# Laboratory for Systems Biology and Bio-Inspired Engineering

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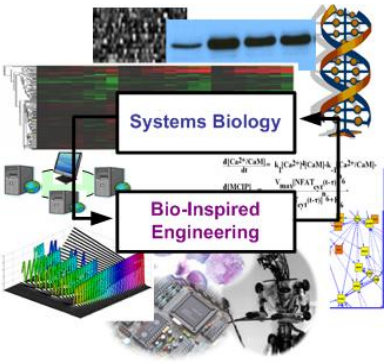
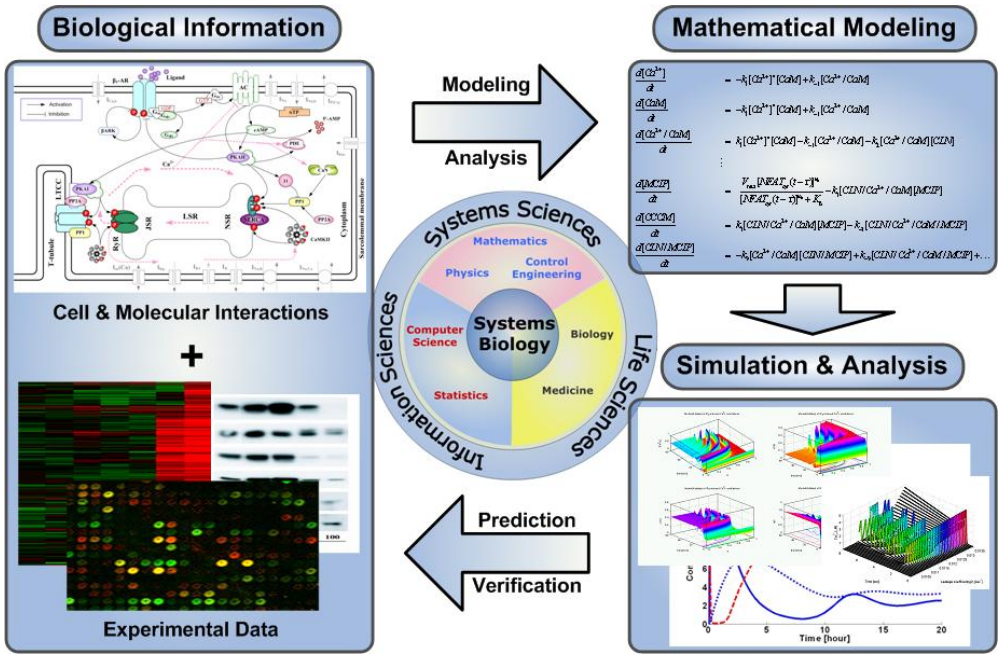
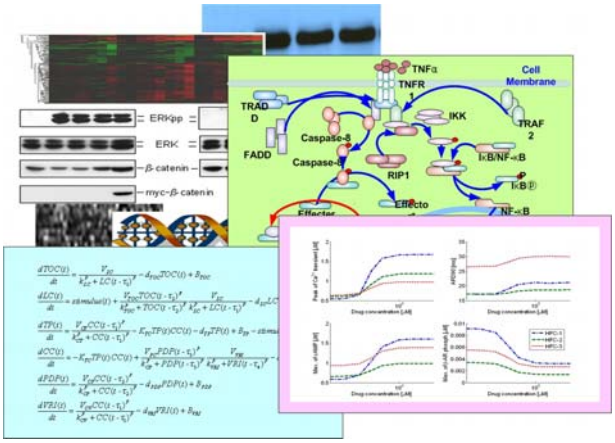
***Prof. Kwang-Hyun Cho***



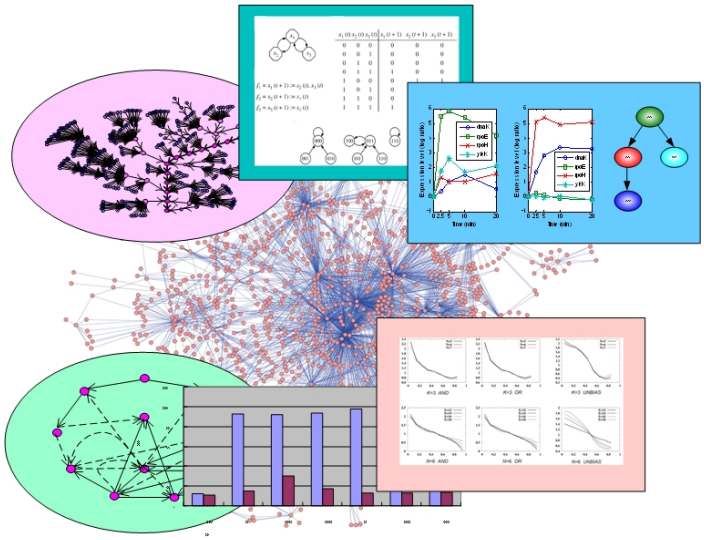

Life sciences witness a shift of paradigm from traditional characterization of individual molecules towards an understanding of interactive pathways and networks. I believe that the role of genes, proteins, metabolites and cells can be understood and defined through their interactions and it is this very focus on intra- and inter-cellular dynamics that I am deeply involved in the emerging area of Systems Biology. For Systems Biology to succeed, we have to cope with the bewildering complexity of cellular systems, covering a wide range of scales in time and space. I think that the two key characteristics are dynamic modeling and integration (fusion) of various informations including genomics, transcriptomics, proteomics, and metabolomics. In this context, our research has been centered on systems-level investigations of cellular signal transduction pathways, reverse engineering of biomolecular regulatory networks, and unraveling hidden cellular dynamics. We will focus on developing a systems biology analysis of cellular information processing by signaling and gene networks in cells with particular emphasis towards understanding cell-fate decisions on proliferation and differentiation. Regulation of the commitment to differentiation is central to many biological processes such as cancer, inflammatory diseases, and neurodegeneration. We have **two long term objectives** in our research. **The first is to create a predictive model for a programmable cell that can be optimized for personalized therapy.** This work has been already underway. **Our second objective is longer term and is to apply the knowledge obtained from the study of biological systems to engineering.** In this way we hope to contribute to engineering innovation using ideas inspired by molecular systems biology. More detailed work plans are described below.



### *Cellular Signal Transduction Pathways*



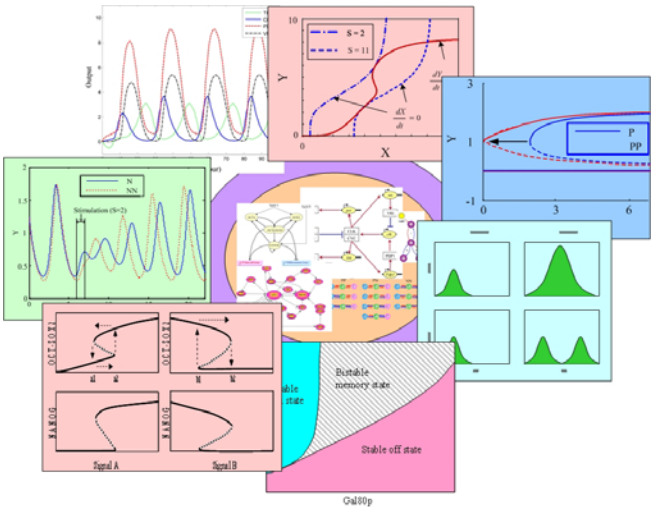

Cells are not running a fixed program but continually elaborating their program by sensing their environment through receptors. To determine how cells *behave* and *interact*, we need to understand how information is transferred among and within cells. Cell signaling or 'signal transduction' is the mechanism by which this transfer of biological information comes about. We have concentrated on signal- and systems-oriented approaches to investigate the flow of information. With regard to specific cellular systems, we have focused on the NF-kappaB, ERK, Wnt, JAK-STAT, and beta-AR pathways. The aim was to identify the functional role of those pathways through quantitative relationships among parameters and variables. Since most of these relationships are nonlinear with varying feedback connections, the problem is non-trivial. We will further investigate various crosstalks among pathways and apply the results for identification of undiscovered drug targets.



### *Biomolecular Regulatory Networks*

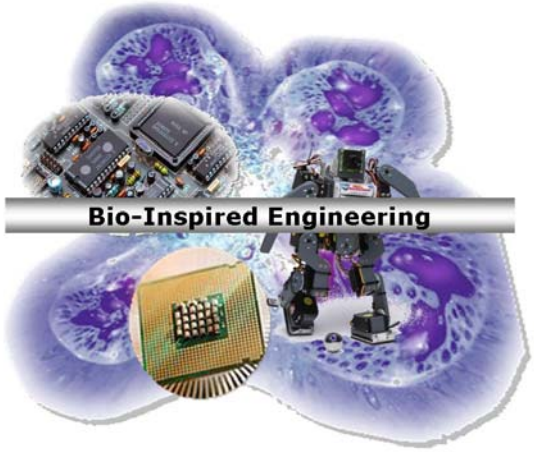
In order to probe complex biomolecular regulatory networks, we believe that one approach is to study their interactive structures. In this respect, We have focused on gene regulatory networks (GRNs) representing interactive structures. Inference of such a GRN for a specific subsystem or an entire genome scale can help us unravel a gene interaction mechanism and we believe that we can further utilize this information to identify novel drug targets and predict their potential, adverse effects. Thanks to the recent development of high-throughput measurement technologies, there is a renewed interest in unraveling hidden GRNs. Various reverse engineering methods have been developed to infer such a GRN. Due to both experimental limitations and methodological complexities, however, a majority of these attempts have not been completely successful. We have been interested in developing new methods by exploiting dynamical properties of temporal expression profiles and will further substantiate those properties through practical case studies.

### *Complex Cellular Dynamics*




Cellular networks are composed of complex interconnections among components, where some subnetworks of particular functioning are often identified as network motifs. Among such network motifs, feedback loops have been considered to play critical roles. Intriguingly, such feedback loops are often found as a coupled structure in many cellular circuits. Hence, we have investigated available informations regarding the coupled feedbacks and came up to a set of three principles. First, positive feedbacks enhance signal amplification and lead to bistable

characteristics. Second, negative feedbacks enhance homeostasis. Lastly, positive and negative feedbacks enable reliable decision by properly modulating signal responses and effectively dealing with noises. Examples include apoptosis decision circuits, circadian regulatory circuits, and cellular memory circuits. We will further investigate various cellular dynamics to uncover their hidden design principles and extend them for bio-medical applications.




***Bio-Inspired Engineering Based on Molecular Systems Biology***

We are currently developing a new realm of engineering: bio-inspired engineering based on molecular Systems Biology. The key concept is application of systems-level knowledge on cellular mechanisms to engineering. This includes, for instance, signal processing systems that mimic cellular signal transduction mechanisms (e.g., bio-inverters/switches, and integrated circuits for complex perception tasks inspired from the brain), large complex systems by applying cellular developmental processes (e.g., bio-inspired VLSI circuits, and networked embedded systems), and robust & non-fragile systems (e.g., autonomous networking systems, and reconfigurable circuits for dynamic routing). The eventual goal is to invent self-organizing systems that can overcome unexpected environmental changes or system failures by reconfiguring internal structures and thereby behave almost autonomously (e.g., evolving digital circuits, and robust integrated circuits capable of “self-repairing” and “self-replication”).

**References**

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3. D. Kim, O. Rath, W. Kolch, and K.-H. Cho, “A hidden oncogenic positive feedback loop caused by crosstalk between Wnt and ERK pathways”, *Oncogene*, Vol. 26, Issue 31, pp. 4571-4579, July 2007.
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5. J. Kim, D. G. Bates, I. Postlethwaite, P. Heslop-Harrison, and K.-H. Cho, “Least-squares methods for identifying biochemical regulatory networks from noisy measurements”, *BMC Bioinformatics*, Vol. 8, No. 8, pp. 1-15, Jan. 2007.
6. D. Kim, Y.-K. Kwon, and K.-H. Cho, “Coupled positive and negative feedback circuits form an essential building block of cellular signaling pathways”, *BioEssays*, Vol. 29, Issue 1, pp. 85-90, Jan. 2007.
7. More than 76 international journal papers published in our lab. (visit http://sbie.kaist.ac.kr for details).