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# SYSTEMS BIOLOGY AS A NEW AREA OF BIOLOGICAL RESEARCH: CHARACTERISTIC TRENDS AND TENDENCIES OF DEVELOPMENT

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A review article is devoted to the general analysis of trends and tendencies prevailing in the development of systems biology as a new area of biological research. It has been shown that systems biology emerged from accumulated knowledge about human genome and living matter. It uses as methodology systems approach which allows to follow simultaneously multiple components of complicated hierarchy in living system due to the opportunities of high throughput technologies in monitoring of vital biomolecules.

***Ключові слова:*** systems biology, humane genome, high throughput technology, metabolome, transcriptome, regulome.

## INTRODUCTION

System biology is a new emerging and challenging area of biological research which unites in itself a comprehensive knowledge accumulated by other sciences, in particular molecular biology, mathematics, computational science, physiology and so forth, and aims in system – level understanding of metabolic pathways that take place in living organism through complex relationships and interplay between genes, protein and metabolites.

As late as in 1948 Norbert Weiner in his book "Cybernetics, on Control and communication in the Animal and the Machine" pointed out the importance of system approach and system level understanding [1]. Later on a pleiad of prominent scholars such as W. Ashby [2], L. Bertallanffy [3] endeavored to apply system theory to biology and to unravel general biological laws governing the existence of living matter. In view of this, a living organism was considered as an opened physical system which consistently acquires, transfers and utilizes external energy from the environmental stocks in order to ensure the realization of physiological control through processing information. However these early attempts faced serious challenges and gradually disappeared from research agendas. The limitations of classical systems biology were thoroughly discussed by R. Rosen who in addition outlined an alternative way for further incarnation of system theory principles and system level understanding in regard to living organisms [4].

Implementation of Human Genome Project was crucial for making a new step in biology towards systems understanding because the scientists received at their disposal a real possibility to follow simultaneously the activities of all genes in genome, to perturb them and analyze transcriptome and proteome on a new induced level of steady state. These tremendous opportunities in biological research have been highly supported by the advent of high throughput technologies in DNA sequencing, microarray, protein mass-spectrometry and metabolic analysis. Thus, from 1985 until 2000 a 2000-fold increase in throughput of DNA sequencing was observed. For example, 96-capillary sequencer can produce approximately 500,000 base pairs of raw DNA sequences per day. Currently it is possible to identify 16-20 residues in 500 000 different sequences simultaneously. Microarray allows visualizing gene activities of up to 40,000-50,000 genes on one glass slide. Mass-spectrometry can identify and quantify with appropriate software thousands of proteins per day. In addition, multiple screening of different parameters of organism metabolic activity through detecting microquantities of low molecular weight metabolites in blood, urine, saliva also has become possible with high efficiency and throughput [5].

Thereby, the development of different sciences such as mathematics, physics, chemistry, molecular biology, genetics, computational science along with emerging of high throughput technologies have prepared the grounds for the advent of systems biology at the end of the second and the beginning of third millennium of our era in biological research.

**The systems biology concept – What is systems biology?**

Biological investigations and theory in 17-19 centuries were based on mechanistic principles and reductionism. In a view of this, every organism was considered as a complex machine which could be analyzed by disassembling and examining its manageable pieces. Therefore a whole organism behavior was supposed to be easily deduced through reassembling pieces. Mechanistic biology was greatly influenced by successes in physics reached in mathematical description of planetary movement and gravity law. As well as in engineering that showed up in construction of clockwork and vapor engine.

However mechanistic reductionist approach denied the essential specialty of orchestration in living systems. Moreover these principles were ineffective in shedding light on great robustness and genetico-physiological individuality of each living organism. In this connection, all further development of biological research which embodied in uncovering of heredity laws and DNA structure doomed step by step evolution of biology towards holism. Noteworthy, a holistic viewpoint was worded up as early as in ancient time by Greek philosopher Aristotle who regarded the whole system as something more complicated than simple sum of its parts [6].

The ongoing physiological research showed great individual variations not only among species but also within species. Thus, organ weights and cell dimensions varied. Yet, each organism possessed its own level of hormones, fatty acids, neurotransmitters, prostaglandins and other active metabolites. All these organism relevant phenotypic differences were named as a norm of reaction, thereby highlighting the phenotypic individuality of a specific organism. The latter was considered as a complex interplay between genotype and environment [7].

Physiology unclosed feedback control mechanisms which are executed through neurohumoral reactions. Thus, food ingestion is accompanied by irritation of different receptors sensitive to flavor, odor and food appearance. The receptors transmit signals to brain and endocrine organs thereby stimulating the production of digestive enzymes. When food digestion is over then catabolites enter in blood circulation and induce down-regulation of target organs to stop the process of food digestion.

The research in biochemistry showed the feedback control in enzyme networks that was stipulated by the existence of allosteric enzymes having regulatory sites in their tertiary structure. In microbiology the genetic analysis of lac-operon in bacteria revealed up- and down-regulation of gene activities through special DNA interacting substances of peptide or ribonucleic nature [8].

The works in non-equilibrium thermodynamics concerning chaos, negentropy and opened living systems proved the existence of coupled processes and their permanent dynamic interplay. Thus, catabolism is linked to anabolism, respiration along with oxidation to ATP-generation through chemiosmotic coupling and proton pump in mitochondria.

Studies of oscillations in yeast glycolysis promoted the elucidation of individual peculiarities between cells similar to the reaction norm incident to multicellular human or animal organisms.

It is necessary to emphasize a great contribution of molecular biology to systems biology concept (table 1). Deciphering of genetic code, creation of recombinant technologies and DNA automated sequencing eventually embodied in determination of genome of Haemophilus influenzae as a first sequenced organism in 1995. By 2001 human genome project was accomplished which provided information about a whole set of genes forming human genome. This achievement made possible to connect different metabolic pathways with gene networks and implement large-scale analysis of gene encoding processes [9].

A series of breakthroughs in molecular biology, techniques, namely polymerase chain reaction (PCR), DNA-DNA hybridization and reverse transcription, allowed for usage of automatization in biology, thereby microarray and pyrosequencing were invented. Besides, the elaborated two yeast hybrid system and immunoprecipitation (ChIp) provided an important information concerning interactions between similar or different molecules, notably protein-protein, protein-DNA, protein-RNA, in great abundance [5].

The efficiency and throughput of microarray allows to follow the whole genome activity on one plate simultaneously. Thereby, the analysis of functional genome in dynamics has become a reality. Development of high throughput techniques in functional genomics stipulated the continuous generation of information concerning genome, transcriptome, proteome and metabolome at large scale in routine. The received data are arranged in databases so that everybody is in position to find whatever information is needed in regard to the structure, activity and function of different genes, RNAs, proteins and metabolites as well as the principal peculiarities concerning multiple interplay between various substances. The databases which are created by bioinformatics distinguish in great accuracy and details. Moreover, through curation any false information is eliminated. The databases serve as helpful tool in systems biology since the information stored therein provides a basis for simulation, analysis and prediction [10].

Thereby, systems biology emerging was determined by historical evolution of different sciences along with creation of special paradigm, accumulation of relevant information and elaboration of system approach. Thus, systems biology is operating with the whole system at a given moment because it disposes necessary information about almost all components composing it. Moreover, all components are considered as special nodes of different pathways in networks (fig.1), the latter being interconnected and linked by definite control mechanisms.

Featuring a living organism as an opened complex system in permanent interaction as well as matter and energy exchange with environment is typical to systems biology which analyzes different states of such a system through performing external perturbations. In consequence, the detected regularities are described by the aid of mathematical formalization and simulation in differential equations, whereby mathematical models of different processes in living organism are being generated. On the next stage, the developed models pass verification and correction through iteration that allows for elucidation of new positive links and interactions. In such a way, which implies the dynamical analysis of the whole system functional activity through decomposing and identifying its functional nodes along with their interplay, systems biology not only comprehends the existing relations but unravels the hidden peculiarities and forecasts the future outcome.

**The systems biology methodology – How has other sciences contributed to systems biology?**

Systems biology as a biological discipline emerged due to significant progress made other disciplines in the area of biology or relative to it areas. Hence systems biology embodied in itself the most vivid tendencies and items of modern science not only in its paradigm but also in methodology which is in general named as systems approach.

Thus biochemistry owing to the works of L.Michaelis and M.Menten on enzymatic kinetics, P.Mitchell on chemiosmotic theory and A. Hill on enzymatic oxidation provided the ideas of simulation and mathematical description for dealing with metabolic processes in living systems. This gave impulse to further development of metabolic control analysis (MCA) in order to elucidate key mechanism of network control in biochemical pathways. In consequence, molecular properties of components in networks were shown to relate to overall network properties that defined intrinsic control incarnation [9].

The accomplishments of molecular biology especially in area of DNA sequencing, microarray and protein large-scale analysis supplied systems biology with the opportunity of global vision, that is, to observe functioning of living system through detecting functional patterns of its components. The possibility of follow the internal behavior of living organism seems to be crucial for asserting the principles of systems biology and its right for long existence. As it was stressed in part 1, system methodology had been attempted for the application to living system, in particular by non-equilibrium thermodynamics, but proved to be barely efficient in biological research. In present situation just entire perception of biological system as a whole through penetration in internal interactions and counteraction of interplay of its components should render flexibility and robustness to systems approach [11, 12].

As long as systems biology simultaneously deals with a whole system consisting of a great deal of components it experiences a great need in computational science and its approaches in order to hold and operate the accumulated data. Currently a lot of databases are available which furnish a large spectrum of different data to the researchers. Databases are helpful also in getting rid from information redundancy and repeating. Apart from this,

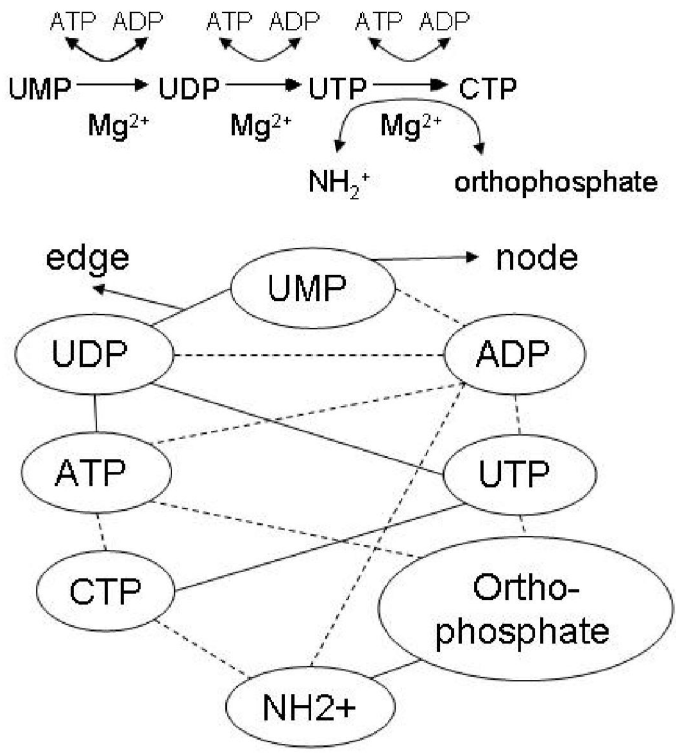


**Fig. 1.** Representation of biochemical pathways in terms of metabolic networks by nodes and edges.

the elaborated special algorithms help to elucidate gene ontogeny and to predict evolutionary links between genes and organisms. Further, special programs make possible database automatic curation and annotating that is of great importance for treating numerous and diverse information [13]. In addition, computer science has provided special programs and algorithms, e.g. MatLab and SSPS statistical package, which facilitate the operation with huge quantitative datasets. Consequently, pairwise similarities between components are found out and further clustering is implemented. Decomposing system on clusters is very valuable for examining different pathologies, e.g. cancer, and diagnostics. Yet, statistical analysis allows for avoiding noise and false conclusions [4]. Systems biology endeavors to apply mathematical language of formulae to describe the processes and component interactions. It makes up different models and verifies their suitability to a specific system. This is a way towards engineering and construction of living processes. Similar things took place in techniques when mathematics penetrated therein. As a result a great deal of various devices and machines were developed. Moreover mathematical formalism has spread out in the area of population ecology whereby population dynamics and species extinction is being described and analyzed [14].

Systems biology frequently utilizes perturbation to disturb system and follow its behavior near the equilibrium point. Therefore systems of differential equations are used for this purpose which detect steady states and show the tendency for system stabilization or destabilization [11].

Physics has contributed a lot to systems biology. The ideas of non-equilibrium thermodynamics and negentropy were very helpful for comprehending living processes. Regarding that entropy or chaos increase is pertinent to any system therefore self organization and information accumulation in vital molecules like DNA, RNA and proteins is impossible without concomitant energy losses. Thus, opposite in nature processes are interconnected, the organism being the intertwining of them. Furthermore, physics and its lows helped to study physical processes in living matter, e.g. electrical conductivity, molecular interactions and atomic decays,and to use physicochemical properties of key molecules in developing throughput technologies [15].

Systems biology has adopted some ideas from cybernetics, in particular system vision. In contrast to cybernetics living system in systems biology is not simplified to separate parts and simple physical interactions.

Rather, each system is analyzed on a new level as a very complex entity with multiple components and very complicated hierarchy. In this view network theory proved to be very helpful for systems biology. Primarily it appeared in ideas of L.Euler and P. Erdos and than was further worked out by A.Barabashi, who proposed to represent living organism in the terms of interconnected nodes with edges(see fig.1). The organism is regarded as a set of different networks functioning in permanent cooperation with each other. However special bottle-neck points exist in these networks which in the whole doom the efficacy of different network interplay [16].

Thereby, systems biology was founded on the ideas and achievements of other disciplines which in turn supplied it by flexible and sound methodology. However systems biology is a quite new science with a completely new understanding of living matter.

**Table 1**

**Key moments on the evolutionary way towards modern systems biology**

| No. | Name | Description | Year(s) |
|---|---|---|---|
| 1 | Non-equilibrium thermodynamics theory | Negentropy and entropy production are two coupled processes essential for life | 1930-1940 |
| 2. | DNA is a hereditary substance | DNA was shown to be responsible for storing and transferring genetic information | 1944 |
| 3. | DNA structure | DNA structure (primary, secondary and tertiary) was deciphered | 1953 |
| 4. | Feedback regulation in metabolism | Feedback control mechanisms in aminoacid synthesis through inhibition | 1957 |
| 5. | Genetic code | Triple nucleotide sequences were determined for all aminoacids including nonsense codons | 1960-1970 |
| 6. | Recombinant DNA technologies | Discovery of reverse transcriptase, restriction enzymes, terminal nucleotidase | 1960-1980 |
| 7. | Analog simulation in microbiology and genetics | Analysis of lac operon by glucose-lactose changes in bacteria deduced gene regulation on transcriptional level | 1960-1965 |
| 8. | Simulation and mathematical analysis in bioenergetics | The laws of energy generation through coupling of respiration and phosphorilation with proton pumping were founded in mathematical form | 1960-1970 |
| 9. | Large-scale simulators of metabolic dissipative structures | Metabolic control analysis proved to be an important approach to characterize interactions in chemical reactions | 1970-1980 |
| 10. | DNA sequencing | Determination of small DNA sequences in different DNA templates | 1980-1990 |
| 11. | Automated DNA sequencing | Automatization of DNA sequencing, pyrosequencing as highthroughput methods | 1990-1995 |
| 12. | In silico biology and mathematical modelling | Genome scale models of viruses and erythrocytes were created | 1990-1995 |
| 13. | Microarray, two yeast hybrid system, protein mass-spectrometry | Invention of high throughput technologies for analysis of transcriptome, proteome and regulome | 1990-2000 |
| 14. | Genome sequencing | Deciphering of Haemophilus influenzae and human genome | 1995-2001 |
| 15. | Bioinformation databases | Accumulation and arrangement of genomics, proteomics, metabolomics data in databases | 1995-2010 |
| 16. | Genome-scale models | Mathematical modeling of large scale processes | 1995-2000 |

**Prospects of systems biology**

System biology is designed to unravel intrinsic peculiarities of living processes. It aims in screening different functional states of living system in conjunction to its components and their interplay in dynamics. Consequently, the new previously masked peculiarities may be unclosed and studied. Hence systems biology deepens our knowledge concerning life. Currently the analysis of the whole transcriptome at once is possible. However, dealing with a whole proteome and metabolome remains to be designed. The research results and the last breakthroughs in the area of high throughput technologies stand for the possibility of attaining this goal in near future. In view of this the complete screening of living organism on all hierarchical levels may become feasible soon. Such an opportunity shall greatly contribute to the drawing up of special algorithms for drug design, pathology diagnostics and metabolome engineering [17]. The further development of systems biology will proceed in tight link with other disciplines such as computer science, mathematics, physics, chemistry, engineering, molecular biology. This implies synergetic cooperation between sciences so that the process of evolutionary progressing in systems biology should greatly accelerate. In consequence, the qualitative jump may occur resulting in replacing descriptive and cognitive modeling by constructive modeling for building new systems with synthesized properties [10].

In this connection, the perspectives for systems biology are indisputable and wide. It is likely that very soon it may merge with medicine in the sphere of diagnostics, drug design and bioimplant construction. Undoubtedly, this will stipulate the gradual transformation of systems biology from purely theoretical biological science into applied biomedical discipline [18].

**CONCLUSION**

Systems biology is a new area of biological research which has emerged with the deciphering of human genome and creation of high throughput technologies for screening transcriptome, proteome and metabolome. The high speed of progressing in systems biology is achieved by interdisciplinary links with highly challenging sciences, namely computational science, bioinformatics, functional genomics, molecular biology, mathematics and physics.

Currently systems biology is mostly a theoretical discipline which makes up a new knowledge through analysis of bioinformatical databases, data mining and dealing with datasets about transcriptome, proteome and metabolome upon living system perturbation by external agents. By the aid of mathematical modeling and simulation systems biology elucidates invisible links between numerous components of living system on different hierarchical levels and then verifies the outcome through iteration and correction [19].

Development of systems biology moves from general description of living processes towards their construction and engineering. The tight link between medicine and systems biology in diagnostics, drug discovery and control as well as metabolome engineering is anticipated.

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## СИСТЕМНА БІОЛОГІЯ ЯК НОВА ГАЛУЗЬ БІОЛОГІЧНИХ ДОСЛІДЖЕНЬ: ХАРАКТЕРИСТИКА НАПРЯМКІВ І ТЕНДЕНЦІЇ РОЗВИТКУ

**Андрейченко С.В.**

Оглядова стаття присвячена аналізу наукових напрямків та тенденцій, що мають місце в розвитку системної біології як нової галузі біологічних досліджень. На фактах і прикладах показано, що системна біологія виникла на основі накопичених знань про геном людини і живу матерію. Як наука системна біологія використовує методологічний підхід, котрий дозволяє одночасно спостерігати за чисельними компонентами складної багаторівневої ієрархії живої системи завдяки можливостям, що виникли при застосуванні сучасних високоефективних технологій по моніторингу життєвоважливих біомолекул.

***Ключові слова:*** системна біологія, геном людини, високотехнологічні методи, метаболом, транскриптом, регулом.

## СИСТЕМНАЯ БИОЛОГИЯ КАК НОВАЯ ОТРАСЛЬ БИОЛОГИЧЕСКИХ ИССЛЕДОВАНИЙ: ХАРАКТЕРИСТИКА НАПРАВЛЕНИЙ И ТЕНДЕНЦИИ РАЗВИТИЯ

**Андрейченко С.В.**

Обзорная статья посвящена анализу научных направлений и тенденций, которые имеют место в развитии системной биологии как новой отрасли биологических исследований. На фактах и примерах показано, что системная биология возникла на основании накопленных знаний про геном человека и живую материю. Как наука системная биология использует методологический подход, который позволяет одновременно наблюдать за многочисленными компонентами сложной многоуровневой иерархии живой системы благодаря возможностям, которые возникли при использовании современных высокоэффективных технологий по мониторингу жизненноважных биомолекул.

***Ключевые слова:*** системная биология, геном человека, высокотехнологические методы, метаболом, транскриптом, регулом.