BIOGRAPHICAL SKETCH

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NAME: Bintu, Lacramioara

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

POSITION TITLE: Assistant Professor of Bioengineering

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
Brandeis University, Waltham, MA	B.S.	05/2005	Physics
University of California, Berkeley, CA	Ph.D.	12/2010	Physics
University of California, Berkeley, CA	Postdoctoral	06/2011	Quantitative Biology
California Institute of Technology, Pasadena, CA	Postdoctoral	12/2016	Systems Biology and Biological Engineering

A. Personal Statement

The research goals of my lab are to develop new tools for mammalian synthetic biology, epigenetic editing and detection of chromatin modifications, and use these tools to elucidate the connection between chromatin dynamics and gene expression at the single-cell level. To get at the basic rules of gene regulation, we quantify the effects of different chromatin regulators on gene expression dynamics in different cell types, analyze combinations of regulators (recruited simultaneously or sequentially), and measure spreading of epigenetic states over time**.** We dissect how these basic rules of chromatin-mediated gene control affect cell fate during differentiation and innate immune response. We use cell-line engineering, flow cytometry, time-lapse microscopy, and next generation sequencing methods. Based on these data, we develop predictive mathematical models of epigenetic control in mammalian cells. My quantitative interdisciplinary training positions me ideally to carry out these research goals. In particular, I have experience developing theoretical models of gene regulation, analyzing the dynamics of transcription through chromatin using molecular biology and single-molecule methods, measuring the dynamics of chromatin regulation in single cells using time-lapse microscopy and flow cytometry, and developing high-throughput functional screens. In addition to the research goals, I am committed to teaching and mentoring, with a focus on quantitative methods, interdisciplinary approaches, effective communication, and collaborative science. My group consists of students and postdocs with diverse training in Bioengineering, Biophysics, Genetics, Biology, Biochemistry, Computer Science, and Applied Math. Our research training, together with access to Stanford's technological resources and knowledge in colleagues' labs, will allow my lab to make major contributions to both chromatin regulation and mammalian synthetic biology.

B. Positions and Honors

Positions and Employment

2004-2005 Research Assistant, Brandeis University, Waltham, MA
2017- Assistant Professor, Department of Bioengineering, Stanford University, Stanford, CA

Other Experience and Professional Memberships

2002 Undergraduate Teaching Assistant for Modern Physics, Brandeis University
2003 Science Teacher in *TOPS (Teaching Opportunities in Physical Sciences),* MIT & Harvard
2005-2006 Graduate Student Instructor, University of California, Berkeley, CA
2009- Member, American Society for Cell Biology

2017- Member, Society for Biological Engineering

Honors

2001-2005 Wien International Scholarship, Brandeis University
2004 Elihu A. Silver Prize for undergraduate research in science, Brandeis University
2005 Phi Beta Kappa
2005 Molly W. and Charles K. Schiff Memorial Award in Science, Brandeis University
2005 Doris Brewer Cohen Endowment Award for best senior thesis, Brandeis University
2006 Outstanding Graduate Student Instructor Award, University of California, Berkeley
2011 Harold M. Weintraub Graduate Student Award for outstanding achievement during graduate studies, Fred Hutchinson Center
2011-2104 Beckman Institute Fellowship for equipment, California Institute of Technology
2011-2014 Jane Coffin Childs Postdoctoral Fellowship
2015-2020 Career at the Scientific Interface Award, Burroughs Wellcome Fund

C. Contributions to Science

1. I helped develop a thermodynamic model that predicts gene expression from a bacterial promoter based on the concentrations and binding affinities of repressors and activators. Since the model is simple, it has proven useful to many researchers and has been used in numerous courses. This research was carried out while I was in the groups of Jané Kondev (Brandeis University) and Rob Phillips (Caltech).

    a. Bintu, L., Buchler, N. E., Garcia, H. G., Gerland, U., Hwa, T., Kondev, J., Phillips, R. (2005). Transcriptional regulation by the numbers: models. *Current opinion in genetics & development*, *15*(2), 116-124. PMC3482385.

    b. Bintu, L., Buchler, N. E., Garcia, H. G., Gerland, U., Hwa, T., Kondev, J., Kuhlman, T., Phillips, R. (2005). Transcriptional regulation by the numbers: applications. *Current opinion in genetics & development*, *15*(2), 125-135. PMC3462814.

2. I used single-molecule methods to measure the direct effect that nucleosomes have on transcription as well as the effect that transcription has on nucleosomes *in vitro*. We found that the polymerase acts as a ratchet, waiting for the nucleosomal DNA to fluctuate free from histones in order to advance. The fate of the histones depends on the speed of the polymerase: for slow polymerases, the histones can be transferred behind the polymerase via a DNA loop; fast polymerases ratchet their way through so quickly that the transfer fails to happen, and the histone octamer dissociates from DNA. These findings act as a knowledge scaffold for the more complex *in vivo* scenarios that involve a larger number of transcription factors and chromatin regulators. I performed this research as a PhD student in Carlos Bustamante's Laboratory at the University of California, Berkeley.

    a. Hodges, C.*, Bintu, L.*, Lubkowska, L., Kashlev, M., Bustamante, C. (2009). Nucleosomal fluctuations govern the transcription dynamics of RNA polymerase II. *Science*, *325*(5940), 626-628. PMC2775800.

    b. Bintu, L.*, Kopaczynska, M.*, Hodges, C., Lubkowska, L., Kashlev, M., Bustamante, C. (2011). The elongation rate of RNA polymerase determines the fate of transcribed nucleosomes. *Nature structural & molecular biology*, *18*(12), 1394-1399. PMC3279329.

    c. Zamft, B., Bintu, L., Ishibashi, T., Bustamante, C. (2012). Nascent RNA structure modulates the transcriptional dynamics of RNA polymerases. *Proceedings of the National Academy of Sciences*, *109*(23), 8948-8953. PMC3384149.

    d. Bintu, L.*, Ishibashi, T.*, Dangkulwanich, M., Wu, Y.Y., Lubkowska, L., Kashlev, M., Bustamante, C. (2012). Nucleosomal elements that control the topography of the barrier to transcription. *Cell*, *151*(4), 738-749. PMC3508686.

3. We showed that recruitment of different chromatin regulators at a target gene controls its expression in an all-or-none stochastic manner. Our single-cell measurements of gene expression as a function of time allowed us to propose a preliminary unified model of epigenetic control. In this model, chromatin regulation can move a gene among three states: active, reversibly silent, and irreversibly silent. Different chromatin regulators are associated with different rates between the three states. This model provides a useful way of

thinking about chromatin regulators, especially in the context of synthetic mammalian engineering. I developed this framework while I was a postdoc with Michael Elowitz (Caltech), and are continuing to work on it in my lab.

   a. Bintu, L.*, Yong, J.*, Antebi, Y.E., McCue, K., Kazuki, Y., Uno, N., Oshimura, M., Elowitz, M.B. (2016). Dynamics of epigenetic regulation at the single-cell level. *Science,* 351(6274):720-4

   b. Tycko, J.*, Van, M.V.*, Elowitz, M.B., Bintu, L. (2017). Advancing towards a global mammalian gene regulation model through single-cell analysis and synthetic biology. *Current Opinion in Biomedical Engineering*, 4:174-193.

4. We recently developed new methods for measuring and controlling gene expression and epigenetic memory. In collaboration with the Bassik lab, we developed a high-throughput assay in which pooled libraries of protein domains are recruited to a reporter gene and transcriptional effects are measured with a sequencing readout. This approach has enabled us to test the majority of Pfam annotated domains, perform a deep mutational screen of the KRAB domain from CRISPRi – resulting in a mutant with increased stability/silencing, and discover new repressor and activator domains as short as 10 amino acids. In addition to testing short domains from human proteins, we have shown that compact nanobodies against endogenous chromatin regulators can also be used to silence gene expression and induce epigenetic memory.

   a. Tycko J, DelRosso N, Hess GT, Aradhana, Banerjee A, Mukund A, Van MV, Ego BK, Yao D, Spees K, Suzuki P, Marinov GK, Kundaje A, Bassik MC, Bintu L. (2020). High-throughput discovery and characterization of human transcriptional effectors. *Cell*,S0092-8674(20)31541-5.

   b. Van MV, Fujimori T, Bintu L. (2021). Nanobody-mediated control of gene expression and epigenetic memory. *Nature Communications*, 12(1):1-2.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/pubmed/?term=Bintu+L

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

U01 DK127419, (MPIs: Bintu, Boettiger, Co-Is: Greenleaf, Spakowitz, Wysocka) 09/15/20-06/30/25
NIH, 4DN initiative, Real Time Chromatin Dynamics and Function
Live-cell multiplex super-resolution imaging of chromatin state transitions
We combine live imaging of gene expression with endpoint chromatin tracing (using oligopaints) in order to investigate the connection between gene expression, epigenetic memory and 3D chromatin structure.
Role: MPI

R35 GM128947, Bintu (PI) 07/05/18-06/30/23
NIH, NIGMS Maximizing Investigators' Research Award
Single-cell analysis and synthetic control of mammalian chromatin dynamics and gene regulation
The goal of this project is measure and model the connection between chromatin regulation and gene expression in different human cell types using synthetic biology and single-cell methods.
Role: PI

Career Award at the Scientific Interface, Bintu (PI) 07/01/15-06/30/21
Burroughs Wellcome Fund
Dynamics of epigenetic regulation at the single-cell level
The goal of this project is to build a quantitative and predictive framework of chromatin-mediated gene control.
Role: PI