COMPUTATIONAL SYSTEMS BIOLOGY

Descriptive details concerning the subject:

· Code : CSB
· Type of subject: Optional
· Credits: 5
· ECTS: 5
· Total hours: 125.0
· Course: 1r. curs
· Term: 3rd (Spring 2008)
· Coordination: Marta Cascante Serratosa
· Department: UB
· Room: Mar 60.122
· Timing: See Calendar and map 2008-2009

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Subject presentation:

· **Presentation:**

The living body is composed of numerous subsystems, large and small, by which the flows of energy, material and information are controlled. During embryogenesis a multicellular organism emerges from a single cell which divides a finite number of times, in a spatially and temporally ordered way, to generate an ensemble of different cells. The aim of developmental biology is to understand how this occurs. -What are the elements that define the different kind of cells? -Where do the instructions for the processes lie? - What is the language of those instructions? Here we shall approach development from a standpoint on which the molecules and the genes, rather than the organism, take centre stage. Therefore, it is misleading to think of the genome as embodying the *blueprint* of an organism. The sequence of the genome contains some of the information to build an organism but this information is very limited. Genes encode proteins and carry information that determines when and where these proteins are made. However, genes do not contain the information that determines how the proteins will assemble, or when, or where and how they will be active. These pieces of information lie in the proteins themselves, which assemble into functional and regulatory networks. This is a hierarchical system involving subsystems such as metabolism, transcriptional control, signal transduction, the cell cycle, and apoptosis at the cell level, though all of these in turn are implemented as subsystems of interacting molecules. At a higher level, populations of cells are the subsystems of various physiological and pathological systems, organ systems, up to the body level.

Traditional study of biological systems requires reductive methods and have generate huge quantities of data in the last decades. In parallel with the data-driven research approach that focuses on speedy handling and analyzing of the huge amount of data, a new approach called 'model driven research' is gradually gaining power. Model-driven research takes the approach that sets

up a biological model by combining the knowledge of the system with related data and simulates the behavior of the system in order to understand the biological mechanism of the system. It is simply called, "Systems Biology". Systems biology aims to model and simulate the various subsystems and their interactions with one another, for the better understanding of life mechanisms. Biology (including molecular biology) has relied on qualitative and verbal modes of reasoning and explanation, but the human brain cannot be relied upon to model such complex systems intuitively.

Computational systems biology demands that all premises in the explanation are made explicit, modes of interaction of components are given a functional form, and the evolution of the system behavior simulated on this basis. Computational systems biology, defined in Wikipedia as the algorithm and application development arm of systems biology**, is also directly associated with** bioinformatics **and** computational biology **and aims to develop and use** algorithms**,** databases **and communication tools to facilitate the integration of large quantities of biological data with the goal of modelling dynamic characteristics of the biological systems . Computational systems biology projects are going on in different laboratories around the world and models can include for example steady-state metabolic flux or the time-dependent response of signaling networks. Algorithmic methods used in these projects require basic concepts on topics such as** optimization**,** network analysis**,** graph theory**,** linear programming**,** grid computing**,** flux balance analysis**,** sensitivity analysis**,** dynamic modeling**, and others that will be presented in the different lectures in this course .**

Many important software projects in computational systems biology are being developed two important markup languages for systems biology are the Systems Biology Markup Language (SBML) and CellML.

In previous courses of this Master several simulation techniques have been already introduced. In this Computer Systems Biology course knowledge on simulation techniques will be expanded and applied to the modelling of biological systems.

The subject is centred in the understanding the translation of a biological problem into a mathematical frame to construct models of i.e. metabolic or signalling networks that permit to answer relevant biological and biomedical questions. Modelling of networks of cellular processes will permit to understand its regulation and to design new therapeutical strategies in multifactorial complex diseases as cancer.

As this is a completely incremental subject, the student is advised of the need of strong interaction with the lecturers and the need of keeping the class material up to date.

· Methodological focus of the subject:

The subject focuses on theoretical classes and hands on work involving the use of simple mathematical computer languages for modelling gene regulatory networks, metabolic pathways and signalling cascades. For Block 2 tyhe students will make use of the ByoDyn web interface (http://cbbl.imim.es/byodyn-web)

also they will need to have installed Gepasi (alternatively Copasi if they master) that they can download from http://www.gepasi.org/gepasi.html

For network analyses, installation of Cytoscape (http://www.cytoscape.org) and Pajek (http://vlado.fmf.uni-lj.si/pub/networks/pajek) are required.

The theoretical classes and hands on sessions to construct models of different intracellular processes networks will be complemented by:

- exercises, individual and for particular chapters/blocks of the course
- Practical tests based on solve exercises related with the different models constructed

Prerequisites in order to follow the itinerary:

· Prerequisites:

This subject does not have any pre-requisite, although previous programming knowledge and notions of basic maths and basic biology and biochemistry are expected

Competences to be attained in the subject

General competences:

Instrumentals:

1. Proficient reading/writing/listening scientific English related to the subject
2. Expertise in formalising in mathematical terms a verbal model in GRN
3. Ability to implement in a computer programme simple dynamical models
4. Knowledge of software for modelling biochemical networks
5. Basic concepts on enzyme kinetics
6. Elements of biology and biochemistry: basic concepts on biochemical network, basic concepts on enzyme kinetics and main metabolic pathways i.e. glycolysis, krebs cycle, pentose phosphate pathway, gluconeogenesis and glycogen metabolism, basic concepts on signalling cascades, basic concepts on gene regulation and expression.
7. Concepts of gene regulation in time and space.

Interpersonal:

1. Group work
2. Ability to solve by yourself a given problem

Systemic:

1. Analysis and synthesis abilities
2. Ability to search for information

Specific:
1. The system's concept. To understand the concept of biological networks. Levels of organisation and description of networks.
2. To know different modes of gene regulation and how cells acquire different identities (fates). Classical concepts in developmental biology.
3. To understand and implement the concept of positive and negative interaction between genes and understand the concept of gene regulatory networks.
4. To understand the different types of dynamical behaviour exhibit by biological networks.
5. To get familiar with the most common mathematical techniques used to analyse the dynamical features of simple gene regulatory networks.
6. To get basic user knowledge of some of the most popular systems biology software tools.
7. To know the basic concepts on enzyme and enzyme kinetics (Michaelis Menten equation).
8. To know basic concepts on metabolism, and main metabolic pathways (i.e. glycolysis, gluconeogenesis, Krebs cycle, pentose phosphate pathways, glycogen metabolism).
9. To understand basic concepts of metabolic network regulation and control.

Learning aims:
· Aims:
To get the ability to understand a biological system of biomedical interest, to transform into mathematical language and to integrate different types of experimental data to validate the model and make predictions.

Evaluation

General assessment criteria:
The evaluation will consists in four parts, with percentages of the total grade indicated in the following list:
1. Work performed in the hands on session, capacity in answer questions done for teachers and lecturers during the theoretical and hands on session, degree of participation in the classes asking questions and participating in scientific discussions and capacity to solve the exercises proposed. (20% of the total grade)
2. Evaluation of the understanding of topological features in biological networks (15% of the total grade)
3. Evaluation of the understanding of gene and/or protein interaction networks (25% of the total grade)
4. Evaluation of the understanding of enzyme kinetics, control and regulation of metabolic networks (40% of the total grade)

competency evaluation	Attainment indicator	Assessment procedure	Scheduling
Instrumentals			
1. Proficient reading/writing/listening scientific English related to the subject	Comprehension of papers related to the subject	Paper reading and oral discussion	Progressive
2. Expertise in formalising in mathematical terms a verbal model in GRN	Ability to follow the class and exercises without any basic handicap	Implicit in the solving of the proposed exercises	Progressive
3. Ability to implement in a computer programme simple dynamical models	High quality presentation of exercises	Implicit in exercises presentation	Progressive
4. Knowledge of software for	Ability to understand	Implicit in hands on	Progressive

	algorithms	transforming biological systems knowledge in mathematical language	
5. Basic concepts on enzyme kinetics	Ability to understand and basic concepts on enzyme kinetics and to use for modelling metabolic networks	Implicit in hands on sessions transforming biological systems knowledge in mathematical language	Progressive
6. Elements of biology and biochemistry: basic concepts on biochemical network, basic concepts on enzyme kinetics and main metabolic pathways i.e. glycolysis, krebs cycle, pentose phosphate pathway, gluconeogenesis and glycogen metabolism, basic concepts on signalling cascades, basic concepts on gene regulation and expression.	Ability to understand chemical concepts in the simulations performed	A set of pencil and paper and practical exercises	exercises taken during the course and practical tests.
7. Concepts of gene regulation in time and space.	Ability to understand how gene expression is regulated at the transcriptional level in different cells and along development proceeds	Implicit in the paper reading given to students	progressive
Interpersonal: 1. Group work	Ability to do team work during hands on sessions	Implicit in the proposed work in hands on sessions	Progressive
2. Ability to solve by yourself a given problem	Correct answer of set of pen and pencil exercises and practical tests	Implicit in exercises and practical tests	Progressive
Systemic: 1. Analysis and synthesis abilities	Enzyme kinetics and sensitivity analysis	Implicit in proposed exercises and tests	Progressive
2. Ability to search for information	Complete exercises proposed	Implicit in exercises proposed	End of term
Specific: 1. The system's concept. To understand the concept of biological networks. Levels of organisation and description of networks.			
2. To know different modes of gene regulation and how cells acquire different identities (fates). Classical concepts in developmental biology.	Undertand the concept of cell fate, patterning, gene regulation in time and space, enhancers	Paper reading and discussion	Progressive
3. To understand and implement the concept of positive and negative interaction between genes and understand the concept of gene regulatory networks.	How genes act sequntially and how to built a geentic network through experim experimental data	Discussion and problem exercice	Progressive
4. To understand the different types of dynamical behaviour exhibit			

5. To get familiar with the most common mathematical techniques used to analyse the dynamical features of simple gene regulatory networks.			
6. To get basic user knowledge of some of the most popular systems biology software tools.	To know the basic utilities of some of the the tools available and to understand that modelling at different levels require different types of tools.	Hands-on tutorials and practical assignments	Progressive
7. To know the basic concepts on enzyme and enzyme kinetics (Michaelis Menten equation).	To be able to derive a kinetic equation and to be able to assign appropriate kinetic equation to differnt enzyme catalyzed reactions.	Hands-on tutorials and practical assignments	Progressive
8. To know basic concepts on metabolism, and main metabolic pathways (i.e. glycolysis, gluconeogenesis, Krebs cycle, pentose phosphate pathways, glycogen metabolism).	To be able to construct a kinetic model of a metabolic network using appropriate software (i.e. gepasi or copasi) using experimental data on kinetics and metabolomics.	Hands-on tutorials and practical assignments	Progressive
9.To understand basic concepts of metabolic network regulation and control.	To be able to analyze control distribution in a metabolic network and to be able to discuss the different patterns of regulation of a metabolic network.	Hands-on tutorials and practical assignments	Progressive

Contents
Block 1: Network Biology

Concepts	Procedures	Attitudes
1. The network abstraction. Basic definitions and issues in converting empirical data into networks (thresholding, time windows, etc.)	1. Theoretical with concrete examples related to biology.	
2. Basic statistical properties of networks (average path length, clustering, degree distribution) and elementary models of them (Erdos-Renyi, Watts-Strogatz and Barabasi-Albert networks).	2. Theoretical classes and hands-on work involving the use of Pajek for network statistics and simulation packages to generate the networks.	To be able to understand the concept of network and its properties (structure, dynamics, regulation, robustness etc...)

robustness. Comparison of scale-free and exponential random networks. Robust networks from optimisation.	hands-on work, involving network statistics in Pajek and experiments using the simulator.
4. Dynamic processes on networks (cf. cascades on networks). Basic models and lessons from them.	4. Theoretical classes and hands on experiments with simulation software.
5. Dynamic networks. Processes that result in networks. The consequences of link-maintenance costs. Advanced network concepts.	5. Theoretical classes and hands on experiments with simulation software.

Block 2: Computational Systems Biology approach to modelling gene regulatory networks

Concepts	Procedures	Attitudes
To understand the basic rules of how an organism develops and cells acquire different identities depending on their combinatorial expression of subsets of genes. Concepts of cell specification, patterning, regulation of gene expression, principles of gene regulatory networks (GRN). To get the molecular structure of cis-elements and learn how from the information encoded in the promoters a gene regulatory network can be built.	Theoretical classes with examples plus an assignment for students involving the comprehension of a very recent paper on GRN in Drosophila	To be able to understand the relevant developmental problems addressed in systems biology
To translate a biological problem into a mathematical frame for solving questions related to the operation of gene networks in living processes. Concepts on dynamical behaviour of gene circuits: switches, multistability, saddle points, feedback regulation, sensitivity to kinetic parameters, robustness, resilent systems.	Theoretical classes and hands on work involving the use of simple mathematical computer languages.	To be able to formulate gene interaction information in a mathematical language. To be able to determine the possible dynamical behaviours displayed by the system. To be familiar with the mathematical techniques to analyse the dynamical features of a regulatory system.
To build intermediate complex regulatory networks that model pattern formation in organisms during development. Description of several levels of biochemical detail for the explanation of pattern formation. Concept of lateral inhibition, boundary	Hands on lecture using systems biology software.	To be able to understand different formalisms that drive to lateral inhibition and boundary formation during development.

formation, Notch-Delta pathway.

Block 3: Computational Systems Biology approach to modelling metabolic networks

Concepts	Procedures	Attitudes
To understand basic concepts on enzymes: catalyst, protein with a catalytical center, acceleration compared to non-catalysed reaction, thermodynamics, type of kinetics, deterministic kinetic modelling of biochemical reactions, regulation of enzyme activity. To understand basic concepts on biochemical reaction and metabolic networks and to translate a metabolic network diagram into a mathematical frame for solving questions related to operation of metabolic networks in health and pathological states:Substrates, products, stoichiometric analysis, network properties, time course, equations describing the system, steady state, Control and regulation of metabolism. Metabolic flux analysis. Targeting pathological states of metabolic networks in multifactorial disease like cancer.	Theoretical classes and hands on work involving the use of simple mathematical computer languages and systems biology appropriate software. Application of the theoretical concepts to solve exercises on enzyme kinetics and metabolic network control: prediction of drug effects on the network and design of strategies for metabolic interventions with drugs.	To be able to formulate metabolic information in a mathematical language. To be able to identify control distribution in a metabolic network and to plan rational drug interventions to alter metabolic pathways. To be able to integrate -omics data in models to determine the dynamical flux distribution in the metabolic network under different environmental conditions, pathological states and as response to drug interventions or enzyme malfunctioning.