

THIAMINE UPTAKE IN YEAST *SACCHAROMYCES CEREVISIAE* – A MODELLING APPROACH

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Abstract

The thiamine metabolism is a complex dynamic system involving different processes such as thiamine transport, utilization, biosynthesis, and gene regulation. For yeast, different cellular components (genes, proteins, metabolites etc.) and the interactions (transcription, biochemical reactions, activation and inhibition) between these components are relatively well known. In order to understand the dynamic properties of the system and to test different mechanistic hypotheses, we set up a mathematical model of the system. This has been done by assigning reasonable mathematical rate expressions and corresponding parameters to the rate variables in a static model, following a systematic modelling framework.

On the way to ultimately describe the whole thiamine cellular network, the first step was focused on a smaller subsystem, namely on the extra- and intra-cellular thiamine (de)phosphorylation and thiamine transport into the cell. Estimation of the numeric values of the involved parameters is done based on published information, quantitative time series measurements of thiamine and its phospho-derivates as well as quantitative analysis of gene expression and protein levels. During the process of the initial data collecting, *in silico* simulations and experimental validation of the model, several new features of the system have been found. Apart from the parameter determinations, we have found a few key characteristics of the systems components. One important observation was that the thiamine transporter Thi7, known for its specificity for free thiamine, possesses also a substantial capacity to transport extracellular thiamine mono-phosphate (ThMP) and thiamine diphosphate (ThDP) from the cell surroundings. Our initial experiments indicated that the activity of Thi7 is downregulated by the availability of ThDP. *In silico* experiments, however, failed to explain possible mechanism of such inhibition and later experiments demonstrated that the intracellular accumulation of ThDP has indeed no effect on the Thi7 activity. The only regulatory step seems to be the transcriptional control. On the other hand, thiamine kinase Thi80 seems to be regulated by the accumulated ThDP. We proposed the mechanism of the inhibition. The reason for this regulation of the kinase might be a protection against ATP depletion in the conditions of high thiamine abundance. Thiamine is stored in the form of free vitamin in the cell.

In our study, modelling process is applied as an iterative procedure between experimental data and simulations and exhibits an example of the approach leading to remarkable acceleration of understanding the studied system.