OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Siegal, Mark Levi

eRA COMMONS USER NAME (credential, e.g., agency login): MS4131.NYU

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 |
| --- | --- | --- | --- |
| Brown University, Providence, RI | Sc.B. | 05/1993 | Biology |
| Harvard University, Cambridge, MA | Ph.D. | 06/1998 | Biology |
| Stanford University, Stanford, CA | Postdoctoral | 11/2004 | Biological Sciences |

# A. Personal Statement

My research contributes to the theoretical and empirical understanding of phenotypic variation and the evolution of complex traits. Through my undergraduate, graduate and postdoctoral education, I gained broad training in molecular, developmental and evolutionary biology, as well as in applied mathematics and statistics. In 2005 I was appointed Assistant Professor in the Department of Biology and Center for Genomics and Systems Biology at New York University, and I was promoted to Associate Professor with tenure in 2011. In the past five years I have authored 26 publications, including high-profile papers in *PLoS Biology*, *PLoS Genetics*, *PNAS* and *Genome Research*. As reflected in the diversity of field-specific journals in which I have recently published (ranging from *Journal of Human Genetics* to *Development* to *Biological Theory*), my work is notable for its creative use of a variety of approaches to address the same core questions. In particular, my laboratory’s main focus is on uncovering the molecular and evolutionary mechanisms that determine the extent to which environmental or genetic perturbations affect complex traits. We pioneered the use of high-throughput microscopic analysis of yeast-cell morphology and growth to quantify phenotypic variation within and between genotypes in different environments. This work has led to important findings about the genetic control of phenotypic heterogeneity, and forms the foundation on which the proposed research program builds.

I aim to run a small, innovative and efficient research group, and I take very seriously my role as mentor. Of the three postdoctoral researchers who have completed their training, one is now a tenured Associate Professor at Rutgers, one holds an endowed Assistant Professorship at Stony Brook, and the third is pursuing a career in industry. All four Ph.D. students who have completed their studies are in postdoctoral positions (at Sloan Kettering, NYU School of Medicine, Yale and UCSF). I am particularly invested in undergraduate education. In addition to mentoring over 20 undergraduates in my laboratory over the past 10 years, I have been Director of Undergraduate Studies for Biology since 2011, and led a major redesign of the introductory Biology curriculum. I also mentor 2–3 students per year who have received a fellowship through NYU’s Collegiate Science and Technology Entry Program (CSTEP), which prepares students from traditionally underrepresented or low-income backgrounds for careers in scientific, technical or health-related professions. My excellence in teaching and mentoring were recognized with the NYU Graduate School of Arts & Science’s Outstanding Faculty Award, and with the NYU College of Arts and Science Golden Dozen Teaching Award.

My research, leadership and mentoring experience prepare me well to lead the research program described in this MIRA proposal. Four recent papers that highlight my scientific contributions are:

Bauer CR, Li S and Siegal ML, 2015. Essential gene disruptions reveal complex relationships between phenotypic robustness, pleiotropy, and fitness. *Molecular Systems Biology* 11:773.

Zhu YO, Siegal ML, Hall DW and Petrov DA, 2014. Precise estimates of mutation rate and spectrum in yeast. *Proc Natl Acad Sci USA* 111:E2310–E2318.

Richardson JB, Uppendahl LD, Traficante MK, Levy SF and Siegal ML, 2013. Histone variant HTZ1 shows extensive epistasis with, but does not increase robustness to, new mutations. *PLoS Genetics* 9:e1003733.

Levy SF, Ziv N and Siegal ML, 2012. Bet hedging in yeast by heterogeneous, age-correlated expression of a stress protectant. *PLoS Biology* 10:e1001325*.*

# B. Positions and Honors

**Positions and Employment**

1998-2004 Postdoctoral scholar, Department of Biological Sciences, Stanford University

2005-2010 Assistant Professor, Department of Biology, New York University

2011- Associate Professor, Department of Biology, New York University

2011- Director of Undergraduate Studies, Department of Biology, New York University

2013- Global Coordinator of Curriculum, Department of Biology, New York University

**Other Experience**

2007-2008 National Evolutionary Synthesis Center working group, “Modeling Variation in Gene Networks”

2008-2015 *Ad hoc* grant reviewer for NSF (2008, 2010-2012); Israel Science Foundation (2009); NIH (2011); Austrian Science Fund (2012); BBSRC (2014); Research Foundation Flanders (2014); Netherlands Organisation for Scientific Research (2014); Danish Council for Independent Research (2014); University of Nebraska Office of Research & Economic Development (2015)

2012-2015 *Ad hoc* member, Genetic Variation and Evolution Study Section, NIH

2014-2015 Guest Associate Editor, *PLoS Genetics* and *PLoS Biology*

**Honors**

1990 CRC Press Freshman Chemistry Achievement Award

1993 Sigma Xi inductee

1993 Maria Caleel Memorial Prize for Excellence in Biology, Brown University

1993 *magna cum laude*, Brown University

1993-1998 Howard Hughes Medical Institute Predoctoral Fellowship

1996-1998 Award for Distinction in Teaching, Derek Bok Center, Harvard University

1998 Walter Fitch Prize, Society for Molecular Biology and Evolution

1998-2000 NSF/Alfred P. Sloan Foundation Postdoctoral Research Fellowship in Molecular Evolution

2000 Fulker Award, Behavior Genetics Association

2001-2003 NIH Individual National Research Service Award Postdoctoral Fellowship

2005-2007 Alfred P. Sloan Research Fellow in Computational and Evolutionary Molecular Biology

2006-2008 NYU Whitehead Fellowship for Junior Faculty in Biomedical and Biological Sciences

2006 National Academies Education Fellow in the Life Sciences

2007-2008 NYU ITS Instructional Technology Faculty Fellowship

2009 NYU Golden Dozen Teaching Award

2009 NYU Graduate School of Arts & Science Outstanding Faculty Award

**C. Contribution to Science**

**1. Advancing transgenic methods for detecting subtle differences in gene function**

In the early days of transgenic analysis using transposable-element vectors, genome-position effects on transgene expression often confounded efforts to detect subtle functional differences between gene variants. As a Ph.D. student, I introduced Cre recombinase into *Drosophila melanogaster* to create the first efficient way of putting transgenes into identical positions in the fly genome (Siegal & Hartl 1996). I applied this method to study lineage-specific effects of genomic position on gene expression (Siegal & Hartl 1998), as well as the consequences of replacing the *Alcohol dehydrogenase* gene of one species with another’s (Siegal & Hartl 1999). This latter work was awarded the Behavior Genetics Association’s Fulker Prize for its resolution of a longstanding controversy involving alcohol tolerance and egg-laying site preference and for the methodological advance it represented. My Ph.D. work also earned me the Walter Fitch Prize of the Society for Molecular Biology and Evolution. Although my specific transgenic method has been eclipsed by other means of site-specific genome engineering, the work continues to be cited nearly 20 years later.

Siegal ML and Hartl DL, 1996. Transgene coplacement and high efficiency site-specific recombination with the Cre/*loxP* system in Drosophila. *Genetics* 144:715–726.

Siegal ML and Hartl DL, 1998. An experimental test for lineage-specific position effects on alcohol dehydrogenase (*Adh*) genes in *Drosophila*. *Proc Natl Acad Sci USA* 95:15513–15518.

Siegal ML and Hartl DL, 1999. Oviposition-site preference in *Drosophila* following interspecific gene transfer of the *Alcohol dehydrogenase* locus. *Behavior Genetics* 29:199–204.

**2. Advancing the theory of phenotypic robustness**

Many cellular and developmental processes are robust. That is, they operate with high fidelity to produce stereotyped outcomes despite environmental and genetic perturbations. Nonetheless, the causes and consequences of robustness in biological systems are poorly understood. As a postdoctoral fellow, I began my work to uncover how mechanisms that constrain variation evolve, and what effects such mechanisms have on subsequent evolution. This initial work, published in a widely cited pair of papers in *PNAS* and *Nature*, studied computational simulations of evolving gene-regulatory networks. The first paper (Siegal & Bergman 2002) showed that simulated networks evolved robustness to mutations even without selection for a specific output, suggesting that robustness might be an intrinsic rather than selected property of complex regulatory networks. The second paper (Bergman & Siegal 2003) showed that the networks accumulated cryptic genetic variation and that this variation could be revealed by deletion of any gene in the network. An indication of this paper’s impact is that it was selected by *Nature* in 2009 as an “Evolutionary Gem”, one of “15 examples published by *Nature* over the past decade or so to illustrate the breadth, depth and power of evolutionary thinking” (doi:10.1038/457008b). Although my laboratory’s major focus is experimental, I continue to contribute to the conceptual understanding of variability in complex traits. I have done this both through modeling (e.g., Siegal et al. 2007) and through integrative reviews that aim to synthesize and orient the field (e.g., Siegal & Leu 2014).

Siegal ML and Bergman A, 2002. Waddington’s canalization revisited: developmental stability and evolution. *Proc Natl Acad Sci USA* 99:10528–10532.

Bergman A and Siegal ML, 2003. Evolutionary capacitance as a general feature of complex gene networks. *Nature* 424:549–552.

Siegal ML, Promislow DEL and Bergman A, 2007. Functional and evolutionary analysis in gene networks: Does topology matter? *Genetica* 129:83–103.

Siegal ML and Leu J-Y, 2014. On the nature and evolutionary impact of phenotypic robustness mechanisms. *Annual Review of Ecology, Evolution, and Systematics* 45:495–517.

**3. Discovering and characterizing genes required for phenotypic robustness**

Studying mechanisms that control phenotypic heterogeneity requires experimental platforms that allow precise control of genotypes and environments, and that accommodate very large sample sizes. Upon establishing my laboratory at NYU, I pioneered the use of high-throughput microscopy to study variation in complex traits at the single-cell level. The first product of this effort was a *PLoS Biology* paper (Levy & Siegal 2008) motivated by my 2003 *Nature* paper, in which we used data from all viable, single-gene-deletion mutants in the budding yeast, *Saccharomyces cerevisiae*, to identify deletions that increase variation in cell morphology. This was the first (and remains the only) genome-wide screen for genes involved in robustness of any trait in any organism. We have since demonstrated that loss of robustness need not imply loss of fitness, an important result when considering the evolutionary consequences of robustness (Bauer et al. 2015). In addition, we refuted a longstanding hypothesis that mechanisms increasing robustness against one type of perturbation also increase robustness against other types. We showed that the alternative histone H2A.Z, which increases robustness against environmental fluctuations, interacts epistatically with mutations but does not increase robustness against their effects (Richardson et al. 2013). Epistasis also figured prominently in work we conducted in collaboration with Hunter Fraser and Himanshu Sinha, in which we showed that deleterious pleiotropic effects of adaptive mutations appear to be mitigated by compensatory mutations (Fraser et al. 2012).

Levy SF and Siegal ML, 2008. Network hubs buffer environmental variation in *Saccharomyces cerevisiae*. *PLoS Biology* 6:e264.

Fraser HB, Levy S, Chavan A, Shah HB, Kowli S, Perez JC, Zhou Y, Siegal ML and Sinha H, 2012. Polygenic *cis*-regulatory adaptation in the evolution of yeast pathogenicity. *Genome Research* 22:1930–1939.

Richardson JB, Uppendahl LD, Traficante MK, Levy SF and Siegal ML, 2013. Histone variant HTZ1 shows extensive epistasis with, but does not increase robustness to, new mutations. *PLoS Genetics* 9:e1003733.

Bauer CR, Li S and Siegal ML, 2015. Essential gene disruptions reveal complex relationships between phenotypic robustness, pleiotropy, and fitness. *Molecular Systems Biology* 11:773.

**4. Elucidating development and function of robust yet rapidly evolving sex-specific structures in flies**

Sex-related traits often show much divergence between species relative to the amount of variation within species. They therefore present an opportunity to study how robust developmental processes evolve. This opportunity attracted me, in my postdoctoral work, to sexual differentiation in *Drosophila*, an excellent model system for both developmental genetics and evolution. I soon learned, however, that knowledge of how sex-specific traits developed was so limited as to make evolutionary comparisons superficial at best. I therefore shifted my focus to developmental, rather than evolutionary, questions. I contributed to the cloning and characterization of *intersex*, a gene required for female differentiation (Siegal & Baker 2005), as well as to the genome-wide discovery of sex-differentially expressed genes (Arbeitman et al. 2004). In my own lab we found key regulators of genital morphogenesis, including some required for the development of sex-specific traits that diverge rapidly between *Drosophila* species (Chatterjee et al. 2011). We also dissected the functions of the secretory cells that line the female sperm-storage organs, which are evolutionarily interesting as a site where female and male reproductive interests collide (Schnakenberg et al. 2011). Our fly work is just now returning to direct study of phenotypic variability. As part of an NSF-funded project we are introducing an *intersex* mutation into a large panel of genetic backgrounds to reveal cryptic genetic variation affecting female differentiation.

Arbeitman MN, Fleming AA, Siegal ML, Null BH and Baker BS, 2004. A genomic analysis of *Drosophila* somatic sexual differentiation and its regulation. *Development* 131:2007–2021.

Siegal ML and Baker BS, 2005. Functional conservation and divergence of *intersex*, a gene required for female differentiation in *Drosophila melanogaster*. *Development Genes and Evolution* 215:1–12.

Chatterjee S, Uppendahl LD, Chowdhury M, Ip PL and Siegal ML, 2011. The female-specific Doublesex isoform regulates pleiotropic transcription factors to pattern genital development in *Drosophila*. *Development* 138:1099–1109*.*

Schnakenberg SL, Matias WR and Siegal ML, 2011. Sperm-storage defects and live birth in *Drosophila* females lacking spermathecal secretory cells. *PLoS Biology* 9:e1001192*.*

**5. Discovering and characterizing a bet-hedging system in budding yeast**

Robustness-conferring mechanisms represent one end of a spectrum of adaptations to cope with environmental uncertainty. At the other end of the spectrum are mechanisms that generate heterogeneity, allowing a population to maximize its long-term fitness by hedging its bets (Levy & Siegal, 2012). To explore variability in fitness-related growth traits, my laboratory developed a novel, microscopy-based method for automated, highly parallel measurement of cell growth rates at the level of individual microcolonies. With this method we can assay, in one overnight experiment, as many as ~200,000 microcolonies divided between as many as 384 different genotype X environment combinations. Using this method we discovered a bet-hedging mechanism in budding yeast, whereby clonally related cells in the same environment grow at different rates and slow growth correlates with tolerance of acute stress (Levy et al. 2012). Moreover, we identified a major component of the bet-hedging mechanism: a gene product (TSL1) whose heterogeneous expression among genetically identical cells correlates negatively with growth rate and positively with stress survival (Levy et al. 2012). In related work in collaboration with David Gresham, we uncovered extensive variation in growth-rate distributions in wild yeast under different low-nutrient conditions (Ziv et al. 2013), which suggests that different ecological pressures might select for different extents and natures of bet hedging.

Levy SF and Siegal ML, 2012. The robustness continuum. *Advances in Experimental Medicine and Biology* 751:431–452.

Levy SF, Ziv N and Siegal ML, 2012. Bet hedging in yeast by heterogeneous, age-correlated expression of a stress protectant. *PLoS Biology* 10:e1001325*.*

Ziv N, Siegal ML and Gresham D, 2013 Genetic and non-genetic determinants of cell-growth variation assessed by high-throughput microscopy. *Molecular Biology and Evolution* 30:2568–2578.

**Complete list of published work in MyBibliography:**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/mark.siegal.1/bibliography/41159849/public/?sort=date>

# D. Research Support

**Ongoing Research Support**

NIH R01 GM086673 Siegal (PI) 4/1/2010 – 3/31/2016 (no cost extension)

*Sources and consequences of phenotypic variation in complex regulatory networks*

The goal of this project is to test whether genes that buffer the effects of nongenetic variation on yeast morphological phenotypes also buffer the effects of genetic variation on these phenotypes.

Role: PI

NIH R01 GM097415 Siegal and Petrov (multi PI) 9/30/2011 – 7/31/2015

*Sequencing yeast lines to measure rates of neutral and deleterious mutations*

The major goal of this project is to characterize the molecular nature and the fitness consequences of a large number of spontaneous mutations by using high-throughput sequencing and sensitive assays of cell growth rates.

Role: PI

NSF IOS-1258078 Siegal (PI) 9/1/2013 – 8/31/2017

*Systematic study of cryptic genetic variation in Drosophila*

The major goal of this project is to characterize the amount and nature of cryptic genetic variation affecting morphological and gene-expression traits in flies, as revealed by genetic perturbations.

Role: PI

**Completed Research Support**

NSF CAREER IOS-0642999 Siegal (PI) 4/1/2007 – 3/31/2012

*CAREER: Phenotypic robustness and diversity: Integrating theory and experiment in genomics research and teaching*

The goal of the research funded by this award is to identify and characterize genes required for buffering of single-cell morphological phenotypes of the yeast *Saccharomyces cerevisiae*.

Role: PI

United States – Israel Binational Science Foundation 2009270

Siegal and Heifetz (multi PI) 9/1/2010 – 8/31/2014

*The role of spermathecal secretory cells in reproduction*

The goal of this project is to study a poorly understood cell type in the *Drosophila* female reproductive tract by transcriptomic and proteomic profiling.

Role: PI