Regulatory property of scaffold protein on MAPK cascade: A qualitative modeling

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Short Abstract — **An integrated mathematical model, which incorporates scaffold proteins into a MAPK cascade, is built. By employing Monte Carlo simulation, regulatory property of scaffold protein on signaling ability for MAPK cascade is investigated theoretically. It is found that scaffold binding increases signal amplification if dephosphorylation is slow. Increasing number of scaffold decreases amplification if dephosphorylation is slow. Scaffold number can control the timing of kinase activation so the time flexibility of signaling is enhanced. For slow dephosphorylation case, scaffolds decrease sharpness of the dose–response curves. We hope our work may provide some predictions for future experiments.**

Keywords —Scaffold protein, MAPK cascade, Mathematical model, Monte Carlo simulation, Regulatory property.

I. Introduction

By a typical motif in signal transduction network, i.e., MAPK cascade, specific signals from cellular membrane are converted into specific gene expression in nuclear and appropriate cell fate. There exists a kind of macromolecule, i.e., scaffold proteins in MAPK pathway. Each scaffold proteins can bind three kinases and form a complex, which often plays important roles on accurate biological response [1].

Most of previous researches are based on the deterministic ordinary differential equation model, however two important factors are important under cell level. (i) The number of protein molecules are low, so the internal noise cannot be omitted [2]. (ii) The spatial effect is also an important factor under small cell size [3]. The enzyme and substrate molecules diffuse in the reaction space with finite velocity, which leads to that the biochemical system cannot be treated with a well-stirred system. As our knowledge, the combined effects of stochastic noise and spatial diffusion are still studied in few researches about the MAPK signaling pathway.

II. Monte Carlo simulation

We propose a mathematical model in which scaffold protein is integrated into the MAPK cascade, then use Monte Carlo simulation [4]. Our Monte Carlo simulation is performed on 2 dimension square lattices 100×100 with reflecting boundary conditions. Each protein molecule (unimolecule or bimolecule) only can occupy one lattice site. Except for scaffold protein, each molecule type is mobile on the lattice through diffusion. Each kinase activation (i.e, phosphorylation) or deactivation (i.e.,dephosphorylation) reaction in the solution is treated by a two-step enzymatic mechanism as below: firstly, the kinase (or phosphatase) and its substrate associate into an intermediate bimolecule complex by a reversible reaction, then the complex disassociate into the active or inactive products by a catalysis reaction At each MC step, all occupied lattice sites are chosen at random with uniform probability. In our simulation, when two appropriate proteins come into contact with each other by diffusion, certain a biochemical reaction may occur. Each stochastic reaction event has one corresponding reaction probability.

III. Conclusion

By our Monte Carlo simulation, it is found that (i) scaffold binding increases signal amplification if dephosphorylation is slow and decreases amplification if dephosphorylation is rapid. Increasing the number of scaffold decreases amplification if dephosphorylation is slow. (ii) Scaffold number can control the timing of kinase activation so that time flexibility of signaling is enhanced. (iii) It is observed that for slow dephosphorylation case, scaffolds decrease the sharpness of the dose-response curves. While for fast dephosphorylation, increasing scaffold number decreases the height of response, but the shape of graded response is sustained. Furthermore, the underlying mechanism and correlation of our results with real biological systems are clarified.

IV. References

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