Systems Biology

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Systems biology is the computational and mathematical modelling of complex biological systems. Systems biology is a biology-based inter-disciplinary field of study that focuses on complex interactions within biological systems, using a holistic approach to biological research. From year 2000 onwards, the concept has been used in the biosciences in a variety of contexts. For example, the Human Genome Project is an example of applied systems thinking in biology which has led to new, collaborative ways of working on problems in the biological field of genetics. One of the outreaching aims of systems biology is to model and discover emergent properties of cells, tissues and organisms functioning as a system whose theoretical description is only possible using techniques which fall under the remit of systems biology. These typically involve metabolic networks or cell signalling networks. (Wikipedia Contributors 2016)

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Systems Biology: A Vision for Engineering and Medicine

Organisms and Hosts Interact in Communities of Life

There is an increasing appreciation that microbes are an essential part of the ecologically-important traits of their host. Organisms do not live in isolation, but have evolved, and continue to evolve, in the context of complex communities and specific environmental conditions. Evolutionary biologists are increasingly able to integrate information across many organisms, from multiple levels of organization and about entire systems to gain a new integrated understanding that incorporates more and more of the complexity that characterizes interdependent species associations. Only when we begin to understand the molecular base for adaptation and interactions of communities of life, can we start to comprehend how ecosystems are functioning.

Addressing Different Levels of Organization of Organisms

Understanding the function of complex biological systems is one of the greatest challenges facing science. The rewards of success will range from better medicines to new engineering materials. The sequencing of the human genome, although of fundamental importance, does not even provide a complete parts list of the protein molecules that exist in a biological organism because of complexities of downstream processing and complex folding required to make a functioning receptor or enzyme from a long chain of amino acids. Furthermore, protein molecules do not function alone but exist in complex assemblies and pathways that form the building blocks of organelles, cells, tissues, organs, organ systems and organisms, including man. The functioning of brain or muscle, liver or kidney, let alone a whole person, is much greater than the sum of its parts.

Figure 1 - Levels of Structural Organization of the Human Body (source - https://cnx.org/contents/Xh_25wmA@7/Structural-Organization-of-the#fig-ch01_02_01)

Internalizing the Complexity – Pushes the Boundary of Systems Thinking Capability

To tackle this problem (understanding biological systems) requires an iterative application of biomedical knowledge and experiment with mathematical, computational and engineering techniques to build and test complex mathematical models. Systems and control engineering concepts, a modular approach and vastly increased computing capacity are of critical importance. The models, once developed and validated, can be used to study a vastly greater range of situations and interventions than would be possible by applying classical reductionist experimental methods that usually involve changes in a small number of variables. This new approach is now termed "Systems Biology". It allows insight into the large amount of data from molecular biology and genomic research, integrated with an understanding of physiology, to model the complex function of cells, organs and whole organisms, bringing with it the potential to improve our knowledge of health and disease. Systems Biology will inevitably become an approach that pervades scientific research, in much the same way that molecular biology has come to underpin the biological sciences. It will transform the vast quantities of biological information currently available into applications for engineering and medicine.

Natural Patterns and Engineered Patterns Can Be a Source of Inspiration - in Both

Directions

Biological organisms are much more complicated than any machine designed by man. However, there are similarities between the way in which organs and whole organisms are assembled from molecules and cells and the design methods used by engineers in the construction of complex systems. The application of such methods to biology will, however, require novel engineering tools to be developed since biological systems possess key features that artificial ones do not. Specifically, biological systems have an exceptional capacity for self-organization and assembly, using rules and mechanisms that have been shaped by natural selection. Biological systems also have significant capacity for continuing self-maintenance through turnover and renewal of component parts. Perhaps the property that distinguishes biological systems most is their ability to auto-adapt their organization to changing circumstances through altered gene expression, or more directly, through signal transduction and modification of proteins. This adaptation culminates at higher levels of organization as evidenced by phenomena such as the development of resistance to antibiotic therapy or tolerance to recreational drugs. The mechanisms by which component parts interact are often highly stochastic in nature; that is, susceptible to the play of chance, which becomes particularly important when only a few components are being considered. Nevertheless, biological systems are robust.

Advancements in Methods for Predicting "What If" in the Behavior of Complex Adaptive Systems

Advances in engineering design and techniques carry a significant potential in driving the progress of Systems Biology. Interventions to biological systems intended to improve health, whether environmental, pharmacological or clinical, need to be carefully thought through and carried out to maximize benefit and reduce harm. The refinement of techniques and tools enables devices and systems to achieve a defined performance within precise tolerance limits, potentially allowing better interventions to complex biological systems. They will be increasingly necessary to permit more reliable system-wide predictions of the effects of biomedical advances and to achieve desired clinical results to a predefined tolerance, or at least to have a quantitative bound on the biological uncertainty.

Transdisciplinary Approaches are Needed to Address the Complex Bio-system Problems

Research in the field of Systems Biology requires close interactions and collaborations between many disciplines that have traditionally operated separately such as medicine, biology, engineering, computer science, chemistry, physics and mathematics. Systems Biology demands a focus on the problem as a whole and therefore a combination of skills, knowledge and expertise that embraces multiple disciplines. The success of leaders in the field of Systems Biology will depend strongly on the extent to which they accomplish the creation of the environment that researchers need to develop an understanding of different working cultures, and manage also to implement strategies that integrate these cultures into shared working practices.

Systems Biology: Relevance to Healthcare

Complex Diseases Demand Systemic Approaches

Over the past few decades, pharmaceutical R&D has focused on creating potent drugs directed at single targets. This approach was very successful in the past when biomedical knowledge as well as cures and treatments could focus on relatively simple causality. Nowadays, the medical conditions that affect a significant proportion of the population in industrialized countries are more complex, not least because of their multifactorial nature. The sequencing of the human genome has led to a considerable increase in the number of potential targets that can be considered in drug discovery and promises to shed light on the etiology of such conditions. Yet, the knowledge of the physiological properties and the role that these targets play in disease development is still limited.

Diminishing Returns in the Single Target Approach to Disease

In terms of drug targets, there is a case that much of ‘the low hanging fruit’ was picked in the period between the late 1940s and the mid-1980s. The decline in output of new molecular entities and medicines recorded over the last 20 years, despite the steadily growing R&D expenditure and significant increase in sales, bears testimony to the fact that advances with new targets are more difficult and that R&D projects have become much more prone to failure. A basic problem is that the many factors that predispose to, and cause, complex diseases are poorly understood let alone the way in which they interact. The very fact that there are multiple drivers for these conditions suggests that a reductionist approach focusing on individual entities in isolation is no longer appropriate and may even be misleading. It is therefore necessary to consider 'novel' drugs designed to act upon multiple targets in the context of the functional networks that underlie the development of complex diseases. Many of the new developments are likely to turn into effective medicines when combinations of drugs are used to exert a moderate effect at each of several points in a biological control system. Indeed, many common diseases such as hypertension and diabetes are already treated with a combination of two or three medicines hitting different targets in the control network that underlies the condition. Investigating the possible combinations by trial and error in man is onerous but feasible with two components. However, it quickly becomes extremely complicated with three components and well-nigh impossible with four or more. Systems Biology, promises to assist in the development of more specific compounds and in the identification of optimal drug targets on the basis of their importance as key 'nodes' within an overall network, rather than on the basis of their properties as isolated components.

Individualized Medicine, Tuned to the Individual and Their Circumstances

Increasingly powerful drugs will be aimed at a decreasing percentage of people and eventually at single individuals. Modelling can be used to integrate in vivo information across species. Coupled with in vitro and in silico data, it can predict pharmacokinetic and pharmacodynamics behavior in humans and potentially link chemical structure and physicochemical properties of the compound with drug behavior in vivo. Large-scale integrated models of disease, such as diabetes and obesity, are being developed for the simulation of the clinical effects resulting from manipulations of one or more drug targets. These models will facilitate the selection of the most appropriate targets and help in planning clinical trials. Coupling this approach with pertinent genomic information holds the promise of identifying patients likely to benefit most from or to be harmed by, a particular therapy as well as helping in the stratification of patients in clinical trials. Symptoms that diagnose a disease do not necessarily equate to a common cause.

Systems Biology is arguably the only research approach that has the potential to disentangle the multiple factors that contribute to the pathogenesis of many common diseases. For example, hypertension, diabetes, obesity and rheumatoid arthritis are known to be polygenetic in origin although individual genes may not have been identified. Ultimately, the prevention of these conditions rests upon a comprehensive approach that engages with each of the more important predisposing factors, genetic and environmental, that operate upon individuals. A systems approach is already proving valuable in the study of complex scientific subjects and the research aimed at the prevention and management of medical conditions. Illustrative examples are neuroscience, cancer, ageing and infectious diseases.

A Healthcare Paradigm Reinforcing the Causes of Health and Not Just the Treatment of Disease

Notwithstanding the hugely important role that Systems Biology plays in understanding disease and designing drugs that treat them, the greatest opportunities may lie in health maintenance and disease prevention. Even modest measures that could retard the effect of ageing on brain, heart, bones, joints and skin would have a large impact on the quality of life and future healthcare demands of older people and consequently on the provision of health services. Young people are vulnerable too. Multifactorial diseases such as diabetes, obesity, allergies and autoimmune conditions are becoming prevalent in younger people and unless effective measures are taken to prevent an early and significant decline in their health, healthcare demand will increase exponentially. It is apparent that multiple and diverse factors interact in determining health, quality of life and ageing. These include genetic makeup, microbiota, diet, physical activity, stress, smoke and alcohol, therapeutic and social drugs, housing, pollution, education, and only a systems approach will permit the understanding of how best to prevent and delay health decline.

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