



Howard Hughes Medical Institute
Research Laboratories

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Investigator

December 2, 2004

Biocomplexity Faculty Search Committee
c/o Professor Rob de Ruyter van Steveninck
Department of Physics
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Dear Selection Committee:

I offer my highest recommendation of Jan Karbowski for a faculty position in your department. Jan has worked with me for the past year and one-half, and I have come to hold him in the highest regard as a scientist. He is a brilliant theoretician with an exquisite sense of how to model biological phenomena. While I am primarily an experimental biologist, I have had an interest in modeling and theory since my undergraduate days, have collaborated with engineers and applied mathematicians on a number of occasions; have worked on software and database development in the context of WormBase, and observed the interactions of modeling and experiment in activities such as the Alliance for Cell Signaling and our new Center for Biological Circuit Design; thus, I have a reasonable understanding of this broad interdisciplinary area. Jan is as good as they get.

I met Jan after he joined Caltech as a Sloan-Swartz Fellow and explained to him the problem of nematode sinusoidal movement. The field has generated an impressive array of genetic reagents to analyze worm movement, there is a complete *C. elegans* neuronal wiring diagram, and we had developed a machine vision system with which to obtain quantitative information about worm movement, but there was no theoretical framework with which to reason about these extensive data sets. We had a number of intriguing observations, such as cuticle (hydrostatic skeleton) mutants with abnormal locomotion, that I could not explain in rigorous terms. Jan took up the challenge and has made impressive and informative progress in modeling this system. Jan first tried a simulation approach; after three months, he understood much of the worm data and had a working simulation, the work moved. However, he felt strongly that he could not deduce principles from the simulation and wanted a mathematical description. Over the past year, he has developed such a mathematical model and has used it to interpret data and make predictions. Several of these predictions have been tested by experimentalists in my laboratory, and borne out.

His current model is multi-partite: it includes muscle biophysics, systems-level biomechanics (including skeleton and muscle), and neuronal circuitry. Jan has done a beautiful job matching the model to our experimental observables. Indeed, he has spent considerable effort on data analysis, for example realizing that there is conservation of certain relationships across nematode species. He has written one paper on the three-part model to capture the overall relationships, and is drafting a second paper on a more detailed neuronal circuit model for which we have had a tight cycle of prediction and experiment. One key result is that slowing down the myosin contraction cycle, affects the frequency of worm movement, indicating that muscle contraction is embedded within a feedback circuit. Jan made quantitative predictions about inhibitory neuron function in *C. elegans* ventral cord circuitry, and worked out a method to test the model, to make

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synaptic transmission defects in specific cells of the circuit and observe the consequence for the sinusoidal locomotion. Jan does not plan to carry out experiments but will rely on collaborations; he is talented enough to make this strategy work (and I only say this about very rare individuals). I would be delighted to continue to collaborate with him on nematode locomotion, but I would also encourage him to work with others as well to expand his contacts in this growing area of research.

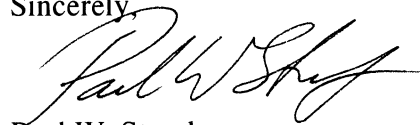
Jan has also engaged in other studies to fill in his time this year (for example when waiting for experimental results). He has a broad range of interests, and we continually discuss areas in which he might apply his considerable talent. Jan has excellent judgment concerning what is interesting in biology, and what is worth formalizing in mathematical terms.

He communicates effectively with biologists, learning the intricacies of experiments, and explaining the essential aspects of his models. I am confident that he will develop many productive collaborations with biologists, as well. Jan writes and speaks well.

At a personal level, Jan has a wonderful dry sense of humor, and is delightful to talk with.

I expect he will not only be highly successful, but also a wonderful colleague and teacher.

Sincerely,



Paul W. Sternberg
Thomas Hunt Morgan Professor of Biology
California Institute of Technology