Computer Simulation of Human Erythrocyte Using the E-Cell System

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1 Introduction

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

In this work, we present a substantially extended version (Fig. 1) of this erythrocyte model. We added the following functions: Simulating pH dependence of enzymes, osmotic balance, electroneutrality, and oxygen and carbon dioxide transportation by hemoglobin. The current model also takes into account the hemolysis and the destructive processing of abnormal erythrocytes in the spleen.

2 Model architecture

- **Kinetic equations with pH dependence.**
  In most of the cases, a bell-shaped pH dependence curve for V_m is assumed, and the following equation is employed to fit the curve

$$V_m = \frac{V'}{1 + \frac{H^+}{K_1} + \frac{K_2}{H^+}} \tag{1}$$

  where K_1 and K_2 are constants, and V' is the pH optimum of V_m. When the pH dependence curve is too far from being bell-shaped, a polynomial is employed instead.

- **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:

$$\Pi_i = RT \sum_{j=1}^{n} \phi_{ij} C_{ij} = RT \sum_{j=1}^{n} \phi_{ej} C_{ej} = \Pi_e \tag{2}$$

  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^+.

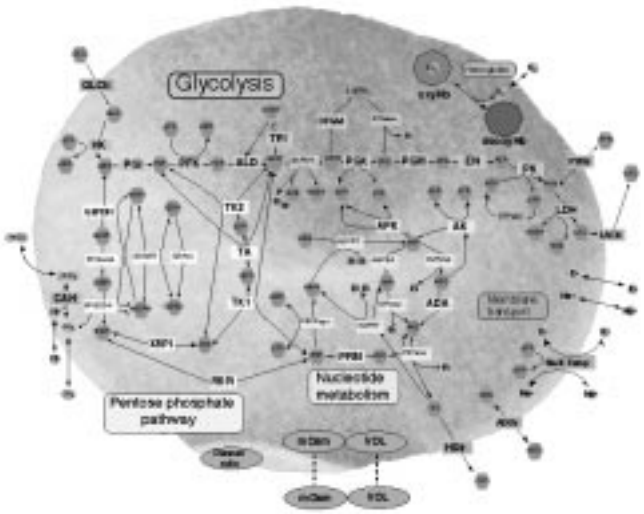

Figure 1: Computer model of Human Erythrocyte.

3 Discussion

The activities of various enzymes in the real erythrocytes change significantly with a small variation in pH. The concentration of proton 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 another factors to compensate increases of molecules.

The extended model we have just constructed takes all 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.

We are also developing a tool for the parameter optimization (Saito *et al.* [2], in this volume), because kinetic parameters reported in the literature sometimes include errors.

Pathological analyses of the effects of enzyme deficiency will be carried out using the extended model.

Acknowledgments

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References

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