Computational Systems Biology

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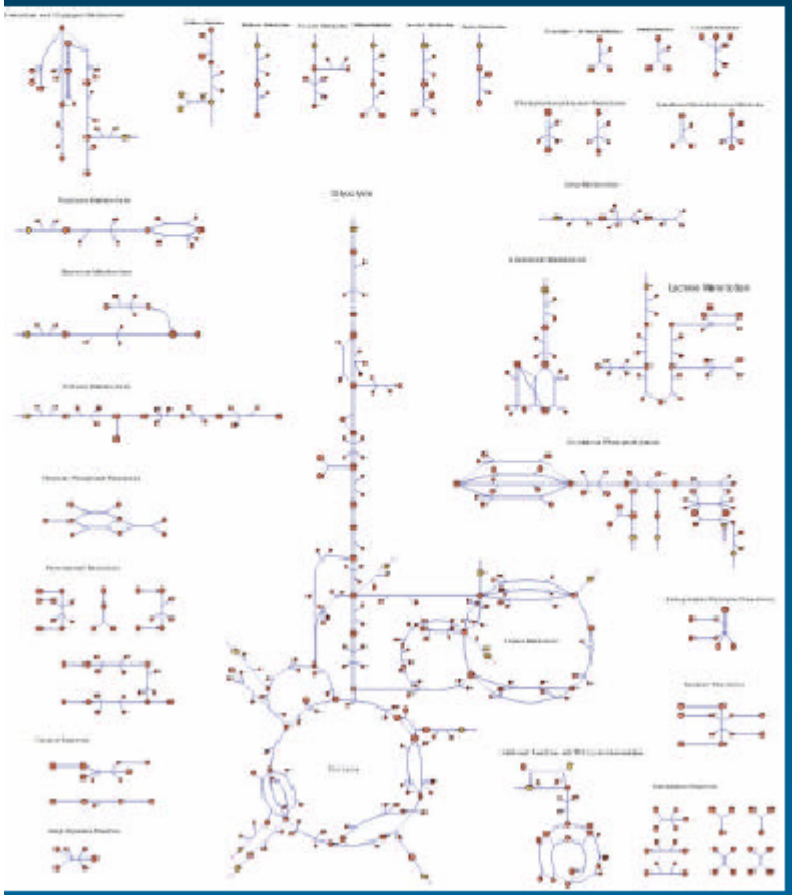
University of Edinburgh, UK

Outline

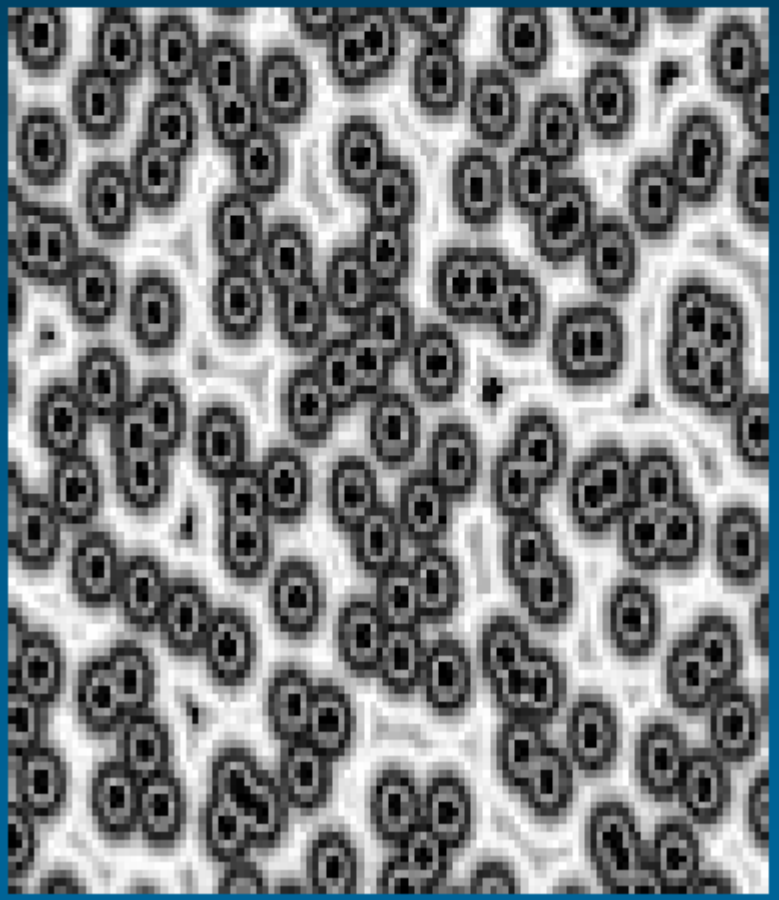
- What is Systems Biology?
- Henrik Kacser and Systems Biology
- Modelling
- Enzyme kinetics
- Metabolic control analysis.
- Constrained based optimization
- Metabolic Example
- Signal transduction Example
- Pathway Editor

Biology is now asking:

If every molecule in a cell is replaced over time, is it still the same cell?

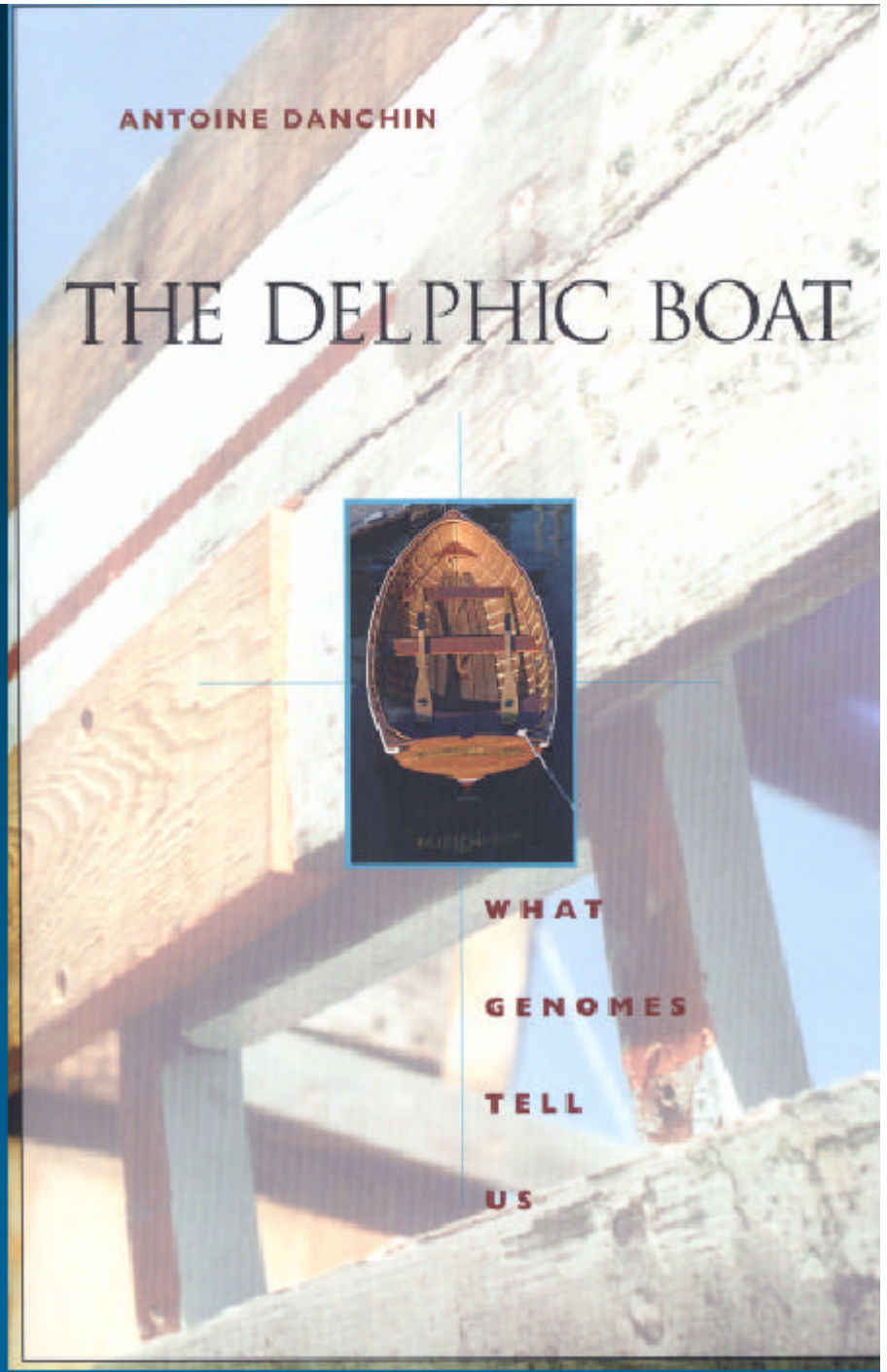


If every cell in an organism is replaced over time, is it still the same organism?



The Oracle of Delphi asked:

If every plank in a boat is replaced over time, is it still the same boat?

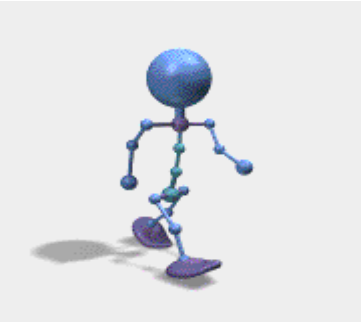


The answer basically is 'yes'

Thus, the interconnections of biological components--the 'blueprint,' the 'circuit diagrams'--of cells are taking center stage in biology:

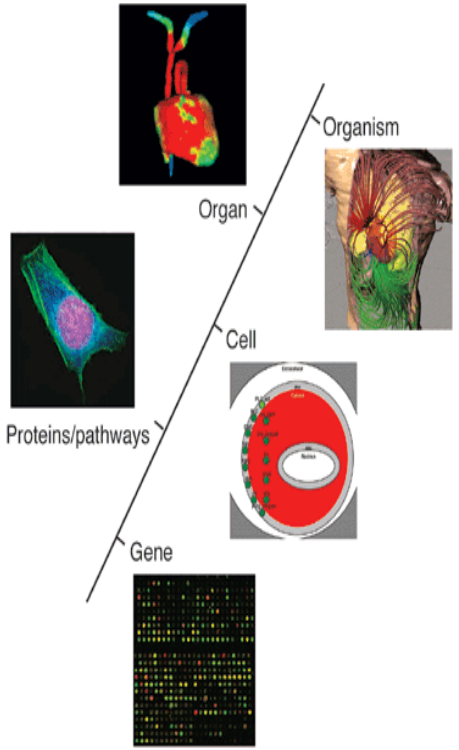
and thus... we have the emergence of systems biology

What is Systems Biology?



is an academic field that seeks to integrate biological data as an attempt to understand how biological systems function.

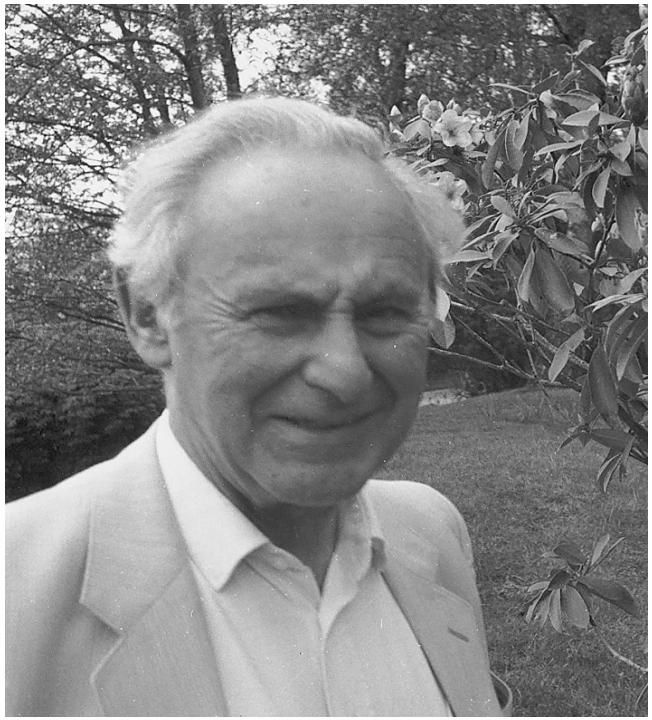
By studying the relationships and interactions between various parts of a biological objects it is hoped that an understandable model of the whole system can be developed



Wikipedia

Henrik Kacser.
Systems Biology. Described in 1957

- "The properties of a system are in fact more than (or different from) the sum of the properties of its components, a fact often overlooked in zealous attempts to demonstrate additivity of certain phenomena. It is with these systemic properties that we shall be mainly concerned"
- "There are no concepts in chemistry or physics equivalent to genes\ regulation\ epigenesis precisely because these are properties only possible in systems of greater complexity than have been subjected to detailed analysis by those sciences"

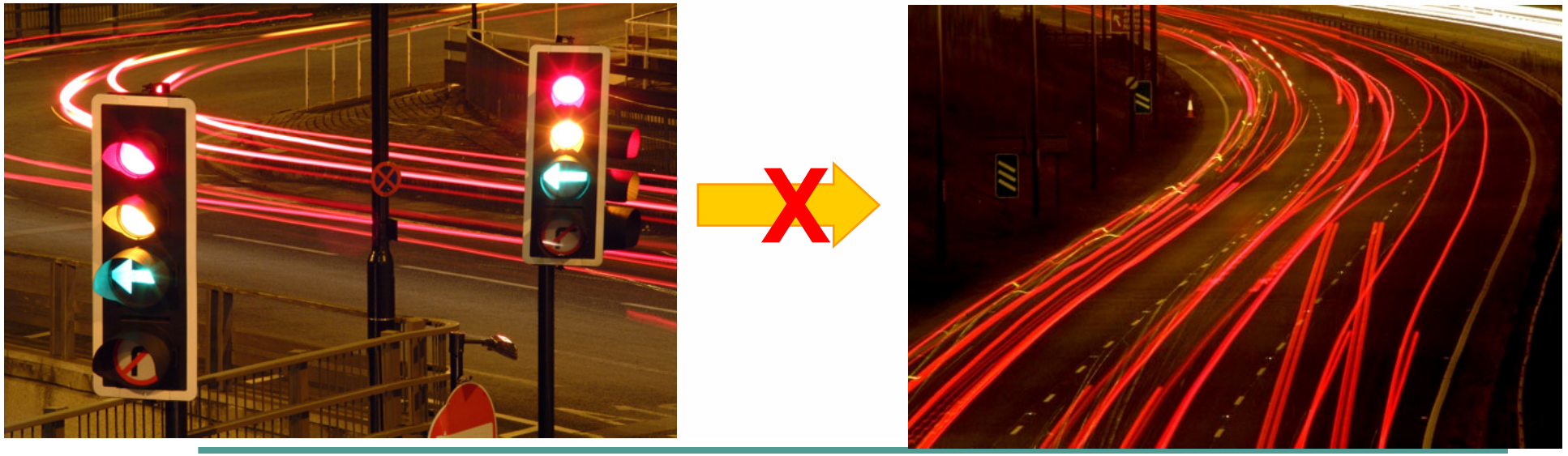


KACSER H 1957 Some physicochemical aspect of biological organisation Appendix to The Strategy of the Genes, (Waddington CH, ed), pp 191-249. London: George Allen and Unwin

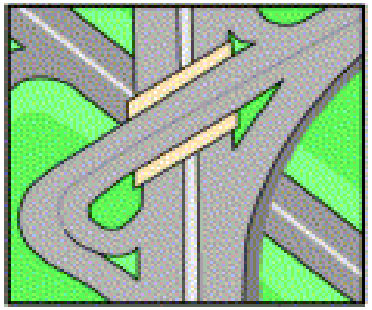
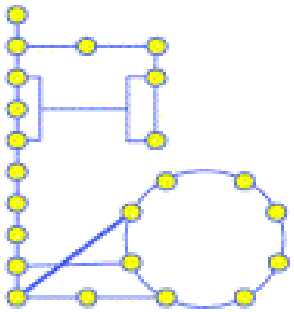
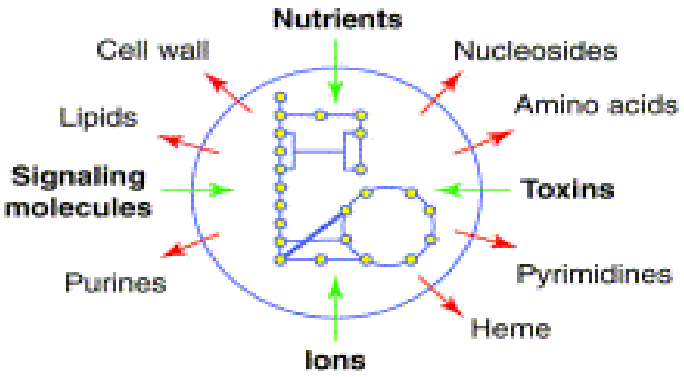
Henrik Kacser. The founder of Metabolic Control Analysis

The expectation that a metabolic pathway will be controlled by a single pacemaker reaction is a fallacy,

Most of the experimental criteria used in the supposed identification of such steps are misleading. Instead, varying amounts of control can be distributed over the enzymes of the pathway, but this is a property of the metabolic system as a whole *and cannot be predicted from the characteristics of the enzymes in isolation.*



KACSER, H. & BURNS, J. A. (1973) The control of flux. *Symp. Soc. Exp. Biol.*27, 65-104.

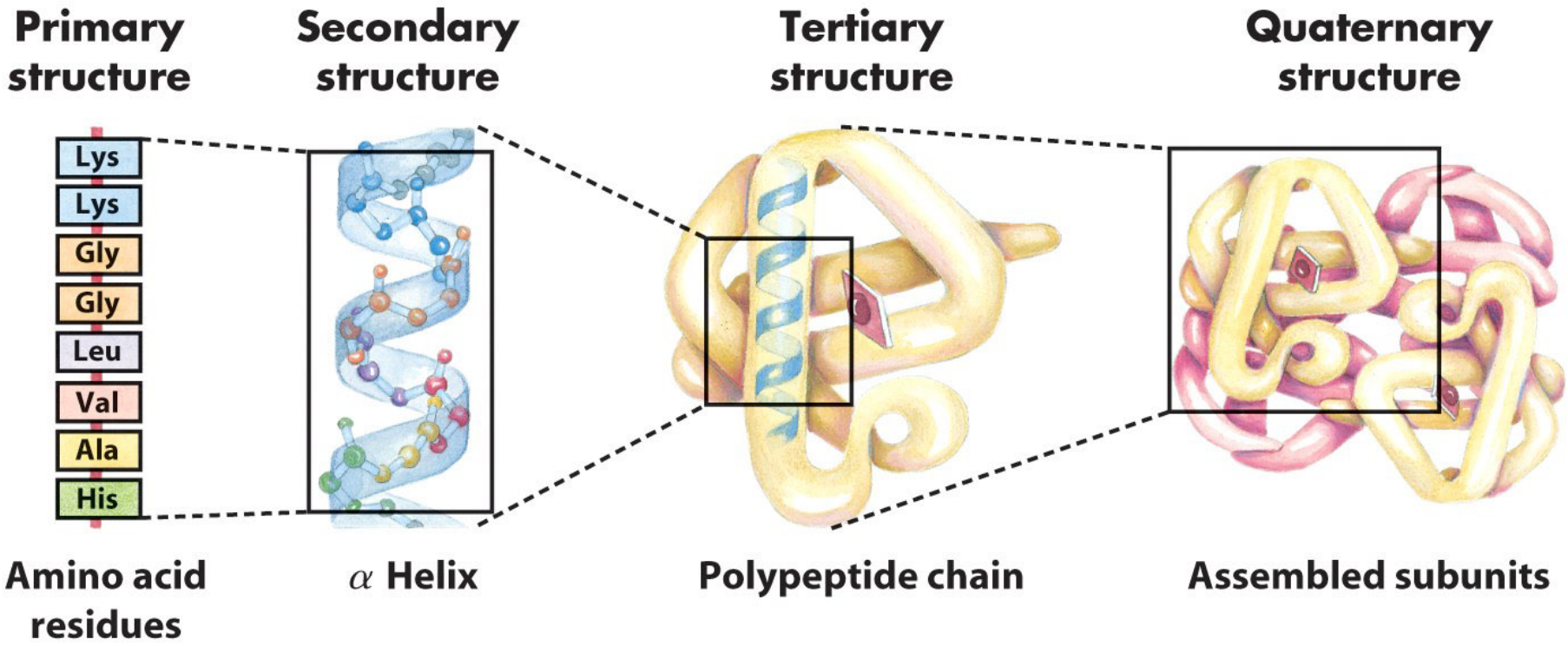
Level of analysis	Traffic simulation	Cellular simulation
List of components	 Isolated roads	 Isolated enzymes
Integration and qualitative analysis	 Road map	 Metabolic map
Mathematical modeling and quantitative analysis	 Traffic patterns	 Flux distributions

TiBS

Metabolic modeling of microbial strains in silico
Markus W. Covert, et al , 2001

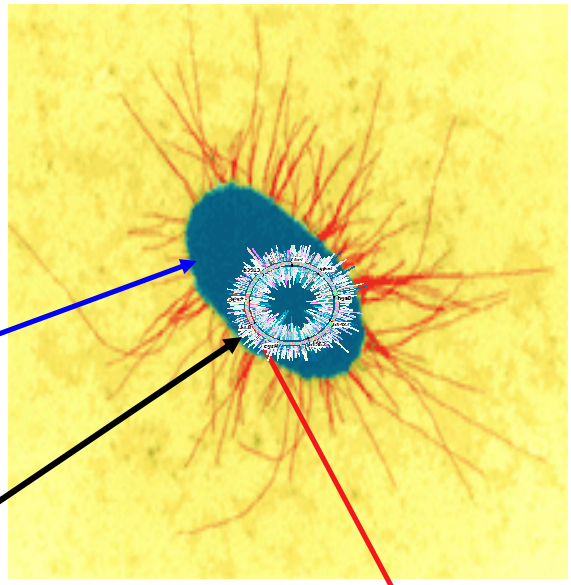
Enzymes

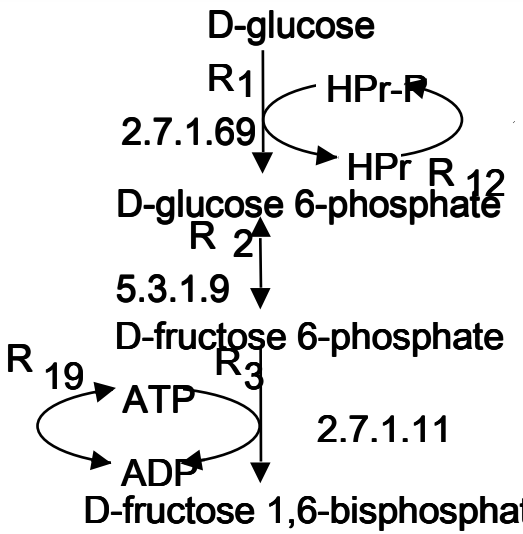
- **Most enzymes are proteins, and their activities depends on the 3D structure of the amino acids that compose them**

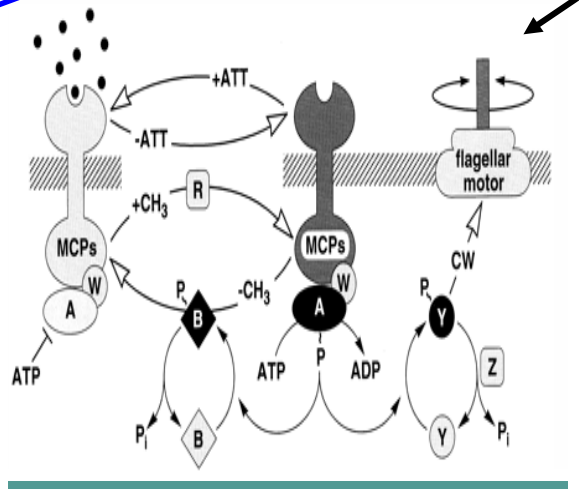


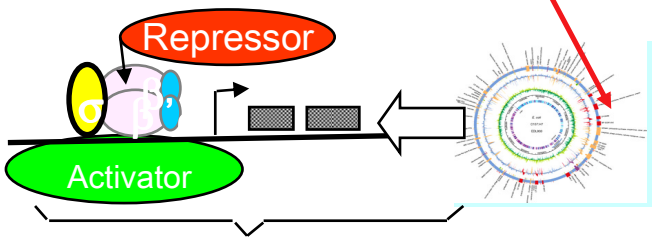
Static Models. The Inventory

- Only connectivity (topology) of the interactions
- Visualised as connection or interaction graph
- Types
  - Metabolic (Metabolomics, metabonomics)
  - Genetic Regulation (Microarrays)
  - Protein-Protein Interactions (Proteomics)



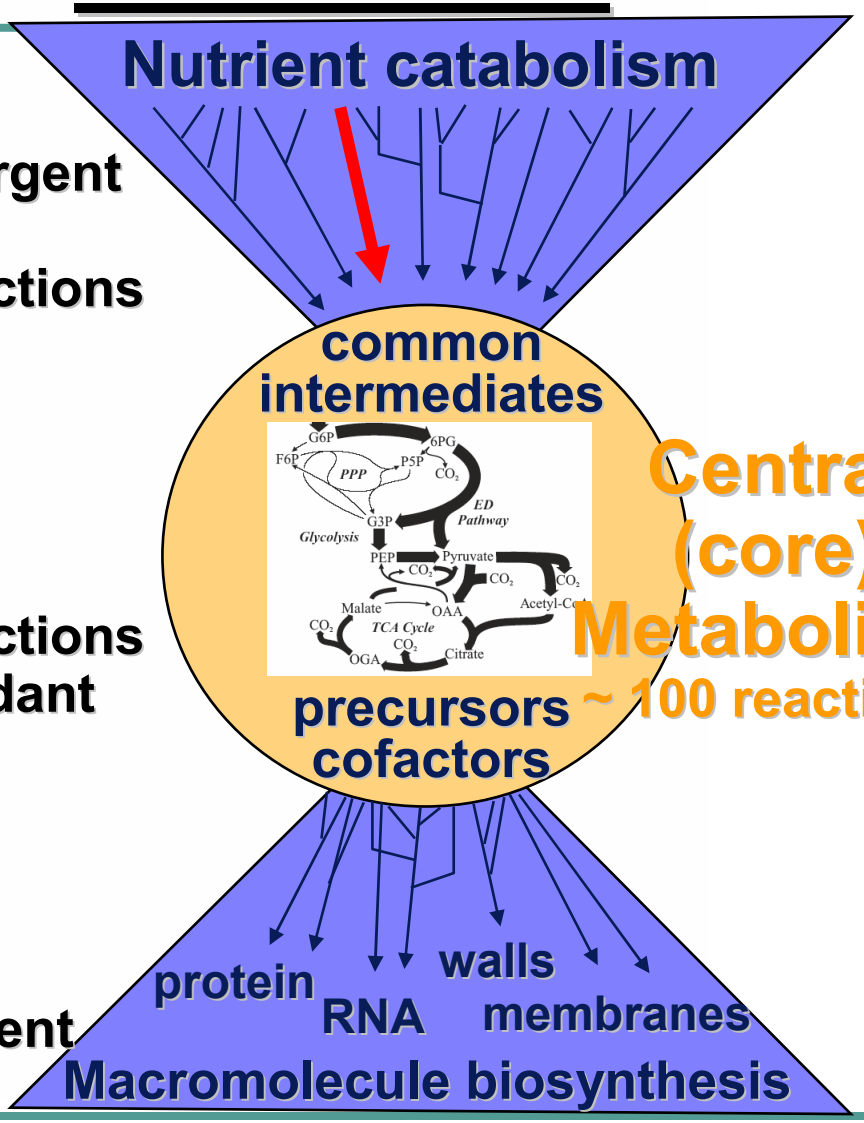






Metabolic network	Protein interaction network	Genetic network

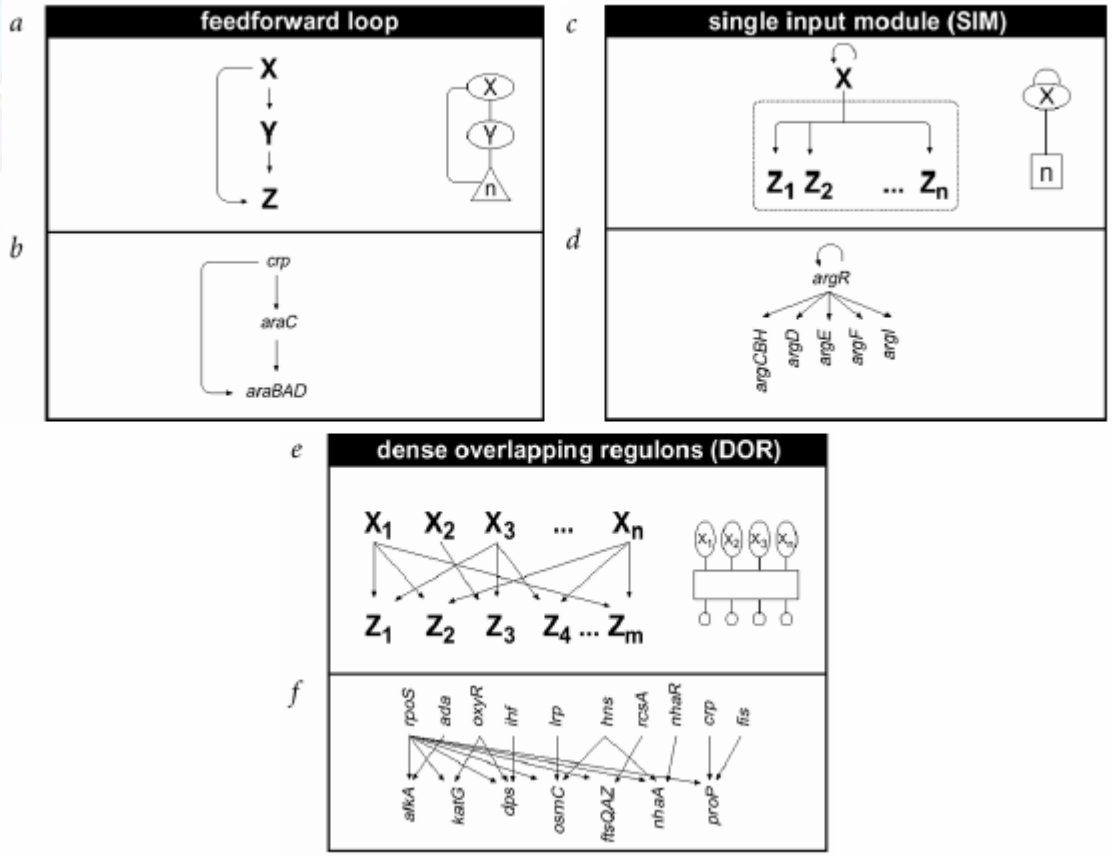
Metabolic Networks



Bow tie structure

Csete & Doyle 2004. Trends Biotechnol. 22: 446

Network motifs

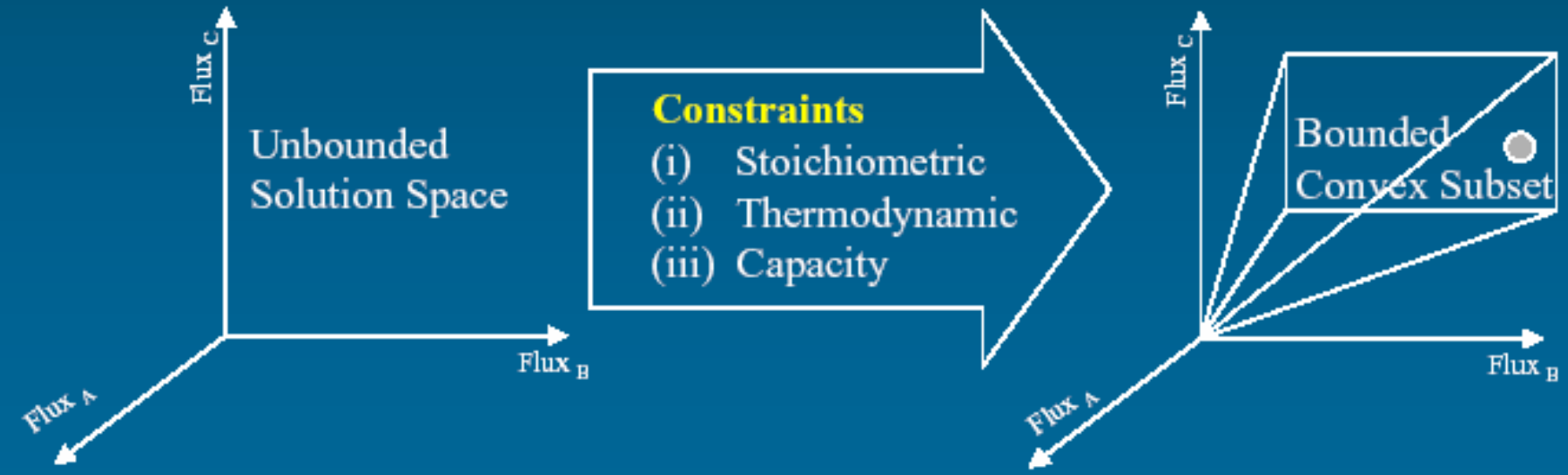


Network motifs found in the E.Coli transcriptional regulation network.

Constraint-based Analysis

How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth?

–Sherlock Holmes, A Study in Scarlet



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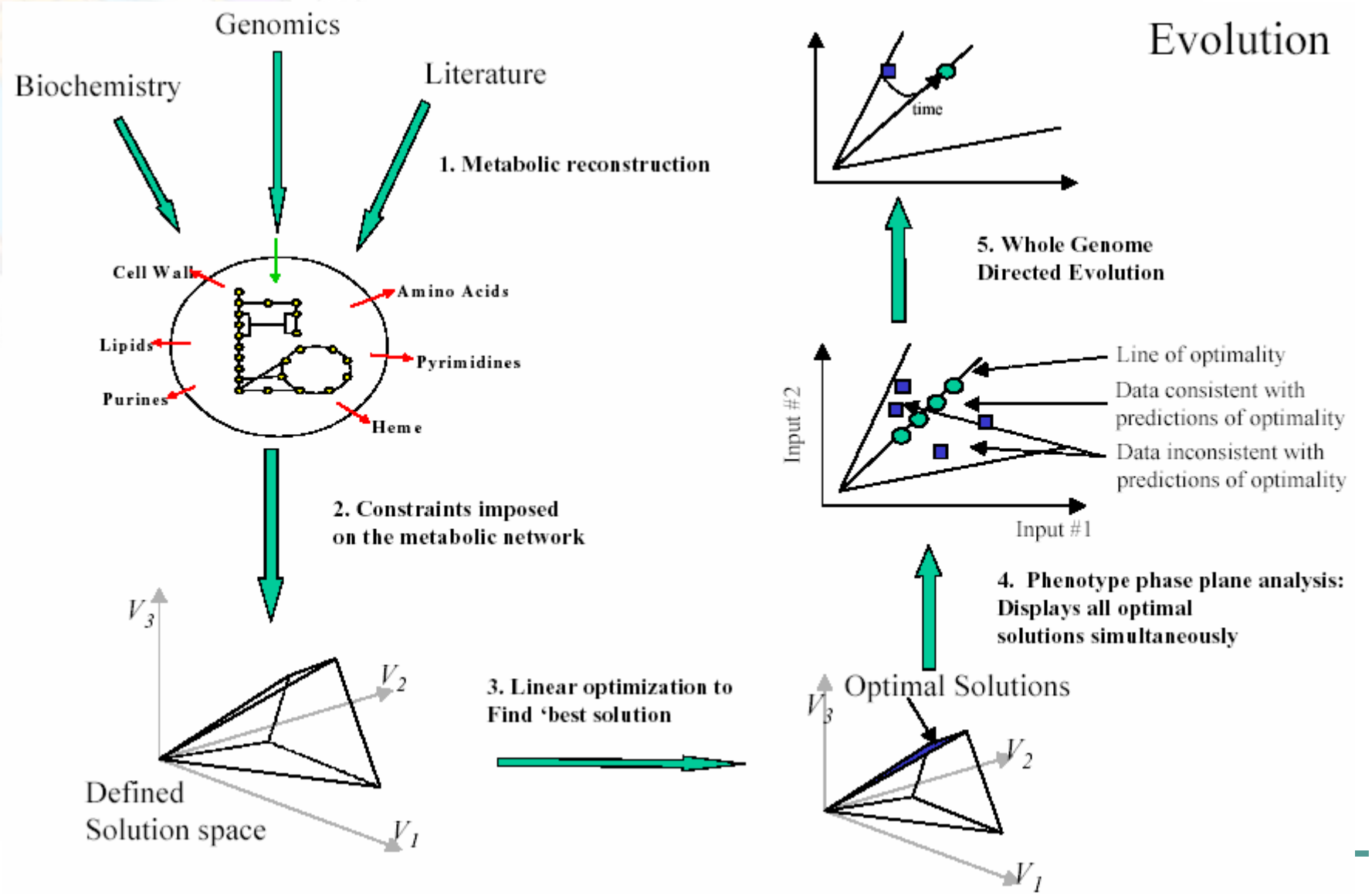
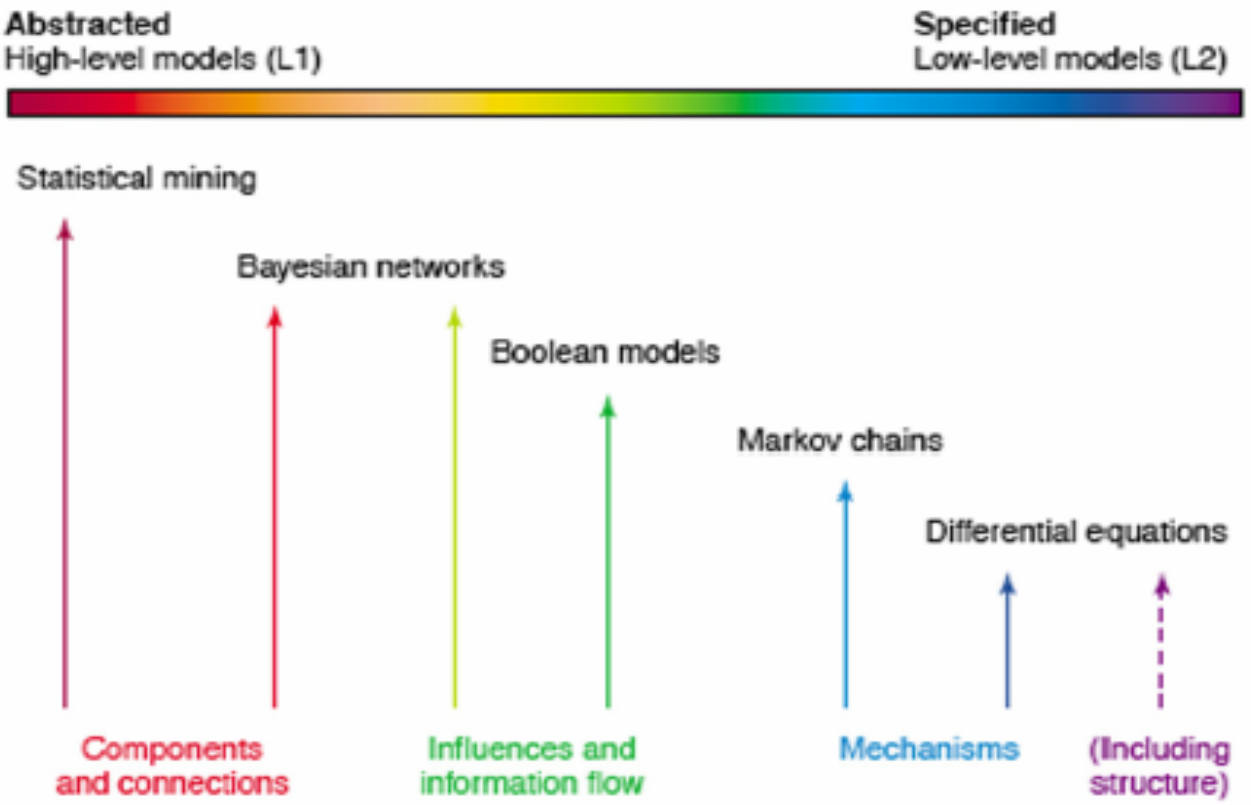
Adaptive Evolution

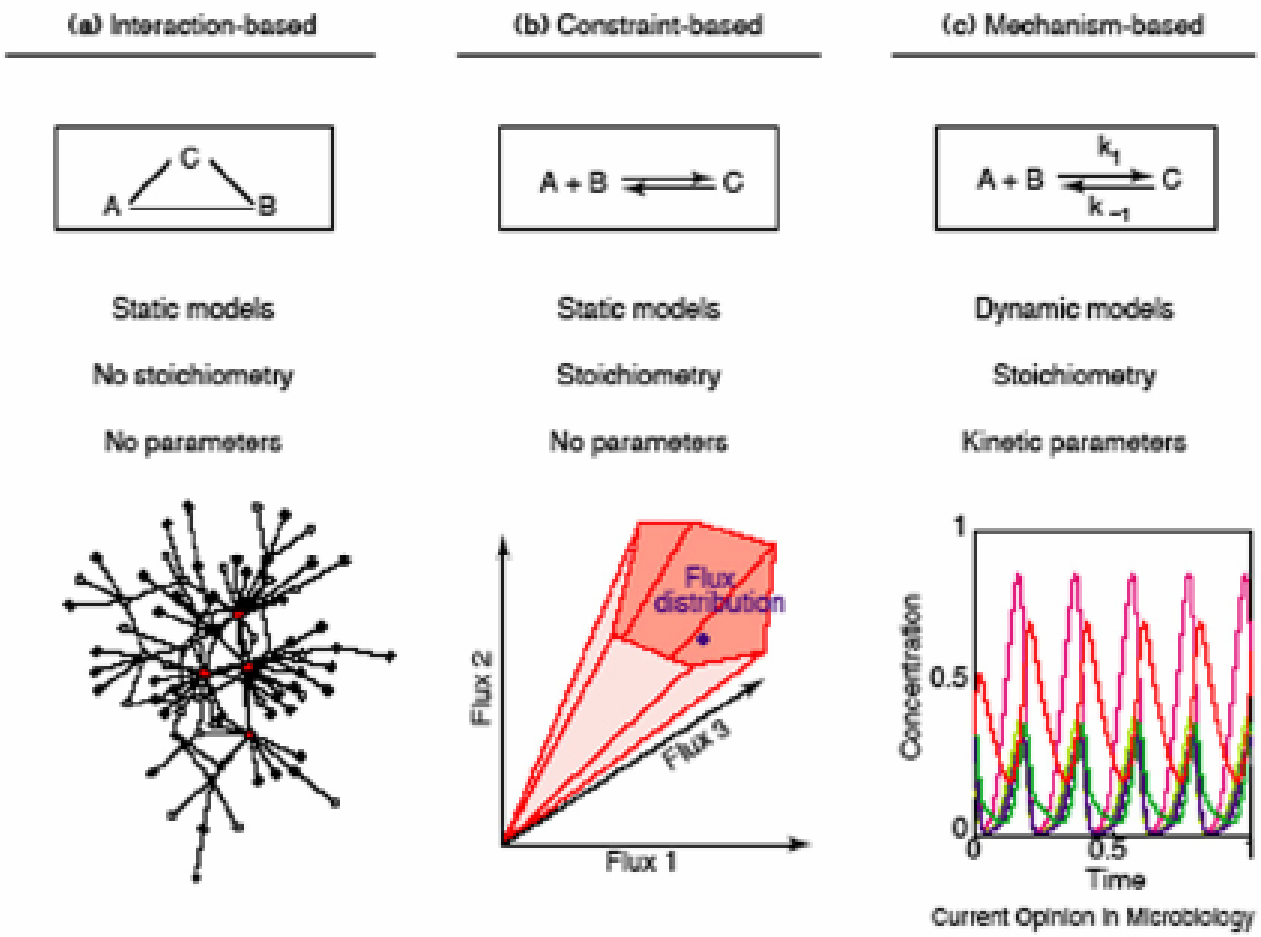


Methods in systems biology



A diverse spectrum of high-to-low modeling approaches (Ideker and Lauffenburger, 2003).

Methods in systems biology



Quantitative Kinetic Models. The TIME

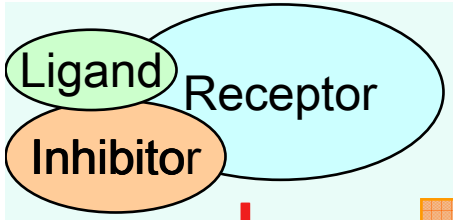
Kinetic models - time dependency incorporated

- Kinetic behaviour (rate laws) added to static model

Kinetic constants by fitting to experimental data

Mathematical model

- Time variation of all concentrations and fluxes can be simulated
- Model analyses possible: sensitivity, linear stability, bifurcation, and asymptotic analysis



\+

Kinetic Model

$R + L \Leftrightarrow R \cdot L$

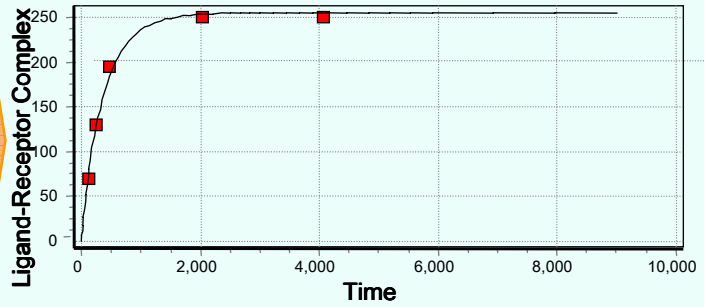
$R + I \Leftrightarrow R \cdot I$

Static model

Mathematical Model

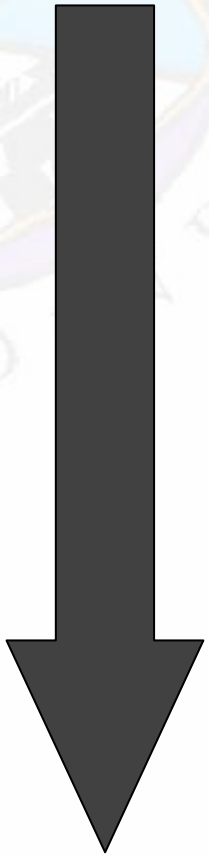
$$
\begin{aligned}
[R]' &= -k_1[R][L] + k_2[RL] - k_3[R][I] + k_4[RI] \\
[RL]' &= k_1[R][L] - k_2[RL] \\
[RI]' &= k_3[R][I] - k_4[RI] \\
[L]' &= -k_1[R][L] + k_2[RL] \\
[I]' &= -k_3[R][I] + k_4[RI] \\
L_0 &= [L] + [RL] \\
I_0 &= [I] + [RI] \\
R_0 &= [R] + [RL] + [RI]
\end{aligned}
$$

Numerical Simulation



Bioinformatics, 1999, Vol 15, 749-758,

Multilevel control of enzyme activity



KM of the metabolic, protein and genetic networks

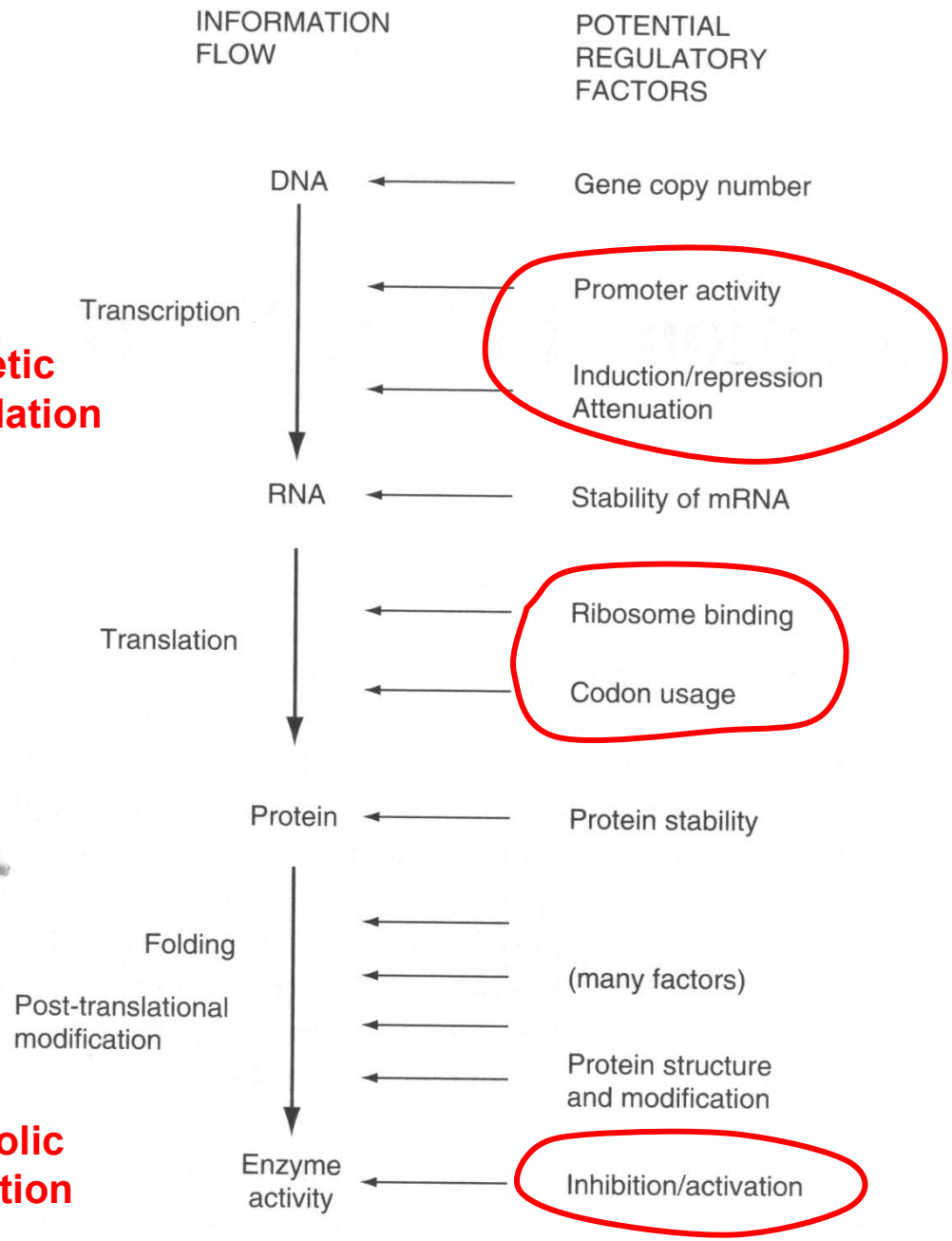


Figure 3.1 Information flow and regulatory factors

Genetic regulation

Metabolic regulation

Main stages of kinetic model development

- Stoichiometry of metabolic pathway and elucidation of the key enzymatic and genetic regulations: Kinetic scheme and N - matrix of stoichiometric coefficients
- System of differential equations describing dynamics of the pathway:

  $dx/dt=N\cdot v(x;e,K)$
  Here, $x=[x_1,\ldots x_m]$ is vector of metabolite concentrations and $v=[v_1,\ldots v_n]$ is vector of rate laws
- Description of individual enzymes:

  - catalytic cycle;

  - derivation of the rate laws for enzymatic reactions;

  - estimation of kinetic parameters of enzymatic reactions from in vitro data, available from literature
- Introduction of gene regulation
- Validation of the whole model using *in vivo* data

Model Analysis. Dynamics

- **Steady State**
- **Damped oscillations**
- **Triggers**

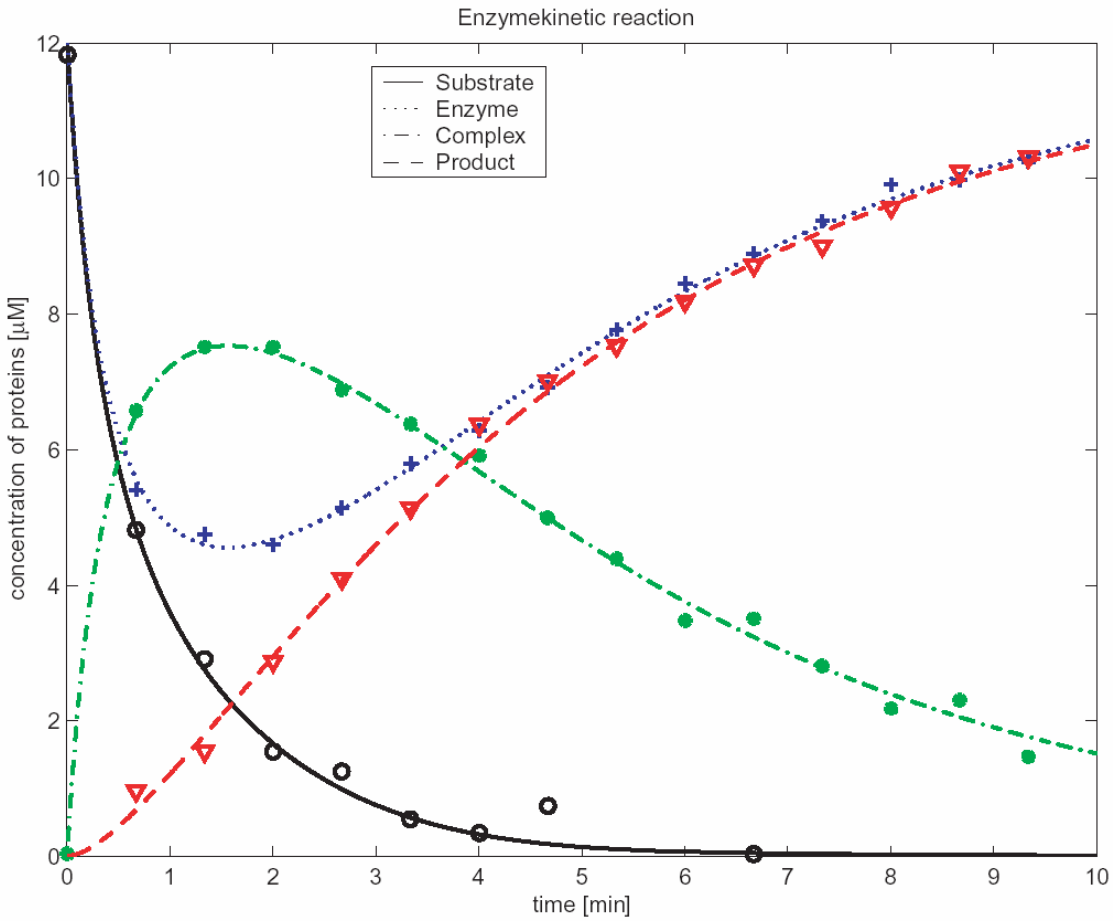
Switches

Oscillation

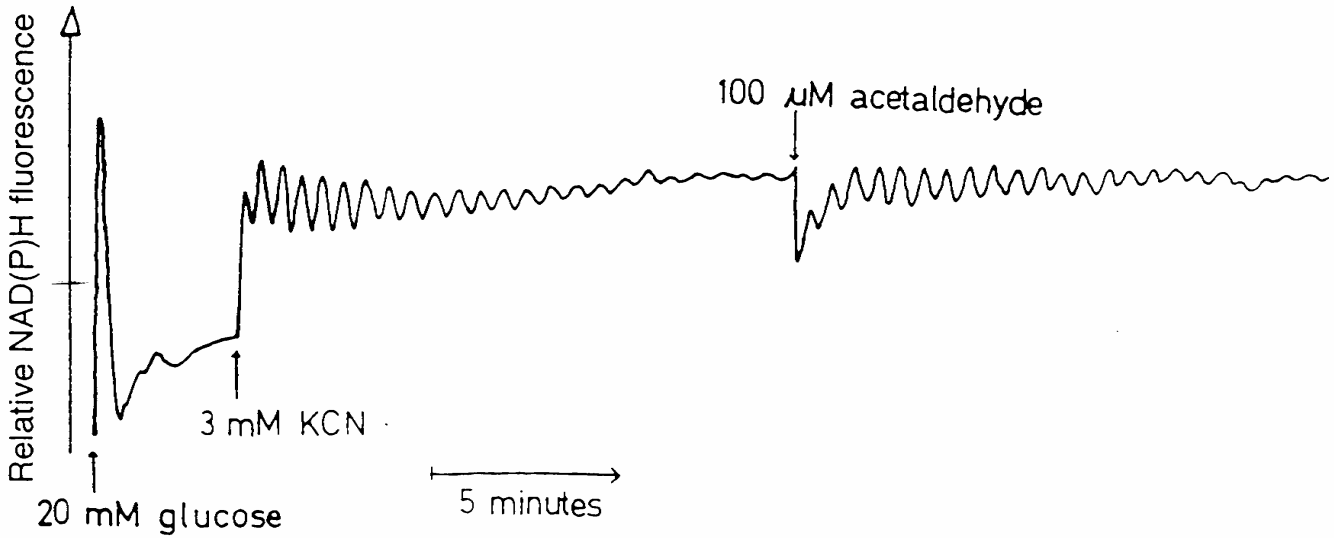
Coupled Oscillations

Chaos

???

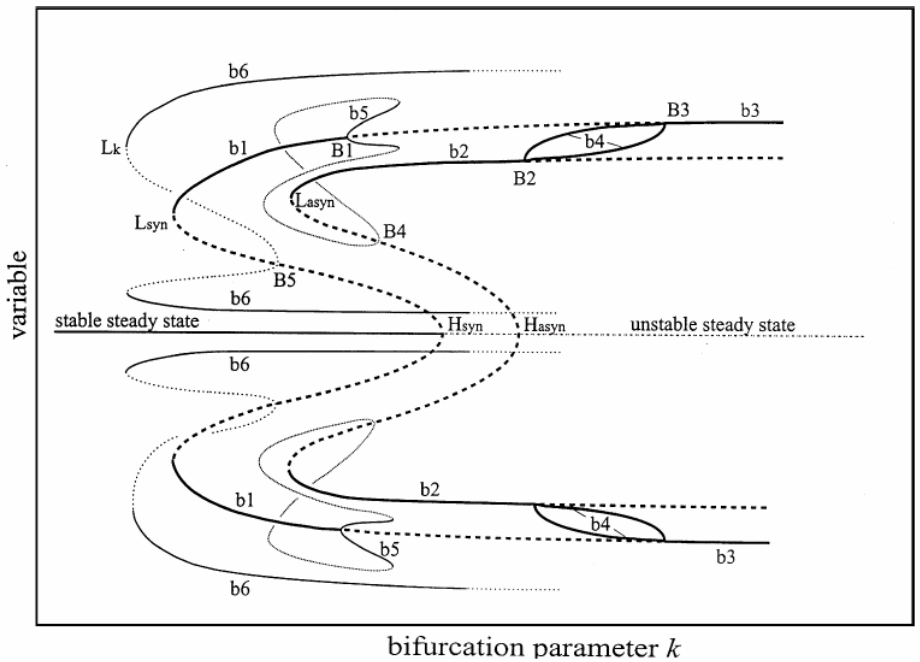


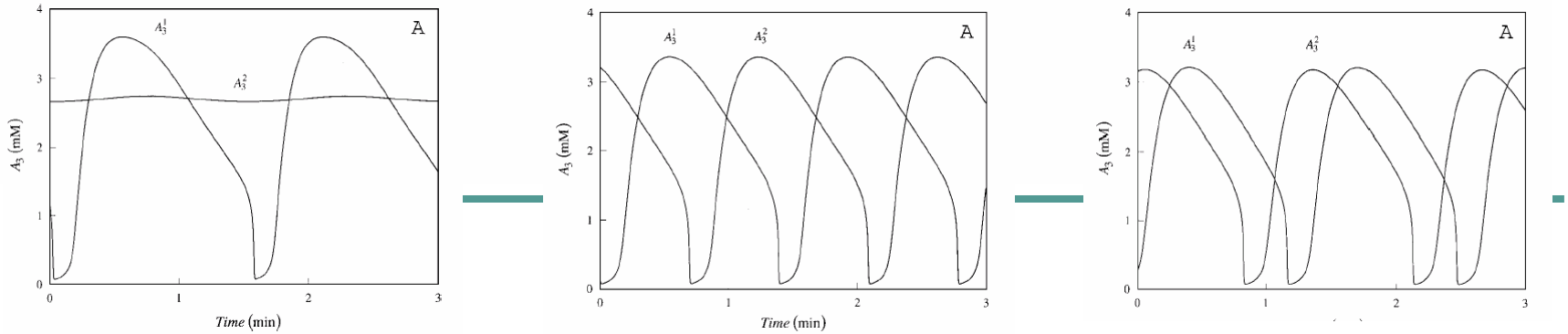
Glycolytic Oscillations



Richard et al. (1996), Eur. J. Biochem. 235, 238-241.

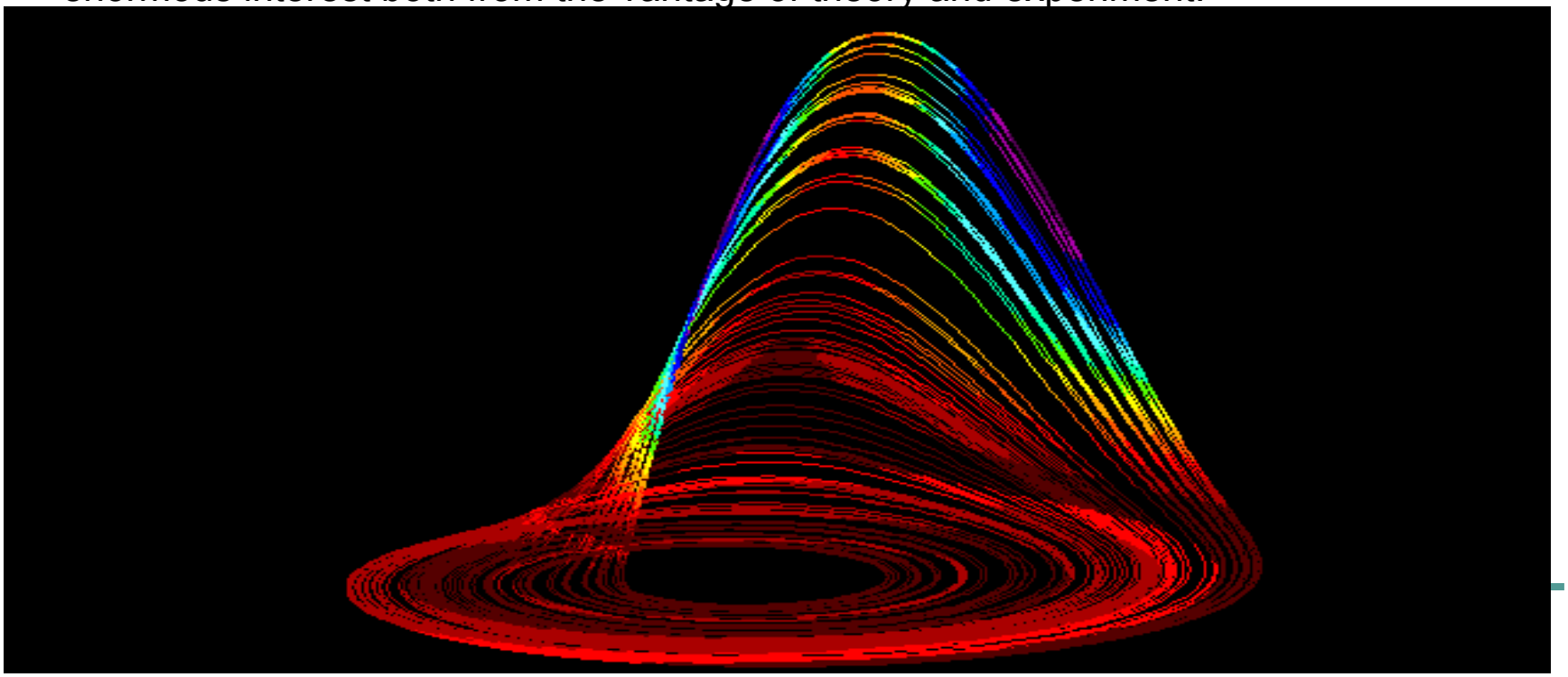
Bifurcation-Analysis: overview about possible modes of dynamical behaviour





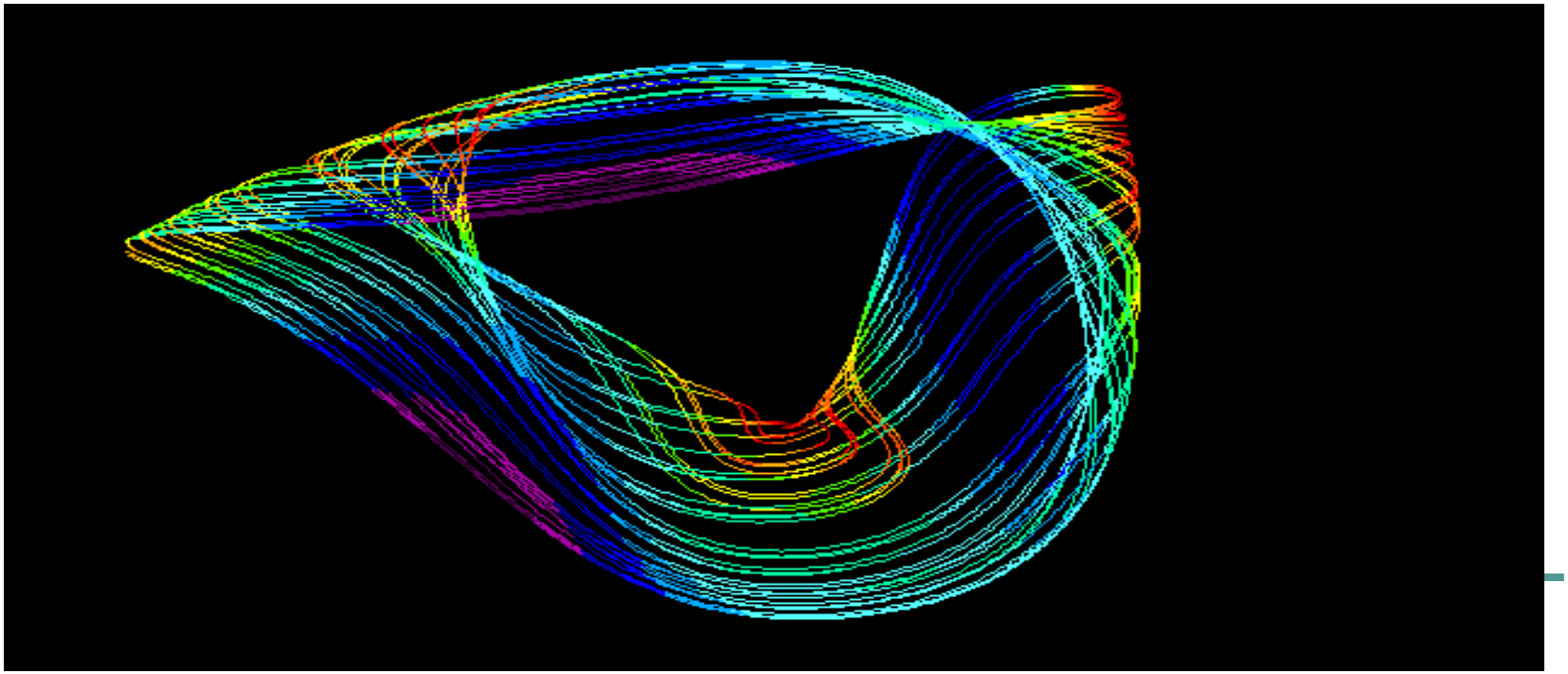
Chaotic kinetic models

Another famous chaotic attractor is due to Otto Rössler[(2)], who set out to find the simplest set of differential equations capable of generating chaotic motion. The chaos (Fig.6) is the so-called "spiral" variety. Rössler's equations can be viewed as a metaphor for chemical chaos, in which regard, it is worth noting that dynamics of the Rössler variety were subsequently discovered[(9)] experimentally in the Belousov-Zhabotinsky and Peroxidase-Oxidase reactions. These chemical oscillators, defying as they do, the old conventional wisdom that all reactions ultimately go to equilibrium, have attracted enormous interest both from the vantage of theory and experiment.



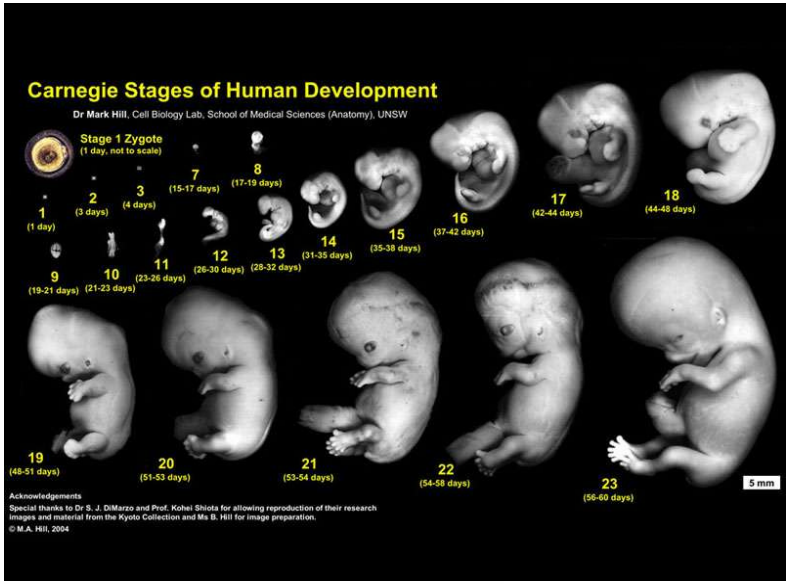
Chaotic kinetic models

- The Mackey-Glass equation models dynamics of white blood cell production in the human body.[10] Because rates of stem cell proliferation entail a time delay, periodic dynamics and chaos can obtain. Indeed, Mackey and Glass have suggested that long-term fluctuations in cell counts observed in certain forms of leukemia are evidence for these behaviors *in vivo*
- Real life is balancing on the edge and could be unpredictable. At the moment, our goal is to make a predictable model, that could be used in pharmaceutical application, to avoid complexity and to work in the range of parameters that produce predictable and re-producible results.

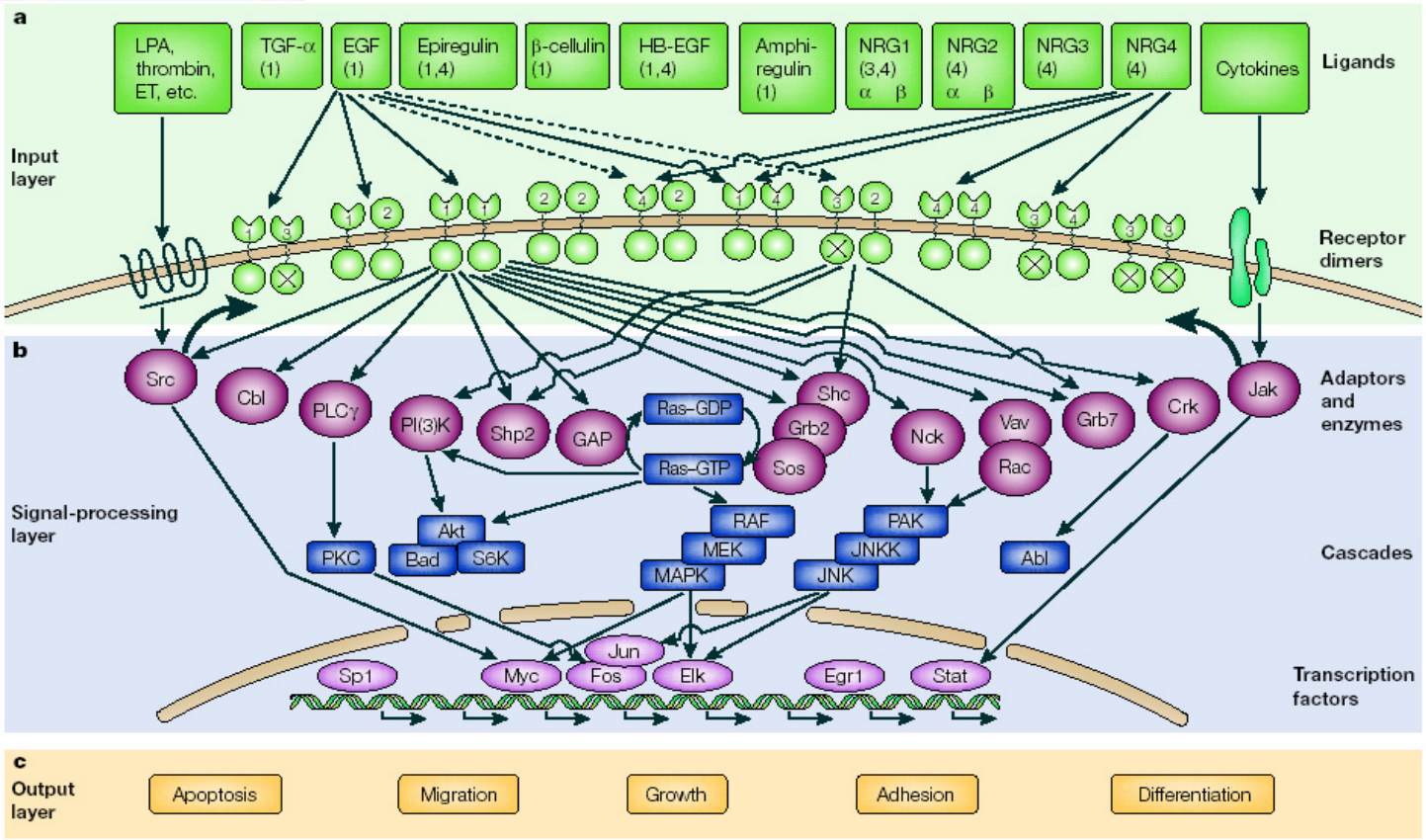


The Modelling Process

- ***Defining the biological scope for the model***
- ***Creating the model***
  - Static model development
    - » Entities and Interactions between them
    - » Data acquisition, mining, curation, and storage
  - Quantative kinetic model development
    - » Collection data on time dependencies
    - » Fitting data to find kinetic parameters
- ***Model validation***
  - **Examining if model makes 'plausible' predictions**
- ***Simulation, visualisation, analysis, and interpretations***
  - **Examine results looking for new biology**
- ***Planning of future experiments***
  - **To enhance model and verify predictions**
  - **To replace some *in vivo* and *in vitro* experiments**



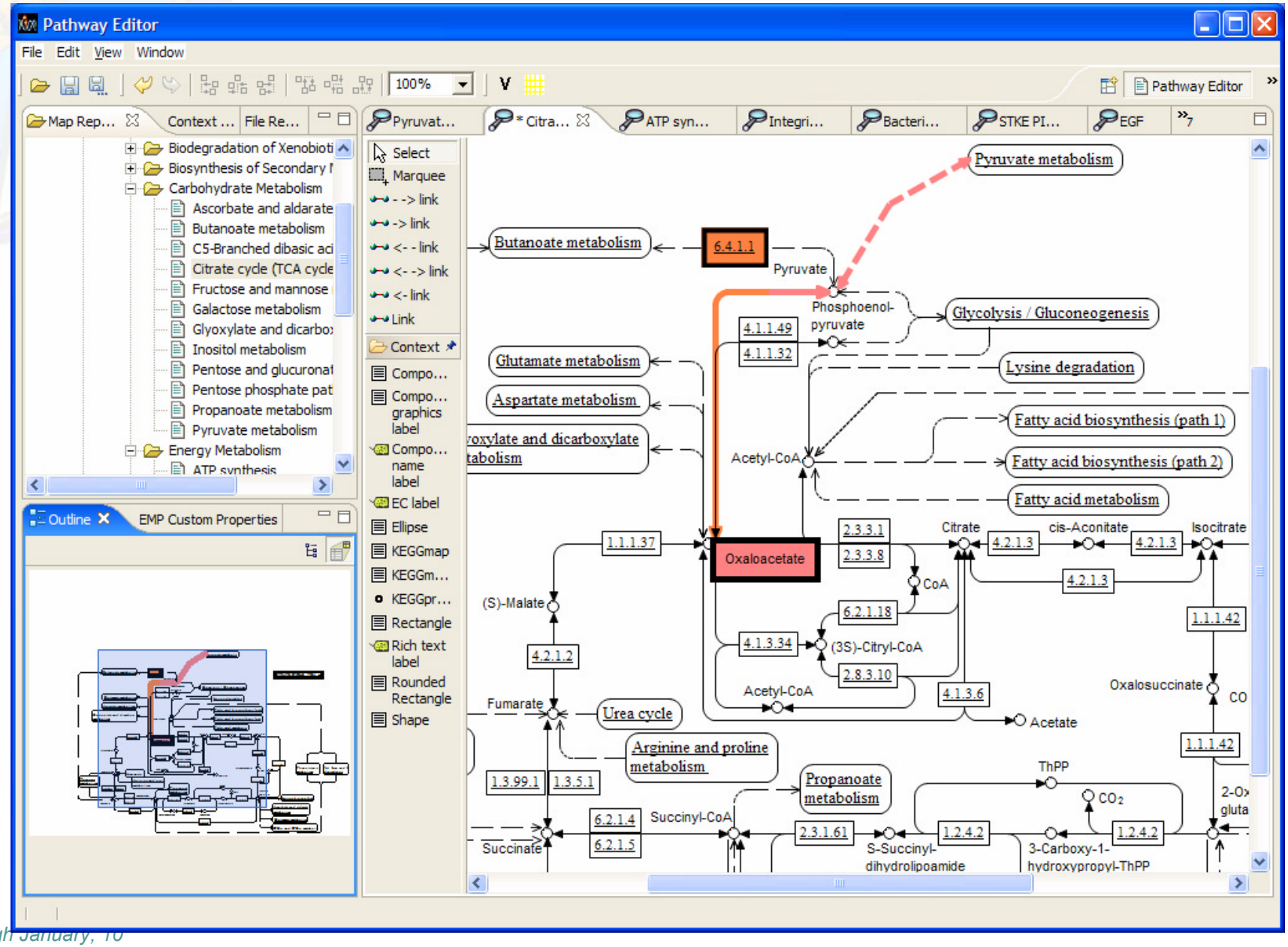
The EGFR signalling network



ErbB pathway becomes hyper-activated in many different cancer cell lines by a range of mechanisms (overproduction of ligands, overproduction or constitutive activation of receptors).

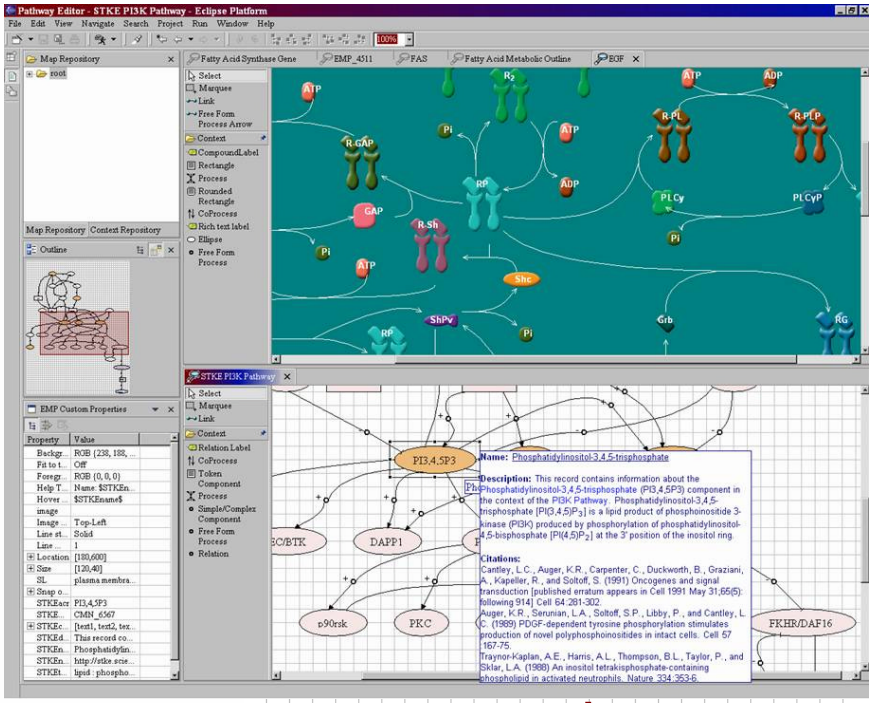
Y. Yarden & M.X. Sliwkowski (2001), Nature Reviews Mol. Cell Biol. 2, 127.

Editable Maps

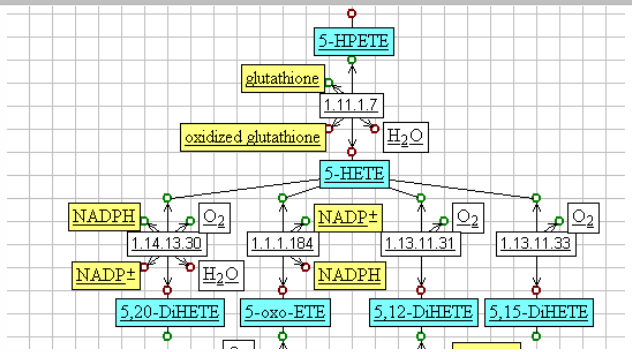


The Edinburgh Pathway Editor (EPE)

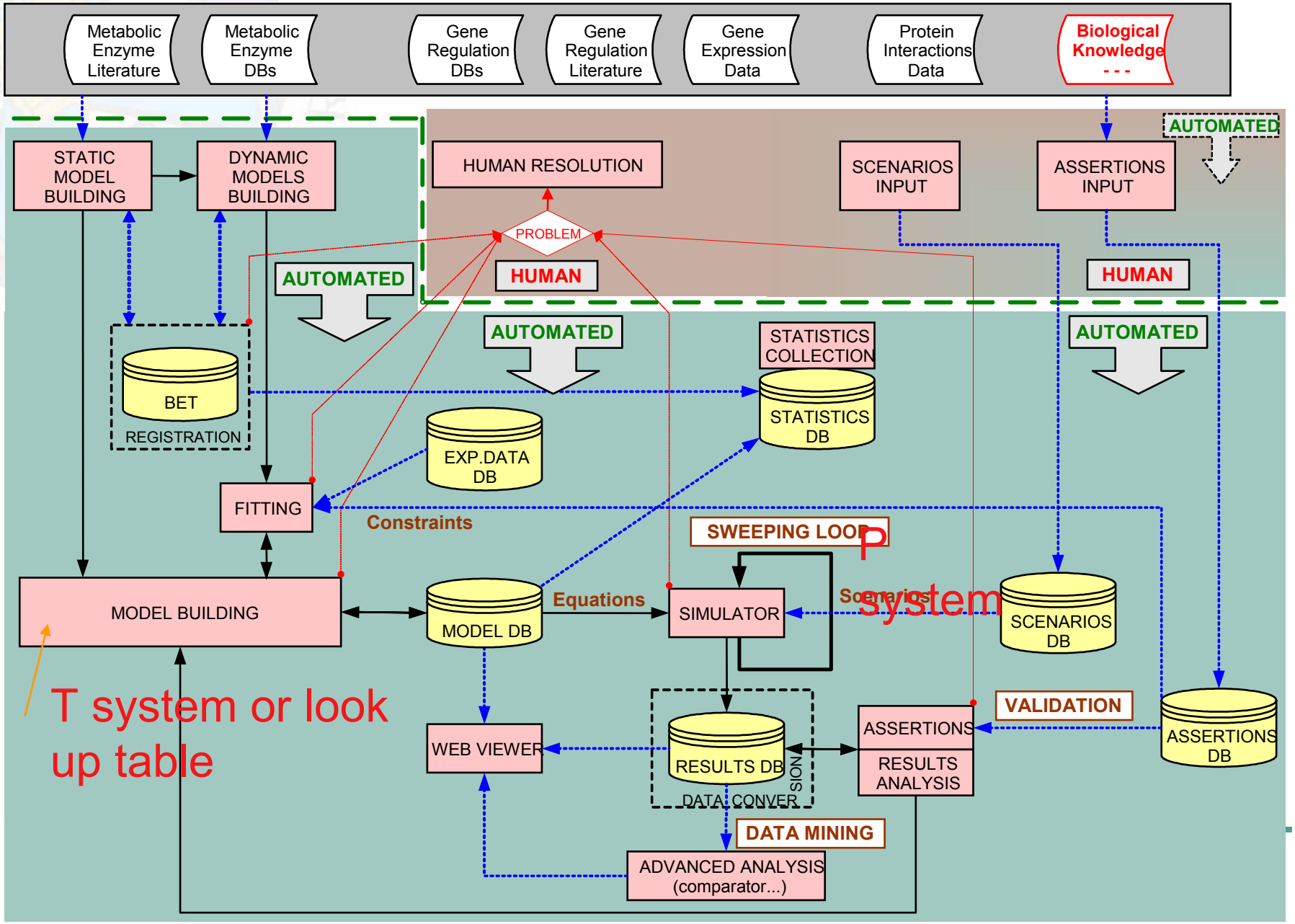
- **Visual annotation of**
  - metabolic, genetic regulatory, signal transduction and other intracellular networks.
  - multicellular, tissue and organism level networks for disease knowledge reconstruction.



- **Consistent and flexible way of data storage**
  - » kinetic information if available
  - » reference, data quality and data confidence
  - » checking biological names against thesaurus and nomenclatures
  - » arbitrary additional user-defined object's properties
- easy data exchange
  - » pathways stored locally in object oriented format (XML)
  - » pathways stored in relational database for enterprise sharing
  - » SemanticWeb (RDF, OWL)
  - » export to different picture formats, including WEB compatible HTML maps
  - » export/import data from/to variety of sources (SBML)



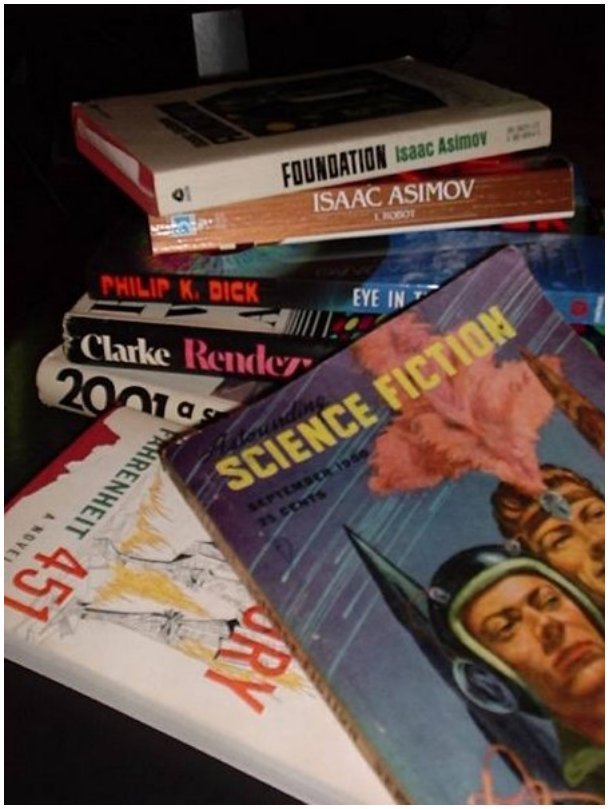
Systems Biology Informatics Infrastructure (SBII)



Use of Systems Biology

Arthur C Clarke's Third Law:

"Any sufficiently advanced technology is indistinguishable from magic"



Is Systems Biology/Modelling:

- an "Esoteric Knowledge"?
- the way to understand biological systems?
- a tool to solve practical problems?

Future for Systems Biology

Medical Informatics

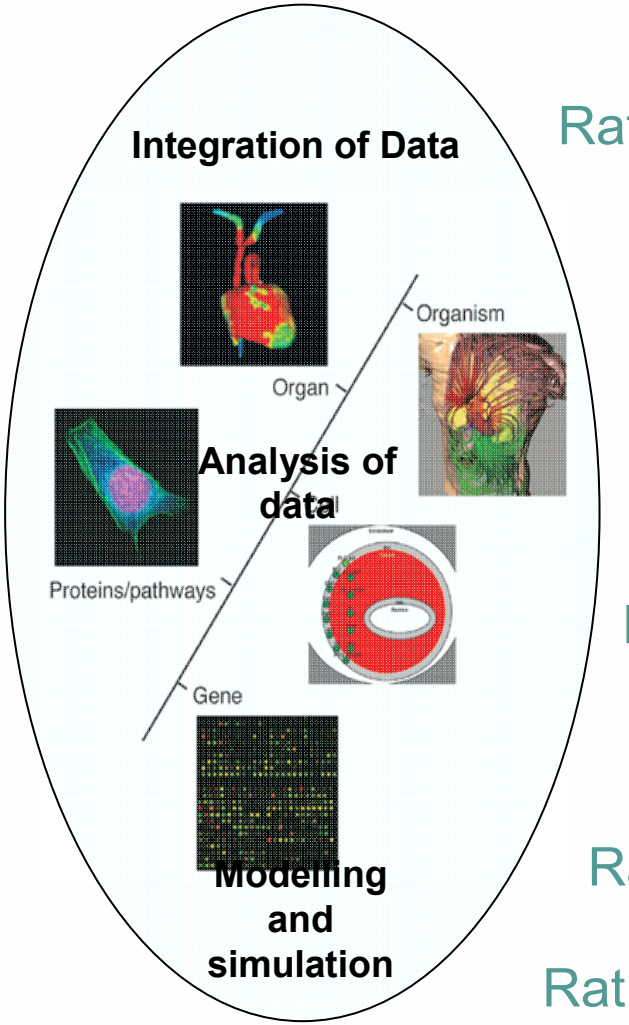
Pre-Clinical/Clinical

ADMET/QSAR

PK/PD

HTP “omics” physiological data,

Bio processing data



Rational therapy design

Rational Toxicology and Safety Assessment

Rational BioMarker Design

Rational Assay Design

Rational Target Design

Rational organism design

Rational process design

References

Welcome to the course

Contact Details

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