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October 31, 2019

Department of Biology
Tufts University
Medford, MA

Dear Faculty Search Committee:

I am thrilled to submit my application for the open faculty position in computational biology at Tufts University. I earned my PhD in bioinformatics from the University of California, San Francisco, and I completed an NIH IRACDA postdoctoral fellowship in the Department of Biology at Stanford University. I am currently completing a postdoc at UC Berkeley in the Department of Integrative Biology.

My research program leverages computational methods and large, noisy datasets to study how ecological and evolutionary processes shape biodiversity in both plant and animal systems. Although Darwinian selection has been highly successful as a conceptual framework to explain the diversification of life on Earth, we still struggle to predict how species will (or will not) adapt to rapid biotic or abiotic change. Moreover, models that seek to predict individual and population variation from genomic data (*e.g.*, polygenic scores) are often inaccurate or positively misleading. My research program takes an evolutionary genetics view of these problems – if we have a better foundational understanding of the mechanistic processes that drive adaptation and trait-variation, we may be more successful in making predictions from genetic data. My postdoctoral research argues that previously undetected signals of weak adaptation can be captured in genomic data, that species composition in California grasslands is highly dependent on the stochastic order-of-arrival (*i.e.*, priority effects), and that evolutionary processes such as explosive growth profoundly affect the interpretation of QTL-mapping studies.

As both a graduate student and a postdoc, I have pursued a commitment to teaching and mentorship. As an IRACDA postdoc, I co-instructed two semester-long courses in evolutionary genetics and ecology at San Jose State University, and trained in a wide variety of evidence-based teaching practices that have the potential to reduce achievement gaps in science. I also initiated a scientific teaching workshop at Stanford, implemented in summer 2017, with the goal of introducing Stanford postdocs to evidence-based teaching approaches. My desire to teach extensively during my postdoc stemmed from my earlier pedagogical training, including a UCSF computational evolutionary genomics course that garnered a Teaching Assistant Excellence Award, an interactive computational evolution workshop that I designed for Stanford undergraduates, and mentorship of numerous summer and undergraduate students. I am currently mentoring an undergraduate research student in a disease modeling project.

As a faculty member at Tufts, I would leverage these experiences to build leading research and teaching programs, help students develop quantitative skills, and encourage students of diverse backgrounds to participate in research in ecology and evolution.

Thank you very much for your consideration.

Sincerely,

Lawrence H. Uricchio

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Education

2015 -	*Postdoc*, UC Berkeley & Stanford University
2014	*PhD*, Bioinformatics, University of California, San Francisco
2011	*MS*, Computer Science, University of Chicago
2009	*MS*, Biophysical Sciences, University of Chicago
2005	*BA*, Physics, Carleton College

Honors & Fellowships

2016 - 2018	NIH IRACDA Postdoctoral Fellow, Stanford University
2015 - 2016	CEHG Postdoctoral Fellow, Stanford University
2014	Discovery Fellow, UCSF
2014	ASHG trainee award for excellence in human genetics research, semi-finalist
2013	Teaching Assistant Excellence Award, UCSF
2012 - 2014	Achievement Rewards for College Scientists Fellow, UCSF
2005	Distinction in the physics major, Carleton College
2005	Phi Beta Kappa (academic honor society), Carleton College
2005	Sigma Xi (scientific research honor society), Carleton College
2005	Magna Cum Laude, Carleton College
2002	Dean's list, Carleton College

Publications

Evolution & ecology

1. Hernandez RD, **Uricchio LH**, Hartman K, Ye J, Dahl A, Zaitlen N. Ultrarare variants drive substantial cis-heritability of human gene expression. *Nature Genetics*, in press, Sep 2019.
2. **Uricchio LH**†. Evolutionary perspectives on polygenic selection, missing heritability, and GWAS. *Human Genetics*, in press, June 2019.
3. **Uricchio LH**†, Petrov DA, Enard D†. Exploiting selection at linked stites to infer the rate and strength of adaptation. *Nature Ecology & Evolution*, 3:977–984, June 2019.
4. **Uricchio LH**†, Daws SC, Spear ER, Mordecai EA†. Priority effects and non-hierarchical competition shape species composition in a complex grassland community. *The American Naturalist*, 193(2):213–226, Feb 2019.
5. **Uricchio LH**‡†, Kitano HC‡, Gusev A, Zaitlen NA†. An evolutionary compass for detecting polygenic selection and mutational bias. *Evolution Letters*, 3(1):69–79, Feb 2019.
6. Goldberg A, **Uricchio LH**, Rosenberg NA. Natural selection in human populations. *Oxford Bibliographies in Evolutionary Biology*, Aug 2018.
7. **Uricchio LH**, Warnow T, Rosenberg NA. An analytical upper bound on the number of loci required for all splits of a species tree to appear in a set of gene trees. *BMC Bioinformatics*, 17(14):241–250, Nov 2016.
8. **Uricchio LH**†, Zaitlen NA, Ye CJ, Witte JS, Hernandez RD†. Selection and explosive growth alter genetic architecture and hamper the detection of causal rare variants. *Genome Research*, 26:863–873, July 2016.
9. **Uricchio LH**, Hernandez RD. Robust forward simulations of recurrent hitchhiking. *Genetics*, 197(1):221–236, May 2014.
10. Maher MC‡, **Uricchio LH**‡, Torgerson DG, Hernandez RD. Population genetics of rare variants and complex diseases. *Human Heredity*, 74(3-4):118–128, Apr 2013.

Statistical genetics

1. Gignoux CR, Torgerson DG, Pino-Yanes M, **Uricchio LH**, Galanter J *et al.* An admixture mapping meta-analysis implicates genetic variation at 18q21 with asthma susceptibility in latinos. *Journal of Allergy and Clinical Immunology*, 143(3):957–969, Mar 2019.

2. **Uricchio LH**, Torres R, Witte JS, Hernandez RD. Population genetic simulations of complex phenotypes with implications for rare variant association tests. *Genetic Epidemiology*, 39(1):35–44, Jan 2015.
3. **Uricchio LH**, Chong JX, Ross KD, Ober C, Nicolae DL. Accurate imputation of rare and common variants in a founder population from a small number of sequenced individuals. *Genetic Epidemiology*, 36(4):312–319, May 2012.
4. Çalışkan M, Chong JX, **Uricchio L**, Anderson R, Chen P *et al.* Exome sequencing reveals a novel mutation for autosomal recessive nonsyndromic mental retardation in the TECR gene on chromosome 19p13. *Human Molecular Genetics*, 20(7):1285–1289, Apr 2011.

Other publications

1. Severson AL‡, **Uricchio LH**‡, Arbisser IM‡, Glassberg EC, Rosenberg NA. Analysis of author gender in TPB, 1991–2018. *Theoretical Population Biology*, 127:1–6, June 2019.
2. Miller LS, Pietras EM, **Uricchio LH**, Hirano K, Rao S *et al.* Inflammasome-mediated production of IL-1β is required for neutrophil recruitment against staphylococcus aureus in vivo. *Journal of Immunology*, 179(10):6933–6942, Nov 2007.
3. Pattanayak AK, Brooks DWC, de La Fuente A, **Uricchio L**, Holby E *et al.* Coarse-grained entropy decrease and phase-space focusing in hamiltonian dynamics. *Physical Review A*, 72(1):013406, Jul 2005.

‡ denotes equal contributions; † denotes corresponding author

In progress

1. Castellano D, **Uricchio LH**, Munch K, Enard D. Viruses rule over adaptation in conserved human proteins. to be submitted: *preprint at* `https://www.biorxiv.org/content/10.1101/555060v1`, 2019.

Dissertation

1. **Uricchio LH**. Models and forward simulations of selection, human demography, and complex traits. UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, 2014.

Teaching	2018	Co-instructor, *Evolutionary genetics* (BIOL 118), San Jose State University*
	2017	Co-instructor, *Ecology* (BIOL 160), San Jose State University*
		****semester-long undergraduate courses for which I led 40-50% of instructional time.***
	2017	Co-founder, *Stanford postdoc pedagogy miniseries*, Stanford University
	2015	Instructor, *Undergraduate Biology Exploration*, Stanford University
	2016-2017	Guest lecturer (twice), *Evolution*, Stanford University
	2014	Graduate teaching assistant, *Computational Evolutionary Genomics*, UCSF
	2013	Graduate student instructor, *Computational Biology*, UC Berkeley
	2009	Guest lecturer, *Genes, Networks, and Cells*, University of Chicago
	2003-2004	Teaching assistant, tutor, & grader, *Introduction to Physics, Classical & Computational Mechanics, Contemporary Experimental Physics*, Carleton College
Mentoring	2016	Student research co-mentor to Alan Aw, Rosenberg Lab
	2013	Student research mentor to Isela Hernandez, Biological Health Sciences Internship Program
	2010	Student research mentor to Sam Neal, Summer Link High School Program
	2006-2007	Co-supervisor/trainer of undergraduate lab members, UCLA
Service	2013-	Invited reviewer for *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, *Theoretical Population Biology*, *Genetics*, *Nature Genetics*, *BMC Evolutionary Biology*, *PLoS Genetics*, *Nature Ecology & Evolution*, *Molecular Biology & Evolution*, *Molecular Ecology*, *Heredity*, *PLoS ONE*, and *G3: Genes, Genomes, Genetics*
	2016	Committee member & session leader, Stanford Postdoc Pedagogy Journal Club
	2015-2016	Committee member, Stanford CEHG diversity outreach committee

Competitive Funding	2016-2018	NIH IRACDA Fellow, Stanford & SJSU ($53,600 per year)
	2016-2017	Stanford Teaching & Mentoring Academy Award ($6,870)
	2015-2016	Stanford CEHG Postdoctoral Fellowship ($50,000)
	2012-2014	UCSF Achievement Rewards for College Scientists Fellow ($12,000 per year)
	2014	UCSF Discovery Fellow ($4,000 for travel & research over 2 years)

Presentations

1. Exploiting selection at linked stites to infer the rate and strength of adaptation. *Evolution Meeting, Providence, RI.* **Talk**, 2019.
2. Genome-scale inference of adaptive evolution: new approaches for answering old questions. *Boise State University, Boise, ID.* **Seminar**, 2019.
3. Genome-scale inference of adaptive evolution: new approaches for answering old questions. *Chapman University, Orange, CA.* **Seminar**, 2019.
4. Evolutionary processes shaping the human genome. *Linfield College, McMinnville, OR.* **Seminar**, 2018.
5. Scientific teaching workshops for stanford postdocs. *Stanford Education Day, Stanford, CA.* **Talk**, 2018.
6. Modulation of adaptation rate by background selection in the human genome. *Bay Area Population Genomics Meeting, Santa Cruz, CA.* **Talk**, 2018.
7. Modulation of adaptation rate by background selection in the human genome. *American Society of Naturalists Meeting, Monterey, CA.* **Talk**, 2018.
8. Designing and implementing scientific teaching workshops for postdocs. *Stanford Teaching and Mentoring Academy seminar series, Stanford, CA.* **Talk**., 2018.
9. An analytical upper bound on the number of loci required for all splits of a species tree to appear in a set of gene trees. *RECOMB Comparative Genomics Meeting, Montreal, Canada.* **Talk**, 2016.
10. Detecting causal genetic variation in populations with complex evolutionary histories. *Univeristy of Washington, Bothell, WA.* **Seminar**, 2016.
11. Explosive growth and the genetic architecture of polygenic traits under selection. *American Society of Naturalists Meeting, Monterey, CA.* **Talk**, 2016.
12. Selection and explosive growth may hamper the performance of rare variant association tests. *Bay Area Population Genomics Meeting, Stanford, CA.* **Talk**, 2015.
13. Recent demography and natural selection hamper the power of rare variant association tests. *American Society of Human Genetics Meeting, San Diego, CA.* **Talk**, 2014.
14. Model-based simulations of selection and demography with implications for heritable phenotypes and rare variant association tests. *UC Berkeley Center for Theoretical Evolutionary Genomics, Berkeley, CA.* **Talk**, 2014.
15. Simulations and inference of simultaneous positive and negative selection. *Society of Molecular Biology and Evolution Meeting, San Juan, Puerto Rico.* **Poster**, 2014.
16. Parameter rescaling for forward simulations of recurrent hitchhiking. *Bay Area Population Genomics Meeting, San Francisco, CA.* **Poster**, 2013.
17. Forward simulations of recurrent selection and demographics with rescaled parameters. *American Society of Human Genetics Meeting, Boston, MA.* **Poster**, 2013.
18. Accurate pedigree-based imputation. *Department of Human Genetics, University of Chicago, Chicago, IL.* **Seminar**, 2011.

References

Associate Professor Ryan Hernandez, PhD *(PhD advisor)*
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Assistant Professor Noah Zaitlen, PhD *(Mentor)*
nzaitlen@mednet.ucla.edu

Assistant Professor David Enard, PhD *(Collaborator)*
denard at email.arizona.edu

Professor Leslee Parr, PhD *(Teaching mentor)*
leslee.parr at sjsu.edu

I believe that equity in science is one of the most pressing issues that must be addressed by my generation of scientists. As an NIH IRACDA fellow, I studied the systemic barriers that have often limited (or prohibited) the participation of women, people of color, and other under-represented groups in science. I also studied many approaches that can promote equity within and beyond the classroom. My commitment to equity in science has been expressed through implementation of these approaches in my teaching, scholarship, mentorship, and service.

Teaching: As a co-instructor of two semester-long courses at SJSU, I was fortunate to serve a broad range of students. In serving a diverse student body, I learned that differences in background and identity can profoundly affect how students experience the classroom (1). In each class, I

1. acknowledge the variation in our backgrounds, identities, and experiences
2. discuss how science has often failed to be inclusive
3. identify ways in which the field is working to improve equity
4. apply evidence-based approaches (*e.g.*, active-learning and values affirmation) to reduce achievement gaps

For example, as an instructor of Evolutionary Genetics at SJSU, I discussed how population genetics had sometimes been misused to justify racism, and how prejudice and economic status have driven the (lack of) diversity among evolutionary biologists. We then explored how institutional efforts (such as fellowship opportunities) are being initiated to promote inclusion, and applied active learning techniques that may reduce achievement gaps.

Scholarship: Women's contributions to science have often been overlooked in fields such as computational biology. For example, female programmers made substantial contributions to many papers in *Theoretical Population Biology* (*TPB*), but were often not credited with authorship (2). Inspired by this work, my colleagues and I studied author gender in *TPB* for the past 18 years (3). We found that while female authorship rates have increased somewhat since the early 1990s, women are still seriously underrepresented as authors in the journal. Our study does not disentangle the various factors that may contribute to this under-representation, but provides data on female authorship that is useful for comparing theoretical evolution & ecology to other adjacent fields, and provides a background against which to assess future efforts to promote equity.

Mentorship: Effective mentorship is critical for increasing diversity in science. Mentorship can be especially impactful when it reaches younger students who may not otherwise consider science majors. In 2013 I was fortunate to work with Isela Hernandez, a high school junior in the former Biological Health Sciences Internship Program for increasing diversity in STEM. She used data from the Exome Sequencing Project to study deviations from Hardy-Weinberg equilibrium. Isela learned to code in Python and analyze modern genetic sequence data, and went on to complete additional research at Occidental College. She graduated as a biology major and is now beginning a career in biotech. As a faculty member, I plan to support summer research opportunities in computational biology for diverse high school students. I've also had the pleasure of mentoring several other summer research students – one such project resulted in co-first authorship with an undergraduate colleague (4).

Service & Outreach: The implementation of evidence-based teaching practices has the potential to improve classroom equity, but such efforts can only be successful if new teachers adopt these best practices. A fellow postdoc and I designed and obtained competitive funding for a teaching workshop to help accelerate the adoption of evidence-based teaching practices by Stanford postdocs. We invited several teacher-scholars to present on a range of topics, including a session on classroom equity. In this session, Prof. Jeff Schinske presented data suggesting that the personal stories of diverse scientists can profoundly change how students perceive the diversity of active scientists (5). I am excited to introduce scientist biographies as a component of the assignments in future courses.

1. C. M. Steele, J. Aronson, *Journal of Personality and Social Psychology* **69**, 797 (1995).

2. S. K. Dung, *et al.*, *Genetics* **211**, 363 (2019).

3. A. L. Severson‡, **L.H. Uricchio**‡, I. M. Arbisser‡, E. C. Glassberg, N. A. Rosenberg, *Theoretical Population Biology* **127**, 1 (2019).

4. **L.H. Uricchio**‡, H. C. Kitano‡, A. Gusev, N. A. Zaitlen, *Evolution Letters* **3**, 69 (2019).

5. J. N. Schinske, H. Perkins, A. Snyder, M. Wyer, *CBE—Life Sciences Education* **15**, ar47 (2016).

My goal as an instructor is to engage students in the process of biological discovery by integrating quantitative training with evidence-based teaching methods. I apply (and iterate upon) this evidence-based approach because I believe that science should be inclusive of all students, and scientific teaching methods have great potential to improve equity in science education. I have applied these approaches in large classes of 40+ students (*e.g.*, *Evolutionary Genetics* at SJSU) and small seminars (*e.g.*, *Computational Evolutionary Genomics* at UCSF).

Evidence-based approaches to student-centered learning

As an NIH IRACDA fellow, I have trained in effective teaching methods such as "backwards design" and active learning. I design new courses by first developing detailed learning objectives, then writing assessments that reflect these objectives, and finally tailoring course content and activities. This backwards design approach has been argued to improve course organization, facilitate the measurement of student progress, and improve learning outcomes. Learning objectives in my courses typically involve mastering core biological and evolutionary concepts, developing quantitative skills, and asking scientifically meaningful questions that can be translated into testable hypotheses. In support of detailed learning objectives, I combine short lectures with active learning methods, including both low-tech approaches (*e.g.*, peer discussion) and high-tech tools (*e.g.*, clickers or computer simulations).

As an instructor for Biology 160 (Ecology) at San Jose State, I regularly designed "think-pair-share" activities, in which students are prompted to independently ponder a question or problem, discuss their ideas with a partner, and finally report back to the class. This method affords students the opportunity to actively engage with the material and potentially correct misconceptions through peer collaboration, and is broadly applicable in both large and small classes. Moreover, the think-pair-share method encourages participation by students who are not regular speakers in class, and may help to make the learning environment more equitable (*1*). Several students expressed positive opinions of these activities in student evaluations of my teaching (*e.g.*, one student wrote that I "highlighted key concepts to know in each lecture along with think-pair and share questions which enhanced my learning, understanding and thinking." Reviews are summarized in Fig. 1). Other examples of learning objectives met through active learning in my classes include:

- *Interpreting scientific data*: In *Evolutionary genetics* at SJSU, I introduced the students to fundamental evolutionary concepts such as inheritance and natural selection through an in-class activity focused on sexual dimorphism of response to infection. Field observations and molecular data (taken from classic papers) allowed the students to generate hypotheses for the evolution of dimorphism, and to employ concrete evolutionary thinking early in the course.

- *Engaging students with current examples*: I created an in-class activity with my colleague Prof. Leslee Parr that focused on the evolutionary and ethical implications of human genetic modification. The students listened to a short podcast on CRISPR, and then participated in a debate over its use in humans. A large proportion of the students participated in the debate, arguing both for and against altering germline DNA.

- *Hands-on coding and algorithm development*: In a *Computational evolutionary genomics* course at UCSF, I taught weekly classes to extend and solidify core concepts through hands-on software development, group exercises, and breakout discussions. The students in this course very kindly recognized my dedication through positive reviews, resulting in my receipt of a Teaching Assistant Excellence Award at UCSF.

A central challenge in teaching computational genomics is that many students experience math anxiety. Moreover, stereotype threat can negatively affect the classroom experiences of students from under-represented groups in science (*2*), and this effect can be especially pronounced in quantitative contexts. Creating an equitable learning environment requires instructors to implement learning strategies to ameliorate the effects of stereotype threat and math anxiety. I am particularly excited about two promising techniques, known as "values affirmation" (*3*) and "scientist spotlights" (*4*). In values affirmation, students reflect on the values that are most important to them before completing an assessment, while scientist spotlights highlight the life stories and accomplishments of diverse scientists working in computational biology (or other fields). These methods have been shown to improve the performance of students from under-represented groups in quantitative fields and help students see

themselves as future scientists. Combining these approaches with bioinformatic modules has the potential to make quantitative learning more equitable across diverse groups of students.

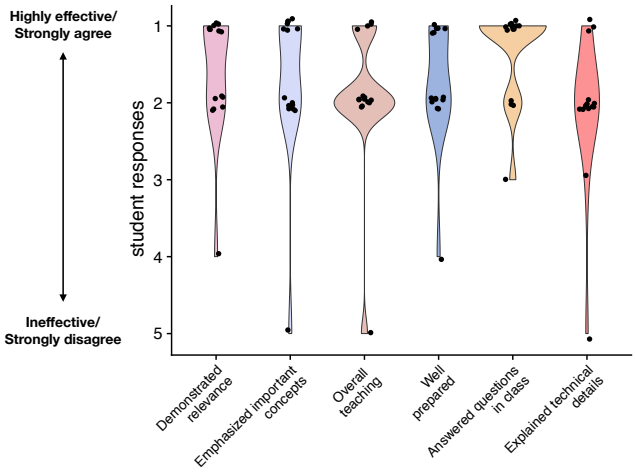

Figure 1: Data from course evaluations in Biology 160 (Ecology), which I co-instructed at SJSU in the Fall of 2017. 15 Students completed the reviews – the data points encode individual student responses, with the violin plots representing the shape of the distribution. Students responded on a five point scale from "strongly agree/highly effective" (1) to "strongly disagree/highly ineffective" (5). Student written comments (each from a different student) included "Very knowledgeable and passionate about subjects", "demonstrated vast knowledge of the plant and environmental subjects that he taught to the class", and "Took time to answer student's questions and ensure we understood slides." *Note that these reviews are specific to me, as my co-instructor was reviewed separately.*

Supporting students of diverse backgrounds

I believe that equity in science is one of the most pressing issues that must be solved by my generation of scientists. As an NIH IRACDA fellow, I studied the systemic barriers that have often limited (or prohibited) the participation of women, people of color, and other under-represented groups in science. I also studied many approaches that can promote equity within and beyond the classroom. My commitment to equity in science has been expressed through implementation of these approaches in my teaching, scholarship, mentorship, and service.

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Courses at Tufts University

I am prepared and excited to contribute to a wide range of existing courses in computational biology, bioinformatics, evolution, and genetics, depending on departmental needs. In addition, I am motivated to develop new upper-level courses that will complement the existing curriculum. One potential upper-level seminar course would focus on critical reading of papers in evolutionary genomics, and how peer review can shape the dissemination of scientific results. The course would simultaneously develop a conceptual basis for understanding and analyzing the scientific evidence presented in contemporary papers along with the skills needed to read these papers critically. With several peer-reviewed journals now publishing scientific reviews and journal correspondence along with the published papers (*e.g.*, *eLife* and *PeerJ*), there is an excellent opportunity for students to see the peer review process through the eyes of scientists, and to examine whether their methodological critiques align with those of more seasoned colleagues. I am currently compiling a list of published papers and accompanying reviews that could be used in this capacity.

In all of my future teaching endeavors, I will draw on my training in genomics, computational biology, evolution, and scientific teaching to challenge students to grapple with difficult concepts in biology. I am tremendously excited to interact with students in the classroom, and look forward to learning along with them.

1. K. D. Tanner, *CBE—Life Sciences Education* **12**, 322 (2013).

2. C. M. Steele, J. Aronson, *Journal of Personality and Social Psychology* **69**, 797 (1995).

3. A. Miyake, *et al.*, *Science* **330**, 1234 (2010).

4. J. N. Schinske, H. Perkins, A. Snyder, M. Wyer, *CBE—Life Sciences Education* **15**, ar47 (2016).

5. S. K. Dung, *et al.*, *Genetics* **211**, 363 (2019).

6. A. L. Severson‡, **L.H. Uricchio**‡, I. M. Arbisser‡, E. C. Glassberg, N. A. Rosenberg, *Theoretical Population Biology* **127**, 1 (2019).

7. **L.H. Uricchio**‡, H. C. Kitano‡, A. Gusev, N. A. Zaitlen, *Evolution Letters* **3**, 69 (2019).

My research revolves around the questions that first drew me to ecology and evolution: why do we observe such tremendous variation within and between species, and how do species respond to changes in their biotic environment? My lab will:

- Investigate how ecological & evolutionary processes affect adaptation rates using comparative genomic data
- Develop novel QTL-mapping techniques that are informed by evolutionary principles
- Analyze eco-evolutionary models to predict how demographic processes affect adaptation in invasive species

What are the ecological and evolutionary factors driving adaptation across species?

Darwinian selection has been hugely successful as a conceptual framework to explain the diversification of life on Earth, but we are only beginning to develop a mechanistic understanding of how selection shapes species at the genetic level. For example, we still know relatively little about the rate and strength of adaptation across species, and almost nothing about the environmental and ecological factors that determine the rate of adaptation. Developing a mechanistic understanding of the determinants of adaptation is crucially important, because it remains unclear how quickly species will adapt to rapid anthropogenically-driven changes. In part, limitations in our current knowledge of adaptation rates are driven by the use of simple bioinformatic tools and conceptual models that make biologically unrealistic assumptions. My work extends these simple models to better capture realistic evolutionary complexity and improve the accuracy of adaptation rate inference.

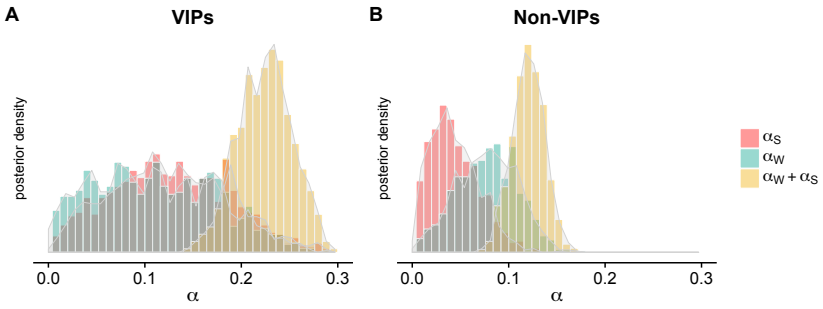

Figure 1: I developed a method to estimate adaptation rate (α) from genomic data that partitions weakly (α_W) from strongly beneficial (α_S) variation. I separately estimated α_W and α_S for proteins that interact with viruses (VIPs) and those that do not (non-VIPs). The larger α_S and $\alpha_S + \alpha_W$ in VIPs suggests that viruses have been an important driver of adaptation in humans.

Recently, I developed a novel approach to adaptation rate estimation that relaxes the simplistic assumptions of previous methods and provides new biological insights into the biotic environmental drivers of adaptation (*1*). Existing methods implicitly assume that beneficial alleles are rarely variable within populations since they tend to rise to high frequency very quickly. In contrast, if weak adaptation is common, beneficial alleles will proceed to high frequency slowly and are likely to appear as variable in sequencing datasets. Using simulations, I found that existing methods tend to underestimate adaptation rate when adaptation is weak – I then developed a new method that extends the existing models to account for mutation of weakly-beneficial alleles. I applied my approach to human genetic data, and found that a model with a high rate of weak adaptation best fits the observed genetic data. Interestingly, the subset of human proteins that are known to interact with viruses supported both stronger adaptation signals and a higher overall rate of adaptation (Fig. 1). These results help to clarify why many previous studies have found surprisingly low estimates of adaptation rate in humans and primates, and provide insight into the fitness costs induced by viral infection.

As a complement to genomic sequence data, large-scale datasets encoding the genetic basis for polygenic traits provide an opportunity to investigate how environmental changes may shape variation in traits under selection. Since selection tends to favor individuals with particular trait values, it is likely to shape the distribution of allele frequencies of trait-altering alleles. Moreover, changes in environment may alter the selection pressures on traits, potentially leaving detectable signatures in the data from association studies. During my postdoc, I developed new software tools that detect the impact of selection on polygenic traits and applied them to human trait data as a proof of principle. I found evidence that shifts in selection pressures on ancestral humans may have altered the relationship between evolutionary fitness and polygenic phenotypes (*e.g.*, BMI and Crohn's disease) (*2*). Ecological genomicists are generating numerous datasets that shed light on the genome-wide basis for heritable traits – such datasets could be readily applied within my inference framework to study the impact of environmental changes on trait distributions across species.

How does selection shape complex phenotypes?

The past twenty years have seen a remarkable burst of progress in our understanding of genetic variation in humans and other species, and many studies have now attempted to map the genetic basis for various complex traits. Nonetheless, the field has been unsuccessful in finding the majority of the causal genetic variants that contribute to phenotypic variation. This problem is sometimes called "missing heritability".

My research applies evolutionary principles to the missing heritability problem. In particular, I use evolutionary models to study the circumstances under which rare alleles can drive substantial variation in common diseases, and I develop bioinformatic methods for studying the evolution of complex traits. Key findings of this work include: a) simple evolutionary models of selection and demography predict that rare variants may contribute substantially to trait variation (*3–5*), b) when selection acts on traits, existing genetic association tools struggle to discover causal variation even in large samples (Fig. 1), and c) genetic variation underlying many human phenotypes, including biomedically relevant traits such as Crohn's disease and RNA expression, harbors evidence for recent natural selection and rare alleles of large effect (*2, 6*). I recently reviewed progress and opportunities for advances in this field (*7*). I suggest that a focus on new statistical tools that leverage our growing knowledge of evolutionary processes will maximize our potential to solve the missing heritability problem. My lab will be well situated to develop such tools and deploy them widely across phenotypes in large, diverse cohorts such as TOPMed.

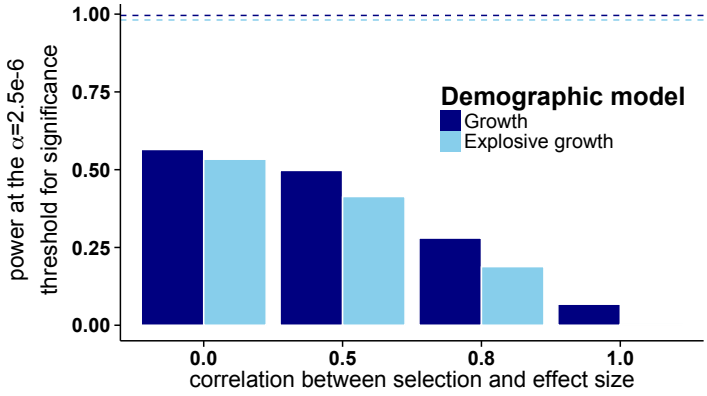

Figure 2: Power (*i.e.*, the probability of detecting a disease-causing locus) for various human evolutionary models inferred from human sequence data. Direct selection on the causal variation for the trait results in a large correlation between selection and effect size, and decreases the ability to detect the causal basis for the trait. Appropriately accounting for human explosive growth (light blue) further reduces power relative to a slower growth model (dark blue). Failing to account for selection results in an overly optimistic estimate of statistical power (dashed horizontal lines). (*Image adapted from (5)*).

How do human disturbances alter ecological interactions in "pristine" systems?

The potential for ecological processes – such as niche differentiation – to explain biodiversity maintenance has attracted much recent attention. However, many previous studies seeking to characterize the ecological processes that can explain coexistence were performed in "pristine" communities in which species have co-occurred over long evolutionary timescales, or in communities with only a few species. My research seeks to address these limitations by asking 1) are the ecological processes shaping invaded communities fundamentally different from "pristine" communities? and 2) how do multi-species outcomes differ from the predictions of models with very few species?

Together with my postdoc co-advisor Erin Mordecai, I used data from experimental competition plots in Jasper Ridge Biological Preserve to measure seed output and demographic rates across a range of competitor densities. I estimated the effect of competition on each species' growth rate and predicted how species composition is likely to change over time in this community. Our results reveal complex outcomes in which no single species is able to dominate (*8*), and the predicted species composition depends on order of arrival (*i.e.*, a priority effect). Interestingly, the strongest priority effects occur between exotic species, but have important implications for the fate of native competitors. Each native species is more likely to persist in combination with a particular exotic species, implying that competition between exotic species modifies the expected outcome of competition between native species. At least one exotic species is predicted to persist with high probability, while California native species persist in only about 20% of the predicted outcomes (Fig. 1). Our results provide a contrast to the earlier studies in pristine systems, and suggest that complex multispecies dynamics may emerge in recently

invaded systems in which species do not have long co-evolutionary histories.

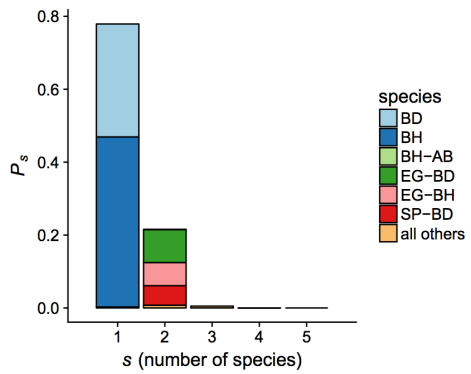

Figure 3: I used data-driven models to predict the most likely outcomes of competition in a system of exotic (AB, BD, and BH) and native (EG and SP) grass species. The x-axis shows the predicted number of species (s) that persist, while the y-axis represents the proportion of simulations that resulted in this outcome (P_s). Each bar is colored by the species composition of the predicted community. In most replicates, exotic species exclude California natives. The next most likely outcome involves coexistence of one native species with one exotic species. The uncertainty in the predicted outcomes is largely driven by randomness in the order of arrival of the exotic species. (Species codes: *Stipa pulchra* (SP), *Elymus glaucus* (EG), *Avena barbata* (AB), *Bromus hordeaceus* (BH), and *Bromus diandrus* (BD)).

Future research directions

1. *Inferring adaptation rates across species.* My postdoc work shows that weak adaptation is likely to be common in humans (*1*), but it is unclear if weak adaptation is common across species. If weak adaptation is common, it could alter our view of the effects of climate change on climate-sensitive species, since adaptation will be driven by alleles that are already polymorphic, and individual alleles will contribute small fitness gains. With genomic data now publicly available from a wide range of relevant species (including plants, birds, mammals, and insects), it is feasible to extend my approach and to test which species support signatures of weak adaptation. By analyzing a diverse set of species, it will be possible to investigate the evolutionary and ecological drivers of adaptation rate, which have been hypothesized to include population size, recombination rate, position in the food web, and rate of pathogen spillover.

2. *Applying evolutionary theory to improve the detection of causal variation.* Existing approaches to detecting casual variation for complex traits are highly sensitive to evolutionary history (*3, 5, 6*). The central problem is that these approaches make assumptions about how causal variation is distributed within and across populations that are inconsistent with evolutionary theory (*7*). This presents a major opportunity to develop novel genetic association techniques based on evolutionary principles (*2, 6*) to improve the rate of discovery of quantitative trait loci in the genomes of humans and other species.

3. *Conservation genomics and modeling selection in declining populations*: My postdoctoral work on exotic plant invasions makes testable predictions about species composition over time (*8*), but we know relatively little about how invasions affect evolutionary robustness to future challenges. The selection pressures induced by competition with invasive plants may differ drastically from those experienced during recent evolutionary history, potentially leading to increases in the frequency of traits that were beneficial during the population decline, but deleterious in natural habitats. My lab will develop eco-evolutionary models that combine polygenic selection and population demography to better understand how brief but intense selection gradients affect future adaptation and population robustness. Collecting genomic (and transcriptomic) time-series data from communities with ongoing invasions could additionally clarify how adaptation contributes to species composition and robustness in systems undergoing rapid change.

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