Introduction to systems biology 2011

Systems biology is a multidisciplinary science, in which mathematics, engineering, physics, computer science and quantitative experimental biology come together to solve biological questions. Communication is key in such a multidisciplinary environment. This is the main aim of the courses in the first year; you will get the basics of these disciplines necessary to be able to communicate with the experts in these fields. In the second year, and through optional courses, you can specialize more into the discipline you like most, e.g. more theoretical, computational or experimental.
In this introductory course we will provide a first overview of Systems Biology, its questions, approaches and methods. This will be done through lectures, studying and discussing case studies, and by a small literature study/project. Together with Fundamentals of Bioinformatics, you will also have the opportunity to refresh and upgrade your knowledge of biology, mathematics and programming, dependent on your background. This course will then prepare you for the rest of the master by providing a context and basic skills.

So what is systems biology? From Wikipedia:

Systems biology can be considered from a number of different aspects:

- As a **field of study**, particularly, 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 (for example, the enzymes and metabolites in a metabolic pathway).
- As a **paradigm**, usually defined in antithesis to the so-called reductionist paradigm (biological organisation), although fully consistent with the scientific method. The distinction between the two paradigms is referred to in these quotations:
  "The reductionist approach has successfully identified most of the components and many of the interactions but, unfortunately, offers no convincing concepts or methods to understand how system properties emerge...the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures, multiple components simultaneously and by rigorous data integration with mathematical models" . Sauer, Uwe; Heinemann, Matthias; Zamboni, Nicola (27 April 2007). "GENETICS: Getting Closer to the Whole Picture". *Science* **316** (5824): 550–551
  "Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different....It means changing our philosophy, in the full sense of the term" . Noble, Denis (2006). *The music of life: Biology beyond the genome*. Oxford: Oxford University Press. pp. 176. ISBN 978-0-19-929573-9
- As a series of **operational protocols used for performing research**, namely a cycle composed of theory, analytic or computational modelling to propose specific testable hypotheses about a biological system, experimental validation, and then using the newly acquired quantitative description of cells or cell processes to refine the computational model or theory. Since the objective is a model of the interactions in a system, the experimental techniques that most suit systems biology are those that are system-wide and attempt to be as complete as possible. Therefore, transcriptomics, metabolomics, proteomics and high-throughput techniques are used to collect quantitative data for the construction and validation of models.
- As a **socioscientific phenomenon** defined by the strategy of pursuing integration of complex data about the interactions in biological systems from diverse experimental sources using interdisciplinary tools and personnel.

This variety of viewpoints is illustrative of the fact that systems biology refers to a cluster of peripherally overlapping concepts rather than a single well-delineated field. However the term has widespread currency and popularity as of 2007, with chairs and institutes of systems biology proliferating worldwide.

Central to most of today's systems biology studies are biological networks: networks of interacting biological molecules. Thus, although systems biology focusses on "whole systems", it is not a holistic approach (as suggested by many, also in the introduction in Wikipedia on the web). It not only looks at the whole, it makes explicit use of the properties of the parts (often found by the classical reductionist approach in biology). These properties can be anything: kinetic properties of enzymes, binding properties, cellular localisation. The idea is to understand the systems behaviour as the result of these component properties and how they interact. Often new properties *emerge* from these interactions.
Yet, there are two schools of thoughts and approaches in Systems Biology, often referred to as *bottom-up* and *top-down* Systems Biology (Fig 1). Both approaches will be taught in this master. Top-down systems biology starts from (high-throughput) data and aims to turn that data into knowledge, often about the interactions between the variables that were measured. Hence, "network reconstruction" is an important activity in top-down SB. Its main mathematical tools are statistical in nature. Its distinction from bioinformatics is blurred: integrative bioinformatics is a branch of bioinformatics that is indistinguishable from top-down SB.
Bottom-up SB starts with known interactions and properties of components, and tries to *construct* systems behaviour as emergent properties. It uses engineering type of approaches and mathematical tools, such as mass balances and differential equations. It uses data of systems behaviour for validation and comparison, more than for construction. In practice, however, these processes and activities are iterative and complementary. Thus, when constructing a model of a pathway, we will need top-down systems biology to find the structure of the network, i.e. the possible interactions between the components. Then we can use information on the individual components to predict how the system behaves when the components interact. This behavior can be tested against available data: in the likely case there is a mismatch, either the structure of the model can be wrong (go back to the top-down SB approach and/or do specific biochemistry to validate/generate better interaction data), or the parameters of the model can be wrong. The latter may be adjusted (fitted) against the data (or, alternatively, more biochemical analyses are needed to obtain the properties of components). In the case of fitting, data that was used initially for validation, has now been used for construction. Validation should then come from a different data set. See Fig 2.
The result of this iterative process is an improvement of our understanding to what extent known properties and interactions can describe and ultimately predict system behaviour. The models are therefore tools for integration of data to generate biological insight; they are not (or should not be) the objectives. Thus, biological questions are central to systems biology: they are the focus of this course. The course does not aim to provide all the technicalities of the approaches. Rather, it provides *the main concepts* and research *questions* of the field. It should provide context and motivation to want to study the techniques later in the master.

Aim of the course

- To make the students aware of gaps in their own background knowledge.
- To make the student acquainted with the major issues, concepts and methodology in systems biology (to be studied in more detail in the master)
- To develop a basic understanding of major biological concepts in genomics and cell

biology that are relevant to current topics in systems biology
- To work together in a group of diverse backgrounds
- To gain hands-on experience in basic modeling as a means of solving systems biology problems

Structure of the course

Schedule (Wed-Thu):

9.00-11.00	Lecture
11.00-12.45	Class mathematics (theory plus exercises)
	– lunch –
13.30-17.00	Assignment

Lectures/class 9.00-12.45:

Week	Day	Room	Topic, contents	Lecturer
1	7 Sept	WN-C624	Introduction; questions, concepts, modeling approaches	BT
	8 Sept	WN-C648	Metabolic networks; steady state, enzymes, solution space	BT
2	14 Sept	TR-3C26	Signal transduction and gene expression	FB
	15 Sept	Artis	Genomics and SB in practice	RK and colleagues
3	21 Sept	WN-P640	Top-down SB; data-driven approaches	HH/JW
	22 Sept	Artis	Genomics and SB in practice	RK and colleagues
4	28 Sept	TR-3C26	Experimental cultivation systems, cellular fysiology	JTM
	29 Sept	Artis	Networks evolve: functional perspective; cancer and SB	BT, HW
5	5 Oct	WN-P640	Dynamics of networks; bottom-up modeling	BT
	6 Oct	WN-C648	Design principles; trade-off, costs and benefits	DM
6	12 Oct	WN-P640	Sensing, sensitivity and control	FB
	13 Oct	WN-C648	Low number biology: noise and single cells	FB
7-8			Project / literature study	
	28 Oct	Artis	Final presentations	

The lectures in Artis are part of a series in the “Artis Academy”, see http://www.artis.nl/artis-academie/colleges/leven-een-microbiele-wereld/ for some more info (in Dutch, however…).

Assignments can be done at home, or in computer rooms that are available in the afternoon. Please check http://vurooster.nl/?course=AM_470631 for an overview.

Lectures: 9.00-11.00

Themes:

Week 1: metabolism, the basis of lots of SB

Week 2: regulation through signalling and gene expression

Week 3: functional genomics and top-down SB

Week 4: cells as systems

Week 5: network properties and constraints

Week 6: cellular decision making

Classes: ***Note that times are different for Mon-Tues, Wed-Thur and Fri!!!***

week 1: short test to identify entry level in Biology, Mathematics and in Programming (together with FoB)

weeks 2-7:

Programming (Mon-Tues): 11.00-12.00 & 13.00-14.00

- Python
- Topics: Syntax, Control, Arrays, Recepies, I/O, functions
- other issues: libraries, string handling (e.g., split), regular expressions
- Toy example to work with: codon tables (translation etc.)
- leading up to the scripting work for the practicals

Mathematics (Wed-Thur): 11.00-12.45

- analytical functions
- differential equations
- linear algebra

Biology (Friday @ UvA: times to be announced):

- metabolism
- signalling
- genomes and gene regulation
- cell biology

Assignments: 13.30-17.00

- Assignments weeks 1-6

  Literature reading and questions

  Modeling practicals
- Project weeks 7-8

  Literature study/project

  report, presentation

Acronym	Lecturer
BT	Bas Teusink
DM	Douwe Molenaar
FB	Frank Bruggeman
RK	Remco Kort
JTM	Joost Teixeira de Mattos
KH	Klaas Hellingwerf
HW	Hans Westerhoff
HH	Huub Hoefsloot

Literature assignment:
In groups work out a topic of interest and prepare a presentation for the minisymposium. Each topic should be supervised by one teacher.

Potential topics:
-metabolic engineering (BT, JTM)
-laboratory evolution (DM, BT)
-population versus single cell (KH, FB)
-cellular decision making (KH, FB)
-SB of GPCR or NR signaling (FB)
-Warburg/Crabtree/… effect (BT, FB)
-genome-scale metabolic models (BT)
-topics from the Artis Academy series (RK, BT, HW)
-top-down systems biology (HH, DM)
…

Proposed question to be addresseds:
-what are the main questions?
-what is/could be the contribution of SB in that field/topic?
-what has been achieved?
-what are the challenges for successful implementation of SB?
-what do you personally have to learn to be able to contribute?
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