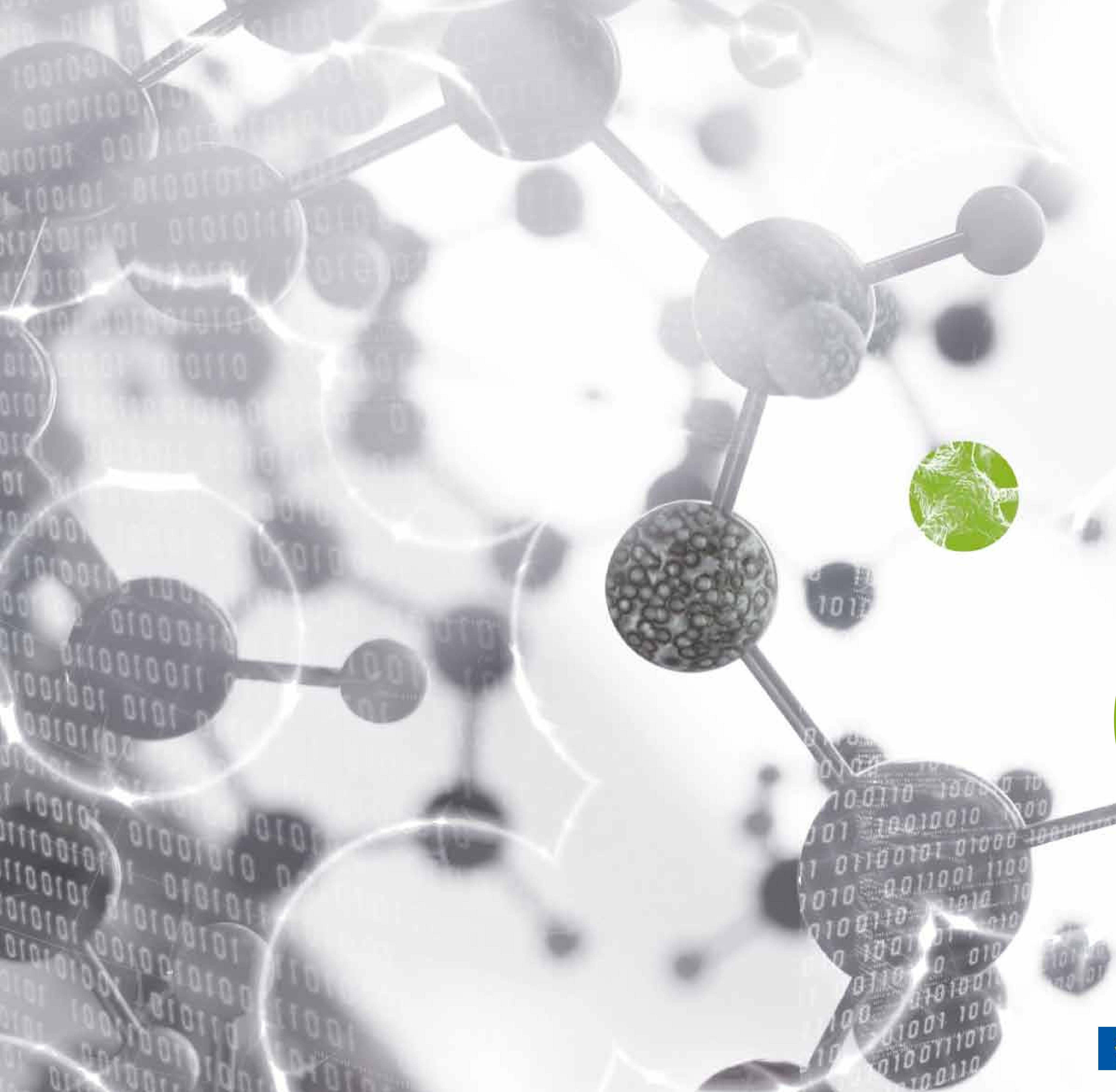

ERASysAPP
ERA-Net for Applied Systems Biology

STRATEGIC
RESEARCH AGENDA

SYSTEMS BIOLOGY IN EUROPE 2016

July 2016

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Summary

The overall conclusions of this Strategic Research Agenda (SRA) are that the field of systems biology has become an important component of the European life sciences. A strong European systems biology community has been formed that is able to take initiatives, such as FAIRDOM (Chapter 5) and ISBE (chapter 7). The 5 most important recommendations in the SRA are summarised below.

1	Develop novel larger-scale and longer-time funding schemes for academic research and for academia-industry collaboration that link molecular and cellular processes with the physiological properties of tissues, organs, complete organisms, up to ecosystems. Such measures will have a major impact on health, food, bio-economy and sustainability.	Chapter 3
2	Make industry, in particular SMEs, aware of the opportunities, costs and timelines of building, validating and exploiting predictive models of biological systems, through dedicated training programmes.	Chapters 4 and 6
3	Increase the efficiency and cost-effectiveness of research projects by making their integrated results (data, procedures, models, maps, etc.) FAIR: **F**indable, **A**ccessible, **I**nteroperable and **R**e-useable. Make the FAIR principle an explicit component of research budgets.	Chapter 5
4	Accelerate the incorporation of systems biology in current academic curricula; developing dedicated multidisciplinary MSc and doctoral programmes and foster life-long training for professionals.	Chapter 6
5	Invest in the development of European Research Infrastructures, such as the European Systems Biology research infrastructure ISBE, and make them the solid bedrock for this Strategic Research Agenda and other European research policies in the biomedical and life sciences.	Chapter 7

1 *INTRODUCTION*

This Stratetic Research Agenda (SRA) on Systems Biology[1] in Europe 2016, is an initiative of the ERA-Sys*APP* project funded by the EC under Framework Programme 7 (FP7). The ERA-Net project fell under the theme of building a European Knowledge Based Bio-Economy by bringing together science, industry and other stakeholders, to exploit new and emerging research opportunities that address social, environmental and economic challenges. In this ERA-Net for Applied Systems Biology, 16 funding agencies and other partners cooperate. It predominantly aims at funding transnational application oriented systems biology research that encourages institutions and scientists from different countries, EU Member States and other countries, to network and share existing resources. This SRA is a follow up of the vision paper Towards a European Research Area for Systems Biology published in 2008 by the ERA-Net ERASysBio[2]. This document was written as a community effort and is based in part on the outcome of the ERASys*APP* workshop on the SRA improvement (2014, Zurich) and several other ERASys*APP* workshops and extensive conversations over a timespan of three years.

The aim of this document is to offer a vision on the development of systems biology in Europe until 2026 as a key component of the life sciences. It is written for scientists, funders, policy makers and industry, that share the vision that the life sciences are essential for our health, food, bio-economy and sustainability. This SRA aims to provoke and focus discussion and to help planning the future.

1 See for a formal description of the term 'systems biology': Box 1 (Section 2.1)

2 https://www.erasysbio.net/lw_resource/datapool/__pages/pdp_2/ERASysBio_Systems_Biology_Strategy_Paper_25-Mar-2008.pdf

This SRA is structured in seven chapters. Chapter 2 presents an analysis of what has been achieved since publication of the 2008 vision paper, followed by a vision for the next 10 years. Chapters 3 through 7 address five major issues that are vital for the development of systems biology and its integration in the life sciences and in industrial innovation. These are:

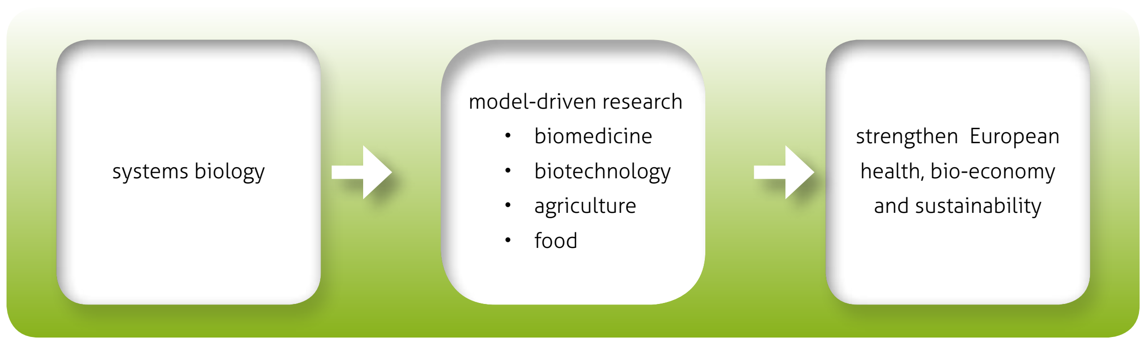
- funding of collaborative research
- partnership of academia and industry
- management of results of research projects (data, procedures, models, maps, etc.)
- education and training
- the role of European research infrastructures

Each chapter starts with a short overview of the present situation, followed by an analysis of how to move forward and what challenges must be faced, and ends with concrete recommendations. The chapters are deliberately somewhat free-standing to allow the reader to concentrate on specific topics without having to go through the complete document. Five appendices have been added to provide background information:

- links to several strategic documents in the field of systems biology
- examples of major investments in systems biology and
- examples of systems biology-driven research projects
- European research infrastructures in the life sciences
- abbreviations and links
- ERASys*APP* partners

Figure 1.

Systems Biology affects the key elements of applications in European health, bio-economy and sustainability.



2 SYSTEM BIOLOGY – THE PAST AND THE NEXT 10 YEARS

This chapter summarises the development of the European systems biology field since the previous Strategic Research Agenda was published in 2008. A vision is presented for the next 10 years outlining how systems biology will become fully integrated in the life sciences and impact on our society. Several of the issues raised below are addressed in more detail in the following chapters, resulting in concrete recommendations.

2.1 The past 10 years

In modern physics, chemistry and engineering predictive computational models play a central role in investigating complex systems. In the past 10 years this approach has also become possible in the life sciences, due to the growing availability of comprehensive data about cells, tissues and organisms. Model-driven research paves the road towards a better understanding of the functioning of complex biological systems (Box 1). In effect, this allows us to interfere with and modify their functioning in a predictable and efficient way.

BOX 1: SYSTEMS BIOLOGY

The research approach of systems biology typically involves collaborations between biology, medicine, engineering, information sciences, mathematics, chemistry and physics.
The heart of the systems biology approach is an iterative process between laboratory experiments and mathematical modelling. Based on large volumes of diverse types of quantitative data at the molecular, cellular, tissue and organ level, algorithms are used to create models that allow predictions about the behaviour of biological systems. The aim is to gain overall understanding of such systems.
Adapted from the definition of the German Federal Ministry of Education and Research (BMBF).

Public investments

National governments and the European Commission have recognised the potential of this development for health, the bio-economy and sustainability. In the past 10 years they have invested over € 750 Million in research programmes in which systems biology and systems medicine have a central role. These efforts have been coordinated and enhanced through dedicated transnational ERA-Net and Coordination Action projects. In addition, a range of FP7 and Horizon 2020 calls implemented systems biology. Examples of national and European major investments are provided in Appendix B.

Industry

Life sciences related industry has started to integrate systems biology approaches in innovation pipelines, albeit at a slower pace than seen in academic research. In particular, pharmaceutical industry and agricultural and microbial biotechnology companies have invested in systems biology. However, high visibility breakthroughs are still scarce. This is mainly due to the complexity of biological systems. System level understanding through building and validating predictive computational models has a high potential for the development of new products, processes and services. However, it often requires larger scale and longer term research efforts than industry is used to. Consequently, companies have been hesitant to make the necessary investments. Smart collaboration between academia and industry should help to overcome this hurdle.

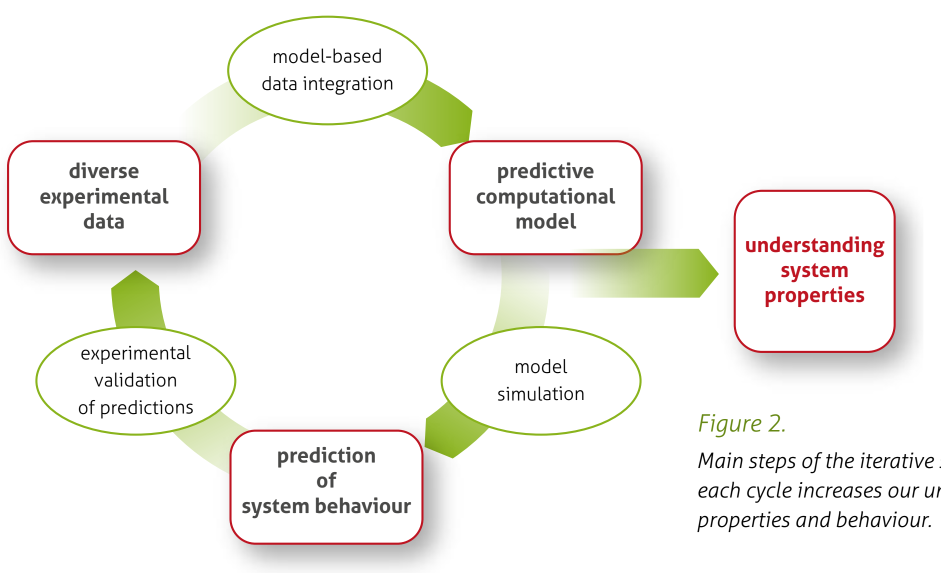


Figure 2.

Main steps of the iterative systems biology cycle: each cycle increases our understanding of system properties and behaviour.

Bridging the gap between molecular biology and physiology

Systems biology is moving from cellular (molecules and cells) to supracellular levels (tissues, organs and complete organisms) in microbial systems, plants and animals, including human beings. For instance, the Virtual Human Heart project[3] produced predictive models of the beating human heart. It gives deep insight about how processes at the molecular, cellular, electrophysiological and tissue levels interact in time and space to generate a beating heart. More recently the Virtual Liver Network[4], funded by the German Ministry of Education and Research (BMBF), has been seeking to develop computational models of the human liver. These integrate quantitative data from all levels of liver organisation, representing human liver molecular networks, physiology, morphology and organ-level function. A number of projects that focus on human organs and tissues are brought together by the international Virtual Physiological Human (VPH) Institute[5]. Similar types of concerted actions have also started in other segments of the life sciences. An example is the Digital Salmon[6] project funded by the Research Council of Norway (Box 2). Similar projects have started for plants.

Systems medicine

Important parallel developments aim to bring systems biology to the clinic. The FP7 Coordination Action project CASyM and the related recent Horizon 2020 ERA-Net project ERACoSysMed are examples of systems medicine initiatives at the European level (Appendix B). In addition, a variety of Framework Programme 7, Horizon2020 and national research programmes focus on systems medicine to improve drug development, diagnostics and treatment strategies.

BOX 2: DIGITAL SALMON

Towards the Digital Salmon: From a reactive to a pre-emptive research strategy in aquaculture (DigiSal)
Systems biology will aid sustainability in salmon farming. Scarcity of fish oil has forced development of novel feedstuffs, challenging the salmon's metabolism as well as our understanding of it.
The project DigiSal will lay the foundations for a *Digital Salmon*: an ensemble of mathematical descriptions of salmon physiology, combining mathematics, high-dimensional data analysis, computer science and measurement technology with genomics and experimental biology into a concerted whole.

Education and training

In 2008, as the previous Strategic Research Agenda on systems biology was published, academic curricula in the field of systems biology hardly existed and postdoctoral training projects had just started. Because curricula in life sciences and biomedicine generally pay limited attention to mathematics, academic education in systems biology had a slow start. Through a steadily growing number of postdoctoral courses an increasing number of scientists with a background in biology, biomedicine, physics, chemistry, engineering and mathematics became interested and proficient in model-driven life sciences. This has sparked a new breed of researchers able to work and teach at the multiple interphases of the life sciences with mathematics, physics and engineering. Also, complementary training of professionals and practitioners is beginning to grow. As a result, a steadily increasing number of universities start to offer MSc and doctoral programmes in systems biology. Steps have been made to accelerate this process through sharing experience and exchanging teaching material and teachers between European universities.

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3 http://physiomeproject.org/research/cardiovascular
4 www.virtual-liver.de
5 www.vph-institute.org
6 http://www.nmbu.no/om/fakulteter/vetbio/institutter/iha/forskning/prosjekter/node/24555

2.2 Reflection on the recommendations in the strategic agenda of 2008

It is enlightening to compare the recommendations in the strategy paper on European systems biology that was published in 2008[7] with the current situation in the field. The analysis shows what issues were successfully tackled by scientists and funding agencies, and those challenges identified in 2008 that still need attention. For practical reasons several 2008 recommendation have been clustered.

Recommendations made in 2008

Recommendation 1: Establish a number of transnational systems biology networks in the ERA and stimulate the establishment of systems biology research structures across the ERA

Considerable progress has been made as the result of several ERA-Net projects and multiple national funding initiatives (Appendix B). A solid European systems biology community has been formed, covering many subfields of the life sciences. This community will be consolidated by the development of the pan-European systems biology research infrastructure ISBE, which will consist of a collaborative matrix of national systems biology centres (see Chapter 7).

Recommendation 2: Encourage the adoption of data management and sharing best practices and of data standards in the ERA

A major step to improve data management and adoption of standards across life sciences communities, has been taken through the transnational FAIRDOM project that started under the auspices of ERASys*APP* and will continue within ISBE. It builds on the FAIR principle that makes research assets (data, tools, operation procedures, models, etc.) findable, accessible, interoperable and re-usable and offers services, tools and software to the scientific community (see Chapter 5).

Recommendation 3: Optimise the education and training in systems biology in the ERA

A growing number of courses and workshops for postdoctoral scientists have been organised in the past seven years, supported by a variety of organisations, including ERA-Net projects. Also, universities are starting to offer systems biology MSc curricula and doctoral programmes or incorporate systems biology components in their regular educational programmes (see Chapter 6).

Recommendation 4: Explore mechanisms to strengthen the academic-industrial links in systems biology in the ERA

Academic-industrial collaboration has been and still is strongly stimulated by national governments and the EC. Many national, transnational and EU funding schemes have enforced collaboration between academia and industry. Nevertheless, there is some concern that these relatively short-term collaborations are not optimal for systems biology types of research, given the large effort that often is necessary to deal with the high complexity of biological systems. Therefore, optimising longer-term collaborations between industry and academia still needs attention (see Chapters 3 and 4).

Conclusions

Considerable progress has been made over the past seven years in developing a strong science base for systems biology and its integration in the life sciences. International collaboration and knowledge exchange have expanded and a start has been made with developing best practices in data management and sharing. Also academic teaching and training has improved and grown. Most importantly, a strong European systems biology community has emerged that is able to take initiatives. FAIRDOM and ISBE are examples (Chapters 5 and 7).

7 https://www.erasysbio.net/lw_resource/datapool/__pages/pdp_2/ERASysBio_Systems_Biology_Strategy_Paper_25-Mar-2008.pdf

BOX 3: UNDERSTANDING A BIOLOGICAL SYSTEM (e.g. cell, tissue, organism)

The promise of systems biology is that it provides understanding of the mechanistic functioning of biological systems at a level that allows us to predict how they behave after changing one or more of their components or their environment.

2.3 Vision for the next ten years

The next step: from molecules and cells to tissues, organs, organisms and ecosystems

In the next ten years systems biology will become a key element in research that aims at understanding complete organisms, encompassing plants, animals, human beings and ecosystems (see Box 3). They will be analysed in terms of networks of molecules, cells, tissues, organs and organisms that dynamically interact in time and space. Model-driven approaches will give insight into the mechanistic functioning of these multi-scale networks. First steps in this direction have already been made, e.g. on salmon, DigiSal, and the Virtual Liver Network (Boxes 2 and 4). The results of this development should allow us to create the necessary basis for effective (personalised) medicine, enhancement of the bio-based economy and sustainability. Importantly, these efforts will reveal basic principles of how living organisms function. This will eventually allow us to influence and alter the properties of living organisms in a rational and predictive way with all its benefits and potential risks. Here systems biology and synthetic biology converge.

This vision is somewhat optimistic and will require commitment and effort. It is not simply a matter of good research and sufficient budget. It also requires fundamental changes in the way we do research, how it is funded and how we educate scientists. Below three major issues are briefly addressed. More detailed discussions follow in the next chapters.

Re-thinking teaching and training

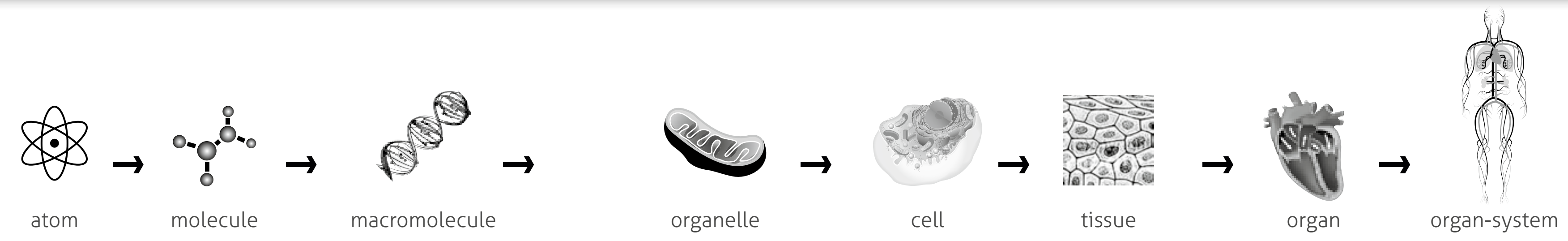
It will be essential to change our mainly mono-disciplinary educational system towards a multi-disciplinary science approach. The aim is to create next generation biologists, medical doctors, physicists, chemists and mathematicians that are able to work and communicate across current disciplinary borders. MSc and doctoral programmes and post-doctoral courses with a systems biology focus exist already in many higher education institutions, but they need to be implemented more broadly. Cooperation and exchange of expertise, teaching material and teachers in European will accelerate the process. A hurdle is that more teachers need to be trained in an interdisciplinary manner before education and training can be implemented broadly. Dedicated training programmes for industry will be necessary to acquaint them with the opportunities that model-driven research and development in the life sciences offer (see Chapters 4 and 6).

Making expertise and resources in systems biology easily accessible

Building, validating and stepwise expansion of good quality predictive models of biological systems require insight into biology that is paired with modelling skills. Such combined expertise is often not readily available. To overcome this limitation a pan-European infrastructure for systems biology (Infrastructure for Systems Biology Europe (ISBE)) is being developed. Together with a number of other European research infrastructures, e.g. ELIXIR (the European Life-Science Infrastructure for Biological Information) covering a broad range of fields and

Figure 3. Complete understanding of a system

The combination of information from various sources on multiple levels – from molecule to full understanding of a biological system



technologies, ISBE constitutes a solid basis for strengthening the research workforce in the life sciences and biomedical sciences (see Chapter 7 and Appendix C).

Making results of research projects findable, accessible, interoperable and re-usable

Integrating experimental data in stepwise expanding computational models requires coordinated research efforts over longer periods of time. Therefore, research results must be available for re-assessment, re-use and integration for a minimum of 10 years. This calls for widely used best practices and standards for structuring and describing data, as well as resources to assist with curation and long-term storage of research assets. The FAIRDOM initiative, initiated by ERASys*APP* and ISBE, is working on this (see Chapter 5).

In short

In the past 10 years systems biology has been fully integrated in the life sciences. Like other subfields it develops rapidly towards tackling more complex systems; a process that will continue. What needs special attention and investments in years to come are what one may call 'cultural changes' in the life sciences. Changes that will enable us to optimally profit from modern life sciences, including systems biology. The next chapter elaborates on this.

3 *Funding collaborative research – a changing life sciences landscape*

In this chapter it is argued that the changing research landscape of the life sciences calls for novel types of funding and larger scale well-managed collaborative research projects.

3.1 Present situation

In the past decade national, transnational and EU-funded research programmes have successfully introduced systems biology into the European life sciences. Examples of EU-supported transnational investments are SYSMO (systems biology of microorganisms), ERASysBio and ERASysBio-plus (general systems biology), ERASys*APP* (application-oriented systems biology) and the recently started ERACoSysMed (systems medicine), linked to CASyM (Coordinating Action Systems Medicine). For a detailed overview see Appendix B. Framework Programme 7 and Horizon 2020 calls show an increasingly focus on the implementation of model-driven approaches in the life sciences, including biomedical research. At the same time, national systems biology research programmes have been initiated in several European countries. These programs mostly focus on the molecular and cellular level. In parallel, there is a development to move to higher biological levels, i.e. tissues, organs and complete organisms and ecosystems. Several are bundled in the Virtual Physiological Human (VPH) Institute[8]. Together, these investments have resulted in a strong systems biology community in Europe and moved systems biology towards the centre stage of the European life sciences.

Lessons learned from 10 years funding programs in systems biology

The promise of systems biology is that it provides understanding of the mechanistic functioning of biological systems at a level that allows us to predict how they behave after changing one or more of their components or their environment. For relatively simple systems, such as metabolic networks of microorganisms, this has been achieved to a reasonable level, creating an important proof-of-principle. For more complex systems, e.g. complete plants or human beings, this level of understanding is still far away.

Tackling highly complex systems needs well-coordinated research efforts between a large number of groups from different disciplines and nationalities over longer periods of time. Long enough to allow the collection of high quality quantitative data and integrating these in predictive computational models, followed by model validation and using the model to understand system behaviour. Current funding schemes are not optimally suited for this: they are too small, too short and often lack adequate research management.

3.2 Challenges

Linking the molecular and cellular level to physiological processes in tissues, organs and complete organisms will be a major research goal in the forthcoming decade, both in health-related research and in biotechnology. The German Virtual Liver Network (VLN) programme is an early example of the former (see Box 4). Developing new types of funding and collaboration schemes that enable us to address highly complex biological systems in a comprehensive way, requires joint efforts of the scientific community, European and national funding agencies and industry. Below we list several challenges that must be faced.

Novel funding schemes

Acquisition of high quality data that cover the different components and the various functions of a biological system is time consuming and therefore expensive. Subsequent building of predictive computational models is only useful if they are thoroughly validated and analysed and give insight into the functioning of systems: this also is an elaborate process. The amount of work needed is often underestimated. Given the volume (1 – 15

8 http://www.vph-institute.org/

BOX 4: VIRTUAL LIVER NETWORK

The Virtual Liver Network (VLN) is a large German research investment tackling a challenge in the life sciences: how to integrate the wealth of data we have acquired in a series of mahematical models that are linked across scales to represent organ functions. As the project is prototyping how to achieve true multi-scale modelling within a single organ and linking this to human physiology, it develops tools and protocols that can be applied to other systems, helping to drive forward the application of modelling and simulation to modern medical practice. It is the only programme of its type to our knowledge that bridges investigations from the subcellular to ethically cleared patient and volunteer studies in an integrated workflow. As such, this programme is contributing significantly to the development of a new paradigm in biology and medicine.
(http://www.virtual-liver.de/)

M€ range) and time span (3 – 5 years) of typical national and European funding schemes, a considerable fraction of systems biology projects is unable to deliver and validate computational models let alone get insight into how systems function. This calls for re-thinking the way the life sciences are funded. Novel funding schemes are required that allow scaling-up over prolonged periods of time. What holds for academic research is also true for collaboration between academia and industry in the field of systems biology. To deliver commercially valuable innovations requires a longer term vision and investments. Current academic-industry cooperation research projects, with a typical timespan of 3 to 5 years, seem too short to be successful and create breakthroughs. The ERA-Net schemes in Horizon 2020 are replaced by the ERA-Net Cofund format[9]. It may be an opportunity to rethink funding formats of systems biology related projects. It is the responsibility of the scientific community, together with national and European funding agencies and industry to critically evaluate research funding and draw relevant conclusions.

Converging of research fields

Systems biology as well as synthetic biology approaches have been found to accelerators for innovation in the industrial biotechnology field. An ERA-Net Cofund Biotechnology[10] is currently being established that encourages the combination of these technology fields to accelerate the process for downstream industrial application. The funding scheme is expected to increase the visibility of potential benefits of a bio-based economy for the society. The significant engagement of industrial partners in these activities will be an important driver to address market needs and facilitate the exploitation of the results. The projects funded under this scheme are expected to benefit from existing knowledge and resources for the development of demonstrators close to the market. Arguably, national funding schemes are expected to follow this example.

Research management

Professional research management is essential for the success of larger-scale research programmes. It should keep research programmes focussed and on track, balance the different interests of the individual researchers, guarantee quality and represent the research programme to the outside world. And all this without hampering scientific creativity. In the life sciences there is remarkably little experience with professional management of research programmes. The few cases that are known , such as the Virtual Liver network, show good and accepted research management that can be highly beneficial. It will be important to invest in the development of adequate management tools that are effective and accepted by the research community. Funding organisations should support this and make it a component of their research budgets. These investments are likely to be highly cost-effective.

9 https://www.era-learn.eu/manuals-tools/p2p-in-h2020/background-information

10 http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/2391-biotec-01-2016.htm

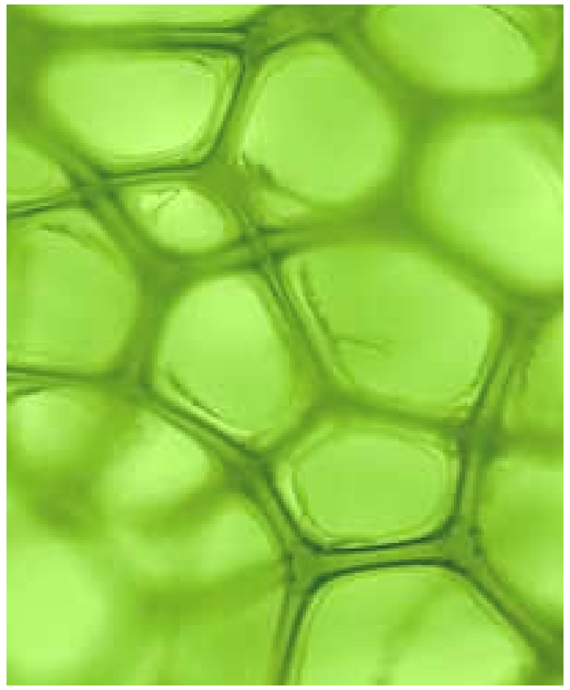
Engagement with society

Linking molecular and cellular mechanisms to physiological processes in tissues, organs, whole organisms and ecosystems will have a major impact on health, bio-based economy and sustainability and therefore on society at large. One example – out of many – are novel decision support systems for medical doctors that help make predictions about what is the best therapy for individual patients. Such tools will be based on predictive models and need to include much more personal biomedical information from the patient than is currently used. Developments like this will need societal consensus to establish the legal framework that ensures data ownership and controls the use of this information for the benefit of the patient. Therefore, it will be essential to involve stakeholders outside the scientific community in developing long-term visions and setting priorities in the life sciences. This also should increase the awareness of what and when research may realistically deliver and what the costs, risks and uncertainties are. The increasing interest of the EU and national funders in Responsible Research and Innovation[11] (RRI, see Box 5) can be used as a vehicle in the process.

BOX 5: RESPONSIBLE RESEARCH AND INNOVATION (RRI)

Responsible Research and Innovation (RRI) is an approach that anticipates and assesses potential implications and societal expectations with regard to research and innovation, with the aim to foster the design of inclusive and sustainable research and innovation.
RRI implies that societal actors (researchers, citizens, policy makers, business, third sector organisations, etc.) work together during the complete research and innovation process in order to better align both the process and its outcomes with the values, needs and expectations of society.

11 https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation



3.3 Recommendations

- Develop novel larger-scale and longer-time funding schemes that allow linking molecular and cellular processes to physiological properties of tissues, organs and complete organisms up to ecosystems.
- Develop research management strategies and tools that ensure efficiency of large-scale research programmes. Make effective research management a standard component of research budgets.
- Involve non-scientific stakeholders in developing and supervising large-scale research programmes. Link to the increased interest of funders and scientists in Responsible Research and Innovation (RRI).

4 *Academia and industry – innovation through systems biology*

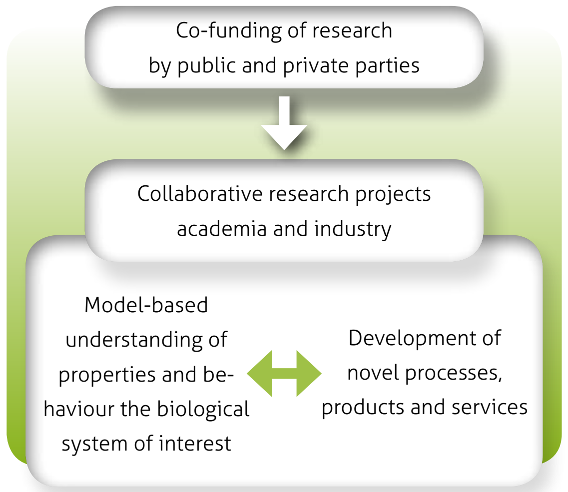
This chapter addresses the growing role of systems biology in collaborations between academia and industry. It is questioned whether current types of collaborative projects are optimally effective. Suggestions for improvement are made.

4.1 Present situation

National governments and the European Commission strongly stimulate collaboration between academia and industry. Many funding schemes require that industrial partners, in particular SMEs, are co-applicants in research projects in order to translate results into services and products. The aim is to increase the impact of life sciences on health and environmentally friendly and safe production of food, chemicals and energy. At the same time this policy seeks to enhance the European bio-economy, making bio-based industry a European spearhead to create jobs and stimulate growth[12]. These efforts have increased industry's awareness of systems biology and initiated a process of incorporating model-based approaches in industrial research and development. Particularly microbial, agricultural industries and pharmaceutical companies have incorporated systems biology in their research programmes.

12 http://www.oecd.org/futures/long-termtechnologicalsocietal-challenges/thebioeconomyto2030designingapolicyagenda.htm

Figure 4. Systems biology: opportunities for collaboration between academia and industry



Current funding schemes are not optimal for academia-industry collaboration

Despite the potential of predictive computational models, systems biology-based breakthroughs in industry are still scarce. It will be important to evaluate how effective present academia-industry collaborations are and to identify how they can be made more successful. At a basic level, teaming up between academia and industry is challenging for both sides. Often there is a mismatch between expectations and research cultures that hamper trust and partnership. Experience shows that systems biology approaches need long-term investments to acquire the necessary high quality data, integrate them in predictive computational models and validate and subsequently exploit models to develop new processes, products and services. Generally, neither public funding agencies nor industry are prepared to commit to such investments. Particularly SMEs struggle with this, because return of investment is not expected to happen soon after the end of a project. This often results in research projects that are at best partially successful in terms of predictive computational models that are useful for industry.

Effective collaboration with industry in research programmes that involve systems biology requires that the industrial partner has a realistic insight into opportunities, limitations, costs and timelines of building, validating and exploiting predictive models. Generally, this knowledge is not sufficiently developed, either in large industry or in SMEs. Development of dedicated basic and advanced training courses for industry is necessary (see Chapter 6).

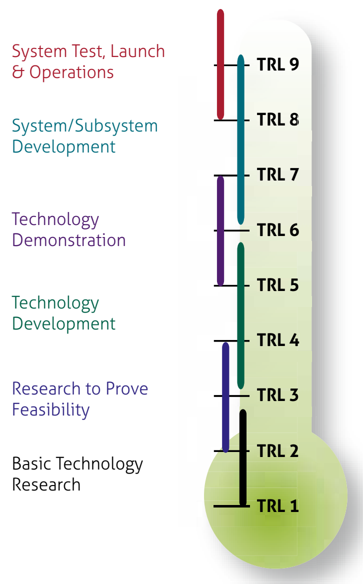
Academia-industry cooperation is common in the broader field of the life sciences. A large-scale example is the Innovative Medicine Initiative (IMI 2) that started in 2014 with a duration of 10 years and a budget of € 3.3 Billion[13]. Here pharmaceutical industry co-funds a EU programme to intensify public-private partnerships in pre-competitive projects. Another example is the Bio-Based Industries Joint Undertaking (BBI, € 3.7 Billion)[14], which has been established following the successful IMI example. So far, systems biology does not play a prominent role in these programmes. In this, ERASys*APP* is a unique transnational ERA-Net programme, as it has been tailored to specifically support application-oriented systems biology research, funding particularly research projects in Technology Readiness Levels 1 – 3 (see Figure 5). Although the funded projects have only 3 years duration, there is considerable engagement of industry. As indicated above, it will be important to critically analyse the results of the funded projects for their impact after the ERASys*APP* programme finishes in 2019.

13 www.imi.europa.eu
14 ww.bbi-europe.eu

Figure 5. Technology Readiness Levels

In order to stimulate innovation and technology in a focused way, funding schemes should define the appropriate Technology Readiness Levels (TRL). TRLs are based on a scale from 1 to 9 with 9 being the most mature technology. The use of TRLs enables consistent and uniform discussion of technical maturity across different types of technology.

More info:
https://en.wikipedia.org/wiki/Technology_readiness_level



4.2 Challenges

There is little doubt that approaches based on predictive computational models are an effective way to tackle complex biological systems. To help society profit from the rapidly growing knowledge base and toolbox of systems biology, in combination with the explosion of analytical technologies (e.g. omics and imaging), a major effort should be made to bring the necessary expertise and knowledge to industry. This requires intense collaboration between industry and academia. Investments in joint academia-industry projects that implement systems biology in innovation pipelines show promising results. However, there are major challenges in public-private collaborations in the field of systems biology that need to be addressed.

Engaging industry in systems biology

The knowledge base available in industry in the field of systems biology should be enhanced. As argued above, insight into opportunities, limitations, costs and timelines of building, validating and exploiting predictive models of biological systems are often limited, both at the scientific and the management level. This makes it difficult, even for the few larger companies that have (often still modest) systems biology departments, to fully benefit from model-driven approaches in the life sciences. This also impairs the development and execution of effective joint academia-industry research projects.

Particularly SMEs may benefit from focussed training programmes that assist industry to optimally position systems biology in their innovation pipelines.

Cooperation between academia and industry needs longer-term projects and improved management

As argued above, systems biology-based research programmes are generally more demanding than classic projects in the life sciences. Data generation, modelling, model validation and exploiting models require more time than the typical 3 to 5 years projects provided by most funding schemes. Given the differences in research culture and aims between academia and industry, collaboration may significantly benefit from professionalising research management. This is particularly true for projects that involve systems biology, because of their inherent complexity and multidisciplinarity. Dedicated training and support in research management through funding agencies and Technology Transfer Offices (TTOs) may help to overcome these hurdles before or in an early stage of collaborative projects.

Non-commercial private organisations

An important group of non-governmental and non-commercial stakeholders that are involved in funding research are charities (e.g. the Wellcome Trust in the UK), foundations initiated by philanthropists (e.g. the Bill and Melinda Gates Foundation) and foundations related to specific companies (e.g. the Novo Nordisk Foundation). Several organisations, operating nationally or internationally, have vested interests in the life sciences and maintain strong links with academia and industry. Often they address major societal issues, for instance enhancing healthcare or sustainability. It will be important to involve them in implementing model-driven approaches to get the necessary deep insight into the functioning of biological systems and exploit that knowledge to address the grand challenges of our society.

4.3 Recommendations

- Evaluate current and past funding programmes that foster academia-industry collaboration and find out how effective they are in implementing systems biology in industrial innovation.

- Depending on the outcome of above evaluation, consider novel types of funding schemes for academia-industry collaborations that use systems biology. These should have a time line and budget that is realistic for the acquisition of high quality data, model building, model evaluation and translating model-based understanding to innovation.

- Develop dedicated training programmes for industry (particularly SMEs) that give insight into opportunities, limitations, costs and timelines of building, validating and exploiting predictive models of biological systems.

- Professionalise research management of projects to overcome differences in expectation and research culture between industry and academia.

- Seek to engage non-commercial private foundations in implementing systems biology to address major societal challenges.

5 *Data and model management – the Rosetta Stone*

This chapter describes the need for good practices in the management of the results of research projects in the life sciences in general and systems biology in particular. It summarises the first steps that recently have been made to achieve this. This is followed by an analysis of major challenges in data management that we will face in the forthcoming years and ends with concrete recommendations for how best to address these challenges.

5.1 Present situation

An urgent problem

A major problem in the life sciences is that a large portion of experimental data cannot be re-used in follow-up research. It is estimated that 80-90 % of all research data is never used by other researchers[15]. This problem exists despite the fact that funding organisations and scientific journals generally require that results are stored in accessible repositories using standard data, as are available for many types of omics data. The key problem is that even if data is available, it tends to be poorly annotated. Therefore, it is unclear how it has been acquired and under what conditions, making re-use for others difficult if not impossible. Relatedly, the multitude of places where data and models can be stored make it difficult to systematically search for specific data. Examples are personal hard-drives (data available on request) and websites that give access to supplementary material belonging to publications or public repositories and databases. The impact of this fragmentation is that it makes life sciences research inefficient and expensive.

Towards a FAIR solution

Adequate management of data, procedures, models, maps and more should ensure that research results are of FAIR quality (see Box 6), i.e. that they are:

- **F** indable: can be searched for after publication
- **A** ccessible: can be read/downloaded by others
- **I** nteroperable: understood clearly in the context of the original experiment
- **R** e-usable: can be used by other researchers

FAIR quality encourages researchers to manage their research using good practice. This involves: (i) formatting research results in consistent ways, (ii) including adequate metadata so that the context of the results can be understood and reproduced, (iii) storing results after publication in open, searchable databases. Such good practice is vital for research, ensuring maximal impact of investments and allowing research assets to be exchanged and re-used more easily between researchers. The key tools required for FAIR data and model production are: standards, dedicated software and searchable repositories.

Community standards

Data and model standards are an essential tool in organising and describing research. Systems biology has standards for formatting and annotating data and models. They are designed by experts with an understanding of what key information will comprise the outcome of an experiment and how it is best structured in a written format. These agreements generally happen at a grass-roots level through the COMBINE community[16]. In addition, there are several relevant top-down standards developed by the International Standards Organisation (ISO)[17]. For instance the recently established ISO Technical Committee on Biotechnology (ISO/TC 276)[18] has a dedicated working group on data integration and processing.

Standardised formats are used to structure knowledge from experiments and models in a consistent way, so that key information can

15 Winkler-Nees, http://www.ariadne.ac.uk/issue64/datacite-2010-rpt

16 http://www.combine.org/

17 http://www.iso.org/iso/home.html

18 http://www.iso.org/iso/home/standards_development/list_of_iso_technical_committees/iso_technical_committee.htm?commid=4514241

be easily found by researchers and by software. Formats exist for structuring models (e.g. SBML, CellML), simulating models (e.g. SBRML, SEDML), visualising models (e.g. SBGN), structuring data (e.g. MzTAB for Proteomics) and structuring investigations (e.g. ISATab). See Appendix D for acronyms and links.

Metadata is information about data or descriptions of data, used to describe knowledge from experiments and models (e.g. strains of an organism, media used for growth, pH, etc.). Standard Operating Procedures (SOPs), which are in-depth descriptions of methods used to produce the data, are key in supporting metadata descriptions. Minimum Information Checklists are used to ensure that data, models and SOPs contain enough description to be understandable. It has been noted that present systems biology standards are not suitable for all types of data. For example,. for physiology models and certain cellular processes, such as transcription, no mature standards are available yet.

Dedicated Software

Research projects require data and model production and analysis. Dedicated software is the best way of running these analyses, because it allows (i) experts and non-experts to run an analysis without the need to rewrite the code, (ii) errors in analysis, resulting from incorrect coding of a method, to be traceable, (iii) automatic structuring and annotation of data and models. There is software in systems biology to assist with model generation (COPASI[19], JWSOnline[20], CellML), model simulation (COPASI, JWSOnline, CellML, and FAME[21]) and visualisation (COPASI, JWSOnline, Cytoscape, Cell Designer). For reliable software used by the community, longevity and continuous development must be guaranteed. Due to the current short-term funding cycles, this cannot be ensured as it often relies on personal engagement of individual researchers.

19 http://www.copasi.org/
20 http://jjj.mib.ac.uk/
21 http://f-a-m-e.fame-vu.cloudlet.sara.nl/ajax/page1.php

Data, protocols, model repositories and commons

Commons are centralised public resources that aggregate the diverse results produced by a research project. Repositories and commons allow data and models to be made available publicly or restricted, for searching and re-use. They are ways of storing and managing data and models.

Most repositories in the life sciences are data-type specific, for example only for storing genome data. This is great for cross-comparing data, but not so useful for model-based data integration. Commons allow data, procedures, models etc. to be interlinked, stored and managed using contextual relationships rather than data type. The most popular commons platform in systems biology is SEEK[22], which uses the Investigations (project context), Study (unit of research), Assay (analytical measurement) format[23] to organise research assets hierarchically. In contrast, presently it is usual for researchers to share their data and models publicly via 'supplementary material' linked to publications, which is neither searchable nor standardised. We therefore need to move away from this traditional mode of sharing.

BOX 6: The FAIR guiding principles for data, models and other research assets

To be Findable: can be searched for after publication

To be Accessible: can be read and downloaded

To be Interoperable: can be understood clearly in the context of the original experiment

To be Re-usable: can be used by other researchers

22 http://fair-dom.org/seek
23 http://isatab.sourceforge.net/format.html

Data, models, procedures, etc. must remain available over a long period of time

In the life sciences, it is important that FAIR research results in repositories and commons remain available, searchable and accessible for longer periods of time. Knowledge and particularly models rely on a stepwise expansion with each step adding more data and novel insight. For this process the older data, models, procedures, etc. must remain available. Presently, a considerable portion of research results are not stored in ways that ensure their accessibility over longer periods of time (e.g. 10 years) due to inadequate maintenance of the repository and/or the unavailability of software to access older data.

5.2 Challenges

Moving forward, FAIR management of research assets should become an integral component of national and European research projects, implemented by all researchers. This will significantly increase opportunities to reproduce, access and re-use data, tools and models over longer periods of time. Research results will be well-structured and annotated according to community best practices, so they can easily be understood and used by other researchers. Importantly, researchers will no longer have to only rely on publication of their work as the de facto yardstick of their impact on a research field. Results of research projects (data, models, procedures, etc.) themselves will become 'first-class citizens', being sharable, understandable, re-usable and citable. Reaching this situation poses several challenges as indicated below.

Convince scientists and enforce FAIR data policy in nationally and EC-funded research

Funding organisations need to accept that making research assets FAIR will cost money and effort. This should be made explicit in grant applications. On the other hand, the findability and re-usability of results will make research significantly more cost-effective and efficient, i.e. saving money. Also publishers should take responsibility by requiring FAIR data management instead of the usual 'supplementary information' for publications. FAIR type data management should become a standard component in doctoral and post-doctoral training programmes for life scientists in general and systems biologists in particular.

Ensure long-term storage and accessibility of data, models, procedures, tools and software

Currently, many archives do not have long-term sustainable funding plans. So, when support runs out, the repositories decline and the data and models are no longer findable and accessible. European infrastructures such as ELIXIR and ISBE could be solutions that enable the sustainability of relevant resources.

5.3 Recommendations

- Make the FAIR concept a guiding principle in funding and publishing.
- Invest in acceptance and implementation of standards and best practices through guidance, training and easy-to-use software.
- Invest in the development and the maintenance of community standards development.
- Make FAIR data management an explicit component in research budgets.
- Invest in ensuring long-term (>10 years) storage and accessibility of research assets.

6 *Education and training – seeding future success*

This chapter stresses the growing need to incorporate systems biology in MSc education and doctoral training. It emphasises that academic education, particularly in the biological and biomedical sciences, should prepare for interdisciplinary research in collaboration with informaticians, mathematicians, chemists, physicists and engineers.

6.1 Present situation

Academic education

The gradual shift from reductionism towards system-level research requires reconsidering academic curricula in biology and medical sciences. However, broad implementation of systems biology approaches is slowed down by the fact that many life scientists in academia and industry have insufficient knowledge of basic mathematics and physics. Therefore they are not prepared to deal with computational models and mathematical analyses. This is in sharp contrast to other fields, especially physics and engineering, where model-based approaches to tackle complex systems are key and fully integrated into education and research.

In the past 5 years several European universities have started to integrate systems biology into their curricula, either by creating dedicated MSc programmes or by incorporating systems biology components in existing programmes. There are two objectives.

- Educate life scientists to be able to collaborate with physicists, mathematicians and engineers.
- Educate scientists with a biology, medical, physics or mathematics background to be able to develop and exploit predictive computational models of biological systems and obtain deep insight into biological systems. An overview of graduate programmes with a focus on systems biology can be found on the Systems Biology Educational portal (SBEDU) on the webpage of ERASys*APP*[24].

One bottleneck is the lack of teaching staff able to operate at the interface of biology and medicine with mathematics, physics and engineering. This is the result of decades of mono-disciplinary education. Similarly, comprehensive text-books in this field are still rare.

Together with ISBE, ERASys*APP* has recently developed a standard systems biology MSc curriculum[25] that is offered as starting material for universities seeking to establish such a curriculum in their institution. This process can be enhanced by the platform for dissemination of teaching material SBEDU[26] maintained by ERASys*APP*. These activities are complemented by other efforts, e.g. the EBI training programme[27], IMI EMTRAIN[28] and activities of ISBE that will start in 2016.

Postdoctoral training

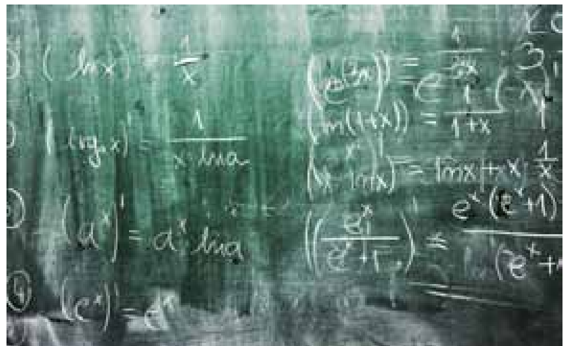
Several transnational European systems biology projects offer postdoctoral training material, including courses, summer schools and workshops. For instance, ERASys*APP* has organised six summer schools and several courses on data management. Additional examples are from the recently completed SysMO, ERASysBio and ERASysBio+ projects, as well as the ongoing CASyM and the ERACoSysMed projects that focus on systems medicine. Training efforts range from creating awareness to exploring specialised aspects of the systems biology field, for instance multi-scale modelling. These European activities are complemented by workshops and courses organised by national parties. Together, these training activities have been and still are crucial in the exchange and development of expertise and building a solid European systems biology knowledge base.

Dedicated training for industry

Translation of academic research to industrial applications has a high priority in many funding programmes. Therefore the industrial perspective needs to be visible in strategies to encourage the uptake and use of systems biology approaches by companies. As outlined in Chapter 4 on academia-industry cooperation, one of the reasons why companies hesitate to incorporate systems biology is that they lack sufficient knowledge about systems biology and insight into its opportunities, limitations and time lines. This calls for training programmes that are dedicated to industry, basic courses on systems biology, as well as specialised ones focussing on specific types of industry, such as the plant biotechnology and pharmaceutical industries.

24 www.erasysapp.eu/training-and-exchange/graduate-study-programs

25 http://www.nature.com/articles/npjsba201611
26 http://www.sbedu.eu/
27 http://www.ebi.ac.uk/training
28 http://www.imi.europa.eu/content/emtrain



6.2 Challenges

Despite the range of local, national and transnational training and education activities, many students and researchers in Europe do not have easy access to good quality systems biology education and training. Incorporating system level, model-driven approaches in academic MSc and doctoral programmes will require serious efforts. In contrast, training at the postdoctoral level is already well-developed. Experience shows that developing systems biology education and training programmes pose a number of challenges[25].

Develop and maintain an international platform for systems biology education and training

The development of good quality multi-disciplinary education and training programmes in systems biology will benefit strongly from a European platform for exchange of expertise, teaching material and teachers. ERASys*APP* has invested in the SBEDU platform, but long-term efforts are required to maintain and continuously update the platform. Here, the Infrastructure for Systems Biology ISBE may take the lead as the pan-European research infrastructure for systems biology.

Make educational programmes accessible for students from other disciplines

Systems biology curricula should attract students with widely different backgrounds, including biology, medicine, physics, chemistry, mathematics, informatics and engineering. But such programmes start with two major deficiencies. First, biology and biomedical students often have limited insight into basic principles of mathematics. Second, students from physics, engineering, mathematics and chemistry generally lack insight into basic molecular and cellular biology. Experience shows that this problem can be solved by creating two or more separate introductory routes (possibly web-based) that will provide the basis for later joint education. Particular attention should be paid to training teachers to act on the interphase of biology and medicine with other relevant disciplines.

Training programmes for industry

As argued in Chapter 4, implementation of systems biology in industrial innovation pipelines requires dedicated training courses. They may focus on generic approaches, limitations, model building with validation and exploiting predictive models. In particular this will be useful for SMEs that generally lack the possibility to hire personnel with training in systems biology. In addition more specialised courses are necessary that focus on specific branches of industry, e.g. plant biotechnology and pharmaceutical industry. To enhance the translation of knowledge and skills from academia to industry it will be useful to involve researchers from companies in academic training programmes. This relies on commitment by industry and academia to team-up.

6.3 Recommendations

- Accelerate the incorporation of systems biology in current academic curricula, develop novel dedicated multidisciplinary MSc and doctoral programmes and foster life-long training for professionals.

- Continue to invest in a European platform for the exchange of expertise in educational programmes in systems biology, building on what has been initiated by ERASys*APP* and ISBE.

- Invest in the development of training courses that are tailored for industry, in particular SMEs, to make them aware of the opportunities and timelines for implementing systems biology in their innovation pipelines.

7 Research infrastructures: all for one, one for all

This chapter briefly addresses the appearance of multiple European research infrastructures, many of them relevant for systems biology. The Infrastructure for Systems Biology Europe (ISBE), which is presently under construction, addresses many of the issues and recommendations in this Strategic Research Agenda.

7.1 Present situation

European research infrastructures are new players in the world of the life sciences. They give scientists easy access to expertise, resources and services. Among others, they are responsible for the development and dissemination of community standards, enhancing education and training and should act as hubs for industrial innovation in Europe by connecting relevant stakeholders.

The ongoing rapid development of high throughput analytics (e.g. omics and imaging), bioinformatics and computational biology enable scientists to tackle increasingly complex biological systems and unravel their functioning at the molecular, cellular and multicellular level. Understanding the functioning of tissues, organs, organisms and ecosystem has become a target of the life sciences (see Chapter 2). Against this background policy makers, funders and scientists agree that novel ways must be developed to make expertise, resources and technical skills easily and widely accessible. The aim of European research infrastructures that are developed in the context of the European ESFRI[29] programme is to strengthen the European scientific workforce and boost translation from academia to industry and onto commercialisation and market penetration.

A landscape of European research infrastructures in the life sciences

Presently, the ESFRI Road Map[30] lists 13 European research Infrastructures in the field of the life sciences and medical sciences. Several of the 13 research infrastructures have recently started their activities, while others are under development. Each covers a specific field or technology (see Appendix C for an overview). From a systems biology perspective this is an important development, as it will give researchers easier access to expertise, data, tools, repositories and services in a broad range of fields and technologies. All of these are necessary to gain comprehensive insight how living organisms function. Two of these research infrastructures are particularly important for systems biology: the Infrastructure for Systems Biology Europe (ISBE) and ELIXIR. ISBE will concentrate on systems biology and work together with ELIXIR. It has entered its construction phase in 2015 and expects to be fully operational in 2018. ELIXIR brings together Europe's bioinformatics resources and is a distributed infrastructure for life-science information that started its activities in 2014.

Parallel to the development of these European research infrastructures, several European countries are developing national roadmaps for infrastructure investments in the life sciences. The need for synergies between the European and national roadmaps is widely recognised.

ISBE: the research Infrastructure for systems biology in Europe

The initiative to develop the European systems biology infrastructure ISBE is important in the context of this SRA, since ISBE plans to address many of the issues and recommendations discussed here and as described in the ISBE business plan[31] (published July 2015). In short, ISBE will consist of a collaborative matrix of national systems biology centres that is coordinated by a central European office. ISBE will offer three types of services to researchers and industry, supporting newcomers in the field, as well as those that are proficient in systems biology.

29 https://ec.europa.eu/research/infrastructures/index_en.cfm?pg=home
30 http://www.esfri.eu/roadmap-2016

31 http://project.isbe.eu/business-plan/

Box 7: A landscape of European infrastructures in the life sciences
13 European research infrastructures in the life sciences have recently started or are under construction (see Appendix C).
ELIXIR (bioinformatics) and BBMRI (biobanking) are two examples of systems biology-related research infrastructures that are already operational as a legal entity, with a number of countries signed in.
To harmonise the activities and access policies of these life sciences research infrastructures a 5 years Horizon2020 project CORBEL started in 2015. It aims at establishing joint services to future users.

- Give academia and industry easy access to expertise, advice and services in modelling of biological systems and related issues, such as experimental design.
- Drive the development and uptake of community standards and good practices according to the FAIR principle (see Chapter 5).
- Foster and enhance national and EU-level education and training programmes (see Chapter 6).

7.2 Challenges

Synergise the activities of multiple European life sciences research infrastructures

The fact that there are 13 established and emerging research infrastructures in the life sciences and biomedical sciences in Europe creates the risk that they become niche-linked silos that focus on their own research community and have little or no interactions with other fields. That would be counter-productive from a systems biology perspective, since by its very nature, systems biology aims at integrating diverse data types and technologies. The CORBEL project[32] addresses part of this problem by aiming at harmonising the activities and the access policies of the infrastructures (see text Box 7). It will be important to closely monitor the results of CORBEL's activities to support it in avoiding the risk of the creating scientific islands.

32 https://www.elixir-europe.org/about/eu-projects/corbel

Figure 6. Infrastructures:

Making the best systems biology expertise and tools accessible to all European scientists and industry: through a pan-European matrix of collaborative national systems biology centres with overlapping and complementary expertise.

Finance European research infrastructures

It is expected that research infrastructures will be mainly financed by national governments. This makes starting new infrastructures a tedious and time-consuming process. More so because multiple new European research infrastructures in the life and biomedical sciences compete for the same limited national budgets. For this reason there is a growing need for these research infrastructures to join forces to the overall benefit of the European landscape. Evidently, it will be necessary to align national and European infrastructures. Another challenge will be to engage the private sector, not only as users but also as co-funders.

Create a coordinating organisation for European systems biology research infrastructures

Creating an institution that coordinates the activities of the European systems biology community and represents them will be advantageous. For instance, in following up the recommendations made in this SRA. To be successful, such an organisation needs the support of all stakeholders, including the European research community and national funders and policy makers. Many of the issues that are raised in this document are also addressed in ISBE's Business Plan. Therefore, it will be useful to explore whether ISBE can play such coordinating role.

7.3 Recommendations

- Invest in the development of the European systems biology research infrastructure ISBE, making it the solid basis for this European systems biology research agenda.
- Enable the European research infrastructures in the life sciences collaborate in a way that ensures easy access and use by all scientists.
- Harmonise regional and national infrastructural road maps with European initiatives that are developed in the context of ESFRI.
- Pursue engagement of industry in the development and financing of European research infrastructures.

Appendix A: Strategic documents

Title	Writers/Inititiative	Year
ISBE Business Plan, July 2015	ISBE	2015
Meeting the Challenges of Industrial Biotechnology in the age of Synthetic Biology – description of a proposed European research infrastructure dedicated to integrative industrial biotechnology	Infrastructure for Industrial Biotechnology (IBISBA)	2015
http://www.ibisba.com/wp-content/uploads/2015/08/IBISBA_an-infrastructrue-for-IB.pdf		
Next steps for European synthetic biology: a strategic vision from ERASynBio	ERASynBIO	2014
https://www.erasynbio.eu/lw_resource/datapool/_items/item_58/erasynbiostrategicvision.pdf		
The CASyM roadmap; implementation of Systems Medicine across Europe	CASyM	2014
https://www.casym.eu/index.php?index=90		
http://project.isbe.eu/wpisbe/wp-content/shared-data/2015/07/isbe-business-plan-first-edition-final.pdf		
Workshop report on the strategic research agenda, ERASysAPP	Report by ERASys*APP*	2014
https://www.erasysapp.eu/publications/strategy-documents		
ERASysBio+ trends and recommendations	R. van Driel	2013
https://www.erasysapp.eu/lw_resource/datapool/_items/item_133/trends_and_recommendations_6_9_13.pdf		
Health Research in HORIZON 2020	Nicole Firnberg	2013
http://ec.europa.eu/health/programme/policy/index_en.htm		
Rethinking the life sciences	T. Swierstra, N. Vermeulen, J. Breackman, R. van Driel, EMBO Reports	2013
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3615664/		
Geneticists push for global data-sharing	E.C. Hayden, Nature	2013
http://www.nature.com/news/geneticists-push-for-global-data-sharing-1.13133		
Systems Biology and P4 Medicine: Past, present, and future	L. Hood, Rambam Maimonides, Med J.	2013
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3678833/pdf/rmmj-4-2-e0012.pdf		
ESF forward look; Personalised medicine for the European Citizen – towards more precise medicine for the diagnosis treatment and prevention of disease (iPM)	European Science Foundation (ESF)	2012
http://www.esf.org/uploads/media/Personalised_Medicine.pdf		
Workshop on ESFRI Research Infrastructures and Joint Programming Initiatives in the field of Biological and Medical Sciences	EC	2011
https://ec.europa.eu/research/infrastructures/pdf/synergies_report_2011.pdf		
Systems biology at work	Martins dos Santos, J. Damborsky, 2010, Current Opinions in Biotechnology	2010
http://loschmidt.chemi.muni.cz/peg/wp-content/uploads/2013/01/cobio10.pdf		
Ethics of Synthetic biology, European commission	European Commission	2009
https://www.erasynbio.eu/lw_resource/datapool/_items/item_15/ege__opinion25_en.pdf		
Systems Biology: Its Past, Present and Potential	Mendoza, Philippine; Science Letters	2009
http://www.philsciletters.org/pdf/200914.pdf		
ICT Infrastructures for E-science	European Commission	2009
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2009:0108:FIN:EN:PDF		
Systems Biology in the European Research Area	ERASysBIO	2008
https://www.erasysbio.net/lw_resource/datapool/__pages/pdp_2/ERASysBio_Systems_Biology_Strategy_Paper_25-Mar-2008.pdf		
ESF Advancing Systems Biology for Medical Applications	European Science Foundation (ESF)	2008
http://www.esf.org/fileadmin/Public_documents/Publications/SPB35_SysBioMed.pdf		
ESF Task Force on Systems biology, ESF report, 2007.	European Science Foundation (ESF)	2007
https://ec.europa.eu/research/biotechnology/eu-us-task-force/index_en.cfm?pg=workshop_past		
The Bioeconomy to 2030: Designing a policy agenda	OECD	2006
http://biotech2030.ru/wp-content/uploads/docs/int/The%20Bioeconomy%20to%202030_OECD.pdf		
Systems Biology: a Grand Challenge for Europe 2004-2005	European Science Foundation (ESF)	2005
http://www.esf.org/index.php?eID=tx_nawsecuredl&u=0&g=0&t=1464973283&hash=08e068043d6ec3d023b49e91fea1175 1451b8106&file=fileadmin/be_user/research_areas/emrc/documents/publications/SPB25SystemsBiology.pdf		

Appendix B: Examples of major investments in systems biology at the European and national level

Examples of major investments in systems biology at European level (2005 – 2016)

Funding scheme	Name	Duration	Coor-dina-tor	Budget Mio EUR EU
FP6, ERA-Net	ERASysBio: ERA-Net for Systems Biology	2003 – 2010	DE	2.95
http://www.erasysbio.net/				
FP6-LIFESCIHEALTH-5	ESBIC-D - European Systems Biology Initiative combating complex diseases	2004 – 2007	DE	0.35
http://cordis.europa.eu/result/rcn/51789_en.html				
FP6, ERA-Net	European Research Area Plant Genomics	2004 – 2009	NL	2.9 + 55
http://www.erapg.org/				
FP6 - Europe STREP	DIAMONDS - Dedicated Integration And Modelling Of Novel Data and prior knowledge to enable Systems biology	2005 – 2007	BE	2.50
ftp://ftp.cordis.europa.eu/pub/lifescihealth/docs/canpr203_en.pdf				
FP6-LIFESCIHEALTH NiO (Network of Excellence)	Computational Systems Biology of Cell Signalling (COSBICS)	2005 – 2008	DE	1.01 +1.68
http://www.2020-horizon.com/COSBICS-Computational-systems-biology-of-cell-signalling%28COSBICS%29-s31077.html				
FP6-LIFESCIHEALTH	STEROLTALK Functional genomics of complex regulatory networks from yeast to human: cross-talk of sterol homeostasis and drug metabolism	2005 – 2008	DE	3.08
http://cordis.europa.eu/projects/rcn/75692_en.html				
FP7 - ERA-Net ERASysBIO	SysMO - Systems Biology of Microorganisms	2005 – 2010	DE	45.7
http://www.sysmo.net/				
FP6-LIFESCIHEALTH	BaSysBio - Systems Biology Initiative for understanding the basic principles that control complex bacterial cell activities	2006 – 2011	FR	16.32
http://cordis.europa.eu/projects/rcn/84986_en.html				
FP6-LIFESCIHEALTH	AMPKIN - Systems biology of the AMP-activated protein kinase	2006 – 2009	SE	2.56
http://cordis.europa.eu/project/rcn/78758_en.html				
IP - Integrated Project FP6-LIFESCIHEALTH	Agron-omics - Arabidopsis GROwth Network integrating OMICS technologies	2006 – 2011	BE	16.7
http://cordis.europa.eu/project/rcn/85221_en.html				
FP6 - Marie Curie actions - Research Training Networks (RTN)	NucSys: Systems biology of nuclear receptors: A nutrigenomic approach to aging-related diseases	2006 – 2009	FI	3.74
http://www.oppi.uef.fi/uku/nucsys/				
FP6 - Europe STREP	GENNETEC: GENetic NETworks: Emergence and Complexity	2006 – 2009	FR	1.48
http://gennetec.csregistry.org/tiki-index.php?page=HomePage				
FP6 and FP7- KBBE ERA-Net	ERA-IB, Industrial Biotechnology	2006 – 2012 2012 – 2015	DE	67.8
http://www.era-ib.net/				
ERA-Net Plus Scheme, FP7	ERASysBio+, The consolidation of systems biology research – stimulating the widespread adoption of systems approaches in biomedicine, biotechnology, and agri-food	2008 – 2013	DE	5.5 + 24
http://cordis.europa.eu/project/rcn/93038_en.html				
FP7 - Infrastructure	ISBE: Infrastructure for Systems Biology	2012 – 2015	UK	4.75
http://project.isbe.eu/				
FP7 - HEALTH Coordination and Support Action (CSA)	Casym: Coordinating Systems Medicine across Europe	2012 – 2016	DE	2.9
https://www.casym.eu/				
ERA-Net, FP7- KBBE	ERASys*APP*	2013 – 2015	DE	2 +15.75
www.erasysapp.eu				

Examples of major national investments (2005 — 2016)

Acronym	Name	Duration	Country	Budget Mio EUR
	Systems of Life – Systems Biology	2001 – 2004	DE	no information
http://www.ptj.de/systembiologie				
	Systems Biology and Bioinformatics	2004 – 2007	FI	10.7
http://www.aka.fi/sysbio				
HEPATOSYS	Systems Biology of Hepatocytes (HEPATOSYS)	2004 – 2010	DE	36
http://www.hepatosys.de/				
FORSYS	Research Units Systems Biology (FORSYS)	2007 – 2011	DE	45
http://www.bmbf.de/foerderungen/6039.php				
QuantPro	QuantPro: Quantitative Analysis to Describe the Dynamic Processes in Living Systems	2007 – 2011	DE	40
http://www.ptj.de/quantpro				
	Helmholtz Alliance on Systems Biology	2007 – 2011	DE	49
https://www.helmholtz.de/en/about_us/networks_and_cooperation/helmholtz_alliances/systems_biology/				
	SystemsX.ch	2008 – 2012 2013 – 2016	CH	100 81
http://www.systemsx.ch/				
NCSB	Netherlands Consortium for Systems Biology (NCSB)	2008 – 2013	NL	30
www.ncsb.nl/				
MedSys	MedSys: Medical Systems Biology,	2009 – 2012	DE	44.2
http://www.ptj.de/medizinische_systembiologie				
SysTec	New Methods in Systems Biology SysTec	2009 – 2012	DE	22
http://www.ptj.de/neue-methoden-systembiologie				
BioEnergieSys	BioEnergieSys: The Systems Biology in BioEnergy	2009 – 2012	DE	5
http://www.genomicscience.energy.gov/biofuels/				
GerontoSys I & II	GerontoSys I & II: Systems Biology of Health in Old Age	2009 – 2015	DE	44
http://www.ptj.de/gerontosys				
CSBR	Three centres for Systems Biology Research (CSBR)	2010 – 2015	NL	13
http://www.nwo.nl/en/research-and-results/programmes/Centres+for+Systems+Biology+Research				
VLN	Virtual Liver Network	2010 – 2015	DE	51
http://www.virtual-liver.de/				
CancerSys	CancerSys: Systems Biology in Cancer Research	2011 – 2013	DE	16.5
http://www.ptj.de/cancersys				
	Development of omics'-methods for quantitative systems biology studies of bacteria (Institutional Research Funding Programme)	2012 – 2015	EE	0.57
e:bio	e:bio: Innovationswettbewerb Systembiologie	2012 – 2022	DE	100
	Epigenomics (Institute)	Since 2002	FR	no information
http://www.epigenomique.genopole.fr/				
G2C	G2C: Genes to Cognition	2014	UK	no information
http://www.genes2cognition.org				
SYSTHER	INREMOS - SYSTHER: Systems Biology Tools Development For Cell Therapy And Drug Development (Virtual Institute)	2005	DE, SI	no information
http://systher.biologie.hu-berlin.de/				
Bilateral call	Innovative Systems Toxicology for Alternatives to Animal Testing (InnoSysTox)	2015-2018	NO	2.9
https://www.ptj.de/innosystox				

Appendix C: European research infrastructures in the life sciences

ANAEE – Infrastructure for Analysis and Experimentation on Ecosystems
AnaEE is an EU science infrastructure project whose goal is to overcome the current fragmentation of ecosystem research in Europe by setting up a coordinated ensemble of experimental fora (ExpeER, AnaEE-S). They are mandated to test, analyse and model ecosystem reactions to climate changes and to develop appropriate management techniques.
www.anaee.com

BBMRI – Biobanking and Biomolecular Resources Research Infrastructure
Modern clinical research will be significantly supported by linking large collections of high quality, well documented samples from humans and model organisms. By integrating data from biobanks and molecular research, and by improving access to metadata, the descriptions and therefore discoverability of biomedical samples will be hugely improved.
www.bbmri-eric.eu

EATRIS - The European Advanced Translational Research Infrastructure in Medicine
In personalised medicine, decisions about treatment options will be supported by access to integrated data and information from multiple reference resources and analysis platforms.
www.eatris.eu

ECRIN – Pan European infrastructure for clinical trials and biotherapy
Data relevant to personalised medicine that is generated by the different research infrastructures will be made available to scientists and clinicians in an ethical, robust and sustainable manner, and mechanisms of interoperability for different data types will be developed. Clinical trial data, biomolecular data and basic research data will be better linked.
www.ecrin.org

ELIXIR – European Life-Science Infrastructure for Biological Information – A Major Upgrade
New discoveries will be facilitated by revealing possible connections between linked and accessible biomolecular, clinical, biobank (tissue sample) and image data.
www.elixir-europe.org

EMBRC: European Marine Biological Resource Center
Links to metagenomics data will help characterise poorly understood ecosystems and cheminformatics data to characterise the activity of isolated natural products.
www.embrc.eu

ERINHA: European Research Infrastructure on Highly Pathogenic Agents
Strains of known species and unknown species of pathogens will be more easily distinguished and accurately identified by linking to biomolecular data. This is important in controlling epidemics and in security applications.
www.erinha.eu

EU-OPENSCREEN: European Infrastructure of Open Screening Platforms for Chemical Biology.
The enormous effort involved in high throughput screening for chemical tools and drugs will be supported by building targeted strategies based on integrated clinical, cheminformatic, and biomolecular data.
www.eu-openscreen.eu

Euro-BioImaging: Research infrastructure for imaging technologies in biological and biomedical sciences
Extensive image data sets representing different biological scales spanning biomolecules, cells, tissues and organisms will be linked, enabling drug-target and biomarker discovery for human disease.
www.eurobioimaging.eu

Infrafrontier - Infrastructure for phenotyping and archiving of mammalian genomes
The mouse is an important model organism for studying human disease. Harmonising ontological descriptions of phenotype in mouse and human and improving links between mouse model data and human data, using diabetes and obesity as examples, will increase the relevance of data that is generated in mouse studies for clinical studies.

INSTRUCT – An integrated Structural Biology Infrastructure for Europe
Structural data on biomolecules will be linked with clinical data, maximising its value by enabling its use in studies of important biological and medical problems.

ISBE – Infrastructure for Systems Biology – Europe
In tackling complex biological problems, ISBE will enable European scientists to implement research from a systems perspective. Through strengthening Europe's economic and scientific competitiveness, ISBE will also improve the quality of life for EU citizens. In addition, industry will be offered the best training, collaborations, services and development of technologies.

MIRRI – Microbial Resource Research Infrastructure
A Pan-European distributed research infrastructure that provides microorganisms services facilitating access to high quality microorganisms, their derivatives and associated data for research, development and application.

Appendix D: Abbreviations and links

Array Ex.
Array Express – archive of functional genomics data.
https://www.ebi.ac.uk/arrayexpress/

BBI Europe
Bio-Based Industries public-private partnership
http://www.bbi-europe.eu/

Bio-economy
The bioeconomy comprises those parts of the economy that use renewable biological resources from land and sea – such as crops, forests, fish, animals and micro-organisms – to produce food, materials and energy.
https://ec.europa.eu/research/bioeconomy/index.cfm

CASyM
Coordination Action for Systems Medicine
www.casym.eu

Cell Designer
A modeling tool of biochemical networks
http://www.celldesigner.org/

CellML
Standard for formatting models, as well as a model repository.
https://www.cellml.org/

COMBINE
Computational Modelling in Biology Network.
http://co.mbine.org

Commons
A commons is centralised public resource that allows the aggregation of diverse content. In systems biology, commons allow data and models to be linked to, stored, and managed using contextual relationships (e.g. all data and models comprising healthy liver tissue from patient X), rather than by data type.
http://fair-dom.org/knowledgehub/data-and-model-repositories-and-commons/

Coordination Action
These are actions under FP7 that cover not the research itself, but the coordination and networking of projects, programmes and policies.

COPASI
COPASI is a software application for simulation and analysis of biochemical networks and their dynamics
http://copasi.org/

CORBEL
Coordinated Research Infrastructures Building Enduring Life-science Services - The CORBEL consortium brings together eleven major new Biological and Medical Research Infrastructures (BMS RI) in Europe. Their resources include biological data, physical biobank samples, imaging facilities and molecular screening centres.
http://www.corbel-project.eu/about-corbel.html

Cytoscape
Cytoscape is an open source software platform for visualizing complex networks and integrating these with any type of attribute data.
http://www.cytoscape.org/

EC
European Commission
http://ec.europa.eu/

ELIXIR
A distributed European infrastructure for life-science information
https://www.elixir-europe.org/

ERA
European Research Area - unified research area to exchange scientific knowledge, technology and researchers
http://ec.europa.eu/research/era/index_en.htm

ERACoSysMed
ERA-Net CoFUND under HORIZON2020 on Systems Medicine
https://www.eracosysmed.eu/

ERA-IB-2
ERA-Net under FP7 on Industrial Biotechnology
http://www.era-ib.net/

ERA-Net
European Research Area network - designed to support public-public partnerships for coordination of joint activities
http://ec.europa.eu/research/era/era-net-in-horizon-2020_en.html

ERASynBIO
ERA-Net under FP7 on Synthetic Biology
https://www.erasynbio.eu/

ERASys*APP*
ERA-Net under FP7 for Systems Biology Applications
https://www.erasysapp.eu/

ERASysBIO
ERA-Net under FP6 and FP7 on Systems Biology
https://www.erasysbio.net/

ESFRI
The European Strategy Forum on Research Infrastructures
http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri

EU
European Union
http://europa.eu/

FAIR
Findable, Accessible, Interoperable and Reusable
make their Data, Operating procedures and Models FAIR
http://fair-dom.org/

FAIRDOM
Findable Accessible Interoperable Reusable Data standard Operating Procedures and Models. Data and model management service facility for Systems Biology
http://fair-dom.org

FAME
Flux Analysis and Modeling Environment
http://f-a-m-e.fame-vu.vm.surfsara.nl/ajax/page1.php

FP7
Seventh Framework Programme. FP7 was the European Union's Research and Innovation funding programme for 2007-2013.
https://ec.europa.eu/research/fp7

Horizon 2020
The EU Framework Programme for Research and Innovation; funding period 2014 – 2020
https://ec.europa.eu/programmes/horizon2020/

IMI
Innovative Medicines Innitiative - created as Public-Private Partnership between the Europan Commission and the European Pharmaceutical industry
http://www.imi.europa.eu/

IMI EMTRAIN
European Medicines Research Training Network
http://www.imi.europa.eu/content/emtrain

ISATab
The Investigation/Study/Assay (ISA) tab-delimited (TAB) format is a general purpose framework with which to collect and communicate complex metadata (i.e. sample characteristics, technologies used, type of measurements made) from 'omics-based' experiments employing a combination of technologies.
http://www.dcc.ac.uk/resources/metadata-standards/isa-tab

ISBE
Infrastructure for Systems Biology Europe.
http://project.isbe.eu

ISO
International Standards Organisation
http://www.iso.org

ISO/TC 276
ISO Technical Committee on standardization in the field of biotechnology
http://www.iso.org/iso/home/standards_development/list_of_iso_technical_committees/iso_technical_committee.htm?commid=4514241

Metadata
Metadata are data that provide information about other data and datasets.

MSc
Master of Science education program

OECD
The Organisation for Economic Co-operation and Development

Omics
The word "omics" indicates the study of a body of information, such as the genome (which is all DNA in a cell), the proteome (which is all the proteins), metabolome (metabolites), transcriptome (RNA transcripts) and autoantibody profiles, among other things.

PPP
Public-Private Partnership - a collaboration between public and private partners.
http://ec.europa.eu/research/industrial_technologies/ppp-in-research_en.html

RRI
Responsible Research and Innovation - an approach in Horizon 2020 with the aim to foster the design of inclusive and sustainable research and innovation.
https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation

SBGN
Systems Biology Graphical Notation
http://www.sbgn.org/

SBML
Systems Biology Mark-up Language
http://sbml.org/

SBRML
Systems Biology Results Markup Language
http://www.comp-sys-bio.org/SBRML.html

SBEDU
Systems Biology Educational platform for exchange of educational material on Systems Biology
http://www.sbedu.eu/

SEDML
Simulation Experiment Description Markup Language
http://sed-ml.org/

SEEK
Systems biology data management platform, which works as an aggregated content commons, and a database.
http://fair-dom.org/SEEK

SME
Small and medium-sized enterprises
http://ec.europa.eu/growth/smes/business-friendly-environment/sme-definition/index_en.htm

SOP
Standard Operating Procedure

SRA
Strategic Research Agenda

SysMO
Systems Biology of Microorganisms
http://www.sysmo.net/

TTO
Technology Transfer Office

VLN
The Virtual Liver Network
http://www.virtual-liver.de/

VPH Institute
The Virtual Physiological Human Institute
http://www.vph-institute.org/

BMBF
Federal German Ministry of Education and Research (Bundesministerium für Bildung und Forschung)
https://www.bmbf.de/

Appendix E: ERASysAPP partners

Estonia	Europe	France
Eesti Teadusagentuur Estonian Research Council	European Commission	INRA Institut National de la Recherche Agronomique

Germany	Iceland	Latvia	Luxembourg
Bundesministerium für Bildung und Forschung; PtJ Projektträger Jülich Forschungszentrum Jülich	rannís		Fonds National de la Recherche Luxembourg

Netherlands	Norway	Romania
ZonMw	The Research Council of Norway	ANCS Autoritatea Nationala pentru Cercetare Stiintifica; uefiscdi

Spain	Sweden	Switzerland
Instituto de Salud Carlos III	Region Västra Götaland; Vetenskapsrådet	SystemsX.ch The Swiss Initiative in Systems Biology