CLEMENS WAGNER, PHD

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Biocomplexity Faculty Search Committee
C/o Prof. Rob de Ruyter van Steveninck
Biocomplexity Institute, Indiana University
Swain Hall West 117,
Bloomington IN, 47405 - 7105

Bern, 26. December 2003

Application for a Junior Faculty Position in Biocomplexity

Dear Professor de Ruyter van Steveninck

Your job advertisement in the October issue of Nature attracted my attention. Due to my background in computational biology I would like to apply for the junior faculty position in Biocomplexity.

Since two years I have an independent research position at the Institute of Pharmacology at the University of Bern in Switzerland. Currently, my research focuses on the relationship between dynamical and topological properties of a network. The details of my investigations are outlined in the section "Research Interests". One of the methods I am using is the concept of elementary modes. It allows for detecting redundant pathways in metabolic systems. Recently, my grant to compute elementary modes of large biochemical networks has been approved by the Swiss National Science Foundation. However, my working contract runs out in April 2005, which drives me to look for a new job in time.

Beside the analysis of networks my scientific background in computational biology encompasses kinetic modeling, stochastic processes, nonlinear dynamics and time series analysis.
In my PhD thesis I investigated electron transfer reaction in the bf-complex, a protein located between the two photosystems in the thylakoid membrane of chloroplasts. During my postdoc I developed a model for the pulsatile secretion of growth hormone (GH) into the circulation and I investigated the interaction of GABA and picrotoxin on the gating mechanism of the $GABA_A$ channel by kinetic modeling. Further, I determined intermediates in protein folding by a kinetic scheme and explored their function on the folding pathway using a stochastic approach.
Nonlinear dynamics of neuronal networks was the major topic when I started my job in Bern. At that time it was thought that unstable periodic orbits of a chaotic attractor might play an

important role to understand brain function. Therefore I developed a simple memory model, which stores information in unstable periodic orbits. The information was then retrieved by a chaos control method. While searching for a simple control algorithm, which needs no computational efforts, I realized that limiters already do the job. In the following I have analyzed the control method of hard and soft limiters of chaotic orbits in detail.

My preferences in teaching are (bio-)physics, nonlinear dynamics, kinetics as well as introduction to neural networks and theoretical neuroscience.

If you need further information about my curriculum or translations of the documents please let me know.

I would be very pleased to get invited for an interview and I am looking forward to hear from you.

Yours sincerely,

Clemens Wagner, PhD.

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GROWTH HORMONE OSCILLATIONS

INTERMEDIATES IN PROTEIN FOLDING

SCALING OF LIMITER CONTROLLED, DYNAMICAL SYSTEMS

NETWORK ANALYSIS

RESEARCH

RESEARCH INTERESTS

Analysis of Biological Networks

Since the seminal papers by Strogatz (small world networks) and Barabasi (scale-free networks) the analysis of biological networks has grown to a major topic in systems biology. I am interested in the relationship between the topology and the dynamics of networks. The goal of my work is to derive functional properties of the systems from the network architecture. In metabolic networks I explore the presence of redundant pathways and in neural networks my interests focus on network topologies that are able to synchronize (Figure 1).

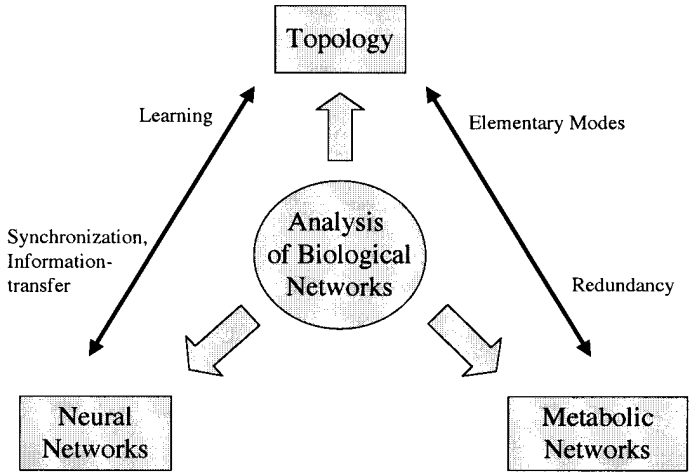

Figure 1 Summary of research interests

Tools

Beside general tools from graph theory – i.e. mean path length, clustering coefficient and degree distributions – I will use the concept of elementary modes to analyze networks. Elementary

modes are minimal sub-networks, which either connect inputs to outputs or form cycles. Further, they are non-redundant, which means that the interruption of a single connection eliminates the complete mode.
Elementary modes are derived from the stationary state of the system. Chemical systems are linear in the flows whereby the linear map is given as stoichiometry matrix. Therefore, elementary modes lie in the nullspace of the stoichiometry matrix due to the imposed steady state condition. In geometric terms the set of normalized elementary modes forms a convex body and all stationary states are internal points of that body.

Algorithms
I have recently developed a new algorithm to calculate the elementary modes of a network. It uses the fact that elementary modes are elements of the nullspace of the stoichiometry matrix. Hence, they can be written as linear combinations of nullspace basis vectors.
However, the analysis of networks by elementary modes is a combinatorial problem. Therefore it is crucial, when studying larger systems, to incorporate results from graph theory in order to improve the algorithm, i.e. nested dissection.

A. Graphs
Although the analysis of networks in terms of elementary modes is derived from the stationary state of the system, the concept also provides a general tool to analyze graphs. For the class of graphs without loops and node degrees larger than 1, the elementary modes represent all possible cycles of the network. This includes Hamiltonian cycles. In this sense, elementary modes yield a new ansatz to solve graph theoretical problems.
However, my major goal is to characterize graphs by their distribution of cycles. Networks may be distinguished by their distribution of the number of cycles versus the cycle length. A closed, nearest neighbor-coupled chain contains only a single cycle whereas a completely coupled chain shows a distribution of cycles of all length. Alternatively, one can study the number and the length of cycles for a given node, in order to investigate the (node)

robustness of the network. In addition, short cycles represent a local property of the network whereas large cycles are associated with global properties.

B. Metabolic Networks

In metabolic pathways of parasites one of the problems for an efficient drug treatment is the presence of redundant connections between inputs and outputs. Therefore, the fact that elementary modes are non-redundant sub-networks can be exploited. As mentioned above, by inhibiting a sole transition the complete elementary mode vanishes. If all elementary modes are eliminated the network is fully blocked. Hence, if the elementary modes are determined, a minimal set of reactions can be identified, which disjoins the input from the output. This requires that each elementary mode contains at least one of these reactions. For a single drug application all elementary modes must have one reaction in common. In contrast, if a single reaction is not sufficient to interrupt the network multiple drugs have to be applied. I have verified the method by comparing the outcome of the elementary mode analysis to the results of inhibitor experiments of the glycolytic pathway in glycosomes of trypanosomes. Here, the elementary mode analysis revealed its elegance and its power of prediction. It encouraged me to investigate pathways in other parasites in order to identify reactions for an efficient drug treatment. In the end, the work should lead to a general redundancy analysis of metabolic networks to characterize the robustness of these systems.

However, the analysis crucially depends on the correct representation of the biological network. Therefore, a further aim is to investigate how elementary modes can be used to support the reconstruction of a pathway.

C. Neural Networks

In contrast to metabolic systems, the output of a node of a neural network is not only driven by the inputs but also by the internal dynamics. Since I am interested in network properties the complex internal dynamics of individual real neurons is ignored and chaotic oscillators are used instead. Whether neurons are indeed able to operate in a chaotic mode or not is still under debate. However, networks of chaotic oscillators warrant for complex behavior and

have been shown to provide qualitative correct results.
Synchronization seems to an important mechanism how different sets of neurons communicate in the brain. Furthermore, it has been hypothesized recently that the brain is size optimized. Therefore, I am looking for network topologies, which synchronize with a minimal density of connections. Progress in morphological studies of the visual cortex revealed a connection density that decays with distance following a power law. These, so called fractally coupled, networks are one possibility to satisfy the above mentioned requirements.
A crucial determinant for fast object recognition is the latency of synchronization onset requiring a fast information transfer between the different sets of neurons. Thus, I examine the speed of information transfer in networks with different architectures.
Fractally coupled networks are scaled networks by construction. An interesting extension of the proposed studies will be the investigation of fractally coupled multiscale networks, an intermediate between scaled and scale-free networks. In principle, this is already realized in the visual cortex where it has been reported that the connection density within a column of neurons is high but it is markedly reduced between the columns.

Significance

Elementary mode analysis is a sophisticated tool to unravel redundant pathways in metabolic systems. An application of the method is the identification of crucial reaction that can be used as drug targets in order to block a network. The analysis might also be applicable to signaling and genetic networks.
The concept of elementary modes can be used to characterize the topology of networks in terms of cycles. From a dynamical point of view cycles are important since they have the ability to destabilize the system.
Synchronization is an important way, how populations of neurons communicate in the brain. In addition, the brain seems to be optimized for size. Thus, the elucidation of a size-optimized network architecture that synchronizes helps to decipher neural communication.

CLEMENS WAGNER, PHD

PUBLICATIONS

1. Tzanela M., **Wagner C.** and Tannenbaum G.S. "Recombinant human growth hormone binding protein fails to enhance the in vivo bioactivity of human growth hormone in normal rats"
   Endocrinology **138** (1997), 5316 - 24.

2. Kiefhaber T., Bachmann A., Wildegger G. and **Wagner C.** "Direct measurement of nucleation and growth rates in lysozyme folding"
   Biochemistry **36** (1997), 5108 - 12.

3. **Wagner C.,** Caplan R.S. and Tannenbaum G.S. "Genesis of the ultradian rhythm of growth hormone secretion: a new model unifying experimental observation in rats"
   Am. J. Physiol. **275** (1998), E1046 - 54.

4. **Wagner C.** and Kiefhaber T. "Intermediates can accelerate protein folding"
   Proc. Natl. Acad. Sci. USA **96** (1999), 6716 - 21.

5. Bieri O., Wildegger G., Bachmann A., **Wagner C.** and Kiefhaber T. "A salt induced kinetic intermediate is on the new parallel pathway of lysozyme folding"
   Biochemistry **38** (1999), 12460 - 70.

6. Buhr A., **Wagner C.,** Fuchs K., Sieghart W. and Sigel E. "Two residues in M2 of the GABA receptor affect both channel gating by GABA and picrotoxin affinity"
   J. Biol. Chem. **276** (2001), 7775 – 77781.

7. **Wagner C.** and Stoop R. "Optimized chaos control with simple limiters"
   Phys. Rev. E **63** (2001), 017201.

8. **Wagner C.** and Stucki J. "Construction of an associative memory using the unstable periodic orbits of a chaotic attractor"
   J. Theor. Biol. **215** (2002), 375 – 384.

9. **Wagner C.** and Stoop R. "Renormalization approach to optimal limiter control of 1d chaotic maps"
   J. Stat. Phys. **106** (2002), 97 –107.

10. Stoop R., Blank D., Kern A., v.d. Vyver J.-J., Christen M., Lecchini S. and **Wagner C**. "Collective bursting in layer IV. Synchronization by small thalamic input and recurrent connections."
    Cogn. Brain Res. **13** (2002), 293 – 304.

11. Stoop R. and **Wagner C**. "Scaling Properties of Simple Limiter Control."
    Phys. Rev. Lett. **90** (2003), 154101-1 – 154101-4.

12. **Wagner C**. "Nullspace Approach to Determine the Elementary Modes of Chemical Reaction Systems."
    To appear in *J. Phys Chem* (accepted)

Non Peer-Reviewed Publications

13. **Wagner C.** and Walz D. "Analysis of b-cytochrome titrations in terms of interacting redox-centers" In Photosynthesis: from Light to Biosphere (Mathis, P. Ed.) Vol II (1995), pp781 – 784, Kluwer Dodrecht.

14. **Wagner C.** and Stoop R. "Universal scaling behavior of flat-topped maps"
    In Control of oscillations, Proceedings of the conference: progress in nonlinear science, in honor of the 100th Birthday of A.A. Andronov (2001)

15. **Wagner C.** and Stoop R. "Enhanced information flow in a chain of fractally coupled chaotic clusters"
    In Frontiers in Artificial Intelligence and Applications, Damiani E., Howlett R.J., Jain L.C. and Ichalkaranje N. (Eds.) (2002), 905 – 909, Amsterdam IOS Press.

16. **Wagner C.** and Stoop R. "The Small World of Fractal Coupling"
    Proceedings of the Conference: Complexity 2003, Aix-en-Provence,France.

INVITED TALKS

1. "*Effects of high energy intermediates on the kinetics of protein folding*" Falter Tagung, Regensburg, Germany (1999).

2. "*Construction of a Memory based on the Properties of a Chaotic Attractor*" Mabic Conference on Biological Computation, Lavin, Switzerland (2000).

3. "*A Minimal Model for the Rhythmogenesis of Growth Hormone Secretion in the Rat*" Seminar, Novartis Research Institute, Vienna, Austria (2001).

4. "*Renormalization Approach to Optimal Limiter Control*" Mabic Conference on Biological Computation, Lavin, Switzerland (2001).

5. "*Correlation based Learning of Synchronization in a Network of Coupled Chaotic Maps*" Mabic Conference on Biological Computation, Lavin, Switzerland (2002).

6. "*Enhanced Information Flow in a Chain of Fractally Coupled Chaotic Clusters*" Knowledge Based Intelligent Information Engineering Systems and Applied Technologies KES02, Crema, Italy (2002).

7. "*The Small World of Fractal Coupling*" Complexity 2003, Aix-en-Provence, France (2003).

8. "*Biological Rhythms: Growth Hormone Oscillations in the Rat*" Seminar Department of Endokrinology, Universität Bern (2003).

9. "*Analysis of Biological Networks*" Seminar, CIIT, Research Triangle, Chapel Hill, North Carolina (2003).

GRANTS

1996	Postdoctoral Fellowship Swiss National Science Foundation and Ciba Geigy Foundation
2001	Josephine Clark Foundation Computer, Backup System
2003	Canadian Institutes of Health Research (CHIR) Minor Applicant (Major Applicant: Prof. G.S. Tannenbaum McGill University, Montreal, Canada) Traveling money and software
2003	Swiss National Science Foundation (SNF) Grant – Application 3100A0-102269 Major Applicant (single) Postdoc

COLLABORATIONS

McGill University, Montreal, Canada
Montreal Children's Hospital Research Institute
Prof. Dr. G.S. Tannenbaum
Effect of Ghrelin on the Rhythmogenesis of Growth Hormone

Weizman Institute of Science, Rohovot, Israel
Department of Biological Chemistry
Prof. Dr. S.R. Caplan
Bifurcations in a Mathematical Model of Growth Hormone Secretion

University and ETH Zürich, Switzerland
Institute of Neuroinformatics
PD Dr. R. Stoop
Neural Networks and Nonlinear Dynamics

University of Bern, Switzerland
Department of Neurology, Motor Research Laboratory
Dr. A. Kälin
Time Series Analysis of Transcranial Magnetic Stimulation Data

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CHEMICAL KINETICS

MATHEMATICS

PHYSICS

TEACHING

CLEMENS WAGNER, PHD

LECTURE

1998 PhD Course, University of Basel, Prof. T. Kiefhaber

Chemical Kinetics

- Rate Equations
- First Order Systems (Geometric Viewpoint)
- Nonlinear Systems: Oscillating Reactions (Volterra-Lottka Model, Brusselator), Limit Cycles, Bifurcations
- Collision Theory
- Thermodynamics and Statistical Mechanics
- Transition State Theory
- Kramers Theory
- Markov Chains

EXERCISES

1997 – 1998 University of Basel, Prof. H.P. Kraft

Mathematics for Students of Natural Sciences

- Calculus: Functions, Series, Differentiation und Integration in one and more Variables
- Linear Algebra: Matrices, Linear Equation Systems, Gaussian Algorithm, Eigenvalues and Eigenvectors

CLEMENS WAGNER, PHD

TUTORIAL

2000 University of Bern, Prof. J. Stucki

Pharmacology
- Antidepressants
- Antibiotics

2003 University of Bern, Lehrauftrag

Physics for Students of Natural Sciences
- Mechanics, Thermodynamics, Electrodynamics and Optics

CLASSES

2002 – 2003 Kirchenfeld Gymnasium (High School),
Prorektor: Herr H. Andermatt

Physics
- Mechanics (Newton)
- Electrodynamics