BIOGRAPHICAL SKETCH

NAME: Elston, Timothy Charles

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

POSITION TITLE: Professor of Pharmacology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date 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

1. Research

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. Currently, my lab integrates computational approaches, including mathematical modeling and quantitative image analysis, with experimental investigations to understand complex cellular behavior. We are particularly interested in understanding network motifs that regulate the spatiotemporal dynamics of cell signaling pathways. We also develop novel computational techniques for quantitative analyses of live-cell images and simulating spatiotemporal models of signaling systems. Current projects in the lab focus on cell fate decisions, migration, polarity establishment and gradient sensing. Part of my research uses yeast *Saccharomyces cerevisiae* as a model organism for studying these processes. 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 signaling pathways in various physiological contexts and their dysregulation in human disease.

2. Training, Mentorship and Service

I have always had a strong commitment to graduate training. I have completed the Mentor Training for Biomedical Researchers course run by the UNC Office of Graduate Education. Before moving to UNC-CH, I served as the Director of the Graduate Program in Biomathematics at North Carolina State University. From 2005-2019, I served as Director of the Curriculum in Bioinformatics and Computational Biology. I have mentored 17 graduate students and 14 postdoctoral researchers; all of whom have gone on to successful careers using the skills they acquired at UNC-CH. I currently have 4 graduate students and 2 postdoctoral researchers in my lab. My philosophy is to provide guidance tailored to the specific needs and career goals of the trainee and to encourage the development of scientific independence

Throughout my career I have made significant contributions to the research community both within and outside the University of North Carolina at Chapel Hill. At UNC-CH, I am currently the Co-Director of the Computational Medicine Program and serve as Chair of the Research Computing Advisory Committee. I was Director of the Curriculum in Bioinformatics and Computational Biology from 2005-2019. Outside of the university, I have served as a standing member of the NIH Modeling and Analysis of Biological Systems (MABS) Study Section and have served on multiple NSF review panels. From 2011-2021 I was on the Board of Reviewing Editors for *Science Magazine*.

<u>Ongoing projects that I would like to highlight include:</u>

U01EB018816 (Haugh) 06/01/2018-05/31/2023

NCSU/NIH

<u>Multiscale modeling of wound healing</u>

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).

U01 CA238475 (Perou, Elston) 06/01/2019-05/31/2024
NCI
Predictive Modeling of the EGFR-MAPK pathway for Triple Negative Breast Cancer Patients
Aim 1: Construct multi-scale models of the EGFR-MAPK signaling network using statistical modeling approaches; Aim 2: Construct mathematical models of the EGFR-MAPK signaling network to investigate mechanisms of drug resistance across multiple time scales; Specific Aim 3: Evaluation of computational models using human breast tumor xenografts and tumors from Phase I and II clinical trials.

B. Positions, Scientific Appointments and Honors

Positions and Employment

2018- Co-Director, Computational Medicine Program
2008- Professor, Department of Pharmacology, University of North Carolina at Chapel Hill
2005-2019 Director of the Graduate Program in Bioinformatics and Computational Biology, University of North Carolina at Chapel Hill
2005-2008 Associate Professor, Department of Pharmacology, University of North Carolina at Chapel
2002-2005 Associate Professor, Department of Mathematics, University of North Carolina at Chapel Hill
2001-2002 Director, Biomathematics Graduate Program, North Carolina State University
1998-2002 Assistant Professor, Department of Statistics, North Carolina State University
1997-1998 Assistant Professor, Department of Physics, DePaul University
1996-1997 Visiting Scholar, University of California at Berkeley
1994-1997 Postdoctoral Fellow, The Center for Nonlinear Studies, Los Alamos National Laboratory

Other Experience

2013-2019 Editorial Board, SIAM Dynamical Systems
2011-2021 *Science*, Board of Reviewing Editors
2009- Chair, Research Computing Advisory Committee
2009-2013 Member, Modeling and Analysis of Biological Systems Study Section, NIH
2006 Chair, Joint SIAM/SMB Life Sciences Conference
2006-2011 Editorial Board, *Journal Theoretical Biology*
2005-2009 Editorial Board, *Mathematical Medicine and Biology*
2004 Chair, Gordon Research Conference, Theoretical Biology and Biomathematics

Academic and Professional Honors

2018- Jeffrey Houpt Distinguished Investigator

C. Contributions to Science

1. Contributions over the past 5 years most related to the current application. The broad focus of my research is to elucidate signaling motifs that allow cells to sense and respond to changes in their environment. To accomplish this goal, we combine computational approaches including mathematical modeling and image analysis with experiments performed in living cells. Recently, we used the pheromone response of yeast to establish regulatory mechanisms that confer memory and adaptation on signaling systems (**a**) and demonstrate how ratiometric sensing can be used for gradient sensing to overcome spatial fluctuations in the distribution of receptors on the cell surface (**b**). We are also interested in determining if the system-level properties we discover in yeast translate to mammalian cells. To this end, we have developed computational techniques for inferring Src activation kinetics from single molecule measurements (**c**) and mathematical models for pattern formation during phagocytosis (**d**).

   a. Pomeroy AE, Pena MI, Houser JR, Dixit G, Dohlman HG, Elston TC, Errede B. A predictive model of gene expression reveals the role of network motifs in the mating response of yeast. Science signaling. 2021;14(670). Epub 2021/02/18. doi: 10.1126/scisignal.abb5235. PubMed PMCID: PMC8193838. [Support: R01GM114136, R35GM127145, R35GM118105 and T32GM067553]
   b. Henderson NT, Pablo M, Ghose D, Clark-Cotton MR, Zyla TR, Nolen J, Elston TC, Lew DJ. Ratiometric GPCR signaling enables directional sensing in yeast. PLoS Biol. 2019;17(10):e3000484.

Epub 2019/10/18. doi: 10.1371/journal.pbio.3000484. PubMed PMID: 31622333; PMCID: PMC6818790. [Support: R35GM127145, R01GM103870 and R35GM122488]

c. Liu B, Stone OJ, Pablo M, Herron JC, Nogueira AT, Dagliyan O, Grimm JB, Lavis LD, Elston TC, Hahn KM. Biosensors based on peptide exposure show single molecule conformations in live cells. Cell. 2021;184(22):5670-85 e23. Epub 2021/10/13. doi: 10.1016/j.cell.2021.09.026. PubMed PMID: 34637702; PMCID: PMC8556369. [Support: R35GM127145, R35122596, HHMI].

d. Herron JC, Hu S, Liu B, Watanabe T, Hahn KM, Elston TC. Spatial Models of Pattern Formation During Phagocytosis. *PLos Comp Bio* (submitted), bioRxiv. 2022:2022.04.11.487979. doi: 10.1101/2022.04.11.487979. [Support: R35GM127145, R35122596]

2. Polarity establishment and gradient sensing. A current interest of my lab is to understand the mechanisms used by cells to polarize and detect gradient chemical gradients. In collaboration with Dr. Daniel Lew, we combined mathematical modeling with experimental analyses to demonstrate how negative feedback in the polarity signaling pathway of yeast ensures robust polarization and the emergence of a single polarity site (**a**) and how the polarity patch undergoes chemotactic movement to locate a mate (**b**). We have used particle-based simulations to put theoretical limits on the time required for cells to reliably determine the direction of a chemical gradient (**c**) and determine the role of molecular-level fluctuations in polarity establishment. Recently, we developed a novel stochastic simulation approach to efficiently simulate models of polarity establishment and investigate the mechanisms that regulate movement of the polarity site (**d**).

   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. Ghose D, Jacobs K, Ramirez S, Elston T, Lew D. Chemotactic movement of a polarity site enables yeast cells to find their mates. Proc Natl Acad Sci U S A. 2021;118(22). Epub 2021/05/30. doi: 10.1073/pnas.2025445118. PubMed PMID: 34050026; PMCID: PMC8179161.
   c. Lakhani, V. and T.C. Elston. 2017. Testing the limits of gradient sensing. *PLoS Comp Bio* PLoS Comput Biol 13(2): e1005386.
   d. Ramirez, S., M. Pablo, S. Burk, D. Lew and T. C. Elston. 2021. A novel stochastic simulation approach enables exploration of mechanisms for regulating polarity site movement. *PLoS Comp Bio* 17(7): e1008525.

3. Signal transduction. My lab develops models of intracellular signaling pathways to understand how cells are able to sense and respond to their environment. Using both theoretical and computational techniques we have determined how molecular switches determine the response properties of signaling pathways (**e**), how kinetic insulation can be used as mechanism for pathway specificity (**f**), demonstrated how dose-to-duration encoding can be used to transmit information (**g**) and how negative regulators can have positive effects on signal output (**h**).

   e. Ghusinga, K. R., R. Jones, A. Jones and T. C. Elston. 2021. Molecular switch architecture determines response properties of signaling pathways. *Proceedings of the National Academy of Sciences*, 118, e2013401118.
   f. 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.
   g. 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.
   h. Houser JR, Ford E, Nagiec MJ, Errede B, Elston TC. Positive roles for negative regulators in the mating response of yeast. Molecular systems biology. 2012;8:586. Epub 2012/06/07. doi: 10.1038/msb.2012.18. PubMed PMID: 22669614; PMCID: 3397415.

4. Quantitative image analysis. My lab develops computational methods for performing quantitative image analysis (**i**-**l**). This work is primarily carried out in collaboration with Dr. 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 (**i**). We also developed SegmentMe, a MATLAB application designed to perform image segmentation and tracking (**j**). SegementMe 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. Very recently, we used deep learning to enable structured illumination microscopy using low light levels and enhanced speed (**l**).

i. 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.

j. 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.

k. 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.

l. Jin, L, B. Liu, F. Zhao, S. Hahn, B. Dong, R. Song, T. C. Elston, Y. Xu and K. Hahn. 2020. Deep learning enables structured illumination microscopy with low light levels and enhanced speed. *Nat Commun* 11,1934.

5. 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 (**m**). 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 (**n**). 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* (**o**). Recently, we developed a stochastic model for gene regulation by the Human Papillomavirus early promoter and used the model to understand how a combination of positive and negative feedback regulation generates stochastic bursts of gene expression (**p**).

m. Kaern, M., W. Blake. T. C.Elston and J. Collins. 2005. Stochasticity in gene expression. Nat. Gen., 6:451-464.

n. T. Kepler and T. C. Elston. 2001. Stochasticity in transcriptional regulation: origins, consequences, and mathematical representations. *Biophys. J.* 81:3116-3136.

o. 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.

p. Giaretta, A., M. T. Toffolo, and T. C. Elston. 2020. Stochastic Modeling of Human Papillomavirus early promoter gene regulation. *J. Theor. Bio.* 486:110057.

Complete List of Published Work:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40962549/?sort=date&direction=ascending