Computational Systems Analysis of the Glycolytic Pathway in *Lactococcus lactis*

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Short Abstract — **The goal of this study is to develop a comprehensive kinetic-dynamic model of the control of carbohydrate metabolism in *Lactococcus lactis* under anaerobic conditions. We have incorporated the dynamic peak and consumption behavior of the intermediate metabolite Fructose-1,6-bisphosphate (FBP) for varying amounts of environmental glucose concentrations in this model. This comprehensive model will be expanded and fine-tuned to account for pH effects and utilized to create acid-resistant *Lactococcus* strains which have the potential of being used as a novel vehicle for the non-invasive delivery of vaccines and therapeutic proteins.**

Keywords — **Glycolysis, *Lactococcus lactis*, Biochemical Systems Theory, systems biology, metabolic pathway modeling.**

I. PURPOSE

One of the grand challenges of computational systems biology is the translation of biological systems into mathematical models that permit analysis, prediction, manipulation, optimization, explanation, understanding, and the discovery of biological design and operating principles [1].

The system under study here is the glycolytic pathway in the bacterium *Lactococcus lactis*. This organism is of high relevance in the food industry, and if it could be manipulated to survive low pH levels in the stomach, it could be used as a novel vehicle for the noninvasive delivery of vaccines and therapeutic proteins [2]. We are now working on the extraction and mathematical interpretation of regulatory and kinetic information obtained from *in vivo* Nuclear Magnetic Resonance (NMR) time series data describing metabolic profiles in *L. lactis* [3]. The integration of this information into fully functional, explanatory models remains to be a challenging task, which we address here.

II. RESULTS

We expanded the present model of glycolysis in *L. lactis* toward anaerobic conditions by accounting for NAD^+ and NADH dynamics. The resulting model is able to capture the accumulation behavior of the intermediary metabolite FBP as well as its consumption.

A. FBP dynamics

An intriguing observation, which had not been fully explained previously, is the accumulation of the intermediary metabolite Fructose-1,6-bisphosphate (FBP), whose peak concentration seems to be independent of the environmental glucose concentrations. Specifically, for series of experiments with increasing glucose concentrations, FBP accumulation shows a plateau, whose length, but not height, varies with substrate availability.

B. Method

The metabolic modeling is performed within the framework of Biochemical Systems Theory(BST) formalism [4,5].
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III. CONCLUSION

We have expanded a preliminary model of the system toward a more comprehensive model which explains the differences in FBP concentrations under anaerobic conditions as well as FBP consumption dynamics.

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