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**Mannitol production in *Lactococcus lactis*: dynamic modeling,
metabolic control and regulation**

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The dynamic modeling of metabolic networks constitutes a major challenge in systems biology. A top-down approach can be conducted using experimental time series of metabolite concentrations, obtained through Nuclear Magnetic Resonance (NMR), and defining the model structure, given as a system of non-linear coupled differential equations. An important class of equations under Biochemical Systems Theory is commonly used, where rates are modeled with power-law functions.

This work addresses the modeling of glycolysis in *Lactococcus lactis*, expanding a study recently conducted (Voit et al. 2006). The metabolic data used correspond to time series representing metabolite concentrations obtained previously by NMR (Neves et al. 2002).

The estimation of the parameters constitutes a major difficulty given the innumerable local minima and rough error surface. Although the obtained model might not correspond to global optima, it can nevertheless provide important insights into the design of the pathway and the function of specific feedforward and feedback activations and inhibitions.

The new features of the model here proposed are 1) introduction of control signals that correspond to genetic regulation through Hill functions on enzyme behavior; 2) dynamics of glucose uptake modeling by the PEP:PTS system with saturation phenomenon; 3) inclusion of new reactions in order to model mannitol production. Preliminary results show that this model is useful for optimization purposes.

References

Neves AR et al (2002) Appl Environ Microbiol **68**, 6332-6342
Voit EO et al (2006) IEE Proc Syst Biol 153, 286-298