ERASysBio
ERA-NET
for Systems Biology

Systems Biology in the European Research Area

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ERASysBio ERA-NET for Systems Biology

Towards a European Research Area for Systems Biology

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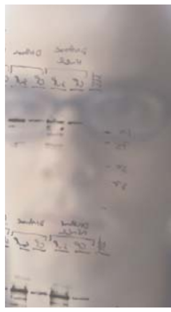

SUMMARY

In recent decades, new techniques in molecular biology and other life sciences have generated a tremendous amount of data on biological systems. An example is the Human Genome Project, which has revealed that knowing the building blocks of the genome does not provide knowledge of the function of these genes or their interactions with other genes and with the environment.

Systems biology integrates mathematics, chemistry, physics, informatics, engineering and other fields to enhance understanding of biological processes. This complex field requires the development of new tools. For example, data sets are used to develop mathematical models for biological processes that are then simulated to provide inputs for further experiments, leading to new and better datasets. Repeating this cycle increases knowledge of the biological processes rapidly.

ERASysBio: the vision

The countries of the European Research Area (ERA) recognise the importance and scientific potential of systems biology. This is reflected in their national policy making and increasing investments. The ERASysBio partnership, which began in 2006 with 16 partners from 13 countries, builds on this by working together to create an international policy to enhance competitiveness.

This strategy paper is an early product of the partnership. It sets out core elements of the 5-10 year vision of the ERASysBio partners and provides a framework for decision-making to advance the field. The document is based on input from the scientific community at two strategic meetings, organised and funded by ERASysBio. It reflects the wide range of topics considered to be critical for driving forward systems biology research in the ERA. Detailed scientific direction within the ERA is being discussed and defined out with this document; through and in dialogue with the scientific community.

People and structures

A vibrant research community that attracts and retains excellent scientists within the ERA is crucial. This starts with training students and early-career scientists in this interdisciplinary field; for example by providing training in one discipline with access and resources for them to develop sufficient know-how in other disciplines. For instance, biology students may train in basic mathematics so as to understand and work with mathematical models.

Established scientists also require (re-)training to update their knowledge on adjacent disciplines. This should be facilitated and encouraged through summer courses and medium- to long-term visits to complementary institutions.

Appropriate structures, both physical and virtual, can help to facilitate interdisciplinary training and mobility. These might include a systems biology centre with a long-term commitment of space, research facilities and staff, which provide the opportunity to interact with, train, attract and engage top-class scientists within and outside the institution. Virtual structures, like networks, are excellent tools for the initiation of collaborations between scientists from different labs and different countries. There is also a need for a structured technological innovation. Generation of high quality data could be coordinated through platforms and made available to the entire community.

Data requirements and standards

It is important that the large amounts of data being generated are of high quality, compatible, accessible and usable. There is a widely recognised and urgent need for standardisation, that at the same time is not too restrictive. This should cover data generation and agreed standards in modelling programmes and databases. The transnational funding programme SysMO is one of the current initiatives aimed at achieving consensus on standards, management and sharing of data.

Public-private partnerships

Industry is increasingly aware of the potential offered by systems biology. Academics and industrialists recognise the importance of joint initiatives to advance systems biology in the ERA. ERASysBio can facilitate the creation of public-private partnerships and play a role in solving issues like intellectual property and open access of data.

Outreach

The ERASysBio partners wish to engage with the wider society, for example through activities for young people, school teachers and general public. The aim is to raise awareness, understanding and involvement in the systems approach to biology.

Young people must be inspired and stimulated towards a career in systems biology, and the public should be engaged regarding the ethical and societal implications of the science.

Funding organisations

At the international level the role of funding organisations represented by the ERASysBio is to jointly pave the way for systems biology research to interact outside the boundaries set by national regulations. This includes both funding mechanisms to stimulate the growth of this scientific field as well as coordination of other complementary activities.

Recommendations

The final chapter provides several recommendations that the ERASysBio partners consider essential to consolidate a strong ERA in systems biology.

- Establish a number of transnational systems biology networks in the ERA
- Encourage adoption of data management and sharing best practices in the ERA
- Encourage adoption of data standards in the ERA
- Optimise the education and training in systems biology in the ERA
- Stimulate the establishment of systems biology research structures across the ERA
- Explore mechanisms to strengthen the academic-industrial links in systems biology in the ERA

The future of systems biology in the ERA is the responsibility of many institutions. We describe actions needed to improve Europe's position. Some recommendations are being pursued by the ERASysBio partners. For others, the consortium will encourage others to get involved and work together.

1. INTRODUCTION

ERASysBio[1] is a transnational funding initiative to support the convergence of life sciences with information technology and systems science. ERASysBio brings together 16 ministries and funding agencies from 13 countries to coordinate their national research programmes in systems biology and agree on a common European research agenda.

Under the ERA-NET scheme the European Commission (EC) finances collaboration between funding organisations and policy makers. The scheme helps establishing the common knowledge base necessary for the development of coherent policies across national borders and encourages joint activities conducted at national or regional level as well as among the European research organisations. Any resulting joint activity or transnational funding programme is funded by the national/regional budgets.

As an ERA-NET[2], ERASysBio is therefore committed to supporting the establishment of the European Research Area (ERA) in the field of systems biology by stimulating and facilitating programme coordination and joint activities in the field; in European Union (EU) Member States and in associated countries.

This paper is jointly presented by the ERASysBio partners and represents the views of the scientific community and funding organisations on present and future directions of systems biology in Europe. These views were captured at two strategic meetings organised and sponsored by ERASysBio in March 2007: the Meeting of the European Systems Biology Centres[3] and the ERASysBio Strategy Conference[4]. The outcomes of these meetings provided the foundations for this paper and the recommendations within.

The paper targets a wide audience, which includes scientists, politicians, policy makers and funding agencies, industry and the public, and aims to provide a framework for further discussions and activities, creative thinking and coordinated action.

Even though systems biology is already rapidly developing at the national level in a number of partner countries, important added value can be achieved through partnership. The ERASysBio partners firmly believe that systems biology offers the ideal opportunity and the vehicle for implementing pan-European collaboration, to strengthen the wider European scientific community towards a greater impact worldwide.

In the context of the number of funding activities being developed at the European level, ERASysBio recognises the need of reinforcing the coherence of the ERA of systems biology. ERASysBio wishes to see complementarity in its current and future activities, and those of other funding organisations, e.g. EC and European Science Foundation (ESF), in order to maximise benefit to the scientific community.

The aim of this paper is to provide a framework for decision-making on what is needed to advance the field, on what the community can do together to be heard internationally as one voice and on what we as funding organisations can do in partnership to assist in this common goal.

2. SYSTEMS BIOLOGY – Biology's Big Bang

Biology research is undergoing a fundamental change. Historically, different disciplines interacted through dialogue within academia. In the 19th century the medieval university model was modernised. The educational system was expanded into many different disciplines, all of which attempted to apply a scientific approach: sociology, political science, history, biology, physics, astronomy, medicine. Every new discipline was studied scientifically and linked to scientific research.

Disciplines diversified and grew in complexity. Biologists faced the challenge of understanding the complexities of living organisms. Over the last 50 years through advances in genetics, molecular biology, biochemistry, cell biology and physiology, biologists have generated groundbreaking developments greatly improving and revolutionising our knowledge of biological processes. These changes were driven on two assumptions: such complex organisms and processes surely require lots of information and the

[1] ERASysBio partner countries are listed on the inside of the back cover.
[2] ERA-NET supports joint activities conducted at national or regional level as well as among the European research organisations, and helps to develop the common knowledge base necessary for the coherent development of policies.
[3] The Meeting of the European Systems Biology Centres was held on 7-8 March 2007 in London, UK, as a preparatory meeting for experts from dedicated Systems Biology Centres. The purpose of the meeting was to identify areas of common interest where links between institutions could be maximised and to consider any specific challenges faced by such cooperation (link http://www.erasysbio.net/Calendar).
[4] The ERASysBio Strategy Conference was held on 27-28 March 2007 in Oxford, UK. The purpose of the meeting was to discuss the views of delegates and funding organisations on a number of relevant topics, e.g. scientific vision, standardisation and integration, public-private partnerships, the skills base and public engagement, and to provide a framework for decision making on future funding mechanisms (link http://www.erasysbio.net/Calendar).

more intricately formed an organism is the more genes it would have in its cells. By completion of the Human Genome Project, biologists were surprised that all animals have approximately the same number of genes for proteins – around 20,000. Yet the human being is more complex than flies and worms. The reality is that only very limited information about function can be inferred directly from the genome, i.e. protein coding regions, so the challenge of unravelling the complexity of living organisms remains. It is dynamic interaction between components in a biological system that seems to provide clues to decipher the overall function and behaviour of biological organisms. Systems biology emerges today as a powerful scientific approach that may help explain why some creatures are more complex than others. It is not intended to replace the classical approach to biology research. Systems biology is a logical and necessary follow-up to the years of reductionist biology that culminated in the sequencing of the human genome. The 'systems' approach assimilates advances from the biological, computational, mathematical, physical sciences and engineering. By taking integrative approaches to address research questions, systems biology promises to yield greater insights than do piecemeal contributions by separate fields. Two-hundred years after the split of disciplines, the growing amount of experimental data and the need for integration is producing the contrary effect, i.e. the condensation of divergent scientific disciplines into a 'new' way of working and thinking – interdisciplinarity.

The expanding shock waves from this 'Big Bang' are enriching biology research with new ideas, new tools and new data. To some extent, the vast generation of data by systems approaches is pushing the analysis beyond our observable horizon, causing biology research to undergo its biggest shake-up in 50 years. It is likely to change our views radically: about how cells self-regulate, how life becomes more complex, how diseases develop and how evolution operates. It may have already changed our vision of ourselves, human beings, and the universe in which we live.

Systems biology aims at understanding the dynamic interactions between components of a living system, between living systems and their interaction with the environment. Systems biology is an approach by which biological questions are addressed through integrating experiments in iterative cycles with computational modelling, simulation and theory. Modelling is not the final goal, but is a tool to increase understanding of the system, to develop more directed experiments and finally allow predictions.

3. INTERDISCIPLINARITY – Rebuilding the Tower of Babel

Systems biology is an emerging field with different possible approaches in different contexts. Intrinsic to systems biology is, however, its interdisciplinary nature and the common aim of achieving quantitative understanding of dynamic biological processes through the use of mathematical and statistical analyses to integrate biological data, in order to develop predictive models of biological behaviour. Research in systems biology requires close interaction between different disciplines and a positive attitude towards working across different cultures. Moreover, it requires the fusion of different disciplines for the birth of a new, connecting field.

Biologists, medical doctors, engineers, chemists, computer scientists, mathematicians and physicists use conventional approaches, which do not necessarily encourage working beyond their fields. Using its own specific language, the reductionist approach to research used by traditional disciplines reduces a problem to its elementary components to study each in isolation. In contrast, the more holistic approach of systems biology focuses on understanding the biological process as a whole using a combination of knowledge, methods, skills and expertise from different disciplines.

This new way of doing biology research requires integrative thinking and doing, a radical culture change for the biosciences, which involves dialogue and genuine understanding between disciplines and the appreciation of giving and sharing for mutual benefit. It requires persistence and determination for the construction of a unified language and a common framework. The benefits of this cultural change are promising to deliver practical and powerful advances in healthcare, industrial biotechnology and environmental sustainability.

This paper will take the reader through a number of topics that were considered essential for the consolidation of systems biology in the ERA. These topics describe the challenges and the instruments to overcome them, the people and students needed, the vast amount of data to be analysed and managed, the benefits of public-private partnerships, scientific achievements to be expected in 5-10 years, and the role of funding agencies in facilitating this process. Interdisciplinarity is at the heart of systems biology approaches and will be found embedded in all topics and throughout the entire paper.

Intrinsic to systems biology is its interdisciplinary nature and the common aim of achieving the quantitative understanding of dynamic biological processes through the use of mathematical and statistical analyses to integrate biological data in order to develop predictive models of biological behaviour.

4. THE SYSTEMS BIOLOGY ERA – Rising to the challenges

The launch of ERASysBio marked the commencement of a large coordination action, in which the partners declared their common interest in systems biology and their commitment to build an ERA as a cornerstone for European knowledge in this field. For this ERA to mobilise research, training and innovation in systems biology to the point of fulfilling the economic, social and environmental ambitions of its society, a number of obstacles must be faced and successfully overcome. In this paper we describe the views of scientists and funding agencies on the nature of these obstacles, their magnitude and possible solutions and recommendations to tackle them.

At present, one of the major challenges faced by the systems biology community is achieving real understanding and adequate communication between the disciplines involved. This interdisciplinary cooperation is the foundation of any successful systems approach and spans from the design of the experiments to the generation of outcomes outlasting the duration of the individual projects. Arising from discussions, it was suggested that the development of infrastructures constituted one of the most important areas where work was required. Establishing trans-national and trans-disciplinary networks, as vehicles to facilitate the exchange of information, ideas, knowledge and expertise, was considered a significant step forward.

The availability, quantity and, most of all, the quality of the data was a central point in the discussions. There was general consensus that the community needs to join forces in the adoption of Standard Operation Procedures (SOPs). Stringent peer-review strategies, including considerations of data standards, management and sharing, should be adopted by journals and funding organisations.

The development of this ERA also requires development of the research community. A great degree of restructuring the curricula of all disciplines concerned in the training of pre- and post-graduates is required. These new structures should provide enough flexibility to allow students to cross-train as part of their academic degree. An appealling and challenging career path is needed to attract and retain researchers: this should measure and recognise their success across disciplines. The networks proposed above can provide a platform for early-career and established researchers as well as for students to enhance their network, knowledge and career opportunities.

As an emerging area, systems biology is not yet attracting enough investment from industry. Industry only now starts to recognise to what extent systems approaches will be an essential facilitator of research across the entire process from concept to product. There was strong consensus for a joint effort to build academic-industrial links and involve the scientific community, industrial partners and the funding organisations.

These challenges will be further elaborated in this paper. The underlying message, constituting the basis of the recommendations, is the need for mutual understanding between individuals and the disciplines of all partners involved.

It is widely agreed that the challenges faced by systems biology call for a fresh perspective on old structures of thinking and communicating, research and collaboration, training and funding mechanisms. Only a community effort targeting all obstacles will create a meaningful advance for systems biology in the ERA. This community has to grow together from all different fields, scientifically and culturally, across political borders and including industry.

5. PEOPLE IN SYSTEMS BIOLOGY – Flexibility and mobility

For Europe and the associated countries in this ERA to consolidate systems biology and to remain competitive in biosciences, biomedical sciences, engineering and the environment, careful consideration should be given to education, training and the career structure of systems biologists. Interdisciplinary scientists are in demand and to ensure influx of adequately educated and excellent scientists, a new approach to education is needed. From an early stage of education throughout career development, the complementation and integration of disciplines should be enabled. Publicly funded institutions are at present the best placed to host the breadth of disciplines needed to develop systems biology and to cope with continuously changing and unpredictable requirements.

Training and education

Several obstacles in current basic university curricula hinder appropriate training in systems biology. It is generally agreed that mathematics is now an essential component in biological research. In order to equip future scientists for a multi-disciplinary field, curricula and structures at universities (graduate and MSc levels) should be updated. This includes state of the art mathematical education for biology students to provide the necessary tools to integrate disciplines at a later stage. Students pursuing a scientific career in this interdisciplinary subject should receive credits when following courses at different groups, faculties or universities. There was also discussion of agreeing on a European curriculum at the MSc level.

The majority of researchers support the idea of current diversity in higher education being turned into a European strength. Exchange of (PhD) students between European institutes should enable them to increase their level of education in systems biology, allow them to taste different flavours of culture as well as gaining expertise in the institute that is most qualified. For this to be a strength rather than an obstacle, credits should be given to students who spend time in a research centre other than their own. Appropriate structures should be established at universities to allow for and coordinate this kind of mobility.

On top of the required changes in basic curricula mentioned above, specialised programmes should be established and linked for systems biology students and early-career scientists. This includes an e-learning platform or web-based tuition for systems biology, targeted to both biologists and non-biologists by generating common toolboxes for applications that overlap different projects.

Being a relatively new and strongly developing field, systems biology needs a shift in education and training of students and early-career scientists, and also requires full attention to established scientists who need to acquire new skills and knowledge. Most of established scientists getting engaged in systems biology are mono-disciplinary trained. For them to learn a subject they are not basically familiar with, training options like summer schools should be provided. For further embedding in the unfamiliar subject, long-term opportunities like discipline hopping should be facilitated.

There are currently great efforts going on all over Europe in this direction that can be exploited and extrapolated. These go beyond the efforts of systems biology centres and institutes alike. Initiatives like the UK doctoral training centres, master courses and summer schools arise across Europe. As an example, the Human Frontier Science Program[5] has introduced a call for cross-disciplinary fellowships targeted to postdoctoral fellows with a PhD degree in the physical sciences, chemistry, mathematics, engineering and computer sciences willing to train in biology.

Mobility

The interdisciplinarity of systems biology and the underlying concept of cooperation between multiple disciplines, require the mobility of people and knowledge between disciplines and institutes. The mobility of researchers was an important aspect that received much attention at both ERASysBio meetings. A number of vehicles to promote mobility of researchers between academic institutions and to and from industry were discussed. Among these was spending time in a complementary institution in the ERA to learn and comprehend the characteristics of another discipline.

A great degree of consensus and flexibility will be required from universities' course directorates (and funding agencies) in order to facilitate rotation of students and scientists. Deviation from the beaten track might be required to develop a successful structure for mobility.

The involvement of industry in training was extensively discussed and was considered a critical area that required special consideration and, in some cases, significant improvement. Fellowships, with the specific requirement for early-career researchers to spend a year in an industrial environment, were proposed as a vehicle to encourage mobility.

Formal re-training of senior scientists was discussed and the UK discipline hopping model was used as an example. An element of flexibility is required as an important component at all career levels to accommodate specific circumstances.

The ERASysBio partners acknowledge that there is a wide spectrum of training needs across the ERA and a great diversity in the national approaches to training. Whatever mechanism is adopted to achieve this goal, we should strive to fulfil training requirements while considering and making the most of these differences within the ERA.

[5] The HFSP supports novel, innovative and interdisciplinary basic research focused on the complex mechanisms of living organisms (link http://www.hfsp.org/).

Career structure

It was recognised that students undergoing training now may face funding gaps in their career in the short term. For example, in the next 2-3 years theorists may have to wait until enough public data are available. The possibility of establishing fellowship programmes of up to 5 years duration to foster these specific careers in sufficient numbers to satisfy the demands of academia and industry was considered.

Career recognition and structure for established scientists was regarded as an important consideration. There was a general perception of a lack of incentives for scientists to cross-train in a different discipline as the risks implied outreached the benefits. Success measures like publications vary significantly across communities, and therefore the metrics for interdisciplinarity to be used in career progression were thought to require careful consideration. For an interdisciplinary community to emerge and develop, a new set of criteria needs to be created to judge both the quality of the science and the career paths of those embarking in this emerging field.

Systems biology brings together people and properties of multiple disciplines to create a unique interdisciplinary field. Acquiring and fostering well trained, new students and early-career scientists, as well as stimulating established scientists to broaden their horizon require motivation, effort and flexibility of all involved in the field of systems biology.

All phases of education, starting at graduate level, should provide a solid base for the scientific career of a researcher in systems biology. Career structure and education are facilitated by well-structured opportunities for mobility between countries, institutions and disciplines.

6. STRUCTURES – The foundation of success

Successfully expanding the ERA in the field of systems biology requires a structural approach. Structures needed to catalyse the interdisciplinarity in the field of systems biology must provide the basis for communication, mobility and interactions in an organised way. Creating structures will provide a flow of knowledge and people, resulting in collaboration and integration of modelling, simulation and practical experiments. Furthermore, the basis for interdisciplinary training and involvement of the industry can arise from the organisation of structures. The size and duration of collaborative projects that arise from facilitating structures were discussed. Opinions ranged from small projects as facilitators of long-lasting collaborations to longer, larger projects integrating a large number of research groups. It was acknowledged, however, that the best collaborations would last beyond the impact and duration of the project itself.

Systems biology centres

The creation of systems biology centres where researchers from different disciplines are physically united within a single, physical environment is proving to be an effective arrangement to provide the necessary tools for interdisciplinary research. Co-location of researchers within a single academic centre offers unique opportunities for capacity building in the immediate term. Established systems biology centres will possess:

- a concentration of research facilities within a single, appropriate and dedicated physical space run under one national programme;
- a long term commitment of space, research facilities and staff within a philosophy of interdisciplinary working;
- a reservoir of skilled technical staff capable of supporting the necessary range of high throughput and other advanced technologies to be deployed, and a commitment to their retention, training and development;
- a matured effective policy and provision for data capture, management and storage;
- a vision and strategy for developing, taking forward and advancing at the cutting edge of integrative systems biology;
- a commitment to reach out, engage and train, and to attract and engage other top-class scientists and engineers from within and outside the institution.

Both the UK and Germany have made substantial investments by establishing centres. The Biotechnology and Biological Sciences Research Council (BBSRC) with contribution from the Engineering and Physical Sciences Research Council (EPSRC) has invested €75M in establishing six Integrative Systems Biology Centres in the UK. In Germany, the Federal Ministry of Education and Research (BMBF) has invested €51M for the funding of the first three years (2007-2009) in establishing four Systems Biology Centres. Other countries, e.g. The Netherlands and Switzerland, have also recognised the advantages of integrating traditionally separate subjects into top class interdisciplinary programmes within a single building or in close proximity.

Structures to serve the people

Virtual structures are as essential as physical structures in the pursuit of a successful research environment. Structured networks and virtual centres offer the opportunity to groups and individuals to work at distant locations and at the same time collaborate and design common projects. Each lab has its own expertise and by joining forces the results exceed individual possibilities. Networks have to serve the scientists; by deliberating with other disciplines, experiments will be co-designed by both experimentalists and computer scientists, subsequently ensuring model-compatibility.

The high level of heterogeneity in the education and training of students across Europe was regarded as advantageous. The diversity in the curricula offers unique skills, of which some are in high demand in systems biology research. It reinforces the need to complement these curricula with facilities for mobility of researchers. The idea of involving scientific societies, such as the Federation of European Biochemical Societies (FEBS) and the Federation of European Microbiological Societies (FEMS), in training and mobility programmes was well supported. The role and participation of ESF in these activities was also discussed.

The interdisciplinary field of systems biology provides challenges for both early-career and established scientists, relating to traditional differences between disciplines. Increasing the transparency of the individual fields will facilitate the mobility of researchers and improve career structure of early-career scientists. There was general consensus to recognise individual scientists by explicit author contributions and publication credits, to facilitate the transition between disciplines. Granting extended fellowships will further reduce the personal risk for the scientist, increasing their motivation to take the plunge.

Technology

The need for technological innovation was extensively discussed. The field of systems biology requires massive technology development, mainly for the generation of data. The idea of creating technological platforms enabling the generation of quality-controlled data, was strongly supported. These platforms should include a research component in order to foster continued technological innovation, and should be established in close collaboration with industry. Technological innovation, leading to an increase in data production, requires more data storage and management. The bioinformatics community has provided a large portion of the input for current computational analyis in systems biology and will continue to play a significant role in addressing the challenges posed by data integration and modelling. Structures will initiate and enable standards and provide databases to be compatible.

A number of requirements for European-level infrastructures were identified. The idea of creating a network of reference centres was supported by a number of participants at the two strategic discussions. Some were also in favour of creating a European Institute of Systems Biology, which would combine theory and advanced experimental facilities, following a model similar to the Newton Institute, the Institute for Advanced Study or the Kavli Institute for Theoretical Physics. The possible role of the European Bioinformatics Institute of the European Molecular Biology Laboratory (EBI-EMBL) e.g. in the archiving and distribution of datasets and models was also raised.

Involvement of industry

In the last few years, industry has become aware of the potential systems biology offers to help tackle complex processes and diseases. Systems biology is being applied in a number of industrial sectors, including pharmaceuticals, biotechnology, biofuels, food, ecology and personal care. The establishment of mixed departments associating academia and industry was proposed as a step towards facilitating close collaboration at a relatively early stage. Using organised structures, industry and academia will be encouraged to meet and collaborate in a way which exceeds the scientific involvement with industry of individual countries.

Providing structures, both physical (buildings) and virtual (networks), is the route of choice for creating a European research environment in systems biology. Precise initiation, stimulation and organisation of structures in systems biology relates to positive development of collaboration initiatives, mobility, education, data generation and sharing, involvement of industry and technological innovation. For the technological innovation to succeed, it seems imperative that technology is first standardised, that high-throughput is used whenever possible, and that quality control becomes essential so the export to public databases is facilitated. The interdisciplinary properties distinct to systems biology require attention of all involved in this field and should be emphasised in the initiatives of European institutes and funding organisations.

7. DATA – A universe expanding

An ever expanding amount of data generated by systems approaches has propelled the understanding beyond non-computational comprehension. Keeping data in the orbit requires them to display the necessary attraction requiring quality, compatibility and accessibility.

Data gathered in the course of publicly funded research are public good and should be openly available to the maximum extent. In addition to serving the public interest, this also advances the entire scientific community. Data produced are not merely of importance to the scientist who initiated and facilitated the work, but also to the wider systems biology community. Only by enabling the whole community to share can we expect the field to advance. As an outstanding example of publicly funded and available data is the Human Genome Project (HGP), where privatisation would have been devastating to the scientific community in particular and the public in general.

In view of the size and number of data sets currently available and being produced, data quality is a topic of great concern to the scientific community. This is also of significant importance to the funders, who are committed to getting the best value for their funds. In order to assure the necessary quality a certain degree of standardisation has to be implemented.

Standardisation

It is generally agreed that standards in systems biology are useful and even necessary to assure data quality. The opinions as to which extent standards are required and at what point they become too restrictive differ. Standardisation in systems biology is not new; many standards in database management, in-vitro and in-vivo experiments and in data modelling already exist. Some standards are generally used (e.g. micro arrays, SMBL and MIAME) or developed for common use (e.g. MIRIAM). Notwithstanding these initiatives, standardisation is not yet developed at large-scale and it is highly dependent on community buy-in and the financial aspects of such large initiatives. Although the need for standardisation is commonly accepted, the rapid developments in systems biology make it difficult to define what standards should look like and how to keep them dynamic. Examples of challenges in systems biology standardisation are the diversity in data sources and changes occurring in databases. Also the route to standardisation is being discussed and opinions differ about the exact way to go, like top-down or bottom-up approaches which are under debate, as well as model-driven versus data-driven approaches. Different opinions might lead to different standards and call for different approaches. We will roughly distinguish here three types of standardisation:

- Epistemic standards: originate from community of users in a bottom-up fashion, e.g. mathematical formalisms. These standards are products of constant evolvement and are not yet fully developed. Therefore these standards should be approached with consideration and have space to mature.
- Evolvable standards: top-down emerging standards, based on the epistemic standards after sufficient maturation of the field, e.g. HepatoSys and SysMO.
- True standards: decided by an official committee, world wide and top-down. A strongly abstracted version from evolvable standards, e.g. post-genomic data production and normalisation, Gene Ontology (GO).

Requirements in systems biology standardisation

Data management, i.e. data collection and integration, needs to make progress quickly. Improvements in data capture, curation, verification and storage are urgently required in order to turn existing databases into much more powerful tools. A series of databases linked to each other and maintained through a common hub was suggested as a starting point. One of the main messages arising from the discussions was that established centres should take the lead in this kind of management. This should, to some extent, be independent of scientists, to ensure efficient integration and to enforce the realisation of such a large and long-term effort.

As mentioned previously, several standards are already successfully implemented and the awareness of the need for standardisation is widespread. In order to obtain large-scale standards, the following subjects should be considered in standardisation activities.

- Databases
  - Database information exchange – central portal system (central vs. local storage)
  - Communication between databases
  - Quality of databases – keep good data, exclude bad data
- In-vitro and in-vivo experiments
  - Description of materials, apparatus, procedures and formulation of results
  - Techniques to be described in SOPs
  - Documentation to preserve information

- Modelling
  - Programming language
  - Principles of modelling, model exchange
  - Documentation to preserve information
  - Quantitative and predictive modelling
- Graphical representation and visualisation of standards

The standardisation of data was regarded as a pre-requisite for the consolidation of systems biology. Confidence in the quality of data that are being generated and the models derived from these data will develop only if the standards originate from a community effort. Data standards can be adopted in the form of Standard Operation Procedures (SOPs).

Efforts already undertaken

Significant efforts are being undertaken to fulfil the infrastructural requirements of large scale data management. Two cases of evolvable standards are being put into place by two large systems biology consortia.

With the start of the German HepatoSys[6] project it became apparent that the volume of the projects required a common data management solution to use the results to the maximum extent. It was agreed that all project partners must have access to all validated data via a common portal and that data were to be produced according to commonly agreed SOPs. The functional specifications were determined from within the project consortium. The volume of the work required entailed the need of additional funding, which was provided to license a platform managing research data, and to integrate and analyse transcriptomic, proteomic and metabolomic data.

In the transnational funding programme SysMO[7] it was required that all projects join in a common effort towards the development of a data management programme. Funding agencies and grant holders are jointly working on a complex proposal which includes the creation of a common portal and the adoption of a Laboratory Information Management System (LIMS) by all members of the 11 funded consortia. SysMO wishes to build their concept, learning from the experiences gained from the HepatoSys programme and other examples world wide. This ambitious plan has the full support from all SysMO funding agencies and promises to become an exemplar, which will require the long-term commitment and engagement of all SysMO grant holders.

Both cases demonstrate how funders and project scientists can work together to facilitate the implementation of data sharing and standardisation. It is desirable that such initiatives will increase in numbers and the implementation will lead to an ERA of higher organisation, providing data sharing and ensuring data quality.

Funding can be the key issue to such large team efforts with the potential to create the momentum needed. Rather than enforcing top down standards and procedures on the community the funders should act as catalysts to help the community to install a higher order in the data galaxy.

The mission of the ELIXIR (European Life Sciences Infrastructure for Biological Information) project is to construct and operate a sustainable infrastructure for biological information in Europe to support life science research and its translation to medicine and the environment, the bio-industries and society. The project is on the current European Strategic Forum for Research Infrastructures (ESFRI) Roadmap. As part of this project an upgrade to the EBI is foreseen. ELIXIR has a preparatory phase funding award from EC Framework 7, which includes a technical feasibility project to assess European data support needs in systems biology and address the potential role of the EBI.

ERASysBio believes that at this point progress towards high quality data will advance effectively through the implementation of data standards, data management and sharing requirements. These requirements must be built in dialogue with the scientific community and provide researchers with a wide choice about the nature of the solution. Only an iterative process of understanding between scientists and programme owners and the commitment of a large number of grant holders in the process will lead to a rapid evolvement and establishment of the necessary data management structures and policies.

[6] HepatoSys is the German network on systems biology of the liver cell, financed by the Federal Ministry of Education and Research. The aim is to arrive at a holistic understanding of detoxification, endocytosis, iron regulation and regeneration processes in mammalian hepatocytes and to be able to present and make these processes accessible in silico, i.e. through computer modelling. For the realisation of these goals funding of €36M has been provided. (www.systembiologie.de)

[7] SysMO is a transnational initiative for the funding of research on systems biology in microorganisms. This pilot call is financed by the German Federal Ministry of Education and Research, the Austrian Federal Ministry of Science and Research, the Netherlands Organisation for Scientific Research, the Research Council of Norway, the Biotechnology and Biological Sciences Research Council of the UK and Ministry of Education and Science in Spain. Eleven consortia are funded under this initiative with financial national contributions from all partners and an overall investment of €28M. (www.sysmo.net)

8. PUBLIC-PRIVATE PARTNERSHIPS – 'For richer or for poorer'

A partnership can be defined as 'a contract between two or more persons who agree to pool talent and money to share profits or loses'. The members of such a venture embark on a relationship which is as exciting as it is risky. So, why is it worth taking the plunge?

The systems approach is promising to enormously benefit our economy by providing applications that help anticipate project failure at an early stage and shorten product development timeframes. This is of particular interest to the (bio)pharmaceutical companies, which are likely to benefit from this new approach in the short term. An example of the potential that systems biology has to revolutionise this sector is the estimate that cell-based systems biology in the USA could reduce drug discovery costs by €330M and reduce development times by three years for each drug released to the market[8].

Academics and industrialists recognise the importance of building relationships as a means to creating more knowledge, more opportunities, and more value through sharing knowledge. The generation of human capital is seen as one of the most important deliverables of such relationships in addition to hard outputs, such as patents, licenses and spin-offs. The benefits of investing in creating teams of academic and industrial researchers with exceptional multidisciplinary and communication skills are immeasurable and outlast the duration of any funded project. Systems biology is still an emergent area and as such, industry is looking for examples of its success in translational application as it considers investing in this approach for the future. The wide dissemination of these success stories will greatly benefit communication and future industry involvement. A selection of the numerous existing academic-industrial collaborations and initiatives across the ERA is listed below.

- The German funding strategies of the Federal Ministry of Education and Research (BMBF) on Medical Systems Biology and Methods in Systems Biology are jointly drafted, organised and executed in collaborations of funders, academia and industry. This concept also applies in the area of systems biology in biofuels, where the Industrial Plant Research Association plays a significant role.
- Different levels of public-private partnership (PPP) are realised in the German HepatoSys programme. This programme is now in a second funding phase with a notable increased involvement and funding from industry. For the 3rd phase it is planned to increase the participation of companies substantially. The German pilot industry project on 'Systems Biotechnology' funded by the BMBF was initiated by the Degussa Company and has been running since March 2007.
- Systems Biology in Plant Breeding is a significant subject in the trilateral funding initiative between Germany, Spain and France. The concept was drafted by the representatives of the French, German and Spanish Industrial Plant Research Associations accompanying the three National Plant Research Programmes.
- In the United Kingdom, the Doctoral Training Centre (DTC) at the Manchester Centre for Integrative Systems Biology trains students for a PhD in Systems Biology with direct links to relevant industries, e.g. AstraZeneca and Unilever. The DTC is fully integrated in industry labs and parts of the course are being taught by industry-related personnel.
- The Centre for Plant Integrative Biology (CPIB) at the University of Nottingham in the UK builds on the strengths and collaborations across four RAE (Research Assessment Exercise) 5-rated schools – the Schools of Biosciences, Computer Science and IT, Mathematical Sciences and Mechanical, Materials and Manufacturing Engineering – and strong industrial links with Syngenta and Unilever.
- The Biotechnology and Biological Sciences Research Council (BBSRC) in the UK has recently launched the Systems Approaches to Biological Research Initiative with an investment of €37M. The projects recommended for funding are an example of effective engagement of university departments with the private sector, and involve interaction from companies representing the pharmaceutical, agrochemical, software, and instrumentation industrial sectors.
- In Norway, a number of small and medium enterprises (SMEs) are working in close collaboration with public organisations: a) Photocure AS, in collaboration with Radium in Oslo to develop tools for cancer diagnostics and treatment; b) Avexxin AS, early stage drug discovery on rheumatoid arthritis and glomerulonephritis in collaboration with the technical University in Trondheim (NTNU); c) Lytix AS, cancer therapy using lytic peptidomimetics in collaboration with

[8] Butcher E (2005) Can cell systems biology rescue drug discovery? Nature Reviews Drug Discovery 4(6), 461-467.

the University of Tromsø; d) Lauras AS, in collaboration with the Biotechnology Centre at the University of Oslo, working on development of immunostimulatory therapy disrupting the hyperactivated cAMP signalling pathway in HIV immunodeficiency.

- In Spain, the Ministry of Education and Science (MEC), within its 'National Strategic Action on Genomics and Proteomics', aims to better position itself in the area of application-oriented research to strengthen the competitiveness in industry. A first and crucial step in rising to this challenge was the formal constitution of INVEGEN, a Spanish association of private companies with interests in diverse sectors (agrifood, forestry, bio-energy, etc), in 2005.
- In France, the French National Research Agency (ANR) provides specific programmes in which one or more SMEs have to be associated to one academic lab to apply and be funded. SMEs are funded at 50-60 % of full cost depending on their size, whereas academia is funded at 100% of additional costs. This programme exists in biology, informatics, and other relevant areas.
- In The Netherlands, TIPharma is a collaborative structure consisting of industrial and academic research teams. TI Pharma conducts groundbreaking, cross-disciplinary research and trains their personnel to improve the efficiency of the entire drug discovery and development process.
- Opened in December 2005 the CoSBi Centre for Computational and Systems Biology is a joint venture between Microsoft Research and the University of Trento. At CoSBi, researchers are focusing on creating the next generation of computational tools that will enable biologists and others working in the life sciences to better understand and predict complex processes in biological systems, which could revolutionise our understanding of disease, and lead to new and faster insights into entirely novel therapies and better vaccines.

The research arena

The creation of exhibition platforms was proposed as a means to provide a stimulating forum where academia and industry can establish new collaborations, find mutual interests and design common research programmes.

The establishment of mixed departments associating academia and industry was proposed as a step towards facilitating close collaboration at this relative early stage. It was recommended that the character of such departments had to be rigorously international, be based on specialised technology and offer expert training. The development of an industry-driven technology platform was identified as a structure that may facilitate realisation of the potential of public-private partnerships in this area. It was suggested that programmes focusing on small projects could provide far more benefits than larger schemes. The generation of start-up companies, led by post-doctoral scientists who are adequately trained in systems biology, might be facilitated by public-private partnerships. These start-ups were thought to be conceived on a project-base fashion.

The critical role of industry in up-taking this new science and exchanging knowledge was extensively discussed. Public-private partnerships were regarded as a way to enhance both the academic excellence and industrial relevance of postgraduate research. The proposal of establishing joint graduate programmes involving academia and industry was thought to be of particular relevance.

There is a range of models and schemes available in a number of partner countries, which facilitate the application of knowledge and new technologies arising from research. The advantages of making use of existing models were extensively discussed and encouraged. Learning from present and future partnerships, and extrapolating and improving current schemes is of relevance. These models and schemes can adopt the form of: a) research grants with different levels of industrial contribution towards the costs of the project; b) 3-4 year studentships to fund science graduates to undertake a research programme designed jointly by academic and industrial partners; c) industry fellowships, which allow academic scientists to carry out research in an industrial environment or industrial scientists to conduct research in academic centres; d) follow-on funds, which provide financial support in the route to commercialisation or licensing.

Some degree of stability in funding is required for these partnerships to foster industrially focused research teams doing research with a visionary approach, delivering long-term benefits and innovation. Such medium- to long-term funding might be matched between public and private sectors.

Freedom of access

Open access resources and open source collaborations are emerging in the biological sciences at high rate, driven by the enormous recent advances in communication technologies. There are clear benefits to such resources as mechanisms for accelerating scientific research. Both will succeed in proportion to the extent of scientific community involvement.

Some experts have strong reservations over the rise in intellectual property (IP) protections as it could hinder discovery. The protections would bar too many scientists from using IP research tools. Surveys carried out in the USA, UK, Germany and Japan by AAAS's Science and Intellectual Property in the Public Interest (SIPPI) project found that tools from software to genetically modified organisms 'remain relatively accessible to the broad scientific community'. This indicates that scientific research may not have been affected significantly by a recent proliferation of technology patents and licensing agreements.

It is the view of the majority of experts that to push research forward, scientists need to draw from the best data and innovations in their field. The full-scale application of an open-source approach to biology was believed to require further exploration in order to free up biological data without violating intellectual property rights.

The business venture

As a result of new collaborations, academics and industrialists enter a binding agreement that is enforceable by law. This new venture risks a loss but promises a profit. The IP often derived from such a venture offers control over the ownership of ideas.

Most scientists participating in the discussions agreed that IP in systems biology requires full attention. There are specific legal issues to this emerging area, which require expert patent lawyers and call for the creation of specific Intellectual Property Rights (IPR). These rights should facilitate academics and industrialists in managing and measuring outcomes and discoveries.

Industry is engaging with the systems biology community and the possibilities it has to offer in the coming decades. Concerted forces between industry and academia create more knowledge, opportunities and value. Some of the present hurdles to be overcome are freedom of data access and intellectual property rights.

9. A 5-10 YEARS VISION FOR SYSTEMS BIOLOGY

'The orchestra of life works without a conductor. We might find that discovery relatively easy to accept for viruses, bacteria, plants, and the simpler animals. But can this really be true for the so-called higher animals, including man? After all, we have a huge brain, with billions of nerve cells. It may well be the most complicated thing in the universe.'
Denis Noble, The Music of Life[9].

In biology there is, at the moment, a sense of barely contained expectation. Systems biology emerges as a powerful tool with the promise to provide the answers to some of the major biological challenges we are facing today. It promises enormous economic and social impact, probably comparable to that in the 20th century from advances in physics, which provided electrification, radio communication, electronics, telephony, internal combustion engines, atomic energy and the internet.

Many of the big challenges facing humanity are biological, or are amenable to biological intervention. For example understanding the complexity of the ageing process and finding solutions to an ever increasing ageing population. The risk of a new virus, spreading infection at a pandemic scale, is another global biological issue. Climate change is also a biological problem as carbon dioxide is released into the air at a greater speed than plants can absorb it.

The future of this revolutionary field is currently being defined. The vision, creativity and determination of talented scientists who decide to make this field their overarching focus, will drive the field to the tipping point, and will leave a legacy of a new generation of scientific leaders. The sharp sight, clear focus and forward looking of funding organisations will identify opportunities, invest public goods and capitalise the immense potential that systems biology has.

Scientists and funding organisations jointly reflected upon the expected deliverables by systems biology in the next 5-10 years, the scientific topics of common interest and the particular strengths that European organisations have to offer (Annex 1). As a result, two main areas were identified where improvement is needed in order to achieve these targets. One was addressing infrastructural needs. It was proposed

[9] Denis Noble, The Music of Life, Biology Beyond the Genome. Oxford University Press Inc., New York, 2006, pp 113

that establishing networks for cooperation and synergy between different countries and different disciplines was a priority. The second major pre-requisite was education in this interdisciplinary field.

A number of biological topics to benefit from advances in systems biology were identified within the biomedical, agricultural, food and environmental sciences. Some scientists anticipate that in the next 10 years a model of the brain will be completed, together with new ways to tackling neural diseases. In 10 years, we will understand why and how we get older, and how to address the health and social issues associated to the ageing process. While in the next few years, systems biology will provide solutions to protect our environment, through advances in bio-based products research, bioremediation, biofuels, and ecosystem health.

The view of the ERASysBio partners is that in addition to funding research projects, the areas where funding organisations can make significant contribution in the next 5-10 years are the training of a new generation of researchers, the adoption of policies on data standards, data management, data sharing and best practice, and the fostering of productive and long-lasting scientific networks.

What can we expect from systems biology in 5 to 10 years? Great advances in biomedicine, agricultural, food and environmental sciences are expected through the setup of realistic goals. A 'man on the moon' success story will put systems biology in the spotlight and demonstrate its full potential. For this to become a reality, systems biology needs firm action towards structuring, training of excellent scientists and adoption of data standards and management.

10. OUTREACH – Spreading the word

Systems biology covers one of the most exciting and challenging areas in modern science as it enables a holistic analysis of individual systems and processes. It also provides a powerful tool to identify, for example, key gene-environment combinations that affect ageing and immune responses. The benefits of this approach are immense and, as the area develops rapidly, some aspects of this research have the potential to raise concerns among the public.

The flow of information and exchange of views between researchers and members of the public is being encouraged by the majority of funding organisations, learned societies and top university departments across the ERA. These organisations recognise that it is essential to foster an environment of trust and to assist in the development of a society that is fully equipped to debate scientific issues. The ERASysBio partners are committed to tell the public about the research they fund but they also need to know what people think about this research to guide their own policies and decisions.

ERASysBio wishes to engage in science outreach – that is, organised activities targeted at our youth, school teachers, and general public to increase their interest, understanding, and involvement in the powerful combination of maths, bioscience, physics and engineering which make up the systems approach to biological research.

Young people and teachers – seeds of change

It is common knowledge that studying traditional sciences is becoming more unpopular among young people. This has enormous implications for the future. Unless effective action is taken, the ERA's long-term capacity to innovate and the quality of its research will be compromised. But what can we do about it?

ERASysBio believes that scientists and funding organisations all have an obligation to rise to this challenge and contribute to address skills shortages and recruitment problems in this area. As a first step, ERASysBio chose to gather the views of scientists and funding organisations on this topic. Reaching young people and teachers was the target audience that received the strongest consensus. The ERASysBio partners are now exploring mechanisms to reach and inspire the new generation through working with science teachers across the ERA.

Synthetic biology – ethical and societal implications in the synthesis of new life

Synthetic biology has gained increased attention in the scientific arena in recent years. In 2005 the EC New and Emerging Science and Technology (NEST) programme published the report 'Synthetic Biology – Applying Engineering to Biology'. The report defined synthetic biology as 'the engineering of biology: the synthesis of complex, biologically-based (or inspired) systems which display functions that do not exist in nature'.

The concept of synthetic biology is closely linked to the scientific agenda of systems biology. Systems biology studies a biological system at various levels in its entirety, ranging from cell networks to cells and complete organisms. It involves the mapping of pathways, gene and protein interactions and logical circuitry of natural organisms at the cellular, tissue and whole-organism level and the integration of this information into a computer model. Systems biology therefore provides the analytical framework in which synthetic biology operates.

Much of current synthetic biology research is not new. However, in the last few years several funding organisations across the world have gradually recognised this area within their remits. These organisations are fully aware of the ethical debate linking systems biology to synthetic biology and the growing concern among individuals in our society regarding the principle of assembling artificial components to form a living organism.

Discussions held at the two ERASysBio strategic meetings emphasised the urge for funding organisations and science experts to explore possibilities to influencing which way the debate develops in the ERA. The BBSRC in the United Kingdom has recently launched a call for networks in synthetic biology. The aim of the call is to help build a community, to foster cross-disciplinary research and to overcome language barriers. It also aims at developing awareness and incorporation of ethical and societal issues at early stages in project development.

The development of the debate in the ERA on ethical and societal implications of systems biology can and should be influenced. ERASysBio is currently exploring possible mechanisms to reach and inspire the new generation through working with science teachers across the ERA.

11. FUNDERS

'Money often costs too much.'
(Ralph Waldo Emerson)

Cost should not dominate when science and thus the public interest are concerned. This is why the ERASysBio partners are committed to paving the way for systems biology scientists to interact outside the boundaries set by national regulations.

Above we have elaborated on the current situation, present and potential initiatives, challenges, needs and responsibilities in systems biology as reflected by the scientific community. The general consensus was that systems biology should continue to rapidly develop in the ERA and major achievements have already been accomplished.

ERASysBio is not a single international effort to boost European systems biology. Many successful initiatives on different subjects, at the local, national and international level were brought up at the meetings, demonstrating the awareness within both the scientific community and funding organisations of their concomitance and of the continuous need for improvement. ERASysBio wishes to see complementarity in its current, and future activities and those of other organisations and funding agencies. Representatives from two major efforts supporting the advancement of systems biology at the European level were invited to the discussion forum provided by the ERASysBio partners. The 'Systems Biology Programme of the European Commission 2002-2013' was presented, highlighting the progress of many of the issues discussed at the meetings.

The ESF has recently launched its scientific forward look, 'Systems Biology: a grand challenge for Europe'. The document shows clearly the tremendous influence of the discussions held at the two ERASysBio strategic meetings on driving ESF future policies in this area. ERASysBio is exploring ways to work with the ESF in addressing the overall challenge of realising the full potential of systems biology research in Europe. In doing so ERASysBio and ESF should define the specific roles that each will play in advancing systems biology in the ERA. Annex 2 provides a summary of EC initiatives and ESF proposals.

SysMO – Systems Biology of Microorganisms

The transnational initiative SysMO is an example of effective cooperation between European funding organisations for the funding of research on systems biology in microorganisms. This pilot call is under the umbrella of activities of ERASysBio, and financed by the Federal Ministry of Education and Research in Germany (BMBF), the Federal Ministry of Science and Research in Austria, the Netherlands Organisation for Scientific Research (NWO), the Research Council of Norway (RCN), the Biotechnology and Biological Sciences Research Council (BBSRC) of the United Kingdom and Ministry of Education and Science (MEC) in Spain. Eleven consortia, including 91 groups across Europe, are funded under this initiative with a financial commitment across all partners of €28M.

All SysMO consortia started their projects in March 2007 but the effort of SysMO funding organisations has not ended there. The SysMO funding partners have embarked on a joint effort to involve all groups from the 11 consortia in a common data management, storage and sharing strategy. The SysMO Data Management Group, composed of representatives from all SysMO projects, is now finalising the content of a proposal with support of all SysMO funding organisations. The proposal promises to tackle specific challenges in the areas of communication, data storage, data exchange and data sharing, and provide solutions that will outlast the duration of the projects. SysMO and its joint data management strategy are becoming an exemplar of an efficient and concerted way to set a European initiative in systems biology that contributes effectively and rapidly to the prosperity of the ERA.

Beyond our frontiers

The United States (US), Japan, Switzerland and the countries of the European Union have all implemented mechanisms to fund systems biology research, with US and Japan being viewed as the most progressive. Central milestones include the founding in the US of the Molecular Sciences Institute in 1996 and the Institute of Systems Biology in 2000, and the launch in Japan of the E-Cell Project in 1996 and the Kitano Symbiotic Systems Project in 1998.

In Japan, the E-Cell Project started in 1996 with the aim of establishing technological bases that will make possible predictive modelling and simulation of cellular systems at the molecular level. The ERATO Kitano Symbiotic Systems Project started at the Sony Computer Science Laboratory in 1998 with the aim to analyse, model and simulate living organisms through innovative IT tools. The level of investment is expected to grow in Japan in the next years as the Council of Science and Technology has identified systems biology as one of its thematic priorities.

In the US, the National Institute of Health's (NIH) Roadmap for Medical Research includes systems biology-related strategic areas. Among these is the US$300M Molecular Libraries Initiative, which includes the NIH Chemical Genomics Center, a national network of molecular screening centres, and the development and expansion of computational and predictive modelling. The National Institute of General Medical Sciences has a dedicated Systems Biology Initiative, which funds centres, research projects and education programmes, with the aim to attract investigators trained in the mathematically based disciplines to study biomedical problems. The National Science Foundation's Integrative Organismal Biology programme supports research aimed at integrative understanding, through advanced computational techniques and interdisciplinary perspectives, from the molecular through the ecosystem levels. Other significant investments in systems biology research include those from the Defence Advanced Research Projects Agency, the Army Research Office, and the Department of Energy.

In Switzerland, systems biology is supported through initiatives such as the SystemsX, a programme funded by ETH Zurich, University of Basel and University of Zurich. The initiative, which is funded by pharmaceutical giant F. Hoffmann-La Roche (Roche), received support amounting to $8.7M from the Swiss Federal Institute of Technology in 2006 and 2007. An additional $17.4M is provided by the local government to construct a new Centre of Biosystems and Engineering in Basel. Additionally, the Department of Biology at the ETH Zurich founded the Institute of Molecular Systems Biology in 2005.

Several international initiatives have been launched to boost systems biology research in the ERA. It is crucial that these initiatives cooperate to maximise the potential of systems biology. The recommendations in this paper therefore do not only highlight the responsibilities of the ERASysBio partners as funding organisations to coordinate their actions, but rather the efforts and commitment that are required from all stakeholders to make this happen.

12. RECOMMENDATIONS

ERASysBio was created to act as a nucleus in the consolidation of systems biology research in Europe and its associated countries. ERASysBio supports joint activities in systems biology conducted at the national and regional level, to harmonise funding and to coordinate initiatives between funding organisations in the ERA. The ultimate goal of ERASysBio is to provide a sound knowledge base that is required for systems biology to mature from a discovery science into an established science, embedded in the policies and strategies of all concerned institutions, public and private organisations and governments across the ERA.

In previous chapters, the ERASysBio partners present an overall picture on the current state, strengths, needs and challenges in systems biology. In listening to the views of a mixed, well-represented audience at its two strategic meetings, ERASysBio has generated a number of recommendations and identified key actions to be put in place.

ERASysBio aims to provide a framework for further discussion and activities of systems biology in the ERA, and emphasises that these recommendations and its actions concern all stakeholders. The ERASysBio partners are currently setting up and launching a number of activities, which promise to have an immediate impact on the direction and consolidation of systems biology in the ERA. These activities include a joint research call, specialised training/summer school schemes and the stimulation of networks between national systems biology centres.

1. Establish a number of trans-national systems biology networks in the ERA

Networks should be established with the aim to link existing systems biology centres and departments alike. These networks should work towards the development of a world-class infrastructure supporting systems biology research in the ERA. Networks should serve as vehicles to facilitate the communication between disciplines, for the exchange of information, data, ideas, knowledge and expertise.

Improvement and strengthening of (electronic) networks, provide communication that subsequently can result into collaboration. These networks will furthermore facilitate training and mobility of both scientists and data over the ERA.

2. Encourage the adoption of data management and sharing best practices in the ERA

Through the adoption of data management and data sharing policies, funding organisations and scientific journals can play an active role. By encouraging the scientific community to consider and incorporate specific requirements for data management and sharing among collaborating teams and with the wider community, they can contribute to the realisation of this radical culture change, reinforce open scientific inquiry and stimulate best practice.

3. Encourage the adoption of data standards in the ERA

The standardisation of data is a pre-requisite to the consolidation of systems biology, also needed to enable data management. The challenge of achieving high data quality requires the joint effort of the scientific community and can be initiated through the adoption of SOPs. Stringent peer-review processes, led by funding organisations and scientific journals, should include considerations of data standards.

4. Optimise the education and training in systems biology in the ERA

Interdisciplinary scientists are in demand and for this a new approach to education is needed at all levels. Publicly-funded institutions are at present the best placed to host the breadth of disciplines needed to develop systems biology. These institutions, together with funding agencies and learned societies, have an active role to play. Some of the actions that can be taken are:

- Encourage universities to bring their curricula up to speed to accommodate the current requirements. Students ought to be credited for exploring the integration of disciplines. The implementation of a centralised and agreed curriculum in the ERA needs to be explored.
- Organisation of international summer schools on specific subjects and at the right level of complexity, for young scientists as well as for established researchers.
- Promote the mobility of students and researchers through a range of funding schemes. A great degree of flexibility is required from institutions and funding organisations for these schemes to provide the best opportunities for exchange across the ERA. Master studentships, PhD studentships, post-doctoral fellowships, and fellowships for established scientists, such as discipline hopping, should be incorporated in this vision.

5. Stimulate the establishment of systems biology research structures across the ERA

The integration of the systems biology community in an interdisciplinary research environment requires the establishment of adequate structures. These should provide tools and technologies, training opportunities and an optimal arrangement for the fast development of this field. These structures can adopt different forms, some examples are summarised below:

- Systems biology centres: The UK and Germany already have made substantial investments and other countries have also recognised the advantages of integrating traditionally separate subjects into top class interdisciplinary programmes under one roof. It is proposed that the model was followed to establish systems biology centres in other countries across the ERA and to bring them into collaboration in research and training.
- Virtual centres: This model offers the opportunity to establish inter-institutional collaborations and integration without a significant financial investment. The model is to be explored in association with Recommendation 1 – Networks.
- Reference Centres: The creation of a European Institute of Systems Biology, which would combine theory and advanced experimental facilities, was discussed.

6. Explore mechanisms to strengthen the academic-industrial links in systems biology in the ERA

Publicly-funded institutions are encouraged to create mixed departments associating industrial partners to facilitate collaborations, provide training and specialised technology in systems biology. Funding agencies are encouraged to extrapolate, improve and promote current schemes, and to consider in association with industry routes for medium- to long-term joint funding schemes. The scientific community in dialogue with industry should explore mechanisms for the full-scale application of an open-source approach to systems biology without violating intellectual property rights.

'All languages are prisons of culture as well as liberators of communication. We need language to communicate, but our languages in turn cloud what we understand. There is no mystical […] culture in which all our problems are solved. The point is rather that cross-cultural experience can help us brake out of our illusions.'
Denis Noble, The Music of Life, 2006[10]

[10] Denis Noble, The Music of Life, Biology Beyond the Genome. Oxford University Press Inc., New York, 2006, pp 117

ANNEX 1 – Targets and areas of common interest in systems biology

STRUCTURE AND TOOLS – Targets for next 5-10 years
- Formation of multidisciplinary teams;
- project management best practice;
- coordinated systems biology training;
- generation and standardisation of tools for handling large databases, for quantitative proteomics, and for the creation of repositories for public data sharing;
- development of methods to assess compatibility of simulation with image data;
- public opinion and understanding of needs and achievements of systems biology;
- firm, established connections with industry.

SYSTEMS BIOLOGY SCIENCE IN EUROPE
1) Anticipated scientific achievements for the next 5 years
- Organisation of knowledge and data into applicable and predictive models, usable for scientists within and outside systems biology community;
- development of good models for defined aspects in single cell systems, e.g. yeast metabolism, signalling, genetic pathways, energy, carbon metabolism in hepatocytes;
- development of models for aspects of multi-cellular organisms, e.g. cellular communication;
- development of models for specific human tissue function/malfunction.

2) Anticipated scientific achievements for the next 10 years
- Reiteration of experiments to allow development of models: expansion;
- extension of building of models to more systems;
- integration of physiological, biochemical and molecular aspects in organ models;
- building of models of complex diseases at multiple levels;
- building of models of plant-environment relationships;
- extrapolation and application of developed models to medical and other systems.

3) Research subjects of pan-European interest
a) Biomedicine
- Multi-factorial diseases/ predictive modelling for complex diseases, e.g. obesity, metabolic syndrome, cancer, cardiac diseases;
- drug development, toxicology, proof of concept prior to clinical trials, personalised medicine;
- metagenomics, considering both organism and its ecological niche;
- aging processes, health and social issues;
- neuroscience, e.g. schizophrenia, Alzheimer's, Parkinson's, depression and others;
- infectious diseases (human and animals), malaria as a pathology model;
- food safety, human nutrition.

b) Agriculture, food, biosafety and the environment
- Energy-related research, e.g. biofuels, atmospheric-carbon capture;
- biomimics, synthetic biology;
- agro-economics, agrobiotech;
- crop breeding for sustainable agriculture;
- combating plant disease;
- metabolic bioengineering;
- non-medical aspects of metagenomics.

ANNEX 2 – Initiatives and proposals by other funding agencies

European Commission initiatives

The information provided on initiatives from the EC is based on the information kindly provided by Dr. Frederick Marcus. The approximately 20 projects in this initiative link many several hundreds of laboratories around Europe. Current funding initiatives include 12 small projects (STREP/CA/SSA, several dozen laboratories; €25M) and 5 large networks (NOE/IP, over 100 laboratories; €60M).

The EC considers Systems Biology to have a wide range of 'dimensions':
- Structures — Gene, Protein, Macro complex, Organelle, Cell, Network, Tissue, Organ, Organism
- Function — Regulatory, Growth, Metabolic, Electrical, Mechanical, Transport
- Data to theory — Empirical Data, Statistical Modelling, Predictive Modelling, Mathematical, Ontologies, Systems Analysis, Physico-Chem Principles, Theory
- Models — Ease of experiments: simple bacteria, rapid reproduction; eukaryotes, still relatively simple, rapid reproduction; single cells as cell lines; fertilised eggs, simple, more difficult to obtain, maintain, artificial environment; in-vivo studies model organisms, complex, more relevant; primates, humans, highly complex and relevant.

Current funded STREP/CA/SSA projects cover a wide range of research areas

- COMBIO P53-MDM2 Spindle systems biology
- COSBICS Signalling systems biology
- DIAMONDS Cell Cycle, yeast-human systems biology
- EMI-CD Systems biology models- complex disease
- ESBIC-D Systems biology of cancer-patients
- YSBN Systems biology of yeast cells
- BIOBRIDGE Integrative Genomics and Chronic Disease Phenotypes
- QUASI&AMPKIN Modelling of signalling pathways
- STREPTomics Streptomyces – protein production
- SYSBIOMED Workshops determining Systems Biology approaches for Medical Applications
- VALAPODYN Intracellular Pathways – Cell Death

Current NOE/IP projects involve > 100 laboratories, and are linked to many worldwide, European and national programmes

- ENFIN Bioinformatics basis for systems biology modelling
- BaSysBio Systems biology of Bacterial transcription
- BioSim Systems biology for medical applications
- EUTRACC Systems biology for transcription in mice
- AGRON-omics Systems biology of leaf development in Arabidopsis

Future funding plans – programmes:

- First call FP7 – 4 Large Scale (€48M)
- Second call FP7 – Several Medium scale (€10s of millions)
- Rest of FP7 – Genomics, SysBio (€100s of millions)
- Plus Infrastructure

Future funding plans – areas:

- Systems biology inter-, intra-cellular processes
- Genetic variation in human health – also provides key infrastructure for systems biology analysis.

The EC has, by funding and linking programmes around Europe, provided a basis for a European Research Area (ERA) in Systems Biology. A strong forward programme is planned, on the basis of projects, workshops and consultations. These activities provide important input to decision making in the ERASysBio context.

European Science Foundation proposals

In August 2005 the ESF published the Policy Briefing on systems biology, a brief report which was the outcome of the ESF Forward Look on Systems Biology in 2004/2005. The report summarises recommendations of needs and requirements that were provided by an international high-level expert group. Currently the ESF is finishing rounding up the full Forward Look report, with more detailed insight into the considerations of the experts and their conclusions. In short the recommendations from the Policy briefing were:

- Establishing a task force to define a European Road map
- Organisation of high-level strategic workshops
- Involvement of specific target groups, e.g. health insurances and regulatory bodies
- Focus on small number of specific targets
- Perform business case studies to explore costs and benefits
- Set up a European Systems Biology Office
- Simulate transnational collaborations and networking with other initiatives
- Establish a European training programme in systems biology

For the full text of the ESF Policy briefing, see: http://www.systembiology.net/esfflshort.pdf

In September to 2007 ESF published its forward look 'Systems Biology, a Grand Challenge for Europe'. The recommendations include a European road map, European reference laboratories, cooperation between industry, academia and funding agencies, public acceptance, training and education, and cooperation between different European systems biology initiatives. Some priority areas were indicated to enforce breakthroughs in the different fields of systems biology.

For the full text of the ESF Forward Look, see: http://www.esf.org/publications/forward-looks.html

ERASysBio partners

Coordination Germany	Forschungszentrum Juelich GmbH (FZJ) Project Management Juelich (PtJ)
Germany	Federal Ministry of Education and Research (BMBF)
Austria	Federal Ministry of Science and Research (BMWF)
Belgium	National Fund for Scientific Research (FNRS)
Finland	Academy of Finland (AKA)
France	French National Centre for Scientific Research (CNRS) French National Research Agency (ANR)
Israel	Israeli Science Foundation (ISF)
The Netherlands	Netherlands Organisation for Scientific Research (NWO) The Netherlands Organisation of Health Research and Development (ZonMw)
Norway	The Research Council of Norway (RCN)
Russia	Russian Foundation for Basic Research (RFBR)
Slovenia	Ministry of Higher Education, Science and Technology (MHEST)
Spain	Ministry of Education and Science (MEC)
Trento, Italy	Autonomous Province of Trento (PAT) Department of University and Scientific Research
United Kingdom	Biotechnology and Biological Sciences Research Council (BBSRC)

Affiliated partners

Luxemburg	National Research Fund of Luxemburg (FNR)
Switzerland	Swiss National Science Foundation (SNF)

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