Exploring metabolic and genetic control of the glycolytic pathway of *Lactococcus lactis*

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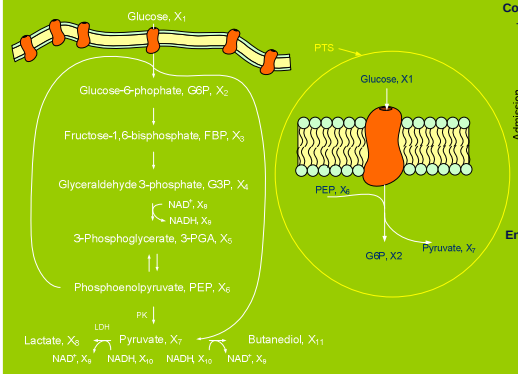
1 Abstract

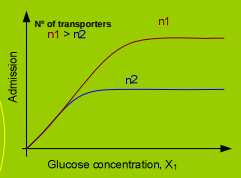
The central goal of this work is to develop methods and algorithms to integrate information from different sources in order to derive effective models for genetic and metabolic networks. The dynamical model of glycolysis in *Lactococcus lactis* was simulated and a recently conducted study was expanded (Voit et al., 2006). The metabolic data used correspond to time series representing metabolite concentrations previously obtained by NMR (Neves et al., 1999; Neves et al., 2002).
In this new model we focused on the glucose uptake by the phosphoenolpyruvate:sugar-phosphotransferase system (PEP:PTS). We speculate that a saturation phenomenon might occur which justifies the second order decay of glucose.

2 Dynamical model of glycolysis in *Lactococcus lactis*

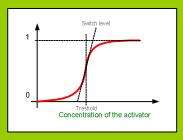
Simplified representation of the glycolytic pathway:



Constant glucose admission through PTS:
- only for high concentrations



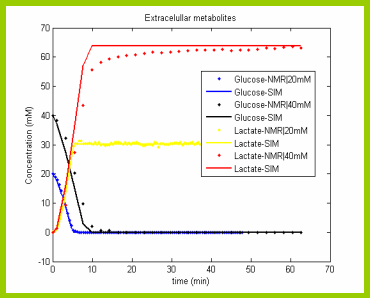
Enzyme allosteric effect model:

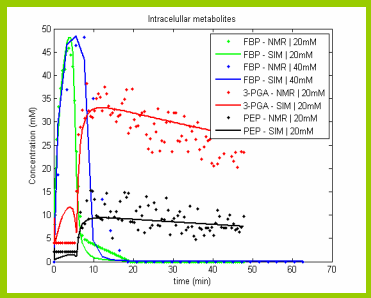


$$\dot{X}_1 = -\beta_1 a\tan(k_1 X_1) X_6$$
$$\dot{X}_2 = \beta_1 a\tan(k_1 X_1) X_6 - \beta_2 X_2$$
$$\dot{X}_3 = \beta_2 X_2 - \beta_3 X_3^{\gamma_3}$$
$$\dot{X}_4 = \beta_3 X_3^{\gamma_3} - \beta_4 X_4 X_9$$
$$\dot{X}_5 = \beta_4 X_4 X_9 + \beta_{6.5} X_6^{\gamma_{6.5}} - \beta_{5.6} X_5^{\gamma_{5.6}}$$
$$\dot{X}_6 = \beta_{5.6} X_5^{\gamma_{5.6}} - \beta_1 a\tan(k_1 X_1) X_6 - \beta_{6.5} X_6^{\gamma_{6.5}} - \beta_6 X_6^{\gamma_6} PK$$
$$\dot{X}_7 = \beta_6 X_6^{\gamma_6} PK + \beta_1 a\tan(k_1 X_1) X_6 - \beta_{7.8} X_7 X_{10} LDH - \beta_{7.11} X_7 X_{10}$$
$$\dot{X}_8 = \beta_{7.8} X_7 X_{10} LDH$$
$$\dot{X}_9 = \beta_{7.8} X_7 X_{10} LDH + \beta_{7.11} X_7 X_{10} + \beta_{10} X_{10} - \beta_4 X_4 X_9$$
$$\dot{X}_{10} = \beta_4 X_4 X_9 - \beta_{7.8} X_7 X_{10} LDH - \beta_{7.11} X_7 X_{10} - \beta_{10} X_{10}$$

3 Diagnostics, simulation and conclusions

Dynamics of metabolite pools in *L. lactis* derived from [6 - ^{13}C] glucose metabolized under aerobic conditions at pH 6.5.





Simulation with two different initial conditions (20mM and 40mM of glucose)

Conclusions:
- The model reveals the same glucose consumption rate for both pulses, like the experimental data
- FBP saturates near 50mM independently of the glucose initial conditions
- Enzyme allosteric effect, like PK and LDH are well modelled as a switch. These enzymes are activated by FBP and responsible for the stationary behaviour of 3-PGA and PEP before glucose exhaustion.

4 Future work

Oscillation behaviour:
In this preliminary work, an oscillatory behaviour was observed when the step between 3-PGA and PEP was modelled considering a small influx and efflux, and not as a closed cycle. However if the influx goes to zero these oscillations stop. A spectral analysis performed over the NMR data revealed what seems to be an oscillatory signal combined with noise. To better understand this behaviour further analysis has to be performed.

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We want to thank Helena Santos, Rute Neves and Eberhard Voit for the helpful discussions. Rodrigo Piedade was partially supported by the FCT project POCTI/BIO/48333/2002 and project MaGiC (IE02ID01004) from INESC-ID.