Dear Dr. Swanson,

I would like to express my interest in the position of Research Scientist in your lab. In the following, I summarize my recent work and my background.

My recent research has been done in collaboration with Dr. Miriam Barlow and members of her lab. It centered around the evolutionary dynamics of antibiotic resistant bacteria. The appropriate model in this setting is one of stong selection and weak mutation. Beneficial mutations occur rarely, and when they do, they quickly go to fixation in the population. The result is a genetically homogeneous (at with respect to antibiotic resistance) cell population punctuated by instantaneous replacements by fitter genotypes. The standard model for stong selection weak mutation was developed in the work of Gillespie. Gillespie's ideas were recently resurrected by Orr, and from Orr have recently been put in use in studying microorganismic population by Weinreich. What can be called the Orr-Weinreich approach has been raised to something of a doctrine in the microbiological community. Paramount in the work of all these authors has been the use of the extreme value theory in probability.

Evolutionary Predictability and Complications with Additivity, written with Miriam Barlow and Kristina Crona was entirely a dissent against the Weinreich model. We have numerous objections, ranging over biological, mathematical, and logical grounds. In our article, we confined ourselves to what we view as a biological flaw in his arguments, namely, not taking into account additivity of fitness effects of mutant alleles. There is much empirical evidence suggesting that the fitness effects of alleles across different loci are additive, or at least approximately so. Weinreich's model completely ignores this aspect. He calculates the probability distribution of all possible evolutionary trajectories to the most fit genotype, and finds that the probabilities of occurence of a great number of the trajectories are marginal. He concludes from this that evolution of microbes is very predictable, since only few trajectories have probabilities large enough to likely to happen. Following the basic spirit Weinreich's model, which, as mentioned above is based on the extreme value theory method set down by Gillespie and Orr, we recomputed the probabilities, but this time taking into account additivity. We found that under this assumption the gulf found by Weinreich between the most likely trajectories and the least likely trajectories decreased significantly. We believe that this refutes to some extent the claim regarding the predictability of microbial evolution.

In our other article, *Adaptive walks of TEM alleles*, with Mirian Barlow, Stephan Jacobs, and Kristina Crona, we attempted to extend the Gillespie-Orr-Weinreich strong selection weak mutation model to take into account geographical distances between bacteria populations. While the model is accurate for *local* cell populations, clinical evidence shows a substantial amount of interlocational genetic variability of resistant bacteria. Perhaps this is not so surprising, but the conventional models for populations under stong selection and weak mutation assume panmicticity, which leads to genetically homogeneous populations. Using the R programming language, we developed a model which took these features into account. We avoided mathematical sophistication, using only the assump-

tions of a mutational rate, instant fixation of a beneficial mutant in a local population, and gradual spread of a beneficial mutant over geographical areas. Not surprisingly, the evolutionary predictions obtained from this model differed significantly from the those obtained with conventional models.

A nice result of abandoning panmicticity may be to provide an evolutionary rationale for the phenomenon of "cross over" or recombination in bacteria. (In single cell organisms, recombination means two cells exchanging genetic material.) In a panmictic population with stong selection and weak mutation, the population spends most of its time in a genetically homogeneous state, in which case what is the point of recombination? Interlocational heterogeneity, however, makes recombination an obvious strategy. Quite simply, suppose that allele A confers antibiotic resistance while allele B at a different locus confers resistance superior to that confered by allele A. Furthermore, assume that the genotype AB confers resistance superior to that of both A and B alone. With interlocational variability, you may have one subpopulation for which A alone has gone to fixation and another where B alone has gone to fixation. With the weak mutation assumption there may be a substantial time lag before the superior genotype AB arises in either population. What is more likely to occur is that the B subpopulation spreads to the A subpopulation, wiping it out. With recombination however, AB genotypes will arise, which are superior in fitness to both A and B. Any gene associated with the process of recombination will thus be selectively favored, since in such a situation it will "ride along" with the conquering AB genotype.

I am trained as a pure mathematician. The knowledge that I've accumulated over the course of my work in biology has been self-taught. I am comfortable with the mathematical models commonly used in population genetics, which include a fair bit of probability theory and PDEs. I am knowledgeable in and have used ideas in probability and statistical theory. The simulations used in our research were coded in R, and I was entirely responsable for their design.

Respectfully Yours,

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CV

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Education

Degrees:

A.B., University of California, Berkeley, 1996 (Mathematics)
Highest Distinction in General Scholarship
Ph.D., University of California, Berkeley, 2001 (Mathematics)

Professional Experience

Aug 1996-May 2001	Graduate Student Instructor, University of California, Berkeley
Aug 2001-May 2002	Research Assistant Professor, University of Nebraska, Lincoln
Jan 2003-April 2005	Visiting Assistant Professor, University of California, Irvine
2006-2007	English Language Consultant (self-employed; living in Stockholm, Sweden)
August 2007-present	Lecturer in Mathematics, University of California, Merced

Recent Research Articles

Adaptive walks of TEM alleles
(with Miriam Barlow, Stephan Jacobs, and Kristina Crona) submitted for publication

Evolutionary Predictability and Complications with Additivity
(with Miriam Barlow and Kristina Crona) submitted for publication

Programming Skills

R

References

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