HARVARD UNIVERSITY
BAUER CENTER FOR GENOMICS RESEARCH

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October 14, 2005

Yves Brun,
Systems Biology/Microbiology Faculty Search,
Department of Biology,
Indiana University,
Jordan Hall 142,
1001 E 3rd St,
Bloomington IN 47405-7005

Dear Yves Brun,

I am excited to apply for the position of assistant professor in systems biology because of the interdisciplinary environment and the resources available at Indiana University. My graduate training was in theoretical physics under Carl Bender at Washington University in St. Louis. Subsequently, I switched my research focus to biology and took a postdoctoral fellowship with Geoffrey West and James Brown at the Santa Fe Institute and Los Alamos National Laboratory. By constructing quantitative theories and comparing predictions to empirical data, I have studied the pervasive effects of metabolism on biological processes such as population growth, developmental time, sleep duration, tumor growth, and cell size. My work is among the first to explicitly and mechanistically connect biological scaling theory, based on individual organisms, to ecosystems and biomedicine. Building upon this work, I am studying environmental effects (*e.g.*, effects of temperature) on ecosystem dynamics and stability. More recently, I have used my time as a postdoctoral fellow at the Bauer Laboratory at Harvard University to continue my theoretical studies of biological systems and to add an experimental component to my research, investigating connections between cellular metabolic rate, cell size, and ploidy with possible implications for cancer development.

Please find enclosed the materials you requested: my research statement, my teaching statement, my curriculum vitae, and several manuscripts by me. The latter are:

V. M. Savage, J. F. Gillooly, J. H. Brown, G. B. West, and E. L. Charnov, (2004). Effects of body size and temperature on population growth, *The American Naturalist* **163(3),** 429-441.

V. M. Savage (2004). Improved approximations to scaling relationships for species, populations, and ecosystems across latitudinal and elevational gradients. *Journal of Theoretical Biology* **227(4)**, 525-534.

V. M. Savage, J. F. Gillooly, W. H. Woodruff, G. B. West, A. P. Allen, B. J. Enquist, and J. H. Brown (2004). The predominance of quarter-power scaling in biology. *Functional Ecology* **18(2)**, 257-282.

V. M. Savage and G. B. West (2005). Biological scaling and physiological time: Biomedical applications. Complex System Science in Biomedicine. Ed. T. S. Deisboeck and J. Y. Kresh, New York, Kluwer Academic.

J. F. Gillooly, E. L. Charnov, G. B. West, V. M. Savage, and J. H. Brown (2002). Biological time: effects of size and temperature on developmental time, *Nature* **417**, 70-73.

Please let me know if you require any further information or materials. Thank you for your consideration.

Sincerely,

Van M. Savage
Systems Biology Postdoctoral Fellow

# Research Statement

Biological systems display extraordinary diversity in form and function. Consequently, molecular, cellular, organismal, population, and ecological processes are often studied separately with little discourse between fields and subfields. However, these specialized studies are likely to miss constraints and connections between different levels of biological organization. Moreover, simple rules from biology, chemistry, and physics often govern biological processes. These rules hold across multiple scales and constrain how levels interact. I construct quantitative theories from which I derive predictions that are tested using empirical data compiled from the literature and from my experiments.

I have previously investigated the effects of body size and body temperature on metabolic rate—the power produced by an organism for growth, maintenance, and reproduction. Due to its fundamental nature, metabolic rate can be used to identify constraints on many biological processes and to connect different levels of biological organization. I have compiled large comparative datasets that demonstrate metabolic rate scales as body size to the 3/4 power (*i.e.*, sub-linearly) and with body temperature as an exponential Boltzmann-Arrhenius factor. Surprisingly, most of the variation in metabolic rate across a broad range of organisms, including unicellular organisms, plants, and animals, is determined by this scaling relationship, collapsing 15 orders of magnitude variation to just one. I and my collaborators developed theory to explain this relationship based on principles from biology, chemistry, and physics. We have also constructed scaling theories to predict the mass and temperature dependence of many other rates, times, and lengths, including population growth and heart rates, developmental and sleep times, and the radius and length of the aorta. These predictions are in excellent agreement with data, and these theories are providing a long-sought foundation for allometric relationships in ecology and physiology.

Many problems are amenable to this scaling approach. I recently co-wrote a book chapter on the potential applications of scaling relationships to cellular energetics, the spread of infectious diseases, tumor growth, sleep, and lifespan. Of these I have investigated sleep and tumor growth the most thoroughly. Based on the hypothesis that cellular repair in the brain occurs during sleep, West and I derived novel, quantitative predictions for relationships between sleep times and body size that agree with empirical data for mammals. We believe this is the first theoretical explanation of the available comparative data for mammalian sleep, and it may aid in distinguishing between several theories about the purpose of sleep. To model tumor growth, we extended our scaling theory for the cardiovascular system to predict scaling of tumor metabolic rate with tumor and host size, allometry of asymptotic tumor size, and tumor growth trajectories. These predictions are consistent with available data, and the trajectories can be used to determine how cancer cells are able to grow quickly and at the expense of the rest of the body. In related work, I am currently investigating theories of aging, including metabolic damage and caloric restriction.

I am also interested in several questions of scale at the cellular level, especially the whole-organism factors that determine cell size, nucleus size, genome size, and organelle densities. In particular, are cell size, nucleus size, and DNA content connected to organismal and cellular metabolic rate, and if so, is there a parsimonious explanation? This could provide clues to the C-value paradox—why does genome size vary by so many orders of magnitude across species and why do some "simple" organisms have such large genomes—by explicitly linking genome size differences across species to temperature through its effects on metabolic rate and cell size. It follows from above that the ratio of average cellular metabolic rate, $B_c$, to cellular mass, $m_c$, decreases with body size, $M$, to the quarter power, and increases with body temperature, $T$, through a Boltzman factor (*i.e.*, $B_c/m_c \propto M^{1/4} e^{-E/kT}$). This relationship demands a tradeoff between average cellular metabolic rate and average cell size

across species but also within species due to naturally occurring temperature gradients. That is, cellular metabolic rate and cellular mass *cannot both* be held constant as body size and body temperature vary, indicating a fundamental constraint.

To begin studying these questions, I am collecting and analyzing data from the literature, and results indicate this is a promising direction to pursue. Experiments targeted specifically at these questions have yet to be performed, so I have initiated a collaboration with David Pellman at the Harvard Medical School to obtain the relevant data. Through this collaboration I am learning experimental methods with which I plan to study systematically the effects of cellular metabolic rate on cell and nucleus size, and conversely, the effects of ploidy (number of chromosome sets) on cell size and physiology. Among other reasons, ploidy is intriguing because cancer cells often exhibit aneuploidy and elevated metabolic rates as compared to healthy cells, so this work could facilitate the discovery of drugs that target the ploidy and metabolic states typical of cancer cells. The Pellman lab has a unique set of resources—tetraploid mouse embryonic stem (ES) and a library of tetraploid yeast deletion strains—that make this experimentally tractable. Currently, I am comparing the viability of tetraploid and diploid mouse ES cells after exposure to an assortment of metabolic inhibitors (*e.g.*, deoxy-D-glucose and oligomycin) at various concentrations. To study the effects of cellular metabolic rate on cell and nucleus size, I will vary yeast cellular metabolic rate by adjusting temperature and nutrient conditions and then, using microscopy and a Coulter counter, measure the response of cell and nucleus size. Based upon these experimental results, I will endeavor to develop theory that disentangles the connections between cell size, cellular metabolic rate, and ploidy. To test the generality of my conclusions, I plan to perform further experiments, possibly with drosophila, in order to study effects of multicellularity and ectothermy.

In parallel to this, I am studying ecosystem processes. I am developing theory for the effects of temperature on predator-prey interactions that are dependent on the organisms' physiology (*e.g.*, ectotherm-ectotherm versus endotherm-ectotherm interactions) and behavior (*e.g.*, active-capture versus sit-and-wait predator strategies). From this I can derive conditions for species coexistence and optimal predator-prey relationships at different temperatures. By characterizing existing food-web data according to this framework, characteristics of systems at different temperatures, such as prevalence of certain predator or prey strategies, can be determined and tested against predictions. In addition, I am helping develop a framework for analyzing the effects of a changing environment on biomass distributions for traits within a functional group. Using fitness functions to connect a trait to the environment, trait distributions can be calculated numerically and followed through time. This framework can accommodate multiple environmental variables, multiple traits, and correlations between the variables and traits. Since the rapid changes in temperature predicted by global warming models would affect physiological processes and species interactions, combining this work is relevant for the prediction and assessment of the impact of global warming on biodiversity and ecosystem functioning. Many theoretical and empirical steps within this framework must be completed before the fully integrated problem can be studied.

In summary, I plan to study cell size and dynamics, physiological processes such as sleep and aging, and ecosystem dynamics. More generally, by combining findings from these ongoing projects, I intend to investigate connections and mutual constraints between the cell and organism and the organism and ecosystem. I feel interactions with Spencer Hall, Viola Ellison, Michael Lynch (with whom I have previously discussed some of these ideas) and others at Indiana University could be very fruitful. Because of the breadth of my interests, I feel a position at Indiana University, with its interdisciplinary approach, resources, and people, would be ideal for achieving these goals.

# Teaching Statement

I feel it is crucial to provide students with a working knowledge of biological systems and to teach them problem solving skills for building upon this knowledge. Teaching a person to think analytically is at the core of what a student should take away from any science course. For students not majoring in biology, it is important to teach them how science affects their daily lives and how to make informed decisions about governmental policies and science reports in the daily news. For biology majors it is crucial to teach them the knowledge pertinent to their course of study and how scientists solve difficult problems using approximation, computational, and other quantitative methods. These important tools often are not taught in traditional biology courses, but they are invaluable to future researchers because they aid in the careful design of experiments and in determining the predictions of a model or theory. I would also strive to cover a range of topics in my courses. This would enable me to teach an array of different methods for approaching biological problems and to demonstrate how similar approaches can be applied to problems from disparate fields.

This year I was a faculty member at the Santa Fe Institute Complex Systems Summer School (SFI-CSSS), where I lectured on complex systems approaches to biological problems. Many students were biologists improving their mathematics or physicists and mathematicians improving their biology. The school also included students with a broad range of backgrounds (*e.g.*, architecture, urban planning, and philosophy of science). I have previously guest lectured for night school and summer introductory physics courses as well. While in graduate school, I was the teaching assistant for several courses for both graduate and undergraduate students. For three graduate level mathematical methods courses, I graded homework papers, provided solution sets, and learned a great deal about teaching mathematical physics by observing the lectures of my graduate advisor, Carl Bender. From this, I learned the importance of engaging students through jokes and everyday examples and of pitching material at a level that assumes intelligence but not necessarily knowledge. I was also teaching assistant for three introductory level courses: The Epic of Evolution (a joint class with the Biology and Earth and Planetary Sciences departments), Physics and Society, and an Introductory Physics. For the introductory physics course, I taught three lab sections in which I gave lectures, assigned final lab grades, and held office hours. For the other courses, I provided solution sets for the tests and homework assignments, held office hours, assisted with in-class demonstrations, and helped assign final grades. Although it is often challenging to teach introductory students, it is a challenge I thoroughly enjoy. Preparing lectures and solution sets forces me to communicate fundamental ideas in simple terms and to think deeply again about some of the most basic principles in physics and biology. Physics and Society connected physics to current issues like global warming, the ozone hole, science versus pseudoscience, and alternative energy sources. The Epic of Evolution explained the basic science behind the Big Bang, the formation of the earth, and evolution.

I am extremely interested in being involved with and helping to create interdisciplinary courses, especially ones with connections to biology, complex systems, and current events. Developing a course similar to the Epic of Evolution mentioned above would be of great benefit to students. There are many exciting interdisciplinary

courses that could be developed within a biology department, especially in relation to health and the environment. Further, interdisciplinary and topical courses are excellent ways to give students a much deeper understanding of the biology that is relevant to their everyday lives, and concurrently, to teach them basic biology and methods of analytical thinking. I would also like to help develop or to be involved with a mathematics course specifically tailored to biologists. It would be an entryway for students into some of the most revolutionary research being currently conducted, and it would provide students with important skills that would enhance their efforts in virtually any field they choose to pursue. Furthermore, I feel my skills make me well suited to teach biology majors how to construct theories and models, to derive predictions from these models, and to test these predictions against empirical data they have collected from the literature or obtained in the laboratory. I would also enjoy teaching an introductory biology course, an ecology course, or an evolutionary theory course.

Mentoring the research of undergraduate and graduate students is one of the most long-lasting contributions a researcher can make, and it is a process that I find fun and rewarding. While at the Santa Fe Institute, I mentored a graduate student from Cornell for one summer, and a senior from Wesleyan University, Alex Herman, for a year and a half. The project with Alex was on the cardiovascular dynamics and allometry of tumor growth. It became his senior thesis and will soon be submitted for publication. Alex is currently an MD/PhD student at the University of California at San Francisco. Two groups from SFI-CSSS have also contacted me about advising them on current projects.

For my undergraduate education, I attended Rhodes College, a small, four-year, liberal arts school. From this experience I learned that discussions outside of the classroom are a crucial part of the learning process, so I believe in being available to the students outside of lectures. Many students who are reserved in class ask excellent questions in smaller settings and thus, learn much more. I greatly value the instruction and mentorship I received while in college and feel strongly about providing quality education to current and future students. I feel Indiana University would be an ideal environment to pursue both my research and teaching interests.