582653 Computational Methods of Systems Biology

Lecturer: Juho rousu
Course assistant: Leena Salmela

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582653 Computational Methods of Systems Biology

- Lecturer: Adjunct professor Juho Rousu
- Course assistant: Dr. Leena Salmela
Course topics

- Graph theoretical analysis of networks (chapters 3-6)
  - Global properties
  - Centralities, motifs
  - Network clustering
- Analysis of biological networks (chapters 8-11)
  - Signal transduction & Gene regulation
  - Protein-protein interaction
  - Metabolic networks
  - Correlation networks
Prerequisites

We will assume that you know at least something about the following

- Introduction to bioinformatics: protein, cell
- Data structures: graphs and networks
- Elementary probability calculus
- Basic linear algebra / Matrix computation
Completing the course

- Exercises (3 sets): 30% of the grade
- Groupwork: (2 sets): 20% of the grade
- Course exam (28.2., 16.00-19.00 A111): 50% of the grade
- Grading: 50% of maximum points gives the grade 1/5, 80% gives 5/5
Lectures

Total of nine lectures:

- Week 1: Mon 17.1
- Week 2: Mon 24.1, Thu 27.1
- Week 3: Mon 3.2
- Week 4: Mon 7.2, Thu 10.2
- Week 5: Mon 14.2., Thu 17.2
- Week 6: Mon 24.2

Note: No lecture on Thursday 20.1 Read chapter 2 (Graph theory) on your own.
Exercises

- 3 sets of exercises during the course, total 30% of the course grade
- Reviewed in the exercise session (24.1, 7.2, 14.2)
- To be completed at home, returned in writing to Leena Salmela (leena.salmela@cs.helsinki.fi), prior to the review session
  - Note: exercise points will be based on the written answers
  - Don’t return your answers late if you want exercise points!
Groupwork

- 2 groupwork assignments, total 20% of the course grade
- Completed in groupwork sessions (31.1., 21.2), 10:15-11:45 + 12:30-14:00
Additional reading

- For more broad coverage of the course topics, you may look at the following books
- There books are not required for passing the course
What is systems biology?

Characterizations from the literature:

▶ “A new field of biology that aims at systems-level understanding of biological systems” (Kitano, 2001)

▶ “Systematic investigation of cells, organs and organisms and of cellular processes…” (Klipp et al. 2005)

▶ “The study of the interactions between the components of biological systems, and how these interactions give rise to the function and behavior of that system” (Wikipedia)
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What is systems biology?

An antithesis to 'traditional, reductionist biology':

▶ Reductionist biology: study of individual components (genes, proteins) of the system, aiming to in depth understanding of how a component behaves

▶ Systems biology: study of the interplay of a set of components in order to understand how they make up the systems behaviour
What is systems biology?

Reductionist and systems approaches need each other for best results:

- Component knowledge carries systems analysis: e.g., if functional annotation of a gene is incorrect, the model of a biological system including that gene is likely to give incorrect predictions as well.

- System analysis for finding crucial components: e.g., analysis of the biological system can reveal components that are the most promising targets for drugs.
Systems biology and genome-wide measurements; ’omics’

- Systems biology relies on genome-wide measurements
- Yield indirect information on the interactions between the components.
  - Genomics: DNA sequences
  - Transcriptomics: mRNA expression
  - Proteomics: protein concentrations
  - Metabolomics: small molecule concentrations
  - Fluxomics: enrichment of stable isotopes in metabolites
Examples of direct measurements of interactions:

- Chromatin immunoprecipitation, ChIP: (right) protein binding to promoter regions of genes ⇒ regulatory interactions

- Yeast-2-hybrid, Y2H (below): protein to protein binding ⇒ protein interactions
Networks and systems biology

- We will concentrate on modelling the interaction networks underlying the biological systems.
- Focus on network structure and how it qualitatively reflects in biological function.
- Quantitative modelling of dynamic, time dependent behaviour (typically: differential equation systems) is not part of the focus of the course.
Physical interactions

Physical interactions (typically: binding of molecules, forming a complex) between molecules:

- Protein and DNA: transcription factor proteins, epigenetic silencers, histones . . .
- Protein and RNA: ribosomes, transcriptase proteins, . . .
- Protein and Protein: protein complexes, (some) metabolic pathways, . . .
- Protein and Small molecule: enzymes, metabolic regulation, signaling, . . .
Abstract interactions

We will often look at abstract or logical interactions between the components, rather than mapping physical interactions:

- Gene regulatory network: 'gene A' negatively regulates 'gene B'
  - Biologically: transcription factor protein produced by A, binds to the promotor region of B, thus repressing the transcription of B

- Metabolite network: metabolite $M_1$ interacts with metabolite $M_3$
  - Biologically: protein C catalyzes a chemical reaction $M_1 + M_2 \implies M_3 + M_4$ between metabolites

- Correlated behavior: gene A has similar behaviour to gene B in a set of experiments—do not necessarily need to have direct regulatory relationship, although often they have
Aims:

- To elucidate the structure of networks, in terms of properties computable from the network:
  - degree distribution, connectedness, path length distributions
- Finding frequently occurring patterns or motif from the network:
  - Regulatory cascades, dense overlapping modules, ...

- Landmark paper of network analysis
- Showed that many natural networks (power grid, co-actor relations, neural network of C. elegans) have similar properties
  - Highly clustered, dense local subgraphs
  - Short average path length between and two nodes (hence the term "small world")
- Small-world networks since found in numerous other networks in biology and other fields of life.
Scale-free networks (Barabasi & Albert, 1999)

- Barabasi and Albert created a simple theoretical model for creating small-world networks
- The resulting network has few nodes with many neighbours and many nodes with few neighbours
- Scale-freeness refers to the mathematical law governing the degree distribution of the nodes

(a) Random network
(b) Scale-free network
Network motifs (Alon, 2005)

- Uri Alon and later many others have studied local subnetworks that can be found in biological networks.
- Network motifs are subnetworks that occur in the network much more often than expected by chance.
- Alon also offers functional explanations why the motifs are present.
Networks in biology

Types of biological networks of interest:

▶ Transcriptional regulation
▶ Signal transduction
▶ Protein-protein interactions
▶ Metabolism
Transcriptional regulation networks

- Often also called 'gene regulatory networks'
- Represented as graphs where nodes correspond to genes
- Directed edges $A \rightarrow B$ correspond to regulatory relations 'product of gene $A$ controls the transcription of gene $B$'
- Positive (enhancer) or negative (repressor) regulation may be indicated by signs or special arrowheads

(Lee et al., Science Vol. 298, 2002)
Transcriptional regulation networks

- In general, not very well known for most organisms
- Fragments of the complete network characterized
- Alon’s network motif work is one of the most notable approach to analyse transcriptional regulation networks

(Lee et al., Science Vol. 298, 2002)
Protein interaction networks

- Protein(-protein) interaction network models two kinds of interactions:
  - Proteins binding to each other and functioning as a complex
  - Proteins catalyzing biochemical reactions sharing a metabolite (enzyme network)
- Represented as undirected networks with proteins as nodes and the interactions as edges
Protein interaction networks

- PPI networks are very much tied to the measurement technology, different network obtained with different methods.
- Scale-free properties found in PPIs: network contains few 'hub' proteins with many neighbors.
Signal transduction networks

- Signal transduction networks model the communication systems by which the cell obtains information from the environment and from other cells (e.g. nutrients, hormones).

- Signal transduction involve heterogeneous interactions: protein-small molecule, protein-protein and protein-DNA.

(MAPK signaling pathway, Wikipedia Commons)
Metabolic networks

➤ Metabolism is responsible of providing the cell with energy and building blocks for cell growth

➤ Metabolic networks are composed of biochemical reactions, catalyzed by enzymes (proteins) and metabolites that participate in the reactions
Metabolic networks

Several representations used, for example

- **Hypergraph**: Metabolites as nodes, reactions as hyperedges (edges with more than two end-points)

- **Bipartite graph**: Reactions and metabolites as nodes, edges connect metabolites to reactions and vice versa

- **Metabolite graph**: metabolites as nodes, edges represent participation in reaction

E.Coli glycolysis, EMP database, www.empproject.com
Metabolic networks

- Study of enzyme kinetics pre-dates the discovery of DNA by a half a century
- Metabolic networks are better characterized for many organisms than other biological networks
- Wide array of dedicated network analysis tools has been developed, together with rigorous theory of metabolic systems
  - Stoichiometric models
  - Functional pathway discovery
  - Analysis of metabolic fluxes (pathway activity in steady state)
  - Metabolic control analysis for modelling metabolic regulation
Correlation networks

The biological networks described before

- some underlying physical interaction (protein-protein, protein-DNA, protein-metabolite) they aim to model
- there typically are dedicated measurements to uncover these interactions
- the networks have undergone significant manual curation
Correlation networks

- High-throughput ‘omics’ data gives a rise to another approach to network construction
- Correlation networks model statistical dependencies between any components (genes, proteins, metabolites)
- There may or may not be an underlying physical interaction behind the correlation
- For example: gene expression and metabolite concentration may be observed correlate in some set of experiments $\Rightarrow$ new previously unknown interaction?
Correlation networks

- Observe a set of components (genes, proteins, metabolites) in a set of experiments
- Construct a correlation matrix to list all pairwise correlations between components
- Graph is extract the by drawing and edge between components that have correlation higher than threshold
Next steps on the course...

- No lecture on Thursday 20.1. Read chapter 2 on your own. Copy to be found on the course homepage.
- Exercise set 1 is available on course web page as well. Exercises come from Chapter 2 of the book.
- Review session of exercises on Monday 24.1. from 10.15. Return answers to Leena on writing before that.
- Next lecture 24.1 at 12.15.