Computational Models of Cardiac Arrhythmia

PATRICK BOYLE
Biomedical Modeling Using Imaging Data
AAPM Annual Meeting, Tuesday, July 16, 2019

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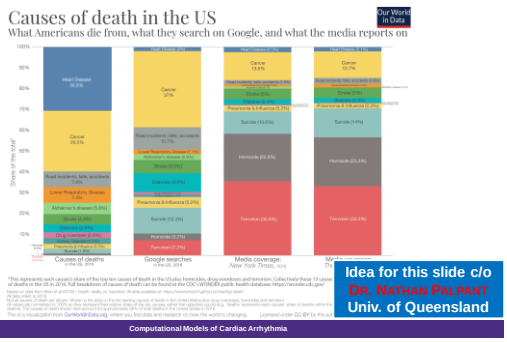
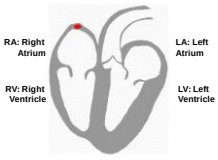


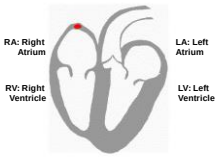
What is cardiac arrhythmia?



Normal heart rhythm, Wikimedia Commons

- **Cardiac excitation** precedes contraction, delivery of blood to body
- **Electrocardiogram** has principal electrical events
- No coordinated excitation = no O_2 delivered to body = **death within minutes**

What is cardiac arrhythmia?

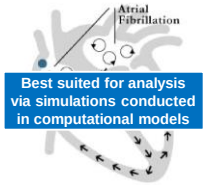


Normal heart rhythm, Wikimedia Commons

- **Cardiac Arrhythmia** Any disruption of heart's intrinsic rhythm regulation
- Some arrhythmias are less lethal than others
- e.g., **Atrial fibrillation** poses no acute threat but increases risk of stroke

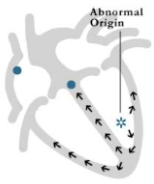
Major arrhythmia categories

Reentrant self-perpetuation



Best suited for analysis via simulations conducted in computational models

Focal/triggered ectopy

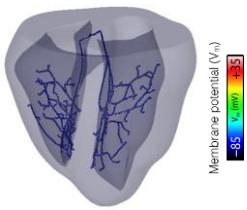


Brigham and Women's Hospital (2015)

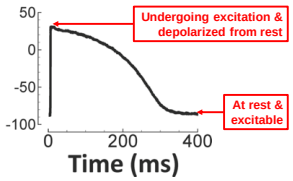
Methodological overview

1. What are we trying to model?
2. How do these models work?
3. How can these models be used?

Excitation at cell and organ scales

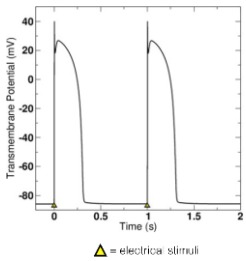


Normal excitation of rabbit ventricles
Boyle et al. (2010) Annals of Biomed Eng



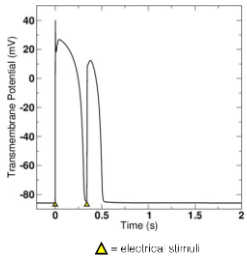
Cardiac action potential (AP)
O'Hara et al. (2011) PLoS Comp Biol

Refractoriness



- **Generally**, two stimuli = two action potentials
- What if we shorten the **coupling interval (CI)**?
- At its extreme, this can lead to complete action potential suppression

Refractoriness



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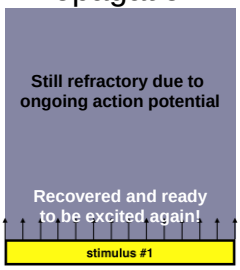
- What if we shorten the **coupling interval (CI)**?
- At its extreme, this can lead to complete action potential suppression
- **Major consequences at the tissue scale!**

Normal AP Propagation in Tissue



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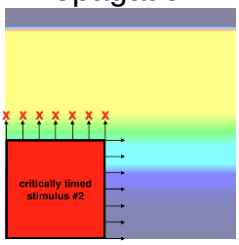


Self-perpetuating excitation = BAD

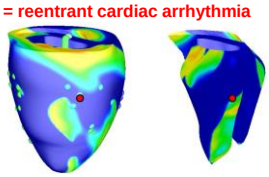
Why do we care so much about reentry?

- Two "ingredients" for reentrant arrhythmia:
  - **Substrate:** state of tissue after stimulus #1
    (i.e., spatially heterogeneous refractoriness)
  - **Trigger:** critically-timed stimulus #2
- Many pathophysiological factors can give rise to these types of pro-arrhythmic substrates and triggers!
- Reentrant arrhythmias are complex; simulations can help explain how they work and reveal new treatments

Conceptual basis of reentrant arrhythmia

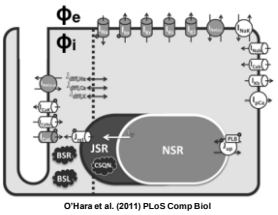
Healthy, beating human heart

+ substrate (disease, genetics, etc.)
+ trigger(s) (ectopic beat, stress, etc.)
= reentrant cardiac arrhythmia

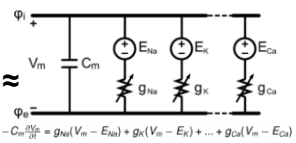


Ventricular fibrillation (Epi/Endo views)
Boyle et al. (2013) Heart Rhythm

Cell-scale building blocks



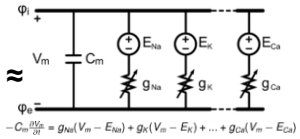
O'Hara et al. (2011) PLoS Comp Biol



Solve ODE system(s) to represent membrane kinetics, leading to realistic models that can **simulate cardiac APs**

Cell-scale building blocks

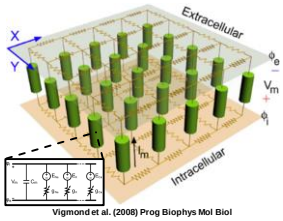
O'Hara et al. (2011) PLoS Comp Biol



$$-C_m\frac{\partial V_m}{\partial t} = g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K) + \ldots + g_{Ca}(V_m - E_{Ca})$$

Solve ODE system(s) to represent membrane kinetics, leading to realistic models that can **simulate cardiac APs**

Tissue-scale building blocks



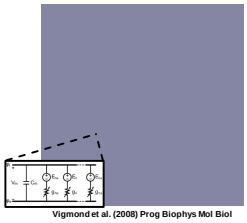
Vigmond et al. (2008) Prog Biophys Mol Biol

- Solve PDE system(s) using finite element analysis to represent propagation
  - e.g., bidomain formulation:

$$\nabla\cdot(\bar{\sigma}_i+\bar{\sigma}_e)\nabla\phi_e = -\nabla\cdot\bar{\sigma}_i\nabla V_m - I_e$$
$$\nabla\cdot\bar{\sigma}_i\nabla V_m = -\nabla\cdot\bar{\sigma}_i\nabla\phi_e + \beta I_m$$

- Must be solved numerically using high-performance computing systems

Tissue-scale building blocks



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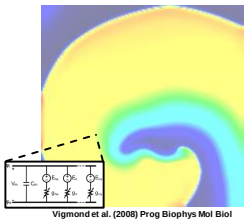

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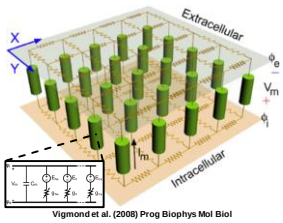

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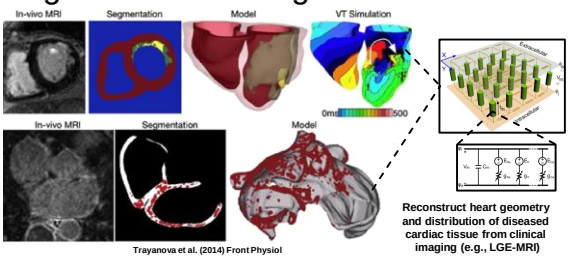
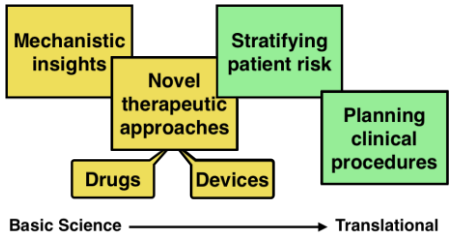
Organ-scale building blocks



Trayanova et al. (2014) Front Physiol

Reconstruct heart geometry and distribution of diseased cardiac tissue from clinical imaging (e.g., LGE-MRI)

Potential applications



Case study #1

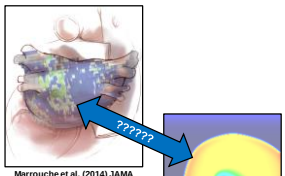
Fast-turnaround patient-specific modeling of atrial fibrillation (AFib)

The AFib epidemic

- AFib is an enormous health problem worldwide
- Most prevalent sustained arrhythmia (1-2%)
- Prevalence on the rise (~2.5× increase by 2050)
- Many patients transition to **persistent AFib** from less severe forms of disease

Persistent AFib is very hard to treat

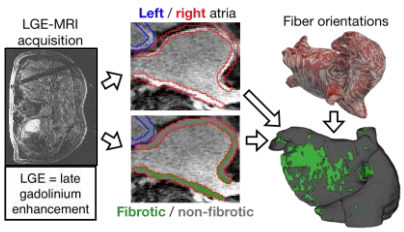
- Long-term ablation success rates are low
- Relationship between **fibrotic remodeling** and **reentrant drivers** of AFib is not well characterized
- **Computational models can be a huge help!**



Marrouche et al. (2014) JAMA

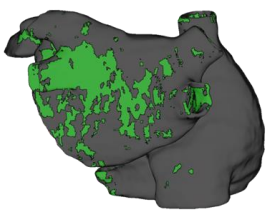
Reentrant driver concept

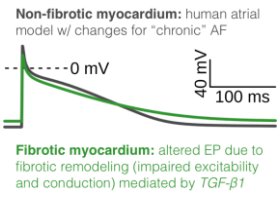
Model reconstruction from LGE-MRI



Zahid et al. (2016) Cardiovasc Res

Model parameterization

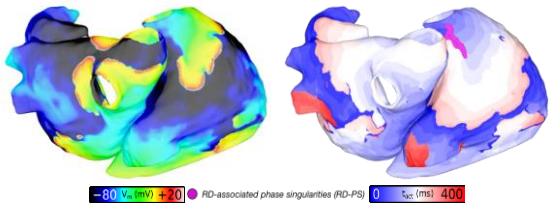




Zahid et al. (2016) Cardiovasc Res

Dynamics of simulated AFib

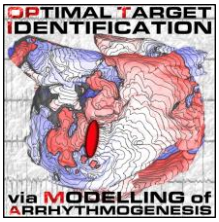
Evolution of $V_m(t)$ **Map of activation times**



Zahid et al. (2016) Cardiovasc Res

Potential value of modeling is high

- Better understand underlying mechanisms of AFib
- Identify patients at risk of developing AFib in the future (e.g., cryptogenic stroke)
- **Patient-specific persistent AFib treatment planning (OPTIMA trial at JHU)**



Boyle et al. (2019) Nature Biomedical Engineering *(IN PRESS)*

OPTIMA Workflow

OPtimal
Target
Identification via
Modeling of
Arrhythmogenesis

Boyle et al. (2019) Nature Biomedical Engineering *(IN PRESS)*

OPTIMA outcomes are good, but...

ID	Rhythm at end of FU	FU duration (days)	Atrial ablation during FU
1	SR	543	No
2	SR	347	No
3	PAF/Afl	417	PAF/Afl
5	SR	399	No
6	SR	302	No
7	SR	315	No
8	SR	264	No
9	SR	239	No
10	SR	197	No

- No recurrence of persistent AF: 10/10
- 4/10 patients had paroxysmal AF/flutter during follow-up, including one repeat ablation

Boyle et al. (2019) Nature Biomedical Engineering *(IN PRESS)*

...uptake will be hindered by complexity!

- **Staggering computational complexity**
  - Model reconstruction: ~0.5-2 days
  - "Substrate stress test": ~2-4 days
  - 15-20 total days of CPU time
- **Difficult to carry out simple parameter sensitivity analyses**
  - *Deng et al. (2017) Chaos: 60k CPU hours to test ±10% APD/CV in 12 atrial models*
- **The JAWS philosophy does not apply**

"We're gonna need more than just a bigger super computer."
–Pat (2019)

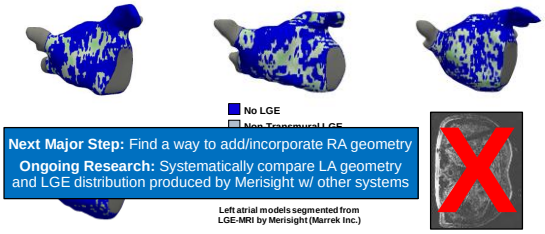
Long-Term Objective: Streamlined framework for atrial model reconstruction and realistic simulation of AFib

- Automate! Automate! Automate!
- Prioritize Validation, Verification, and Uncertainty Quantification (VVUQ)
- Produce clinically actionable results within a suitable timeframe

Issue: Atrial image segmentation can be time consuming and labor intensive

- **Solution?** 3rd party image segmentation service
  - Every AFib ablation patient at UW LGE-MRI pre-procedure
  - Every scan gets processed off-site (Merisight, Utah)
- **Benefits:** no time spent on image segmentation or processing, consistency, ease of clinical integration
- **Drawbacks:** loss of precise control, current workflow produces single LA surface w/ normalized LGE values

3rd party image segmentation



Next Major Step: Find a way to add/incorporate RA geometry

Ongoing Research: Systematically compare LA geometry and LGE distribution produced by Merisight w/ other systems

Left atrial models segmented from LGE-MRI by Merisight (Marrek Inc.)

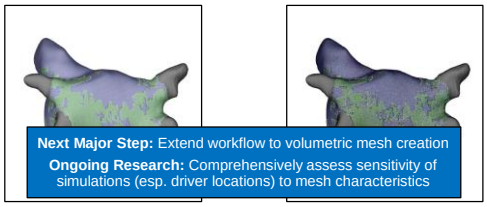
Issue: Mesh generation and refinement are time-consuming and unreliable

- **Meshes produced by Merisight** are too coarse for running cardiac EP simulations, have weird elements
- **Commercial software options** (Simpleware ScanIP, Materialise Mimics) are $$$, produce meshes suitable for different types of finite element analysis and nearly always involve a GUI (i.e., death to automation)
- **Solution?** Explore Open Source Software (OSS) for potential solutions that can be run from command line

Fully automated (re)-meshing

Original mesh extracted from Merisight VTK file

Production-quality mesh produced by gmsh (OSS)



Next Major Step: Extend workflow to volumetric mesh creation

Ongoing Research: Comprehensively assess sensitivity of simulations (esp. driver locations) to mesh characteristics

Geuzaine & Remacle (2009) Int J Num Meth Eng

Issue: Simulation run-times are long

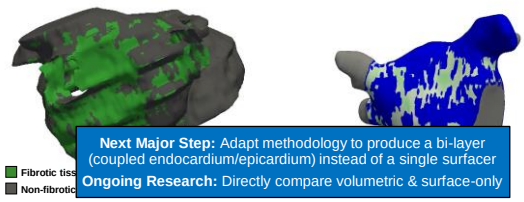
- **Computational complexity** impairs rapid turnaround times (clinical applications) and makes it challenging to carry out VVUQ (e.g., sensitivity analysis, etc.)
- **Solution?** Surface-only instead of volumetric models
- **Benefits:** huge performance boost, simpler meshing
- **Drawbacks:** information on transmurality abandoned

Using surface-only meshes is not a new idea!
e.g., Labarthe et al. (2014) Europace; Roney et al. (2016) Europace; Hwang et al. (2018) PLoS One; many others

Simplified geometry (no transmurality)

Volumetric bi-atrial mesh

Surface-only mesh of LA

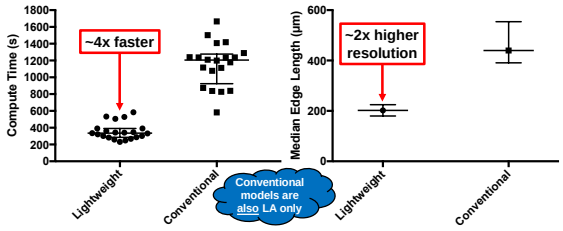


Fibrotic tiss
Non-fibrotic

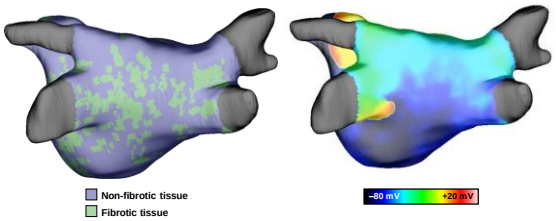
Next Major Step: Adapt methodology to produce a bi-layer (coupled endocardium/epicardium) instead of a single surfacer

Ongoing Research: Directly compare volumetric & surface-only

Performance of new models is great!



Simulated AFib in new models



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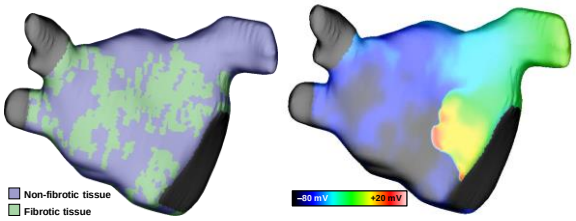


Simulated AFib in new models

- Reentrant drivers are **qualitatively similar** to those seen in conventional models
- Dynamic localization to **fibrotic tissue boundaries**
- High spatiotemporal **stability** (i.e., little meandering)

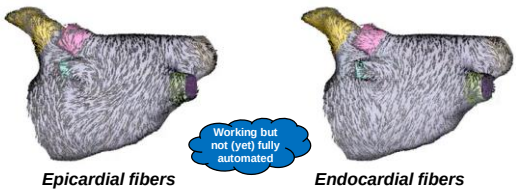
- **Key distinction:** Lack of chaotic activity and/or transient reentry in areas peripheral to driver
  - Consequence of surface only vs. volumetric models?

Next steps

Model Framework Features	Lightweight	Conventional*
Completely automated	Yes	No
Rapid compute time	Yes	No
High mesh resolution	Yes	No
Reentrant arrhythmia inducible	Yes	Yes
Realistic fiber orientations	No	Yes
Atrial thickness, transmural fibrosis	No	Yes

1. Map fibers from atlas geometry via new **UAC method**
2. Approximate transmurality via **bi-layer surface models**

Preliminary data: UAC fiber mapping



Epicardial fibers *Endocardial fibers*

UAC = Universal Atrial Coordinates

Roney et al. (2019) Med Imag Anal

Conclusions

A streamlined simulation framework is within reach!

If successful, this research promises to realize personalized computational models that could “follow the patient” in their electronic health records, **with near-real-time updates**

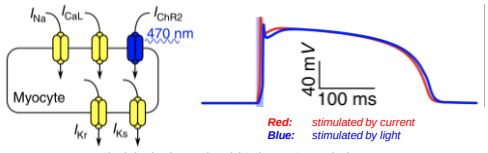
The new computational framework is not yet ready for showtime (validation is still needed), **but it will be soon!**

Case study #2

Exploring anti-arrhythmia approaches based on cardiac optogenetics

“Optogenetics”: genetic encoding of light-sensitive proteins in excitable cells

- Channelrhodopsin-2 (ChR2) light-gated NS cation channel
- Irradiation with blue light elicits a large depolarizing current



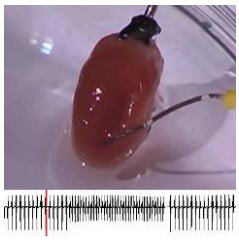
Simulation data from Boyle et al. (2013) Nature Communications

Noteworthy advantages of optogenetics

- Different opsins alter cell behavior in different ways
- Contact-free perturbation
- Patterned illumination = exquisite spatial and temporal precision
- *Selective expression in specific cells/tissues = selective stimulation*

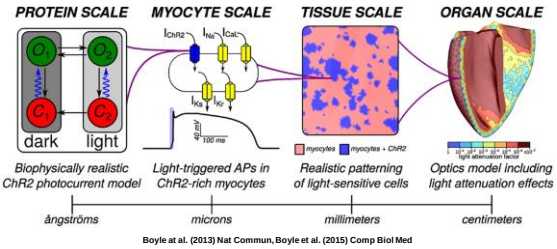
Deisseroth lab experiment, Stanford University
http://www.youtube.com/watch?v=v7uRFVR9BPU

Optogenetic stimulation of the heart



Bruegmann et al. (unpublished, 2010)

Comprehensive modeling framework



Boyle et al. (2013) Nat Commun, Boyle et al. (2015) Comp Biol Med

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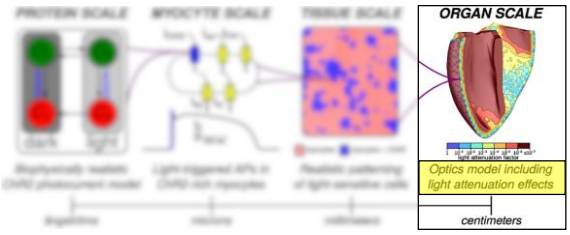
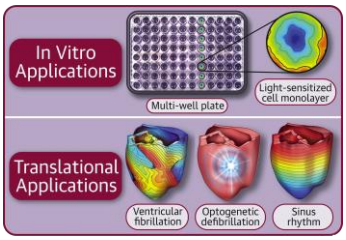


Boyle at al. (2013) Nat Commun, Boyle et al. (2015) Comp Biol Med

A novel approach to arrhythmia therapy?



Boyle et al. (2018) JACC EP State-of-the-art Review

A novel approach to arrhythmia therapy?

As a clinical treatment?

- Optogenetic defibrillation, pacing, APD modulation
- Two key prerequisites:
  - Light sensitization via gene/cell therapy
  - Illumination

As an experimental tool?

- New assays to quantify EP properties (contact-free, high-throughput)
- Patterned illumination can impose contrived scenarios (e.g., rotors)
- Light-based modulation of non-EP properties

A novel approach to arrhythmia therapy?

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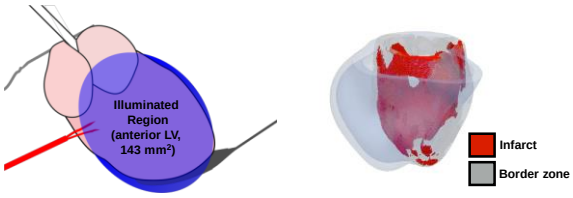
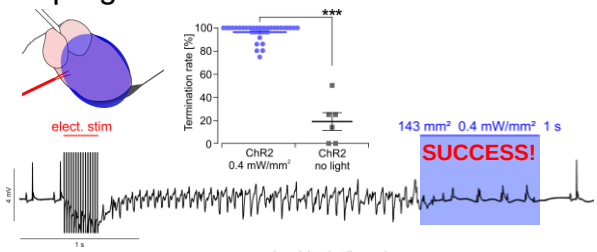
Optogenetic defibrillation

In perfused mouse hearts **In a simulated human heart**



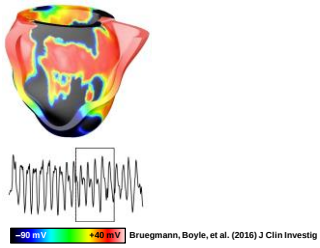
Bruegmann, Boyle, et al. (2016) J Clin Investig

Optogenetic defibrillation



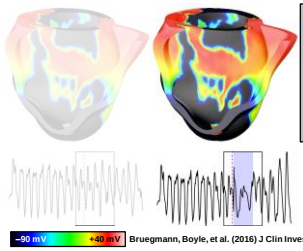
Bruegmann, Boyle, et al. (2016) J Clin Investig

Optogenetic defibrillation



Bruegmann, Boyle, et al. (2016) J Clin Investig

Optogenetic defibrillation



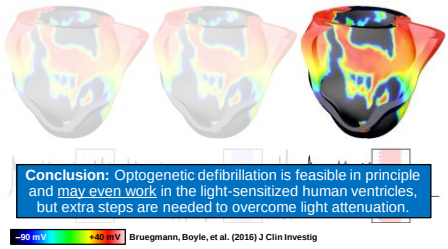
Blue light failed to defibrillate the heart!

Likely cause: attenuation from photon scattering and energy absorption

Possible solution: **RED light**

Bruegmann, Boyle, et al. (2016) J Clin Investig

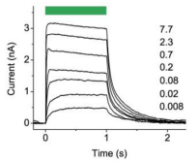
Optogenetic defibrillation



Conclusion: Optogenetic defibrillation is feasible in principle and may even work in the light-sensitized human ventricles, but extra steps are needed to overcome light attenuation.

Bruegmann, Boyle, et al. (2016) J Clin Investig

Optogenetic defibrillation/cardioversion via anion channelrhodopsins (ACRs)

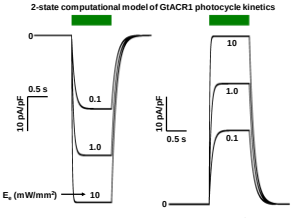


Govorunova et al. (2016) Sci Rep
(V_{clamp} = *0 mV in NRVMs*)

- **GtACR1:** Green Light Sensitive Anion Channel
- Conducts anions and elicits strong currents in cardiomyocytes
- GtACR1 reversal potential near that of chloride ions (approx. –40 mV)

Optogenetic defibrillation/cardioversion via anion channelrhodopsins (ACRs)

2-state computational model of GtACR1 photocycle kinetics



Karathanos et al. (unpublished)

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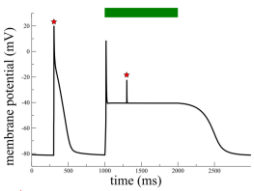
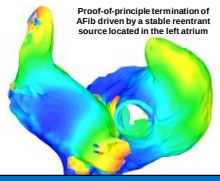




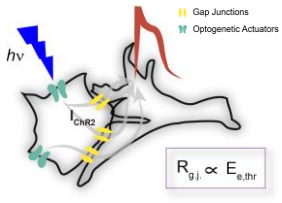
Proof-of-principle termination of AFib driven by a stable reentrant source located in the left atrium

Preliminary Conclusion: Arrhythmia termination via GtACR1 is feasible

Karathanos et al. (unpublished)

OptoGap: Light-based assay for cell-cell electrical coupling

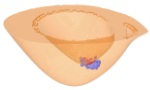
- No direct quantitative method to assess electric coupling in multi-cellular tissue preparations
- **Selective ChR2 expression** in one type of cells (e.g., FBs)
- Threshold irradiance to elicit excitation ($E_{e,thr}$) is proportional to inter-cellular gap junction resistance (R_{gj})
- **Feasible at organ scale**



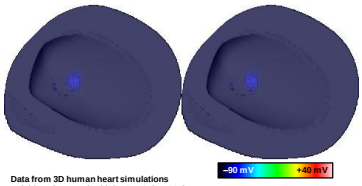
Yu et al. bioRxiv pre-print (doi: 10.1101/171397)

OptoGap: Light-based assay for cell-cell electrical coupling

Truncated view of ventricular apex with light-sensitized cells coupled to native myocytes in a restricted volume

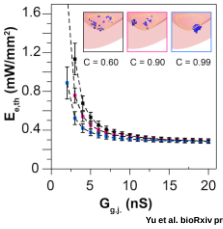


Side-by-side comparison of excitation pattern in response to light stimuli that are just below (left) and just above (right) $E_{e,thr}$



Data from 3D human heart simulations
Yu et al. bioRxiv pre-print (doi: 10.1101/171397)

OptoGap: Light-based assay for cell-cell electrical coupling



- Relationship between $E_{e,thr}$ and coupling holds for a variety of spatial patterns of ChR2+ cells
- Contactless, potentially high-throughput, scales to tissue/organ levels

Yu et al. bioRxiv pre-print (doi: 10.1101/171397)

Conclusions

~10 years on, cardiac optogenetics has emerged as a **vibrant and rapidly-growing field**

Development of a **comprehensive framework for computational modeling** has helped drive progress

New opsins and illumination strategies have created opportunities for optogenetics-based innovation, both experimentally and as a potential new treatment approach

Cardiac Systems Simulation Lab
UW Department of Bioengineering

Clinical EP team at UW Medical Center

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Arun Sridhar
Zeinab Birjandian
Sakher Sarairah

Optogenetics

Emilia Entcheva
Cookie Yu
Thomas Karathanos

AHA Funding SDG16-30440006 (PI: Boyle)

NIH **NIH Funding DP1-HL123271 (PI: Trayanova)**

Collaborators: **Johns Hopkins N Trayanova**

Collaborators: **CARP consortium G Plank, E Vigmond**

OPTIMA Team (JHU)

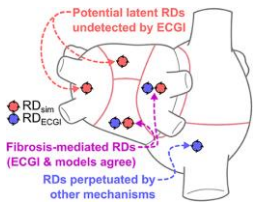
Simulations	Clinical EP
Natalia Trayanova	Hugh Calkins
Patrick Boyle	Saman Nazarian
Sohail Zahid	Joseph Marine
Dong Dong Deng	Hiroshi Ashikaga
Adityo Prakosa	David Spragg
Michael Murphy	Ronald Berger
William Franceschi	Tarek Zghaib

OPTIMA Patient Characteristics

ID	Age	Sex	BMI	LA % fibrosis	RA % fibrosis	LA VI (mL/m²)	RA VI (mL/m²)	CHA_2DS_2-VASc	# Prior Ablations	Reconnected PVs (if any)
1	69	M	31	35.8	38.65	73.3	62.5	2	1	No
2	60	M	26	26.7	5.8	35.5	52.6	0	0	
3	73	M	27	46.9	34.4	87.8	74.4	5	3	No
4	72	F	34	0.7	5.5	59.3	58.7	2	0	
5	68	M	25	32.9	34.9	71.0	46.7	2	1	RSPV, RIPV
6	67	M	29	19.7	15.6	43.3	38.2	2	0	
7	49	M	35	25.4	7.2	42.4	43.7	1	1	No
8	71	M	27	24.8	33.9	32.3	26.0	1	1	LSPV, LIPV, RIPV
9	72	M	23.8	11.9	3.1	28.5	38.2	2	2	LSPV
10	59	M	40.2	15.8	6.8	41.9	34.4	1	0	
	66±7	9(90%)	30±5	24.1±12.4	18.6±14.2	51.5±20	47.5±14.6	2[1;2]	1[0;1.5]	

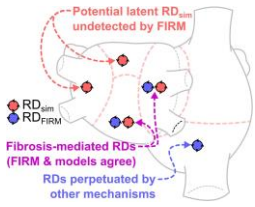
Comparison to clinical data

Boyle et al. (2018a) Front Physiol



19/42 regions w/ RD on ECGI had RD in simulations

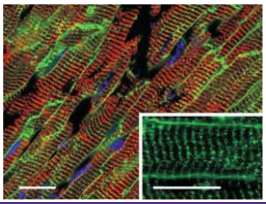
Boyle et al. (2018b) Front Physiol



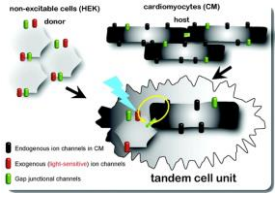
20/24 regions w/ RD on FIRM had RD in simulations

The dawn of cardiac optogentics

Bruegmann et al. (2010) Nature Methods
Green = ChR2-EYFP; Red = myocytes



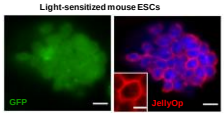
Jia et al. (2011) Circ Arrhyth Electrophysiol
Light-sensitive donor cells coupled to myocytes

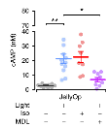


Optogenetic modulation of sympathetic tone

- Standard techniques lack spatial/temporal precision
- **JellyOp:** light-sensitive GPCR (activates G_s only)
- **Light stimulation** (2.9mW/mm^2 5min), isoprenaline infusion (1µM 5min) led to similar increases in cAMP levels

Light-sensitized mouse ESCs

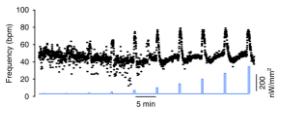




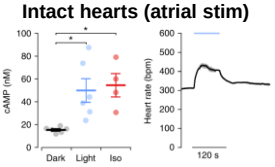
Makowka et al. (2019) Nat Commun

Optogenetic modulation of heart rate

Isolated myocytes



Intact hearts (atrial stim)

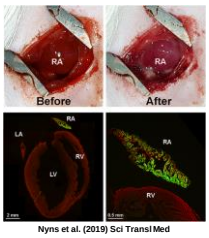


Makowka et al. (2019) Nat Commun

Exciting implication for future research: fine-grain spatial and temporal control of sympathetic tone may be possible, e.g. study effects of heterogeneity, gradients

Closed-chest, automated optogenetic termination of atrial fibrillation in mice

- Gene painting technique used to light-sensitize RA
- Selective expression of ReaChR (red-sensitive)
- System is fully automated and self-contained
- AFib termination “in vivo” and in perfused hearts



Nyns et al. (2019) Sci Transl Med

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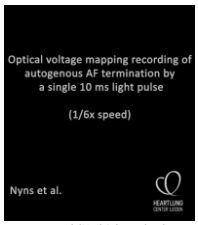
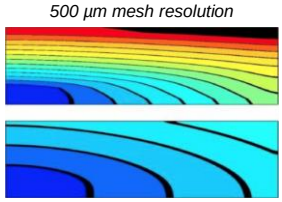


Nyns et al. (2019) Sci Transl Med

Computational complexity

- Ionic models have 20+ state variables
- µs-order time steps required due to ODE system stiffness
- Millions of nodes due to stringent resolution limit (max: 200-300 µm)

500 µm mesh resolution



100 µm mesh resolution

Niederer et al. (2009) Philos Trans A Math Phys Eng Sci

Computational complexity

- Ic
  s
- µ
  re
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Even with the best available optimizations, clinically relevant simulations of cardiac electrophysiology require HOURS OR DAYS OF RUNTIME ON DOZENS OF CPUS IN PARALLEL

100 µm mesh resolution

Niederer et al. (2009) Philos Trans A Math Phys Eng Sci