Business Plan

First Edition

July 2015

Update of
2014 Business Case

Project funded by the European Commission under the Seventh Framework Programme for Research and Technological Development

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Vision

To create a European research infrastructure in the field of systems biology that empowers scientists to understand how living organisms function to a level that allows rational and effective intervention in how biological systems operate. This allows life science researchers to deliver solutions that address societal grand challenges in health and quality of life, bio-economy and sustainability.

Mission

By interconnecting national systems biology centres and making their collective expertise, resources and services easily accessible for all European researchers, ISBE will bring systems biology within easy reach of scientists.

Through ISBE, researchers will be able to gain efficient access to the best systems biology expertise, resources and services including state-of-the-art facilities, data, models, tools and training.

ISBE will set, improve and promote standardisation of biological data, tools and models as well as operating procedures, ensuring that resources from different laboratories, countries and sectors can be integrated and become re-usable.

Iterating ISBE’s plans

As the Preparatory Phase of Infrastructure for Systems Biology in Europe (ISBE) comes to an end, the project is publishing this preliminary copy of its business plan. This is an update of the ISBE business case, published in November 2014. This business plan outlines the rationale for ISBE, the physical infrastructure, the plans for services and access, the legal and governance structure and financial aspects of the research infrastructure. It also sets out how ISBE will be built during the interim phase from 2015 till 2018, with the commencement of “ISBE-light”.

A living document

In order to be successful, ISBE must map onto current and future community needs. It is therefore a key task of the project to engage regularly with stakeholders and potential funders to develop a research infrastructure that meets the needs of our broad and diverse community. As such the ISBE business plan is a living document that will continue to evolve during the course of the Interim Phase and regular updates are planned to publicly refresh this document.

The present document is a preliminary version of the business plan. A more definitive plan will be published early in the interim phase.

Executive summary

The modern life sciences are making big steps in analysing living organisms. This is fuelled by the development of powerful technologies, such as genomics, proteomics, metabolomics, imaging and many more, resulting in important new insight and a true data deluge. Despite these successes our understanding of how living systems function is still remarkably limited. Here, ‘understanding’ is defined as being able to correctly predict the functioning of systems after changing their components or their environment.

Systems biology is a branch of the life sciences that can create understanding through integrating multiple and diverse data sets in quantitative computational models. These models are able to predict the behaviour of biological systems based on experimental data about the interplay of molecules, cells and tissues in time and space. This level of understanding can make a huge impact on health, biotechnology and sustainability, whilst fuelling the bioeconomy. As such, national governments and the European Commission have recognised the importance of systems biology, investing considerably in the past decade. In ISBE European countries are joining forces in a research infrastructure for systems biology by building on national strengths to meet European needs.

Infrastructure for Systems Biology Europe (ISBE) will bea knowledge-based research infrastructure that will add value to national and European investments by empowering European researchers across academia, clinics and industry to implement systems biology approaches. It will enable easy access to expertise, resources and training and offer hands-on support in building and using computational models based on model-compliant high quality data. To be effective, ISBE will take responsibility for the development and implementation of community standards to make data, models and tools re-usable over prolonged periods of time. This is essential for progress in the life sciences and, importantly, makes research more efficient and cost-effective.

ISBE’s offerings to the scientific community are based on surveys of the needs of different user communities and potential provider institutions in Europe. ISBE will consist of a collaborative and synergistic matrix of national systems biology centres with overlapping and complementary expertise, each centre being tightly linked to its national systems biology research community. Activities of the centres will be coordinated and overseen at the European level by a central ISBE office, headed by an ISBE director and a supervisory board of stakeholders.

ISBE’s national centres will be financially supported directly by their national governments. For the central office, a membership fee is proposed related to the gross national product of a country. The European Research Infrastructure Consortia is being considered as the preferred legal basis for ISBE.

1. Introduction

Over the past sixty years the life sciences have developed at an ever increasing pace. The discovery of the double helix structure of DNA in the early 1950s may be taken as the starting point of the molecular biology revolution, which radically changed our understanding of living systems. Scientific and technological progress in molecular and cell biology in the years that followed has included cloning, sequencing of the human genome, and the ever growing power of -omics technologies and other methodologies that allow genome-wide analysis of the molecular components of life. This has led to the dawning of a new biological age that is now beginning to give us deep insight into how living systems function, with a rapidly growing impact on human health, food, sustainability and economy.

1.1 Big data: converting information into understanding

The traditional approach to research in the life sciences has been one of reductionism. However, the data explosion in the life sciences, including health-related research, means that biological data can no longer be analysed and interpreted in a useful way without taking into account the broader context of the living organism. Because of exponentially growing volumes of data and the complexity of biological systems, new approaches had to be developed to integrate the diverse data sets of molecules, cells and tissues and convert this 'information' to 'understanding'. Here, 'understanding' means the ability to successfully predict how biological systems behave after changing environmental conditions or altering molecular components.

> **Systems biology**
>
> The research approach of systems biology is interdisciplinary and typically involves collaborations from the fields of biology, medicine, engineering, information sciences and mathematics, chemistry and physics.
>
> The heart of the systems biology approach is an iterative process between laboratory experiments and mathematical modelling, using computers. Based on large volumes of quantitative data at the molecular, cellular, tissue and organ level, algorithms are used to create models which allow predictions to be made of the behaviour of complex biological systems with the aim of gaining an overall understanding of the system.
>
> *Adapted from the definition of the German Federal Ministry of Education and Research (BMBF).*

Converting data to understanding is systems biology, which addresses the emergence of biological function from the dynamic interactions of the components of biological systems. It embraces systems theory, an approach that is fully incorporated in other areas of science and in engineering. Biological systems are highly dynamic, with many components and interactions. Thus their functioning can only be understood by building quantitative and predictive computational models based on experimental data. This is at the heart of systems biology and it is this knowledge-based approach that is the central offering of the

Infrastructure for Systems Biology Europe (ISBE) to the life sciences community.

€2,000B

Value of EU bioeconomy sectors in 2012

1.2 The central role of the life sciences in our society

Our rapidly growing capacity to understand and rationally alter living systems is beginning to have a major impact on human health, food and feed production and sustainability. Metabolic engineering of microorganisms and the integrated model of the beating human heart, which predicts the, often counter intuitive, effects of potential drugs, are just two examples (see ISBE publication *Success Stories in Systems Biology,* 2015[1] and Appendix 1).

The economic effects of these developments in the life sciences cannot be overestimated. The importance of the bioeconomy in Europe is growing rapidly. The EU's bioeconomy sectors in 2012 were worth € 2,000 billion in annual turnover and account for more than 22 million jobs representing approximately 9% of the EU workforce.[2] The systems biology approach is a strong research base that translates into industrial products and processes and in healthcare. This is a primary reason for recent significant investment in systems biology for the European life sciences community. This has also been reflected more widely by significant international investments, such as the Institute of Systems Biology in Seattle and the Systems Biology Institute in Tokyo to support their considerable and growing research effort in this area.

To make this effort both effective and efficient requires the creation of an environment, an infrastructure, for systems biology in Europe that is capable of coordinating and leveraging the science base. This is the aim of the ISBE described in this document.

1.3 Infrastructure for Systems Biology Europe (ISBE)

The aim of ISBE is to make resources, expertise and training in systems biology readily accessible to European researchers, clinicians and industry, including SMEs, and to actively support their research efforts. ISBE builds on over a decade of national and EU support in systems biology and will coordinate and synergise future investment. It will actively support researchers in:

- addressing how the dynamic interactions between biological components (molecules, cells, tissues, organs) leads to the functioning of living organisms in a constantly changing environment,
- creating predictive computational multi-scale models of living systems, up to complete organisms, representing these interactions,
- exploiting such models to generate major socio-economic benefits in areas including pharmaceuticals and healthcare, agricultural science, energy and the environment.

The ISBE research infrastructure will consist of a matrix of interconnected national centres of excellence in systems biology, coordinated and managed at the European level.

Building understanding of the functioning of hugely complex biological systems is a process that takes time, in which predictive models improve and expand stepwise. Therefore, it is essential that data, procedures and models can be re-used and are accessible over long periods of time. A primary function of ISBE will be to

[1] http://zenodo.org/record/21393

[2] Innovating for Sustainable Growth: A Bioeconomy for Europe; COM (2012) final; European Commission: Brussels, Belgium, 2012

harness the community in the development and implementation of standards and operating procedures that enable and promote re-usability. Through the ISBE infrastructure, European researchers from across the life sciences will have access to the best systems biology research expertise, tools, services and training via a single portal.

1.4 This document

This document provides details of the ISBE research infrastructure, including the strategy for developing and positioning the infrastructure as a central element of the European research landscape, and describes its structure, services, finance and governance. This is the result of the collaborative activity of 23 research institutions and funding agencies in 11 European member states in the context of the European Strategy Forum on Research Infrastructures (ESFRI) Roadmap and is supported by a three year Seventh Framework Programme (FP7) grant of the European Commission (2012-2015). In July 2015, the Preparatory Phase of ISBE ends and the process of building the research infrastructure begins. It is expected that ISBE will be fully functional from 2018.

Researchers analyse mass spectrometry data (*Image courtesy of University College Dublin*)

2. The ISBE strategy: building on national strengths to meet European needs

This section describes the vision and strategy for ISBE, outlining how the research infrastructure will be positioned in the broad European research landscape to achieve maximum impact for the research base. Subsequently, Chapter 3 details its services, structure and functioning.

2.1 Investments in systems biology

Since the turn of the century there have been significant investments in establishing major systems biology centres, both in their capital fabric (buildings and equipment) and in developing expertise through training programmes and appointments at research faculties. Similar investments have been and are still being made in systems biology departments and groups at universities and research centres. An example is the €147 M investment in systems biology made by the Biotechnology and Biological Sciences Research Council (BBSRC) in the United Kingdom by 2012, which accounted for 12% of its total investment in biological sciences in the past 10 years. However, wider dissemination and uptake of such model-driven approaches in Europe is still relatively slow. It is now timely to ensure that coordination and access to existing resources and skills is developed broadly across both national research bases and Europe-wide, in order to gain optimal impact from prior investments in capital and expertise.

€147M

Investment in systems biology by UK BBSRC to 2012

2.2 Converting information into understanding

The ongoing challenge in the life sciences is to convert the huge amount of biological data that we produce into understanding of how living systems function to a level that enables successful prediction of their operations and of changing their components or networks (see ISBE publication *Success Stories in Systems Biology*, 2015). Intelligent, computational model-driven approaches are essential to deal with the extreme complexity of biological systems. This is a game-changing goal for the life sciences for the next ten years and is made possible by recent rapid technological developments, such as genomics, proteomics, metabolomics, advanced imaging, bioinformatics and our rapidly increasing understanding of tissues and organs. This has been recognised by national funding organisations and the European Commission, resulting in significant investments and many major research programmes dedicated to systems biology in the past 10 years.

2.2.1 European investments in systems biology

European investment in systems biology initially focussed on the development and use of predictive models, so far mostly at the molecular level, such as metabolic networks within cells. More recently, there has been a clear shift towards the implementation of systems biology approaches within biomedical research (known as 'systems medicine') and across the biotech industry. Recent examples include the transnational programme Coordinating Action

Systems Medicine (CASyM), the ERANet projects ERACoSysMed and ERASys*App* and various EU programmes that are part of the Bio-Based Industries (BBI) funding scheme (see *Appendix 3* for an overview of European investment).

Recent developments include the use of multi-scale modelling, which aims at understanding the functioning of complete organs and organisms as the result of the dynamic interplay in time and space of molecules, cells, tissues. Here, molecular and cellular biology meet physiology. Such integrative efforts are already creating a strong basis for new avenues in biomedical and pharmaceutical research. Examples include the virtual human heart[3], the Virtual Liver Network[4] , the Human Metabolic Atlas[5] and other projects within the international Virtual Physiological Human (VPH) programme.[6]

2.2.2 Bottlenecks

Whilst prior investments have created a solid knowledge base for systems biology in a number of European countries, dissemination and uptake is still slow. Reasons include:

- Protocols for properly planning and executing experiments and acquisition of high quality, quantitative data that can be integrated in computational models are not yet widely used.
- Expertise required to build and use high quality predictive computational models is limited and will not grow without widespread integration into biological and biomedical academic curricula, while lack of suitable for training for industry is also inhibiting take up.
- Integrated stewardship of results is still in its infancy. This includes annotation and curation of model-compliant data sets and making them findable and re-usable over prolonged periods of time.
- Slow translation of systems biology approaches into clinically and commercially usable application.

2.2.3 ISBE's offerings

ISBE's vision is that systems level approaches should be within reach of all European life scientists to accelerate a fast adoption and translation into new research findings and industrial applications. This will increase the competitiveness of the European Research Area as well as in health and the bio-economy industry. ISBE therefore intends to make the necessary expertise, services, tools and resources easily and openly accessible to scientists in academia, hospitals and clinics and for industry, in particular SMEs. This process will be enhanced by European education and training programmes and a range of community activities, such as the development and implementation of standards (see Chapter 3).

2.3 ISBE amalgamates national strengths to meet European needs: a two-tier infrastructure

ISBE's strategy is to support the European Research Area by building on existing national investments, expertise and strengths and harnessing the experience of national and transnational initiatives in systems biology, such as the ERANET programmes (see Appendix 3 for further details). ISBE will not have a research programme itself. Rather, it supports research projects and programmes of its users, i.e. individual researchers, research groups and research consortia.

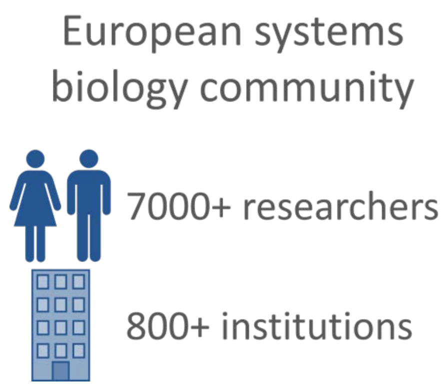
ISBE will consist of a European matrix of national systems biology centres that offer expertise, services and resources. The activities of the centres will be coordinated at the European level by a central office. Each centre will be

3 http://thevirtualheart.org/
4 http://www.virtual-liver.de/
5 www.metabolicatlas.org
6 http://www.vph-institute.org/

tightly linked to national systems biology research groups and therefore well-embedded within the local research community. The collaborating national ISBE centres will offer a broad range of expertise, services and resources to life scientists in academia, clinics and industry across Europe through a single ISBE web-based portal.

2.4 Fitting ISBE in the European life science landscape

The proposed ISBE services, detailed in Chapter 3, are built on extensive consultations with future user and provider communities during the ISBE Preparatory Phase (2012-2015). This document is based on these consultations as summarised below.



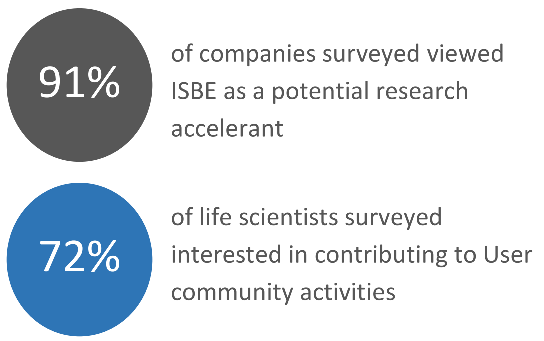
2.4.1 Systems biology community: users and providers

The European systems biology community is made up of more than 7,000 researchers working in more than 800 European research institutions[7] (further information is available through ISBE's European Systems Biology Community website, community.isbe.eu and in Appendix 4). Only a small proportion of these institutions (15%) are specifically dedicated to systems biology, while the rest are institutions dedicated to a wide variety of areas of the life sciences such as microbiology, plant physiology and medicine.

This broad and vibrant community consists of systems biology users and specialists. It represents an important segment of the potential user-base of ISBE while also including several of the institutions that will provide the expertise, tools and resources for ISBE's national Systems Biology Centres. To understand the existing landscape, ISBE carried out an in-depth survey of the potential provider community, including detailed, direct consultation with over 50 institutions about their resources and expertise, as well as their interests and needs as providers and as users of ISBE (see Appendix 4 for further details).

2.4.2 Stakeholders in the life sciences and beyond

Surveys and interviews have been carried out with stakeholder groups in academia, hospitals and clinics and industry, including SMEs, as well as with national funders and scientific journals, to inform the ISBE strategy (see Appendices 5 and 6 for further details).



2.4.3 The European research infrastructures landscape

The 2010 ESFRI Roadmap lists 13 research infrastructures in the life sciences, including ISBE. They complement each other, together forming a strong basis for the development and dissemination of knowledge and the provision of services. The essence of systems biology is to integrate diverse data and technologies to

[7] Based on ISBE's literature analysis of the period 2010-2013

obtain a complete picture of biological systems. Building on this vision, ISBE is already collaborating with the 12 other biomedical ESFRI research infrastructures to harmonise and optimise their procedures and offerings, through the Horizon 2020 funded programmes COordinated Research Infrastructures Building Enduring Life-science Services (CORBEL) and RItrain (see Appendix 7 for further details).

2.5 Timeline of the development of ISBE

Building a European research infrastructure such as ISBE is a long-term process. Planning ISBE grew out of discussions within ERASysBio that led, in 2009 to the submission to ESFRI. This resulted in ISBE's inclusion in the ESFRI Roadmap 2010. This enabled ISBE to obtain funding through the EU FP7 Infrastructure programme to fund its Preparatory Phase (2012-2015) in which 23 research institutions and funding organisations in 11 countries collaborated. The publication of the present Business Plan is the culmination of these efforts and is the result of broad and intensive discussion and consultation aiming to design an optimal European research infrastructure for systems biology.

Since systems biology is a relatively new and rapidly developing field in the life sciences, the Preparatory Phase was primarily intended to:

- map and analyse the European systems biology community
- explore the potential user and provider-base in academia, hospitals, clinics and industry, including SMEs
- develop a simple, easily accessible and affordable structure for operation of the research infrastructure

In the forthcoming Interim Phase (2015-2018) the ISBE research infrastructure will be built in a stepwise fashion (see Section 6) until it reaches full functionality in 2018, 10 years after the ISBE initiative was conceived.

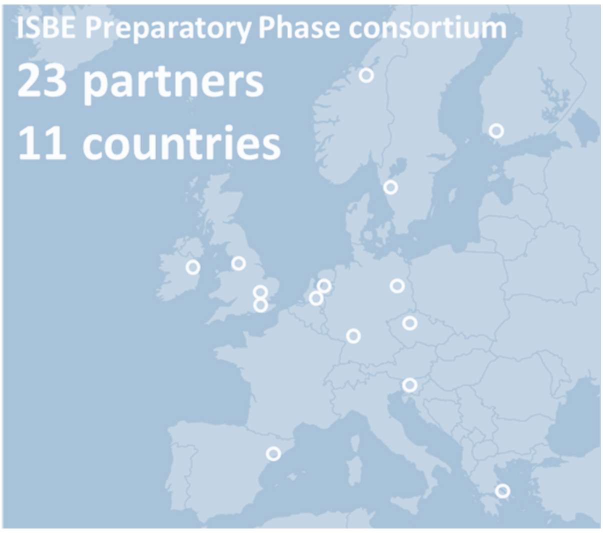


Figure 2.1 ISBE Preparatory Phase consortium

2.6 Next sections

Details of the proposed services, structure and functioning of ISBE are presented in Section 3. Its proposed governance structure and financial basis set out in Sections 4 and 5.

Figure 2.2 The three phases of ISBE

3. The research infrastructure

This section describes how the ISBE research infrastructure will function. It starts with defining the challenges of its ***user communities*** and how its portfolio of ***services and resources*** will meet these user needs. Subsequently, the ***architecture of the infrastructure***, ISBE's ***access policy*** and its ***service providers*** are presented.

Academic and clinical challenges	Quantitative data that can be integrated through computer modelling Ready availability of basic and advanced training in systems biology Easy access to curated computer models, tools and model relevant data and related expertise
Industrial challenges	Standards for data and models that make results interoperable Access to and knowledge of existing tools, resources and repositories Engagement with networks of academic expertise (particularly for SMEs) Provision of high quality and certified training courses in systems biology

Table 3.1: Summary of challenges arising from sectorial surveys (full details in Appendices 5 and 6)

3.1 Who will use the infrastructure and what will ISBE offer?

The ISBE infrastructure is designed to meet the needs of three broad and interlinking life science research communities in academia, clinicians, and industry. The mapping and stakeholder engagement analyses have identified the key challenges for the different user groups that the infrastructure can address (Table 3.1).

ISBE will offer services and resources that are valuable for all branches of the life sciences, independent of the type of organism or biological system studied. Systems biology creates a strong unifying and theory-based foundation in the life sciences. The different types of services are outlined below.

3.1.1 Resources for storing, sharing and interoperating research assets

ISBE will provide efficient access to core research assets of systems biology, i.e. maps, models, data, and tools. Assets will include (i) user research assets that are managed and curated by ISBE to ensure quality and reproducibility and (ii) publicly available model-compliant research assets that have been selected by ISBE. These will be made available in a cataloguing resource which contextualises information according to biological phenomena rather than data type. For example, assets describing the human liver will be organised together, along a hierarchical map of the liver. This method of organising resources will not transfer data, maps, models and tool physically, but will work with links, pointers and web services, leaving the items at a repository managed locally or by collaborating research infrastructures (such as ELIXIR, the European life science data management research infrastructure) with whom ISBE has developed a number of guiding principles for effective management and sharing of data.[8]

Figure 3.1 ISBE services

Offering systematic asset management tools to ISBE users will enhance the 'findability' and 'integratability' of data, models, SOPs, maps, software and tools. This will considerably enhance the efficiency of life sciences research and increase its impact on society. It is stressed that this aspect of ISBE's activities is generic, i.e. not restricted to specific fields or levels of complexity in biology, biotechnology and health-related research.

Research assets will be attributed to their authors' profiles, which will be made available in a cataloguing resource. This constitutes a valuable source for life scientists who want to complement their research efforts with high quality results from other studies. It is an additional way of creating impact by easy deposition into specialised data sources provided by other research infrastructure such as ELIXIR. In this context ISBE will offer expertise for direct curation of models, standard operating procedures (SOPs) and data, tools and protocols linked to them, with persistent identifiers (for example digital object identifiers (DOIs)) for easy access, attribution and citation. Centralisation of access to assets in ISBE will increase the breadth of audience and, as a result, the impact that published assets can have. This will incentivise researchers to deposit their data, tools, models and maps.

ISBE will ensure sustained and dedicated public resources for research asset management over the long-term. Helping establish sustainable funding models for all resources is considered key for systems biology research asset management. The resources will also provide, in conjunction with research infrastructures such as BBMRI and ELIXIR, provisions for commercially and personally sensitive data.

> **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 appropriate outcomes from systems biology research.

3.1.2 Stewardship and standardisation to make data, models and tools re-usable

ISBE will offer an online 'Knowledge Hub' providing best practice material and tutorials to assist researchers in making their research assets FAIR compliant, that is *f*indable, *a*ccessible, *i*nteroperable, and *r*eproducible (see Appendix 7 for further details of FAIRDOM). The

[8] Detailed recommendations and the background and context for data management and sharing at the RIs can be accessed here: https://zenodo.org/record/8304#.VXBZkNKrS70

material will include identifying the most suitable formats, ontologies for annotation, and best practice usage of them, for a wide variety of research assets. Importantly, this will make maps, data, tools and models re-usable over prolonged periods of time, in follow-up research projects and by other researchers, adding significant value to research investment. In this context, a key activity of ISBE will be advocacy for the development and adoption of best practice, community standards, and minimum description models, setting in motion their habitual use by the community. ISBE's support to make research assets of its users re-usable over prolonged times will make research more efficient and considerably improve its cost-effectiveness.

Community standards and best practices for maps, data, tools, models and SOPS

Supporting the experimental design phase with expert knowledge ensures suitable data is collected for downstream use. After this, advice on integration of data into models, followed by model validation is important. The framework which supports the scientific process, the collaborative data infrastructure, needs to support storage and access to the data and models, as well as access to infrastructure services that assist with data and model analysis including simulation software for models, and data analysis software. A mediating layer is needed that simplifies the accessibility and usability of the software for the users, allowing smoother interoperating of the research assets in different analysis software, and also makes the storage and availability of research assets in multiple platforms simpler for the user.

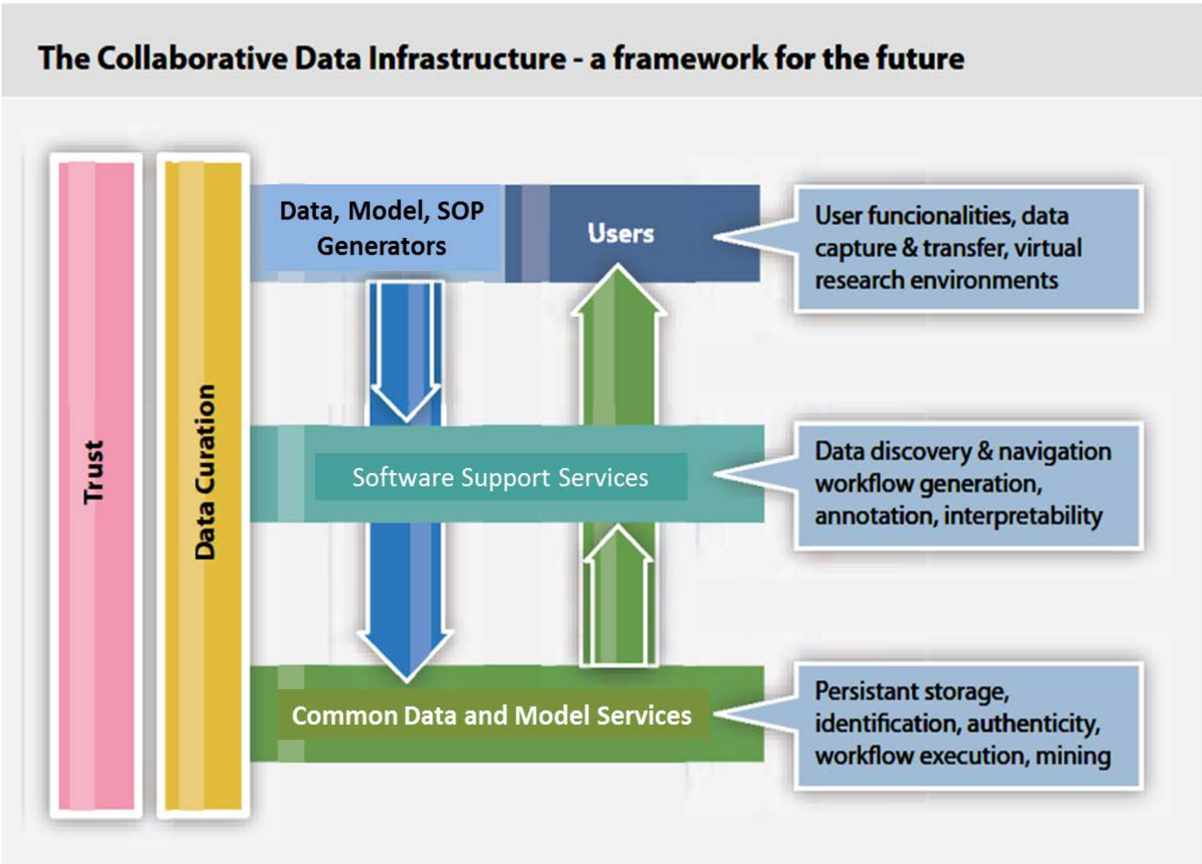


Figure 3.2 Structural elements required for e-infrastructure supporting systems approaches.

Data curation refers to the skills and due process that are involved in formatting and annotating data, models, and SOPs to a suitable standard, and how they will be stored, maintained, and eventually disposed of over their lifetime. This can include direct curation by centre experts, training of producers/users to curate their own data and models, and must also involve clear management plans for length of storage and privacy requirements. Data curation components involve:

(i) the development of community standards and best practices for maps, data, tools, models and SOPS;
(ii) the provision of brokerage services to bring researchers in contact with external research infrastructures or institutes with experimental design and data generation capabilities in compliance with ISBE standards;
(iii) Training to disseminate better data management practices throughout the community.

The single most important aspect is trust. Service providers must trust researchers to format, annotate, and make their data and models available according to a base level of requirements; providers must trust the infrastructure to store and maintain their data, models, and SOPs for the lifetime of their data management agreement – including the security of sensitive research assets, and the ability to maintain intellectual property rights where appropriate. Providers also must trust that they can get adequate acknowledgement and credit if their research assets are reused in other projects – much like with paper citations at present.

3.1.3 Modelling of biological systems based on integration of diverse data sets

Modelling is at the heart of systems biology. ISBE will support life scientists, either proficient or unskilled in systems biology, in developing and using quantitative and predictive computational models to understand the functioning of complex biological systems. These services include model-supported data integration and data analysis, model analysis and validation, model-based simulation and analysis of system behaviour, and model construction. Increasingly, this involves integration of highly diverse data sets and a variety of pre-existing models, in multi-scale models that span large time scales and length scales.

ISBE will offer a wide range of modelling approaches for systems ranging from subcellular molecular networks through to cells, tissues, and organs up to complete organisms in their dynamic environment. In this ISBE will draw on a broad range of genome wide maps, Boolean, Bayesian, and Petrinet models, all the way up to multi-scale models that harbour mixtures of multidimensional, stochastic and partial differential equation models and integrate the molecular, cellular and physiological levels.

As scientists that are not experienced in modelling of biological systems are a major target of its services, ISBE will enable a wide range of researchers to use computational modelling to integrate diverse data sets and explore, predict and test the behaviour of complex biological systems in biotechnology and health research. This will support the conversion of information about systems into system level understanding.

3.1.4 Facilitating model-compliant data generation

Most existing biological data sets are unsuitable for systems biology modelling: they are incomplete, unannotated, or have been acquired for other purposes. Researchers active in the systems biology field generally require precise data obtained under defined experimental conditions which must be described adequately if they are to be validly reused. Improving the generation of model-compliant data is not simple and requires, firstly, systems biology compliant experimental design, and then a strong framework of activities that support a smooth pathway from data, model, SOP and other research asset generation, through to storage, followed by search, access, and reuse by downstream users. The structural elements required can be seen in Figure 3.2.

To address this, ISBE will facilitate the generation of data suitable for systems biology through: (i) the development of community standards and best practices for maps, data, tools, models and SOPS; (ii) the provision of brokerage services to bring researchers in contact with external research infrastructures or institutes with experimental design and data generation capabilities in compliance with ISBE standards; and (iii) support in the experimental design phase and throughout the data generation, integration, modelling and model validation process, in order to obtain model-compliant data.

3.1.5 Community activities

The ISBE user and provider communities are the infrastructure's greatest resource. ISBE will harness their expertise in a range of community-led activities across its systems biology and life science stakeholders:

- integral map, model and data curation
- development and implementation of community standards, in collaboration with the life science community and international systems biology journals
- foster the maintenance and development of systems biology formatting and annotation standards, such as Systems Biology Markup Language (SBML), Simulation Experiment Description Markup Language (SED-ML), and Minimum Information Required In the Annotation of Models (MIRIAM)
- promote the development of standards for the exchange of information between models dealing with time varying but spatially lumped processes, such as CellML, and spatially and time varying processes, such as FieldML.
- serve as a contact for worldwide initiatives and collaborations in systems biology-related fields
- be a key player in the collaboration between and the harmonisation of activities of the thirteen life sciences ESFRI research infrastructures in the context of the CORBEL programme
- cooperate with and contribute to harmonisation between European systems biology-oriented research programmes and activities, such as Virtual Physiological Human, ERASys*App*, Coordinating Action Systems Medicine (CASYM), ERACoSysMed and ERASynBio
- promote, support and contribute to the organisation of international congresses in the field of systems biology
- develop and maintain the European Systems Biology Community website (community.isbe.eu) as a portal for networking and community engagement

3.1.6 Training and education

Education and training in systems biology is vital for ensuring the effective adoption of systems biology approaches to tackle today's societal challenges. ISBE's ambition is to train a new generation of systems biologists equipped with the cross-disciplinary skills that will be important not just for systems biology but that also have applications in many areas of academia, government, industry, consultancy and other non-governmental organisations.

ISBE's multi-faceted training strategy consists of the following key elements:

User training and continued professional development

ISBE's national Systems Biology Centres will provide bespoke training to ensure effective utilisation of its tools, services and resources. This training will range from starter courses for novices to specialised training for experts and tailored courses for industrial users. ISBE will work with, and learn from, other research infrastructures to develop a training strategy which encompasses a range of learning methods to ensure maximum efficacy.

Education

Together with ERASys*App,* ISBE has developed a core curriculum for Masters level students in systems biology which will be disseminated through various communication channels (publication, website and conferences) and implemented as a pilot project through interested universities.

Dissemination of information on education and training

ISBE will maintain a comprehensive and up-to-date database of systems biology-related education, courses, workshops and conferences and make this information openly available. If ISBE identifies major gaps in knowledge dissemination or development, it will lobby national and European organisations to take the initiative, or will develop courses itself.

Training of staff managing and operating research infrastructures

The complexity of research infrastructures and the exploitation of their full potential requires suitably trained managers and technical operators. As a key participant in the recently funded Horizon 2020 CORBEL and RItrain projects, ISBE is working with other European research infrastructures to develop and support the training of staff managing and operating research infrastructures including the exchange of staff and best practices between facilities. The development and establishment of a Masters in Research Infrastructure Management within the RItrain project will contribute to the supply of human resources with the requisite skills.

€1.69M awarded to ISBE partners through the H2020 COordinated Research Infrastructures Building Enduring Life-science Services (CORBEL) programme

€185k awarded to ISBE partners through the H2020 RItrain project

3.1.7 Why would scientists make use of ISBE's services?

All components that ISBE will offer are in principle available also outside the infrastructure. Why then would scientists involve ISBE? The answer to this question is summarised below.

- The various services of ISBE in relation to modelling, research assets management and training and education are offered individually, as well as a coherent package, tuned to the needs of the user.

- ISBE's services will be of guaranteed high quality.
- Many European researchers do not have (easy) access to expertise and services that will be offered by ISBE.
- National funders that invest in nSBCs will have a vested interest in urging their research communities to use their services.

Clearly, this will only work if ISBE indeed is able to convince its potential users that its services are valuable for them. This requires continuous quality and efficiency control of ISBE.

3.2 How will ISBE be organised?

ISBE will build on existing European resources and draw on the national technological and scientific strengths of its providers to offer a comprehensive portfolio of services and resources. ISBE will map onto existing national structures and coordinate and synergise facilities under a single banner, creating ease of access for its users. This will stimulate growth in the user-base of existing resources, providing a return on existing investments while keeping coordination costs minimal.

The core of ISBE will be a distributed knowledge-based infrastructure of national Systems Biology Centres (nSBCs) across Europe, offering interconnected and complementary services and resources both nationally and transnationally (figure 3.3).

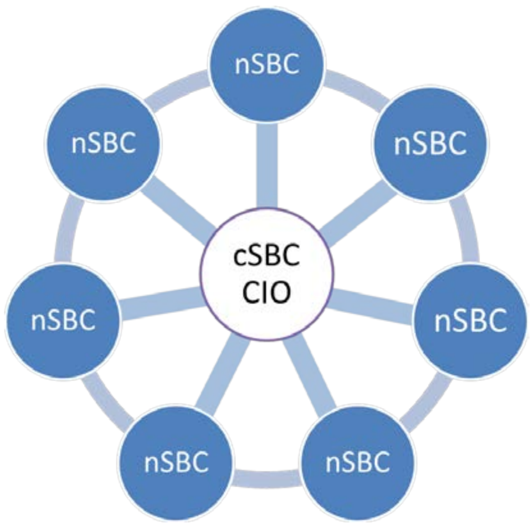


Figure 3.3: ISBE two-tier structure

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 an integrated range of services
- provides coordinated services with other European research infrastructures

3.2.1 Building on national strengths

AT THE NATIONAL LEVEL

Coordination

activities coordinated by a national Systems Biology Centre (nSBC)

Providers

operational delivery by systems biology centres of excellence within member states

Users

provision of resources and services to national users, and beyond

National Systems Biology Centres (nSBCs) are the cornerstone of the ISBE research infrastructure. Embedded in their national life science community, each will deliver the portfolio of standard ISBE services and resources as outlined in Section 3.2 as well as bespoke services based on the expertise of institutions in their country. nSBCs will serve (i) their national user-base including academia and industry, (ii) transnational users, as well as (iii) multinational projects. Trans- and multinational activities will run through collaborations of two or more nSBCs that are coordinated through the Central ISBE Office (CIO) and the coordinating SBC (cSBC), (see Section 3.3.2 for further details). Managing individual nSBCs within the context of the ISBE infrastructure will be the responsibility of the relevant national authority.

In principle, a country will maintain one nSBC which will constitute the primary vehicle for providing services to the national community. This nSBC may be a single national institution or a distributed centre drawing expertise from a number of different institutions in a country. The nomination and selection process for nSBCs is described in Section 6.2.4.

3.2.2 Coordination at the European level

AT THE EUROPEAN LEVEL

Coordination
strategic coordination and support of transnational service activities by a single coordinating Systems Biology Centre (cSBC), with administration and management by Central ISBE Office (CIO)

Integration
resource integration to obtain stronger functionality through synergy

Collaboration
collaborative activities with EU and international research infrastructures

Outreach & Communication
coherent outreach programme to promote ISBE to potential user communities and fostering of existing stakeholders through effective communication

Standardisation
lead development of pan-European community standards

Quality control
monitoring of service demand and quality control

Organisational structure: the Central ISBE Office and the coordinating nSBC

The *Central ISBE Office (CIO)* will be responsible for central management, administration and executing the Governing Board's decisions of ISBE and working with the Management Group to undertake delivery. It will integrate, coordinate, monitor and oversee:

- overall operations and strategy development of ISBE, including nominations and selection of new nSBCs (see Section 6.2.4 for further details)
- functional links between nSBCs, including commissioning of novel services, resources and activities
- quality control of nSBCs and the European matrix of centres
- liaison with national and European funding organisations, external cooperation, partnerships with other research infrastructures, including other ESFRIs, and international organisations in or outside Europe

To give the CIO rapid and easy access to scientific competences in the field of systems biology, it will be physically linked to one of the nSBCs, which fulfils the role of *coordinating Systems Biology Centre* (cSBC). The role of the cSBC is to advise the CIO on matters relating to the coordination of user support, stewardship and teaching and training. Also, with the help of the cSBC, the CIO will maintain an overview of the scientific and technical capabilities of all nSBCs. This will enable the CIO to identify gaps in expertise as early as possible.

The scientific expertise of the cSBC will support the CIO to manage complex and extensive user requests that require cooperation of two or more nSBCs working together. The CIO will support pan-European community activities including training and development of community standards. The function of cSBC will be performed by a nominated nSBC.

3.3 Scalability of ISBE's services

Given the present and near-future developments in the life sciences, the need for the kinds of services offered by ISBE will increase steadily. This requires an infrastructure with services that are scalable and can be adapted rapidly to changing needs of its users. Therefore, the nSBCs should be flexible, both with respect to the volume of support activities and their range of expertise. This is one of the aspects that must be agreed upon in the covenants that ISBE will have with each of the national funders that finance an nSBC. The development of the volume and the types of support that ISBE offers will be coordinated by the CIO.

3.4 How will users access ISBE?

ISBE will be openly accessible to all researchers from European academia, hospitals, clinics and industry, including SMEs. It will not have a research programme itself. Rather, it will support research projects and programmes of its users, i.e. individual researchers, research groups and research consortia. Access to the infrastructure will be easy and efficient through a central web portal. ISBE will support users that are proficient in systems biology, as well as those that are inexperienced in the field. This will enhance the dissemination and implementation of systems biology in all branches of the life sciences and the impact of systems biology for society. After first contact through the ISBE web portal, users will be linked to one of the nSBCs that is able to offer the requested services, or to a number of nSBCs for more complex services. In all cases the user will have a single ISBE officer as contact person.

Access to the majority of ISBE's web-based resources and simple consultancy activities will be free of charge. Services that are more elaborate, such as modelling, model validation and data collection, will require a fee based on a contract between ISBE (or the relevant nSBC) and the user. It is expected that in most cases costs will be covered through national or European grants. In many cases user projects will already have undergone peer review through a funding organisation. If so, ISBE will accept the user without further screening. If not, ISBE will carry out its own quality check based on a simple peer review process.

Cost models for the above will be developed together with national funders and the nSBCs. Training and education activities will be developed and offered through the nSBCs. Costs for ISBE clients will depend on the user-type, activity and the tariff defined by the nSBC.

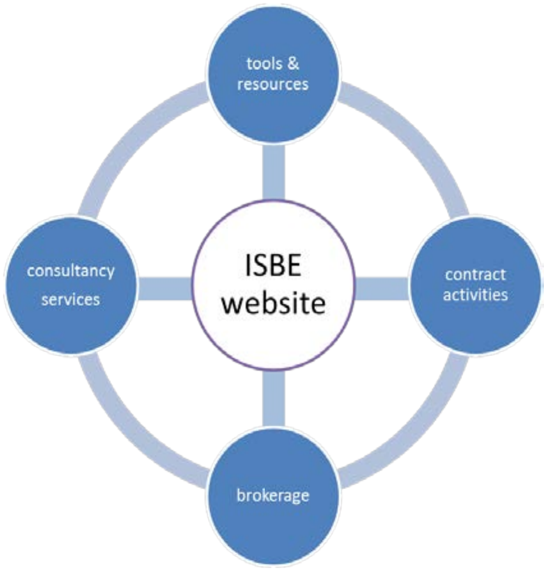


Figure 3.4 User access

ISBE will be a gateway to services provided by linked research infrastructures and provide brokerage services to introduce users to services outside of the remit of ISBE including systems biology compliant data generation and experimental design that is not performed within the infrastructure.

3.5 Who will provide ISBE's services?

A range of national research programmes in many countries have resulted in a broad and substantial systems biology base in Europe, including those established on support from a series of transnational ERA-Net programmes, or supported by FP6, FP7 and Horizon 2020 awards. ISBE will serve as the coordinator of this expertise, fostering new user-bases and providing a single entry point.

90% Percentage of audited systems biology centres positive about contributing to ISBE

Leading systems biology centres in most European member and associated states have been identified during ISBE's Preparatory Phase. Within each of the national communities, ISBE has pinpointed the leading centres and addressed a number of them to audit their capacity and interest in providing systems biology services and resources to a broad audience (see Appendix 4 for details). Prominent researchers in more than 40 institutions across Europe have been consulted, and more than 80 available systems biology resources have been identified with this exercise (figure 3.4).

Almost all of institutions surveyed (90%) recognised the value of offering their expertise and services to a broader community of users via a pan-European infrastructure, and thus manifested interest for being part of ISBE as a provider. A portion of these resources are already available to very variable numbers of users (from between 5 and 15,000 per month), but their sustainability and interoperability is often at risk. In fact, most of the resources surveyed by ISBE were funded primarily on short-term, unspecific grants, with less than 10% operating with stable funding arrangements. In this context, a broadening of user bases through ISBE will be beneficial and improve sustainability.

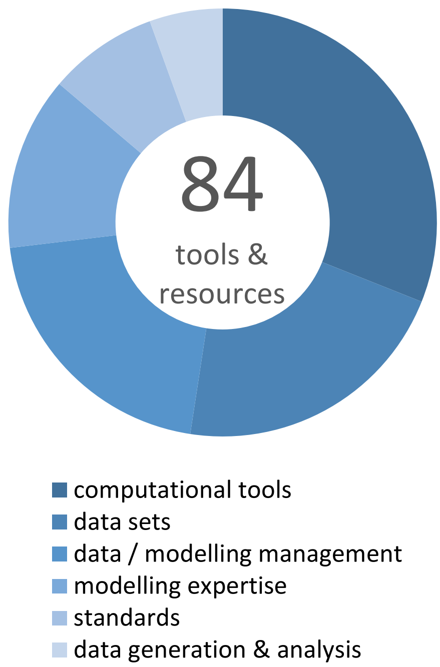


Figure 3.5 Number of resources identified through ISBE audit with potential to be offered through a systems biology research infrastructure

4. Legal and governance from 2018 onwards

4.1 Legal structure – European Research Infrastructure Consortium (ERIC)

ISBE requires its own legal personality in order to obtain funding, manage budgets and establish legal agreements with the national Systems Biology Centres (nSBCs). This legal entity can coherently engage with users, providers, national ministries, funding agencies and the European Commission. The Preparatory Phase has identified the European Research Infrastructure Consortium (ERIC) mechanism as being the most appropriate legal model for ISBE. This allows ISBE to become a legal entity with a European identity and to benefit from tax exemptions. The ERIC framework has already been ratified by many EU member states and allows membership for countries outside the EU.

Table 4.1 summarises how the ERIC structure is suitable for ISBE.

ERIC legal document describes:	**Advantages of the ERIC structure:**
Legal structure	Utilises the existing ERIC framework mechanism that allows for rapid agreement by countries who have already agreed to the framework
Support of the organisational structure	Will allow for funding of the Central ISBE Office coordination functions for periods longer than 5 years
Eligibility to apply for EU funding	Can apply for EU funding in its own right as an 'international partner'
Ability to engage with multinational research programmes	Presents a single European entity able to engage directly with large multinational consortia on behalf of the national Systems Biology Centres (nSBCs)
Establishment and operation of strategic and financial framework, and work programmes	Can provide support for standing bodies tasked with strategy development and financial planning that shares good practice between centres, together with obtaining independent external advice, notably on ethical issues
Effectiveness of collaboration with other European RIs	Provides a single European entity able to formalise strategic and operational links to other RIs
Liability and Intellectual Property administration	CIO is able to establish collaboration agreements with nSBCs
Duration	Sets out period of effectiveness, dates for entry into force, conditions for accession of new members, obligations and conditions for possible termination and consequences

Table 4.1: The ERIC legal document and its advantages

4.2 Legal agreements for individual national Systems Biology Centres

While the nature and mechanisms for coordination of nSBCs would be outlined in the ERIC, direct agreements between ISBE and the nSBC will be required to ensure efficient coordination of services across centres. All nSBCs will be established by entering into a pre-agreed Service Level Agreement (SLA) with ISBE that will define, in a fair and transparent manner, the commissioning of services, resources and other activities that will be offered. The SLAs will formally define those services and resources that are to be offered through ISBE and define the levels of services expected by users, as well as the obligations for the nSBCs in maintaining their availability. An nSBC may be a single institution or a single institution may act in a capacity to represent several other nationally-located institutions responsible for providing aspects of the nSBC services.

4.3 Governance and management

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 (figure 4.1).

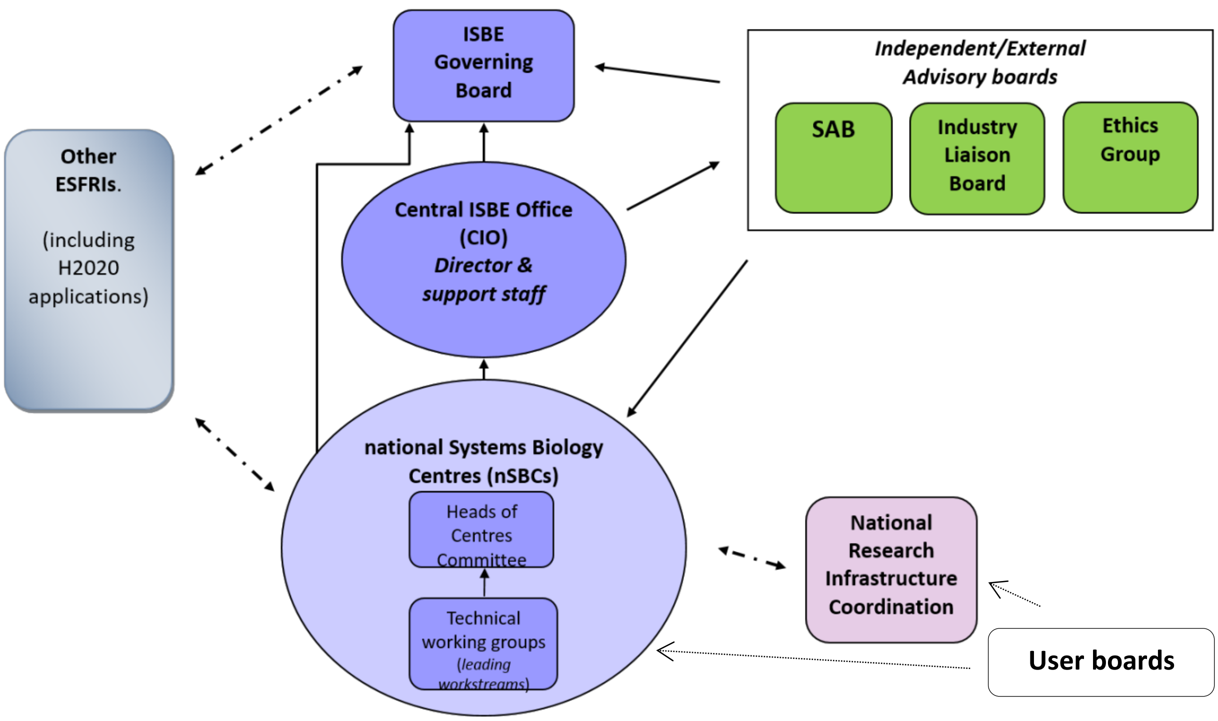


Figure 4.1: Organisational diagram of the main standing bodies of ISBE and key areas of interaction during the legal phase from 2018 onwards

4.3.1 Procedure for identification of Central ISBE Office and nSBCs

The location of the host institution for the CIO for the Legal Phase has yet to be identified. The host country will be identified during the Interim Phase (2015-2018).

The procedure and eligibility criteria for approving further nSBCs will also be developed in the Interim Phase, with evaluation processes set out in the ERIC. While the CIO may be situated at the same institution as an nSBC, there will be clear mechanisms that separated their responsibility and functions to allow independent operation and avoid conflict of interest.

4.3.2 Governing Board

The *Governing Board* will be the central decision making body with high-level oversight, supervising the CIO on behalf of the member states. It will be responsible for ISBE's strategy and budgets, as well as approval of prospective nSBCs. Representatives will be drawn from and nominated by national funding bodies, together with scientific experts identified by the national funder and tasked with representing the interests of their national communities.

4.3.3 Heads of national Systems Biology Centres

The *Heads of Centres Committee* will provide operational coordination across the nSBCs and will be responsible for maintaining effective operations across the nSBCs and developing strategic plans, for agreement by the Governing Board. Members will be the directors of the nSBCs, together with the director of ISBE.

4.3.4 Executive management and technical working groups

The ISBE director is expected to have significant experience coordinating collaborative programmes, notably those with significant elements community outreach and industrial involvement. As head of the CIO, the Director will be appointed by the Governing Board. The Director will be responsible for executing the Governing Board's decisions, and management of the central budget. The CIO will organise the scientific evaluation and monitoring of nSBCs, as well as managing SLAs and the interface with other ESFRIs. The CIO will also coordinate internal communications and outreach aspects on behalf of the centres.

In support of this, cross-centre *Technical Working Groups* will lead the delivery of the specific technical and training work streams. These boards will coordinate the delivery of community-led activities.

4.3.5 External feedback and input – advisory boards

Understanding user needs is crucial to the success of ISBE. ISBE will draw from the widest possible international expertise to gain insight in how best to meet emerging community needs and opportunities across all sectors, combined with ensuring the continued delivery of cutting edge technologies.

ISBE will establish three main advisory panels, described below, giving independent external advice to enable:

- effective and efficient operations
- suitable oversight and monitoring
- independent audit
- prioritisation of ethical considerations
- a flexibly managed portfolio of expanding resources services by adapting activities within nSBCs as well as bringing in new nSBCs, including the amendment and termination of existing activities at nSBCs, and proposals for novel services to address emerging challenges.

Scientific Advisory Board (SAB)

The *Scientific Advisory Board (SAB)* will be the main sources of external advice from academia for both the Governing Board and executive. A key role is SAB's evaluation of nSBC applications against a pre-agreed evaluation process, and their subsequent monitoring to advise the Governing Board on decisions such as to renew or terminate nSBCs.

Industry Liaison Board (ILB)

The *Industry Liaison Board (ILB)* will be the main source for wider coordinated consultation of stakeholders within the commercial sector. Its separate identity from the SAB underlines the importance of addressing industrial interest in working collaboratively with academic systems biology researchers. The SAB also will draw from the ILB membership.

Ethical Board (EB)

The *Ethical Board (EB)* will consider the ethical implications of ISBE's activities such as managing information from plant, animal and human experimentation, together with the related issues of data security and access. It will draw expertise from the nSBCs as well as the SAB and ILB. ISBE will build on links being established within the CORBEL project across ESFRIs for the consideration of legal and ethical issues for data exchange and protection in transnational research collaborations. This will include ensuring appropriate collection and storage of patient samples; regulations on working with genetically modified organisms, and guidelines for accommodation and care of lab animals.

User Boards

ISBE *User Boards* will engage representatives from different user sectors to ensure effective feedback on services and activities, and their involvement in developing novel targeted activities.

4.3.6 Liaison with other research infrastructures

ISBE will work closely with other research infrastructures building on existing activities, such as those currently supported through CORBEL and RItrain (see Appendix 7), to deliver joint activities and avoid redundancy of operations. Representatives of other research infrastructures will also be invited to attend meetings of standing and advisory bodies. Where longer term agreements are needed, ISBE will work with other research infrastructures to develop appropriate Memoranda of Understanding.

5. Finance model for the Legal Phase: 2018 and beyond

This section describes the proposed cost model of the ISBE Legal Phase from 2018 onwards. This model is similar to that implemented by or proposed for other European research infrastructures, including BBMRI, ECRIN and ELIXIR. The proposal is provided as guidance for negotiations with national funding agencies and governments, recognising that it makes certain assumptions that will be subject to ongoing review.

The proposed cost model of ISBE has five main components:

- national Systems Biology Centres (nSBCs)
- the Central ISBE Office (CIO)
- further expansion of ISBE
- services and community activities
- funding through third parties

Full details of these models are provided in Appendix 9, with a summary of the main aspects described below.

5.1 Cost model for the national level: nSBCs

When considering how contributions to ISBE will add value, it is important to understand the overall costs across all the nSBCs. The operational costs of each nSBCs will be covered at the national level, with many of these services and resources often already receiving national support. Further national support in the context of ISBE will enhance national investments and uptake by their growing national user base. ISBE will make national investments more cost-effective by providing access to a broader user and provider base at the European level.

Table 5.1 summarises three potential scenarios presenting a range of services that nSBCs may provide in the first five years of ISBE's Legal Phase, starting 2018. These estimates are based on existing operational and staff costs for research institutions in the UK and the Netherlands and therefore need modification for costs in other European countries. Estimates include staff costs, running costs and overheads.

Table 5.1: three possible scenarios for three possible sizes of nSBC at the start of ISBE's Legal Phase (2018 – 2022)

	Annual operational costs (k€)					Total (5 yrs)
	2018	**2019**	**2020**	**2021**	**2022**	
small nSBC	200	300	400	450	500	**1850**
medium nSBC	350	600	700	800	900	**3350**
large nSBC	600	700	1250	1500	1700	**5750**

5.2 Cost model for European operations: CIO

The CIO, headed by the ISBE director, will coordinate the development and maintenance of the portfolios of services, resources and community activities and takes responsibility for ISBE's finance, governance and outreach. It is estimated that in total six full time equivalent staff (FTEs) will be the optimal to monitor and coordinate overall operations and oversee ISBE strategy development all services and resources. Table 5.2 summarises the expected costs of the CIO for the first three years of ISBE's Legal Phase (2018-2022). A detailed overview of anticipated support staff, expertise and operational costs is presented in Appendix 9.

In practice, levels of national member state contributions should reflect their relative size. To support the CIO, ISBE therefore proposes to use a similar Gross Domestic Product (GDP) based subscription model to that currently employed by other ESFRIs. It is anticipated that additional contributions such as 'in-kind' support of indirect costs may come from the country that hosts the CIO.

5.3 Further expansion of ISBE

ISBE will expand its budget in two ways, i.e. through stepwise increased national budgets of its nSBCs and by acquiring funding at the European level through the CIO.

5.3.1 Stepwise increase of national budgets

Once established, ISBE is designed to grow with expanding user demand, as well as new countries joining over time. The ISBE infrastructure model allows for its subsequent expansion over time, in a manner that can respond to evolving user demands be developing the scope of services and resources it supplies (see tables 5.3 and 5.4).

Table 5.2: expected costs for the Central ISBE Office (assuming 6FTEs)

	Annual operational costs (k€)					**Total**
	2018	**2019**	**2020**	**2021**	**2022**	
CIO	625	675	710	765	785	**3560**

Table 5.3: projected growth in number and value of commitment of the differing sizes of nSBCs in the first five years of the Legal Phase (2018-2022)

Construction of ISBE nSBCs	2018	2019	2020	2021	2022
small nSBCs	**2** (400 €k)	**2** (600 €k)	**4** (1600 €k)	**6** (2700 €k)	**8** (4000 €k)
medium nSBCs	**2** (726 €k)	**3** (1614 €k)	**3** (2160 €k)	**4** (3276 €k)	**5** (4550 €k)
large nSBCs	**1** (600 €k)	**2** (1410 €k)	**3** (37870 €k)	**4** (6180 €k)	**5** (8200 €k)
Total number of nSBCs	**5**	**7**	**10**	**14**	**18**

5.3.2 European level funding

There are increasing opportunities in the Horizon 2020 scheme for developing European research infrastructures. Examples are the recently awarded grants for the CORBEL (harmonizing activities of life sciences research infrastructures) and RItrain (training research infrastructure personnel) programmes in which ISBE participates. Another example is the transnationally funded FAIRDOM programme, which will be integrated in the ISBE activities. Together, this presently represents a European level budget for ISBE of ~€4.6M. The CIO will, together with the nSBCs, make a continuous effort in expanding European funding of ISBE.

5.4 Services and community activities

A detailed cost model for ISBE services for all user types will be developed in conjunction with nSBCs and relevant national funders based more exactly on the specific services a centre will provide.

5.5 Reviewing legal agreements

As ISBE develops in the legal phase, the CIO will develop legal documentation for concluding agreements with nSBCs and collaborative agreements with other ESFRIs for ISBE services. This would also require legal advice, and further iterations of the financial plan will need to properly cost this element.

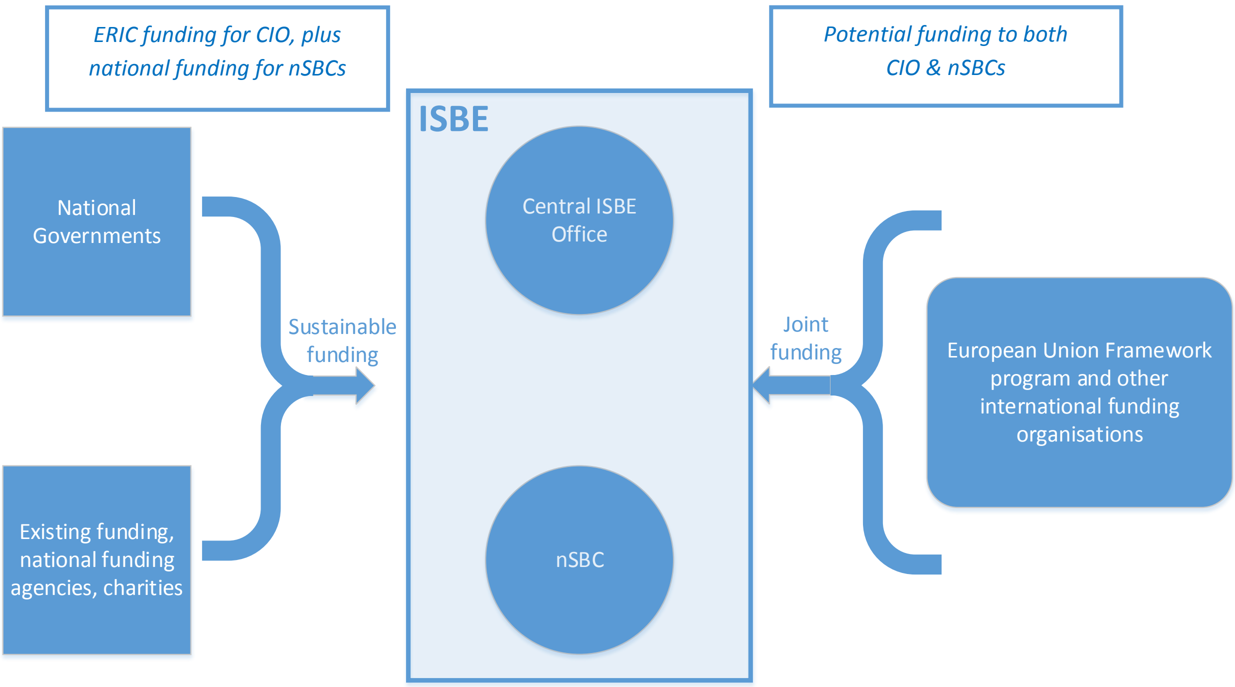


Figure 5.1 ISBE's funding streams

6. The Interim Phase: building the infrastructure

By the end of the ISBE Interim Phase (2015-2018) a fully functional ISBE will be established as a legal identity. This section describes the mechanisms and timeframe of how ISBE will be rolled out up until its formal start in 2018.

The Interim Phase has five major objectives:

- reach formal agreement with national funding organisations about ISBE's legal structure and budget for the Legal Phase
- make available an initial portfolio of services and resources to European scientists: ISBE-light
- establish ISBE's governance and management structure
- establish the European distributed knowledge-based infrastructure of interconnected nSBCs
- harmonise ISBE's operations with those of other research infrastructures in the life sciences, primarily through the CORBEL and RItrain programmes

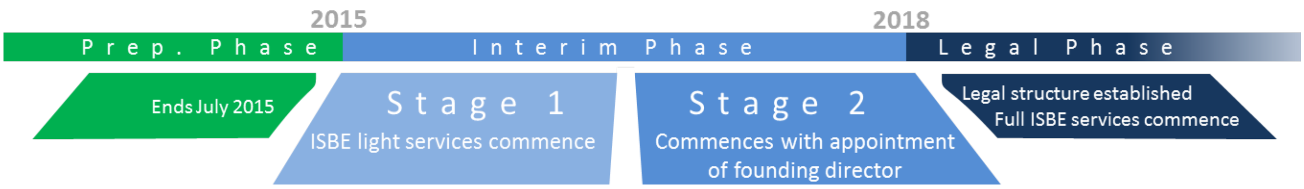


Figure 6.1 Timeline of the Interim Phase

6.1 Two-stage structure of the Interim Phase

The Interim Phase will consist of two distinct stages. Interim Phase Stage 1 will begin in August 2015, immediately after the end of the Preparatory Phase (see figure 6.1). The aim of Stage 1 is to have at least three national funding organisations signing a Memorandum of Understanding (MoU) within the first year of the interim phase. This stage will establish an interim governance and management structure capable of commencing delivery of the 'ISBE-light' operational portfolio. Negotiations with funders will continue to establish commitment for financial support. This should ensure an adequate budget for the construction of ISBE during Interim Phase Stage 2. The start of Stage 2 is marked by the appointment of the founding director, who takes responsibility for building the research infrastructure.

6.2 Interim Phase Stage 1 (2015-2016)

6.2.1 Objectives

The major objectives of Stage 1 are (i) to continue activities on the national and European level, initiated during the Preparatory Phase, and (ii) secure Stage 2 budget, and (iii) start delivering ISBE-light services.

This comprises the following processes:

- establish an interim governance structure
- formally involve at least three national funding organisations on the basis of a MoU
- identify and pursue further European funding opportunities

- negotiate with national funders and key stakeholders to establish the budget for Stage 2
- select a founding director as soon as the Stage 2 budget is secured
- identify the host country for the Central ISBE Office (CIO) and the coordinating Systems Biology Centre (cSBC)
- start the procedure to identify and select nSBCs that will be formally established in Stage 2
- commence delivery of a portfolio of web-based services and resources called 'ISBE-light'
- operate ISBE-branded activities through the CORBEL, RItrain H2020 projects and FAIRDOM, with continuing partnership with other ESFRI research infrastructures and national infrastructural programmes

6.2.2 Stage 1 management

The management at the outset of the Interim Phase will reflect the commencement of the operations of 'ISBE-light' web-based services and resources with the formation of the **ISBE Interim Committee (IC)** body

The ISBE Interim Committee (IC) will (i) ensure inclusive negotiations with both national funders and key stakeholders that are required to establish the budget for Stage 2, (ii) select the founding director, and (iii) start the procedure to identify and select nSBCs that will be formally established in Stage 2. The IC will consist of all Management Team and Intergovernmental Working Group members and draw on members of the Preparatory Phase Steering Committee who have expressed their interest in further engagement.

This IC will identify further European funding opportunities for ISBE, as well as coordinate strategic interactions with other ESFRIs. In addition, steps will be taken to form user community forums and an Industry Liaison Board.

The Interim Committee and the Management Team will be chaired by a full time Interim Coordinator, who will be responsible for the development of ISBE during Stage 1.

The Management Team (MT) is a sub-committee of the IC, which will consist of those involved in the delivery of ISBE-light's portfolio of services, and coordination across ISBE-branded activities through the CORBEL and RItrain H2020 projects and FAIRDOM.

The Intergovernmental Working Group (IWG) is another sub-committee of the IC, which will draw together representatives of national funding organisations who have expressed an interest in supporting ISBE.

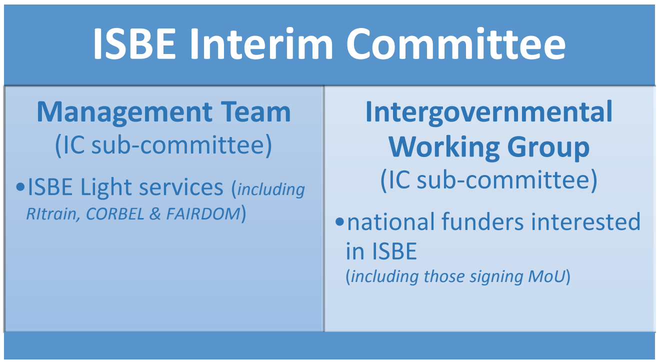


Figure 6.2 Relationship of the three initial governance bodies at the start of Stage 1

6.2.3 Stage 1 budget

The costs of Stage 1 are estimated to be minimally € 250k for 12 months (see Table 6.1and Appendix 9, Table 1). Contributions are expected via financial and in-kind contributions through ISBE stakeholders and national funders.

6.2.4 Securing the budget for Interim Phase Stage 2

Negotiations with national funding agencies should result in the signing of a MoU and associated financial support, or another type of agreement, in which they declare interest in participating in building ISBE and contribute to a budget for Stage 2.

6.2.5 Selection process of nSBCs and the host country for the Central European Office (CIO)

The selection of nSBCs in Interim Phase Stage 2 requires an open and transparent procedure, which will be agreed with national funding organisations and research communities. The same holds for the host country of the CIO.

6.2.6 ISBE-light services

To expand awareness of ISBE in the scientific communities and maintain the momentum and interest developed during the Preparatory Phase, ISBE will offer in Stage 1 and Stage 2 a portfolio of four types of web-based services and resources.

Most ISBE-light services will be available free of charge to users. They will be operated and supervised by systems biology centres of excellence that have an interest in continued involvement in ISBE. ISBE-light will commence as soon as possible after the start of Interim Phase Stage 1. Services will continue in Stage 2, forming a solid basis for a complete portfolio in ISBE's Legal Phase.

ISBE-light will offer three types of services:

a. Modelling services and resources

ISBE's modelling services aim to lower the threshold for biologists to incorporate computational modelling in their research. In this early stage of ISBE development, clients will be directed to a ready-to-use web-based modelling platform, linked to relevant model resources. Target communities for these services are researchers in academia and industry with varying levels of training in mathematics and statistics and in computer and information science.

For the initial ISBE-light services, ISBE will focus first on modelling frameworks that have (i) a large potential user base, and (ii) standardised ways of asking research questions. By doing so, one can span a large space of questions with a well-defined set of query parameters. In addition, users can pose a wide range of questions by filling in a form and uploading their own data or models, similar to what is already common place in bioinformatics.

b. Access to tools, standards and model-compliant data and maps

For ISBE-light, ISBE will engage with the existing FAIRDOM initiative[9], a joint action of the ERANet ERASys*App* with ISBE. FAIRDOM aims to establish a data and model management service facility for systems biology. This is intended to operate under the ISBE-light umbrella. ISBE-light services will aim for web-based access to tools, archives, model-compliant data and maps which will focus on:

- making software available with user guides that support and improve research asset management from instrument to publication
- supporting the establishment of research asset management planning for grants
- developing an online 'knowledge hub' which
  - identifies and characterises different tools and standards that can be used within projects
  - identifies public repositories and characterises them according to the type of data that they contain, and what standards are used in conjunction with the repository
  - identifies and categorises minimum information models for different research-asset types
  - providies data-templates that are semantically capable for a range of different data-assay types

c. Education and training

Services will aim at dissemination of information on training and education in systems biology and will include:

[9] http://fair-dom.org/

- dissemination of information on training and postgraduate education in systems biology (in collaboration with ERASysApp), through the ISBE community portal
- dissemination and implementation of a core curriculum through the ISBE website, publication, Erasmus+ and low cost networking meetings
- dissemination of courses (summer and winter schools, workshops, advanced training) that ISBE partners are involved in

d. Liaise with scientific journals

ISBE is currently exploring a synergistic role between ISBE and scientific journals on

- ISBE being a rich source of multidisciplinary expertise in systems biology, spanning a broad range of biological fields, disciplines and skills
- ISBE taking initiatives in developing and disseminating community standards and standard operation procedures (SOPs) in the systems biology field

6.2.7 Embedding of ISBE in the European research landscape during the Interim Phase

In Interim Phase Stage 1 ISBE will be embedded in European-level systems biology initiatives and national systems biology communities and it will actively contribute to the harmonisation of ESFRI research infrastructures in the life sciences field. Figure 6.3 schematically maps the various interactions and how they relate to interim governance structure

6.3 Interim Phase Stage 2 (2016-2018)

Stage 2 will commence with the appointment of the founding director and will end with the establishment of ISBE as a legal entity. The major responsibility of the founding director is therefore to develop ISBE's legal identity and operational processes.

6.3.1 Objectives

The objective of Stage 2 is to develop a legally-based and fully functional ISBE. This includes the following:

- establish the Central ISBE office (CIO), the coordinating SBC (cSBC) and ISBE's governance structure
- continue empowering ISBE-light and organise the transition of ISBE-light towards a fully operational ISBE by developing a broad portfolio of services, resources, community activities and training and education programmes together with the nSBCs and in dialogue with user communities
- establish a collaborative federation of nSBCs that will be fully operational in the Legal Phase
- negotiate the operational budget of ISBE Legal Phase
- develop the legal basis for ISBE, preferentially an ERIC
- continue developing partnerships with other European research infrastructures, primarily through the CORBEL and RItrain projects

6.3.2 Stage 2 management and budget

The management structure from Stage 1 for the ISBE Interim Committee and the ISBE-light Management Team will be modified at the start of Stage 2 as part of the stepwise migration of the Interim Phase governance structure towards that described for the Legal Phase (in section 4).

Stage 2 requires a budget of approximately € 1.6 M for two years (2016-2018; see Table 6.1 and Appendix 9, Table II), comprising:

- salary of the founding director and CIO staff
- operation costs of the Central ISBE Office (CIO)
- activities to develop and coordinate the European matrix of collaborating nSBCs and ISBE's portfolio of services and resources

ISBE will negotiate with national funding agencies that are MoU signatories, as well as other national funders, to agree on conditions for sustainable funding of ISBE in its Legal Phase. ISBE will seek their contribution to the central budget to support the CIO and coordinating and community activities. In parallel, agreement should be reached about national funding of the individual nSBCs and the coordinating SBC.

6.3.3 Selection of nSBCs

The open and transparent nomination and selection process for nSBCs will be executed along the lines agreed on in Stage 1. Provisions will be made to give users in European countries without an nSBC access to ISBE's resources and services.

6.3.4 Central ISBE office (CIO), coordinating SBC and governance structure

Negotiations in Stage 1 will identify the host country of the interim CIO. The founding director will head the interim CIO and establish the governance structure for the legal phase (see Section 4 for further details).

6.3.5 Adapting the Governance structure towards the legal phase

Modification of the governance structure for Stage 2 will be fully defined in Stage 1. At present it is anticipated that the IC sub-committees will be fully integrated into the Interim Committee, in anticipation of migration the full ESFRI bodies in the Legal Phase. Finally groups expecting to form nSBCs will be invited to form a "Candidate nSBC working group" (anticipated to grow into the legal phase 'Heads of Centres Committee').

6.3.6 Central ISBE office (CIO), coordinating SBC and governance structure

Negotiations in Stage 1 will identify the host country of the interim CIO. The founding director will head the interim CIO and establish the governance structure for the legal phase (see Section 4 for further details).

6.3.7 Legal basis for ISBE

An important aim of Stage 2 is to agree on the legal status of ISBE. The current preference is an ERIC. However, we expect that the development of the ISBE structure for the legal phase will continue and therefore the suitability of ERIC, including the potential for a transitional legal structure to facilitate to foundation of ISBE will be kept under dynamic review. Decisions will be made based on discussions with national funding organisations and governments. Establishing ISBE's legal status marks the transition of the Interim Phase to the Legal Phase.

6.3.8 Portfolio of services, resources, community activities and training and education programmes

Together with the nSBCs and relevant research communities, ISBE will develop and establish its portfolio of services, resources and community activities within the framework outlined in this Business Plan. This will build on the activities of ISBE-light that started in Stage 1. The portfolio will grow steadily in Stage 2 and in the subsequent Legal Phase, constantly adapting to the developing needs of ISBE's users.

6.3.9 Engagement with the user-base in academia, hospitals/clinics and industry

A major task of the founding director will be to develop relationships with different user communities, including academia, hospitals/clinics and industry/SMEs. This will build on the expertise in translational research for those centres providing ISBE activities to enhance translation and create a coherence forward look for systems approaches from a joint academia-industry perspective. A vital part of this will involve establishing user committees and advisory boards.

6.4 Summary of costs of the Interim Phase and current funding

2020 CORBEL and €185k for the RItrain project consortia that aim at harmonisation and collaboration with other ESFRI life sciences research infrastructures (see Appendix 7). In addition the FAIRDOM project that intends to interact with ISBE under the ISBE-light umbrella of activities has received €2.7M. ISBE will continue to build on the success of the recent CORBEL and RItrain awards, by seeking additional funding through the Horizon 2020 programme, as well as from other parties.

ISBE Interim phase		
	FTEs	Cost (k€)
Interim phase stage 1 (2015 - 2016)	1	250
Interim phase stage 2 (2016 - 2018)	4	1500
Total (k€)		**1650**

Table 6.1 Summary expected costs for ISBEs Interim phase

6.5 Coordination with ELIXIR on ensuring synergies to address community needs

In developing its portfolio ISBE recognises the key links it has already forged with ELIXIR as part of developing the CORBEL and RItrain proposals. In addition the FAIRDOM project addresses the overlapping data standards requirement across both Research Infrastructures. ISBE and ELIXIR will continue to work closely in ensuring a common strategic framework for delivery of services and resources that avoids duplication and redundancy of provision. As a first stage both RIs are committed to formalising their relationship and further defining their interface, be developing a common strategic document on joint working early in 2016.

6.6. Key Performance Indicators for the ISBE Interim Phase (2015-2018)

ISBE has identified three areas where it will monitor and review of its activities until the end of the Interim Phase to determine if the project has been successful. Analysis of the 11 key performance indicators (KPIs) will show what aspects of the research infrastructure need special attention at the beginning of the Legal Phase. The areas are summarised in Figure 6.4. which lists 11 KPIs that allow an objective and quantitative assessment of ISBE's activities. Their assessment is explained in table 6.2. The KPIs create a clear compass for the process of developing ISBE during the Interim Phase. The first integral evaluation is foreseen at the end of the Interim Phase and should help to decide whether ISBE is ready to enter its Legal Phase in 2018. In a later stage of ISBE's development these KPIs can be adapted for assessment of ISBE's performance during its Legal Phase.

As a key part of developing a robust risk mitigation strategy, ISBE will make full use of independent advice from its advisory boards to draw in industry and other major stakeholders, together with engaging other ESFRIs to understand and implement best practice for auditing outputs developed across the ESFRI family.

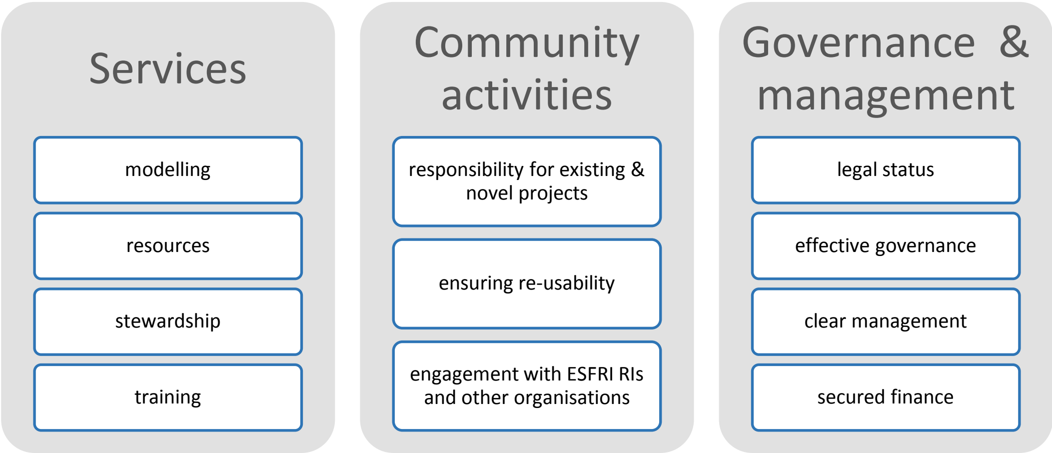


Figure 6.4: Key performance indicators are grouped according to the 3 main pillars of ISBE operations.

Table 6.2: KPIs to be assessed at the end of the Interim Phase

Category	Component	Quantity/quality measured	Assessment criteria
services	**1. modelling services**	number of users with positive user satisfaction and submitted publication acknowledging ISBE essential support	number of support requests and user evaluation forms)
	2. resources	number of users and user satisfaction with acknowledgement in publications	through evaluation forms
	3. stewardship	number of users and user satisfaction with acknowledgement in publications of help in stewardship	through user evaluation forms
	4. teaching and training	number of users of training courses and user satisfaction number of hits on education and training database uptake of core curriculum	through user evaluation forms through website analytics report based on meetings/survey

Category	Component	Quantity/quality measured	Assessment criteria(date/number/success threshold)
community activities	**5. assume responsibility for ongoing and new community activities**	impact of collaboration with communities (e.g. VPH, ERASysApp, CASyM, repositories, ELIXIR, journals)	reports of evaluation meetings with communities and report
	6. make results re-usable	contribution to FAIRDOM programme	report summarising activities and achievements
	7. engagement with other research infrastructures	activities in context of CORBEL and RItrain	reports summarising activities and achievements
governance and management	**8. legal structure**	establishment of a legal identity (e.g. ERIC)	5 or more countries sign
	9. management and coordination	demonstrate effective functioning of CIO and coordinating SBC	evaluations of Supervisory Board and Board of heads of nSBC
	10. matrix of cooperating interim nSBCs	demonstrate synergistic and coordinated matrix of nSBCs	overview of coordinated activities and collaborative actions in matrix by CIO
	11. governance	demonstrate an effective governance structure; show effective exchange with the different Advisory Boards (SAB, Industry Liaison Board and Ethics Board); show satisfaction of nSBCs and funders with ISBE	annual reports of Supervisory Board; annual reports of Supervisory Board and Board of heads of interim nSBC; annual reports by individual boards

6.7. Measuring Wider Impact

In addition to understanding and measuring the direct outputs of ISBE and its services, it is also important to develop appropriate metrics to understand how we have supported the delivery of the research of those communities using ISBE. During the Interim Phase ISBE will consider the needs for longer term monitoring of services and their users, ISBE plans to demonstrate to its funders how its activities and services:

- have influenced the development of a highly skilled work force
- have fostered the usage of data and model standards, and appropriate tools
- have aided in development of collaborations of provider and users at scientific institutions in Europe and worldwide
- have encouraged closer collaboration between academia, the industry to the benefit of the EU bioeconomy.
- have enhanced the application and integration of systems approaches in the biosciences by acting as a 'knowledge broker' of choice
- have facilitated the rapid uptake of novel and innovative technologies across all biomedical sectors

Appendices

APPENDICES

1. Showcases
2. ISBE Preparatory Phase partners
3. Overview of significant previous and current major European coordinated support programmes for systems biology
4. Audit on Systems Biology service provision in Europe
5. Survey of life scientists in academia and hospitals
6. Survey of industrial needs in systems biology
7. Joint activities with other ESFRIs
8. Examples of existing national systems biology infrastructures
9. Details of the ISBE financial model
10. Abbreviations

appendix 1 Showcases

The following systems biology showcases are an extract from Success Stories in Systems Biology (2015) and are available from the ISBE website, www.isbe.eu.

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

Further Information

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

BE-Basic Foundation
www.be-basic.org

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

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

Further Information

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

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

appendix 2 ISBE Preparatory Phase partners

Imperial College London

BBSRC 20 Years of Pioneering Great British Bioscience

MANCHESTER 1824 The University of Manchester

Universiteit van Amsterdam

UCD Dublin

MDC Max-Delbrück-Centrum für Molekulare Medizin Berlin-Buch in der Helmholtz-Gemeinschaft e.V.

Turun yliopisto University of Turku
Bioteknikan keskus Bioteknikcentrum Centre for Biotechnology

dkfz. German Cancer Research Center in the Helmholtz Association

Universität Heidelberg Zukunft seit 1386 BioQuant

Norwegian University of Life Sciences

C4Sys

CRG Centre for Genomic Regulation

NIB National Institute of Biology

Univerza v Ljubljani

EMBL-EBI

University of Gothenburg

Wageningen UR For quality of life

Heidelberg Institute for Theoretical Studies HITS

VU University Amsterdam

Chalmers

NWO

Republika Slovenija Ministrstvo za izobraževanje, znanost in šport

BRFAA Biomedical Research Foundation Academy of Athens

ISBE ASSOCIATE PARTNERS

appendix 3 Overview of significant previous and current major European coordinated support programmes for systems biology

Start Date: 2006

Number of Partner Countries: 13 (plus 2 affiliates)

The ERASysBio partnership began with SysMO (Systems Biology of Microorganisms). A transnational funding initiative to support the convergence of life sciences with information technology & systems science. The ERASysBio Coordination Action came from a Specific Support Action (SSA) that had already laid the foundations of this new network. It brought together funding agencies from 13 countries including Israel and Russia, with affiliated partners, Luxembourg and Switzerland. It aimed to build not only on national programmes in systems biology but also upon several European efforts springing from EUREKA, the European Science Foundation, the European Molecular Biology Laboratory and several other EU-supported projects.

The ERASysBio+ partner countries are: AT, DE, ES, FI, FR, IL, LU, NL, SI and the UK. Non-partner countries with groups participating in the transnational research projects are: IT, IS, US and ZA.

Total amount: €69.7M	**Groups involved:**
◦ €28M for SysMO1 and €17.7M for SysMO2	◦ 11 transnational research projects involving 91 groups in SysMO
◦ €24M- €18.5M from the partner countries and €5.5M through the ERA-NET Plus scheme of the EC.	◦ 16 transnational consortia from 14 countries in ERASysBio+.

Start Date: 2013

Number of Partner Coutries: 13

This initiative was launched to coordinate and enhance research opportunities in the emerging scientific field of Systems Biology. A total of 16 funding agencies/partners cooperate within the novel ERA-Net for Applied Systems Biology ERASysAPP. This ERA-Net predominantly aims at funding transnational Applied Systems Biology research, encouraging institutions and scientists from different countries, EU Member States as well as others, to network and share existing resources.

1st call - November 2013 "Transforming Systems Biology Knowledge into Applications"	**2nd call - October 2014**
Its first joint transnational call on focused mainly on application-oriented research approaches to tackle major scientific and societal challenges. 7 that started in autumn 2014awards were funded, comprising more than 46 research groups from 10 countries,.	The second joint call on research teams from ten participating countries to set up international research consortia and to submit joint project proposals, and aim to encourage scientists to collaborate and share resources beyond national boundaries.

Start Date: 2012

Number of Partner Coutries: 11

The Coordinating Action Systems Medicine (CASyM) is a multidisciplinary European consortium that joined forces to develop an implementation strategy (road map) for Systems Medicine. It has 22 partners from 11 countries, and is funded under the FP7 program with €2.9 M for 4 years (2012-2016).

Duration: 4 years (2012-2016) The CASyM road map is driven by clinical needs: It aims to identify areas where a systems approach will address clinical questions and solve clinical problems.

Goals

- **Developing a strategic European wide road map for Systems Medicine**
- **Fostering integration, networking and communication among relevant communities**
- **Building a sustainable Systems Medicine community**

Start Date: 2015

Number of Partner Coutries: 11

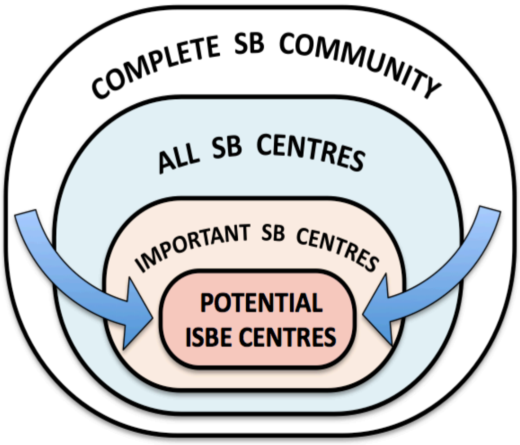
The ERA-Net ERACoSysMed "Collaboration on systems medicine funding to promote the implementation of systems biology approaches in clinical research and medical practice" is the first ERA-Net on Systems Medicine under the EU framework programme Horizon2020. The 14 funding bodies of ERACoSysMed joined forces to support transnational research consortia that demonstrate the feasibility and socio-economic benefits of systems medicine in clinical practice. In the first, co-funded call national financial contributions will be complemented with an EU contribution (co-fund model).

First ERACoSysMed Joint Transnational Call – opened 16 February 2015

The first Call with EU co-funding aims at the development of Proof of Concept and success stories (demonstrator projects) in Systems Medicine to improve understanding and show the utility of this approach in a clinical setting. Projects were requested that specifically demonstrate the translation of Systems Biology approaches into medical research and practice (Proof of Concept).

appendix 4 Audit on Systems Biology service provision in Europe

Goal: obtain evidence of the current systems biology service provision in Europe and of the interests of potential ISBE providers



The Audit addresses the current and future SB service provision in Europe both qualitatively, by discussing with the experts their interest and wants in providing services to / using from a pan-European infrastructure; and quantitatively, by recording data about individual resources offered by the SB centres, its actual use, funding, and sustainability.

NB ISBE Audit on systems biology provision is a fact-finding mission, and is not related to the selection process of the centres that will be part of the operational ISBE. An in-depth and formal process of selecting ISBE centres is still to be undertaken.

Protocol: to delimit the current and future provision of systems biology services and resources in Europe, ISBE has performed a 3-step Auditing exercise, which culminated in direct consultation of several systems biology centres across Europe.

I. **Analysis on systems biology research landscape in Europe** An extensive exploration was done to find all institutions performing systems biology research in Europe (Step1),
II. **Identification of Key national experts**: - Identification at the national level the main systems biology actors (Step 2, by curation of listed information by local experts in each of the ISBE participating countries); and
III. **Consultation Phase** - Personally contacting a country-by-country list of systems biology centres and recognized researchers that have been (Step 3).

This Audit has been coordinated by Centre for Genomic Regulation, Barcelona (James Sharpe and Joaquim Calbó), under ISBE preparatory phase Work Package 5 (community building and synergies), and performed with the help of several members of the ISBE team.

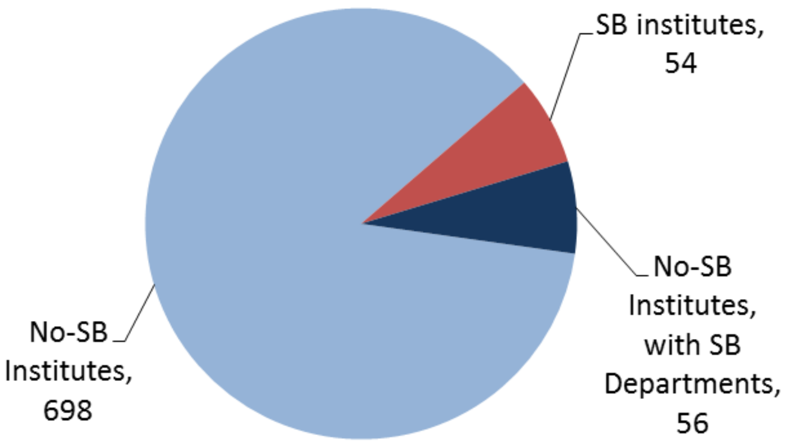
STEP 1 - ANALYSIS ON SYSTEMS BIOLOGY RESEARCH LANDSCAPE IN EUROPE

Data collection: web search + literature search + ISBE survey.

Main focus: Institution level.

Outcome: Broad estimation of community size and distribution across Europe. The figures include institutes and researchers who contributed to SB papers, even if they may not consider themselves as part of the SB community.

Category	Number
Institutes:	808
Nr. of countries:	27
Nr. of researchers:	>7000
o Nr. of researchers with affiliation:	1455
Nr. of papers:	1620
Nr. of group leaders (web search):	866



Main findings:

- *Similar country-distribution found for institutions and for researchers (not shown)*
- *Countries with larger numbers of centres and researchers contributing to SB are UK and Germany, followed by Spain, The Netherlands, France and Italy, and with smaller figures by Switzerland, Belgium, Austria and Sweden.*
- *Different countries use the phrase "Systems Biology" in different ways, and some countries do not use it much. This seems to be related to past national funding schemes.*
- *Most Systems Biology research is carried out in institutes or departments which do not explicitly focus on SB*

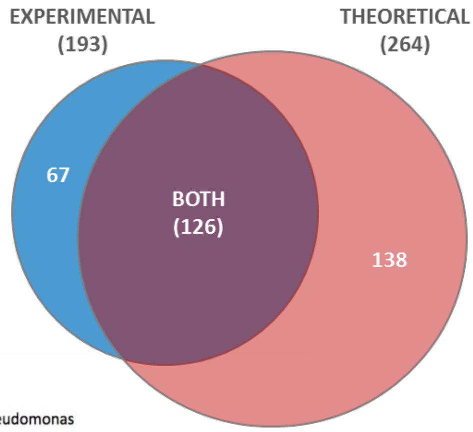
STEP 2- IDENTIFICATION OF KEY NATIONAL EXPERTS

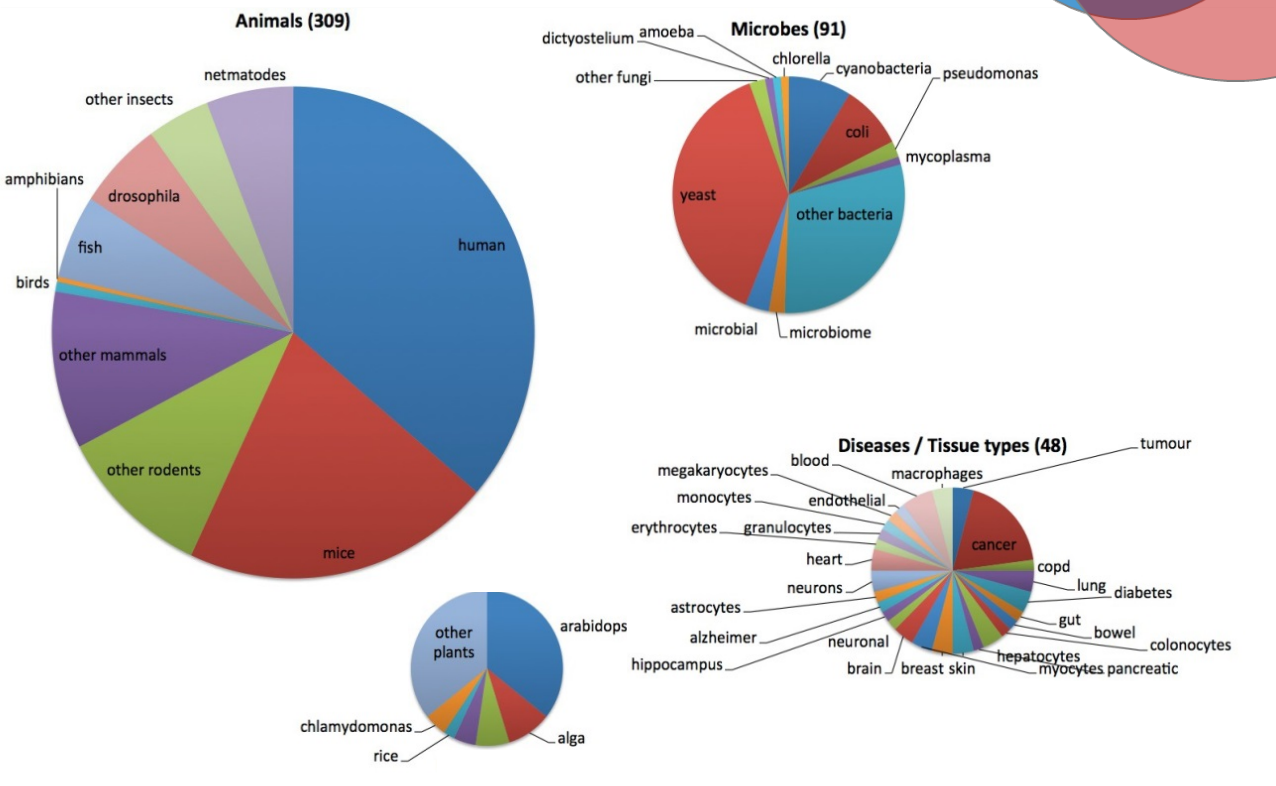
Data collection: Analysis to identify and describe, country-by-country, the most relevant centres and systems biologists, from data generated in Step 1. Experts within ISBE identified the centres with higher SB activity, and provided in detail information about the SB scientists in those centres.

Focus: Researchers and institutions

Outcome: Information about expertise, approaches, and frequency of the different topics. The results reflect the perception of the systems biology community as a whole.

Category	***Number***
Institutes:	*87*
Countries:	*11*
Nr. of researchers:	*~500*





Main findings:

- *Most of the identified researchers use a purely theoretical (138) or mixed (126) approach, while only the 15% (67) are purely experimentalists.*
- *The topics of interest, model systems and experimental approaches cover a very broad field (animals, plants, microbes), although research on humans, and in particular on human health is relatively prevalent.*

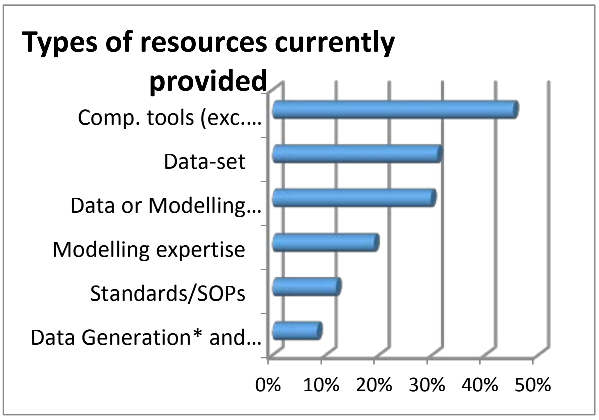
Step 3- Consultation Phase

Data collection: A series of semi-structured interviews with about 50 leading researchers from relevant SB centres in Europe, performed by ISBE participants.

Focus: Potential interest and motivation of centres to be involved in the future development of ISBE, both as providers or users of SB services.

Outcome: Quantitative data on the type or resources offered and its current funding.

Category	Number
Researchers interviewed:	49
Institutions(*see list below*):	48
Countries:	9
Resources identified:	82



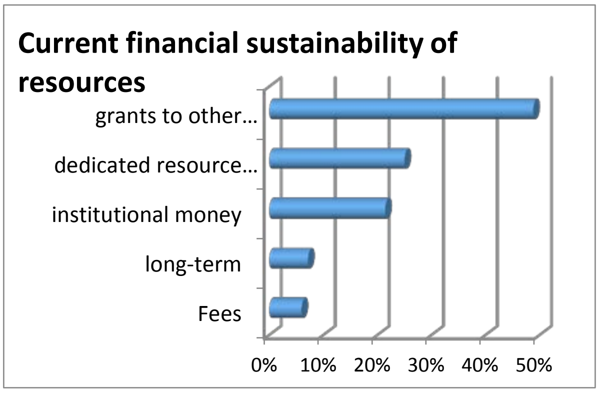
MOTIVATIONS TO BE INVOLVED WITH ISBE:

as Providers

- Access to expertise
- Networking
- Make tools available
- More Users
- Develop Standards
- Sustainability
- Visibility

as Users

- Access to modelling expertise
- Access to curated datasets
- Standards and stewardship
- Access to tools
- Access to models
- Data management
- Access to training (underestimated)
- Data generation



Main findings:

- *Majority of interviewees (49) were positive about contributing to ISBE (~90%)*
- *Very few publically-used online resources have stable funding.*
- *Motivation to contribute included:*
    - *a) Wider visibility and sustainability for the resources they provide.*
    - *b) A network to help find a wider range of suitable scientific collaborators.*
- *Interests in using ISBE are: access to modelling expertise, tools and data-sets.*
- *Current resources mostly provide: computational tools, data-sets and management.*

Institutions included in Step 3:

Country	Institution
Czech Republic	Institute of Chemistry and Biochemistry, University of South Bohemia; Department of Experimental Biology at Masaryk University; Laboratory of Bioinformatics at the Institute of Microbiology; Global Change Research Center-Czechglobe.
Germany	Max Delbrück Center for Molecular Medicine; Institute of Toxicology and Genetics (ITG), Karlsruhe institute of Technology (KIT), European Zebrafish Resource Centre; Department Computational Molecular Biology of the Max-Planck- Institute for Molecular Genetics; Integrative Research Institute for the Life Sciences (IRI) Institute for Theoretical Biology (ITB); Systems Biology of Signal Transduction Division at the German Cancer Research Center (DKFZ); University of Heidelberg; Berlin Institute for Medical Systems Biology (BIMSB); HITS GmbH; Institute of Computational Biology (ICB), Helmholtz Zentrum München; Department of Mathematics at TU Munich; Center for Systems Biology Dresden, a joint project of MPI-CBG and MPI-PKS in collaboration with the TU Dresden; Department for Plant Systems Biology, Center of Life and Food Sciences Weihenstephan TU Munich; BioQuant Center Heidelber (Institute of Applied Mathematics Heidelberg, Center for Modeling and Simulation in the Biosciences (BIOMS), Institute for Theoretical Physics).
Ireland	Systems Biology Ireland, University College Dublin; Centre for Systems Medicine, Royal College of Surgeons Ireland
The Netherlands	Department of Bioinformatics, BIGCAT; Maastricht Centre for Systems Biology (MaCSBio); Amsterdam Data Science – Life Science Node; CSBB – Centre for Systems Biology and Bioenergetics; CWI – Centrum Wiskunde & Informatica; TUE-CBIO – Computational Biology Group; CMSB – Centre for Medical Systems Biology.
Norway	Department of Biotechnology, Norwegian University of Science and Technology (NTNU); Department of Animal and Aquacultural Sciences (IHA), Norwegian University of Life Sciences (NMBU)
Slovenia	Department of Biotechnology and Systems biology, National Institute of Biology; Department of Knowledge Technologies, Josef Stefan Insitute; Institute of Physiology, Faculty of Medicine, University of Maribor; Centre for Functional Genomics and Biochips, Faculty of Medicine, University of Ljubljana; Faculty of Computer and Information Science, University of Ljubljana.
Spain	IRB Lleida/Lleida University; IRB Barcelona; Centre for Genomic Regulation (CRG); Department of Molecular Biology and Biochemistry, University of Malaga
Sweden	The Linköping Centre for Systems Biology, Biomedical Engineering, Linköping University; Department of Biology and Biological Engineering, and Department of Mathematical Sciences, Chalmers University of Technology; University of Gothenburg
United Kingdom	Centre for Integrative Systems Biology and Bioinfomatics (CISBIO), Imperial College London; University of Edinburgh; EMBL-EBI; Babraham Institute; Centre for Plant Integrative Biology; Centre for Integrated Systems Biology of Ageing & Nutrition (CISBAN); INSIGNEO; Oxford Institute for Integrative Systems Biology

Appendix 5 Survey of life scientists in academia and hospitals

Report on ISBE telephone survey conducted with senior level academic scientists and medical researchers

- ***Identifying systems biology requirements/needs of senior level academic and medical researchers***
- ***Raising awareness about ISBE***

Objective

The aim of the telephone survey was to:

1. Map how scientists from academia and clinical research are implementing systems biology approaches in their work
2. Identify challenges faced by these researchers and opportunities for ISBE
3. Raise awareness about the new concept of an European infrastructure on systems biology to the interviewees

The outcome of the survey is being used to align and tailor ISBE's portfolio of services and resources to the most important needs of researchers.

Method

Structured and scripted telephone interview of 19 senior academic and clinical scientists (principle Investigator, department Head, director) in 10 countries. Their scientific interests were mostly in health, pharma and plant sciences. They were not involved in any way in the development of ISBE. The survey was carried out by Instinctif Partners, UK (http://instinctif.com/).

Overall findings

1. The majority of interviewees were interested to hear more about ISBE and recognised its importance to systems biology research in Europe.
2. Generation of standardised data that can be integrated into computer models was the ISBE offering cited as being most important to the interviewees. This was then followed equally by both basic, advanced or user tailored teaching in systems biology as well as access to existing computer models, tools and model relevant data followed with equal importance. This was also reflected and correlated with the challenges that many of the interviewees said they experienced with their current systems biology approaches.
3. The interviewees were highly supportive of ISBE as shown by the majority expressing a willingness to share their data and models, subject to IP and publication. Additionally, 72% of interviewees were willing to participate in the ISBE User Advisory Board which would provide advice and feedback to ISBE.

Specific findings

4. Almost all interviewees were involved in research in which computational modelling was important.
5. 12/19 had heard about ISBE. Awareness of ELIXIR was also 12/19. For other life sciences ESFRI research infrastructures it was significantly less.
6. Interviewees showed a strong need for (i) standardised and integratable data, (ii) basic and advances teaching and training in system biology, (iii) access to curated models and model-compliant data and (iv) advise and support about computational models.
7. 14/19 interviewees are interested in becoming engaged with ISBE as early users and/or becoming member of a Users Advisory Board.

Appendix 6 Survey of industrial needs in systems biology

- ***Identifying systems biology requirements/needs of industry including small and medium enterprises (SMEs)***
- ***Develop portfolio of services to meet industrial needs***

Objective

The aim of the survey was to:

1. Map how scientists from a range of industrial sectors, including health, agriculture and ICT, in a variety of European countries are implementing systems biology approaches in their work
2. Identify challenges faced by these sectors and areas that ISBE can address through its services
3. Raise awareness about the new concept of an European infrastructure on systems biology to the interviewees

The outcome of the survey is being used to align and tailor ISBE's portfolio of services and resources to the needs of industry.

Methodology

Structured and scripted telephone interview of 40 questions with senior representatives of 17 companies involved in the area of systems biology from 7 countries. Their areas of interest included health, pharma, biotechnology, bioinformatics, agriculture and ICT. Results have been validated with the interviewees and at an ISBE industry engagement event in Brussels in June 2015. The survey was carried out by ISC Intelligence, Belgium (www.iscintelligence.com). A further survey on data management and intellectual property was carried out to further elucidate areas in which ISBE can be of benefit to industry, including * interviews with **.

Findings

1. 96% of interviewees applied computational and predictive modelling in their organisations and 70% stated that systems biology was critical to the future of their company.
2. Collaboration is central to systems biology: 88% of organisations collaborate with academia or research organisation and 56% collaborate with companies in other industries, and SMEs in particular stated that mechanisms to access collaborators in academia would be very welcome.
3. Lack of knowledge of existing resources and concerns about proprietary research were identified as primary barriers to research by those surveyed, with these two areas of specific areas of concern for SMEs.
4. Interviewees identified the following as key services for ISBE (i) standardize and ensure interoperability of data (74%); (ii) access to systems biology resources including tools, data, maps, models and standards (59%); (iii) stewardship and curation of model-compliant data and models making results re-usable (46%); and (iv) modelling of biological systems based on integration of diverse data sets (41%).
5. The majority of those surveyed (91%) stated that ISBE services would act as a research accelerant for their company, while 63% identified the proposed provision of bespoke industry training would be of benefit to them while 42% cited the potential to improve networks of collaborators as a major draw.
6. ISBE could provide some form of regulatory advice regarding IPR to its clients specifically to SMEs as this is currently lacking. Building on the best practice of other research infrastructures, primarily EATRIS, and the recommendation of industry representatives, it is suggested that intellectual property rights should be managed on a case by case basis rather than a ‘one size fits all’ policy.

appendix 7 Joint activities with other ESFRIs

A7.1 CORBEL (2015 – 2019)

CORBEL (COordinated Research Infrastructures Building Enduring Life-science Services) is a 4 year project in response to the Horizon 2020 (H2020) INFRADEV-4 call. It will start in Fall 2015 and aims to enhance the integration and harmonization of actions between all 13 European biomedical research infrastructures.

The main goal of CORBEL is to establish a collaborative framework of shared services between the ESFRI Biological and Medical research infrastructures that transforms the efficiency, productivity and impacts of biomedical research and its translational into medicine in the EU (and beyond). This will be achieved by delivering the following objectives:

- forge effective partnerships with user communities
- develop unique solutions to users' needs
- implement a portfolio of generic, shared services that facilitate user access to data, samples and instrumentation through common access policies and shared resource portal

CORBEL's budget is € 14.8 M (2015-2019) of which € 1,5 M is spend through ISBE partners.

A7.2 RItrain (2015 – 2019)

The goal of Horizon 2020 RItrain (Research Infrastructures Training Programme) is to identify the competency requirements for the professional management of European research infrastructures (RI) and design a training programme to fulfil these requirements. Its highest priority is those professionals who are already working in research infrastructures, including directors, project managers, heads of HR, legal representatives and communications experts. However, by designing a flexible, modular programme, the project will also be able to provide a new qualification aimed at *future* managers within research infrastructures – the Master in Research Infrastructure Management.

The RItrain consortium has identified four major objectives for this application.
1. Definition of required competencies in distributed RIs throughout the lifecycle of an RI, from the initial preparatory phase through to operational maturity.
2. Mapping of these competency requirements to existing training courses and programmes.
3. Development and piloting of a comprehensive curriculum, at master's level (EQF level 73), incorporating existing training opportunities and creating new content to fill the gaps.
4. Development of continuing professional development, including a series of webinars based on how real challenges in research infrastructures have been overcome, and a staff-exchange programme.

RItrain's budget is €1.9M of which €185.7k will be spend through ISBE partners.

A7.3 FAIRDOM

FAIRDOM is a joint action of ERA-Net EraSysAPP (ending December 2015) and European Research Infrastructure ISBE (starting Autumn 2015) to establish a data and model management service facility for Systems Biology. The €2.7m project was funded in 2014 for 3 plus 2 years. Its prime mission is to support researchers, students, trainers, funders and publishers by enabling Systems Biology projects to make their Data, Operating procedures and Models, Findable, Accessible, Interoperable and Reusable (FAIR).

FAIRDOM builds on the outcomes of the successful SysMO-DB and SyBIT data management projects, uniting their tool and database development as well as their experience serving large systems biology projects. The project will achieve this by:

- The FAIRDOM Open Software Platform and toolset to manage data, models and projects that combines standards, the SEEK4Science and openBIS tool suites and community tools.
- A centrally hosted, public FAIRDOMHub - a “Systems Biology Community Commons” - for independent researchers, projects and programmes. Researchers can manage their projects and project assets in a secure way. Journals, funders and communities have a resource for shared and published data, models and methods. FAIRDOMHub brings together already established programme SEEKs for SysMO, VLN and independent project SEEKs.
- A Facility of support services for curation, training, and data management planning for the EraSysAPP projects.
- A European Knowledge community for standards, data and model management expertise, FAIRDOM users and developers, and developers of Systems Biology tools and resources. We run workshops and summer schools, and will develop a library of standard templates for data, model and SOP management.
- Working with stakeholders - funders, policy makers, research infrastructures, journals and standards initiatives - to foster FAIR data and model management in Systems Biology. We work actively with COMBINE and ISBE, as well as other national initiatives.

<u>FAIRDOM is supported by 4 National Funders</u>

- Biotechnology and Biological Sciences Research Council (BBSRC) in the UK.
- The Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung – BMBF) in Germany
- The Netherlands Organization for Scientific Research (Nederlandse Organisatie voor Wetenschappelijk Onderzoek NWO) in the Netherlands.
- SystemsX (SystemsX.ch) in Switzerland

appendix 8 Examples of existing national systems biology infrastructures

C4SYS, Czech Republic

What is it?
The Czech distributed infrastructure for systems biology, linking the diverse Czech systems biology research community into ISBE

What does it provide?
A multi-purpose national platform for academia and industry offering easy and rapid access to systems biology expertise. Its broad portfolio includes approaches to build and exploit predictive maps and models of complex biological systems ranging from molecular to whole organism level; design of efficient experimental data collection design fit for modelling with stewardship of relevant data, models and maps. C4Sys services comprise consulting, support through contract activities, development of standards, and teaching and training.

Who does it serve?
Primarily serving its national community, it also makes services available to international users, including as part of world-wide international research networks and collaborations. C4SYS provides staff and resources to ensuring longer term maintenance and curation.

How is it structured?
Led by Prof. Rudiger Ettrich, Ph.D. (INSB), it is a collaboration between the host - Institute of Microbiology, Academy of Sciences of the Czech Republic, and three partnering institutions: Masaryk University in Brno, University of South Bohemia in Ceske Budejovice, Global Change Research Center - Academy of Sciences of the Czech Republic.

- The central management team and 11 groups,
- covers 21 scientists, 13 technical and 11 administrative staff,
- National-level agreements with the research infrastructures CIISB (Instruct), Czech-BioImaging and ELIXIR-CZ to enhance synergy.

How is it funded?
A priority project on the national roadmap since 2011, it gained national infrastructure status in 2015. 70% of the overall costs are met by the Ministry of Education, Youth and Sports (MEYS) until 2022, with 30% from partner institutions.

SYSBIO Italy, Italy

SYSBIO Italy is an organized, multidisciplinary and inclusive scientific community devoted to the understanding of complex biological processes for biosociety development.

Led by prof.Lilia Alberghina, in Milan and Rome, running experimental and computational research activities for Systems Biology in Yeast; Cancer cell proliferation; of ageing and neurodegeneration.

What does it provide?

World-class tools for metabolomics; provides skills in modeling (Flux Balance Analysis and multiscale dynamic models), together with software libraries and applications for high-performance analysis of experimental models. SYSBIO Italy would intend to provide within ISBE two types of services:

- Data acquisition and analysis & model construction, plus multi-scale dynamic models
- Metabolic profiling, pathways identification, & flux analysis, together with Flux Balance Analysis

What does it support

SYSBIO Italy will serve high-quality scientific research centres in academia, and high value added economic activities within biopharmaceutical and industrial biotech companies, intended support the EU *Excellent Science* and *Industrial Leadership* pillars for economic growth.

How is it structured?

SYSBIO Italy runs under an agreement between the Italian National Research Council (CNR) and the University of Milano-Bicocca (UNIMIB). This affiliates a total of 60 researchers within CNR institutes (IBFM, IASI) and UNIMIB departments (Biotech&Biosciences, ICT), of which 50% are young scientists (PhD, postdocs).

How is it funded?

Funded by the Italian Ministry of Education, University, and Research (MIUR), and is included in the Italian Roadmap for Research Infrastructure.

appendix 9 Details of the ISBE financial model

STAGE 1 INTERIM PHASE COST MODEL (Aug 15 - Jul 16)

The model for primary activities in stage one, ensures the continuation on discussions established in the preparatory phase by the Steering Committee, whilst expanding deliberations to establishing the interim bodies, beginning activities under ISBE-light, and continuing the programme of outreach.

Table I: Overview of costs for the ISBE Interim Phase stage I (all costs are in k€)

Expenditure		Costs (k€)
Personnel Costs	*Project Officer (1 FTE)*	*70*
Investments/facilities	*Consumables*	*4*
	Hardware + software	*10*
	Running costs	*1*
Portfolio of web-based services		*35*
Travel and conferences		*10*
Outreach and coordination		*20*
Total (k€)		**150**

STAGE 2 INTERIM PHASE COST MODEL (Aug 16 - July 18)

The model envisages the appointment of the founding director as the beginning of Stage 2 with specific resources to provide defined support for personnel within the interim Central ISBE office to provide secretarial support interim bodies, with staff effort for outreach and community engagement activities as well as providing for the costs of delivering the central portal for ISBE-light.

Table II: Overview of costs for the ISBE Interim Phase stage II (all costs are in k€)

Expenditures		FTE	Costs (k€)
Personnel	*Director*	1.00	*390*
	Web manager	0.70	*130*
	Secretary	0.20	*40*
	Public relation manager	0.50	*95*
	Liaison officer (project manager)	1.00	*95*
	training and education developer	0.60	*95*
Investments/facilities			
	Consumables		*26*
	hardware + software		*87*
	Running costs		*30*
Portfolio of web-based services			*250*
Travel and conferences			*137*
Outreach and coordination			*125*
Totals (investments and Personnel costs) (k€)			**1500**

LEGAL PHASE COST MODEL - CIO (Aug 2018-2022 onwards)

The model for the legal phase envisages the expansion of personnel at the CIO in order to support the newly agreed national Systems Biology Centres that take over delivery of operations from the ISBE-light organization. This is reflected in the need to support a broader range of standing bodies and support technical and operational coordination working groups across the nSBCs. Support for outreach and community engagement activities is similarly enhanced to deliver the central portal for ISBE as a legal entity.

Table III: summary of personnel and operational costs for the Central ISBE Office for the first 5 years of the legal phase (2018-2022) (all costs are in k€).

	2018	2019	2020	2021	2022
Personnel	495	530	545	560	580
Operational costs	130	145	165	205	205
Total	**625**	**675**	**710**	**765**	**785**

Table IV Summary of estimated fulltime equivalents (FTEs) and personnel costs for the Central ISBE Office for the first 5 years of the legal phase (2018-2022) (all costs are in k€)

Expenditures			**Legal phase**				
			2018	**2019**	**2020**	**2021**	**2022**
Personnel Costs	*Director (1.0 FTE)*		165	175	180	180	185
	Web manager (1.0 FTE)		70	70	70	70	75
	Secretary(0.5 FTE)		30	30	35	35	40
	Public relation manager(0.4-0.5 FTE)		30	30	35	35	40
	Liaison officer (project manager) (1.0 FTE)		70	75	75	80	80
	QC officer (0.75-1.0 FTE)		70	75	75	80	80
	training and education developer (0.8-1.0 FTE)		60	75	75	80	80
Subtotal Personnel FTE			**5.45**	**6.00**	**6.00**	**6.00**	**6.00**
Subtotal Personnel costs			**495**	**530**	**545**	**560**	**580**

Table V: Summary non-staff operational costs for coordinating for the Central ISBE Office for the first 5 years of the legal phase (2018-2022) (all costs are in k€)

Investments/ facilities in the legal phase							
			2018	2019	2020	2021	2022
CIO Office functions	*Consumables*		5	5	5	10	10
	hardware		10	15	15	20	20
	Software		10	10	15	15	15
	Running costs		5	5	5	10	10
Subtotal			**30**	**35**	**40**	**55**	**55**
Portfolio of web-based services			40	50	60	75	75
Travel and conferences			10	10	15	15	15
Outreach and coordination			50	50	50	60	60
Subtotal			**100**	**110**	**125**	**150**	**150**
Subtotal Investments			**130**	**145**	**165**	**205**	**205**
Totals (investments and Personnel costs) (k€)			**625**	**675**	**710**	**765**	**785**

LEGAL PHASE COST MODEL - nSBCs (Aug 2018-2022 onwards)

The model for estimated that likely cost for the differing sizes (small, medium & large) of national Systems Biology Centres (nSBCs) ***NB*** *that the support for these centres is anticipated to continue to be met through national funding programmes and opportunities and is provided in advance of the more exact modelling of costs for services that would follow the identification of the actual services, activities and resources that a member state would itself propose during the interim phase.*

Table VI: Summary of estimated fulltime equivalents (FTEs) and costs for a **small** national Systems Biology Centre for the first 5 years of the legal phase (2018 - 2022) (all costs are in k€)

Expenditures	S		Legal phase				
			2018	**2019**	**2020**	**2021**	**2022**
Personnel FTE	*Administrative; Integration and modelling; Steward & standardisation*		2.0	3.0	4.5	5.0	5.0
Subtotal Personnel costs			**140**	**240**	**320**	**350**	**390**
Investments/ facilities	*Consumables; hardware; Software; Running costs*		25	25	35	40	50
Portfolio of web-based services			15	15	20	20	25
Travel and conferences			10	10	10	15	15
Outreach and coordination			10	10	15	15	20
Totals (investments and Personnel costs) (k€)			**200**	**300**	**400**	**450**	**500**
							1,850

Table VII: Summary of estimated fulltime equivalents (FTEs) and costs for a **medium** national Systems Biology Centre for the first 5 years of the legal phase (2018 - 2022) (all costs are in k€)

Expenditures			Legal phase				
			2018	**2019**	**2020**	**2021**	**2022**
FTE Personnel							
	Administrative		0.4	1.0	1.0	1.0	1.0
	Integration and modelling		1.5	3.0	3.0	4.0	4.0
	Steward & standardisation		1.6	2.0	4.0	4.0	4.0
Subtotal Personnel FTE			**3.5**	**6.0**	**8.0**	**9.0**	**9.0**
Personnel Costs	*Administrative*		28	70	70	70	75
	Integration and modelling		105	210	210	280	300
	Steward & standardisation		112	140	280	280	300
Subtotal Personnel costs			**245**	**420**	**560**	**630**	**675**
Investments/facilities							
	Consumables		30	30	40	40	50
	hardware		5	5	10	10	15
	Software		10	10	10	20	20
	Running costs		3	3	10	10	15
Portfolio of web-based services			30	30	40	40	50
Travel and conferences			20	20	20	34	45
Outreach and coordination			20	20	30	35	40
Totals (investments and Personnel costs) (k€)			**363**	**538**	**720**	**819**	**910**
							3,350

Table VIII: Summary of estimated fulltime equivalents (FTEs) and costs for a **large** national Systems Biology Centre for the first 5 years of the legal phase (2018 - 2022) (all costs are in k€)

Expenditures			Legal phase				
			2018	**2019**	**2020**	**2021**	**2022**
FTE Personnel	*Administrative*		1.0	1.0	2.0	2.0	2.0
	Integration and modelling		2.0	3.0	5.0	8.0	8.0
	Steward & standardisation		2.0	2.0	6.0	6.0	6.0
Subtotal Personnel			**5.0**	**6.0**	**13.0**	**16.0**	**16.0**
Personnel Costs	*Administrative*		70	70	140	140	150
	Integration and modelling		140	210	350	560	600
	Steward & standardisation		140	140	420	420	450
Subtotal Personnel costs			**350**	**420**	**910**	**1,120**	**1,200**
Investments/facilities							
	Consumables		60	60	80	80	100
	hardware		15	20	25	30	35
	Software		20	20	20	35	35
	Running costs		5	5	15	20	20
Portfolio of web-based services			70	80	100	120	100
Travel and conferences			40	40	40	60	60
Outreach and coordination			40	60	70	80	90
Totals (investments & Personnel costs) (k€)			**600**	**705**	**1,260**	**1,545**	**1,640**
							5,750

LEGAL PHASE COST MODEL - SCALABILITY OF ISBE (Aug 2018-2022 onwards)

The ISBE infrastructure model allows for scalability in size and over time, responding to the actual ISBE user numbers it serves and the scope of services and resources requested by the European users. This is an estimate, based on current communication with national funding organisations, of the development of ISBE.

Table IX: projected growth in amount of nSBCs of ISBE in the first 5 years of the legal phase

Construction of ISBE: nSBCs	2018	2019	2020	2021	2022
small nSBCs	2	2	4	6	8
medium nSBCs	2	3	3	4	5
Large nSBCs	1	2	3	4	5
Total number of nSBCs	5	7	10	14	18

Table X: projected growth in relation to amounts of nSBCs and expected costs (k€) of ISBE in the first 5 years of the legal phase

Construction of ISBE	2018	2019	2020	2021	2022
small nSBCs	400	600	1600	2700	4000
medium nSBCs	726	1614	2160	3276	4550
Large nSBCs	600	1410	3780	6180	8200
Total Costs (k€)	**1726**	**3624**	**7540**	**12156**	**16750**
					41796

Appendix 10 Abbreviations

BBSRC	Biotechnology and Biological Sciences Research Council
BMBF	German Federal Ministry of Education and Research
C4SYS	Czech distributed infrastructure for systems biology
CASyM	Coordinating Action Systems Medicine
CellML	Cell Markup Language
CIO	Central ISBE office
CORBEL	COordinated Research Infrastructures Building Enduring Life-science Services (Horizon 2020 funded programme)
cSBC	coordinating Systems Biology Centre
DOIs	digital object identifiers
EB	Ethical Board
ERACoSysMed	Framework Programme 7 Collaboration on systems medicine funding to promote the implementation of systems biology approaches in clinical research and medical practice
ERANet	Framework Programme 7 ERA-NET scheme for cooperation and coordination of research activities carried out at national or regional level in the Member States
ERASynBio	Framework Programme 7 ERA-Net for Systems biology
ERASysApp	Framework Programme 7 ERA-Net for Applied Systems Biology
ERASysBio	Framework Programme 7 ERANet in Systems biology
ELIXIR	European Life Science Data Infrastructure
ERIC	European Research Infrastructure Consortium
ESFRI	European Strategy Forum on Research Infrastructures

FAIRDOM	joint action of ERA-Net EraSysAPP and European Research Infrastructure ISBE to establish a data and model management service facility for Systems Biology
FieldML	Field Markup Language - a declarative language for representing hierarchical models using generalized mathematical fields
FP7	European Commission Framework Programme 7
GDP	Gross Domestic Product
IC	ISBE Interim Committee
ILB	Industry Liaison Board
ISBE	Infrastructure for Systems Biology Europe
KPIs	key performance indicators
MIAPE	Minimum Information About a Proteomics Experiment
MIRIAM	Minimum Information Required In the Annotation of Models
MoU	Memorandum of Understanding
MT	ISBE Interim Management Team for ISBE-light
nSBC	national Systems Biology Centre
RItrain	Horizon 2020 funded Reseach Infrastructures Training Programme
SBML	Systems Biology Markup Language
SED-ML	Simulation Experiment Description Markup Language
SLA	Service Level Agreements
SMEs	Small and Medium-sized Enterprises
SOPs	Standard Operating Procedures
VPH	Virtual Physiological Human programme