

# The MetaGenoReg project

**Towards an understanding of the interrelations  
between metabolic and gene regulation**

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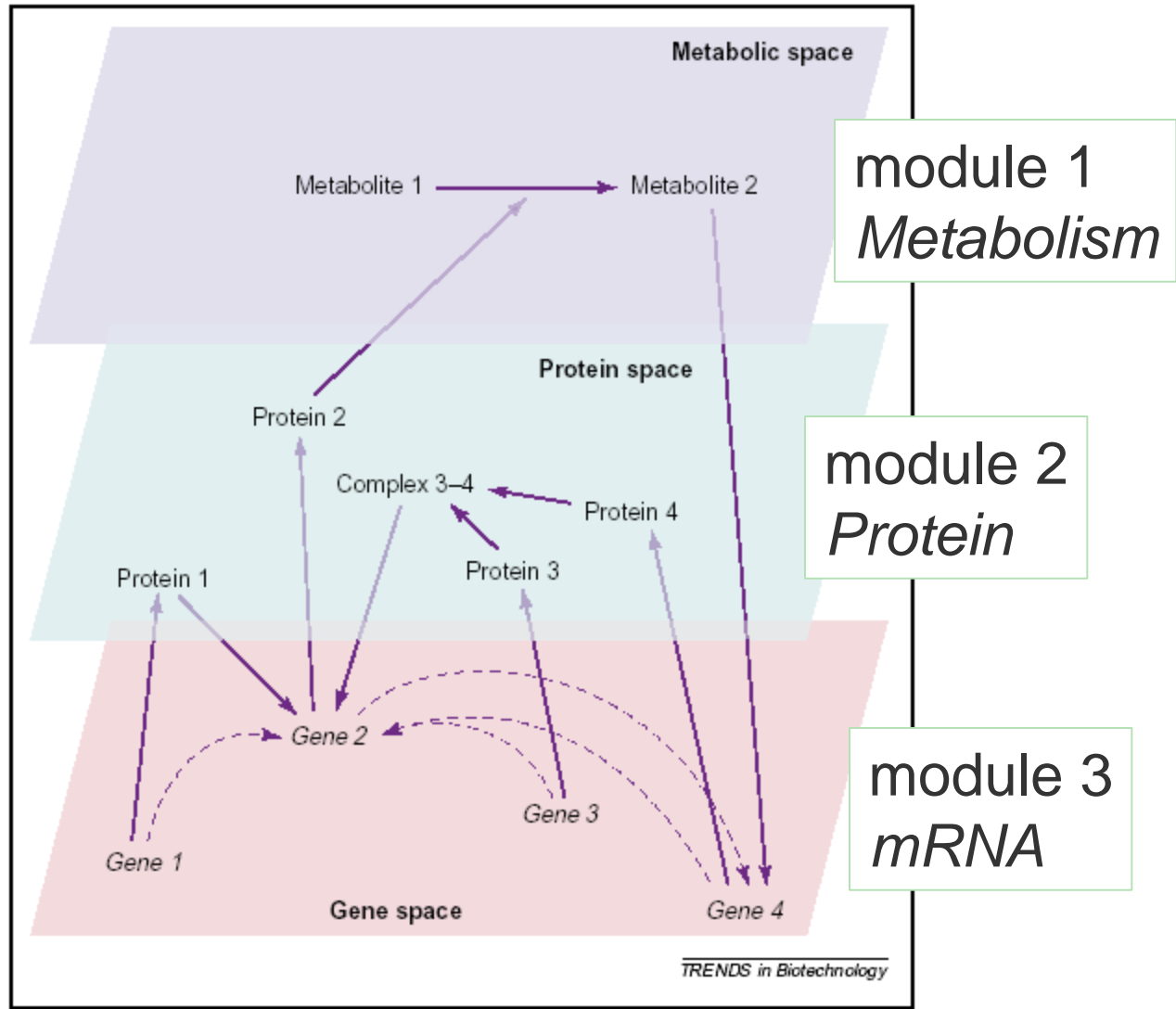


# General question of biological regulation

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- Cellular regulation involves **several levels**, including:
  - Gene regulatory networks
  - Metabolic regulation
- **These levels interact:**
  - Gene expression impacts metabolism through changes in enzyme concentrations
  - Conversely metabolism influences gene expression
- What is the **rationale** articulating both types of regulation?
  - Are they interchangeable ?
  - How much are they constrained?
  - What is the relative importance of gene and metabolic regulation?

# Modular 'hierarchical' analysis



# MCT and regulation analysis

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- Metabolic Control Theory provides for sensitivity analysis **around steady-states**
- MCT can handle **modular, hierarchical networks**  
(Kahn & Westerhoff, 1991; Bruggeman *et al.*, 2002)

However:

- **MCT is not well adapted to abrupt transitions**
- Rigorously it cannot treat transients between remote steady-states
- Strong non-linearities must be captured differently
- Therefore one needs a different approach

# Combining both types of regulation

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## Outline

- **Reduce** and **simplify** in order to understand the system's behaviour
- Develop a method for **joint modelling** combining **different approximations** suited to both types of regulation
- **Measure** their respective contributions

# Which reduction, which approximations?

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- Decompose the system into a **slow** (gene) and a **fast** (metabolic) component
  - fast algebraic subsystem (quasi steady-state hypothesis)
- Variable aggregation
- Strongly cooperative effects to be approximated by **step functions**
- Various types of **linearization** of metabolic responses

# PL model for gene regulation

de Jong *et al.* (2003) *Bioinformatics* 19:336-344

- Approximate promoter responses by step functions:

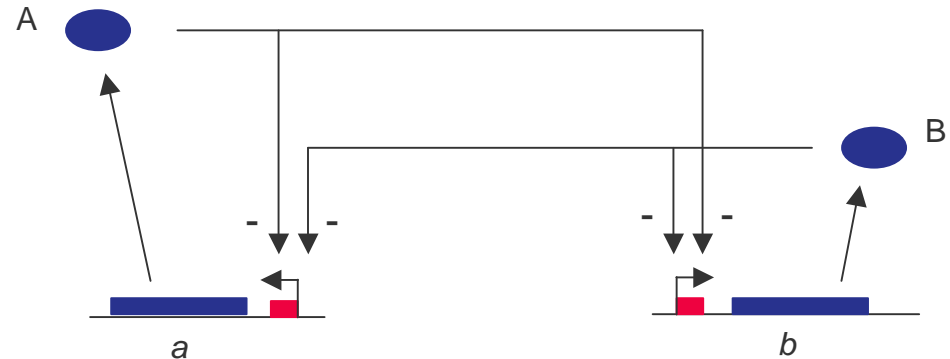
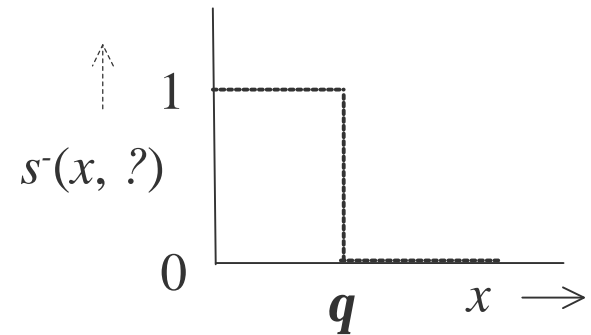
$$\dot{x}_a = k_a s^-(x_a, q_{a2}) s^-(x_b, q_{b1}) - g_a x_a$$

$$\dot{x}_b = k_b s^-(x_a, q_{a1}) s^-(x_b, q_{b2}) - g_b x_b$$

$x$  : protein concentration

$q$  : threshold concentration

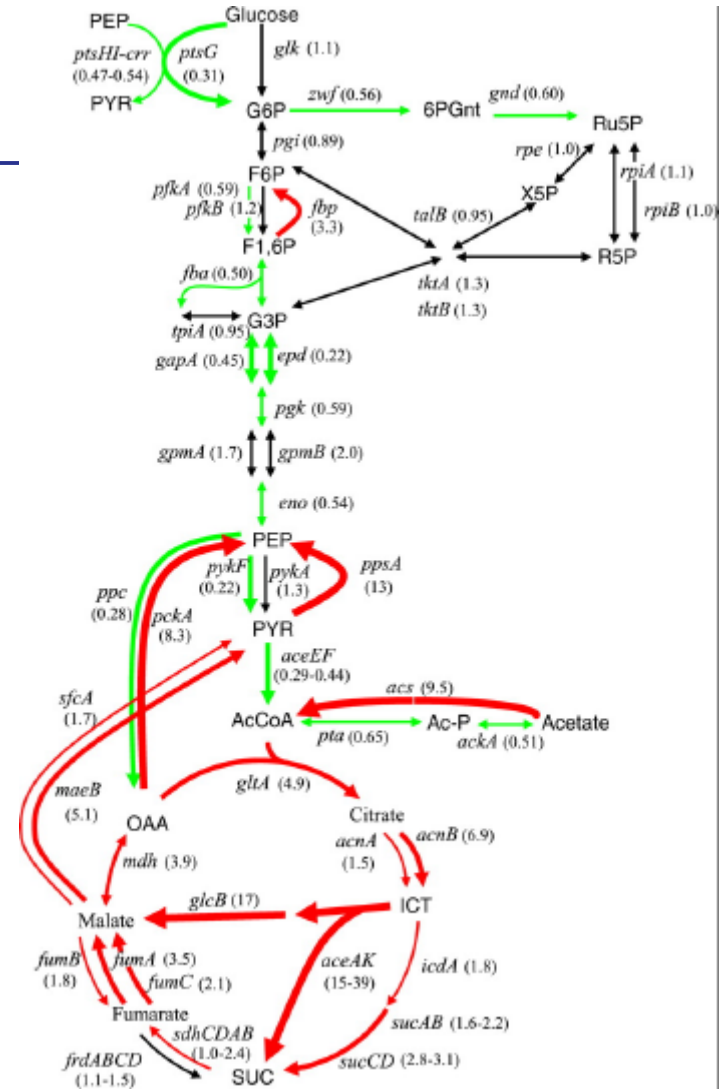
$k, g$  : rate constants



- Piece-wise linear (PL) differential systems

# Glucose-acetate diauxie

- Well-characterised transition in *E. coli*
- Involves major changes
  - at the metabolic level: gluconeogenesis vs. glycolysis
  - at the gene expression level
- Strong interaction between metabolic and gene expression levels



Oh et al. (2002), *J Biol Chem.* 277(15):13175-83.



# Assessment and use of simplified model

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- Benchmark model entirely specified with ODEs
- ‘Toy’ system to assess different **reductions** and **approximations**
- **Comparison** of simplified models with complete ODE model
- Parameter **estimation** for the simplified model on the basis of experimental data generated in the project:
  - Metabolic (concentrations and fluxes:  $^{13}\text{C}$  NMR, IC-MS)  
Jean-Charles Portais, Toulouse
  - Gene expression (enzyme activities, microarrays, reporter genes)  
Hans Geiselman, Grenoble



# Roles of metabolic and gene regulation

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- Study the metabolic response in the model **when gene regulation is abolished**
- Evaluate (quantify) the **contribution of gene regulation** to the metabolic response
- Conversely calculate the **contribution of metabolic effects** to gene regulation
- Understand the **biological rationale** underlying the distribution of regulation between metabolism and gene expression

# Partners and support

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- Hidde de Jong, Delphine Ropers, INRIA Grenoble
- Daniel Kahn, INRIA HELIX & Lyon 1 University
- Jean-Luc Gouzé, INRIA COMORE, Sophia-Antipolis
- Hans Geiselmann, CNRS-UJF Grenoble
- Jean-Charles Portais, INRA-INSA Toulouse
  
- Agence Nationale pour la Recherche
- EU



# Fellowships available on MetaGenoReg

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- Thesis fellowship, 2007-2010

Application deadline: April 30

- Post-doctoral fellowships, 2007-2009

- Contact  **INRIA**

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