SBG Journal Club

‘Perspectives on Systems Biology’

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Overview

1. Introduction
2. Characteristics of Biological Systems
3. Design Patterns and Control Principles
4. System Structure Identification
5. System Behaviour Analysis
6. Software Platform
7. Conclusion
1. Introduction

• Ultimate goal in biological research – To explain every detail and principle of biological systems.
• 1953, DNA Structure (Watson & Crick or Franklin??).
• Emergence of molecular biology.
• Rapid progress - complete sequencing of genome.
• Identification of genes, elucidation of protein functions, linking genes, proteins and diseases.
1. Introduction

• However, understanding of molecular-level mechanisms will not provide us with understanding of biological systems as systems.
• Genes and proteins are components of the systems.
• While understanding a system’s constituents is important, it is not sufficient.
• Systems Biology – system-level understanding of biological systems.
1. Introduction

• To understand biological systems as systems:
  1. Structure of the systems (components and structural relationships)
  2. System behaviours and characteristics
  3. Methods controlling the states and behaviours of the system
  4. Methods by which systems with desired functions are designed and built
2. Characteristics of Biological Systems

- Emergence - most complex systems are assumed to be composed of large no. of simple components emerge to exhibit complex behaviours.
- In many cases, components of the system are assumed to be homogeneous.
- But biological systems (cells, proteins, genes) are heterogeneous, hence more complex.
Thus, biological systems are best char. by:
1) Heterogeneity of components
2) Complexity of components
3) Selectivity of interactions

3. Design Patterns and Control Principles

- Structures of biological systems are formed through evolution.
- Evolution selects circuits that are more likely to be functional.
- But there is no guarantee they are optimally designed for their function.
- Hence we should - identify patterns of design, create a library, develop methods to identify which is used in a specific biological system.
3. Design Patterns and Control Principles

- Many biological circuits have common control mechanisms.
- Robustness and stability are commonly achieved by using:

  1) Feedback loops
     - sophisticated control system.
     - closes loop of signal circuits.
     - attains desired control of system.
     - e.g. Negative feedback.
3. Design Patterns and Control Principles

2) Redundancy
   - Improve a system’s robustness against damages to its components.
   - Multiple pathways to accomplish function.
   - e.g. MAP Kinase pathway, futile cycle (??).

3) Modular design
   - Prevents damage from spreading without limit.
   - Eases evolutionary up-grading of some of the system components.
4. System Structure Identification

- To understand a biological system, we have to first identify its structure (components, their functions, interactions).
- Difficulty – structure of system cannot be inferred from experimental data based on some principles or universal rules, because systems evolved via a stochastic process.
- There can be multiple solutions to one given problem.
- Example: Stripe-pattern formation
  - *Pomacanthus* (turing wave); marine angel fish.
  - *Drosophila melanogaster* (even-skipped (eve) gene); fruit fly.
  - Same phenotype, different mechanisms.
4. System Structure Identification

Fig 1. Possible Genetic Regulatory Network for Stripe Patterns
4. System Structure Identification

- Approaches for Structure Identification:
  1) Bottom-Up Approach
     - Construct a gene regulatory network from independent experimental data.
     - Suitable when most of the genes and regulatory relationships are relatively well understood.
     - Aim: to build a precise simulation model so that dynamical properties of system can be analyzed by changing parameters.
4. System Structure Identification

- Approaches for Structure Identification:
  2) Top-Down Approach
    - Infer gene regulatory network from high-throughput DNA microarray data and other new measurement technologies.
    - Clustering methods are suitable for handling large-scale data but do not directly provide network structures.
    - Hence some heuristics must be imposed.
4. System Structure Identification

• Approaches for Structure Identification:
  3) Hybrid Approach
    - It is likely that some knowledge should be assumed in the process of gene network inference.
    - Use of trustworthy knowledge can significantly reduce the kinds of network structures feasible.
    - Hybrid approach appears to be a promising and practical method.
4. System Structure Identification

- Computational Challenges:
  ‘Given a set of noisy expression profiles, experimental data, and partially correct networks, find a set of plausible gene regulatory network topologies and their associated parameters.’
  - Parameters are important, for experimental validation.
  - GA and simulated annealing are common parameter optimization methods.
  - Caution: Multiple parameter sets may generate simulation results equally well fitted to experimental data.
5. System Behaviour Analysis

- To have system-level understanding, we need to understand the robustness and stability of the system.
- In engineering systems, increasing complexity increases stability and robustness of a system.
- Is that the same for biological systems?
- *Mycoplasma* has 400 genes; live under narrowly specific conditions, vulnerable to environmental fluctuations.
- *E.coli* has 4,000 genes; live in varying environments.
- Evolved genetic and biochemical circuits (-ve feedback) for stress responses and basic behavioural strategies.
5. System Behaviour Analysis

- Feedback in biological systems?

Fig 5. p53 related feedback loop
5. System Behaviour Analysis

- Redundancy in biological systems?

Fig 6. Redundancy in MAP Kinase Cascade
6. Software Platform

- Systems biology research requires software systems for data collection, simulators, parameter optimization, data visualization, analytical tools.
- Simulation is important for understanding the behaviour of existing systems.
- Hence, we need highly functional, accurate, user-friendly simulator systems.
- Simulator needs to be coupled with parameter optimization tools, a hypothesis generator, and a group of analysis tools.
- Algorithms underlying these softwares need to be designed for biological research. -- Cellware?
7. Conclusion

• Systems biology is an emerging field in biology aiming at system-level understanding of biological systems.
• Requires a range of new analysis techniques, measurements techniques, experimental methods, software tools, and concepts for looking at biological systems.
• There is still a long way to go before deep understanding of biological systems can be achieved.
• Author believes that systems biology will be the dominant paradigm in biology.
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--- The End! ---

Thank you for your attention.