BIOGRAPHICAL SKETCH

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NAME: Lezon, Timothy R.

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

POSITION TITLE: Assistant Professor of Computational and Systems Biology

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
University of Illinois at Urbana-Champaign	B.S.	05/1997	Engineering Physics
Pennsylvania State University	Ph.D.	05/2007	Physics
University of Pittsburgh	Postdoctoral	10/2010	Computational Biology

A. Personal Statement

My current research focuses on maximizing the useful information extracted from phenotypic screens, and applying this information toward understanding cellular systems biology and disease progression. High content analysis (HCA) is a cornerstone of the University of Pittsburgh drug discovery approach; it can also serve as a valuable source of information on the systems biology of the cell. Using locally generated HCA data as input, I develop mathematical models to explore the origins of cellular phenotypic heterogeneity, to predict its response to chemical perturbagens, and to infer from it functional relationships between biomolecules. I have developed methods for quantifying and comparing heterogeneity, and for predicting its time evolution; I am actively working to streamline experimental design to efficiently identify optimal drug combinations. In line with this work, my role in the present project will focus on developing tools that can be used to analyze cancer progression at the intra- and inter-cellular levels.

My expertise in constructing novel mathematical models for systems biology extends from a graduate background in the physics of protein folding. Using concepts from statistical physics, I investigated how many-body interactions among amino acid residues can promote protein-like structures. Many of the computational aspects of this work translated to the field of protein structural dynamics, where I used it in my postdoctoral training for parameter optimization and for modeling physical interactions between proteins. Only recently have I shifted focus from structure to systems biology, where the same mathematical concepts and computational principles apply. Cell-level phenotypic data of the types generated here are well-suited for both statistical and detailed mechanistic models, and the project represents a natural extension of my present work.

a. Suofu Y, Li W, Jean-Alphonse FG, Jiao J, Khattar NK, Li J, Baranov SV, Leronni D, Mihalik AC, He Y, Cecon E, Wehbi V, Kim J, Heath BE, Baranova OV, Wang X, Gable M, Kretz E, Di Benedetto G, **Lezon TR**, Ferrando L, Larkin TM, Sullivan MLG, Yablonska S, Wang J, Minnigh MB, Guillaumet G, Suzenet F, Richardson RM, Poloyac S, Stolz DB, Jockers R, Witt-Enderby P, Carlisle DL, Vilardaga J-P, Friedlander RM. *Dual role of mitochondria in pruducing melatonin and driving GPCR signaling to block cytochrome c release*. Proc. Natl. Acad. Sci. USA 114:E7997-E8006 (2017). PMID: 28874589

b. Pei F, Li H, Henderson MH, Titus SA, Jadhav A, Simeonov A, Cobanoglu MC, Mousavi SH, Shun T, McDermott L, Iyer P, Fioravanti M, Carlisle D, Friedlander RM, Bahar I, Taylor DL,

Lezon TR, Stern AM, Schurdak, ME. *Connecting neuronal cell protective pathways and drug combinations in a Huntington's disease model through the application of quantitative systems pharmacology*. Scientific Reports (*In Press*).

B. Positions and Honors

Positions and Employment

1997-1999	Manufacturing Engineer, Merkle-Korff Industries, Des Plaines, IL
2001-2007	Graduate Research Assistant, Pennsylvania State University, University Park, PA
2007-2010	Postdoctoral Associate, Department of Computational Biology, University of Pittsburgh
2010-	Assistant Professor, Department of Computational & Systems Biology, University of Pittsburgh
2012-	Systems Biology Team Leader, University of Pittsburgh Drug Discovery Institute

Other Experience and Professional Memberships

2001-2010	Member, American Physical Society
2009-2011	Member, Biophysical Society
2012-2013	Member, American Society for Cell Biology

Honors

2001-2005	NSF Integrative Graduate Education and Research Traineeship (IGERT) Fellow

C. Contribution to Science

1. **Network Inference** – A unifying thread throughout my research career has been the application of statistical methods and information theory to understand complex biological systems. As part of my thesis work I introduced a novel method for inferring the structure of yeast gene interaction networks through the use of entropy maximization. During my postdoctoral years I applied these same concepts to theoretical investigations of protein structural dynamics, showing that the predictions of coarse-grained protein models can be improved through the introduction of energetic frustration. Working with the Drug Discovery Institute, I am showing the value of generalized entropy as a measure of cellular diversity and heterogeneity.

    a. **Lezon TR**, Banavar JR, Cieplak M, Maritan A and Fedoroff N. *Using entropy maximization to infer genetic interaction networks from gene expression patterns.* Proc. Natl. Acad. Sci. USA 103:19033-19038 (2006). PMID: 17138668; PMCID: PMC1748172
    b. **Lezon TR** and Bahar I. *Using entropy maximization to understand the determinants of structural dynamics beyond native contact topology.* PloS Comp. Biol. 6:e1000816 (2010). PMID: 20585542; PMCID: PMC2887458
    c. Erdem C, Nagle AM, Casa AJ, Litzenburger BC, Wang Y, Taylor DL, Lee AV and **Lezon TR**. *Proteomic screening and lasso regression reveal differential signaling in insulin and insulin-like growth factor I pathways*. Mol Cell Proteomics 15:3045-3057 (2016). PMID: 27364358; PMCID: PMC5013316

2. **Analysis of Heterogeneity** – A critical component of phenotypic drug discovery is properly handling cell-to-cell variability. The mean cellular response of a population to a treatment often fails to capture the rich array of responses of its members, introducing the possibility that therapeutic strategies that are effective in some subset of a cell population may not be effective in others. Further, our research has shown that patterns of cellular heterogeneity carry information on disease state, allowing heterogeneity to act as a prognostic marker. As part of an industrial/academic collaboration, I have developed methods and algorithms for characterizing cellular heterogeneity and using it to predict disease progression.

a. Gough A, Chen N, Schurdak M, Shun TY, **Lezon TR**, Boltz R, Reese C, Wagner J, Vernetti L, Grandis J, Lee A and Taylor DL. *Identifying and Quantifying Heterogeneity in High Content Analysis: Application of Heterogeneity Indices to Drug Discovery*. PLoS One 9:e102678 (2014). PMID: 25036749; PMCID: PMC4103836
b. Spagnolo DM, Gyanchandani R, Al-Kofahi Y, Stern AM, **Lezon TR**, Gough A, Meyer DE, Ginty F, Sarachan B, Fine J, Lee AV, Taylor DL and Chennubhotla SC. *Pointwise mutual information quantifies intra-tumor heterogeneity in tissue sections labeled with multiple fluorescent biomarkers*. J Pathology Informatics 7:47 (2016). PMID: 27994939; PMCID: PMC5139455
c. Gough A, Stern AM, Maier J, **Lezon T**, Shun T-Y, Chennubhotla C, Schurdak ME, Haney SA and Taylor DL. *Biologically relevant heterogeneity: Metrics and practical insights*. SLAS Discovery 22:213 (2017). PMID: 28231035
d. Spagnolo DM, Al-Kofahi Y, Zhu P, **Lezon TR**, Gough A, Stern AM, Lee AV, Ginty F, Sarachan B, Taylor DL, Chennubholta C. *Platform for quantitative evaluation of spatial intratumoral heterogeneity in multiplexed fluorescence images*. Cancer Research (in press).

3. **Protein Structural Dynamics** – During my postdoctoral appointment I employed elastic network models (ENMs) to understand the global dynamics of proteins and biomolecular assemblies. I developed methods for incorporating effects of membranes into coarse-grained models of proteins, and I used them to demonstrate the large-scale asymmetrical dynamics of the yeast nuclear pore complex. I further used mathematical modeling to highlight the important role of the membrane in determining the functional dynamics of the Glt_{Ph} neurotransmitter transporter. These methods are available in the NIH-funded ProDy protein dynamics analysis software package. I have also quantified the extent to which noise – such as crystal lattice vibrations – influences the values of experimentally measured crystallographic temperature factors, and suggested methods for accounting for this noise when calibrating dynamical models of proteins.

    a. **Lezon TR**, Sali A and Bahar I. *Global motions of the nuclear pore complex: insights from elastic network models.* PLoS Comp. Biol. 5:e1000496 (2009). PMID: 19730674; PMCID: PMC2725293
    b. **Lezon TR** and Bahar I. *Constraints imposed by the membrane selectively guide the alternating access dynamics of the glutamate transporter Glt_{Ph}*. Biophys. J. 102:1331-1340 (2012). PMID: 22455916; PMCID: PMC3309413
    c. **Lezon TR**. *The effects of rigid motions on elastic network model force constants*. Proteins 80:1133-1142 (2012). DOI: 10.1002/prot.24014. PMID: 22228562; PMCID: PMC3294121
    d. Bergman S and **Lezon TR.** Modeling global changes induced by local perturbations to the HIV-1 capsid. J Mol Graphics Modelling 71:218 (2017). PMID: 27951510

4. **Protein Folding** – In early research I explored the basic physical principles that give rise to universal properties of globular proteins. Using a variety of mathematical and computational approaches, I demonstrated that protein folds are consistent with the conformations adopted by marginally compact flexible tubes. I showed that the three-body interactions that are central to defining local curvature of continuous tubes are also instrumental in determining which fold will be adopted by an amino acid sequence. I developed an information-theoretical method for protein structure prediction and advanced the paradigm that protein folds represent a unique state of matter, not unlike liquid crystals.

    a. **Lezon T**, Banavar JR and Maritan A. *Recognition of coarse-grained protein tertiary structure.* Proteins 55:536-547 (2004). PMID: 15103618
    b. **Lezon TR**, Banavar JR, Lesk AM and Maritan A. *What determines the spectrum of protein native state structures?* Proteins 63:273-277 (2006). PMID: 16470841
    c. **Lezon TR**, Banavar JR and Maritan A. *The origami of life*. J. Phys.: Cond. Matt. 18:847-888 (2006).

D. Research Support

Informatics Tools for Tumor Heterogeneity in Multiplexed Fluorescence Images
Role: Research Faculty $96,456 ADC
A collaborative team will develop software for use by cancer biologists and clinicians to quantitate, interpret and visualize spatial intratumor heterogeneity as a first step toward constructing diagnostics based on both cancer biomarker expression levels and spatial relationships between cancer and stromal cells.

NIH – UL1 TR001857 (Reis) 07/01/2016-06/30/2021 3.6 Cal
University of Pittsburgh Clinical and Translational Science Institute
Role: Co- Investigator $25,000 ADC
The goal of this project is to establish clinical and translational science as a distinct discipline, moving actionable research findings into practice and prevention settings, and improving health at the individual and population levels.

NIH 1U24TR001935 (Schurdak) 09/22/2016–08/31/2018 2.4 Cal
University of Pittsburgh Tissue Chip Testing Center
Role: Co-Investigator $667,916 ADC
This project leverages integrated drug development expertise, established infrastructure, and a pioneering microphysiological system database (MPS-Db) to test and characterize the performance of tissue chip organ systems to guide optimal application in drug safety and efficacy testing.