BIOGRAPHICAL SKETCH			
NAME Daniel S. Fisher		POSITION TITLE David Starr Jordan Professor of Science	
eRA COMMONS USER NAME			
EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Cornell University	B.A.	1975	Mathematics and Physics
Cambridge University		1975-76	Churchill Scholar
Harvard University	A.M.	1978	Physics
Harvard University	Ph.D.	1979	Physics

A. Personal Statement

I am a theoretical physicist who spent much of my career working in a wide range of areas of condensed matter physics, particularly non-linear and collective dynamical phenomena including exotic low temperature phases of matter, spin-glasses and other disordered materials, nano-scale quantum mechanical transport, superconductivity, fracture, and earthquakes. Over the past fifteen years my primary interests have turned to biology, including cellular biophysics and neuroscience. But my primary focus has been on developing quantitative understanding of evolutionary dynamics -- of microbial populations, the adaptive immune system, and most recently, cancer. This research has involved, in an essential way, a combination of theory, mathematical modeling -- both abstract and biologicallly concrete -- close collaborations with experimental groups, and development of means for extracting useful information and understanding from deep sequencing of environmental and laboratory microbial populations, and immune repertoires. My extensive experience as a broad statistical physicist has been invaluable for my research in biology.

Over three decades as a professor I have trained many outstanding PhD students almost all of whom have gone on to academic research careers at top institutions, including Harvard (two), Cal Tech, UCSB, UCSC, Emory, Syracuse (two), and Universities of Chicago, Wisconsin, Texas, Colorado, Paris, and Athens. Although I do not have an experimental laboratory, I have been the primary advisor of a number of students and postdocs working on both theory and experiments in biology, several of whom have gone on to become leading experimental biologists, including the two faculty at Harvard and others now faculty at Duke, UCSD, and Cambridge. In addition, although I have not published in neuroscience, I have been the secondary advisor for four theoretical neuroscience PhD students.

B. Positions and Honors.

Positions

1979-90: AT&T Bell Laboratories, Member of Technical Staff, Theoretical Physics
1987-90: Princeton University, Professor of Physics and Applied & Computational Mathematics
1990-2007: Harvard University, Professor of Physics and Applied Physics
2007-present: Stanford University, Professor of Applied Physics and, by Courtesy, of Biology and of Bioengineering

Selected Other Activities

- Gordon Research Conference, Chair, 1986
- NSF Institute for Theoretical Physics, UCSB, Chair of Advisory Board, 1990-91
- Bauer Center for Genomics Research, Harvard, Fellows Selection and Advisory Committee, 2000-06
- Center for Brain Science, Harvard, Head of Planning and Faculty Search for 2001
- Canter for Non-Linear Studies, Los Alamos Nat'l Lab, External Advisory Committee, 2008-10
- James Simons Foundation, advisor on Simons Investigators program and development of Mathematical Modeling of Living Systems program, 2011-15
- Paul Allen Foundation, Advisory Group on New Frontiers in Biosciences, 2013 & 2015
- Board on Physics and Astronomy, National Academies of Science, Engineering, and Medicine, 2015-18

Selected Honors

- Bergman Memorial Award, 1985
- Fellow of American Physical Society, 1986

- Exceptional Contribution Award, AT&T Bell Laboratories, 1986
- Sloan Research Fellow, 1988-92
- Fellow of American Academy of Arts and Sciences, 1999
- Onsager Prize of American Physical Society, 2013
- Member, National Academy of Sciences, 2015

C. Contributions to Science

1. Theory of evolutionary dynamics of large populations.

In large microbial populations, many beneficial mutations arise each generation and the fitter mutant lineages compete with each other and accumulate further beneficial mutations before any of them can fix in the population. The complex interplay between clonal interference and accumulation of multiple mutations is exceptionally difficult to analyze and simulations are of only limited utility as keeping track of the diversity is not possible even for population sizes reachable in laboratory experiments, and, even if this could be done, understanding which features are universal within broad classes of models and which particular to the details of the model simulated would not be possible. Thus frameworks for undersanding universality brought from physics as well as development of new methods have been crucial.

My research on asexual poulations began with the thesis work of Michael Desai which analyzed the simplest model, and continued with showing the generality of the results and, most interestingly, the statistics and dynamics of the genetic diversity created and maintained in large continually evolving populations. Some of the predicted features of the diversity have since been seen in sequencing from the long term evolution experiments of Richard Lenski's group as well as in HIV evolution in individual humans. These clearly show the differences between the conventional picture of mostly neutral evolution punctuated by occasional selective sweeps, and the continual evolution picture in which large populations explore many evoltuionary directions in parallel.

The effects of recombination on the evolutionary dynamics of large populations is highly complex as it involves the interplay between the largely-asexual accumulation of mutations on single genomes, and recombination between anomalously fit genomes that are anomalously far apart genetically so that their luckiest offsping can become the fittest individuals in the population. A key step in understanding how recombination increases rates of adaptation was carried out with two physicist collaborators, and further work is now in preparation on the effects of extremely low rates of genetic exchange relevant for bacterial and some viral populations. This latter shows how a recombination rate that is only of order an inverse power of the population size can already dramatically change the evolvability.

a. Aleksandra Walczak, Michael M. Desai, and **Daniel S. Fisher**, (2013) Genetic Diversity and the Structure of Genealogies in Rapidly Adapting Populations, *Genetics* 193, 565-585
b. Richard A. Neher, Boris I. Shraiman, and **Daniel S. Fisher** , (2010) Rate of Adaptation in Large Sexual Populations. *Genetics* **184**, 467 – 481. PMCID: PMC2828726
c. Oskar Hallatschek and **Daniel S Fisher**, (2014) The Acceleration of Evolutionary Spread by Long-range Dispersal, PNAS 111, E4911ÐE4919

2. Laboratory evolution experiments

With several experimental collaborators, I have been involved in experimental projects that broke completely new ground in control and depth of measurements in laboratory evolution experiments. I initiated a collaboration with Andrew Murray to test the quantitative predictions of the theory that Michael Desai and I had developed on how the rates of adaptation and distribution of fitness within a population depended on population size and mutation rate. The experiments were also carried out by Desai, our to-become joint student who is now a star in the field (and – highly unusually -- training both theory and experimental students).

With Gavin Sherlock, Sasha Levy, and Dmitri Petrov, my group, especially a joint postdoc Jamie Blundell, developed the theory and means of analysis needed to understand the mutational and selection dynamics of half a million barcoded lineages as they acquired beneficial mutations – the first development and extensive use of DNA barcoding and extremely deep sequencing. This collaboration has continued in multple directions and several involved and others are starting to use the tools developed for studying dynamics of cancers.

In a more exploratory project, I initiated a collaboration with Tad Fukami on the evolution of "niche construction" whereby populations modify their environment to change their competitive fitness against

other types. We found that, starting from a single clone, *Pseudomanas fluoroescens* rapidly evolved several types with complex interactions illustrating how rapidly ecology can emerge even in the simplest of selective conditions. Hints of subtle ecological interactions developing rapidly in other evolution experiments has been one of the motivations for my group's developing theoretical work on evolution of microbial ecological diversification.

a. Michael M. Desai, **Daniel S. Fisher**, and Andrew W. Murray (2007). The Speed of Evolution and Maintenance of Variation in Asexual Populations. *Current Biology* **17**, 385-394. PMCID: PMC2987722
b. Sasha Levy, Jamie Blundell, Sandeep Venkataram, Dmitri Petrov, **Daniel S Fisher** and Gavin Sherlock, (2015) Quantitative Evolutionary Dynamics Using High-Resolution Lineage Tracking, *Nature* 519, 181–186

3. Dynamics of bacterial circadian clocks

The cyanobacterium, *Synechococcus elongatus,* has a remarkably precise cell-autonomous circadian clock whose core is a three protein oscillator that can be reconstitutued and functions well *in vitro.* Although some of the basic interactions between the component proteins were known and the key role of a phosphorylation de-phosphorylation cycle in hexamers of the KaiC protein already investigated, I showed that the known interactions and model could not possibly result in sustained oscillations. I conjectured that the crucial missing feature was a special role of singly-phosphorylated KaiC in inhibiting further phosphorylations and developed a simple model of relaxation-oscillator-like dynamics based on this conjecture. I then interested Erin O'Shea in initiating a program to measure the essential dynamics of the four different, heretofore indistinguishable, phosphoforms of KaiC. With one minor modification from the preliminary experimental data, the predictions of the basic model were supported by the experiments and it provided a frameowrk for guiding further experiments in our collaboration and many more since. This is a now classic example of how theory can drive experiments in cellular biophysics.

4. Fine-scale diversity of environmental microbial populations

Studying microbial populations by amplifying, sequencing, and analyzing conserved portions of their genomes, most commonly 16S rRNA, is extensively used. But for studying within species strain diversity, it is very difficult to disentangle such fine-scale diversity from amplification and sequencing errors. With a collaborator Devaki Bhaya, we were interested in studying the diversity of a single thermophillic *Synechococcus* species in a Yellowstone hot sping, for which her group had genomes of two isolates, metagenomic data, and ~ 200 amplified and deeply sequenced regions of the genomes. Finding that existing state-of-the art algorithms for error correction were woefully inadequate for the task, we developed our own algorithm, DADA, which was further developed by Susan Holmes' group into a now-becoming widely used tool, DADA2, considered the best for a wide range of applications.

The scientific investigations, which to extract the maximum information required using much additional biological information and other statistical methods and models developed for the purpose: these led to striking discoveries. The first paper showed that the population has such a high rate of homologous recombination that linkage correlations only extend tens of bases along the genome. And the frequency correlations between synonymous polymorphisms gave hints of the evolutionary dynamics of the population being inconsistent with neutral drift but consistent with our predictions from dynamics driven by extensive hitchhiking. A second soon-to-be-submitted paper carries out extensive analysis of the diversity and considers potential evolutionary/ecological scenarios that could potentially explain it, showing that there are problems with all of these – but the inconsistencies would not have been discovered by any conventional analyses.

5. Physics of disordered systems

One of my main contributions to physics is the development of understanding of the roles of randomness – disorder in the structure of materials - in a wide range of contexts. For this body of work I was awarded the Onsager Prize, the top American-awarded prize in statistical physics.

D. Research Support.

ACTIVE

R01 GM110275 (Gavin Sherlock, PI) 5/10/2014 – 2/28/2018
NIH NIGMS
Systematic Molecular Analysis of Antagonistic Pleiotropy
Role: Co-Investigator
Major goals: characterization of the extent and role of antagonistic pleiotropy in evolution, and determining at a molecular level how lineages carrying an antagonistically pleiotropic allele can escape from its deleterious effects.

2U2C2015-003 1/1/2016 – 12/31/2018
Stand Up to Cancer/Memorial Sloan-Kettering Cancer Center (Ross Levine, PI)
The Genetic, Epigenetic & Immunological Underpinnings of Cancer Evolution through Treatment
Role: Co-Investigator
Major Goals: Modeling evolutionary processes underlying development of drug resistance in cancers, with focus on AML and EGFR lung cancers

1545840 6/15/2016 – 5/31/2019
National Science Foundation
Collaborative Research: The genetic, epigenetic, and immunological underpinnings of cancer evolution through treatment
Role: PI
Major Goals: Modeling evolutionary processes underlying development of drug resistance in cancers, with focus on AML and EGFR lung cancers

PHY-1607606 9/15/2016 – 8/31/2021
National Science Foundation
Evolutionary Dynamics and Diversity in High Dimensions
Role: PI
Major Goals: Theoretical development of models for understanding fine-scale microbial diversity and evolutionary dynamics together with analysis and modeling of data on sequencing of environmental microbial populations.

COMPLETED

DMS-1120699 9/15/2011 - 8/31/2014
National Science Foundation
Deep Sequencing of Microbial Populations: Disentangling Diversity, Dynamics and Errors
Role: PI
Major Goals: Developing methods for analyzing and extracting useful information from deep sequencing data and applying these to thermophillic cyanobacterail populations

PHY-1305433 9/1/2013 – 8/31/2017
National Science Foundation
Recombination, Genetic Interactions, and Observable Evolutionary Dynamics
Role: PI
The major goal of this project is analyzes models of the evolutionary dynamics of large microbial populations especially the effects of recombination and epistatic interations between mutations.