

# ALTENBERG SEMINARS IN THEORETICAL BIOLOGY

*Summer 2005:*  
*Systems Biology*

**Hörsaal 1, Biozentrum, Althanstrasse 14, at 6.15 p.m.**

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## *The Program at a glance:*

14 April 2005

Debora HAMMOND (Sonoma State University, California):

["Organization in Living Systems: Exploring the Genealogy of General Systems Theory"](#)

28 April 2005

Olaf WOLKENHAUER (Universität Rostock):

["Systems Biology: There is Nothing More Practical Than a Good Theory!\(!\)"](#)

12 May 2005

Albert GOLDBETER (Université Libre de Bruxelles):

["Systems Biology Approaches to Circadian Rhythms: From Molecular Mechanisms to Physiological Disorders"](#)

9 June 2005

Bas TEUSINK (Universiteit Wageningen):

["Systems Biology: Something Old, Something New? A View on Systems Biology from the Perspective of Cellular Metabolism"](#)

23 June 2005

Mihajlo MESAROVIC (Case Western Reserve University, Cleveland, Ohio):

["Search for Organizing Principles in Complex Systems Biology: A Challenge for General Systems Theory"](#)

## *The topic*

“If someone were to analyze current notions and fashionable catchwords, he would find ‘systems’ high on the list. The concept has pervaded all fields of science and penetrated into popular thinking, jargon and mass media.”

These words are taken not from contemporary literature, but from Ludwig von Bertalanffy’s introduction to his 1968 book, *General System Theory*. In Bertalanffy’s view, classical science in its diverse disciplines “tried to isolate the elements of the observed universe — chemical compounds and enzymes, cells, elementary sensations, freely competing individuals, what not — expecting that, by putting them together again, conceptually or experimentally, the whole or system — cell, mind, society — would result and be intelligible.” The science of his day, however, began to take seriously the challenge of “wholeness,” which Bertalanffy characterized as “problems of organization, phenomena not resolvable into local events, dynamic interactions manifest in the difference of behavior of parts when isolated or in higher configuration, etc.; in short, ‘systems’ of various orders not understandable by investigation of their respective parts in isolation.”

Chong and Ray (2002), writing in *Science*, claim that Bertalanffy’s characterization “remains an effective definition of systems biology as practiced today with the integration and application of mathematics, engineering, physics, and computer science to understand a range of complex biological regulatory systems.” Contrary to what latter-day systems biologists such as Hood (2002) like to suggest, the “machine-organism,” constituted in scientific practice as a “technical-natural object” for us, and conceptualized as a “command-control-communication system” in terms of coding and copying, communication and replication, long predated the bioinformatics revolution and “technical wizardry” (Hood) associated with the Human Genome Project, as Haraway (1981-82) has made clear in a lucid analysis of sociobiology; see also Fell (1996) and Voit (2000) on the development of metabolic control analysis and biochemical systems theory in the 1970s.

More importantly, Chong and Ray’s conciliatory stance diverts attention from the enduring conflict between the organicist view of life embraced by Bertalanffy — which made him wary of one-sided concentration on the physicochemical or molecular level at the expense of the higher levels of biological organization — and the mechanistic view that made “the world of the organisms (appear) a product of chance, accumulated by the senseless play of random mutations and selection; the mental world as a curious and rather inconsequential epiphenomenon of material events.” That mechanistic explanation of complex living systems can go hand in hand with the acceptance of a strong form of emergence — for instance, in cell biology — is a very recent insight of philosophers of biology (Boogerd et al. 2005).

Today, “systems biology,” if defined at all (many of its practitioners refrain from doing so and jump on the bandwagon without further ado), is understood in all sorts of ways, not all of which promise much conceptual or practical progress (but see Alberghina and Westerhoff 2005). Actors with a continued stake in single-level explanations include scientists who were disappointed about the fact that deciphering full genomes did not yield the promised revelations, but also “corporate stakeholders who would like to believe that a patentable entity — a gene, a protein, a drug that affects a metabolic step — has a unique causal relationship to a biological function or trait, such as blood pressure, obesity, or depression” (Newman 2003): The promise of predictive biology (Stark et al. 2003) and predictive medicine (Bell 2003; Kitano 2004) requires that the machine-organism be malleable by us.

The “delay” between early pronouncements of the systems paradigm and the current wave of systems biology is often presented as having been necessary, “primarily to accumulate sufficient descriptions of the parts to enable a reasonable reassembly of the whole” (Chong and Ray 2002). Thus, in a way that is reminiscent of naive Baconian induction, the HGP is taken to illustrate the concept of discovery science — “the idea that all the elements of the system (that is, the complete genome sequence and the entire RNA and protein output encoded by the genome) can be defined, archived in a database, and made available to facilitate hypothesis-driven science and global analyses” (Hood and Galas 2003). In a similar vein, Kitano (2002) identifies areas where attempts to derive systems-level understanding are still thwarted by the absence of required extensive and precise information.

Mesarovic (2003) corrects this data-driven view of the enterprise by picturing systems biology as based on a triad of holistic experimentation, software tools to unravel information from a wealth of data, and system science to help transform information into understanding. He illustrates the role of system science in this triad by a quote attributed to Darwin: “How odd is it that anyone should not see that all observation must be for or against some view if it is to be of any service?”

Notwithstanding successes in the exploration of systems as diverse as the regulation of galactose in yeast, or early embryonic development in the sea urchin, or the whole heart (Hood and Galas 2003; Noble 2002), it is obvious that from a biocomplexity point of view, “there is a lack of tools of thought

for dealing with integrative issues” (Paton 2002). Kitano’s (2004) exploration of the inherent properties of robust systems and of the trade-offs between robustness, fragility, performance, and resource demands suggests one promising way to go, as does Wolkenhauer’s (2002) and Mesarovic et al.’s (2004) insistence that explanations in terms of how the categories of systems are organized to function in ever changing conditions are more relevant than numerical predictions.

## REFERENCES

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Stark J, Callard R, Hubank M (2003) From the top down: Towards a predictive biology of signalling networks. *Trends in Biotechnology* 21: 290–93.

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*Abstracts and biographical notes*

**Debora HAMMOND**  
*Hutchins School of Liberal Studies,  
Sonoma State University, CA, USA*

**Organization in Living Systems:  
Exploring the Genealogy of General Systems Theory**

Thursday 14 April

***Abstract***

Given the key role played by Ludwig von Bertalanffy in the articulation of General Systems Theory, Vienna is an ideal location in which to explore the evolution of that tradition. Drawing from my recently published history, *The Science of Synthesis: Exploring the Social Implications of General Systems Theory* (U Press of Colorado, 2003), I will provide an overview of the roots of systems theory, examining the relationship between the emergence of organismic concepts in biology in the early twentieth century and other parallel developments in engineering, management, cybernetics, information theory, ecology and social theory. I will then provide a brief overview of the contributions of the five founders of the Society for General Systems Research: Ludwig von Bertalanffy, Kenneth Boulding, Ralph Gerard, James Grier Miller, and Anatol Rapoport, highlighting the biological dimensions of their work.

***Biographical note***

Debora R. Hammond joined the faculty of the Hutchins School of Liberal Studies in 1997 as Assistant Professor of Interdisciplinary Studies (1997-2002) and is currently Associate Professor of Interdisciplinary Studies (2002-present). She studied history at Stanford University (BA, 1974) and history of science at the University of California at Berkeley (PhD, 1997), under the mentorship of Professor Carolyn Merchant in the Department of Environmental Science, Policy and Management, drawing from both fields in her research on the history of systems thinking. She served as Provost/Director of the Hutchins School (2001-2004), and is currently incoming President of the International Society for the Systems Sciences.

***Selected publications***

Hammond DH, Wilby J (2005) The life and work of James Grier Miller. *Systems Research and Behavioral Science* (upcoming issue).  
Hammond DH (2004) Reflections on the role of dialogue in education and community building. *Systems Research and Behavioral Science* 21: 295—301.  
Hammond DH (2004) Ecopsychology. In: Kresh S, McNeill JR, Merchant C (Eds), *Encyclopedia of World Environmental History*, 402—07. Routledge.

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**Olaf WOLKENHAUER**

*Systems Biology and Informatics, University of Rostock*

**Systems Biology: There is Nothing More Practical Than a Good Theory! (?)**

Thursday 28 April

***Abstract***

A new paradigm should challenge the way research has been conducted previously. I am going to present systems biology as a merger of control theory with molecular and cell biology. In our view, the central dogma of systems biology is that feedback dynamics give rise to cell function. The concepts of feedback regulation and control of pathways and the coordination of cell function are emphasized as an important area of research in systems biology. A conceptual framework for modelling multiple pathways and their coordination is presented. The hurdles and risks for this area are discussed from the perspective of dynamic pathway modelling. Most of all, the aim of the presentation is to promote mathematical modeling and simulation as a part of molecular and cell biology. Systems Biology is a success if it is widely accepted that there is nothing more practical than a good theory.

***Biographical note***

Olaf Wolkenhauer received his Dipl.Ing. and BEng. in Control Engineering from the University of Applied Sciences, Hamburg and the University of Portsmouth, U.K. in 1994. He received his PhD from the University of Manchester Institute of Science and Technology (UMIST) in 1997 for his work on possibility theory with applications to data analysis. Between 1997 and 2002 he held a research lectureship at the Control Systems Centre, UMIST. In 2002 he received a joint senior lectureship between the Department of Biomolecular Sciences and the Department of Electrical Engineering and Electronics. In 2003 he accepted the Chair in Bioinformatics and Systems Biology at the University of Rostock.

***Selected publications***

- Wolkenhauer O, Mesarovic M (2005) Feedback dynamics are the basis for the coordination of cell function. *Molecular BioSystems* (accepted).
- Wolkenhauer O, Ullah M, Wellstead P, Cho K-H (2005) The dynamic systems approach to control and regulation of intracellular networks. *FEBS Letters* 579: 1846–53.
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Wolkenhauer O(1997) Qualitative uncertainty models using random set theory. In: Liu X, Cohen P, Berthold M (Eds), Advances in Intelligent Data Analysis, Reasoning About Data, 609—20. Springer.

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**Albert GOLDBETER**  
*Unité de Chronobiologie théorique,  
Faculté des Sciences, Université Libre de Bruxelles*

**Systems Biology Approaches to Circadian Rhythms:  
From Molecular Mechanisms to Physiological Disorders**

Thursday 12 May

***Abstract***

Oscillations abound in biological systems. Rhythmic behavior arises in genetic and metabolic networks as a result of nonlinearities associated with various modes of cellular regulation. In view of the large number of variables involved and of the complexity of the intertwined feedback processes that generate oscillations, a Systems Biology approach based on computational models and numerical simulations is needed to clarify the molecular mechanism of cellular rhythms. Among biological rhythms those with a circadian (close to 24 hours) period are conspicuous by their ubiquity and by the key role they play in allowing organisms to adapt to their periodically varying environment. In all organisms studied so far circadian rhythms originate from the negative auto-regulation of gene expression. Computational models of increasing complexity will be presented for circadian oscillations in the expression of clock genes in *Drosophila* and mammals. When incorporating the effect of light, the models account for phase shifting of circadian rhythms by light pulses and for their entrainment by light-dark cycles. Stochastic simulations permit to test the robustness of circadian oscillations with respect to molecular noise. The model for the mammalian circadian clock will be used to address the dynamical bases of physiological disorders of the human sleep-wake cycle. The example of circadian rhythms shows how Systems Biology can be used to address issues ranging from the molecular mechanism to physiological disorders in genetic regulatory networks.

***Biographical note***

Albert Goldbeter is the Head of the Unit of Theoretical Chronobiology at the Université Libre de Bruxelles (ULB). His domains of research are the theoretical modeling of cellular rhythms, nonlinear phenomena in biochemical systems, computational cell biology, systems biology, and chronobiology. Dr. Goldbeter studied chemistry at the ULB (PhD, 1973). From 1973 to 1975 he was a post-doctoral EMBO fellow at the Weizmann Institute of Science, Rehovot, Israel. In 1979-80 he worked as a Visiting Research Associate and in 1989 as the Visiting Miller Research Professor at the University of California, Berkeley. Dr. Goldbeter has also been a Visiting Professor at the Université de Paris VI in 2002. He has been the Scientific Secretary of the Chemistry Committee of the International Solvay Institutes for Physics and Chemistry, Brussels, since 2002. He is a member of the Belgian Royal Academy of Sciences and of the Belgian National Committee on Biophysics. He has won the Merck Sharp & Dohme Scientific Prize, granted by the Belgian National Fund for Scientific Research (FNRS), in 1991, and was the Laureate for 2004 of an International Blaise Pascal Research Chair in Ile-de-France Region, France. He is a member of the editorial boards of the *Journal of Theoretical Biology* and of *Comments on Theoretical Biology*, and member of the advisory boards of *Biophysical Chemistry*, the *Journal of Biological Rhythms*, *Chaos* (1991-1995), and of the *Journal of Biosciences*. He has published some 160 articles.

***Selected publications***

Antoniou I, Goldbeter A, Lefever R (Eds) (2004) *Complexity : Microscopic and Macroscopic Aspects*. Proceedings of workshop held in honor of Ilya Prigogine on the occasion of his 85th birthday. *International Journal of Quantum Chemistry* 98(2): 59–280.  
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**Bas TEUSINK**  
*NIZO food research B.V., Wageningen Center for Food Sciences*

**Systems Biology: Something Old, Something New?**  
**A View on Systems Biology from the Perspective of Cellular Metabolism**

Thursday 9 June

***Abstract***

In this lecture I will show some examples of traditional Systems Biology (if I may use that anachronism), where relatively simple mathematical models give fundamental insight in the regulation of cellular metabolism. I will then move to modern Systems Biology, which owes its popularity to the (functional) genomics revolution. I will show some examples of genome-scale approaches in data analysis and modeling, and will hint at directions for how old and new Systems Biology may be combined.

***Biographical note***

Bas Teusink studied Chemistry at the University of Amsterdam. After graduation in 1993 on the topic of glycolytic oscillations in yeast, he started his PhD work in the group of Mathematical Biochemistry at the University of Amsterdam, under supervision of Prof. Hans Westerhoff. The subject of the thesis was to understand the systemic behavior of yeast glycolysis in terms of the properties of the constituent enzymes and their interactions.

In 1996 he obtained a Marie Curie fellowship to work in Manchester for one year in the lab of Prof. Stephen G. Oliver, at that time the coordinator of the Yeast functional analysis program EUROFAN. Together they developed a concept now well known as metabolomics, i.e., the use of metabolite concentration changes to characterize deletion strains of hypothetical genes. In 1999 he defended his PhD thesis entitled: "Exposing a Complex Metabolic System: Glycolysis in *Saccharomyces cerevisiae*."

At the end of 1998 he joined the group of Prof. Louis Havekes at TNO Prevention and Health at Leiden University, to study the interactions between glucose, fatty acid, and lipoprotein metabolism in several transgenic and knockout mouse models. The focus was on the use of tracer dynamics for accurate flux measurements in mice.

In 2002 he started at NIZO food research, where he is now working on a project for the Wageningen Center for Food Sciences, on the use of functional Genomics tools for improvements in industrial fermentations of lactic acid bacteria. He is also a visiting scientist at the bioinformatics group of Prof. Roland Siezen at the Radboud University Nijmegen. The research focuses on building models of the metabolic networks for managing and interpreting high throughput data generated by the functional genomics techniques used to follow the global responses of lactic acid bacteria to environmental conditions and to metabolic engineering.

***Selected publications***

Teusink B, van Enckevort FHJ, et al. (2005) In silico reconstruction of the metabolic pathways of *Lactobacillus plantarum*: Comparing predictions of nutrient requirements with growth experiments (submitted).

De Roos B, Duivenvoorden I, Rucklidge G, Reid M, Ross K, Lamers RJ, Voshol PJ, Havekes LM, Teusink B (2005) Response of apolipoprotein E\*3-Leiden transgenic mice to dietary fatty acids: Combining liver proteomics with physiological data. *FASEB J* Mar 8 (Epub ahead of print)

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Teusink, Walsh MC, et al.(1998). The danger of metabolic pathways with turbo design. *Trends Biochem Sci* 23(5): 162—9.

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**Mihaljo MESAROVIC**  
*Department of Electric Engineering and Computer Science,  
Case School of Engineering, Case Western Reserve University, Cleveland, Ohio, USA*

**Search for Organizing Principles in Complex Systems Biology:  
A Challenge for General Systems Theory**

Thursday 23 June

***Abstract***

The principal challenge facing systems biology is complexity. According to Hood, “Systems biology defines and analyzes the interrelationships of all of the elements in a functioning system in order to understand how the system works.” With 30,000+ genes in the human genome the study of all relationships simultaneously becomes a formidably complex problem. Hanahan and Weinberg raised the question as to whether progress will consist of “adding further layers of complexity to a scientific literature that is already complex almost beyond measure” or whether the progress will lead to a “science with a conceptual structure and logical coherence that rivals that of chemistry or physics.” At the core of the challenge is the need for a new approach, a shift from reductionism to a holistic perspective.

However, more than just a pronouncement of a new approach is needed. I suggest that what is needed is to provide a conceptual framework for systems biology research. I propose that the concept of a complex system, i.e., a system of systems as defined in mathematical general systems theory (MGST) is central to provide such a framework. I further argue that for a deeper understanding in systems biology investigations should go beyond building numerical mathematical or computer models — important as they are. Biological phenomena cannot be predicted with the level of numerical precision as in classical physics. Explanations in terms of how the categories of systems are organized to function in ever changing conditions are more revealing. Non-numerical mathematical tools are appropriate for the task. Such a categorical perspective led me to propose that the core of understanding in systems biology depends on the search for organizing principles rather than solely on construction of predictive descriptions (i.e., models) that exactly outline the evolution of systems in space and time. The search for organizing principles requires an identification/discovery of new concepts and hypotheses.

***Biographical note***

Mihajlo Mesarovic is Cady Staley Professor of Systems Engineering and Mathematics in the Department of Electrical Engineering and Computer Science, Case School of Engineering, Case Western Reserve University. He holds a PhD from the Serbian Academy of Science. He is the founder, with Y. Takahara, of the Mathematical Theory of General Systems (abstract systems theory). He is the founder of the journal *Mathematical System Theory* (Springer). Dr. Mesarovic became internationally famous through his collaboration with Eduard Pestel on the second report to the Club of Rome, *Mankind at the Turning Point* (1974), which was translated into seventeen languages. Systems Biology research at the Systems Research Center at Case was established in 1969 with Mesarovic, Robert Plonsey, and David Fleming, and in 1973 grew into the Bio-Medical Engineering Department, which was probably the first biomedical department jointly in the Medical School and School of Engineering. The current Center for Computational Genomics is an interdisciplinary research center, established for enhancing the CWRU research and training effort towards understanding the human genome.

***Selected publications***

Mesarovic MD, Sreenath SN, Keene JD (2004) Search for organising principles: Understanding in systems biology. *Systems Biology* 1: 19–27.  
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