Computer Simulation of Human Erythrocyte and its Application to Analyses of Enzyme Deficiencies

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1 Introduction

We previously reported a computer model of the human erythrocyte [1], which has three major metabolic pathways, including glycolysis, the pentose phosphate pathway, and nucleotide metabolism, in addition to Na^+/K^+ pumps, some transport systems, and magnesium complexation. The model has reached the steady state, which indicates that it is very closed to approximating the real erythrocyte.

In this work, we carried out the simulation of enzyme deficiencies such as that of Pyruvate kinase. The obtained data sets from these simulation experiments were similar to the conditions of real erythrocytes with enzyme deficiencies.

We also expanded our simulation model of the erythrocyte to enhance its robustness and tolerance (Figure 1), adding the following functions: pH dependence of enzymes, osmotic balance, electroneutrality, and oxygen and carbon dioxide transportation by hemoglobin.

2 Method and Results

2.1 Simulation and analysis of pyruvate kinase deficiency and other deficiencies

PK is a key enzyme that produces ATP in the glycolysis pathway, and mutation of the PK enzyme reduces its activity. We modified the kinetic parameters of PK to fit for the three types of mutant, and the simulation experiments were carried out respectively with steady state concentrations corresponding to those of the normal erythrocyte. The amount of ATP was gradually reduced and eventually exhausted (Figure 2). The longevity of our computer model in these experiments turned out to be much shorter than that of the real erythrocyte with PK mutation. This difference is presumably due to the fact that the initial concentrations in this simulation were set too far from the concentrations of the real PK mutant cell in the steady state. To solve this problem, we are currently trying to determine a steady state of the PK mutant by using the mathematical method. We are also trying to represent the condition of oxidative stress with our Model, to simulate the Glucose-6-phosphate dehydrogenase (G6PDH) deficiency. The results of the simulation experiments will also be presented.

2.2 Architecture of expanded model

- **Osmotic balance and electroneutrality.**
  The erythrocyte has to balance osmotic pressure while maintaining electroneutrality on both sides of the membrane. For the erythrocyte to be in an osmotically stable environment, the water activity of both the extracellular and intracellular fluids should be the same: The intracellular volume is changed to satisfy this equation. In this model, we assume that the plasma has an infinite volume. The law of electrical neutrality of solutions applies within and outside the erythrocyte; there must be the same number of positive ionic charges and negative charges in solution.
- **Oxygen and carbon dioxide transportation by hemoglobin.**
  We adopt a thermodynamic model of hemoglobin, which represents the binding affinity of hemoglobin molecules to ligands such as O_2, CO_2, 2,3-DPG, and H^+.

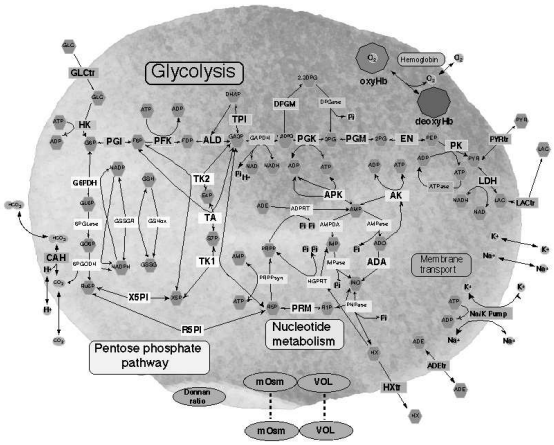

Figure 1: Computer model of Human Erythrocyte.

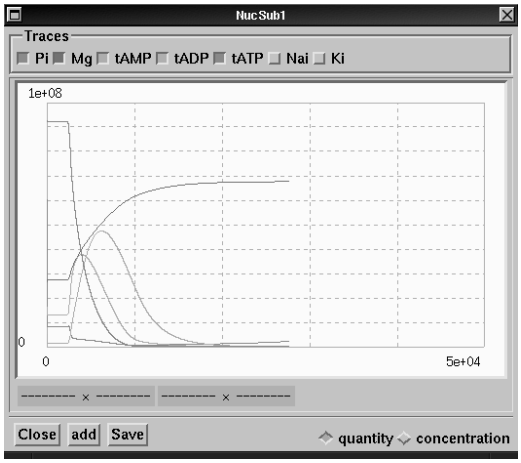

Figure 2: Effects of PK mutant on ATP.

3 Discussion

The activities of various enzymes in the real erythrocytes change significantly in response to a small variation in pH. The concentration of protons is regulated by the buffer effect of hemoglobin and carbonic acids. These form an important compensation mechanism to regulate the activities of enzymes. Osmolality and membrane potential are other factors that help compensate for increases of molecules. The extended model we constructed takes all of these factors into account, and is expected to be significantly more stable than the basic model. We are currently analyzing the performance of the extended model in detail.

Pathological analyses of the effects of enzyme deficiency will be carried out using the extended model. We also plan to expand our simulation model to achieve greater accuracy of the cell state in enzyme deficiencies as follows: isozymes of rate-determining enzymes, metabolite diffusion and localization, dynamic changes of the cell shape, and oxidative stress.

References

[1] Matsushima, R., Kawase, A., Watanabe, N., Nakano, H., Saito, K. and Tomita, M., Modelling of human red blood cell using the E-Cell simulation system, *Genome Informatics*, 9:248–249, 1998.

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