Systems Biology: An Overview

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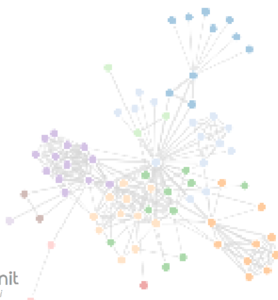
The Theseus' Paradox: The Ship of Theseus

Plutarch - AD 46

If you replace the planks of a boat, is it still the same boat?

Let's Take Some Planks



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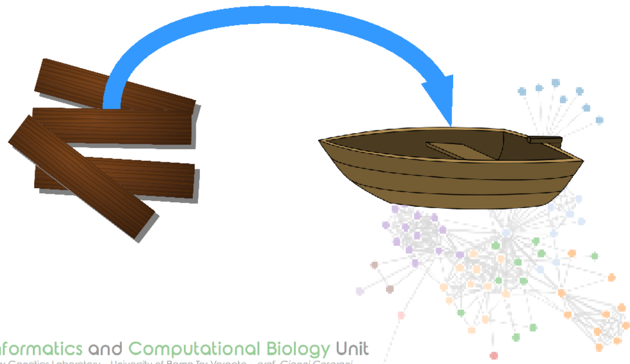
Let's Build a Boat



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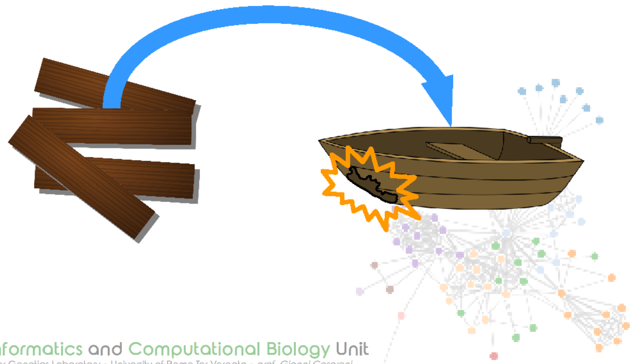
We Got Hit!



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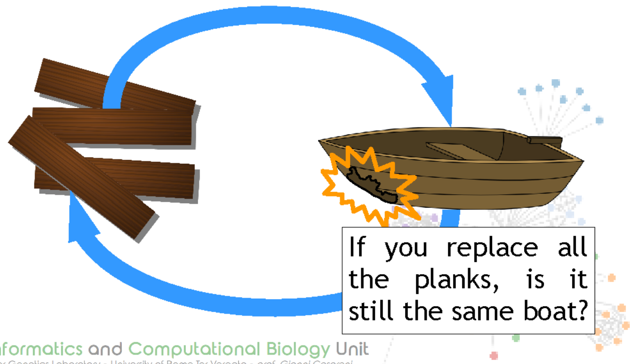
OK, Let's Repair Our Boat



If you replace all the planks, is it still the same boat?

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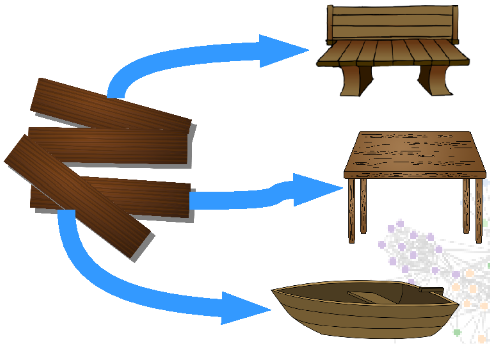
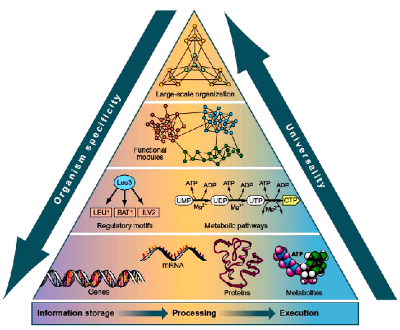
What's the Boat Then? Emergence



Emergence

- Some characteristics emerge from the cooperation of single entities
- In general, the properties of a complex system that are not detectable from the study of single entities are called "**Emergent Properties**"
- Emergent properties are NOT the summations of the properties of the system's entities
- (Biology) If we replace molecules and other entities over time, we still obtain the same cell. The same molecules or the same proteins can be in different cells.

Systems Biology



Oltvai & Barabasi, Life's complexity pyramid, *Science* 2002

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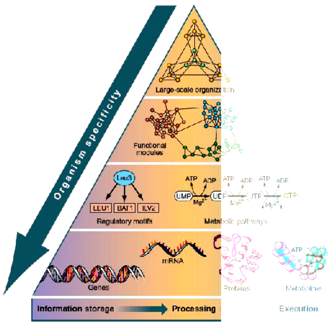

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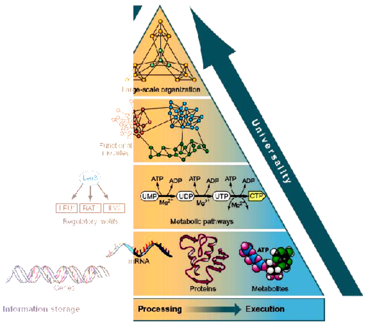

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Systems Biology and Emergence

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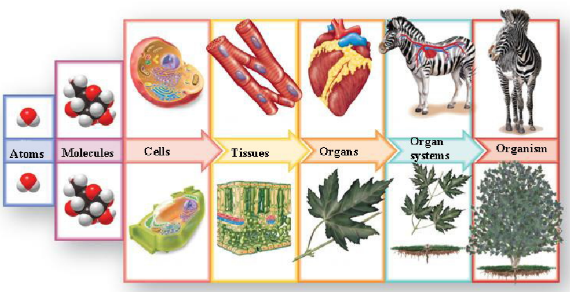
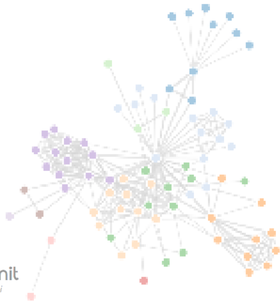


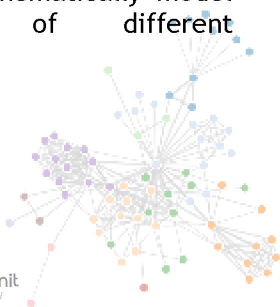
Systems Biology

• Systems Biology...



Systems Biology

• Systems Biology relies on **Systems Theory** to computationally and mathematically model **biological systems** of different complexities.



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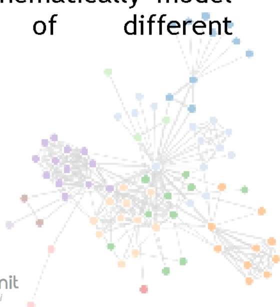
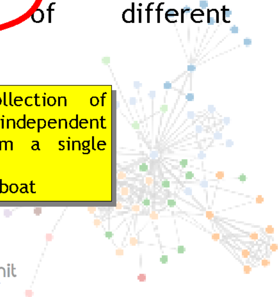


Systems Biology

- Systems Biology relies on Systems **Theory** to computationally and mathematically model **biological systems** of different complexities.

A system is a collection of interactions and/or independent components that form a single object.
E.g.: A cell, a tissue, a boat



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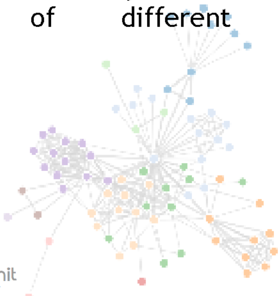
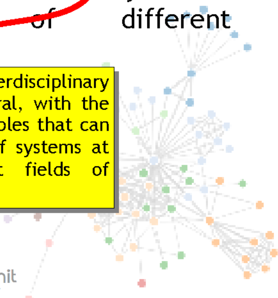


Systems Biology

- Systems Biology relies on **Systems Theory** to computationally and mathematically model **biological systems** of different complexities.

Systems theory is the interdisciplinary study of systems in general, with the aim to clarify those principles that can be applied to all types of systems at any levels in different fields of research.



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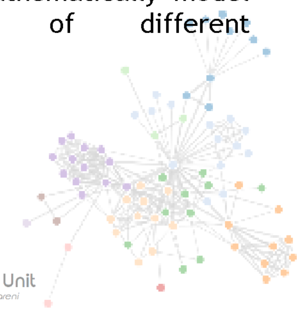

Systems Biology

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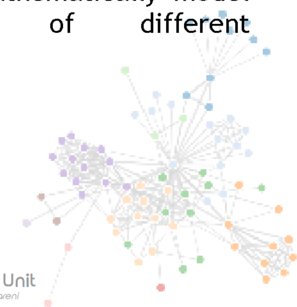
A biological system is a complex network of biological entities.



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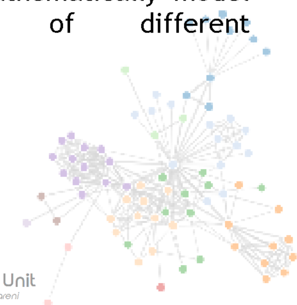


Systems Biology

- Systems Biology relies on **Systems Theory** to computationally and mathematically model **biological systems** of different complexities.

A biological system is a complex network of biological entities.

In the context of network theory, a complex network is a graph (network) with non-trivial topological features - features that do not occur in simple networks as lattices or random graphs but often occur in graphs that represent real systems. A complex network typically has many vertices (nodes) and, most importantly, many connections (edges)

Systems Biology

- Systems Biology relies on **Systems Theory** to computationally and mathematically model **biological systems** of different complexities.

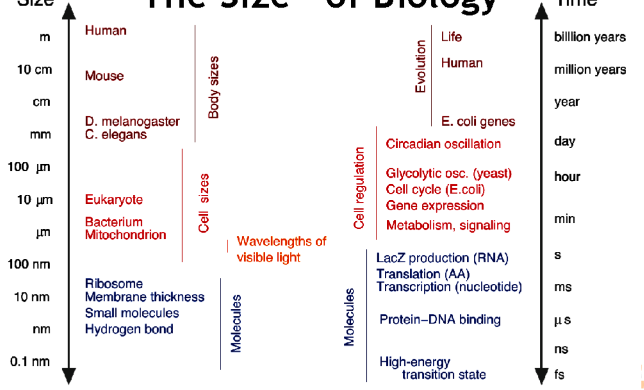
- It focuses on…

Systems Biology

- Systems Biology relies on **Systems Theory** to computationally and mathematically model **biological systems** of different complexities.

- It focuses on the development and use of algorithms, data structures, visualization, and in general on methods to mimic biological behaviours on a computer.

“The Size” of Biology



What is a Model?

A **model** is an object or concept that is used to represent something else. It is reality scaled down and converted to a form we can comprehend.

A **mathematical model** is a model whose parts are mathematical concepts, such as constants, variables, functions, equations, inequalities, etc.

Walter J. Meyer

Modelling and its Benefits

In Systems Biology we can define a model as an abstract representation of dependent or independent entities such as DNA and proteins that explain certain characteristics or a particular phenomenon.

Modelling and computer simulations help us understanding the nature and dynamics of processes and to predict future developments.

Mathematical Model

- It is a **description of a system** that uses concepts and **mathematical languages**. It consists of **relationships** and **variables**

Discrete Models

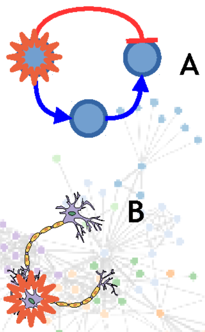
Systems that exhibit switch-like behaviour

Two examples:

A) Gene regulatory networks, in which at a given moment a gene can be expressed or not expressed and can influence the expression of other genes

B) Neuronal networks, in which a neuron can be either active or at rest

These systems can be analysed with the Boolean models.

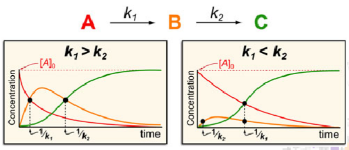


Mathematical Model

- It is a **description of a system** that uses concepts and **mathematical languages**. It consists of **relationships** and **variables**
- A **discrete model** treats as objects and states as fixed units, such as particles in a molecular model.

Continuous Models

Systems that vary in time. We want to study how rates influence the system we are studying. Biochemical reactions in general exhibit continuous behaviours: Michaelis-Menten, Mass-Action etc...



Mathematical Model

- It is a **description of a system** that uses concepts and **mathematical languages**. It consists of **relationships** and **variables**
- A **discrete model** treats as objects and states as fixed units, such as particles in a molecular model.
- A **continuous model** represents objects and states as varying units, like the temperature variation in a room.

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Two Ways of Modelling

Top-Down

1)Begin with data set (often very large scale)
2)Use statistical methods to find patterns in the data.
3)Generate predictions based on the structure within the data

Examples

- ???

Bottom-Up

1)Begin with hypothesis of biological mechanism.
2)Write down equations describing how components interact.
3)Run simulations to generate predictions.

Examples

- ???

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Two Ways of Modelling

Top-Down

1) Begin with data set (often very large scale)
2) Use statistical methods to find patterns in the data.
3) Generate predictions based on the structure within the data

Examples

- Network analysis
- Clustering
- Principal components
- Partial least-squares regression
- Gene set enrichment

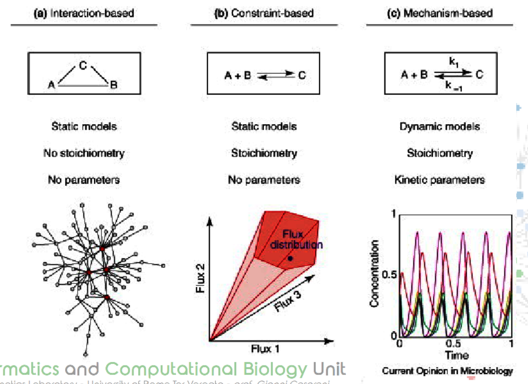
Bottom-Up

1) Begin with hypothesis of biological mechanism.
2) Write down equations describing how components interact.
3) Run simulations to generate predictions.

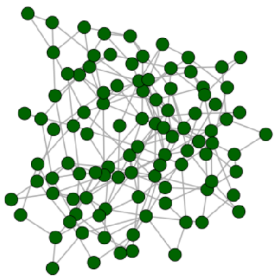
Examples

- Ordinary differential equations
- Dynamical systems
- Parameter estimation
- Partial differential equations
- Stochastic models

Approaches to the Mathematical Modelling of Cellular Networks



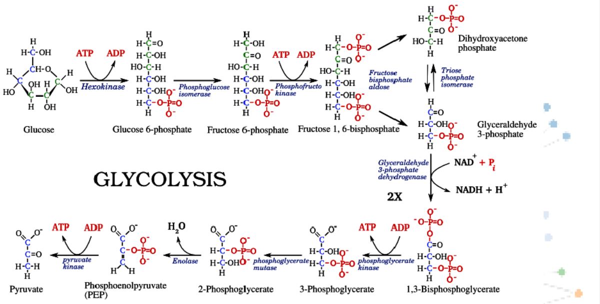
Interaction-Based



Recalling previous lecture

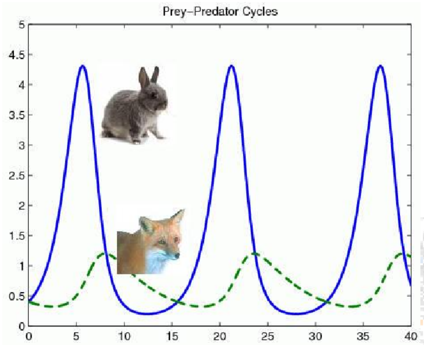
- Network Classification
- Degree distribution
- Central nodes
- Central interactions
- Clusters => Functions
- …

Constraint-Based



Mechanism-Based

A simple Prey-Predator Model



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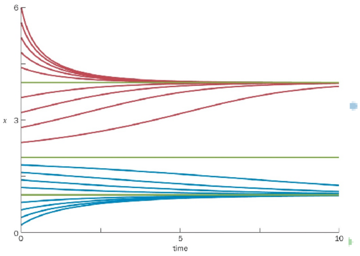
Steady-State Analysis

$$dx/dt = -0.1(x-1)(x-2)(x-4)$$

x	dx/dt
0	0,8
0,2	0,5472
0,4	0,3456
0,6	0,1904
0,8	0,0768
1	0
1,2	-0,0448
1,4	-0,0624
1,6	-0,0576
1,8	-0,0352
2	0



For x = 2 the derivative is 0 thus the slope of the curve is 0.

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Analysing a Model

- Steady-state analysis
  A condition in which none of the variables change in number, amount, or concentration. This does not mean that nothing is happening but it rather refers to thermodynamic equilibrium.
- Stability analysis
  Stability analysis assesses the degree to which a system can tolerate perturbations. E.g.: the system will returns to a steady state after a small perturbation.
- Parameter sensitivity
  How much a system is affected by small alterations in variables and parameter.

Stability Analysis

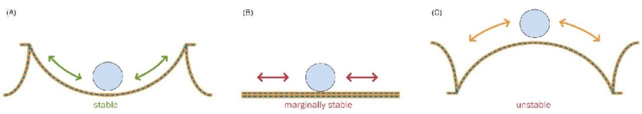

Figure 4.15 A First Course in Systems Biology (© Garland Science 2013)

Stability analysis assesses the degree to which a system can tolerate perturbations.

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Parameter Sensitivity

Sensitivity analysis is a crucial component of any systems analysis, because it can quickly show if a model is wrong.

Good, robust models usually have low sensitivities, which means that they are quite tolerant to small, persistent alterations, in which a parameter remains altered.

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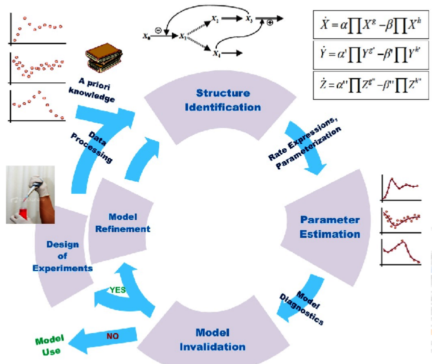
Systems Biology is Modelling



Conclusions

- Systems Thinking, the Ship of Theseus
- Emergence
- Reductionism vs. Universality
- Systems Biology (Systems Theory)
- Different time and size scales
- Modelling
  - Discrete vs. Continuous
  - Top-Down vs. Bottom-Up
- Approaches
  - Interactions, constraints, reactions
- Analysis
  - Steady-States, Stability, Parameter Sensitivity