ERASysBio+
trends and recommendations

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1. This report

In the past decade considerable investments in systems biology have been made by the European Commission and national funding agencies. ERASysBio+ (2008-2013) is an example in which 11 countries joined forces and together with the EC invested 24 M€ in 16 transnational research projects in the field of systems biology. In parallel the ERASysBio programme was dedicated to build a European systems biology community by (i) developing a European Agenda for Systems Biology, (ii) stimulating the formation of networks between European Systems Biology centres, and (iii) coordinating training and education in systems biology.

This report presents a personal vision on the development of systems biology in Europe, starting from the outcome of the ERASysBio+ programme and resulting in a number of recommendations.

Systems biology

In this document systems biology is understood as formlated in the call for proposals of the e:BIO programme of the German Ministry of Education and Research (BMBF).

The research approach of systems biology is characterized by a collaborative way of working in the form of cooperations between different disciplines – from engineering, information sciences and mathematics up to physics, chemistry, biology and medicine. The heart of the systems biology approach is the iterative process between laboratory experiments and quantitative and predictive modelling using computers, i.e. model-driven experiments and experimental data-driven models. Based often on large volumes of quantitative data, algorithms are used to create models that allow predictions to be made of the behaviour of complex biological systems with the aim of gaining an overall understanding of the system.

http://www.bmbf.de/foerderungen/15679.php
(minor textual adaptations made by the author)

2. Is ERASysBio+ successful?

The answer to this question depends on what one accepts as the most important success factors. Below a few of these are analysed. Sections 3 and 4 address how funding schemes can be made more effective and the quality of research can be improved.

a. ***Setting a strategic systems biology agenda***

ERASysBio produced a strategic document *Systems Biology in the European Research Area* [1] (March 2008), which is an interesting point-of-reference for a vision on systems biology and the high expectations this new approach in the life sciences. Importantly, the recommendations in that document are - five years later - still valid and to the point. Evidently, despite the high expectations of systems biology, changing the life sciences towards a more quantitative and systematic approach is a slow process that needs perseverance, patience and a long-term vision.

b. ***Building a systems biology community and infrastructure***

An important result of the ERASysBio and ERASysBio+ programmes is the creation of a European systems biology community. To this end, four meetings of systems biology centres in Europe have been organised in the period 2007 – 2011. These events effectively stimulated many formal and informal contacts between systems biologists. For instance, these programmes created a solid basis for the ESFRI initiative *Infrastructure for Systems Biology Europe* [2] (ISBE). ISBE will become a pan-European infrastructure that will make high-end systems

[1] http://www.erasysbio.net/lw_resource/datapool/__pages/pdp_2/ERASysBio_Systems_Biology_Strategy_Paper_25-Mar-2008.pdf
[2] http://isbe.eu/

biology expertise and hardware available for researchers in academia and industry. Presently, a comprehensive business plan for this systems biology infrastructure is being developed supported by a FP7 grant. It is expected that ISBE will begin to offer services in 2016.

c. ***The ERASysBio+ research programme***

Although formal reports of the 16 research consortia are not yet available, the recent ERASysBio+ symposium in Berlin (June 2013) presented a comprehensive overview of what has been achieved scientifically. Taking the development of predictive models based on experimental data sets as the major success factor of systems biology research projects, a substantial fraction of projects did not fully achieve. Importantly, this is not necessarily a judgement about the quality of the research performed, e.g. measured in terms of the classical criterion of number and quality of publications. Similar results seem true for other national and international systems biology funding schemes, although no systematic analysis has been carried out so far. Evidently, the promises made about the systems biology aspect in the grant applications often are too high, the selection procedures may not be optimal, or the complexity of the biological systems that are tackled often is underestimated. Most probably it often is a combination of the three.

d. ***Education and training***

Education and training in systems biology has been an essential component of the ERASysBio programme. A variety of workshops and summer schools have been organised. Among others, these activities have contributed to decisions made by many universities and research schools to develop BSc, MSc and/or post-graduate curricula in systems biology. Systems biology involves a tight cooperation between different disciplines, including biology, medicine, chemistry, physics, informatics, mathematics and engineering. Education and training in systems biology therefore require novel teaching programmes at the interfaces of these disciplines. Teaching material must be developed and teachers be found that are capable to cross borders between disciplines.

e. ***Conclusion***

In conclusion, the ERASysBio and ERASysBio+ programmes have been successful, particularly in creating a European systems biology community and a systems biology agenda.

3. Towards an updated strategic agenda for systems biology

Starting from the analyses in the previous section, below a number of issues are addressed that may be incorporated in an updated version of the strategic systems biology agenda.

a. ***Entering a new phase in implementing and exploiting systems biology***

Investments in the past 10 years have positioned systems biology in the lime light as a logical and promising toolbox to tackle complex biological systems by importing and adapting paradigms from other disciplines. We discovered that biological systems are highly complex and therefore often require bigger efforts and therefore larger investments than anticipated. This learning curve now should come to an end, asking for firm decisions of researchers, funding agencies and policy makers, enabling us to make a next step. It requires re-thinking of the

way we carry out and fund research in the life sciences (see section 4 for suggestions). If we don't do so, society will not fully profit from the potential benefits that the life sciences offer.

b. ***How can we make systems biology research projects more successful?***

The observation that systems biology research projects tend to be only partially successful in terms of developing and exploiting predictive models of complex biological systems needs attention (section 2c). Systems biology research projects are more demanding than the classic research efforts we are used to, if we accept that developing and exploiting effective models are an explicit success criterion. Classic research projects often are considered successful if they add information and/or knowledge, resulting in peer reviewed publications. In contrast, systems biology projects not only must fulfil that same criterion, but also they should produce and exploit predictive computational models. This makes systems biology projects significantly more difficult than most classic research projects in the life sciences. More often than not, the effort that is required to fulfil this second criterion is underestimated, both by project applicants and by referees that are expected to select the most promising proposals.

In application/industry-oriented systems biology projects, such as ERASys*App* which was launched January 2013 (first call Fall 2013), an additional requirement must be fulfilled, i.e. models must be instrumental in applied life and biomedical sciences and biotechnology. Obviously, this calls for very well thought-out proposals and effective selection.

Researchers, funding agencies and selection panels should become aware of the extra criteria that must be met to make systems biology projects successful. Among others, the feasibility aspect of systems biology project proposals should become a much more prominent component in funding decisions.

c. ***Systems biology: is our funding system fit for it?***

Two issues re-occur in many documents that address the future of systems biology: (i) big promises about what systems biology may bring society in terms of health and economy, and (ii) a lack of showcases to underscore these claims. The strategic ERASysBio document *Systems Biology in the European Research Area* (March 2008) is a good example. Why is it that the systems biology approach does not (yet) lives up to its expectations?

The answer is directly related to what is discussed above in section 3b: we tend to underestimate what it takes to unravel biological systems. Here we must ask ourselves how effective present national and European funding schemes are for systems biology. Most may be too small to overcome the 'complexity hurdle' that must be overcome in systems biology projects, as is argued in a recent paper in EMBO Reports [3]. In short, we must ask ourselves how to scale the size of systems biology research projects to the complexity of the systems that are tackled, taking into account that 'simple' biological systems do not exist. In any case, this issue should be discussed and analysed in order to be successful in systems biology funding schemes.

[3] This and related issues have been addressed in a recent publication by Swierstra et al. (2013) Re-thinking the life sciences, EMBO Rep. 14, 310-4.

One could argue that up-scaling is not necessary, because the results of many smaller projects can be added up. However, this is still an enigma in the life sciences due to a lack of good standards in experimentation, reporting, data acquisition, etc. So moving forwards in (many) small steps is not an option in the life sciences.

It is important to stress that there seems to be no alternative to using predictive computational models to unravel complex systems that are typified by dynamic interactions of many components and broad time-scales and length-scales. In physics, chemistry and engineering such model-based approach is fully accepted. In the life sciences we still in the process of getting used to it. In the past 10 years we discovered what it takes to do so for biological systems in terms of amount, diversity and quality of data sets needed. It is essential that we adapt the way we do research and how we fund it to this new insight.

d. ***Systems biology and community building in the life sciences***

The life sciences are remarkably poorly organised. There is no organisation that speaks up on behalf of this community, or that is able to guide discussions about issues such as indicated above [3]. This situation hampers the development of systems biology, because it depends on a broad agreement on standards at all levels: data acquisition, data formats, etc. Such agreement is essential for integration of diverse data sets from different laboratories in computational models. Failing to develop such standards will make that a significant part of research efforts in the life sciences will turn out to be essentially useless.

Developing standards is a major research challenge by itself. Presently it only seems to be worth the effort in the context of large and well-organised research communities. Examples are the transnational SysMO programme [4] and the German Virtual Liver Network [5]. Because representative organisations in the life sciences are lacking, the European funding agencies are in the best position to take the lead in this discussion.

e. ***Education and training in systems biology***

As argued in section 2d, developing adequate education and training in systems biology is essential for the life sciences in general and systems biology in particular. Therefore, European training programmes remain important. Such programmes may help the numerous initiatives at European universities to initiate BSc, MSC and postgraduate educational programmes in systems biology and integrate them with existing curricula in biology, medicine and others. Sharing across Europe of experience, expertise, teaching material and teachers may avoid inventing wheels and make efforts more effective.

4. Recommendations

a. Explore whether classic funding schemes are adequate for systems biology research projects. Take into account the research efforts that are required to develop and exploit predictive computational models of biological systems.

[4] SysMO: Systems biology of Microorganisms (http://www.sysmo.net/)
[5] http://www.virtual-liver.de/wordpress/en/

Given the high complexity of biological systems consider among others the following issues.

i. Is funding of relatively small projects – small in relation to the complexity of the problem addressed – an effective way to enhance our understanding of biological systems?
ii. Is funding of consortia of collaborating research groups a more cost-effective and productive way of funding life sciences research?

b. In considering research consortia take into account the following issues.
    i. Standardisation is essential for adding up results from different research groups. Here, for instance require that effective SOPs (standard operating procedures) are developed, adequately tested and made available to the scientific community. Accept that these and other standardisation efforts require a significant part of the research budget.
    ii. Adequate research management is essential to make larger collaborative research efforts successful. Note that there is remarkably little expertise in research management in the life sciences.

c. Improve the quality of systems biology-oriented research projects.
    i. Make development and exploitation of predictive computational models an essential component of proposals.
    ii. Require convincing risk analysis and contingency plans with respect of reaching the project goals.
    iii. Ensure that selection panels put a strong emphasis on the feasibility of the project.
    iv. There is a strong trend to exploit systems biology approaches in application-oriented research projects (e.g. clinical, industrial). Here, be even more critical about the issues addressed in recommendations a, b and c. Challenge applicants to be competitive in writing realistic proposals, rather than the usual 'optimistic' and overpromising ones.

d. Stimulate the establishment of platforms that aim to organise and effectively represent the European life sciences community. Although this is largely uncharted territory, challenge the community to experiment with this issue and facilitate such experiments.

e. Continue the development of European systems biology training and education programmes. In particular, coordinate the numerous efforts of universities throughout Europe in developing BSc, MSc and postgraduate education and training programmes by exchanging experience, expertise, teaching material, teachers, etc.