BIOGRAPHICAL SKETCH

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NAME: Guy Sella

eRA COMMONS USER NAME (credential, e.g., agency login): GUYSELLA

POSITION TITLE: Associate Professor

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
Tel Aviv University, Tel Aviv, Israel	B. Sc.	10/1993	Physics and Mathematics
Hebrew University, Jerusalem, Israel	M.A.	10/1997	Neural Computation
Tel Aviv University, Tel Aviv, Israel	Ph.D.	10/2001	Mathematics
Weizmann Institute of Science, Rehovot, Israel	Postdoctoral	04/2003	Mathematics and Computer Science
Hebrew University, Jerusalem, Israel	Postdoctoral	01/2005	Center for the Study of Rationality

A. Personal Statement

My group studies the evolutionary processes that give rise to genetic and phenotypic differences between individuals, populations and closely related species. To these ends, we use mathematical models to better understand these processes and apply statistical analyses to identify their footprints in data and make inferences about them. We are particularly interested in the evolutionary causes of adaptation and disease, but we also study a variety of other topics. Currently, our main research foci are to (i) elucidate the population genetic processes that give rise to variation in human quantitative traits within and between populations; (ii) quantify the effects of linked selection on genetic variation and learn about the underlying modes of selection (notably, selective sweeps and background selection) in humans and other taxa; and (iii) characterize how life history effects on mutation have affected polymorphism and divergence in autosomes and sex chromosomes of great apes.

B. Positions and Honors

Positions

2005-2006 Visiting Assistant Professor, Department of Biological Sciences, Stanford University
2006-2010 Lecturer, Department of Ecology, Evolution and Behavior, Hebrew University
2009-2013 Visiting Assistant Professor, Department of Ecology and Evolution, University of Chicago (summer quarters and spring 2010)
2010- 2013 Senior Lecturer, Department of Ecology, Evolution and Behavior, Hebrew University (tenured in 2012)
2013- Pres. Associate Professor (non-tenured), Department of Biological Sciences, Columbia University

Honors

1997-1999	Fulbright Award to study at Stanford University (in Marc Feldman's lab)
1998	Prize for Excellent Ph.D. project, Tel Aviv University
2001-2003	Koshland Postdoctoral Fellowship, Weizmann Institute of Science
2003-2005	Horowitz Postdoctoral Fellowship, Hebrew University
2006-2009	Flegg Fellowship for Young Researcher, Hebrew University

Selected Services (Since 2013)

Co-organizer, Symposium on "Evolutionary Genetics of Complex Disease Susceptibility and Other Polygenic Traits", SMBE Meetings, Chicago, US (2013).
Guest Associate Editor, *PLoS Genetics* (2015 - Present).
Co-organizer, New York Area Population Genomics Meeting, Columbia, New York, NY (2017).
Ad-Hoc Member, NIH GVE Study Section (Feb. 2017)
Reviewer of manuscripts submitted to Evolution, Genetics, Genome Research, J. Mol. Evol., Mol. Biol. Evol., Gen. Biol. Evol., Physical Biology, PLoS Biology, PLoS Genetics, PLoS Computational Biology, Nature Comm., PNAS and Science.
Reviewer of grants submitted to the Israel Science Foundation, United States-Israel Bi-national Science Foundation, Minerva Foundation, European Research Counsel (ERC) and NIH.

C. Contributions to Science

1. Learning about natural selection in the genome from its effects on neutral diversity levels

Both positive and negative selection at linked sites affect neutral diversity levels nearby. Our work over the past decade has contributed to considerable progress in using these footprints to learn about natural selection and its effects on genetic diversity in humans and other taxa. In our earlier work, we discovered that neutral diversity levels are negatively correlated with rates of protein evolution in the *D. simulans* genome, indicating selective sweeps are common. Alongside other lines of evidence, this work contributed to overturning the neutralist view of molecular evolution, suggesting pervasive adaptive evolution in Drosophila (Macpherson et al. 2007 and Sella et al. 2009). When we looked in humans, the results were more nuanced: while we found strong evidence for the effects of linked selection, it was unclear whether it resulted from selective sweeps or background selection (Cai et al. 2009). To overcome these limitations, we developed a more direct way to visualize and quantify the genomic effects of sweeps by looking at how average diversity levels vary with genetic distance from different kinds of substitutions. This approach further strengthened the evidence for pervasive adaptation in Drosophila and allowed us to derive more reliable estimates of the genomic rate of beneficial substitutions and the strength of selection driving them (Sattath et al. 2011). In contrast, our results in humans demonstrated that classic selective sweeps, in which a new beneficial mutation rises rapidly to fixation, were extremely rare in recent human evolution (Hernandez et al. 2011). This work has led the field to shift attention to other modes of adaptation in humans, notably selection on standing variation and polygenic selection. More recently, we developed a method to infer the effects of background selection and selective sweeps jointly, using more information about variation in diversity levels along the genome and considering selection at non-coding as well as coding regions (Elyashiv et al. 2016). Applying this method to data from *D. melanogaster* allowed us to: (i) predict neutral diversity levels along the genome, explaining ~70% of the variation on the 1Mb scale; (ii) show that linked selection has had a considerably larger effect on diversity levels throughout the genome than previously appreciated; (iii) find the first evidence (to our knowledge) for pervasive sweeps in a non-coding annotation (i.e., in UTRs); and (iv) distinguish between the effects of sweeps resulting in substitutions and other modes of linked selection (e.g., background selection). Application of this method to human data is underway.

Elyashiv, E., Sattath S., Hu, T., McVicker, G., Strutsovsky, A., Andolfatto, P., Coop, G. and G. Sella (2016). A genomic map of the effects of linked selection in Drosophila. *PLoS* Genet **12**: e1006130. PMCID: PMC4990265
Hernandez, R. D., Kelley, J. L., Elyashiv, E., Melton, S. C., Auton, A., McVean, G., 1000 Genomes Project, Sella G.[+] and M. Przeworski[+] (2011) Classic selective sweeps were rare in recent human evolution. *Science* **331**: 920-4. [+]*Joint senior authors*. PMCID: PMC3669691
Sattath, S., Elyavish, E., Kolodny, O., Rinott, Y., and G. Sella (2011) Pervasive adaptive protein evolution apparent from diversity patterns around amino-acid substitutions in *Drosophila simulans*. *PLoS Genet* **7**: e1001302. PMCID: PMC3037414
G. Sella, D. A. Petrov, M. Przeworski, and P. Andolfatto (2009) Evidence for pervasive natural selection in the Drosophila Genome? *PLoS Genetics* **5**: e1000495. PMCID: PMC2684638
J. J. Cai, J.M. Macpherson, G. Sella* and D. A. Petrov* (2009) Pervasive hitchhiking at coding and regulatory sites in humans. *PLoS Genet* **5**: e1000336. PMCID: PMC2613029 **Co-supervised this work*.
J. M. Macpherson*, G. Sella*, J. C. Davis, and D. A. Petrov (2007) Genome-wide spatial correspondence between non-synonymous divergence and neutral polymorphism reveals extensive adaptation in Drosophila. *Genetics* **177**: 2083-89. PMCID: PMC2219485 **Joint first authors*.

2. Recent human demographic history had little effect on the mutation load

Recent demographic history has profoundly affected the distribution of genetic variation in human populations, leading to considerable interest in whether it also shaped the burden of genetic disease (i.e., the mutation load) in modern human populations (Simons & Sella 2016). In collaboration with Jonathan Pritchard (Stanford University), we used population genetic models and statistical analyses of exome data to demonstrate that these effects had little or no impact on the average burden of deleterious mutations (Simons et al. 2014). We focused on three demographic models applicable to human populations, using theory and simulations to study demographic effects on mutation load over the range of selection and dominance parameter regimes. Among other results, our analysis revealed that changes to the population size do not affect the mutation load that stem from strongly selected variants, so long as they are partially dominant. More generally, we showed that recent changes in population size likely had little impact on the burden of deleterious mutations and therefore that differences among extant human populations are not expected. This prediction is supported by our analysis of two large exome sequence data sets, which despite providing high power, show no significant difference in the burden of damaging mutations between individuals of west African and European ancestry. A parallel study from Reich, Sunyaev and colleagues *(*Nat Genet *2015)*, used a similar statistical approach to arrive at the same conclusions based on data from additional human populations.

Simons, Y., Turchin, M., Pritchard, J. K.[+], and G. Sella[+] (2014). The deleterious mutation load is insensitive to recent population history. Nat Genet **46**: 220–224. PMCID: PMC3953611 [+]Joint senior authors.
Simons, Y. and G. Sella (2016). The impact of recent population history on the deleterious mutation load in humans and close evolutionary relatives. *Curr Opin Genet Dev* **41**: 150-158. PMCID: PMC5161708

3. Life history effects on the molecular clock helps to clarify the chronology of hominid evolution

Our estimates of split times among closely related species are predicated on the neutral molecular clock: the assumption that the rate at which neutral substitutions accumulate on a lineage equals the rate at which mutations arise. However, recent estimates of the mutation rate based on sequencing human pedigrees suggest split times between humans and our closest living relatives that are seemingly at odds with the fossil record, generating considerable confusion about the chronology of human evolution. We have shown that accounting for the effects of life history (i.e., of sex-specific generation times, age of onset of male puberty and rates of spermatogenesis) on the molecular clock can resolve this apparent contradiction and explain several other puzzling observations in hominid and mammalian evolution. Specifically, we have shown that taking these effects into account can explain both: (i) the puzzlingly low X-to-autosome ratios of substitution rates in humans and chimpanzees and differences in rates of autosomal substitutions among hominine lineages and (ii)

why the “generation time effect” on the molecular clock is stronger in short-lived species, e.g., why the generation time has a major influence on yearly substitution rates in the mammalian phylogeny but only a subtle one in human pedigrees. Our results further suggest how to translate pedigree-based estimates of human mutation rates into split times among extant hominoids (apes), accounting for sex-specific life histories. In so doing, they help to bridge the gap between estimates of split times based on fossil and molecular evidence, in particular suggesting that the human-chimpanzee split may have occurred as recently as 6.6 MYA.

Amster, G. and G. Sella (2016). Life history effects on the molecular clock of autosomes and sex chromosomes. *Proc Natl Acad Sci USA* 113: 1588-1593. PMCID: PMC4760823
Gao, Z., Wyman, M.J., Sella, G. and M. Przeworski (2016). Interpreting the dependence of mutation rates on age and time. *PLoS Biol* **14**: e1002355. PMCID: PMC4711947

4. Drawing analogies between models of molecular evolution and statistical physics

It is often surprisingly difficult to solve even the simplest models of molecular evolution analytically, limiting our ability to study their behavior and its sensitivity to specific modeling assumptions. We have shown that a precise mathematical analogy can be drawn between models of nearly neutral evolution and thermodynamic systems, in the parameter regime in which the evolutionary process can be treated as a succession of mutant fixations, each of which occurs on the genetic background of the population’s previous common ancestor (Sella & Hirsh 2005). The analogy is powerful because it allows for the machinery of statistical physics to be applied to the analysis of evolutionary models. Specifically, it implies that: (i) for any fitness landscape, the probability of observing a fixed genotype at steady state depends only on its fitness and on the population size, leading to simple general expressions for this distribution and (ii) contrary to a basic tenet of the Nearly Neutral theory of molecular evolution, the frequencies of adaptive and deleterious substitutions at steady state are equal; in fact, it establishes a “detailed balance” by which this equality holds for any effect size; and (iii) there is an evolutionary analogue of the Second Law of Thermodynamics for these models, in which a “free fitness function”, which balances between natural selection and stochastic drift, never decreases. This result can be viewed as an extension of Fisher’s Fundamental Theorem to finite populations.

G. Sella and A. E. Hirsh (2005) The application of statistical physics to evolutionary biology. *Proc Natl Acad Sci USA* **102**: 9541-46. PMCID: PMC1172247
G. Sella (2008) An exact steady state solution of Fisher's geometric model and other models. *Theor Pop Biol* **75**: 30-4. PMID: 18996138

5. Genes and genetic codes co-evolution explains the organization of the Standard Genetic Code

The standard genetic code, the mapping used (with minor variations) throughout the domains of life to translate genes into proteins, is organized in a way that makes it extremely efficient at minimizing the effects of errors in replication and translation. Although such an organization seems to be adaptive, its evolution cannot be explained by selection alone as, in order to make a code more robust to errors, natural selection would have to change an existing code—a type of change that could be catastrophic for an organism, introducing new amino acids into virtually every protein. With these considerations in mind, David Ardell and I set out to understand how the co-evolution of genes and genetic codes could have led to the organization of the standard code. We developed a mathematical model that captures the co-evolutionary relationship between genes and genetic codes, and derived rules of code modification that follow from this co-evolution in the presence of errors in replication and translation. Using this approach, we were able to demonstrate that this co-evolution results in the error-minimizing organization and redundancy observed in the standard code.

D. H. Ardell and G. Sella (2001) On the evolution of redundancy in genetic codes. *J Mol Evol* **53**: 269-81. PMID: 11675587
G. Sella and D. H. Ardell (2002) The impact of message mutation on the fitness of a genetic code. *J Mol Evol* **54**: 638-51. PMID: 11965436
D. H. Ardell and G. Sella (2002) No accident: genetic codes freeze in error-correcting patterns of the standard genetic code. *Phil Trans Roy Soc B* **357**: 1625-42. PMCID:PMC1693064
G. Sella and D. H. Ardell (2006) The coevolution of genes and genetic codes: Crick's frozen accident revisited. *J Mol Evol* **63**: 297-313. PMID:16838217

List of Published Work in Google Scholar: https://scholar.google.co.il/citations?user=twTA3A4AAAAJ&hl=en

D. Research Support

Ongoing:

PI, R01 GM115889 08/2015-07/2020
The Population Genetics of Disease Risk and Other Quantitative Traits
The main goals are to understand how selection, pleiotropy and demography shape the genetic architecture of quantitative traits in humans. The research is related to, but does not overlap with the one proposed by Dr. Berg (e.g., because it focuses on continuous additive traits under stabilizing selection rather than on complex diseases that are described by the liability threshold model and are subject to directional selection).

Completed Since 2013:

Co-PI, R01 GM083228 07/2009-06/2014
Adaptive Evolution of Non-Coding DNA and Gene Expression Divergence in Drosophila

PI, Israel Science Foundation 1492/1 10/2010–09/2013
Characterizing Adaptation in Drosophila using Genome-Wide Patterns of Genetic Variation