Foreword

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There are many different ways to define Systems Biology. In Lyon, we have chosen an integrative view, which aims at bridging the gap between biologists generating data and mathematicians studying differential equations, to make it short.

Within the frame of the Idex2 project, BioSyL was sought for contributing in the shaping of an interdisciplinary research community, that would associate all biological disciplines and up to the "natural sciences'' academic college. This workshop was a first step in that direction. The organizing committee (Benjamin Audit, Arezki Boudaoud, Hubert Charles, Fabien Crauste, Olivier Gandrillon, Francois Gueyffier, Daniel Kahn, David Rousseau and Jacqueline Marvel) identified the 4 following scientific topics:

1. Training the next generation of System Biologists

2. Multiscale modeling

3. Systems Biology vs. Synthetic Biology

4. Networks for Biologists

The aim of the workshop was to get inspiration from eminent members of the Systems Biology community worldwide, both from a scientific and from an organizational point of view. The four morning sessions were therefore completed by 4 separate round tables in the afternoon, on the same topics. These round tables were dedicated to tackling three series of questions aimed at building a road map for the Lyon community in Systems Biology:

1. What are the burning questions that need to be addressed, both from a cognitive and from a technological point of view?

2. What are the unifying projects that should be developed?

3. What are the infrastructures (equipment, platforms, web-based resources, ...) that should be built.

This one day workshop proved to be a very efficient way to propose answers to those questions. What is below is the result of that workshop, for which we have to thank all those who attended, both outside guests and members of the Lyon community, who actively participated in shaping this roadmap.

Round table 1.

Training the next generation of System Biologists

(Marija Cvijovic, Hubert Charles, Mathilde Calvez)

1) Burning questions: What is the ideal program for training in system biology?

Make the program attractive for students.

Currently, a lot of students do not enter the existing SB trainings (in particular mathematicians who already have their own math trainings tackling some biological questions).

- Students have to be told about SB: what it is, why SB can be useful, why it is not only a tool but also a scientific field per se, etc.
- Need to tell the students about the importance of SHS linked to SB (societal aspect of SB, biotechnologies...).
- tell students that training in SB could give them new knowledge to make them more competitive when looking for a job.

It is important to emphasize that independent of the life science field – methods, tools, approaches that are learnt by the students within Systems Biology program are a horizontal expertise and can easily be transferred to other areas where flexibility and interdisciplinarity are desired.

Make a list of the current training units that already exist in Lyon (and of the specialists that are not currently involved in trainings but that could be able to give lectures in the new SB master).

- See if these trainings/courses overlap or not, determine which ones could be complementary, identify the missing units...
- Then, need to define a **reference curriculum** and determine the specifications that are required to validate the SB program.
- With these defined specifications and the list of the existing units, then it becomes possible to choose a list of courses to create the SB master, or to pick up some of these courses to build individual SB curricula.

Training must be in English.

- All the work and publications are done in English nowadays, people need to be fluent in English to interact with other scientists and share their work and knowledge. Moreover, doing the lectures in English would allow attracting foreign students and lettting them enter the SB degree (which would not possible if all the lectures are done in French). Doing the lectures in English would also allow inviting foreign specialists to give lectures in this SB degree.

Link the training with possible careers.

- As SB is a very large field, it is difficult for students to clearly define potential jobs that they could do after the SB training (and convince their parents that these jobs are not fancy ones).
- Need to define jobs in which students can identify themselves. For that, one approach could be to identify existing or potential careers (e.g. by asking the Industry for giving seminars on the jobs

they offer, by offering internships, industrial master thesis projects...) and to make a list of the jobs that are available in the region.
Practice should be encouraged. The "do it yourself" way of thinking is also favourable for SB.
SB master should be owned by the Université de Lyon, to escape from the departments and make the SB training as much interdisciplinary as possible (although UdL is organized in colleges that are not really propitious for interdisciplinarity).

2) What are the unifying/integrating projects that should be developed?

Students should be specialists in one domain, but have awareness of other fields.
Deal between either taking the students as early as possible (while they are still "generalists" and have knowledge in several fields), or taking them later, once they are already specialized in one field, to allow them interacting with each other and taking benefits of each other background. One counter example, the BIM students at INSA are not specialist and are equally formed between biology, math and computer sciences.
Allowing more flexibility between the existing programs.
- To allow students being specialist in their field but also having awareness of the other domains: need to make bridges between the existing programs within a school, or even between schools.
- Need to adapt scholar schedules to allow students following several courses belonging to different programs (currently these bridges are often possible in theory, but impossible in practice due to incompatible schedules).
Label the different paths leading to the SB degree.
- System of colors (the color depending on the main background) to identify the units that would allow students to validate the SB master.
- A minimal number of units should be required to validate the SB degree.
- Need to offer the possibility of specialization (optional lectures, internships in labs of student's choice...).
Facilitate joined master degree projects: e.g. in labs, make mathematicians work with biologists on a same project.
One big SB training, or several SB trainings in each field/school (e.g mathematics for biologists, or biology for mathematicians...)?
- It depends on the existing programs/skills/teachers in Lyon, on the master's owner (University versus departments), on the beginning of the program (license = generalist students -> unique program; master = specialists so different programs required?)
- One possibility could be to create a unique program, which begins by a given period of specialized lectures depending on the field of origin of students (e.g. biologists do mathematics, while theoreticians go in the lab doing experiments). Following this first period of specialized lectures, students could all follow the same classes to make them have the same general knowledge in SB. Then, a last period of specialization (optional lectures, internships...) could allow students specializing in their SB field of interest.

3) What are the infrastructures that are required?

Students need to learn how to use the infrastructures and centers (imaging, computation, genomics platform...).
Students should be aware of the potential uses of these infrastructures, the time experiments would take using these infrastructures, the cost of experiments...
Develop remote trainings (MOOCS, online courses)
- To complete individual curricula (online courses on SB fields that are not developed during the training) or to give advanced knowledge (for students to specialize in one particular SB field).
- As SB is a very large field, everything cannot be developed during the training: MOOCS could thus be a good solution to get lectures on things that were not evoked in the training, or to get lectures from specialists that are not in Lyon and could not directly give lectures in the SB training.
Summer schools / PhD and/or PI trainings
Develop "Do It Yourself" and fab labs?

Round table 2.
Multiscale modeling

(Alfonso Bueno-Orovio, Christophe Arpin, Olivier Gandrillon)

1) Burning questions?

a) **How many different scales can we couple?** This is an important question that raises both theoretical and practical issues. Regarding experiments, one question concerns the type of data that can be acquired at different scales (including both time and space scales, scaling up to the population level to account for experimental and individual variability). For a given project, the first question should be: what are the currently existing multiscale models? What are the available types of data? What is already feasible or do we need either mathematical or computational development to achieve our goal?

b) **How to assess the validity of a stochastic multiscale model when fitted onto noisy data?** This is a fundamental question in Systems Biology: since the data are noisy by essence (both due to technical and to biological noise) and since repetitions of a given model can also vary (in the case of a model incorporating a stochastic component), how can we address the validation of such frameworks for their application to Biology?

c) **How to model coupling of genotypes and phenotypes**? This is by essence a multiscale question that couples both spatial aspects (from DNA to organisms) and time-dependent scales (from minutes to years). It has been suggested that a "Genopheno club" could be envisaged to work on this particular point.

2) What are the unifying/integrating projects that should be developed?

a) **Coupling of molecular causes to disease progression.** This question is not unrelated to the previous one. It implies to model the metabolism and intra-cellular biochemical pathways (molecular scale) in regards to disease (organ/organism/population scales).

b) **Personalized modeling.** This is in line with the objective to progress in the field of personalized medicine. This should concern punctual analyses but also longitudinal follow-ups. This is probably the next step from the point 2a above.

c) **Aging.** Although aging should not be viewed as a risk factor but as a goal, the same kind of questions and approaches can be deployed as for 2a and 2b.

3) What are the infrastructures that are required?

a) **Training for biologists.** A crucial need for training of biologists has been pointed out. It could rely on online solutions like Moocs. It should be based on practical examples. The best approach would rely on a combination of both web-based tools and real human-to-human IRL interactions.

b) **Reinforce the modeling community of biologists.** This could be developed upon the existing BioSyl community to be enlarged to a critical mass. It is important that all fields of biology should be enrolled into the systemic vision.

c) **Development of a web-based repository.** The BioSyL website could be used for that purpose. It would consist in collecting the relationships between scales and relevant formal tools. For example: I want to model a population of animals, what are the available formalisms? If now I want these animals to behave according to some internal function, what would be the recommended formalism?

d) **Increase facility of access to computing facilities.** There will be a greater need for High Performance Computing (HPC). In Lyon we have numerous computing resources, but their access and learning curve should be facilitated to newcomers.

e) **Development of a "Galaxy-like" tool for multiscale modeling.** This is probably a very long term (if attainable) goal. Let's say I want to model a liver cancer. Then I can go to the "Cell Type Module", select hepatocytes. From those I go to the "Molecular modules" and select "Growth module", which I modify to turn it into an "uncontrolled growth" mode, and plug it with the cellular module. Then I can confront the behavior of that model to an existing set of data registering the behavior of hepatocellular carcinomas at cellular and molecular scales.

Round table 3.

Systems Biology vs. Synthetic Biology

(Jerôme Bonnet, Corinne Dorel, Daniel Kahn)

Burning questions

If system biology is well implanted, represented and known in Lyon, synthetic biology is a more recent approach, which most scientists would like to better understand.

1. First of all, we have to ensure that people understand and use common concepts and vocabulary. This will pave the way to the creation of the BioSysSyn community.

Actions

We suggest to organize in Lyon a Thematic Day "BioSysSyn" to the attention of students and academic, but also companies. It is important to emphasize that socio-economic partners have to be involved in such an approach. For example, a first session should be dedicated to answer the questions "what is synbio, what is sysbio?"

2. Ethical and societal questions

We recommend to involve humanities from the very beginning of the process.

3. Methods to reliably and quickly combine biological functions.

Also, how to combine modeling and testing approaches quickly.

Deal with evolution.

Projects

It appears premature to talk about "projects" right now. The first goal is to build a community and understand each other. Then, unifying/integrating projects will be developed.

Resources

Several propositions were made to develop a "BioSysSyn" community, some virtual as the project to set up an online resource, directory of people with their expertise, or the idea to integrate with GDR. A Spring School, organized by GDR could be an unifying project complementary to the thematic day proposed above. However, real estate resources would certainly boost the emergence of BioSysSyn projects, such as the access to a FabLab, a Biofab or, let's dream: the **"Lyon Institute of systems and synthetic biology".**

Round table 4

Networks for Biologists

(Tariq Enver, Françoise Monéger, Jacqueline Marvel, Benjamin Audit)

1) What are the burning questions that need to be addressed, both from a cognitive and from a technological point of view?

Two main scientific questions were identified as being relevant to network approaches in biology:

i. Cell differentiation and development;
ii. Multi-scale biological data integration: from molecule to tissue to organism to environment.

These questions raise a number of practical issues that need to be addressed:

- What are the appropriate methods to build and integrate different types of networks? Issues that were raised and need to be addressed include: (1) the nature of links used to create the interactions and their heterogeneity: Protein/protein interaction networks, Gene regulatory networks (DNA/protein interactions), Gene co-expression networks, Food webs, Between- or within-species interaction networks; (2) the quality of the available information and it completeness; (3) the scale at which biological processes are represented.
- How can stochasticity be taken into account? There is a need for probabilistic approaches to assess noise, homogeneity/heterogeneity and variability. In terms of standardization between labs/experiment the relevance of defining *invariants* is being questioned?
- How can we include temporal order in network representations? There is a need for tools to go from static to spatio-temporal, dynamics and quantitative networks.
- Standards are required to define *high quality* data and facilitate data sharing. This encompasses the problems of data normalization and biological data validation at the network level.
- How can analysis focusing on specific pathways (sub-network studies) be compared to *whole network* approaches? This is related to the problem of global biological interpretation of network-science results. To which extent is the study of biological networks a more powerful tool compared to the study of individual network components (genes, proteins, ...); how can one extract biological meaning or hypothesis from network studies and what is the best way to test them at the global network level?

2) What are the unifying projects that should be developed?

Questions raised in point 1) naturally led to unifying projects with methodological motivations in relation to: modeling/representation of biological processes (ontology) for constructing

meaningful biological networks, the integration of heterogeneous datasets an multi-scale temporal networks. It was also suggested that on a biological question of interest to a large community for example: cell differentiation and development one could generate a large data set of high quality and completeness that would be made available to the community at large.

Examples of methodological projects for biological networks:

- Reconstruction / construction of networks, network inference. Can stochasticity (noise, heterogeneity of the measurements) be used to infer a network given that the network should be robust with respect to noise? What are the structures of biological networks? There is a need for a biological network science that would allow the identification of common rules;
- Dynamic-quantitative-network representation and analyses;
- Validation of networks (all minus one versus global networks, sensitivity to missing data);
- Generalization of knowledge: How do we proceed from simple networks to complex/large networks; from simple model organisms (unicellular) to more complex situation (mammals, plants, ...);
- Analytical tools for stochastic network modeling. Tools for multi-scale simulations.

3) What are the infrastructures (equipment, platforms, web-based resources, ...) that should be built?

In order to progress together towards the above goals, create multidisciplinary interactions between teams and to share tools or results, the panel identified the need for an infrastructure for *Interdisciplinary Social Networking*. A Society for Networks at Université de Lyon (SoNUL) would work as a platform facilitating scientific exchanges between disciplines. It was also suggested to have regular user-friendly meetings in a relaxed atmosphere. (la loi Evin nous empêche d'en dire plus)

A possible unifying resource for SoNUL would be funding for platform usage and human workforce costs for data generation, storage and curation:

- Data generation: Measurement of important model parameters i.e half life and synthesis rate of proteins and RNAs;
- Data mining: Validate and distributing high-quality normalized data for computational scientist of Université de Lyon;
- Sharing of tools (Cf Rulbi / PRABI ?)