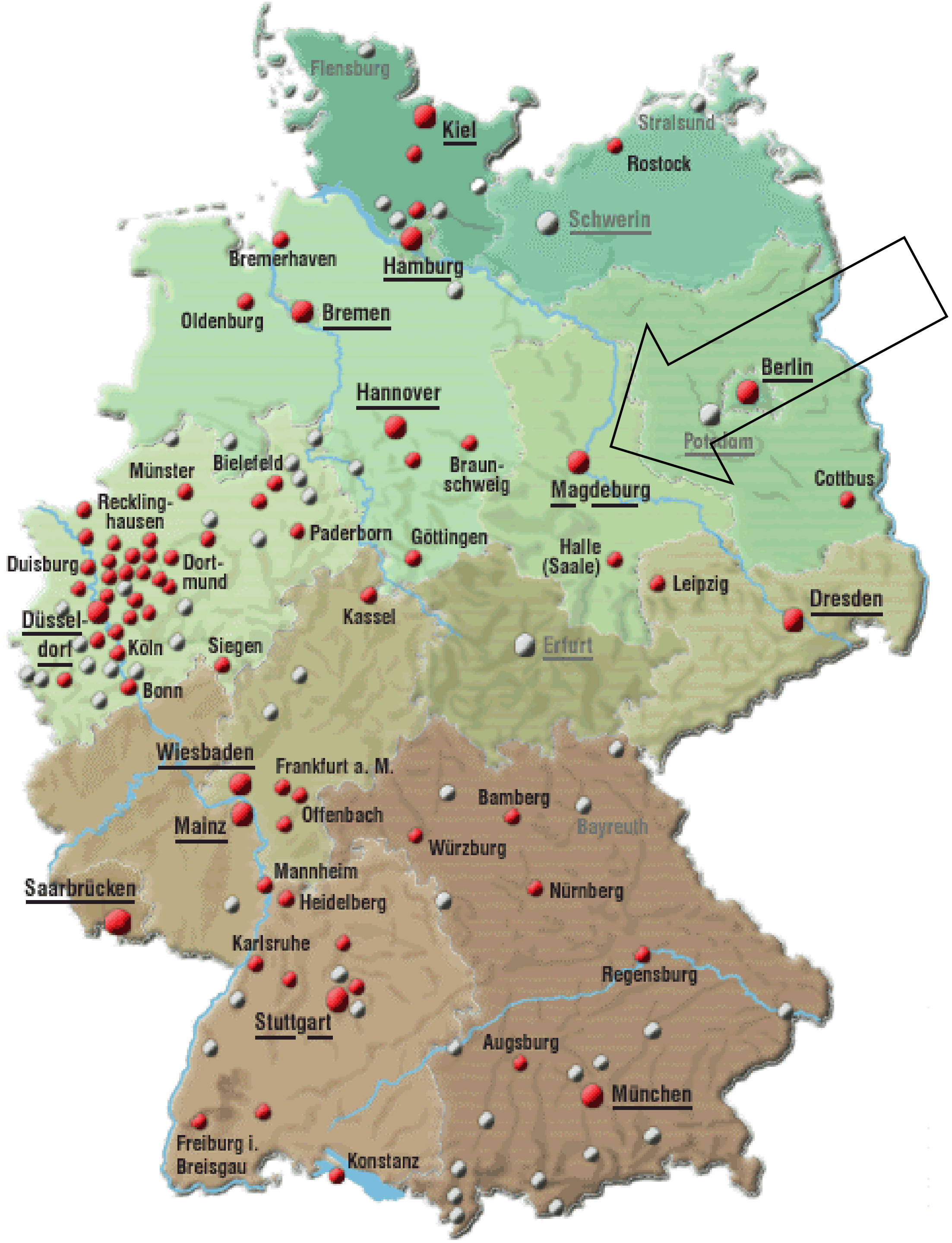
Max Planck Institute
for Dynamics of Complex Technical Systems
Magdeburg

Networks of Signal Transduction and Regulation in Cellular Systems

E.D. Gilles

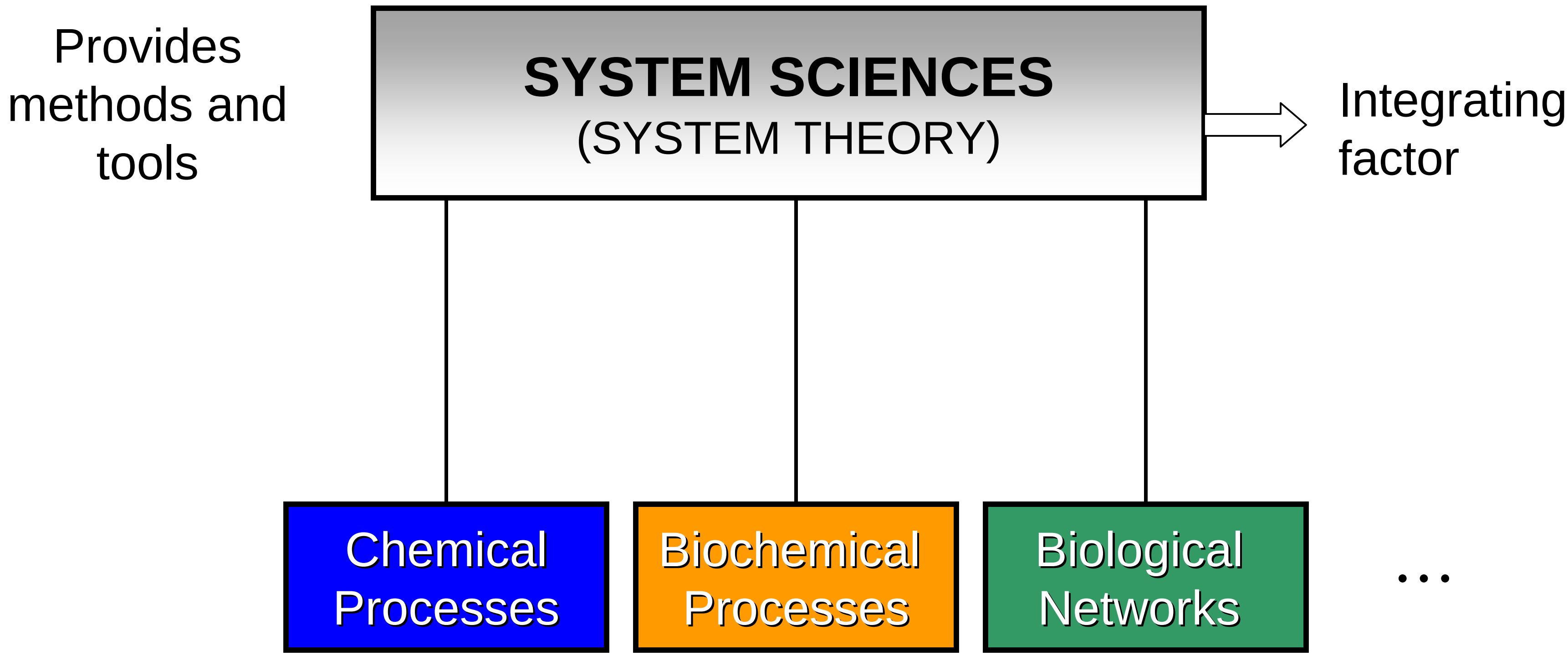


Magdeburg –
Capital of
Saxony-Anhalt

MAX PLANCK INSTITUTE
FOR DYNAMICS OF COMPLEX TECHNICAL SYSTEMS
MAGDEBURG

- Founded in 1996 as 1st Max Planck Institute of Engineering
- Start of research activities in 1998
- 4 departments:
  - Process Engineering (Sundmacher)
  - Bioprocess Engineering (Reichl)
  - Physical and Chemical Fundamentals (Seidel-Morgenstern)
  - System Theory (Gilles)

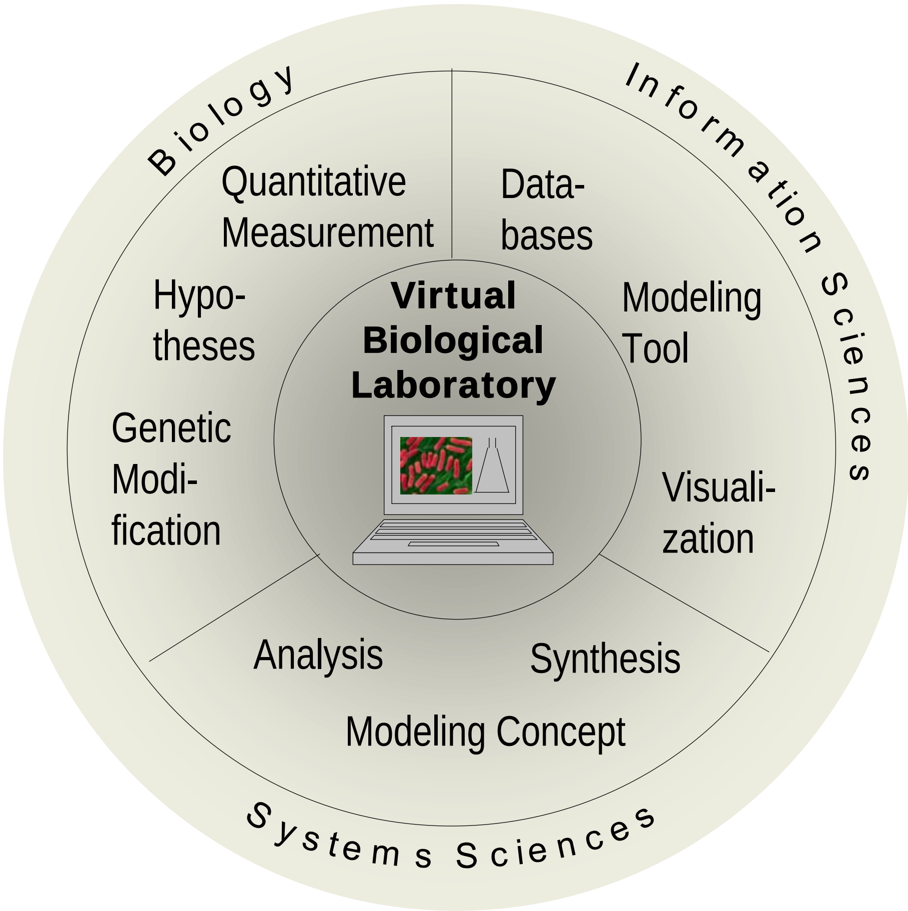
BROAD SPECTRUM OF PROCESSES TO DEAL WITH:



SYSTEMS BIOLOGY

„Systems biology is the synergistic application of experiment, theory, and modeling towards understanding biological processes as whole systems instead of isolated parts.“

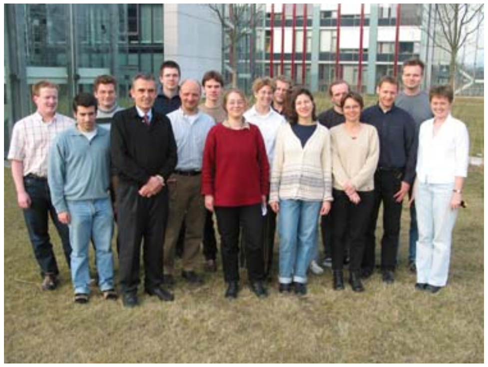
Systems Biology Group/Caltech



Interdisciplinary approach towards a quantitative and predictive biology

MAX-PLANCK-INSTITUT
DYNAMIK KOMPLEXER
TECHNISCHER SYSTEME
MAGDEBURG

RESEARCH GROUP:
SYSTEMS BIOLOGY



- Research activities started in 1998
- 17 employees working in our group
- Continuous extension of research activities on metabolic regulation and signal transduction
- Interdisciplinary composition of research group
- Close cooperation with a network of external biology groups
- Fermentation laboratory to perform experiments for model validation and hypotheses testing
  - Quantitative determination of cellular components
  - Construction of isogenic mutant strains of *E.coli* and other microorganisms

OBJECTIVES OF RESEARCH

- Improved understanding of cellular systems
- New solutions for biotechnological and medical problems (drug target identification)

APPROACH

- Detailed mathematical modeling
- Close interconnection between theory and experiment
  - Model validation
  - Model-based design of experiments
  - Formulation and testing of hypotheses
- System-theoretical analysis of dynamics and structural properties
- Decomposition into functional units of limited autonomy
- Model reduction

COMPLEXITY AND ROBUSTNESS

Complex Technical Processes

Powerful concepts to cope with increasing complexity

- Modularity techniques
- Hierarchical structuring
- Redundancy and diversity

Biological Systems

Similar features of structuring

- Natural modularity →decomposition into functional units of limited autonomy
- Hierarchical structuring of regulation
- Redundancy and diversity of pathways, sensors and other key units

Objectives of these concepts in both fields

- Robustness of functionality
- Reduction of fragilities

Methods and tools developed in engineering, also appropriate for biological systems

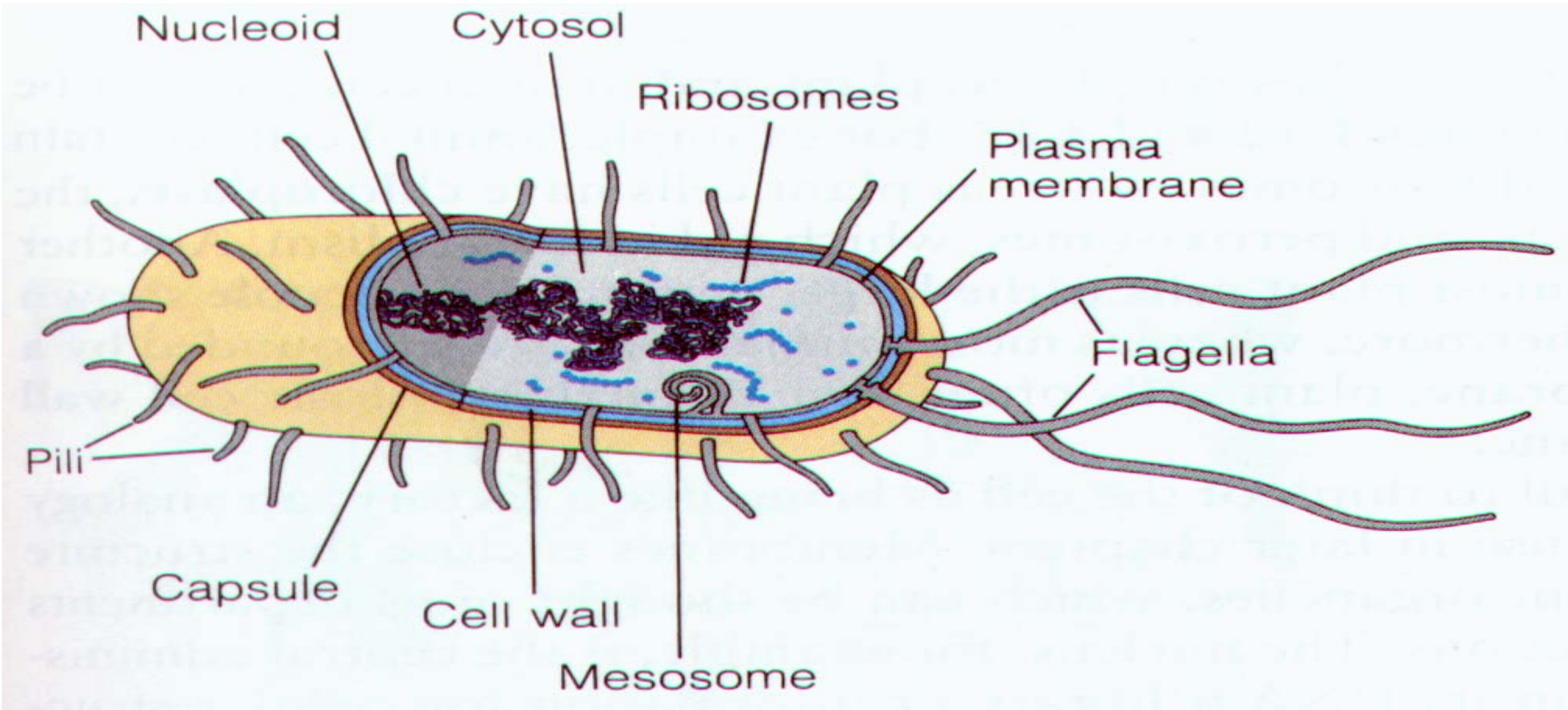
Control Theory, Nonlinear Dynamics, System Theory …

SIGNAL TRANSDUCTION AND REGULATION IN BACTERIAL CELLS

- Bacteria are ideally qualified to be studied in systems biology

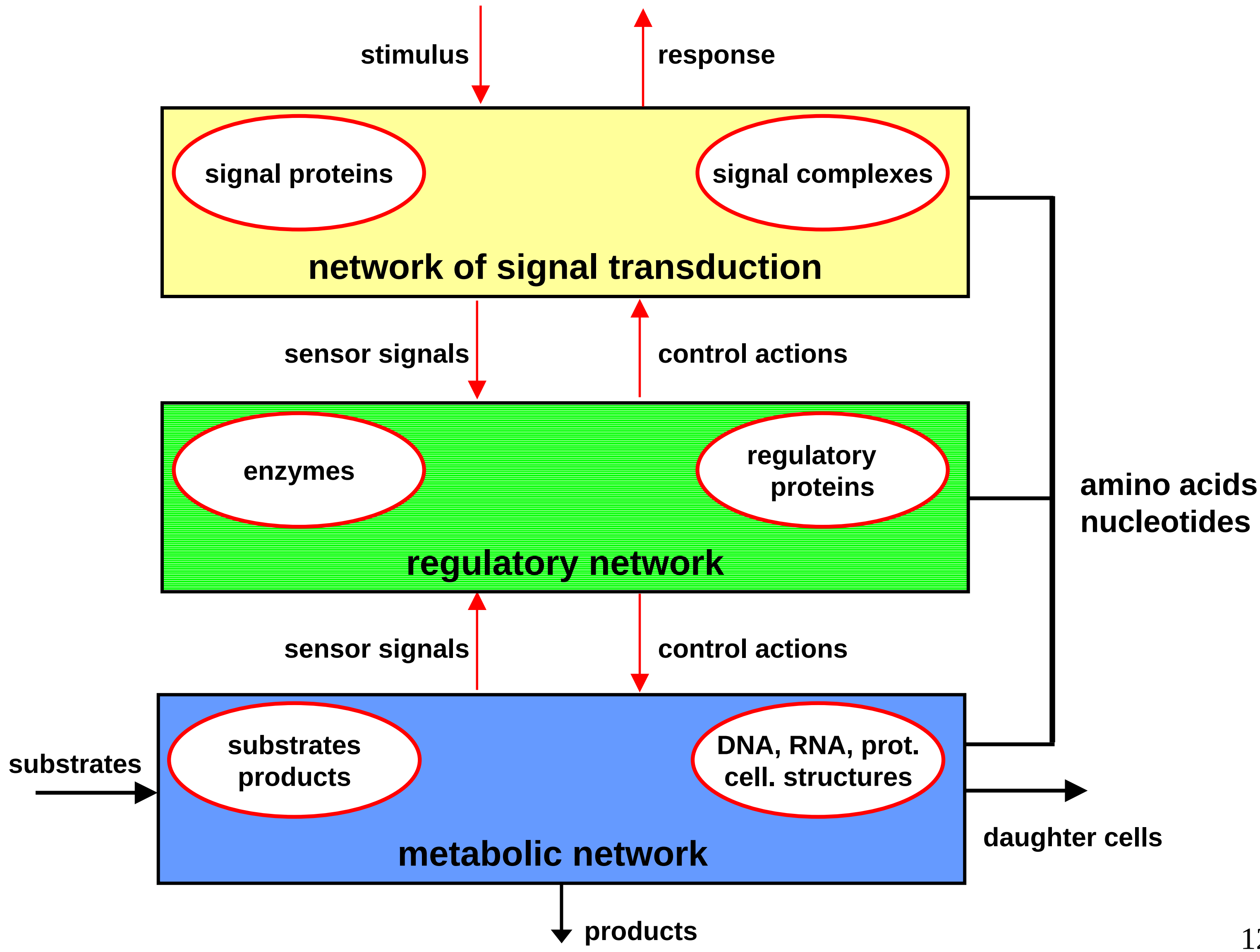
- Bacteria are very sensitive and respond very efficiently to changes in their environment
- Bacteria have a limited complexity compared to higher cells and multicellular organisms
- Well established experimental methods for large scale cultivation and genetic manipulations are available
- Lots of biochemical and genetic data are on-hand
- Broad spectrum of applications in biotechnology, medicine, agriculture

PROCARIOTIC CELL

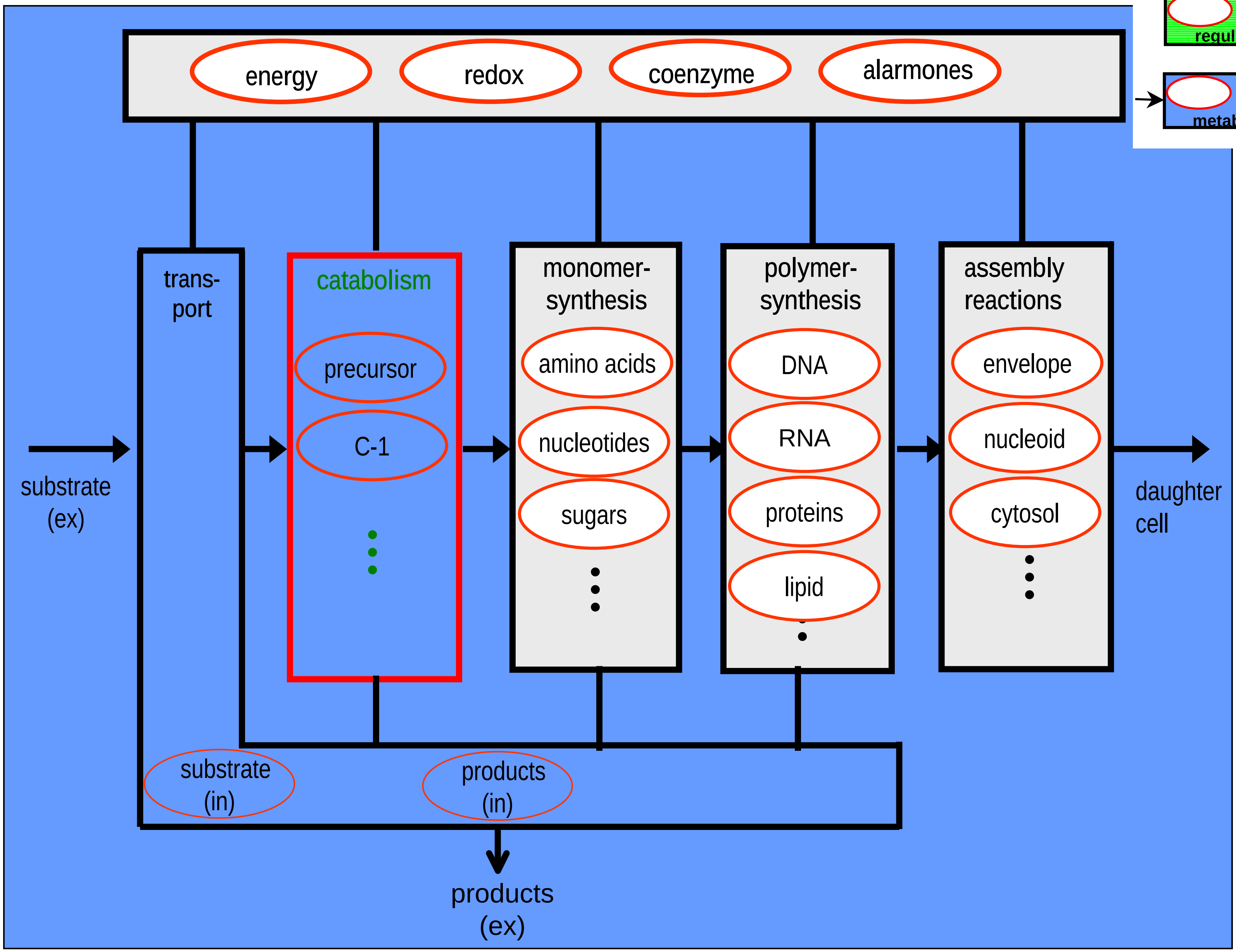


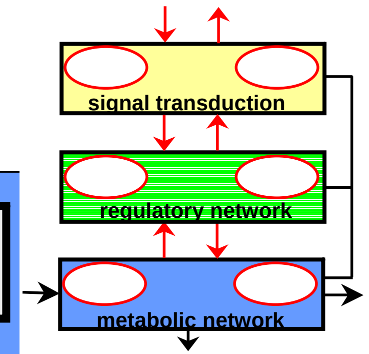
4800	**genes**
50	**metabolic units**
100	**genetically controlled regulatory units**
2500	**proteins**
50-70	**sensors**

SIGNAL ORIENTED DESCRIPTION OF A BACTERIAL CELL

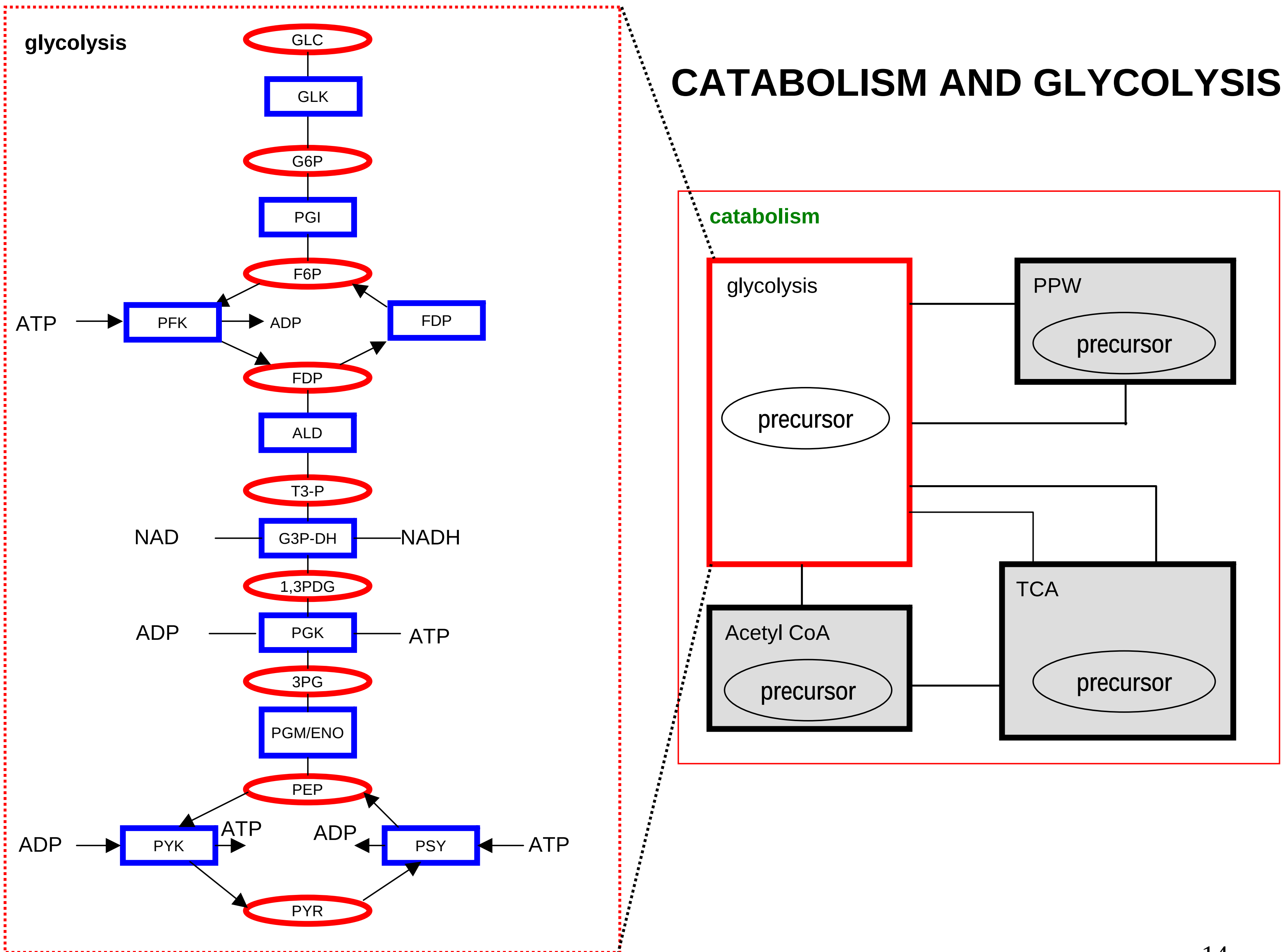


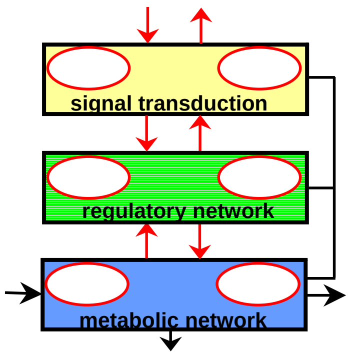
METABOLIC NETWORK



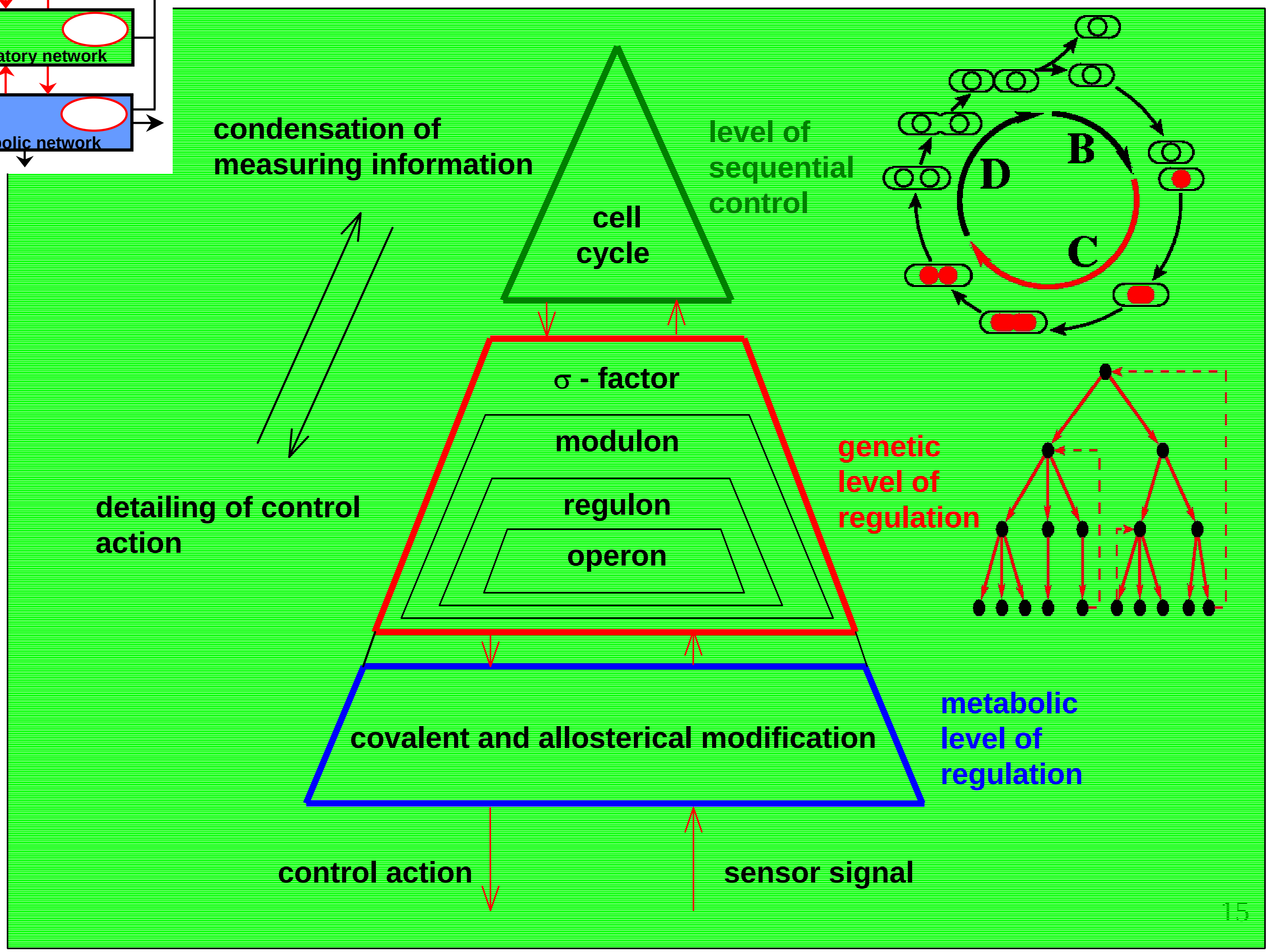


CATABOLISM AND GLYCOLYSIS

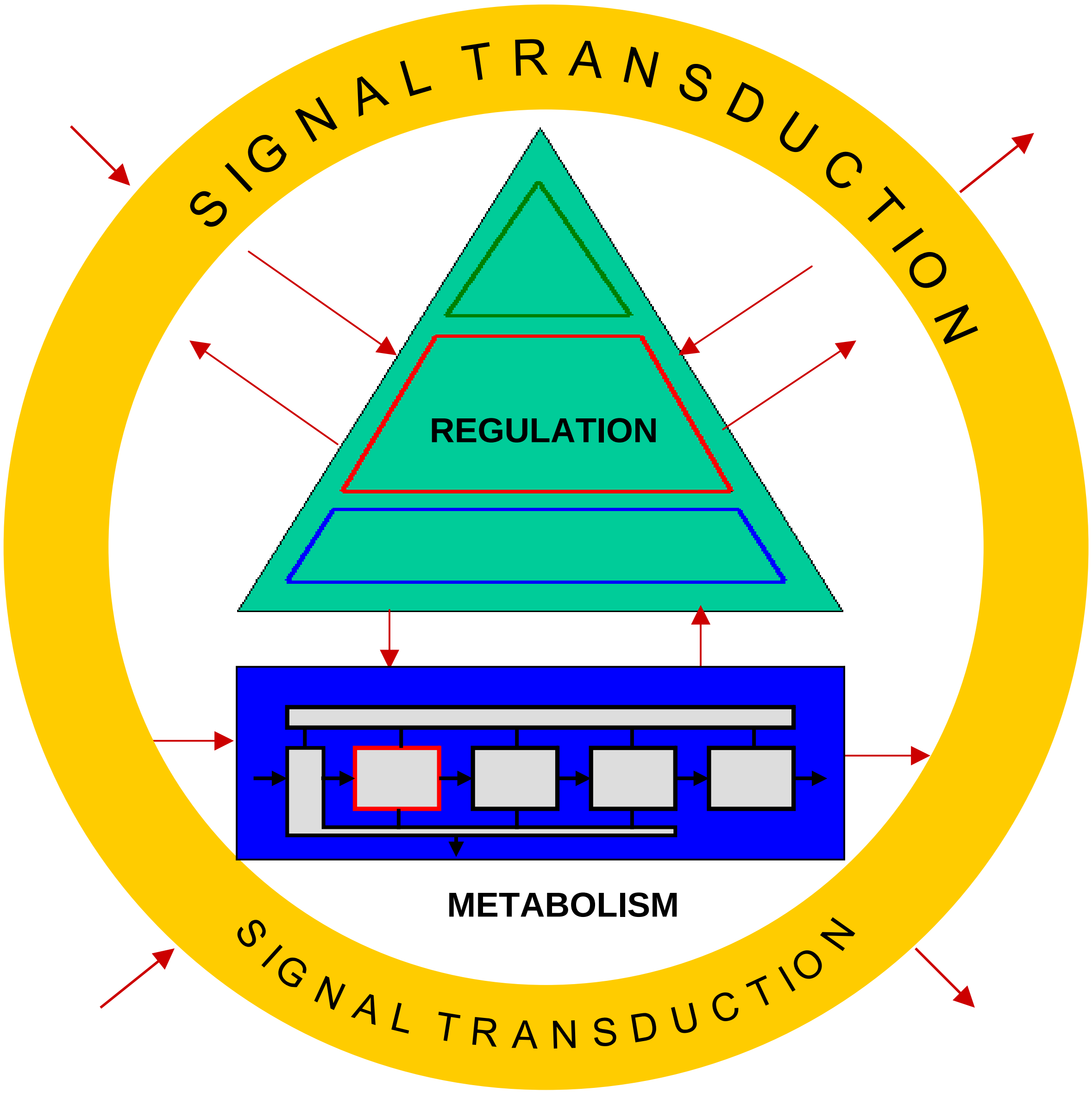




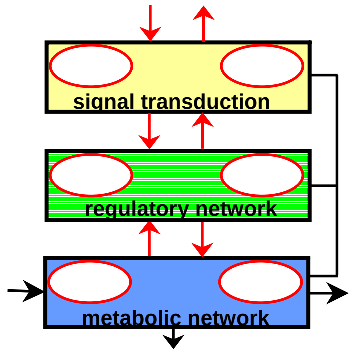
REGULATORY NETWORK

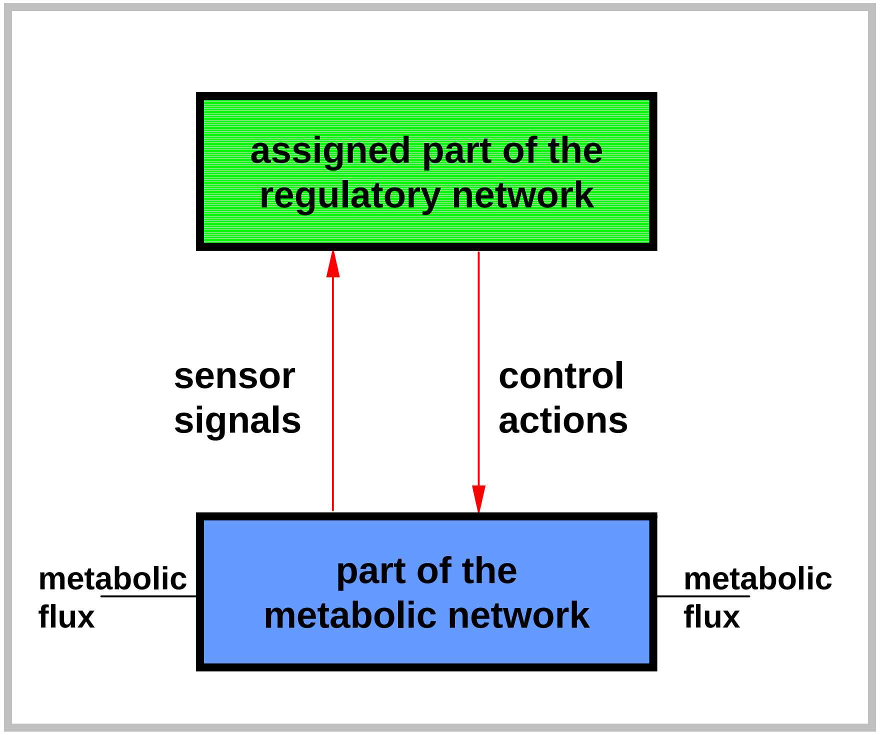


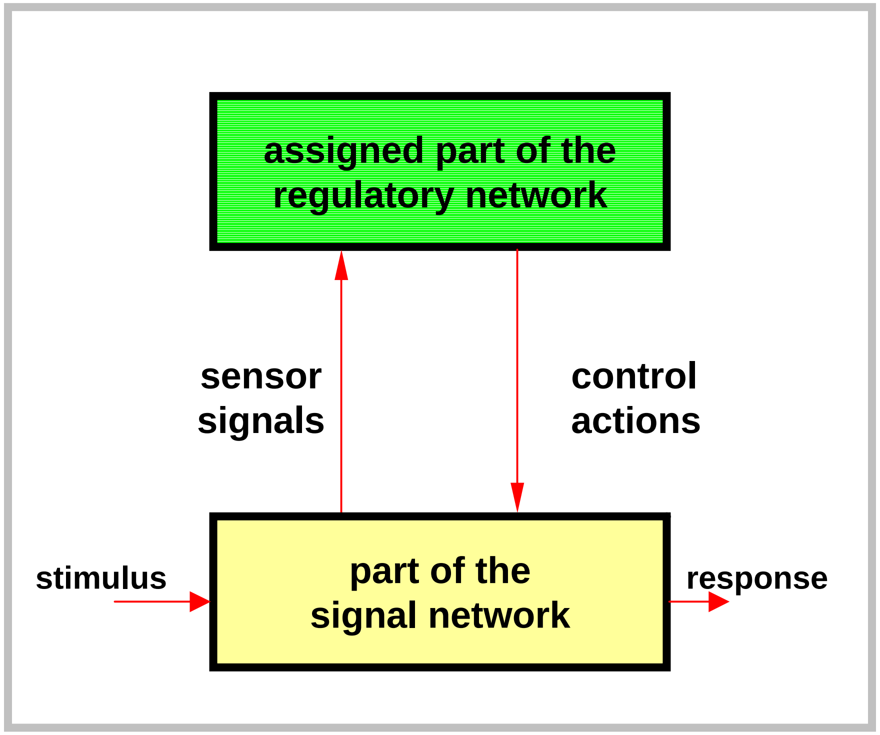
BACTERIAL CELL



CELLULAR FUNCTIONAL UNIT







functional unit
of metabolism with regulation

functional unit
of signal transduction with regulation

CRITERIA TO DEMARCATE CELLULAR FUNCTIONAL UNITS

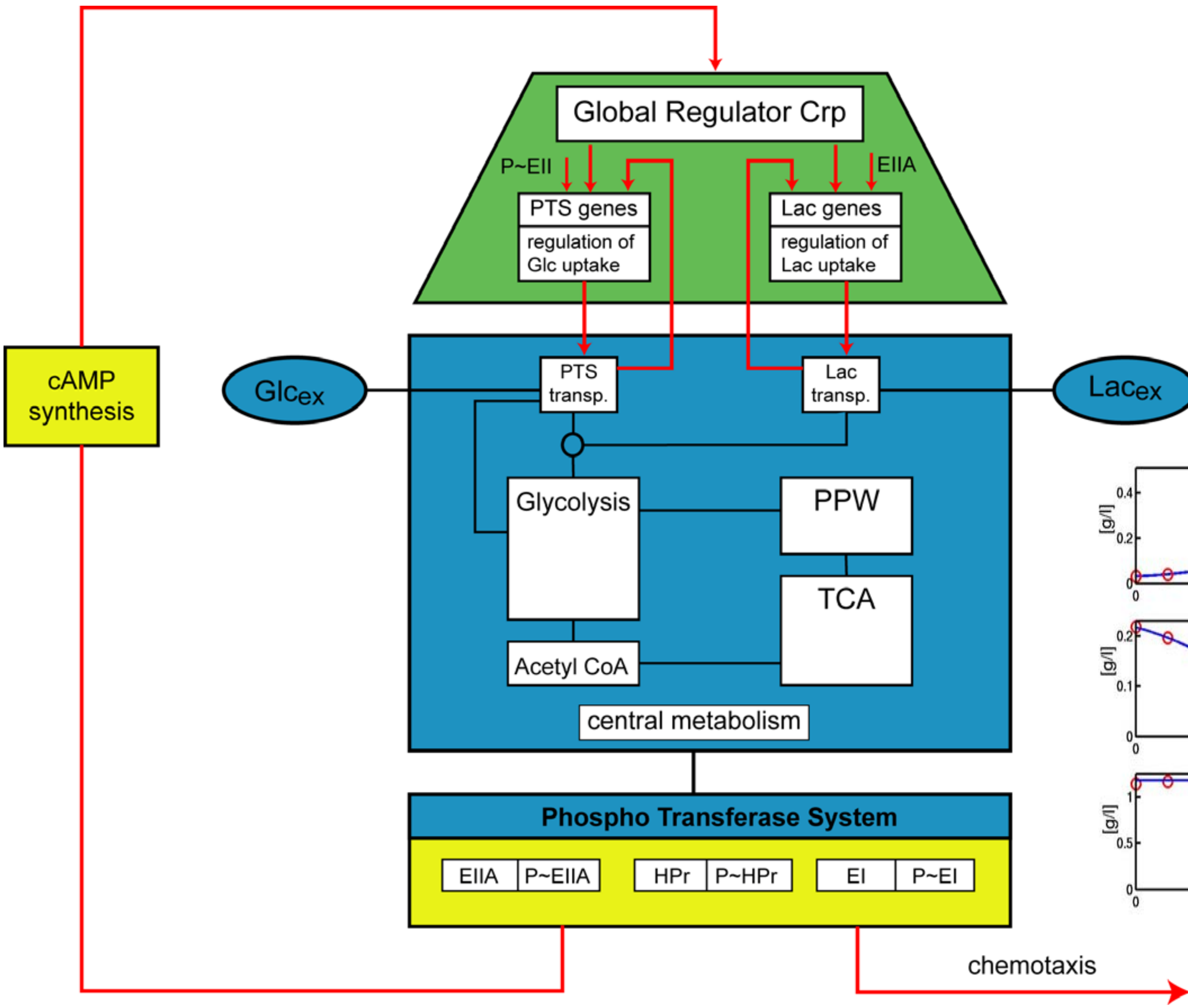
- Physiological function:
  Components of a functional unit fulfil by interaction common physiological task (quest for food, respiration, sporulation, stress management ...)

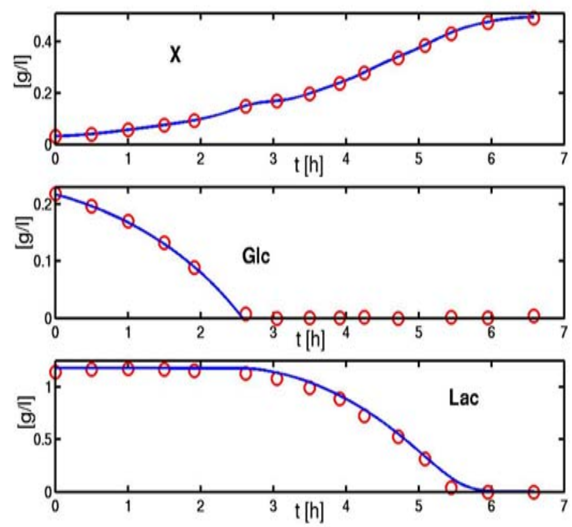
- Genetic structuring:
  Genes of a functional unit are expressed in a coordinated way (operon, regulon, modulon)

- Regulation:
  A functional unit owes a certain degree of autonomy to closed control circuits in its interior

- Signal transduction:
  The components of a functional unit establish a network of transfer elements for signal processing and signal integration

CATABOLITE REPRESSION IN *E. coli*

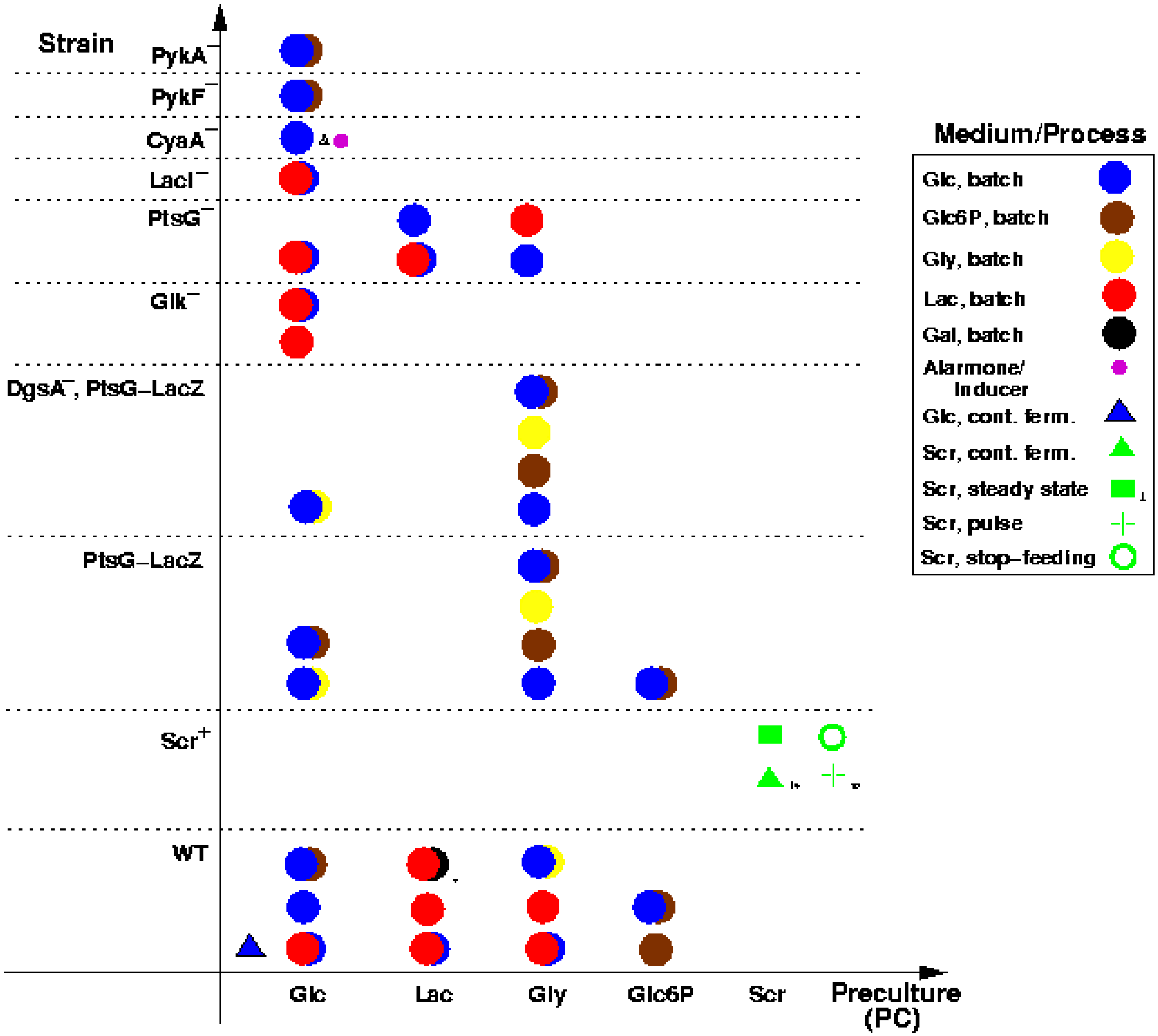




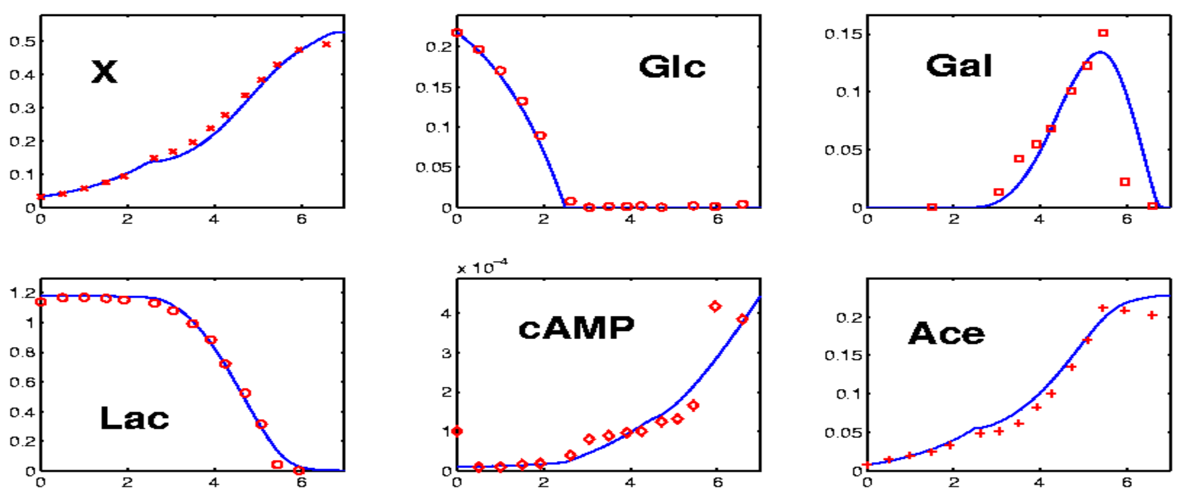
VALIDATION OF THE MODEL BY EXPERIMENTS

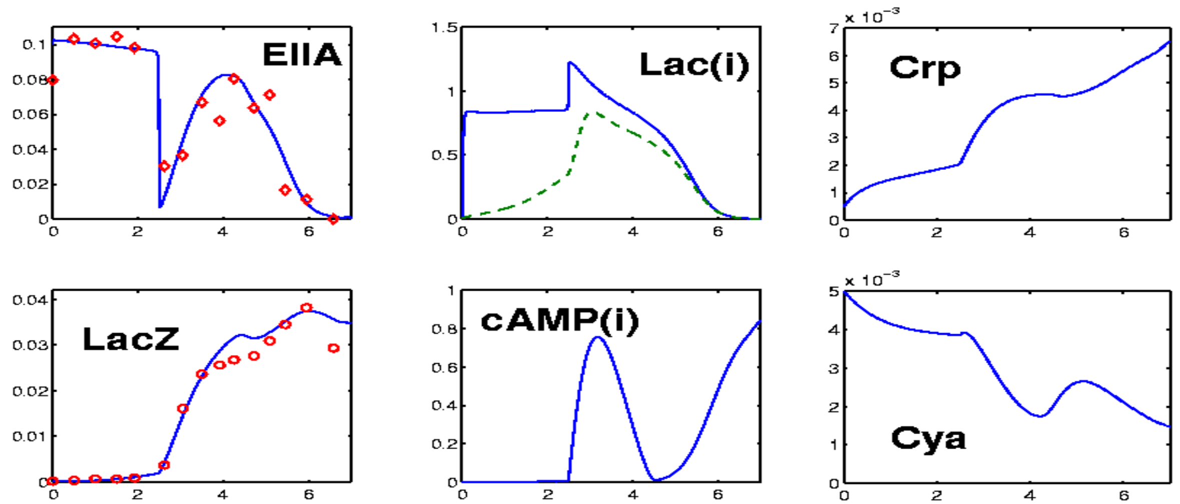
- Experimental strategy
  - Isogenic mutant strains
  - Different mixtures of the main substrates
  - Different preculture conditions
  - Batch experiments (µ is constant)
  - Feeding strategy (µ is changing)
  - Continuous culture (µ is constant, but sub-maximal)
- Time dependent measurement of components
  - Extra cellular carbohydrates
  - Glycolytic metabolites (Glc, Glc6P, F6P, Pep, Prv)
  - Degree of phosphorylation (EIIA, P~EIIA)
  - Enzyme activity (LacZ)
- Desired and in preparation
  - PCR technology
  - Transcriptome (cDNA arrays)
  - Proteome

EXPERIMENTS WITH DIFFERENT STRAINS AND CULTURE

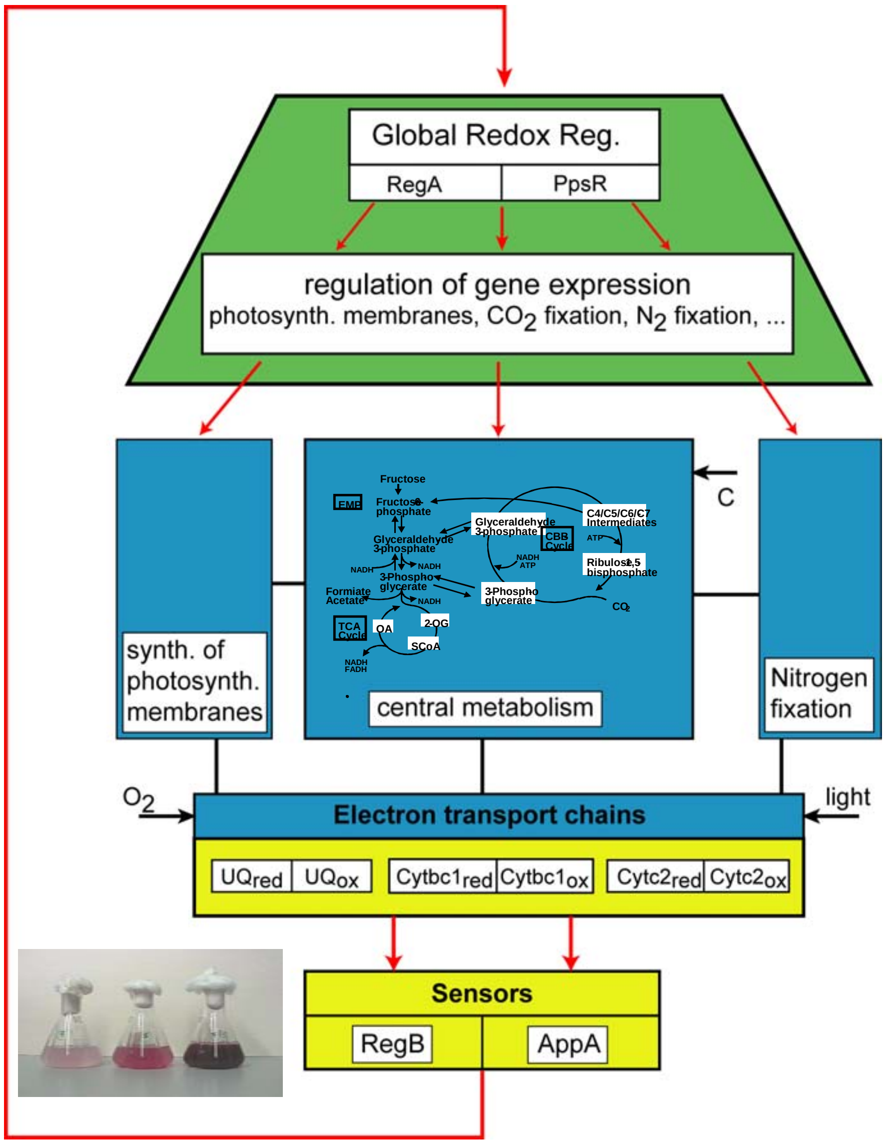


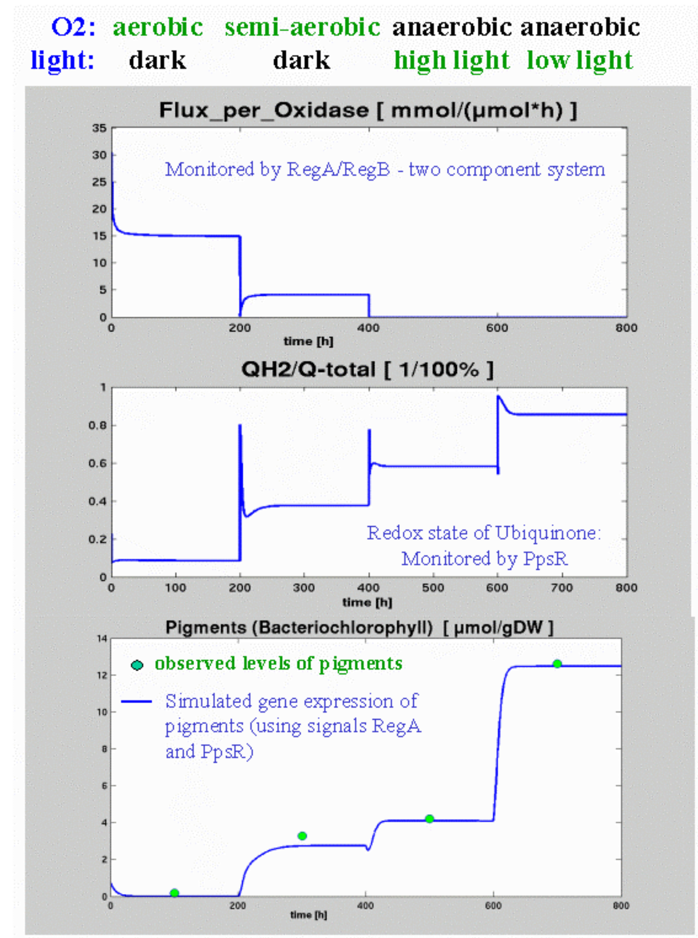
COMPARISON SIMULATION – EXPERIMENT
(wild type)





REDOX CONTROL OF PHOTOSYNTHETIC BACTERIA

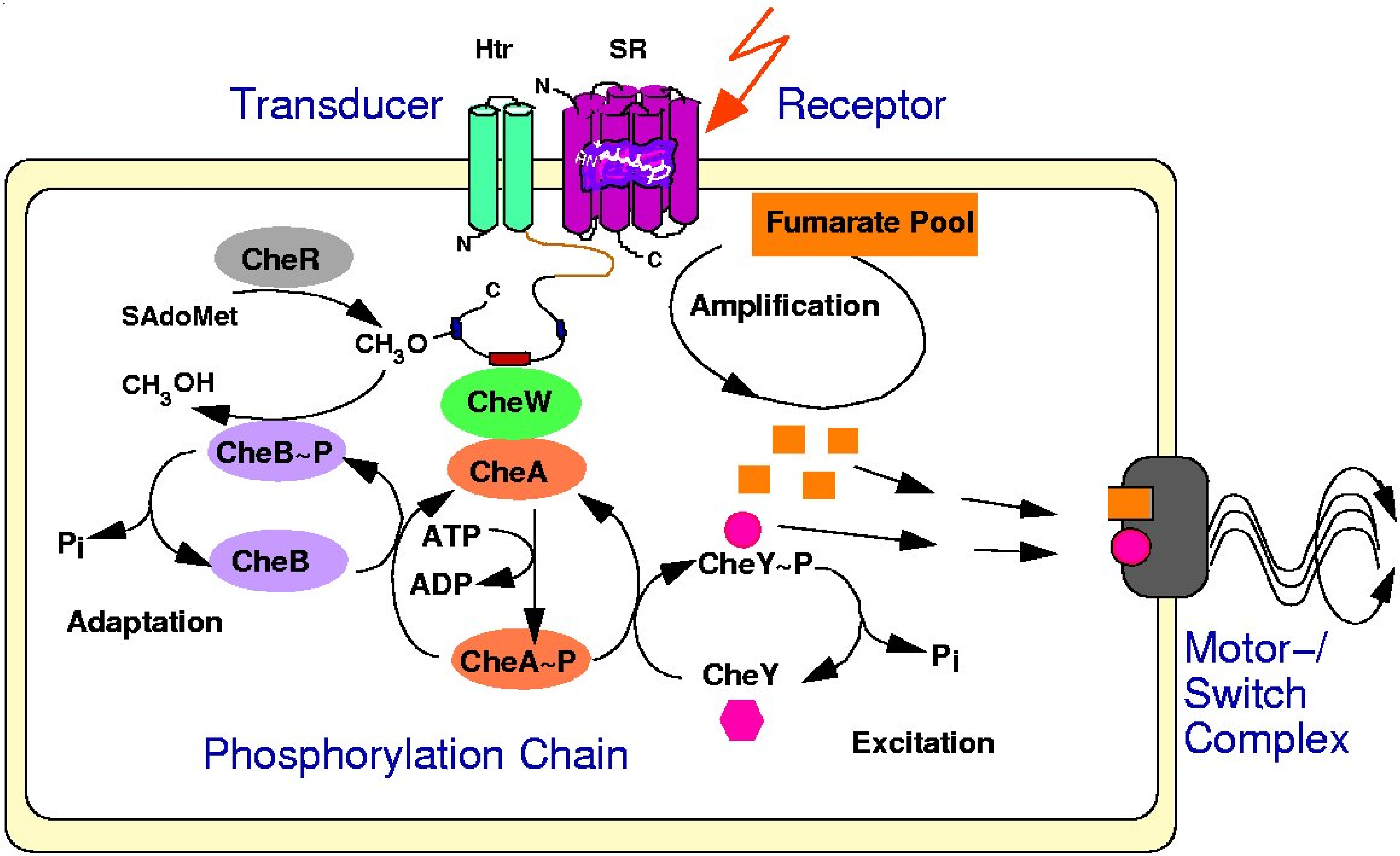




PHOTOTAXIS IN HALOBACTERIUM SALINARUM

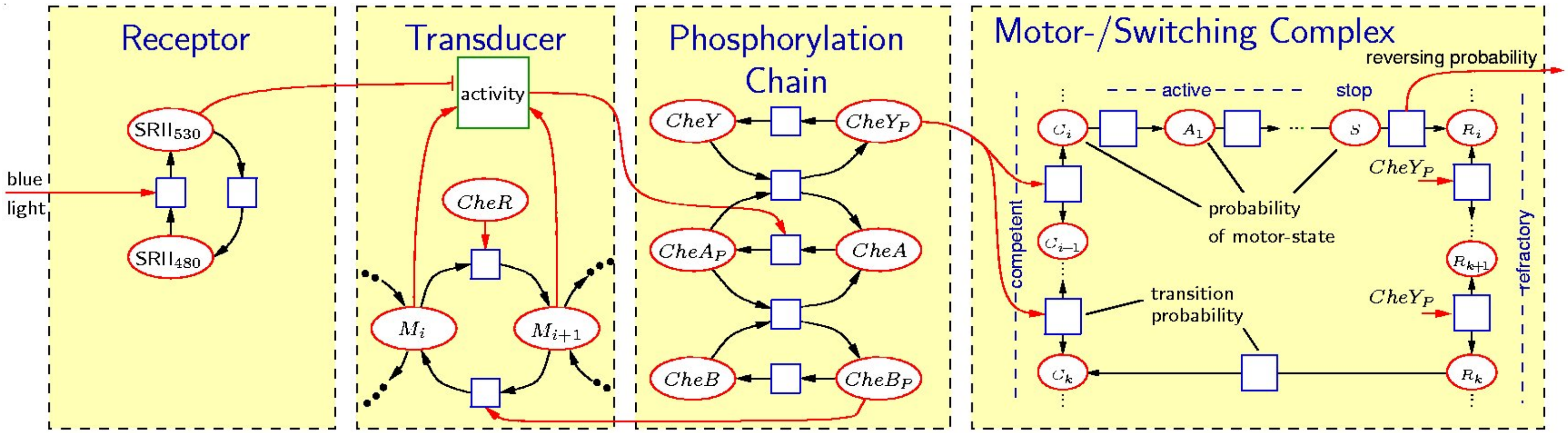
- Orange light as energy source for photosynthesis through the light driven proton pump bacteriorhodopsin.
- Simple kind of colour vision (blue, orange, ultraviolet).
- H. swims to those sites where optimal light conditions exist.
- Continues to swim in forward direction when sensing increasing intensity of orange light.
- Flees blue or ultraviolet light by reversing its swimming direction

PHOTOTAXIS IN HALOBACTERIUM SALINARUM

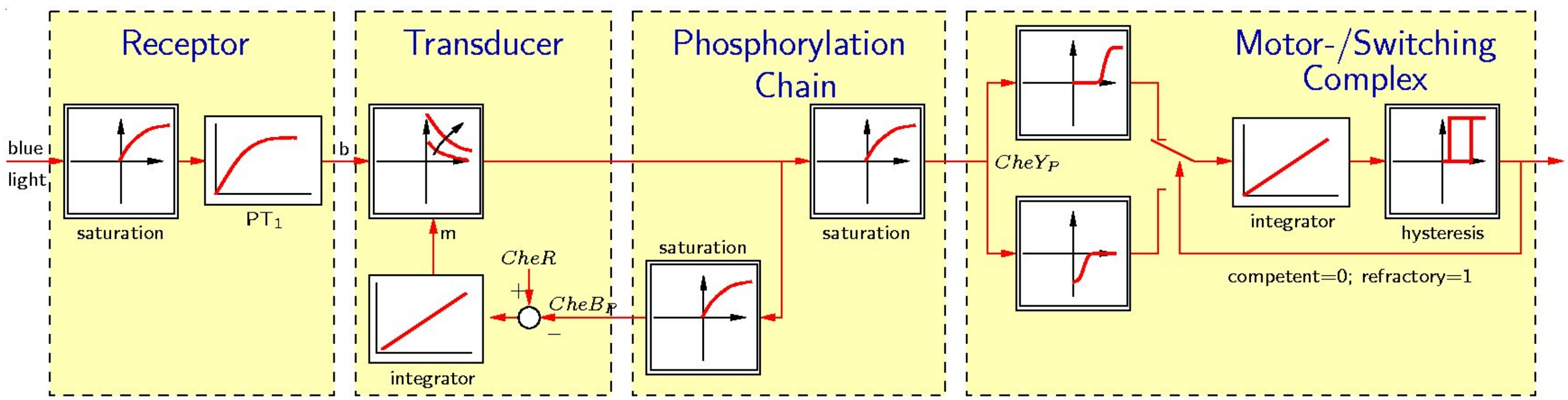


BLOCK-DIAGRAM OF PHOTOTAXIS

MOLECULAR ORIENTED:



SIGNAL ORIENTED:



THANK YOU!