BIOGRAPHICAL SKETCH

NAME: Finzi, Laura

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

POSITION TITLE: Full Professor

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Bologna, Bologna, Bo	BS	06/1984	Industrial Chemistry
University of New Mexico, Albuquerque, NM	PHD	05/1990	Chemistry
University of New Mexico, Albuquerque, NM	Postdoctoral Fellow	12/1990	Biophysics
University of Oregon, Eugene, OR	Postdoctoral Fellow	01/1992	Biophysics
Brandeis University, Waltham, MA	Postdoctoral Fellow	06/1993	Biophysics

A. Personal Statement

I am a single-molecule biophysicist working in the area of DNA-protein interactions and transcriptional regulation. I pioneered single-molecule DNA manipulation and microscopy methods that have been milestones in the field. For example, the article describing a first-generation magnetic tweezer used to measure the elastic properties of DNA[(a)] has been cited more than 2400 times and as a landmark in the field in the first NASEM decadal Report on Biological Physics/Physics of Living Systems. The first real-time observation of DNA looping by the lac repressor[(b)] is another milestone in the field. My research has led to several advances in our understanding of DNA mechanical properties and of mechanisms of transcription regulation. Supported by *NIGMS*, and using complementary atomic force imaging, tethered particle microscopy, and magnetic tweezers, my group and I discovered (i) key features of ubiquitous looped-based mechanisms of gene regulation (invited talk, Symposium on "*Biophysics of Epigenetic Switches*" 2014 Biophysical Society Meeting), and (ii) the fundamental role of DNA supercoiling in tuning such switches [(c,d)] (invited talks, Symposium on "DNA supercoiling" at the 2018 Biophysical Society Meeting; 2023- TORC talks, an Ireland-UK collaboration). Other areas of investigation include the protein-DNA interactions providing the scaffolding of chromosomes and the effect of macromolecular crowding on the structure and function of the genome (invited talk, "*The fluid versus gel nature of the genome Symposium*" 2024 Biophysical Society Meeting). Ultimately, we aim at understanding the interplay between the different forces that act on the genome with the long-term goal of predicting a spatio-temporal map of genome transactions as a function of force and DNA torsional state to better understand gene regulation and aid a broad range of areas such as drug discover, personalized medicine, engineering of smart biomaterials. Our extensive experience in the use of single-molecule techniques to study DNA-protein interactions, a multipronged approach including experiments, instrument development and a diverse network of national and international collaborations are foundational to the success of our research.

a. Smith SB, Finzi L, Bustamante C. Direct mechanical measurements of the elasticity of single DNA molecules by using magnetic beads. *Science* 1992 Nov 13;258(5085):1122-6. PubMed PMID: 1439819.

b. L. Finzi and J. Gelles, "Measurement of Lac Repressor-mediated loop formation and Breakdown in Single DNA Molecules", *Science,* 1995267, 378-380. PMID: 7824935.

c. Finzi L, Dunlap D. Supercoiling biases the formation of loops involved in gene regulation. *Biophys Rev*. 2016 Nov;8(Suppl 1):65-74. PubMed PMID: 28510212; PubMed Central PMCID: PMC5418503.

d. Finzi L, Olson WK. The emerging role of DNA supercoiling as a dynamic player in genomic structure and function. *Biophys Rev*. 2016 Nov;8(Suppl 1):1-3. PubMed PMID: 28510213; PubMed Central PMCID: PMC5418505.

B. Positions, Scientific Appointments and Awards

2023- Fellow of the American Physical Society

2023- Faculty, Biomedical engineering graduate program, Emory University, Atlanta, GA

2019- Faculty, Winship Cancer Institute, Emory University, Atlanta, GA

2016- Affiliated Faculty, Chemistry Department, Emory University, Atlanta, GA

2015-2022 Faculty, Biochemistry, Cell and Developmental Biology Graduate Program, Emory University, Atlanta, GA
2012- Full Professor, Physics Department, Emory University, Atlanta, GA
2007-2011 Affiliated Faculty, Emory Computational and Life Science (CLS) Initiative, Atlanta, GA
2005-2012 Associate Professor, Physics department, Emory University, Atlanta, GA

Other Experience and Professional Memberships

Reviewer for various peer-reviewed, scientific journals such as *Cell*, *PRL*, *PRE*, *PNAS*, *Journal of Molecular Biology*, *Biophysical Journal*, *Nucleic Acids Research* (*NAR*), *European Biophysics J*, Nature Publishing Group (npg) Journals, *eLife*, JoVE, etc.

2023 Reviewer for NSF Div-Bio Infrastructure Major Research Instrumentation (DBI-MRI)
2023 Reviewer (NASEM) Ford Foundation Fellowships, Physical Sciences, Mathematics, & Computer Science (undergraduates, graduates, postdoc).
2021 Reviewer for NIH ZRG1 F04B-H Biochemistry and Biophysics of Biological Macromolecules
2020 Reviewer for NIH (NIAID and MGA).
2020 – 2022 Co-founder and co-Chair of the Biophysical Society "Single molecule forces, visualization and manipulation" Subgroup.
2021-present Founder and Chair of the Diversity, Equity and Inclusion (DEI) Committee of the Emory Physics Department
2021 Member, Biophysical Society Nominating Committee
2019-2022 Member, Emory Academic Standards Committee
2018-2021 Member, Emory Tenure and Promotion Advising Committee to the University President
2018-2021 Member, Emory Tenure and Promotion Advising Committee to the University President
2018 Reviewer of NIH Preapplications for a Biomedical Technology Research Resource (X02)
2017 Organizer and Chair, Southeastern Single-Molecule Biophysics Networking Meeting, April 6-9.
2017-2020 Co-Chair, Emory Faculty Science Council
2016-present Co-founder and Chair, Women in Science at Emory (WiSE)
2016-present Member, *Biophysics Reviews* Editorial Board
2015-2015 Site reviewer, NIH P41 center "National Biomedical Technology Resource to Address Challenges Related to RNA Research.
2015-2015 Chair, Biophysical Society, Nanoscale biophysics Subgroup
2014-2014 Vice-Chair, Biophysical Society, Nanoscale Biophysics Subgroup
2013-2016 Member, Emory Tenure & Promotion Committee
2013-2013 Co-organizer, Atlanta Area Molecular and Cellular Biophysics Symposium
2013-2013 Member, Emory Committee for the Enhancement of the Undergraduate Experience
2012-2018 Standing member, NIH Molecular Function and Structure C (MFSC) study section
2012-2015 Member, Emory Undergraduate Curriculum Committee
2011-2013 Member, Biophysical Society Executive Board
2011-present Reviewer, Dutch Government (FOM), Belgian Research Council, Swiss National Science Foundation, Australian Research Council
2010-2013 Member, Biophysical Society Program Committee
2010-2010 Member, Biophysical Society Nominating Committee
2010-present Reviewer for promotion cases at various domestic and foreign Universities
2009-present Member, American Physical Society
2008-2014 Member, *Biophysical Journal* Editorial Board (two terms)
2008-2011 Director of Graduate Studies, Emory University, Physics Department
2008-2011 Elected member, Biophysical Society Council
2008-2010 Member, Biophysical Society Special Programs Committee
2008-present Ad hoc reviewer for NSF and HFSPO.
1989-present Member, Biophysical Society

Honors (selected from last 5 years)

2024 Invited Speaker and Chair, *The fluid vs. gel nature of the genome* Synposium, 68th Biophysical Society Meeting, Philadelphia, Feb 10-14.

2023 Invited speaker, *TORC Talk.* Online online seminar series, on the importance of DNA supercoiling in gene regulation, and the physical mechanisms as to how this is achieved. An Ireland-UK initiative.

2023 Invited speaker, *School on Biophysics*, Ettore Majorana Foundation and Centre, Erice, Italy, Oct 16-20.

2022 Publication (a) in the personal statement above has been cited more than 2400 times and has been judged to be a landmark in the first NASEM decadal report on the field of Biological Physics/Physics of living systems.

2022 Keynote speaker, *International School of Physics Enrico Fermi* on "Multimodal and Nanoscale Microscopy", Varenna, Italy, July 11-16th.

2022 Invited speaker, American Physical Society, Div. Biol. Phys, *Living Histories series*, April 20.

2021 Keynote speaker, *Nanoscopy 2.0*, 6th NIC@IIT, Italian Institute of Technology, Genova, Italy, Nov 29 - Dec 3.

2020 Invited speaker, *XXII Annual Linz Winter Workshop on Force Spectroscopy*, Linz, Austria, Jan 31-Feb 3.

2018 Invited Speaker and co-Chair *DNA supercoiling Symposium*, 62nd Biophysical Society Meeting

C. Contributions to Science

1. *Technique and Instrumentation development*. During my career, I built several microscopes of novel design and contributed substantially to the development of the analysis of data gathered with the tethered particle motion (TPM) technique. These technical achievements proved valuable in the understanding of structure and function of a variety of systems from the thylakoid membranes of chloroplasts to DNA transactions and I have helped other investigators across the world set up the TPM technique, among whom are Francesco Pavone (LENS, Italy) and Rob Phillips (CalTech); related software is available on my group website. Thus, I am recognized as one of the best-known experts of this technique[a,b]. Recently, my group designed and implemented a new prototype of electro-magnetic tweezers for single-molecule manipulations which minimizes mechanical vibrations[c]. The article was highlighted in *SciLight* (DOI: 10.1063/10.0006622), the publication of the American Institute of Physics (AIP) that shawcases most innovative research. Additionally, we devised an algorithm to track a single particle in bright field which allows fast and accurate characterization of the S/N ratio in magnetic tweezers data[d].

   a. Suleyman Ucuncuoglu , David A. Schneider, Eric R. Weeks, David Dunlap, Laura Finzi, Multiplexed, Tethered Particle Microscopy for Studies of DNA-Enzyme Dynamics. *Methods Enzymol*. 2017; 582:415-435. PubMed PMID: 28062044; PubMed Central PMCID: PMC5388542.

   b. Daniel T. Kovari, Yan Yan, Laura Finzi, David Dunlap, Tethered Particle Motion: An Easy Technique for Probing DNA Topology and Interactions with Transcription Factors. *Methods Mol Biol*. 2018; 1665:317-340. PubMed PMID: 28940077; PubMed Central PMCID: PMC6089228.

   c. Daniel T. Kovari, David Dunlap, Eric. R Weeks, Laura Finzi, "Model-free 3D localization with precision estimates for brightfield imaged particles", *Optics Express*, 2019; **27**, pp. 29875-29895. PMC6825595.

   d. Joe Piccolo, Josh Mendez Harper, Daniel Kovari, David Dunlap, Laura Finzi, “Force spectroscopy with electromagnetic tweezers”, *Journal of Applied Physics* 2021; **130,** 134702; DOI: 10.1063/5.0060276

2. *DNA mechanics*. I pioneered single-molecule studies of DNA mechanics (ref. *a* in the Personal Statement above). Since then, using single molecule approaches, my collaborators and I have investigated how the bending and torsional elasticities of DNA change in different physiologically relevant conditions. For example, we adapted a statistical mechanics-based model to show that DNA *force-vs-extension* curves can be used as a macroscopic readout of the number of proteins bound to DNA[a]. We also investigated the effect of ionic strength on protein-induced DNA unwinding[b]. Since, DNA elasticity plays an important role in enzyme activity, we used diaminopurine (DAP)-substituted DNA, which is stiffer than normal DNA, to elucidate mechanistic differences between gyrase and human topoisomerase II[c]. Given its utility as an analytical tool and its newly found presence in several bacteria and phages genomes, we characterized DAP-DNA torsional elasticity[d] and plan to continue to use this substituted double helix to understand the role of DNA stiffness in tuning DNA interactions.

   a. Sachin Goyal, Chandler Fountain, David Dunlap, Fereydoon Family, Laura Finzi, Stretching DNA to quantify nonspecific protein binding. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2012 Jul;86(1 Pt 1):011905. PubMed PMID: 23005450; PubMed Central PMCID: PMC3653181.

b. Alexander Zhang, Yan Yan, Fenfei Leng, David Dunlap, and Laura Finzi, "Ionic strength modulates HU protein-induced supercoiling." BIORXIV/2021/464438

c. Monica Fernández-Sierra, Qing Shao, Chandler Fountain, Laura Finzi, David Dunlap, *E. coli* Gyrase Fails to Negatively Supercoil Diaminopurine-Substituted DNA. *J Mol Biol*. 2015 Jul 3;427(13):2305-18. PubMed PMID: 25902201; PubMed Central PMCID: PMC4457584.

d. Domenico Salerno, Francesco Mantegazza, Valeria Cassina, Matteo Cristofalo, Qing Sha, Laura Finzi, David Dunlap, "Nanomechanics of negatively supercoiled diaminopurine-substituted DNA", *Nucleic Acids Res*. 2021; Oct 29, PubMed PMID: 34718727; PubMed Central PMCID: PMC8599871.

3. *Loop-based genetic switches and DNA supercoiling/topology*. Protein-mediated DNA looping is a ubiquitous regulatory mechanism involved in the most fundamental processes of the cell from packaging to, for example, recombination and repair. In transcription, operation of many genetic switches relies on protein-induced DNA loops. The open and closed conformations of the loop correspond to ON or OFF states of the switch. Understanding the parameters that regulate the activity of a switch and make it responsive to changes in the external environment is essential to the understanding of transcriptional regulation. Using the lysogeny/lysis genetic switch of the λ bacteriophage, my group discovered some of the essential features of looped-based genetic switches. We demonstrated that i) the number of binding sites at the closure of the loop and their binding affinity affect the thermodynamic stability of the loop and allow for cooperative interactions that create a tunable switch, ii) non-specific binding can be a significant synergistic factor that tweaks the dynamics of the switch, and renders it robust, yet sensitive to external changes, iii) DNA supercoiling toggles the switch in response to the health status of the cell. We further discovered that protein-mediated loops are complex structures that trap supercoiling and may endure significant torsional stress. Since DNA supercoiling is an inherent feature of all genomes, we have more recently investigated the interplay between protein-mediated looping and supercoiling. We found that DNA supercoiling lowers the free energy of DNA loop formation by the paradigm lac repressor (LacI) protein[(a)] and that unwinding, and not nucleoid associated proteins, can drive LacI-mediated looping to 100% even in the presence of physiologically relevant levels of tension[(b)]. We have also shown that protein-mediated looping in supercoiled DNA generates large topological domains that may enable co-regulation of distant genes[(c)]. We found that negative supercoiling is a determinant parameter that finely tunes the probability of LacI-mediated DNA looping on the timescale of *E. coli*'s doubling time[(d)].
   a. Ding Y, Manzo C, Fulcrand G, Leng F, Dunlap D, Finzi L. DNA supercoiling: a regulatory signal for the λ repressor. *Proc Natl Acad Sci U S A*. 2014 Oct 28;111(43):15402-7. PubMed PMID: 25319264; PubMed Central PMCID: PMC4217475.
   b. Yan Y, Leng F, Finzi L, Dunlap D. Protein-mediated looping of DNA under tension requires supercoiling. *Nucleic Acids Res*. 2018 Mar 16;46(5):2370-2379. PubMed PMID: 29365152; PubMed Central PMCID: PMC5861448.
   c. Yan Yan, Yue Ding, Fenfei Leng, David Dunlap, Laura Finzi, Protein-mediated loops in supercoiled DNA create large topological domains. *Nucleic Acids Res*. 2018 May 18;46(9):4417-4424. PubMed PMID: 29538766; PubMed Central PMCID: PMC5961096.
   d. Yan Yan, Wenxuan Xu, Sandip Kumar, David Dunlap, Laura Finzi, "Negative DNA supercoiling under tension makes protein-mediated looping deterministic and ergodic within the bacterial doubling time", *Nucleic Acids Res.* 2021 PubMed PMID: 34723343; PubMed Central PMCID: PMC8599721.
4. *Transcription and its regulation*. We investigate transcription by single RNA polymerases, including the less-studied, but essential RNA polymerase I, which transcribes ribosomal RNA and is responsible for more than 60% of all transcriptional activity in eukaryotes. We study the effect that protein-induced topological rearrangements of DNA have on elongating *E. coli* RNA polymerase (RNAP). Using AFM, we compared three roadblocks (LacI, λ CI and 186 CI) that exemplify the three main mechanisms with which transcription factors interact with DNA and regulate transcription: looping, looping by cooperative interaction of several proteins and wrapping[(a,b)]. We discovered that while proteins securing a loop turn into strong roadblock for an approaching RNAP, even if bound to a weaker binding site, proteins that close a loop, or wrap DNA via multiple cooperative interactions are generally much weaker roadblocks. This indicates a rule of thumb to assess roadblocks. TPM experiments revealed that, independently of affinity, LacI bound at the promoter-proximal operator became a stronger roadblock when securing a loop. In contrast, LacI bound to a distal operator was a weaker roadblock in a looped configuration suggesting that RNAP might more easily displace LacI obstacles within a torsion-constrained DNA loop[(c)]. Since protein junctions can efficiently block the diffusion of DNA supercoiling, these data indicate that the positive supercoiling generated ahead of a

transcribing RNAP may facilitate the dissociation of a roadblock. Magnetic tweezers measurements showed that pauses are indeed shorter when RNAP encounters obstacles on positively supercoiled than on relaxed DNAand that at similar winding levels of the DNA template, RNAP pause duration decreased with tension[(c)]. In recognition of these contributions, we have been recently invited to review the field[(d)].

a. Vörös Z, Yan Y, Kovari DT, Finzi L, Dunlap D. Proteins mediating DNA loops effectively block transcription. Protein Sci. 2017 Jul;26(7):1427-1438. PubMed PMID: 28295806; PubMed Central PMCID: PMC5477534.
b. Yue Lu, Gustavo Borjas, Christine Hendrickson, Zsuzsanna Vörös, David Dunlap, Keith Shearwin and Laura Finzi, "Proteins mediating different DNA topologies block RNAP elongation with different efficiency." *FEBS Letters*, 2022, **596**, 1994-2006; doi:10.1002/1873-3468.14447. Editor's choice-Journal cover.
c. Wenxuan Xu, Yan Yan, Irina Artsimovich, David Dunlap and Laura Finzi, "Positive supercoiling favors transcription elongation through lac repressor-mediated DNA loops", *Nucleic Acids Research* 2022, 50, 2826-2835. PubMed PMID: 35188572; PubMed Central PMCID: PMC8934669.
d. Jin Qian, Wenxuan Xu, David Dunlap and Laura Finzi "Single-molecule insights into torsion and roadblocks in bacterial transcript elongation", *Transcription*, 2021 Aug;12(4):219-231. PubMed PMID: 34719335; PubMed Central PMCID: PMC8632135.

5. *Theoretical approaches*. We use and develop theoretical approaches as needed[(a-c)]. Recently, since RNAP pausing is relevant to the analysis of several of our current measurements, we developed a thermodynamic model for the prediction of pausing[(d)].

a. Sachin Goyal, Chandler Fountain, David D. Dunlap, Fereydoon Family, Laura Finzi, "Stretching DNA to quantify non-specific binding", *Physical Review E*, **86**, 011905, 2012. PMCID: PMC3653181
b. Wenxuan Xu, Laura Finzi and David Dunlap "Energetics of twisted DNA topologies", *Biophysical Journal*, 2021,*120*, Issue 16, 3242-3252. PubMed PMID: 33974883; PubMed Central PMCID: PMC8391063.
c. Jin Qian, David Dunlap, and Laura Finzi, Basic mechanisms and kinetics of pause-interspersed transcript elongation, *Nucleic Acids Research* (2020) *49*, 15-24. PubMed PMID: 33330935; PubMed Central PMCID: PMC7797061.
d. Jin Qian, David Dunlap and Laura Finzi, "Thermodynamic Model of Bacterial Transcription." *Physical Review E*, 1 October 2022; Vol. **106**, No. 4; DOI: 10.1103/PhysRevE.106.044406.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40647244/?sort=date&direction=descending