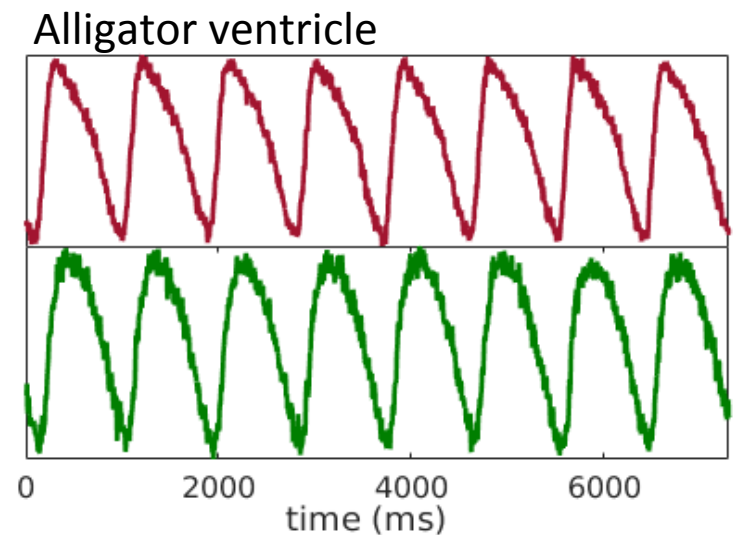
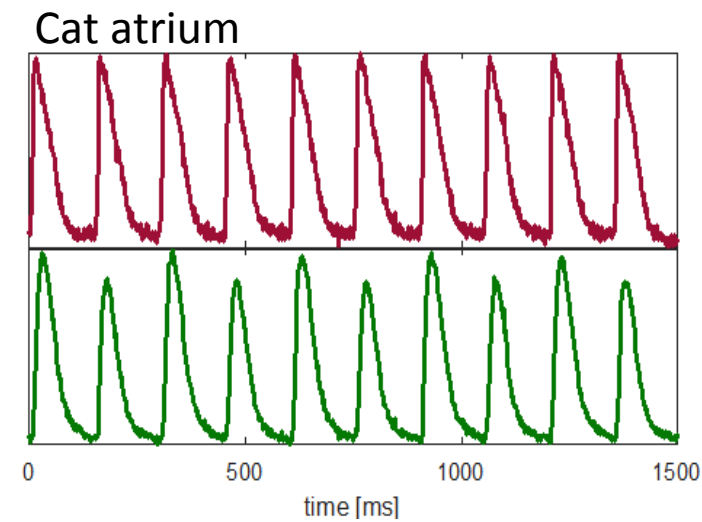
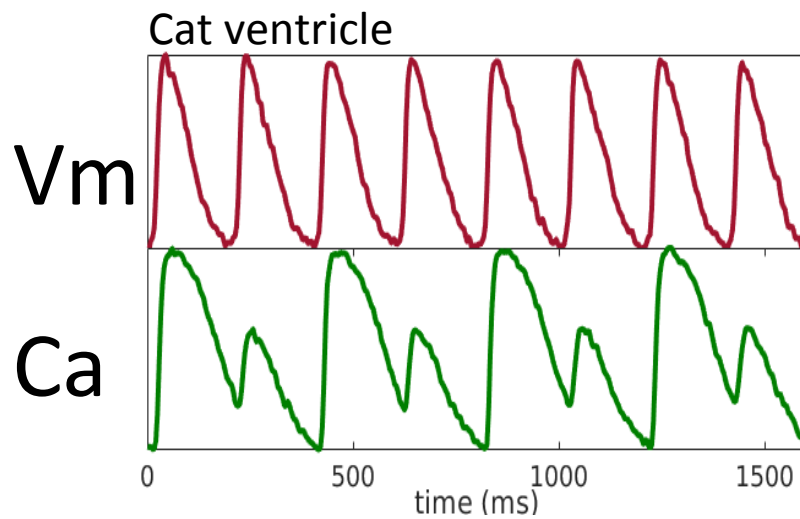
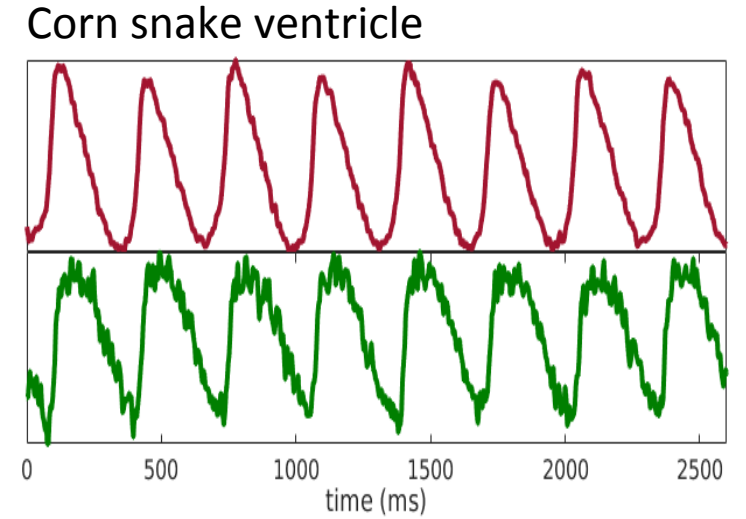
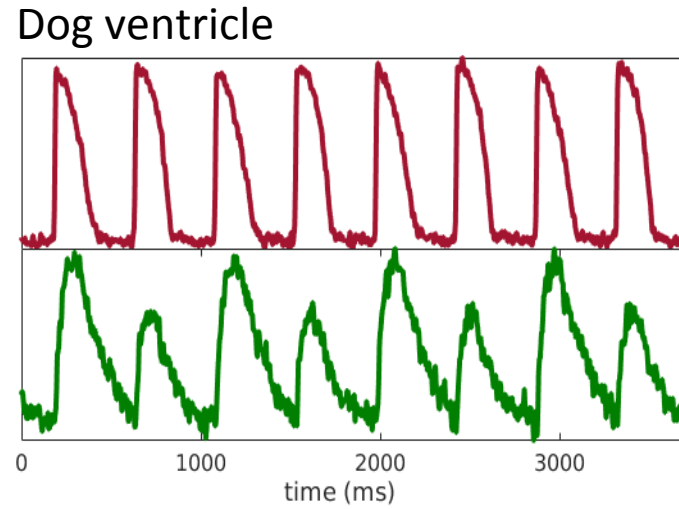
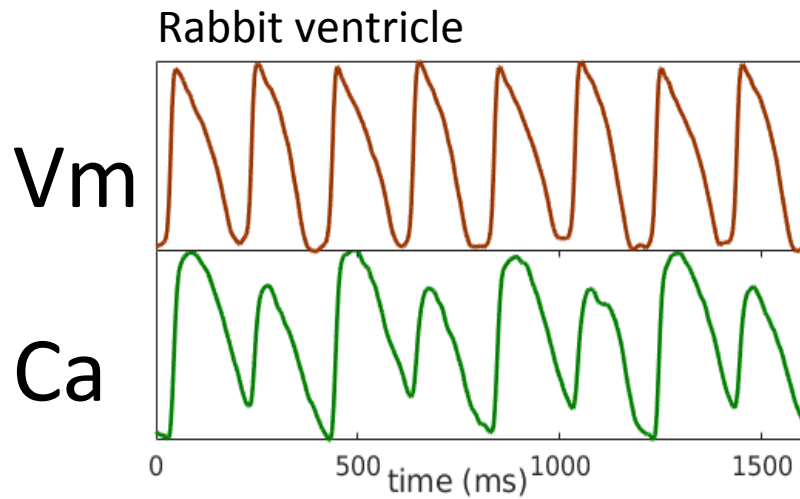




# Constant diastolic interval control in zebrafish and unexpected results

Conner Herndon, Flavio Fenton  
Georgia Institute of Technology

# Flavors of cardiac dynamics

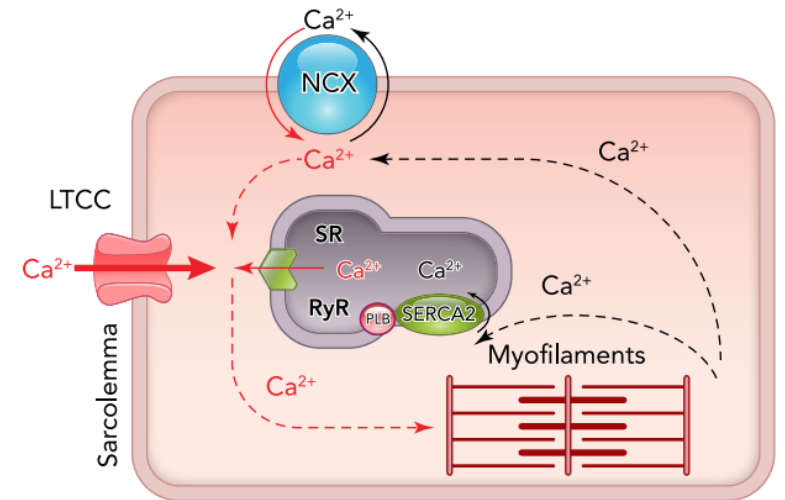
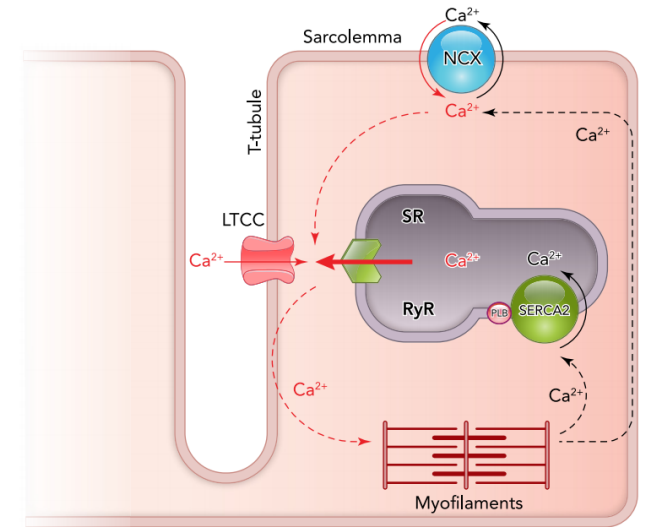




# What about species with less active dynamics for intracellular calcium handling?

In Endotherms, cardiac contraction relies primarily on calcium from the sarcoplasmic reticulum

In ectotherms, cardiac contraction relies primarily on the transmembrane influx of calcium from the extracellular space

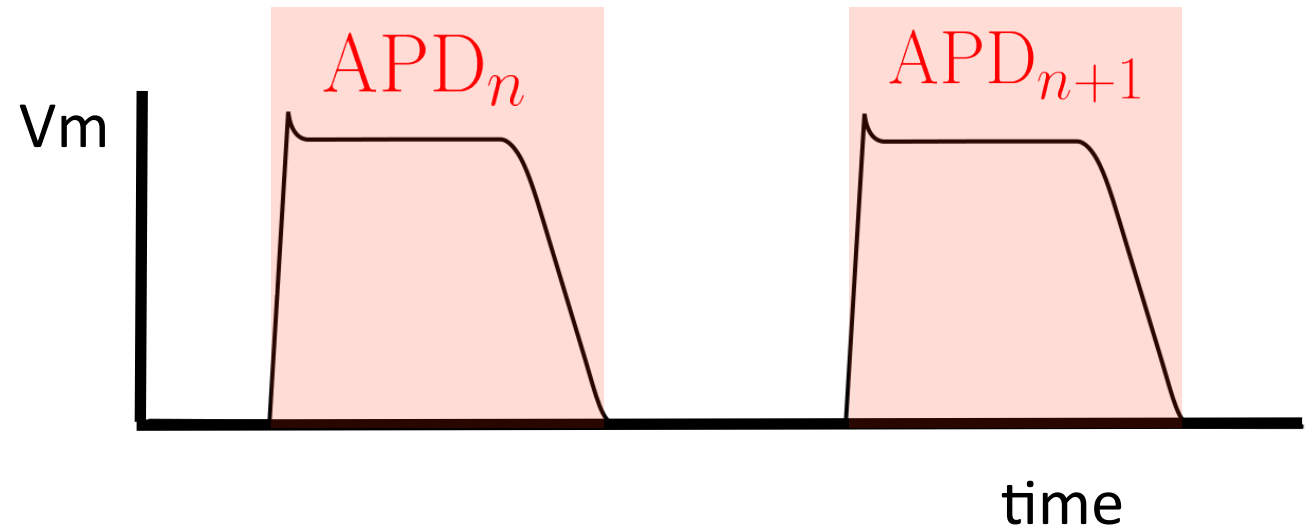




# Restitution

Suppose that the **action potential duration (APD)**

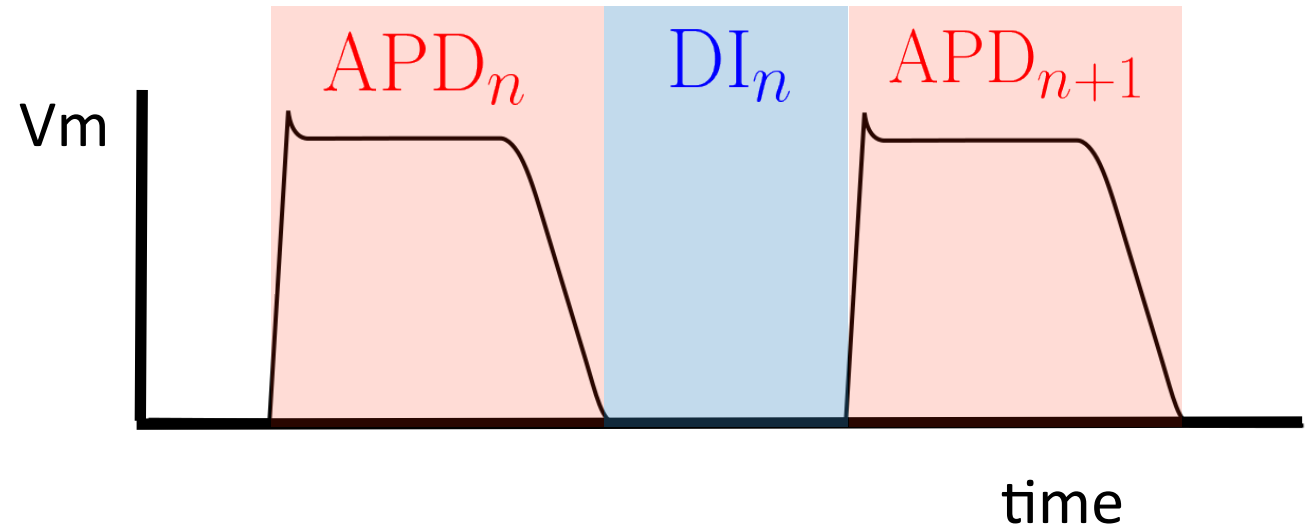
$APD_{n+1}$



# Restitution

Suppose that the **action potential duration (APD)** is a function of the previous **diastolic interval (DI)**

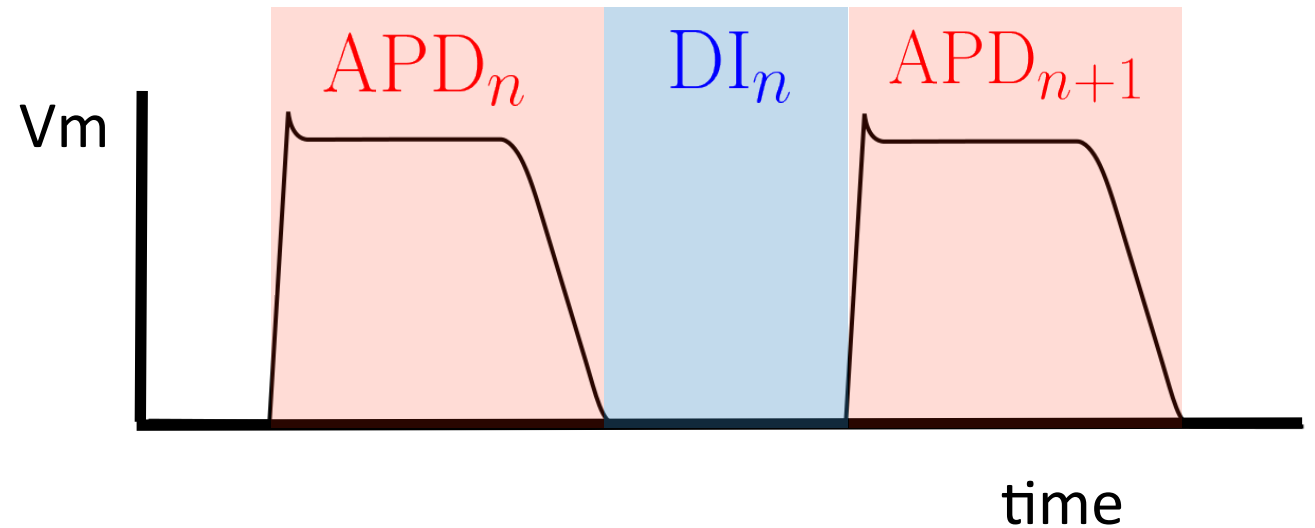
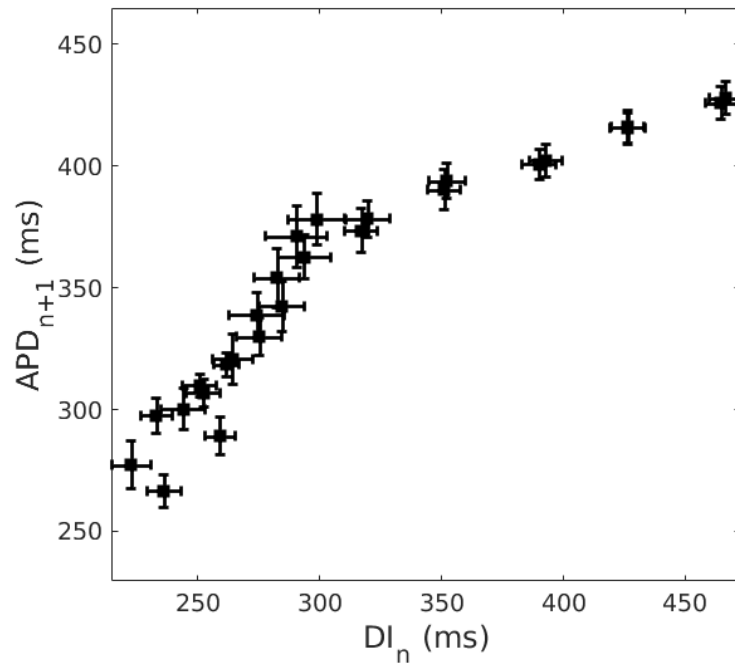
$$APD_{n+1} = f(DI_n)$$



# Restitution

Suppose that the **action potential duration (APD)** is a function of the previous **diastolic interval (DI)**

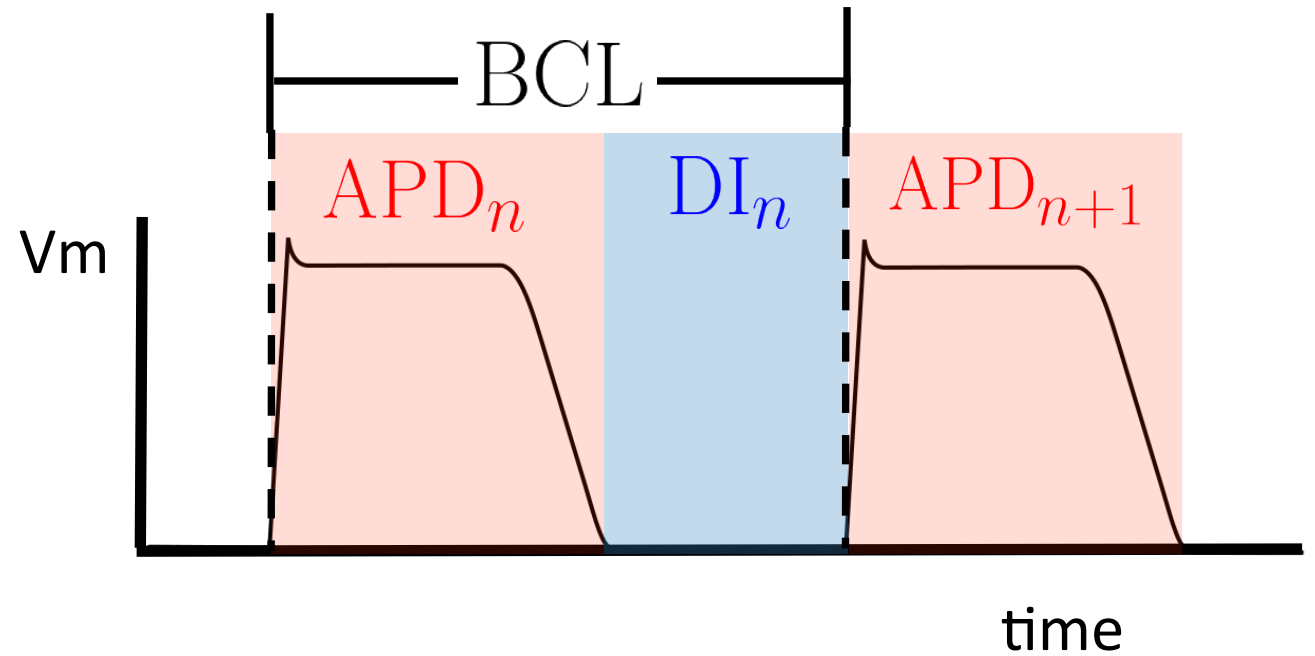
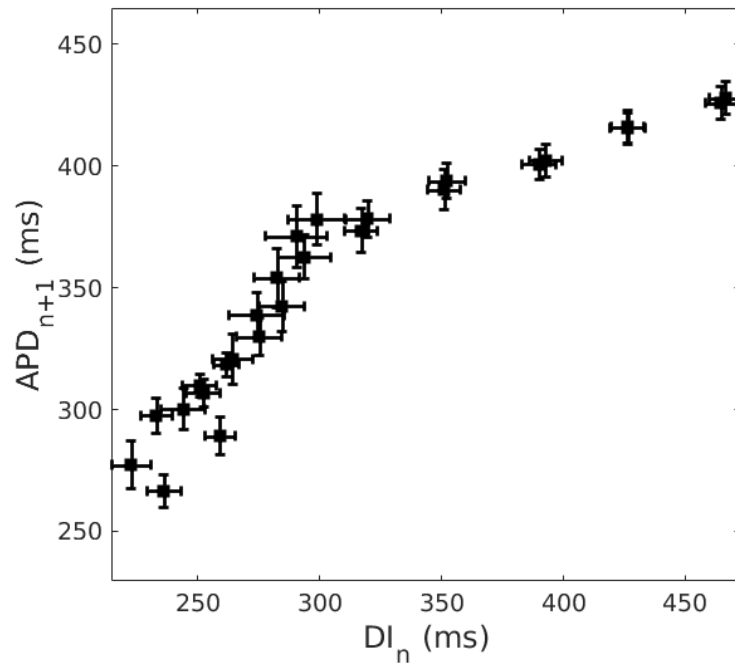
$$APD_{n+1} = f(DI_n)$$



# Restitution

For constant basic cycle length (BCL),  $BCL = APD_n + DI_n$

$$APD_{n+1} = f(DI_n)$$

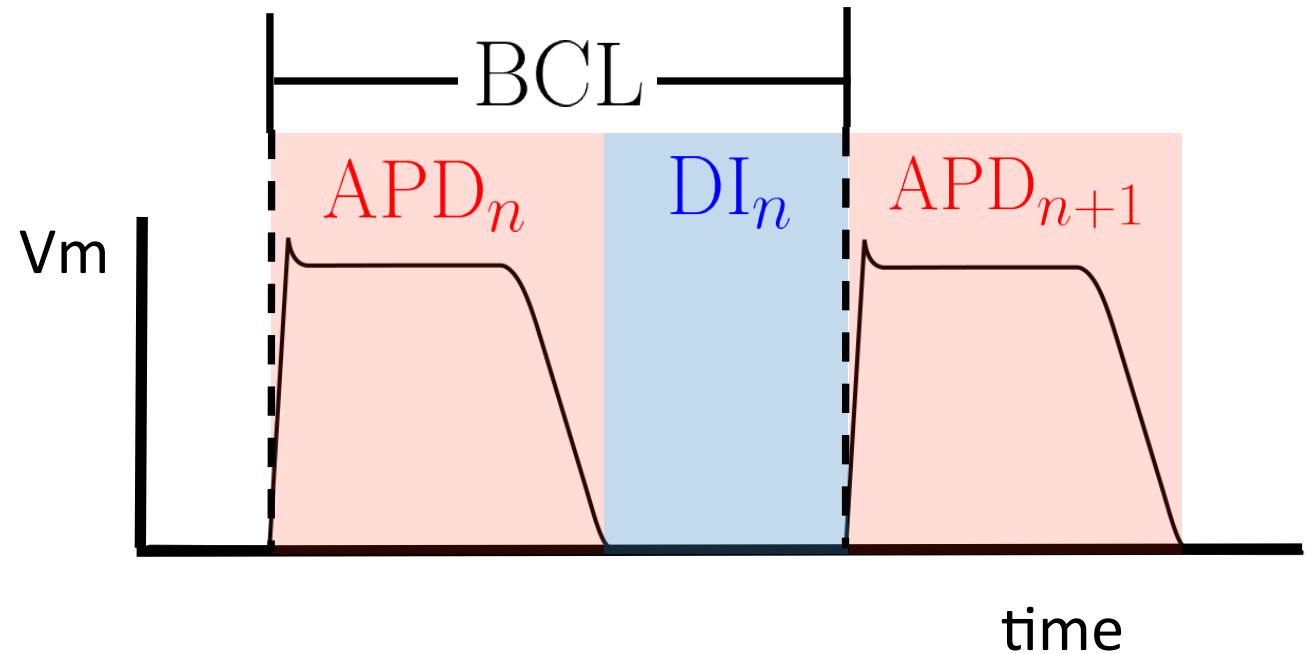
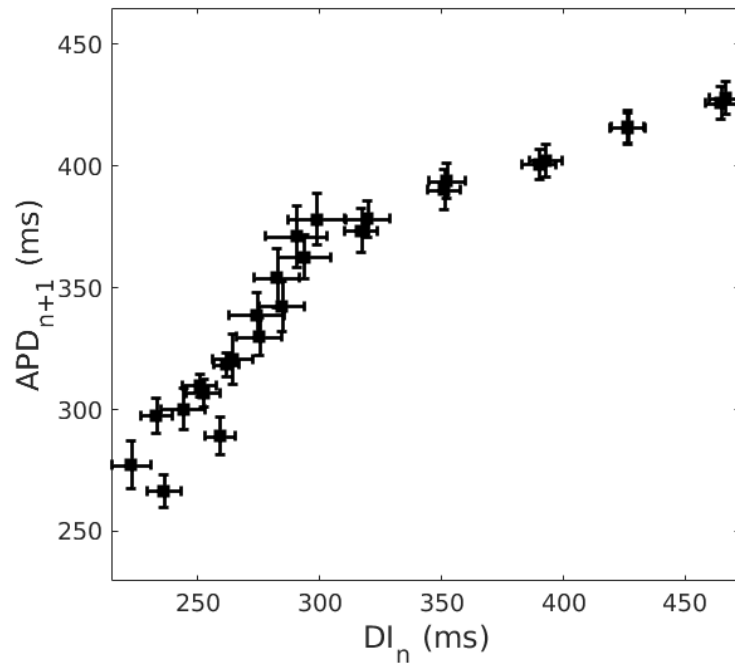


# Restitution

For constant basic cycle length (BCL),  $BCL = APD_n + DI_n$

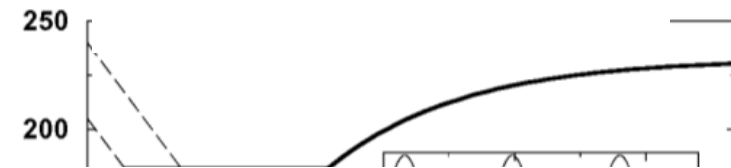
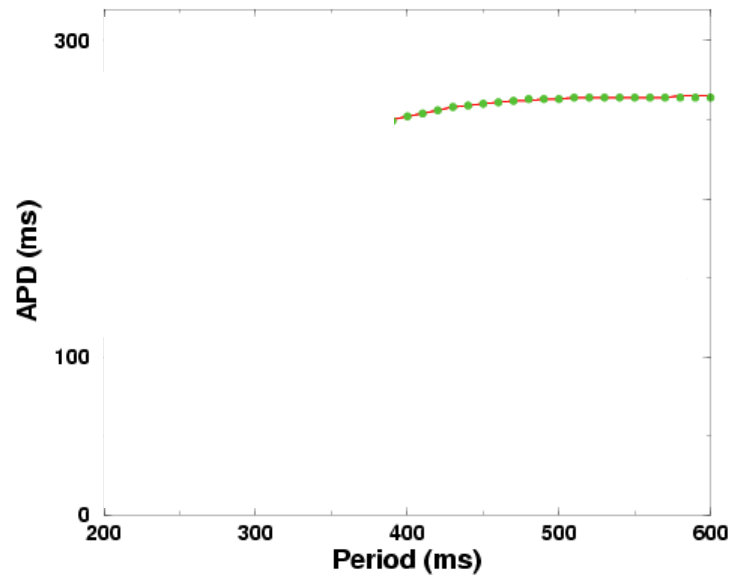
$$APD_{n+1} = f(BCL - APD_n)$$

$$APD_{n+1} = f(DI_n)$$



# Restitution

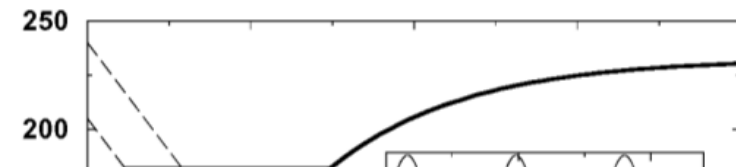
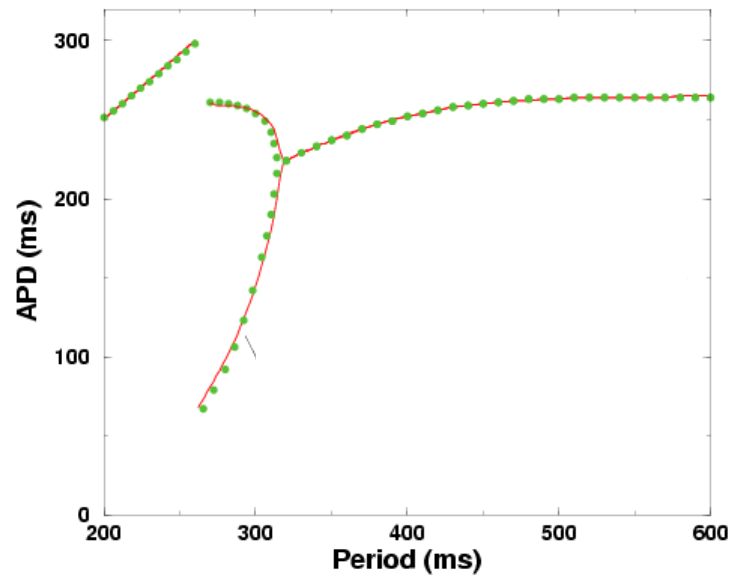
With the restitution function, a given stimulus period will tell us the corresponding action potential duration (APD)



# Restitution

With the restitution function, a given stimulus period will tell us the corresponding action potential duration (APD)

And when it bifurcates





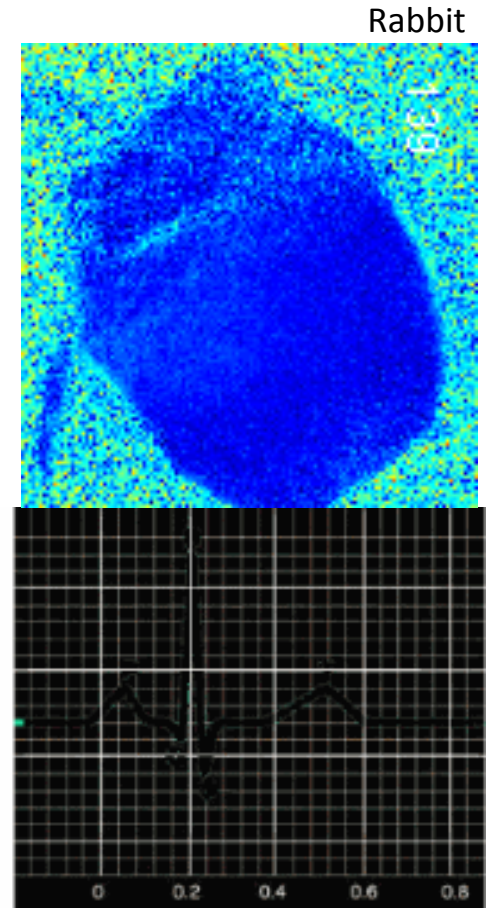
# Optical Mapping

- Fluorescent dyes track the transmembrane voltage and intracellular calcium
- 500 frames per second
- 128x128 pixels

Canine right atrium



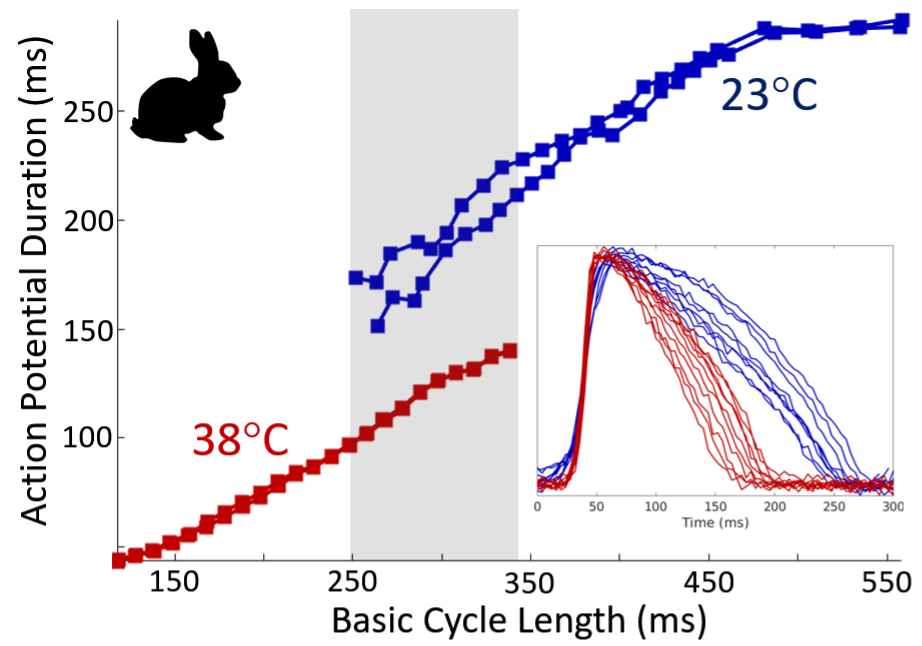
Canine left ventricle

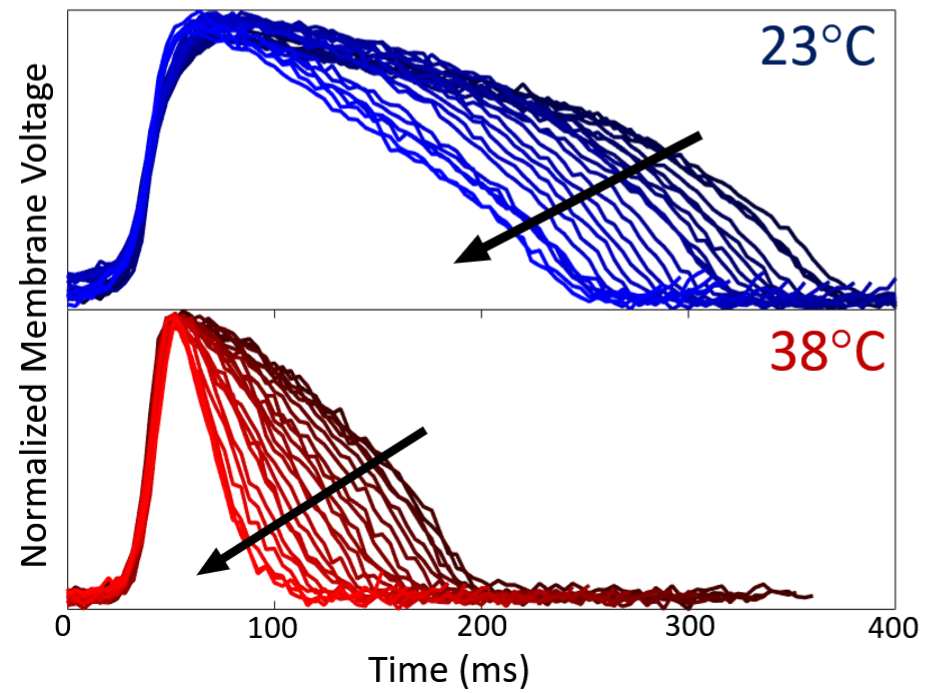
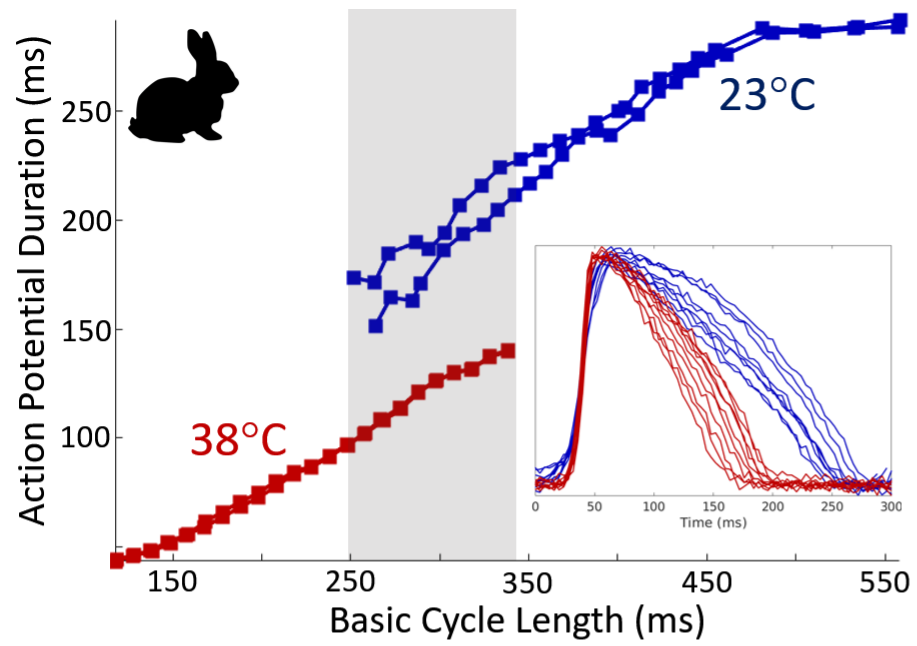










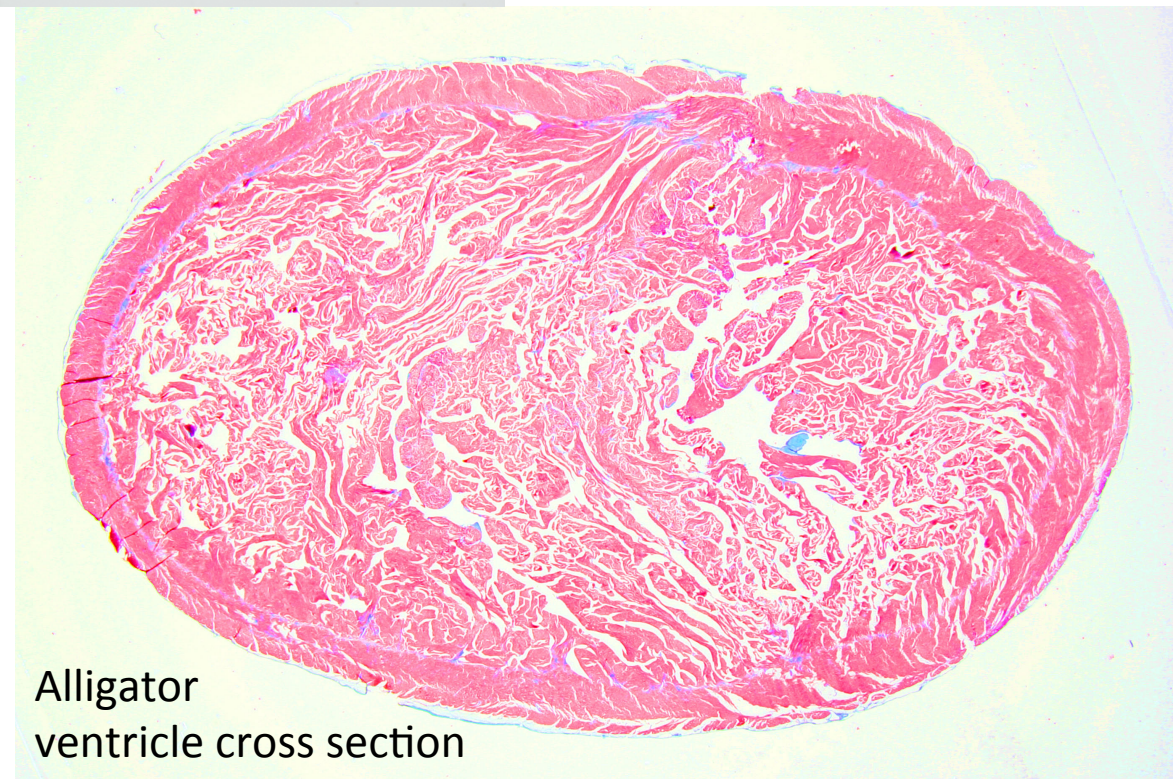
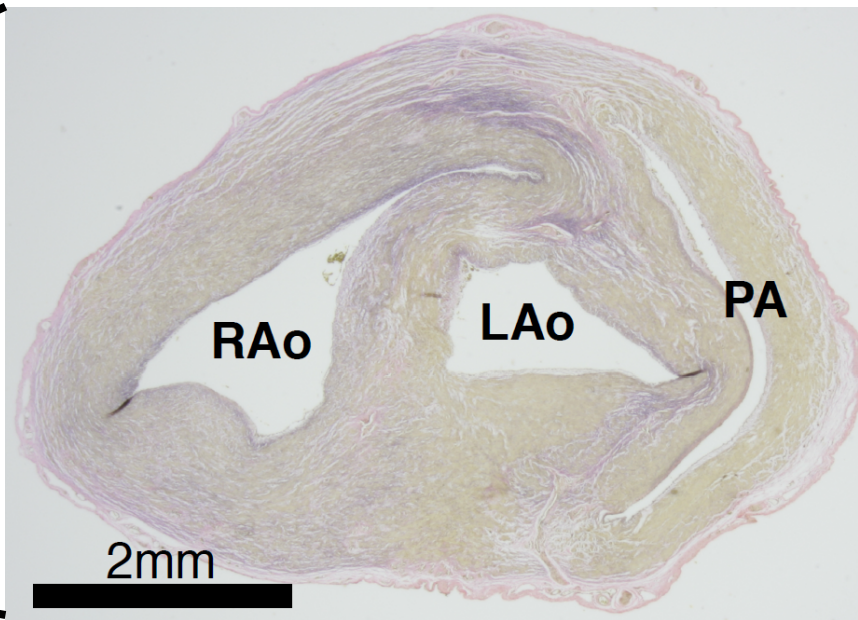
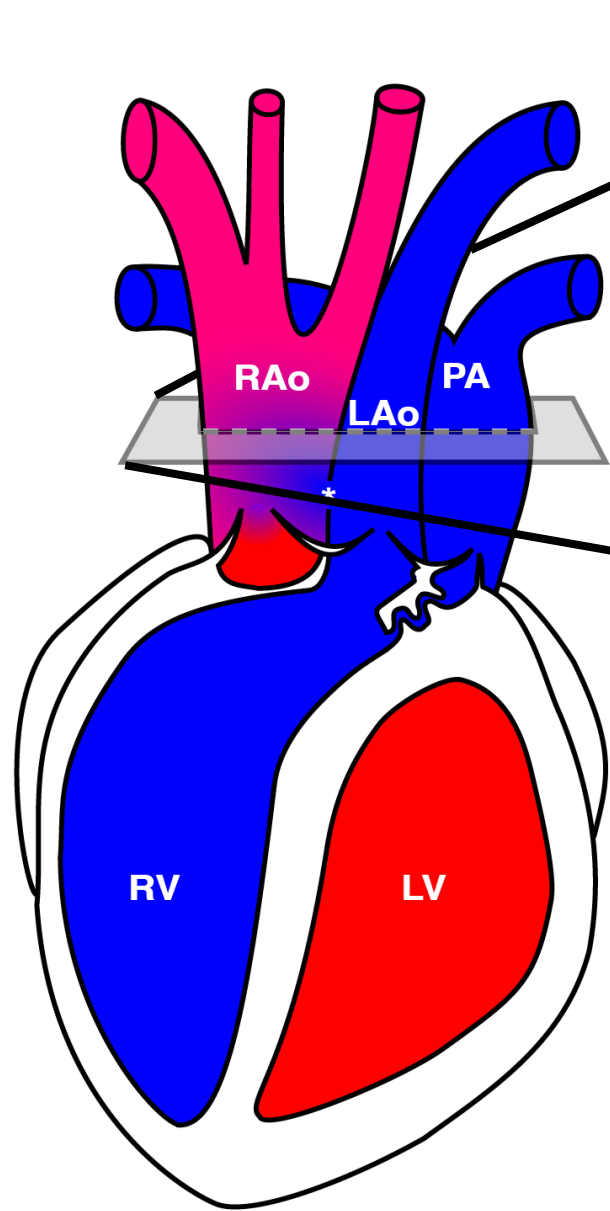


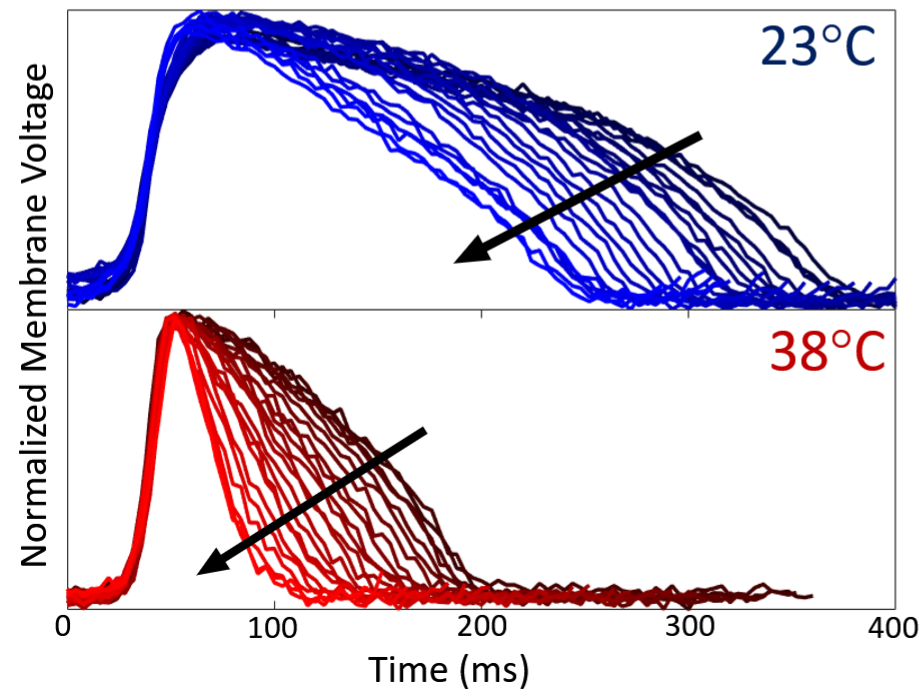
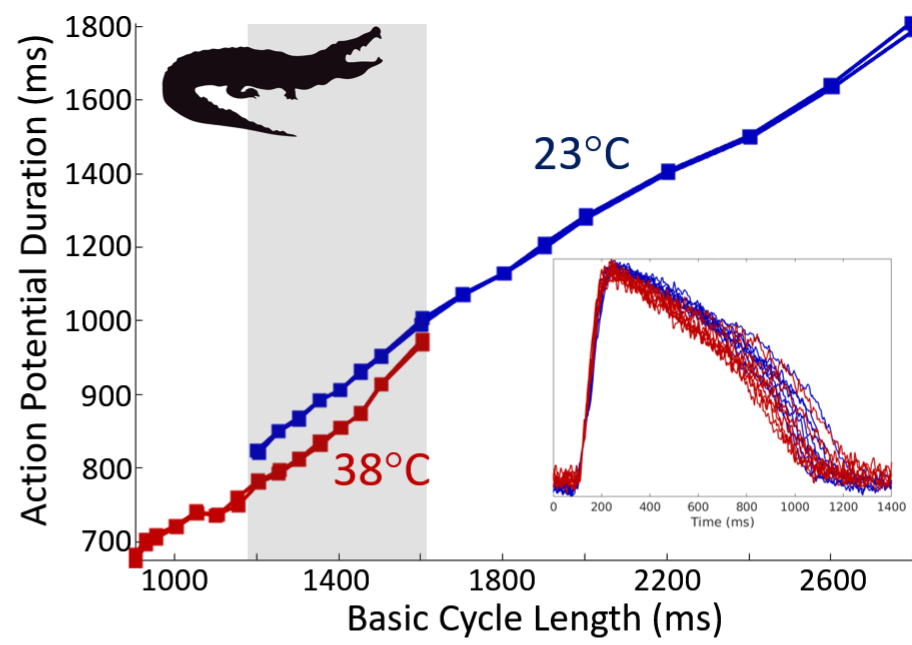
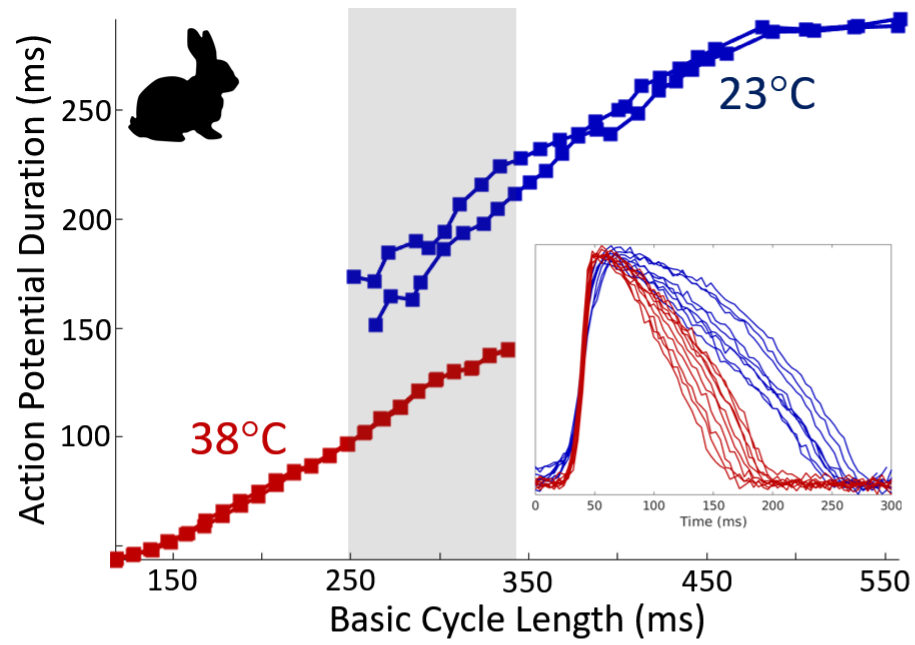




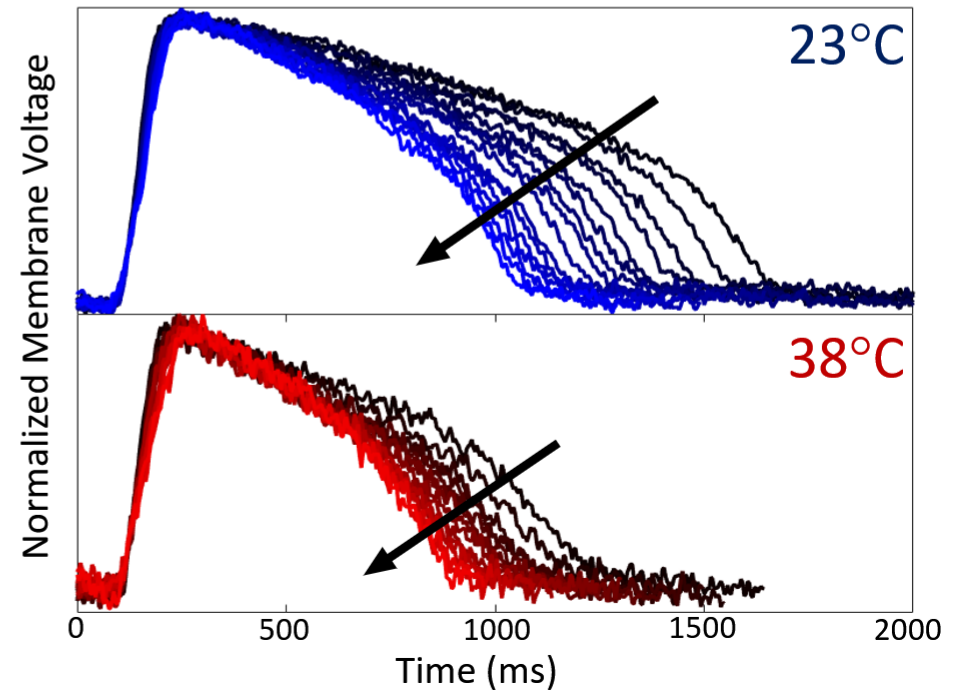
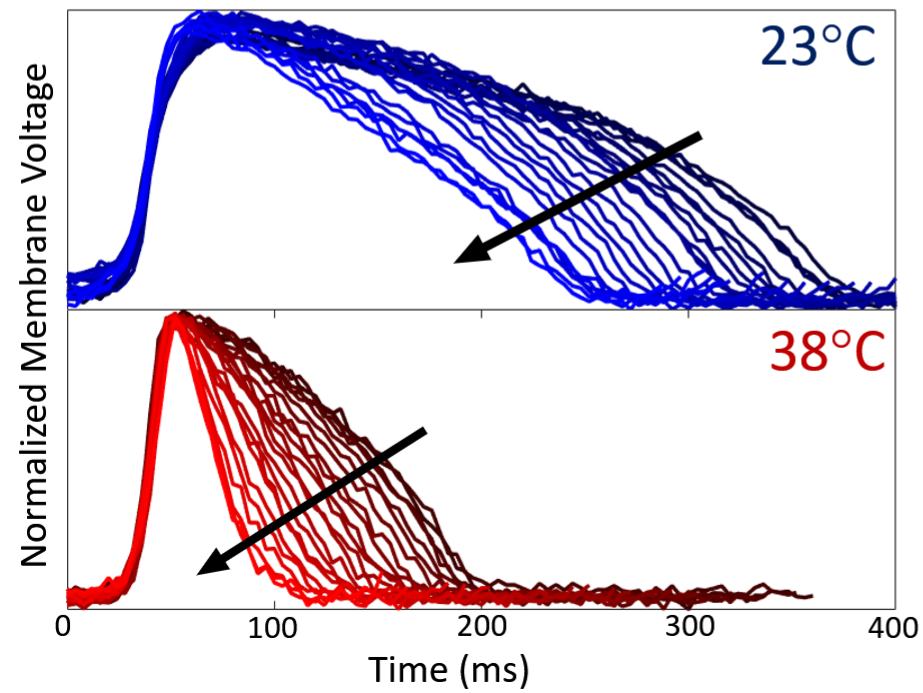
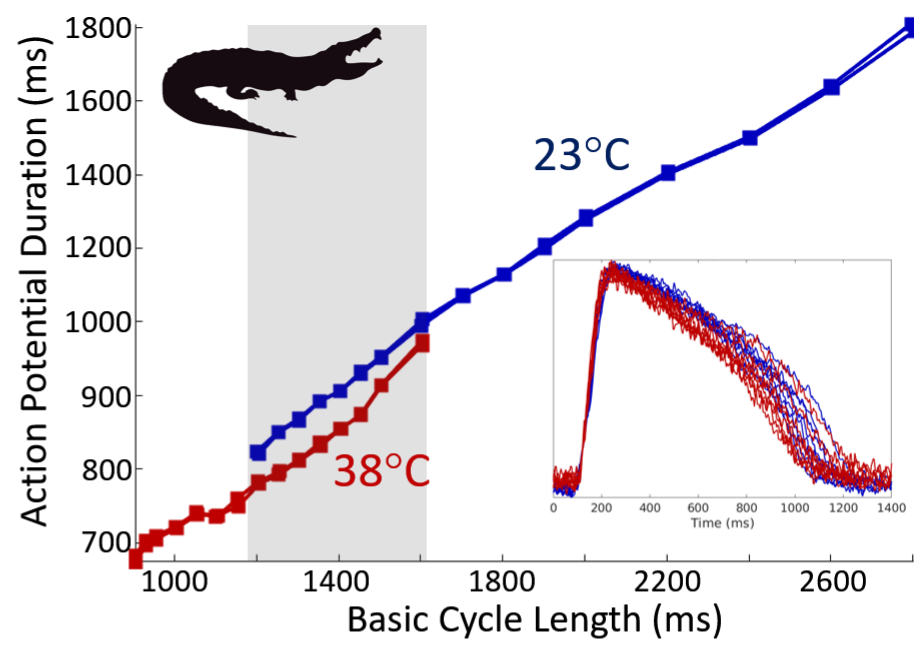
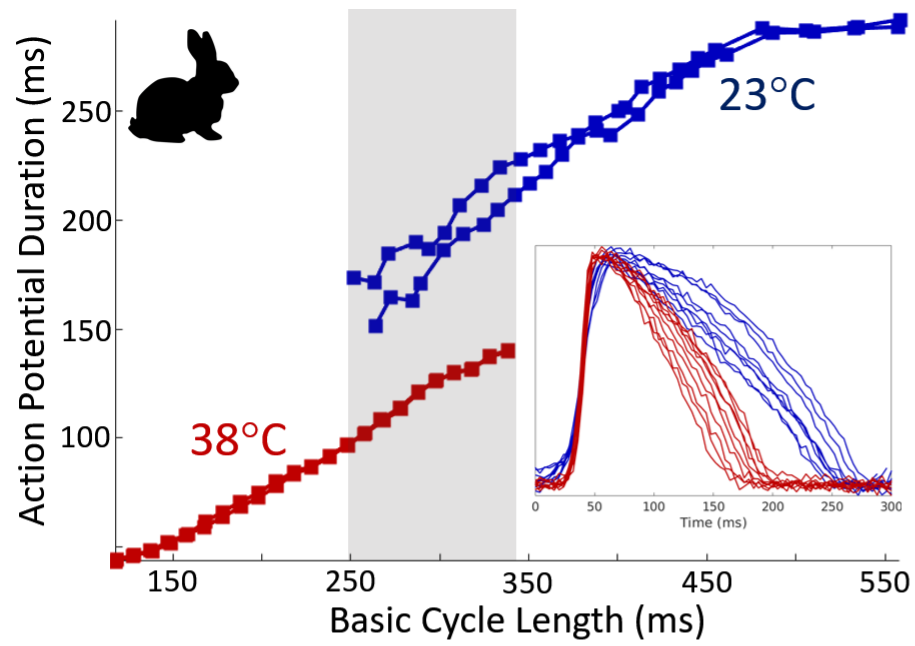


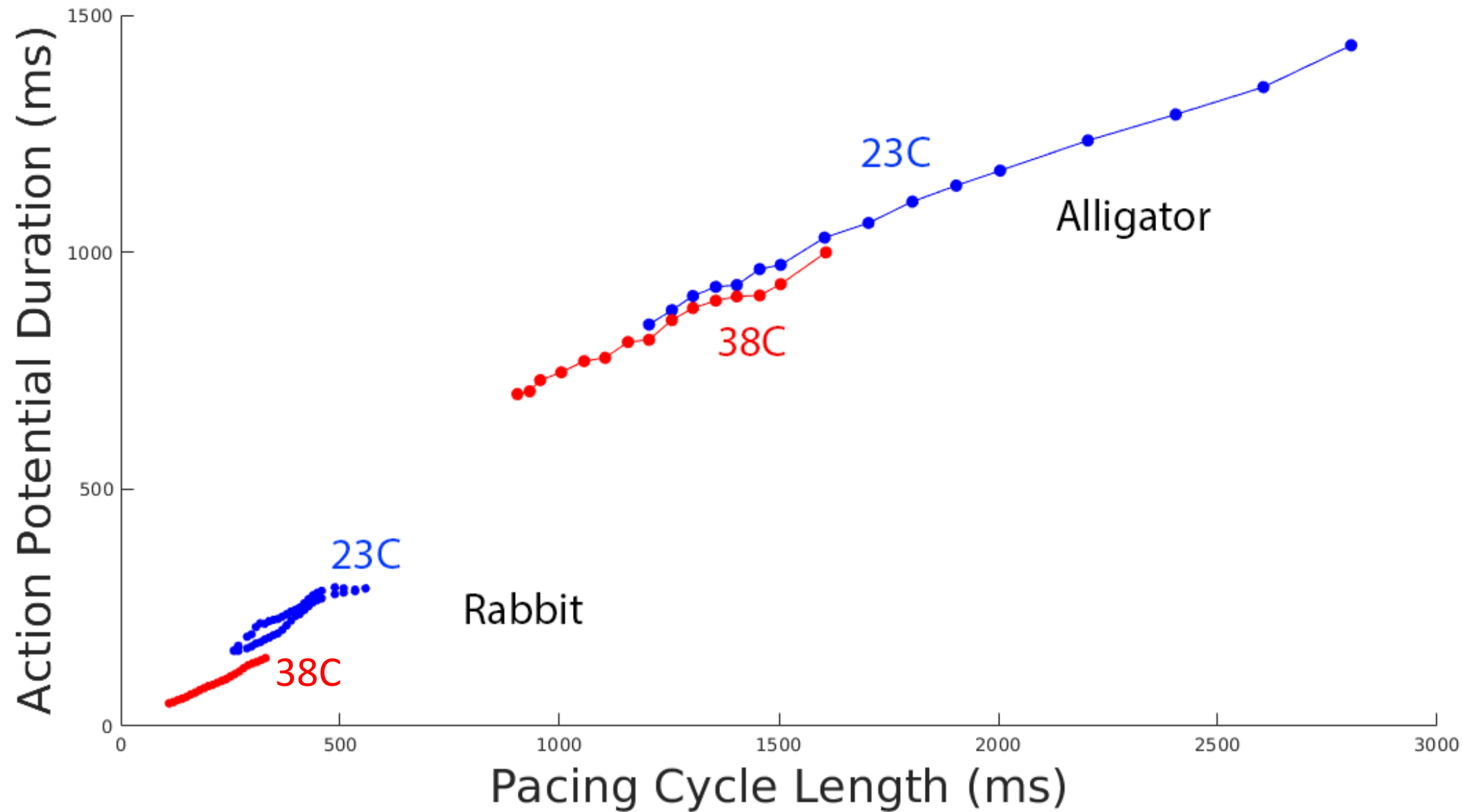




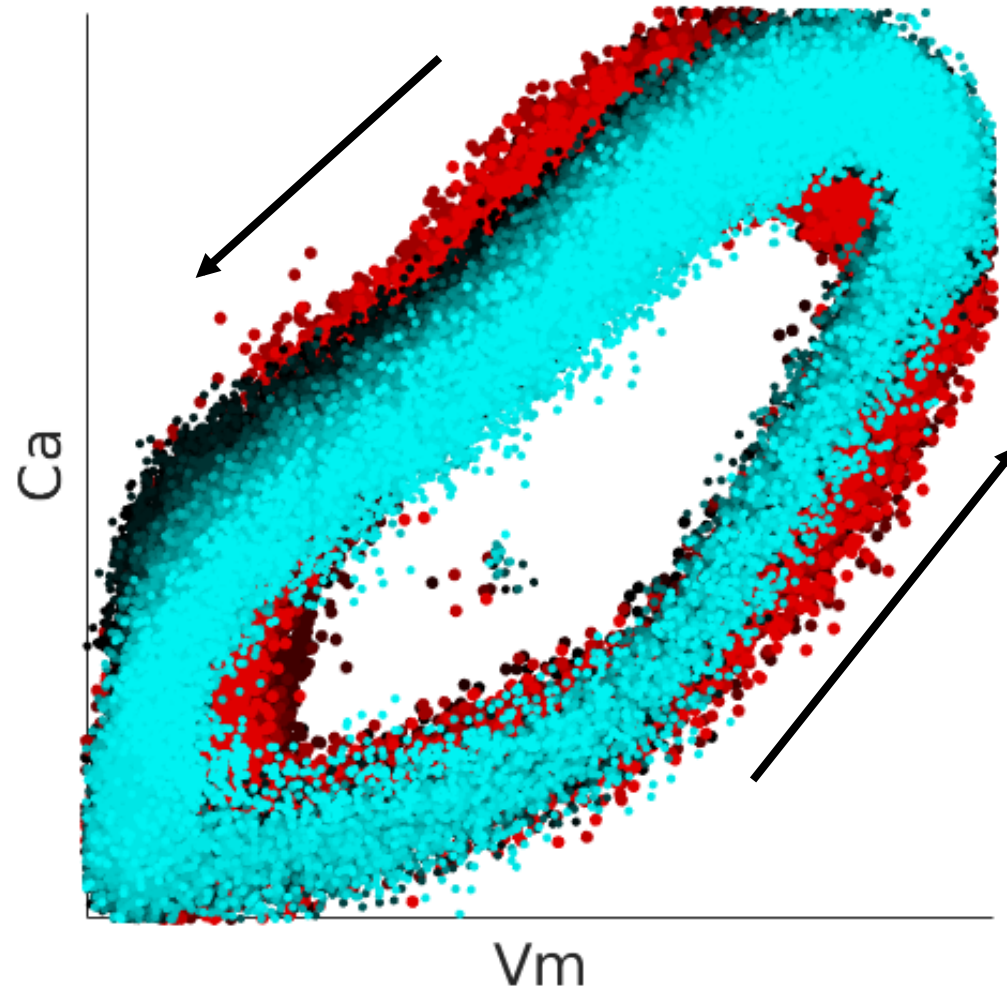




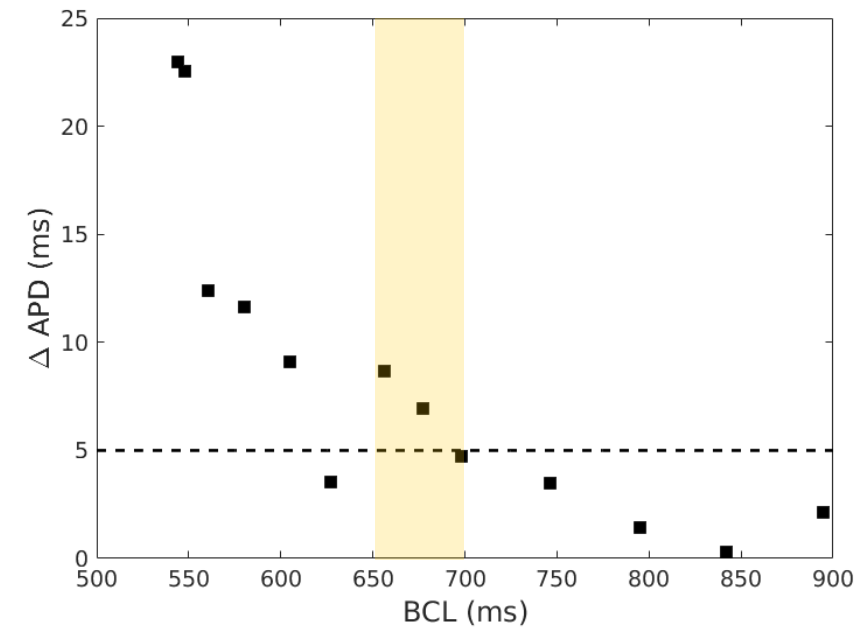
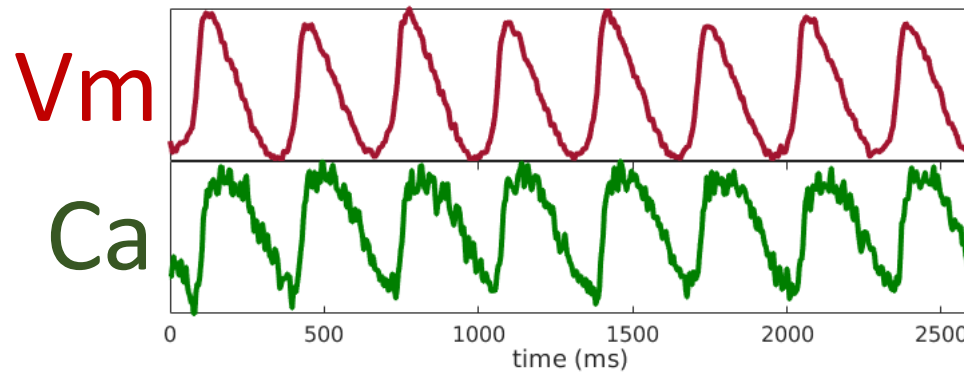
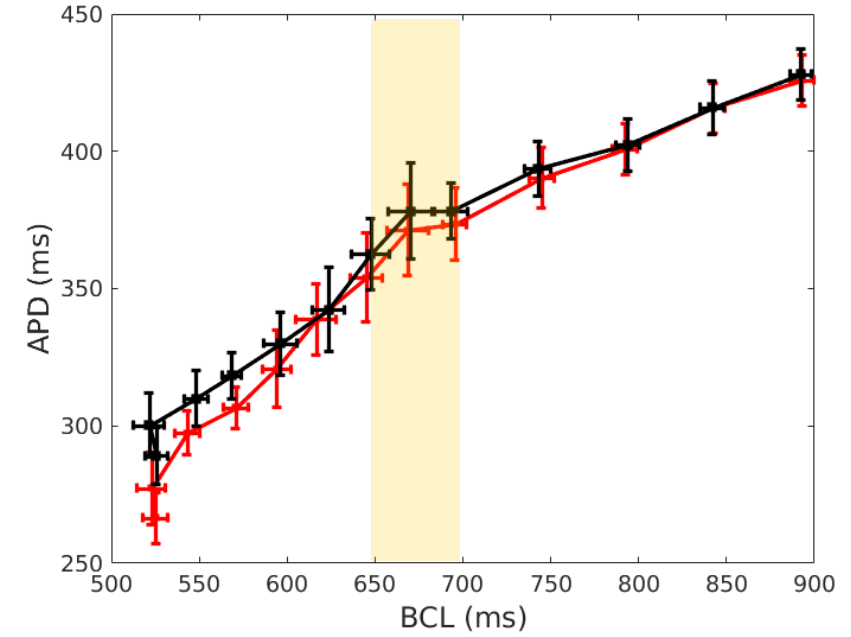
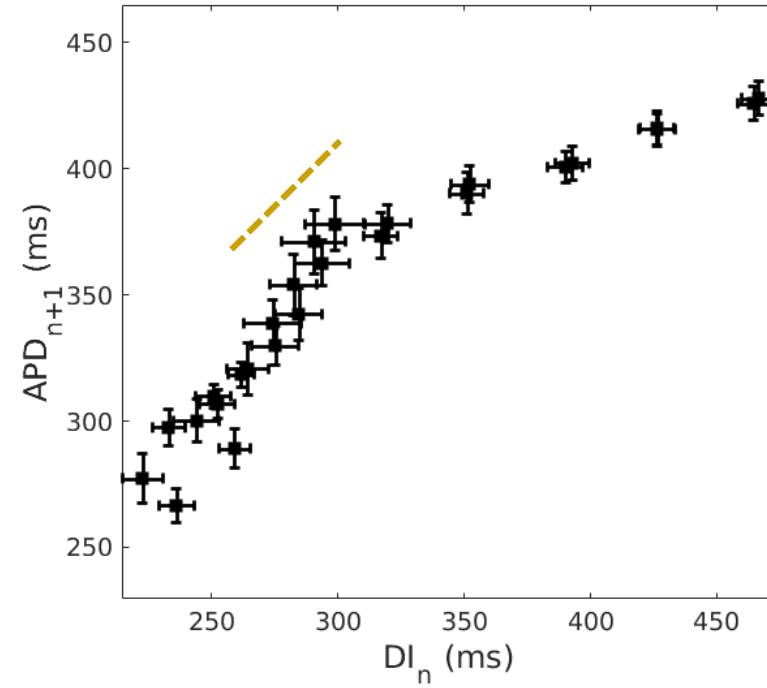




The relationship between  $V_m$  and  $Ca$  in the alligator changed very little across all pacing cycle lengths and both temperatures



# Corn Snake



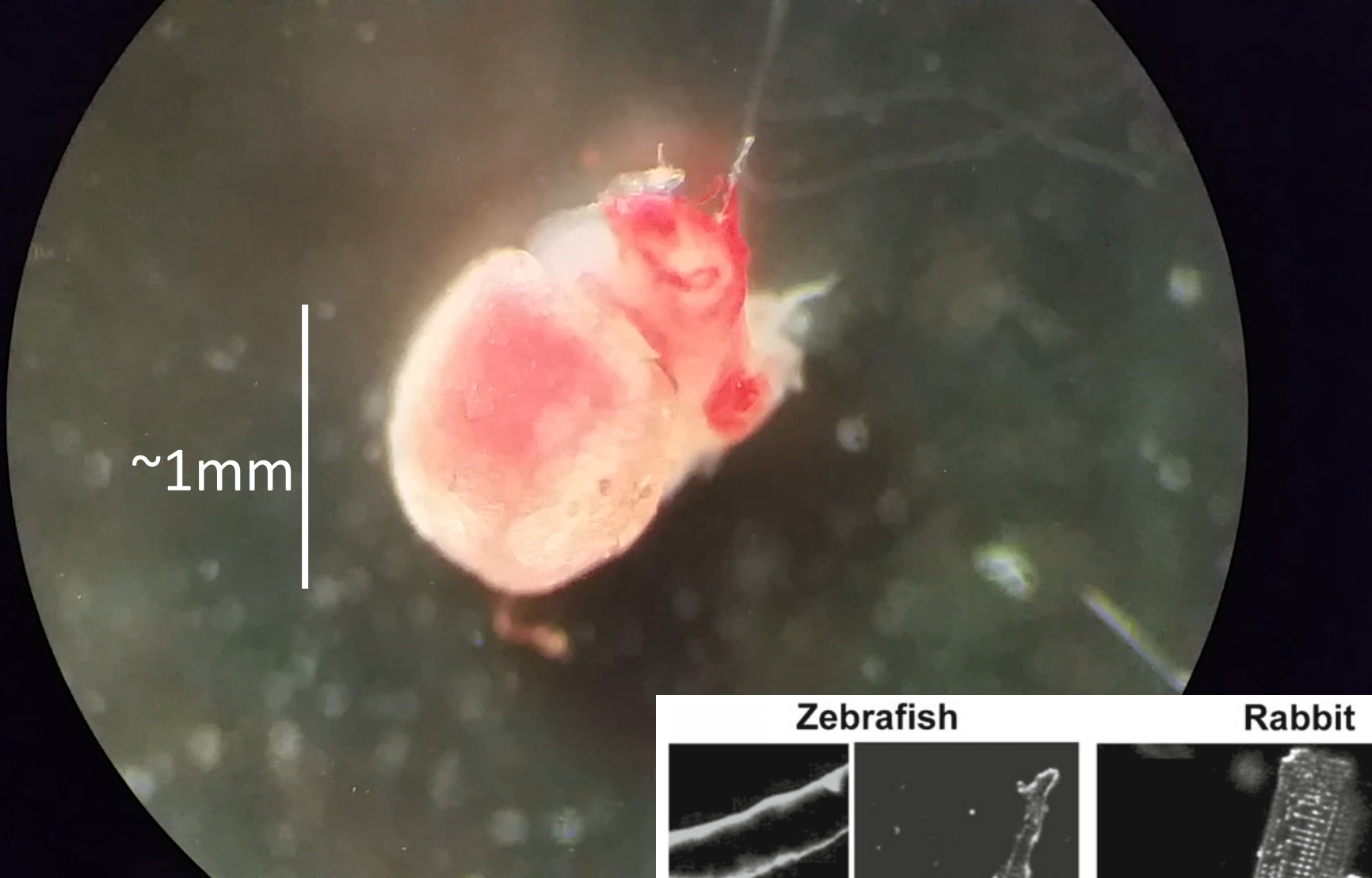
constant diastolic  
interval control



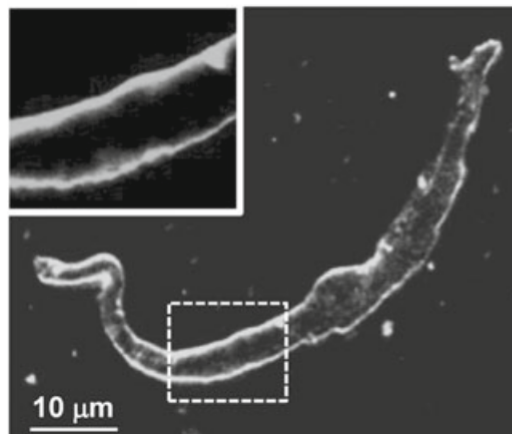
~1cm



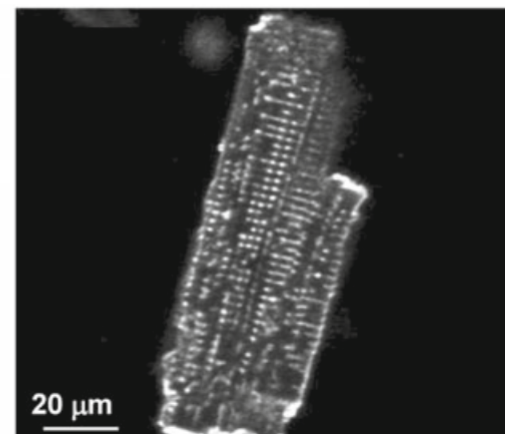
~1mm



Zebrafish



Rabbit





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# Progress in Biophysics and Molecular Biology

journal homepage: [www.elsevier.com/locate/pbiomolbio](http://www.elsevier.com/locate/pbiomolbio)

## Cardiac Ca<sup>2+</sup> signalling in zebrafish: Translation of findings to man

Chantal J.M. van Opbergen, Stephanie M. van der Voorn, Marc A. Vos, Teun P. de Boer  
Toon A.B. van Veen<sup>\*1</sup>

Department of Medical Physiology, Division of Heart & Lungs, University Medical Center Utrecht, The Netherlands

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Received 31 January 2018

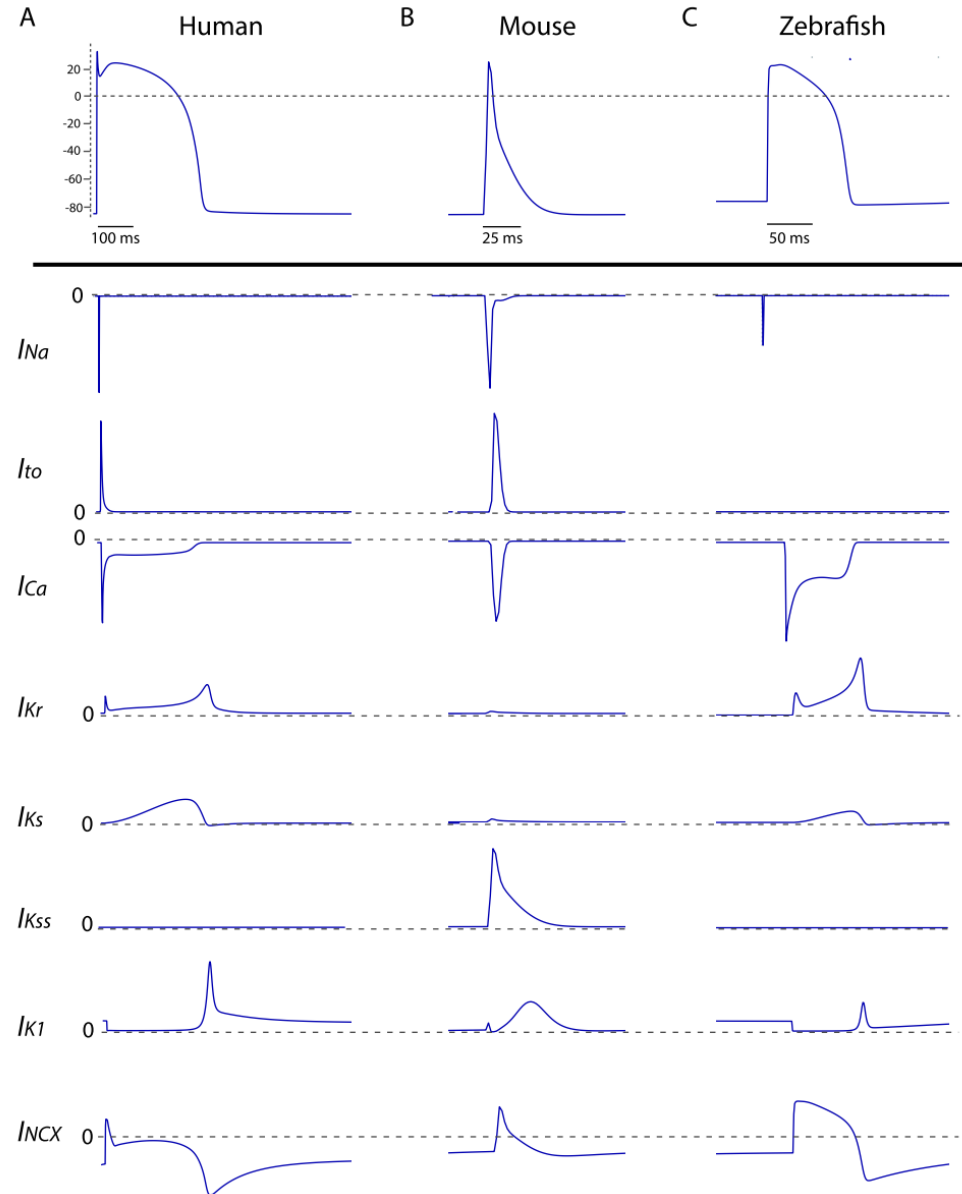
Received in revised form

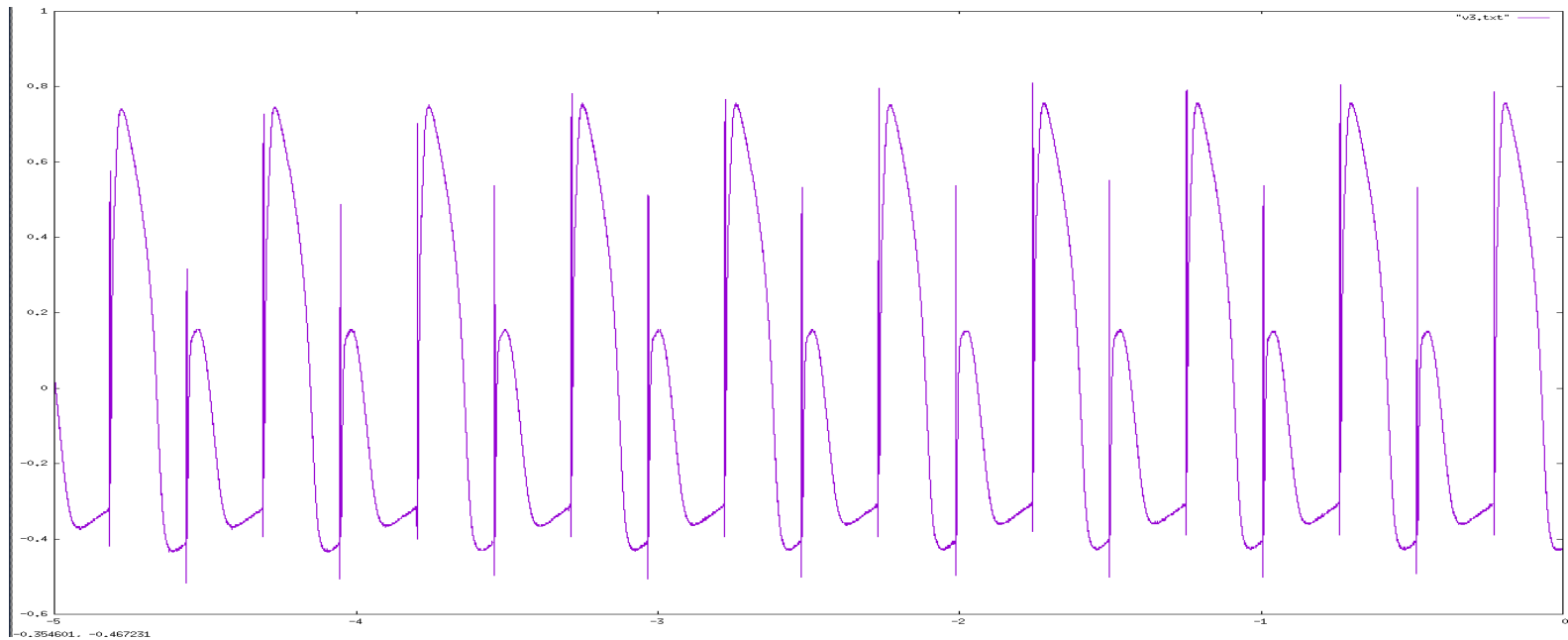
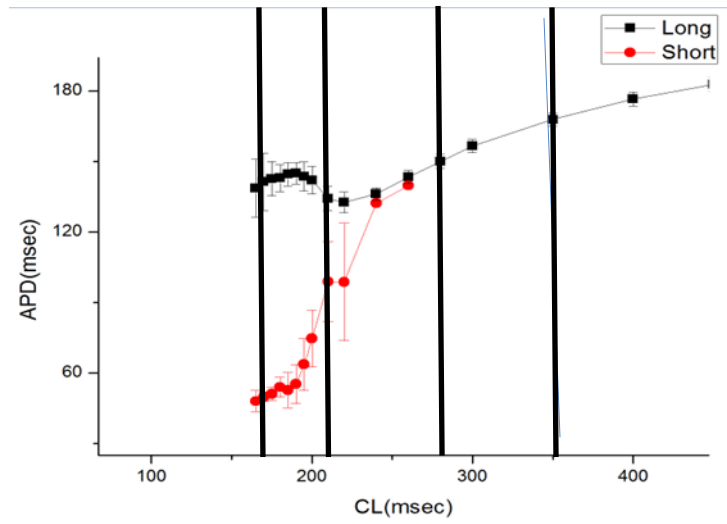
9 April 2018

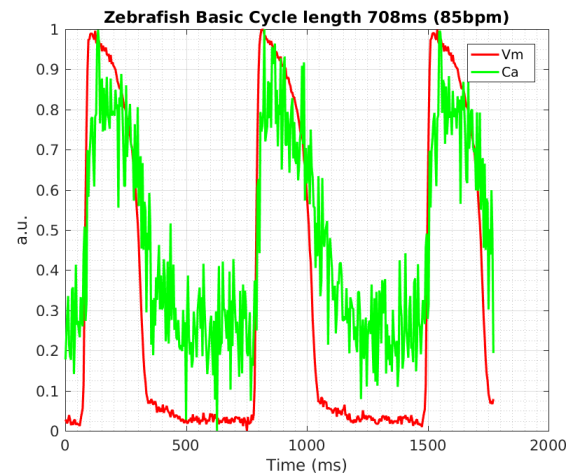
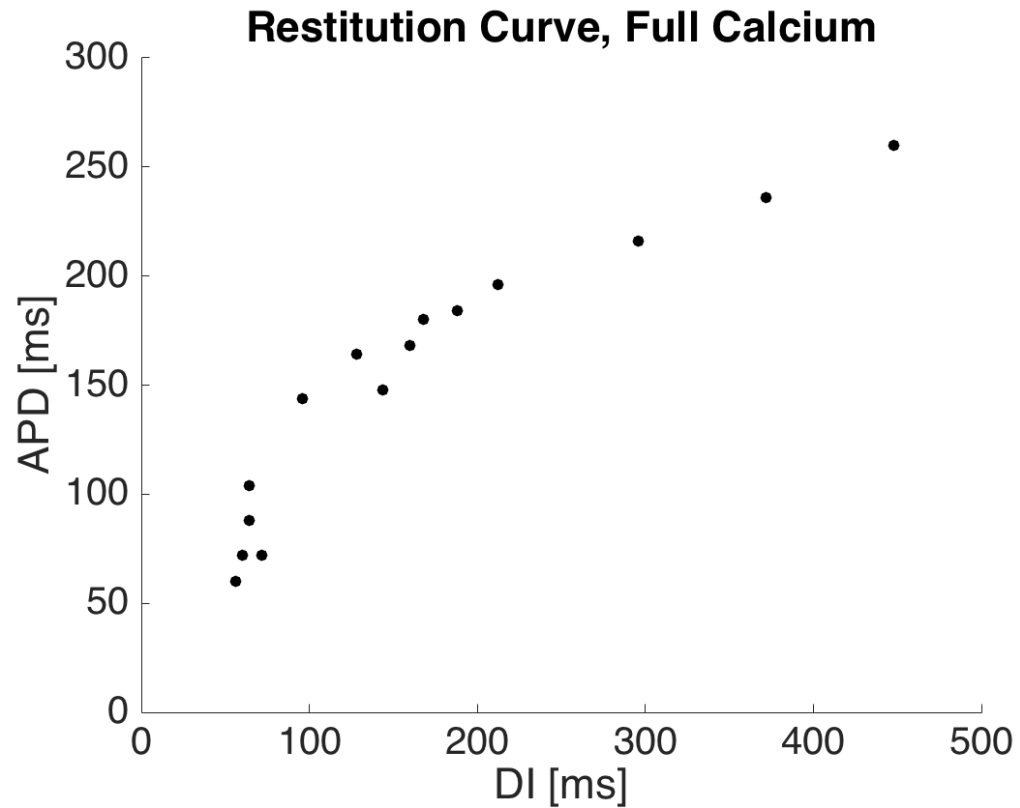
Accepted 4 May 2018

### ABSTRACT

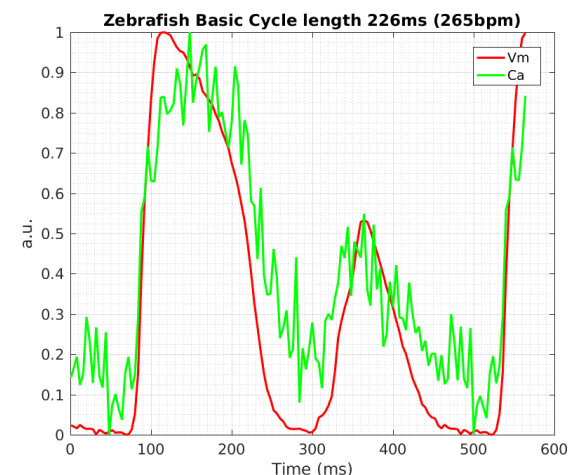
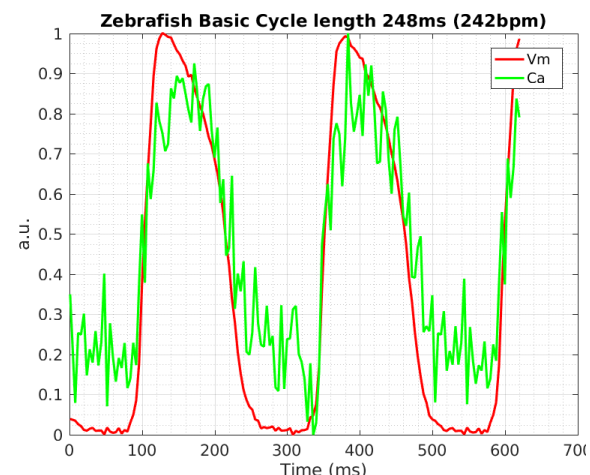
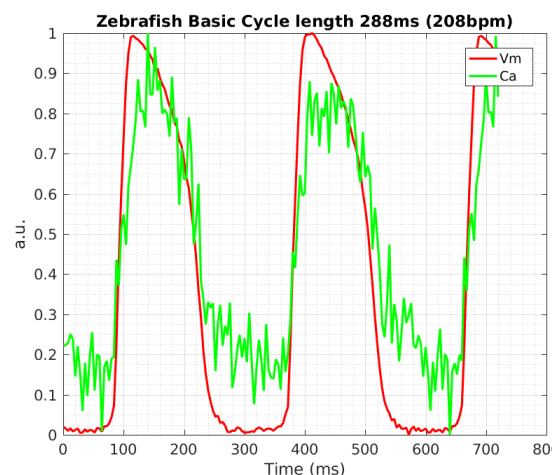
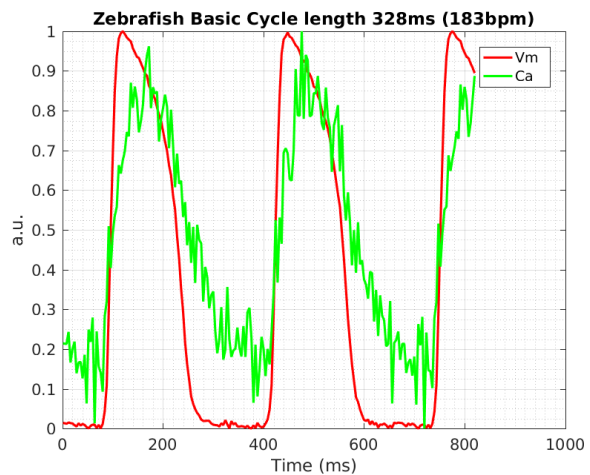
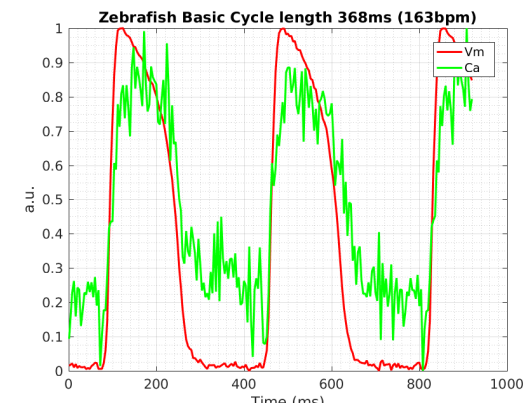
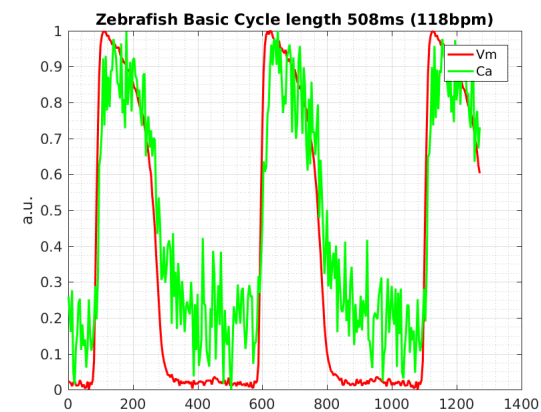
Sudden cardiac death is a leading cause of death worldwide, mainly caused by high activation patterns in the heart. Currently, murine models are the most popular underlying molecular mechanisms of inherited or acquired cardiac electrical abnormalities. Numerous electrophysiological discrepancies between mouse and human raise the question whether mice are the optimal model to study cardiac rhythm disorders. Recently it has been



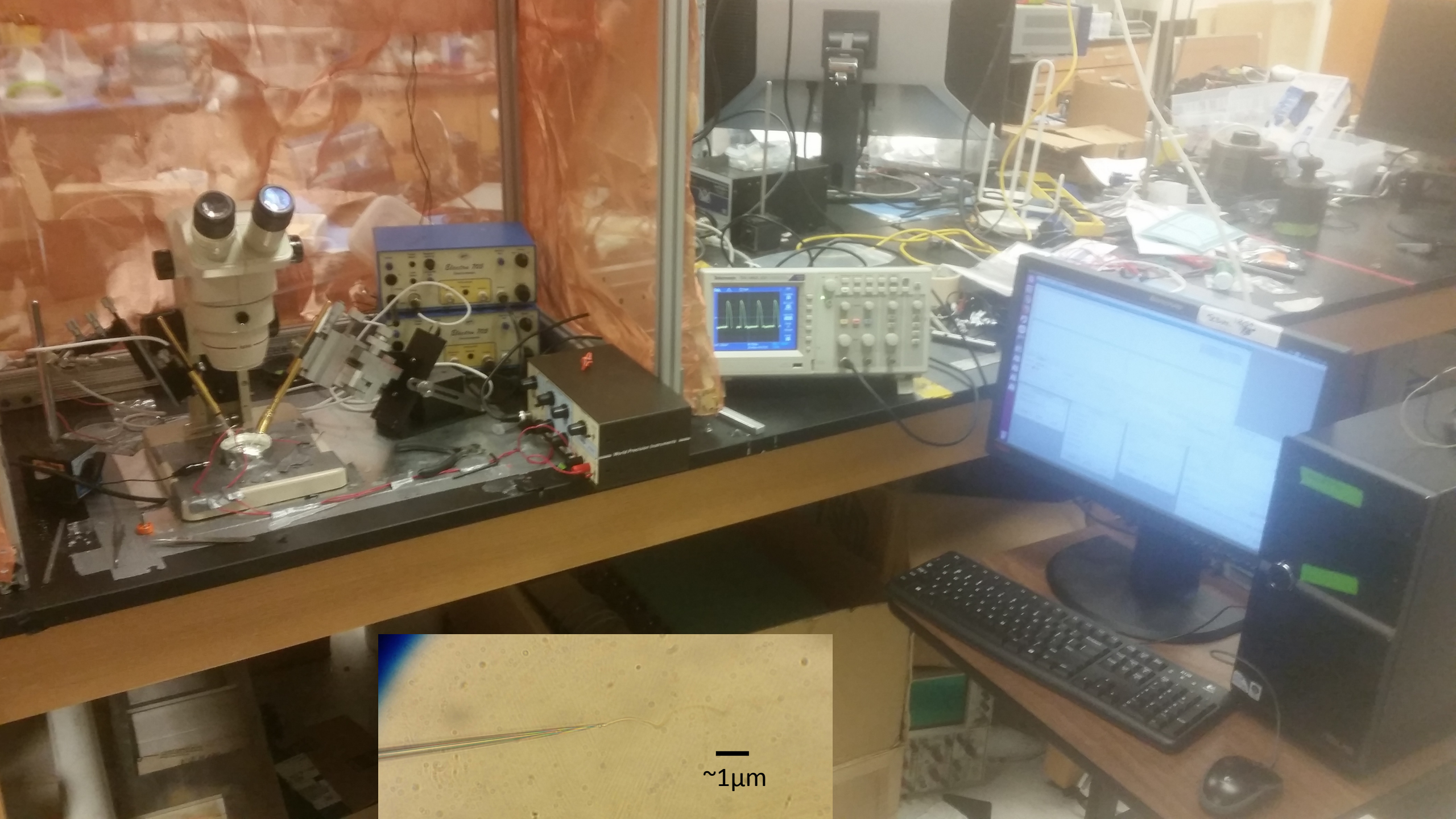




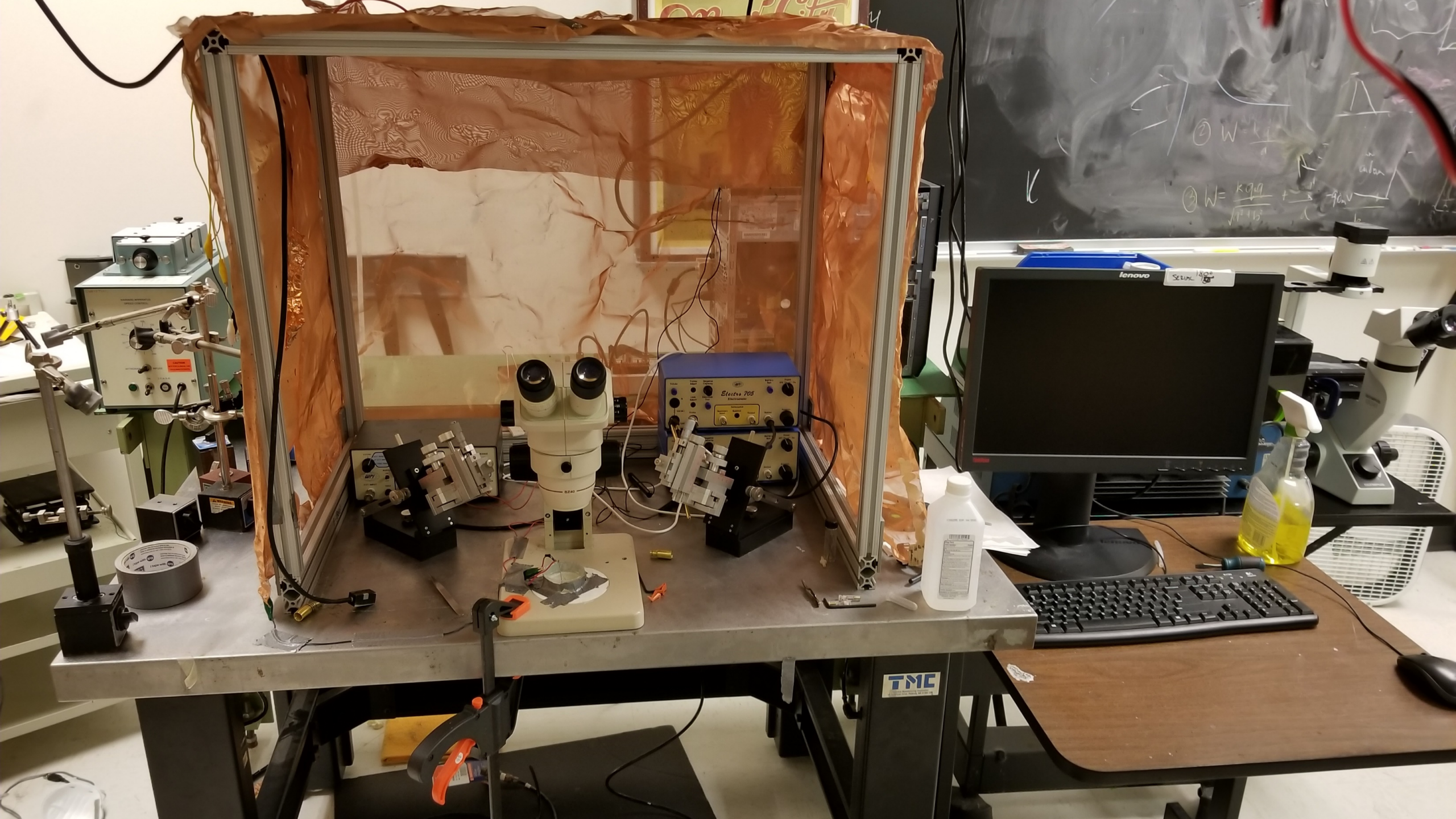
Tim Farmer



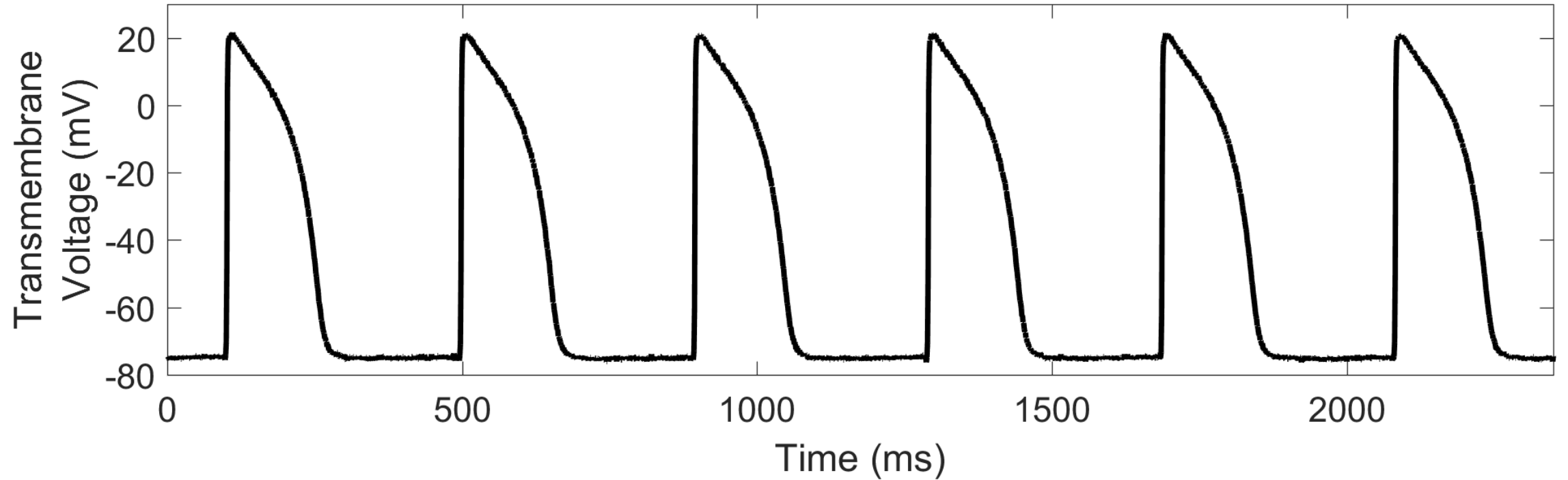






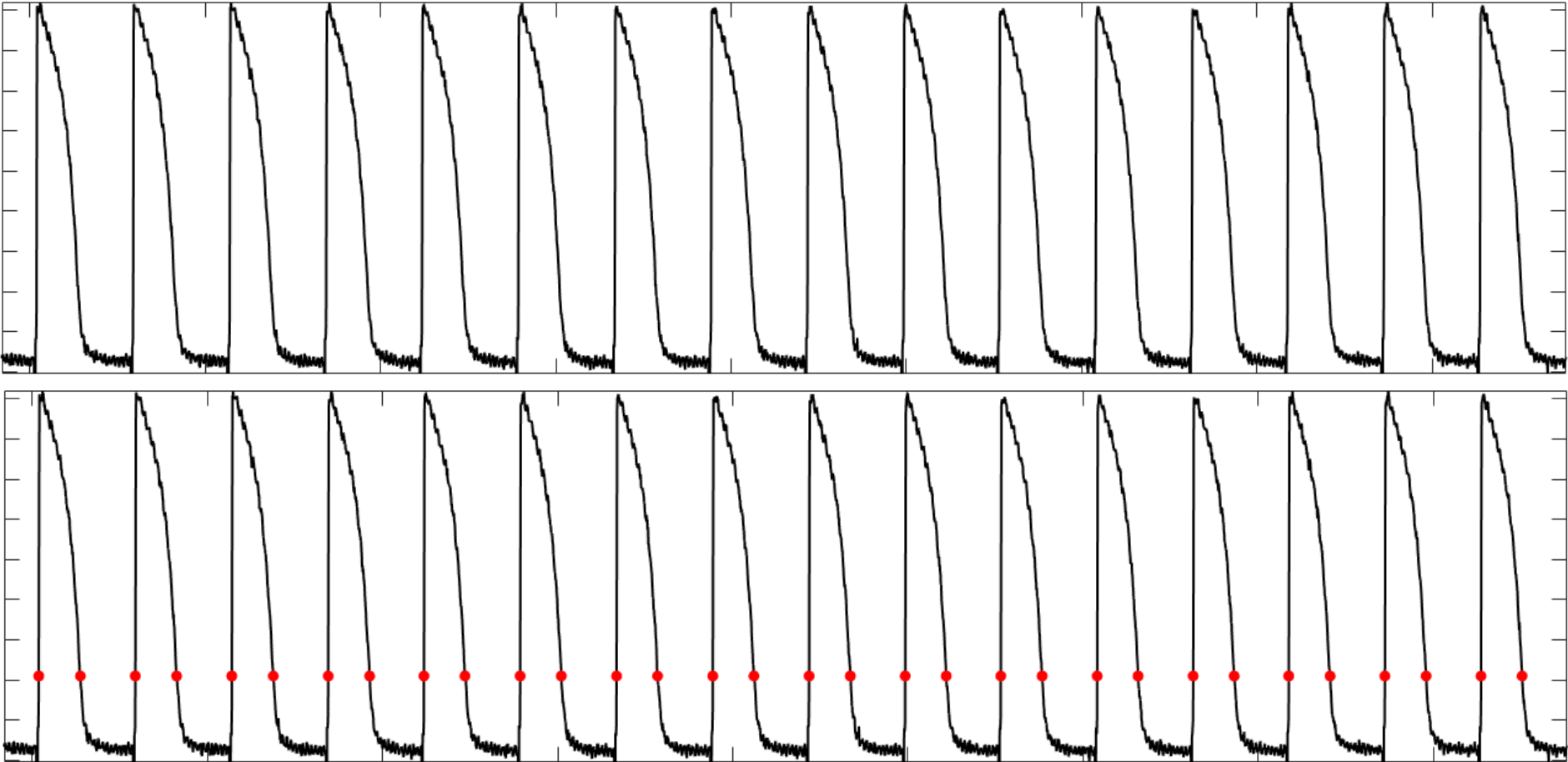


# Microelectrode recordings



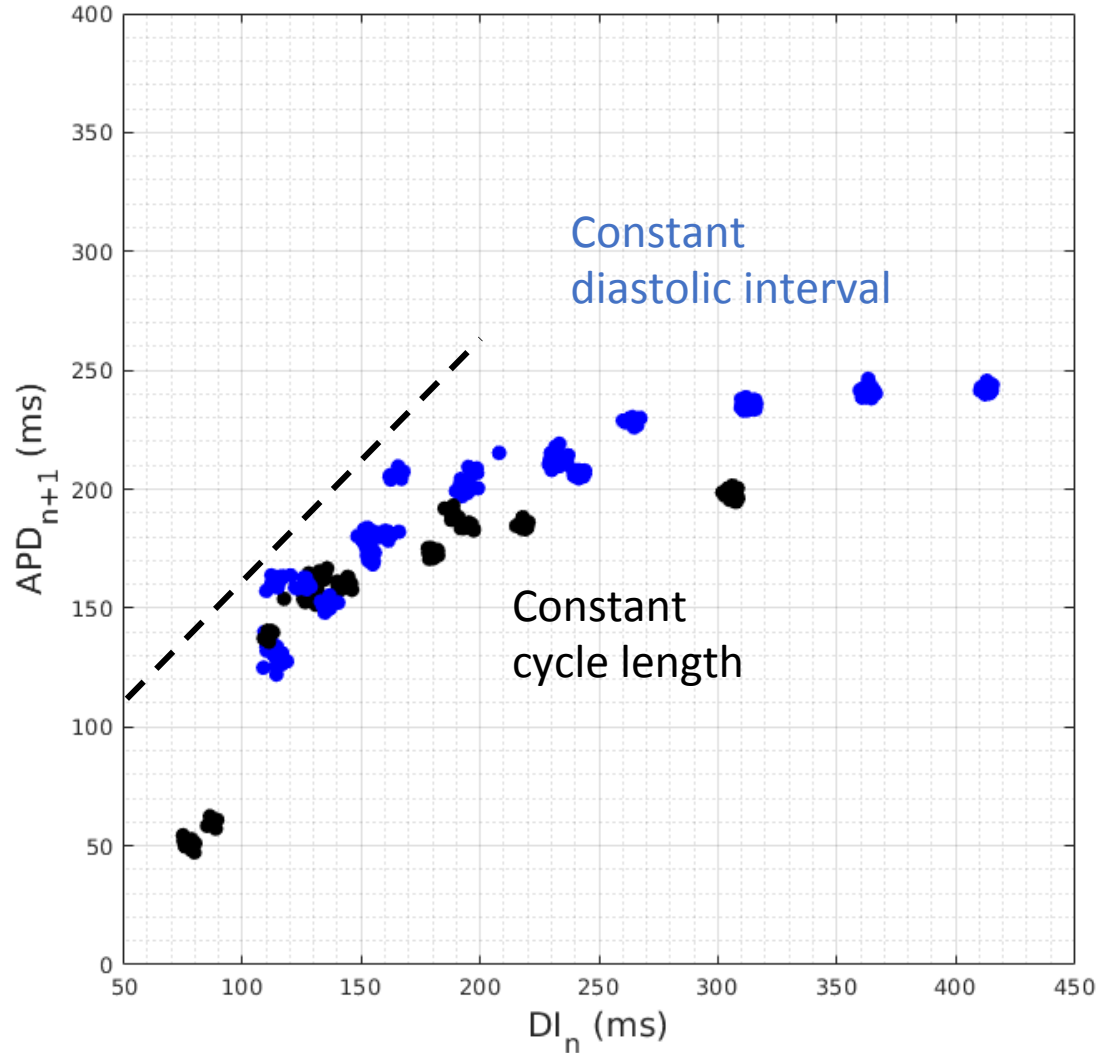


# Constant diastolic interval in real time

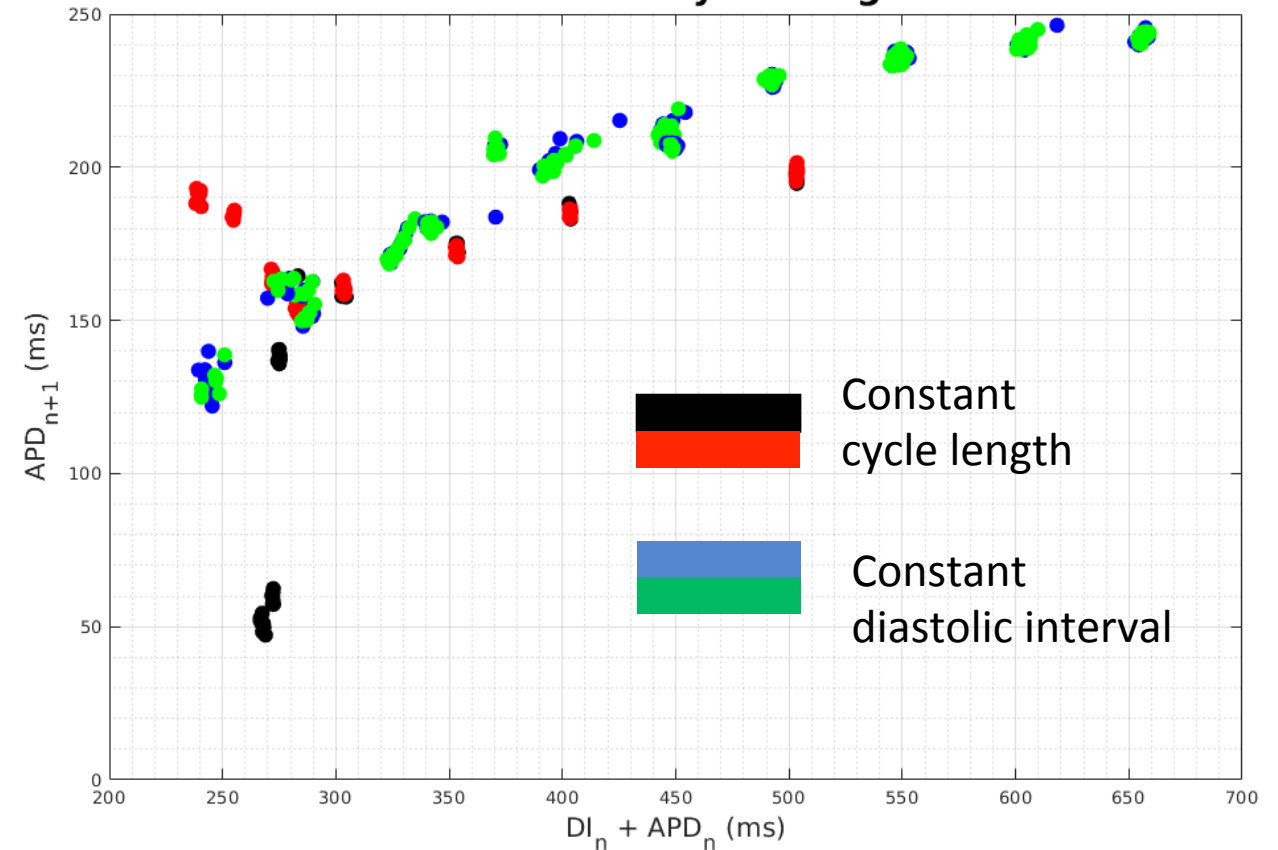


# Constant Diastolic Control with Microelectrode Initial Results

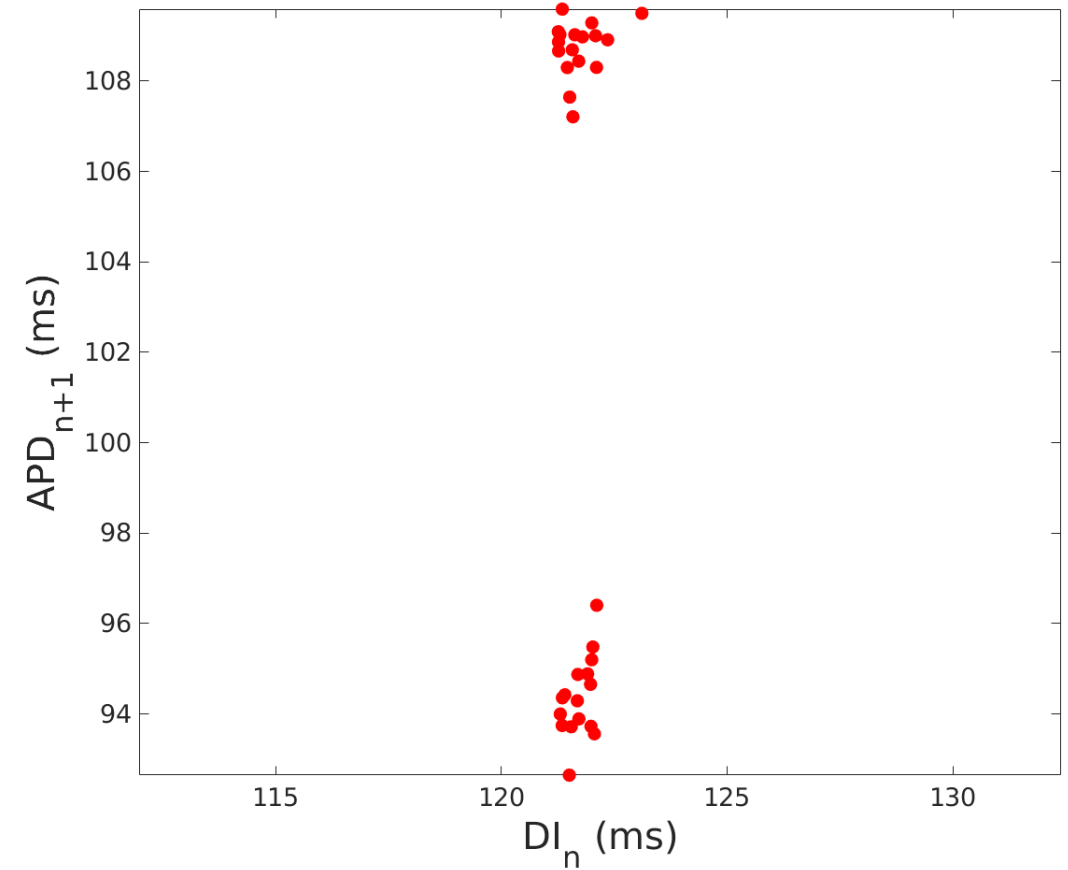
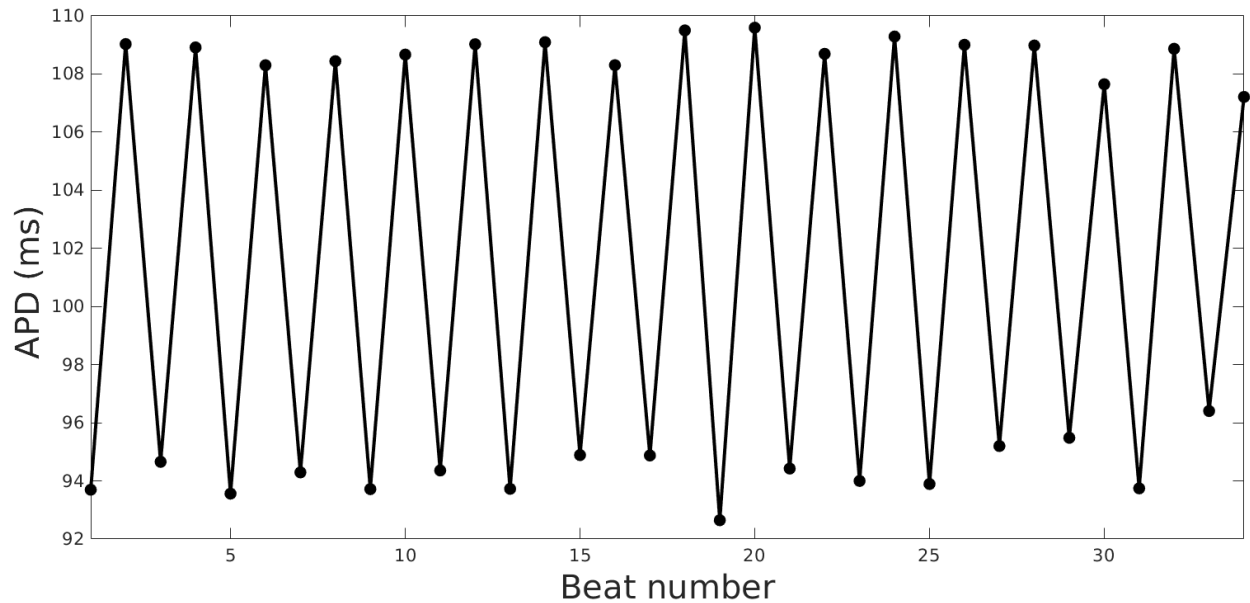
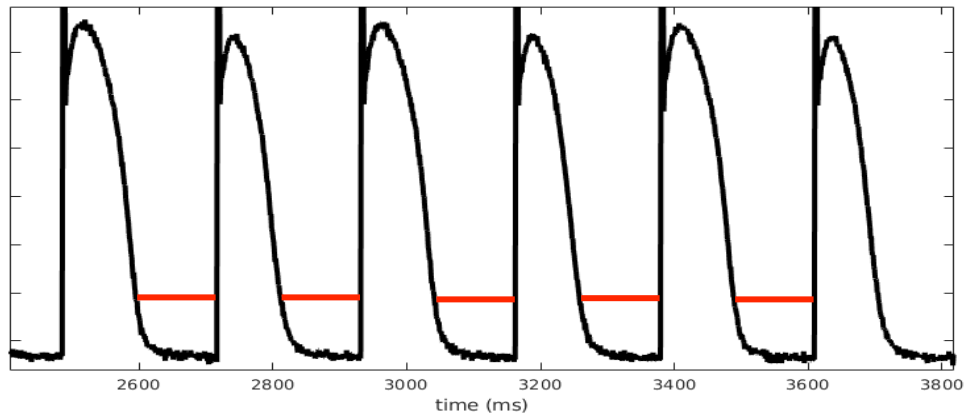
## Restitution



## APD versus Cycle Length



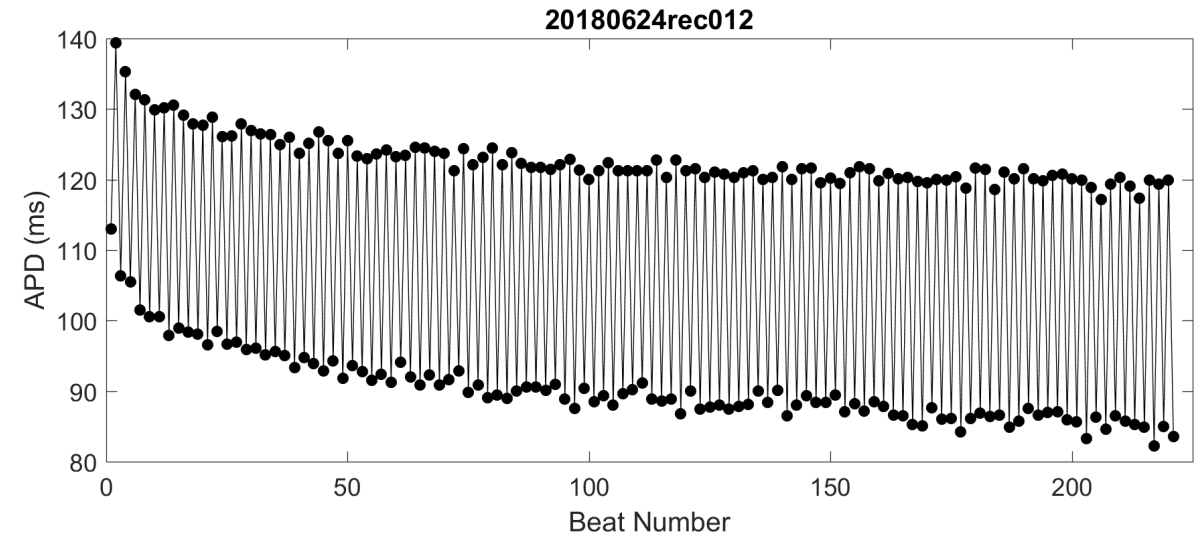
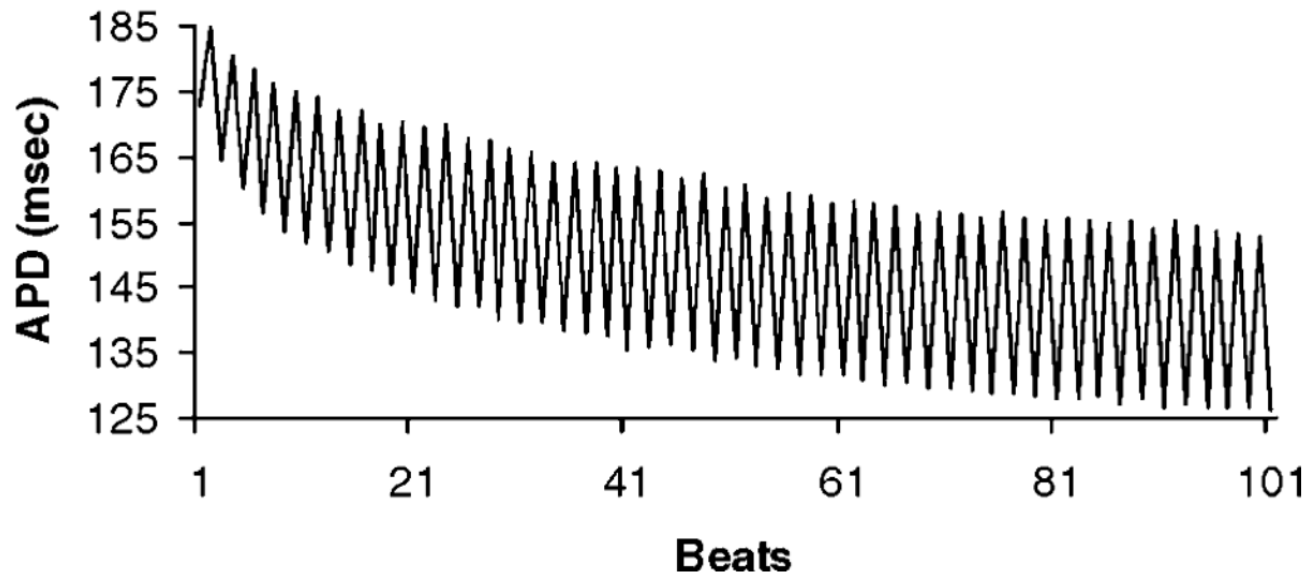
Repeated experiments showed the appearance of alternans during constant diastolic interval pacing



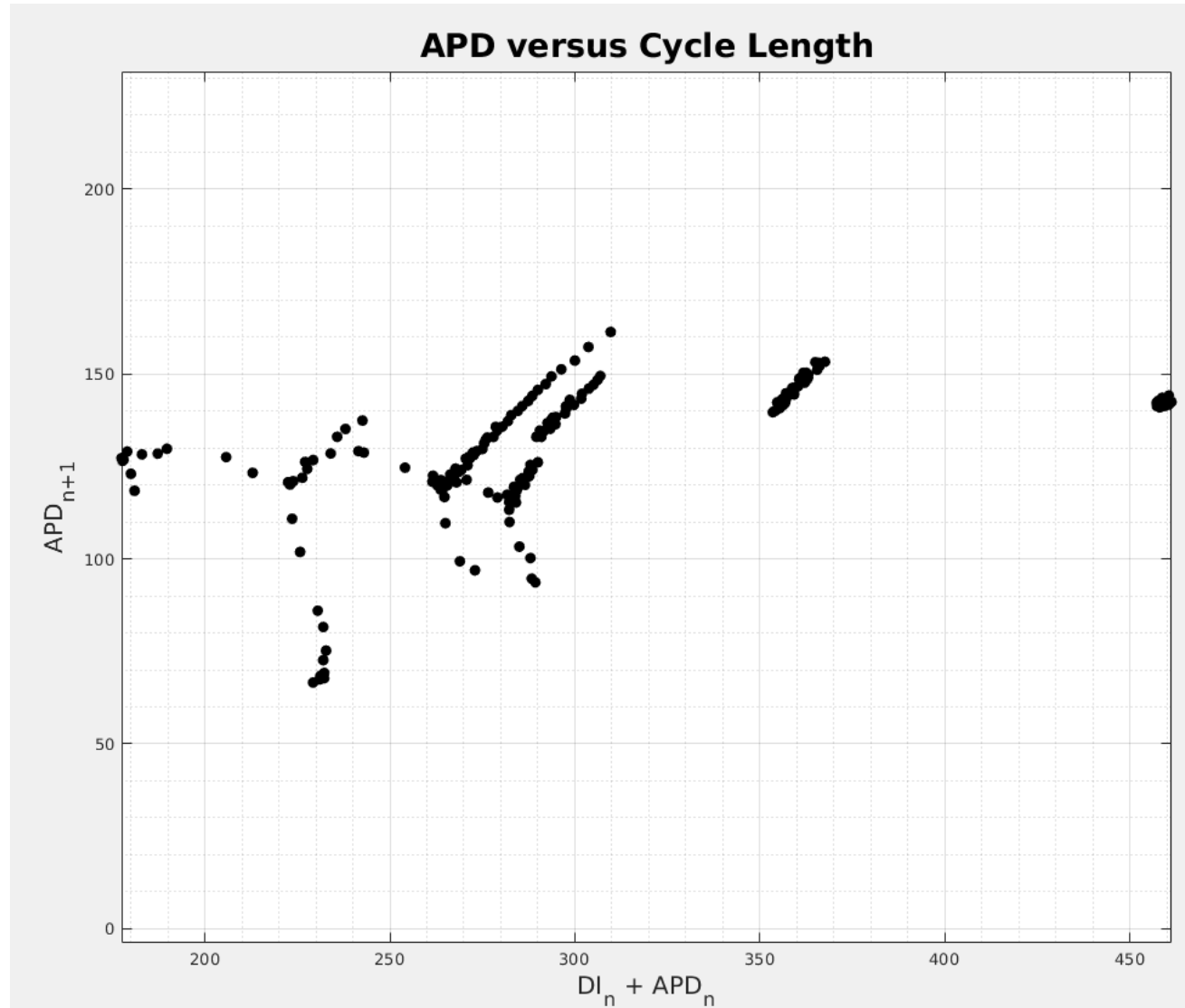
# Mechanism of Repolarization Alternans Has Restitution of Action Potential Duration Dependent and Independent Components

RUNZE WU, M.S.,\* and ABHIJIT PATWARDHAN, PH.D.\*,†

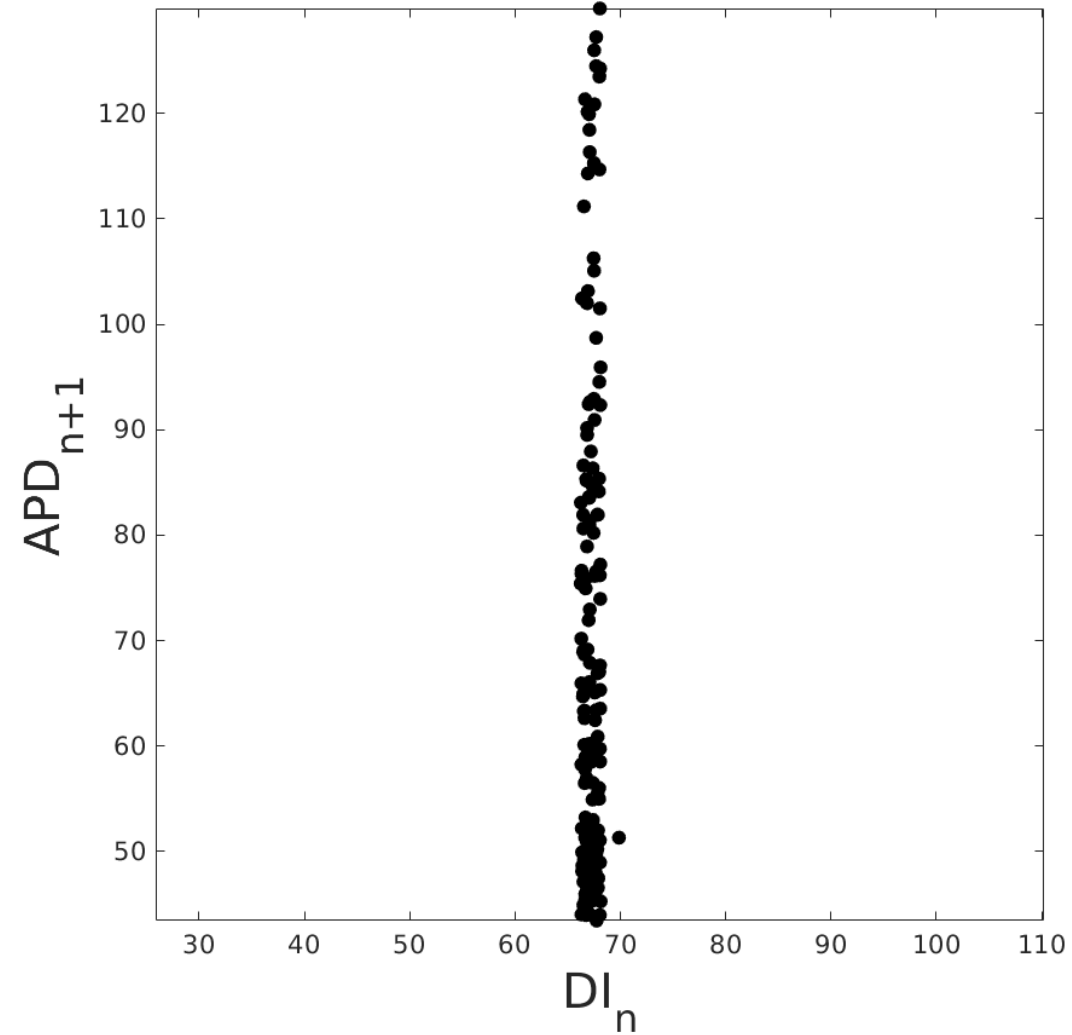
From the \*Center for Biomedical Engineering, and †Division of Cardiovascular Medicine, University of Kentucky, Lexington, Kentucky, USA



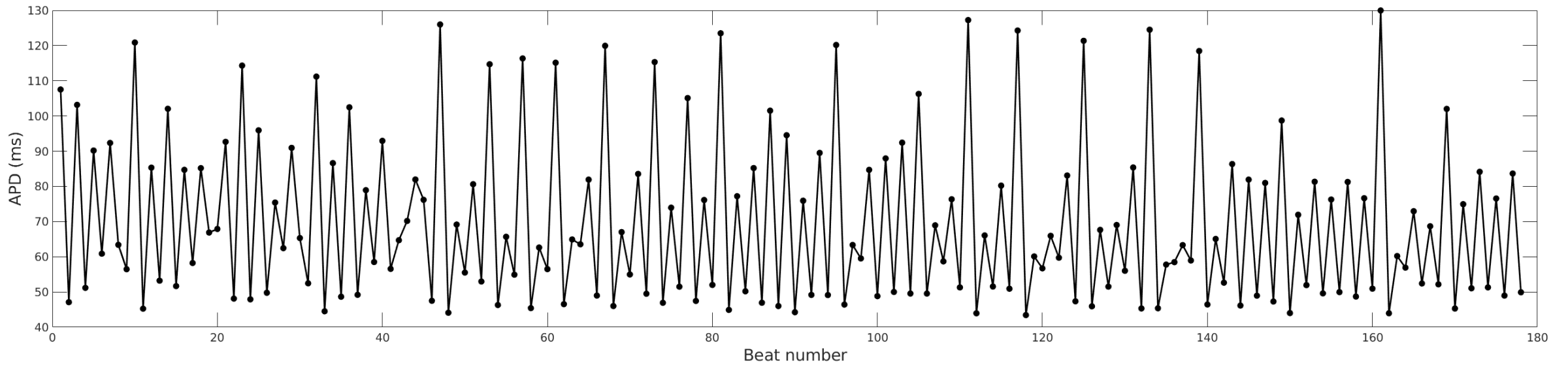
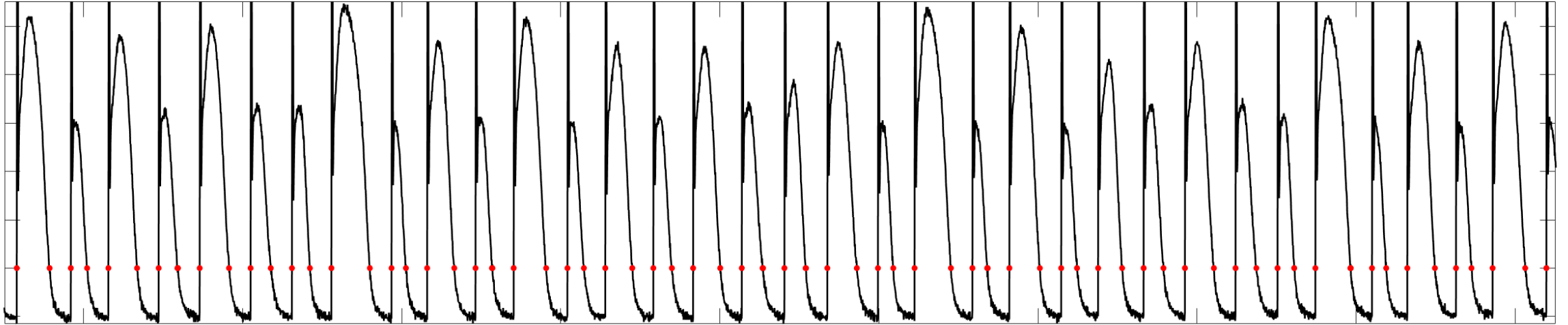
During constant DI pacing, action potential durations reduce and bifurcate



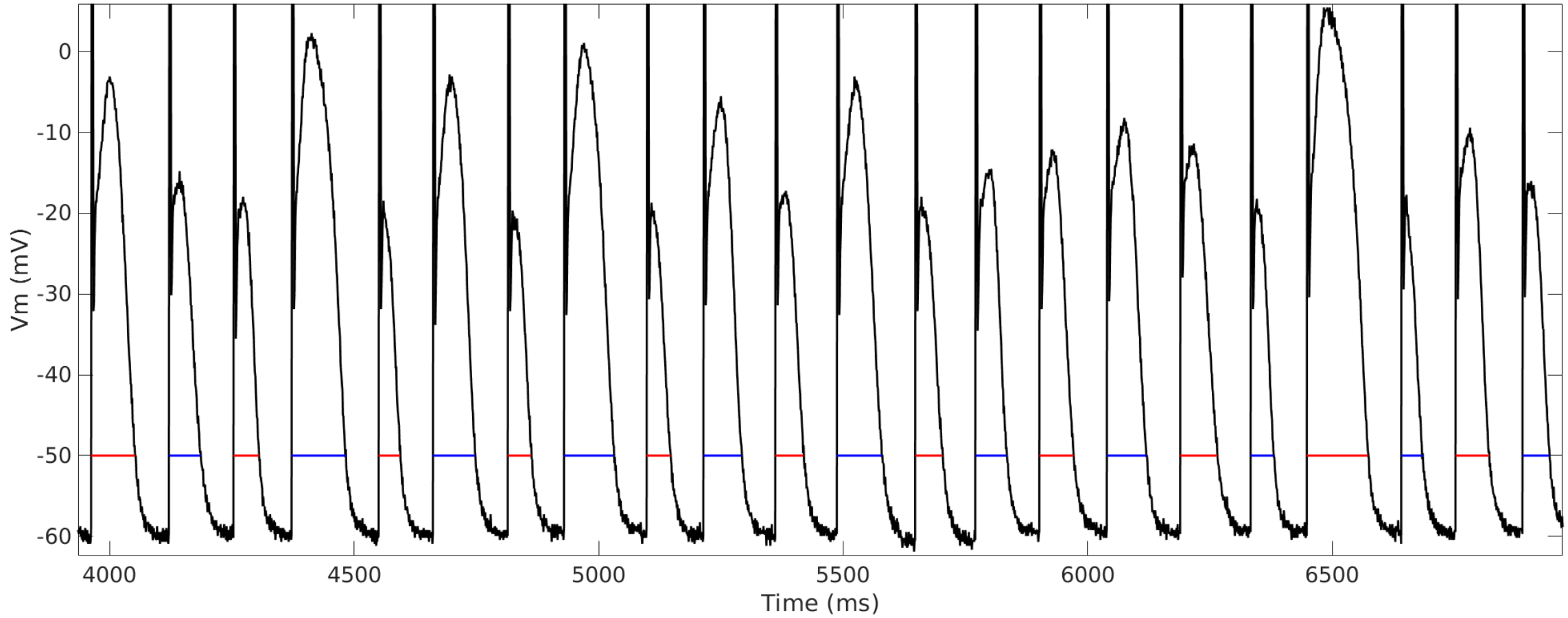
It gets worse.



# Constant diastolic pacing can yield erratic behavior

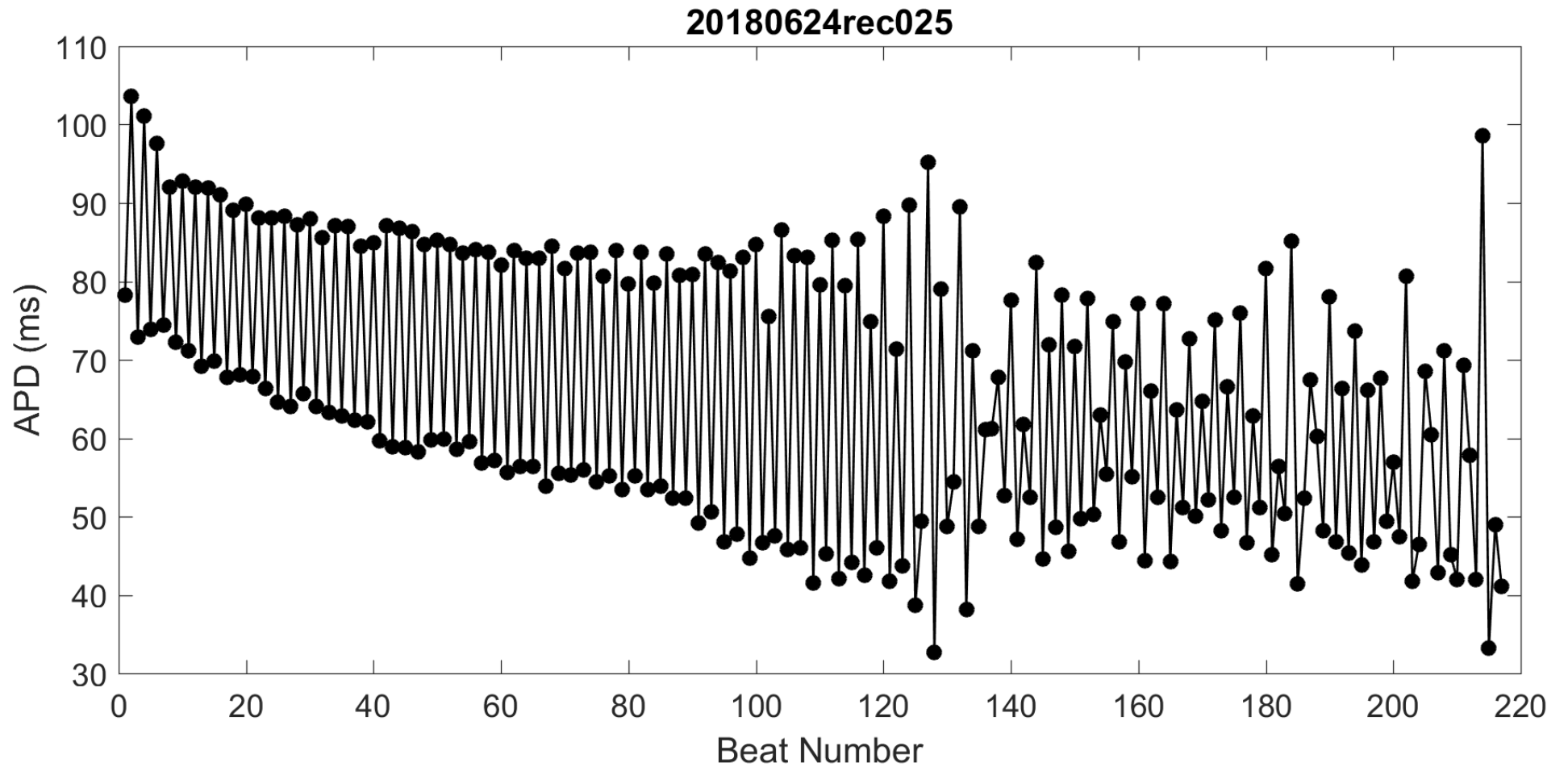
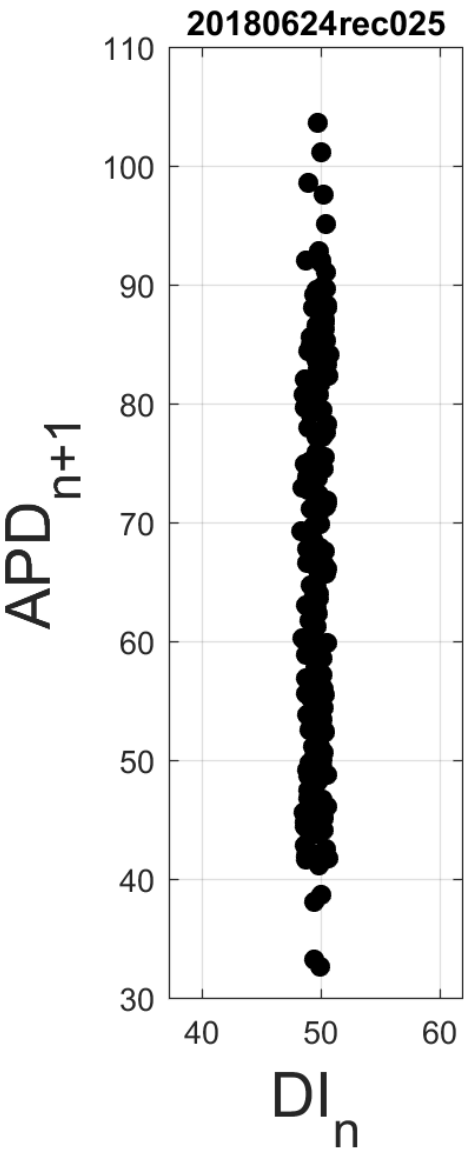


20180531rec067 Even/Odd beats





# Alternans breaking into aperiodic behavior



# Conclusions

- Cardiac dynamics can differ across species subject to different evolutionary pressures
- Many models predict control of alternans under constant DI pacing
- Constant DI pacing did not suppress alternans in zebrafish

# Future Work

- Perform constant DI control on other species such as frog, guinea pig, rabbit, ferret, dog, cat, pig, lost children

# Flavio Fenton's CHAOS lab

- Abouzar Kaboudian
- Ilija Uzelac
- Andrea Welsh
- Yanyan Yi
- Diana Chen
- Hector Velasco



Henry Astley

University of Akron

# Undergrad indentured servants

- Zoha Naqawe
- Tony Aportela
- Hannah Phillips
- J. Tim Farmer
- Daniel Gurevich



Tomasz Owerkowicz

CSUSB

