DANA-FARBER CANCER INSTITUTE | Children's Hospital

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October 18, 2005

To members of Systems Biology/Microbiology Faculty Search,

I am writing to express my strongest support for Van Savage's application for assistant professor at Indiana University.

Savage is currently a systems biology postdoctoral fellow at the Bauer Center for Genomics Research at Harvard University. Savage, a physicist by training, is interested in defining the scaling relationships between temperature, cell size metabolism, and DNA output (ploidy). This is a central question in biology with a broad impact on evolution, ecology, growth control and cancer. During a postdoctoral fellowship at the Santa Fe Institute, Savage had a leading role in the discovery that in many animals cell size increases slowly with body size and decreases exponentially with temperature, whereas unexpectedly metabolic rate remains roughly constant. Savage has authored numerous articles and has developed an international reputation for his theoretical work.

Savage is now making a major shift in his research training: he wants to develop experimental skills that will enable him to directly test his theories as well as discover new phenomenon to which he will apply his computational skills. Savage therefore has been working in my laboratory, while maintaining his relationship with the Bauer Center. My group has been studying how cell physiology is altered when the ploidy of a cell is changed. We have developed approaches for studying this problem using yeast, Drosophila tissue culture cells, and mice. Our studies in yeast and mice suggest that one important consequence of altered ploidy is genetic instability. We have unpublished data that tetraploidy of mouse mammary epithelial cells can initiate tumerogensis, validating an old hypothesis first formulated by Theodor Bovari. Two areas of research are directly relevant to Savage's work. First, in the process of identifying genes that are required for the survival of tetraploid yeast (ploidy-specific lethal functions) we have generated a library of matched diploid and tetraploid yeast strains lacking each of the non-essential genes (4,700 tetraploid deletion strains). We are in the process of characterizing cell size in all of these strains in an attempt to identify genes involved in scaling cell size to genome size. Savage will be involved with this project and also initiate studies on how this scaling is affected by nutrients and temperature. In addition, we have interesting preliminary data that altering ploidy in embryonic stem cells may alter metabolism. By gene set enrichment analysis, we find that glycolysis is significantly upregulated in tetraploid cells. This is consistent with data from yeast, and could form the basis for selection of polyploidy cells in a wide variety of biological contexts. This may include the selection for genome doublings that occur frequently during evolution.

I am committed to helping Savage acquire the experimental skills that are necessary for him to attack these fundamental problems. My lab is set up for all of the experiments, including the functional genomic experiments in yeast. Other postdoctoral fellows in my laboratory are training Savage in the necessary experimental methods. We are excited to have Savage take the lead on following up these preliminary findings.

I think Van Savage is an ideal candidate for an assistant professor in Systems Biology. His physics background gives him superb computational skills, and he has already thought deeply about these biological problems. He has a strong record of previous accomplishment. His interests are also a perfect match for collaborating with my laboratory; we will be able to provide him with unique reagents and experience with experimental approaches.

I am very impressed with Savage's determination to blend theoretical and experimental approaches. This is a rare, but powerful combination. In this respect, Savage reminds me of Alexander van Oudenaarden, a physicist at MIT who has applied computational modeling to many systems biology problems. I think Savage could have a similar stellar career trajectory. I think he is just the sort of scientist that should be hired for one of the new positions in systems biology at Indiana University, and has potential to bring great credit to the program.

Sincerely,

David Pellman, M.D.
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Dana-Farber Cancer Institute
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October 14, 2005

Systems Biology/Microbiology Faculty Search
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Dear Yves Brun,

I take great pleasure in recommending Van Savage for a faculty appointment at Indiana University. Van was a post-doctoral fellow with me for three years following his graduation from Washington University, St. Louis, where he had written a doctoral thesis in quantum field theory under the guidance of Carl Bender. His record, both as a graduate student and as an undergraduate, was outstanding and, as a consequence, he had received several honors and awards. Among these was a highly competitive NSF Physics Graduate Fellowship at the Santa Fe Institute (SFI), where I first met him. At that time my primary appointment was at Los Alamos but I spent part of my time at SFI. I was sufficiently impressed with Van during this period that I strongly encouraged him to apply for a post-doctoral appointment. Since I felt it would be mutually advantageous for him to experience the atmosphere of a large lab as well as that of a small, more intimate, institute, I suggested a joint appointment for him with Los Alamos. It is a measure of his abilities, accomplishments, and potential at that time that he was offered highly competitive institution-wide post-doctoral fellowships at both the SFI and Los Alamos.

During his time at SFI/Los Alamos, Van became very interested in work that I had become involved in concerning the implications and ramifications of a fundamental quantitative theory for the origin of universal scaling laws in biology. These laws are the result of general principles underlying the function, structure, and organization of much of life ranging from molecules and cells to mammals, plants, and ecosystems. This work has been developed over the past few years and has received a great deal of attention in both the popular and scientific press including, for example, several feature articles about it in both *Science* and *Nature*. After arriving at SFI, Van almost immediately joined our collaboration that includes the well-known ecologist/biologist, James Brown, of the University of New Mexico. Van very quickly and diligently learned a great deal of biology and became very much an equal partner in much of our work. In particular, he was central in conceptually understanding the critical role of temperature in biological processes, and, in particular, on its role in metabolism and growth during ontogeny. Two papers were written on this, one published in *Science*, the other in *Nature*. These ideas were extended to understand some basic questions in ecosystem population dynamics, where Van took the lead. Unfortunately, a lack of sensitivity on my part to the "cultural" differences between physics and biology regarding order of authors resulted in Van not being first author on some of these. More recently we have been investigating some potentially, very exciting, questions concerning genome lengths and their relationship to cell size, body size, structure and function. This has raised some very challenging conceptual and technical problems regarding the relationship between molecular dynamics, intra-cellular and mitochondrial transport, and informational structures. Van has been playing a central role as we grapple with these issues and has the lead role in writing forthcoming papers. Other related recent work is summarized in a paper that is just being submitted to *Science* exploring the dynamics, growth, structure, and vasculature network geometry of tumors. The paper presents a quantitative, analytic, predictive theory of tumor growth and angiogenesis which provides a point of departure for understanding and predicting generic properties of specific tumors, such as the percentage of necrosis and details of blood flow and vessel sizes.

I have been extremely impressed by Van's technical skills, creativity, and his ability to learn new things very quickly, and not in a superficial fashion; he has excellent intuition and rapidly focuses on the central issues. He typically asks probing and challenging questions that have led to new ways of looking at the problem, and is persistent until he gets a satisfactory answer. I should emphasize that our collaboration is highly interdisciplinary involving physicists, chemists, and biologists and is a successful example of what will surely be seen more and more at the interface of physics with the life sciences. Van is in a very strong position to take advantage of this. An imperative attribute of this kind of trans-disciplinary research, which Van has mastered admirably, is the ability to get to the essential heart of the problem and to be able to express it in simple pedagogical terms. Consequently, Van gives very clear presentations, making complex problems transparent; as such, I am confident that he will develop into a superb teacher. When Van left us he moved to the Bauer Genome Center at Harvard to meet the challenge of being a lone theoretical-minded post-doc among wet lab biologists. I strongly urged him to take this position since I feel that it is crucial for theorists to interact strongly, almost daily, with their experimental colleagues if they are to have any serious impact. Van has risen to the challenge admirably and gone further by getting involved in the lab as an active experimental biologist. In little over four years Van has transformed himself from an abstract theoretical physicist into a highly creative biologist who has the potential to make significant contributions to the field

Incidentally, as a "straight" theoretical physicist, Van has written several excellent papers. His collaborators have included my ex-colleague, Fred Cooper (who now runs the theoretical physics program at the NSF), Sir Michael Berry, the famous mathematical physicist, and, of course, his thesis advisor, Carl Bender, himself a highly distinguished mathematical physicist. All of these have spoken very highly of Van. With his migration into biology Van has demonstrated at an early stage of his career that he is maturing into an excellent researcher with broad and flexible interests. He has a very pleasant, warm personality and is outgoing without being aggressive. I have very much enjoyed working with him and have certainly missed having him as a day-to-day collaborator and colleague. He is creative, has broad interests, thinks deeply about the big questions, yet does not shrink from the details nor from the specific, has excellent technical skills, already done excellent work, is highly interactive and a very good citizen.

I have no hesitation in placing Van near the top of other young biologists and ecologists that I have either worked or interacted with; he is certainly competitive with some of the best. For example, I judge him comparable to John Wilkins, who just joined us after being a Junior Fellow at Harvard, and to my ex-post-doc Brian Enquist, now a Professor at the University of Arizona who was named among the top ten "brilliant young scientists" of last year, and to Drew Allen, also my ex-post-doc, now at NCEAS, UC Santa Barbara. I would rate him potentially better than Jamie Gillooly, also my ex-post-doc, now an Assistant Professor at the University of Florida, who just received this year's Bartholomew Award, and better than Josh Weiss at Princeton. Frankly, it's too early to tell whether Van will make truly major contributions but I do believe that he has the right combination of talents and has chosen an unusual and challenging path to position himself to do so.

In conclusion, I am delighted to give Van Savage my strongest recommendation. Should you require further information or feedback please feel free to contact me.

Yours sincerely,

Geoffrey B. West
President
Distinguished Research Professor

GBW:dlu

Washington University in St. Louis

ARTS & SCIENCES

Department of Physics

October 11, 2005

Yves Brun
Systems Biology/Microbiology Faculty Search,
Department of Biology
Indiana University
Jordan Hall 142
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To whom it may concern:

With this letter I strongly recommend that Van Savage be awarded a nontenured job position. Van has a strong ability to do research, to teach, and to work with students. Van has an interdisciplinary background that extends from theoretical physics to mathematical biology. He has great mathematical, computational, and communication skills. Savage would be ideal for such a position.

I was Savage's PhD thesis advisor at Washington University in St. Louis. Having passed and done well on his PhD qualifying examination in 1997, Van began his thesis research with me on the topic of PT-symmetric quantum-mechanical systems. At this point I already knew Van well and had a high regard for his intellectual abilities. Van had already taken four graduate courses in mathematical physics from me, Physics 501-502 (topics include: complex variables, partial differential equations, nonlinear waves, transform theory, variational principles) in 1997-1998 and Physics 503-504 (topics include: differential and difference equations, asymptotics, perturbation theory, summation theory, expansion of integrals, WKB theory, boundary layer theory, multiple scale analysis, graph theory) in 1996-1997. His performance in these courses was excellent. For example, in 501 he was one of the top five students in a class of 21. Also, Van had served as my TA in Physics 171 and in several graduate courses; he was extremely responsible and hard working and extremely well liked by the students in these courses.

Van showed enormous intellectual development in the course of carrying out the research for his PhD thesis and in subsequent collaboration on research. For his thesis he completed and published five papers with me in mathematical physics and a sixth with Prof. Claude Bernard.

Van's thesis research is on a startling new area of quantum mechanics involving non-

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Hermitian Hamiltonians. The PCT theorem, a fundamental symmetry of quantum field theory, is derived from the assumption of Lorentz invariance and positivity of the spectrum of the Hamiltonian. Van's thesis asks the question, what happens if we assume only Lorentz invariance and PCT symmetry? Hamiltonians having this property need not be Hermitian, but, except when PCT is spontaneously broken, the energy levels of such Hamiltonians are all real and positive! We have examined some quantum-mechanical and quantum-field-theoretic systems whose Hamiltonians are non-Hermitian but obey PCT symmetry. These systems have weird and remarkable properties, and the classical theories underlying these quantum systems also have strange and interesting behaviors. Hamiltonians such as these may be regarded as complex deformations of conventional Hermitian Hamiltonians. Thus, in effect, Van studied the analytic continuation of conventional classical mechanics and quantum mechanics into the complex plane. On one of Van's papers, one of his coauthors is Michael Berry, famous for having discovered the Berry phase. Van's work with Bernard involves numerical lattice calculations for non-Hermitian quantum field theories.

The ultimate objective of Van's thesis research is to make some predictions concerning the Higgs particle. This may be regarded as the most important particle in modern particle physics because it contributes the property of mass to all other known particles. In all of this research Van has made strong and significant contributions in hard work, detailed calculations, and, most importantly, in creative and original ideas; Van deserves credit for at least half of the work in the six papers above.

Van's thesis research was certainly much more than enough for a PhD. However, WHILE HE WAS A GRADUATE STUDENT, he took a research position at the Santa Fe Institute working with Dr. Geoffrey West on theoretical biophysics. Simultaneous with his thesis research he also began publishing papers with West on applications of scaling and renormalization group analysis to biology. Since leaving Washington University and accepting a joint postdoctoral position at the Los Alamos National Laboratory and the Santa Fe Institute, he has made significant contributions to the research program of G. West and his collaborators. Van has completed many more papers on biophysics with West. Several of these papers are published in Nature.

Over the time I have known him, I have seen Van develop into a first-rate researcher. He is a highly competent applied mathematician, having mastered the full range of asymptotic and perturbative methods, including matched asymptotic expansions, fancy applications of the method of steepest descents, and summation theory. He is a first-rate numerical analyst and programmer. He has written efficient Monte Carlo routines, and long and detailed FORTRAN, C, MACSYMA, Mathematica, and MAPLE programs. He has an excellent knowledge of quantum field theory. He is fully experienced at doing weak-coupling as well as strong-coupling and nonperturbative calculations in physics. He understands renormalization, dimensional regularization, functional integrals, critical phenomena, diagrammatics, and semiclassical methods. Also, he has a broad and thorough knowledge of general physics. Van compares favorably with previous PhD students I have had (David Griffiths, now tenured at Reed, and the coauthor of numerous textbooks in physics; Tom Banks, now tenured at Rutgers; Larry Mead, now tenured at the University of Southern Mississippi; Stefan Boettcher, now at Emory; Peter Meisinger, now at Boeing in St. Louis, Q. Wang, now a postdoc at the University of Connecticut.). Van is not as good as Banks but is better than Griffiths, Mead, and Meisinger, and equal to Boettcher and Wang at comparable times in their careers.

Van already has an unusually strong publication record. He is a creative and an extremely bright, eager, and hard-working physicist. He has made strong contributions to our collaborative research efforts and he has been equally useful in his new environment as a postdoctoral research fellow at Los Alamos and the Santa Fe Institute. Van has a charming, warm, open, and very friendly personality and an excellent sense of humor. He explains ideas well and is an excellent teacher and lecturer. Van has a first rate career ahead of him as a teacher and researcher. I strongly recommend him for a nontenured position.

Sincerely yours,

Carl M. Bender
Professor of Physics

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October 14, 2005

Yves Brun,
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Department of Biology,
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Jordan Hall 142,
1001 E 3rd St,
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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

Van M. Savage
Systems Biology Postdoctoral Fellow