Biophysical Networks

Systems biology refers to the understanding of biological network behavior through the application of modeling and simulation tightly linked to experiment. The "network" aspect of biological systems has become especially prominent recently as a result of the understanding that complex phenotypes (disease states such as cancer or diabetes, or the infection of a host by a virus or bacterium) are governed by the behavior of genetic networks rather than single genes.

The network-centric approach to biology is already yielding insights into complex disease pathways and shows great promise in the identification of novel disease readouts, as well as potential (vectoral) drug targets for implementation of control measures by small molecules, RNAi's, monoclonal antibodies, and other approaches.

In the case of bacterial infections, the network analyses that detail the attacking pathogens and subsequent hijacking of host cells span multiple scales (temporally and spatially), including sequence knowledge of viruses and bacteria, gene regulation, protein-protein interactions between hosts and pathogens, immune-receptor signaling, and ultimately organ-level analyses of physiological responses.

Why Is Systems and Control Relevant?

Regulation, tracking, interactions, adaptation, robustness, communication, signaling, sensitivity, identification, dynamics, stability/instability, and causality are all concepts that are crucial in biomedical systems and have counterparts in the systems and control domain. Control and systems theory can be harnessed for:

- Understanding and treating diseases,
- Disease inference and tracking of progression using novel assays,
- Novel (molecular) drug treatment, and
- Developing systems methodologies for implementing personalized medicine.

Complex Biophysical Networks

Control and dynamics tools can be used to interrogate complex signaling networks, such as those responsible for apoptosis (programmed cell death; Figure 1). Key modules within the network can be isolated, such as the crosstalk between two different TNF receptors (Figure 2) and elementary control principles can be used to elucidate the role of positive and negative feedback between receptors on the dynamic response of the system to perturbations.

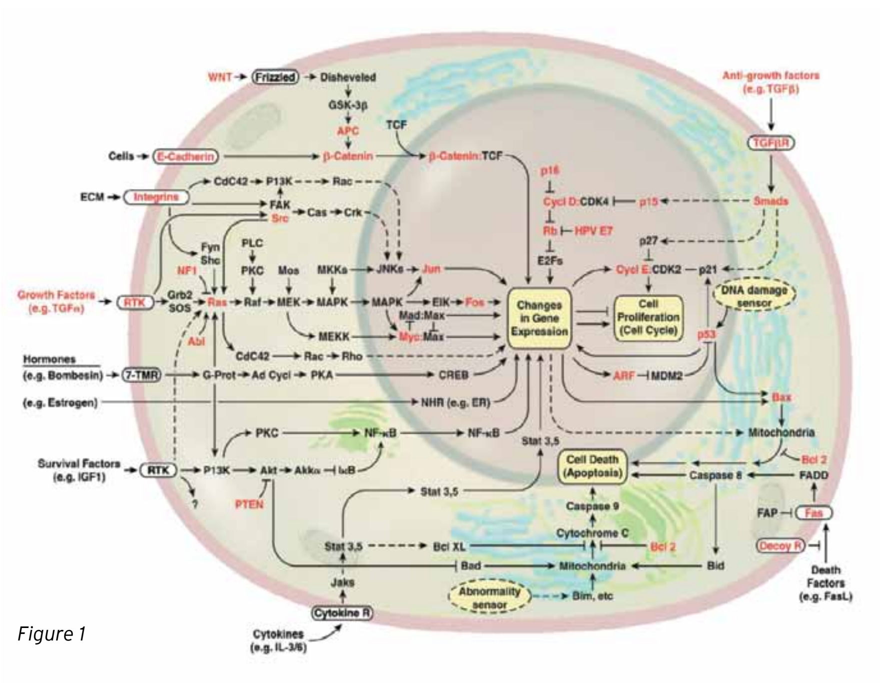

Figure 1

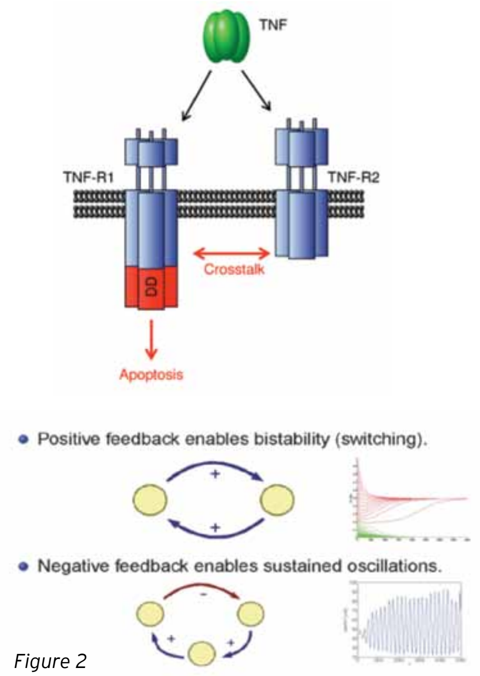

Figure 2

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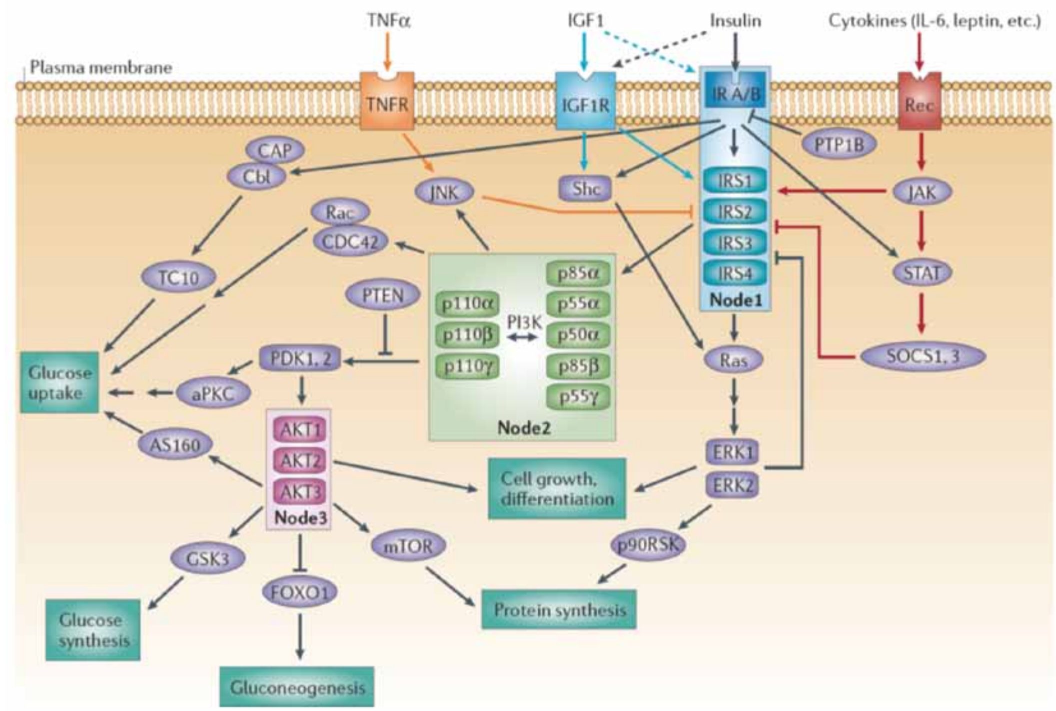
Example: Type 2 Diabetes

Type 2 diabetes is a metabolic disorder primarily characterized by hyperglycemia and insulin resistance. An estimated 350 million people worldwide will be affected by the year 2030. In the U.S. today, 14 million have type 2 diabetes, with associated annual medical costs of $132 billion. The disease is linked to obesity from high caloric intake combined with low physical activity. Current drugs are ineffective, and the consensus is that we do not understand the disease well enough (from a molecular network level) to choose appropriate drug targets. Biophysical networks are extremely "noisy" due to molecular-scale fluctuations.

The combination of systems modeling of the biophysical network with robustness analysis (sensitivity of candidate drug targets in the face of molecular noise) is a visionary and exciting prospect.

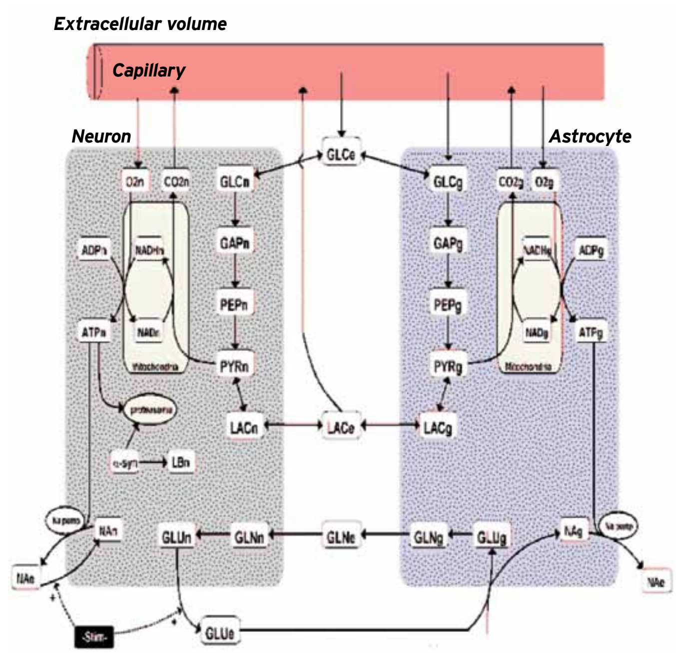


Example: Parkinson's Disease

Worldwide approximately 6.3 million people are living with this disease. A conservative cost estimate for treatment is $14,000 per patient year. Total costs are poised to rise sharply with population aging.

The causes of neuronal degeneration in Parkinson's are poorly understood: no clear genetic marker has been identified; toxin exposure and stress have been postulated with mixed results; metabolic changes with aging are clearly correlated, but precise mechanisms are unclear.

Systems biology can help integrate diverse insights into the disease and thereby elucidate key dynamic interactions and causative factors.



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