

BIOGRAPHICAL SKETCH

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NAME Elston, Timothy Charles	POSITION TITLE Professor of Pharmacology		
eRA COMMONS USER NAME (credential, e.g., agency login) telston			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Georgia Institute of Technology	B. S.	1988	Physics
Georgia Institute of Technology	Ph. D.	1993	Physics
Los Alamos National Laboratory	Postdoctoral	1993-1997	Biophysics

A. Personal Statement

I received my graduate training in physics with an emphasis on statistical physics and nonlinear dynamics. As a postdoctoral researcher, I became interested in applying tools from these fields to problems in biophysics and cell biology. In particular, my lab integrates computational approaches, including mathematical modeling and quantitative image analysis, with experimental investigations to understand complex cellular behavior. We also develop novel computational techniques for quantitative analyses of live-cell images and simulating spatiotemporal models of signaling pathways. Current projects in the lab focus on cell fate decisions, polarity establishment and gradient sensing. The primary model system we use to study these cellular functions is the yeast *Saccharomyces cerevisiae*. Our investigations combine microfluidic technology with live-cell microscopy to observe cellular behavior in well-controlled environments. This experimental platform provides a powerful system for developing and validating predictive models of cellular function. My lab also is involved in multiple collaborative projects to investigate these fundamental cellular processes in physiological contexts and their dysregulation in human disease.

B. Positions and Honors

1994-1997 Postdoctoral Fellow, The Center for Nonlinear Studies, Los Alamos National Laboratory
1996-1997 Visiting Scholar, Department of Molecular and Cell Biology, University of California, Berkeley
1997-1998 Assistant Professor, Department of Physics, DePaul University
1998-2002 Assistant Professor, Department of Statistics, North Carolina State University
2001-2002 Director of the Graduate Program, Biomathematics Graduate Program, North Carolina State University
2002-2005 Associate Professor, Department of Mathematics, University of North Carolina at Chapel Hill
2004 Chair, Gordon Research Conference, Theoretical Biology and Biomathematics
2005-2008 Associate Professor, Department of Pharmacology, University of North Carolina at Chapel Hill
2005-2009 Editorial Board, *Mathematical Medicine and Biology*
2005- Director of the Graduate Program in Bioinformatics and Computational Biology, University of North Carolina at Chapel Hill
2006- Editorial Board, *Journal Theoretical Biology*
2006 Chair, Joint SIAM/SMB Life Sciences Conference
2008- Professor, Department of Pharmacology, University of North Carolina at Chapel Hill
2009- Member, Modeling and Analysis of Biological Systems Study Section, NIH
2009- Chair, Research Computing Advisory Committee
2011- *Science*, Board of Reviewing Editors

C. Contributions to Science

1. Motor proteins. As a postdoctoral fellow working with Dr. George Oster, I became interested in the mechanisms used by motor proteins to convert chemical energy into directed motion. My work during this time focused on energy transduction in the rotary motors ATP synthase (a) and the bacterial flagellar motor (b). These studies demonstrated how linear proton fluxes could be converted into rotary motion. More recently, I have worked on force generation by the motor protein dynein (c). This work developed the first computational model for two-headed dynein that couples conformational changes of the motor's subunits to the biochemical steps involved in ATP hydrolysis. I have also developed fast and efficient numerical methods for simulating stochastic models of motor proteins (d).
 - a. Elston, T. C., H. Wang and G. Oster. 1998. Energy transduction in ATP synthase. *Nature* 391:510-513.
 - b. Elston, T. C. and G. Oster. 1997. Protein turbines I: the bacterial flagellar motor. *Biophys. J.* 73:703-721.
 - c. Tsygankov, D., A., A. Serohijos, N. Dokholyan and T.C. Elston. 2011. A Physical Model Reveals the Mechanochemistry Responsible for Dynein's Processive Motion. *Biophys J.* 101:144-150.
 - d. Wang, H. C. Peskin and T. C. Elston. 2003. A robust numerical algorithm for studying energy transduction in motor proteins. *J. Theor. Biol.*, 221:491-511.

 2. Noise in gene regulation. As an assistant professor at North Carolina State University, I became interested in the origins and consequences of noise in gene expression and signaling pathways (a). Together with Dr. Tom Kepler, we developed some of the initial theories into how molecular level noise can qualitatively change the dynamical behavior of simple gene networks (b). Working with Dr. Jim Collins, my lab developed predictive stochastic models for gene expression that were then validated using engineered gene networks in *E. coli* (c). My lab also has developed stochastic models of signaling pathways, and used these models to demonstrate how even small levels of noise can influence the temporal behavior of these systems (d).
 - a. Kaern, M., W. Blake, T. C. Elston, and J. Collins. 2005. Stochasticity in gene expression. *Nat. Gen.*, 6:451-464.
 - b. T. Kepler and T. C. Elston. 2001. Stochasticity in transcriptional regulation: origins, consequences, and mathematical representations. *Biophys. J.* 81:3116-3136.
 - c. Guido, N., X. Wang, D. Adalsteinsson, D. McMillen, J. Hasty, T. C. Elston, and J. J. Collins. 2006. A bottom-up approach to gene regulation. *Nature*, 439: 856-860.
 - d. Wang, X., N. Hao, H. Dohlman and T. C. Elston. 2006. Bistability, Stochasticity and Oscillations in the Mitogen Activated Protein Kinase Cascade. *Biophys. J.* 90: 1961-78.

 3. Signal transduction. When I moved to the University of North Carolina at Chapel Hill, I became interested in cell signaling. In collaboration with Drs. Henrik Dohlman and Beverly Errede, my lab developed models of the yeast pheromone response pathway to understand how these cells are able to sense and respond to their environment. These investigations demonstrated how dose-to-duration encoding can be used to transmit information (a) and how kinetic insulation can be used as mechanism for pathway specificity (b). Recently, we have combined live-cell microscopy in microfluidic devices with mathematical modeling to understand receptor dynamics (c). In collaboration with Dr. Alan Jones, my lab also has developed models for glucose sensing in *Arabidopsis* (d).
 - a. Behar, M., N. Hao, H. Dohlman and T.C. Elston. 2008. Dose-to-duration encoding and signaling beyond saturation in intracellular signaling networks. *PLoS Comput. Biol.* 4: e1000197.
 - b. Behar, M. H. Dohlman, and T. C. Elston. 2007. Kinetic insulation as an effective mechanism for achieving pathway specificity in intracellular signaling networks. *Proceedings of the National Academy of Sciences*, 104: 16146-51.
 - c. Venkatapurapu, S., J. Kelley, G. Dixit, M. Pena, B. Errede, H. Dohlman and T.C. Elston. 2015. The RGS protein Sst2 regulates receptor dynamics during the mating response of yeast. *Mol. Biol. of the Cell* (published on line before print).
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- d. Fu, Y., S. Lim, D. Urano, N. Phan, T.C. Elston and A. Jones. 2014. Reciprocal encoding of signal intensity and duration in a glucose sensing circuit. *Cell* 156:1084-1095.
4. **Polarity establishment and gradient sensing.** Recently my lab has become interested in understanding the mechanisms used by yeast to polarize and detect gradients of mating pheromone. In collaboration with Dr. Daniel Lew, we combined mathematical modeling with experimental analyses to demonstrate how negative feedback in the polarity signaling pathway ensures robust polarization and the emergence of a single polarity site (a). Our work with the Lew lab, also has revealed a new mechanism for gradient sensing in which movement of the polarity site is dependent on the concentration of pheromone (b). Finally, we have investigated the role of the scaffold protein Ste5 (c) and the protease Bar1 (d) in gradient sensing.
- a. Howell, S., M. Jin, C. Wu, T. Zyla, T. C. Elston, and D. Lew. 2012. Negative feedback enhances robustness in the yeast polarity circuit. *Cell* 149: 322-333.
- b. Dyer, J.M., Savage, N.S., Jin, M., Zyla, T.R., Elston, T.C., and Lew, D.J. (2013). Tracking shallow chemical gradients by actin-driven wandering of the polarization site. *Curr Biol* 23, 32-41.
- c. Hao, N., S. Nayak, M. Behar, R. Shanks, M. Nagiec, B. Errede, J. Hasty, T. C. Elston and H. G. Dohlman. 2008. Regulation of cell signaling dynamics by the protein-kinase scaffold Ste5. *Molecular Cell* 30:649-56.
- d. Jin, M., B. Errede, M. Behar, W. Mather, S. Nayak, J. Hasty, H.G. Dohlman and T.C. Elston. 2011. Yeast dynamically modify their environment to achieve better mating efficiency. *Science Signaling* 4(186):ra54.
5. **Quantitative image analysis.** A new direction for my lab is the development of computational methods for performing quantitative image analysis (a-d). This work is primarily carried out in collaboration with Drs. Denis Tsygankov and Klaus Hahn. We developed the open source MATLAB application *CellGeo*, a user-friendly computational platform to allow simultaneous, automated tracking and analysis of dynamic changes in cell shape (a). We also developed *SegmentMe*, a MATLAB application designed to perform image segmentation and tracking (b). *SegmentMe* automates the process for monitoring growth and division of individual yeast cells, enabling the rapid and systematic generation of quantitative metrics for measuring and interpreting changes in gene expression.
- a. Tsygankov, D., Bilancia, C.G., Vitriol, E.A., Hahn, K.M., Peifer, M., and Elston, T.C. (2014). *CellGeo*: a computational platform for the analysis of shape changes in cells with complex geometries. *The Journal of cell biology* 204, 443-460.
- b. Tsygankov, D., Chu, P.H., Chen, H., Elston, T.C., and Hahn, K.M. (2014). User-friendly tools for quantifying the dynamics of cellular morphology and intracellular protein clusters. *Methods in cell biology* 123, 409-427.
- c. Karginov, A.V., Tsygankov, D., Berginski, M., Chu, P.H., Trudeau, E.D., Yi, J.J., Gomez, S., Elston, T.C., and Hahn, K.M. (2014). Dissecting motility signaling through activation of specific Src-effector complexes. *Nature chemical biology* 10, 286-290.
- d. Chu, P-H., A. Karginov, D. Tsygankov, M. Berginski, S. Gomez, T.C. Elston, and K. Hahn. 2014. Rapidly activated Src family protein analogs reveal isoform differences in generation of cell morphodynamics. *PNAS* 111:12420-12425.

Complete List of Published Work:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40962549/?sort=date&direction=ascending>

D. Research Support

For Multiple Principle Investigator (MPI) awards * denotes contact PI.

R01 GM079271 (MPI - Elston*, Errede, Lew)

09/01/2006 – 08/31/2018

NIH/NIGMS

Spatiotemporal Modeling of Signal Transduction in Yeast

This project will use mathematical modeling to understand various aspects of the yeast pheromone response pathway. In particular, rate equation and stochastic models will be used to investigate the mechanisms that regulate transcription from the FUS1 promoter, and spatial models based on reaction-diffusion equations will be used to determine the role that protein localization plays in regulating pathway activity.

R01 GM078994 (MPI - Elston*, Jacobson)

04/01/2006 – 03/31/2017

NIH/NIGMS

Cytoskeletal Oscillations: Mathematical Modeling Integrated with Experiments

The goal of this project is to discover the mechanism that underlies cytoskeletal oscillations. This will be accomplished by developing a mathematical model that couples the biochemical network that regulates actin-dependent contractility to force generation by myosin.

R01 GM103870 (MPI - Lew*, Elston)

05/01/2013 – 04/30/2017

NIH/NIGMS

Gradient Tracking and Chemotrophism

This project will develop and analyze mathematical models to understand the molecular mechanisms that allow yeast to detect and track shallow gradients of mating pheromone. The models will be validated using live-cell imaging and other experimental approaches.

MCB-1158054 (MPI - Jones*, Elston)

01/01/2012 – 06/30/2016

NSF

G Protein Activation through Uncoupling Regulator of G Signaling Protein, AtRGS1

This project combines mathematical modeling and experimental analysis to study signaling through G-protein coupled receptors in Arabidopsis. Our working hypothesis is that glucose and/or sugar metabolites activate the G protein pathway by regulating the coupling between the RGS portion of the receptor and G-protein. We will develop a model to quantify this mechanism and suggest experiments to validate the model.

U01 EB018816 (PI Haugh, Bear, Elston)

07/01/2014 – 06/30/2019

NIH

Multiscale modeling of wound healing

This project seeks to develop a predictive, multi-scale model of the proliferative phase of wound healing, incorporating 1) receptor-mediated signal transduction (molecular scale), 2) self-assembly of contractile actomyosin structures (supra-molecular scale), 3) morpho-dynamics and statistics of cell migration (cellular scale), and 4) collective cell behavior in vivo (tissue scale).

R01 GM114136 (MPI - Elston*, Dohlman, Errede)

05/01/2015- 04/30/2019

NIH/NIGMS

Mechanisms of noise regulation in cell fate transitions

This project seeks to elucidate the mechanisms that regulate noise during cell fate transitions in yeast. In particular, we use microfluidic devices and fluorescent imaging to follow single cells in well controlled environments, quantitative image analysis to characterize fluctuations in signaling and gene expression, and stochastic modeling to suggest and test noise regulation mechanisms.
