Publications of the Academy of Finland 8/09

Systems Biology and Bioinformatics Research Programme 2004–2007 (SYSBIO)



Evaluation Report





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Description

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Author(s)	Evaluation panel			
Title	Systems Biology and Bioinformatics Research Programme 2004-2007 (SYSBIO). Evaluation report.			
Abstract	The Systems Biology and Bioinformatics R in 2003 and ran for four years from 2004 the mented jointly by the Academy of Finland nology and Innovation, Tekes. The main ob was to promote an integrative and holistic a processes at the systems level. Multidisciplin ity were essential characteristics of the Prog integrating role in the projects. Twenty-one emy of Finland and the Finnish Funding As The programme was funded with a total sur In 2008, after the end of the Programme, ternational evaluation Panel to assess the Pr on the following issues: planning of the rese SYSBIO Research Programme, success of t and objectives, contribution to researcher an working, applicability of research and impo the future. The members of the evaluation I Panel), German Cancer Research Center, Pr of Denmark, Professor Marta Cascante, Un Rand, University of Warwick, Great Britair secretary of the Panel). The Panel concluded that some of the ma scientific quality, added value) whereas som were only attained in part. The evaluation p many, was the first country to establish syst Finland has been particularly successful in c life science community and has been able to ematical groups into life science application success, Finland has not yet achieved the cri ity of systems biology. The Panel emphasizz technical infrastructure and software platfor continuation of funding for systems biology, field of systems biology.	esearch I rough to and the I ojective o pproach narity, im gramme, y research gency for m of 10.7 the Prog cogramme earch Pro the imple nd expert ortance to Panel wer rofessor S niversity on and Dr and Dr and not tee (e.g. im oanel not tee (e.g. im oanel not tems biol dissemina o attract H . The Par itical mas ed the im rms creat y and the	Programme (SYSBIO) was launched 2007. The Programme was imple- Finnish Funding Agency for Tech- f the SYSBIO Research Programme in research on complex biological terdisciplinarity and transdisciplinar- with bioinformatics having a central a projects were funded by the Acad- r Technology and Innovation, Tekes. 7 million euro. ramme Steering Group set up an in- e as a whole and to reflect especially ogramme, scientific quality of the ementation of the Programme goals t training, collaboration and net- o end-users and recommendations for re Professor Roland Eils (chair of the Søren Brunak, Technical University of Barcelona, Spain, Professor David Michaela Reichenzeller (scientific tives were attained succesfully (e.g. ternational and national networking) ed that Finland, together with Ger- ogy as a research priority. Therefore, tting systems biology thinking in the high-level computational and math- nel was concerned that, despite this ss required for long-term sustainabil- portance of sustained support for ted within the programme as well as e training of young researchers in the	
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I INTRODUCTION

1.1 Background

Publication of the preliminary nucleotide sequence of the human genome at the turn of the millennium was one of the milestones in modern biology. Yet this information package of 3,000,000,000 nucleotides marks only the beginning for modern "postgenomic" research on molecular genetics and life sciences in general. A characteristic feature of such research is the generation of increasing amounts of raw data requiring advanced informatics services and tools to process this information into biological knowledge.

Multidisciplinarity and integration are characteristic features of postgenomic research. Genes, gene products, their regulatory networks and interactions with the environment must be analysed as components of higher-order structures, metabolic pathways or entire cells and organisms. This type of integrative and holistic approach has been termed **systems biology**. Research defined as systems biology is characteristically multidisciplinary and dependent on **bioinformatics**, the computer-assisted analysis of biological data. Close collaboration of biologists, biochemists, physiologists, chemists and physicists with computational biologists and mathematicians is essential.

Since the mid-1990s, the research programmes of the Academy of Finland have provided targeted support to research, networking, researcher training and infrastructures in the field of biotechnology and molecular biology in Finland. The Research Programmes on Genomics, Cell Biology, Molecular Epidemiology and Evolution, Structural Biology and Biological Functions ("Life 2000") as well as the Research Programme on Mathematical Methods and Modelling in the Sciences comprise a continuum providing long-standing support to the various aspects of molecular biology and biotechnology. The Research Programme on Systems Biology and Bioinformatics (SYSBIO) is a logical extension of this support.

The planning of the Research Programme on Systems Biology and Bioinformatics was carried out in close cooperation between the Finnish Funding Agency for Technology and Innovation Tekes.

1.2 The scope of the SYSBIO programme

The Research Programme on Systems Biology and Bioinformatics covered the following fields:

Structural biology

- structural analysis of biomolecules and their complexes
- preference for multidisciplinary proposals involving several research fields, ranging from chemistry, biochemistry and physics to computer science and medicine *Functional genomics and proteomics*
- postgenomic research on humans as well as on all model organisms

- research areas included genomics, transcriptomics, proteomics and metabolomics, and the techniques used in these fields
- preference for multidisciplinary approaches for the elucidation of the interplay of cellular and subcellular structures as well as metabolic pathways

Molecular genetics

• the genetics of multifactorial human diseases, gene-environment interactions and model organisms

Bioinformatics, biomathematics, and computational biology

• basic research and method development in bioinformatics, biomathematics and computational biology

Ethical, social and cultural aspects

• the ethical and socio-economic aspects of systems biology and bioinformatics.

1.3 Objectives of the SYSBIO programme

The main objective of the Research Programme was to promote an integrative and holistic approach in research on biological processes at the systems level. Multidisciplinarity, interdisciplinarity and transdisciplinarity were essential characteristics of the Programme, with bioinformatics envisioned to play a central integrating role in the projects.

Specific aims were to

- create new knowledge through high-quality, multidisciplinary collaborative research in the field of systems biology and bioinformatics,
- promote efficient and synergistic use of the existing resources and infrastructures,
- develop research environments, methodologies and cooperation among researchers,
- promote efficient researcher training and mobility of researchers, taking the multidisciplinary nature of the Research Programme into account,
- promote application of technologies both in basic research across disciplines, and in research and development aiming for protected intellectual property and commercialisation of research results,
- generate more information on and knowledge of the ethical and socio-cultural dimensions of systems biology and its applications among researchers and in society.

Dissemination of the research results was considered very important in order to increase the impact of the Research Programme.

1.4 Implementation of the SYSBIO programme

The Systems Biology and Bioinformatics Research Programme ran for four years from 2004 through to 2007. The Programme was coordinated by the Academy of Finland and implemented jointly by the Academy of Finland and the Finnish Funding Agency for Technology and Innovation Tekes. Each funding agency applied its own procedures and criteria in making its funding decisions.

Academy of Finland

The Board of the Academy of Finland allocated EUR 9 million to the Programme. The call for applications was launched in April 2003 as a two-stage process.

Altogether 105 plans of intent were submitted to the Academy. Of these, 56 were individual applications and 49 consortium applications. Applied funding came to a total of about EUR 68 million. The programme Steering Group with the aid Dr Roland Eils, Germany, and Gunnar von Heijne, Sweden, selected 38 applications for the second stage according to previously determined criteria. The selection criteria in the first-stage call were: the application's relevance for the SYSBIO programme (i.e. how well the application met the objectives of the programme), the applicant's expertise in the field, innovation and scientific quality.

The international evaluation panel rated the full applications using the following criteria: relevance of the project to the Programme, scientific quality and innovativeness of the research plan, feasibility of the research plan, competence and expertise of the applicant and the research team, national and international networks, and research and training environment. The panel members were: Dr Roland Eils, DKFZ, Germany (chair), Director Charles Auffray, CNRS, France, Dr Peer Bork, EMBL, Germany, Professor Hans Prydz, University of Oslo, Norway, Professor Jesper Tegnér, Stockholm University, Sweden, and Professor Hans V. Westerhoff, Vrije Universiteit, Netherlands (vice-chair). The programme Steering Group made the recommendations for funding in November, on the basis of the scientific evaluation made by the panel. The official funding decisions of the Academy of Finland were made by a subcommittee.

Finnish Funding Agency for Technology and Innovation Tekes

Tekes funding for the programme was EUR 1.7 million. Besides the general criteria of the Programme, Tekes emphasized collaboration with industrial partners.

Funded projects

Altogether 21 research projects (17 funded by the Academy of Finland and four funded by Tekes) involving 54 research groups were funded in the programme. Thirteen of the projects were consortia and eight were individual projects.

1.5 The coordination of the programme

The Research Programme was managed and supervised by a Steering Group, assisted by the Programme Manager, Dr Sirpa Nuotio.

The Steering Group of SYSBIO (19 March 2003 – 31 Dec 2003)

- Professor Marja Makarow, Research Council for Health (chair)
- Professor Annele Hatakka, Research Council for Biosciences and Environment (vice-chair)
- Professor Mats Gyllenberg, Research Council for Natural Sciences and Engineering
- Professor Juha Sihvola, Research Council for Culture and Society
- Professor Peter Slotte, Research Council for Biosciences and Environment
- Professor Eero Vuorio, Research Council for Health

- Senior Technology Adviser, Adjunct Professor Erja Heikkinen, Finnish Funding Agency for Technology and Innovation
- Senior Technology Adviser Pentti Nummi, Finnish Funding Agency for Technology and Innovation

The Steering Group of SYSBIO (28 Jan 2004 – 31 Dec 2006)

- Professor Marja Makarow, University of Helsinki (chair)
- Professor Kalervo Väänänen, Research Council for Health (vice-chair)
- Professor Annele Hatakka, University of Helsinki
- Professor Mats Gyllenberg, University of Helsinki
- Professor Juha Sihvola, Research Council for Culture and Society
- Professor Karl Åkerman, Research Council for Biosciences and Environment
- Adjunct Professor Ulla Ruotsalainen, Research Council for Natural Sciences and Engineering
- Senior Technology Adviser, Adjunct Professor Erja Heikkinen, Finnish Funding Agency for Technology and Innovation
- Senior Technology Adviser Teija Palko, Finnish Funding Agency for Technology and Innovation

The Steering Group of SYSBIO (12 Jan 2007 – 31 Dec 2008)

- Professor Marja Makarow, University of Helsinki (chair)
- Professor Jaakko Astola, Research Council for Natural Sciences and Engineering (vice-chair)
- Professor Mats Gyllenberg, University of Helsinki
- Professor Reijo Lahti, Research Council for Biosciences and Environment
- Professor Pia Vuorela, Research Council for Health
- Senior Technology Adviser Pauli Saarenketo, Finnish Funding Agency for Technology and Innovation

1.6 Facts about the SYSBIO programme

List of projects and funding, see Annex 5.

- Average funding for projects was 86% of the funding applied for
- The projects reported close to EUR 2 million in additional funding from other sources
- More than 2,300 person months were done in these projects, the average being 138 person months per project
- Of the reported person months
 - 64% consisted of work by persons with a MSc degree
 - 25% consisted of work by persons with a PhD degree
- Person months do not include work done <u>without</u> a salary from the project (e.g. most of the senior researchers)
- 27 PhD and 18 MSc degrees were earned in the SYSBIO programme
- Altogether 318 articles were published in refereed scientific journals, producing an average of 19 articles per project
- Researchers appeared 16 times in TV or radio programmes
- 17 patent applications were filed
- Projects were involved in cooperation with researchers from 14 different countries.

2 EVALUATION PROCEDURE

The Steering Group commissioned a scientific evaluation of the programme in October 2008. The Evaluation Panel members were Professor Roland Eils (chair of the Panel), German Cancer Research Center, Professor Søren Brunak, Technical University of Denmark, Professor Marta Cascante, University of Barcelona, Spain, Professor David Rand, University of Warwick, Great Britain and Dr Michaela Reichenzeller (scientific secretary of the Panel). The Steering Group was responsible for the general planning of the evaluation. The Programme Coordinator organised the self-evaluation of the programme and compiled the self-evaluation data. The researchers who took part in the programme and who responded assessed the general success of the programme as well as their own contribution with self-evaluations (see Annex 1. Self-evaluation form for projects). In addition, most of the researchers submitted final reports to the Academy of Finland. The deadline for report material was 30 April 2008. The Evaluation Panel had access to the documentation produced about the programme and the submitted reports of each project (see Annex 2. Material for the evaluation). The material for the evaluation was sent to the Panel members in July 2008. The Evaluation Panel met at the Academy of Finland in October 2008. For this meeting, each project was assessed by the full Panel, and this material was used as a basis for discussions and interviews. Interview sessions with 19 Principal Investigators or senior researchers and 17 young researchers were organised during the Evaluation Panel meeting. A discussion meeting was also held with the Programme Coordinator but unfortunately no members of the Steering Group were available for discussion. (See Annex 3. Agenda for Evaluation Panel meeting.) The aim of the evaluation was to estimate the extent to which the SYSBIO research programme had succeeded in fulfilling its original objectives. The evaluation also aimed to provide feedback on the success of the programme and its coordination as well as other information that is useful for purposes of science policy planning and decision-making. The Panel was expected to assess the programme as a whole and to reflect especially on the following issues: planning of the research programme, scientific quality of SYSBIO, success of the implementation of the programme goals and objectives, contribution to researcher and expert training, collaboration and networking, applicability of research and importance to end-users and recommendations for the future (see Annex 4. Panel assignment).

3 SCIENTIFIC QUALITY OF THE PROGRAMME

Our opinions are based on the reports that were available to us and the interviews that we conducted with representatives of 16 of the projects. Of these, we judged that 6 of the 16 projects are outstanding. Each of these is an excellent example of systems biology in practice and is internationally competitive or internationally leading in terms of the general scientific achievements. The top-rated projects were:

- The project *Linking developmental, computational and evolutionary biology of mammalian teeth* led by Jernvall, Fortelius and Thesleff was very highly regarded by the Panel. This was a beautiful example of how the systems biology approach can add great value to an already impressive research programme. The project was an evo-devo investigation of tooth shape development predicting evolutionary patterns of mammalian teeth development using a total systems view. The approach successfully crossed scales of integration from the underlying gene networks to three-dimensional models of tooth shape using in-silico and in-vitro experiments. In addition, analytical and data management tools were developed.
- The project Signaling pathways and gene regulatory networks leading to generation of a lymphocyte phenotype pathogenic in asthma and allergy led by Lahesmaa, Aittokallio, Koski and Oresic similarly impressed the Panel. This project created an integrated data platform that was used to model the signalling pathways and gene regulatory networks critical for the development of understanding of the Th2 lymphocyte pathogenic in asthma and allergy. It combined a broad range of molecular data that was successfully integrated. The Panel was particularly impressed by the added value by which a cross-disciplinary collaboration has resulted in a highly successful molecular biology group sustainably taking up a systems biology approach and by the way that two relatively junior group leaders established significant groups.
- The project *Deciphering the circuitry leading cancer cells to premature senescence* led by Mäkelä, Klefström, Ojala, Vidaland and Västrik had a broad aim of identifying pathways by which activation of certain oncogenes result in antiproliferative events. Despite a change of direction this project produced two very high-profile papers which have already had a significant impact. This project has been very strong in combining experimental work and data generation with computational analysis. The activity on extraction of protein-protein interaction networks represents a strong example of computational analysis and infrastructure that broadens the data diversity scope which otherwise in SYSBIO is very focused on gene expression data.
- The project *Computational Processes in Living Cells* led by Petre, although largely theoretical, was regarded by the Panel as highly innovative and showing great potential. The Panel strongly recommends that this should be taken forward with a greater involvement of the relevant biological communities.
- The Panel was impressed by the successful and innovative combination of first-rate molecular biology, bioinformatics and modelling in the project *Systems level*

architecture of GDNF mediated neurotrophic action led by Saarma. This aimed to carry out an analysis of GDNF family ligand signalling and the theoretical model was used to predict the functional outcome of the signalling network under complex conditions. The experimental group emphasised the significant extent to which their research approach had been modified by the incorporation of a modelling component as a result of the SYSBIO initiative.

• The project *CompGenome* led by Mannila very successfully developed and applied computational tools to (a) describe genomic and functional variation including novel hierarchical methods for segmentation and for finding and analysing haplotypes, and (b) techniques for the identification of rearrangements, duplications, and other large-scale variations in genomes. There was also some high-quality computer science research produced. The Panel particularly commends the fact that this project linked across to the abovementioned project led by Jernvall et al.

Six of the projects were judged to be up to our expectation level in terms of their engagement with systems biology and these contained aspects that were internationally competitive. Four projects were judged to be somewhat disappointing although some of these contained elements that were nationally or internationally competitive. All of the latter projects suffered either from a lack of crossdisciplinary involvement, from not being at the cutting edge of their field, or for being rather incremental.

In addition to the 16 projects mentioned there was an ethics project, *Ethical and Social Aspects of Bioinformatics*, led by Häyry. The Panel considered that this was well linked internationally with many publications and had good international visibility.

Although many components in this initiative must be regarded as functional genomics rather than systems biology, it was one of the earliest in Europe and the potential community that it addressed was smaller than in many European countries. In view of this, we feel that the programme can be judged to have been very effective and successful in terms of scientific quality. The early start of the programme meant that the emphasis started from expertise in functional genomics with projects that should prepare the ground for systems biology. The fact that two thirds of the projects fully achieved this goal with one third achieving it at an internationally leading level can be regarded as a significant success.

Because of the early starting date of this initiative there was an overwhelming focus on high-throughput, genome-wide data, primarily from microarrays, while there was a relative absence of metabolic, proteomics and imaging data. Moreover, the bioinformatics had a narrow focus with a concentration on microarray data analysis and structural bioinformatics. There is an urgent need for diversification of this effort and a closer linking to the emerging key themes of systems biology. There was some evidence that this was already happening (as mentioned in the context of one of the highlighted projects above).

The Panel is concerned that, despite this success, Finland has not yet achieved the critical mass required for long-term sustainability of systems biology. Moreover, unlike other countries such as Germany and the UK, Finland does not seem to have given as high a priority to developing a more quantitative, predictive and integrative approach to biology. This was reflected in the decision to only continue the special funding for systems biology through a new e-science initiative. It was also reflected in the fact that, although they valued the combination of experiment, modelling and bioinformatics, none of the postdocs or PhD students whom the Panel interviewed regarded themselves as system biologists or thought that, within Finland, this was a marketable career choice.

3.1 Applicability of research and importance to end-users

While there were some excellent examples of high-value tools and methods of significant use to the biological research community, the Panel was somewhat disappointed with the tools produced by the bioinformatics groups. In other Academy-funded projects than this, the Panel felt there was little in terms of tools or methods that would be of interest to end-users outside the biological research community. The Panel felt that this situation was to be expected from a programme like this that focused on basic science. The Panel was impressed by the software package Chipster and judged that it was already being used in the research community and had a good chance of being taken up by other end-users in fields such as the pharmaceutical industry.

4 Success of the implementation of the programme goals and objectives

The vision of systems biology is often described as having two major components: data-driven modelling and integration of different experimental domains, and more theoretical approaches working from first principles and assumptions formulated mathematically. The Finnish systems biology programme has clearly included several projects within both areas as well as activities which combine the two.

However, the 2003 call from the Academy of Finland was formulated very broadly with topics which in many other countries would have been termed functional genomics. The call also explicitly included the topic of structural biology, which is a more traditional discipline that is weakly linked to systems aspects in the life sciences. Similarly, molecular genetics does not *per se* target systems aspects but will often focus on single genes and their variation.

The match between the programme goals and objectives and the research projects should be viewed taking this broad formulation into account. The Panel found that it was consequently also important to focus on evidence of transition from traditional research areas to more systems-oriented analysis of cells and organisms, and that this aspect was also highly important in relation to the evaluation of success.

Overall, several of the disease-oriented experimental groups have clearly been excellent in driving projects towards becoming truly multidisciplinary, while some of the groups within structural biology and bioinformatics have continued their traditional line of research without embarking on novel types of systems-level analysis. In some cases strong computer science groups have linked themselves with strong experimental groups, which is also a good sign, and further adds to the potential for expanding systems biology in the Finnish setting. In this sense the program has indeed contributed to enhancing interdisciplinary and multidisciplinary approaches in research.

As mentioned above, many of the projects would more naturally be categorised as being part of functional genomics. One goal within systems biology is to transcend a particular experimental domain, and combine different, often complementary, data types and produce more systems-oriented descriptions of biological mechanisms. In the SYSBIO project, the dominating high-throughput data type produced and analysed stems clearly from transcriptomics experiments. From a systems biology perspective this is a weakness, and the weakness also extends to the bioinformatics activities where algorithms and methods for analysing expression data also dominated strongly. The activities in the Mäkelä group on protein-protein interaction networks represent an example of a good exception to this tendency. Otherwise many of the bioinformatics activities were indeed continuations of old research plans, and it is noteworthy that several of the most original examples of new computational methods were developed within the experimental projects.

The financial scope of the programme clearly imposed severe limitations on the potential for starting new, genuine systems biology-oriented efforts. The funding

level for each participating group (often limited to one FTE or less) made the programme work somewhat like EU funding, where the funding model can add to the activity level in well-established labs (in Finland often in centres of excellence), but is not suited to starting up new research groups. The scale of projects matters particularly within systems biology – the area expands significantly in many other countries with dedicated departments being formed at universities and research institutes. In Finland, systems biology is still strongly viewed as an 'interface' topic, not as an independent research field, for example with its own graduate school. From what the Panel learned, it also seems that it is not possible to obtain a PhD in systems biology as such, but that the topic is attached to other, more conventional degrees.

4.1 Functioning of the consortia and interaction with the Steering Group

In the call text, the research plan for consortia was to be formulated jointly by all partners. It is therefore surprising that the final reports were made by individual subgroups, and this made it more difficult to assess the productivity and synergy of the consortia as such. This is a clear example of management problems which should have been handled by the Steering Group.

Overall, the role and responsibilities of the Steering Group were not clear to the Panel. It was, for example, unclear to the Panel to what extent the Steering Group requested that joint meetings between the groups were held at regular intervals. Several consortia in fact had very limited interaction between the participating groups and reported few joint papers or none at all. Furthermore, the Steering Group does not include leading PIs from the projects. This model is unusual and the Panel finds that the strategy of leaving these matters to the consortium leaders cannot be recommended. The budget of the SYSBIO programme roughly corresponds to one single FP7 'integrated project' (budgets often at the level of EUR 12 million), and the need for coordination and fertilization of synergy in these projects is comparable to what would have been needed in the SYSBIO effort. The Panel learned during the site visit that most of the Steering Group members representing different stakeholders had essentially been inactive, and this fact obviously undermines the usefulness of this particular management model (for details see General Recommendations in Chapter 6 below).

The SYSBIO programme has held three annual meetings where highlights and progress reports have been presented. In addition, there have been several topical meetings, winter schools, courses and other activities such as a fact-finding mission to Cambridge and London. These activities have been well planned and closely related to the scope of SYSBIO.

The general level of these activities has been reasonable, but perhaps close to the minimum expectation for this type of country-wide effort. Again, a more active role played by the Steering Group could have secured a more intense outreach, which would have been of particular importance for a programme where part of the rationale was to inspire and encourage Finnish researchers in relation to the shift of paradigm into systems biology. The coordination report includes the information that the SYSBIO project did not even manage to update project web page descriptions annually, and that part of the website was lost during reformatting in 2007.

4.2 Added value

The Panel found that the programme indeed has had clear added value. However, the added value is not evenly distributed among the projects; for some it has been extensive and has led to significant changes in research strategies and establishment of new infrastructures and networks, while others have continued to apply conventional approaches without adding modelling or simulation aspects to their work. In a few cases, SYSBIO has also clearly led to new international collaboration (for example, in the context of ERANET), with India and the US. The links with industry have been quite limited, although not entirely absent.

5 CONTRIBUTION TO RESEARCHER AND EXPERT TRAINING

During the last few years, many countries, such as Japan, USA, the UK or Germany have promoted systems biology programmes and have set up systems biology institutes to promote researcher training in this new field. In order to be competitive in the field, young researchers must learn about the methods that are indispensable for systems biology research, including mathematical modelling, computational approaches, bioinformatics, bioimaging, microarray analysis, proteomics, metabolomics and others. The choice of Master programmes in systems biology and specialized courses on offer is increasing in Europe. If Finland wants to be in the first line of competitive research on systems biology in Europe, it will not only have to promote excellent research projects in the field but also ensure that training of PhD and postdocs in the field is guaranteed. Although annual symposia and a few courses have been organized within the SYSBIO programme, they did not necessarily provide practical interdisciplinary training.

In many cases, a four-year programme seems not to be enough to complete a PhD in Finland, according to what the panel was told by the students in the interview. As a result, some of the PhD students appointed at the beginning of the programme may be able to finish their PhD theses within the funding period, but others will need to continue for another few years, which could raise some difficulties for some consortia if funding were discontinued.

Even though some of the consortia produced outstanding results in terms of research quality in the systems biology field, it became clear from the interviews that fellows in the consortia missed a full training in systems biology covering expertise in a very wide range of theoretical and technical methods from different disciplines such as bioinformatics, physiology, imaging techniques and the different '-omics' fields.

The panel considers it an excellent idea to organize a discussion session with PhD students and young postdocs involved in the funded projects. The panel was very happy to see that a large number of students came and that they were open for discussions and expressed their opinions on the programme. Th panel made several suggestions concerning things they would like to see implemented in a programme like this to complement and improve their training in systems biology.

During the one-and-a-half-hour discussion with the students, the panel collects the following impressions from their comments:

- Training in both experimental work and theory has been provided to the students in only a few cases. Most of the students do either experimental or computational work only. Moreover, some commented that they would appreciate if more multidisciplinary training was implemented in future systems biology programmes.
- The students expressed the need for more collaboration between laboratories with different expertise. They would appreciate if meetings between experimental and computational fellows/postdocs working in a consortium could be organised on a more regular basis. Some students reported that they have held such weekly or monthly 'sit-together-meetings' in their consortia and that they consider this very positive.

- The students think that it would be a very good experience to be able to attend hands-on courses composed of both experimentalists and theoreticians to promote teamwork.
- From the students' comments, the panel realized that several of them had never attended international training initiatives in systems biology, such as the FEBS courses, which are usually open to all young researchers. The panel concluded together that it would be a good idea to spread information about such offers more efficiently and that funding for attending international courses should be provided.
- We also concluded that it would be a good idea to implement the appropriate channels, i.e. a Wiki or a webpage, to keep them informed on international training initiatives and to facilitate discussion forums and exchange of results and tools between them and other experts.
- Some of the students commented that there is also a lack of supervisors that have a strong background in both experimental and computational science, resulting in the opinion that it was sometimes difficult to find all the training they required for their project in a single lab. The students further commented that they would appreciate co-supervised PhD projects between complementary labs, especially with respect to promoting the objectives of the systems biology programme in Finland.

In conclusion from our discussions with the PIs and PhD students, the panel strongly recommends that intensified training should be an integral part of any multidisciplinary programme. Establishing a training programme in the consortia integrated in a research programme such as SYSBIO will help young researchers in the early phase of their career to become the interdisciplinary systems biology researchers of tomorrow. Furthermore, this will ensure the generation and maintenance of critical mass in this field that is necessary to make Finland's systems biology internationally competitive.

In addition to specific hands-on courses, the panel strongly recommends that the project funding includes funds to ensure the mobility of PhD students within the consortia, in order to conduct truly interdisciplinary research. It has already been shown in different multidisciplinary fields that programmes combining first-class research with student mobility (such as the Marie Curie programme funded by the EU) are very successful and produce very competitive young researchers. The panel therefore strongly recommends that PhD students need to rotate through two or three labs of the consortia and that PhD research projects as well as mobility programmes need to be included in the grant application. Co-supervision of PhD projects and guaranteed mobility will allow the students to learn the state-of-the-art methods in the different disciplines, which are required in systems biology.

Even though the efforts within the programme to provide training courses and symposia have been very valuable and appreciated by the students, the panel concludes that training of young researchers in Finland in the field of systems biology is not sufficient to be internationally competitive in systems biology. A student mobility programme should be created to match the research programme. Finally, we suggest the introduction of co-supervised PhD projects which would promote efficient interdisciplinary research. These aspects should be specifically addressed in a future call for a multi-disciplinary programme such as the systems biology programme

6 Collaboration and networking

The reports and presentations of the SYSBIO programme members show that a substantial number of research groups within this systems biology programme extended or established their collaborations with other Finnish groups within the funding period of SYSBIO. Although there were groups that used the potential for national collaborations to a high extent, such as the Salminen or Kallioniemi laboratory, with few exceptions these collaborations only partially supported aspects of bringing experimental work and modelling together in systems biology. An excellent example of highly efficient national collaboration was the work of the Jernvall consortium, which managed not only to establish a close collaboration among the groups of Jernvall, Fortelius and Thesleff, but also produced a number of highimpact publications in the field of systems biology during the funding period. More recently, the Mannila group had also started collaboration with the Jernvall group and is expected to produce joint publications from this collaboration. These kinds of collaborations were acknowledged by the Panel as very promising.

It was obvious to the panel that during the funding period a number of international collaborations were also started. The Lahesmaa consortium collaborated well within the consortium and, in addition, initiated a number of international collaborations with groups from the UK, Japan, and more recently also with an Indian research group. As a spin-off, a systems biology project at the University of Turku was established. The Mäkelä consortium established national and international collaborations that contributed to the success of the consortium. The Tekes-funded project on the simulation of microarray and microscopy data by the group of Yli-Harja developed international collaboration with the Canadian group of Stewart Kauffmann, which will be continued in the future. The second Tekes project by the Korpelainen group, which has developed a user platform for data management and analysis of microarray data called Chipster, has created it as an open source tool. As such it will be available for the research community and, thanks to their international contacts, it will be installed on several servers in different countries, including Germany and the US. Research cooperation among the different consortia was only established in two cases: the collaboration between the Jernvall and Mannila groups and the Kangasjärvi and Kaski groups. In our opinion, this did not reflect strong networking and it would have been nice to see more of these powerful examples of network collaboration.

A total of nine research groups have published joint articles, but most of the publications that were released during the funding period were not dependent on their collaboration. It was clearly visible to the Panel that collaboration with the existing Centres of Excellence has promoted the scientific work and output of these groups, as seen for the Lahesmaa or the Mannila consortium. The panel suggests to all funded members that they should extend the level of international collaboration through e.g. other EU projects or NIH-founded projects as seen in the case of the Mannila consortium, which extended its collaboration to UCLA in an NIH-funded project on schizophrenia research.

With regard to collaboration with end-users, only the Tekes projects by Korpelainen and Ruusuvuori can be mentioned. Korpelainen intends to distribute the software tool to researchers abroad, which makes it a useful tool for researchers all over the world. Meanwhile, Ruusuvuori has established collaboration with an industrial company that could further promote the applicability of the software development to end-users.

7 Summary and suggestions

The panel saw that there were some groups that managed to build up a number of national and international collaborations that promoted the establishment of a systems biology branch in Finland. Unfortunately, there were also groups which did not establish any or only weak collaboration, even though the projects themselves were considered by the evaluation panel as successful, though not with respect to systems biology. It would be of high importance for these groups to establish cooperation with computer scientists for the future maintenance of systems biology projects in Finland. This is also highly recommended for other groups which mainly relied on existing collaboration and therefore did not manage to include systems biology in their projects. The degree of networking among groups from different consortia was low, and consequently the Panel would recommend more emphasis on this in future systems biology programmes.

Since it was very difficult for the evaluation panel to assess the extent of collaboration on the basis of the publication list, we would like to suggest for the future that consortia and groups put their publications into different categories: (i) joint publications within the consortium and (ii) with other consortia and (iii) other publications.

7.1 Recommendations for the future

Finland received high international recognition for being the first nation, together with Germany, to establish systems biology as a research priority. Thanks to this early start, Finland was particularly successful in disseminating systems biology thinking in the life science community and was able to attract high-level computational and mathematical groups into life science application. These very promising early developments are at risk if sustained funding for systems biology is not secured for the next five-ten years.

The Panel shares the major concern raised by a number of PIs in the final interviews: the continuity of systems biology projects and sustained support for technical infrastructure and software platforms created within the programme are of utmost importance. Continuation through institutional support, funding by Tekes or by the EU can only partially compensate for the lack of a systems biology programme. The Panel strongly advises to further promote and fund systems biology in Finland. An integration of systems biology into other programmes such as the eScience Programme is certainly welcomed, although not sufficient on its own. The Panel suggests introducing two measures for sustained integration of systems biology in Finland. First, an internationally visible centre for systems biology should be established. Here, we suggest installing a Centre of Excellence in systems biology. Any of the internationally outstanding consortia mentioned in Chapter 2 could contribute to the establishment of such a centre. This would bring Finland up to a European scale in systems biology and would match existing systems biology centres established in Germany, the UK and elsewhere. Second, a critical mass of systems biology research in Finland must be secured. Here, the panel strongly recommends renewing a programme in systems biology to complement institutional and international funding.

The Panel was surprised to see a lack of programme-wide teaching and training activities within the SYSBIO programme. Mostly, students and young researchers were trained on the job only, which the Panel considered insufficient. In many other national and international systems biology programmes, training and teaching are an instrumental part of the programme. This is even more important for a new and multidisciplinary research field such as systems biology, where education of young researchers still presents a major obstacle in developing systems biology on a national level. The panel advised that a future programme should set aside a certain percentage of the budget for such training activities.

Obviously, the Steering Group has played an important role in setting up the SYSBIO programme and in the selection of projects or consortia to be funded within the programme. It was not clear to us, however, what the tasks and involvement of the Steering Group were in the programme during the funding period. According to international standards, the panel suggests that a two-level hierarchy is introduced into future programmes. The Steering Group should act as a supervisory board for the programme, whereas the operational tasks within the programme should be handed over to a programme committee that consists of elected PIs within the programme. This will put the programme committee into a position to better direct the programme and reserves the right to oversee the entire progress of the programme for Research Council members. The Steering Group should also include international experts in the field who complement the expertise of the Research Council members.

The final reports were partially of poor quality, incomplete and difficult to assess due to the fuzziness of the posed questions. The panel recommends that the final reporting should be changed as follows: 1) There should be only one report for one consortium instead of having one from each PI in the consortium. 2) In the selfevaluation forms the PIs should be asked to highlight the most important results and rank them, and

to highlight publications that are joint publications between different PIs in the consortium and/or carried out by funded personnel. Further, extramural and intramural funding deriving from the programme should be noted explicitly. To motivate the PIs in producing complete final reports we suggest, according to international standards, that a certain percentage of funding (e.g. 10%) is held back until all final reports have been received and accepted by the Academy.

The Panel finally suggests that for an interdisciplinary programme such as systems biology, the Academy should consider putting mechanisms in place for promoting joint programmes across Research Councils, e.g. by reserving a certain percentage of the budget for interdisciplinary projects or by offering incentives to the Research Councils for establishing cross-council projects.

ANNEX I. SELF-EVALUATION FORM

SYSTEMS BIOLOGY AND BIOINFORMATICS RESEARCH PROGRAMME 2003-2007 EVALUATION FORM



This evaluation questionnaire is part of the final evaluation of SYSBIO research programme. Please, fill in one questionnaire for each SYSBIO project (i.e. consortium) partner by **30.4. 2008.**

Please, remember also to submit a research report to the Academy by **30.4.2008** (online services/reporting).

Objectives of the Systems Biology and Bioinformatics Research Programme (SYSBIO, 2003-2007)

The main objective of the SYSBIO Research Programme is to promote an integrative and holistic approach in research on biological processes at the systems level. Multidisciplinarity, interdisciplinarity and transdisciplinarity are essential characteristics of the Programme, with bioinformatics envisioned to play a central integrating role in the projects.

specific aims of the SYSBIO Research Programme

- create new knowledge through high-quality, multidisciplinary collaborative research in the field of systems biology and bioinformatics,
- promote efficient and synergistic use of the existing resources and infrastructures,
- develop research environments, methodologies and co-operation of researchers,
- promote efficient researcher training and mobility of researchers, taking the multidisciplinary nature of the Programme into account,
- promote application of technologies both in basic research across disciplines, and in research and development aiming to protected intellectual property and commercialisation of research results,
- increase information on and knowledge of the ethical and socio-cultural dimensions of systems biology and its applications among researchers and in society.

Dissemination of the research results is considered very important in order to increase the impact of the Programme.

A. SYSBIO RESEARCH PROGRAMME

General discussion of the objectives of the SYSBIO research programme. Were the objectives relevant and achievable?

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Did the research field gain any added value for having a programm If yes, how?	ne compared to normal research grants?
Did SYSBIO research programme enhance multi- and/or transdisci how? How could it be enhanced in the future?	iplinarity in your research area? If yes,
Did SYSBIO research programme enhance the development of you	r research area? If yes, how?
How did the coordination manage its task in trying to achieve the the coordination? If so, how? Did you find the arranged events use supported you more?	objectives? Did your project benefit from ›ful? How could the coordination have
	v
How essential the SYSBIO funding was for your research? Has the positions the members of your research group have today? Was th research plan?	funding affected the type of academic ne funding sufficient compared to the
Have you benefited from engaging with SYSBIO programme regard	ling
Indicate your opinion by marks. 1=not at all 5= very much	
	1 2 3 4 5
researcher training	
scientific work	
multidisciplinary collaboration with other researchers	
mobility of researchers	

How would you define systems bioology and why?What are the future poin your research area? To what direction should systems biology develo suggestions/recommendations (to the Academy) for future activities.	pssib p? Yo	ilitie our	es an	d po	ossibl	a chall	enges
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B. SELF-EVALUATION							
How did your project contribute to the objectives of the programme?							
		I					
	Ψ.	I					
Objectives and results of the project							
Please, estimate							
Indicate your opinion by marks. 1 = not at all 5= very well, very much							
	1	2	3	4	5		
to what extent did you achieve your objectives	\odot	$^{\odot}$	$^{\circ}$	$^{\circ}$	0		
how innovative your results are compared to other research in your field	0	0	$^{\circ}$	$^{\circ}$	0		
to what extent did multidisciplinarity become concrete in your project	0	0	$^{\circ}$	$^{\circ}$	0		
the multidisciplinarity of the project	O	0	0	0	0		
Please, describe the objectives of the project, to what extent did you ac scientific results and achievements, including innovativeness (novelty) your field.	hive in co	you mpa	r obj iriso	jecti n to	ves, t othei	he ma [.] resea	in Irch in
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What were the greatest obstacles in reaching your goals? What (if any) research plan?	chan	ges	wer	e ma	ide to	the o	riginal
	A	I					
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The national and international collaboration of the project. Describe you collaboration with industry, clinical settings and collaboration between u	ır coo unive	oper	atio es a	n. Pl nd r	ease, esear	specif ch ins	fy titutes.

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The applicability of the results. How could your results be utilized? Who could benefit your results? What would be the best long-term impact indicators of your results? When do you think your results could start showing impact?

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Communication of the results. How did/does the project communicate with end users? Has your results of SYSBIO been presented or published in any media outside the scientific community? If yes, what media and when? who initiated the publicity?

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How did multidisciplinarity become concrete in your project? How has the cooperation within consortium worked?

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Lähetä		

ANNEX 2. MATERIAL FOR THE EVALUATION

- Programme Memorandum
- Programme brochure
- Call text
- Explanation of the selection process
- Members of the evaluation panel October 2003
- Minutes of the evaluation panel October 2003
- List of the funded projects
- Applications including research plans and project descriptions
- Coordination report 2003–2007
- Programmes of arranged SYSBIO events
- Introduction to Academy of Finland (in CD)
- Final research reports
- Self-evaluation forms
- Technical data summary

ANNEX 3. AGENDA FOR EVALUATION PANEL MEETING

SYSBIO EVALUATION 15-17 October 2008

OCT 15

19:00Arrival and welcoming dinner

OCT 16

9:00	Panel meeting at the Academy of Finland,		
	vinionvuorenkatu 8, room 455		
9–10	General discussion		
10-13:30	Interviews in groups Ariae Kangaciärri Saarma		
	Final (Coldman) Laberman Ruchanen Rousu (Penttilä)		
	Vlänne Holm Salminen (Johnson) Detre		
	Jernvall, Panula, Mäkelä		
13:30-14	Lunch		
14–17:30	Interviews in groups and discussion		
	Hautaniemi (Kallioniemi), Kaski		
	Tekes projects: Korpelainen, Ruusuvuori (Yli-Harja)		
17:30	End of panel meeting		
18:00-	0– Science Gala at Vanha Ylioppilastalo		
OCT 17			
9:00	Panel meeting at the Academy, meeting room 564, 5th floor		
9:30	Interview: Mannila		
10–12	2 Interview with young researchers of the projects as a grou 17 young researchers from the SYSBIO groups		
12–13	Lunch		
13–	Discussion and finalising the report		
	Departure		

ANNEX 4. PANEL ASSIGNMENT

The Assignment

Evaluation of the Systems Biology and Bioinformatics Research Programme (SYSBIO)

Dear Professor NN,

The Academy of Finland has launched the evaluation process of the Systems Biology and Bioinformatics Research Programme. The scientific evaluation of the programme will be carried out by an international evaluation panel. The members of the evaluation panel are

- Professor *Roland Eils*, German Cancer Research Center, Germany, Chair and members
- Professor Søren Brunak, Technical University of Denmark, Denmark
- Professor Marta Cascante, University of Barcelona, Spain
- Professor David Rand, University of Warwick, Great Britain
- Dr Michaela Reichenzeller, German Cancer Research Center, Germany, will serve as a scientific secretary for the evaluation panel.

With this assignment we, on behalf of the Academy of Finland, confirm your membership in the evaluation panel of the Systems Biology and Bioinformatics Research Programme.

The objective of the evaluation is to estimate to which degree the Systems Biology and Bioinformatics Research Programme has succeeded in fulfilling the objectives originally set for it in the Programme Memorandum. Of specific interest are the programmatic approach, added value and programme impacts, interdisciplinarity, multidisciplinarity, applicability of research, networking, and dissemination of results.

In the Evaluation Report, the panel is expected to assess *the programme as a whole* and reflect especially the following issues:

- 1. Planning of the research programme
 - Preparation of the programme and planning of the contents of the programme
 - Research projects funded and funding decisions in creating the necessary preconditions for the programme
- 2. Scientific quality of the programme
 - Scientific quality and innovativeness of the research
 - Scientific competence of the consortia
 - Contribution to the deepening of understanding of systems biology

- 3. Success of the implementation of the programme
 - Concordance with the objectives of the research programme
 - Functioning of the programme
 - Added value of the programme
 - Contribution to enhancing inter- and multidisciplinarity in research
 - Scientific and administrative coordination
- 4. Contribution to researcher and expert training
- 5. Collaboration and networking
 - Collaboration within the programme, especially interdisciplinary collaboration
 - Collaboration with other Finnish groups
 - International cooperation
 - Collaboration with the end-users
- 6. Applicability of research and importance to the users
 - Contribution to promoting the applicability of research results
 - Relevance and importance to end-users
 - National and international impact of the programme
- 7. Recommendations for the future (including the justification for the recommendations)

The panel will have its meeting on 15–17 October 2008 in Helsinki at the Academy of Finland, Vilhonvuorenkatu 6. The preliminary schedule for the panel meeting is as follows:

15 October (day 1) 2008 Arrival in Helsinki, get-together dinner

16 October (day 2) 2008Panel meeting at the Academy of Finland

17 October (day 3) 2008Panel meeting, Departure from Helsinki – late flights

The work will include examination of the reports, self-evaluation assessments, publications and other products of the programme and discussions with researchers, Programme Steering Group, key stakeholders, and programme coordination during the panel meeting. There will also be periods reserved for intensive work of the panel including the preparation and drafting of the Evaluation Report. Technical assistance will be provided during the meeting.

Further details of the meeting and the evaluation material will be sent to you later. If you have anything to ask please do not hesitate to contact us.

Thanking you in advance for your cooperation,

Yours sincerely,

Marja Makarow, Professor Chair of the SYSBIO Steering Group

Merja Kärkkäinen SYSBIO Programme Manager

Annex 5. List of the projects and funding

The projects funded by the Academy of Finland

Bayesian Latent Class Modelling for Functional Genomics: Combining Experimental Results and Data Base Knowledge (FGBayes) Arjas Elja, 445 260 € Understanding Glucuronidation: A Systems Biology Approach Goldman Adrian, 194 300 € Finel Moshe, 194 300 € Vihinen Mauno, 194 300 € Ab initio protein structure prediction Holm Liisa, 260 570 € Ethical and Social Aspects of Bioinformatics Häyry Matti, 244 890 € Linking developmental, computational and evolutionary biology of mammalian teeth Jernvall Jukka, 450 290 € Fortelius Mikael Thesleff Irma Molecular recognition: automated reconstruction and analyses of large molecular complexes Johnson Mark, 207 140 € Nyrönen Tommi, 142 860 € Salminen Tiina, 137 140 € Cheng Holland Systems biology approach for analysis of transcriptional regulation: Hox-gene circuits in cancer Kallioniemi Olli-Pekka, 194 380 € Astola Jaakko, 253 310 € Monni Outi, 218 000 € The function of the plant RCD1-ROL gene family: a systems biology approach Kangasjärvi Jaakko, 279 990 € Keinänen Markku, 216 170 € Combining multiple data sources in functional genomics for improving genome-wide inferences Kaski Samuel, 186 960 € Castrén Eero, 151 430 € Hollmén Jaakko, 166 010 € Knuutila Sakari, 199 310 € Signaling pathways and gene regulatory networks leading to generation of a lymphocyte phenotype pathogenic in asthma and allergy

Lahesmaa Riitta, 246 540 € Aittokallio Tero, 211 400 €

Koski Timo, Oresic Matej, 211 400 € CompGenome: New computational techniques for analysing the structural and functional landscape of the mammalian genomes Mannila Heikki, 325 710 € Jalanko Anu, 86 990 € Kere Juha, 86 990 € Palotie Aarno, 86 990 € Peltonen-Palotie Leena, 183 430 € Deciphering the circuitry leading cancer cells to premature senescence Mäkelä Tomi, 198 220 € Klefström Juha, 155 530 € Ojala Päivi, 155 540 € Vidal Marc, 46 160 € Västrik Imre, 46 160 € Genetic control of neurodegeneration in zebrafish Panula Pertti, 262 270 € Lehesjoki Anna-Elina, 189 260 € Vesterinen Jaana, 189 260 € Experimental and computational analysis of physiological regulation at transcriptome, proteome and metabolome level Penttilä Merja, 237 010 € Holm Liisa, 150 860 € Ketola Raimo, 190 860 € Rousu Juho, 191 020 € Computational Processes in Living Cells Petre Ion, 249 360 € Systems level architecture of GDNF mediated neurotrophic action Saarma Mart, 440 000 € Global approaches to study actin filament regulation in the muscle sarcomere Ylänne Jari, 202 430 € Carpén Olli, 160 000 € Lappalainen Pekka, 160 000 €

The projects funded by Tekes

Simulation of modern gene activity measurements: From microarrays to microscopy Yli-Harja Olli, Tampere Technical University
Probabilistic methods for microarray data analysis Heikkonen Jukka, Helsinki University of Technology
Development of data management and analysis environment for microarray data. Korpelainen Eija, CSC-Tieteellinen laskenta Oy
Computer-Aided methods as tools to find new bioactive compounds. Poso Antti, University of Kuopio The Systems Biology and Bioinformatics Research Programme (SYSBIO) was launched in 2003 and ran for four years from 2004 to 2007. The programme was implemented jointly by the Academy of Finland and the Finnish Funding Agency for Technology and Innovation Tekes. The main objective of the SYSBIO Research Programme was to promote an integrative and holistic approach in research on complex biological processes at the systems level. The programme comprised 21 research projects.

In 2008, an international evaluation panel was set to assess the programme as a whole and to reflect especially on planning of the research programme, scientific quality of the SYSBIO programme and success of the implementation of the programme goals and objectives. This report includes the results of the evaluation and the recommendations of the panel.



Vilhonvuorenkatu 6 • PO Box 99, 00501 Helsinki Tel. +358 9 774 881 • Fax +358 9 7748 8299 www.aka.fi/eng • viestinta@aka.fi



