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SYSBIO Centre of Systems Biology

Vision

To create a pan-European infrastructure for systems biology that empowers life scientists to understand living organisms to a much higher precision and in a predictive way. This allows intervention in the functioning of biological systems in a predictive and rational manner. The infrastructure enables scientists in academia, the health sector and industry to access and exploit the full potential of data-driven computational modelling of complex biological systems with the required reproducibility and validation. It provides the expertise, tools and resources to address current and future grand challenges in healthcare, agriculture and industrial biotechnology, thereby enhancing the wealth and well-being of the European citizens.

Mission

To construct and manage a distributed infrastructure of interconnected systems biology centres that provides resources and services, coordinated at the national and European levels. This will allow the wide use of data suitable for model-driven analyses and prediction of biological systems, and its application to understand their functioning from a multi-discipline and multi-scale perspective. This will be achieved by providing:

- community access to findable, accessible, interoperable and re-usable (FAIR) models, data, biological maps and tools, that fosters synergy with existing services and standards
- effective aggregation and interlinking of related datasets and models, in order to preserve the provenance and shared understanding of systems biology experiments
- support for the generation of model-compliant data, and the building and use of data-driven models of complex biological systems,
- effective stewardship of data and models that allows their re-use now and in the future (FAIR compliant), independent of short term funding and national strategies,
- promoting the development and adoption of community standards and best practices for the generation and curation of data and models,
- enhanced education and training in systems biology.

Contents

Foreword

As is well known, over the last sixty years or so, there has been a major revolution in molecular and cell biology which has, most recently, generated enormous, complex data sets and shows no sign of slowing down. Whilst it is impossible to define a starting point in these developments, there is no doubt that two points in time are of particular significance. The first of these is the double-helix model of DNA by Watson and Crick[1], published in Nature in 1953 and the initial sequencing of the Human Genome[2], also published in Nature in 2001. In parallel with developments in molecular and cell biology there have been major developments in information and communication technology. Nowadays, access to large amounts of computer power is ubiquitous in professional circles, as is the wide availability of broadband internet connections in industrialised countries. The third major component which is having an impact on many areas of life science is the application of systems and control theory, which is derived from engineering and physics.

As a result of these developments, the traditional reductionist approach to understanding biological systems is changing. In the past, the reductionist approach, where complexity was broken down into smaller, simpler, and easier to understand, components was driven by an inability to analyse or assay biological systems holistically. This inability was often driven by a lack of the relevant technology and/or an inability of the human brain to understand and retain the connections between the multi-billions of data points involved.

This has resulted in the development of a different approach to the analysis and understanding of biological systems, namely the development of systems biology. The field of systems biology has been developing over the last 20 years in different universities, research institutes and companies around the world in various forms. Over the last one and a half decades the field of systems biology has developed to a point where there are now a number of major co-ordinated activities ongoing within individual research universities and companies. In the case of universities, it is typically in the form of institutes or centres of systems biology.

Whilst these developments have resulted in research which has produced many important research papers, the research was taking place in institutes/centres which were not co-ordinated with each other. As acquiring and analysing the data needed to take an integrated systems approach is complex and requires researchers to work across scientific disciplines and boundaries, it was clear that cross institution and cross country collaborative working was needed. As a result, within the European context, various leading researchers in systems biology across Europe decided in the mid-2000s to work together towards establishing an Infrastructure for Systems Biology across Europe. These developments were supported by some initial funds from the European Commission which resulted in the development of the early stages of what is now called The Infrastructure for Systems Biology Europe (ISBE). ISBE is now part of the European Strategy Forum on Research Infrastructures (ESFRI).

[1] Watson J.D. and Crick F.H.C.. (1953) A Structure for Deoxyribose Nucleic Acid Nature 171 737-738

[2] Lander E.S. et al. (2001) Nature 409 860-921

This collaborative approach was also needed for Systems Biology to realise its commercial potential. Over the past ten years or so major industrial /academic collaborations have investigated biological systems as diverse as tomato ripening[3] to drug discovery for new pharmaceuticals[4].

This Foreword is by way of introduction and support for the business case to which it is attached. I strongly support the strategy described in the business case of developing pan-European infrastructure for systems biology which comprises interrelated domains of services, tools and resources in five main areas of activity: modelling and data integration resources and services; stewardship; standardisation; model-compliant data integration; and education and training. In my view, as a leading European Scientist in the field of systems biology in agri-science, I warmly support and endorse the development of the systems biology infrastructure. I believe that such a development has the potential to provide major support for the European Bio-Economy.

Stuart John Dunbar

Senior Syngenta Fellow, Head of Bioscience; Syngenta, UK

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[3] Tomato Quality http://www.foodsecurity.ac.uk/research/current/tomato-quality.html

[4] Benson N, Cucurull-Sanchez L, Demin O, Smirnov S, van der Graaf P. (2012) Reducing systems biology to practice in pharmaceutical company research; selected case studies. Adv Exp Med Biol. 736 607-15

Executive summary

If the second half of the twentieth century is considered to be the 'digital age' with the introduction of high-powered digital computers, and freely available data via the internet then the first half of the twenty-first century may well be considered as the 'biological age'. Our ability to sequence DNA increasingly quickly, accurately and inexpensively has opened up a new vista for biological research. This 'omics' revolution is best illustrated by the publication of the draft human genome sequence in 2001; the ensuing data deluge showed that this acceleration was part of a wider series of developments in the life sciences with tremendous potential in areas such as drug development, personalised medicine, and sustainable agri-systems. This was recognised by OECD who stated that biotechnology could contribute up to 2.7% of the GDP of OECD countries in 2030[5], with many leading world economies, such as Germany, UK and the USA, identifying the bioeconomy as the next important growth area. This expansion will largely be driven by knowledge-based industries, an area ideally suited for exploitation by the strong European science base.

The challenge for the life sciences in the coming decades will be how we best utilise the deluge of data, and systems biology will be central to this endeavour. In contrast to traditional biological reductionist research – breaking down biological phenomena into constituent parts and analysing these components in isolation – systems biology integrates diverse datasets to allow us to understand biological processes across multiple temporal and spatial scales. This approach is built on the utilisation of computational models in an iterative process of experimentation and modelling, enabling researchers to simulate, explore and predict behaviour of the biological system under investigation. [*See Section 1*]

Over the last decade, systems biology has flourished across Europe and worldwide with advances in high throughput 'omics' technologies, modern computational power and the high speed information exchange of the internet. It is now vital to spread this expertise rapidly throughout the life sciences, together with the tools to undertake even more detailed scientific investigation.

The creation of ISBE will ensure that previous and planned national and international investments will be maximised for the European Research Area to gain added value from European level coordination. It will capitalise on this momentum by providing easy access to services, tools and resources, as well as training and education in systems biology across Europe, to tackle pressing societal grand challenges in health, agriculture and bio-economy. [*See Section 2*]

Realising ISBE - Meeting infrastructure needs for systems biology

This document explains our vision to create a pan-European infrastructure for systems biology (ISBE) that facilitates the use of model-driven approaches to understand complex biological systems, enabling their function to be altered in a rational and predictive way.

[5] The Bioeconomy to 2030, designing a political agenda, OECD, 2009

The delivery of the ISBE strategy will be achieved at a pan-European level across interrelated domains of the services, tools and resources in five main types of co-ordinated activity:

- modelling and data integration resources and services
- stewardship
- standardisation
- model-compliant data generation
- education and training

These co-ordinated activities will be interlinked to greatly improve findability, accessibility, interoperability and re-usability of data, in accordance with the FAIR initiative. [*See Section 3*]

ISBE will comprise a two layer 'hub and spoke' model. At the national level, the national Systems Biology Centre (nSBC) would typically be hosted by a leading university or research institute, linking to other universities and research institutes, all contributing to ISBE. For each country it is envisaged these centres would build upon the installed base of facilities and expertise in line with the national strategies of individual European member states, with provision of resources derived from most of the major previous national investments in systems biology infrastructure. At the European level, the hub for the whole of ISBE will be the Central ISBE Office (CIO) for administrative, legal and governance aspects, with one of the nSBCs coordinating of the operational delivery, including responsibility for pan European issues relating to standards and training. It is envisaged that this structure will link countries with the ability to provide most, if not all, of the facilities and expertise required to realise the ISBE vision, with other countries that have smaller or less well developed research communities that may be able to provide only certain aspects of the vision. The ISBE services will have different modalities including web-based resources, consultancy and contract activities. [*See Sections 4 & 5*]

Underpinning these activities will be a multi-faceted education and training strategy which will provide support of postgraduate education in systems biology through development of core curricula, competency based short courses for users, training for nSBC staff in collaboration with other research infrastructures and an up-to-date database of systems biology courses, workshops and conferences. [*See Section 6*]

ISBE will not operate in isolation, it will integrate its services with complementary biomedical research infrastructures, projects and initiatives to maximise synergies, avoid overlaps and exchange expertise. ISBE is actively engaging with all biomedical European Strategy Forum on Research Infrastructures (ESFRI's[6]) to tackle cross-cutting issues through its involvement in the CORBEL proposal (Coordinated Research Infrastructures Building Enduring Life-science Services) in response to the Horizon 2020 INFRADEV-4 call. ISBE will continue to explore avenues for harmonised access and service provision with other ESFRIs and EU initiatives in all aspects of its planned operations, including ISBE education and training strategy, and coherent industrial engagement. [*See Section 7*]

ISBE will be a sustainable, long term infrastructure, with robust and effective financial, legal and governance structure that supports efficient operations and strategic planning. Funding for nSBCs will come primarily from member states, reflecting their national excellence and priorities. This

[6] http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri

presents an opportunity for additional investment to enhance national coordination in countries with prior significant investments. Other countries may also identify new investment opportunities in those national research centres that would be involved in an nSBC. [*See Sections 8 & 9*]

Through ISBE, the European life sciences research community will come together to provide a range of integrated research 'toolkits' that allow all life scientists to implement computational modelling and systems approaches in their research. This will be accompanied by the development of software to facilitate modelling of complex systems and development of standards and interoperability, making research more efficient. ISBE is poised to enable ready access to state of the art systems biology infrastructure that can further enhance European competitiveness and social wellbeing by creating a common source of systems biology services, archives, repositories, tools, standards, data, models and training. This document demonstrates how ISBE will provide integration and coordination of such resource and services at multiple levels.

This document precedes the more comprehensive ISBE Business Plan that will be published in July 2015 at the end of the final year of the Preparatory Phase of ISBE. The Business Plan will describe in greater detail the key issues touched upon in this Business Case:

- the need for the ISBE infrastructure
- ISBE's structure and how it will function
- ISBE's main users and how they will access the infrastructure
- proof of interest from key stakeholders
- ISBE's financial, legal and governance structure
- how the infrastructure will be built and maintained and its quality assured

This business case therefore sets out how ISBE will provide a robust infrastructure that addresses European and national research strategy needs for the life sciences. It outlines the rationale of ISBE's future delivery and potential scope for how it can be achieved, as the project continues to engage more widely in shaping this vision.

SECTION 1
Introduction to systems biology

"We are now awash with genomic, proteomic and metabolomics data. The problem is to understand it. Simply accumulating yet more data will not solve that problem."

Denis Noble

Since the beginning of this century, the ongoing development of powerful new analytical technologies has driven an ever-growing deluge of biological data. This data has the potential to provide great insights into areas including human biology, medicine and evolution. However, understanding dynamic biological systems at the molecular level is such an immense task that a new approach has been developed to guide the interpretation and integration of data and how they relate to the functioning of the living system as a whole. Systems biology has a strong and proven potential to unravel the complex mechanisms that underlie biological processes[7]. Thereby systems biology is a key component in the developments in biological and biomedical research, which have been identified as 'key innovation drivers' in the European Union[8], at the forefront of new growth and competitiveness.

1.1 The emergence of a systems-based approach

Scientific research, from Newtonian mechanics and particle physics, to genetics and molecular biology, has historically focused on the reductionist principle, whereby the behaviour of complex systems is explained from the properties of their components using simplistic models. With the growing availability of digital computing in the latter half of the twentieth century, the need for reductionism reduced. In physics and engineering, researchers were quick to develop the computational techniques that allowed them to tackle much more complex problems through modelling, systems theory and signal and data processing.

Systems biology

Biological processes are the result of complex and dynamic interactions within and between cells, organs and entire organisms. Systems biology is a field of research which aims to enhance our understanding of and even predict such processes of life. It follows an interdisciplinary approach and combines the latest experimental methods in biology with knowledge and technologies in the fields of mathematics, computer science, physics and engineering. This iterative cycle of laboratory experiments and modelling explains the special potential of systems biology.

Adapted from the definition of the German Federal Ministry of Education and Research (BMBF); http://www.bmbf.de/en/1140.php

These techniques also form the basis of systems biology. In the past fifteen years systems research has become embedded across a range of biological and biomedical fields. This has been driven by the growing abundance and complexity of large biological data sets, the development of tools and techniques with which to perform comprehensive, genome-wide analyses, and the capacity to share these via high speed connection between disparate research groups and disciplines.

[7] Detailed case studies are provided in appendix 1

[8] http://ec.europa.eu/research/bioeconomy/biotechnology/policy/index_en.htm

Using a systems approach, life scientists are now able, for the first time, to study the complex and dynamic interplay between the components of a system (be it at the level of a cell, tissue, organ, organism or population). This can now go beyond understanding function, to enable intervention in the behaviour of the system in a predictive and rational manner. Model-driven, multi-scale analysis is at the heart of this approach.

1.2 Integration, iteration and insight

1.2.1 Systems biology continuously integrates modelling and experimentation

In the systems biology approach, cutting-edge technology platforms, such as genomics, metabolomics, proteomics and phenomics, are used to produce multiple and diverse datasets about a biological system. The data are integrated in a computational model, enabling researchers to simulate, explore and predict behaviour of the biological system under investigation. Further experimental work validates and refines the model, which in turn provides predictions that feed into future experimental design.

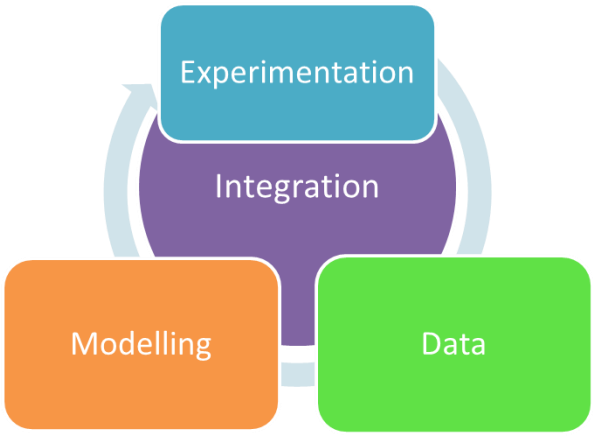

Fig. 1.1: Systems biology can be described as the iterative cycle of integrating data-driven modelling and model-driven experiment.

This iterative cycle (Fig. 1.1) produces deep insights into biological functions and processes: each cycle increases our understanding. The incremental increase in understanding that is developed can be used, for example, in further cycles to explore what goes wrong when a biological system becomes diseased and then how to prevent, diagnose and treat that disease.

1.2.2 Systems biology works across different disciplines and scales

Systems biology is not carried out in isolation by biologists, the skillset necessary to carry out this process of repeated experimentation and modelling requires the integration of technologies and expertise from an array of research fields and disciplines. The unique multidisciplinary approach involves several levels of collaborations between molecular biologists, geneticists, computer scientists, physicists, mathematicians and engineers. While this enables innovative, novel approaches to previously intractable problems, achieving synergy between the different disciplinary backgrounds requires special attention.

Interdisciplinary research is also essential in covering the huge scales in time and size that span biological systems (Fig. 1.2). For instance, human ageing takes decades. In contrast, the chemical processes that underlie the ageing process are measured in milliseconds or less. Hence, to understand the molecular basis of ageing we must consider processes with rates that differ 10^{12} fold. Similarly, we deal with human beings, measured in metres, in which key molecules are measured in nanometres: a 10^{9} fold difference in length. Multi-scale systems are typical in biology and can only be addressed by advanced (multi-scale) modelling approaches. This is the very heart of the systems biology field.

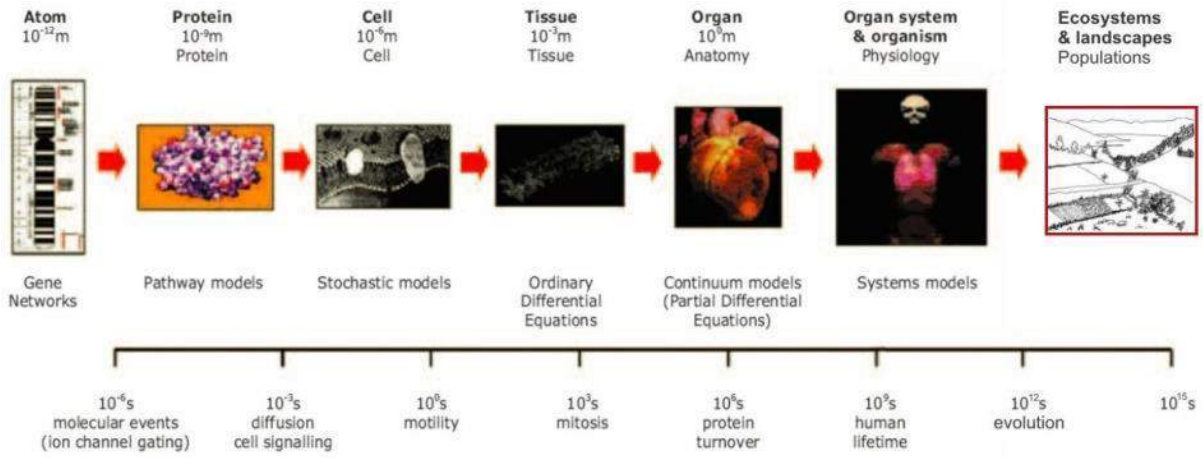

Fig. 1.2: Spatial and temporal levels encompassed by biological systems[9]

1.3 Rationale for ISBE

The ethos behind the *Infrastructure for Systems Biology – Europe* (ISBE) is to connect the existing expertise needed for systems biology, resources and services at a national and European level and then link them to other pan-European research infrastructures to develop a coherent infrastructure. This will enable past, present and future biological and biomedical research investments to be used more effectively and efficiently, with the added benefit that the systems biology approach can be brought to a wide range of new users and new applications, thus maximising the benefits of previous and planned investments in systems biology.

[9] *Based on* Hunter P, Robbins P & Noble D (2002). *The IUPS human physiome project*. European Journal of Physiology **445**, 1-9.

Section 1 Summary & guide to other sections

This section introduces the field of systems biology. The following Sections expand the individual aspects of the infrastructure.

- The strong and diverse community structure within European systems biology research and the need to make systems biology approaches easily accessible in academia, medical research and industry are expanded in *Sections 2 and 3.*
- The resources, services and associated expertise that ISBE will offer and the physical structure of the infrastructure and its centres are dealt with in *Sections 4 and 5.*
- The way ISBE will develop training resources and support systems biology education to facilitate access by users at all levels of expertise are outlined in *Section 6*
- Co-operation between ISBE and other European life sciences research infrastructures and organisations are described in *Section 7*
- The governance, legal and financial aspects of the infrastructure are dealt with in *Sections 8 and 9.*
- The way ISBE will be rolled out in the forthcoming years is explained in *Section 10.*

SECTION 2
Systems biology in Europe

2.1 The systems biology community

In the past ten to fifteen years numerous research groups and institutions across Europe and beyond have started to use systems biology approaches. During this time support from national research funders, together with the EU was extensive as illustrated by investments in the ERASysBio partnership[10] (*see box*) Together they cover a wide range of different fields within biological and medical sciences, as well as in applied research areas, such as industrial and agricultural biotechnology. A considerable number of national, transnational and European systems biology oriented research programmes have been initiated.

The vitality of the systems biology field is underscored by the growing number of academic systems biology training programmes at the undergraduate and postgraduate level. However, this rapid development and uptake of systems approaches in the life sciences has been fragmented and heterogeneous, meaning that specific expertise is not easily and seamlessly accessible for researchers in Europe. Therefore, it is timely to develop common standards and best practices needed to make data and models robust and re-useable. ISBE is the answer to these issues.

ERASysBio ERA-NET for Systems Biology

The ERASysBio partnership began in 2006 with SysMO (Systems Biology of Microorganisms).

Total amount: €69.7M

- €28M for SysMO1 and €17.7M for SysMO2
- €24M- €18.5M from the partner countries and €5.5M through the ERA-NET Plus scheme of the EC.

Groups involved:

- 11 transnational research projects involving 91 groups in SysMO
- 16 transnational consortia from 14 countries in ERASysBio+.

Whilst external estimates of the true size of the community using systems biology and potential utility are scarce, an internal review by ISBE of active systems biology showed 7500 researchers publishing as authors in systems biology journals world-wide.

"Systems approaches to disease are key for dealing with complexity. Having a systems biology infrastructure (and strategy) is vital for this."

Lee Hood
The Institute for Systems Biology, Seattle, USA

[10] http://www.sysmo.eu/ & http://www.erasysbio.net/ERASysBio_PLUS_Projects

Examples of national systems biology investments

Denmark

Centre for Biosustainability at the Technical University of Denmark received ~€150M funding for systems biology approaches.

Germany

BMBF has committed ~€65M for 'e:Bio: Innovations Competition Systems Biology', and expects spend of over €100M for 'e:Med: Paving the Way for Systems Medicine'.

Italy

CNR have supported a €4.5M national distributed network for systems biology involving Milan, Rome, and Naples with funding for 3 years.

Netherlands

Netherlands Consortium for Systems Biology received €30M until 2013, with Centres for Systems Biology Research receiving a further €13M until 2015.

Norway

The 10 year BIOTEK2021 programme began in 2012 with an expected annual budget of ~€20M.

UK

In 2012, 12% (~€147M) of BBSRC's overall Investment was on systems biology.

2.2 Investment to date

In the early years of this century systems biology was identified as a major research priority in several European countries, with parallel significant and directed funding support. This investment sought to combine expertise from different disciplines, including informatics, physics, mathematics and engineering in order to tackle the complexity of biological systems. Support by national funders to build the systems biology community focused on establishment of national centres of excellence and research infrastructures, together with funding for collaborative research programmes and training programmes across the life sciences portfolio. Many of these funders also coordinated support with the European Commission at the European-level, notably via ERANet programmes under EU Sixth and Seventh Framework Programmes such as ERASysBio and ERASysBio+. Moreover, a substantial number of FP7 and Horizon 2020 research programmes have systems biology elements.

These funding schemes have led to the development of a number of prominent European systems biology centres which have individually invested in developing model and data management resources and in making these broadly available to the life sciences community. This has been accompanied by the development of a broad range of teaching programmes that integrate biology, chemistry, physics, mathematics and engineering approaches. Yet, in spite of these investments, and resulting state of the art research, there remains a lack of infrastructural integration that is restricting the potential of systems biology from being fully harnessed by the biological and biomedical sciences to catalyse the community Europe-wide.

2.3 Challenges across different sectors

Systems biology can contribute greatly across the pressing societal grand challenges in health, agriculture and bio-economy, briefly touched upon below.

2.3.1 Health

While twentieth century scientific advances succeeded in protecting people from diseases that caused them to die young, with developments in antibiotics and drugs, the challenges of European healthcare in the twenty-first century will be to cope with ageing populations with complex diseases such as cancer and Alzheimer's, or increasingly where patients present more than one condition.

> The global market for medicines is forecast to grow from €775bn in 2011 to €978bn by 2016, with industry growth averaging 5.1% per year from 2013 to 2020
>
> (UK Government: Strength and Opportunity 2013)

Europe is faced with an ageing population, with affiliated challenges in healthcare provision. Recent European Commission reports have highlighted the correlation between increasing population age and increased public spending on healthcare[11]. The EC, through its Healthy Ageing programme, is seeking to adapt EU policies and strategies to meet the demands associated with this significant demographic shift.

Systems biology's emphasis on combining knowledge from multiple biological processes leaves it uniquely placed to combat diseases and the multi-factorial mechanisms that underlie them. The model-based approach of systems biology is essential to unravelling the complex molecular, cellular and organ basis of such diseases, allowing more effective and rational approaches to prevention, diagnosis and personalised treatment schemes. It is through the power of these models to integrate diverse data sets that we can now begin to properly predict responses to specific interventions and provide new and personalised therapies.

"To enable clinicians to efficiently use all the data available to stratify patients and personalise treatment, a toolbox of modelling technologies and related expertise is essential. ISBE has a major role to play in giving medical practitioners access to this toolbox, enabling them to harness the power of systems medicine approaches in their everyday work."

Professor David Harrison
The University of St Andrews, UK
& Chair, CASyM steering committee

[11] http://ec.europa.eu/economy_finance/publications/european_economy/2012/2012-ageing-report_en.htm

The European Commission has estimated that, without new approaches, average healthcare spending could rise from 7-9% of GDP by 2060

EFPIA: Health & Growth: A vision towards a life sciences strategy for Europe

Systems biology is also key to overcoming the problem that many existing drugs and therapies have no or even an adverse effect on patients. Individualised genome sequencing, transcriptomics, proteomics and metabolomics combined with systems biology based analyses, begin to allow a much more successful, rationalised and personalised treatment plans for the patient.

2.3.2 Agriculture

In agricultural sciences, systems biology approaches are widely used to tackle issues that relate to sustainable food production. Varieties of drought and salt resistant crops, are needed to overcome the world-wide shortage of fresh water to expand overall outputs. Understanding of the relevant processes in plants has opened new avenues to modify molecular and cellular networks and thereby the creation of crops that provide commercially viable yields under previously unfavourable conditions.

EU agriculture has a share of 18% in world food exports, worth €76bn

European Commission, Research & Innovation, Bioeconomy, Agriculture and Forestry

Control of flowering time is another area being tackled by a systems biology approach. This is an exceptionally important economic issue because it allows farmers to optimise yields by defining the best time of the year for crops to be harvested.

A single fungal wheat pathogen (*Septoria tritici*) can reduce wheat yields by 3-40%

UK Plant Science: Current status and future challenges. A report by the UK Plant Sciences Federation (January 2014).

Finally, an area underpinning sustainable energy production is to develop a better understanding of the light harvesting and photosynthetic systems of plants and green algae that will facilitate enhancements to their butanol producing metabolic networks. Linking such complex systems and fine tuning their functioning is now typically addressed through systems biology approaches. A considerable number of European research groups are active in these and related agricultural fields.

2.3.3 Industrial biotechnology

The food industry is one of the largest and most important manufacturing sectors in Europe, and systems biology approaches are giving cutting edge producers an international competitive advantage. Understanding molecular, cellular networks of microorganisms, plants and animals, which have been defined and integrated by systems research, enables a predictable and rational approach to their genetic and metabolic engineering. For instance, systems biology research groups across Europe are utilising computational models in the development of new food products and new plant and animal breeding regimes.

The IB market is estimated to develop from about €28bn in 2013 to ~ €41bn in 2020, and up to ~ €52bn in 2030. This represents an annual compound average growth rate of 4%.

BIO-TIC Overcoming hurdles for innovation in industrial biotechnology in Europe, Market Roadmap: Draft 2, 2014
& NNFCC The Bioeconomy Consultants: Biobased Chemicals – Markets, Innovation & Opportunity, 2013

2.4 Economic impact and commercial adoption

> The European pharmaceutical industry is the 5th largest sector within the European Union, whose production value for 2012 is estimated at 210 billion euro, with Europe having 26.7% of the World pharmaceutical market.
>
> EFPIA: The European Pharmaceutical Industry in a Global Economy: What drives EU exports of pharmaceuticals overseas?

The Organisation of Economic Co-operation and Development (OECD) has placed strong emphasis on the fact that biological resource centres (such as ISBE) are an essential part of the infrastructural requirements for the proper development of bio resources and their explicit role for industry[12]. In parallel, the European Union has substantially invested in programmes such as IMI[13], EMTRAIN[14], EIT[15] and the development of platforms such as KIC[16] to stimulate public-private research and training initiatives. A prerequisite for industry to participate in these programmes is the willingness to promote an open innovation model and exploitation of results. In this context the collaboration and coordination between research infrastructures, including ISBE, in the ESFRI Biomedical Infrastructure Cluster (see Section 7), should play a key role in increasing the output of these programs.

Despite these and other public-private efforts, commercial parties and particularly SMEs face the same problems as the academic sector: they have difficulties in finding and involving the necessary expertise and resources in systems biology. Large companies may have the possibility to invest in (often costly) solutions to tackle some aspects of this problem. SMEs, that lack both budget and manpower, cannot easily overcome this hurdle. Other obstacles hindering industrial research and innovative capacity are the duplication of efforts, difficulty of integrating private and public data and lack of standards. A positive development in solving this problem is that a collaborative landscape is developing, with a range of pre-competitive coalitions in research areas such as human health, environment, energy, and food technology. Here ISBE services and resources, and also matchmaking, would boost collaborations between private and public research efforts.

> Each Euro invested in EU-funded bioeconomy research and innovation is estimated to trigger €10 of value added in bioeconomy sectors by 2025
>
> NNFCC The Bioeconomy Consultants: Biobased Chemicals – Markets, Innovation & Opportunity, 2013

[12] OECD, 2007
[13] http://www.imi.europa.eu/
[14] http://www.emtrain.eu/
[15] http://eit.europa.eu/
[16] http://eit.europa.eu/activities/innovation-communities

Section 2 Summary

- Systems biology has been developed in the past 10 to 15 years by major investments by national funders and the EC.
- Expertise and resources in the field of systems biology are fragmented and not readily available or accessible to wider user groups.
- Systems biology approaches are an essential component in overcoming big challenges in e.g. the health, agriculture and biotechnology sectors.
- A systems biology infrastructure will boost public-private partnership in the life sciences, particularly for SMEs.

SECTION 3
ISBE: meeting needs and widening access

This section outlines the challenges of access to modelling and data integration expertise and resources, stewardship and standardisation and education and training. It highlights how ISBE will address these key challenges to maximise benefits for both ISBE's users and providers. These challenges apply to all parts of the life sciences. Here, ISBE is already working closely with other research infrastructures and initiatives to combine and synergise expertise and resources (see Section 7 and Appendix 2).

As outlined in Sections 1 and 2, systems biology can be described as the iterative process of data-driven modelling and model-driven experiments. Each cycle increases the insight into how the system that is investigated functions, as predictive and quantitative models allow simulation of the behaviour of complex systems under a variety of conditions. This approach is currently being employed by research groups in industry and academia across Europe and the world to produce novel findings and knowledge. Spectacular examples are the deep insight into the regulation of the beating of the human heart by integrating molecular, cellular and tissue level studies in a comprehensive quantitative and predictive computational model[17]. Similarly, ongoing studies on the human liver take a similar approach in unravelling how this organ functions[18]. For these and more examples illustrating the power of systems biology approaches see the case studies in Appendix 1.

Access to the expertise, tools and resources required to implement the iterative systems biology cycle into research projects is limited to a relatively small group of systems biology experts. This constraint impedes a broad implementation of systems biology in research projects. ISBE will enable the life sciences to overcome this hurdle by giving easy access to expertise, services and resources that are essential for systems biology.

ISBE will ensure the development of best practices and community standards for the generation, curation and annotation of data and models. Through this route, ISBE will sustain high quality research and add value to previous investment by enabling the re-use, expansion and integration of data sets and models (Sections 4 and 5). These activities will be supported by the provision of information and training to meet the disparate needs of the various communities that will use the infrastructure (Section 6).

[17] http://videolectures.net/eccs07_noble_psb/
[18] http://www.virtual-liver.de/

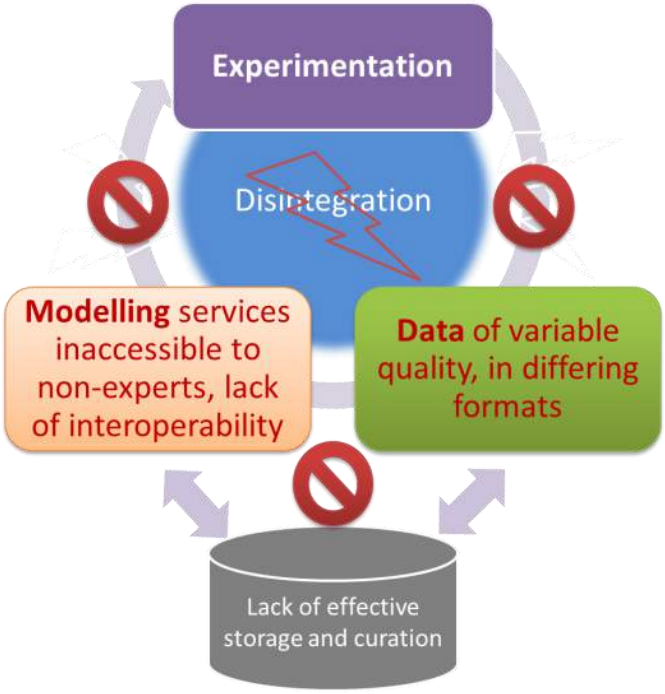

Fig 3.1: Currently, reductionism in combination with lack of modelling services and standards hampers the integration of data and getting insight in how biological systems function.

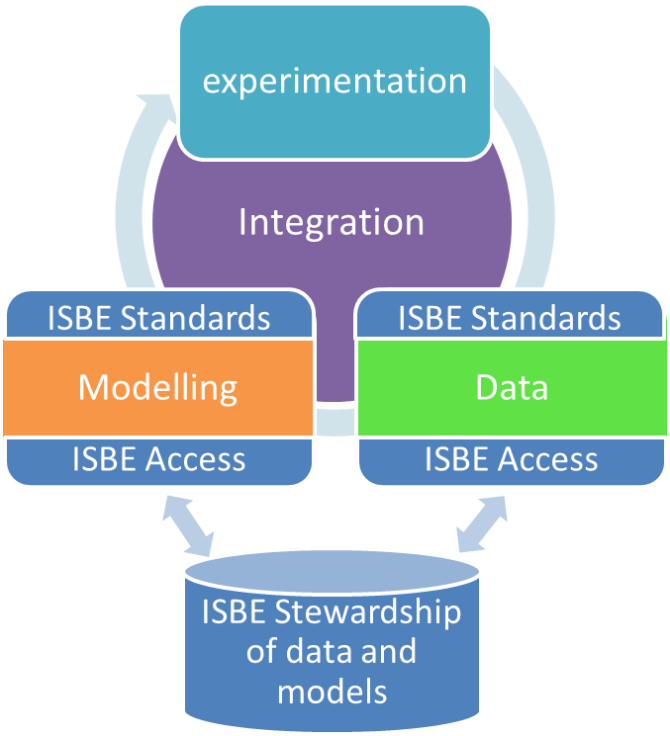

Fig. 3.2: ISBE will enable a more efficient and widespread uptake of systems biology research by providing support in computational modelling, model-compliant experimentation, systems biology compliant data, model and SOP stewardship together with the development and implementation of community standards, linked to relevant training and education.

3.1 Modelling resources and services

One of the key challenges in gaining a wider adoption of systems biology is providing access of modelling to a multidisciplinary user-base. Systems biology is already impacting upon the diverse areas of medicine, pharmacology, food production and agriculture. It is envisaged that the users of ISBE services will come from across these and others sectors, from both basic and applied science. To meet the needs of these groups, services, resources and consistent education, training and information is required.

Recent advances in software for constructing and analysing models (such as Copasi, JWS online, Cell Designer) have illustrated how well-designed, intuitive tools can greatly increase accessibility. However, a much wider variety of integrated services are required to meet the needs of a diverse user-base, from software and tools for hands-on users to consultancy service with trained modellers. Despite a range of local, national and transnational efforts, most students and researchers in Europe do not have easy access to good quality systems biology education and training.

To meet these and other challenges ISBE will do the following:

ISBE will *collect, develop, maintain and make available a wide range of tools and resources for the construction of maps of biological networks and predictive computational models of complex biological systems. This must be combined with expertise to analyse the quality of maps and models and to do model simulation and model validation. Algorithms and workflows used for system analysis will be transformed to toolboxes and software packages that are made widely available. ISBE will provide consultancy services with modelling experts for planning experiments for model construction; pairing of data experts and modellers for collaboration and construction of models from experimental data.*

ISBE will *develop its European strategy for systems biology training and education, in cooperation with its national Systems Biology Centres (nSBCs) and other European stakeholders, to*

Multiscale modelling

What is multiscale modelling?
Systems biology seeks to understand the functioning of living organisms in a quantitative and predictive way, and in terms of the interactions in time and space between molecules, cells, tissues and organs. Multiscale modelling is central to this endeavour, developing models that span multiple spatial and temporal scales, enabling us to understand and predict processes that occur across different scales. Examples include the Virtual Heart of Denis Noble and colleagues, which is now accepted by the United States Food and Drug Administration (FDA) and some pharmaceutical companies as an alternative to animal testing of drugs for cardiac toxicity. Another example is the Virtual Liver Network, bringing together 70 German research groups across 40 institutions. (See case studies: Appendix 1).

Why is it difficult to do?
There are multiple challenges, from bringing together the array of necessary expertise and resources to integrating disparate models and data sets. Technical issues include ensuring cross compatibility of measurements and models, unit consistency of merged models, changing parameter constants through model layers and the cross compatibility of formats. Furthermore, these are often ongoing projects that extend beyond standard funding cycles; the Virtual Heart has been in development for over 40 years.

What can ISBE do to help?
By harnessing Europe's biological modelling expertise, developing standards and best practice and maintaining pre-existing and future models and data, and providing a reliable, sustainable infrastructure, ISBE can help to make multiscale modelling the norm rather than the exception.

"Life Science researchers risk losing access to high-quality databases such as the very popular resource KEGG with 400,000-500,000 monthly users, which is struggling to find ways for its continuous support, and ISBE could be a solution for maintaining the sustainable provision of such resources."

Hiroaki Kitano
The Systems Biology Institute, Tokyo, Japan

3.2 Stewardship

Stewardship helps to ensure that important digital research assets are FAIR (findable, accessible, interoperable and re-usable). For research assets to be FAIR they must be adequately formatted, annotated, validated, interlinked and safeguarded for future use. This is an important role: if research assets have value, someone must manage them, make them discoverable and maintain them to ensure that they remain usable. Beyond traditional stewardship, systems biology requires specialist interlinking of the diverse research assets that comprise investigations. In doing so, value and impact is added to previous research. However, with project funding often limited in duration, resources are not readily available to maintain the valuable research assets being produced. Where research assets have been made available, there is often a lack of formatting and insufficient annotation, or their long-term storage is not guaranteed, making the data and models unsuitable for effective re-use. This presents the risk of making the potential exploitation of such research inefficient at best, or even completely absent.

Research Assets

The heterogeneous nature of systems biology means that outcomes from research are quite broad. We therefore use the term *research assets* to include data, models, SOPs, network maps, software, tools, and any other discipline appropriate outcomes from systems biology research.

Initiatives such as the BioModels database, a repository of computational models of biological processes, which is operated by the European Molecular Biology Laboratory European Bioinformatics Institute (EMBL-EBI)[19], and the JWS Online model database[20] have illustrated a user demand for an infrastructure to effectively steward models (for a case study see Appendix 1). For data, initiatives such as Metabolights[21], a database run by EMBL-EBI for metabolomics data; Gene Expression Omnibus (GEO)[22], a database for genomics data run by National Centre for Biotechnology Information (NCBI); and Human Imaging Database[23] (HID), run by the Biomedical Informatics Research Network (BIRN), have demonstrated a user demand for infrastructure to store and steward data. The next stage is to integrate these resources into a single resource usable by the whole community, known as a commons. NIH in the US has already started an initiative to generate a North

[19] http://www.ebi.ac.uk/biomodels-main/
[20] http://jjj.mib.ac.uk/
[21] http://www.ebi.ac.uk/metabolights/
[22] http://www.ncbi.nlm.nih.gov/geo/
[23] http://www.birncommunity.org/about/overview/

American Commons. Here in Europe we have seen growing demand in SEEK, software that supports a commons originally designed to support consortia projects. We must now build on such initiatives to generate a European Commons, incorporating the stewardship of research assets and the implementation of standards, in order to add value to existing and future research.

ISBE will *work with the systems biology community to maintain and develop sustainable archives, repositories, and commons in order to ensure that they are suitable for supporting the changing nature (volume, variety, velocity, veracity) of research assets.*

ISBE will *ensure that research assets produced* ***within*** *the infrastructure are structured and annotated according to the community state-of-the-art. These will then be curated before storage in a public archive or repository, persistent identifiers (e.g. DOIs), provenance and semantic linking to related research assets. Their usability will be constantly monitored and, where needed, formatting and annotation will be updated to reflect the current state-of-the-art throughout its lifetime. Software to operate the models will be made consistently available for the lifetime of usability of the model. Research assets may be replaced or updated where more relevant research assets are generated beyond of the lifetime the original.*

ISBE will *develop and provide access to* ***best practice*** *recommendations for formatting and annotating research assets produced outside of the infrastructure, as well as long-term storage in archives and repositories, with persistent identifiers (e.g. DOIs), and semantic linking between related research assets. This will be provided for the lifetime of the research assets, and importantly software for running the models will be consistently maintained to ensure the model is usable during its lifetime.*

ISBE will *collaborate with other research infrastructures, projects and initiatives focusing on the stewardship of data to ensure that protocols and resources are synergised. In particular, there will be close links with ELIXIR where data will be stewarded in accordance with common guidelines to be agreed between ELIXIR and ISBE.*

3.3 Standardisation

The data in systems biology projects can be obtained from many sources, using a broad variety of methods. In order to construct computer models, the data must be structured, combined and integrated. The successful application of systems biology tools relies greatly, therefore, on the standardisation of the formats and associated metadata descriptions. It is essential to uniformly format and semantically interlink research assets that are related to each other, for instance within large multinational coordinated projects.

On a broader scale, standards in research assets allow for discovery, exchange, analysis, integration and re-usage between research labs, institutes and industry, and provide users with models that are interoperable on a number of analysis platforms. By enabling the re-use of research assets, research is made considerably more efficient and economical.

"ISBE can represent a solution for the long-term availability of vital community tools, such as the Systems Biology Markup Language (SBML) that is used by over 250 software systems and thereby thousands of monthly users, and which is struggling to find ways for its continued support beyond 2016."

Mike Hucka
California Institute of Technology, USA

The current usage of standards within the community is low. A number of factors influence this, including the lack of suitable standards, usability of standards and the different requirements from funding bodies and journals for standard usage. An additional overarching challenge is the breadth of the systems biology community, the research areas and disciplines it encompasses, many with their own protocols and operational procedures. Efforts towards standardisation in systems biology have been distributed between standards that are applicable across the field and those are that are discipline specific[24], thus utilisation remains limited. For standards to be adopted, they must have community buy-in and be implemented on a sufficient scale for benefits to be realised. Recently systems biology has demonstrated how models can become central engines of data integration, only thereby making the data predictive of real life systems.

[24] Examples of standards that are applicable across the field include Systems Biology Markup Language (SBML), Minimal Information Required In the Annotation of Models (MIRIAM), Systems Biology Ontology (SBO) while FASTA and Minimum Information About a Microarray Experiment (MIAME).

ISBE will *actively promote and support the development of standards, software and algorithms that support modelling analysis within the European systems biology community, working with all stakeholders to maximise uptake. The provision of these resources will make routine building and analysis of models accessible by a wider section of the community. Centralised resources for making algorithms and software will allow users to generate standard operating procedures (SOPs) for their modelling analysis that ensure reproducibility, and provenance of their results.*

ISBE will *work with research communities and scientific journals to develop dedicated archives, repositories, tools, and standards that support the wider provision of resources for systems approaches. These resources will be catalogued for easy discoverability through an online portal. Standard workflows will be established for routine analyses in which a number of operations, tools, and databases are combined in a way that they can be used by non-experts.*

ISBE will *work closely with relevant European and international research infrastructures, projects and initiatives in the development of community-accepted SOPs for data generation, linked to ISBE's stewardship activities. ISBE will work in conjunction with ELIXIR, a European research infrastructure focused on the collection, quality control and archiving of biological data. By developing common standards, ISBE will work with ELIXIR in adding value to ELIXIR's data sets by making them compatible and reusable by researchers undertaking systems biology projects*

3.4 Generation of model-compliant data

Systems biology models require data that are fit for modelling, both when models are built and for their validation. More often than not, disparate data sets must be combined and integrated (e.g. microscopy and proteomics and metabolomics) posing severe constraints on experimental and analytical procedures. This includes issues such as precision of data, sample preparation, data acquisition protocols and data analysis methodologies. To support the life sciences community ISBE will do the following.

ISBE will *provide access through its nSBCs to services of data generation facilities that are able to provide model compliant data. Either such facilities may be integrated into the nSBC, or the nSBC may liaise with such facilities provided by other infrastructures, projects or initiatives.*

3.5 Education and Training

The promotion of training and education in systems biology at all levels is an essential pre-requisite to realising the vision of ISBE. Experience shows that developing good quality education and training programmes in systems biology requires overcoming a number of obstacles; namely, the intrinsic multi-disciplinary nature of systems biology, and training at the interface of mathematics and biology, in particular. In order to address these challenges, ISBE will develop a multi-faceted education and training strategy (*as also described in section 6*):

> ***ISBE will*** *develop core curricula for postgraduate training, and provide short courses and online training for users and nSBC professional staff. This will be combined with dissemination of information on courses and meetings via an up-to-date database.*

Section 3 Summary

ISBE expects to have a broad range of users: academia, hospitals, clinics and industry. Scientists that want to implement systems biology in their research projects will be supported by ISBE through:

- Services in three tightly linked domains: modelling, model-compliant data generation, stewardship and standardisation.
- Diverse data and model exchange in a standardised manner that is accessible and understandable between all sectors.
- Access to data and models to ensure that researchers can progress the systems biology life-cycle by becoming an ISBE user.
- Developing and maintaining tools and software that makes it easier to model biological data.
- Meeting future-proof operational needs of systems biology.
- Developing and offering an education and training programme in systems biology.

SECTION 4
The ISBE infrastructure: interconnected national Systems Biology Centres

This Section describes the structure of ISBE, consisting of interconnected and cooperating national Systems Biology Centres (nSBCs), and presents how it will operate and be managed, and what the eligibility criteria are for institutions interested in joining ISBE as a service provider.

4.1 The infrastructure

The core of ISBE will be a group of national Systems Biology Centres (nSBCs) across Europe offering interconnected, and complementary services at the national and the European level. This will create a European infrastructure that

- covers all facets of the rapidly developing field of systems biology,
- synergises past, present and future national and European investments in systems biology,
- has a highly flexible capacity to provide a range of services.

Figure 4.1: ISBE will be a 2-tier 'hub and spokes' model: that coordinates the delivery of operations by nSBCs at the national level and the strategic coherence across the nSBCs at the European level.

Potentially a single institution may seek to act as an nSBC by being a stand-alone service provider, mostly serving their national users. Alternatively, two or more nSBCs may combine their activities to offer specialised or more extensive support on a project-by-project basis. Each nSBC will be embedded in its national systems biology community. An nSBC may have a distributed structure, uniting diverse expertise in a country, or it may be housed at a single location.

4.2 Building on national strengths

ISBE will build on existing European resources, and draw on the technological and research strengths of its members, to provide a coherent and comprehensive package for users of the infrastructure. Where possible, ISBE will map onto existing structures and coalesce facilities under a single banner, creating ease of access for users and avoid duplication of resources for providers. As highlighted in Section 2, national infrastructures for systems biology currently exist in Europe, stemming from national funding priorities and historic investment. For example, in the UK, Germany, the Netherlands, the Czech Republic and Italy, funding councils have made significant investments in systems biology to date, reflecting national research strategies; ISBE is at present undertaking an audit of existing infrastructure to understand current national strengths and priorities. ISBE will build on these and other national research facilities and expertise in line with national strategies. In this way ISBE will be able to both integrate these facilities and broaden access to their services. In doing so, past, current and future investment of national funding organisations and governments will be strengthened. Under the ISBE umbrella each country will be able to continue to develop its own distinct scientific expertise, resources, services and community activities.

4.3 An integrated European infrastructure

Research is increasingly moving away from single groups working on individual projects towards larger distributed teams and consortia that require access to high-end knowledge, expertise and services. This is key in fully realising the European Research Area. By integrating systems biology activities at a European level, ISBE will facilitate complex and comprehensive research programmes able to compete on an international scale, boosting European research competitiveness and meeting the needs of its governmental, academic and industrial stakeholders. ISBE will also work with countries with no current national access to systems biology resources and expertise by enabling access to state of the art systems biology infrastructure and assisting in the establishment of new national infrastructures.

At a European scale nSBCs will be interconnected, enabling users' needs to be matched to an array of international providers' resources and expertise. ISBE will interlink the complementary expertise in its nSBCs, creating a strong common point of delivery for research assets and services.

4.4 Managing the infrastructure

4.4.1 The coordinating SBC

It is expected that a significant fraction of user support will be handled by individual nSBCs. Managing individual nSBCs within the context of European infrastructure will be the responsibility of the national authorities. More complex or extensive user requests may require the cooperation of two or more SBCs working together to provide the requested services. This will require a continuously updated overview of the scientific and technical abilities of all nSBCs and coordination of their services. In particular, the development of standards and ISBE's teaching and training activities will require coordination of the activities of ISBE's nSBCs. This will require a deep insight into underlying scientific issues. Also, ISBE needs to keep track of the expertise of the nSBCs and identify new developments and gaps in expertise and services that need attention. To do so, a nominated nSBC will become the coordinating SBC (cSBC) of the infrastructure. In summary tasks of the cSBC, beyond those of a nSBC, will be:

- keeping an up-to-date overview of the expertise and services of all nSBCs,
- coordination of nSBCs working in tandem as required to provide ISBE services,
- coordination of the stewardship activities and the development of community standards (Section 5),
- quality control of the services provided by ISBE.

4.4.2 The Central ISBE Office

The central management, administration and governance of ISBE will be carried out by the Central ISBE Office (CIO), which will be physically linked to the cSBC. It will monitor and coordinate overall operations and oversee ISBE strategy development, including:

- nominations and approval process for new nSBCs,
- links between nSBCs, including commissioning of novel services, resources and activities,
- liaison with ISBE member state funding organisations, external cooperation, such as partnerships with other Research Infrastructures, including other ESFRIs, and international organisations in or outside the EU.

4.5 Becoming a national ISBE Systems Biology Centre

Taken together, the ISBE nSBCs will provide a range of unique expertise or services that will contribute to delivering the continuity and positive impact to their national communities, whilst ensuring that ISBEs operates as an effective and cohesive provider giving European added-value. What is missing here is that each centre must provide something unique. Listed below are a set of eligibility criteria for national research institutions interested in becoming an ISBE nSBC.

i. located in and supported by a EU Member State or Associated State
ii. a single legal entity will be identified to represent the institution(s) forming the nSBC
iii. subscribe to the aims and strategies of ISBE
iv. evidence of a reliable and effective governance and management structure and financial stability
v. contribute where possible to the three domains of expertise and services of ISBE: (i) modelling, (ii) stewardship and standardisation, and (iii) model compliant data acquisition
vi. proven high scientific quality in ISBE relevant fields of expertise and facilities
vii. contribute to the ISBE-driven development and implementation of community standards and SOPs
viii. participate in ISBE training and education activities

To host the Central ISBE Office (CIO) an nSBC should be able to show that it has the expertise and resources to carry out the additional tasks listed in Section 4.4.2. Decisions on accepting nominations from prospective nSBCs will be made by ISBE's Governing Board (Section 8.2.1).

Section 4 Summary

- ISBE will form an integrated European distributed infrastructure of national Systems Biology Centres (nSBCs) with overlapping and complementary expertise.
- Depending on the services that are requested nSBCs may act individually or several nSBCs may team up.
- Individual nSBCs are managed and financially supported at the national level.
- At the European level, scientific services of nSBCs are coordinated by a coordinating SBC; coordination of administrative and managerial activities will be done by the Central ISBE Office.
- ISBE defines eligibility criteria and a selection procedure for candidate ISBE nSBCs.

SECTION 5

How ISBE will serve its users

This section describes the services and resources that ISBE will offer to the users, proficient or unskilled in systems biology, and how users will gain access to the infrastructure. ISBE's services and resources will be made available to a wide variety of users from across academia and industry in Member States and Associated Countries.

5.1 Services

ISBE will offer a range of interrelated services that help users to implement the full iterative systems biology cycle, i.e. experimental data-driven modelling combined with model-driven experiments. ISBE's services and standardisation efforts will make data and models re-usable and interoperable, with all services tailored to the need of the individual user. Examples are presented as persona models in Appendix 2.

ISBE, via the nSBCs, will offer its users three main types of services. Their relative weight will differ between nSBCs, depending on national priorities and expertise.

i. *Modelling of biological systems based on integration of diverse data sets*
   ISBE will support life scientists, proficient or unskilled in systems biology, in developing quantitative and predictive computational models of biological systems by integrating diverse data sets. ISBE will offer a wide range of modelling approaches for systems ranging from subcellular molecular networks to cells, tissues, organs and complete organisms. These services will be complemented by model analysis and validation and model-based simulation to gain insight into the behaviour of systems.
ii. *Stewardship and standardisation*
   To make the results of research projects FAIR it is essential to format and semantically link research assets using community-adopted standards and annotations, and make them available in a *commons* interface. This is essential to make results re-usable and to expand data and models in a stepwise manner as research projects progress. In this context ISBE will develop and promote best practices, community standards and standard operating procedures (SOPs) that are easy to use and can be widely implemented by life science communities.
iii. *Generation of integratable and model-compliant data*
   Generation of data sets that can be integrated and are fit for modelling requires careful planning and execution (experimental design). ISBE's nSBCs may have links to institutions that are able to do this, or have in-house facilities. This would use established omics and bioimaging technologies to deliver model compliant datasets.

These services will be offered in various modalities, meeting the full range of needs of diverse life science communities.

i. *Web-based access to repositories and archives*
   ISBE will offer curation of models and data, tools and protocols linked to them, throughout the life-time of the research projects and beyond, with digital object identifiers (DOIs) for easy access, attribution and citation. This will make data, tools and models re-usable over prolonged periods of time, in other research projects and by other researchers.
ii. C*onsultancy*
   Users may contact ISBE to get information and advice from experts about the use of

systems biology and how to implement it in (small or large) research programmes.*(see also section 5.6)*

iii. C*ontract activities*

ISBE nSBCs, individually or in groups (depending on the requested service), will offer to guide or to carry out those components of research projects that require specific expertise. This includes the following activities.

a. design of experimental approaches and efficient workflows that allow the development of quantitative and predictive models of complex biological systems
b. acquisition of data that are fit for modelling
c. model-driven integration of diverse data sets
d. development of quantitative and predictive models
e. validation and analysis of models
f. model simulation to gain insight into the behaviour of complex systems

iv. *Training and education*

ISBE will provide information and access in relation to a wide range of training and education programmes in the field of systems biology: see Section 6. It will also develop outreach activities towards a range of stakeholders.

5.2 Resources

Complementary to its services described above, ISBE will offer web-based access to a variety of resources. These will help researchers to develop their own systems biology approaches.

i. *Tools*

- to enable non-experts to construct maps and computational models that are based on experimental data
- to analyse and validate models and share them with others
- to carry out model simulations

ii. *Data, maps and models*

- selected, curated and annotated public data sets that are fit for modelling
- curated and annotated maps and models in standardised formats

iii. *Community standards and SOPs*

- information about formats, standards and SOPs that are accepted and used by the systems biology community

Advanced technologies

Current established advanced technologies for systems biology include microarray, next generation sequencing, single cell, proteomics, metabolomics, imaging, and dynamic modelling.

As ISBE advances, so too will the breadth of established advanced technologies.

5.3 Community activities and information

The users and providers of ISBE will form an active community who will take responsibility for developing modelling and data standards, best practices and standard operating procedures as outlined above. This will enable life scientists to structure, annotate and store their data and models and means that their results will become re-usable and can be merged with those of others.

ISBE will reference its community activities with other international organisations and initiatives that develop best practices, standards and resources, including the following:

- International Society for Systems Biology (ISSB)
- International Society for Computational Biology (ISCB)
- the Physiome Project
- the Virtual Physiological Human (VPH) project
- transnational programmes such as ERASys*App*, ERASynBio, Coordinating Action Systems Medicine (CASyM)
- Commonwealth Scientific and Industrial Research Organisation (CSIRO)
- Bio-platforms Australia
- the Systems Biology Institute of Japan (SBI)
- Innovative Medicines Initiative (IMI)
- various biomodel repositories

In doing so, ISBE will be the European component in an international network of expert reference centres that facilitates the international development and acceptance of best practices, standards and SOPs in the life sciences, in general, and systems biology in particular. The ISBE community, in the form of a Technical Board (Section 8.2), will drive the development of a European strategy for systems biology training (Section 6), as well as pooling and communicating up-to-date information about the international systems biology community, including workshops, conferences and training courses.

Utilising the expertise from across the infrastructure, the ISBE will maintain a dialogue between its provider and user communities to foster community cohesion, and will instigate a science and technology watch to ensure its services remain state of the art.

"ISBE would provide a sustainable bioinformatic and modelling infrastructure in Europe that would underpin the Virtual Physiological Human community."

Peter Hunter
Auckland Bioengineering Institute,
The University of Auckland, NZ

5.4 Industry, innovation and commercialisation

As outlined in Section 2.4, European industry is faced with many of the same problems as academia in dealing with the complexity of biological systems. Customised model-based approaches, effective stewardship, standardisation and access to selected and annotated fit-for-modelling resources will be highly beneficial to industry. Therefore, interacting with industry is an important target of ISBE. In particular, SMEs have difficulties in getting access to the necessary expertise and services. Given the large number and diversity of European SMEs, ISBE will mostly act through SME platforms, which exist in most countries, to make its services known.

Industry will benefit from the ISBE infrastructure through:

- easy access to the best multidisciplinary research expertise, training, experimental and modeling facilities, repositories of data and models
- enhanced public–private partnership and data integration
- improved data sharing through standardisation
- reduced costs through the re-usability of tools, data, maps and models

Appendix 2 presents examples (persona models) of how ISBE may interact with different types of users.

5.5 Providing access to diverse skills and expertise

There is a wide range of skills and expertise that will be required from staff at ISBE nSBCs that will provide the services, maintain the resources and ensure training and user outreach. ISBE is committed to ensuring both maximum exchange of knowledge and best practice across the nSBCs, and also to foster the continuing professional development of these staff, in order to ensure optimal service provision by ISBE.

Data modelling and integration, together with stewardship and standardisation provides the potential to establish a broad community of modellers, programmers, software engineers and web service managers. In addition these groups have the opportunity to be linked closely to research and technical personnel involved in the generation of model-compliant data (including quality control).

Provision of training and education resources and services will draw on the strength of existing trainers at centres of expertise forming nSBCs. These will be set in the broader context of staff skilled in providing web-based services, combining together to deliver a coherent ISBE outreach and engagement programme for our user community, including industry.

5.6 User access to ISBE

Access to the infrastructure will be easy and efficient through a central web portal. By default, users will subsequently be linked to one of the nSBCs, where possible their local centre.

i. *Web-based services: access to resources and information*
ISBE will offer free web-based access to resources and community information, as outlined in Sections 5.1 and 5.2, including:
- selected curated and annotated tools, data, maps and models
- information about best practices, standards and SOPs
- information about community activities and meetings

ii. *Education and training*
ISBE will develop core curricula for postgraduate training, and provide short courses and online training for users and, training of nSBC professional staff. This will be combined with dissemination of information on courses and meetings via an up-to-date database.

iii. *Provision of expert advice and consultation*
Users who require basic advice or information from an expert will be linked, via the ISBE web portal, directly to a staff member of one of the nSBCs, preferably the nSBC in the country of the user. This nSBC will either provide the requested information itself, or identify experts in one or more other nSBCs and link the client to them. Contact will be by email, telephone, Skype, etc.

iv. *Contract activities*
ISBE services requiring more extended nSBC staff efforts will be subject to the following procedure.

The web portal will be the first point of contact, where potential users will provide condensed basic and standardised information about the requested services (e.g. experimental design, workflows, model-compliant data generation, modelling, model analysis, validation and simulation). The user is then linked to an nSBC staff member and, on the basis of a scientific project plan (e.g. a grant application to a funding organisation) a formal agreement, time planning and a cost estimate are made. Each contract activity is supervised by (one of) the participating nSBC(s). Throughout the project, contact between ISBE and the client is through one of its staff members. Procedures for academics and industry will be essentially the same, except for, when necessary, IP-related issues, for which ISBE will have specific procedures.

Section 5 Summary

- ISBE targets users in European academia, hospitals and industry
  - without experience in systems biology or skilled in model-driven research

- ISBE will provide the following main services
  - modelling of biological systems based on integration of diverse data sets
  - stewardship and standardisation
  - generation of integratable and model compliant data
  - training and education
  - develop community standards and best practices

- ISBE services will have different modalities
  - web-based resources
  - consultancy
  - contract activities
  - training, education and outreach

- ISBE will make data, tools and models re-usable
  - through annotation, curation and semantic linking

SECTION 6

Education and training activities

This section elaborates on ISBE's vision for a pan-European strategy for systems biology training and education, with cooperation across the national Systems Biology Centres (nSBCs) and other European stakeholders.

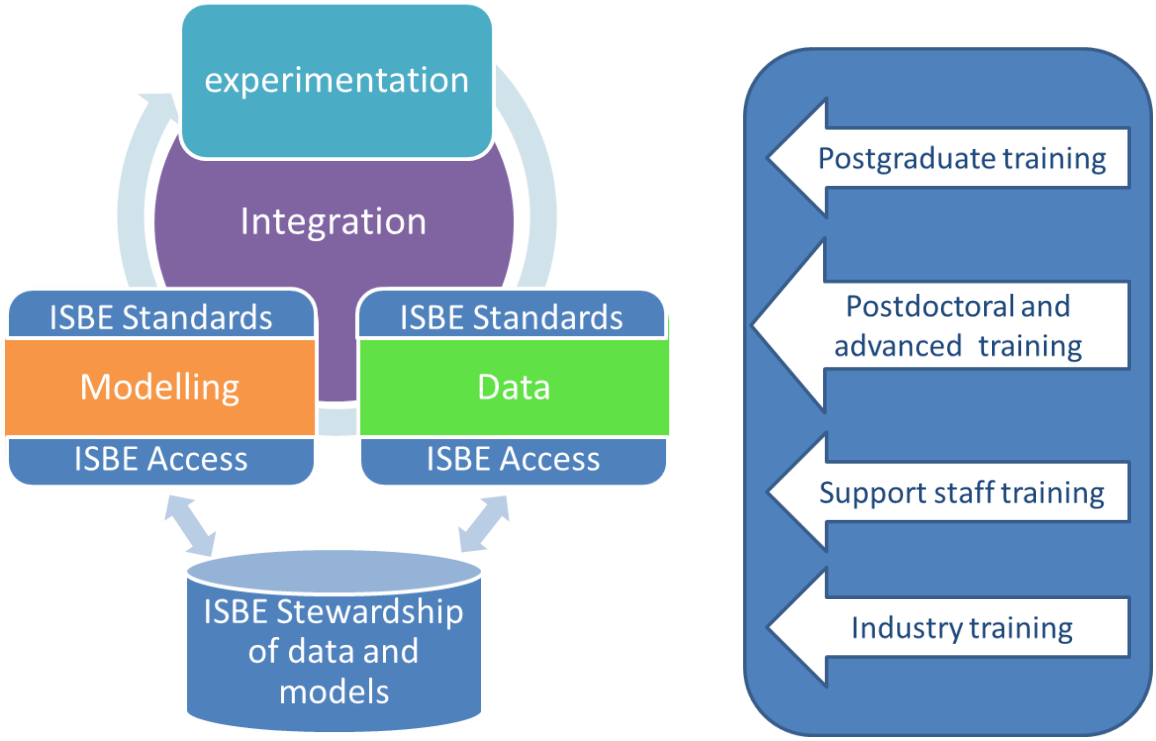

Figure 6.1: ISBE will provide multiple avenues for training in systems approaches.

6.1 What is available and what is needed

At present, training in systems biology is predominantly in countries where there has been significant strategic investments in the research base. A number of universities have developed Masters programmes dedicated to systems biology, or have included specific components relating to systems biology in other educational life sciences tracks. In addition, there are a limited number of specific PhD programmes and short courses addressing systems biology. Again, these tend to be focussed in countries where there has been a strategic investment in the field.

Several transnational European systems biology research programmes, such as the recently completed SysMo[25] and ERASysBio[26] programmes contained considerable training efforts. These have continued, at least in part, through the new ERASysApp[27] and ERASynBio[28] programmes. Also

[25] http://www.sysmo.net/
[26] http://www.erasysbio.net/
[27] https://www.erasysapp.eu/
[28] https://www.erasynbio.eu/

the European Molecular Biology Organisation and the Federation of European Biochemical Societies are active in this field.

Despite this range of local, national and transnational efforts, most students and researchers in Europe do not have easy access to good quality systems biology education and training. Experience shows that developing good quality systems biology education and training programmes requires overcoming a number of obstacles:

- Interdisciplinary teaching
  The intrinsic multi-disciplinary nature of systems biology calls for teachers who are able to operate at the interface of biology (or medicine), mathematics, physics and engineering. These are often difficult to find.
- Students with widely different backgrounds
  Systems biology teaching programmes and courses attract students from different disciplines – biology, medicine, mathematics, physics and engineering. Such students have widely different backgrounds and speak different scientific languages, therefore requiring tailored educational programmes, at least initially.
- Rapid developments in systems biology
  Systems biology is a rapidly developing field and it is essential that its researchers are familiar with the state-of-the-art.
- Lack of mathematical training for biologists
  University education in biology and medicine across Europe contains variable levels of mathematics. As a result, students and researchers are often not equipped with the skills necessary to utilise systems biology approaches.
- Lack of awareness of what systems biology can do for the life sciences more generally
  Since systems biology is still an emerging field , researchers are often not aware of the value of systems biology approaches.

ISBE's strategy for systems biology training and education in Europe aims to overcome these hurdles.

6.2 A multi-faceted education and training strategy

The ISBE training strategy will focus on the development and dissemination of best practice in systems biology training and education at the Masters, PhD and postdoctoral level. ISBE, as a distributed research infrastructure, is in a unique position to develop and maintain access to sustainable, high quality and state of the art training in systems biology. Key elements of the training strategy are:

- Postgraduate training (Masters and PhD): development of core curricula and establishment of a network of ISBE postgraduate training activities[29].
- Training of post-doctoral and advanced researchers, focussing mainly on ISBE's users, and including specialist short-courses based on the competences required within various target groups. To include, for example, accredited modular courses appropriate for continuous professional development, e-resources, online training courses, summer schools, train the trainer courses and a range of advanced lecture courses.

[29] Support for postgraduate training network to be sought, in part from EC H2020 ITN calls

- Training of nSBC professional staff (managers and operators) to maximise effective use of ISBE and other ESFRI infrastructures (to be coordinated with other ESFRI training activities[30]) to include:
    - Managers of research infrastructures: to develop skills such as leadership and team-building, marketing and communication, strategic planning, stakeholder management, project management, human resource management, service quality and management, performance measurement, budgeting and control.
    - Technical support staff of research infrastructures; focussing on harmonisation and integration with other research infrastructures as well as expertise specific to ISBE, including data management, security, user engagement; service development; systems administration and ethical and legal compliance.
- Promoting cultural change to enable integrative, interdisciplinary approaches to systems biology training and education.
- Disseminating information relating to training, making all relevant training findable and accessible to researchers from both academia and industry.
    - In this rapidly expanding field, there is a continuous need for courses and workshops that disseminate, critically evaluate and expand new insight and knowledge. A variety of such courses and workshops are organised by a wide range of organisations. ISBE will maintain a comprehensive database of systems biology-related courses, workshops and conferences and make this information available to the life sciences community. If ISBE identifies gaps in knowledge dissemination or development, it will urge national and European organisations to take the initiative, or will develop courses itself.
- Maintaining an online catalogue of experimental and modelling techniques, allowing (non-expert) researchers to identify what these can provide and what their limitations are.
- Providing customised training for industry.
  Industry has a need for systems biology training courses, tailored to their specific needs. ISBE will develop such bespoke courses in collaboration with industry partners.

Section 6 Summary

ISBE will develop a multi-faceted education and training strategy which will provide:

- support of postgraduate education in systems biology through development of core curricula.
- competency based short courses for users.
- nSBC staff training in collaboration with other RIs.
- an up-to-date database of systems biology courses, workshops and conferences.
- customised training for industry.

SECTION 7
Cooperation with other life sciences research infrastructures and organisations

A key principle of ISBE will be to ensure a sustainable infrastructure that maintains state-of-the-art services and expertise and the broadest possible utility. ISBE will therefore continue to develop and optimise resource and technology provision and the storage of tools, models and curated data at nSBCs across Europe. These will allow for ongoing incorporation of novel and emerging tools and resources, combined with coordinated consultation of users. ISBE is committed to cooperate and tune its activities and services with other research infrastructures (RIs), projects and initiatives to maximise synergies, avoid overlaps and exchange expertise.

The ESFRI Roadmap 2010 lists 13 European Research Infrastructures (RIs) in the life sciences, including ISBE, that are under construction or in their planning phase[31]. In this context, ISBE actively participated in the preparation of the CORBEL proposal (Coordinated Research Infrastructures Building Enduring Life-science Services) in response to the Horizon 2020 INFRADEV-4 call. CORBEL aims to harmonise the actions and joint development of the 13 European Research Infrastructures by integrating user access, data management, ethical and legal issues, training as well as common services at interfaces across ESFRIs. Through ISBE's strong role in integrating life sciences technologies, data and services between the ESFRI Research infrastructures in life sciences, it will be an integral part of the ESFRI community.

There are huge potential benefits from facilitating the exchange of information developed within one community so that it can be applied to the range of different biological research domains, across a large variety of samples. However, this exchange can only happen where the data and models meet with recognised international standards and are closely linked to the communally accessed repositories, even when these are held outside ISBE centres. Coordinated engagement with non-ISBE systems biology centres and relevant ESFRIs will ensure that all potential for joint action is realised. This also affords the opportunity to focus on the common training and development needs of professionals working in these different ESFRIs, or organisations representing them.

ISBE is actively engaging with all ESFRI Research infrastructures in life sciences, including those in translational, marine and microbial research, and is tackling cross-cutting issues relating to data, resources and technologies. An inventory has been made of common interfaces between ISBE and other biological and medical sciences RIs that underscores the importance of cooperation and is summarised in Appendix 3.

[31] http://ec.europa.eu/research/infrastructures/pdf/esfri-strategy_report_and_roadmap.pdf

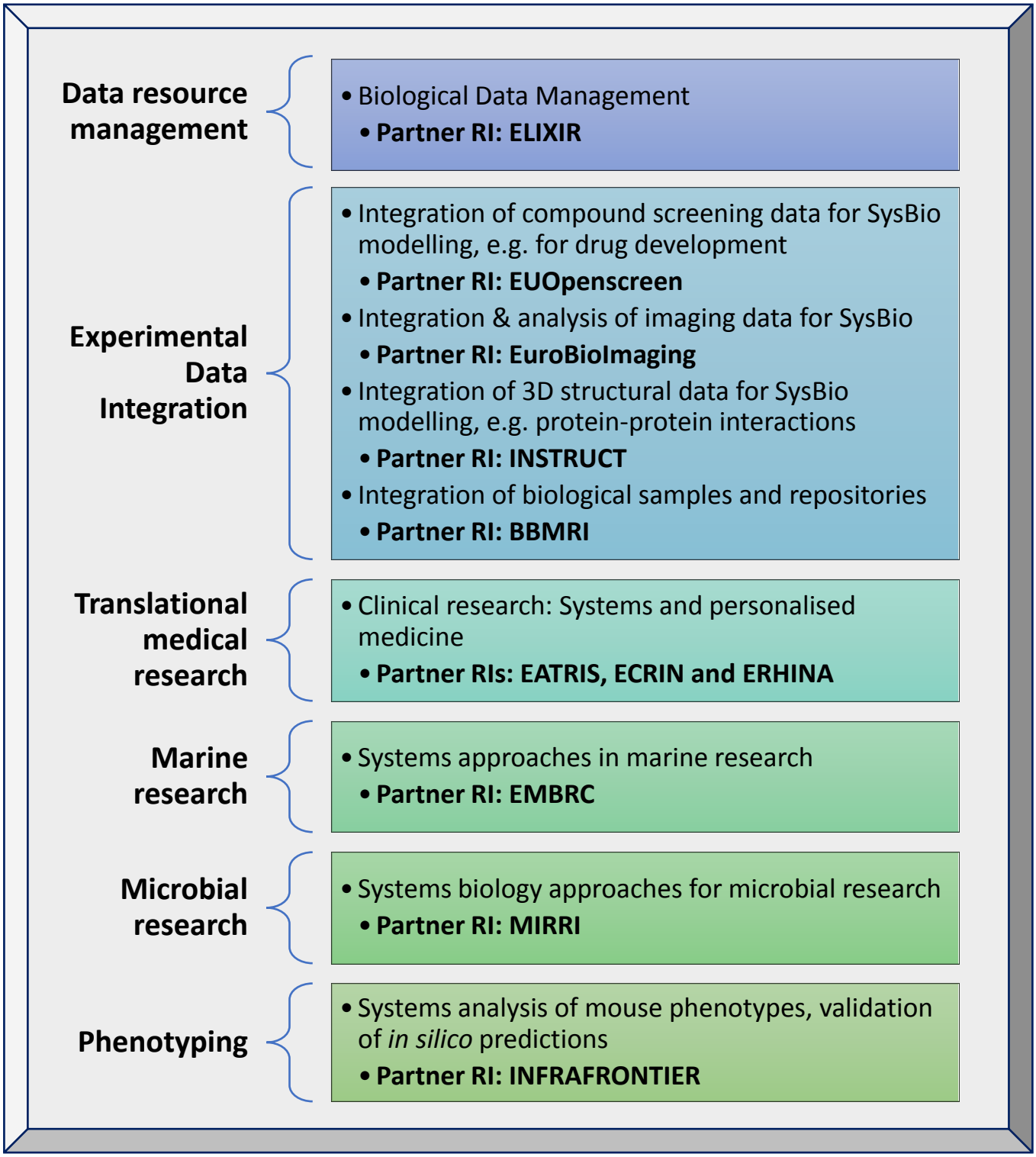

Diagram 7.1: illustrating the key areas of interface with other Biological and Biomedical Science ESFRIs

ISBE is working together with other Research Infrastructures, as well as other relevant projects and initiatives including CASyM[32] and ERASys*APP*[33], to develop common strategies that support access to biological data and samples linked with experimental resources and expertise and will expand this activity once operating. This will strengthen the joint development and facilitate the rapid uptake and availability of tools, services and data management.

Section 7 Summary

ISBE will ensure its ongoing significance, and facilitate the rapid uptake of systems approaches by European users in concert with other ESFRIs.

- ISBE will maintain its provision of state-of-art services and expertise, and broadest possible utility through coordinated consultation of its users. This will allow for ongoing incorporation of novel and emerging tools and resources
- ISBE is actively engaging with all European biomedical ESFRIs to tackle cross-cutting issues through its involvement in CORBEL proposal (Coordinated Research Infrastructures Building Enduring Life-science Services) in response to the Horizon 2020 INFRADEV-4 call.
- ISBE will continue to explore avenues for harmonised access and service provision with other ESFRIs and EU initiatives in all aspects of its planned operations, including ISBE education and training strategy, and coherent industrial engagement.

[32] https://www.casym.eu/
[33] https://www.erasysapp.eu/

SECTION 8
Legal structure and governance

This section describes the legal identity of ISBE, including legal agreements with the nSBCs and ISBE's governance structure. To be a viable long term infrastructure, ISBE will require a robust and effective financial, legal and governance structure that supports efficient operations and strategic planning. This will flexibly allow future inclusions (and departures) of both member states and centres involved in providing ISBE services, activities and resources of excellence in Europe.

8.1 Legal structure

ISBE requires its own legal personality in order to obtain funding, manage budgets, negotiate and operate legal agreements with nSBCs. As a single legal entity it can coherently engage with users, providers and stakeholders from industry, national ministries and funding agencies, the European Commission and other funders. ISBE will appoint and employ a director to engage with external stakeholders, leading outreach and advocacy for the infrastructure, together with administrative staff to support the standing bodies required for planning and operations across the national centres. The Central ISBE Office (CIO) will be based in the cSBC. Its tasks are described in Section 4.4.2.

8.1.1 Legal identity - ERIC

The preparatory phase has identified the European Research Infrastructure Consortium (ERIC)[34] mechanism as being most appropriate long-term model for ISBE. This allows ISBE to become a legal entity with a European identity that could also benefit from tax exemptions. In addition, countries that have already ratified the ERIC framework would not require further Parliamentary ratification. ERIC also allows membership for countries outside the EU.

The ERIC agreement will outline the key aims for ISBE and define the legal framework of relationships between nSBCs, including the application processes. Several other ESFRI projects have already opted to develop the ERIC status as the long-term legal model of choice.

8.1.2 Legal agreements for Individual Centres

Pre-agreed Service Level Agreements (SLAs) will define the commissioning of services, activities and resources that will be offered in a fair, transparent and legally acceptable manner. Their exact nature may vary across individual centres.

On application, each candidate nSBC will define the resources and technical services to be offered, in line with the ISBE provider eligibility criteria (see Section 4.4). Once approved, SLAs would establish an institution's status as an nSBC, and procedures for managing the delivery of services, financial provisions, quality control, IP and liability for the duration of that agreement.

NSBCs may be single institutions (i.e. a single legal entity providing all services), or several institutions combining to provide an integrated package. Where a nSBC is located at more than one institution, the SLA will also outline how these component institutions will offer unified technical support and advice, as well as coherent commissioning of further ISBE services. Each nSBC will define its own

[34] http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=eric

'Head of Centre' and establish for themselves their own processes for internal coordination and monitoring of tasks and responsibilities.

8.1.3 Legal agreements between other ESFRIs, Research Infrastructures, projects and initiatives

The CIO will coordinate interactions with other organisations to ensure efficiency of operations, and coherent engagement. However, it is also recognised that this does not preclude individual nSBCs entering bilateral legal agreements with other institutions.

8.2 Governance

The ISBE governance structure will provide for effective and timely management and monitoring of operations across the nSBCs. It will provide suitable external scientific and technical advice and operate with transparency and clarity in its procedures, including the nomination and election of members (fig. 8.1).

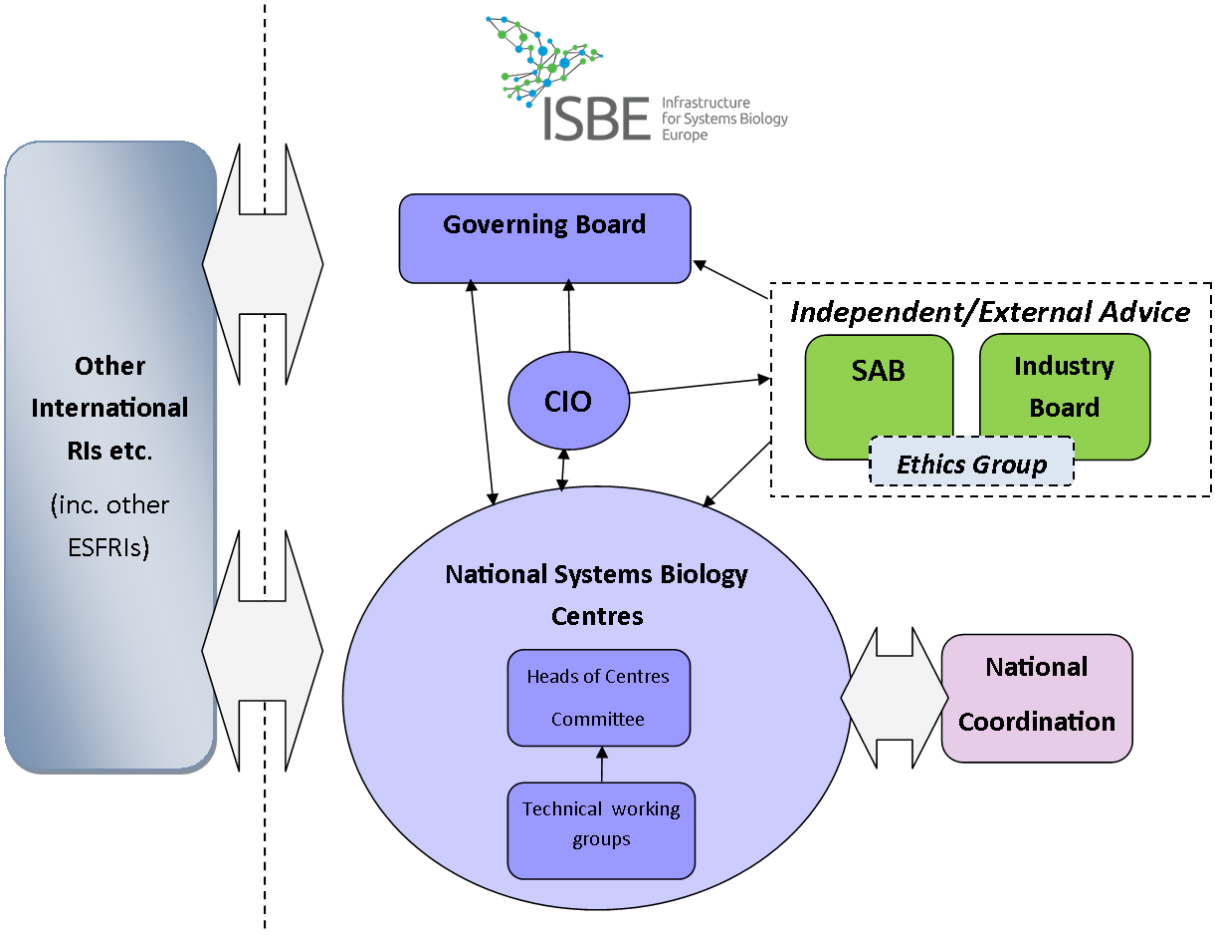

Figure 8.1: Organisational diagram of the main standing bodies of ISBE and key areas of interaction

8.2.1 Oversight and decision making - Governing Board and Heads of Centres Committee

The *Governing Board* will provide central decision making and high-level oversight, with supervision of the CIO on behalf of the member states. It will approve ISBE strategy and budgets, as well as approve prospective nSBCs. Representatives will be drawn from national funding bodies, together with scientific experts from their national communities.

Coordination for operations and planning across the nSBCs will be provided by the *Heads of Centres Committee*. It will consist of all heads of nSBCs and will report to the Governing Board, primarily but not limited to providing strategic advice.

8.2.2 Effective coordination - Executive Management, and Technical working groups

The CIO, headed by the ISBE Director, will report to the Governing Board. It will execute the Governing Board's decisions, manage the central budget and organise the scientific evaluation of centres, as well as manage collaboration agreements (ie. SLAs) with nSBCs.

Cross-centre '*Technical working groups'* will consider specific technical and training aspects of ISBE operations that are of key importance to ISBE. They will coordinate specific communications and knowledge flow on operational aspects, as well as advise other ISBE standing bodies on future needs. Notably, these boards will coordinate the delivery of community-led focus activities.

8.2.3 External advice - User and Stakeholder Engagement

Understanding user needs across all sectors, combined with ensuring the continued delivery of cutting edge technologies, is crucial to the success of ISBE. The *Scientific Advisory Board (SAB)* and the *Industrial Liaison Board (ILB)* will be the main sources of external advice from both academia and Industry respectively, for both the Governing Board and Executive.

The SAB will regularly evaluate all applications for prospective nSBCs against a pre-agreed evaluation process (see Section 4.4), and will the monitor performance and service delivery of nSBCs. The SAB will also advise the Governing Board on decisions to renew or terminate nSBCs.

The Industry Liaison Board will enable wider consultation of stakeholders within the commercial sector, including advice on industry needs as well as reviewing opportunities for joint funding.

8.2.4 Ethical issues - Ethical Board

It is important to consider the ethical implications of ISBE's activities involving information from animal and human experimentation, together with the related issues of data security and access. ISBE will build on existing interactions with BBMRI and other ESFRIs for the consideration of legal and ethical issues for data exchange and protection in trans-national research collaborations, including ensuring appropriate collection and storage of patient samples; regulations on working with genetically modified organisms, and guidelines for accommodation and care of lab animals.

The *Ethical Board* will draw expertise from the nSBCs as well as the SAB and Industry Liaison Board. This board will consider the societal and environmental impact and any other relevant legal issues relating to ISBE operations.

Section 8 Summary

ISBE will be a sustainable, long term infrastructure, with robust and effective financial, legal and governance structure that supports efficient operations and strategic planning.

- ISBE aims to adopt ERIC as its long-term legal personality.
- The CIO will employ the ISBE director, and administrative staff that will support the standing bodies, and operations across all nSBCs.
- The CIO will operate legal agreements with each of the nSBCs, as well as being the legal body for agreements with other Research Infrastructures, including other ESFRIs.
- Across all nSBC's, ISBE will establish standing bodies that will ensure:
  - involvement of funders and scientists from member states in the overarching governing board
  - internal technical coordination and strategic planning
  - external expert advice from Industry, users and other stakeholders
  - due consideration of ethical issues

SECTION 9
Finance

This section outlines the operational costs of the ISBE infrastructure as well as how these costs will be met. ISBE aims to increase value for money and return on current and future national investments by building on existing national resources, services and activities. National contributions from member states hosting nSBCs will contribute to the operational budget of the Central ISBE Office (CIO). Operating costs for nSBCs will be met through existing national funding mechanisms, i.e. existing competitive processes, and/or strategic resourcing of host institutions.

ISBE's five year financial plan will be transparent and create the basis for long-term financial planning and sustainability. The ISBE Governing Board will review the plan annually to ensure operational flexibility.

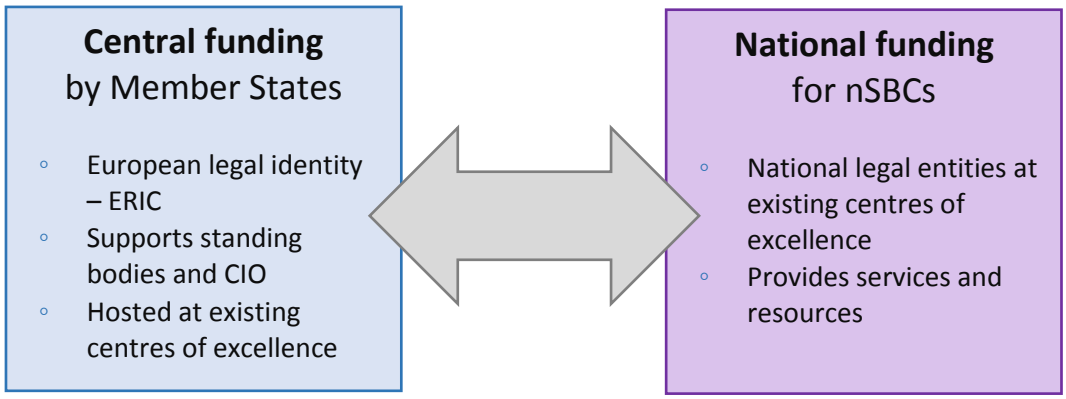

Diagram 9.1: Funding and legal aspects of ISBE and the role of the central office in providing ISBE coordination, while the centres deliver services and resources to the users.

9.1 Operational costs

ISBE intends to use a similar Gross Domestic Product (GDP)-based subscription model to other BMS ESFRIs, such as BBMRI, ECRIN and ELIXIR, to support the ISBE Director and executive functions at the CIO. The levels of national member state contributions may be modified to reflect aspects such as the relative size of the national provider- or user-base. Additional contributions or via 'in-kind' support of the indirect costs might come from the country hosting the CIO.

ISBE will not be a funding organisation for providing additional resource to nSBCs. However, ISBE anticipates that national funding agencies would examine opportunities to focus modest additional investments that will enable ISBE to build on the past national bioscience facilities and e-infrastructure to better realise systems approaches (estimated to be in the order of €62k per annum per country, more details can be found in table 3 in Appendix 4). It is therefore probable that countries will nominate ISBE centres already involved in providing services to their national biological and medical science community for other ESFRIs, such as ELIXIR and Euro-BioImaging.

9.1.1 Costs for Central ISBE Office (CIO)

The CIO will comprise the ISBE director and administrative staff, as well as the project manager, training and education officer and a public relation manager. In Year 1, costs will be € 100k and in total 1 FTE. This grows with additional personnel (e.g. project managers, web manager, training and education manager) to 5 FTE in year 5: costs € 600 k (see Table 9.1, more detailed information in Table 6, Appendix 4). Further growth will depend on scale of services and resources and on the number of nSBCs. Total contribution of € 1.6M for first 5 years.

Table 9.1 Annual Operations/ FTEs Yr1/ Cost Yr 1 (k€)/ etc.

Annual operation costs (k€)	FTEs Yr 1	Cost Yr 1	FTEs Yr 2	Cost Yr 2	FTEs Yr 3	Cost Yr 3	FTEs Yr 4	Cost Yr 4	FTEs Yr 5	Cost Yr 5	Total
CIO	1	**100**	2	**200**	3	**300**	4	**400**	5	**600**	**1600**

9.1.2 Costs for nSBCs

It is anticipated that several of the systems biology centres considering involvement in ISBE will already provide local or national level services. This offers great opportunities for coordination at the European level to provide added value through collaboration.

The ISBE project has developed cost models as examples for the different types and range of plausible ISBE services, including estimates for 'small', 'medium' and 'large' nSBCs. Costs of individual centres once fully operational (year 5) would be about € 2.5M (see Table 9.2).

Table 9.2 Summary of expected costs depending of the nSBC centre size for a national funder

Summary of expected costs for a national funder in 2019				
Size of centre	Staff costs (€k)	investments / facilities (€k)	training and outreach (€k)	**Total costs (€k)**
Small	500	100	15	**615**
Medium	1000	200	50	**1250**
Large	2000	500	55	**2550**

It is assumed that contributions for nSBCs would grow over the first five years of operation. Growth is dependent on personnel, etc. (further details are provided in Appendix 4[35] and a summary is shown in the Table below).

[35] Details cost estimates of capital; staff; consumables; travel; meetings; indirect costs elements are provided in appendix 4.

Table 9.3 Initial cost profiling by ISBE establishing the ISBE national Systems Biology Centres

Annual operation	Year 1 costs (k€)	Year 1 staff (FTE)	Year 5 costs (k€)	Year 5 staff (FTEs)
Small nSBC	**100**	**1**	**600**	**5**
Medium nSBC (2x)	**500** (2 x 250)	**4** (2x2)	**2500** (2x 1250)	**20** (2x10)
Large nSBC (2x)	**800** (2x400)	**8** (2x4)	**3500** (2x 1750)	**40** (2x20)
Total (k€)	**1400**	**13**	**6600**	**65**

In year 5 (2019) total operational costs of ISBE would be about € 6.6M per annum. This is likely to incorporate elements of wider prior investment in national research infrastructures in the order of € 1.13M to € 2M per annum per country, depending on the size of the national research community. Further engagement with funders and providers in 2014-15 will allow ISBE to finesse this estimate.

In the above table ISBE has assumed that nSBCs will:

- have a central entry point via the Central ISBE Office (CIO) however, primarily service will be via their own national communities
- maintain associated staff and resources
- retain the obligation for ensuring the longer term maintenance and curation of the resources being provided
- provide fair, and equitable access to all ISBE users, either via a transparent 'user-pays' charging structure, and/or free-to-user basis via pre-agreed national contributions to the centre.

9.1.3 Ratio of ISBE services provided by a nSBC in 2019

ISBE will enable users to fully implement the systems biology cycle focussing on experimental data-driven modelling combined with model-driven experiments. As mentioned in section 5.1 ISBE's nSBCs will offer four interrelated services. The relative weight of these four components will differ between nSBCs, depending on national priorities and expertise and will be determined at the national level in response to national user demand and/or national strategic prioritisation.

From the cost model detailed in Appendix 4, estimates for both integration and modelling, and data generations activities are comparable (both ~25% of investment costs and 15% of personnel costs), with the majority of likely investment (~35%) and personnel costs (~50%) to support stewardship & standardisation activities. Training and education is the smallest component (15% of investment costs) as ISBE will be working together with on-going initiatives for the delivery of activities. Finally, personnel costs for training and education together with administrative costs is estimated at ~20%.

Further engagement with funders and providers in 2014-15 will allow ISBE to finesse these estimates.

9.2 Inception and development

9.2.1 Expected size and scope on establishment (post-2015)

It is expected that for a viable minimum start-up, with sufficient scale and range of activities to realise the ISBE mission, will require the equivalent of two large, one small and two medium size centres (i.e. 5 countries). ISBE therefore currently anticipates that to be established as a legal entity at least 5 member states, and associated nSBCs would need to commit to ISBE.

Section 9 Summary

ISBE will increase value for money and return on existing and future national systems biology investments by incorporating them in a European context.

- Operating costs for national nSBCs will be met through existing national funding mechanisms. Costs for the CIO will be met by national contributions related to their GDP.
- ISBE's five year financial plan will be transparent, enable long-term financial planning and ensure sustainable services.
- ISBE has provided detailed examples of costs models for establishing and running ISBE.
- ISBE intends to start once at least 5 member states have agreed to join.

SECTION 10
Building ISBE – action plan

This section describes the anticipated roll out of ISBE in 2015-2017 and beyond. The Preparatory Phase of ISBE will finish in July 2015 with the primary output of delivering a comprehensive ISBE Business Plan that describes the ISBE infrastructure. The Business Plan will describe in greater detail the key issues touched upon in this Business Case:

- the need for the ISBE infrastructure
- ISBE's structure and how it will function
- ISBE's main users and how they will access the infrastructure
- proof of interest from key stakeholders
- ISBE's financial, legal and governance structure
- how the infrastructure will be built and maintained and its quality assured

Following this, it is expected that an 'Interim Phase' of at least 2 years will be required to finalise negotiation of the legal agreement for establishing ISBE and the financial contributions from national funder representing member states, as well as the identification of associated nSBCs.

ISBE will be active during the interim phase through the participation of associated institutes in the harmonizing and integrating activities of the CORBEL project (if granted). Thus, it will fine-tune its activities and development with the other ESFRI Research infrastructures in life sciences and establish exemplary services at common interfaces with other RIs, even before being operational.

Upon agreement of the legal structure (from 2017 onwards) ISBE will commence operations as a legal entity, whilst continuing to explore and realise potential for inclusion of further member states and associated nSBCs, together with concluding links with wider infrastructures, notably other ESFRIs.

10.1 Establishing ISBE

ISBE aims to provide to both existing and new users of systems approaches. This community continues to grow. The ESFRI Assessment Group Report recognised the requirement for an Interim Phase to develop pan-European infrastructures, which allows the identification of founding centres, and provides time for negotiations to finalise a longer-term legal framework.

While it is not possible to state exactly how large ISBE would ultimately become, it is expected that within the first couple of years of operation at least 10 national centres will start to deliver services under the ISBE umbrella.

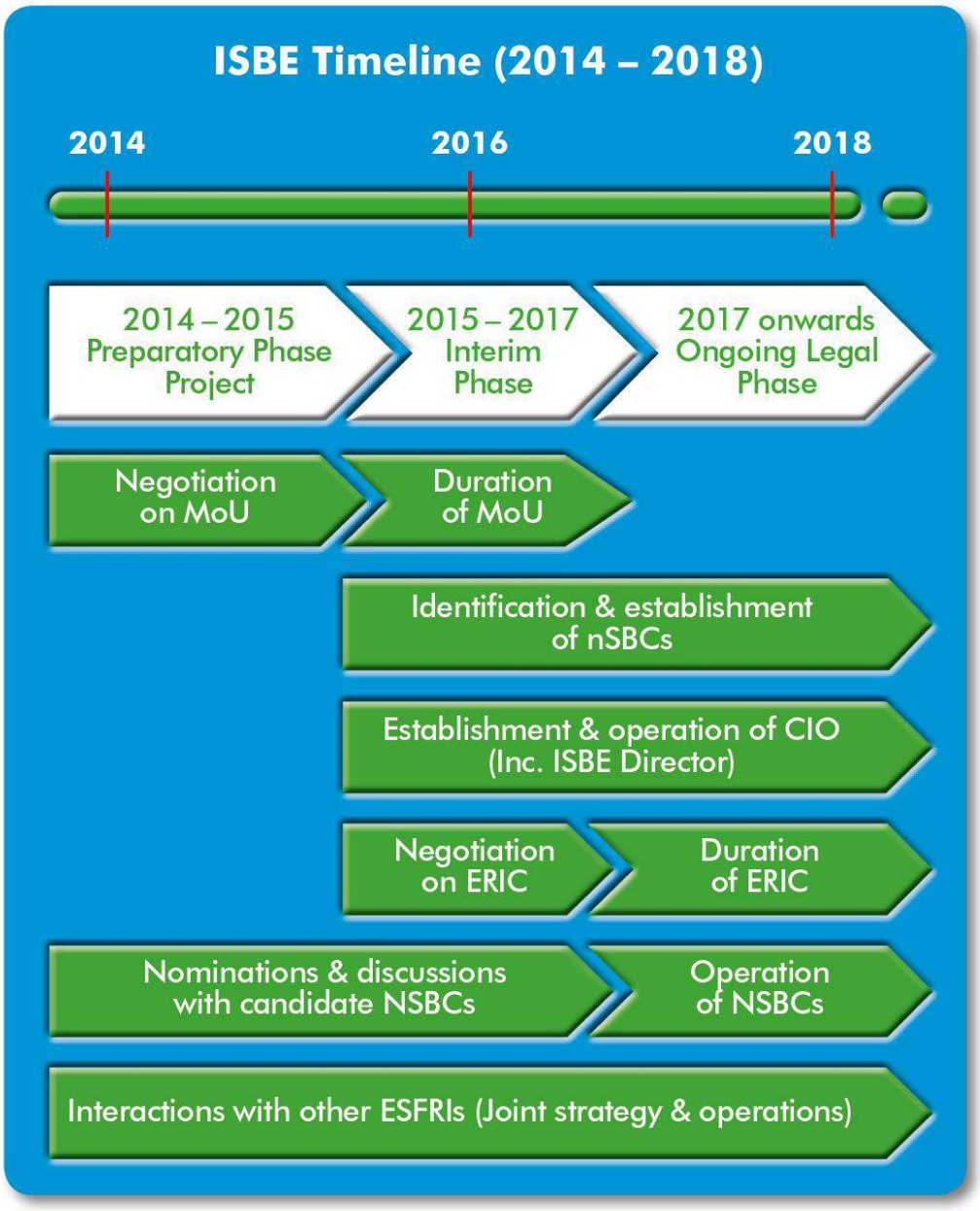

Figure 10.1: An overview of the timeline and the steps in ISBE's establishment and further development.

10.1.1 Completing the preparatory phase (2014-2015)

ISBE is identifying potential nSBCs by December 2014 and developing the process for establishing the interim boards and panels necessary to support ISBE beyond the end of the Preparatory Phase period, as of August 2015. ISBE will continue discussions with potential centres and associated funding bodies, including through ISBE's audit of the potential provider-base during 2014. This will be followed by an open nomination process in 2015 that will require candidate centres to detail existing or planned financial national support, together with endorsement by both the host institution and an associated national research ministry or funding body.

ISBE is developing a Memorandum of Understanding (MoU) for presentation to national funding bodies by December 2014, with the intention of gaining signatures by July 2015. The MoU will also require signatories to identify financial support activities beyond the end of the preparatory phase. ISBE would also continue to liaise with other ESFRIs during this time, and play an active role in coordinated ESFRI Research infrastructures in life sciences applications for EC funding.

Key actions

- Development of draft Memorandum of Understanding (MoU) and negotiation with national funding bodies from potential member states for financial support for 2015 onwards.
- Consultation with potential nSBCs and initial nominations of candidate nSBCs.
- National workshops and roadshows involving users, national funding bodies and commercial stakeholders.
- Engagement with other ESFRIs, including for joint applications to the EC.
- Identification of the host for the Central ISBE Office and coordinating SBC.

10.1.2 Commencing the Interim Phase (2015-2017)

In order to develop plans to allow the start of operations, many, if not all, of the standing bodies and associated management and secretariat functions will be established. The Interim Phase will follow immediately after the end of the Preparatory Phase (August 2015) and is expected to last 2 to 3 years. During this period ISBE will establish bodies for ongoing negotiations of the ERIC, and continued stakeholder engagement.

Funding from MoU signatories will be used to appoint a Director to coordinate the ongoing discussions between candidate nSBCs to develop technical frameworks for joint operations. The Director will also lead outreach and advocacy activities to promote coherent engagement with the systems biology community and other ESFRIs.

The main role of the ISBE CIO will be to support ongoing negotiations of the ERIC agreement with MoU signatory countries, whilst also seeking wider support from additional partners and operate further calls for nominations of candidate nSBCs.

Key actions

- Development of draft ERIC agreement and negotiation with national funding bodies from potential member states for financial support for 2017 onwards.
- Consultation with candidate nSBCs to establish joint operations.
- Establishment of interim boards.
- Appointment of Director and other CIO staff.
- Operate academic and commercial stakeholder engagement programme.
- Ongoing engagement with other ESFRIs, to identify joint activities.

10.1.3 Establishing the legal agreement and subsequent operations (2017 onwards)

ISBE would be considered to be a mature infrastructure upon establishment of the ERIC to establish ISBE as a legal entity. It then intends to grow to incorporate further member states and associated SBCs, including those that may not be ready to join at the outset. Those countries considering involvement in ISBE would have observer status in advance of joining.

Key actions

- Signing of ERIC, and agreement of first 4-5 year financial cycle.
- Official appointment of nSBCs and agreement of service level agreements (and launch of pilot services).
- Operation of ISBE Governing Board and other standing bodies.
- Official agreements with other ESFRIs and other International research organisations.

10.2 Engaging Stakeholders - Communication strategy of ISBE

To ensure ISBE's success, an appropriate communication and marketing strategy is vital to make it well known among policy makers, funders and users. The Central ISBE Office (CIO) will be responsible for managing the development and marketing of the ISBE 'brand'. It will coordinate and execute outreach activities to promote ISBE with appropriate tools, including the designing and maintenance of the ISBE webpage as the central entry point to information about and access to ISBE.

Based on the stakeholder analysis, ISBE's ongoing communication strategy will:

1. Raise awareness of ISBE's services, goals and context with all stakeholders.
2. Ensure the promotion and dissemination of successful ISBE coordinated projects to all stakeholders.
3. Provide strategic outreach to other projects and relevant initiatives (including the individual ESFRI Research infrastructures in life sciences and e-Infrastructures, relevant IMI projects and ESFRI Research infrastructures in life sciences industry partners) to support the implementation of the common solutions developed.

10.3 Key challenges

Building the ISBE infrastructure is a complex process that confronts us with a number of hurdles. Therefore ISBE is already developing a risk management process for all phases, including a detailed risk register and Key Performance Indicators (KPIs), which will be detailed in the Business Plan. In advance of this ISBE has outlined the four key challenges to successfully realising ISBE's vision and mission, indicated below.

a. Getting commitment from sufficient EU member states

A critical pre-condition for entering the Interim Phase (2015 – 2017) is that ISBE has the commitment from a minimum of 5 member states. Such commitment should include funding of nSBCs and a contribution to the central costs of the ISBE infrastructure. To meet this challenge we actively involve national funding agencies in developing the ISBE infrastructure and its financial and governance structure.

b. Convince the wider life sciences community that computational modelling is a necessity

The ambition of ISBE is to considerably expand the use of systems biology approaches in academia, medical and clinical environments and in industry. Although a significant base of systems biology related research is present in Europe, ISBE's aim is to team up life scientists in a wide range of research fields with scientists that are proficient in systems biology.

This requires a professional information and PR strategy that makes clear how systems biology can boost research and how ISBE makes systems biology expertise, tools and resources easily accessible. This strategy is presently developed and will be executed starting Autumn 2014.

c. Participation of big industry and SMEs is essential

The potential impact of systems biology on the bio-economy and sustainability can only be realised if European industry embraces systems biology-type of approaches in its R&D strategy. The information and PR strategy indicated above will have a strong component that aims at European industry, in particular pharma and green and white biotechnology.

d. Connecting with the wider European Research Infrastructures

The ESFRI process has galvanised the development of Europe-wide research infrastructures for biology, with larger distributed consortia being established to address the key, grand challenges. Such Europe-wide platforms require similarly coordinated infrastructure across the entire breadth of the biological sciences. By continuing discussion with the other ESFRIs on joint operational and strategic goals, ISBE can facilitate such complex and comprehensive research activities.

It is also recognised that national providers will be linked to several ESFRIs, enabling users' needs to be matched to a vast array of international providers' resources and expertise. ISBE will consider how to interlink the complementary expertise of potential nSBCs, creating a common source of services, archives, repositories, tools, standards, data, models and training.

Section 10 Summary

ISBE plans a three-phase programme of establishment and growth in order to deliver to both existing and new users of systems approaches.

- The completion of the preparatory phase (until July 2015) will establish a MoU, with identified funding from signatory states for support the next phase. Nominations process for candidate nSBCs will also begin, and the CIO will be identified.
- An interim phase (2015-17), operating under the MoU, will appoint the director and establish and operate the interim bodies. Nominations of candidate nSBCs will continue, and the negotiation of the ERIC agreement will be concluded.
- ISBE will be established following 5 signatories of the legal agreement (ERIC) that is expected by end of 2017. This will mark the start of the first 4-5 year financial operational, and funding cycle. Standing boards will be established, and ISBE, as a legal entity, will conclude legal agreements with nSBCs and other ESFRIs.
- ISBE will continue to consult stakeholders on their needs across all phases.
- ISBE is already developing a risk management process for all phases, including a detailed risk register and KPIs

APPENDIX 1

Case studies

Success stories in systems biology

ISBE Infrastructure for Systems Biology Europe

A MODEL THAT GETS TO THE HEART OF SYSTEMS BIOLOGY

PROF. DENIS NOBLE DISCUSSES THE DEVELOPMENT OF HIS WORK IN CARDIAC CELL MODELLING FROM 1960 TO THE PRESENT

BIOGRAPHY

DENIS NOBLE IS A BRITISH BIOLOGIST WHO WAS THE FIRST TO MODEL CARDIAC CELLS, DETAILED IN TWO PAPERS IN *NATURE* IN 1960. HE WAS EDUCATED AT UNIVERSITY COLLEGE LONDON AND MOVED TO OXFORD IN 1963 AS FELLOW AND TUTOR IN PHYSIOLOGY AT BALLIOL COLLEGE. FROM 1984 TO 2004, HE HELD THE BURDON SANDERSON CHAIR OF CARDIOVASCULAR PHYSIOLOGY AT OXFORD UNIVERSITY.

He is now Professor Emeritus and co-Director of Computational Physiology. His research focuses on using computer models of biological organs and organ systems to interpret function from the molecular level to the whole organism.

Your heart: without it, you wouldn't survive very long. So medicine strives to keep it healthy and fix it if something goes wrong. Yet the heart's central role in our bodies can also make it difficult to test out new clinical approaches in humans. One way to get around this is to build a mathematical model that predicts how the heart will behave, and today the 'virtual heart' approach is helping to make drug discovery and testing safer.

> "Middle out means that you start at one level - which might be in the middle, in our case it's the cell. Then you reach down to individual molecules and you reach up to the organ."

The heart model has its origins in 1960, and its growth since then exemplifies the systems biology approach of using modelling and experimental data to enable new insights. It began when Denis Noble and his PhD supervisor Otto Hutter worked with heart tissue at University College London. They were interested in a type of electrical 'gate' in heart cells called the potassium channel, and Noble wanted to develop a mathematical model of the heart to explore its actions.

He based his work on a 1952 mathematical model that described the characteristics of excitable cells, and to build up the model Noble managed to wrangle some time on the Ferranti Mercury Computer in London. He sat in on maths lectures to get up to speed with the formulae and spent late nights punching in machine code in his allotted time between 2 and 4am.

Soon his work paid off and the heart model began to work. "It didn't take too long to get to the point where rhythm was coming out of the equations," recalls Prof Noble, who is today an Emeritus Professor at Oxford University and President of the International Union of Physiological Sciences. Papers in the prestigious journal *Nature* followed swiftly, and since then the heart model and experimental data have closely intertwined, building up our knowledge of how this key organ works.

In some cases, the model has informed the experiments - Noble recalls how in the early 1960s his model put paid to a method of using double probes to stimulate heart tissue in the lab: the maths clearly showed that the experimental approach was disrupting heart cell function. In other cases, experimental findings enhanced the model. "By about 1967, the existence of calcium channels had been demonstrated, and that was the first point at which it was obvious that the model would have to be expanded," says Prof Noble. "That process of expanding and taking more and more into account has gone on ever since."

In the decades since he punched machine code into the Mercury, Prof Noble has worked with collaborators around the world to build up the heart model and shed new light on how ion channels work. Meanwhile, computer technology grew too, enabling more sophisticated modelling and the development of a virtual organ. The growth of the heart

model exemplifies the 'middle-out' approach that Prof Noble has long supported. "Middle out means that you start at one level - which might be in the middle, in our case it's the cell," he explains. "Then you reach down to individual molecules and you reach up to the organ."

> We used computation to show why ranolazine's combination of actions would be expected to be synergistic and that provided data about the drug as it went through regulatory approval.

The mathematical approach can also offer a safe and ethical support to look for new medications and anticipate side-effects, says Prof. Noble, explaining how in one case the heart model showed in the late 1970s that blocking a newly discovered ion channel would have interesting clinical effects. "We were able to show that a blocker of this mechanism would not stop the heart, that it would slow it," he says. "So a pharmaceutical company looked for and found a compound that did that, and it is now out there as an approved drug - ivabradine."

In another case the heart model helped to explain the dual-action effects of a compound called ranolazine, explains Prof Noble. "We used computation to show why its combination of actions would be expected to be synergistic," he says. "And that provided data about the drug as it went through regulatory approval."

He now sees potential for the virtual heart to continue informing drug discovery and regulation, thereby reducing risks in drug development. "Many side effects of drugs hit the heart and cause arrhythmia, that has in the past been the cause of withdrawal of drugs," he says. "And many of the companies have got out of this kind of work, it's too risky so we are looking to see if you can use the model to filter at an early stage synergistic actions of potential drugs. Getting it right in the early stages [of drug discovery and development] is a good idea, and this is where the model can help."

Words: Claire O'Connell
January 2014

ACKNOWLEDGEMENTS

ISBE would like to thank Denis Noble for his assistance.

Further Information

Denis Noble's website
www.musicoflife.co.uk

ISBE
www.isbe.eu

European Systems Biology Community
community.isbe.eu

Full image credits can be found at isbe.eu/imagecredits
Full citations can be found at isbe.eu/case-studies

CURRENT DEVELOPMENTS IN CARDIAC CELL MODELLING

Premature heartbeats explained as a change in the stability properties of the dynamical system of the heart cell during the course of an action potential (Tran *et al.*, 2009).

Tissue electromechanics models show how infarctions can cause **arrhythmia**.

Multiscale models of electrophysiology illustrate how cellular action potentials give rise to the **electrocardiogram (ECG)** measured macroscopically on the surface of the body (Sundnes *et al.*, 2006).

Multiscale, multiphysics models can account for the effects of **genetic mutations** at levels from ion-channel structure, function, and macroscopic current; cell, tissue and organ function

CAPACITIES

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ANSWERING BIG QUESTIONS
WITH A SMALL BUG

LUIS SERRANO FROM THE CENTRE FOR GENOMIC REGULATION IN BARCELONA EXPLAINS HOW HIS RESEARCH ON A SMALL BACTERIUM CAN HELP US TO UNDERSTAND OTHER LIVING SYSTEMS AND HOW IT CAUSES DISEASE

BIOGRAPHY

THE CENTRE FOR GENOMIC REGULATION IN BARCELONA IS AN INTERNATIONAL BIOMEDICAL RESEARCH INSTITUTE OF EXCELLENCE WHOSE MISSION IS TO DISCOVER AND ADVANCE KNOWLEDGE FOR THE BENEFIT OF SOCIETY, PUBLIC HEALTH AND ECONOMIC PROSPERITY.

Dr Luis Serrano is Director of CRG and leads the Design of Biological Systems research group. The group works toward a quantitative understanding of biological systems to an extent that one is able to predict systemic features, with the hope to rationally design and modify their behaviour.

Given enough technology and know-how, could we completely understand how an entire living system works? It's an ambitious suggestion, but Dr Luis Serrano and colleagues at the Centre for Genomic Regulation in Barcelona are in the process of finding out.

Living organisms vary hugely in size and complexity, so the researchers in Barcelona have chosen their focus wisely: a small bacterium called *Mycoplasma pneumoniae*, a single cell organism that has a relatively simple metabolism.

> "If you have enough results and enough money and enough know-how, would you fully understand a living system?"

The microbe is of clinical relevance because it can cause atypical pneumonia in humans, explains Dr Serrano, but the main reason for selecting it as a model organism is its manageable size.

"It is one of the smallest bacteria you can grow in the lab," he says. "And the whole idea of the project has been to ask if you have enough results and enough money and enough know-how would you fully understand a living system."

To find out more about *M. pneumoniae* Dr Serrano's group and collaborators at the European Molecular Biology Laboratory have been analysing the main biochemical components of the bacterial cell, how they respond under different conditions and how the components fit together to form a functioning system.

Much like a car, a cell has various components that need to work both in their own right and together for the system - or car - to work. In the car, an engine, gears and wheels function individually and together to make the car go. In a cell, molecular systems involving DNA, RNA, proteins and sugars work in synchrony to run the living system, and Dr Serrano has been looking at these systems.

"We acquire the relevant data from the cell - we are looking at its metabolism, its transcriptome [RNA], the proteome [proteins in the cell]," he says. "But we are not looking at every protein individually, we try to get the whole picture: so we are not looking at every screw in the car, we are looking at the main components."

By perturbing the cells and seeing how each system reacts, Dr Serrano and co-workers have been bringing a larger picture into focus of how the system as a whole responds to changes in its environment.

"We explore how it responds to factors like exposure to drugs, changes in temperature or changes in nutrients," he says. "Our approach is a little like if you wanted to analyse the nervous system of the human you could apply something very hot and if the person jumps then the nervous system has responded."

One of the biggest findings to emerge is that *M. pneumoniae* has sophisticated mechanisms for controlling how its genes are expressed.

The microbe has two systems of 'methylation' - a form of tagging on DNA that can determine whether genes are switched on or silenced. "We know the bacterium has very strong methylation and there are two systems, one is general, and there is another more specific system that we don't know what it is doing," says Dr Serrano.

> Having such insights ... may also offer routes to engineer the microbe as a drug-delivery platform to bring medications to specific sites in the human body.

In addition, the small bacterium contains a relatively large amount of 'non-coding RNA', an observation that has now also been made in more complex bacteria as well as in eukaryotic cells, which are the types of cells that make up plants and animals.

"It looks now like bacteria have as large a proportion of non-coding RNA as eukaryotes," says Dr Serrano. "I think this is something that is characteristic of all branches of life."

The team also saw that the cell can read stretches of its DNA either classically or in a 'staircase' pattern - once more this was a surprise to see in the tiny cell, notes Dr Serrano, and the phenomenon has since been observed in other species of bacteria too.

The big challenge is now to integrate the large volumes of data from the tiny Mycoplasma and to sift out the signal from the noise.

"We have been looking at proteomics, transcriptomics, chemogenomics, everything," says Dr Serrano. "And now we want to put it together in a way that makes sense. So we are trying to integrate everything into a big model but this is not easy. You might find 100 proteins acetylated or 60 proteins phosphorylated - how much of this is noise and how much is biologically significant? Which ones are really doing something and which ones are just passing by?"

In the longer term, having such insights into the bacterium could help to understand how it causes disease, and it may also offer routes to engineer the microbe as a drug-delivery platform to bring medications to specific sites in the human body.

But for now Dr Serrano is driven by the ultimate goal of getting that complete picture of a living organism. "When I give talks everyone is excited and amazed by the amount of information and what we are doing," he says. "And the impact will be that we come out with a model that will explain the whole cell in detail. Then we will say for the first time that we understand the whole thing."

Words: Claire O'Connell

October 2013

ACKNOWLEDGEMENTS

ISBE would like to thank Centre for Genomic Regulation in Barcelona for their assistance, in particular Luis Serrano and his colleagues.

Further Information

Centre for Genomics Regulation
crg.es

European Systems Biology Community
community.isbe.eu

ISBE
www.isbe.eu

Full image credits can be found at isbe.eu/imagecredits

COMPLICATIONS ASSOCIATED WITH *MYCOPLASMA PNEUMONIAE*

Lobar consolidation
Abscess
Bronchiolitis obliterans
Necrotizing pneumonitis
Acute respiratory distress syndrome
Respiratory failure

Design of Biological Systems Group, 2013

Mycoplasma pneumoniae

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MODEL SUPPORT

DEVELOPMENTS IN STANDARDS-BASED INFORMATION INFRASTRUCTURES ARE HELPING BIOLOGISTS TO INTERROGATE 'BIG DATA'

BIOGRAPHY

(L-R) Dawie van Niekerk, Johann Eicher, Danie Palm and Jacky Snoep (JWS Online team, University of Stellenbosch)

JWS ONLINE IS A SYSTEMS BIOLOGY TOOL FOR SIMULATION OF KINETIC MODELS FROM A CURATED MODEL DATABASE. JACKY SNOEP IS PROFESSOR OF BIOCHEMISTRY AT STELLENBOSCH UNIVERSITY, SOUTH AFRICA.

One of the big challenges for biological research is its full maturation into a 'big science' discipline, capable of tackling big, complex questions in a coordinated fashion. The inherent complexity and diversity in biology makes the maturation harder for the life sciences than it was for physics, but a growing adoption of standardisation, data-sharing strategies and attempts to address big questions in truly collaborative efforts are speeding up the process.

The ongoing development of systems biology, which integrates computer-based mathematical modelling of living systems with experimental observation, represents an important strand of this process of maturation. An essential element of this is the development of robust, standards-based information infrastructures capable of managing large quantities of data and software code in readily accessible formats. JWS Online and BioModels represent two significant and complementary model management initiatives, which are contributing to the 'digitisation' of biology by enabling researchers to explore previously developed models of diverse biological processes.

JWS Online, originally developed in 2000 at Stellenbosch University (SU; Stellenbosch, South Africa), is now co-developed at the University of Manchester (UM; Manchester, United Kingdom) and the Vrije Universiteit (VU; Amsterdam, Netherlands). It played a prominent role in pioneering the concept of providing researchers with online, centralised access to biological models. It includes a simulation environment that enables scientists to run individual models remotely, eliminating the need for painstaking recoding work that would be otherwise necessary. "It's a lot of work to code mathematical models from the literature, and it's error-prone," says Jacky Snoep, Professor of Biochemistry at Stellenbosch University. "Every researcher who wanted to use these models would have had to do the same work."

the 'digitisation' of biology

JWS Online now contains some 200 curated models, which have been rendered into a standard format using Systems Biology Markup Language (SBML), the de facto standard for creating computational models of biological processes. The system is also employed by the FEBS Journal, to test models that are submitted for review along with papers. Reviewers have access to the JWS toolset, via a secure site, and can run the models, to ensure that the data contained in the paper can be reproduced by the model.

JWS Online has been incorporated into the SEEK collaboration environment (PubMed: 21943917), originally developed for the SysMo project on the systems biology of microorganisms. The SEEK is a mature data and model management platform for large-scale systems biology projects. "The data and model management structure we set up for the SysMo project is currently the best system available, and its approach is likely to evolve into a standard," says Snoep.

BioModels Database, developed at the European Bioinformatics Institute (EBI; Hinxton, UK) since 2005, was created in response to the needs of the community for a model repository. It reflects the growing number of models published in the literature and provides them in a computationally reusable form. These models originate from a plethora of domains representing work that spans decades of refinement. Notable examples include:

- Synthetic biology (BIOMD0000000012)
- Neurobiology (BIOMD0000000020)
- Oncology (BIOMD0000000234)
- Virology (BIOMD0000000463)
- Immunology (BIOMD0000000243)
- PK/PD – Systems Pharmacology (BIOMD0000000490)

> a true database, which can be interrogated dynamically

BioModels Database is now by far the field's largest repository of biological models, having amassed more than 1,000 manually curated biological models. Each of these models are described in peer-reviewed publications, manually curated to verify that the model in the database is capable of reproducing the published results, and is extensively annotated to specify the biological entities that are represented within the model. Additional annotations are also provided that link the model itself to further information such as mathematical concepts, ontological terms (including those that reference biological processes), and to other models (allowing hierarchical analysis on model lineages). Over 300 journals recommend deposition of models directly to the database in their submission guidance notes to authors.

With the ever-growing means by which 'big data' is generated, there is an ever-evolving need to deal with it. The BioModels team has recently introduced a means to automatically manage models from large data sets; Besides the 1,000+ curated models, BioModels also now contains an additional 140,000 models which were generated automatically from representations of biochemical pathways taken from multiple sources. Collectively, these models cover domains such as metabolism, signal transduction, electrophysiology, population and ecosystem dynamics, pharmacokinetics and pharmacodynamics, and mechanisms of disease. "We are fulfilling the classical library function in this domain—we have the record of the developed models," says Henning Hermjakob, head of the EBI's proteomics services team.

BioModels is not just a passive repository—it is a true database, which can be interrogated dynamically. Models can be readily downloaded or can be run remotely using several different tools, including the JWS Online simulation environment. A 'Model of the Month' feature enables new users to learn about important individual models in a largely jargon-free way; BioModels provides a variety of teaching materials and resources, and can be regarded, says Hermjakob, as a portal to the world of modelling.

Modelling biological systems continues to evolve from being an early-stage endeavour. The field has taken major steps in recent years, culminating in the publication of the first whole-cell computational model, which predicts a cell's phenotype (or visible characteristics) from its genotype (or genetic make-up) (Karr *et al.*, 2012). JWS Online and BioModels are both vital components of the information infrastructure supporting these efforts.

Words: Cormac Sheridan
January 2014

ACKNOWLEDGEMENTS

ISBE would like to thank Jacky Snoep, Henning Hermjakob, Camille Laibe and Nick Juty for their assistance.

Further Information

JWS Online
jjj.biochem.sun.ac.za

BioModels Database
www.ebi.ac.uk/biomodels

The SEEK
www.seek4science.org

SysMo
www.sysmo.net

Path2Models
code.google.com/p/path2models

ISBE
www.isbe.eu

European Systems Biology Community
community.isbe.eu

Full image credits can be found at isbe.eu/imagecredits
Full citations can be found at isbe.eu/case-studies

BioModels Database serves as a reliable repository of computational models of biological processes, and hosts models described in peer-reviewed scientific literature. Recently it has also begun to incorporate models that can be automatically generated from 'big data' pathway resources. Henning Hermjakob is team leader of Proteomics Services at the European Bioinformatics Institute, based in Hinxton, Cambridge.

A Growing Database

2005	2013	
Models	**20**	**1000+**
Species	**300**	**400,000+**
Cross-References	**1000**	**1,000,000+**

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VIRTUAL LIVER NETWORK

A COLLABORATIVE SOLUTION TO HEPATIC DISEASES

PUBLICLY-FUNDED GERMAN FLAGSHIP INITIATIVE IS LEADING THE WAY IN LIVER RESEARCH

BIOGRAPHY

SINCE ITS BEGINNING IN APRIL 2010, THE VIRTUAL LIVER NETWORK HAS ENGAGED GROUND BREAKING AREAS OF SYSTEMS BIOLOGY IN A COORDINATED AND FOCUSED ATTEMPT TO SHOW THAT MODELLING AND SIMULATION CAN HELP TACKLE THE CHALLENGES OF UNDERSTANDING THE DYNAMICS OF BIOLOGICAL COMPLEXITY.

Dr Adriano Henney is Programme Director of the VLN. Dr Henney has a PhD in Medicine and many years academic research experience in cardiovascular disease in laboratories in London, Cambridge and Oxford, and worked with AstraZeneca exploring strategic improvements to the company's approaches to pharmaceutical target identification, and the reduction of attrition in early development.

Systems biology has now reached a new stage of maturity. No better proof is the existence of an audacious research project called the Virtual Liver Network (VLN). It provides an excellent example of how systems biology is now yielding a level of detail and quantitative data in biology at a scale not previously attained. "We need to do research in biology at the scale of what astrophysics has done," explains Adriano Henney, Programme Director of the VLN.

The aim of the VLN is to design a dynamic mathematical model of the human liver. This model will represent, rather than fully replicate, the liver's physiology and morphology. More importantly, it will also integrate the wealth of data we have acquired post-genome through multiple models. Its ultimate goal is to represent the multiple liver functions, including detoxification, the fight against inflammation and the production of biochemicals necessary for digestion.

> €50M flagship initiative is supported by the German Federal Ministry of Research and Education

This so-called multi-scale modelling is a challenge. "The ability to model across scales of time and space is not easily done in biology," explains Dr Henney. What makes this project possible is the data crunching capabilities of bioinformatics and the power of new computer modelling. This combined approach enables the integration of quantitative data from the sub-cellular levels to the whole organ. Ultimately, better treatments for the many liver-related diseases are expected to be produced.

This €50M flagship initiative is supported by the German Federal Ministry of Research and Education, BMBF. Research teams that were previously in competition are gathered under the VLN umbrella for five years, until 2015. "This is the first example of an investment in systems biology of this size in a single country that focuses on delivering solutions to clinicians, and aiming to do so using simple to use formats," Adriano Henney points out.

The VLN involves a distributed network of research teams spread over Germany, in 70 laboratories. This approach is unique in international research in the biosciences. No team in the USA, Japan or any other country has managed to perform such an intricate geographically distributed research collaboration. Nor has any other research effort integrated the most fundamental biological research directly through to clinical studies in patients.

An organ as seemingly anodyne as the liver harbours surprising complexity. Using modelling and simulation to tackle this complexity, VLN scientists have been able to show, according to Dr Henney, "that we can use it to highlight inaccuracies in our current knowledge of physiological processes within this vital organ". Specifically, the results of the team lead by Prof. Rolf Gebhardt, Deputy Director of the Institute of Biochemistry at the

University of Leipzig, point to inaccuracies in our knowledge of liver steatosis, or fatty liver disease. The team found that challenging liver cells, called hepatocytes, by external fatty acids, results in accumulation of triglycerides in fat droplets. However, it only results in minor changes in the central metabolism of the liver, against all expectations. The team also found that the influence of insulin on fatty acid biosynthesis in liver was previously strongly overestimated, while that on the conversion of carbohydrates into fatty acids was rather underestimated. These findings led to a patent likely to have a high impact on future therapies of steatosis and related diseases.

> Integrating the most fundamental biological research directly through to clinical studies in patients

Crucially, the project aims to translate the basic research into clinically-relevant applications for doctors. A team working on a showcase of the inflammatory process in the liver has developed a user-friendly interface for doctors, available on a tablet. This team is led by Prof. Steven Dooley, a specialist of molecular hepatology at the Mannheim Medical Faculty, and Jens Timmer, an expert in dynamic process modelling at the University of Freiburg. These inflammation models are available to professionals without the need for extensive training and can be used to help patients understand their illness.

Further concrete results of the VLN project have potential applications in medicine. They include two patents on potential biomarkers for steatosis, which are pending. These disease indicators could ultimately be used as a diagnostic test predicating the onset of fatty liver disease.

The network's research efforts also draw on expertise from industrial collaborators, including German pharmaceutical company Bayer Technology Services. Industry partners have studied some genetic variants connected to the way individuals metabolise drugs. This team is led by VLN leadership team member, Lars Küpfer. The team's findings will help identify patients more likely to benefit from treatment. Previously, liver toxicity has been the reason for the failure of a significant proportion of novel medicines. Now, systems biology is opening new avenues for drug discovery.

For now, the team hopes to extend the funding by another five years, to create the prototype of a true multi-scale model within a single organ and link it to human physiology.

To meet the challenges of 21st Century medicine to deliver more effective therapies, we need a deeper understanding of the complexity of common disease and the dynamic interplay of genes and environment that underpins it. Systems biology offers potential solutions, examples of which are being pioneered in the Virtual Liver Network.

Words: Sabine Louet
January 2014

ACKNOWLEDGEMENTS

ISBE would like to thank the leadership team of the Virtual Liver Network for their assistance, in particular Adriano Henney.

Further Information

Virtual Liver Network
virtual-liver.de

ISBE
www.isbe.eu

European Systems Biology Community
community.isbe.eu

Full image credits can be found at isbe.eu/imagecredits

VLN FACT FILE

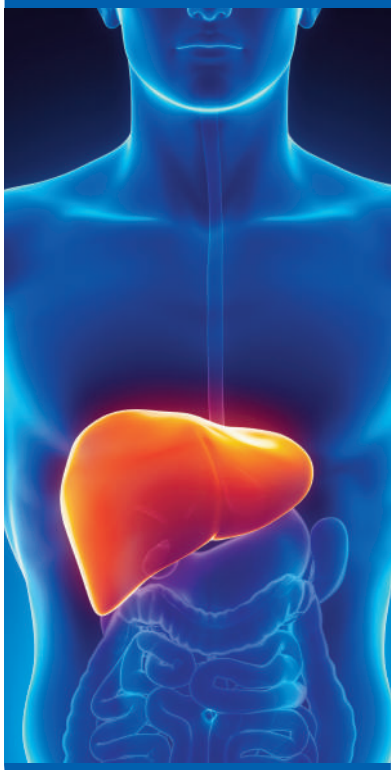
German government-funded initiative

€50M investment over 5 years

70 research groups

41 Institutions

250 Scientists



CAPACITIES

ISBE Infrastructure for Systems Biology Europe

SEEK AND YE SHALL FIND DATA

KATY WOLSTENCROFT FROM THE UNIVERSITY OF LEIDEN DISCUSSES HOW THE WEB-BASED SEEK PLATFORM IS ENABLING SCIENTISTS GREATER ACCESS TO AND MORE INTELLIGENT USE OF THE VAST REPOSITORIES OF BIOLOGICAL DATA BEING AMASSED

BIOGRAPHY

THE SEEK PLATFORM IS A WEB-BASED RESOURCE FOR SHARING HETEROGENEOUS SCIENTIFIC RESEARCH DATASETS, MODELS OR SIMULATIONS, PROCESSES AND RESEARCH OUTCOMES. IT PRESERVES ASSOCIATIONS BETWEEN THEM, ALONG WITH INFORMATION ABOUT THE PEOPLE AND ORGANISATIONS INVOLVED.

Dr Katy Wolstencroft is an Assistant Professor at the Leiden Institute of Advanced Computer Science (LIACS), teaching courses in bioinformatics and computer science. Dr Wolstencroft previously was a Research Fellow in the School of Computer Science, University of Manchester working on scientific workflows with the Taverna workbench, and Systems Biology data and model management with the SEEK platform.

The increasing data intensity of biological research, which is closely linked to the increasing complexity of scientific collaboration, has created an urgent need for new tools to allow researchers to navigate the ever-expanding information universe. Systems biology, the emerging discipline that seeks to map precisely all of the dynamic processes within living cells and organisms, has created very particular data management requirements. At its core is a tight coupling between experimental data and data modelling, as predictions and hypotheses based on computer models are tested experimentally, which can lead to further refinements in the model or to revisions in certain parameters. The scale and complexity of the data that are generated require standards of data stewardship that represent significant challenges to biologists and data management specialists alike.

> "an ambitious attempt to capture the complexities of systems biology research ... to maximise the use and reuse of the data that are generated"

The SEEK platform is a commons interface which has grown out of a large-scale European project on the systems biology of microorganisms (SysMO). It represents an ambitious attempt to capture the complexities of systems biology research within a web-based data management and collaboration environment, in order to maximise the use and reuse of the data that are generated. The platform extends into the systems biology domain concepts and standards developed under the semantic web initiative of the World Wide Web Consortium (W3C), an ongoing effort to present disparate forms of information in machine-readable formats, to enable more sophisticated forms of data searching and analysis across distributed systems.

SEEK was developed by researchers based at the University of Manchester (UK), the Heidelberg Institute for Theoretical Studies (Germany) and the University of Stellenbosch (South Africa) in response to a requirement on the part of SysMO's funders that its grantees, who are distributed across more than 100 institutions located in six countries, share data and data models. Before SEEK there was no obvious way to do this in any kind of comprehensive or controlled fashion. Researchers shared data by exchanging very basic forms of documentation, such as spreadsheets, by setting up project-specific wikis or by using generic web-based or cloud-based collaboration environments, which are not adapted to the specific methodologies or information architectures of systems biology.

The SEEK system acts both as a repository, which allows users to publish and share data and models, and as a registry, which provides links to relevant data sources and models hosted elsewhere. Its main components include an assets catalogue, which holds data files, protocols, workflows, models and

publications; a 'yellow pages' feature, which contains information on SysMO participants and their host institutions; and an access control feature, which enables user to control third party access to their data.

One of the main challenges inherent in its design was to create a system that was sufficiently powerful and robust to be useful, while not placing an excessive burden on its users. Biological information is inherently heterogeneous and complex. Systems biology generates multiple types of data, including various species of 'omics data (genomics, transcriptomics, proteomics, metabolomics, etc.), imaging data and enzyme kinetics data. To enable all of this to be managed coherently in a web environment, data and accompanying models and experimental protocols need to be 'annotated' or described in a precisely defined manner, and the relationships between the various elements must also be specified.

> "The SEEK ... eliminates what would otherwise represent a significant overhead for users"

The SEEK system can generate this 'metadata'—or data about data—on the fly, as users deposit data held in commonly used file formats, such as spreadsheets, using predefined templates. This eliminates what would otherwise represent a significant overhead for users. "There are not that many incentives for people to spend time curating and annotating their data and their models," says Katy Wolstencroft , a member of the SEEK development team at Manchester (now at the University of Leiden, in the Netherlands.).

The system also draws on the ISA framework (Investigation, Studies, Assays), an emerging software standard for managing biosciences data.

SEEK can be readily adapted for any systems biology project. Its user base has, in fact, grown to more than a dozen other implementations since it became available via an open source licence in 2010. These include the European Virtual Institute of Malaria Research (EVIMalaR), a Network of Excellence established under the European Commission's 7th Framework Programme (FP7), which has deployed SEEK to develop a comprehensive picture of research activity within the network. The Virtual Liver Network, which comprises 70 research groups distributed across Germany, has implemented SEEK to enable its members to find and share data, models and processes that relate to liver function—at multiple levels of organisation, from the individual cell up to the complete organism. Other users include: Unicellsys, another FP7 project, which is developing a quantitative understanding of the control of and coordination of cell growth in response to internal and external triggers; JenAge, a German research initiative on the systems biology of ageing; and ROSage, another German project, which is exploring the role of reactive oxygen species in the aging process.

SEEK is part of a wider ecosystem of standards-compliant, open-source systems that will, ultimately, facilitate greater access to and more intelligent use of the vast repositories of biological data that are being amassed globally.

Words: Cormac Sheridan

December 2013

ACKNOWLEDGEMENTS

ISBE would like to thank Katy Wolstencroft for her assistance, along with Prof. Carole Goble at the University of Manchester.

Further Information

The SEEK platform
www.seek4science.org

ISA framework (Investigation, Studies, Assays)
www.isacommons.org

SysMO
www.sysmo.eu

ISBE
www.isbe.eu

European Systems Biology Community
community.isbe.eu

Full image credits can be found at isbe.eu/imagecredits

SEEK IN USE

SEEK
SysMO Systems Biology of Microorganisms
ERASysBio Plus
Pistoia Alliance
unicellsys
EVIMalaR
JENAGE Jena Centre for Systems Biology of Ageing
Centre for Systems Biology Magdeburg MaCS
RosAge Reactive oxygen species and the dynamics of ageing
sybacol
CISBIC
eagle genomics
SBCancer.
Newcastle University Centre for Synthetic Biology and Bioexploitation
University of Birmingham Systems Science for Health

CAPACITIES

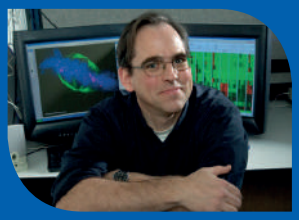
ISBE Infrastructure for Systems Biology Europe

MERRIMACK FOLLOWING A SYSTEMS PATH TO DRUG DISCOVERY

US PHARMACEUTICAL COMPANY BASES ITS BUSINESS ON A SYSTEMS APPROACH AND IS REAPING THE REWARDS

BIOGRAPHY

MERRIMACK PHARMACEUTICALS IS A BIOPHARMACEUTICAL COMPANY DISCOVERING, DEVELOPING AND PREPARING TO COMMERCIALIZE INNOVATIVE MEDICINES PAIRED WITH COMPANION DIAGNOSTICS FOR THE TREATMENT OF CANCER. MERRIMACK APPLIES A SYSTEMS BIOLOGY-BASED APPROACH TO BIOMEDICAL RESEARCH, THROUGHOUT THE RESEARCH AND DEVELOPMENT PROCESS.



Peter Sorger PhD is a Professor of Systems Biology at Harvard Medical School and holds a joint appointment in MIT's Dept. of Biological Engineering and Center for Cancer Research. Sorger was co-founder of the MIT systems biology program CSBi, Merrimack Pharmaceuticals and Glencoe Software.

Birgit Schoeberl is Senior VP of Research with responsibility for discovery and clinical stage projects. She is an internationally recognised leader in Systems Biology. She has been with Merrimack since the very beginning and has been integral to develop the Systems Biology platform.

Merrimack Pharmaceuticals is a NASDAQ-listed biopharma company that has confidently placed its chips on a systems biology approach to cancer drug discovery. The power of a systems approach is to reveal not just individual components of a system, but how each part connects.

Peter Sorger, Professor of Systems Biology at Harvard Medical School, helped found the company while at MIT in partnership with serial entrepreneur Anthony Sinskey, Professor of Microbiology, MIT. Cofounders, Ulrik Nielsen and Gavin MacBeath are still with the company in senior positions.

The very beginning of Merrimack came partly out of dissatisfaction with the myriad explanations in the literature of the induction of apoptosis by anticancer drugs, Sorger recalls. They decided it was necessary to understand the key physiological pathways involved in drug response and that that would require a mix of computational modelling and dynamic modelling.

> "About 80% of the cost of drugs today is in yesterday's failures, so the number one target for systems biology is to change that"

Merrimack remains rooted in the principles of grafting quantitative biology, computational models and engineering to understand the signalling pathways that are involved in disease in a holistic way and then using these insights to identify drug targets, engineer novel therapeutics and identify biomarkers. Today, Merrimack has a market capitalization of over $900m, has around 270 people on staff and 6 drugs in clinical development.

Sorger believes firmly that systems biology offers a new path to drug discovery that will be far more efficient. "About 80% of the cost of today drugs is in yesterday's failures, so one target for systems biology is to change that: so to reduce the rate at which drugs fail and to incrementally improve the process by linking the science back to critical decision making in a company."

Merrimack's core values include drilling into the complex biology behind cancer. So far this has yielded the six molecules in clinical development. In November, the company reported news for Phase 2 studies in the treatment of women with ER/PR2, HER2 negative breast cancer with the inhibitor MM-121. A positive signal was shown in a subpopulation of patients that would potentially benefit from targeted therapy. The findings support ErbB3 signaling as an important pathway of resistance for breast, ovarian and lung cancers.

"MM-121 is a monoclonal antibody against ErbB3 but is not as active in HER2 overexpressing or amplified tumours. Therefore we designed a second molecule, MM-111, which targets ErbB3 in HER2 overexpressing tumours," says Birgit Schoeberl, Merrimack SVP of Discovery. "Based on our preclinical research, we defined five different biomarkers that would be predictive of ErbB3 activity in tumour samples and designed our clinical trials to test this hypothesis." She added

that, with the retrospective analysis of the five biomarkers in Merrimack's clinical samples they were able to identify a subgroup of patients with the same response biomarkers across NSCLC, ovarian and metastatic breast cancer who appear to benefit from the treatment with MM-121.

This is the first time we've gone from an *in silico* preclinical biomarker hypothesis to the ultimate translation into the clinic says Schoeberl, which is a "big moment for Merrimack and I think for systems biology in general. The predictive biomarkers will help identify which patients may benefit from MM-121, which completed six Phase 2 clinical trials in collaboration with Sanofi." Merrimack recently regained worldwide rights to develop and commercialise MM-121 in June 2014 from the cancer arm of French pharma giant Sanofi.

Merrimack pairs up an experimentalist and a modeller in a "discovery pod" and looks to understand the biology before setting off to develop certain drug candidates. "Early on we made some proof-of-concept antibodies targeting ErbB3 and showed that the insights derived from the model translated into the inhibition of cell proliferation, before starting an antibody campaign and selecting the lead molecule," says Schoeberl.

The approach of going under the hood early on to get a good understanding of the biology is essential to Merrimack's philosophy. It is about understanding how a drug targeting a specific disease gene will really work when it gets into a complex human patient, for example. The approach should allow for a better understanding of which patients will respond to which drugs. It could also kill drugs off earlier, says Schoeberl, reducing resource loss through expensive late failures.

"Making a drug should ideally be much more like designing a car or an airplane where it is not a trial and error process. There is a lot of design and modelling and simulation that happens even before a car is built," she says. "We aspire to design and engineer our drugs based on clearly defined design criteria." At the moment, the highest number of failures and most money gets spent before Phase I trials (Tollman *et al.*, 2012). "I believe that Systems Biology applied to target identification and preclinical drug development could increase success rates across the industry," adds Schoeberl.

"In the future a novel drug that comes out and costs US$180,000 per year per patient and is unknown if it will work in 50% of the people it is prescribed to, it is not going to be tolerable," adds Sorger. The systems biology route should mean a more quantitative and also more predictive approach; big pharma is unlikely to turn, however. It is not structured to do so and has no culture of systems biology. Chances are, agrees Sorger, new systems companies are likely to be spun out of universities and research institutes, as was the case with Merrimack.

> "This is the first time we've gone from an *in silico* preclinical biomarker hypothesis to the ultimate translation into the clinic"

Schoeberl herself is a chemical engineer by training, having started her career initially in the oil industry. Her background exemplifies the cross-disciplinary nature and quantitative underpinnings of a systems approach. Schoeberl then did a PhD in systems biology in her native Germany because she was always fascinated by biotechnology. "The concept of systems understanding and systems dynamics is what you do in chemical engineering. It was a good background and the biology I basically learnt along the way."

Words: Sabine Louet
January 2014

ACKNOWLEDGEMENTS

ISBE would like to thank Merrimack Pharmaceuticals for their assistance, in particular Peter Sorger, Birgit Schoeberl and Debbie Tseng.

Further Information

Merrimack Pharmaceuticals
www.merrimackpharma.com

ISBE
www.isbe.eu

European Systems Biology Community
community.isbe.eu

Full image credits can be found at isbe.eu/imagecredits

MERRIMACK FACT FILE

2000 Founded by scientists from Harvard and MIT

2011 Announces $77M in private financing

2012 Launch on NASDAQ

270+ Employees

$900M Company value

6 Cancer drugs in clinical development

Based on 2014 figures

ISBE Infrastructure for Systems Biology Europe

BLUEPRINTS OF LIFE

BAS TEUSINK FROM THE NETHERLANDS PLATFORM FOR SYSTEMS BIOLOGY DISCUSSES THE REMARKABLE DEVELOPMENTS IN HIS RESEARCH MADE POSSIBLE BY THE APPLICATION OF SYSTEMS BIOLOGY APPROACHES

BIOGRAPHY

THE NETHERLANDS PLATFORM FOR SYSTEMS BIOLOGY FOSTERS SYSTEMS BIOLOGY APPROACHES IN THE RED, GREEN, WHITE AND BLUE SECTORS OF THE LIFE SCIENCES, CREATING SYNERGIES BETWEEN SYSTEMS BIOLOGY RESEARCH INSTITUTES/GROUPS AND OTHER STAKEHOLDERS IN SYSTEMS AND SYNTHETIC BIOLOGY, BIOTECHNOLOGY AND MEDICINE.

Prof. Dr. Bas Teusink developed the Kluyver Centre Systems Biology programme; he is Full Professor in Systems Bioinformatics at IBIVU, VU Amsterdam.

We must understand component parts to get to grips with a complicated machine. Once you build such a machine yourself, you can tweak and adopt it. Industry understands how to do this, but has not done so well in deconstructing the live machinery critical for the fermentations at the core of so many food and pharmaceutical processes – the microbial cells.

Bas Teusink at the Netherlands Platform for Systems Biology (SB@NL) is mapping out the design of microbial cellular networks by asking two straightforward but big questions: what makes the cell's biochemical network tick and why did evolution choose that design? His group's modelling of cells' metabolic blueprints on a genome scale is yielding some dramatic successes relevant to industrial fermentation processes.

His group worked in conjunction with the Kluyver Centre for Genomics of Industrial Fermentation, now part of the BE-Basic Foundation, an international public-private partnership that develops industrial bio-based solutions. This collaboration is putting pep into the R&D of industries that rely on innovation in industrial fermentation, optimising what is a critical step in many food, beverage and pharma processes. The aim is to boost performance and robustness of industrial microbes by revealing how the genome and environment interact.

Recently Teusink's group doubled output of a certain toxin, a vaccine component essential for a highly contagious but preventable disease that kills thousands each year. "We could deconstruct the metabolic network of the organism based on its genome," Teusink explains. "In this case it was grown in a traditional production process where a historically defined medium was used." A big pharma company is involved, but cannot be named.

Improving the medium would have meant trial and error, but Teusink's team instead modelled around 1500 reactions underpinning the cell. They realized an ingredient in the growth medium impeded production. Teasing out the metabolic networks also showed them that the cells would be able to use alternative substrates to the ones that inhibited production. They did the heavy lifting in silico, along with experimental test, successfully predicting an improved formula.

> "...it's only now, because of our model, that we can understand thirty years of research..."

"You can design all sorts of hypotheses this way about the media. You can ask what are the minimal inputs I need to support growth or what are the cheapest materials," Teusink explains. The end result: higher productivity at lower costs. But Teusink's systems biology approach has also yielded a fundamental breakthrough, solving a three decade long mutant mystery, recently published in *Science* (van Heerden *et al.*, 2014).

Researchers had struggled with a particular mutant in yeast for years, but couldn't figure out this strange phenotype. It can't grow on glucose, something yeasts normally prefer above all else. Glucose is degraded in a metabolic pathway called glycolysis – Greek for breaking down sugar. It turns out there are two solutions to the problem of degrading glucose in these cells; with the mutant form you have a 99.9% chance of not growing on glucose, but this means that there is still a tiny subpopulation of the mutant that can thrive on it. "This small subpopulation was 1 in 10,000, but we now realize that there are two states these yeast can be in," says Teusink.

When this "bistability" phenomenon was further investigated it turns out 7% of wild type cells by chance do not grown on yeast either and normally just die off when fed it. Genetically the two yeast types in both groups are the same, but chance gives rise to heterogeneity in the system. "This now explains all these weird phenotypes in mutants that people have generated in this field. So it's only now, because of our model, that we can understand thirty years of research."

> "Biology is complicated and you need the maths"

So far so basic, except that glycolysis is a central pathway in life and these subpopulations are everywhere and are particularly important during transitions – such as at the start of a fermentation process when microbes meet a large batch of sugar. "In these transitions we often see that only part of the population starts to grow and the other part dies or does nothing. Suppose that you inoculate a million cells in your milk or your fermentation vat, but only half these cells start doing something. This will lead to a delay in your production [a lag phase]," Teusink explains. Once you understand this split in your population it is possible for you to add something to the media as a pre-treatment to cut down on this delay.

All sorts of processes could benefit from a greater understanding of why only some cells start to grow. Teusink says his yeast work shows that sometimes the average response seen in a population of cells is no such thing - it is actually the sum of two completely different behaviours caused by bistability. Such noise in life is becoming clearer as technological advances improve single-cell measurements and the theory behind cellular network architecture advances; computers will need to run even faster to keep up with network models, Teusink predicts.

Teusink, from his base in Amsterdam, believes Europe must try harder when it comes to training biology students. Today glycolysis is taught as a pathway that goes from A to B, a static process; students are instructed that certain genes are involved, but what does this really mean? "The way we should actually teach this is to make a model of this pathway and let students play with it to see how it actually behaves. It's not so trivial, and stability and steady state concepts today are not clear to students," says Teusink. "Biology is complicated and you need the maths."

Words: Anthony King
March 2014

ACKNOWLEDGEMENTS

ISBE would like to thank Bas Teusink and former director of the Kluyver Centre Jack Pronk for their assistance.

Further Information

Netherlands Platform for Systems Biology (SB@NL)
biosb.nl/sbnl

BE-Basic Foundation
www.be-basic.org

ISBE
www.isbe.eu

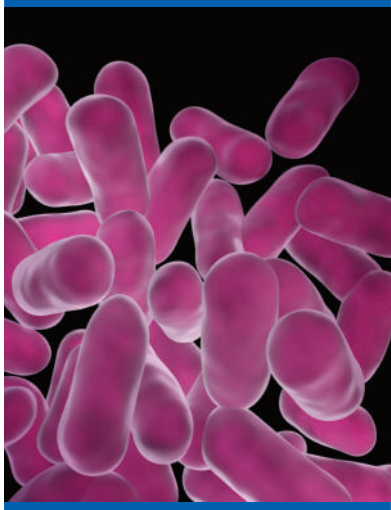
European Systems Biology Community
community.isbe.eu

Full image credits can be found at isbe.eu/imagecredits
Full citations can be found at isbe.eu/case-studies

BE-BASIC FACT FILE

Public-private partnership between:
27 Industrial partners
7 Research Institutes
13 Universities

Since 2011:
447 peer reviewed papers
8 patents filed
8 start ups



Lactobacillus bacteria

CAPACITIES

APPENDIX 2

Persona models

Examples of how ISBE interacts with different types of users

Persona Model 1: ISBE and the researcher

'Sarah' is the leader of a Computational Biomedicine group based in the United Kingdom. She is looking to model the changes in iron metabolism within cancerous cells. The project requires generation of 6 different data sets (a mixture of high throughput and single cell analysis) which Sarah does not have the expertise for in her group. The expertise for producing the data is distributed across 3 different nSBCs, and the data is legally sensitive. Sarah also wants to couple her model with an already available ISBE cell cycle model.

What ISBE will offer

The raw data is collected, structured, and annotated according to available and agreed SOPs in two of the nSBCs. The raw data is then stored in an embassy cloud, to be accessed and post-processed by the third nSBC, according to relevant SOPs, into sharable formats (structured and annotated according to community and ISBE defined minimal standards). The share-format data is loaded into ISBE specific databases, and made available privately (length defined by user/ISBE/legal requirements) to Sarah in a data-unified interface.

The model is constructed by Sarah's group through consultation with her local nSBC to ensure that its structure and format is compatible with the cell cycle model Sarah wants to integrate it with. After the full model is constructed and integrated with the cell cycle model, it is uploaded into a relevant ISBE model database where it can be kept private, or shared with collaborators until publication. At the point of publication the model and data are made available to the public subject to legal restrictions governing the data. The model is curated such that all data can be directly linked and identified with model components.

Impact

5 sets of high quality data are released into the public domain, and are available for other projects to use, subject to legal restrictions. Provenance of the data and model are available and will be tractable through the lifetime of the data and model. The public can access the model and simulate it using ISBE simulation services. Other researchers can (re-)use the data and model for their own research, and satellite work based on this work will be tractable by the community. Sarah's group can be credited for their input into new projects.

Persona Model 2: ISBE and the national research council

A national research funding (NRF) body wants to ensure that the systems biology research it funds has the highest impact possible both in Europe and globally. They have identified that one of the key weaknesses in long-term asset storage from their funded projects is accessibility and (re-)usability. They want to devise a strategy to be implemented on all future funded projects that will overcome these issues.

What ISBE will offer

The NRF can consult with ISBE about its requirements for future systems biology projects. Data handling frameworks will be established between funder and ISBE, and a full set of recommendations for data and model formatting, annotation, and storage will be defined and made available for reference by holders of future successful grants. Training courses can be designed by ISBE and made available voluntarily, or mandatorily to future grant holders.

Impact

When funding projects with public money, especially those with large budgets, it is vital that all assets of suitable quality are made available to the public. By establishing data management and stewardship practices early, and making this a requirement to researchers it improves the likelihood that funded research will achieve higher impact. The development of suitable training made available to grant holders increases the likelihood of the practices being followed correctly. A centrally managed framework means that groups do not have to waste time and resources developing their own formatting, annotation and storage procedures, and therefore reduces the burden and the cost to the researchers whilst allowing the funder to achieve its goals.

Persona Model 3: ISBE and the citizen

'Joe' is diabetic and as an avid amateur biologist is interested in how his blood sugar level impacts the metabolic behaviour of his organs.

What ISBE will offer

The Consensus Human Diabetes Model is stored in a standardised format in an ISBE managed model database. The database is searchable using key-words allowing Joe to find the model quickly. The model has several associated links including the open-access paper it was published in - with a public summary, the patient data that was used to build the model, and services for simulating the model. After reading the paper Joe can understand the basics about what the model does. After launching the simulation, he alters the blood glucose levels through many different ranges. After spotting some clear changes in behaviour, he uses identifiers in the model that link to external resources, in order to understand their function. Joe soon discovers the wide-reaching impact that deviations in his blood sugar levels can have over the short and long-term. He signs up to receive automatic notifications for when the model is updated.

Impact

An open, well managed, and easily accessible infrastructure is not just useful for research scientists; it is also a powerful resource for the enquiring public. The careful storage, annotation, and linking of resources within ISBE has allowed someone with little expert knowledge to gain access to information that impacts their understanding of a common disease.

Persona Model 4: ISBE and the scientific journal

'Systems Biology at Multi-Scale' is an open-access journal dedicated to publishing the growing number of multi-scale models developed within the systems biology community. They have strict policies for publishing models: (i) all data used to construct the model must be available in the public domain, fully annotated to ensure reproducibility, and directly traceable to and from the model; (ii) All models must be publicly available, structured and annotated according to community standards, and simulatable for (re-)use by the community. (iii) The model must be able to reproduce all the finding in the paper; (iv) The data and model must be guaranteed to be available, and (re-)usable, in the public domain for at least 10 years post-publication.

What ISBE will offer

The Journal can work directly with its local nSBC to turn the requirements into a functional set of formats and annotations for authors to follow. The nSBC can train staff from the journal in data and model curation, submission and interlinking. ISBE can provide temporary data and model areas that are private for reviewers to access. Upon publication the data and models will be referred to the trained journal staff who can ensure the formats, and metadata standards of the data and model are suitable, that acceptable cross linking is present, and that the model produces the findings in the paper correctly. This is then submitted to permanent, publicly accessible (subject to any legal restrictions) storage facilities, where the model and data can be viewed in a unified interface. The data will be stored there for a minimum the lifetime of 10 years required by the Journal.

Impact

Journals want to publish high impact, highly cited research. A barrier to this is often the lack of availability of the datasets and models included in journal papers. Poor availability of these assets prevents other researchers assessing the quality of the research, and also being able to use the research to build on within their own work. This will reduce the impact of the research on the community to the detriment of the journal.

APPENDIX 3
Key areas of interface between ISBE and other biomedical research infrastructures

Data and tools

Management of biological data	**Partner RI: ELIXIR**

- Complementarities in provision of access to computing and data resources, data storage and data mining.
- Systems biology data has unique requirements not covered by ELIXIR; ISBE fills this void and is proactively engaging with ELIXIR to avoid duplication of resources and harmonize activities.

Data integration between RIs	**Partner RI: BioMedBridges**

- BioMedBridges aims to provide seamless access to high-capacity computing and data resources, combining all BMS-RIs for IT/data harmonization and data standardization.
- ISBE currently associated partner. In continuation of BioMedBridges, the CORBEL project ('Coordinated Research Infrastructures Building Enduring Life-science Services'; proposal submitted in response to the Horizon 2020 INFRADEV-4 call), will be built on the work of BioMedBridges on data sharing and further extend it to the establishment of common services, harmonised access policies and portals, ethical, legal and social implications, and innovation support and training.

Integration and analysis of diverse imaging data for Systems Biology approaches	**Partner RI: EuroBioImaging**

- EuroBioImaging provides access to novel imaging and image analysis technologies.
- Existing synergies between the two RIs at the common interfaces (e.g. automatic imaging facilities, analysis and integration of high-throughput imaging data) are being explored and will be further developed in the CORBEL project.

Integration of 3D structural data for systems biology modelling	**Partner RI: INSTRUCT**

- Collaborative activities between ISBE and the structural biology RI INSTRUCT could include establishment of streamlined processes on diverse platforms, i.e. a software for integrating structural data into systems wide modelling analysis, e.g. for the prediction of protein-protein (drug-target) interactions from the 3D structure of the individual molecular components.
- Collaborations with INSTRUCT together with EU-OPENSCREEN and other RIs for an integrated compound analysis research pipeline will be elaborated as part of the CORBEL project.

Integration of screening data for systems biology approaches including drug development	**Partner RI: EU-OPENSCREEN**

- EU-OPENSCREEN, the European Infrastructure of Open Screening Platforms for Chemical Biology, integrates high-throughput screening platforms and chemical resources for hit discovery and optimisation.
- Collaborations with ISBE in systems-wide compound analysis as well as for small molecule projects are foreseen, together with other RIs, and also as part of the CORBEL project.

Integration of biological resources and technologies	Partner RI: BBMRI

- The Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) manages biological specimen and data for biomedical research.
- Collaboration potential with ISBE exists for integrating data, samples and repositories with ISBE's modelling expertise into one process pipeline. It is aimed to establish an exemplary service pipeline in a specific use cases as part of the CORBEL project.

Translational medical research

Translational research: Systems and personalised medicine	Partner RIs: EATRIS, ECRIN and ERINHA

- **The clinical research infrastructure ECRIN** foresees value in utilising ISBE's modelling expertise for the prediction of compound (drug) selection, to model the safety/ toxicity of drugs, as well as to predict the efficacy of treatment.
- Topics of common interface with **EATRIS (European Infrastructure for Translational Medicine)** are rare diseases, personalized medicine, as well as biomarker development. There is potential for collaborations between EATRIS and ISBE in the translation of compounds into drugs.
- There is potential for **ERINHA (European Research Infrastructure on highly pathogenic agents)** to utilise ISBE's modelling expertise to identify compounds against high-risk pathogens.

Marine research

Systems approaches in marine research	Partner RI: EMBRC

- The European Marine Biology Research Infrastructure EMBRC allows access to marine ecosystems; areas of potential collaborations cover data generation, integration, analysis and modelling, as well as data storage.
- There is collaboration potential for the systems wide analysis of uncharacterized organisms, natural products, biodiversity and ecosystems.
- Utilising ISBE's expertise in -omics strategies could allow for the understanding of microbial-dominated pelagic ecosystems and biogeochemical drivers.
- Collaborations in the coupling of physical, chemical and biological metadata to systems biology analyses of communities, ecosystems, and processes offer great opportunities for novel approaches in marine science research. Deep sea and polar biodiversity could be examined to exploit for biotechnological potential.
- ISBE and EMBRC will be collaborating within a joint use case to be implemented in the CORBEL proposal (if granted).

Microbial research

Systems biology approaches for microbial research	**Partner RI: MIRRI**

- The microbial resource infrastructure MIRRI provides access to novel natural products and organisms.
- MIRRI could use ISBE's expertise for the characterization of microorganisms and systems wide analysis.
- ISBE stewardship expertise will facilitate access to microbiological data, for data mining, the integration of data from publications, patents, to introduce the use of SOPs, as well as in all other aspects of all e-infrastructures.
- ISBE's modelling expertise offers collaboration potential for the integrated analysis of uncharacterized organisms/ biological material.

Phenotyping

Systems analysis of mouse phenotypes	**Partner RI: INFRAFRONTIER**

- INFRAFRONTIER is providing tools for the systemic phenotyping, archiving and distribution of mouse models.
- Potential areas for collaboration with ISBE are the full level systems analysis of the mouse including the modelling of pathways and molecular effects.
- Within the CORBEL proposal, it is aimed to validate ISBE's genotype-to-phenotype predictions in mouse models provided by INFRAFRONTIER.

APPENDIX 4
Details of national Systems Biology Centre cost estimates

ISBE has developed detailed cost models for the different types and range of plausible ISBE services resulting in estimates for 'small', 'medium' and 'large' national Systems Biology Centres (SBCs), which are detailed in the tables below. The size of each centre is based on the expected activities in relation to the services that a national SBC will provide. However the exact composition of a national centre is to be determined by the national government of the country hosting that SBC. The presented cost models (Staff costs are calculated using the average of UK and Dutch wages) are to open discussions with national governments and national funding agencies.
This appendix starts with a summary of expected activities, the staff and the costs base in year 1. Next, a detailed FTE and costs table is provided for each size-type of national SBC. Lastly the expected FTEs and costs for the central Office (CIO) of ISBE are provided.

A. Summary overview

Table A4.1: Summary of the activities that SBCs will provide and the necessary staff.

Summary of activities		Summary of staff
coordination	day-to-day management	director, project manager, secretary
Services and Standardisation	modelling and data integration	modellers and programmers
	stewardship and standardisation	community worker, software developer, web service manager
	model-compliant data generation	post-docs and technicians
	repository and archives (long-term storage and curation of models, maps, data, tools and protocols)	Scientist
	training, education and outreach. Organising workshops, conferences and training courses	training and education officer
resources	tools, data, maps and models	web manager/ community worker
	community standards and SOPs	Scientist

Table A4.2: Summary of expected annual costs (2019) of a small, medium or large SBC.

Summary if expected costs in 2019				
Size of centre / country	**Staff costs (€k)**	**investments / facilities (€k)**	**training and outreach (€k)**	**Total costs (€k)**
Small	466	120	14	**600**
Medium	932	239	27	**1198**
Large	1863	478	54	**2395**

B. Small national Systems Biology Centres

Table A4.3: Summary of estimated fulltime equivalents (FTEs) and costs for a **small** national Systems Biology Centre both for the interim phase (-2017) and the first two years of the operational phase (2018-2019)

		Interim Phase		Operational phase	
		-2017		2018 - 2019	
FTEs small SBC		***FTE***	**€k**	***FTE***	**€k**
	Administrative	*0,6*	93	*1*	139
	Integration and modelling	*0,42*	80	*0,7*	133
	Stewardship & standardisation	*1,56*	300	*2,6*	450
	Data generation	*0,54*	78	*0,9*	116
Total staff effort		***3,12***	**551**	***5,2***	**838**
Investments/facilities	*Integration and modelling*		24		36
	Stewardship & Standardisation		56		57
	Data generation		27		41
Running costs			50		75
Training & Outreach programme			17		24
Other			6		9
Subtotal investments			**180**		**242**
Total ISBE small SBC costs			**731**		**1080**

C. Medium national Systems Biology Centres

Table A4.4: Summary of estimated fulltime equivalents (FTEs) and costs for a **medium** national Systems Biology Centre both for the interim phase (-2017) and the first two years of the operational phase (2018-2019)

		Interim Phase		Operational phase	
			-2017		2018 - 2019
FTEs medium SBC		***FTE***	**€k**	***FTE***	**€k**
	Administrative	*1,2*	186	*2*	279
	Integration and modelling	*0,84*	160	*1,4*	266
	Stewardship & standardisation	*3,12*	600	*5,2*	900
	Data generation	*1,08*	155	*1,8*	233
Total staff effort		***6,24***	**1101**	***10,4***	**1678**
Investments/facilities	*Integration and modelling*		48		72
	Stewardship & Standardisation		111		114
	Data generation		54		81
Running costs			100		150
Training & Outreach programme			33		47
Other			12		18
Subtotal investments			**358**		**482**
Total ISBE medium SBC costs			**1459**		**2160**

D. Large national Systems Biology Centres

Table A4.5: Summary of estimated fulltime equivalents (FTEs) and costs for a **large** national Systems Biology Centre both for the interim phase (-2017) and the first two years of the operational phase (2018-2019)

		Interim Phase		Operational phase	
			-2017		2018 - 2019
FTEs large SBC		***FTE***	**€k**	***FTE***	**€k**
	Administrative	*2,4*	371	*4*	557
	Integration and modelling	*1,68*	320	*2,8*	531
	Stewardship & standardisation	*6,24*	1200	*10,4*	1800
	Data generation	*2,16*	310	*3,6*	465
Total staff effort		***12,48***	**2201**	***20,8***	**3353**
Investments/facilities	*Integration and modelling*		96		144
	Stewardship & Standardisation		222		228
	Data generation		108		162
Running costs			200		300
Training & Outreach programme			66		94
Other			24		36
Subtotal investments			**716**		**964**
Total ISBE large SBC costs			**2917**		**4317**

E. Central ISBE Office (CIO)

Table A4.6: Summary of estimated fulltime equivalents (FTEs) and costs for a **large** national Systems Biology Centre both for the interim phase (-2017) and the first two years of the operational phase (2018-2019)

		Interim Phase		Operational phase	
			-2017		2018 - 2019
FTEs Central ISBE Office		***FTE***	**€k**	***FTE***	**€k**
	Director	*0,6*	97	*0,9*	145
	Web manager	*0,6*	39	*0,9*	58
	Secretary	*0,6*	33	*0,9*	49
	Public relation manager	*0,6*	43	*0,9*	65
	Liaison officer (project manager)	*1,2*	86	*1,8*	129
	Lawyer	*0,3*	36	*0,45*	53
	Scientists	*0,6*	43	*0,9*	88
	Training and education developer	*1,2*	86	*1,8*	129
Total staff effort		***5,7***	**463**	***8,55***	**716**
Investments/facilities					
	Consumables		4,5		7,5
	Hardware		15		25
	Software		15		22,5
Running costs			46		68
Training & Outreach programme			68		125
Other			5		10
Subtotal investments			**153,5**		**258**
Total Central ISBE Office costs			**616,5**		**974**

BBMRI	Biobanking and Biomolecular Research Infrastructure
BMS	Biological and Medical Science
CASyM	Coordinating Action Systems Medicine
CIO	Central ISBE Office
CORBEL	Coordinated Research Infrastructures Building Enduring Life-science Services
cSBC	Coordinating Systems Biology Centre
CSIRO	Commonwealth Scientific and Industrial Research Organisation
DOI	Digital object identifier
EATRIS	European Infrastructure for Translational Medicine
EC	European Commission
ECRIN	European Clinical Research Infrastructure Network
EFPIA	European Federation of Pharmaceutical Industries and Associations
EIT	European Institute of Innovation & Technology
EMBL-EBI	European Molecular Biology Laboratory European Bioinformatics Institute
EMBRC	European Marine Biological Resource Centre
EMTRAIN	European Medicines Research Training Network
ERIC	European Research Infrastructure Consortium
ERINHA	European Research Infrastructure on Highly Pathogenic Agents
ESFRI	European Strategy Forum on Research Infrastructures
EU	European Union
EU FP6	European Union Sixth Framework Programme
EU FP7	European Union Seventh Framework Programme
FAIR	Findable, Accessible, Interoperable and Re-usable
FDA	United States Food and Drug Administration
FTE	Full Time Equivalent
GDP	Gross Domestic Product
ILB	Industry Liaison Board
IMI	Innovative Medicines Initiative
ILB	Industry Liaison Board
IP	intellectual Property
ISBE	Infrastructure for Systems Biology - Europe
ISCB	International Society for Computational Biology
ISSB	International Society for Systems Biology
KPI	Key Performance Indicators
MIAME	Minimum Information About a Microarray Experiment
MIRIAM	Minimal Information Required In the Annotation of Models
MIRRI	Microbial Resource Research Infrastructure
MoU	Memorandum of Understanding
NIH	National Institute of Health, USA
NNFCC	National Non-Food Crops Centre, UK
nSBC	National Systems Biology Centre
OECD	Organisation for Economic Co-operation and Development
RI	Research Infrastructure
SAB	Scientific Advisory Board
SBI	Systems Biology Institute, Japan
SBML	Systems Biology Markup Language
SBO	Systems Biology Ontology
SLA	Service Level Agreement
SME	Small and Medium Enterprise
SOP	Standard Operating Procedure

Abbreviations