Revisiting the Epidermal Growth Factor Pathway Model.

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【Introduction】

Traditionally, the study of life sciences has essentially been qualitative, quantitative approaches being ruled out by the complexity of life systems. Nowadays, this is no longer true since computers now make it possible to manipulate a very large amount of data and perform complex computations. Our objective is hence to use computers to challenge the study of biological systems, aiming at biochemical pathways. More specifically, we focus on the study of the *epidermal growth factor* (EGF) pathway.

【Process and Method】

It is grossly impractical to perform enough biological experiments to gather enough data about many biochemical pathways. For this reason, we base out study on a model of the EGF pathway first proposed by Kholodenko . We argue that the original model is incomplete and hence propose an extension. More specifically, Kholodenko's model lacks a pathway between PI3-kinase and PLC γ that we introduce into the model.

Kholodenko's model is characterized by two types of differential equations, namely Michaelis-Menten and mass-action. We hence modified both equations to account for the new pathway. Although the existence of the pathway between PI3-kinase and PLC γ was established, we could find no quantitative analysis about it in the literature. For this reason, we have set the parameter of the new pathway to some arbitrary value . We then made a comparative analysis of both models (Kholodenko's original model and the extended one) using sensitivity analysis.

【Results and discussion】

When simulating the EGF pathway with the extended model, we could validate it with the experimental data studied by Kholodenko. In addition, we could also demonstrate the

superiority of the extended model when differences between both models led us to interesting discoveries.

・ Meaning of steady state in signaling models

The steady state data obtained from the extended model reaches the initial state. On the contrary, the steady state data obtained from Kholodenko's model does not reach the initial state. This shows the importance of steady state analysis.

・ Biological Meaning of Kholodenko's Model

We could observe that the flux of phosphorylation and dephosphorylation around the EGF receptor is extraordinarily high compared to other flux.

・Characteristics of the signal generating pathway.

From the pathway between PLC γ and SOS-Grb2, we could find a simple system of the signal generating pathway.

・Meaning of sensitivity analysis in a signaling pathway.

When the flux in the pathway is high, the effect of the pathway on the concentration is only determined by the flux, and not by the coefficients.