Systems Biology – An Overview

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1 Introduction

Systems Biology is an emerging field in Life Sciences which has evinced interest among the community of physicists, chemists, mathematicians and researchers involved in computational modelling to a significant extent. A simple PubMed search would yield more than 25,000 articles in the past two years, with this term appearing either in the title or in the abstract as against three articles in the earlier century. A closer look at the recent articles (which use the term Systems Biology) reveals a systematic work covering computational or experimental efforts to define a system completely. Systems level understanding has dominated themes of discussion in biological sciences for decades. Advances in Molecular Biology, genome level sequencing and interpretations and high throughput measurements at the molecular and imaging level have enabled a new paradigm of understanding a system, its dynamics and the contribution of individual molecules to the performance of a system. Emergence of new and finer techniques in molecular biology enables a systems level understanding grounded with the understanding at the molecular level.

Now, let us align this discussion to a general observation in science. We all know that complex systems are prevalent in the Physics, Engineering, Chemistry and Biology we have discussed over years. The complexity in the system occurs due to a large number of variables in the system, their non linear equations, the kinetic equations and transport equations that describe the system, the network among the variables in the system like Feed Back Loops or gene circuits or networks. Newer techniques and tools in the field have enabled visualization of materials structure and biological molecules at the nano and atomic scale. It is now possible even to determine genome organization and architecture and the molecular players that network to initiate signalling cascades in the cell. Thus one can observe finer kinetic processes, signalling loops and spatio-temporal organization patterns that add to the complexity of the network. Such data sets

become substrates on which one can develop theories of complex function and behaviour. This forms the basis of Systems Biology.

1.1 Understanding Biology at the Systems level

What does a 'systems level understanding' actually mean? Molecular Biology techniques focus on biomolecules - molecules such as nucleic acids and proteins, their sequence, structural and function inside the cell. Systems Biology tries to understand a system which is built of these molecular components. If one wants to measure the interactions in a system, one notices that the interactions vary with respect to molecules; the molecules exhibit properties on their own as well as the properties they acquire through interactions. Thus a biological function emerges because of the collective behaviour of the molecules in the system and not because of molecules in isolation. The structure of the system, the network topologies, the functionality of the constituent components and their dynamics constitute the synergistic system. In a simple language this means that systems Biology attempts to understand the structure and dynamics of a system as a whole rather than understanding its genes and proteins in isolation. The following properties provide a systems level understanding of a biological system.

1. **Systems Structure**-Gene interactions, biochemical pathways, intracellular mechanisms
2. **Systems Dynamics**- Metabolic, sensitivity and dynamic analysis to study system behaviour
3. **Control Method**- Modulation of mechanisms that regulate cell states
4. **Design Method**- Using basic principles and simulations to modify and construct biological systems with desired properties.

Systems Biology does not confine itself to a single organism or single set of macro molecules or to specific techniques. It tries to integrate all these and it is rather heterogeneous.

1.2 What does one require for a systems level understanding?

To carry out an analysis at the systems level, one requires a comprehensive set of quantitative data. Such quantitative data can be obtained from experiments, genome sequencing efforts and molecular network data or from projects such as the Alliance for Cellular Signalling (AfCS) which encompass large scale quantification of cellular data with the sole aim of simulating cellular models. A systems level analysis involving modelling should be explored at the preliminary stages of the project. This would facilitate identification of bottle necks in measuring certain quantities required for building the final model and also to overcome difficulties due to insufficient and inaccurate data which will not add value for model building.

Measurements should be precise and comprehensive and demand the following factors for precise definition.

1. **Factor Comprehensiveness**
   eg. the number of mRNA transcripts or proteins that can be measured simultaneously.
2. **Temporal Comprehensiveness**- The time scales in which such minute measurements are made.
3. **Parameter Comprehensiveness**- Simultaneous measurements of functional parameters inside the cell such as protein phosphorylation, localization, mRNA concentration, etc. Experiments planned with a modelling approach can clearly predict areas where accuracy is most essential and areas where it is not so important. This approach helps in optimal allocation of resources.

Systems Biology therefore facilitates understanding of

- Biological structure as well as network architecture of the system.
- Qualitative and quantitative dynamics of the system supported by predicted modelling
- Control points in the system
- Design methodologies for the system.

This integration of modelling with quantitative experimentation helps us to obtain information not yielded by experimental approaches alone. Systems Biology thus generates key hypothesis that augments our understanding of the complex interactions or functions of biological systems. An often quoted example is the phenomenon of calcium signal transduction in which calcium oscillations where predicted through computational modelling. Calcium dynamics on CaMPK 2, the stochasticity on single calcium channels influencing the dynamics of the system have been investigated in detail through experimental and modelling approaches.

1.3 Computing and Systems Biology

Integration of computing into the analysis of the biological system leads to a better understanding of the functional components of the system. The Systems Biology Markup Language (SBML) is an elegant format to represent models of biological processes. One can simulate metabolic reaction, cell signalling systems and logical function exhibited by the biological system. SBML2LATEX converts SBML files into LATEX files. MATLAB, the versatile tool for engineering calculations has integrated a SBML tool box built on top of libSBML. This tool facilitates the use of SBMLs in MATLAB. Molecular interaction networks, gene expression profiles, protein-protein interactions, can be visualized using “Cytoscape”, an open source tool which facilitates plug-in development using its open API based on JAVA. We have “hands –on” modules on these tools as we learn the essentials of Systems Biology.

I welcome all students of Life Sciences, Chemical Engineering, Mathematics and Computer Science to this course on Systems Biology. The course would help us understand a major transition paradigm that has occurred in biology which enhances our understanding of complex cellular and regulatory systems. I hope you will enjoy how this transition from the molecular to the systems level would be aided by computation and mathematical modelling, experimental design and high throughput experimentation that help us describe the complete behaviour of the system.

This course has been split into four major modules, the first of which addresses gene control and genetic switching. This is followed by Systems Biology in developmental systems and in a functional cell-cell communication paradigm. We would discuss an interesting aspect of Quorum sensing in marine bacteria and design a genetic circuit that can precisely control population in an *E.coli* system using an elegant genetic engineering approach. We also discuss here, how threshold gene expression dictates patterning and cell fate decisions in a Drosophila embryo. Two inspiring lectures on these themes by Bony Bassler and Eric Wieschaus are a part of this module. These promise to be the exciting components of the module. The third module covers modelling the lysogeny-lytic decisions in Lambda phage- the virus that infect bacteria and the most intensive and interesting computational challenge of chemotaxis in *E.coli* system.

The last module opens an interesting paradigm that connects the dynamic gene switching behaviour to the logic gates we observe in electronic circuits. We would discuss here the concept of Transcription Networks and Feed Forward Loops of AND and OR logic that occur as recurrent motifs in the genome. We would also try to understand how such naturally occurring loops in the genome can act to induce delays in the circuit or act as sign sensitive accelerators which speed up the response time in the circuit. This course will be also be supported by reading of key papers that revolutionised the understanding of this field.

2 References

2.1 Text Book

1. Uri Alon**,** An Introduction to Systems Biology: Design Principles of Biological Circuits, 2/e, *CRC Press*, (2006).

2.2 Literature References

1. Kitano et al., Systems Biology: A Brief Overview**,** *Science*, (2002), 295, 1662-1664.
2. John Ross et al., Complex Systems: From Chemistry to Systems Biology**,** *PNAS,* (2009), 106, 6433–6434.