

# Computer Modeling of JAK/STAT Signal Transduction Pathway

Satoshi Yamada<sup>1</sup>

Akihiko Yoshimura<sup>2</sup>

yamada@bio.crl.melco.co.jp

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, interferon, JAK, STAT

## 1 Introduction

Cytokines regulate important cellular responses through signal transduction pathways. The computer modeling is a useful method to understand dynamic characteristics or regulatory mechanisms of signal transduction pathways. The ultrasensitivity of the mitogen-activated protein kinase cascade was shown by the simulation study [2]. Many cytokine receptors transduce signals by receptor bound JAK kinase. JAK/STAT pathway is one of main signal transduction pathways initiated by cytokines. SOCS1, which is induced by JAK/STAT pathway, binds JAK and inhibits its kinase activity [4]. To understand the regulatory mechanisms by induced SOCS1, we developed the model of JAK/STAT pathway and investigated its dynamics by the computer simulation.

## 2 Method and Results

The model of JAK/STAT pathway initiated by interferon- $\gamma$  is shown in Figure 1(1). The binding, phosphorylation, dephosphorylation, synthesis of mRNA and protein, and degradation of them were described in differential equations, and solved mathematically by using Runge-Kutta-Gill method. The synthesis of mRNA and proteins were included in the model. A cell was divided into two compartments, cytoplasm and nucleus. The phosphorylated STAT1 dimer was reported to be transported to nucleus and work as transcription factors [3], and dephosphorylated STAT1 monomer was transported from nucleus to cytoplasm. Other transports through the nuclear membrane except mRNA's transport to cytoplasm were ignored. An unidentified phosphatase for STAT1 in nucleus (PPN) was assumed to explain STAT1's dephosphorylation in nucleus, and that in cytoplasm (PPX) was also assumed. The dissociation constants for protein bindings, kinetic constants for the phosphorylation and the dephosphorylation, and initial concentrations of proteins were estimated based on the experimental data.

Figure 1(2) shows the time course of signal transduction and protein synthesis. Phosphorylated STAT1 dimer (active transcription factor) was accumulated in nucleus, and then decreased gradually by SOCS1's inhibition (left). Without SOCS1 production, almost all STAT1 were kept in nucleus as active transcription factors (right). These results were qualitatively agreed with the experimental time course (Figure 1(5)). Since without SOCS1 production high concentration of active transcription factor was sustained (Figure 1(3)), anti-virus protein was produced much more than that with SOCS1 (Figure 1(4)). This overproduction of anti-virus protein is considered to be a cause of the hyperresponsiveness of SOCS1<sup>-/-</sup> mice [1].

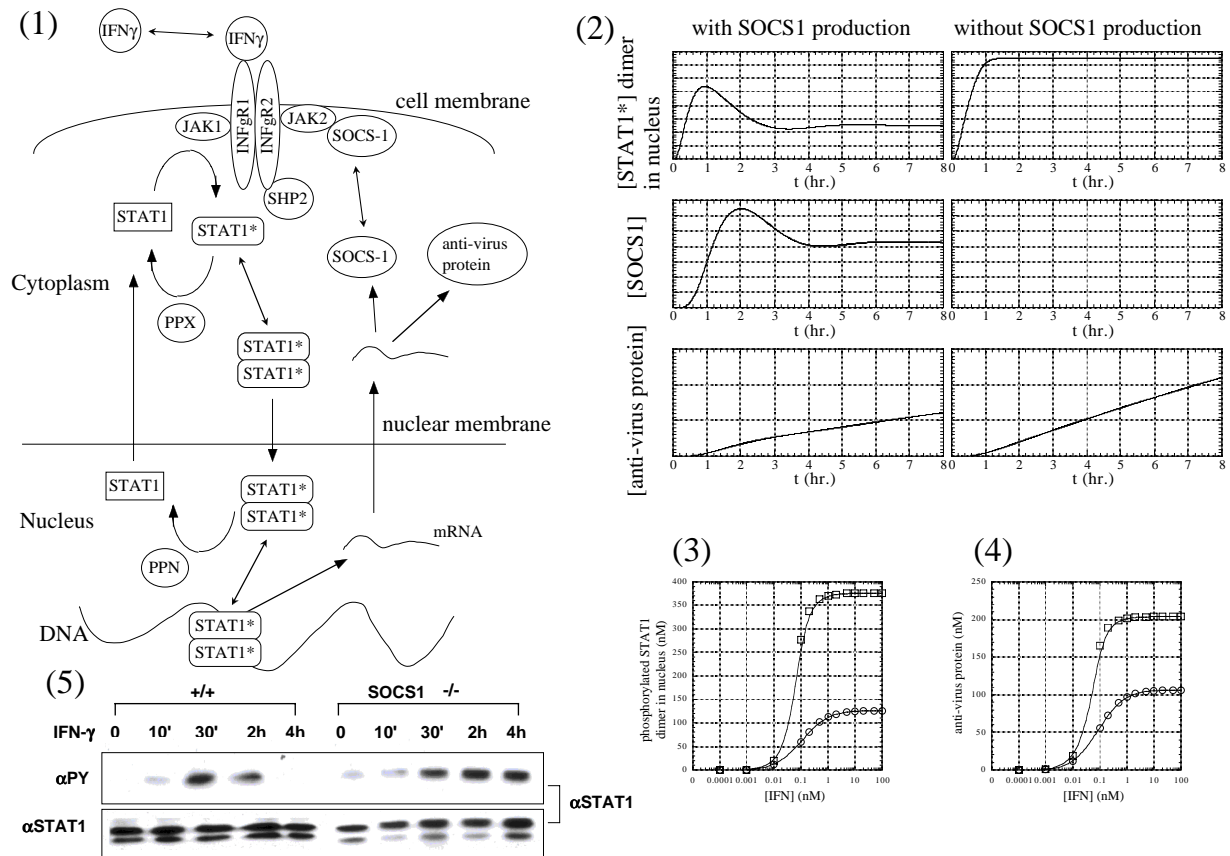


Figure 1: The model of JAK/STAT pathway initiated by interferon- $\gamma$  and simulation result. (1) The model of JAK/STAT pathway, (2) the time course of phosphorylated STAT1 dimer in nucleus, induced SOCS1, and induced anti-virus protein, with SOCS1 production (left) and without SOCS1 production (right), (3) [IFN- $\gamma$ ] dependence of phosphorylated STAT1 dimer in nucleus at the steady state (after 16 hr.) with SOCS1 production ( $\circ$ ) and without SOCS1 production ( $\square$ ), (4) [IFN- $\gamma$ ] dependence of an anti-virus protein with SOCS1 production ( $\circ$ ) and without SOCS1 production ( $\square$ ), (5) experimental time course induced by interferon- $\gamma$  of STAT1 phosphorylation (upper) and STAT1 (lower) of SOCS1 +/+ (left) and SOCS1 -/- (right) mouse embryonic fibroblasts.

## References

- [1] Alexander, W. S., Starr, R., Fenner, J. E., Scott, C. L., Handman, E., Sprigg, N. S., Corbin, J. E., Cornish, A. L., Darwiche, R., Owczarek, C. M., Kay, T. W., Nicola, N. A., Hertzog, P. J., Metcalf, D., and Hilton, D. J., SOCS1 is a critical inhibitor of interferon gamma signaling and prevents the potentially fatal neonatal actions of this cytokine, *Cell*, 98:597–608, 1999.
- [2] Huang, C.-Y. F. and Ferrell, J. E., Jr., Ultrasensitivity in the mitogen-activated protein kinase cascade, *Proc. Natl. Acad. Sci. USA*, 93:10078–10083, 1996.
- [3] Köster, M. and Hauser, H., Dynamic redistribution of STAT1 protein in IFN signaling visualized by GFP fusion proteins, *Eur. J. Biochem.*, 260:137–144, 1999.
- [4] Yasukawa, H., Sasaki, A., and Yoshimura, A., Negative regulation of cytokine signaling pathways, *Annu. Rev. Immunol.*, 18:143–164, 2000.