PS 229

Identification of Protein-metabolite Interactions that Mediate Allosteric Enzyme Regulation in Bacterial Metabolism

H. Link[1], U. Sauer[1]

[1]ETH Zürich, Institute of Molecular Systems Biology, Zürich, Schweiz

Submitted by: H. Link

The last decade has seen major advances in experimental method development for protein-protein and protein-DNA interaction analysis, and we are making great strides towards mapping such interaction networks. In sharp contrast, methods to identify protein-metabolite interactions have not advanced significantly. The gold standard is still classical *in vitro* biochemistry to analyze suspected interactions one by one. Here we set out to identify *in vivo* relevant protein-metabolite interactions that mediate allosteric enzyme regulation from dynamic metabolite concentration data.Specifically, we focus on central carbon metabolism of *Escherichia coli* during 60 second carbon source shifts between glycolytic and gluconeogenic substrates. The key input are dynamic concentration data from more than 50 metabolites and their dynamic ^{13}C carbon labeling profiles, measured with UHPLC tandem mass spectrometry (Büscher et al., 2010). We observed that during short substrate switches *E. coli* immediately redirects flux. Next we ask which regulatory mechanisms enable these rapid yet very robust changes. Therefore, structurally different kinetic models of glycolysis/gluconeogenesis that cover almost ten thousand combinations of allosteric feedback and feed-forward loops were evaluated with regard to multiple performance criteria. One criterion was the prediction of metabolite and labeling profiles observed in the experiments, others were robustness (homeostasis) and efficiency (futile cycling) during the switches. With this approach we could identify the allosteric interactions that are relevant for regulating shifts between glycolysis and gluconeogenesis.

Büscher, JM, et al., (2010), Anal. Chem., 82, 4403.

PS 230

Applications of a Mathematical Model of the Bovine Estrous Cycle

C. Stötzel[1], M. Boer[2], J. Plöntzke[3], S. Röblitz[4]

[1]Zuse Institute Berlin (ZIB), Numerical Analysis and Modeling, Berlin, Deutschland; [2]Wageningen UR Livestock Research, Animal Breeding and Genomics Centre, Lelystad, Niederlande; [3]Free University Berlin, Clinic for Animal Reproduction, Faculty of Veterinary Medicine, Berlin, Deutschland; [4]Zuse Institute Berlin (ZIB), Numerical Analysis and Modeling, Berlin, Deutschland

Submitted by: C. Stötzel

In animal sciences, increasing amounts of data have become available throughout the last years, but systems biology approaches to understand and relate these data are still limited. In cooperation between mathematicians and veterinary scientists, we explore dynamic relations between functional components in the bovine estrous cycle. Constructed on the whole-organism level, the model describes the growth and decay of follicles and corpora lutea, as well as the key hormones involved. The mechanisms, which are mostly regulatory, form a closed feedback loop which generates successive estrous cycles of on average 21 days. A former version of the model, which was presented at the ICSB 2010, was extended and now consists of 15 ordinary differential equations with 59 parameters. Delays have been eliminated, and mechanisms for luteolysis have been improved. In this presentation, we point out two applications of the model. Concurrent with increased milk yield, a decrease in dairy cow fertility has been observed during the last decades. A better understanding of follicle development could help to improve pregnancy rates. A normal bovine estrous cycle contains 2 or 3 waves of follicle development, and ovulation takes place in the last wave. The reason for cycles being of the 2 or 3 wave's type is unclear. We analyze the influence of several biologically plausible parameters on the number of follicular waves per cycle. Varying some of the model parameters that regulate follicle growth rate or time point of luteolysis leads to a change in the model output from 3 to 2 waves per cycle. Numerical experiments suggest that the number of waves per cycle depends on the coupling of two oscillators in the model. Synchronization protocols aim to synchronize the estrous of individual cows. The goal of such hormonal treatments is to facilitate timing of following artificial insemination, independently of estrous cycle stage at the start of the protocol. We show that the simulations of our model agree with observations from synchronization studies and with measured progesterone data after administration of synthetic prostaglandin F2alpha. In particular, a restart of the cycle after a single virtual injection of PGF2alpha on various days of the cycle can be obtained with the model. In the future, we plan to improve the model towards the simulation of individual variability. For example, stochastic models for folliculogenesis or hormonal pulse patterns will be analyzed.

PS 231

Dynamics of General mRNA Translational Control

K. Chandrasekaran[1], T. You[1], G. Coghill[1], A. Brown[2]

[1]Institute of Medical Sciences, Institute of Complex Systems and Mathematical Biology, Aberdeen, United Kingdom; [2]Institue of Medical Sciences, Aberdeen Fungal Group, Aberdeen, United Kingdom

Submitted by: K. Chandrasekaran

A deterministic model that describes the general messenger RNA (mRNA) translation, via Gcn2, in *S. cerevesiae* is presented. The model is essentially a simplification of the comprehensive general mRNA translation model proposed by Tao et al [T. You et al, Yeast, 27, 10, pp785 – 800, 2010] and was developed with an aim to understand the dynamics of cystolic amino acid levels under normal and stress conditions. It can be shown that besides the steady state regime, the model also predicts oscillatory dynamical regimes that under certain specific conditions. Mechanisms governing the change in the dynamical regimes (i.e., from steady state to oscillatory) and the factors affecting the frequency of the oscillations are discussed.