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Biocomplexity Faculty Search Committee,
c / o Prof. Rob de Ruyter van Steveninck,
Department of Physics
Indiana University
Swain Hall West 117
Bloomington IN, 47405-7105

To the Search Committee,

I am writing in reference to Jason Mezey's application for your recently advertised faculty position in biocomplexity. Jason is an evolutionary biologist who is working at the seam between genomics, development, evolutionary biology and statistics, knit together with computational skills. Jason was a post-doctoral fellow in my laboratory from 2000 to 2003. He departed last year for another postdoctoral position with Sergey Nuzhdin at UC Davis. We have interacted a good deal over that period on several different projects, so I know him quite well. In summary, Jason is an exceptional applicant.

Overall, Jason was a wonderful addition to the lab. He received good but somewhat narrow training from Wagner and Kim at Yale, doing quite original research. He rapidly mastered the fly wing experimental system used in my lab, and is making himself an expert in *Drosophila* genetics and genomics, aided by the expertise that he is gaining in Nuzhdin's more molecular lab at Davis. He is interactive, and has good ideas that have pushed ahead my research over the last few years.

Jason's interests are in how the many genes that influence the phenotype of an organism interact to bring that phenotype about. This is a complex and difficult problem. Evolutionary biologists have resorted to very simple models of this relationship between genotype and phenotype, even as developmental and molecular biologists have demonstrated the intricacies that are actually involved. Jason is one of those who would like to correct this situation by introducing more realistic assumptions into evolutionary thinking. These questions are particularly crucial now that functional genomics, the study of organisms at the level of whole genomes, is becoming possible. To what extent do we need to know how all genes are expressed and function to understand evolution? To what extent can we find simple commonalities that underlie all this complexity? These are the big questions that Jason's work addresses.

Jason's skills have expanded over the years to include a wonderful variety of techniques including expression arrays, QTL mapping, quantitative genetics and analytical and numerical theory. One of the most important niches that he fills is the invention and validation of novel statistical approaches to the new sorts of data that are now becoming available.

Jason's work with me provides many examples of his diverse skills and intellectual qualities. He has recently completed some very exciting work estimating the dimensionality of genetic variation in wing shape. The background for this is the speculation of scientists such as Gould that the possibilities for evolution are heavily constrained by the combination of genetics and development. We measured 20 aspects of wing shape simultaneously in a very large quantitative genetic experiment (16,000 individual in 750 families). Our first question is how many of those 20 aspects of shape can vary independently of the others – that is, what is the dimensionality of wing shape? What we expected to find was perhaps five or 10 significant, independent aspects of shape, and, due to a lack of power, being left to test the genetic variation in the other aspects of shape by other means. Instead we found significant genetic variation in ALL 20 aspects of shape. Jason spent a great deal of time devising techniques to test this fundamentally important finding, inventing at least two new techniques for doing so. The most conservative of these tests still shows 17 or more dimensions are variable, essentially confirming the original result. This result, if confirmed in a variety of systems, should fundamentally reorder our thinking on the role of constraints vs. natural selection in shaping phenotypic variation.

Jason brought QTL analyses to my lab, which allowed us to exploit our automated system for measuring everything about *Drosophila* vein morphology in just a couple of minutes per individual. Wings are attractive for study because there is a tremendous amount of background knowledge about their development. Jason has studied recombinant lines developed by Sergey Nuzhdin of UC Davis. These lines are unusual in that they were founded from a cross between two wild flies from a natural population, and therefore inform us about a more typical reference population than the usual wide cross. He has found evidence for at least 18 loci affecting variation in some aspect of wing shape within this single-pair cross, a remarkably high number. In addition, he checked for interactions between the QTLs and mutations in the important wing developmental pathways involving hedgehog and decapentaplegic. Three of the QTLs showed strong interactions with many of these mutants, implicating these pathways as the site of genetic variation influencing wing shape. In order to complete this project, Jason had to develop a novel analysis, because he discovered that the previous analyses of this experiment were flawed. This manuscript has just been accepted at Genetics.

In addition to these projects, Jason has been devising and testing techniques for comparing variation in multivariate samples. The goal of this work is to see if simple rules for variation exist, and, if they exist, work out how to detect them. We

have a substantial collaborative investigation of one increasingly popular technique for looking at complex multivariate data, common principal component analysis. Our first paper together was a cautionary tale about the naive interpretation of CPC analysis. Jason has also turned this work around, and has a really exciting paper in *Genetics* that shows that the conditions under which the principal components remain the same in two populations are very restrictive. Essentially, this is only likely if the phenotype really has a modular genetic architecture. This means that the common finding of no differences between populations is potentially telling us something fundamental about the lack of modularity of phenotypic variation. He also has substantial unpublished work on both the advantages and disadvantages of common principal component analysis's much more useful big brother, common space analysis. His work will be the foundation on which all others in this area need to build. I suspect that this will prove to be one of his most valuable niches as a scientist – figuring out how to use the fantastically complex data that genomic and other sorts of surveys can be used to answer biological questions.

During his thesis work, Jason studied the pattern of effects of QTLs affecting a suite of characters in the mouse mandible. He found evidence that the pattern is not random, but that interacting parts tended to be affected in common by genetic events. If this is generally true, this finding has profound implications for evolution and development. It suggests that the highly successful reductionist approach of breaking down organisms and biological processes into their component parts and then studying the parts has important limitations. Natural selection operates on whole organisms, so Jason's result is in one sense expected, but the implications are profound.

While at FSU, Jason eagerly took advantage of our open structure, and threw himself into new areas of interest. Jason has been an active participant in several discussion groups in the department that include ecology, evolutionary genetics, systematics and statistics. These have very much improved the breadth of his experience, the fruits of which are now beginning to show.

I have heard Jason speak to scientific conferences and in a class-room setting. He is very effective in both. He has mastered the art of presenting energetic enthusiasm, which is very engaging at both levels. He carefully prepares for such opportunities, so his presentations are clear, and of high intellectual quality.

Jason was the sole instructor for Evolutionary Biology during summer 2001, which is a required course of biology majors here. Despite the fact that this was Jason's first teaching experience, the course was very positively received by the students. He seems to have engaged their interests effectively, despite covering a range of difficult topics. His office hours were usually quite well-attended, suggesting that he was respected and trusted by the students.

Jason's record here suggests that he is ready for the larger responsibilities of a

faculty position. He was a good citizen, willing to take on his share of administration of my lab, help entertain visitors, give presentations, etc. I am sure that he would be a willing and effective participant in administrative duties. His capacity and willingness to work long hours expanded to the absurd levels necessary to succeed in academic science.

Finally, Jason was also very well-liked by other students and post-docs in the department. He became an informal advisor to many graduate students on statistical issues, and on "how to be a scientist". He was an important part of a very healthy network of scientific and personal interactions that make this a good place to be. We all miss him.

In summary, I recommend Jason very highly. I am sure that he will continue to generate high quality ideas and the data to test them in the years ahead. I expect him to be one of the intellectual leaders in the evolution of complex systems.

Feel free to contact me for further information.

Sincerely,

A handwritten signature in black ink, appearing to read "David Houle". The signature is fluid and cursive, with a prominent initial "D" and a long, sweeping underline.

David Houle
Associate Professor