BIOGRAPHICAL SKETCH

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NAME: Jeffrey J. Saucerman

eRA COMMONS USER NAME (credential, e.g., agency login): jjs3gnih

POSITION TITLE: Professor of Biomedical Engineering and Cardiovascular Medicine

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
Pennsylvania State University, University Park, PA	B.S. (Hons)	05/2000	Engineering Science
UC San Diego, La Jolla, CA	M.S.	05/2002	Bioengineering
UC San Diego, La Jolla, CA (w. Andrew McCulloch)	Ph.D.	08/2005	Bioengineering
Loyola University of Chicago (w. Don Bers)	Postdoc	06/2006	Physiology

A. Personal Statement

The overall goal of my research program is to advance the field of cardiac systems biology, which aims to develop a systems-level understanding of how signaling networks control cardiac remodeling. We develop innovative methods that combine computational models of signaling networks and cardiac physiology with cellular imaging and biochemical approaches such as high-content microscopy and RNA sequencing. I have a strong quantitative background in engineering, computational modeling, and machine learning. Much of our recent work has focused on developing computational and imaging approaches scalable to large and poorly characterized networks regulating heart disease and development. I have obtained grants from the NIH, NSF, AHA, and university/foundation/industry partnerships to support my research.

Mentoring undergraduate, graduate, and postdoctoral trainees is one of the most important and rewarding aspects of my job. I am committed to leading a laboratory that is committed to scientific rigor, training, mentoring, and to promoting an inclusive and supportive scientific environment. I have mentored >50 undergraduate, 18 graduate (>50% from underrepresented backgrounds), 9 postdoctoral trainees, 6 staff, and 5 faculty members. My trainees have won a range of internal (23) and external fellowships (16; NIH, AHA, NSF, Beckman). My trainees achieved subsequent placement in MS (3), PhD (14), MD (17) or MD/PhD (3) programs, medical residency (2), post-docs (5; HHMI, MIT, Harvard, NIH, UCSD), and ultimately positions as tenure-track faculty (4; Clemson U., Rutgers, UC Boulder, Messiah College), industry (18; AstraZeneca, BMS, Novartis, Merck, Pfizer, Regeneron), and government (NIH, FDA).

Recent publications on image analysis:

A. A.R. Nelson, S. L. Christiansen, K. M. Naegle, and J. J. Saucerman, “Logic-based mechanistic machine learning on high-content images reveals how drugs differentially regulate cardiac fibroblasts,” Proc Natl Acad Sci U S A 2024 Jan 30;121(5):e2303513121 PMCID: PMC10835125.

B. Woo LA, Wintruba KL, Wissmann B, Tkachenko S, Kubicka E, Farber E, Engkvist O, Barrett I, Granberg KL, Plowright AT, Wolf MJ, Brautigan DL, Bekiranov S, Wang QD, Saucerman JJ. Multi-omic analysis reveals VEGFR2, PI3K, and JNK mediate the small molecule induction of human iPSC-derived cardiomyocyte proliferation. iScience. 2024 Jul 11;27(8):110485. PMCID: PMC11338145.

C. Woo L, Tkachenko S, Ding M, Plowright AT, Engkvist O, Andersson H, Drowley L, Barrett I, Firth M, Akerblad P Wolf MJ, Bekiranov S, Brautigan DL, Wang QD, *Saucerman JJ. High-content phenotypic screen for compounds that induce proliferation of human iPSC-derived cardiomyocytes. J Mol Cell Cardiol. 2019 Feb;127:204-214.

D. Sutcliffe MD, Tan PM, Fernandez-Perez A, Nam Y-J, Munshi NV, *Saucerman JJ. High content analysis identifies unique morphological features of reprogrammed cardiomyocytes. Scientific Reports 2018 8:128. PMCID: PMC5775342.
E. M. Chowkwale, M. L. Lindsey, and J. J. Saucerman, "Intercellular model predicts mechanisms of inflammation-fibrosis coupling after myocardial infarction," *J Physiol*, vol. 601, no. 13, pp. 2635–2654, Jul. 2023, doi: 10.1113/JP283346.
F. T. G. Eggertsen and J. J. Saucerman, "Virtual drug screen reveals context-dependent inhibition of cardiomyocyte hypertrophy," *Br J Pharmacol*, vol. 180, no. 21, pp. 2721–2735, Nov. 2023, doi: 10.1111/bph.16163.
G. Hota SK, Rao KS, Blair AP, Khalilimeybodi A, Hu KM, Thomas R, So K, Kameswaran V, Xu J, Polacco BJ, Desai RV, Chatterjee N, Hsu A, Muncie JM, Blotnick AM, Winchester SAB, Weinberger LS, Hüttenhain R, Kathiriya IS, Krogan NJ, Saucerman JJ, Bruneau BG. Brahma safeguards canalization of cardiac mesoderm differentiation. Nature. 2022 Feb;602(7895):129-134. PMCID: PMC9196993.

Highlighted current projects:

NIH/NHLBI R01 (mPIs: Saucerman (contact), Abbate, Toldo) 8/12/2024-4/01/2028
Modeling of cell-specific LRP1 Signaling in acute myocardial infarction

NIH/NHLBI R01-HL162925 (multiPIs Saucerman (contact), Wolf) 4/01/2022-3/31/2026
Systems Pharmacology Model of Cardiac Hypertrophy

NIH/NHLBI R01-HL160665 (multiPIs Saucerman (contact), van Berlo) 1/01/2022-12/31/2025
Computational and Experimental Modeling of Cardiomyocyte Proliferation

U. Virginia Coulter Translational Research (multiPIs Abbate, Saucerman, Toldo) 9/1/2023-12/31/2024
Alpha-2-Macroglobulin to Enhance Cardiomyocyte Survival After Myocardial Infarction

NIH/NHLBI R01-HL158718 (PI: Wolf; co-I: Saucerman) 8/01/2021-6/30/2025
DYRK1a as a therapeutic target to treat myocardial infarction

NIH/NHLBI R01HL159945 (PI: Bilchick; co-I: Saucerman) 8/13/2021- 7/31/2025
Multiscale Models for Predicting Short and Long-term Outcome of Cardiac Resynchronization Therapy

Highlighted recent projects:

NIH/NHLBI R01-HL137755 (multiPIs Saucerman, Holmes) 7/01/2017-6/30/2023 (NCE)
Systems Pharmacology Model for Spatial Control of Cardiac Fibrosis

UVA School of Medicine Vivian Pinn Scholar Award (PI: Saucerman) 01/01/2018 – 12/30/2023
Systems biology of cardiac regeneration

Novartis (PI: Saucerman) 4/08/2021-4/07/2023
Hypothesis generation using cellular network models

B. Positions and Honors

Positions

2020-	Professor of Biomedical Engineering and Cardiovascular Medicine, University of Virginia
2022	Interim Vice Chair of Biomedical Engineering, University of Virginia
2013-2020	Associate Professor of Biomedical Engineering, University of Virginia, Charlottesville, VA
2006-2013	Assistant Professor of Biomedical Engineering, University of Virginia, Charlottesville, VA
2015-	Faculty Member, Center for Membrane Physiology, UVA
2008-	Faculty Member, Center for Public Health Genomics, UVA
2006-	Faculty Member, Robert M. Berne Cardiovascular Research Center, UVA
2005-2006	Postdoctoral Fellow, Stritch School of Medicine, Loyola University of Chicago, Maywood, IL

Other Experience and Professional Memberships

2023-	Co-Editor, JMCC Special Issue on Molecular Networks in Cardiac Remodeling
2023, 2024	Chair, Netflux and Logic-Based Network Modeling Meeting
2023	Reviewer, AIMBE Fellows – Systems Biology
2023	Ad hoc member, NIH Modeling and Analysis of Biological Systems Study Section
2022-	Associate Editor, Biophysical Journal
2020-2021	Co-Editor, JMCC Special Issue on Computational Models of Cardiovascular Regulation
2018-	Editorial Board, Cellular Signaling
2014-	Advisory Board, Keck Center for Cellular Imaging, UVA
2013-	Associate Editor, PLOS Computational Biology
2010-	American Heart Association Professional Member; Council on Basic CV Sciences
2015-	Cardiovascular Training Grant Advisory Committee, UVA School of Medicine
2002-	Biomedical Engineering Society, Member
2020-2021	NIH/NHLBI Mentored Transition to Independence (MTI) Study Section, Ad Hoc Member
2021	Reviewer, Dutch Research Council
2020	Program Committee, Interagency Multiscale Modeling Consortium Meeting
2019	Chair, Search Committee for General Faculty, UVA Biomedical Engineering
2019	Session Chair, Systems Pharmacology, Interagency MSM Meeting, Bethesda, MD
2019	Session Chair, K-12 Dissemination, Interagency MSM Meeting, Bethesda, MD
2018	Search Committee, Assistant Dean of Research Search, UVA School of Medicine
2018	AHA Career Development Program Study Group
2016-2018	Chair, Dean's Research Advisory Committee, UVA School of Medicine
2017	NIH Predictive Multiscale Models U01 Study Section
2017	NSF Computer & Information Science & Engineering Study Section
2015-2016	Member, Dean's Research Advisory Committee, School of Medicine
2016-2017	Chair, AHA Bioengineering Bsc 3 Peer Review Study Group
2015-2017	Chair, UVA Biomedical Data Sciences Faculty Search Committee
2015	Cardiovascular Systems Biology Session Chair, AHA Scientific Sessions
2014-2017	Vice President for Research Internal Review Committee, UVA
2014-2015	Co-Chair, AHA Bioengineering Bsc 3 Peer Review Study Group
2014	Participant, Leadership in Academic Matters course, UVA
2009	Visiting Fellow, Isaac Newton Institute for Mathematical Sciences, Cambridge University, UK
2002	Research Visitor with Denis Noble and Peter Kohl, University of Oxford, UK

Honors

2023-	Fellow, American Institute for Medical and Biological Engineering
2023	UVA Biomedical Engineering Graduate Mentoring Award
2018	Vivian Pinn Scholar Award, U. Virginia School of Medicine
2014	Thelma R. Swortzel Collaborative Research Award, with Zhen Yan
2014-	Fellow of the American Heart Association, Council on Basic Cardiovascular Sciences
2013	NSF Faculty Early Career Development (CAREER) Award
2012-	Member, Academy of Distinguished Educators, U. Virginia School of Medicine
2012	Dean's Excellence in Teaching Award, U. Virginia School of Medicine
2008	National Scientist Development Grant, American Heart Association
2007	FEST Distinguished Young Investigator Grant, University of Virginia
2000-2005	Whitaker Foundation Graduate Fellowship
2000	Francis H. Fenlon Award (outstanding undergrad thesis), The Pennsylvania State University
1997-2000	Schreyer Scholar, The Pennsylvania State University

C. Contributions to Science

1. Computational modeling of inflammation and fibrosis signaling networks. Using our logic-based network modeling methods, we developed the first computational model of the cardiac fibroblast signaling network (Zeigler+ JMCC 2016), identifying and validating context-dependent regulators of fibrosis. We have also applied this approach to model macrophage activation, finding that opposing cues generate a distinct cell phenotype that we validated by RNA-seq (Liu+ J Immunol 2021). Our recent studies expanded on this work to

predict drug responses (Zeigler+ CPTPSP 2021) and in vivo dynamics of intracellular (Zeigler+ Mat Biol 2020) and intercellular (Chowkwale+ J Physiol 2023) signaling, which is an alternative approach here for Aim 2.

a. Zeigler AC, Chandrabhatla AS, Christiansen SL, Nelson AR, Holmes JW, Saucerman JJ. Network model-based screen for FDA-approved drugs affecting cardiac fibrosis. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 11. PMCID: PMC8099443.

b. Nelson AR, Bugg D, Davis J, Saucerman JJ. Network model integrated with multi-omic data predicts MBNL1 signals that drive myofibroblast activation. iScience. 2023 Mar 27;26(4):106502. PMCID: PMC10119756

c. Chowkwale M, Lindsey ML, Saucerman JJ. Intercellular model predicts mechanisms of inflammation-fibrosis coupling after myocardial infarction. J Physiol 2023 Jul;601(13):2635-2654. Editor's Choice. PMCID: PMC9859968.

d. A.R. Nelson, S. L. Christiansen, K. M. Naegle, and J. J. Saucerman, "Logic-based mechanistic machine learning on high-content images reveals how drugs differentially regulate cardiac fibroblasts," Proc Natl Acad Sci U S A, vol. 121, no. 5, p. e2303513121, Jan. 2024, doi: 10.1073/pnas.2303513121.

2. *Computational modeling of cardiomyocyte signaling networks*. For >20 years, I have developed methods for building and analyzing large-scale computational models of cell signaling networks. We developed the logic-based differential equations approach to model biological networks, which we showed to retain much of the predictive capability of a detailed biochemical model while requiring only network topology. More recently, we have developed methods for systematic revision of logic-based DE models using global parameter estimation and structural inference with or new CLASSED method (Khalilimeybodi+ PLOSCB 2020; van de Graaf+ JMCC 2023). We recently applied this approach to develop the first model of cardiac differentiation, revealing a pair of saddle-node bifurcations critical for cardiomyocyte commitment (Hota+ Nature 2022). We recently created the first model of cardiomyocyte survival (Grabowska+ JMCC 2022), which we expand here with LRP1 signaling and its regulation of ischemia-reperfusion cell death.

a. Hota SK, Rao KS, Blair AP, Khalilimeybodi A, Hu KM, Thomas R, So K, Kameswaran V, Xu J, Polacco BJ, Desai RV, Chatterjee N, Hsu A, Muncie JM, Blotnick AM, Winchester SAB, Weinberger LS, Hüttenhain R, Kathiriya IS, Krogan NJ, Saucerman JJ, Bruneau BG. Brahma safeguards canalization of cardiac mesoderm differentiation. Nature. 2022 Feb;602(7895):129-134. PMCID: PMC9196993.

b. Saucerman JJ, Tan PM, Buchholz KS, McCulloch AD, Omens JH. Mechanical regulation of gene expression in cardiac myocytes and fibroblasts. Nat Rev Cardiol. 2019 Jun;16(6):361-378. PMCID: PMC6525041.

c. Khalilimeybodi A, Paap AM, Christiansen SLM, Saucerman JJ. Context-specific network modeling identifies new crosstalk in β-adrenergic cardiac hypertrophy. PLoS Comput Biol. 2020 Dec 18;16(12):e1008490. PMCID: PMC7781532.

d. Grabowska ME, Chun B, Moya R, Saucerman JJ. Computational model of cardiomyocyte apoptosis identifies mechanisms of tyrosine kinase inhibitor-induced cardiotoxicity. J Mol Cell Cardiol. 2021 Mar 3;155:66-77. PMCID: PMC8154673. Cover Image.

e. Clark AP, Chowkwale M, Paap A, Dang S, Saucerman JJ. Logic-based modeling of biological networks with Netflux. bioRxiv [Preprint]. 2024 Jan 15:2024.01.11.575227.

3. High-throughput microscopy of large-scale cardiac signaling networks. We published the first high-throughput microscopy customized for cardiac myocyte phenotypes (Amanfu+ 2011, Bass+ 2012). We have applied these methods to validate computational model predictions, discover mechanisms regulating reversal of cardiac myocyte hypertrophy and identify pathways differentially controlling myocyte size, shape, gene expression, and sarcomeric organization, and screen for compounds that induce CM proliferation. In fibrosis, we have combined network models with high-throughput microscopy to identify how several drugs activate myofibroblasts.

a. Ryall, K. A., V. J. Bezzerides, A. Rosenzwieg, Saucerman JJ. Phenotypic screen quantifying differential regulation of cardiac myocyte hypertrophy identifies CITED4 regulation of myocyte elongation. J Mol Cell Cardiol, 2014 Jul;72:74-84. PMCID: 4078663.

b. Sutcliffe MD, Tan PM, Fernandez-Perez A, Nam Y-J, Munshi NV, Saucerman JJ. High content analysis identifies unique morphological features of reprogrammed cardiomyocytes. Scientific Reports 2018 8:1258 doi:10.1038/s41598-018-19539-z. PMCID: PMC5775342.

c. Woo LA, Tkachenko S, Ding M, Plowright AT, Engkvist O, Andersson H, Drowley L, Barrett I, Firth M, Akerblad P, Wolf MJ, Bekiranov S, Brautigan DL, Wang QD, Saucerman JJ. High-content phenotypic assay for proliferation of human iPSC-derived cardiomyocytes identifies L-type calcium channels as targets. High-content phenotypic screen for compounds that induce proliferation of human iPSC-derived cardiomyocytes. J Mol Cell Cardiol. 2019 Feb;127:204-214. PMCID: PMC6524138.

d. Anders R. Nelson, Steven L. Christiansen, Kristen M. Naegle, Jeffrey J. Saucerman. Logic-based mechanistic machine learning on high-content images reveals how drugs differentially regulate cardiac fibroblasts. bioRxiv 2023.03.01.530599, ***in press at Proc Natl Acad Sci***.

4. *Modeling β-adrenergic signaling in heart.* As a graduate student, I developed the first computational model of a cardiac signaling pathway, focusing on β-adrenergic signaling and its regulation of cardiac excitation-contraction coupling. To our knowledge, these studies were the first mechanistic simulations of candidate therapies in a signaling pathway, integration of a signaling pathway with cell physiology, and effects of a gene mutation on the ECG (which was validated in a subsequent clinical case study). As a pre-tenure focus of my lab, we extended these models with recently identified components of β-adrenergic signaling (e.g. phospholemman, CaMKII), a wide range of β-blockers (explaining how β-blockers can both suppress and enhance β-adrenergic responsiveness), receptor polymorphisms, and performing our own experimental validations in adult cardiomyocytes. These models continue to be used by numerous academic labs (Ni+ Cardiovasc Res 2023) and several companies (Bristol Meyers Squibb).

a. Saucerman JJ, Brunton LL, Michailova AP, McCulloch AD. Modeling beta-adrenergic control of cardiac myocyte contractility in silico. J Biol Chem. 2003;278(48):47997-8003.

b. Soltis AR, Saucerman JJ. Synergy between CaMKII substrates and beta-adrenergic signaling in regulation of cardiac myocyte Ca(2+) handling. Biophys J. 2010;99(7):2038-47. PMCID: 3042590.

c. Yang JH, Saucerman JJ. Phospholemman in a negative feed-forward regulator of Ca2+ in β-adrenergic inotropy. J Mol Cell Cardiol. 2012 May;52(5):1048-55. PMCID: PMC3327824.

d. Amanfu RK, Saucerman JJ. Modeling the Effects of β1-Adrenergic Receptor Blockers and Polymorphisms on Cardiac Myocyte Ca2+ Handling. Mol Pharmacol. 2014 Aug;86(2):222-30. PMCID: 4127930.

5. *Compartmentation of cellular signaling*. We have integrated computational models and live-cell imaging to identify new mechanisms for subcellular compartmentation of cell signaling, which is fundamental to the specificity of many signaling pathways. We were the first to integrate computational modeling of cell signaling with FRET biosensors, demonstrating that cAMP gradients lead to gradients in PKA-mediated phosphorylation (Saucerman+ PNAS 2006). We found that these gradients were caused not only by cAMP degradation but also by physical barriers and cAMP buffering (Saucerman+ PNAS 2006), which was recently experimentally validated by my previous collaborator (Zhang+ Cell 2020). Together with Dr. Zhang, we predicted and validated a nuclear PKA signaling complex (Sample+ Nat Chem Biol 202), along with discovering a role for nuclear PKA in cardiac myocyte hypertrophy (Yang+ JMCC 2014). We developed the first computational models of signaling on A-kinase anchoring proteins (AKAPs) and developed the scaffold state-switching model which mechanistically explains how scaffold proteins can amplify, accelerate and insulate cell signaling (Greenwald+ JBC 2014).

a. Saucerman JJ, Zhang J, Martin JC, Peng LX, Stenbit AE, Tsien RY, McCulloch AD. Systems analysis of PKA-mediated phosphorylation gradients in live cardiac myocytes. Proc Natl Acad Sci U S A. 2006;103(34):12923-8. PMCID: 1568947.

b. 1Sample V, 1DiPilato LM, 1Yang JH, Ni Q, *Saucerman JJ, *Zhang J. Regulation of nuclear PKA revealed by spatiotemporal manipulation of cAMP. Nat Chem Biol. 2012;8(4):375-82. PMCID: 3307945.

c. [1]Greenwald EC, [1]Redden JM, *Dodge-Kafka KL, *Saucerman JJ. Scaffold state-switching amplifies, accelerates and insulates PKC Signaling. J Biol Chem. 2014 Jan 24;289(4):2353-60. PMCID: 3900978.

d. Yang JH, Polanowska-Grabowska RK, Smith JS, Shields CW, *Saucerman JJ. PKA catalytic subunit compartmentation regulates contractile and hypertrophic responses to β-adrenergic stimulation. J Mol Cell Cardiol, 2014 Jan;66:83-93. PMCID: 3927644.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/jeffrey.saucerman.1/bibliography/40918420/public/