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“An ISBE document which defines a core curriculum for systems biology plus sector options”

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A1: Table summarizing the flow of Systems Biology Master level programme

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1. Executive Summary

Systems Biology is an approach to biology and medicine that has the potential to lead to a better understanding of the mechanisms by which genotype determines phenotype. The approach aims at elucidating how the interaction of genes, molecules, cells, tissues or organisms determine biological function by employing experimental data, mathematical models and computational simulations. Consequently, Systems Biology has also become part of the educational portfolio at many universities either as free-standing programmes or as part of genomics and bioinformatics curricula. However, the scope and content of those programmes differs very widely making it difficult for employers and students alike to determine into which type of employment, role or career Systems Biologists would fit. Since Systems Biology is inherently interdisciplinary, education within this field meets numerous hurdles including departmental barriers, availability of expertise locally as well as lack of career paths, teaching material and example curricula.

As interdisciplinary education generally builds on excellence and a strong foundation in one relevant discipline it is suggested that education in Systems Biology generally should start at Master's level.

This report provides the guidance to:

(1) Define the skills that students should have acquired within a Master's programme in Systems Biology anywhere in Europe (or the world).

(2) Outline a possible basic educational curriculum with flexibility to adjust to different application areas and local research strengths.

(3) Describe possible career paths for students that have undergone such an education.

Recommended concepts will help to lift the status and impact of existing programmes and to establish new programmes where Systems Biology is not yet part of the portfolio, recruiting students and teachers to such programmes, shaping Systems Biology careers and instigating collaborations between programmes.

Conclusion:

Interdisciplinary education, in general, and within Systems Biology, in particular, has to overcome a number of different obstacles that are summarised below:

- Education is organised according to disciplines/departments at many higher education institutes. The fact that departments "own" the educational programmes and the financial resources to arrange them directly counteracts interdisciplinary education. A more appropriate model would allocate resources directly to programmes that distribute tasks and resources in accordance with the needs for interdisciplinary education.
- At many institutions all of the appropriate competencies in experimental and theoretical sciences may not be available. Exchange of staff or availability of online courses may be approaches to solve such issues.
- Students may be poorly prepared or not be aware of the systems approach to biology, because high school and bachelor programmes may not touch upon those. Existing biology education is traditionally non-quantitative, while this is a hallmark of the systems-level approach. The community certainly needs to work on penetrating high-school and bachelor levels of education as well.
- There is presently a lack for career paths and job profiles for Systems Biologists.
- There is a lack of example or model curricula that could guide institutions that either want to set up a new programme or that wish to benchmark their existing programme.
- Lack of textbooks and teaching material.

ISBE, as a distributed research infrastructure, is in a unique position to set standards and maintain access to sustainable, high quality and state-of-the-art training in systems biology.

This ISBE report offers ways to structure the Systems Biology education landscape and provide common grounds for both students to plan their education and career and for employers to recruit Systems Biologists into appropriate positions. It represents the basis for further activities towards establishment of a curriculum and processes for a multicentre Systems Biology/Medicine training programme (Deliverable 10.3) and it builds upon the review of the current systems biology education in Europe (Deliverable 10.1).

2. Overcoming challenges in interdisciplinary educational programmes

We collected experts in Systems Biology and education performers at two workshops held in Heidelberg (November, 2014) and Gothenburg (March, 2015), respectively. Our discussions resulted in proposals for **(1) desired entry skills for Systems Biology Programme (2) the generic skills and competences that Systems Biology students should have acquired in relevant programmes, (3) educational topics and approaches that could lead to acquire those skills and (4) possible career paths for Systems Biologists**.

2.1 Entry skills for Systems Biology Programme

A major challenge for any interdisciplinary educational programme concerns the background or entry skills of the students. It is important that the cohort of students in a Master's programme should come from different backgrounds; ideally comprising a mixture of students with an experimental and theoretical background. For Systems Biology programmes students with a background in Biology, Medicine, Physics, Chemistry, Mathematics, Engineering and Computer Science should be considered. This means that the programmes will be entered by students that should have skills in experimental or theoretical sciences but at the same time may have very limited knowledge of biology and/or mathematical modelling. It may therefore be necessary to introduce students before or at the beginning of the programme to basic principles in biology or mathematics.

This report suggests the following introductory topics:

For experimentalists:

- Linear Algebra
- Differential and integral calculus
- Differential equations
- Numerical analysis and algorithms
- Multivariate calculus

For theoreticians:

- The cell concept and cell organization: cell diversity, prokaryotes and eukaryotes, organelles, cytoskeleton and cell structure
- Basic and quantitative biochemistry and physiology: macromolecules, the function of membranes and membrane structure, what drives life: basics of thermodynamics, catabolism and anabolism, basic protein structures, protein properties: enzymes, antibodies, affinities

- Genetics and inheritance: genomes and chromosomes, epigenetics, genetic variation, DNA replication and repair, viruses and transposable elements
- Gene expression: from DNA to RNA: transcription, from RNA to proteins: translation, gene regulation
- Cellular responses: receptors and signalling, cell division, apoptosis and cell death, protein sorting, protein secretion
- Multi-cellularity: the function of tissues, hormones, development, causes of disease
- Evolution: selection and adaptation, basic population genetics
- Techniques: genetic model organisms, DNA technology and sequencing

2.2 General skills acquired in a Systems Biology educational programme

To reflect the interdisciplinary systems approach, and its way of thinking and operating, it is essential to define the competencies that students should have acquired in a Systems Biology educational programme.

This report suggests that graduates from a Systems Biology Master's programme should have acquired the following skills:

- An understanding of the type of biological, medical or bioengineering questions that can be approached by integrating experimental data collection with mathematical modelling.
- Formulating research problems such that they can be solved by an integrated experimental/mathematical approach.
- A good appreciation of the Systems Biology iterative cycle: modelling, prediction and experimental verification.
- A well-developed ability to communicate scientific questions across experimental and theoretical disciplines and to collaborate across discipline borders.
- A good awareness of different types of modelling and their applicability to research problems as well as in-depth understanding and hands-on experience in specific mathematical modelling approaches.
- A good awareness of the type of data generation approaches that are suitable for a given research problem and in-depth understanding and hands-on experience in specific experimental techniques.
- Skills in data handling, management and visualisation, including an awareness of statistical analyses suitable for different types of data and experimental designs.
- An ability to critically assess evidence and scientific argumentation in integrative studies of biological systems based on an understanding of both experimental and theoretical/computational biology (medicine, bioengineering).

2.3 Career paths for students that have undergone a Systems Biology education

There is today no career description for Systems Biologists. Increasing numbers of opportunities where flexibility and interdisciplinary are desired will result in a broader spectrum of job opportunities for students that have completed an education in Systems Biology than pure Biologists or Mathematicians, Computer Scientists etc.

The following are areas where the students that completed a Systems Biology programme will find future jobs and opportunities to further develop their skills.

- Academia is increasingly moving into interdisciplinary recruitments
- Business spin-off, for instance in synthetic biology
- Biotechnology and bioengineering companies
- Data analysis sectors (banks, insurance, consultancy, policy making)
- Pharma (drug discovery, diagnostics, *in silico* clinical trials)
- Public health clinical medicine, multifactorial diseases
- Fine and bulk chemicals incl. biofuels
- Bioremediation; environmental monitoring; sustainable and predictive resource management
- Agro-biotech; Food biotech
- Science and research management

2.4 Role of ISBE

Our effort wishes to offer ways to structure the Systems Biology education landscape and provide common grounds for both students to plan their education and career and for employers to recruit Systems Biologists into appropriate positions.

To maintain access to sustainable, high quality and state-of-art training in systems biology ISBE will:

- Raise interest in the opportunities and challenges to operate across disciplines to solve the biological, medical and bioengineering challenges of the 21th century.
- Raise awareness of cross-disciplinary approaches in high school and bachelor programmes as a strategy for recruiting students to interdisciplinary programmes
- Facilitate collaboration and exchange between Systems Biology education performers.
- Make expertise available via exchange of students and teachers.
- Raise awareness of employers to understand the skills and competences that Systems Biologists have acquired in their education.

- Be a bridge between academic and private sector recruiters to develop the career paths for students that have undergone interdisciplinary training.

3. Suggested basic core curriculum for Systems Biology Education

The aim of this report is to suggest a basic core curriculum for Systems Biology education at the Master's level. This report builds on the review of the current systems biology education in Europe (Deliverable 10.1) and will serve as a basis for further activities towards establishment of a curriculum and processes for a multicentre Systems Biology/Medicine training programme (Deliverable 10.3)

In order to build basic educational programmes we have divided Systems Biology education into five distinct areas and have broken those down into topics that we believe should be covered by any programme in the field. The advantage of this approach is that it provides an opportunity to apply our recommendations within already existing programmes rather than suggesting specific courses that may be too inflexible and hence limit this possibility.

After completing a Master's level programme in Systems Biology students should be true experts/specialists in some of the areas below while having sufficient knowledge of the other areas to productive communicate and collaborate with an expert/specialist.

Mathematical and computational concepts

- Linear Algebra - stoichiometric modelling – genome scale metabolic reconstructions and models; stability analysis – stability of genetic circuits
- Nonlinear dynamics - signalling cascades, kinetic metabolic models, pattern formation, enzyme dynamics, cell differentiation, cellular decision
- Stochastic modelling - gene expression circuits, cell motility, ion channels, protein-protein interaction, diffusion.
- Spatial modelling - morphogenesis, cell communication, tissue formation, crowding, biofilms
- Control theory - design and analysis of metabolic pathways, gene expression circuits, Pharmacokinetics and Pharmacodynamics (PKPD)
- Discrete and logic models - genetic networks, signalling networks, cellular differentiation
- Complex network analysis - metabolic networks, protein interaction networks, gene – disease networks

- Optimisation - metabolic engineering, genome scale metabolic models, parameter estimation in signal transduction networks, reverse engineering

Networks and processes of life

- Metabolic networks – as relevant for metabolic engineering and diseases; fluxes, kinetics, rates, stoichiometry
- Signalling networks – as relevant for information processing, and engineering of cells and organisms; dynamics, feedbacks, adaptation
- Gene regulation networks – as relevant for cellular decision making and differentiation, bi- and multi-stability
- Cell and population networks – as relevant for development, pattern formation, disease, infection and ecology; cell variability
- Genetic networks – as relevant for multifactorial traits and diseases, epistasis, genome-wide association studies (GWAS)
- Protein (and other types of) interaction networks – complex inference and functional modules
- Oscillatory processes – as relevant for cell cycle, circadian rhythms etc.

Scientific programming

- Programming: e.g. Matlab or Mathematica, Python, Perl, Java, R, C, C++
- Tools for genome scale metabolic models (GSMM), kinetic modelling (stochastic and deterministic), network analysis: e.g. Copasi, Cytoscape, OptFlux
- Standards: e.g. SBML, SBGN, MIRIAM

Bioinformatics and statistics

- DNA, RNA and protein sequence analysis
- Integrative bioinformatics- interoperability, ontologies, semantics, databases, standards
- Genomics of communities, meta-genomics
- Molecular evolution
- Complex phenotype-phenotype relationships - genome-wide association studies for human diseases and desirable traits in plants, animals and microbes
- Data analysis - standard algorithms, basics of supervised and unsupervised statistical learning, data integration
- Statistical inference - use of appropriate statistical tests, reverse engineering
- Machine learning - clustering; neural networks, random forest

Experimental design, measurement, analysis, interpretation and knowledge generation

- Quantitative imaging/microscopy - single cell analysis, flow cytometry, image analysis, cell variability
- Global and high-throughput data - genetic, transcriptional, proteomic and metabolic networks
- Biochemical in vitro assays for quantitative properties of proteins, reactions and interactions
- Handling and culturing of cells and organisms
- Quantitative and time resolved experimental methods at low throughput – levels of biomolecules, modifications
- Principles of system perturbations – genetic, experimental, pharmacological perturbations to test, challenge and control systems
- Principles of systems engineering – systems design, genetic and biological engineering, evolutionary approaches

Appendix:

A1: Table summarizing the flow of Systems Biology Master level programme

<table>
<tr><td rowspan="3">Entry skills</td><td colspan="2">Introductory module</td></tr>
<tr><td>Experimental background</td><td>Theoretical background</td></tr>
<tr><td>• Linear Algebra
• Differential and integral calculus
• Differential equations
• Numerical analysis and algorithms
• Multivariate calculus</td><td>• The cell concept and cell organization: cell diversity, prokaryotes and eukaryotes, organelles, cytoskeleton and cell structure
• Basic and quantitative biochemistry and physiology: macromolecules, the function of membranes and membrane structure, what drives life: basics of thermodynamics, catabolism and anabolism, basic protein structures, protein properties: enzymes, antibodies, affinities
• Genetics and inheritance: genomes and chromosomes, epigenetics, genetic variation, DNA replication and repair, viruses and transposable elements
• Gene expression: from DNA to RNA: transcription, from RNA to proteins: translation, gene regulation
• Cellular responses: receptors and signalling, cell division, apoptosis and cell death, protein sorting, protein secretion
• Multi-cellularity: the function of tissues, hormones, development, causes of disease
• Evolution: selection and adaptation, basic population genetics
• Techniques: genetic model organisms, DNA technology and sequencing</td></tr>
</table>

Suggested basic core areas for Systems Biology Education	Masters level programme in Systems Biology	
	Mathematical and computational concepts	• Linear Algebra - stoichiometric modelling – genome scale metabolic reconstructions and models; stability analysis – stability of genetic circuits • Nonlinear dynamics - signalling cascades, kinetic metabolic models, pattern formation, enzyme dynamics, cell differentiation, cellular decision • Stochastic modelling - gene expression circuits, cell motility, ion channels, protein-protein interaction, diffusion. • Spatial modelling - morphogenesis, cell communication, tissue formation, crowding, biofilms • Control theory - design and analysis of metabolic pathways, gene expression circuits, Pharmacokinetics and Pharmacodynamics (PKPD) • Discrete and logic models - genetic networks, signalling networks, cellular differentiation • Complex network analysis - metabolic networks, protein interaction networks, gene – disease networks • Optimisation - metabolic engineering, genome scale metabolic models, parameter estimation in signal transduction networks, reverse engineering
	Networks and processes of life	• Metabolic networks – as relevant for metabolic engineering and diseases; fluxes, kinetics, rates, stoichiometry • Signalling networks – as relevant for information processing, and engineering of cells and organisms; dynamics, feedbacks, adaptation • Gene regulation networks – as relevant for cellular decision making and differentiation, bi- and multi-stability • Cell and population networks – as relevant for development, pattern formation, disease, infection and ecology; cell variability • Genetic networks – as relevant for multifactorial traits and diseases, epistasis, genome-wide association studies (GWAS) • Protein (and other types of) interaction networks – complex inference and functional modules • Oscillatory processes – as relevant for cell cycle, circadian rhythms etc.
	Scientific programmin	• Programming: e.g. Matlab or Mathematica, Python, Perl, Java, R, C, C++ • Tools for genome scale metabolic models (GSMM), kinetic modelling (stochastic and deterministic), network analysis: e.g. Copasi, Cytoscape, OptFlux • Standards: e.g. SBML, SBGN, MIRIAM

	Bioinformatics and statistics	• DNA, RNA and protein sequence analysis • Integrative bioinformatics- interoperability, ontologies, semantics, databases, standards • Genomics of communities, meta-genomics • Molecular evolution • Complex phenotype-phenotype relationships - genome-wide association studies for human diseases and desirable traits in plants, animals and microbes • Data analysis - standard algorithms, basics of supervised and unsupervised statistical learning, data integration • Statistical inference - use of appropriate statistical tests, reverse engineering • Machine learning - clustering; neural networks, random forest
	Experimental design, measurement, analysis, interpretation and knowledge generation	• Quantitative imaging/microscopy - single cell analysis, flow cytometry, image analysis, cell variability • Global and high-throughput data - genetic, transcriptional, proteomic and metabolic networks • Biochemical in vitro assays for quantitative properties of proteins, reactions and interactions • Handling and culturing of cells and organisms • Quantitative and time resolved experimental methods at low throughput – levels of biomolecules, modifications • Principles of system perturbations – genetic, experimental, pharmacological perturbations to test, challenge and control systems • Principles of systems engineering – systems design, genetic and biological engineering, evolutionary approaches

General skills acquired in a Systems Biology educational programme
• An understanding of the type of biological, medical or bioengineering questions that can be approached by integrating experimental data collection with mathematical modelling. • Formulating research problems such that they can be solved by an integrated experimental/mathematical approach. • A good appreciation of the Systems Biology iterative cycle: modelling, prediction and experimental verification. • A well-developed ability to communicate scientific questions across experimental and theoretical disciplines and to collaborate across discipline borders. • A good awareness of different types of modelling and their applicability to research problems as well as in-depth understanding and hands-on experience in specific mathematical modelling approaches. • A good awareness of the type of data generation approaches that are suitable for a given research problem and in-depth understanding and hands-on experience in specific experimental techniques. • Skills in data handling, management and visualisation, including an awareness of statistical analyses suitable for different types of data and experimental designs. • An ability to critically assess evidence and scientific argumentation in integrative studies of biological systems based on an understanding of both experimental and theoretical/computational biology (medicine, bioengineering).
Career paths for students that underwent a Systems Biology education
• Academia is increasingly moving into interdisciplinary recruitments • Business spin-off, for instance in synthetic biology • Biotechnology and bioengineering companies • Data analysis sectors (banks, insurance, consultancy, policy making) • Pharma (drug discovery, diagnostics, *in silico* clinical trials) • Public health clinical medicine, multifactorial diseases • Fine and bulk chemicals incl. biofuels • Bioremediation; environmental monitoring; sustainable and predictive resource management • Agro-biotech; Food biotech • Science and research management