Prediction of Abnormal Cardiac Rhythms with a 1D Dynamical Model

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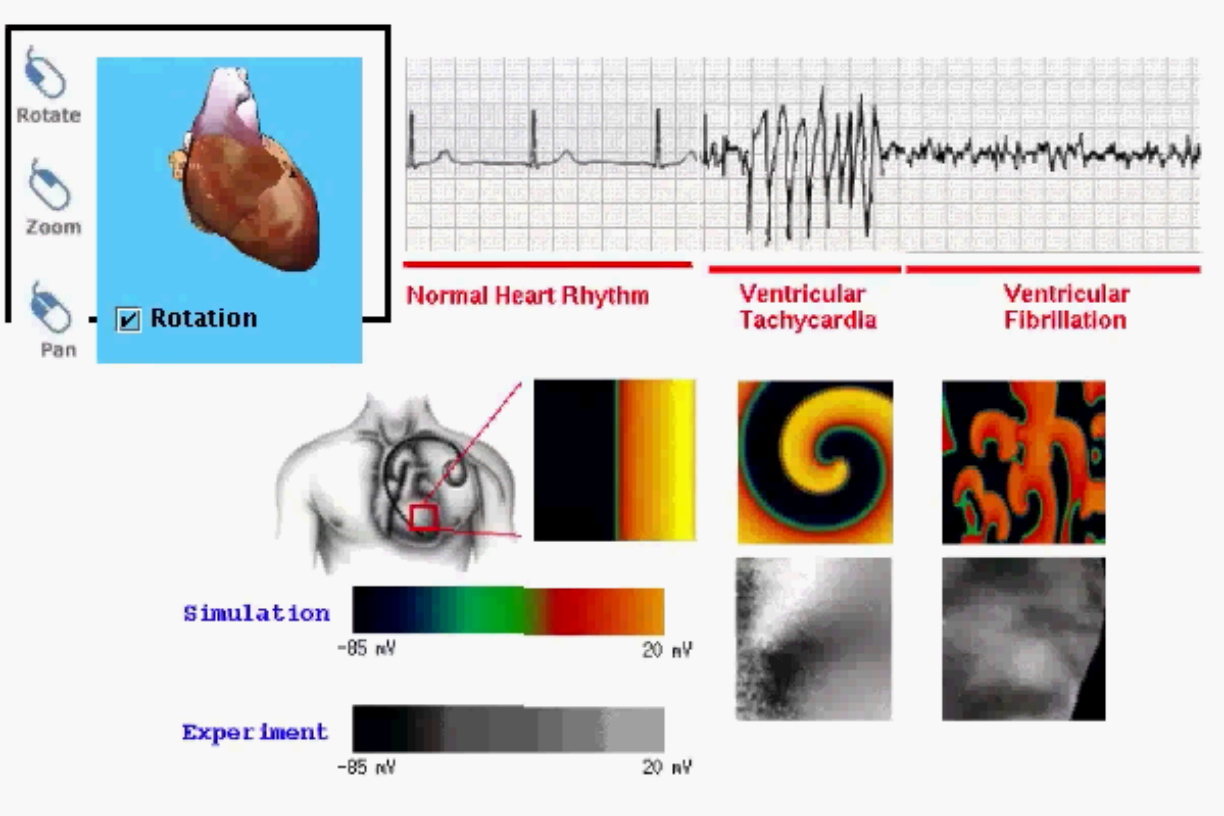
Motivation

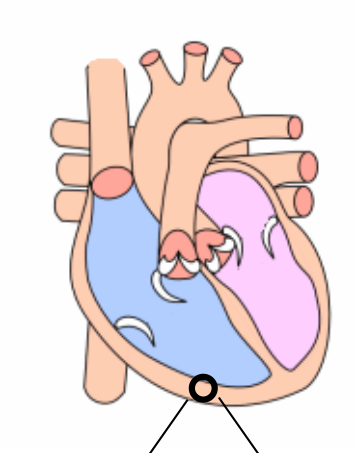
- Ventricular fibrillation (VF) is an uncoordinated heart rhythm that results in loss of effective blood pumping
- Sudden cardiac death (SCD) is a leading cause of death in the industrialized world, responsible for approx. 180000--450000 deaths in US annually
- A substantial proportion of SCDs are thought to be due to VF
- SCDs are rare, in that they affect up to ~0.1% of the US population each year
- VF is often preceded by a sequence of premature beats

Ventricular Fibrillation

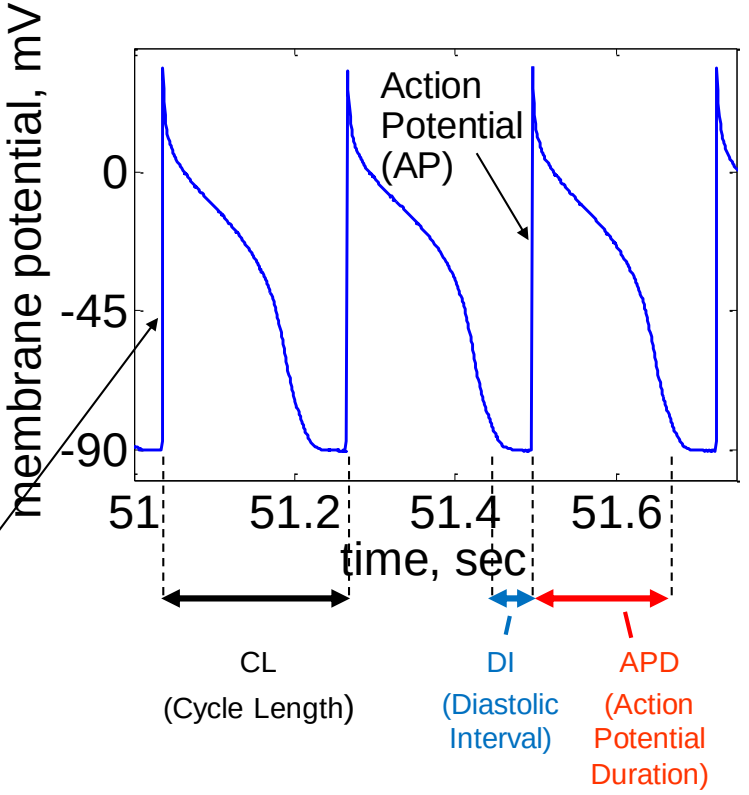


c/o Flavio Fenton and Elizabeth Cherry, http://thevirtualheart.org

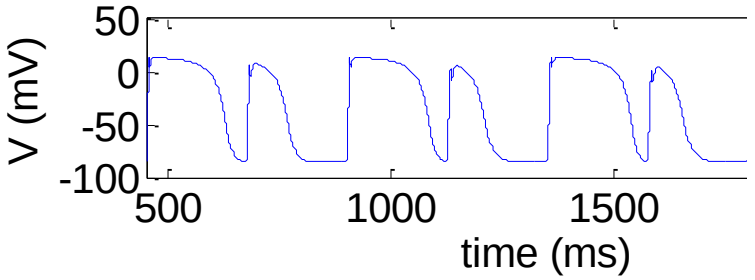
Terminology



(membrane potential)



Alternans: beat-to-beat alternation in APD

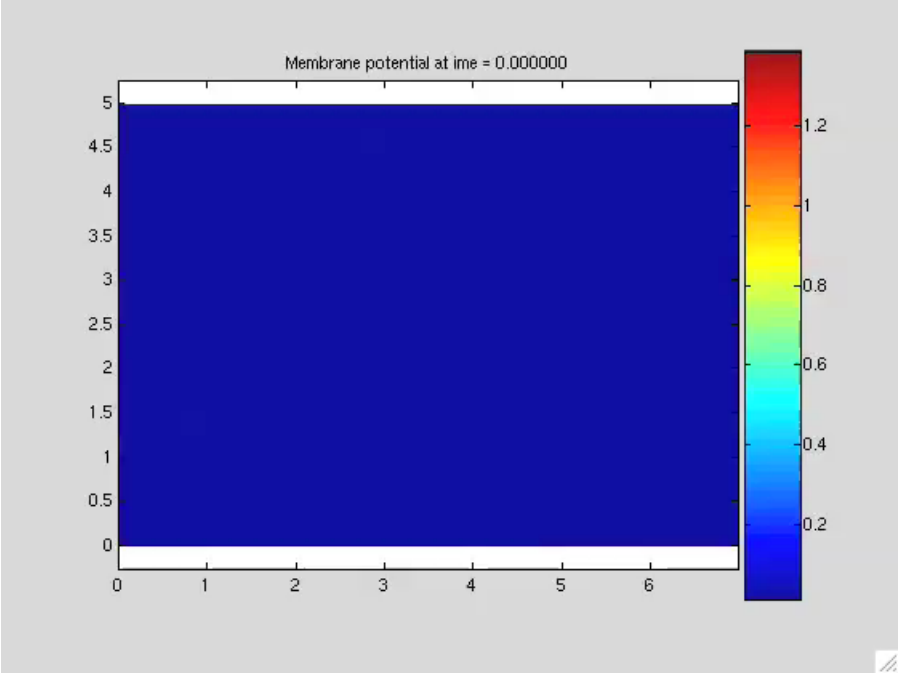


Progression to VF

- Proposed mechanism: Premature beats induce alternans, conduction block, leading to reentry and VF

Simulated ventricular tissue

(2D sheet)



c/o Niels Otani

Background

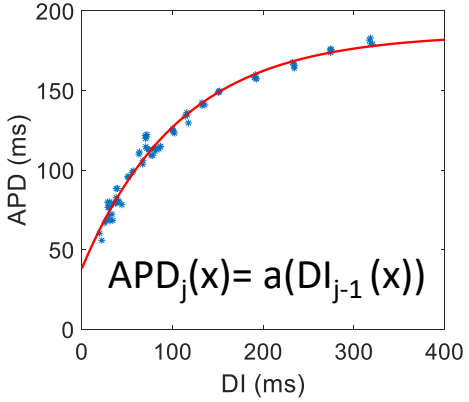
- Many models of cardiac electrical activity have been developed
  - ODE, PDE, difference equations, cellular automata, etc.
  - Phenomenological: lower dimensional, e.g. Noble model (1962), 4 variables per cell
  - Detailed: higher dimensional, e.g. Iyer-Mazhari-Winslow model (2004), 67 variables per cell

- Our approach
  - Use simple nonlinear 1D model to predict alternans, block, VF, following premature beats *in vitro* (Muñoz, et al., 2018)
  - Advantages of simple model: few parameters, and can quickly simulate large numbers of different premature beat sequences

Coupled Maps Model

(Fox *et al.*, 2003, Otani, 2007)

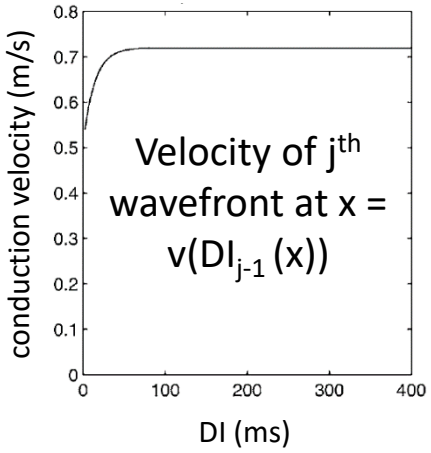
action potential duration (APD) restitution function



x = distance along fiber

j = cycle index

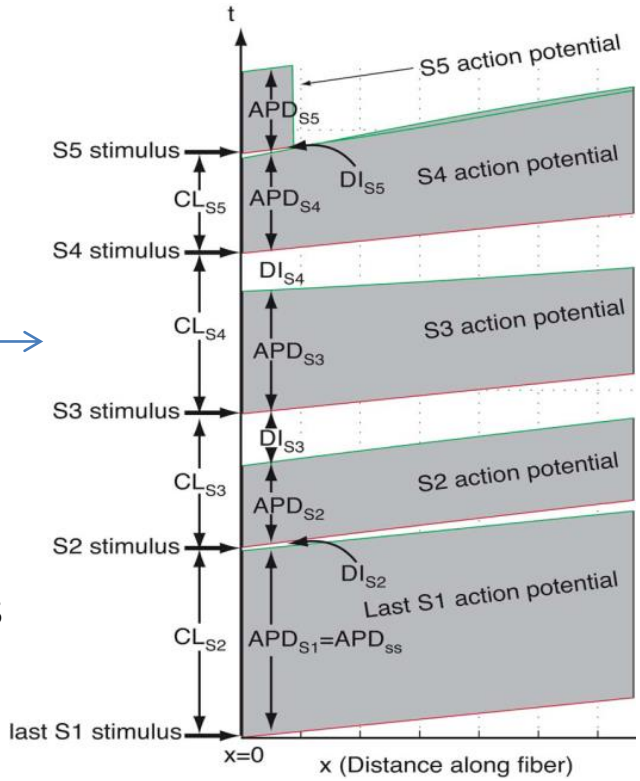
conduction velocity (CV) restitution function



Coupled Maps Model

Inter-stimulus intervals (CL_2, CL_3, CL_4, CL_5)

space-time plot



Coupled Maps Model

(Fox *et al.*, 2003, Otani, 2007)

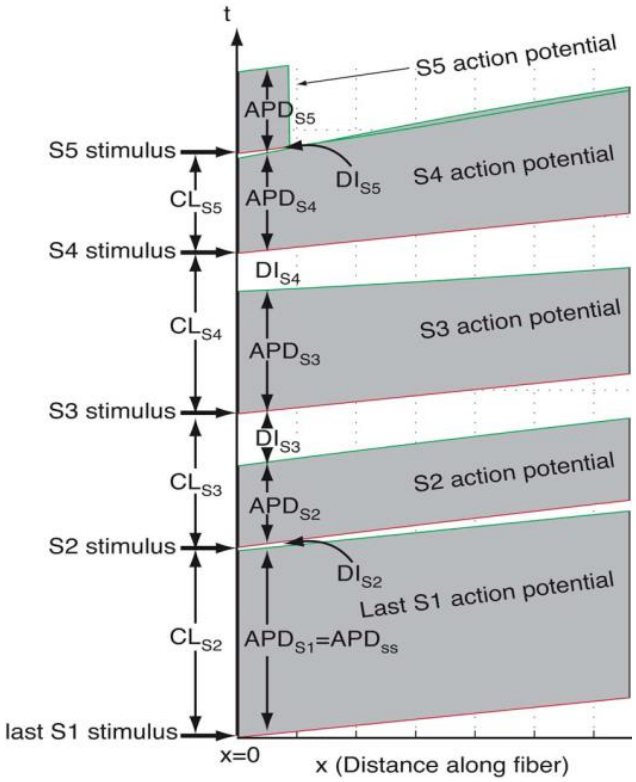
x = distance along fiber (7cm, Δx = 0.025cm)
j = cycle index
i = cell index

$$APD_j(x_i) = a(DI_{j-1}(x_i))$$

$$CL_j(x_i) = CL_j(x_0) + \sum_{k=1}^{i-1} \Delta x / v(DI_j(x_k)) - \sum_{k=1}^{i-1} \Delta x / v(DI_{j-1}(x_k))$$

$$DI_j(x_i) = CL_j(x_i) - APD_j(x_i)$$

space-time plot



Premature stimulus sequences that caused distal block in the model were found to be likely to induce VF *in vivo* (Gelzer, *et al*. 2008, 2009)

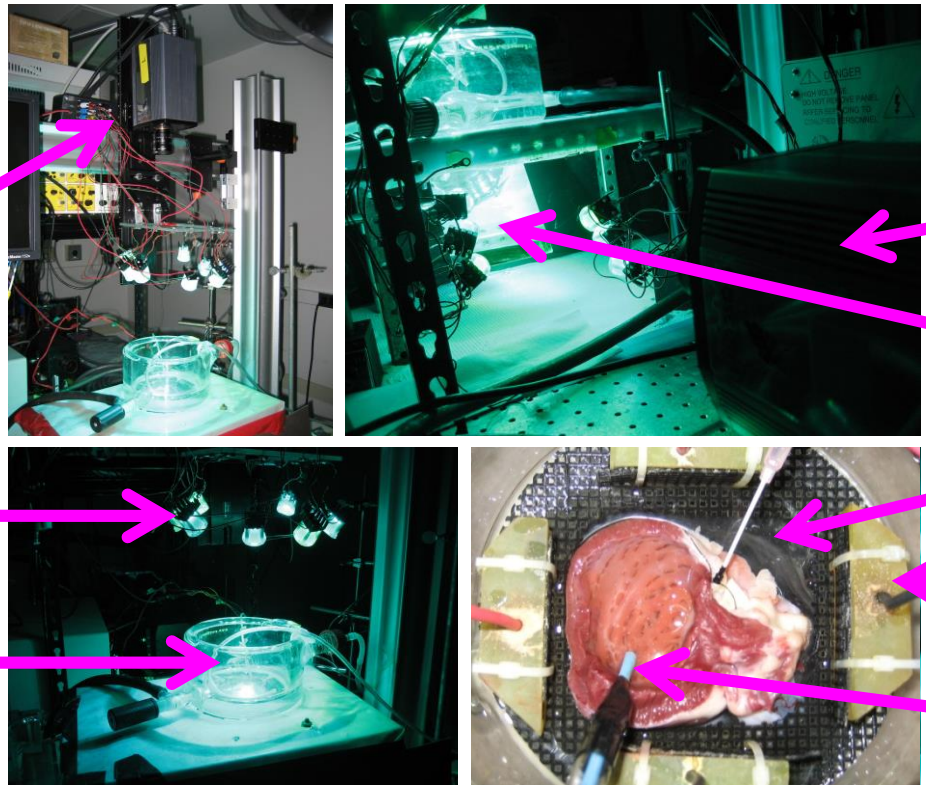
Background

- Gelzer et al. (2008, 2009): premature beat sequences that caused block in the coupled maps model were found likely to induce VF in canine hearts in vivo

- Shortcoming of in vivo setup: can only take measurements at two locations. Can detect VF, but not alternans or block

- Solution: use optical mapping in vitro (n=9 right ventricles), allows detection of alternans, block, VF

Optical Mapping Setup



Cascade 128+ camera

Cascade 128+ camera

mirror

LED units

heat bath including optical-grade bottom

perfusion inflow

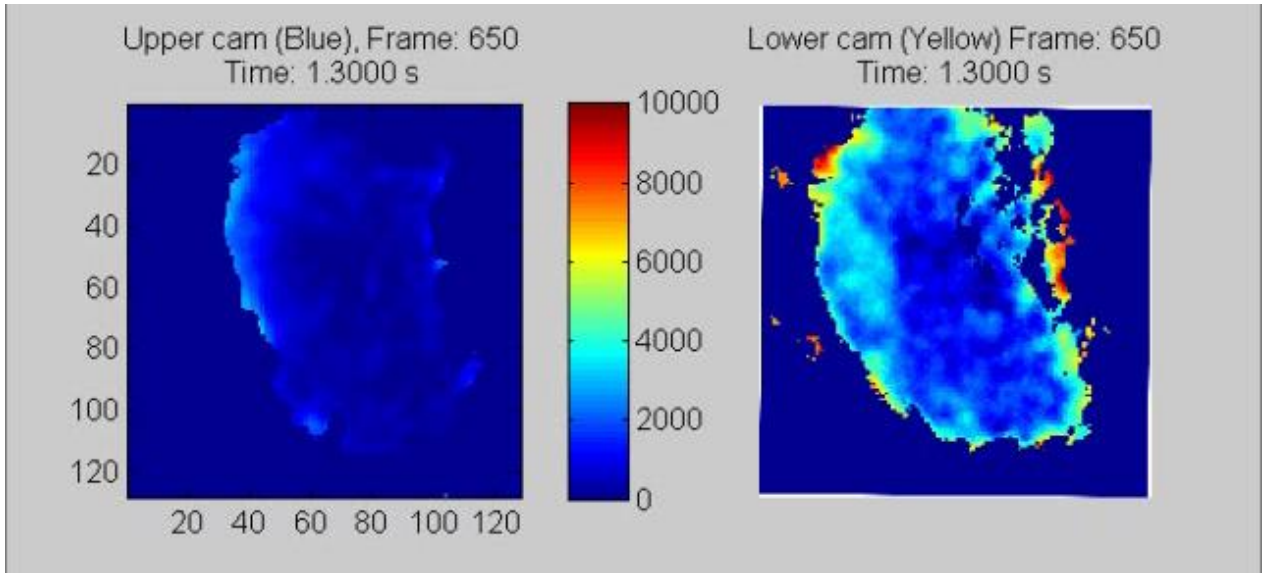
far-field stimulation electrode

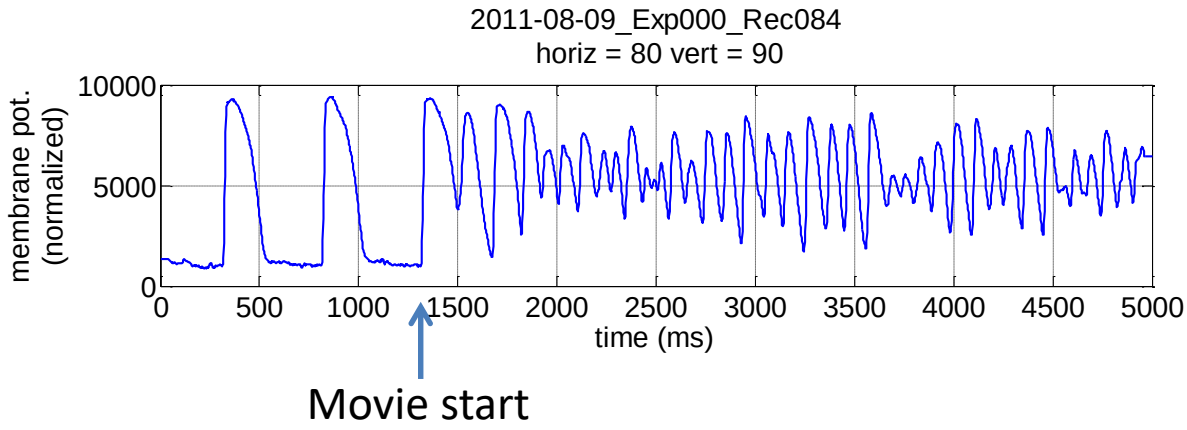
bipolar stimulation electrode

Optical Data Example

Endo

Epi





Methods

- For purposes of comparison, use same methods as in past in vivo studies
- Collect APD restitution data from *in vitro* preps
- Use historical CV restitution data (Riccio et al., 2009)
- Test different combinations of premature stimulus timings *in vitro*
- Compare model simulation results with *in vitro* measurements

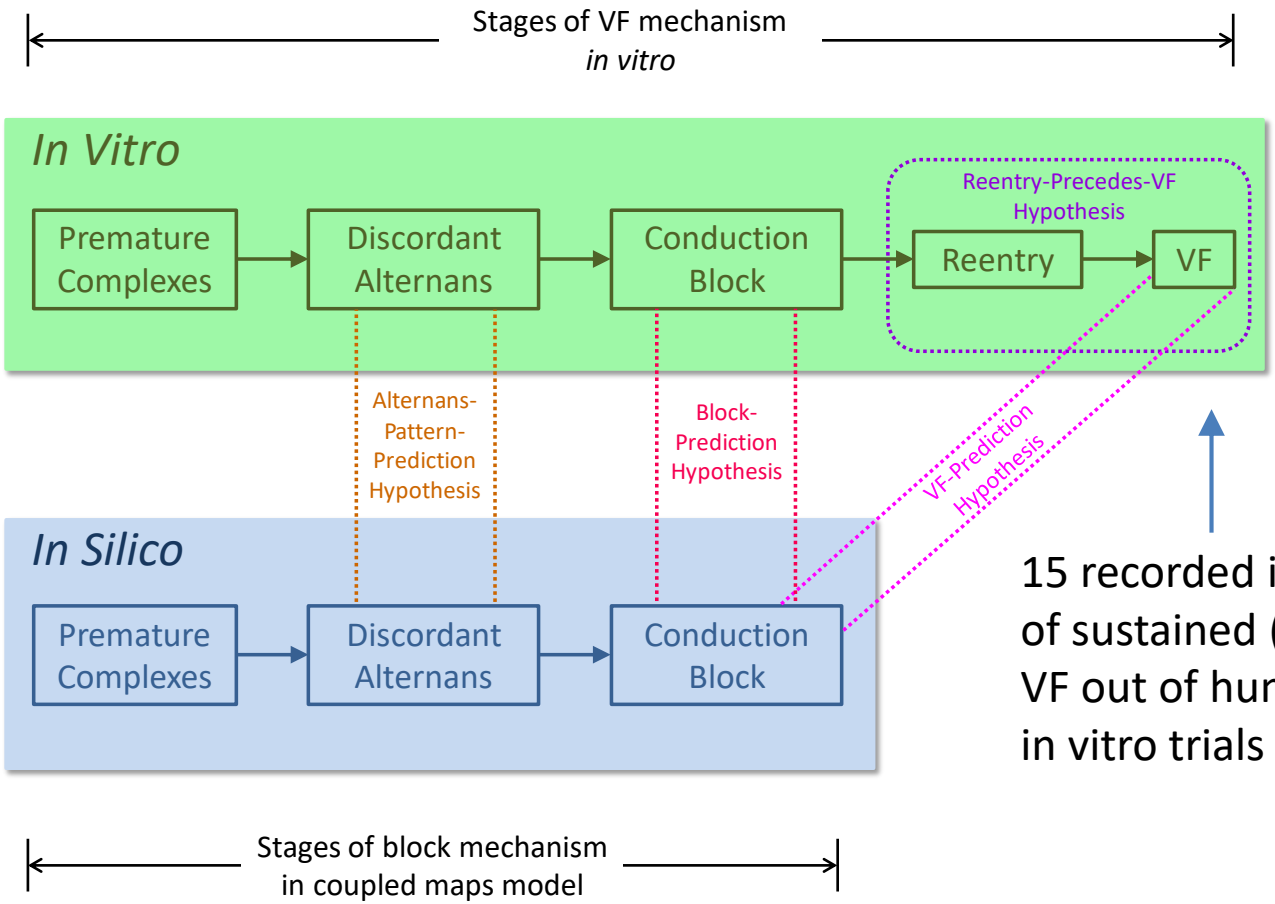
Methods

- Alternans Prediction
  - Compare model predictions with observations for randomly-selected trials
  - Use Bayesian approach to compute posterior probabilities that measured APs followed any given pattern

- Block Prediction
  - Compare model predictions with observations for randomly-selected trials
  - Use generalized estimating equation (GEE) logistic-regression approach
  - GEE model: dependent variable is measured block, explanatory variable is model-predicted block, with clustering by dog

- VF Prediction:
  - Run >100000 simulations and partition premature beat sequence space into blocking/non-blocking categories. Compare blocking/non-blocking predictions with VF/no-VF observations
  - A GEE logistic regression approach was used here as well

Model vs. Experiment

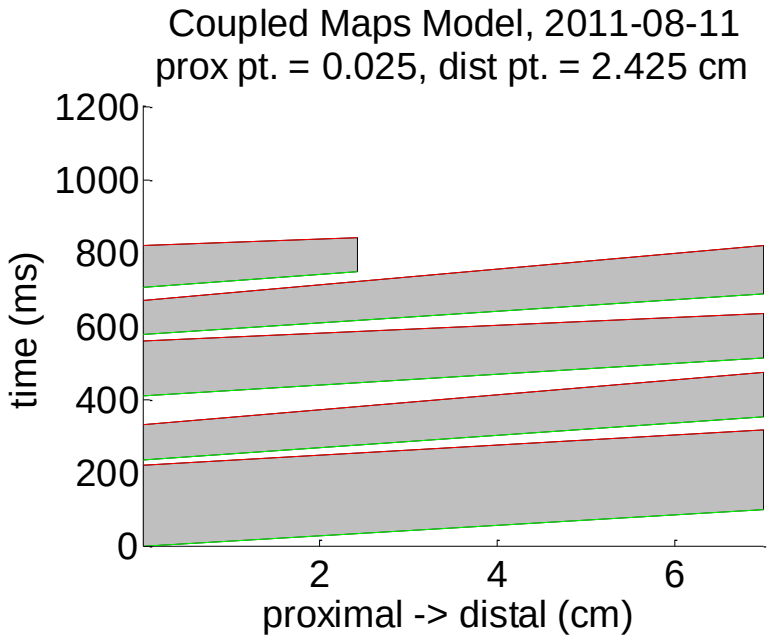


15 recorded instances of sustained (≥ 30 sec) VF out of hundreds of in vitro trials

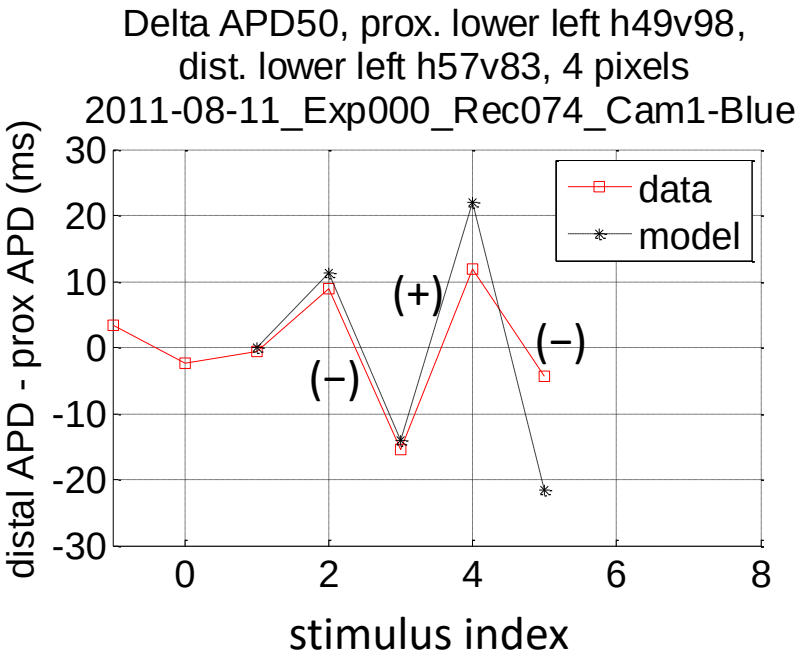
Muñoz, et al., Discordant Alternans as a Mechanism for Initiation of Ventricular Fibrillation In Vitro, *Journal of the American Heart Association*, 2018

Simulated vs. Measured Δ APDs

Space-time plot



Δ APD plot



Report Card for Model

- Alternans:
  - Sign patterns for APD and DI spatial gradients were more likely to follow model-predicted pattern (posterior probs. of 91% and 82%) than would be expected if none of the possible patterns were preferred (1/8 = 12.5%)

- Block:
  - Wald test applied to GEE model: effect of coupled maps model prediction was significant ($p < 1 \times 10^{-15}$, coeff. 44.36)
  - Accuracy = (# correct predictions)/(# total events) = 72%
  - Model predicted fewer instances of block (50%) than actually occurred (78%)

- VF:
  - Wald test applied to GEE model: effect of coupled maps model prediction was significant ($p = .0046$, coeff. 1.63)
  - Accuracy = (# correct predictions)/(# total events) = 79% in vitro (compare with 90% in vivo)
  - Model predicted more instances of VF (21%) than actually occurred (8%)

Possible Improvements to Model

- Calibrate APD restitution (APDR) parameters from location closer to electrode
- Calibrate CV restitution (CVR) parameters from in vitro data. Main obstacle: only have 2D imaging of 3D CV quantity
- Allow spatial variation in APDR and/or CVR parameters
- Include electrotonic effects

Parameter Sensitivity Ratios

- Determine which parameters or settings have larger impacts on predicted values

- For quantity q and parameter p, sensitivity ratio is

$$\frac{\delta q}{\delta p} = \frac{q - q_0}{q_0} \frac{p_0}{p - p_0} = \frac{\Delta q}{\Delta p} \frac{p_0}{q_0}$$

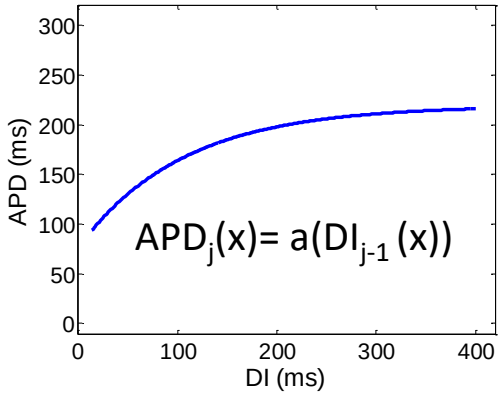
- Let q = mean magnitude of alternans gradient; N=4 premature stimuli

$$q = \frac{1}{N-1} \sum_{i=2}^{N} \left| \frac{\Delta APD_i}{\Delta x} \right|$$

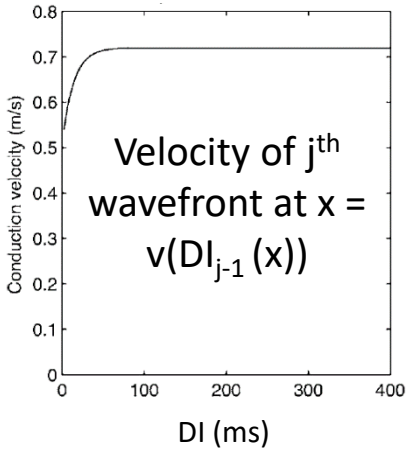
- Larger q means more severe alternation

Parameter Sensitivity Ratios

action potential duration (APD) restitution function



conduction velocity (CV) restitution function



- $APD = a(DI) = A + Be^{-DI/C}$
- $CV = v(DI) = \alpha\,(1 - e^{-(DI-\beta)/\gamma})$
- Rest. params. A, B, C, α, β, γ
- Example: sensitivity ratios for one trial, +5% parameter perturbation

δq/δA	δq/δB	δq/δC	δq/δα	δq/δβ	δq/δγ
0.0	2.7	-1.5	-0.9	-0.6	1.8

Conclusions and Future Work

- Model is a significant predictor of VF
- Predicts measured alternans but under-predicts conduction block
- Possible application: improved stimulus algorithms for anti-arrhythmic devices
- Future work: compute parametric sensitivities over a wider range of conditions

Acknowledgments

Collaborators

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  - Effiba Armah (BS, RIT)
  - Weiye Lin (BS, Cornell)
  - Min Chul Shin (BS, Cornell)
- Faculty:
  - Anna Gelzer (UPenn)
  - Flavio Fenton (GA Tech)
  - Robert Gilmour, Jr. (UPEI)
  - Niels Otani (RIT)
  - Wei Qian (UDel)

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- Thank you for attending!
- Questions?