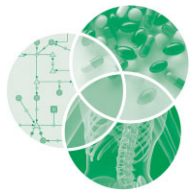
Editorial Commentary



Pathways, networks, and systems medicine—the meeting place of the Aegean and the mind

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Each year, Aegean Conferences organizes an international conference on pathways, networks, and systems medicine, where biomedical researchers engaged in systems biology-related efforts present their latest research developments. Systems biology and medicine focuses on deciphering mechanisms at multiple levels, reconstructing networks in cells, tissues and organs, measuring and predicting phenotypes, building quantitative models that describe and simulate normal and pathological physiological functions, and then testing the validity of these models and predictions experimentally. This issue combines peer-reviewed articles of conference presentations as well as recent reviews on related topics. Most of the articles in this issue deal with methods for identifying protein networks, including detection of proteins and networks across physiology. Two articles describe regulatory networks, one with modeling and another with culling network information from scientific literature.

For decades high throughput biology has been associated with genome sequencing and transcriptomic analysis. DNA microarrays, which exploit the multiplexing of oligonucleotides through complementarity, have become a standard tool for the biologist. But unlike nucleic acids, proteins do not possess complementary binding partners and their detection has hitherto been done through painstaking low throughput approaches. Recently protein microarrays, which utilize the binding of proteins to specific ligands, antibodies, lipids, or nucleic acids, have been designed and are becoming useful for detection and quantitative estimation of protein abundance. In an overview article, Hu et al. describe the technology associated with functional protein microarrays. The fabrication of protein microarrays involves understanding surface chemistry to array the proteins, high throughput protein production, and protein printing on surfaces. The detection of binding to ligands, proteins, lipids, or nucleic acids often involves label-dependent methods where radioisotopes or fluorescent dyes are used for signal changes upon binding. Chemiluminescence has also been employed for this purpose. Label free methods deploy surface plasmon resonance and in specific cases mass spectrometry can be used. This overview article provides a detailed insight into the design, fabrication and utilization of the functional protein microarrays, and discusses the outlook for the future.

In a companion focus article, Merbl and Kirschner describe protein microarrays for genome-wide analysis of posttranslational modifications. While there are nearly 200 covalent modifications that have been described in the literature, phosphorylation continues to be the most widely studied, followed by glycosylation and ubiquitination. An interesting methodology for quantitative phosphoproteomics utilizes isotopically labeled phosphate containing moieties including kinases and ATP and on protein-chip phosphorylation that can be elegantly detected with autoradiography or other methods. For other modifications, fluorescent antibody-based approaches have provided quantitative measurements and these approaches have been used in differential proteomics to detect changes in post translational modifications. This focus article describes the power of these methods for mechanistic biology.

While functional protein arrays can help map interactions between proteins and ligands, proteins and proteins, and proteins and nucleic acids, they often fail in being able to measure protein–lipid interactions. In their advanced review, Arumugam et al. describe the development and application of protein–membrane interactions. Cell membranes, in addition to being chemically heterogeneous, are also structurally diverse and this structural polymorphism is responsible for specific cellular

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mechanisms and phenotypes such as membrane trafficking, membrane protrusions, cytokinesis, cell signaling, and communication. This advanced review describes specific assays to study protein membrane interactions when the membranes are in different lipid systems such as liposomes, lipid tubes, monolayers, and bilayers. The authors present elegant examples such as detection of clathrin-mediated endocytosis and actin-based motility in cells with the development of minimal lipid systems.

Two focus articles round out the protein interaction technologies and applications. In the first, Nita-Lazar describes the quantitative analysis of phosphorylation-based protein signaling networks in the immune system by mass spectrometry. The technical details of mass spectrometric methods for investigating phosphoproteomics aid readers in understanding the power and limitation of the methods. The other focus article by Nibbe et al. presents the applications of protein–protein interaction detection methods for identifying networks and sub-networks in disease. It also provides an insight into development of models that elucidate the differences between normal and diseased states.

New technology is emerging for studying alterations in regulation of genetic mechanisms and networks and this forms the theme of two advanced review articles in this volume. In a state-of-the-art review on an epigenetic change, Shoemaker et al. describe the mediators and dynamics of DNA methylation. Methylation of cytosine in CpG dinucleotides is a common feature employed by eukaryotic cells. The authors describe the presence of this phenomenon in both plant cells and human embryonic stem cells. Although methylation of DNA has become a subject of numerous studies in recent years, few studies have focused on the role of methylation in the dynamics of cellular processes. This review describes the role of methylation in cellular reprogramming. The most intriguing part of this article is the proposal of hydroxymethylcytosine as a new cytosine modification.

Understanding of methylation signatures has begun to elucidate the role of methylation in complex mammalian regulatory mechanisms. Another advanced review by Glubb and Innocenti describes the mechanisms of genetic regulation in gene expression. The authors focus specifically on the regulation of drug metabolizing enzymes and transporters. Multiple mechanisms that alter the functional specificity of an enzyme exist; these include epigenetics, polymorphisms, transcriptional regulation through transcription factors, and post-transcriptional interference with various small RNAs. This advanced review presents multiple methods available for investigating these mechanisms of genetic expression regulation, with special emphasis on enzymes and transporters that are involved in drug response.

Most of the technologies described in the articles in this issue are directed at *in vitro* and *ex vivo* systems. However, it would be beneficial to observe the biomolecular parts list and their interactions in real animal models. The zebrafish by virtue of its anatomical transparency lends itself to direct visualization of components, interactions and biological processes and is beginning to serve as an important model system in the study of development and pathologies. In a focus article, Deo and McRae outline the study of multiple organ systems, their function and regulation in zebra fish through direct observations of the genes, proteins, and networks. The power of direct observation in phenotypic exploration and discovery in zebrafish cannot be underestimated and provides a powerful validation tool for systems biology approaches.

Scientific literature grows at a phenomenal rate with the avalanche of journals and the increasing role of instrumentation in biology. The efficient use of the mushrooming literature continues to pose challenges to researchers. In an advanced review, Deftereos et al. present novel methods for high throughput literature analysis and they apply these to drug repurposing and adverse event predictions. The authors present a platform for trolling the clinical outcome search space through the ABC algorithm. Validated discoveries offer the promise for use of such automated approaches in the future. In another advanced review, Kaznessis provides the framework for mathematical modeling of biological systems from molecules to species. The methods are grounded on thermodynamics. The author uses systems biology as a tool for developing mathematical models and presents a modular strategy developing models that can be simulated across scales.

The Aegean Conference provides a forum for discussion of development across themes described above and perhaps will lead in the future to a Galilean dialog on systems biology and medicine.

