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)
SYSTEM SCIENCES
(SYSTEM THEORY)

BROAD SPECTRUM OF PROCESSES TO DEAL WITH:

- Chemical Processes
- Biochemical Processes
- Biological Networks

Integrating factor

Provides methods and tools
“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
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 …
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

network of signal transduction

sensor signals
control actions

timulus
response

signal proteins
signal complexes

enzymes
regulatory proteins

substrates
products
DNA, RNA, prot. cell. structures

stimulus
response

amino acids nucleotides

substrates
products
daughter cells

regulatory network

metabolic network
METABOLIC NETWORK

- **Energy**
- **Redox**
- **Coenzyme**
- **Alarmones**

**Transport**
- Precursor
- C-1
- ...

**Catabolism**
- Precursor
- C-1

**Monomer-Synthesis**
- Amino acids
- Nucleotides
- Sugars
- ...

**Polymer-Synthesis**
- DNA
- RNA
- Proteins
- Lipid

**Assembly Reactions**
- Envelope
- Nucleoid
- Cytosol
- ...

**Substrate** (ex)

**Products** (in)

**Products** (ex)

**Signal Transduction**

**Regulatory Network**

**Metabolic Network**
REGULATORY NETWORK

condensation of measuring information

level of sequential control

σ-factor

modulon

regulon

operon

detailing of control action

cellular cycle

covalent and allosterical modification

control action

sensor signal

gene

operon

regulon

modulon

condensation of measuring information

level of sequential control

σ-factor

detailing of control action

control action

sensor signal

covalent and allosterical modification

metabolic level of regulation

signal transduction

regulatory network

metabolic network
BACTERIAL CELL

SIGNAL TRANSDUCTION

REGULATION

METABOLISM
CELLULAR FUNCTIONAL UNIT

assigned part of the regulatory network

sensor signals
control actions

part of the metabolic network

metabolic flux

functional unit of metabolism with regulation

assigned part of the regulatory network

sensor signals
control actions

stimulus
response

part of the signal network

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*

Global Regulator Crp

PTS genes
regulation of Glc uptake

Lac genes
regulation of Lac uptake

PTS transp.

Lac transp.

Glycolysis

PPW

TCA

Acetyl CoA

central metabolism

Phospho Transferase System

EIIA  P~EIIA  HPr  P~HPr  EI  P~EI

cAMP synthesis

GlCex

LaCex

chemotaxis

graphs showing the concentration of X, Glc, and Lac over time.
VALIDATION OF THE MODEL BY EXPERIMENTS

- **Experimental strategy**
  - Isogenic mutant strains
  - Different mixtures of the main substrates
  - Different preculture conditions
  - Batch experiments ($\mu$ is constant)
  - Feeding strategy ($\mu$ is changing)
  - Continuous culture ($\mu$ is constant, but sub-maximal)

- **Time dependent measurement of components**
  - Extra cellular carbohydrates
  - Glycolytic metabolites (Glc, Glc6P, F6P, Pep, Prv)
  - Degree of phosphorylation (EIIA, $P\sim$EIIA)
  - Enzyme activity (LacZ)

- **Desired and in preparation**
  - PCR technology
  - Transcriptome (cDNA arrays)
  - Proteome
EXPERIMENTS WITH DIFFERENT STRAINS AND CULTURE CONDITIONS
COMPARISON SIMULATION – EXPERIMENT
(wild type)
REDOX CONTROL OF PHOTOSYNTHETIC BACTERIA

Global Redox Reg.
RegA  PpsR

regulation of gene expression
photosynth. membranes, CO₂ fixation, N₂ fixation, ...

synth. of photosynth. membranes

central metabolism
Nitrogen fixation

O₂: aerobic  semi-aerobic  anaerobic anaerobic
light: dark  dark  high light  low light

Electron transport chains

UQ_red  UQ_ox  Cytb1_red Cytb1_ox  Cytb2_red Cytb2_ox

Sensors
RegB  AppA

Flux_per_Oxidase [mmol/(μmol*h)]

QH2/Q-total [1/100%]

Pigments (Bacteriochlorophyll) [μmol/gDW]

observed levels of pigments
Simulated gene expression of pigments (using signals RegA and PpsR)
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

Transducer

Receptor

Fumarate Pool

Amplification

Motor-/Switch Complex

Phosphorylation Chain
BLOCK-DIAGRAM OF PHOTOTAXIS

MOLECULAR ORIENTED:

SIGNAL ORIENTED:
THANK YOU!