European Science Foundation Policy Briefing

Systems Biology: a Grand Challenge for Europe

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Foreword

Thanks to spectacular advances in the "-omics"[1] disciplines and in information and communication technologies, the biosciences are heading for another revolution: Systems Biology, targeting pathways, cells, organs and complete organisms by integrating experimental data with computational and theoretical approaches. Systems Biology combines concepts from different scientific disciplines to obtain an integral understanding of complex biological systems in terms of their components and their interactions.

A better understanding of the underlying mechanisms of life should open perspectives for a deeper insight into human diseases and the development of new therapies. Thus, Systems Biology promises to have a profound impact on medical research, including drug development and biotechnology.

The integrative character of Systems Biology might be one reason for the fascination of younger scientists for this subject, encouraging them to overcome borders between disciplines and to foster collaboration far beyond national borders. European policy makers should seize this unique opportunity in order to counter the impending lack of young investigators. In addition, the expertise from Eastern European countries should be integrated into the framework of a European Research Area (ERA) in Systems Biology.

The success of European Systems Biology in a global arena will essentially depend on a better coordination of national and European efforts, a rapid adaptation of training schemes and long-term investment in cutting-edge research, which requires immediate and determined action.

This Science Policy Briefing represents an ambitious endeavour moderated by the European Science Foundation (ESF) to set up a European action plan towards a Grand Challenge for European Systems Biology.

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Introduction

Biological and biomedical research is undergoing revolutionary developments that have an immense and lasting impact on society. These developments involve other sciences, including physics, chemistry, mathematics and informatics. They enable us to know and measure the properties of the molecules that constitute life. We are now capable of revealing the complete sets of chemical reactions, interactions and dynamic structures through which molecules, cells and organs determine the functioning of living organisms, including humankind. Integrating the rapidly growing amounts of data available on these components and their interactions and generating understanding on how they govern life is termed *Systems Biology* or *Integrative Biology*.

As Systems Biology progresses, multifactorial diseases (such as diabetes, arthritis, heart failure and cancer) might be understood in terms of failure of molecular components to cooperate properly. Consequently, complex diseases may be approached and treated in a much more rational and effective way.

It should be Europe's ambition to be at the forefront of pinpointing the molecular and systemic causes of diseases, aiming at the rational design of targeted therapies and drugs.

This brief report is the outcome of the ESF Forward Look on Systems Biology in 2004/2005, involving an international high-level expert group, whose members agreed upon specific recommendations

[1] The term "-omics" describes the genome-wide study of entities, in this case the DNA, RNA, protein, or other molecular components of cells, tissues, or organisms.

dedicated to the recent needs and requirements of European Systems Biology. The recommendations are summarised at the end of this report. Input from representatives of industry was taken into account. A full Forward Look report will provide more detailed insight into the considerations of the experts and their conclusions.

This briefing is intended to trigger targeted efforts of relevant stakeholders, including the ESF and its member organisations, governments, the European Commission, European industry and European academia.

Impact of Systems Biology

Systems Biology involves the goal-oriented and systematic gathering of knowledge at all levels, from molecules to entire living organisms, and the subsequent integration into comprehensive and quantitative computer models. These will enable the accurate simulation of the processes of life[2]. Not only will this provide key insights into the functioning of living organisms, more importantly it will uncover underlying principles of how life itself operates. The societal and economic potential and value of such knowledge is immense.

Health

Models based on Systems Biology may well facilitate the more accurate prediction of the properties and behaviour of living organisms in its physiological, pathological and technological context. Integrative Biology is expected to have a major impact on the paradigm shift in medical research towards dynamic multidrug treatments and personalised medicine[3]. It will allow a more cost-effective development of drugs and therapies for major diseases that plague our society today.

Biotechnology

Molecular knowledge of microorganisms, plants and animals gathered from and integrated by Systems Biology-related research will enable a more predictable and rational approach to their genetic and metabolic engineering. This has the potential to change green and white biotechnology in fundamental ways. The rational development of new food products, the production of special chemicals and novel approaches to plant breeding come within reach, as the huge amounts of information about genes, proteins and metabolic pathways can now be integrated using mathematical models and integrative bioinformatics. Eventually, Systems Biology approaches may largely replace animal testing. Systems Biology is a key to innovation in the area of biotechnology. As the food industry is the largest sector in EU manufacturing, it may be among the Systems Biology outlets with the greatest economic potential. This may help to increase the average education base of this important branch of industry and consolidate one of Europe's most important export flows to the USA.

Socio-economic potential

Systems Biology contributes to Europe's endeavour to take a leading position in the generation of new products such as drugs, therapies and biotech-based goods and knowledge. By increasing the safety and efficiency of biotechnological production processes, Systems Biology has the potential to strengthen Europe's economic competitiveness and to improve the quality of life for EU citizens.

Europe should decide whether it chooses to lead in these areas or to become a net importer of Systems Biology-based knowledge and products.

European Strengths

Opportunities for Europe should be seen in their global and historical perspectives. Systems Biology has developed into two major branches[4]. One originates from functional genomics with its genome-wide sequencing and microarray analyses. This has developed rapidly in Japan and the USA. That

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[2] Proof of this concept is the model of the human heart that integrates the molecular, cellular and organ levels in a quantitative and predictive manner (see Noble *Modelling the heart: from genes to cells to the whole organ.* Science 295:1678-1682 (2002)).

[3] The ultimate goal of this new field is to tailor drugs and therapies precisely to the needs of individual patients. Personalised medicine has the important potential to improve the safety and efficacy of medical treatment.

[4] See Westerhoff and Palsson *The evolution of molecular biology into Systems Biology.* Nat Biotech. 22:1249-52 (2004).

approach provides insights into transcriptional patterns and related processes. However, it gives little information about how the dynamic interplay between the molecular components of living organisms results in their function or dysfunction.

The second branch is the bottom-up and hypothesis-driven approach of Systems Biology that aims at discovering how the properties of living organisms arise from the interactions between their molecular components. Historically, this type of approach has a solid basis in Europe (including the Eastern European countries) in theoretical biology and physiology. This is the branch of Systems Biology where Europe is traditionally strong.

European Systems Biology: Current Status and International Context

Recently, national and transnational funding programmes on Systems Biology have been launched in Finland, France, Germany, the Netherlands, Switzerland and the UK and in some of the new EU member states[5]. The European Commission is funding collaborative research projects and coordination activities related to Systems Biology (e.g. ERASySBio) under the 6th Framework Research Programme (FP6)[6] and will implement the topic in FP7[7]. Further transnational activities have been set up in the EUREKA framework (InSysBio), the International *E. coli* Alliance (IECA), the SysMO initiative and the Yeast Systems Biology Network (YSBN). These projects represent important steps towards coordination, networking and sharing of resources in Systems Biology in Europe and clearly show that its importance is broadly acknowledged.

Major investments have recently been made in the USA in the field of Systems Biology. The Alliance for Cellular Signaling[8] initiated by the Nobel prize winner Alfred Gilman and the Genomes to Life Initiative[9] of the US Department of Energy represent prominent examples of large-scale activities. Furthermore, the Institute of Systems Biology in Seattle[10] (co-founded by Leroy Hood) and the Molecular Sciences Institute in Berkeley[11], which was set up in 1996 by the Nobel Laureate Sidney Brenner, have achieved an international reputation as pioneering research institutes dedicated to Systems Biology-related research.

In 1996 Japan launched the E-cell Project[12], followed two years later by the Kitano Symbiotic Systems Project[13], which includes research projects with the California Institute of Technology and various other research labs outside Japan. Other Asian countries, including Singapore, China and Taiwan have also entered the international competition by investing large sums in this promising domain.

Despite the large number of ongoing European initiatives in the field of Systems Biology, it is evident that their scope is too limited to achieve major breakthroughs in health and biotechnology in a reasonable time frame and to compete successfully with the USA and the Far East.

The Grand Challenge: Giving Europe the Lead in Life Sciences

Despite the major investments in life sciences in Europe and elsewhere, existing initiatives lack a strategy that results in efficient integration of and synergy between different programmes and that can overcome the fragmentation of the R&D landscape in life sciences. The Grand Challenge for Europe is to strive for a leadership position in life sciences by creating breakthroughs in health and biotechnology.

[5] EUSYSBIO : Survey on the current status of Systems Biology-related research in New Member States & Associated Candidate Countries, the Russian Federation & Newly Independent States, Western Balkan Countries and the People's Republic of China

[6] Examples of Systems Biology-oriented projects funded under FP6 are: EUSYSBIO, ERASysBio, BIOSIM, QUASI, BIOSAPIENS, COMBIO, EMI-CD, COSBICS, DIAMONDS.

[7] COM (2005) 119 final 'Building the Europe of knowledge'

[8] Alliance for Cellular Signaling: http://www.signaling-gateway.org/

[9] DOE's Genomes to Life program: http://doegenomestolife.org/

[10] Institute for Systems Biology : http://www.systemsbiology.org/]

[11] The Molecular Sciences Institute: http://www.molsci.org

[12] E-Cell Project : http://www.e-cell.org/

[13] The Kitano Symbiotic Systems Project: http://www.symbio.jst.go.jp/symbio/index.html

This is beyond the capabilities of individual European countries and industries. It requires a goal-oriented, pan-European effort and new creative ways of organising, coordinating and funding biomedical and biotechnological research in academia and industry. Furthermore, it needs a change in programme management and scientific culture by encouraging more collective efforts and cooperation.

In spite of attempts to do otherwise, most European granting systems for biomedical and biological research result in incremental advances by (small groups of) individual scientists, rather than an individual's contribution to larger efforts that may have much greater impact[14]. Meeting the Grand Challenge requires an approach that resembles the Human Genome Project, but has more dimensions and is of greater complexity. It calls for cross-border cooperation on a scale new to biological and biomedical research. Such a programme is highly ambitious and demands an objective-driven approach similar to that taken by the USA in the last century in landing a man on the Moon and returning him to Earth.

Meeting the Grand Challenge for European Systems Biology requires a robust multisource financing model. It will need novel ways of cooperation between industry and non-profit organisations, including governments, the European Commission and charities.

Making Choices

To achieve significant results in a reasonable time, it is essential that Europe initially concentrates on a limited number of targets. Choosing targets should be done carefully. They should create enthusiasm and at the same time expectations that can realistically be met in the context of science, industry and politics, and society at large. Linking choices to key issues in human health and in biotechnology is important.

The following considerations should be taken into account.

- Build on expertise that is available in European industry and academia.
- Concentrate on issues that contribute significantly to improving health of European citizens and economic competitiveness.
- Set realistic goals for a 5- to 10-year time horizon and broader objectives for a period of 20 years.
- Implement an approach that leads to the rapid development of generic knowledge, of tools in data acquisition and integration and of complex quantitative modelling.
- As the Grand Challenge progresses, take advantage of the generation and integration of new knowledge to pick up speed and address a broader range of issues, as was done in the Human Genome Project as it moved from a curiosity-driven to a technology-driven approach.

A first survey by the experts involved in this Forward Look identified the following *examples* of Europe-wide targets.

- Full molecular understanding of the bacterium *Lactococcus lactis*, the single cellular eukaryotic yeast *Saccharomyces cerevisiae* and the *human hepatocyte* (liver cell), which are biotechnologically and medically highly relevant. At the same time they represent robust systems for developing generic tools for integrating multilevel biological information. A concerted and goal-oriented European effort focusing on these issues could significantly enhance the health of EU citizens and industrial competitiveness.
- An ambitious and outstandingly relevant health issue is the *metabolic syndrome*, which includes obesity and type-II diabetes. A concerted European Systems Biology effort promises to make a substantial contribution to effective treatment and prevention of this complex disease in the next five to ten years, thereby addressing an immensely important biomedical, economic and societal issue.

A European Action Plan

Since no single country or industry is able to manage such a large-scale initiative by itself, it is imperative to launch a European concerted and objective-driven effort. Such a project will differ decisively from all endeavours that currently define the European

[14] See Liu *Cell* 121:505 (2005).

biomedical and biotechnological research landscape. Below, we address some key aspects of how a Europe-wide programme could meet the major requirements of the Grand Challenge. An action plan may consist of the following steps:

1. A task force to develop a European road map

A small task force should be created in which the major stakeholders are represented, including top scientists, industry, European science organisations and funding agencies, and representatives of the European Commission. This group of people should undertake the following:

- define road maps for the Grand Challenge for the next 10 and 20 years;
- draft a financial plan;
- propose an adequate research management structure that allows cost-effective, goal-oriented, large-scale research efforts;
- define new concepts for effective technology transfer and commercialisation of results;
- make a cost-benefit analysis.

The task force may be based on senior officers from European international funding and science organisations as well as from industries with major Systems Biology-related activities in Europe.

2. European Reference Laboratories (ERLs)

A cost-effective coordination of the European Systems Biology programme, as proposed here, requires the support of a consortium of European Reference Laboratories (ERLs). ERLs are research institutes that combine all relevant scientific disciplines and the know-how to provide outstanding expertise for core aspects of Systems Biology. They should be accessible to investigators from all over Europe to obtain the necessary introduction and training in this field.

ERLs should develop the scientific basis for standardisation and quality control of experimentation, which will then be implemented by the ESBO. In current biological and biomedical research, standardisation and quality control systems play only a limited role. As a result, data obtained by different research groups cannot easily be combined. This is particularly true for quantitative studies. Since heading for a complete understanding of complex biological systems crucially depends on properly handling such data, it is imperative that academia and industry define adequate standards and that these standards are implemented into databases. At the same time such standards should remain adaptable to changes as knowledge increases.

ERLs should be responsible for the following aspects of the Grand Challenge:

- development of generic tools for data integration and data storage that can be implemented by the ESBO;
- development of tools for the validation of data generated by the participating research groups;
- development of relevant training programmes in collaboration with the ESBO;
- providing excellent experimental facilities and expert advice on Systems Biology and its methodologies.

3. Cooperation between industry, academia and charities

A European large-scale effort as outlined in this paper requires a re-thinking of the present practices of cooperation between industry, academia and charities. All parties should contribute to and benefit from the programme but with a clear understanding of what belongs to the public domain and what is rightfully the proprietary information of private companies. An appropriate and sustainable public-private partnership model has to be developed. Re-evaluation of the notion of intellectual property will be investigated, distinguishing accurately between efforts leading to generic pre-competitive tools and those addressing specific commercial biomedical and biotechnological objectives.

4. Public acceptance

A major European effort as addressed in this report will be viable only if the general public accepts and endorses the underlying ideas and goals of the Grand Challenge for European Systems Biology. To achieve this, careful communication and explanation will be necessary from the onset, with initiatives in social sciences and ethics accompanying the Systems Biology research. A broad and open debate will enable the public to be aware of the socio-economic benefits, but also of any potential risks of the Grand Challenge, allowing a balanced and objective monitoring of the further development of this field from the very beginning.

5. Training and education

In contrast to the present practice of educating scientists in the classical disciplines, the Systems Biology approach requires new thinking across scientific borders. New interdisciplinary BSc, MSc and PhD teaching and training programmes should be implemented as a matter of urgency to address this issue. In this respect, an open debate with responsible European stakeholders and higher education institutions (e.g. universities) should be initiated.

6. Financing the Grand Challenge

The Europe-wide approach proposed here will require a higher level of funding than that provided by vehicles available now. We propose that a new financial model is developed based on cooperation between national, international, industrial, charities and EC-related organisations. It will be a major challenge to align this heterogeneous set of parties so as to produce a synergistic cooperative programme.

7. A European Systems Biology Office (ESBO)

Systems Biology depends on a close cooperation of a broad range of scientific disciplines, including medicine, pharmaceutics, biology, physics, chemistry, mathematics, nanosciences and ICT. Furthermore, a European effort of the scale foreseen here will involve numerous research groups from all over Europe, in connection with non-European initiatives.

This cross-border cooperation should be supported by an independent coordinating body that has an overview of ongoing activities, a timetable of planned research and an awareness of areas where information is missing and how these gaps should be filled. Furthermore, this body, named the European Systems Biology Office (ESBO), should foster international networking and be responsible for the management of public relations affairs of the Grand Challenge. The Office should mediate between the scientific, industrial and political stakeholders and provide them with expert advice.

The ESBO should raise awareness of ethical, socio-economic and intellectual property right (IPR) issues relevant to a European Systems Biology programme. Other important tasks may include questions related to training of undergraduate and postgraduate students and other scientists, as this is seen as a major bottleneck in Systems Biology. Furthermore, the ESBO should be charged with data storage and the implementation of a quality control system and standardisation in experimentation.

Recommendations

- Establish a task force to define a European road map. This could be mediated by the ESF.
- Organise a high-level strategic workshop for national and European funding agencies, industry and charities to develop an appropriate financial model for the Grand Challenge. In addition, this high-level group should work out a strategy plan aimed at the integration of ongoing activities in the field.
- Involve specific target groups, such as patient organisations, health insurances, regulatory bodies and publishing groups. It is important that they contribute to the development of the Grand Challenge.
- Concentrate on a small number of specific targets that are of major importance for human health and have a substantial impact on economic growth. The chosen targets should allow the exploitation of European strengths and expertise. Defined milestones should be achievable within 10 years.
- Perform business case studies to explore the costs and benefits of Systems Biology in general and of the Grand Challenge in particular. A review of the socio-economic value of such a large-scale approach would provide reliable data to funding institutions and policy makers on the expected outcome of the programme.
- Set up a European Systems Biology Office (ESBO) and identify research institutes that could serve as European Reference Laboratories (ERLs), providing appropriate expertise, resources and facilities for the Grand Challenge.
- Stimulate transnational collaboration and networking with other ongoing Systems Biology initiatives throughout the world to act in a synergistic manner and profit from their experiences.
- Establish a European training programme in Systems Biology to provide young investigators with the appropriate background. The programme could include regular summer schools, courses, graduate schools, BSc and MSc programmes.

ESF Forward Look on Systems Biology

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