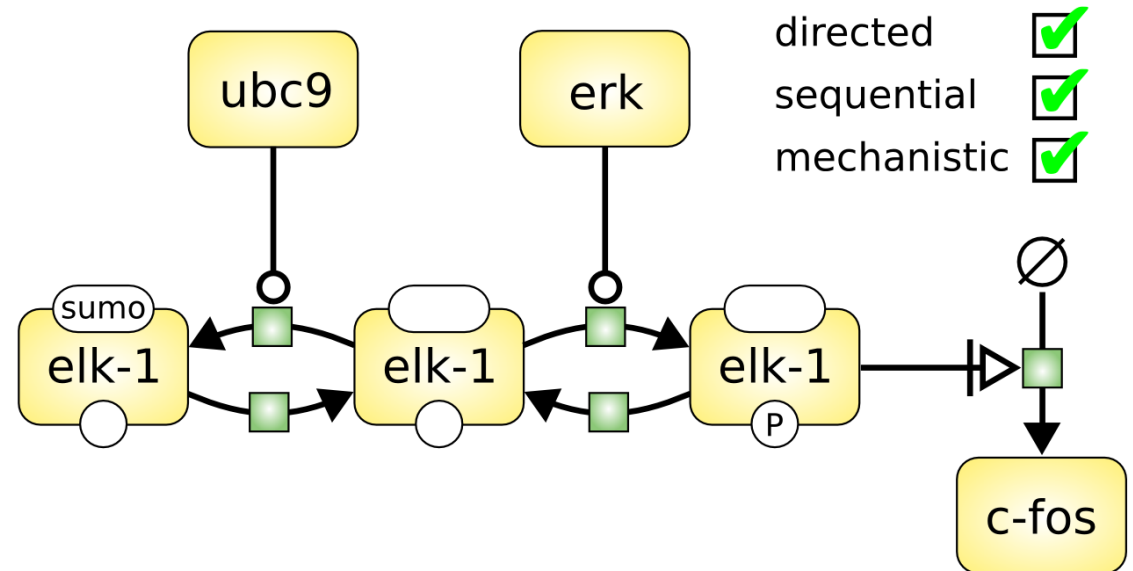
n.lenovere@gmail.com

The four views of molecular systems biology

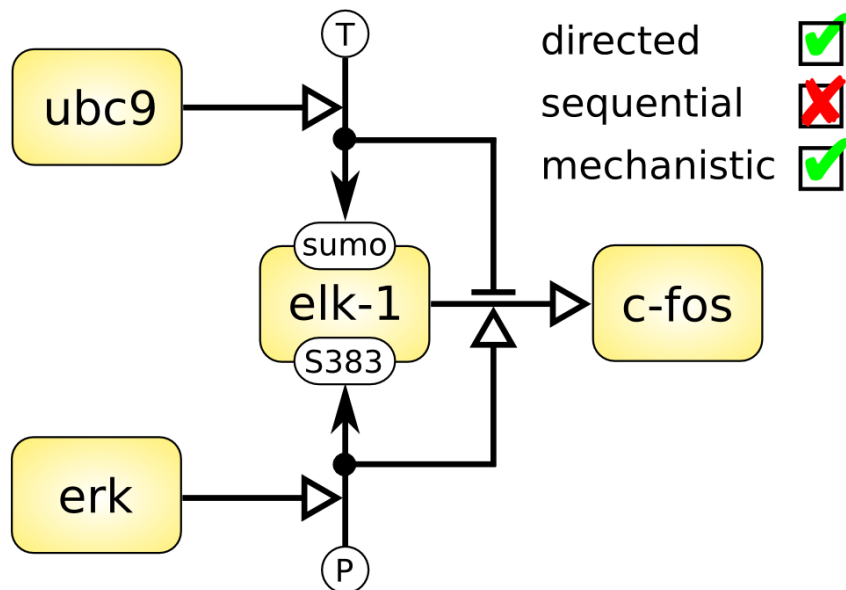
a interaction network



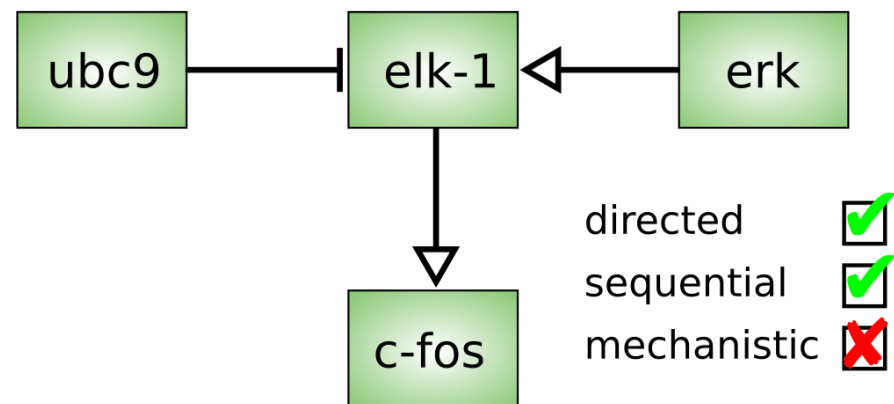
c process descriptions



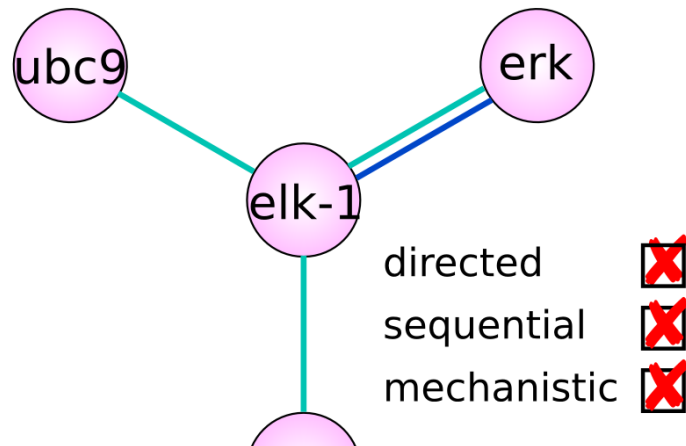
b entity relationships



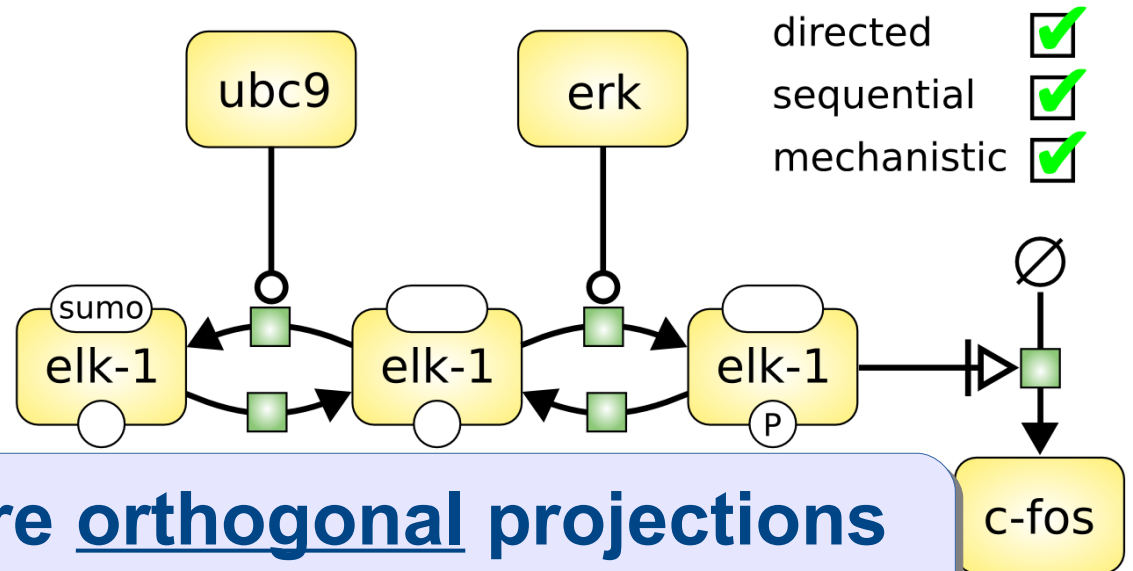
d activity flows



a interaction network

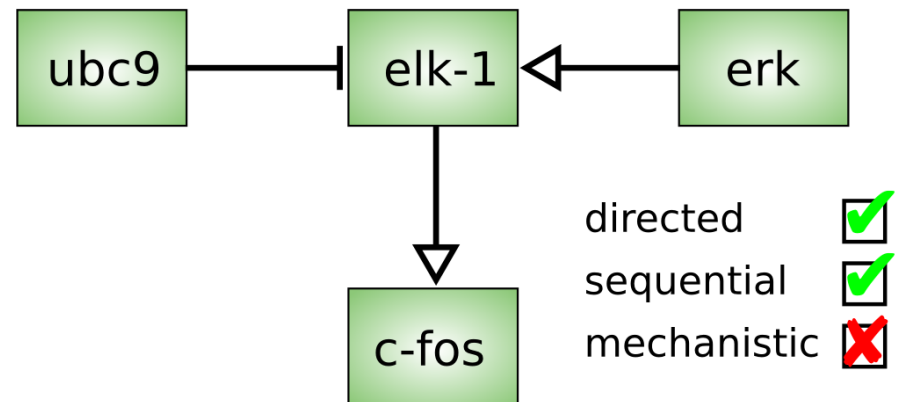
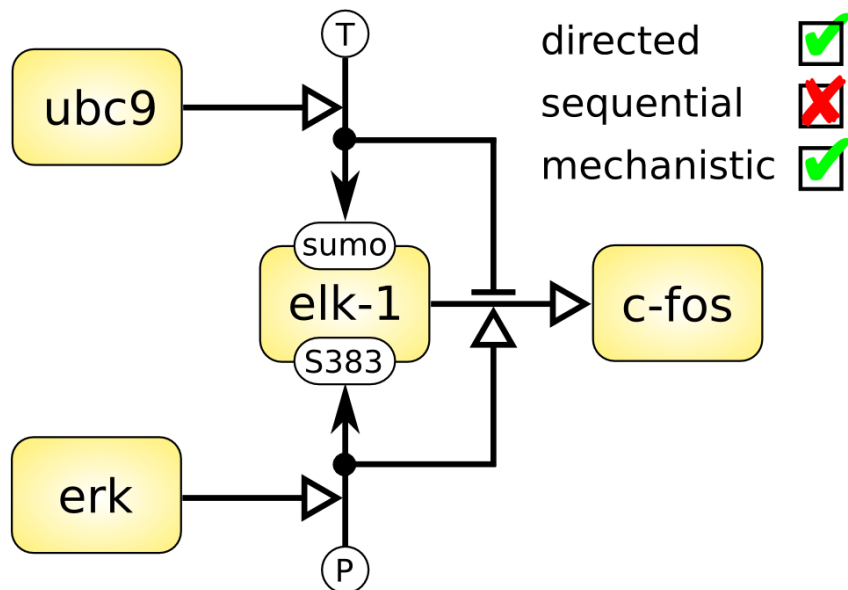


c process descriptions

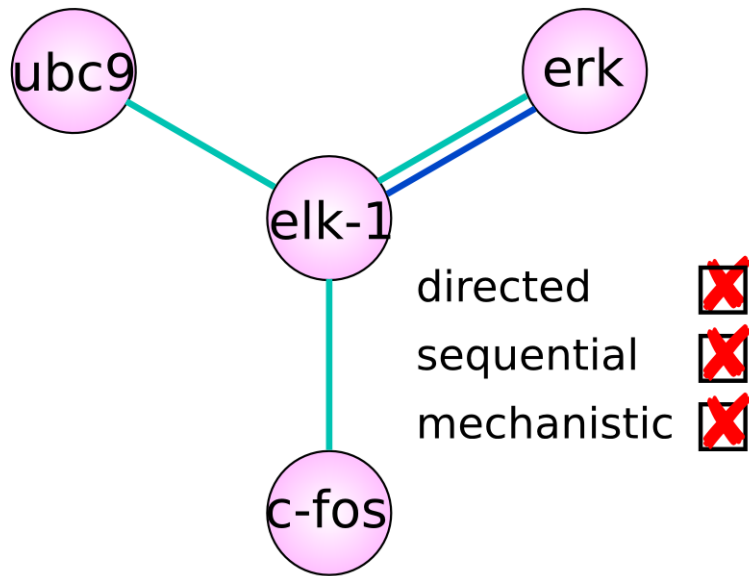


The four views are orthogonal projections of the underlying biological phenomena

b ent



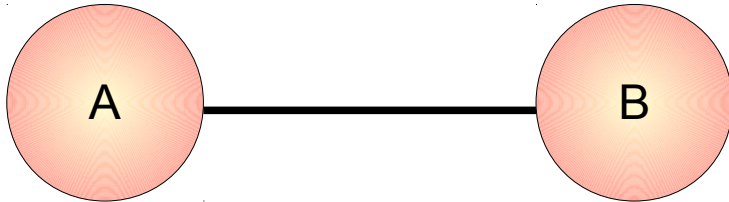
Interaction networks



- Statistical modelling
- Functional genomics
- IntAct, DIP, String

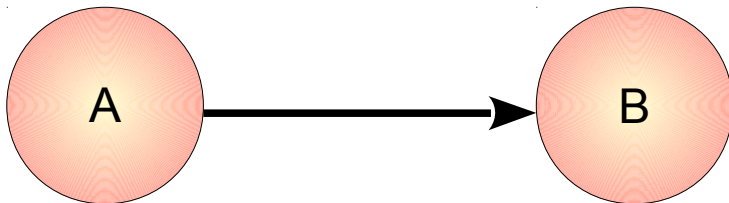
more on Monday

Undirected, directed, signed



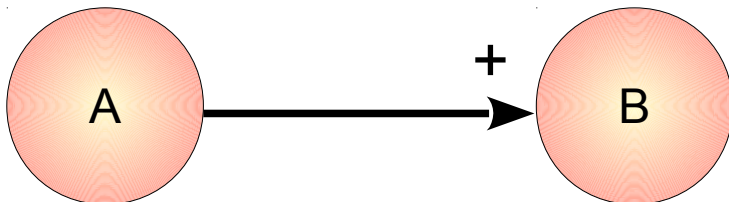
Undirected

“A interacts with B”



directed

“A influences B”

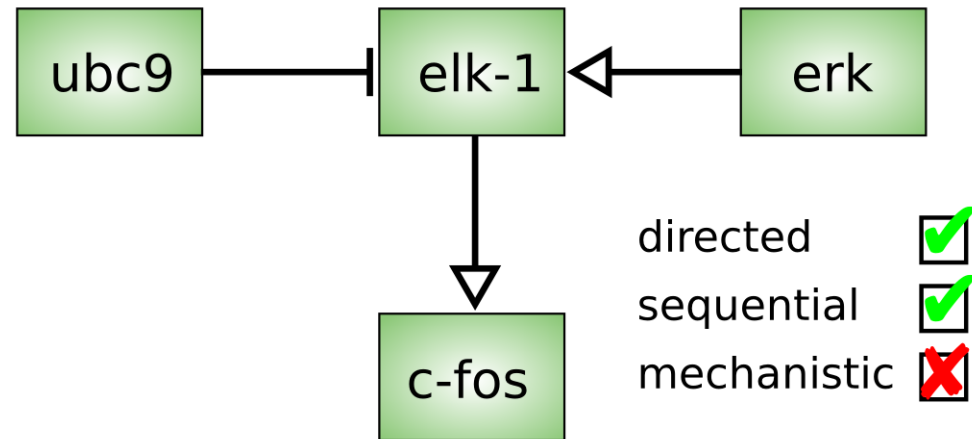


Signed

A influences positively B

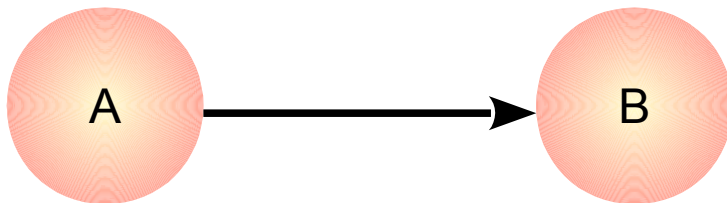
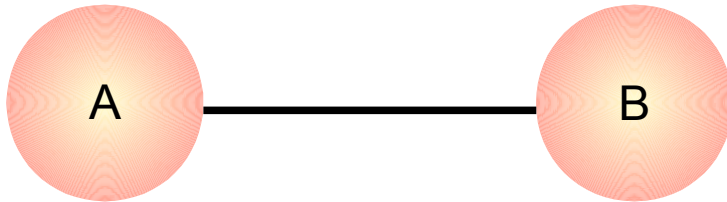
Activity Flows

- Logical modelling
- Signalling pathways, gene regulatory networks
- KEGG non-metabolic, STKE

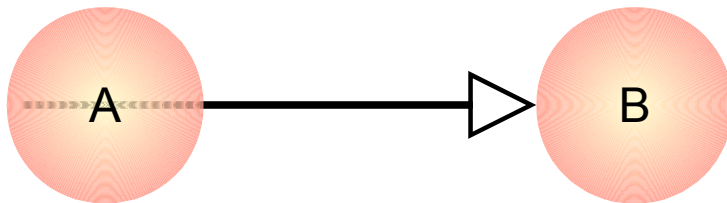


more on Tuesday

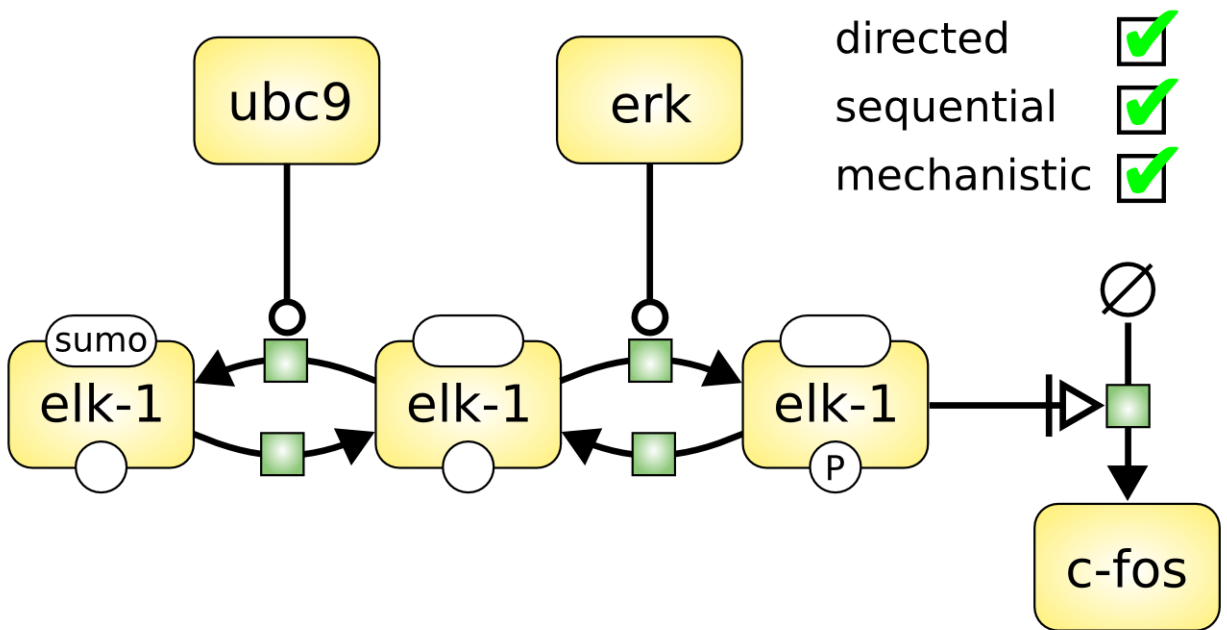
Undirected, directed, signed



A signed interaction network
is equivalent to an activity flow



Process Descriptions

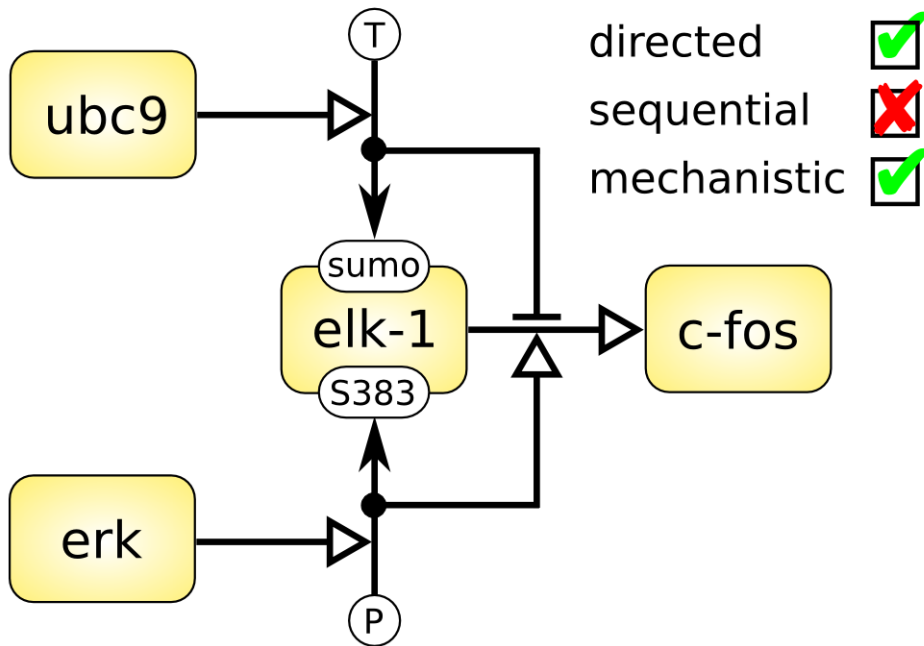


- Process modelling
- Biochemistry, Metabolic networks
- Generally within “closed world”
- Subjected to combinatorial explosion
- KEGG metabolic, Reactome

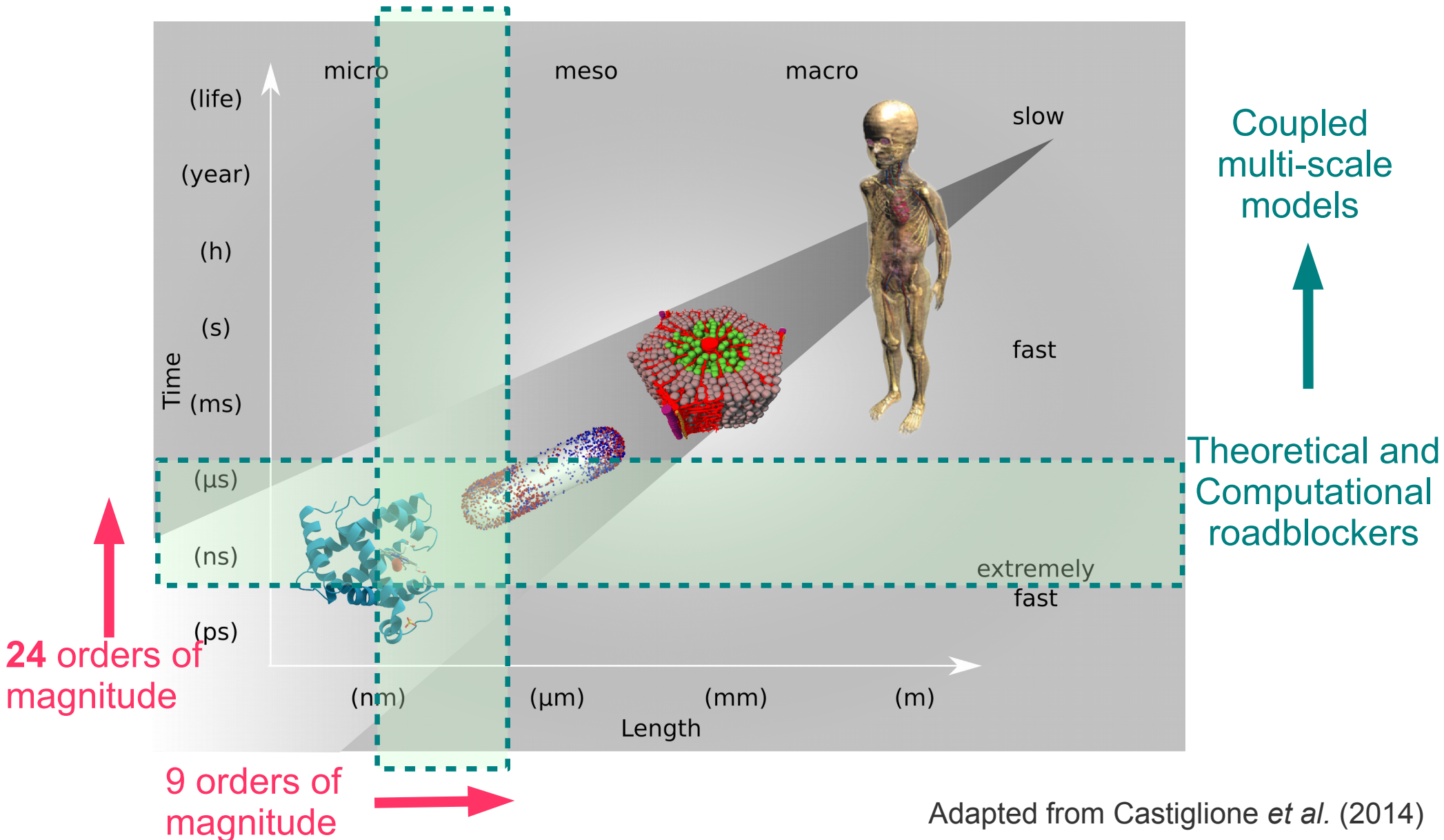
[more on Wednesday](#)

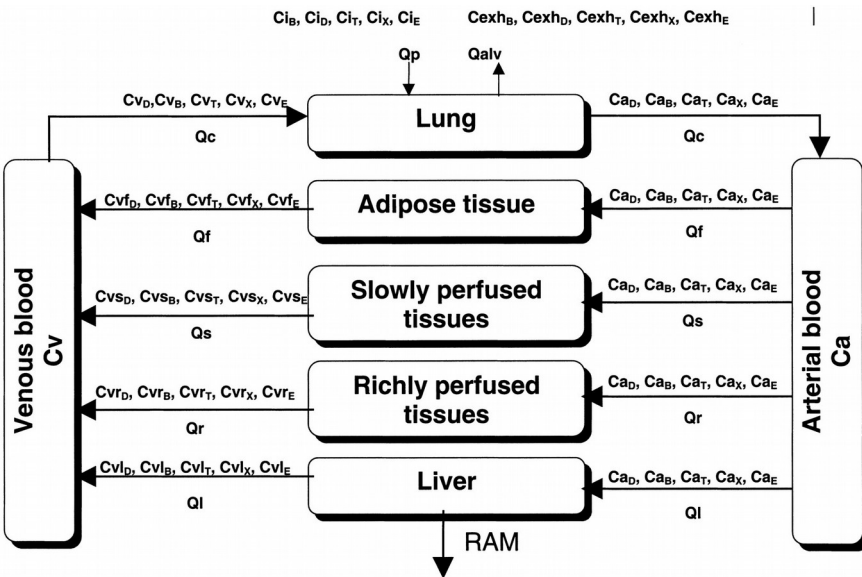
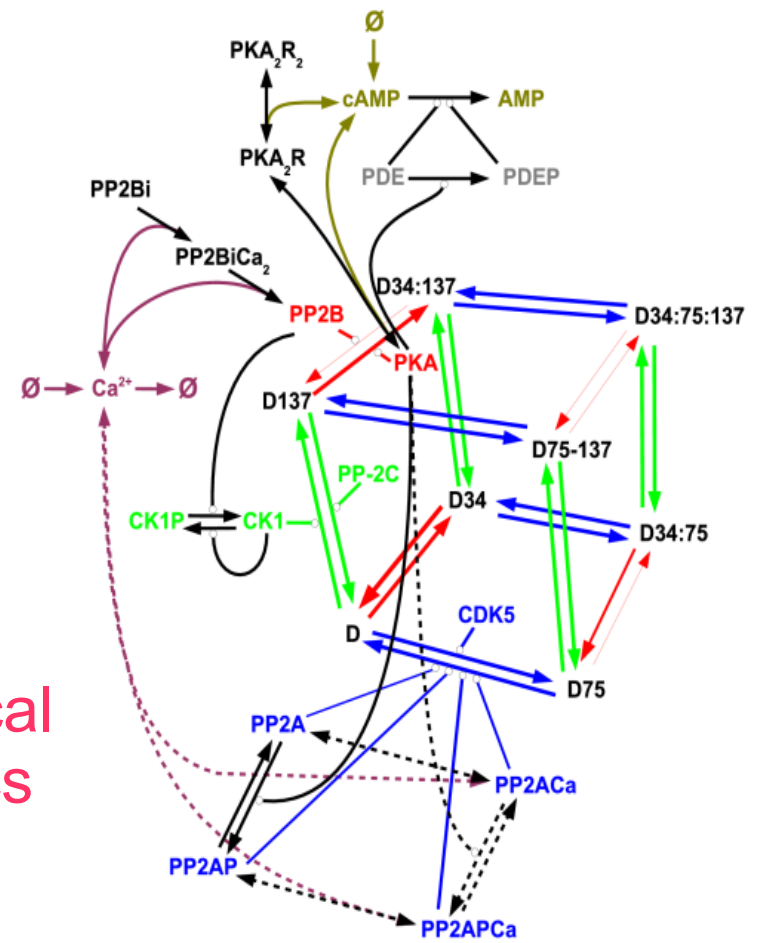
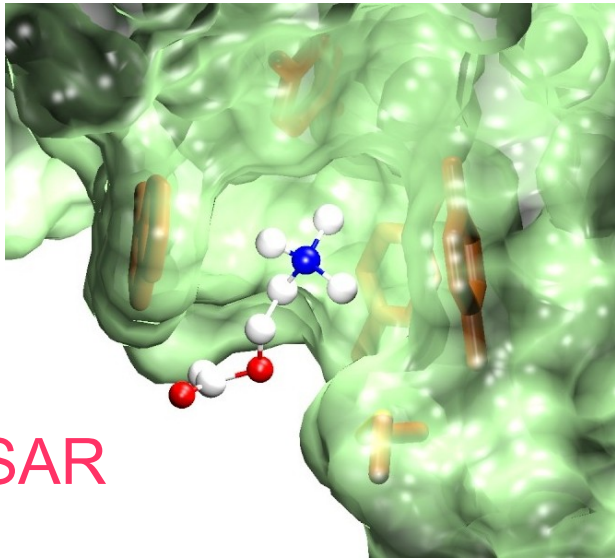
Entity Relationships

- Rule-based modelling
- Molecular Biology
- “Open world”
- Independent rules: no explosion
- Molecular Interaction Maps



The problem of scales



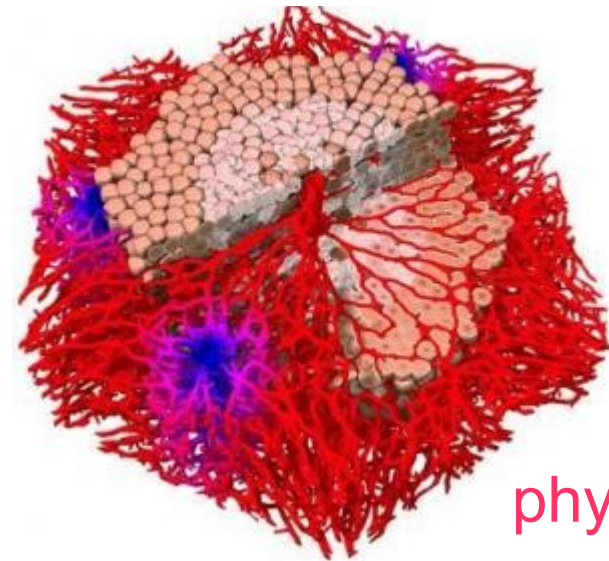


$$RAM_D = \frac{V_{max_D} C_{vD}}{K_{mD} \left(1 + \frac{C_{vD}}{K_{iD}} + \frac{C_{vT}}{K_{iD}} + \frac{C_{vX}}{K_{iD}} + \frac{C_{vE}}{K_{iD}} \right) + C_{vD}}$$

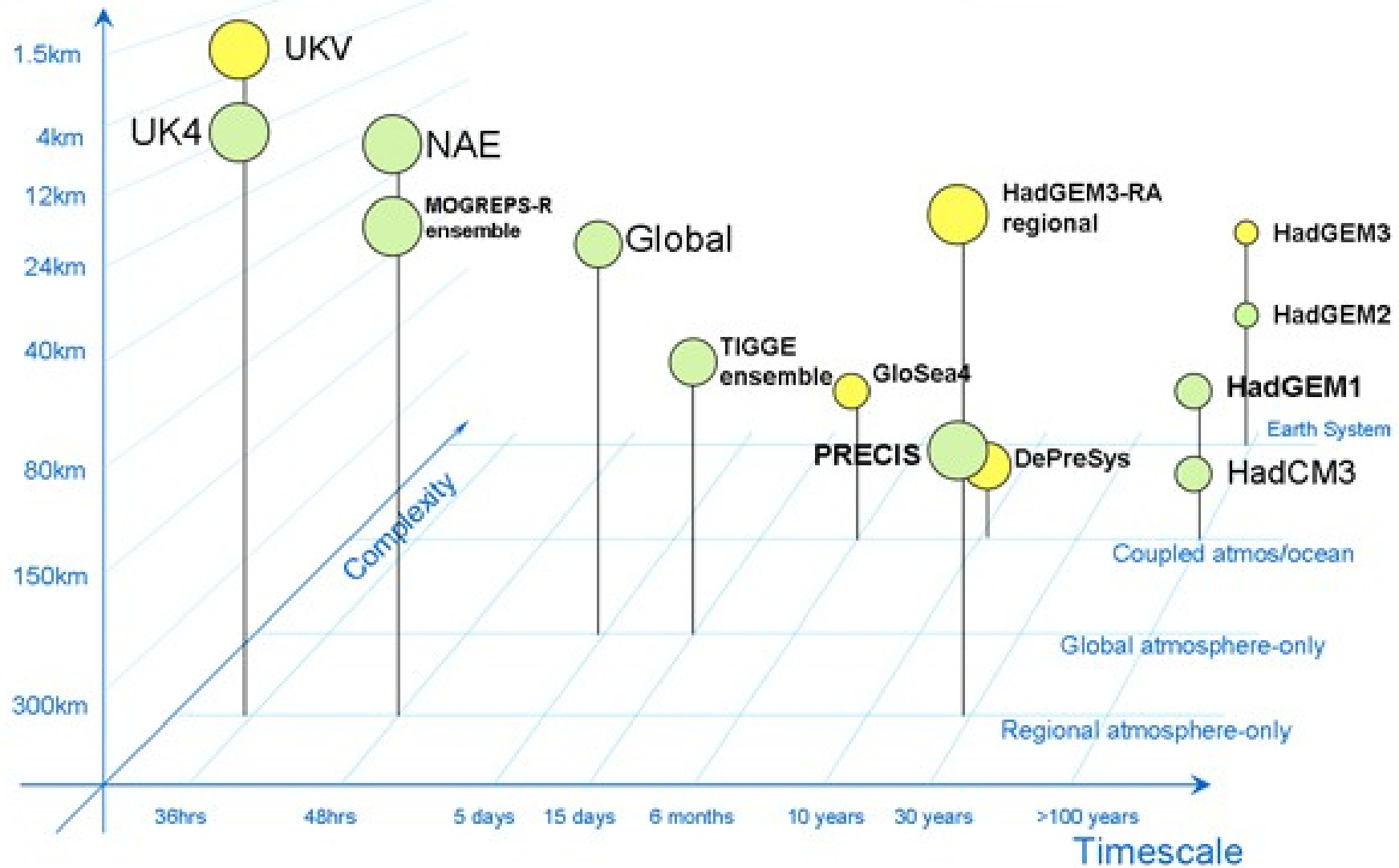
$$RAM_B = \frac{V_{max_B} C_{vB}}{K_{mB} \left(1 + \frac{C_{vD}}{K_{iB}} + \frac{C_{vT}}{K_{iB}} + \frac{C_{vX}}{K_{iB}} + \frac{C_{vE}}{K_{iB}} \right) + C_{vB}}$$

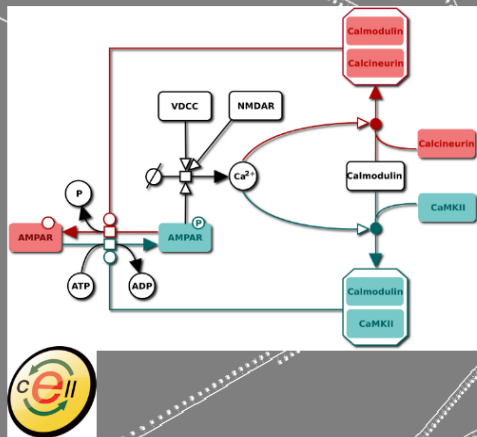
$$RAM_T = \frac{V_{max_T} C_{vT}}{K_{mT} \left(1 + \frac{C_{vD}}{K_{iT}} + \frac{C_{vB}}{K_{iT}} + \frac{C_{vX}}{K_{iT}} + \frac{C_{vE}}{K_{iT}} \right) + C_{vT}}$$

$$RAM_E = \frac{V_{max_E} C_{vE}}{K_{mE} \left(1 + \frac{C_{vD}}{K_{iE}} + \frac{C_{vB}}{K_{iE}} + \frac{C_{vX}}{K_{iE}} + \frac{C_{vT}}{K_{iE}} \right) + C_{vE}}$$



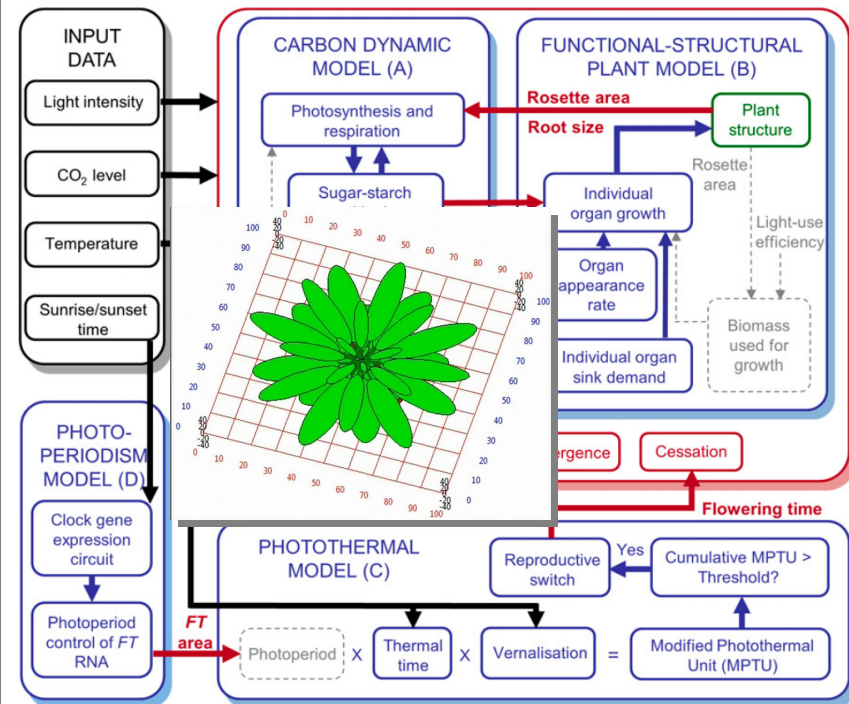
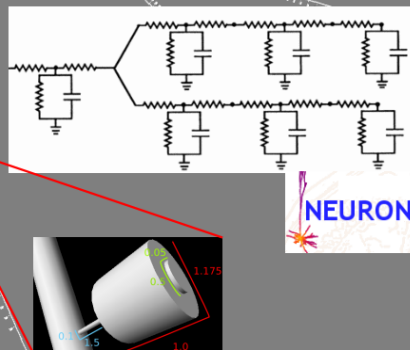
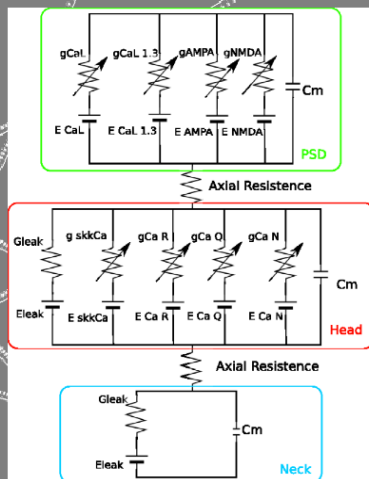
Atmospheric
grid length



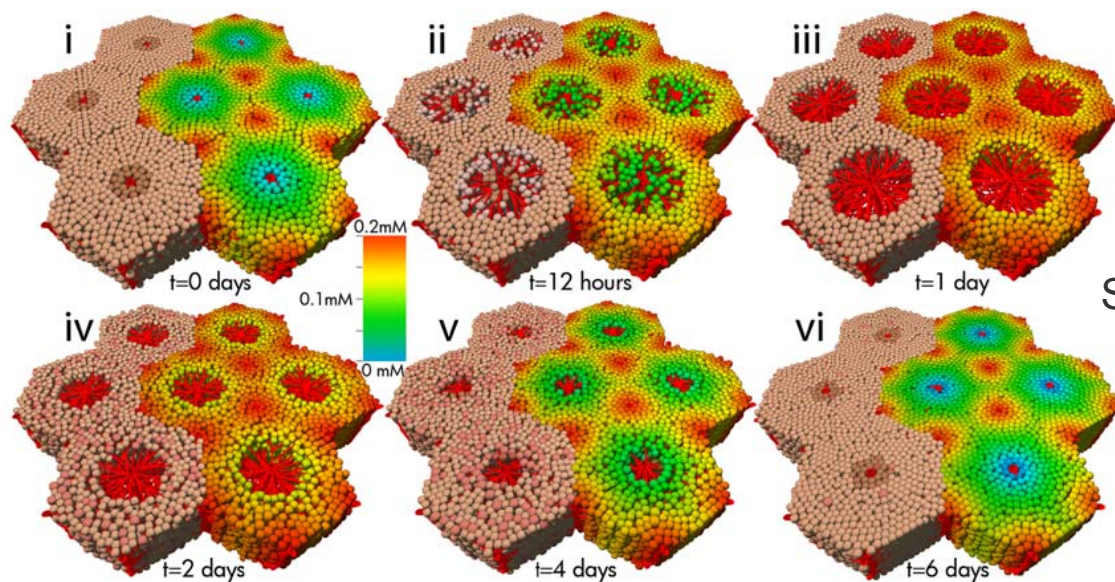


1504 spines
4761 compartments
16362 channels

Mattioni, Le Novère (2013)

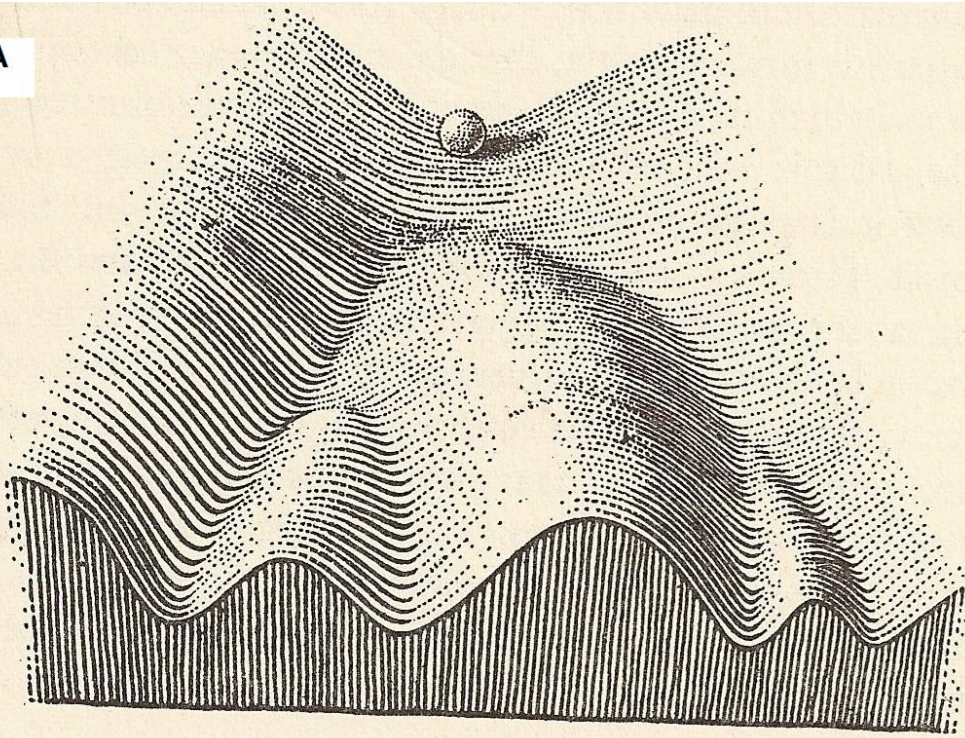


Chew *et al.* (2014)



Schliess *et al.* (2014)

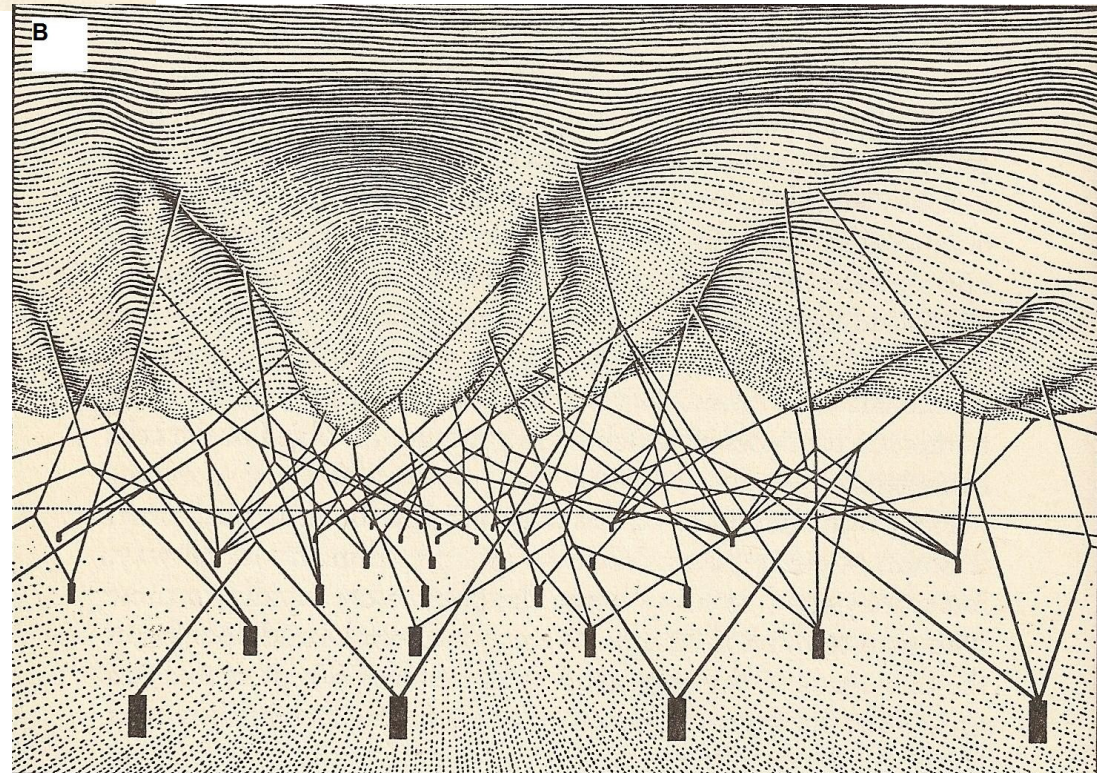
A



Emergent properties and the gene-system-phenotype puzzle

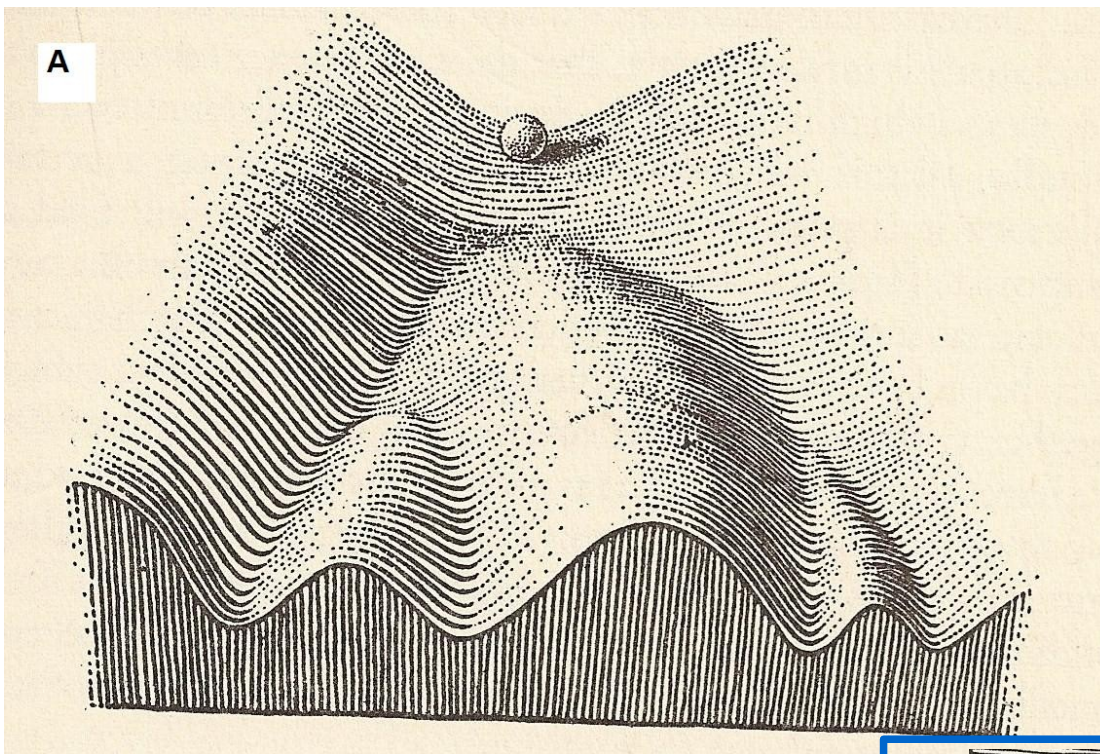
Waddington C.H., Kacser H (1957)
The Strategy of the Genes:
A Discussion of Some Aspects of
Theoretical Biology.
George Allen & Unwin

B



Emergent properties and the gene-system-phenotype puzzle

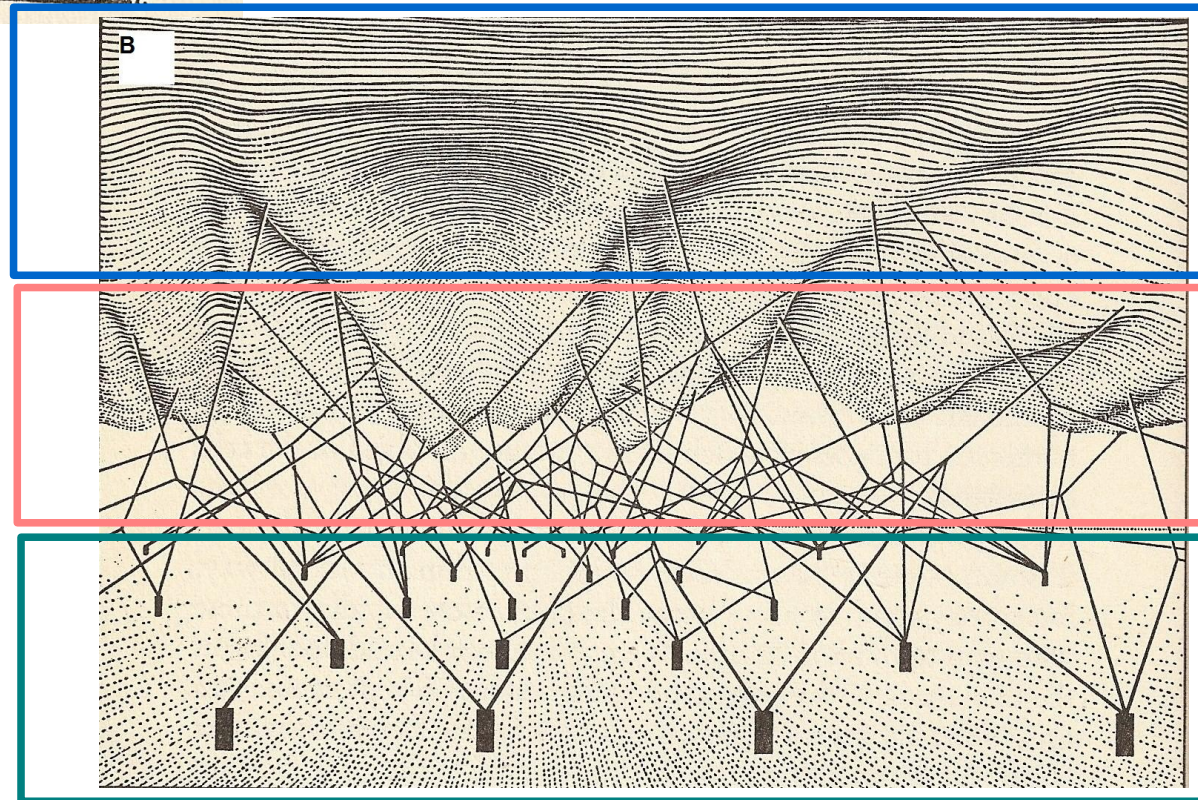
Waddington C.H., Kacser H (1957)
The Strategy of the Genes:
A Discussion of Some Aspects of
Theoretical Biology.
George Allen & Unwin



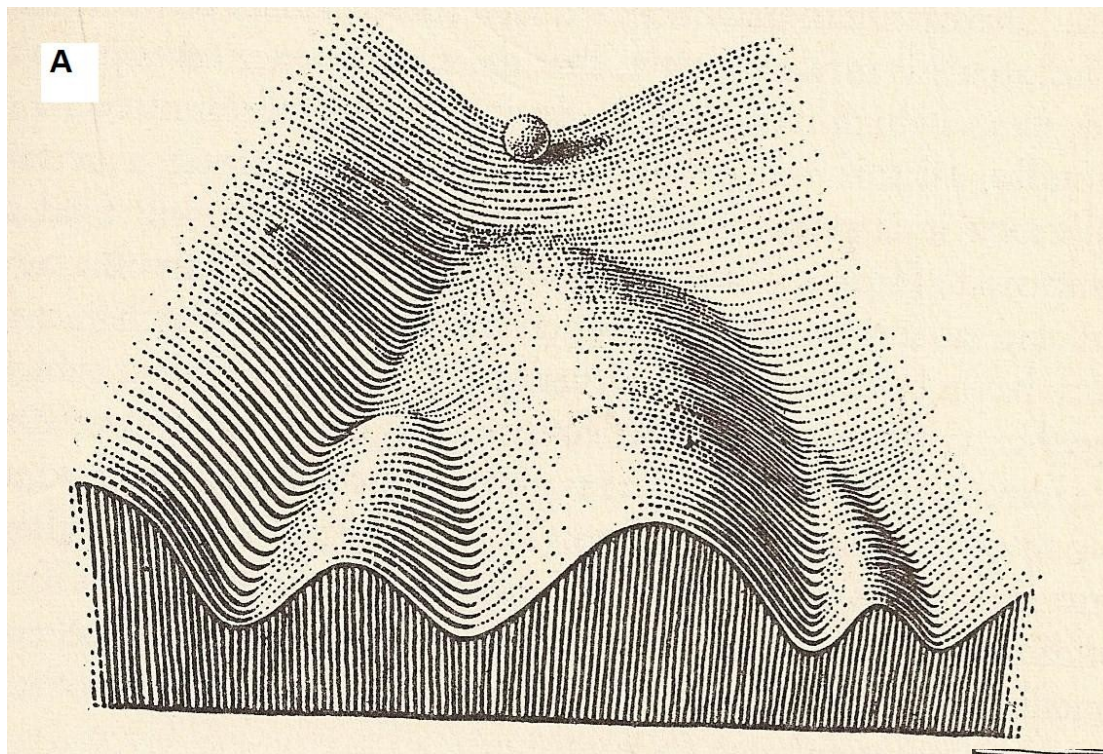
physiology ← phenotype

systems
biology ← system

genetics ← genotype

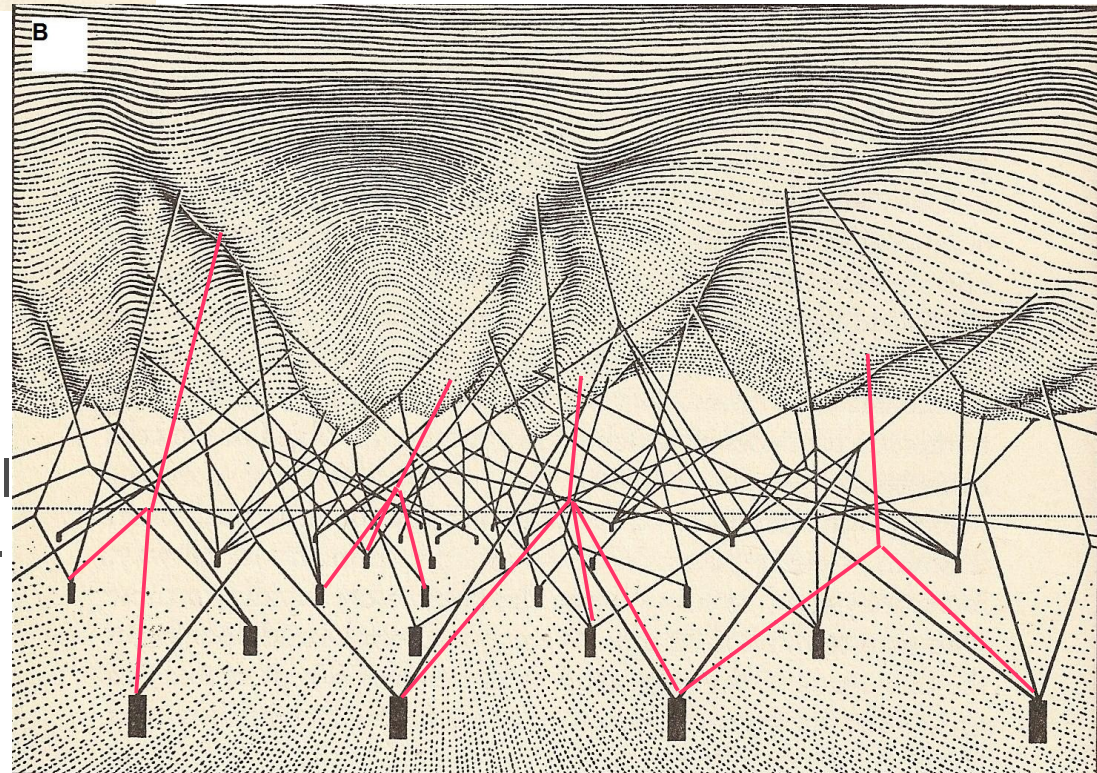


Emergent properties and the gene-system-phenotype puzzle



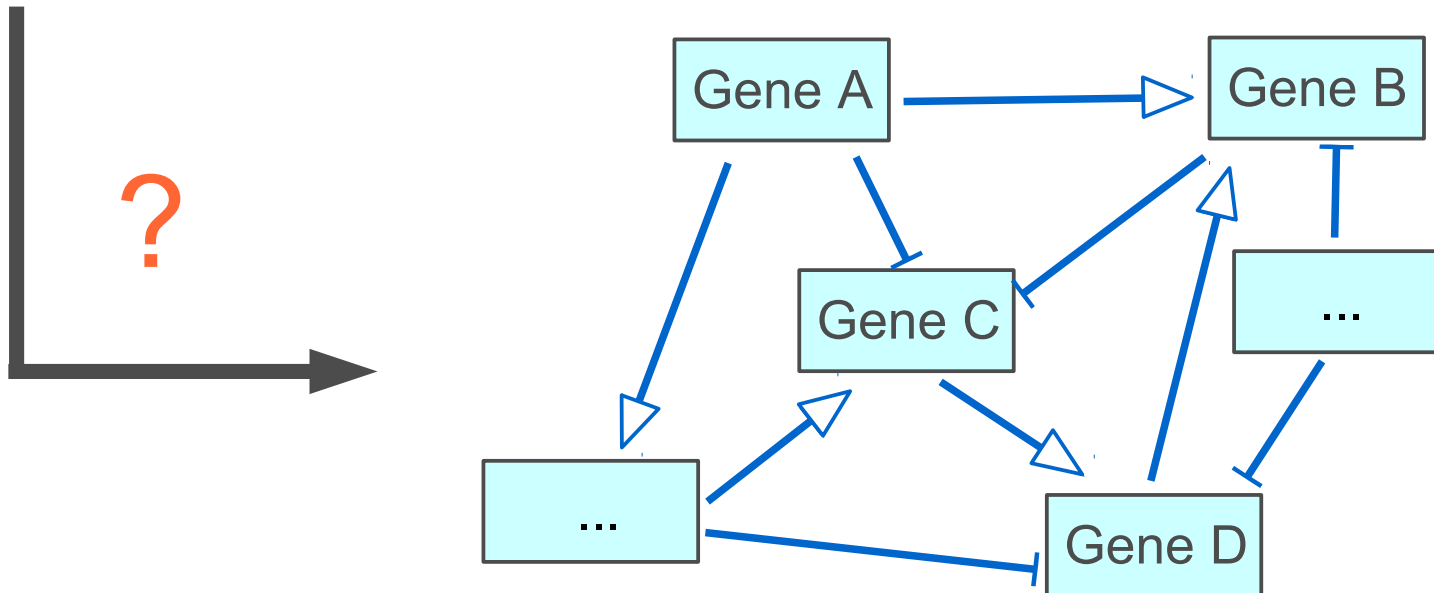
Waddington C.H., Kacser H (1957)
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Many networks can theoretically generate the same phenotype, and this happens, in a synchronous (sister cells with same phenotype but different transcript/prote/metabol/omes) and diachronous manner (*omes of a cell changes over time but same phenotype).

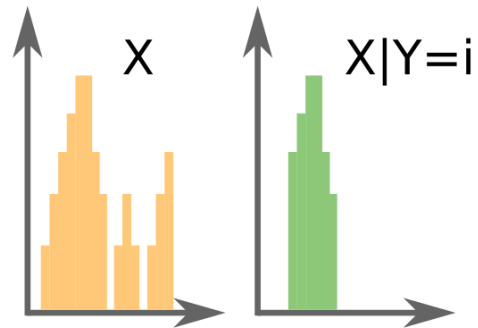


Reverse engineering is hard ...

	Gene A	Gene B	Gene C	Gene D	...
Phenotype X	✓	✗	✓	✗	
Phenotype Y	✓	✗	✗	✓	
Phenotype Z	✗	✓	✓	✗	
...					

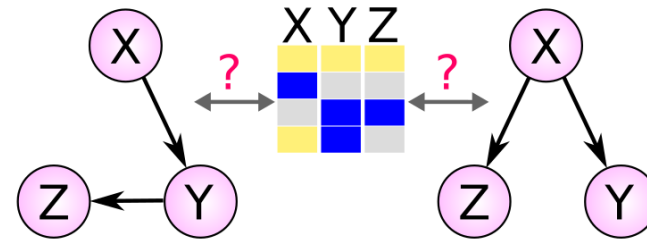


b Information theoretic



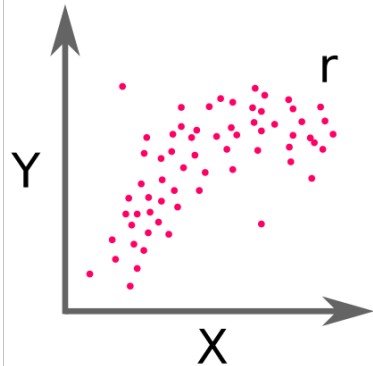
$$I(X, Y) = H(X) - H(X|Y)$$

c Bayesian inference



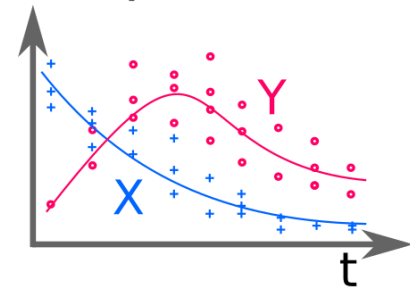
$$P(X|Y) = \frac{P(Y|X)P(X)}{P(Y)}$$

a Correlation

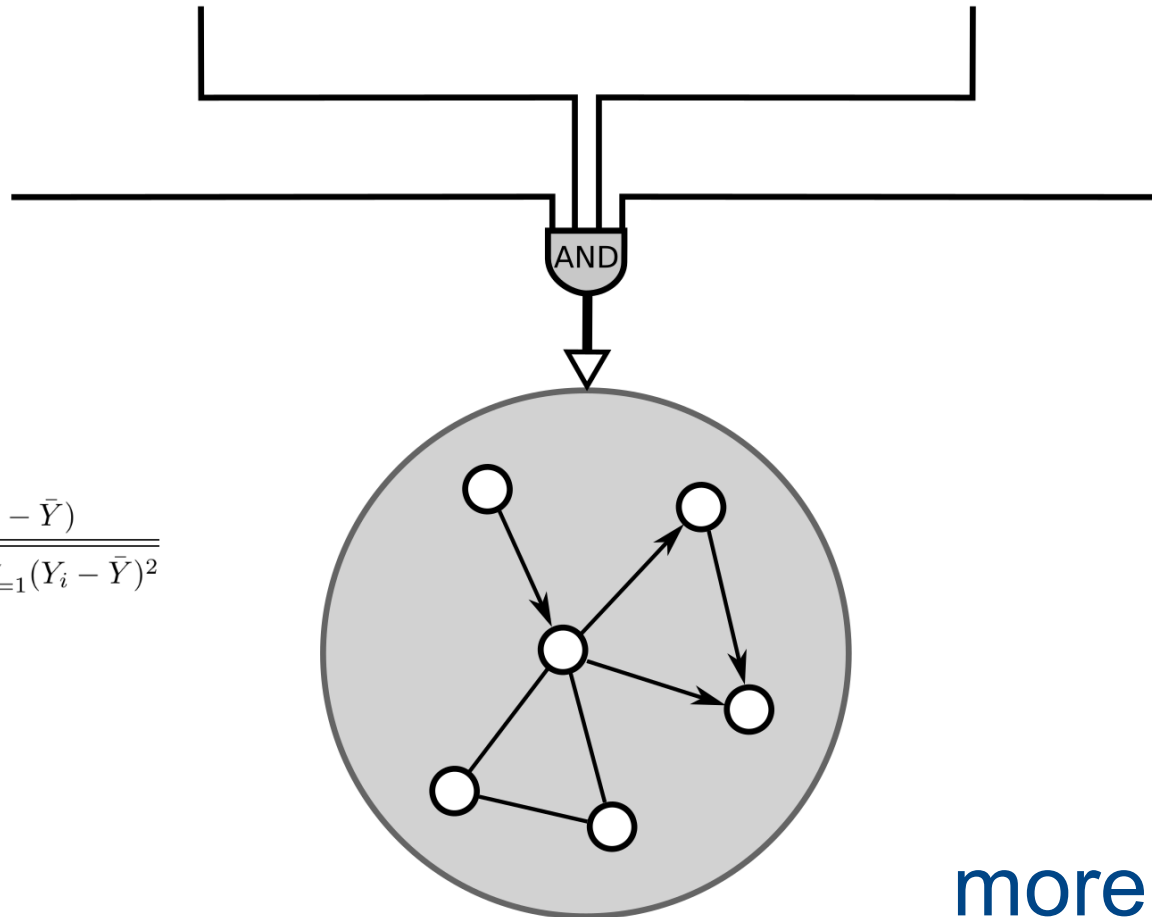


$$r = \frac{\sum_{i=1}^n (X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^n (X_i - \bar{X})^2} \sqrt{\sum_{i=1}^n (Y_i - \bar{Y})^2}}$$

c Differential equation

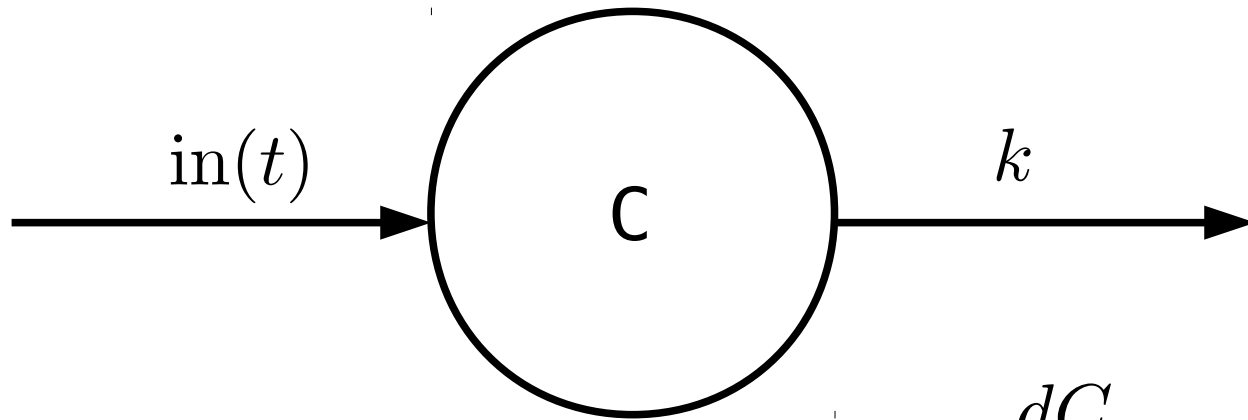


$$\frac{dx_i}{dt} = \sum_{j=1}^n a_{i,j} x_j$$

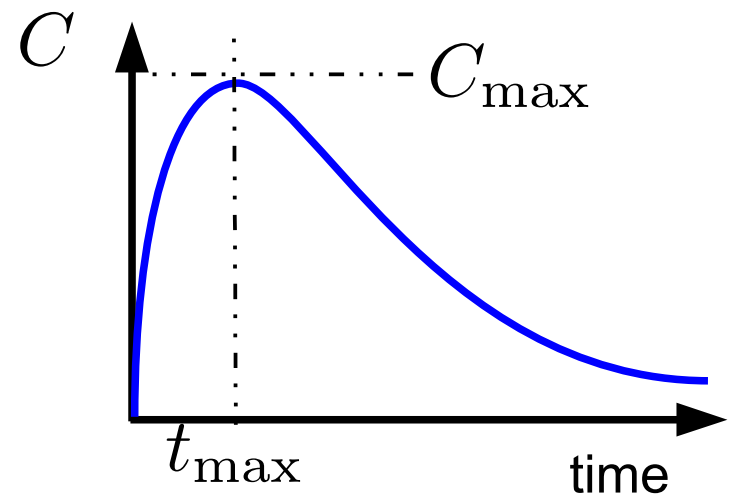
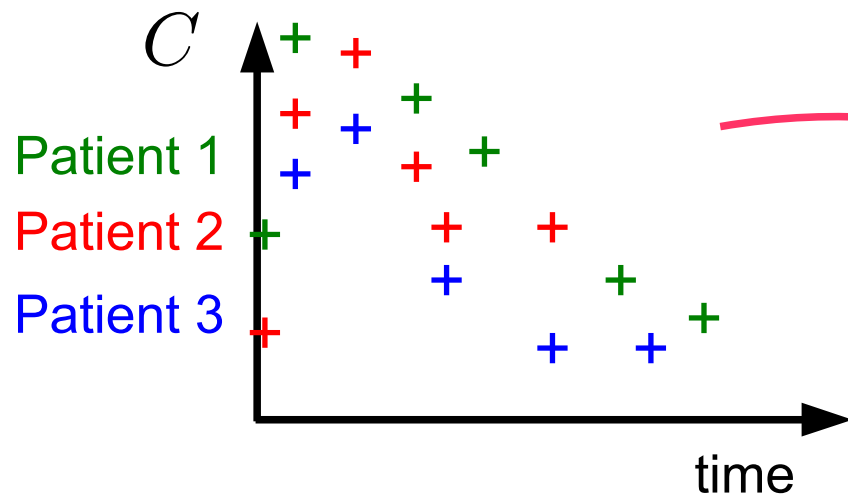


more on Monday

Drug discovery modelling: pharmacometrics

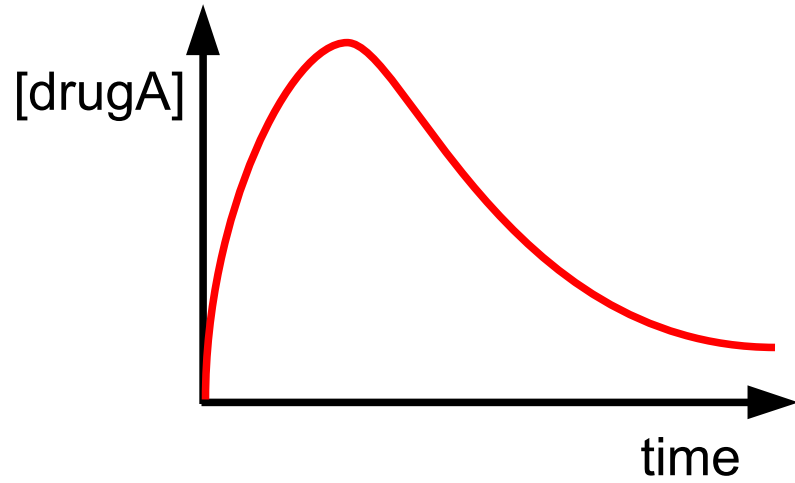


$$\frac{dC}{dt} = \text{in}(t) - k \times C$$

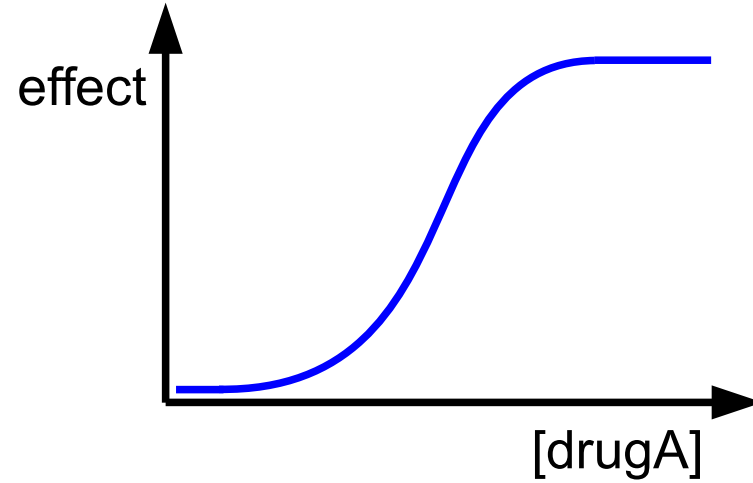


Drug discovery modelling: pharmacometrics

PK

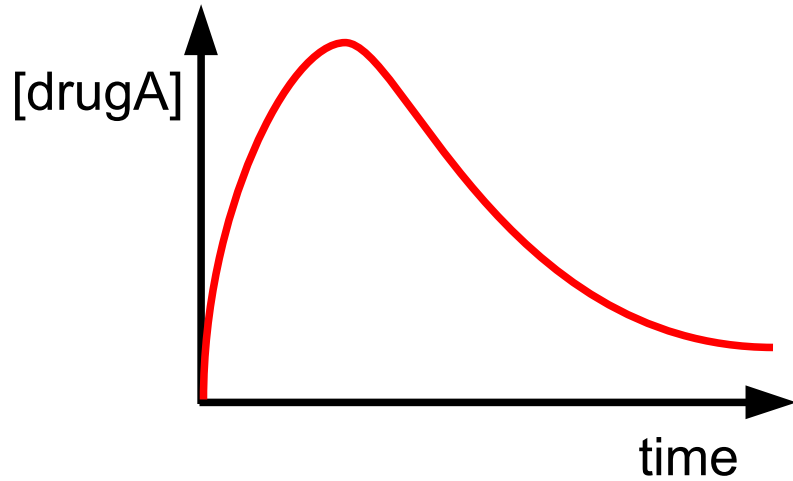


PD

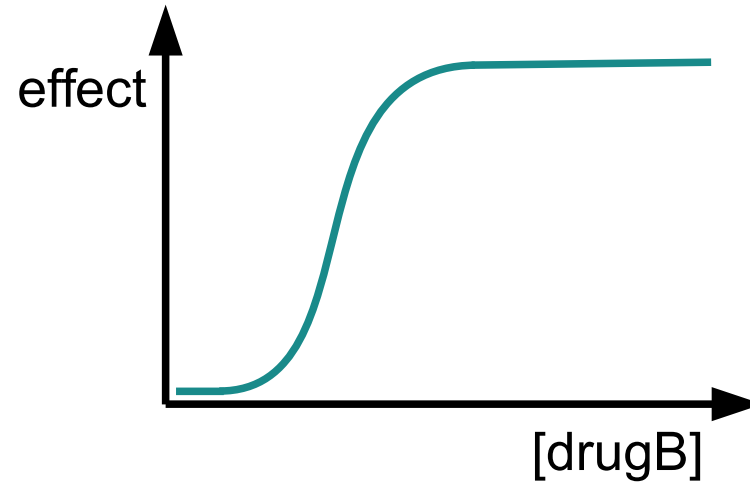
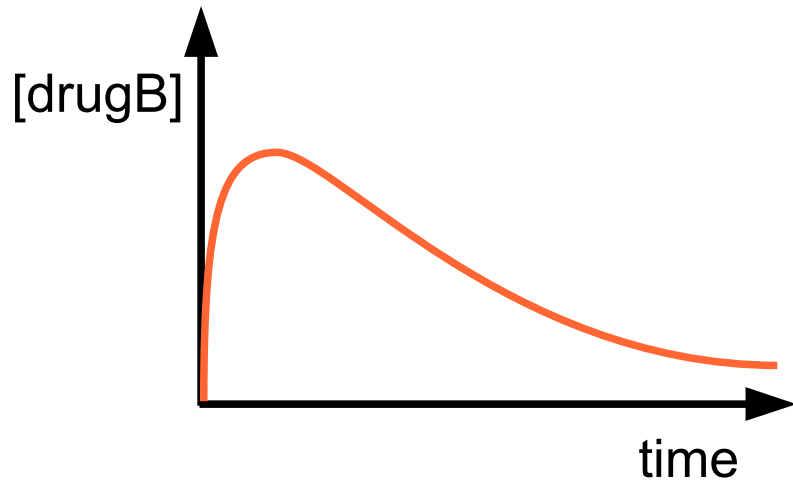
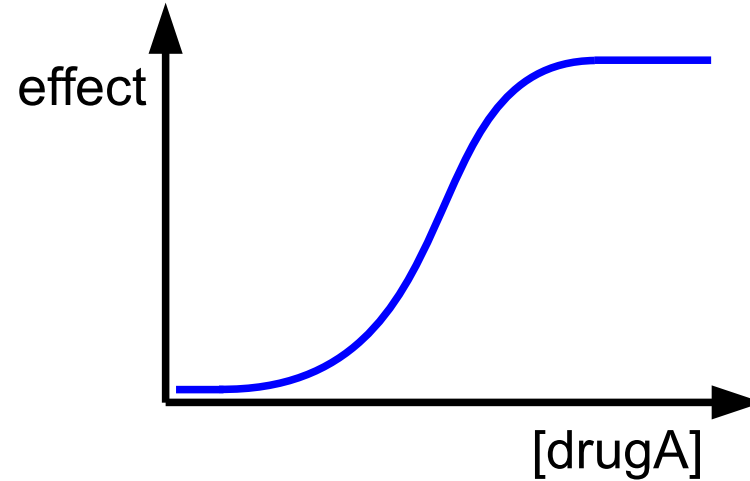


Drug discovery modelling: pharmacometrics

PK

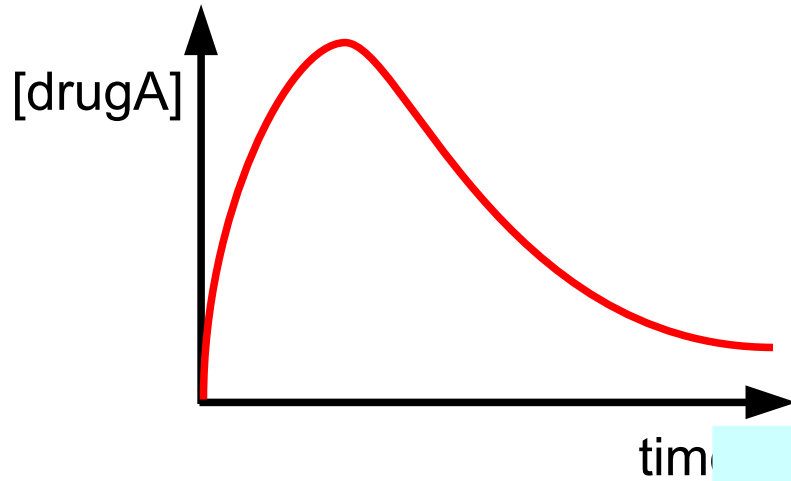


PD

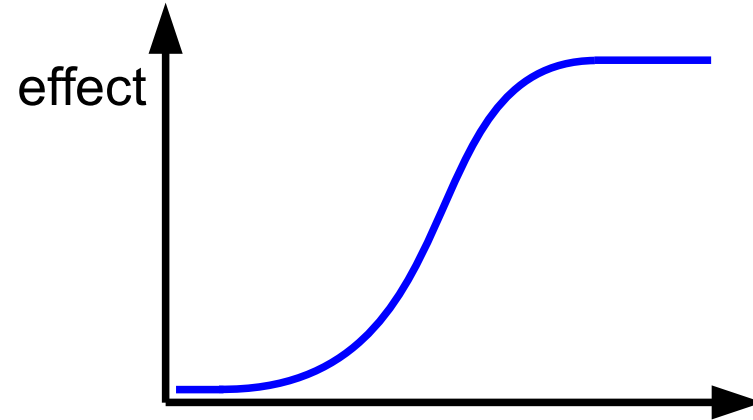


Drug discovery modelling: pharmacometrics

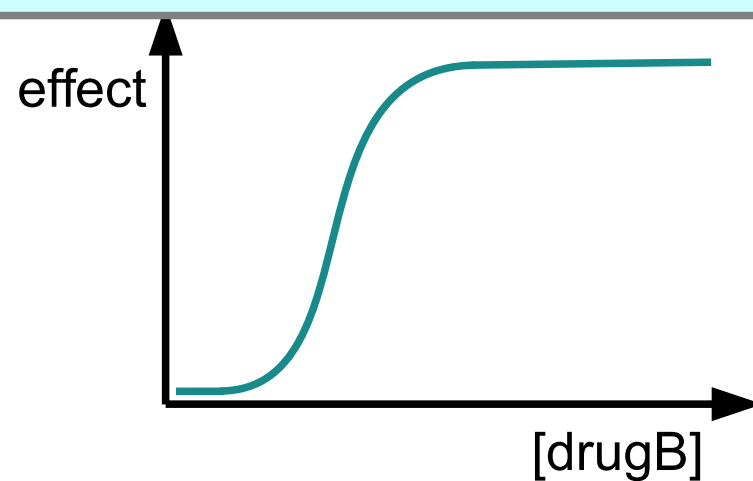
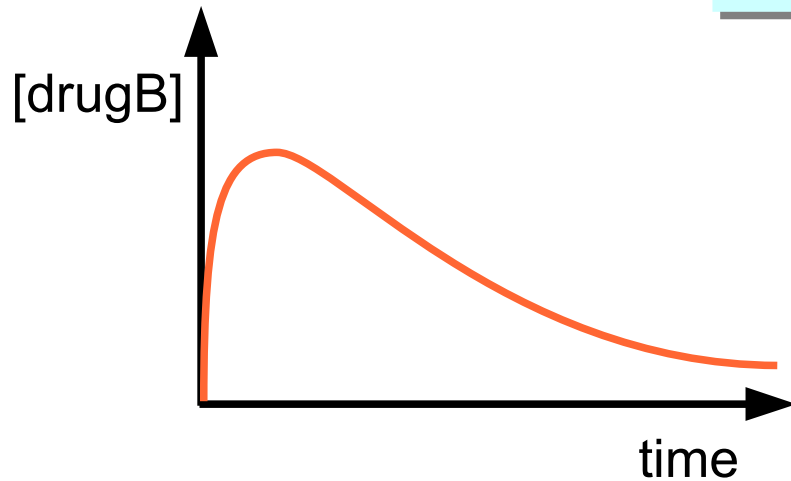
PK



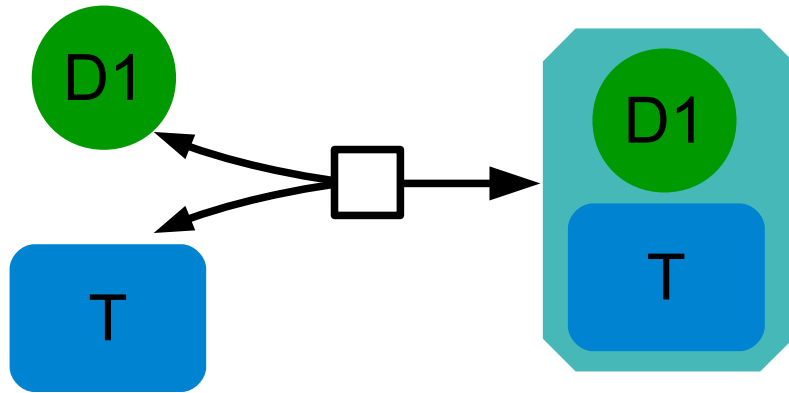
PD



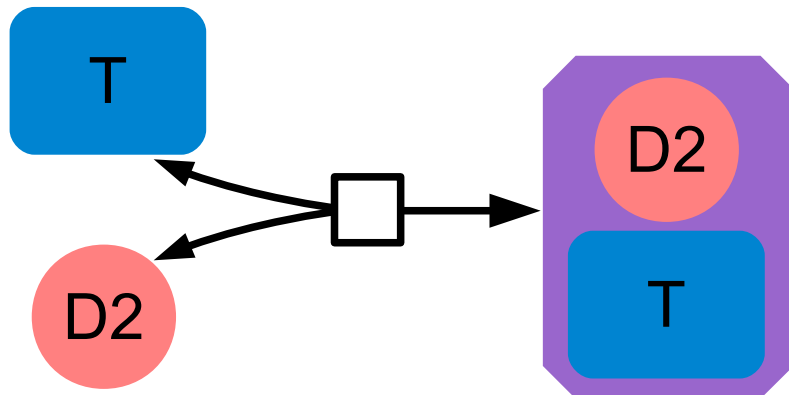
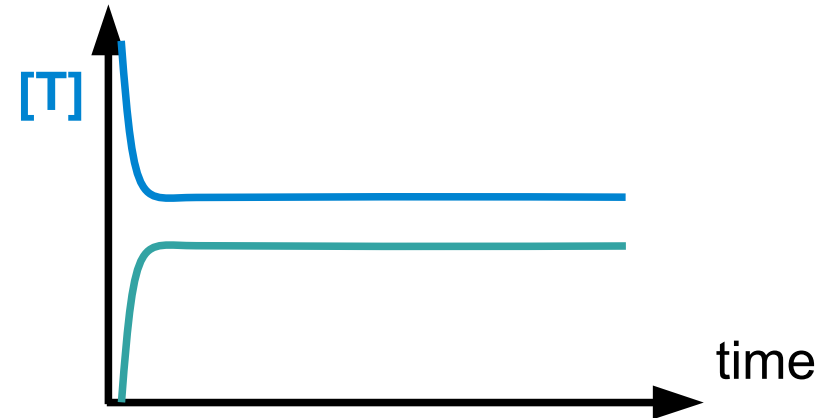
Effect of A+B?



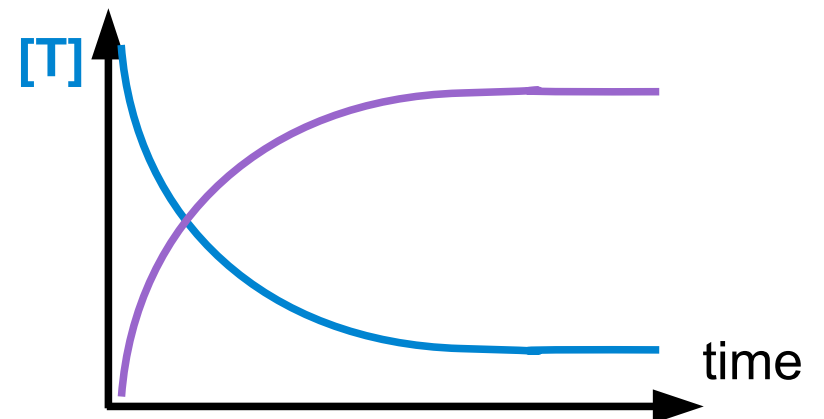
Systems modelling



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

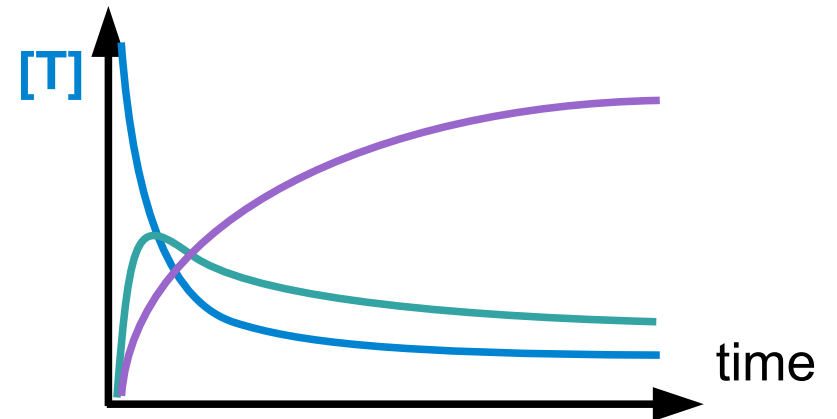
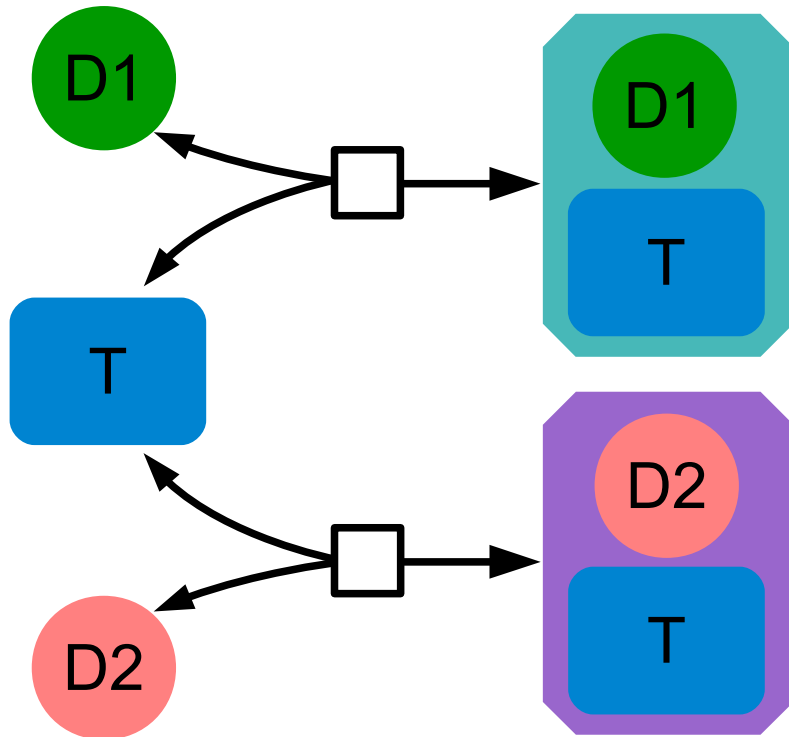


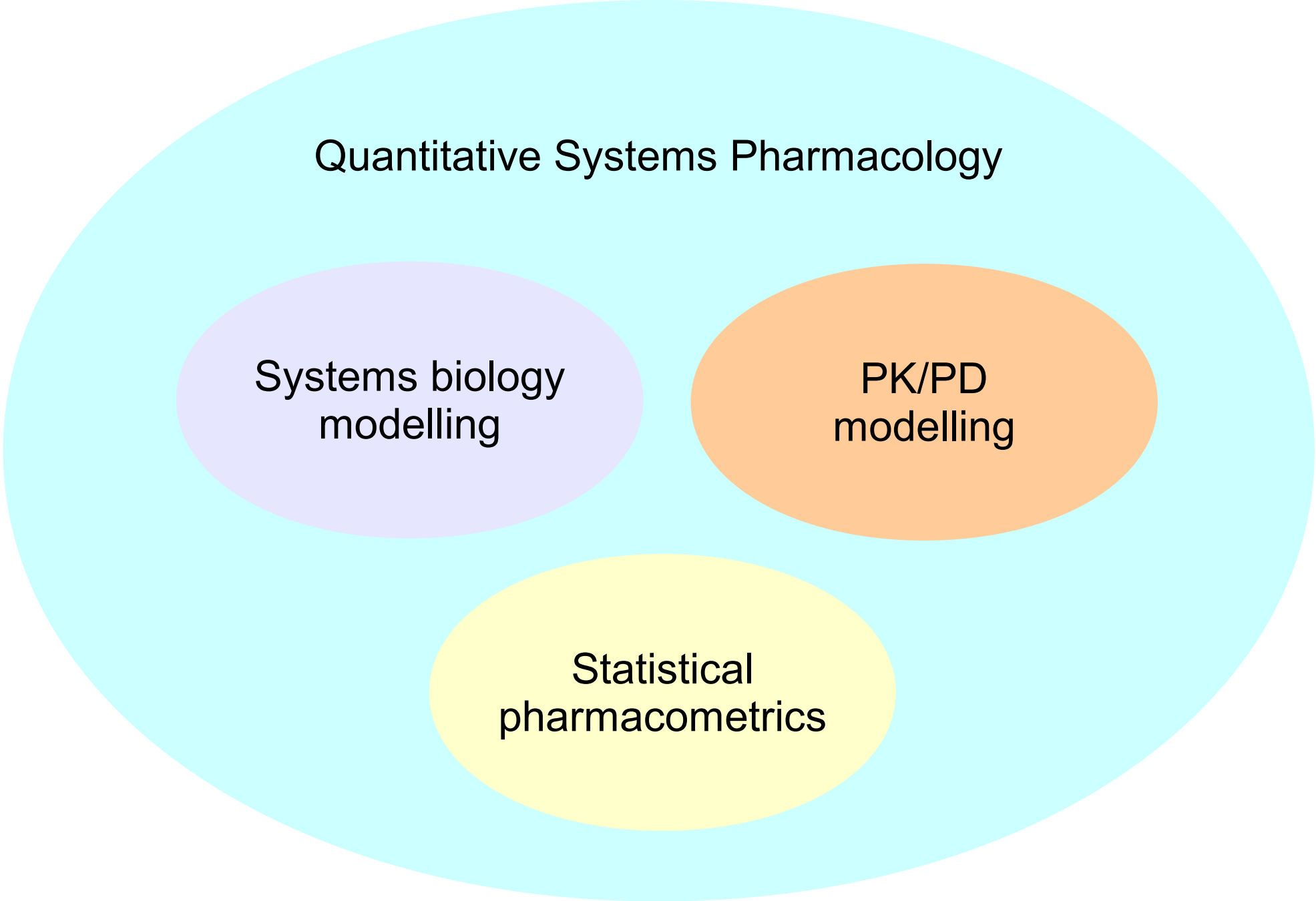
$$\frac{d[T]}{dt} = -k2 \times [T] \times [D2]$$



Systems modelling

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





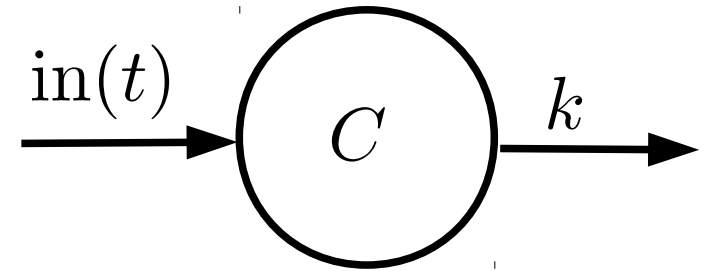
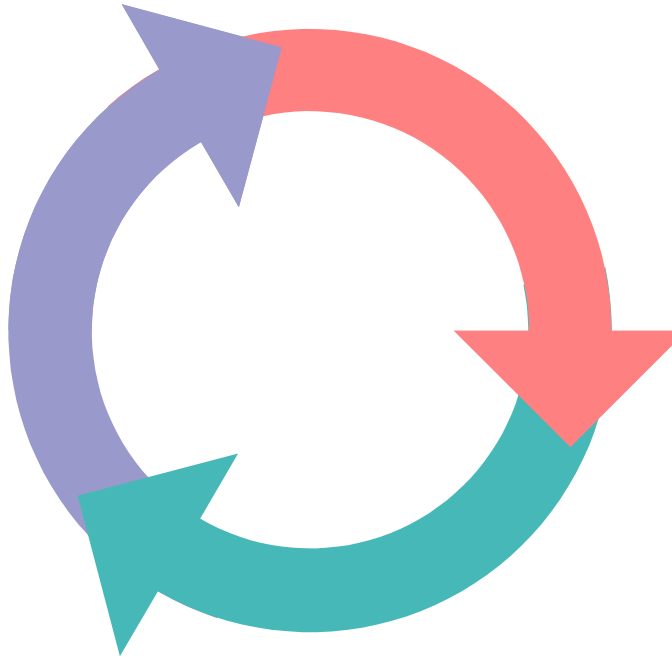
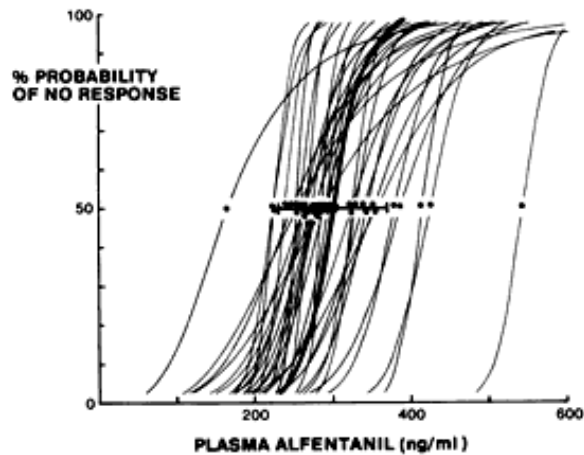
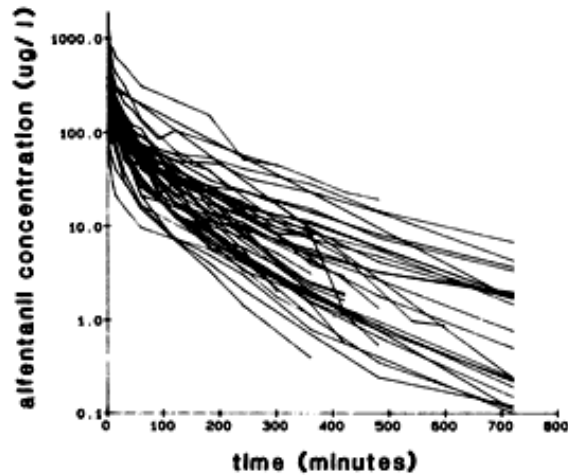
Quantitative Systems Pharmacology

Systems biology
modelling

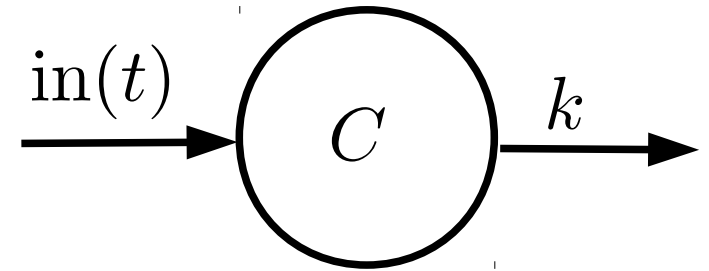
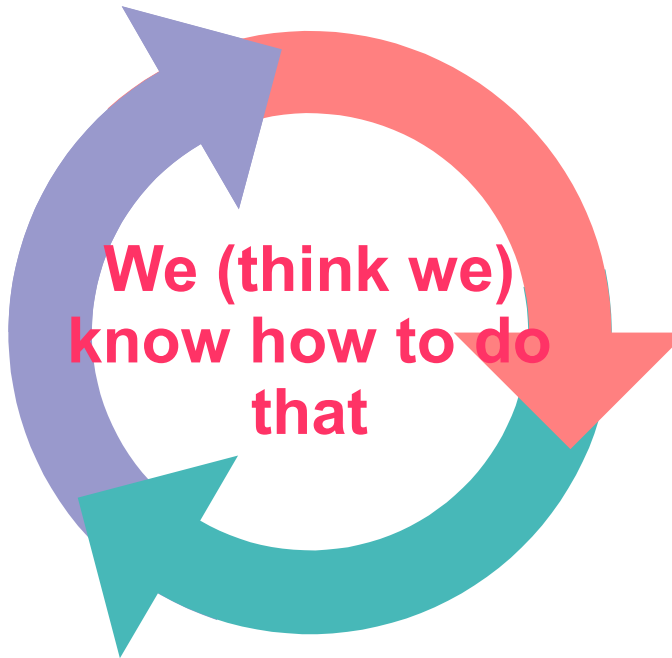
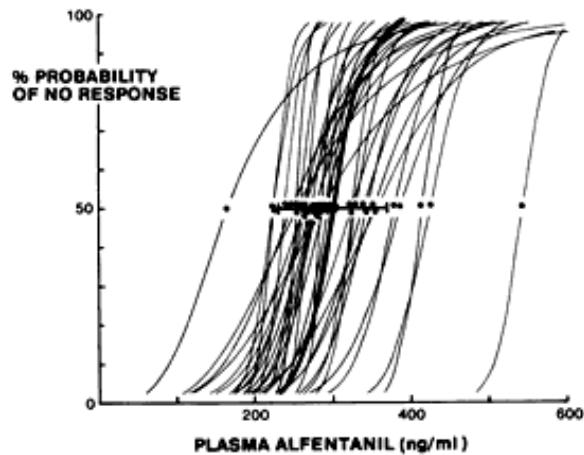
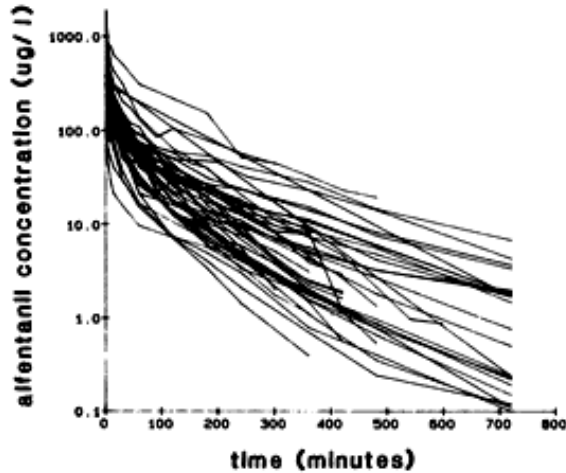
PK/PD
modelling

Statistical
pharmacometrics

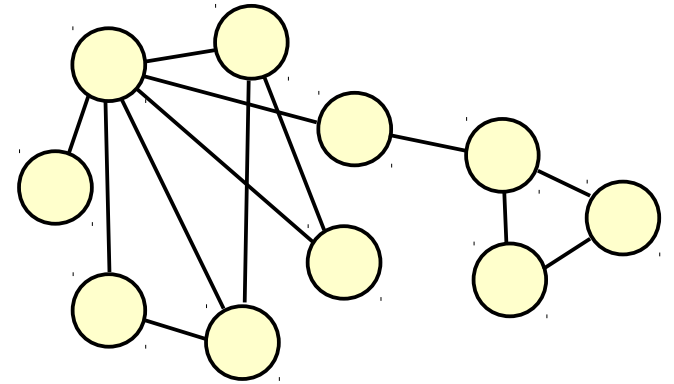
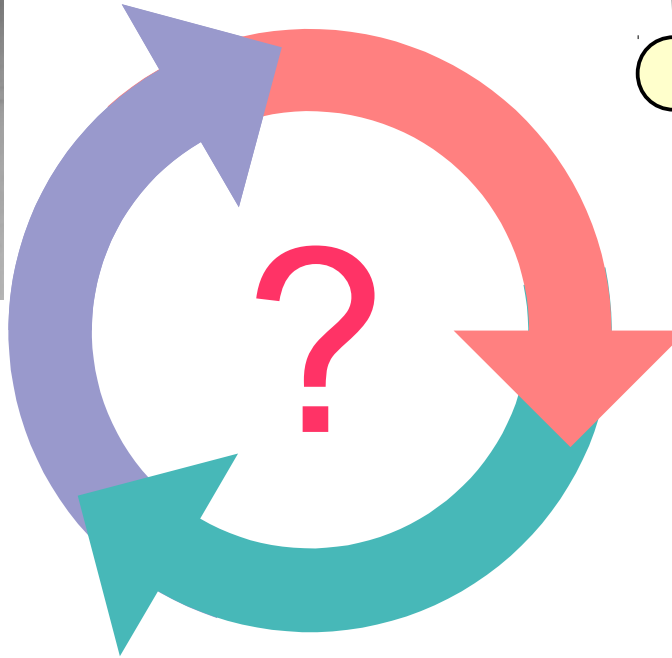
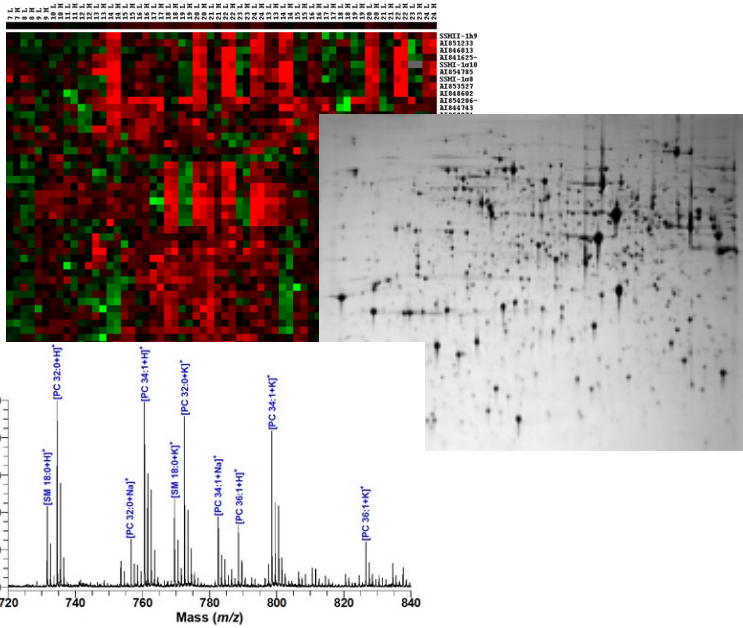
Drug discovery and pharmacometrics models

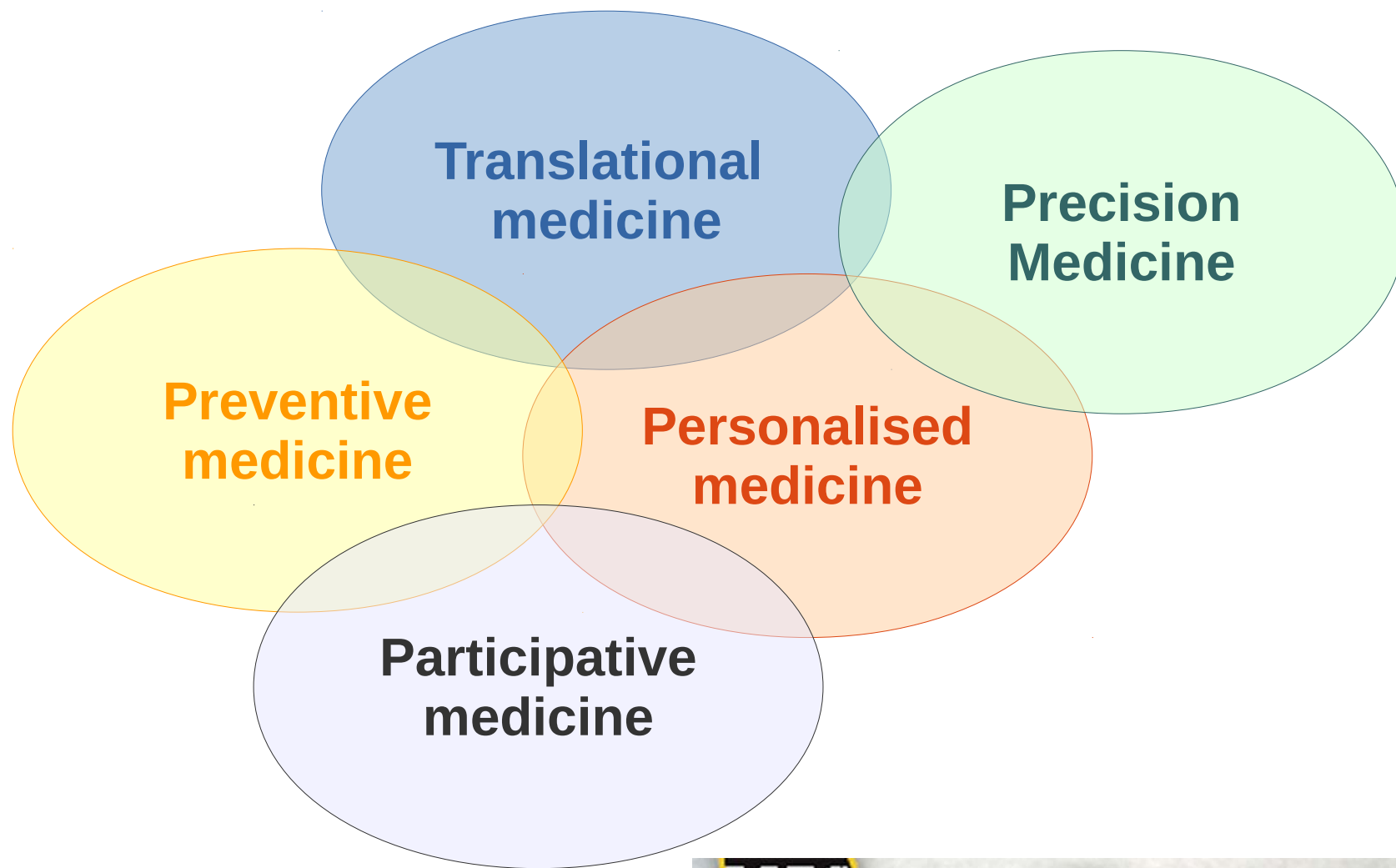


Drug discovery and pharmacometrics models



Drug discovery and omics





Systems Biology

Edda Klipp, Wolfram Liebermeister, Christoph Wierling,
Axel Kowald, Hans Lehrach, and Ralf Herwig

A Textbook

 WILEY-
BLACKWELL

DYNAMIC MODELS

 IN BIOLOGY

STEPHEN P. ELLNER AND
JOHN GUCKENHEIMER



