

Towards Simulation of Whole Metabolic Pathways in Human Erythrocyte

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1 Introduction

We have previously reported the simulation of the glucose-6-phosphate dehydrogenase (G6PD) deficiency in human erythrocyte using E-CELL system. In this previous work, we showed that the glutathione metabolism, including two biosynthesis pathways for the reductive form of glutathione (GSH) and the active export system of oxidative glutathione (GSSG), has a significant role in the simulation of this deficiency, and that the half-life of the erythrocyte was drastically elongated by these pathways. From these results, insignificant pathways for normal erythrocytes could be essential in abnormal conditions. This indicates that the whole metabolic pathways should be included in the simulation model, if this model focuses on the simulation of abnormal conditions such as enzyme deficiencies. Toward the whole human erythrocyte model, in this work, we implemented some pathways into previous models using hybrid simulation algorithm.

2 Methods and Results

We used a hybrid method that is combination of the dynamic model and the static model (Nakayama *et al.* in this meeting). With this method, we could construct flux based models into the previous model that was constructed with kinetic equations. The flux based method we used is the flux balance analysis (FBA). The mass balance constraints in a metabolic network can be represented mathematically by a matrix equation:

$$S \cdot v = 0$$

The matrix S is the $m \times n$ stoichiometric matrix, where m is the number of metabolites and n is the number of reactions in the network. The vector v represents all fluxes in the metabolic network, including the internal fluxes and transport fluxes. The optimal v vector was determined and defined the steady-state metabolic flux distribution.

We constructed the model using this approach and implemented pathways as follows: (i) Touster (urate) cycle: xylitol is metabolized and NADP is produced as the metabolites. (ii) The cysteine metabolism stands at the intersection of two pathways: remethylation to methionine, which requires folate and vitamin B12 (or betaine in an alternative reaction); and transsulfuration to cystathionine, which requires pyridoxal-5'-phosphate. (iii) The fructose metabolism processes fructose into fructose-6-phosphate, and the galactose metabolism processes galactose into glucose-6-phosphate. These metabolites are used in glycolysis as an initial substrate.

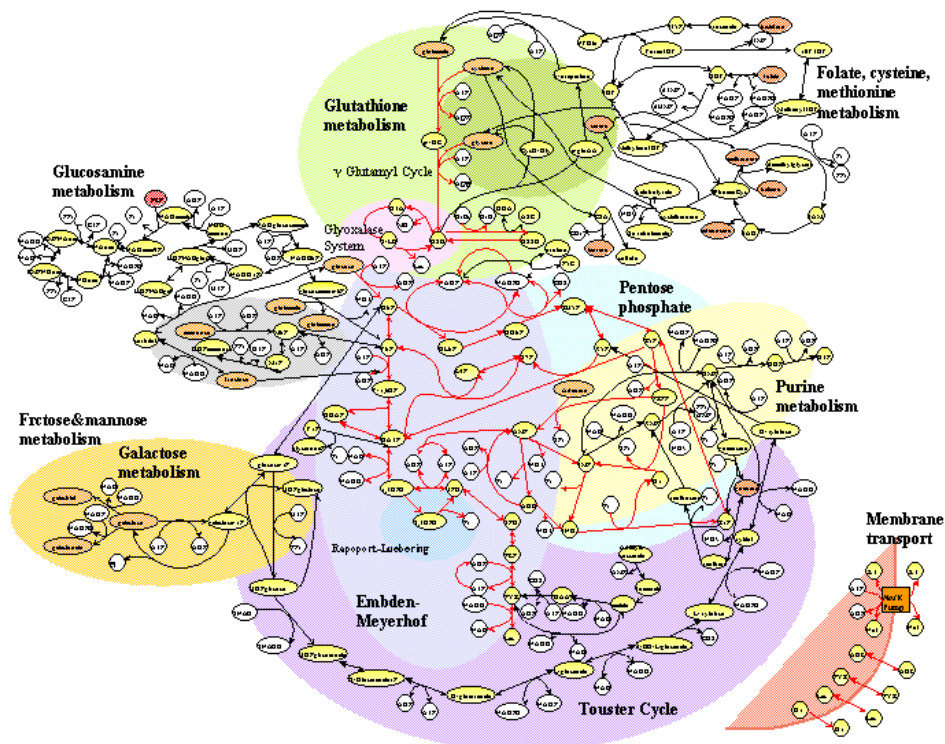


Figure 1: The metabolic pathways of the model constructed in this work (Reactions of previous model are shown with red arrows).

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References

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