Meeting report

Biological networks: from physical principles to biological insights

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A report on the Fourth Georgia Tech and UGA International Conference on Bioinformatics 'Biological Networks: From Genomics to Epidemiology', Atlanta, USA, 13-16 November 2003.

The Fourth Georgia Tech International Conference on Bioinformatics was entitled 'Biological Networks: From Genomics to Epidemiology' and it assembled an interdisciplinary group of physicists, mathematicians, computer scientists and biologists all working on understanding biological networks. The conference was organized by Mark Borodovsky (Georgia Institute of Technology, Atlanta, USA) and Eugene Koonin (National Center for Biotechnology Information, Bethesda, USA) and primarily covered three active research areas: computational reconstruction, analysis, and simulation of biological networks. An avalanche of experimental data coming from various genomics and 'interactomics' projects means that the three focal areas are currently experiencing an exponential growth in results and publications. In spite of the computational flavor of the conference, a productive interaction between theory and experiment was clearly evident, as the majority of the participants either collaborates with, or directly uses data from, experimental labs.

Presentations covered several types of biological network: protein-protein-interaction, genetic, regulatory, and metabolic. While these types of networks represent different cellular processes, they all share common organizational and functional principles. At the meeting, molecular networks were studied at different spatial scales, from the whole network level, via biological pathways and modules to the level of elementary topological motifs. Several exciting talks highlighted rapid progress in the field.

Adam Arkin (University of California, Berkeley, USA) described how methods of nonlinear dynamics and game theory can be used to determine the optimal evolutionary strategies for bacterial growth in stochastic environments. He demonstrated how the inherent stochasticity of biological processes could help bacteria survive in uncertain environments. Arkin also presented a comprehensive comparative analysis of the chemotaxis modules from different bacteria. Variations in the structure of the chemotaxis module between bacteria lead to differences in the sensitivity to the kinetic parameters defining the chemotaxis response. It turns out that the modules are usually sensitive to only a few 'crucial' parameters, which could increase the 'evolvability' of the modules, while insensitivity to other parameters ensures robustness, and resistance to the effects of deleterious mutations. It is likely that similar studies, which include not only comparison of a parts list but also a detailed dynamic analysis, represent an important next step in comparative genomics.

Albert-Laszlo Barabasi (University of Notre Dame, USA), who pioneered the statistical analysis of biological networks, described how scale-free behavior is shared by a vast array of networks. Scale-free networks contain highly connected hubs, which usually represent highly conserved and essential proteins. Barabasi showed that, in addition to static networks, several dynamic biological networks - such as co-expression networks and the networks formed by metabolic fluxes - also exhibit scale-free properties. He also demonstrated that biological networks display a high degree of modularity and that highly interconnected modules are hierarchically organized into larger structures. In a related analysis Ricard Solé (University Pompeu Fabra, Barcelona, Spain) showed that important properties of biological networks, such as scale-free distributions and modularity, could emerge as a by-product of the rules of network evolution, rather than as a consequence of functional selection. Martijn Huynen (University of Nijmegen, The Netherlands) also demonstrated how a simple mechanistic model, without selection, can account for the observed architecture of biological networks.

Andreas Wagner (University of New Mexico, Albuquerque, USA) devoted his talk to the intriguing question of the evolution and robustness of biological networks. He showed how protein networks evolve in terms of changes in interactions partners, cellular localization, and regulation. Sergei Maslov (Brookhaven National Laboratory, Upton, USA) also showed an interesting difference in evolutionary rates between the protein-protein interaction and regulatory networks. An important property of biological networks is robustness toward genetic mutations. Robustness toward deleterious mutations can be caused by gene duplications - the loss of function in one copy can be compensated for by the other copy - or by more complicated network effects, such as use of alternative metabolic routes. Wagner presented several lines of evidence suggesting that in *Saccharomyces cerevisiae* 25-50% of gene deletions are compensated for by duplicate genes. Both Wagner and Maslov showed results based on *Caenorhabditis elegans* 'deletions' obtained recently using RNA interference (RNAi), demonstrating how quickly the data from large-scale experimental projects are currently used to investigate the principles of biological network organization.

Joel Bader (Johns Hopkins University, Baltimore, USA) presented a recently published work on the two-hybrid protein-protein interaction map of *Drosophila melanogaster*. This fly map contains more than 20,000 interactions and is the first interactome map for a multicellular organism. Importantly, because the two-hybrid methods are known to contain a significant number of false positives and negatives, Bader presented a computational method to detect high-confidence interactions. The resulting high-confidence map contains 4,679 proteins and 4,780 interactions. The *D. melanogaster* interactome map represents a rich source of information, and will certainly be analyzed for years to come. The initial analysis of this network showed a deviation from the power-law distribution commonly observed in biological networks. Additionally, statistical analysis shows a two-level network organization: short-range structures, representing protein complexes, and larger components presumably representing inter-complex connections.

Leonid Mirny (Massachusetts Institute of Technology, Cambridge, USA) has shown that there is a similar organization in the yeast protein-protein interaction network and he presented several algorithms to identify such structures. Importantly, structures derived from static data such as pairwise protein-protein interactions can correspond to either protein complexes, where all proteins come together at the same time (for example, the ribosome or spliceosome), or to dynamic functional modules where different interactions are realized at different times, for example, signaling pathways or cell-cycle control modules. Mirny also presented stochastic simulations of a cell-signaling pathway emphasizing that even such a simple module can achieve non-trivial filtering of the signal.

As we investigate the regulatory networks that are widespread in modern organisms, it is also interesting to study ancient regulatory interactions. Riboswitches are spatial structures of mRNA that can bind small molecules and change mRNA conformation, and they may represent the oldest system of gene-expression regulation. Fascinating work on riboswitches was presented by Mikhail Gelfand (Center GosNIIGenetika, Moscow, Russia), whose group's work demonstrates that riboswitches appear to control protein concentrations by regulating both transcription and translation. Riboswitches were found to regulate the metabolism of, for example, vitamins, amino acids and purines, and are conserved over very large phylogenetic distances. Gelfand also presented some initial work on the evolution of regulatory networks involving riboswitches.

The goal of explaining the observed distribution of protein-domain families in sequenced genomes led Koonin and colleagues to develop the Birth, Death, and Innovation Model (BDIM). By changing the parameters in the BDIM, researchers can investigate how different evolutionary processes shape the observed distributions of domain families. While the simplest linear BDIM shows an excellent fit to the observed distribution of domain-family sizes in genomes, the introduction of stochasticity into the model leads to prohibitively large evolution times. Koonin demonstrated how changes in the model could speed up evolution, at least *in silico*.

In my view, the presentations at the conference clearly demonstrate that many of the organizational principles of biological networks, such as the dominance of scale-free distributions, modularity, hierarchical organization, and optimality, have been firmly established and accepted by the field. Currently, the cutting-edge studies are directed at understanding two major questions: first, what is the functional importance of these organizational principles? And second, how have these principles emerged and shaped the evolution of biological systems? Appropriately, the last slide of the conference (presented by Huynen) explicitly contained these questions; their answers will shed light on 'generic laws' or 'design principles', which are common in physics and engineering, but so far have eluded biology. The official program is available at the conference website [http://opal.biology.gatech.edu/GeneMark/conference/index.cgi].