

Review Article

Systems Medicine: Dawn of a New Era in Biomedical Science

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1. Systems biology : Definition and relevance to medical science.

Biological systems are inherent with immense complexities. The behavior of such complexities at every level of organization, from molecules, cellular structural activities, tissues and organs to organisms, and the ecosystems in which they reproduce, grow and meet their programmed end points in life cycles, - both in normal and perturbed conditions is the broad nomenclature that has become acceptable as "Systems Biology". An important conceptual as well as working axiom on which such a definition is given is derived from the premise that biological functions as system properties are different from those of the interacting components.

Presently, technologies are driving the high throughout DNA sequencing, and analysis of transcriptomes, proteomes and metabolomes. The variations and functional differences of the human genome, and their ramifications on human health and

disease conditions are rapidly being understood by strides made in instrumentation and technologies in biochemistry, biophysics and analytic methodologies. These include mass spectrometry, chromatography, nuclear magnetic resonance, which coupled to powerful computational and mathematical tools have yielded mathematical and computational strategies and instruments to develop a 'systems approach' to unravel networks concerned with functions and regulation, of immense complexities in biological systems.

There is a great need to develop these and other tools on methods and concepts to integrate the vast data from different levels of life processes, characteristic of human life and development, physiology and disease, - the last one in its susceptibility, resistance (immunity) and intervention facets.

Work thus far undertaken and ongoing in medical genomics has somewhat overcome the limitations of genome-wide studies to identify disease associations, and has identified a modest number of loci pointing to their association to susceptibility to several common diseases as well as complex ones. We are witnessing recently in this field that systems approaches are beginning to shed light and provide tools for a deeper understanding into the mechanisms of human diseases. Much promise is indicated by such development of systems biology approach

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of diagnostic and prognostic markers (of greater clinical significance and value for application in clinical practice) for cancer and several other diseases. At another level, systems approaches will usher a paradigm shift in drug development, targets for such approaches being network events and components and multiple pathways which influence these events. More than token or peripheral interaction between academic clinicians and industry can be expected, as a robust and productive partnership. A very welcome outcome of systems approach in this context would relate to concepts and practices from Western and Eastern cultures finding in each other, complementary phenomena to draw from. Outcome of such developments will mean that gaps in healthcare between the two worlds may get gradually narrower.

Systems biology has its origins in the sciences of physiology, biochemistry and biology, cellular as well as molecular. Recently, it has integrated into this amalgam advances in genomics and bioinformatics. Systems theory and engineering sciences in the designing and in modeling biological complexities are deployed. Synthetic biology may become an extension of genetic engineering in designing and fabricating functional systems from component modules.

2. Structure to Function: Driven by Technology.

The early achievements in DNA sequencing and data acquisition and processing software for assembly of sequence and interpretation involved very large budgets (multibillion dollar), thousands of researchers spread across the globe, and a whole decade. Such an effort on the human genome triggered

genome sequencing of many other life forms. From this point onwards, technology has galloped exponentially, to include mega sequencing of DNA, cutting cost and time astonishingly lower, and faster levels of performance respectively. The third generation sequencing which is widely used currently opens the possibility of correlations between genotypes and disease phenotypes. Microarray technology used for expression profiling has benefitted by extensive sequencing of partial and complete cDNA collections. It is now possible to find variations in expression of many gene transcripts under normal and perturbed states.

Genome and transcriptome sequences can be a source to derive a nearly complete list of genes. By extending such a task, one can derive a list similar to it of proteins. This is bound to revolutionize proteomics. At present, mass spectrometry can identify peptides, and not complete proteins. Multiple reaction monitoring with mass spectrometry is the most powerful and rapid target approach in proteomics available. Single cell proteomics is also making rapid progress. Nano materials under development will expectedly be the next generation proteomic analysis tools.

Metabolomics is exploiting the nuclear magnetic resonance technology to analyze complex sets of metabolites in body fluids and tissues. These measurements will reflect normal and disease states. This technology is also being deployed to observe interactions with gut microbes and several environmental factors. Additional biomarkers receiving significant attention are lipidomics and glycomics as biomarkers which are complementary to other

omics that are already receiving attention in the cascade of life processes.

It is significant to note at this point in the progress of this 'New Biology' of which systems Biology (a major offshoot of which is systems medicine) that technologies of high-throughput and astonishing speed which have been developed in the evolution of the several omics have required rigorous procedural standards, quality assurance protocols as well as software development and database architecture. New Biology laboratories addressing systems biology have emerged with a new culture in their practices and lexicon. Independent validation of results revealed by omics studies need "chemical-genetics" based screening and these are being performed by cell microarrays and RNA interference.

3. Biochemistry, new physiology and mathematical sciences lead to pathological biology.

Advanced biochemistry as most of us learnt and understood, included wall charts, illustrated and static, published in text books as well. Currently, with large amounts of data on all types of biological components, there is shift to identifying their interactions, formations of macromolecular structures, transient or permanent and computational patterns as metabolic, protein, micro RNA and then regulatory networks. This emerging network biology will perhaps reveal the scientific basis for the robustness of biological systems facing changing environments.

In a rapidly evolving strategy for integrative computational physiology, a project which is yet another - Ome, "the physiome

project" is being developed on the foundations of over five decades of molecular modeling of excitable cells. Such efforts deploy ordinary and partial differential equations and finite element lattices for geometric modeling of human organs. These approaches have gradually led to the evolution of computational physiology with its own lexicon and language for modeling. For example, the beating heart, contracting muscle and breathing lung in all of which initial models have become available. Many efforts currently being made in computational neuroscience can be eventually expected to merge with systems biology.

Importance of contributions from mathematics, physics and informatics for the emergence of systems biology cannot be sufficiently acknowledged. They are immense and pervasive. Yet, to gain deeper insights into multiple levels of organization and timescale characteristics of life processes, it is felt that more theoretical advances may be needed. This has to be moderated by the awareness that biological data have to be tested by a hypothesis driven studies. There are some developments in this direction on scale relativity theory etc., which are beyond the scope of this review, though very significant.

Medical genomics currently, utilizes high speed sequencing data, computational tools and knowledge bases to build links between genes, biological functions and many a wide range in diseases. Pathological biology and connections to clinical research and drug discoveries are gainful outcomes and represent the current features of genomic medicine as practiced and applied.

Genetic maps of the human genome wherein the identified mutations which affect hundreds of genes involved in inherited disorders have been the outcome of the first generation genome maps. However, associations between common complex traits and genetic polymorphism are yet to be confirmed in studies conducted independently though the picture is changing rapidly. Diabetes, Obesity, Breast and Lung Cancer are some examples. Future progress will relate to genomic polymorphism between individuals, including monozygotic twins. Copy number variations and epigenetic modifications will receive serious attention. Integration of physiopathology, network biology and DNA variations will begin to provide novel insights into the mechanism of several diseases, e.g., diabetes, obesity etc; Systems biology has greatly facilitated studies on cancer. The importance of epigenetic variations which regulate / control transcriptional events that sustain differentiation of normal and cancer stem cells are some outcomes which are highlighted currently.

4. Some expected outcomes in the new era of systems medicine.

Discovery of useful biomarkers for classification and diagnosis of cancer subtypes are the expected yield from transcriptome and proteome analysis of cancer specimens, coupled to functional appraisal and modeling of pathways and networks. Such biomarkers will include those that reveal subtypes, prognosis, prediction of intervention and treatment responses and identification of targets for drug development in terms of perturbation sites. Similarly, systems approach has impact on

studies in immunological diseases, inflammation, tuberculosis, autism, Alzheimer's disease, asthma, cardiovascular and other metabolic diseases. It is of great interest that "regulation of energy metabolism appears to have a central role" is a common biological theme of many of these studies.

We can surmise fairly with a degree of certainly from the foregoing that perturbation of fundamental biological processes are at the root of human diseases and that systems approaches help elucidate the mechanisms and in designing therapeutic interventions. Treatments in the future may consist of multiple drugs to interact with key interconnected components within functional modules. In a sense, they will reflect the manner in which biological systems function and maintain themselves by adapting to changes brought about by development, environment, physiology and pathology. It is of great interest that traditional systems of medicine of the East, Chinese and Indian in origin have similar principles underlying their approaches, though evolved empirically, they seem to touch upon a similar framework of reference in logic. Synergistic effect of combining Western Medicine with the Chinese medicine components in the treatment of leukemia seem to yield positive outcomes. Also studies on metabolome to analyze composition of herbal medicines to delineate their therapeutic properties and modulatory effects of gut microflora on human metabolic phenotypes in response to health or disease all represent a 'West meets East' framework of integrative systems medicine. We may have to traverse still some vast terrains of new knowledge and

insights. This does not detract from an exciting future for medicine which has acquired a 'systems' dimension, thanks to the integration of all the basic sciences, chemistry, physics and mathematics in the new era of systems biology. Adherence to evidence as the underpinning of medical science may expand its vistas and scope without sacrifice of the fundamental tenets of science.

Suggested reading

[The key references to the topic under review number over several hundreds. Only a few which are in the nature of milestones or reviews in the field are suggested for reading]

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Source of Support: Nil Conflict of Interest: Nil
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