Systems biology – interaction science of biology and information technology

Tatjana Zukova, Egils Stalidzans

Latvian University of Agriculture, Faculty of Information Technology

Abstract

Systems Biology (SB) is science about behaviour and interaction of elements in functioning biological system integrating experimental and computational research. SB as a new interdisciplinary branch promotes holistic approach to biological processes. Definitions, short history and bibliography of SB underline interdisciplinary character of SB. Roles and used research methods of specialists from branches like biology, information technology, system analysis, mathematicians and others are described. Proportions of different specialists in SB research teams are analysed.

Information creation cycle by iterative progress of experimental and computational approaches is seen as main tool towards validated holistic model of biological object or process. Chemical kinetic, network and other modelling methods of elements and their interactions within biological objects are described.

Results of SB in research and economy by the year 2025 are forecasted to indicate expected directions and speed of its development. Strategic documents of European Union SB development to reach expected results of 2025 in medicine, pharmacy, food production, environmental projects, agriculture, chemistry indicate status and possible role of European and neighbour countries in European SB.

Key words: *systems biology, modelling, validation, holistic approach.*

Introduction

Technical progress supported by science has made many courageous ideas possible. Still technical and scientific progress has negative aspects due to poor forecasts of its impact to environment and other biological objects. Of course, progress has impact also on humans in form of stress, health problems and ecological catastrophes. Independent on human-driven progress nature brings own biological problems that need to be solved (new diseases, disfunction of ecological balance).

Problems with involved biological objects are the hardest as biological objects are not human made. Biological problems can be solved only by detailed understanding of processes in their full complexity as disturbance of balance is much easier than fine task to get it back.

Progress of genetics and information technologies brings preconditions for biosciences to get into next step of *in silico* (computer) simulation of complex life process. This new branch named System Biology (SB) combines concepts from molecular biology, engineering sciences, mathematics in a holistic approach in studies of biological systems, for example living cells, organisms, plants, animals, humans and ecological processes.

Holistic approach based model of a biological object or process becomes a tool, which can either confirm or deny new hypotheses about elements and interactions of a functioning biological system as model and its original (biological object) can be compared in dynamic behaviour. Validated model can become a tool for intensive experiments before implementation of another ‘progressive’ invention of humans.

Goal of this paper is to illustrate the history, current status and perspectives of SB worldwide and specifically for European Union based on different information sources. Paper should give possibility to assess how attractive and useful is SB for a particular research group. Special attention is paid to specialists of engineering sciences and information technologists.

Definition of SB

There are different definitions of SB available showing different accents of SB mission.

- SB research behaviour and interactions of elements in functioning biological system (Palsson, 2000, Ideker et al., 2001).

- SB can be defined as understanding of complex biological systems integrating experimental and computational research (Kitano, 2002).

- SB studies how properties of live forms arise from interaction of their components (Reiss, 2005).

Systems biology approaches comprise (Reiss, 2005):

- The enumeration of network and pathway components in complex biological contexts,
- The reconstruction and mathematical modelling of networks, pathways or living systems,
- The mathematical representation of networks based on quantitative biological datasets,
- The mathematical analysis and simulation of networks to assess their properties and Biological experiments to verify or falsify mathematical models of biological systems.

Definitions demonstrate interdisciplinary art and wide scientific area covered by SB. That results in tendency of SB to split in subbranches.

Short history of SB

History of SB and its name itself is young. Still there are discussions regarding name and definitions of SB. Other proposed names as ‘mathematical biology’, ‘quantitative biology’ and ‘holistic biology’ partly describe the methods and approaches of SB. Still the name Systems Biology is the most known name that includes all aspects mentioned in other names. Development dynamics of SB can be estimated by bibliometric data to trace the development of SB since the 1990s (Reiss, 2005). The analysis shows a very rapid increase of systems biology (core systems biology) publications since 1990 resulting roughly 400 publications in 2004. The first publications originated in Japan in the middle of the 1990s (Figure 1).

Since 2000 the USA has taken the lead, European countries followed with a time lag of about three years. Among the European countries Germany and the United Kingdom showed the highest publication activities. In addition, France and the Netherlands contributed a considerable number of publications. Japan exhibits a comparatively low publication activity which does not reflect the perception by the research groups responding to the benchmarking survey within project EUSYSBIO (Reiss, 2005) were Japan was considered as a key actor in systems biology.

SB as a multidisciplinary science

Biology has been mostly qualitative and describing during last decades comparing to technical sciences. To reach understanding of complex processes of system as optimal control, adaptation and memory it is necessary to analyse components as well as their interactions within biological objects.

SB represents holistic approach looking at a system in all its complexity and moving towards biology as a quantitative and exact science. Only quantitative and holistic description of biological processes by its components and their interactions can confirm or deny correctness of understanding of visible behaviour.

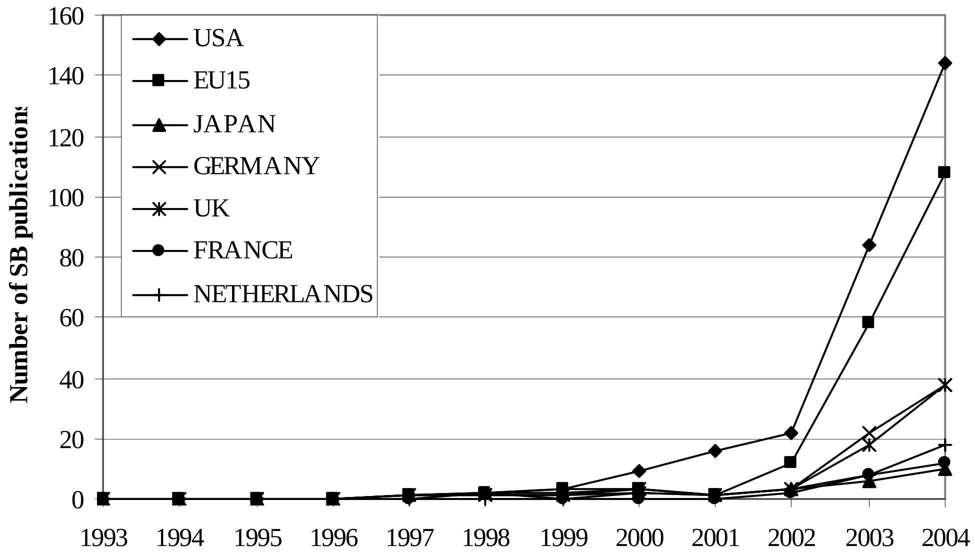

Figure 1: International publication activities in SB between 1993 and 2004 (Reiss, 2005)

Taking into account huge amount of data to be processed and understood new methods are necessary as it can not be managed by human intuition. Therefore mathematical modelling becomes a central mean of process description. SB develop to a multidisciplinary branch where biologists, information technologists and system analysts join to put existing knowledge in a simulation model that can be compared to visible behaviour of biological process (Figure 2).

Goal of SB is a validated model of investigated object allowing computer experiments (*in silico*) instead of experiments in nature (*in vivo*) or in artificial environment (*in vitro*).

That would be the way to predictive biology – possibility to predict processes in quantitative way. This kind of model might become precondition to allow any activities in biological or ecological field only after simulation of planned activity as it is done at nowadays with technical systems.

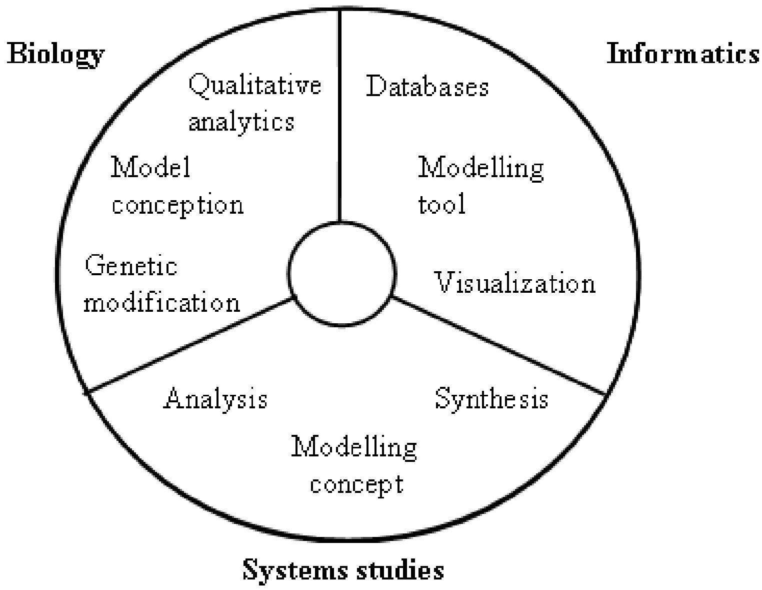

Figure 2: Systems biology as multidisciplinary science (Reiss, 2002)

Figure 3 illustrate regional differences regarding proportion of different specialists in SB teams (Reiss, 2005). Looking at Europe, USA and Japan in teams clearly dominate biologists by about 40%while other specialists are divided in different specialities represent about 60% which still underline SB as a interdisciplinary science. USA research groups show higher interest in specialists from engineering field and the lowest percentage of biologists. A bottleneck in expanding of research groups is personal specialised in medicine, system studies and mathematics and biophysics. Size of SB research groups is about 8 full time researchers. Number of research groups is growing.

Funds for SB come mainly from governmental institutions and national project funding covering about 70% financing. Exception is Japan by over 90% (Reiss, 2005).

Each group of specialists has specific means and methods of contribution in SB approach (Table 1).

Input of informatics is modelling and simulation. Modelling is the main method in representing and validation of data and complex knowledge in SB. Amount of data used in SB due to its holistic approach is far away from capacities of human brain to cover and analyse it. Computer by means of modelling becomes tool allowing operate and prepare version of biological object function in understandable form. Of course, process representation by model request participation of specialists like system analysts, information technologists as discussed earlier. Their cooperation with biologists might give new methods and tools for rapid development of SB.

Some aspects of SB research like insufficiency of information and low quality of data request specialised methods of data mining (experiments, expert surveys) as well as data processing (Stalidzans, 2005; Stalidzans and Markovitch, 2005 b).

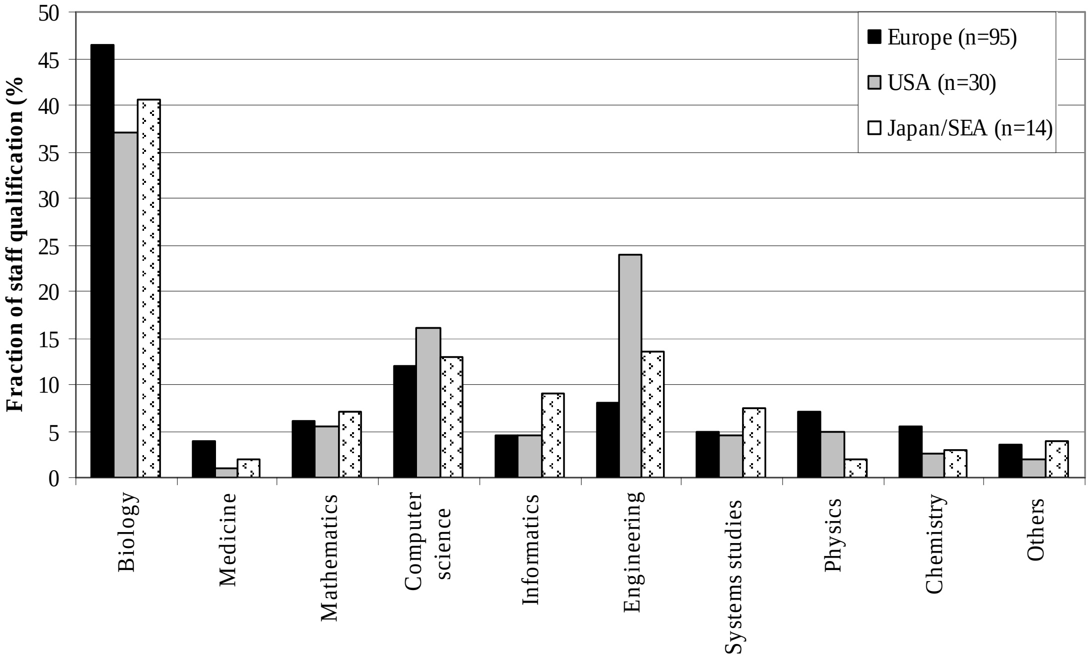

Figure 3: Qualification profile of staff in systems biology research units in different countries (n-number of respondents per country) (Reiss, 2005)

Model in SB has to perform knowledge and understanding about behaviour and interaction of elements of a functioning biological system. That means understanding of system level of biological object. This approach request following basic characteristic (Kitano, 2000):

1. Structure of system. Separate parts of biological system as well as their structural relationships.
2. Dynamics of system. Behaviour of system in time under different internal and external circumstances.
3. Control of system. Research on mechanisms of systems control.
4. Principles of construction have to be identified and used in system analysis.

Based on above-mentioned data a mathematical model can be developed. Hypothesis can be checked in parallel *in silico* (computer simulations) and in vitro (live experiments). Modelling and simulation has three important functions:

1. Presentation way of researched biological object.
2. Gives method to plan experiments to confirm or deny hypothesis performed on a model.
3. Model is a summary of knowledge status in universal form. It acts as a coding of biological knowledge that is necessary in communication of research community.

Modelling specialists should generate new tools and methods for SB or adapt the existing ones from engineering sciences.

Existing computer models for processes in cell level can be divided into two groups: chemical kinetical models and network models (Reiss, 2002).

Chemical kinetic models try to present the processes within a cell as a system of chemical equations. Concentration of molecules of different substances determines interactions in chemical reactions and status of the whole system. Chemical reactions are represented mathematically in form of differential equations where the start and end products are linked by speed constant of possible chemical reactions.

Normally this art of systems with differential equations are too complex to have explicit solution. Still it is possible to go step for step modelling sequential states of system.

Table 1

Prevalence of methods used for systems biology research (n-number of respondents per country) (Reiss, 2005)

Informatics (n=147)		Mathematics (n=115)		Biology (n=127)	
Modelling	81.6%	Parameter estimation	71.3%	Network analysis	59.8%
Simulation	69.4%	Sensitivity analysis	60.9%	System perturbation	48.8%
Algorithms	66.0%	Robustness	49.6%	Genetic modification	46.5%
Databases	50.3%	Stability analysis	48.7%	Transcriptome analysis	46.5%
Visualization	44.2%	Bifurcation analysis	40.0%	Molecular interaction analysis	44.1%
Data mining	41.5%	Metabolic control analysis	34.8%	Cell culture	41.7%
Data annotation	19.0%	Flux balance analysis	30.4%	Genome analysis	40.2%
Data repositories	17.7%	Adaptation	16.5%	Proteome analysis	33.1%
Data access	16.3%			Metabolome analysis	26.0%
Standardisation	16.3%			Single molecule measurement	18.1%
				Physiome analysis	16.5%
				Cell isolation	15.7%

Network models are discrete simulation in form of a network of nodes and oriented relation links. Nodes represent amount or concentration of definite molecules and relation links represent effect of state of a node to the neighbour node. Each node has function how all the influences of linked nodes determine the state of the node itself. It can be simplified assuming that nodes can have only two states. For instance it can be used to indicate if a molecule exist or not or a gene is present or not. At the starting point all the states of nodes are defined. The following states can be calculated by functions of nodes. Network models still are quite far from reality as biological systems can have more then just two states.

Processes of control within biologic system can be described and simulated as a set of control interacting loops (Stalidzans, Markovitch, 2005a).

SB expects new tools from information technologists and mathematicians to develop representation of biological systems easier way.

Generally a computer based model of biological unit is not the final product of SB. Model has to be seen as a mean for holistic approach of SB. Model has to represent real system as good as possible. That is a representation of knowledge status that can be compared with original – investigated biological unit.

Biological systems analysed by SB

Driving force of SB are human needs. Biggest financial support would flow towards SB development for humans (understanding of its functioning, healthcare). On the other hand humans are one of the most complex biological objects and the way to their understanding might start by investigation of simpler organisms as yeast cells. Table 2 show used biological systems in SB research (Reiss, 2005). Humans are by far the most interesting object in Europe compared to USA and Japan. That can be caused by high research level of human diseases like cancer. Yeast is very interesting system in all the world as it is short way to understand basics of living cell to move then to more complex systems.

Table 2

Biological system used for systems biology research (n-number of respondents per country) (Reiss, 2005)

	Europe (n=95)		USA (n=31)		Japan/SEA (n=16)	
Humans	54	61%	9	30%	4	27%
Yeast	50	57%	17	57%	7	47%
Animals	42	48%	12	40%	8	53%
Bacteria	35	40%	14	47%	6	40%
Plants	14	16%	0	0%	3	20%

Agriculture seems to be more interesting as a field of application of SB then convenient object of research.

Directions of SB development

Table 3 is related to directions of SB research. Intensive work on tools and methods of SB indicates early stage of research activities. More than 70% of respondents deal with basic mechanisms again indicating early stage of research.

Items as standardisation, data handling and data validation that are important as a base in every emerging science seem to be less interesting at the moment. That is another indication about early stage of science.

Expectations of results of SB in 2025

Perspectives of SB development accordingly to EUSYSBIO project report (Reiss, 2005) can be divided into scientific and economical ones.

Science will get closer to general understanding of living systems. Later progress will come to detailed pathways and networks of living systems. In science in general biology will change from mainly descriptive into a quantitative, analytical and statistical science.

Table 3

Objectives of systems biology research (n-number of respondents per country) (Reiss, 2005)

	Europe (n=95)		USA (n=31)		Japan/SEA (n=16)	
Development of tools and methods	70	74%	28	90%	14	88%
Elucidation of basic mechanisms	69	73%	22	71%	14	88%
Applications in medicine	46	48%	10	32%	6	38%
Development of databases	28	29%	9	29%	3	19%
Pharmaceutical applications	25	26%	5	16%	6	38%
Validation	16	17%	7	23%	0	0%
Applications in food production	14	15%	0	0%	1	6%
Standardisation	13	14%	3	10%	2	13%
Environmental applications	7	7%	5	16%	1	6%
Applications in agriculture	6	6%	0	0%	1	6%
Applications in chemistry	6	6%	2	6%	4	25%

In gene and genome level dynamics of changes will be described more detailed in general and particularly the ones of human. SB of a cell will develop in sense of quantitative modelling technologies in connection with experimental data integration. Spatial and dynamic processes of a single cell will be clearer. Yeast cell as the most investigated cell will be understood so far that 40% of all metabolic pathways will be understood, 50% of all protein-protein interactions will be known and 60% of all signalling pathways will be defined.

The most interesting organism – human body should be so far understood in 2025 that strategies for curing of 80% of all diabetes, 20% of all cancer and 50% of multifunctional diseases will be developed. SB will bring better understanding of nervous system. Integration between mind and body will be understood at an 80% level.

Strategies of plant biotechnology and food breeding will be developed. Understanding of internal biological processes will bring progress towards quantitative science in precision agriculture.

Economical aspects of SB development in 2025 will bring changes into structure of research and engineering in general. Research will become less time consuming due to more intensive experiments in modelling (*in silico*) instead of time and money consuming live experiments (in vivo) preventing vast of research and development money. This will bring other approach to control tools and methods of biological systems.

Economic impact on health will be seen as increase of quality and efficiency of research and development resulting in more complex understanding of drug impact. SB will lead to multi-drug therapies. Individualised diagnostics and medications will develop personalised medicines. In area of diagnosis SB will implement living biosensors.

Environmental applications of SB can be very wide. It can start by very global issues of ecosystems to impact of individual molecules. SB could bring explanations of environmental toxicology of various substances, assessment of the interaction of plant biotechnology, human health and agricultural economy. Very important direction will be development of microorganisms or plants as alternative sources of energy.

Coordination of European SB

SB research in EU countries is most developed in Germany, UK, France and Netherlands. Still SB as high priority interdisciplinary science needs involving of more partners to reach research level of USA and Japan.

Within earlier mentioned project of 6. Framework programme "The Take-off of European Systems Biology" EUSYSBIO investigation of SB relevant research status and key actors in new EU member states, associated candidate countries, Russian Federation and New Independent States of former Soviet Union, Western Balkan countries and Peoples Republic of China is done (Survey, 2004). The goal of research was to find out potential in terms of highly qualified scientists in mathematics, bioinformatics, systems engineering etc. for later development of strategy of their integration into European activities.

Survey indicates very fragmentary activities relevant to SB in investigated countries. There is a lack of interorganisational coordination to develop SB systematically. There are several countries where no SB relevant activities were found (new member states: Malta, Slovakia, New Independent States of former Soviet Union: Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Tajikistan, Turkmenistan, Ukraine, Uzbekistan, Western Balkan countries: Albania, Bosnia and Herzegovina, Croatia, Macedonia, Yugoslavia). Russia is exception from other countries as there is high level research in SB related items (bioinformatics, computational and systems biology) and research groups are linked together by joint seminars and conferences since several years. Actually many lead SB scientists in Europe and USA are originally from Russian institutes. Thus EU strategy should be improvement of cooperation between the Russian Federation and EU.

In Eastern Europe biocomputing and modelling are not related to SB and genomics. They concentrate more to technical applications of methods in medical engineering or bioprocessing technologies. That experience can bring new tools into SB and broaden definition of SB itself.

Modelling activities in Eastern Europe are done mostly in technology departments or faculties of computer sciences and engineering sciences. Strong interdisciplinary orientation to develop SB field as converging technology field between engineering sciences, computer and systems sciences as well as life sciences would help Eastern European research groups to participate in future research projects.

Integration of Eastern Europe research groups should take place right from the beginning of European SB research projects.

Conclusions

System Biology (SB) is science about behaviour and interaction of elements in functioning biological system integrating experimental and computational research.

Japanese scientists in the middle of 1990s make first scientific publications on SB. Bibliometry indicate rapid increase resulting roughly 400 publications worldwide in 2004. USA, Japan and European Union are the leading SB centres in the world.

SB is interdisciplinary science of biology, informatics, system studies and others as newest developments of specific branches are necessary for SB progress. 35-45% of SB researchers are biologists. Typical size of research group is about 8 full time scientist equivalent.

Main biological systems used for SB research are humans, yeast cells, animals, bacteria and plants. Yeast cell is at the moment the preferred biological system for research.

SB applications are expected in medicine, pharmacy, food production, environmental projects, agriculture and chemistry. Main methods used in SB by specialists of informatics are modelling, simulation, algorythmisation, data bases, visualisation and data mining. Main methods of mathematics are parameter estimation, sensitivity analysis, robustness analysis, and stability analysis. Main methods of biologists used in SB are network analysis, system perturbation, genetic modification, transcriptome analysis, molecular interaction analysis, cell culture and genome analysis.

Leading EU countries in SB research see necessity of cooperation between EU and neighbouring countries to increase the SB research progress and get to the leading position in the world.

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