December 22, 2003

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

Dear Dr. de Ruyter:

I am responding to your advertisement for junior faculty positions as part of the new Biocomplexity Institute at Indiana University. I am presently conducting postdoctoral research in the laboratory of Dr. Eve Marder at Brandeis University, where I combine theoretical, experimental, and hybrid dynamic clamp methods to investigate pattern generation, stability and homeostasis in individual neurons and small neural networks.

In recent work at Brandeis, I developed a computational method that makes use of the constantly increasing performance of computers to construct and analyse large-scale databases of computational model neurons and networks. Such databases provide a flexible tool for the systematic investigation of non-linear systems at all levels of biological complexity. I am particularly interested in joining the Biocomplexity initiative at Bloomington, because it promises to attract investigators working on a wide variety of biological systems and to thus provide a range of exciting possibilities for the application and further refinement of the database approach I pioneered.

Coming from a physics background, I received my PhD from the Technical University in Munich, Germany, for research on small neural networks that I designed and modelled at the Max-Planck-Institute for Biochemistry with Dr. Peter Fromherz. Both at the Max-Planck-Institute and at Brandeis, I have come to appreciate interdisciplinary work with colleagues and students from a wide variety of fields, including physicists, biologists, chemists, mathematicians, physicians, and engineers. I am convinced that the Biocomplexity Institute and the Bloomington campus in general will provide a similarly stimulating environment with ample opportunity for fruitful interactions, and I would love to both contribute to and benefit from that environment.

In the past, I have enjoyed interacting with students enrolled in physics, biology, biophysics, and neuroscience programs, and I am excited about the opportunity to teach specialized and core courses in the physics or biology department at Indiana University.

I am enclosing my curriculum vitae and a statement of my research interests, and I have arranged for letters of recommendation to be sent to you from Dr. Peter Fromherz, Dr. Eve Marder, and Dr. Larry Abbott.

Thank you for considering my application. I very much look forward to hearing from you in the application process.

Sincerely,

Astrid Prinz

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PAST, PRESENT, AND FUTURE RESEARCH

Summary
In my future research, I plan to combine newly developed computational methods and dynamic clamp experiments to investigate how tightly neuronal and synaptic properties need to be regulated to achieve functional network performance, and how such regulation can be achieved at the cellular and synaptic level.

The background: neural networks can perform the same function in different ways

My pre- and postdoctoral research was motivated by the desire to understand neural systems at the cellular and small network level. In the course of my studies I monitored action potential propagation along the neurites of leech cells [1], investigated the role of a potassium current in shaping the activity of hippocampal neurons [2], engineered and analyzed geometrically simple networks of snail neurons coupled by electrical synapses [3, 4], and investigated the effect of synaptic input strength and duration on oscillatory neurons [5].

A vital part in all of these studies was the use of computational models to elucidate the behavior of neurons and neural networks beyond what is possible with purely experimental approaches. These modeling studies taught me that neural systems can often perform their function in many different ways. This is supported by the experimental finding that functionally equivalent neural behavior can result from very different combinations of ion conductances in a neuron's membrane [6].

Similarly, theoretical results suggest that neurons and neural systems are better described as a set of possible combinations of neural and synaptic properties that all generate similar behavior – a "solution space" – rather than a single, unique combination of membrane and synaptic currents [7-10]. Due to on-going turnover of molecular components and varying environmental conditions, homologous neural systems in different animals – or the same network at different times during an animal's life-span – are thought to achieve the same function with varying combinations of underlying membrane and synaptic properties.

The concept of similar neural system behavior from different underlying cell and synapse properties raises several important questions: What are the combinations of cellular and synaptic properties that can generate a desired behavior? How tightly do the different parameters have to be regulated? How do neurons and neural networks achieve this regulation? In my future research, I wish to address these questions through a combination of computational and experimental methods described in the following sections.

The database approach: mapping neural behavior with brute force

Neural activity arises from complex interactions between non-linear dynamic components, like voltage-dependent ion channels, synaptic processes, and cellular signaling cascades. To understand which combinations of these components will result in functional neurons or networks, it is often not sufficient to vary one cellular or synaptic parameter at a time. During my postdoctoral research, I developed a computational method [11] that solves this problem by systematically exploring the high-dimensional

parameter space of a neural system and characterizing the behavior of many different combinations of cellular and/or synaptic properties.

I used this approach to generate a database of model crustacean stomatogastric ganglion (STG) neurons by varying the maximal conductances of a conductance-based model [11] and to create a database of network models of the pyloric pattern generator circuit in the STG [12]. Preliminary analysis of these databases has confirmed that similar electrical activity can be generated by neurons and networks with different membrane and synaptic conductances. Furthermore, first results from the database of network models indicate that pattern generation in the pyloric circuit can rely mostly on cellular, mostly on synaptic, or on a mixture of cellular and synaptic properties. I plan to continue the analysis of these existing databases to gain further insights into the operation of STG neurons and circuits.

Furthermore, I am eager to pioneer the promising technique of database construction in other neural systems. The two databases mentioned above were constructed by varying maximal membrane or synaptic conductances, while leaving many other parameters, like activation thresholds and time constants, unchanged. The technique could also prove powerful if applied to multi-compartment models of extended neurites, or if more than just maximal conductances were varied.

Beyond neural systems, the database approach can be applied to any complex biological system that can be mathematically described. I am convinced that the diverse range of model systems that will be investigated at the Biocomplexity Institute would provide an ideal setting for the beneficial application of the database technique to a variety of non-linear systems.

Staying grounded in experiments: dynamic clamp verification of model predictions

The database studies outlined in the previous section have led and will continue to lead to predictions about the relative importance of different cellular and synaptic parameters in generating a particular behavior. For example, preliminary results from the database of model pyloric circuits [12] indicate that functional pyloric rhythms can be generated with different synaptic strengths that can, in the case of most synapses in the circuit, range over several orders of magnitude of synaptic conductance. However, one particular synapse, from the lateral pyloric (LP) to the pyloric (PY) neuron, appears to require much tighter regulation; if the strength of this synapse exceeds a certain value in the simulation, pattern generation breaks down.

To validate results from purely computational database studies, I intend to test such predictions through dynamic clamp manipulation of biological cells or circuits. The dynamic clamp is an electrophysiological technique that injects computer-generated currents into biological neurons to mimic the effects of synaptic or membrane conductances [13, 14]. In the above example, I plan to use the dynamic clamp to artificially increase the strength of the synapse from the LP to the PY neuron in the biological circuit and to thus test how sensitively the output of the biological circuit depends on this synapse conductance.

Modeling and probing regulation of cellular and synaptic properties

If proper network function can be achieved with a variety of different combinations of cellular and synaptic properties, how do neural systems regulate their properties to

remain in this "solution space" despite molecular turnover and environmental variability? Experimental and theoretical results suggest that individual neurons and small networks can achieve such functional homeostasis [15-19], and it appears that intracellular calcium signals may play an important role in linking neural activity to signaling cascades that regulate expression levels of membrane and synaptic proteins [3, 4, 18, 20].

Neuron and network "solution spaces" obtained with the database approach provide an ideal basis for theoretical explorations of the regulatory mechanisms that underlie functional homeostasis. Using existing and future databases, I plan to address questions such as: Do intracellular calcium signals distinguish between functional and non-functional network configurations? What other signals could be involved in regulatory pathways at the cellular and synaptic level? Are the proposed regulatory mechanisms sufficient to restore proper network function in response to different network perturbations?

These computational studies will be guided by experimental investigations of the regulatory behavior of biological networks. I will use the dynamic clamp to simulate physiologically meaningful perturbations in biological networks, such as the addition of neuromodulatory currents or the artificial up- or down-regulation of a subset of synaptic or membrane currents. The reaction of biological networks to such perturbations will inform the refinement of models of homeostatic regulation in neural networks.

References

1. Prinz, A.A. (1996). Optische Detektion der elektrischen Signalausbreitung in Neuronen. Diploma thesis. Universitaet Ulm, Ulm, Germany.
2. Kupper, J., A.A. Prinz, and P. Fromherz (2002). Recombinant Kv1.3 potassium channels stabilize tonic firing of cultured rat hippocampal neurons. Eur J Physiol 443: 541-547.
3. Prinz, A.A. and P. Fromherz (2000). Electrical synapses by guided growth of cultured neurons from the snail Lymnaea stagnalis. Biol Cybern 82: L1-L5.
4. Prinz, A.A. and P. Fromherz (2003). Effect of neuritic cables on conductance estimates for remote electrical synapses. J Neurophysiol 89: 2215-2224.
5. Prinz, A.A., V. Thirumalai, and E. Marder (2003). The functional consequences of changes in the strength and duration of synaptic inputs to oscillatory neurons. J Neurosci 23: 943-954.
6. Golowasch, J., L.F. Abbott, and E. Marder (1999). Activity-dependent regulation of potassium currents in an identified neuron of the stomatogastric ganglion of the crab *Cancer borealis*. J Neurosci 19: RC33.
7. Bhalla, U.S. and J.M. Bower (1993). Exploring parameter space in detailed single neuron models - simulations of the mitral and granule cells of the olfactory bulb. J Neurophysiol 69: 1948-1965.
8. De Schutter, E. and J.M. Bower (1994). An active membrane model of the cerebellar Purkinje-cell. I. Simulation of current clamps in slice. J Neurophysiol 71: 375-400.
9. Foster, W.R., L.H. Ungar, and J.S. Schwaber (1993). Significance of conductances in Hodgkin-Huxley models. J Neurophysiol 70: 2502-2518.
10. Goldman, M.S., et al. (2001). Global structure, robustness, and modulation of neuronal models. J Neurosci 21: 5229-5238.

11. Prinz, A.A., C.P. Billimoria, and E. Marder (2003). An alternative to hand-tuning conductance-based models: construction and analysis of databases of model neurons. J Neurophysiol JN-00641-2003.
12. Prinz, A.A., D. Bucher, and E. Marder (in preparation).
13. Sharp, A.A., et al. (1993). Dynamic clamp: computer-generated conductances in real neurons. J Neurophysiol 69: 992-995.
14. Prinz, A.A., L.F. Abbott, and E. Marder The dynamic clamp comes of age. Submitted.
15. Golowasch, J., et al. (1999). Network stability from activity-dependent regulation of neuronal conductances. Neural Comput 11: 1079-96.
16. Soto-Trevino, C., et al. (2001). Activity-dependent modification of inhibitory synapses in models of rhythmic neural networks. Nat Neurosci 4: 297-303.
17. Marder, E. and A.A. Prinz (2002). Modeling stability in neuron and network function: the role of activity in homeostasis. Bioessays 24: 1145-1154.
18. Liu, Z., et al. (1998). A model neuron with activity-dependent conductances regulated by multiple calcium sensors. J Neurosci 18: 2309-2320.
19. MacLean, J.N., et al. (2003). Activity-independent homeostasis in rhythmically active neurons. Neuron 37: 109-120.
20. Turrigiano, G., L.F. Abbott, and E. Marder (1994). Activity-dependent changes in the intrinsic properties of cultured neurons. Science 264: 974-977.