Post-transcriptional feedback control of polyamine metabolism in yeast: an integrated modeling and experimental investigation

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A new predictive model of the polyamine metabolism in the yeast Saccharomyces cerevisiae was developed with the help of a systems biology approach incorporating enzyme kinetics, statistical analysis, control engineering and experimental molecular biology of translation. This quantitative model of the polyamine control system reproduces experimental data and predicts polyamine content under normal conditions and at various decease-induced scenarios that cannot be seen from experiments. Possible applications of this model are in pharmacology, toxicology, cancer research and neurodegenerative disorders studies.

***Keywords* — ribosomal frameshifting, kinetic pathway modelling, polyamine metabolism, optimization**.

I. INTRODUCTION

THE aim of this systems-level analysis is to uncover the design principles relative importance of the different control mechanisms, robustness and fragility of the regulation of polyamine biosynthesis in health and disease states. The polyamine molecules putrescine, spermidine and spermine are involved in a number of important cellular processes such as transcriptional silencing, translation, protection from reactive oxygen species and coenzyme A synthesis [1]. Components of the polyamine pathway are also potential targets for cancer therapeutics [2], as unregulated polyamine synthesis can trigger uncontrolled cell proliferation. Conversely, polyamine depletion can cause apoptosis. In the cell, polyamine concentrations are regulated by multiple mechanisms, including feedback control of Spe1 by the protein antizyme, which is synthesised via a +1 ribosomal frameshift during translation of the antizyme mRNA [3].

II. MODEL DEVELOPMENT

Experimental time course data to describe polyamine biosynthesis came from average of measurements from many yeast cells. Hence we analyze such data by the help of deterministic dynamical models [4] with stochastic effects [5] represented by uncertainty ranges of kinetic parameters and probabilistic models of cellular regulation.

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A. Estimates for model parameters

To derive reliable estimates for model parameters an optimization problem was considered to fit mathematical prediction to time course data. The steady state measurements serve as a benchmark for the deterministic equations for the yeast wild type model.

B. Network motifs

To analyze available data sets three models are introduced. This technique not only efficiently describes available data sets but also delivers robustness of the model of wild yeast polyamine metabolism by considering separately its crucial functional motifs/modules representing essential cellular functions. During optimization of chosen cost function the minimization of deviation between model prediction and measurements of each of three models was performed using several algorithms [6,7].

III. CONCLUSION

The main aim of this systems biology study is to derive and validate comprehensive model for polyamine biosynthesis in wild type Saccharomyces cerevisiae yeast. The approach consists of assembling three optimized modules originated from the genetic knockouts in wild type yeast. The role of ribosomal frameshift is emphasized in polyamine biosynthesis regulation.

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