Integrative Cardiac Dynamics

https://www.kitp.ucsb.edu/activities/cardio18

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Final Report on program held on June 25, 2018 - July 20, 2018

Introduction

The Integrative Cardiac Dynamics program brought together a broad range of scientists interested in the dynamics of cardiac arrhythmias. The participants included theoretical physicists, mathematicians, cardiac physiologists, cell biologists, and medical doctors. These scientists represented a broad spectrum of expertise with the sole purpose of understanding the fundamental mechanisms that cause dangerous electrical and mechanical activity in the heart. The KITP offered a unique setting where these researchers could spend a substantial amount of time together discussing scientific questions. To our knowledge, there are very few venues that promote such intense and prolonged discussion. Most scientific meetings in the field of cardiac dynamics consists of many more participants for a much shorter amount of time with little time for in-depth discussions and collaborations borne on-site. ***Therefore, we feel that the KITP offers a unique setting to promote truly impactful interdisciplinary work.*** As a result, a substantial number of participants established new collaborations. In many cases, it was clear that this connection would not have been made without the excellent atmosphere provided by the KITP.

Organization

This was a 4-week program that was organized around four general themes. Each week was devoted to mostly one theme. However, week 3 & 4 were mixed due to the logistics of integrating short-term visitors. Week 1 centered mostly on subcellular calcium dynamics and signaling. Week 2 talks explored gene regulatory mechanisms and new modeling techniques that accounted for genetic variability. Weeks 3 & 4 focused on the latest advances on imaging, mechanistic understanding and control of emergent phenomena such as spiral waves and reentrant activity in the intact heart, and their clinical applications. Each week day we had 2 talks, one at 9:00am and the next at 10:30am, with ample discussion of each and with a clear break between the talks. On Tuesday and Thursday we had an additional talk at 2:00pm, which was usually given by an affiliate. Fenton delivered the Blackboard Lunch talk on 07/02, open to broader audience. Talk

scheduling was done with the online system and the weekly schedule was completed on the Friday before each week. During the week the organizers made changes with the program officer David Kaczorowski, who quickly updated the online schedule. It should be noted that most participants relied on the KITP website to keep track of the schedule changes.

The talk sessions were highly interactive, thought-provoking and friendly. Almost all talks lasted a full one hour and a half even though all speakers were urged to prepare to speak only for 30 minutes. This was due to the high level of engagement of all participants in the friendly atmosphere. Remarkably, this level of engagement was sustained and applied to essentially every talk during the 4-week period of the program. The KITP Auditorium was ideal and provided an excellent atmosphere which promoted interactions between speaker and audience. Overall, the level of interaction during talks was truly outstanding and many participants have praised this aspect of the workshop, not present in any other professional meeting in the field. It should be mentioned that KITP staff was also highly competent and promptly solved all technical issues that arose. On one day a talk was delivered through Skype and the staff still managed to record the audio.

After the talks, participants typically went to lunch together in small or larger sub-groups, and proceeded to interact in their offices, hallway, courtyard, or around KITP. The organizers urged speakers to form small groups and use many of the convenient common spaces in the courtyard and lobby at the KITP. On several occasions groups of up to 5 participants held meetings to discuss specific topics of mutual interest. Once again, the KITP design and layout were ideally suited for these short informal meetings between a few participants. It should be noted that during week 1 the courtyard was occupied by a conference which made such meetings inconvenient. However, the following 3 weeks were clear and meeting participants had better access to the common spaces.

In the evening, participants often gathered for dinner in the dining room of Munger Hall. Each Thursday we organized a barbeque in the outdoor space for all. The Munger facilities for social and scientific interaction are truly outstanding. Credit should be given to James Brill for excellent organization, and for providing the basic resources to handle these activities.

Accomplishments & new collaborations

There were several research directions covered in the program:

Subcellular remodeling and Ca waves. Week 1 was mostly focused on Ca signaling in cardiac myocytes and their role in the genesis of cardiac arrhythmias. A key topic that was explored is the role of the subcellular architecture of myocytes. Specifically, there was intense interest on the role of remodeling of the spatial relationship between ion channels in the heart. Gorelik showed tantalizing new experimental evidence that L-type Ca channels migrated to the cell boundaries from t-tubules. Also, Wasserstrom and Shiferaw argued that in ventricular myocytes in heart failure remodeled so that t-tubules retract forming a substrate that supported arrhythmogenic Ca waves. Echebarria and Lacalle pointed out that Ca waves cannot propagate in cardiac myocytes given what is known about the cell architecture and buffering. However, Sato presented new experimental data and simulations showing that the cell's intrinsic heterogeneity is crucial for the propagation of Ca waves. Overall, the interactions this week were intense and highly productive. It was clear at the end that a great deal of work remains to be done and that better mechanistic understanding of the Ca cycling system will be an important topic in the field. Potential new collaborations that emerged from these discussions are:

- *Echebarria, Lacalle, Shiferaw, Wasserstrom:* Will investigate how waves propagate in ventricular heart failure cells where the cell architecture is substantially modified from normal. Echebarria and Lacalle have recently developed a detailed subcellular modeling framework that can be combined with Shiferaw's more phenomenological approach. These, combined with confocal linescan imaging from Wasserstrom, will form the basis of a new research direction.
- *Wasserstrom, Shiferaw, Lacalle:* Will explore how remodeling affects the homeostasis of calcium in atrial myocytes in heart failure. The expertise of the researchers is complementary and a new collaboration was initiated.
- *Shiferaw, Lacalle, Echebarria, Karma, Sato, Sobie:* Will investigate a general framework for calcium wave propagation. The mechanism of transition from calcium sparks to waves is still unknown. Combination of detailed computational modeling and experimental measurements will reveal fundamental mechanisms of wave propagation.

Cell-cell communication mechanisms and spatio-temporal instabilities. Several talks, e.g. by Weinberg, Pertsov and others triggered a discussion on cell-cell communication mechanisms alternative to mainstream-considered gap-junctional propagation. When “ephaptic” coupling is considered, i.e. mechanisms of

excitation dependent on the electric fields in the nanospace at the intercalated disks, some non-trivial effects emerge. These discussions inspired newly formed collaborations.

- *Otani, Karma, Pertsov, Weinberg:* An ongoing mystery in the study of electrical alternans in the heart (the beat-to-beat alternation of properties of propagating electrical waves) is why the coherent regions of in-phase alternations are as small as they are in experiments, when standard theory suggests they should be much larger. During this conference, it was proposed that "ephaptic" coupling (as opposed to standard gap junction coupling) between cells may be responsible for this effect. During the workshop, Otani constructed a computer model of this effect, and showed, preliminarily, that ephaptic coupling can create much smaller in-phase regions. Further discussions can define the experiments needed to validate this new idea, which may reconcile some discrepancies between models and experiments.
- *Karma, Entcheva:* A collaboration has been initiated to reconcile a striking discrepancy between model-based prediction of conduction velocity profiles during discordant alternans and experimental findings based on calcium imaging in cell culture. New modeling and analysis will help uncover the mechanism of pattern formation of calcium alternans during reentrant arrhythmias.
- *Sato, Entcheva, Bub:* Perturbation theory and spatio-temporal patterns in triggered arrhythmias were discussed and what a basic set of experiments would be. Cell patterning and optogenetic approaches may help design such experiments.
- *Gorelik, Entcheva:* Experiments to quantify hetero-cellular coupling combining the nano-scale ion scanning conductance microscopy and cell-selective optogenetic perturbations were discussed. The method can bring new insights about cell communication in the heart and the dynamics of contacts.

Population models, better empirically-validated models. Talks by Sobie, Krogh-Madsen, Simonetti and Karma spearheaded discussions on model building. High-throughput functional measurements (Entcheva) and detailed spatiotemporal measurements of cardiac dynamics in different species (Fenton) can aid in this process.

- *Krogh-Madsen, Entcheva:* We discussed "smart" approaches for efficient model building and in what cases all-optical technology can help scale these up.
- *Sobie, Entcheva:* Discussions of data analytics using results from high-throughput all-optical electrophysiology in human iPS-derived cardiomyocytes took place.

Towards better understanding of cardiac electromechanics. Recent advances in 3D ultrasound imaging of cardiac mechanical waves (Christoph, Luther) sparked interest in developing computational modeling of cardiac electromechanics, which has been lagging compared to electrophysiological models.

- *Christoph, Luther, Karma:* A computational study of the spatiotemporal organization of cardiac mechanical waves is being conducted and will be submitted for publication. Particularly, the non-locality of elastic interactions is explored and its effect on the dynamics of electrical waves. This work can further aid ultrasound imaging of 3D cardiac dynamics.
- *Luther, Christoph, Bub, Kay, Entcheva:* Discussions took place on developing a grant application by leveraging the recent motion tracking algorithms and imaging of mechanical waves (Luther, Christoph) along with optogenetic actuation methods (Entcheva, Bub, Kay) to uncover fundamental properties of electromechanical waves in cell culture and in the whole heart. Such experiments can inform better models in this area.
- *Otani, Christoph, Luther:* Ideas were discussed to develop a framework for predicting electrical waves from measurements of mechanical waves in cardiac tissue.

Control of alternans and other instabilities. Optogenetic control. Talks by clinicians or clinically-immersed scientists (Ashikaga, Bernus, Stevenson and Tolkacheva) spearheaded discussions on how to help clinicians by leveraging basic science knowledge.

- *Talkachova, Karma:* Work on control of alternans at the whole heart level using constant DI pacing and ECG as an input will be further explored to understand the mechanism and to establish this as an alternative control strategy to constant cycle length pacing.
- *Bub, Entcheva, Kay:* Discussions for cell-specific optogenetic control in the area of neuro-cardiology took place, prompted by Kay's presentation using transgenic mice with light-sensitive sympathetic and parasympathetic nerves. In vitro and in vivo experiments will be performed to suggest new strategies for control of cardiac arrhythmias.
- *Biktashev, Biktasheva, Bub, Entcheva:* Various ideas for model-driven spatiotemporal feedback control of cardiac waves were discussed, including resonant drift. Such ideas are ideally tested in 2D in vitro experimental systems, and optogenetic methods can help implement them.
- *Otani, Cherry, Fenton, Sato:* Mathematical analysis of calcium-driven alternans was discussed. We developed a novel control protocol for this alternens.

Linking the ECG and heart rate heart print with ionic models describing diseased state. Leon Glass gave an excellent presentation outlining his previous efforts to develop a statistical analysis of ECG signals in order to construct a heart print that can be used for risk stratification. This talk stimulated discussions with Karma, Shiferaw, Ashikaga and Sato to develop more effective algorithms to characterize various diseased states. In particular, discussions centered around the possibility that ECG patterns of diseased patients contain information about the underlying cellular instability. Potential collaborations that arose from these discussions are:

- *Karma, Glass, Sato, Ashikaga and Shiferaw:* Will analyze a cardiac repository developed by Glass and collaborators which contains ECG patterns of patients with a range of cardiac defects. Shiferaw and Sato proposed to study statistical signatures of key Ca dependent instabilities to see these can be detected in ECG patterns. Karma proposed to study LQT patients to explore if EAD patterns in cells from these patients can be linked to fluctuations patterns seen in the ECG. Ashikaga, who is a practicing clinician – a cardiac electrophysiologist at Johns Hopkins Medical School - offered to acquire data from patient's Holter monitors.
- *Talkacheva, Weinberg:* Heart rate variability will be explored by combining experimental data (Talkacheva) and computational modeling (Weinberg) to potentially explain unexpected results in isolated rabbit hearts. Grant application is planned.
- *Kay, Weinberg:* Experimental data (Kay) will be used in conjunction with computational models to understand long-term changes in heart rate modulation during heart failure in mice.

Developing tools to guide clinical procedures and/or analyze patient's data. Talks by clinicians or clinically-immersed scientists (Ashikaga, Bernus, Stevenson and Tolkacheva) spearheaded discussions on how to help bring basic science knowledge into the clinic to guide procedure and/or interpret data from patients.

- *Pertsov, Ashikaga:* An algorithm for guidance of 20-electrode lasso catheter for radio-frequency atrial ablation in patients was discussed. Ashikaga will provide data for retrospective analysis to attempt to improve the future catheter guidance in ablation targeting abnormal activity sites.
- *Fenton, Cherry, Bernus:* Data assimilation approach will be used to reconstruct 3D dynamics based on whole heart transmural data obtained by Bernus at Bordeaux.
- *Fenton, Ashikaga, Kaboudian, Grigoriev:* Development of methods of quantifying spiral waves in the clinical setting was discussed.
- *Fenton, Sato:* Integration of mathematical models and physical systems was discussed.

This list of collaborative projects is non-exhaustive. Many other ideas were discussed and the interactions at the workshop likely will continue beyond this meeting. All participants were impressed and grateful for the unique creative atmosphere at the KITP.

Efforts at achieving participation by groups underrepresented in physics

The coordinators recognize the paucity of women and minorities in the field of cardiac dynamics. In this program we focused our efforts to increase the representation of women and minorities across different career stages, and actively worked to secure their participation. The organizers gave priority to the women and minority applicants, and solicited these applicants during the early stages of organization. Dr. Emilia Entcheva volunteered to serve as the diversity coordinator, and specifically encouraged minority and women researchers in our field to apply. As a result, 30% of participants were female (40 reported their gender, 28 male and 12 female), and two participants were of African origin (Ethiopia, Botswana).

List of participants (in alphabetical order)

- Hiroshi Ashikaga
- Olivier Bernus
- Irina Biktasheva
- Vadim N. Biktashev
- Gil Bub
- Elizabeth Cherry
- Blas Echebarria
- Emilia Entcheva
- Flavio H. Fenton
- Simonetta Filippi
- Alessio Gizzi
- Leon Mark Glass
- Julia Gorelik
- Eleonora Grandi
- Roman Grigoriev
- Mehran Kardar

- Alain S. Karma
- Matthew Kay
- Trine Krogh Madsen
- Enrique Alvarez Lacalle
- Tim Lewis
- Stefan Luther
- Laura Munoz
- Niels F. Otani
- Arkady M. Pertsov
- Zhilin Qu
- Guy Salama
- Daisuke Sato
- Yohannes Shiferaw
- Eric A Sobie
- William G Stevenson
- Conrad Bertrand Tabi
- Elena G. Tolkacheva
- J. Andrew Wasserstrom
- Seth H. Weinberg
- James Nathaniel Weiss

Affiliates

- Diandian Chen
- Jan Christoph
- Conner Herndon
- Abouzar Kaboudian
- Shihori Kamimoto
- Ilija Uzelac

Integrative Cardiac Dynamics: Publications to Date (October 1, 2018)

1. Girish S. Ramlugun, Belvin Thomas, Vadim N. Biktashev, Diane P. Fraser, Ian J. LeGrice, Bruce H. Smaill, Jichao Zhao, and Irina V. Biktasheva, Dynamics of cardiac re-entry in micro- CT and serial histological sections based models of mammalian hearts, ArXiv e-prints (2018), arXiv:1809.01186.
2. Yohannes Shiferaw, Gary L. Aistrup, and John A. Wasserstrom, Synchronization of triggered waves in atrial tissue, Biophysical Journal 115 (2018), no. 6, 1130 – 1141.

Integrative Cardiac Dynamics
Schedule of Talks

Speaker	Title	Date
Andy Wasserstrom (Northwestern University)	Why is t-tubule remodeling such a problem in the failing heart?	June 26
Yohannes Shiferaw (CSUN)	Synchronization of stochastic calcium waves in atrial cells	June 26
Alessio Gizzi (Bio-Medico Univ.)	Cardiac electro-mechanics & mechano-electric feedback: The Stress-Assisted diffusion approach	June 26
Julia Gorelik (Imperial College)	Non-optical nanoscale functional imaging for studying ion channels/beta-adrenergic receptors in cardiovascular system	June 27
Daisuke Sato (UC Davis)	How to set the heart on fire	June 27
Guy Salama (University of Pittsburgh)	How stochastic intracellular Ca2+ release elicit arrhythmias in bradycardia and LQT2	June 28
Zhilin Qu (UCLA)	Short-term memory induced complex APD dynamics in cardiac myocytes	June 28
Conner Herndon (Georgia Tech)	Constant diastolic interval control in zebrafish and unexpected results	June 28
Blas Echebarria (Barcelona Tech)	Modeling the effects of microstructure on calcium dynamics in atrial cells	June 29
Enrique Alvarez Lacalle (UAM)	How to determine calcium homeostasis by analyzing the behavior of ion currents	June 29
Laura Munoz (RIT)	Control, Estimation, and Modeling of Cardiac Action Potential Dynamics	July 2
Ele Grandi (UC Davis)	In silico evaluation of efficacy and safety of atrial fibrillation selective pharmacotherapy	July 2
Seth Weinberg (VCU)	Sodium channel mutations and signaling at the intercalated disk	July 3
Vadim Biktashev (University of Exeter)	Two examples of coping with small parameters: time-stepping for Markov chains, and propagation in thin layers	July 3
Eric Sobie (Mt Sinai)	Slow delayed rectifier current protects ventricular myocytes from arrhythmic dynamics across multiple species	July 3
Alain Karma (Northeastern)	Variability and compensation of cardiomycoyte ionic conductances at the population level	July 5
Jim Weiss (UCLA)	Stabilizer cells: A novel gene therapy approach to treat cardiac arrhythmias	July 5
Irina Biktasheva (Liverpool)	Cardiac re-entry dynamics in MRI- and micro-CT based models of the heart	July 6
Leon Glass (McGill)	Some open questions about dynamics of cardiac arrhythmias	July 6
Emilia Entcheva (George Washington)	All-optical cardiac electrophysiology	July 9
Matt Kay (George Washington)	Spatiotemporal control of neurotransmitter release from intrinsic cardiac autonomic neurons	July 9
Trine Krogh-Madsen (Cornell)	Global optimization of cardiac myocyte models	July 10

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Speaker	Title	Date
Arkady Pertsov (SUNY Upstate)	Atrial Fibrillation:Drivers and Triggers	July 10
Ilija Uzelac (Georgia Tech)	Eliminating Cross Talk in Simultaneous Optical Mapping of Voltage and Calcium in Cardiac Tissue using the Semasbestic point	July 10
Hiroshi Ashikaga (Johns Hopkins)	Causality, Information Flow and Fibrillation	July 11
Alena Talkachova (University of Minnesota)	Prevention and control of cardiac arrhythmias	July 11
Flavio Fenton (Georgia Tech)	Initiation of arrhythmias via amplitude alternans & termination of arrhythmias via low energy synchronization	July 12
Stefan Luther (Max Planck)	Electromechanical Vortex Filaments during Cardiac Fibrillation	July 12
Ilija Uzelac (Georgia Tech)	Eliminating Cross Talk in Simultaneous Optical Mapping of Voltage and Calcium in Cardiac Tissue using the Semasbestic point	July 12
William Stevenson (Vanderbilt)	The challenge of intramural ventricular arrhythmia substrates	July 13
Roman Grigoriev (Georgia Tech)	Topological Analysis of Fibrillation	July 13
Simonetta Filipi (Rome)	Spatiotemporal correlation uncovers fractional dispersion in cardiac tissue	July 16
Gil Bub (McGill)	New methods for imaging and controlling waves in cardiac tissue	July 16
Elizabeth Cherry (RIT)	Reconstructing cardiac dynamics using data assimilation	July 17
Tim Lewis (UC Davis)	Threshold Dynamics in Excitable Media: Fast Waves, Slow Waves, and Reflections	July 17
Niels Otani (RIT)	New and not-so-new methods for stopping rotating action potential waves	July 18
Olivier Bernus (Bordeaux)	Novel Insights into Human VF Dynamics	July 18
Jan Christoph (MPI-DS)	Electromechanical Vortex Filaments during Cardiac Fibrillation	July 19
Abouzar Kaboudian (Georgia Tech)	Near Real-Time Study of Complex Human Cardiac Cell Models Applied to Cardiac Tissue in a Web-Browser	July 19