BIOGRAPHICAL SKETCH

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NAME: Petrov, Dmitri A.

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POSITION TITLE: Michelle and Kevin Douglas Professor of Biology, Dept. of Biology, Stanford University

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Moscow Institute of Physics and Technology, Moscow Russia	M. Sc.	6/1989	Physics and Biology
Harvard University, Cambridge, MA	Ph.D.	6/1997	Evolutionary Biology
Harvard University Society of Fellows, Cambridge, MA		8/2000	Evolutionary Biology
Harvard Medical School Research Fellow, Boston, MA		8/2000	Genetics

A. Personal Statement

My research has focused on understanding the basic forces in evolution such as mutation, recombination, and natural selection. I started my career in physics, continued to classical and molecular genetics, and received my Ph.D. in evolutionary biology and genetics. My broad training allows me to run a laboratory that combines theoretical, computational, and experimental approaches in a range of organisms including yeast, viruses, *Drosophila*, mouse models of cancer, and humans. I started as an Assistant Professor in the Department of Biological Sciences at Stanford in 2000, was promoted to Associate Professor (with tenure) in 2005, to Professor in 2009, and to Endowed Chair in 2011. **My current research program remains broad in the array of approaches and study systems employed, but with a specific focus on uncovering the dynamics of rapid evolutionary adaptation**. We quantify rapid adaptation in a variety of systems using state of the art measuring techniques. We carry out this work both in the lab using experimental evolution in yeast and mouse models of cancer and in the field using Drosophila semi-natural field experiments and samples from the natural populations. **My lab has been productive with 53 published papers as well as 11 biorxiv preprints that are currently in review in the last 5 years (since 2015).** These papers have already been cited ~2000 times with 20 papers cited more than 30 times each.

My key focus is on training of students and postdocs. **14 out of 18 former postdoctoral scholars in the lab hold tenure-track or tenured faculty positions with the other 4 working as scientists in the biotech industry and national labs.**

I have been active in the evolutionary and population genetics community. I would specifically mention my role in founding and running as co-chair all three Population, Evolutionary, and Quantitative Genetics (PEQG) conferences (2016, 2018, and 2020). This is the first GSA-sponsored conference based on a topic rather than on an organism and has been very well received. I hope it will continue for many years to come. I have also founded and run over 20 Bay Area Population Genomics (BAPG) conferences that bring ~150 researchers from around the Bay Area to one of the local Universities twice a year. BAPG focuses on the research of graduate students and postdocs and introduces faculty who recently moved to the area to the local community. I have raised funds from local companies and managed to keep the conference entirely free for the participants. I have also been a permanent member and currently serve as the chair of the GVE study section.

Google Scholar: https://scholar.google.com/citations?hl=en&user=Kh9REfEAAAAJ **(h = 69, i10 = 143)**

B. Positions and Honors

1989-1990	Junior Scientist, Institute of Molecular Genetics, Moscow
1990-1992	Research Assistant, Washington University, Department of Genetics
1997-2000	Junior Fellow, Harvard University Society of Fellows
1998-2000	Research Fellow, Department of Genetics, Harvard Medical School
2000-2005	Assistant Professor, Department of Biological Sciences, Stanford University
2005-2009	Associate Professor, Department of Biology, Stanford University
2009-2011	Professor, Department of Biology, Stanford University
2011-now	Michelle and Kevin Douglas Professor, Department of Biology, Stanford University
2014-2020	Associate Chair, Department of Biology, Stanford University
2016-now	Director, Program for Conservation Genomics, Center for Comp. Evol. & Human Genomics

Honors:

1995-1997	Teaching excellence awards (1995 twice, 1997), Harvard University
1996	Walter Fitch Prize for Best Student Paper, SMBE, Tucson, Arizona
1998	Harvard University William F. Milton Fund Award
2003	Alfred P. Sloan Foundation Research Fellow
2003	Terman Award, Stanford University
2005	Hellman Faculty Award
2008	Chambers Fellow
2013	Walter P. Kistler Prize and Research Award in Population Genetics and Society

C. Contributions to Science – focus on last 5 years (members of the Petrov Lab are listed in bold)

Below I focus on topics that we have been actively pursuing over the past 5 years. I will thus not mention our previous work focused on transposable elements and genome evolution (evolution of genome size, mutational rates and biases, and GC content). I will also not discuss the work on the evolution of codon bias.

1. Inference of rate and dynamics of adaptation from genomic data.

Adaptation by natural selection is the central process in evolution. Although the principles of adaptation by natural selection have been long established, the extent to which specific traits have been shaped by natural selection remains unknown. These questions remain particularly controversial at the level of molecular evolution. The dominant model of molecular evolution, the Neutral Theory, states that practically all polymorphisms within populations and substitutions between species are due to neutral mutations, with natural selection relegated to the weeding out of deleterious mutations.

My lab contributed to establishing that molecular adaptation is much more common and consequential than previously appreciated. We were first to use whole-genome polymorphism data to demonstrate that regions of high functional (nonsynonymous) divergence harbor surprisingly low levels of neutral (synonymous) polymorphism. This pattern is difficult to explain under the assumptions of the Neutral Theory, but is fully predicted if recurrent adaptation is common. We used these patterns to infer that adaptation in Drosophila is not only frequent, but is commonly driven by strong selection, with selection coefficients on the order of 1% of even larger.

Macpherson, J.M. *, Sella, G. *, **Davis, J.C.**, and **D. A. Petrov**. (2007). Genomewide spatial correspondence between nonsynonymous divergence and neutral polymorphism reveals extensive adaptation in Drosophila. *Genetics*, **177**, 2083-2099. (*these authors contributed equally)

We also detected signatures of abundant and recurrent selective sweeps in humans and showed that previous failed attempts were due to the confounding effect of background selection in functionally rich regions. We further used the variation in background selection to quantify *both* the strength and rate of adaptive evolution in the human genome as well as developed the asymptotic McDonald-Kreitman test that accurately estimates rates of adaptation in the face of the confounding effects of slightly deleterious mutations.

Much of our recent effort went to using genomic data to pinpoint the **causes of adaptation** with a particular focus on the role of viruses and other pathogens in the human evolution specifically and mammalian evolution more broadly. We have argued that viruses in particular have been an exceptionally powerful driver of adaptive molecular evolution including driving adaptive introgression between modern and archaic humans.

Enard, D., **Cai, L**., Gwennap, C., and **Petrov, D.A.** Viruses are a dominant driver of protein adaptation in mammals. (2016). *Elife*, **5**:e12469

Most approaches to detecting cases of genomic adaptation by *de novo* mutations had assumed a model of hard selective sweeps that involved a single sweeping adaptive mutations. We decided to test this model by closely investigating known cases of contemporaneous adaptation, specifically that of evolved resistance to pesticides. Our study of evolution at the target of organophosphate pesticides, *Ace*, in *D. melanogaster* demonstrated that adaptation was in fact driven not by a single mutation in a hard selective sweep, but rather by multiple co-occurring and simultaneously sweeping adaptive mutations in a pattern known as a soft sweep. We argue that this demonstrates that adaptation in *D. melanogaster* is not limited by mutation, implying a much larger current effective population size relevant to strong adaptation than what is implied by long-term averaged levels of neutral variation. It also demonstrated that complex adaptations can arise rapidly even when they require multiple mutations.

Karasov, T.*, Messer, P.*, and D.A. Petrov. (2010). Evidence that adaptation in Drosophila is not limited by mutation at single sites. *PLoS Genetics* 6: e1000924; (* contributed equally).

Motivated by these observations, we focused on developing theory of soft selective sweeps, devising statistics to detect both hard and soft sweeps in genomic data, and validating theory and empirical results with positive controls of known adaptation. We developed a suite of haplotype statistic (H12, H2/H1 and H) and used them to demonstrate that recent and strong adaptive events in *D. melanogaster* left signatures of soft selective sweeps. Using genomic data to quantify dynamics and modes of adaptation precisely and comprehensively remains the central focus of my lab.

Garud, N. Messer, P.W., Buzbas, E., and **Petrov, D.A.** (2015). Evidence that selective sweeps in *Drosophila melanogaster* are primarily soft. *PLoS Genetics*, **11**: e1005004.

2. Rapid evolution on seasonal scales in Drosophila.

Although adaptation is often believed to be a slow process, there is abundant evidence that adaptation can be rapid, at times occurring on scales of just a few generations and thus interacting with ecological processes. *D. melanogaster* is a case in point, with populations appearing to evolve substantially over the course of a single season, from Spring to Fall. Spring flies tend to have lower rates of reproduction than Fall flies, but have comparatively greater ability to survive stress and have a longer life span. In collaboration with the lab of Paul Schmidt at U. Penn, we are mapping rapid adaptation on seasonal timescales at the genomic level and discovered that hundreds of polymorphisms recurrently shift in frequency possibly by as much as 20% from Fall to Spring and back. Most of the seasonal polymorphisms appear very old, with some even shared with *D. simulans*, indicative of long-term balancing selection. These data challenge the current dogma that highly polygenic adaptation must be driven by mutations of weak effect. Understanding of the nature of these long-term balanced alleles should shed much light on the process of adaptation and on the maintenance of fitness-related variation in populations.

Bergland, A.O, Behrman, E.L., O'Brien, K.R., Schmidt, P.S., and **Petrov, D.A.** (2014). Genomic evidence of rapid and stable adaptive oscillations over seasonal time scales in Drosophila. *PLoS Genetics*, **10**: e1004775.

We have replicated this finding by studying seasonal evolution across 20 populations across the North America and Europe. Further we were able to determine that particularly hot summers and particularly cold falls at specific locations can shift the direction of adaptive response.

Machado*, H.E., Bergland*, A.O., **Taylor, R**., **Tilk, S**., Behrman, E., Dyer, K., Fabian, D.K, Flatt, T., Gonzalez, J., Karasov, T.L., Kozeretska, I., Lazzaro B.P., Merritt, T.J.S., O'Brien, K., Rajpurohit, S., Roy, P.R., Schaeffer, S.W., Schmidt, P.**#** and **D. A. Petrov#**. Broad geographic sampling reveals predictable and pervasive seasonal adaptation in Drosophila. *Elife*, (in revision); (* and # - contributed equally); on Biorxiv.

The study of seasonal adaptation in natural populations is an essential component of this work. However, it is necessarily limited in assigning causality specifically to natural selection as it is virtually impossible to prevent the possibility of local migration. It is also limited in terms of replication. To address these problems, we collaborate with Paul Schmidt who established an experimental orchard which contains now more than 60 large cages capable of supporting populations of Drosophila of up to 200,000 individuals in each cage. Using these cages Paul's and our labs are dissecting the phenotypic and genomic basis of adaptation on monthly timescales and are establishing the existence of rapid adaptive tracking in response to momentary ecological and environmental pressures. The focus on the understanding of adaptive dynamics in these semi-natural populations is the key part of our research focus for the next 5 years.

3. Quantification of adaptation using high-resolution lineage tracking in *S. cerevisiae*.

The key problem in studying adaptation is that of small numbers. We often do not have enough repeated trials of adaptation and do not capture enough well-defined adaptive events to build a predictive theory. Instead the field has had to rely primarily on individual examples. In collaboration with the labs of Gavin Sherlock and Daniel Fisher, my lab co-developed a high-throughput system for studying adaptation using experimental evolution of *S. cerevisiae* with ultra-diverse molecular barcodes that allows us to probe evolutionary process of adaptation at unprecedented level of resolution.

Levy*, S., **Blundell*, J.R., Venkataram, S., Petrov, D.A.**, Fisher, D.S., and Sherlock, G. (2015). Quantitative evolutionary dynamics using high-resolution lineage tracking. *Nature*, doi:10.1038/nature14279; (* contributed equally).

Venkataram, S.*, Dunn, B.*, **Li, Y**., Argawala, A., Chang, J., **Ebel, E., Geiler-Samerotte, K.,** Herrisant, L., **Blundell, J**., Levy, S.F., Fisher, D., Sherlock, G.[#], and **Petrov, D.A**[#]. (2016). A comprehensive genotype-fitness map for adaptive mutations in yeast. *Cell*, **167**, 1–12; (* and [#] contributed equally).

Li, Y. [*], **Venkataram, S. , Agarwala, A.,** Dunn, B., **Petrov, D.A**. [#], Sherlock, G. [#], Fisher, D.S. [#] (2018). Hidden complexity of yeast adaptation under "simple" evolutionary conditions. *Current Biology,* **28**: 515-525. (* and [#] contributed equally)

Li, Y., **Petrov, D.A*** and Sherlock, G.*. (2019). Single nucleotide mapping of the locally accessible trait space in yeast reveals pareto fronts that constrain initial adaptation. *Nature Ecology and Evolution*, **3**: 1539–1551. (* contributed equally).

My lab is currently utilizing the barcoding system to investigate: (i) the nature of adaptation in progressively more complex environments and the patterns of fitness tradeoffs, (ii) evolution of generalists and specialists, and (iii) the phenotypic properties of adaptive mutations of large effect with specific focus on modularity and pleiotropy of such mutations. We are also adding high throughput CRISPR approaches (CRISPEY) to investigate properties of a large number of mutations within key signaling pathways that are often targeted by adaptation and to compare phenotypic and fitness properties of polymorphisms segregating in natural populations with those of *de novo* adaptive mutations.

4. Cancer Evolution

In collaboration with the lab of Monte Winslow we have extended the barcoding technology to study the **fitness landscape and dynamics of tumor growth in the mouse model of lung adenocarcinoma**. The approach --Tuba-seq -- utilizes lentivirus delivery system and a combination of CRISPR and Cre/lox to uniquely barcode individual cells in the lung that carry specific tumor-driving genetic alterations. Using this system we can generate thousands of tumors in a single mouse lungs carrying specific alterations in tumor suppressors and oncogenes, alone or in combination, and then measure their growth after a period of time by sequencing of the barcode region in the bulk DNA sample. The essential feature is that multiple genetic alterations can be assayed within the same animal allowing for very precise and rapid quantification of tumor suppressor effects.

Rogers, Z.N.*, **McFarland, C.D**.*, Winters,I.P., Naranjo, S., Chuang, C.-H., **Petrov, D.A.**, and Winslow, M. (2017). Tuba-seq: a quantitative and multiplexed approach to uncover the fitness landscape of tumor suppression in vivo. *Nature Methods*, doi:10.1038/nmeth.4297 (*contributed equally)

Rogers*, Z.N., **McFarland*, C.D.**, Winters, I.P., Seoane, J.A., Brady, J.J., Yoon, S., Curtis, C., **Petrov, D.A.** [#] and Winslow, M.M.[#] (2018). The fitness landscape of tumor suppression in lung adenocarcinoma *in vivo*. *Nature Genetics*, **50**, 483–486 (* and [#] - contributed equally).

Li, C.*, Lin, W.-Y.*, Rizvi, H., Cai, H., **McFarland, C.M**., **Rogers, Z.**, Yousefi, M., Winters, I.P., Rudin, C.M., **Petrov, D.A**.[#],and M.M., Winslow[#]. (2020). Quantitative *in vivo* analyses reveal a complex pharmacogenomic landscape in lung adenocarcinoma. *Nature Cancer (in review)*; *Biorxiv;* (* - contributed equally; # corresponding authors).

We have shown that individual tumor suppressive mutations can have a strong fitness effect (~20% faster growth), show substantial epistasis with each other, and that they generate substantial variation in sensitivity to cancer therapies. We are currently building fitness and epistatic maps of tumor suppression for all major tumor suppressors (~50), learning how tumor growth and initiation vary with age, with the immune system status, and in response to therapies. We are also extending the platform to allow us to induce genetic diversity in growing tumors and to assay phenotypic states of thousands tumor cells using single-cell sequencing using expressed barcodes.

This work is carried out in conjunction with genomic analyses of the human cancer data where we specifically focus the effects of hitchhiking on tumor growth dynamics. We have argued in a recent preprint that passenger mutations in cancer are not “mere passengers” but instead generate substantial deleterious load. Complete linkage in cancer is not allowing tumors to weed out such mutations and instead tumors deal with the accumulating deleterious load by upregulating protein folding and degradation pathways. This discovery has identified a virtually universal vulnerability of cancer and changing how we think of passenger mutations.

Tilk, S., Curtis, C.**, Petrov, D.A**.*, **McFarland, C.D.*** (2019). Most cancers carry a substantial deleterious load due to Hill-Robertson interference. *Nature*, *in review*; *Biorxiv*; (* - co-corresponding authors).

5. Theory of rapid evolution.

While much of our focus is on the empirical investigations of rapid adaptation in large populations, we are also strongly interested in building theoretical models of rapid evolution. I will highlight specifically these three projects:

(i) the theory of soft selective sweeps from de novo mutations in populations of fluctuating size and especially in evolutionary rescue: **Wilson, B.A**, Pennings, P.S. and **Petrov, D.A**. (2017). Soft selective sweeps in evolutionary rescue. *Genetics*, **205**: 1573-1586;

(ii) interactions among very strong evolutionary forces such as strong mutation, migration, and selection and the possibility of measuring these parameters in relation to each other: **Feder, A.F.**, Pennings,P.S, Hermisson, J. and **Petrov, D.A**. (2019) Evolutionary dynamics in structured populations under strong population genetic force. *G3*, **9**, 3395-3407;

(iii) theory of adaptation under fluctuating selection and the finding that very modest amounts of “segregation lift” in which dominance of the currently favored allele remains on average above 0.5 is sufficient to both maintain diversity and lead to allele frequency fluctuations: **Wittman, M. J., Bergland, A.O**., Feldman, M.W., Schmidt, P.S., and **D. A. Petrov**. (2017). Segregation lift: A general mechanism for the maintenance of polygenic variation under seasonally fluctuating selection. *Proc. Natl. Acad. Sci.*, **114**: E9932-E9941.

We continue our work on the theory of rapid evolution with a specific focus on the nature of genotype-phenotype-fitness maps that are consistent with very large effect adaptive mutations and the evolution of generalists and specialists in eco-evolutionary scenarios.

D. Additional Information: Research Support over the past 5 years

Ongoing Research Support

GM118165-01 (MIRA grant) (Petrov) 05/01/2016-04/30/2021
NIH/NIGMS
Genomics of rapid adaptation in the lab and in the wild
Role: PI

ALA, Lung Cancer Discovery Award 11/1/2019-10/31/2021
Principal Investigator

TRDRP, High Impact Pilot Research Award, 11/15/2019-11/14/2021
Principal Investigator

R01CA234349 (Winslow/Petrov) 06/01/2019-05/31/2024
Unravelling mechanisms of tumor suppression in lung cancer
Role:co-PI

R01CA231253 (Winslow/Petrov) 09/01/2018-08/31/2022
(PQ4) Quantitative and multiplexed analysis of gene function in cancer in vivo
Role:co-PI

Completed Research Support

R01CA207133-01 (Winslow/Petrov) 07/05/2016-06/30/2019
A Quantitative multiplexed platform for the pharmacogenomic analysis of lung cancer
Role:co-PI

R01 GM115919 (Petrov) 09/01/2015-05/31/2019 (relinquished due to MIRA rules)
NIH/NIGMS
High-resolution study of adaptation in haploid and diploid populations of yeast
Role: PI

R01GM10036601 (Petrov) 05/15/2012-04/30/2016
NIH/NIGMS
Adaptation in 6 Dimensions

Role: PI