Harvard Medical School
DEPARTMENT OF SYSTEMS BIOLOGY

200 Longwood Avenue
Alpert 536
Boston, Massachusetts 02115-5730

Walter Fontana phone: (617) 432-5474 fax: (617) 432-5012 walter@hms.harvard.edu

October 25, 2005

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

Letter in support of Dr. Van Savage

Writing a letter in support of Van Savage is a real pleasure. Recalling what he has achieved and imagining what his future might hold is truly exciting.

I first met Van four years ago when I was a research professor in residence at the Santa Fe Institute (SFI) in Santa Fe, New Mexico. Van held a Postdoctoral Fellowship that was split between SFI and Los Alamos National Laboratory. At SFI he did phenomenal work in the biological scaling group of Geoffrey West (now President of SFI). Simultaneously, at Los Alamos, he worked with Fred Cooper (a former student of Shelly Glashow and now NSF Program Director for particle physics) on the Gross-Neveu model of quark/gluon plasmas that occur when smashing gold atoms into each other at high energies. Prior to his years in New Mexico, Van did graduate work with Carl Bender at Washington University in St. Louis, MO, developing techniques for computing eigenvalues of non-Hermitian matrices with charge-parity-time (CPT) symmetry.

I will focus on Van's biological interests, as these constitute the dominant component of his foreseeable activities in science. I would like to emphasize, however, that it is precisely the pairing of his passion for biology with his formal skills and training that constitutes the hallmark of a new breed of scientific minds that will lead biology to a wholly new level. Van has the requisite knowledge and the skills to make his passion for biology consequential.

At SFI Van made substantial contributions to the scaling project of Geoffrey West. Roughly, in the past eight years West *et al.* developed a theory capable of explaining why metabolic rate (energy production) scales with a 3/4 power in the body mass of organisms across species. This empirical scaling law holds remarkably well over almost 30 orders of

magnitudes from elephants to the molecular processes of mitochondrial oxidative phosphorylation. Consider that the range of mass between Earth and Milky Way "only" spans 18 orders of magnitude. The theory of West *et al.* explains biological scaling in terms of the structure and physics of evolutionarily optimized transport networks, such as the vascular system. Metabolic rate is a central state variable of living systems that is connected to many other macroscopic state variables, such as aging, developmental and gestation times, growth rates, and respiratory rates. The significance of this work consists in distilling a fundamental intelligibility from a staggering biological diversity. It identifies coarse-grained variables and their interrelations central for a macroscopic description of living systems. While such a description enjoys autonomy from its underlying microscopic (i.e. molecular) implementation, its formal derivation from the latter is (and will continue to be) a major source of fundamental theoretical and practical insight.

Van's work at SFI, and later at Harvard's Center for Genome Research, included a detailed theoretical explanation (within West's framework) of the empirically observed deviations from the 3/4 power law. (He computed corrections to the overall volume of transport networks in the theory. These corrections become relevant at smaller body sizes or masses.) In addition, Van collected large amounts of data on metabolic rate, body size, temperature, genome lengths, cell sizes, and analyzed these data to extract empirical interdependencies. In particular, there was a dispute over whether the exponent is 3/4 or 2/3 (which would suggest a less "deep" surface-to-volume argument). Van helped settle that controversy.

Most importantly, Van pushed the theory into completely new territory by extending its range of application from organismic maintenance to growth in ecology and ontogeny. He was the first to establish a connection between metabolic scaling and ecosystems research by investigating population growth, species diversity, carrying capacity and their interdependency.

His most anxiously awaited results and perspectives, however, are coming from his original approach to cancer (or ontogenetic growth in general) within the scaling framework. This is the line of work he intends to pursue vigorously in the near future. Van is collaborating with Harvard's David Pellmann at Dana Farber to collect more data on scaling in tumor growth, and to test several predictions suggested by his theory.

A further area that awaits a connection with the metabolic scaling theory is biological aging. Van is determined to pursue this connection. It is in this area that I had many thought-provoking discussions with him. (I'm setting up a team of theorists and experimentalists to combine mathematical, computational and empirical approaches to aging in *C.elegans*.)

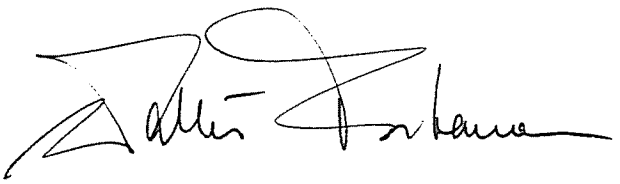
Van represents a formidable synthetic style of thought that amalgamates mathematical abstraction with an attention to empirical data and detail. His training and research experience cover a broad range of quantitative skills and topics from physics to biology. He is completely autonomous in his thinking. His ability to absorb new knowledge and

techniques is second to no one I know. His numerous and lively delivered lectures or impromptu seminars sparkle with insights.

Van is at an early stage of a career that transcends disciplines. He has already published extremely well for a theoretician – *Nature*, *Science*, *Proceedings* – and his productivity is accelerating. He is well connected and respected within the scientific community. He held appointments in the past that were predicated on freedom of choice and action, and he has proven to possess the plasticity and originality needed for turning such opportunities into personal and intellectual growth for his own benefit and those of others that had the privilege of interacting with him. The institution that can hire Van will be noted and envied.

I would be delighted to answer any questions you might have in regard to his application.

Sincerely,



Walter Fontana, Professor