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: Dunn, Alexander

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

POSITION TITLE: 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)	END DATE MM/YYYY	FIELD OF STUDY
California Institute of Technology, Pasadena, CA	BS	06/1998	Chemistry
California Institute of Technology, Pasadena, CA	Ph.D.	06/2003	Chemistry
Stanford University School of Medicine, Stanford, CA	Postdoc	12/2008	Biochemistry

A. Personal Statement

The goal of our laboratory is to discover the biophysical mechanisms underlying the construction of cells and tissues. Our lab has used genetically encoded, fluorescent molecular tension sensors to measure forces transmitted between adjacent epithelial cells (Borghi *et al.*, PNAS 2012; Price *et al.*, Nat. Comm. 2018). These experiments, along with in vitro single-molecule optical trap measurements (Buckley *et al.*, Science 2014), clarified how physical linkages between neighboring cells are established—a finding with important implications for our understanding of embryonic development and cancer biology. Complementary work examining integrin-based linkages to the extracellular matrix revealed the importance of a previously understudied integrin state in mediating cell adhesion (Chang *et al.*, ACS Nano 2016) and motivated an update to the molecular clutch hypothesis, the dominant model for how cells exert cytoskeletally generated forces on their surroundings (Tan *et al.*, Science Adv. 2020; Miller *et al.*, Nat. Comm. 2022). Single-molecule biophysical measurements also revealed that the molecular linkages between cell adhesion complexes and the F-actin cytoskeleton are intrinsically directional (Huang *et al.*, Science 2017; Owen *et al.*, PNAS 2022), suggesting how cellular adhesions can seed long-range order in the actin cytoskeleton. Recently, we expanded into the field of cryo-electron tomography (cryoET), a technique that provides direct insight into the molecular-scale organization of complex subcellular structures, with the sarcomere being a primary example (Engel *et al.*, J. Struct. Biol. 2021; Engel *et al.*, Nat. Commun. 2025).

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2016 - 2024	Associate Professor, Dept. of Chemical Engineering, Stanford University
2012 -	Fellow, Stanford ChEM-H Institute, Stanford University
2010 -	Member, Stanford Cardiovascular Institute, Stanford University School of Medicine
2009 - 2016	Assistant Professor, Dept. of Chemical Engineering, Stanford University
2004 -	Professor, Dept. of Chemical Engineering, Stanford University

Honors

2016 - 2022	HHMI Faculty Scholar, Howard Hughes Medical Institute
2010 - 2015	NIH Director's New Innovator Award, NIH
2008 - 2013	Career Award at the Scientific Interface, Burroughs Wellcome Fund
2003 - 2006	Jane Coffin Childs Fellowship, Jane Coffin Childs Memorial Fund for Medical Research
1998 - 2003	Hertz Graduate Fellowship, Fannie and John Hertz Foundation
2018	Tau Beta Pi Teaching Award, Stanford University
2008	James H. Clark Faculty Fellowship, Stanford University
2008	K99/R00 Pathway to Independence Award (declined), NIH
2003	Herbert Newby McCoy Award (outstanding Ph.D. thesis), California Institute of Technology

Scientific Service and Appointments

2026	Chair, Signaling Through Adhesion Receptors Gordon Research Conference
2023-present	Founder and Co-organizer of the Living Matter Interest Group, a Bay Area colloquium series hosted by the Chan-Zuckerberg Biohub
2024	PI for R13 to fund the Signaling Through Adhesion Receptors Gordon Research Conference
2017-2022	Standing Member, Intercellular Interactions (ICI) NIH study section
2024	Vice Chair (elect), Signaling Through Adhesion Receptors Gordon Research Conference
2021	Co-organizer ASCB subgroup “How Cells Build on the Micron Scale” ASCB national meeting
2020	Co-organizer ASCB subgroup “Cytoskeletal Ensembles Across Scales” ASCB national meeting
2019	Co-organizer ASCB subgroup “Mechanics of Large Cellular Machines” ASCB national meeting
2018	Program committee, ASCB national meeting
2017	Chair, Mechanobiology Subgroup, Biophysical Society
2017-present	Editorial Board Member, Molecular Biology of the Cell
2016 – 2021	Editorial Board Member, Biophysical Journal
2016	Chair for American Institute of Chemical Engineers National Meeting, Areas 15d/e.
2014 – 2018	Scientific Advisory Board, Myokardia, South San Francisco, CA
2013	DARPA/Hertz Foundation Future Ideation Session, Arlington, VA
2013	NSF Proposal Review Panel, Directorate of Engineering
2013 – 2016	Secretary, Cellular Mechanobiology Subgroup, Biophysical Society

C. Contribution to Science

1. **Mechanosensing at cell-cell adhesions.** Until relatively recently it was not known how, and even whether, cells might sense mechanical forces generated by their neighbors. We developed a fluorescent, genetically encoded molecular force sensor to, for the first time, directly measure the forces transmitted between neighboring cells (Borghi _et al._ PNAS 2012). This study provided conclusive evidence that the adhesion protein E-cadherin acts as a linkage between the cytoskeletons of neighboring cells and that this cell-cell linkage experiences constitutive mechanical tension. In addition, we used a single-molecule optical trap assay to show that the mechanical linkage between the E-cadherin complex and F-actin acts as an exquisitely sensitive force sensor (Buckley _et al._ Science 2014). In subsequent work, we used an updated version of this assay to identify the probable molecular mechanism that underlies force sensing. Together, these studies provide a firm mechanistic basis for understanding how mechanotransduction can occur at cell-cell contacts, a result with important implications for our understanding of both embryonic development and cancer biology. In more recent work, we extended these studies to reveal an unexpected role for vinculin and α-catenin in generating long-range polarity the cytoskeleton. We have likewise used genetically encoded force sensors to determine when and where desmosomes transmit mechanical forces between adjoining cells in simple epithelia. In total, these studies have materially advanced our understanding of how cells sense and transmit mechanical forces at cell-cell junctions.
    a. Bax NA, Wang A, Huang DL, Pokutta S, Weis WI, Dunn AR. Multi-level Force-dependent Allosteric Enhancement of αE-catenin Binding to F-actin by Vinculin. *J Mol Biol.* 2023 Mar 1;435(5):167969. PMCID: PMC9957948.
    b. Wang A, Dunn AR, Weis WI. Mechanism of the cadherin-catenin F-actin catch bond interaction. *Elife*. 2022 Aug 1;11 PMCID: PMC9402232.
    c. Price AJ, Cost AL, Ungewiß H, Waschke J, *Dunn AR, *Grashoff C. Mechanical loading of desmosomes depends on the magnitude and orientation of external stress. *Nat Commun*. 2018 Dec 11;9(1):5284. PMCID: PMC6290003.
    d. Huang DL, Bax NA, Buckley CD, *Weis WI, *Dunn AR. Vinculin forms a directionally asymmetric catch bond with F-actin. *Science*. 2017 Aug 18;357(6352):703-706. PMC5821505.
2. **Mechanosensing at integrin-based adhesions.** We have made important contributions to the current understanding of how cells sense mechanical forces at integrin-based adhesions to the extracellular matrix (ECM). When we joined the field, surprisingly little was known about how integrin-based mechanosensing occurs at the molecular level. Even the magnitude of forces experienced by individual integrins was uncertain, with estimates ranging from <1 to >100 pN. This knowledge gap made it difficult to formulate models of how cellular adhesion works at a physical level. We developed FRET-based molecular tension

sensors (MTSs) to directly visualize the traction forces exerted by single integrins. We found that the majority of integrins transmit forces <3 pN, much less than the maximal loads supported by integrin-ligand bonds. These and other data indicate that a large pool of minimally tensioned integrins plays an essential role in providing cells and tissues with mechanical integrity. In subsequent work, we used single-MTS measurements, theory, and single-molecule imaging to perform a direct, molecular-scale characterization of how cells transmit cytoskeletal forces though adhesion complexes to the extracellular matrix. These data motivated a reevaluation of the consensus, "molecular clutch" model for how cells transmit cytoskeletal forces to their surroundings. A revised model can account for our results and suggests how mechanical stability can arise from the dynamical properties of the actin cytoskeleton. Finally, we used a single-molecule optical trap assay to demonstrate that talin forms a force-sensitive catch bond with F-actin that requires dimerization and is exquisitely directional, with appreciable binding lifetimes only when the actin filament is oriented in the direction compatible with myosin-based force generation. In combination with parallel studies of vinculin and αE-catenin (see above), these data support a unified model for how cellular adhesion complexes can seed long-range cytoskeletal organization at the cell and tissue levels.

a. Miller CM, Korkmazhan E, Dunn AR. Extraction of accurate cytoskeletal actin velocity distributions from noisy measurements. *Nat Commun*. 2022 Aug 13;13(1):4749. PMCID: PMC9376101.

b. Owen LM, Bax NA, Weis WI, Dunn AR. The C-terminal actin-binding domain of talin forms an asymmetric catch bond with F-actin. *Proc Natl Acad Sci U S A.* 2022 Mar 8;119(10):e2109329119. PMCID: PMC8915792.

c. Tan SJ, Chang AC, Anderson SM, Miller CM, Prahl LS, Odde DJ, Dunn AR. Regulation and dynamics of force transmission at individual cell-matrix adhesion bonds. *Sci Adv.* 2020 May;6(20):eaax0317. PMCID: PMC7228748.

d. Chang AC, Mekhdjian AH, Morimatsu M, Denisin AK, Pruitt BL, Dunn AR. Single Molecule Force Measurements in Living Cells Reveal a Minimally Tensioned Integrin State. *ACS Nano*. 2016 Dec 27;10(12):10745-10752. PMCID: PMC5886374.

3. **Emergence of cell- and tissue-level organization across length scales.** In recent work we have expanded our focus to the broader question of how living systems self-organize on a variety of length scales. In one such study, we used time-lapse 3D imaging and mathematical modeling to understand the physical mechanisms by which a solid mass of cells develops a hollow opening, or lumen. These experiments revealed that lumen formation is intrinsically coupled to the geometrical constraints imposed by creation of a non-stick apical domain, suggesting a deep linkage between the fields of physical biology and cell polarity and helping to explain lumen shapes observed in a wide variety of developmental contexts. In complementary work, we used a single-molecule optical trap assay to discover that ezrin, which links the apical membrane to the actin cytoskeleton, forms a complex that slides along F-actin. In so doing, ezrin provides a dynamic linkage that allows the cell membrane and the actin cortex to undergo rapid remodeling while still resisting the physical forces that might otherwise cause membrane rupture. In conceptually related work, we used a combination of single-molecule imaging and sophisticated modeling to demonstrate that the highly unusual gliding motility used by the eukaryotic parasite *Toxoplasma gondii* arises from spontaneous, self-organizing flows in the actin cytoskeleton. Finally, in collaboration with *Drosophila* geneticists, we are dissecting the physical and molecular mechanisms that underlie planar cell polarity, the development of long-range order in epithelial tissues. Our studies show that signal amplification and error correction in this pathway are intrinsically coupled to the cooperative assembly and dynamics of large planar cell polarity signaling clusters. More broadly, this work is beginning to reveal general design principles by which condensates and related mesoscale macromolecular assemblies implement robust signal transduction across diverse cellular contexts.

a. Nissen SB, Weiner AT, Suyama K, Bosch PS, Yu M, Song S, Gu Y, Dunn AR, Axelrod JD. Cluster Assembly Dynamics Drive Fidelity of Planar Cell Polarity Polarization. *bioRxiv*. 2025 Jan 31; PMCID: PMC11526938.

b. Hueschen CL, Segev-Zarko LA, Chen JH, LeGros MA, Larabell CA, Boothroyd JC, Phillips R, Dunn AR. Emergent actin flows explain distinct modes of gliding motility. *Nat Phys*. 2024;20(12):1989-1996. PMCID: PMC11631758.

c. Korkmazhan E, Dunn AR. The membrane-actin linker ezrin acts as a sliding anchor. *Sci Adv*. 2022 Aug 5;8(31):eabo2779. PMCID: PMC9355349.

d. Vasquez CG, Vachharajani VT, Garzon-Coral C, Dunn AR. Physical basis for the determination of lumen shape in a simple epithelium. *Nat Commun.* 2021 Sep 23;12(1):5608. PMCID: PMC8460836.

4. **Physical biology of the peripheral and central nervous system.** The Dunn lab has a long-term interest in the physical biology of neurons. In initial work, we examined how peripheral neurons withstand the large mechanical strains generated by body movement. We used a combination of atomic force microscopy (AFM) measurements, laser axotomy, and genetically encoded, fluorescent tension sensors to demonstrate that touch-responsive neurons (TRNs) in C. elegans are under mechanical pre-stress, and that this prestress protects the neurons from physical damage. In more recent work, we used FRET-based molecular tension sensors to probe the molecular mechanisms that underlie the migration of neural stem cells, which must travel large distances in the brain to repair damage from injury or infection. These data demonstrate a tradeoff between cell adhesion strength and migration speed, with excessive adhesion limiting neural stem cell migratory ability in aged mice. Finally, we have used a magnetic tweezers assay to demonstrate that latrophilin, an adhesion GPCR that localizes to neuronal synapses, is potently activated by physiological levels of mechanical force. These data motivate the hypothesis that mechanical cues may help to control neuronal synapse formation and remodeling.
   a. Zhong BL, Lee CE, Vachharajani VT, Bauer MS, Südhof TC, Dunn AR. Piconewton Forces Mediate GAIN Domain Dissociation of the Latrophilin-3 Adhesion GPCR. *Nano Lett*. 2023 Oct 25;23(20):9187-9194. PMCID: PMC11801148.
   b. Yeo RW, Zhou OY, Zhong BL, Sun ED, Navarro Negredo P, Nair S, Sharmin M, Ruetz TJ, Wilson M, Kundaje A, Dunn AR, Brunet A. Chromatin accessibility dynamics of neurogenic niche cells reveal defects in neural stem cell adhesion and migration during aging. *Nat Aging.* 2023 Jul;3(7):866-893. PMCID: PMC10353944.
   c. Krieg M, Stühmer J, Cueva JG, Fetter R, Spilker K, Cremers D, Shen K, Dunn AR, Goodman MB. Genetic defects in β-spectrin and tau sensitize *C. elegans* axons to movement-induced damage via torque-tension coupling. *Elife*. 2017 Jan 18;6 PMCID: PMC5298879.
   b. Krieg M, Dunn AR, Goodman MB. Mechanical control of the sense of touch by β-spectrin. *Nat Cell Biol.* 2014 Mar;16(3):224-33. PMC4046587.

5. **Endothelial cell response to fluid flow.** Little is presently known about how endothelial cells respond to spatial variations in fluid shear stress such as those that occur locally during embryonic development, at vascular and heart valve leaflets, and at sites of aneurysm formation. In earlier work, we built a novel flow device that exposes endothelial cells to gradients of shear stress (Ostrowski et al. Biophys. J. 2014). Using this and related devices, we discovered that endothelial cells are exquisitely sensitive to both the magnitude and spatial gradients in wall shear stress. In subsequent work, we determined that the G protein–coupled receptor (GPCR) sphingosine 1-phosphate receptor 1 (S1PR1), a protein known to be critical for vascular development, is required for directional cell migration in response to flow. Work in collaboration with Kristy Red-Horse (Stanford U.) revealed that endothelial cells migrate upstream in the developing cardiac vasculature, and that this migration is controlled in part by signaling through CXCL12 and CXCR4. More recently, we examined the response of cells to combined spatial and temporal variations in wall shear stress, such as occur at branch points in the blood and lymphatic vasculature. These studies revealed that endothelial cells integrate both forms of flow information to regulate intracellular signaling through calcium, NFAT, and other pathways. Over the longer term, we aim to build on these results to discover the molecular mechanisms that drive vascular and lymphatic valve formation, with the long-term goal of growing transplantable valves in an in vitro setting.
   a. Michalaki E, Surya VN, Rodríguez-Hakim M, Fuller GG, Dunn AR. Response of lymphatic endothelial cells to combined spatial and temporal variations in fluid flow. *FASEB J*. 2023 Dec;37(12):e23240. PMCID: PMC11863998.
   b. Michalaki E, Surya VN, Fuller GG, Dunn AR. Perpendicular alignment of lymphatic endothelial cells in response to spatial gradients in wall shear stress. *Commun Biol.* 2020 Feb 6;3(1):57. PMCID: PMC7005002.
   c. Surya VN, Michalaki E, Fuller GG, Dunn AR. Lymphatic endothelial cell calcium pulses are sensitive to spatial gradients in wall shear stress. *Mol Biol Cell.* 2019 Mar 21;30(7):923-931. PMCID: PMC6589782.
   d. Chang AH, Raftrey BC, D'Amato G, Surya VN, Poduri A, Chen HI, Goldstone AB, Woo J, Fuller GG, Dunn AR, Red-Horse K. DACH1 stimulates shear stress-guided endothelial cell migration and coronary

artery growth through the CXCL12-CXCR4 signaling axis. *Genes Dev.* 2017 Jul 1;31(13):1308-1324. PMCID: PMC5580653.

Complete List of Published Work in My Bibliography

90 peer-reviewed publications, **32** publications and preprints 2021-present

https://www.ncbi.nlm.nih.gov/myncbi/alexander.dunn.1/bibliography/public/