

Stephen Proulx
Center for Ecological and Evolutionary Biology
5289 University of Oregon
Eugene, Oregon 97403-5289
email:proulx@uoregon.edu

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Biocomplexity Faculty Search
c/o Ms. Yana Teterina
Department of Physics
Indiana University
Swain West 117
727 East 3rd Street
Bloomington, IN 47405-7105

Dear Search Committee:

I am applying for the faculty position in Biocomplexity. I have included my CV, and a statement of research and teaching interests. A full set of reprints are available at www.proulxresearch.org.

My research applies mathematical tools to problems in evolutionary biology and genetics. My technique involves deriving an analytical model to understand general underlying principles, then creating a numerical model that includes more specific detail. This technique, a combination of analytical and numerical methods, allows the exploration of more complex models, especially those that require computational solutions.

My pursuit to understand the underlying dynamics of evolution has led me to work with colleagues in a number of fields, including behavioral ecology, statistical genetics, and population genetics. Among other topics, I have explored

- the evolution of female mating preferences,
- methods of inferring genetic interactions at the synapse of *C. elegans*, and
- the accumulation of deleterious mutations in genetic networks.

This wide range of research topics reflects my firm belief that fundamental insights into evolutionary processes can only be obtained through an integrative approach.

My current research uses population genetic models to investigate the evolution of genetic networks. The recent explosion of genomic data potentially allows us to answer new kinds of questions about the evolution of genetic systems, but a complete understanding of these data can only come after an integrative theory of genome evolution is complete. To contribute to this integrative theory, my current lines of study are

- the evolution of canalization in genetic networks,
- divergence in genes during duplication, and
- the micro-evolution of genetic regulation.

I believe my research interests would both complement and enhance current research at the Indiana University. My interests overlap with several areas of research in the department, including modeling regulatory networks and the dynamics of developmental systems. In addition, my interests in modeling the evolution of genetic networks and the micro-evolution of genetic regulation would provide new directions for the program.

Sincerely,

Stephen Proulx

Research and Teaching Statements

Stephen R. Proulx

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1 Research Overview

In my research I use mathematical and computational tools to solve problems in evolutionary biology. My background includes formal training in both biology and pure and applied mathematics. This dual-path training has given me a comprehensive set of techniques that allows me to find and use the best method for solving new biological problems, crafting elegant solutions that encompass the appropriate level of complexity.

Building on my research experience in behavioral ecology, statistical genetics, and population genetics, I am currently examining the evolution of genetic networks, the accumulation of genetic variation in genetic networks, and the evolution of developmental regulation. This focus has developed during the past two years of my association with the University of Oregon, where I have been an active member of the NSF-funded IGERT program in Evolution, Development, and Genomics. My current research is funded by an NIH NRSA fellowship and promises to be an area of increasing interest.

2 Previous Research

Behavioral Ecology

Traditional models of male display assume that display traits are made once, last forever, and have a fixed cost. I have created game theoretic models of male display that incorporates the timing of signaling costs and the effects of aging. This work shows that signaling is generally more “honest” among older males, which is a novel explanation for the observed female preference for older mates (**Figure 1**). Because the amount of future reproduction available decreases as individuals age, the optimal signaling strategy shifts to higher levels of signaling for all males. However, the relationship between quality and signal changes as males age so that a tighter relationship between male quality and signal exists in older age groups.

Statistical Genetics

I have worked with colleagues in molecular genetics to understand the functional relationship between gene products at the synapse of *C. elegans*. I designed a maximum likelihood method to test for genetic interactions between partially recessive mutations at known loci. The estimates of the genetic interactions were obtained from an analytical model, but a computational approach was required to define confidence intervals and conduct hypothesis testing. By applying this method we were able to both verify known physical interactions (validating the method), and infer novel interactions between gene products.

Population Genetics

My research in population genetics has included studies of sexual selection, sex allocation, genetic dynamics in

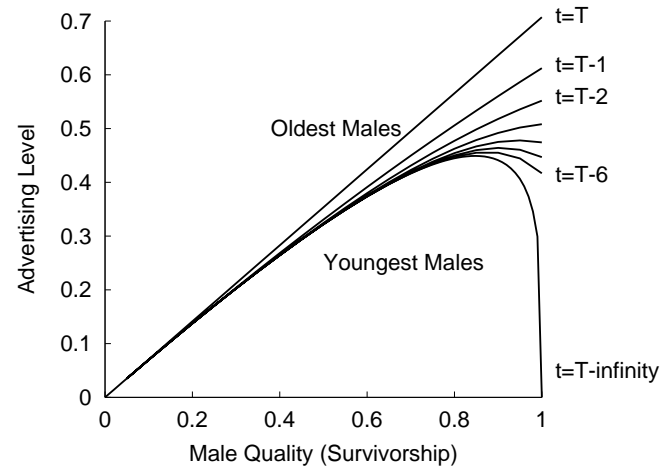


Figure 1: Signaling as a function of quality for several age classes. In older age classes signaling increases with quality.

stochastic environments, and virulence evolution. A major theme of my research is concerned with the interaction between sexual selection and adaptation in both space and time. I have shown that the mating system can have a large influence on whether populations survive climate change or introductions to novel environments and affect the rate of adaptation to novel conditions. Further, sexual selection can enhance the ability of a species to achieve local adaptation and maintain genetic variation along a spatial gradient. This creates a feedback cycle that strengthens selection for female mating preferences and local adaptation simultaneously. By focusing on the dynamics of adaptation and mating system evolution, I have shown that speciation is not the most likely response to spatial variation, but rather that sexual selection can maintain both local adaptation and gene flow simultaneously.

I am generally interested in the role that stochasticity plays in adaptive evolution and the creation of neutral genetic variance. As biologists we often attempt to predict the outcome of evolution as though it were a deterministic process, despite the fact that it is inherently stochastic. A more valid view of adaptive evolution embraces its inherent uncertainty, focusing on the relative probability of observing different adaptive states. I have taken this approach by studying trait evolution both when individuals face random variance in their ability to reproduce and when whole populations face random environmental variance. For the case of individual variance, I have derived both methods to bound the fixation probability of a novel allele, as well as diffusion approximations to calculate fixation probabilities. This method represents an important improvement on previous methods, as is shown by its ability to predict simulation results (**Figure 2**). I have applied this method to sex allocation in finite populations and have shown that allocation to the more risky sex will be reduced, a pattern observed in plants with risky pollination syndromes.

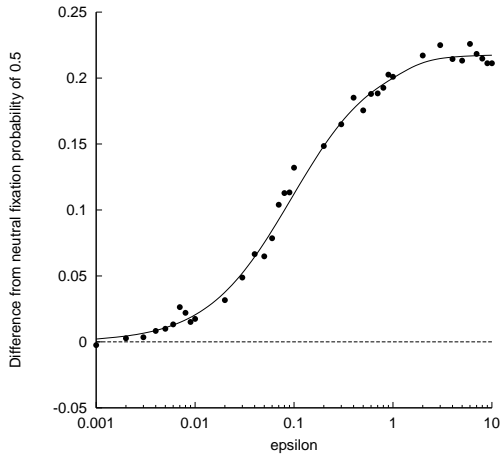


Figure 2: The curve represents the predicted fixation probability from the diffusion approximation while the dots represent observed fixation probability from simulations.

3 Current Research

Canalization and Genetic Networks

One of the central themes of organismal biology is the functional integration of the organism as a whole. Changes in one part or system of an organism are likely to have cascading effects through its other systems and impact seemingly unrelated functions. These cascading effects make the organism susceptible to perturbations in the environment or in the genome. On the other hand, regulatory interactions among different systemic elements allow the organism to lessen the impact of these cascading effects through buffering, feedback, and compensation. Thus when evolution reduces the effect of perturbations on the output of the genetic network, this is referred to as canalization.

I have developed a general framework for studying the strength of selection on canalization. The simple result is that selection on canalization is at most equal to the fitness load minus the per gene mutation rate ($L - \mu$). For load induced by mutation alone, canalization is only favored when the number of interacting genes is large, as is the case for heat shock proteins. However, the fitness load induced by both spatial and temporal variance can be large, providing ample selection for canalization even when only a few genes are involved. This implies that ecological processes play an important role in shaping genetic interactions and genomic structure.

The Micro-Evolution of Regulatory Control

The regulatory control of genes involved in development has recently received increased attention due to experimental advances. One of the striking features is that positive regulation occurs at a broad level while inhibitory regulation is more important in determining where genes are expressed. I am currently developing models that include

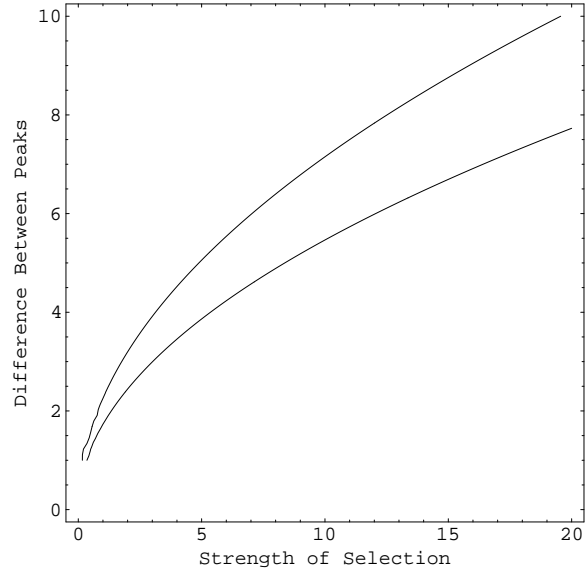


Figure 3: The critical strength of selection for allelic divergence. The top curve is for duplicated genes while the bottom is for single loci. Only parameters between the two curves allow divergence of duplicate loci without causing divergence at a single locus.

both population genetics and developmental dynamics to investigate the micro-evolution of regulatory control during development. My preliminary results suggest that positive regulation of spatial expression can only evolve by major changes, while inhibition control can evolve by small steps. This suggests that the present patterns of genetic control evolved because of historical constraints rather than due to the system level properties of control structures.

The Evolution of Gene Families

Most evolutionary models of gene duplication focus on events that occur after the duplication has become fixed in the population. However, important genetic dynamics can occur before gene duplication and alter the selective pressures on duplication itself. I have derived population genetic models of allelic diversity in genes that can potentially perform multiple functions. My results show that evolutionary divergence between alleles at a single locus is typically required for divergence to be maintained after a duplication event (**Figure 3**).

These results suggest that the creation of gene families is not allowed by relaxed selection following duplication events, but rather precedes duplication. When allelic divergence occurs at a single locus, heterozygote advantage is created. Once heterozygote advantage has evolved, there is selection for gene duplication through a form of canalization. Thus, the creation of gene families before duplication can help to explain why gene duplicates are maintained in evolutionary time.

4 Teaching Experience and Interests

Teaching Experience

I have gained valuable teaching experience over the past 10 years, ranging from guiding field courses to one-on-one tutoring to lecturing for large classes. As a postdoctoral researcher at the University of Toronto, I served as a lecturer for the evolution seminar course taken by graduating honors students. This has given me an opportunity to conduct an entire course, from syllabus design to grading.

As a graduate student I acted as a teaching assistant for a wide variety of classes, including ecology, mathematical biology, and a field course on desert ecosystems. In addition to acting as a teaching assistant, I also had the opportunity to give lectures for many of these classes. As a lecturer, I discovered that one of the many hang-ups students face in introductory ecology is applying mathematical knowledge to specific problems. For example, students often have trouble understanding differential equations describing population growth, as they have typically learned how to integrate functions only in abstract terms.

While completing my graduate studies, I tutored advanced placement high school students in physics, calculus, and biology. This brought home the conceptual difficulties inexperienced students have, difficulties that must be addressed to successfully teach ecology and evolutionary biology. Both at university and in preparatory programs, I found it helpful to provide physical analogies to processes students come into contact with in their everyday lives, such as driving a car or draining a bath tub. Once I translated the concepts into those terms, the students understand the concepts much more readily.

My first year in graduate school was also the first year that my advisor, Fred Adler, taught his course “Mathematics for Life Scientists.” I acted as TA during this first year, and later took part in researching and designing “problem sets” for his book *Modeling the Dynamics of Life*. As I worked through the problem sets with Dr. Adler, I learned how to break down even the most complex problems, like pressure regulation in the human eye, into manageable parts that students can work through. Acting as a TA for this class was a unique experience as it offers an alternate pathway for undergraduates to learn calculus: students learn calculus from examples in biology. When these students are later asked to apply calculus in biology classes, they are more prepared than students with a traditional calculus background. I anticipate applying these lessons to a modeling course for biologists at the undergraduate/graduate level.

Teaching Philosophy and Goals

As an instructor, my main goal is to clarify the conceptual underpinnings of biological phenomenon. While I find this type of teaching particularly effective in subjects that are

primarily conceptual in nature, such as ecology and evolution, experimental design and statistics, and theoretical biology, I believe it is an excellent way to introduce students to biology.

Often, introductory courses give students the impression that biology is mostly a descriptive science, filled with lists of species, structures, and associations. While it is true that understanding biology requires an expanded vocabulary and concept base, the courses that most excite students are often inspired by current research that is focused on understanding patterns and phenomena at a conceptual level.

My main teaching method is this: I take a problem and break it down into components, describing each component as simply as possible. Once the students have a good grasp on the new information, I teach them to see the individual components as part of an interactive system. This method helps to guide students to a deeper understanding of biological processes as a whole and gives me the opportunity to introduce students at an early stage to the conceptual nature of biology. I can actually show them that working their way up the learning curve will indeed lead to more exciting studies.

I believe that avid interest on the part of both the instructor and the student is a necessary ingredient to successful learning. Like many instructors, I find much personal satisfaction in watching my students succeed in their studies. The students’ enthusiasm as they discover new ideas renews my own interest in the topic at hand and inevitably leads to an increase in my own knowledge.