Analysis of Complex Systems

Lecture 1: Introduction

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www.dynamic-connectome.org

Preliminaries - 1

Lecturers

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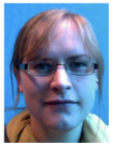
Practicals



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Preliminaries - 2

- Coursework (specification on NESS):
  - Network analysis 50% due Fri 2 Mar 5pm
  - Dynamical systems 50% due Fri 9 Mar 5pm

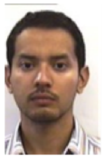
- Module contents:
  - Introductory lecture (today)
  - Network analysis (1st week and next Monday)
  - Dynamical systems (2nd week)
  - Dynamical systems (3rd week)

Preliminaries - 3

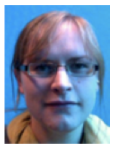
- Practical uses the widely used Matlab environment (installed on your cluster)
- To try at home:
  - Free licence from university IT service
  - Matlab student bundle
    (10 included toolboxes £55)
  - Matlab student version (£29)
  - free version Octave (not 100% compatible)

Team (current and alumni)

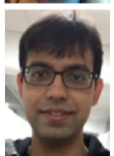
Luis Peraza
PostDoc



Frances Hutchings
PhD student



Nishant Sinha
PhD student

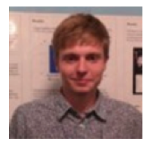


Sol Lim
PostDoc

Roman Bauer
Now faculty

Chris Hayward
PhD student

Joe Necus
PhD student



Peter Taylor
Now faculty

Yujiang Wang
Now faculty

Chris Papasavvas
PostDoc

Jinseop Kim
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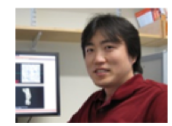

Michael Mackay
PhD student

Chris Thornton
PhD student

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Collaborators

Justin Dauwels

Sydney S. Cash

M. Brandon Westover

Funders

EPSRC Engineering and Physical Sciences Research Council

wellcome

BBSRC bioscience for the future

http://www.dynamic-connectome.org

@ConnectomeLab

Outline

- Complex Biological systems and selected problems
- Complex Systems approach
- Network analysis
- Dynamical systems

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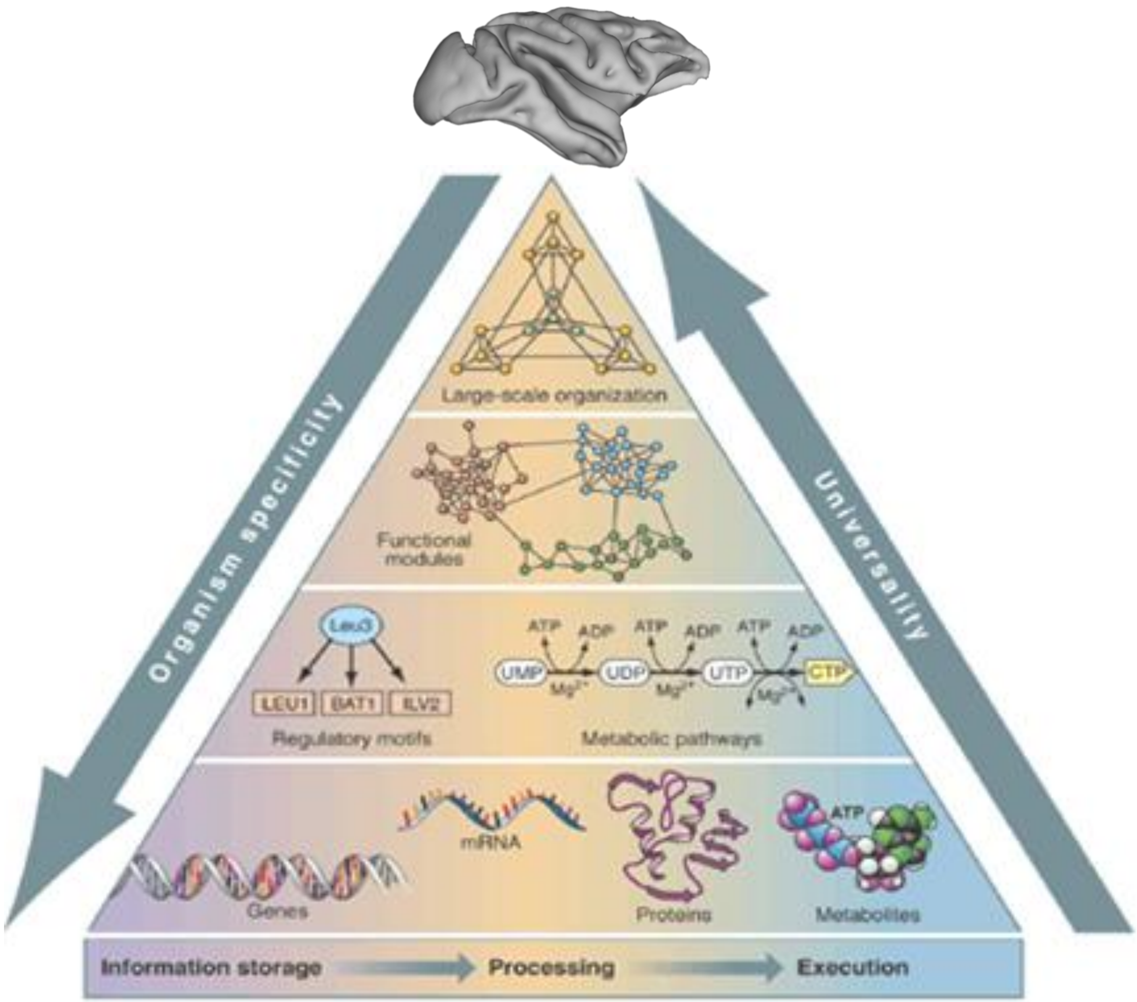
Complex Biological Systems

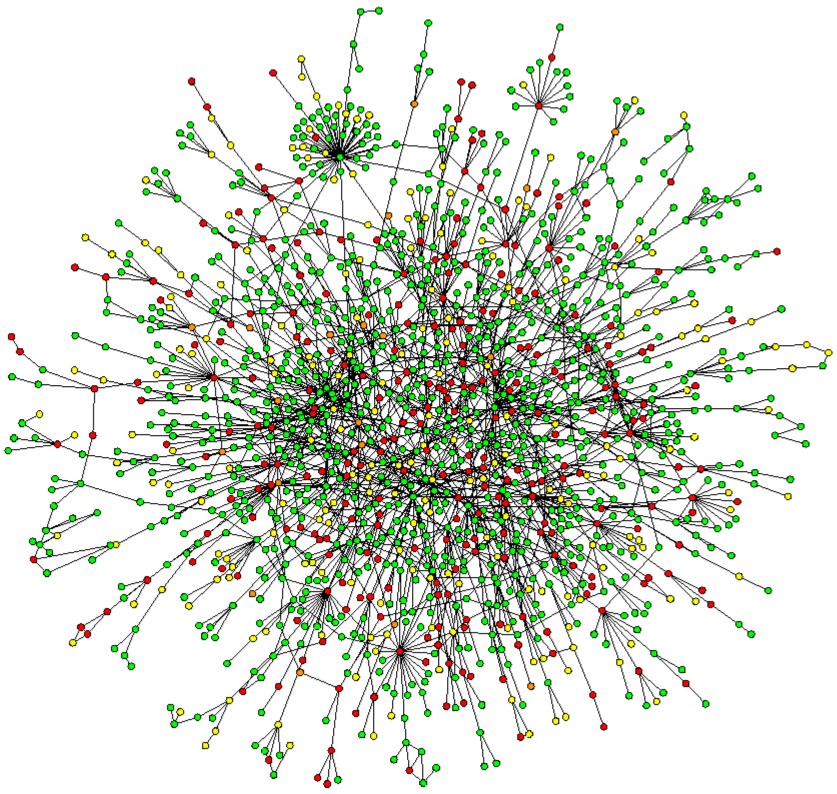


Life's Complexity Pyramid [Z. N. Oltvai and A.-L. Barabási, Science 298, 763 (2002)]

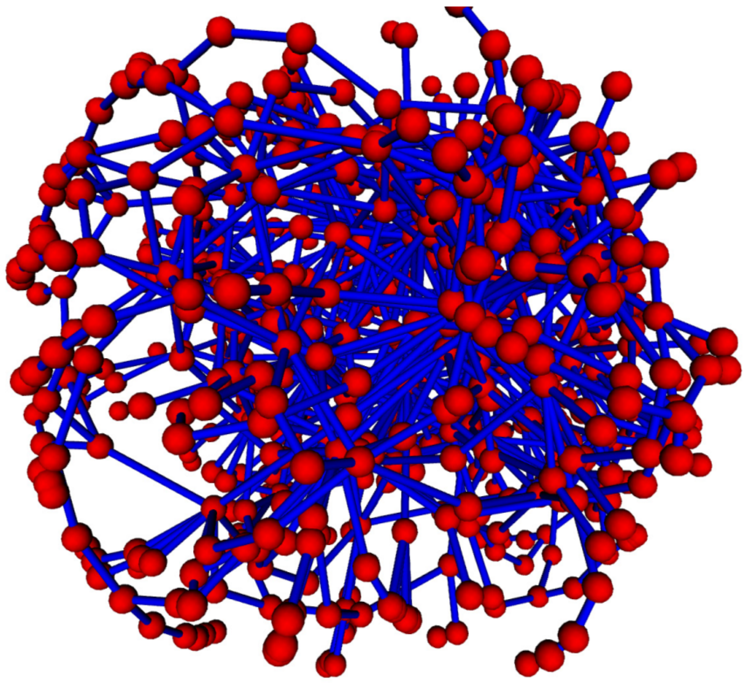
Cellular systems

- Interactions between proteins, lipids, metabolites

Yeast (*Saccharomyces cerevisiae*) protein-protein interaction network

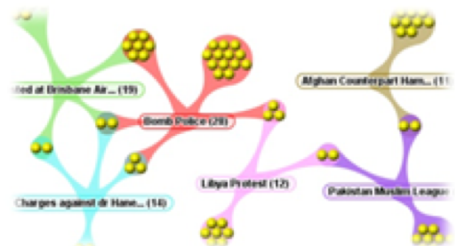


(Jeong et al., Science, 2000)



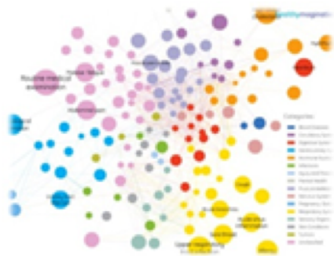
(Hilgetag & Kaiser, Bioforum, 2005)

Graph Analytics



Government/Security
- Patterns of Activity Analytics
- CyberThreat Discovery
- Tax Fraud Discovery
- Crime Prediction

...



Healthcare
- Personalized Treatment
- Fraud Detection
- Efficacy of Care
- Adverse Event Clustering
- Disease Prediction

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Energy/Resources
- Location Discovery
- Field Production Analysis
- Contingency Analysis
- Climate Modeling

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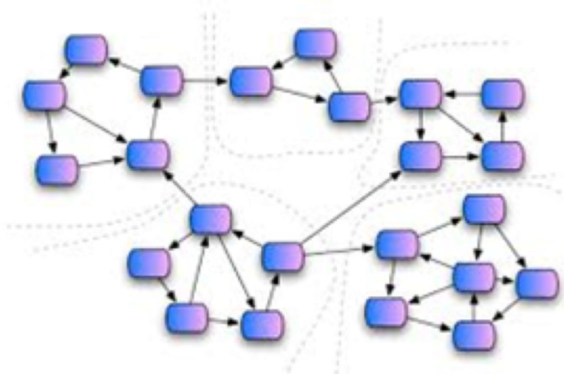

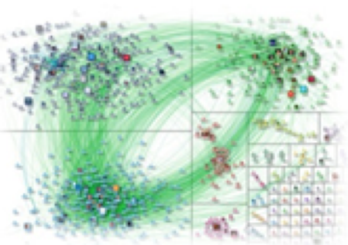

Telecom/Media
- Influencer Discovery
- Churn Analytics
- Behavior Analytics

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Life Sciences
- Drug Discovery
- Drug Repurposing
- Clinical Trial Mining

...

...

Financial Services
- Market Sensing
- News/Trading Analytics
- Counterparty/Risk
- Insider Threat
- AML/Compliance

Outline

- Complex Biological systems and selected problems
- **Complex Systems approach**
- Network analysis
- Dynamical systems

Systems

- System units and interactions between them
- E.g., gene regulation system: the units are genes, the interactions are the regulatory interactions
- E.g., protein interaction systems: the units are proteins, the interactions are the protein interactions

System evolution

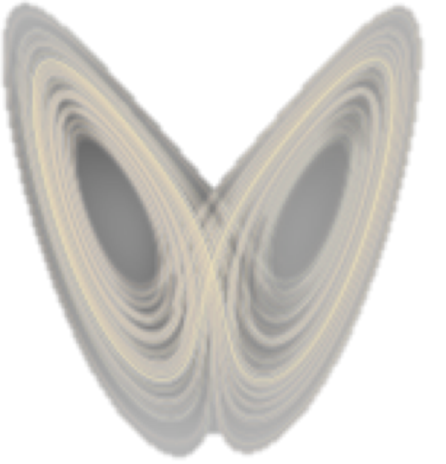
- System state: set of units and set of current interactions between units
- Rules: a set of active interactions is followed by another set of interactions, new units may become active depending on the system's state, some units may stop to be active

System analysis

- Description of the system *state*:
  current units and interactions
- Analysis of the system's *evolution*:
  rules of state change, description of the state changes for some limited or unlimited future

- What is a *complex* system?

Complex systems

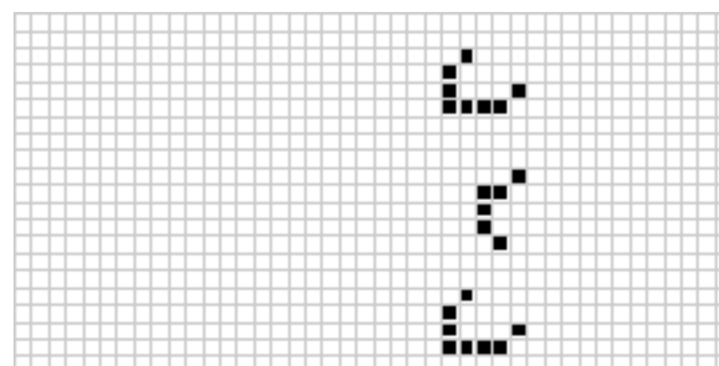


- A complex system is a system composed of interconnected parts that as a whole exhibit one or more properties not obvious from the properties of the individual parts (**emergence**)
- Not obvious: hard to predict or unpredictable (**dependence on initial conditions**)
- E.g., the evolution of a cell, stock market, weather forecast (Edward Lorenz)

Emergence

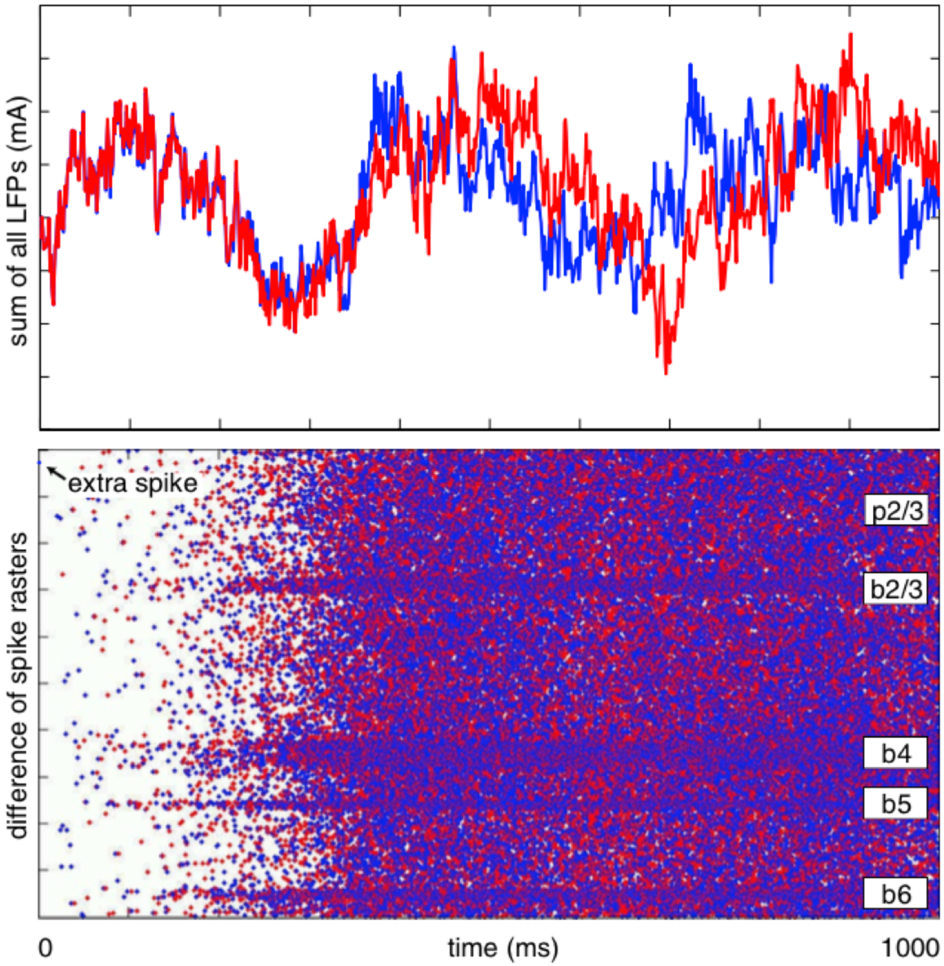
Conway's Game of Life (the origin of *cellular automata*)

1. Death: if the count is less than 2 or greater than 3, the current cell is switched off.
2. Survival: if (a) the count is exactly 2, or (b) the count is exactly 3 and the current cell is on, the current cell is left unchanged.
3. Birth: if the current cell is off and the count is exactly 3, the current cell is switched on.



Martin Gardner (1970). Mathematical Games – The fantastic combinations of John Conway's new solitaire game "life". Scientific American 223. pp. 120–123

Dependence on initial conditions



Simulation of 100,000 neurons:
Effect of one additional activation at the beginning of the simulation

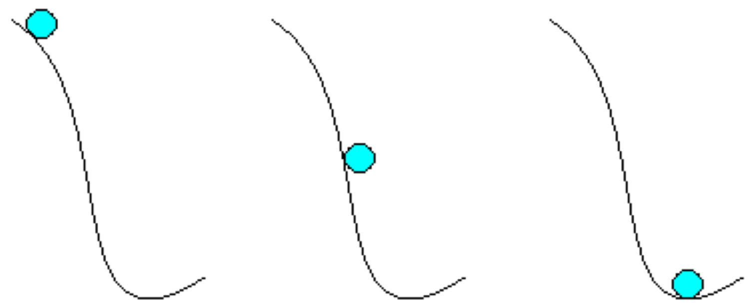
-> divergent system dynamics after half a second

A small change in initial conditions can lead to a massive change in the long-term behaviour of the system

Izhikevich & Edelman, PNAS, 2008

No analytic solutions for long-term behaviour

- The description of the evolution of the system cannot be summarized in a simple way
- Simple system: ball rolling down on a slope into a valley
- Complex system: double pendulum



Gene regulation systems

- Couple / several / many participant genes
- Possibly highly variable balance of product protein quantities
- → complex system

Protein-protein interaction systems

- Many units and interactions
- Hard to predict and describe the evolution of this system
- Hard to predict the effects of simple changes (e.g., blocking the activity of a couple of proteins)
- → complex system

Analysis methods

- Simplification and abstraction
- Capture key features of the system
- Analysing a model system
- Ignoring non-key features and factors (and hopefully not missing key features!)

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- **Network analysis**
- Dynamical systems

“Network Science”

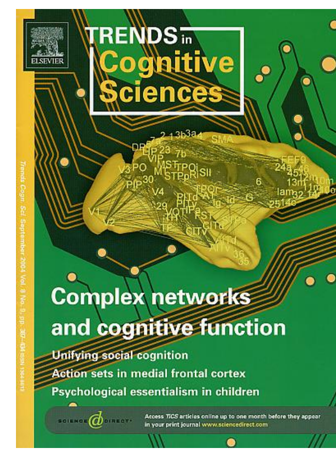
Rapidly expanding field:

Watts & Strogatz, *Nature* (June 1998)

Barabasi & Albert, *Science* (October 1999)

Modelling of SARS spreading over the airline network
(Hufnagel, *PNAS*, 2004)

Identity and Search in Social Networks
(Watts et al., *Science*, 2002)



The Large-Scale Organization of Metabolic Networks.
(Jeong et al., *Nature*, 2000)

Organisation and dynamics of neural systems
(Sporns, Chialvo, Kaiser, Hilgetag, Trends in Cognitive Sciences, 2004)

Why use network analysis?

- Many diseases are due to failures of multiple genes
→ single gene knockouts will not be sufficient

- Combinatorial explosion of possible gene knockout combinations (example for 1k genes):

  single gene knockout: $1000 = 10^3$
  double gene knockout: $1000 * 999 \approx 10^6$
  triple gene knockout: $1000 * 999 * 998 \approx 10^9$
  …

- Network analysis can help to predict combinations which are more likely to lead to performance changes
→ reduced costs for drug discovery (hopefully!)

Outline

- Complex Biological systems and selected problems
- Complex Systems approach
- Network analysis
- **Dynamical systems**

Dynamical systems

- E.g., gene regulatory networks
- Formulation as a set of interdependent differential equations
- $dX / dt = a * X + b * Y$
- $dY / dt = c * X + d * Y$
- X and Y are quantities of proteins

Why use dynamical systems theory?

- Theoretically feasible:
  many parameters for computer simulations can now be measured (e.g. gene expression or protein interaction data)
- Computationally feasible:
  Increase in processing power
  (quad-core microchips today; 100-core in 2010)
- Economically desirable:
  In silico experiments are cheaper than wet lab experiments

  → **simulation-based science** (e.g. e-cell project)

Summary - 1

- The state of systems (Cells, genome, organisms) is given by the set of units or nodes (e.g. proteins) and interactions or edges (e.g. protein-protein interaction) between units
- The state of the system evolves over time (e.g. gene expression or metabolite concentration changes) and can lead to observable changes in behaviour, e.g. anaerobic metabolism → aerobic metabolism (not all state changes lead to large-scale changes!)

Summary - 2

- Problem: describe the evolution of protein quantities knowing gene regulatory networks
- Problem: find key functional proteins to damage or restore cell functionality

- Complex systems
- Analysis of complex systems
  - Graph structure analysis
  - Dynamical systems analysis

Q&A - 1

1. What could be nodes or edges for the interaction between cells?
2. Is it true that cell behaviour can be seen as direct interactions between nucleic acids ?
3. Is it true that proteins are encoded by genes ?
4. Is it true that the evolution of a gene regulatory network is relatively simple and can be described easily ?

Q&A - 2

5. Is it true that a way to find antibiotic targets is to analyse the protein interaction network of the bacteria ?
6. Is it true that the dynamical systems analysis can be applied to the analysis of protein interaction networks ?
7. Is it true that graph models use nodes and edges to describe a system ?