Q & A: Frederick Cohan

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In graduate school I became interested in Ernst Mayr’s ideas on species and speciation, particularly his idea that a species is a cohesive body, whose divergence is opposed by various forces of evolution, and that the splitting of species marks the origin of lineages that no longer cohere. Species were thought to be cohesive mostly as a result of recurrent genetic exchange among them, but I was interested in finding whether cohesion might also operate through natural selection, even among isolated populations. Using Drosophila fruit flies, I tested whether populations from different parts of a species’ range might be channelled to respond in the same way to the same environmental challenge (Mayr’s prediction) or whether even geographically close populations might already be predisposed to diverge under uniform natural selection (my prediction, which proved to be correct). My experiments made me wonder whether there actually are important limits to cohesion across a large species.

How did you get interested in bacteria?

Following the pioneering work in microbial population biology of Levin, Hartl, Istock, and Hall, some zoologically oriented population biologists were realizing by the early 1980s that bacteria offer a very nice model system for studying general questions about evolution. I had the opportunity when I was at the University of Arizona to learn about evolutionary microbiology and genetic transformation of Bacillus from Conrad Istock and John Spizizen. I started out using Bacillus as a tool for studying general issues in evolutionary adaptation, including the evolution of sex (in collaboration with Richard Michod), as well as compensatory evolution, which I studied in my first few years at Wesleyan.

But the bug about species continued to stir in my head as I became steeped in microbiology. Early on in my career at Wesleyan, I realized that some ideas that zoologists and botanists had developed about cohesiveness of species might apply to bacteria. While I was preparing lectures for my first course at Wesleyan, in ecology, I realized that the key to lineages becoming irreversibly separate in the bacterial world was that they had to diverge ecologically. At the time I didn’t know much about microbial ecology, but I could see how, at least in principle, natural selection could...
limit diversity within an ecologically homogeneous population, while it could not prevent divergence between populations that had become distinct in their ecology. Eventually my students and I developed a more comprehensive theory of speciation in bacteria, which took into account that generally useful genes could transfer from species to species while each species retained its integrity as an ecologically distinct unit — ideas that had been stewing in my imagination since my first introduction to hybridization in oaks.

So, this was the beginning of my interest in bacterial speciation. Since then, my students and I have studied resistance to gene transfer across species. We’ve also developed a much more nuanced approach to species that takes into account more of the realities of bacterial ecology that were outside my understanding in the beginning. Also, the work has benefitted from my collaboration with David Ward, from whom I have learned a great deal of bacterial ecology and physiology, and from my collaboration with Danny Krizanc, who has helped me become a much more effective algorithmist.

How do you see your contributions to microbial evolution and ecology? I think the most important message from our work is that bacteria have a history of rapid and recent ecological diversification that is still ongoing, and that much of the ecological diversity in bacteria is unappreciated by the species demarcations of bacterial systematics. Moreover, it is possible through the computational methods we have developed in our lab to discover the ecological diversity among very close relatives, even when we don’t know ahead of time what the ecological differences among the populations are. We have found our approach to be useful in identifying the ecological dimensions in which speciation occurs.

I think we will have ultimately succeeded in our work when we can present an ‘idiot’s guide’ to the discovery and characterization of the full and most recent ecological diversity within any unknown bacterial taxon, without requiring any prior knowledge about the taxon. The idea is to develop universal molecular and genomic tools for identifying evolutionary groups likely to represent the most newly divergent species within a focus taxon, and then to develop ways to characterize the ecological diversity among the species. This will involve finding ways to leverage what we already know and can most easily find out from other organisms, to interpret the ecological message from an organism’s genome and its associations with other organisms. I think that many subfields of microbiology, including epidemiology, biotechnology, and genomics, will benefit from recognizing and characterizing the most closely related, ecologically distinct populations of bacteria.

Other aspects of our work are more controversial, such as whether there are significant cohesive populations of bacteria, as we have hypothesized. At this point, it won’t bother me if we’re not correct on this, as we have modelled various kinds of cohesive and non-cohesive bacterial species — I would just like to know which models are right. As in many areas of evolutionary biology, I suspect the answer will be the percentage of times that one model versus another is more appropriate.

What is your favourite paper? At the Evolution Society meeting at Asilomar, I saw Michael Donoghue present a paper on the importance of taking phylogeny into account in comparative biology, later published in 1989 in Evolution (43, 1137). Up to that point, I was a population geneticist with no training or interest in phylogenetics, and here Donoghue was telling us, so compellingly, that you can’t do meaningful work in evolutionary biology without taking phylogeny into account. I was so grateful for that message, as I don’t see how any of our work on the origin of bacterial species in the last two decades would have been possible without a phylogenetic context.

What advice would you offer someone starting a career in biology? I have found some advice given to me by my postdoctoral mentor Tim Prout to be of lasting value. He suggested that an experiment should be designed so that, no matter which way the biology turns out, the work will still make an important contribution. Following this advice means that we’re always finding out interesting things about how nature works, regardless of whether some really interesting or novel hypothesis is supported.

Over the years, I have come to understand that this advice is actually more than a strategy for research productivity — it is also a recipe for encouraging integrity among all of us working together on a project. Criticisms of science often focus on the vulnerability of science to fraud because science depends so urgently on the honesty and integrity of all participants. However, I think this kind of criticism makes a false dichotomy of the value of results — that one set of results will lead to a researcher’s success while another set of results will lead to failure. If we inculcate into our students the idea that we are finding out how nature works, and all results are of value, this takes a lot of pressure off of integrity.

My other bit of advice deals also with the design of experiments, as well as the taking of data. I suggest that our students should think really hard about how their data might be useful to the project at hand, as well as to future researchers who might come across our data and would want to use it to test some hypothesis beyond our current imagination. Thus, they should record all the data, within reason, that could possibly be interesting for posterity. This is advice that I believe will grow in value as original data sets are increasingly published on-line.

To make this point a little more dramatically, I’d like to tell you about a famous baseball game that I was lucky enough to see in my childhood. On September 9, 1965 (already baseball fans will know what I’m talking about), I went to see a Los Angeles Dodgers game, along with my Little League baseball team and our fathers, and we were delighted to see that Sandy Koufax, the greatest left-handed pitcher of all time, was on the mound for the Dodgers. This turned out to be the evening that he pitched his ‘perfect game’, meaning that he didn’t allow a single batter to reach first base.

The Dodgers had recently led a radio campaign to teach all the kids of the Los Angeles area how to score a baseball game, meaning that we knew how to record data on the outcome of every at-bat. Somewhere around half way through the game, we all knew that this game could be a truly significant event in baseball history, and I was very pleased that I was keeping an accurate record of every
at-bat, including which fielders were involved, and so on. At that point, I was amused to see that my friend Kyle was also keeping score, but that he marked every at-bat with a simple and uninformative ‘X’ when each batter was retired; consequently, his whole data sheet on the opposing team was just one string of Xs after another.

Although I was feeling the superior data collector, I realized afterward that although I had recorded the game the way I was taught, my data collecting was not up to the task of recording the most significant memory of that game (besides that Koufax pulled off the perfect game). Somewhere around the seventh inning Koufax reached Ball 3 and no strikes, just one errant pitch away from ruining his perfect game. This is the moment when all sound left the stadium and the suspense of the game became indelibly burned into our memories. It turns out that my standard approach to data collecting, including how each batter was put out but not including the count or order of balls and strikes, did not account for the possibility that one might want to have a record of how close Koufax had come to failing. So, Koufax is telling us to use our imagination about where our data might lead, and what might be most truly important.

**What is your favourite course to teach?** I teach courses at all levels, from non-majors’ and introductory courses to graduate courses. My favourite course is my newest one, on global change and infectious disease, directed to majors in Wesleyan’s new, interdisciplinary Environmental Studies program, and more generally to non-scientists interested in the environment. This course is particularly rewarding for me because it reaches the people who I believe are most likely to make progress on our climate crisis — the policy makers, pundits, and artists of the future who will need to persuade public opinion to make the necessary choices. While there is much to be learned in the science of global climate change, I don’t think that what scientists like me will contribute will be as important as the contributions of those who will try to persuade the public to commit themselves to avoiding climatic catastrophe.

**KASH and SUN proteins**

**Daniel A. Starr**

**What are KASH proteins?** KASH proteins (Klarsicht, ANC-1, Syne homology) are C-tail-anchored membrane proteins, which are targeted specifically to the outer membrane of the nuclear envelope. The defining feature of KASH proteins is the carboxy-terminal KASH domain that consists of a hydrophobic region spanning the outer nuclear membrane and 6–30 residues in the perinuclear space. The perinuclear domains of KASH proteins are often highly similar; for example, 13 of 20 residues are identical between Caenorhabditis elegans ANC-1 and human Syne/ Nesprin-1 and -2. Other KASH proteins have shorter and/or divergent perinuclear sequences. Due to a lack of homology, additional KASH proteins likely remain to be discovered. KASH proteins also have large, non-conserved cytoplasmic domains.

**What are the names of mammalian KASH proteins — Syne or Nesprin?** In 2000–2002, around the time of the discovery of KASH proteins, two mammalian KASH proteins were independently identified by at least six groups. They were originally named Syne-1 and -2 because of their roles in anchoring nuclei at the neuromuscular junction. Today, many call these proteins ‘Syne’, but the majority of the field uses the term ‘Nesprin’ (for nuclear envelope with spectrin repeats) for the proteins and SYNE for the genes. Neither name is perfect, because not all KASH proteins contain spectrin repeats. Furthermore, the term Nesprin refers exclusively to mammalian KASH proteins and excludes the functional roles elucidated from studies of KASH proteins in other model systems.

**What are SUN proteins?** SUN proteins (for Sad1 and UNC-84) are integral components of the inner nuclear membrane with conserved, carboxy-terminal SUN domains that localize to the perinuclear space. SUN domains consist of approximately 175 residues and are conserved across all eukaryotes. The nucleoplasmic domains of SUN proteins are not conserved, but nonetheless interact with structural components of the nucleoskeleton; many interact directly with lamins. The presence of multiple SUN proteins in a single organism (at least five in humans), their various isoforms, and their ability to form multimers complicates the studies of their functions.

**How are KASH proteins targeted to the outer nuclear membrane?** The nuclear envelope is a specialized extension of the endoplasmic reticulum, complicating trafficking of KASH and SUN proteins to specific membrane domains. The outer nuclear membrane is contiguous with the endoplasmic reticulum, and the inner and outer membranes are connected at nuclear pores. Although a KASH domain alone is sufficient to target a heterologous protein to the outer nuclear membrane, recruitment of KASH proteins to the outer nuclear membrane requires both KASH and SUN domains, as a mutation in either one blocks the targeting of KASH proteins to the outer nuclear membrane. In agreement with these genetic data, KASH and SUN proteins physically interact in the perinuclear space to connect the inner and outer nuclear membranes and to maintain the even spacing of these membranes. Together, SUN and KASH proteins form bridges that span both membranes of the nuclear envelope (Figure 1).

**What is the LINC complex?** LINC (linker of nucleoskeleton and cytoskeleton) complexes connect the nucleus to the cytoskeleton. The nucleoskeleton, which provides structure to the nucleus, is made of lamins, inner nuclear membrane proteins, and chromosomes. It is separated from the cytoskeleton by the nuclear envelope. Forces generated in the cytoplasm must be transferred across both membranes to the nucleoskeleton. KASH and SUN proteins are central to the transfer of this force because they form the bridge across the nuclear envelope. The cytoplasmic domains of KASH proteins interact with a variety of components of the cytoskeleton. SUN proteins, in turn, interact with the nucleoskeleton. The entire chain of