

# Computer Modeling of Ras-MAPK Signal Transduction Pathway

Satoshi Yamada<sup>1</sup>

Yamada.Satoshi@wrc.melco.co.jp

Akihiko Yoshimura<sup>2</sup>

yakihiko@bioreg.kyushu-u.ac.jp

<sup>1</sup> Advanced Technology R&D Center, Mitsubishi Electric Corporation, 8-1-1  
Tsukaguchi-Honmachi, Amagasaki, Hyogo 661-8661, Japan

<sup>2</sup> Medical Institute of Bioregulation, Kyushu University, 3-1-1 Maidashi, Higashi-ku,  
Fukuoka 812-8582, Japan

**Keywords:** computer simulation, signal transduction, Ras, MAPK, EGF, FGF

## 1 Introduction

Ras-MAPK cascade signal transduction pathway is a main pathway initiated by growth factors, which induce cell division, cell survival and the differentiation. Different growth factors induce different cellular responses even if their signals are transduced through same pathway (Ras-MAPK pathway). For example, EGF induces cell division in PC12 cells, but NGF or FGF induces the differentiation. Although several computer models of Ras-MAPK pathway were developed [1, 4], they did not show these differences. We developed the model of Ras-MAPK pathway showing the difference between EGF responses and FGF responses.

## 2 Method and Results

The model of Ras-MAPK pathway initiated by EGF or FGF is shown in Figure 1(1). The binding, phosphorylation, dephosphorylation, GTP exchange, GTP hydrolysis, synthesis of mRNA and protein, and degradation of them were described in differential equations, and solved mathematically by using Runge-Kutta-Gill method. In this model, Michaelis-Menten approximation was not used because the condition for its approximation is not satisfied in the signal transduction pathway. SOS binds to receptor through adaptor protein Grb2, and activates membrane-bound Ras. In FGF pathway, FGF receptor substrate 2 (FRS-2) is phosphorylated by receptors, and acts as a membrane anchor for Grb2-SOS complex [2].

Because there are more FRS-2 than EGF receptors, more Ras were activated in FGF pathway. This produces sustained activation of ERK and Elk (see Figure 1 (2) right panel). FGF stimulation produces transient and sustained activation, but EGF produces only transient one (Figure 1 (2) left panel). The sustained activation of ERK by FGF stimulation is considered to induce the differentiation of PC12 cells. EGF stimulation to the cells with the overexpression of EGF receptors showed responses similar to FGF stimulation (sustained activation of ERK and differentiation) [5]. Figure 1 (3) shows the dependency on the receptor concentration. As the receptor concentration increases, the sustained activation by EGF increases (Figure 1 (3) left). This result explains the above overexpression experiment. Responses on FGF stimulation showed no dependency on FGF receptor concentration (Figure 1 (3) right) because phosphorylated FRS-2 concentration is nearly constant. Sprouty is induced by Ras-MAPK pathway and inhibits Ras-Raf interactions. It inhibits FGF signals but not EGF signals [3]. In this model, Sprouty production is included only in FGF pathway and Sprouty binds to Raf and inhibits Raf activation. Simulation results showed RasGTP increase around 2hr.

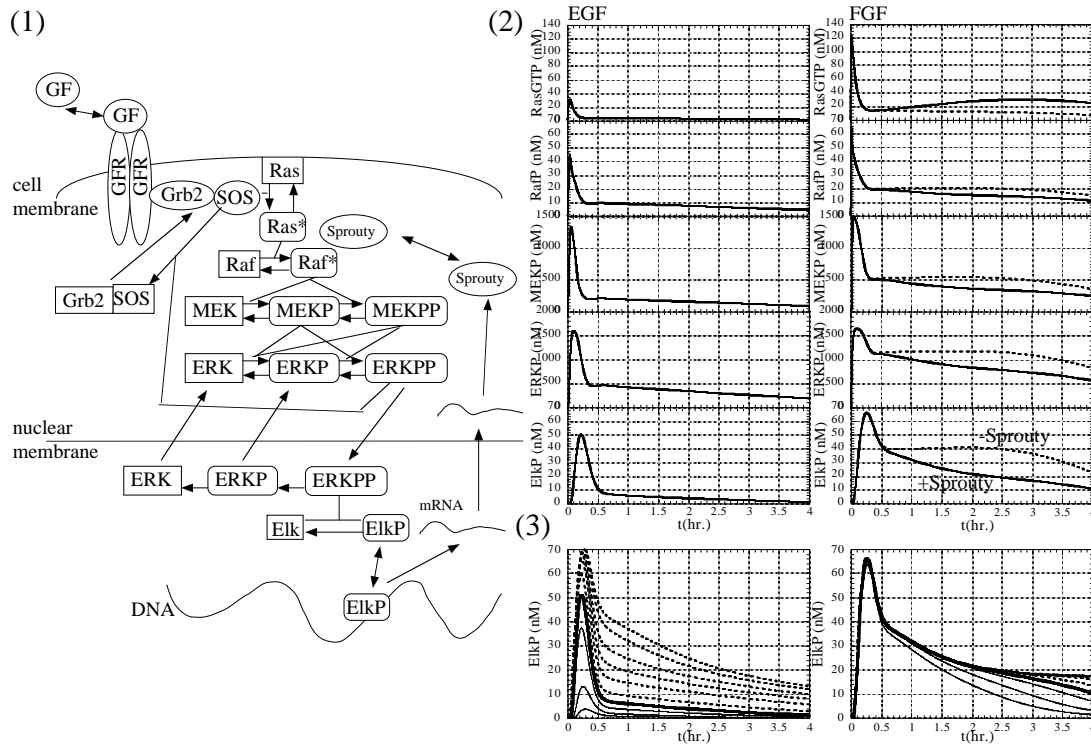


Figure 1: The model of Ras-MAPK pathway and simulation results. (1) The model of Ras-MAPK pathway, (2) the time course of RasGTP, phosphorylated Raf, phosphorylated MEK, phosphorylated ERK and phosphorylated Elk, in EGF pathway (left) and in FGF pathway (right), (3) the time course of phosphorylated Elk with various concentration of receptors in EGF pathway (left) and in FGF pathway (right). bold line: normal condition, thin lines: 1/2, 1/5, 1/10 concentration of receptors, dotted lines: \*2, \*5, \*10, \*20, \*50, \*100.

with Sprouty and increase in sustained activation of ERK without Sprouty (Figure 1 (2) right panel, dotted line), which was consistent with experimental data.

## References

- [1] Brightman, F.A. *et al.*, Differential feedback regulation of the MAPK cascade underlies the quantitative differences in EGF and NGF signalling in PC12 cells, *FEBS Letters*, 482:169–174, 2000.
- [2] Hadari, Y.R. *et al.*, Critical role for the docking-protein FRS2 $\alpha$  in FGF receptor-mediated signal transduction pathways, *Proc. Natl. Acad. Sci. USA*, 98:8578–8583, 2001.
- [3] Sasaki, A. *et al.*, Identification of a dominant negative mutant of Sprouty that potentiates fibroblast growth factor- but not epidermal growth factor-induced ERK activation, *J. Biol. Chem.*, 276:36804–36808, 2001.
- [4] Schoeberl, B. *et al.*, Computational modeling of the dynamics of the MAP kinase cascade activated by surface and internalized EGF receptors, *Nature Biotechnol.*, 20:370–375, 2002.
- [5] Traverse, S. *et al.*, EGF triggers neuronal differentiation of PC12 cells that overexpresses the EGF receptor, *Curr. Biol.*, 4:694–701, 1994.