Syllabus

Subject

Subject / Group 11010 - Systems Biology / 1
Degree Master's in Physics of Complex Systems
Credits 3
Period 2nd semester
Language of instruction English

Professors

Lecturers	Office hours for students					
	Starting time	Finishing time	Day	Start date	End date	Office / Building
Tobias Galla	15:00	16:00	Tuesday	18/02/2020	22/05/2020	IFISC 103
Manuel Alberto Matias Muriel	14:00	15:00	Tuesday	01/10/2019	29/05/2020	Desp. 211 (Edif. Instituts Universitaris)

Context

INSTRUCTORS

Manuel Matias holds PhDs in Chemistry (1990) and Physics (1997) and has five 6-year terms ("sexenios") recognized by ANEP. Although his recent research is in Nonlinear Dynamics (Bifurcation Theory, Synchronization, ...), in the last years he has become interested in the quantitative description of some collective phenomena in Cell Biology from the viewpoint of Systems Biology.

Tobias Galla completed his undergraduate degree in Münster (Germany) in 1999, and his DPhil at the University of Oxford (UK) in 2004. He has then worked at the International Centre for Theoretical Physics in Trieste (2004-2007), Italy and at the University of Manchester, UK, first as a Lecturer, then Senior Lecturer, then Reader. His research interests include stochastic and disordered systems, in particular applications to questions in evolutionary dynamics, game theory, and gene regulatory systems.

COURSE
This is an optional course of the Structural Module of the master of Physics of Complex Systems. The main objective of the course is to highlight general principles of molecular and cellular biology from the viewpoint of physics and complex systems science. The course will provide tools for the mathematical and computational study of emergence of system-wide phenomena in biological systems from the interaction of the microscopic constituents.

How does life emerge from the myriads of interactions between molecules? Why are biological systems so resilient and versatile? What are the main building blocks in the control systems of life? While the study of molecular processes has advanced biology at an exhilarating pace over the last 50 years, it is very hard to answer any of these questions from looking at processes at the molecular level alone. In fact, the vast majority of cellular processes do not result from the simple juxtaposition of independent components of the cell’s machinery (e.g. individual genes or proteins), but on the interplay between multiple elements working together as a system. Thus, a system-level approach is necessary, requiring an understanding of the broader structure of biological systems, their common building blocks and of the general principles on which they are

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built. The importance of taking a system-level approach is amplified by the vast amount of biological data that is now available, for example from high-throughput gene sequencing. The data is so vast that it is sometimes hard to see the forest from the trees; making sense of the incredible resource of biological data requires an integrated approach,beyond looking at biological processes at the molecular level.

Approaching biology from the systems perspective reveals several common features: Regulatory circuits perform information processing tasks. Living systems adjust their behaviour by processing incoming stimuli and taking decisions in response. They are robust to changing environmental conditions. Biological systems can adapt to external stresses. They are often relatively insensitive to parameter changes, and they show so-called `graceful degradation', that is to say the system's function only degrades slowly under damage, instead of immediate catastrophic failure. Biological systems also maximize the balance between cost and benefit; this can be interpreted as fitness optimised by evolution.

How does biology achieves this? None of these properties of biological systems cannot be understood from only looking at their features at the molecular level. They are system-wide properties emerging from the interaction of the constituents. From a physics perspective, systems biology amounts to constructing a macro-description of a system from the microscopic processes of the constituents. This course takes you on the exciting journey of applying ideas from physics and complex systems to biological dynamics. In particular we will look at:

1) The structure of biological systems: this includes for example the network of gene interactions and biochemical pathways;

2) Their dynamics: how a system behaves over time under different conditions; this includes ananalysis using ideas from dynamical systems theory (e.g. phase space, bifurcations, ...), and from stochastic process modelling;

3) Control methods and information processing: mechanisms that systematically control the state of a cell, or allow a biological system to react to changes in its environment;

4) Design principles: strategies to modify and construct biological systems with desired properties;

An understanding of how structure of biological systems relates to their functioning is also important from an evolutionary perspective. Comparing different biological architectures and systematically classyfing them allows one to understand why certain regulatory circuits have been modified by evolution, and why others are stable over long evolutionary time scales.

Requirements

Recommended

The course assumes knowledge of the concepts covered by the core courses "Dynamical Systems and Chaos" and "Complex Networks" of this Master. We will also use some ideas from the course on "Stochastic Processes".

Skills

Specific

* E8: To know how to characterize generic behavior of dynamical systems and their instabilities
* E11: To know how to apply dynamical systems techniques to physical, chemical, biological and social systems
* E15: To understand the main concepts and techniques of complex networks

Generic

* TG1: To be able to describe, both mathematically and physically, complex systems in different situations
* TG2: To acquire the capacity to develop a complete a research plan, covering all steps from bibliographic research, strategy to reaching conclusions
* TG3: To be able to write in a clear, precise and rigorous way the different steps of the research process and to present the results to an expert audience

Basic

* You may consult the basic competencies students will have to achieve by the end of the Master's degree at the following address: http://estudis.uib.cat/master/comp_basiques/

Content

The aim of this course is to offer an introduction to the emerging field of systems biology. Systems biology is a young and interdisciplinary field at the borders of biology, biochemistry, physics, mathematics, computer science and engineering. It bridges areas which used to be disconnected in the past, such as molecular biology and genetics, on the one hand, and cell and tissue biology, embryology, etc., on the other hand. This is achieved by integrating the microscopic processes at the level of genes, proteins, etc. into macro-level descriptions of cells, tissue, and organisms. One organizing idea is that of biological networks, i.e., the aim is to understand how different biological elements interact and produce collective behaviour. There are several key elements and motifs used by nature to build biological networks. Biological systems are robust, exhibiting a high tolerance in their operational ranges. They make an efficient use of resources, and are versatile information processing systems. These demands imply constraints on their structure.

In this course we will focuson quantitative approaches. We will use theoretical models to predict the overall qualitative behaviour of biological systems, and to understand how to change the behavior of these systems and to engineer them, in the spirit of the emerging field of synthetic biology.

Range of topics

1. Introduction
   Introduction of the scope and approach of the course. Some basic biological concepts: DNA transcription and translation.

2. Transcription Networks
   Basic concepts: activators and repressors. Michaelis-Menten kinetics and Hill input functions. Elements of transcription networks. Dynamics of simple gene regulatory systems.

3. Network Motifs I
   Autoregulation: negative and positive.

4. Network Motifs II

Feed-forward loop gene circuits: coherent and incoherent. Single-input modules. The multi-output feed-forward loop.

5. Network Motifs at work
   Developmental transcription networks. Signal transduction networks. Motifs for information processing: multi-layer perceptrons. Negative feedback and oscillator motifs.
6. Stochastic aspects of biological systems
   Noise induced by low copy numbers in biological systems. Effects of noise on gene circuits and cellular decision making. Mathematical description and computer modelling.
7. Oscillations in biological systems
   Design principles of biological oscillators. Delayed negative feedback. The segmentation clock.
8. Robustness of biological circuits
   An example: bacterial chemotaxis. Response and exact adaptation. Robust patterning and precision in development.
9. Biological systems in changing environments
   Models of biological systems in changing environments; bed-hedging and phenotypic switching.
10. Kinetic Proofreading
   Kinetic proofreading of the genetic code. Recognizing self and non-self by the immune system.
11. Demand Rules for Gene Regulation
   Evidence of demand rules. The selection pressure for optimal regulation.
12. Optimal Gene Circuit Design
   Cost, benefit and fitness functions of biological circuits.

Teaching methodology

Workload

The novelty of the material for students with a Physics background implies a number of theory classes where the main new biological concepts will be explained. On the other hand, students with a more biological background should have no problem with this course after having passed Dynamical Systems and Complex Networks in the first semester. The course is structured such that, while fundamental concepts are given in each chapter (motifs, robust behavior, proofreading, optimality of biological systems, etc.), the concepts are illustrated with a broad number of biological examples that will allow to increase the biological knowledge of the class, with examples like sensory and developmental transcription networks, signal transduction networks, bacterial motility, including chemotaxis, morphogen patterning, RNA translation, etc.

The goal is that the student is able to work sucessfully with these concepts and this will be accomplished through the assignment of a small number of exercises and mainly with a small individual project, chosen between the instructor and the student. This project will be related to recent research topics and will involve the use of the ideas and methods developped during the course.

In-class work activities (0.75 credits, 18.75 hours)

Modality	Name	Typ. Grp.	Description	Hours
Theory classes	Theory classes	Large group (G)	Lectures given by the professor(s), in which theoretical concepts and applications are explained.	17
Practical classes	Practical sessions	Large group (G)	Solution of examples, work on specific problems, and questions.	1.25
Assessment	Oral presentation	Large group (G)	Each student will be given an individual assignment covering one or several of the topics of the course. In addition to a written report, the student will give an oral presentation attended by all students inthe class, and by the professors.	0.5

At the beginning of the semester a schedule of the subject will be made available to students through the UIBdigital platform. The schedule shall at least include the dates when the continuing assessment tests will be conducted and the hand-in dates for the assignments. In addition, the lecturer shall inform students as to whether the subject work plan will be carried out through the schedule or through another way included in the Aula Digital platform.

Distance education tasks (2.25 credits, 56.25 hours)

Modality	Name	Description	Hours
Individual self-study	Implementation of the assignment	The student carries out the individual assignment, prepares a report, and prepares and delivers an oral presentation.	30
Individual self-study	Study and understanding theoretical concepts	This activity aims at the understanding of the theoretical concepts,techniques and applications discussedin the lectures.	14
Individual self-study	Exercises	The student will work on exercises assigned by the lecturers, and submit solutions in written form.	12.25

Specific risks and protective measures

The learning activities of this course do not entail specific health or safety risks for the students and therefore no special protective measures are needed.

Student learning assessment

The evaluation will be based on the participation in class, homework (assigned exercises) and of the "small project" on a subject related to a recent topic already mentioned.

Frau en elements d'avaluació

In accordance with article 33 of Regulation of academic studies, "regardless of the disciplinary procedure that may be followed against the offending student, the demonstrably fraudulent performance of any of the evaluation elements included in the teaching guides of the subjects will lead, at the discretion of the teacher, a undervaluation in the qualification that may involve the qualification of "suspense 0" in the annual evaluation of the subject".

Oral presentation

Modality	Assessment
Technique	Oral tests **(retrievable)**
Description	Each student will be given an individual assignment covering one or several of the topics of the course. In addition to a written report, the student will give an oral presentation attended by all students inthe class, and by the professors.
Assessment criteria	Accuracy and quality of the work as well as the clarity in the oral exposition.

Final grade percentage: 20%

Implementation of the assignment

Modality	Individual self-study
Technique	Papers and projects **(retrievable)**
Description	The student carries out the individual assignment, prepares a report, and prepares and delivers an oral presentation.
Assessment criteria	Suitability of the introduction and motivation. Accuracy of the work. Clarity of the ideas and explanations. Relevance of the conclusions. Quality of the written report.

Final grade percentage: 40%

Exercises

Modality	Individual self-study
Technique	Papers and projects **(retrievable)**
Description	The student will work on exercises assigned by the lecturers, and submit solutions in written form.
Assessment criteria	Accuracy of the answers. Clarity and quality of the explanations.

Final grade percentage: 40%

Resources, bibliography and additional documentation

Research on the topic taught in this course is quite recent (mostly from the 21st century). As a main source we will use the pioneering book by Uri Alon. Another interesting resource is the recent book "Cell Signaling", that stresses the interconnection between the traffic of signals arriving atacell and the role of signalling systems as information processing devices. This will be complemented by the frequently updated book Molecular Biology of the Cell (now in its 6th edition). We recommend it as a reference for particular biological and molecular details of systems studied in specific examples and the project. Other resources are seminal research papers in systems biology, which we will highlight as the course progresses. This will be complemented by specific bibliography for the project to be carried out by the students.

Basic bibliography

Uri Alon, *An introduction to Systems Biology: Design Principles of Biological Circuits*, (Chapman & Hall/ CRC, Boca Raton, FL, 2007)

Complementary bibliography

Bruce Alberts et al., *Molecular Biology of the Cell*, (Garland Science, New York, 2014) (6th Edition).
Wendell Lim, Bruce Mayer, and Tony Pawson, *Cell Signaling*, (Garland Science, New York, 2015).

Other resources

1. J.J. Tyson, K.C. Chen, and B. Novak, *Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell*, Curr. Opin. Cell Biol. **15**, 221-231 (2003).
2. J.E. Ferrell, *Self-perpetuating states in signal transduction: positive feedback, double-negative feedback and bistability*, Curr. Opin. Cell. Biol. **14**, 140-148 (2002)
3. W. Ma, A. Trusina, H. El-Samad, W.A. Lim, and C. Tang, *Defining Network Topologies that Can Achieve Biochemical Adaptation,* Cell **138**, 760-773 (2009).
4. N. Barkai and B.Z. Shilo, *Variability and Robustness in Biomolecular Systems*, Mol. Cell **28**, 755-760 (2007).
5. B. Novak and J.J. Tyson, *Design principles for biological oscillators*, Nat. Rev. Mol. Cell Biol. **9**, 981–991 (2008).
6. L.S. Tsimring, *Noise in Biology*, Rep. Prog. Phys. **77**, 026601 (1-29) (2014).
7. A.C. Oates, L.G. Morelli, and S. Ares, *Patterning embryos with oscillations: structure, function and dynamics of the vertebrate segmentation clock*, Development **139**, 625-639 (2012).

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