BIOGRAPHICAL SKETCH

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NAME: **Leighton T. Izu**

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

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	Completion Date	FIELD OF STUDY
University of Hawaii (Manoa)	B.A. *with Distinction*	05/1979	Mathematics
University of Hawaii (Manoa)	B.A.	05/1979	Psychology
State University of New York at Buffalo	Ph.D. *Highest Distinction*	05/1990	Biophysics
State University of New York at Buffalo	Post-Doc Fellow	07/1995	Electrophysiology
University of Maryland, Baltimore	Post-Doc Associate	07/2000	Cardiac Modeling

A. Personal Statement

Biological systems seem to have endless variations, but underlying this vast variability are a few common themes that repeat and combine to give rise to the miracle of life. By casting these important common themes in mathematical forms, I have the joy of discovering the underlying physical principles and the mathematical simplicity of some complex behaviors in biological systems and, in particular, the excitation-contraction coupling system in the heart. My main research interest is to understand how non-linear dynamic systems (i.e. the electrical system, Ca^{2+} control system, contractile system) interact in the heart to control cardiac function, and how dysregulation in the sub-systems or their uncoupling can engender dynamic instabilities that lead to cardiac arrhythmias. Understanding the non-linear dynamic systems behavior holds the key to understanding exactly how cardiac arrhythmias are triggered that may lead to sudden cardiac death and heart failure.

I have been doing cutting-edge research in cardiac modeling for over 25 years. Coming from mathematics and biophysics background, I always strive to solve fundamental problems in cardiac excitation-contraction coupling and arrhythmia mechanisms. I have developed innovative mathematical methods to study the stochastic Ca^{2+} sparks and the non-linear dynamics of Ca^{2+} control system. My modeling work is often based on the first physical principles and rigorous mathematical treatments (with proofs) that build a solid foundation for not only solving the specific problem but also leading to general applications. My current work focuses on developing the new "**Functional Connectome"** approach to understand a fundamental question in biology: ***how are myriad cellular processes are coordinated to produce the whole-cell response to an external stimulus, such as the cardiomyocyte's auto-regulation behavior in response to mechanical loading?*** I chose the phrase "Functional Connectome" because the connections and coordination between the cellular subsystems that enable the cell to produce appropriate ***functional*** output is–in my mind–no less impressive and important than the neural connection map of the brain, called the Connectome.

The proposed Functional Connectome project builds on my expertise in nonlinear dynamical systems modeling and using linear algebra and other mathematical tools to identify patterns of coordinated changes in complex biological systems. Drawing strength from my multi-disciplinary training and professional experiences in mathematics, cardiac modeling, and experimental biology (electrophysiology, Ca^{2+} imaging, mechanics), I am uniquely qualified to lead this interdisciplinary project combining mathematical modeling with experimental investigations to develop the conceptual and mathematical platform of Functional Connectome and use it to elucidate how multiple Ca^{2+} handling processes in the cardiomyocyte are coordinated to autoregulate contractility to compensate for mechanical load changes in the heart.

B. Positions and Honors.

Employment Positions

1991 - 1995	Postdoctoral Fellow, State University of New York at Buffalo, NY
1995 - 2000	Postdoctoral Associate, University of Maryland, Baltimore, MD
2000 - 2002	Instructor, University of Maryland, Baltimore, MD
2002 - 2004	Assistant Professor, University of Maryland, Baltimore, MD
2005 - 2008	Assistant Professor (tenure track), University of Kentucky, Lexington, KY
2009 - 2020	Associate Professor (tenured), University of California, Davis, CA
2020 -	Full Professor (tenured), University of California, Davis, CA

Awards and Distinctions

1979	B.A. (*with Distinction*), University of Hawaii at Manoa, Honolulu, HI
1979 - 1982	Woodburn Fellowship, State University of New York at Buffalo, Buffalo, NY
1990	Ph.D. (*with Highest Distinction*), State University of New York at Buffalo, NY
1996	AHA Maryland Affiliate Postdoctoral fellowship (declined to accept NRSA)
1996 - 1998	NIH NRSA Postdoctoral Fellowship (HL09651)
2000 - 2002	National Center for Supercomputing Applications (MCB00006N)
2001 - 2003	AHA-Mid Atlantic Affiliate Beginning Grant-In-Aid (0160400U)
2002 - 2006	NIH Mentored Quantitative Research Career Development Award K25 (HL068704)

Society Membership and Grant Review Panels

2005, 2009	Reviewer for National Institutes of Health (NIH) grant study section on Mathematical Analysis of Biological Systems [**MABS**].
2002 - 2005	Reviewer for American Heart Association (AHA) Mid-Atlantic grants
1991 - present	Member of Biophysical Society
1996 - present	Member of American Heart Association / American Stoke Association

C. Contributions to Science

Research Theme: Mathematical Analyses of Complex Biological Systems

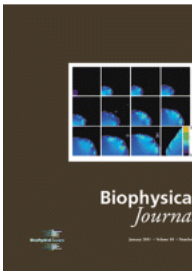
I have long been interested how complex dynamical systems become unstable and using these insights to understand how arrhythmias arise. Heart muscle cells are fascinating, first, because they have many dynamic systems that interact with one another and, second, because a critical element of the calcium control system is inherently stochastic. Therefore, to understand how excitation-contraction (E-C) coupling in the cardiomyocyte works and how arrhythmogenic activities can arise requires combining two areas of mathematics: ***nonlinear dynamics*** and ***probability theory***. I feel fortunate that these are the two areas of mathematics that I truly enjoy and have honed professional expertise and intuition.

The central theme of my research is to apply mathematics to gain both qualitative and quantitative understanding of complex biological systems. The strength of my research stems from combining classical mathematical analyses, computational modeling, and experimental biology to achieve an in-depth understanding of biological systems at two levels: one is the distillation of mathematical simplicity and underlying connections of seemingly complex biological behaviors; and another is to develop realistic models of biological systems based on and tested by experimental data.

Mathematical analyses of nonlinear dynamic Ca^{2+} signaling system

A common thread that runs through my research is understanding how the spatial geometry of Ca^{2+} handling system affect Ca^{2+} signaling dynamics. At the time of my PhD study in theoretical biology, models of Ca^{2+} oscillations had no spatial dependency (well-mixed models); my PhD research (with Robert A Spangler at SUNY-Buffalo) was the first to examine how diffusion of Ca^{2+} affected Ca^{2+} dynamics (in a 1-dimensional space model). I discovered that coupling the Ca^{2+} diffusion in cytosol to the SR Ca^{2+} release and uptake generated a very rich set of complex Ca^{2+} oscillations (***Ref. 1, 2***). In the cardiomyocyte, because Ca^{2+} is released from the SR from brief stochastic openings of ryanodine receptors in the form of spatially discrete Ca^{2+} sparks, my later models of the Ca^{2+} control system combined stochastic processes with nonlinear dynamics (***Ref. 4, 6***). We were the first to publish a model of Ca^{2+} waves arising from stochastically occurring sparks in a 2-dimensional geometry (***Ref. 4***).

In the early phase of Ca^{2+} study in the field, I developed methods and software for confocal Ca^{2+} image processing and analyses. For example, I developed statistical analyses of Ca^{2+} spark amplitudes (***Ref. 3),*** which became the classical analysis method in the field. I also developed probability analyses of large populations of stochastic Ca^{2+} sparks that shows how spontaneous Ca^{2+} waves arise from near synchronous Ca^{2+} sparks (***Ref. 4)***. These works set the foundation for linking stochastic molecular level events (Ca^{2+} sparks released from RyR clusters) to the cellular level spontaneous Ca^{2+} waves that lead to cardiac arrhythmias. *[Ctrl-click to follow link]*



Ref.4

1. **Izu, L. T.*** (1994). *Cardiac calcium oscillations in a diffusion equation with nonlinear boundary conditions*. Proceedings of Dynamic Systems and Applications. 1:151-158.
2. **Izu, L.T.*** and R.A. Spangler (1995). *A class of parametrically excited calcium oscillation detectors.* Biophys. J. 68:1621-1629. PCM ID: PMC1282058
3. **Izu, L. T***, W.G. Wier, and C.W. Balke (1998). Theoretical analysis of the Ca^{2+} spark amplitude distribution. Biophys. J. 75:1144-1162. PMCID: PMC1299790
4. **Izu, L. T.***, W.G. Wier, and C.W. Balke (2001). *Evolution of cardiac calcium waves from stochastic calcium sparks.* Biophys. J. 80:103-120. PMCID: PMC1301217

Modeling the Ca^{2+} signaling system in the cardiomyocyte based on experimental data

In the next phase of Ca^{2+} study, I further developed more realistic models of the Ca^{2+} signaling system in the cardiomyocyte by taking two major steps forward. (**A**) Based on experimentally measured RyR cluster distribution geometry in 3-dimensional (3-D) space, I developed a more realistic 3-D Ca^{2+} signaling system model (***Ref. 5, 6***). (**B**) I employed large-scale computer simulations in collaboration with Sandia National Laboratory to study computationally and analytically the role of spatial distribution of RyR clusters on spontaneous Ca^{2+} wave generation and propagation (***Ref. 6***).

Our modeling study predicted that the 3-D spatial distribution of RyR clusters (Ca^{2+} release unit) are critically important for maintaining the stability of the Ca^{2+} control system, because the Ca^{2+}-induced Ca^{2+} release (CICR) mechanisms requires optimized spatial separation of RyR clusters to avoid 'chain reaction' in a positive-feedback system (***Ref. 6***). Our model prediction was put to experimental test in the case of Familiar Hypertrophic Cardiomyopathy (FHC). Prompt by our model prediction, Dr. Jil Tardiff (U. Arizona) examined several mouse models of FHC; significantly, her data show a close correlation between shortened sarcomere length in FHC hearts (which shortens the spatial distance of RyRs) and increased arrhythmogenic activities and sudden cardiac death (J.Clin.Invest. 104:469-81).

I continue to improve Ca^{2+} signaling models by developing more sophisticated image data processing and detection methods to process tens of thousands of Ca^{2+} sparks (***Ref. 7***), and using the big data set to empower more advanced statistical analysis (***Ref. 8***) to understand the conditions that give rise to arrhythmogenic Ca^{2+} waves (***Ref. 9***).

5. Chen-Izu, Y., McCulle, S.L., Ward, C.W., Soeller, C., Allen, B.M., Rabang, C., Cannell, M.B., Balke, C.W., **Izu, L.T*.** (2006). *Three-dimensional distribution of ryanodine receptor clusters in cardiac myocytes.* Biophys. J. 91:1—13. PMCID: PMC1479079
6. **Izu, L. T.***, S.A. Means, Y. Chen-Izu, J.N. Shadid, and C.W. Balke (2006). *Interplay of Ryanodine Receptors Distribution and Calcium Dynamics.* Biophys. J. 91:95-112. PMCID PMC 1479049
7. Banyasz, T[&], Chen-Izu, Y[&], Balke CW, **Izu, Leighton T.*** (2007) *A New Approach to the Detection and Classification of Ca^{2+} Sparks.* Biophysical J. 92:4458-4465 PMCID: PMC 1877760
8. **Izu, L. T.***, Banyasz T, Balke CW and Y Chen-Izu. (2007) *Eavesdropping on the Social Lives of Ca^{2+} Sparks.* Biophysical J 93:3408-3420. PMCID PMC 2072070.
9. **Izu, L.T*.**, Y. Xie, D. Sato, T. Bányász, and Y. Chen-Izu. *Ca^{2+} waves in the heart.* J. Mol. Cell. Cardiol. 58:118-124 (2013). PMCID: PMC3660086

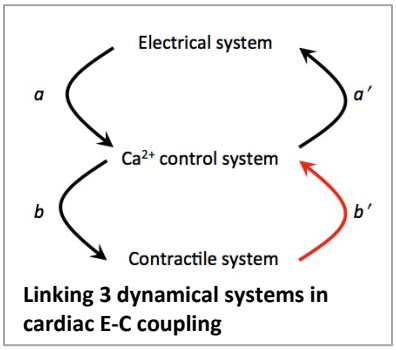
Interdisciplinary Study on Cardiac Excitation-Ca^{2+} signaling-Contraction Coupling (ECC)

Being a mathematician, I love the theoretical studies, but I also realize that mathematical models need to be rooted in physiological reality and modelers need to have a thorough understanding of the meaning and limitations of experimental results. Therefore, part of my post-doc training was devoted to experimental work in the areas of electrophysiology and Ca^{2+} imaging. *Ca^{2+} imaging*: I do experimental work on Ca^{2+} imaging using confocal fluorescence microscope. Localized Ca^{2+} release takes the form of sparks, puffs, quarks, and embers. Automatic detection of these localized releases depended on *a priori* assumptions on what the release should look like. I developed an "agnostic" method for detecting localized Ca^{2+} release

based on probability theory without *a priori* assumptions on the release should look like (***Ref. 7***).
Electrophysiology: I did patch-clamp experiments to study ion channels to gain experience with bench electrophysiology (***Ref. 10***).
I also use mathematical analyses to aid experimental design to develop a new way of measuring the submembrane Na^+ concentration (***Ref. 11***).

10. Shorofsky, S.R., **Izu, L**., Wier, W.G. and Balke, C.W. *Ca^{2+} sparks triggered by patch depolarization in rat heart cells*. Circ. Res. 82:424-29 (1998). PMID: 9506702
11. Hegyi, B. Banyasz, T. Shannon, T.R., Chen-Izu, Y., **Izu, L.T***. *Electrophysiological Determination of Submembrane Na+ Concentration in Cardiac Myocytes.* Biophysical J. 111:1304-15 (2016). PMCID: PMC5034366

Integration of electrophysiology, Ca^{2+} signaling, and contractile mechanics in cardiac modeling: The classic picture of excitation-contraction (E-C) coupling in mammalian hearts has the electrical system triggering Ca^{2+} release from the SR (*arrow a* in figure) that then causes muscle contraction (*arrow b*). Many studies have elucidated the effect of Ca^{2+} back onto the electrical system (*arrow a′*). Results from our modeling study (ref 8) indicated that changes in the contractile system could affect the Ca^{2+} control system (*red arrow b′*). This contractile system to Ca^{2+} control system link allows the continuous and circular flow of information between the three dynamical systems that control e-c coupling. We have tested this using the 'Cell-in-gel' system to impose mechanical loads on individual cardiomyocytes (***Ref. 12***). One of the key findings was that the Ca^{2+} transient *increased* when the myocyte was mechanically loaded suggesting the existence of *autoregulatory mechanism that sensed the mechanical load and adjusted the amount of Ca^{2+} release to compensate for the load* (***Ref. 13***).



Linking 3 dynamical systems in cardiac E-C coupling

12. Jian, Z., Han, H., Zhang, T. , Puglisi, J. , **Izu, L. T.**, Shaw, J. A. , Onofiok, E. , Erickson, J. R. , Chen, Y. J. , Horvath, B. , Shimkunas, R. , Xiao, W. , Li, Y. , Pan, T. , Chan, J. , Bányász, T. , Tardiff, J. C. , Chiamvimonvat, N. , Bers, D. M., Lam, K. S., and Chen-Izu, Y*. *Mechanochemotransduction during cardiomyocyte contraction is mediated by localized nitric oxide signaling.* Science Signaling 7, 317:ra27 (2014). PMCID: PMC4103414
13. Chen-Izu, Y.* and **Izu, L.T.***. *Mechano-chemo-transduction in cardiac myocytes.* J. Physiol. 595(12):3949—3958 (2017). PMCID: PMC5471413

Applied Mathematical Study of Fundamental Problems in Biology
As mathematician, I always strive to tackle fundamental problems in biology using applied mathematics. Currently I am studying the following topics that are related to cardiac modeling but also have much broader implications in biological systems.
Study of Population Variability*:* Biological populations have diversity. There is considerable debate on whether diversity (or variability) is beneficial, harmful, or inconsequential. I've tackled this problem by reframing the question to ask: "*What is the optimal level of population variability that maximizes benefit to the population?*" The mathematical framework I developed to answer this question (***Ref 14***) is applicable to a surprisingly broad set of systems including increasing resolution in measurement systems (i.e. noise filtering for image processing, digital analog-to-digital converter), maximizing tax revenues, maximizing pollen collection by honeybees, and maximizing flow rate of accurate information from distributed sensors.
The Functional Connectome (FC): A fundamental problem in cellular biology is understanding how multiple cellular processes are coordinated to produce the cell's response to an external stimulus. Here we develop a new way to address this fundamental problem by combining dynamic systems modeling with linear algebra methods (singular value decomposition) to determine the pattern of coordination amongst cellular subsystems that underlie the cell's response. In this project, we will develop the mathematical framework of FC and apply it to study the pattern of changes in Ca^{2+} signaling system in cardiomyocyte.
The FC and variability: In cardiomyocytes population, we found cell-to-cell variability in the functional expression of ionic currents (***Ref 15***). I will apply the FC approach to understand how the myocyte is able to maintain normal action potentials in spite of significant variability in ion channels' expressions.

14. **Izu, L.T***., T. Bányász, and Y. Chen-Izu. *Optimizing Population Variability to Maximize Benefit.* PLoS ONE 10(12): e0143475 (2015). PMCID: PMC4674128
15. Banyasz T, Horvath B, Jian Z, **LT Izu**, Chen-Izu Y*. *Sequential dissection of multiple ionic currents in single cardiac myocytes under action potential-clamp*. J Mol Cell Cardiology 50:578-581. (2011) PMCID: PMC3047417

List of Publications *[Ctrl-click to follow link]*

Google Scholar: Leighton T. Izu (Complete list) NIH NCBI website (partial list)

D. Research Support

Active grants

NIH/NHLBI R01 HL149431 12/20/2019 – 11/30/2024

PD/PI: Izu Leighton T, mPI: Chen-Izu Y

"The Functional Connectome of the Mechanically Loaded Cardiomyocyte"

NIH/NHLBI R01 HL141460 01/02/2019 – 11/30/2023

PI: Chen-Izu Y, co-Investigator: Izu LT

"MECHANICAL LOAD EFFECT ON CARDIAC EXCITATION-CONTRACTION COUPLING"

NIH/NHLBI R01HL123526 08/01/2015 – 7/30/2020

PI: Ye Chen-Izu; co-Investigator: LT Izu

"Novel Cell-in-gel device for studying mechano-chemotransduction at single cell level"

This grant is to develop a novel cell-in-gel system to control mechanical stress at the single cell and molecular levels to study the mechano-chemo-transduction in live cardiomyocytes.

Completed grants *(Selected)*

NIH/NHLBI 1R01HL105242 12/01/10 - 11/30/15

PI: McCulloch, A; co-Investigator: Izu LT

"Multi-Scale Systems Models of Murine Heart Failure"

NIH/NHLBI R01 HL090880 6/2009-5/2014

PI: Izu LT, co-I: Y. Chen-Izu

Sarcomere Length Shortening and the Destabilization of the Ca^{2+} Control System in Cardiac Cells -- Linking Contractile Dysfunction to Arrhythmias

NIH/NHLBI R01 HL071865 7/2003-6/2008

co-Investigator: Izu LT

Mechanisms of Excitation-Contraction Coupling in Atrial Cells

Veteran's Administration Merit Award 10/2002—9/2007

co-Investigator: Izu, LT

Cellular Mechanisms of Excitation-Contraction Coupling in Cardiac Atrial Cells

NIH HL068704 K25 Quantitative Research Career Development Grant 1/2002/-11/2006

PI: Izu LT

Calcium Waves in Atrial Cells

National Center for Supercomputing Applications 6/2000-6/2002

PI: Izu LT

Calcium sparks and calcium waves in heart cells.