9th meeting of

European
Study
Group on
Cardiovascular
Oscillations

Role of Temperature and Tissue Size on Nonlinear Cardiac Dynamics

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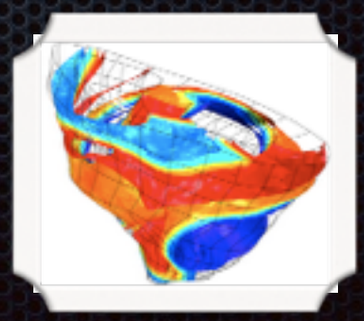


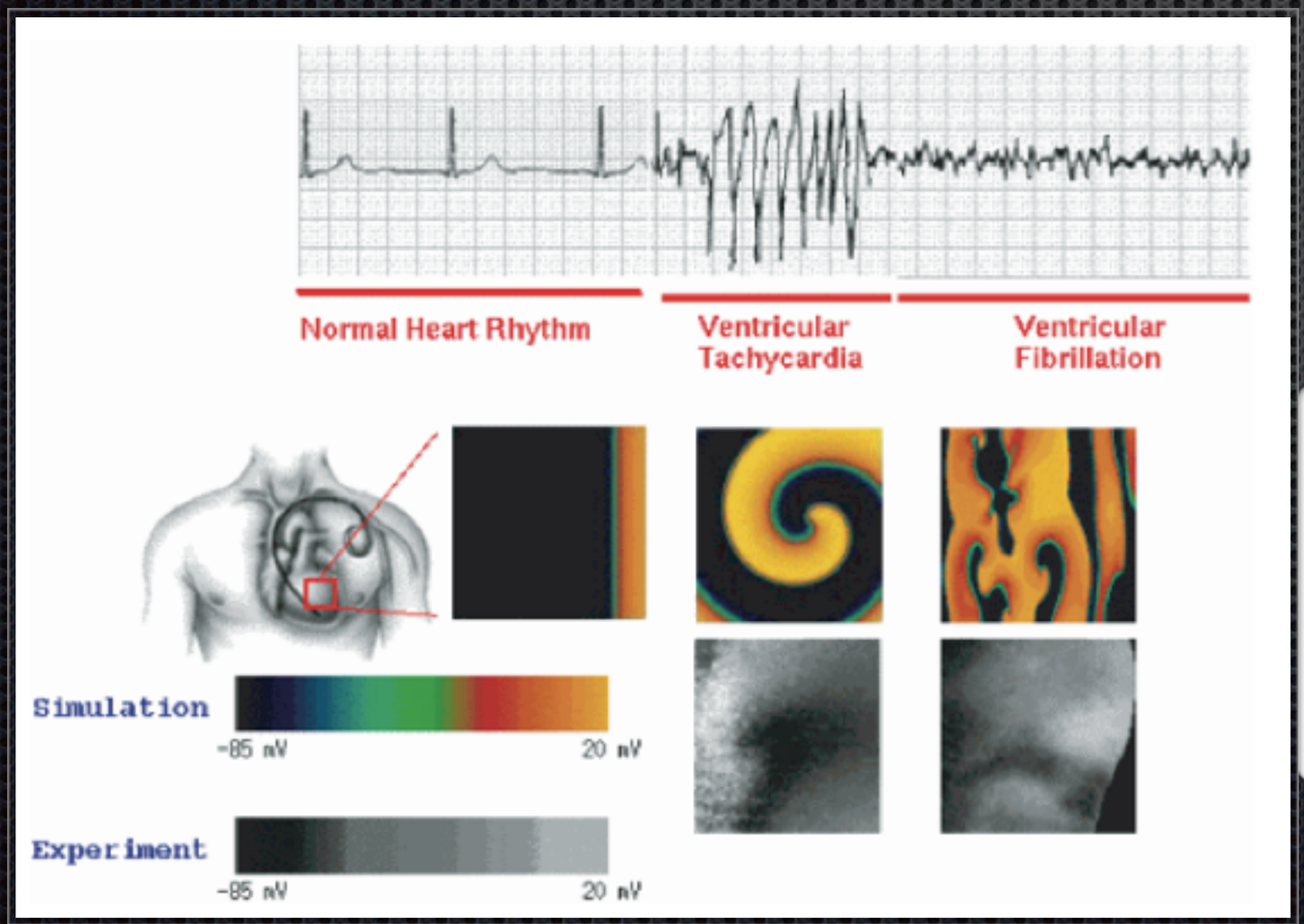
Outline

- **Cardiac Arrhythmias and Temperature Effects**
- **Experimental Setup and Data Analysis**
- **Mathematical Modelling**
  - **Model tuning**:
    - temporal dynamics
    - spatio-temporal dynamics
- **Alternans**: bifurcation analysis
- **Arrhythmias**:
  - domain size and temperature effects
- **Conclusions**

Cardiac Arrhythmias

Cardiac Rhythm Transition

The 'standard' induction of Ventricular Fibrillation measured via the ECG goes from Normal Rhythm - to - Ventricular Tachycardia - to - Ventricular Fibrillation

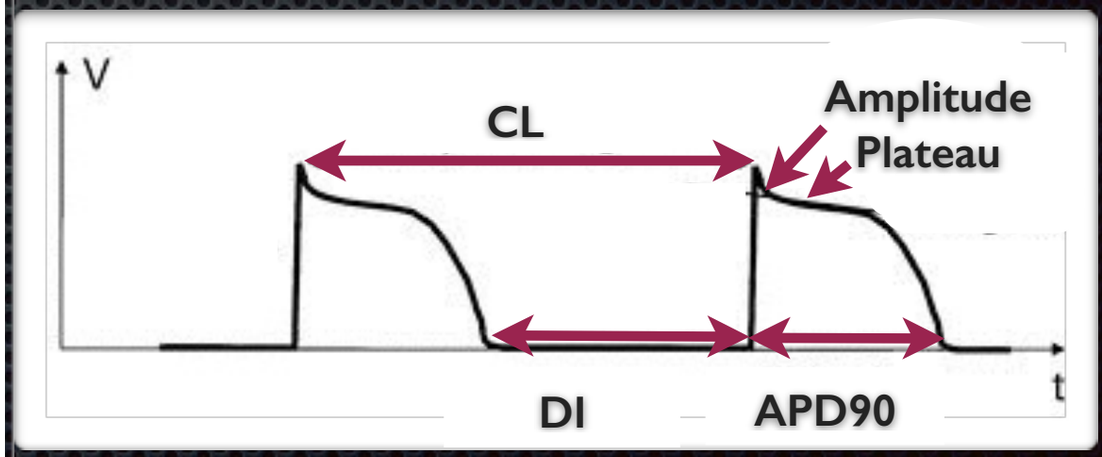


Flavio H. Fenton

Cardiac Alternans

Restitution Curves

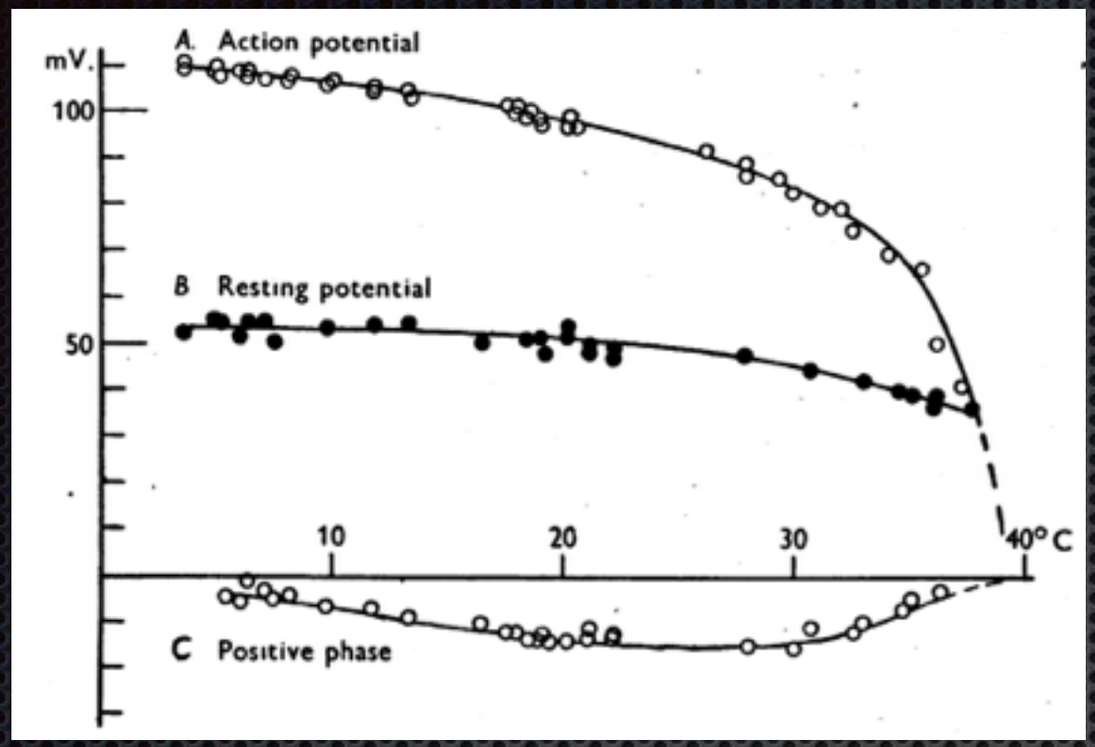
- APD vs. CL
- APD vs. DI
- CV vs. CL
- CV vs. DI

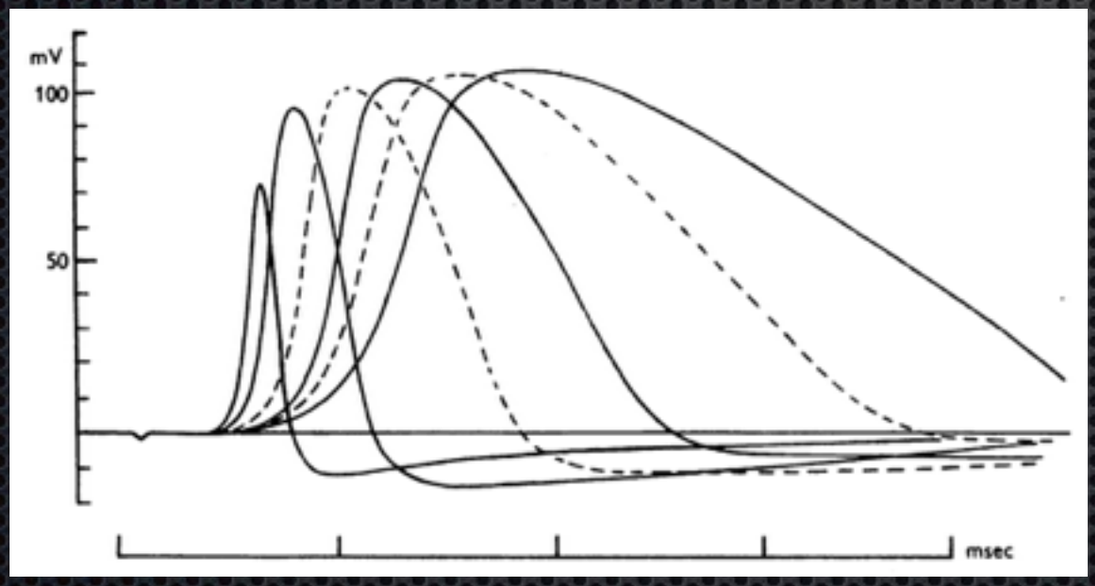


Fenton Scholarpedia 2008

F.H.Fenton

Temperature Effects on Excitable Systems

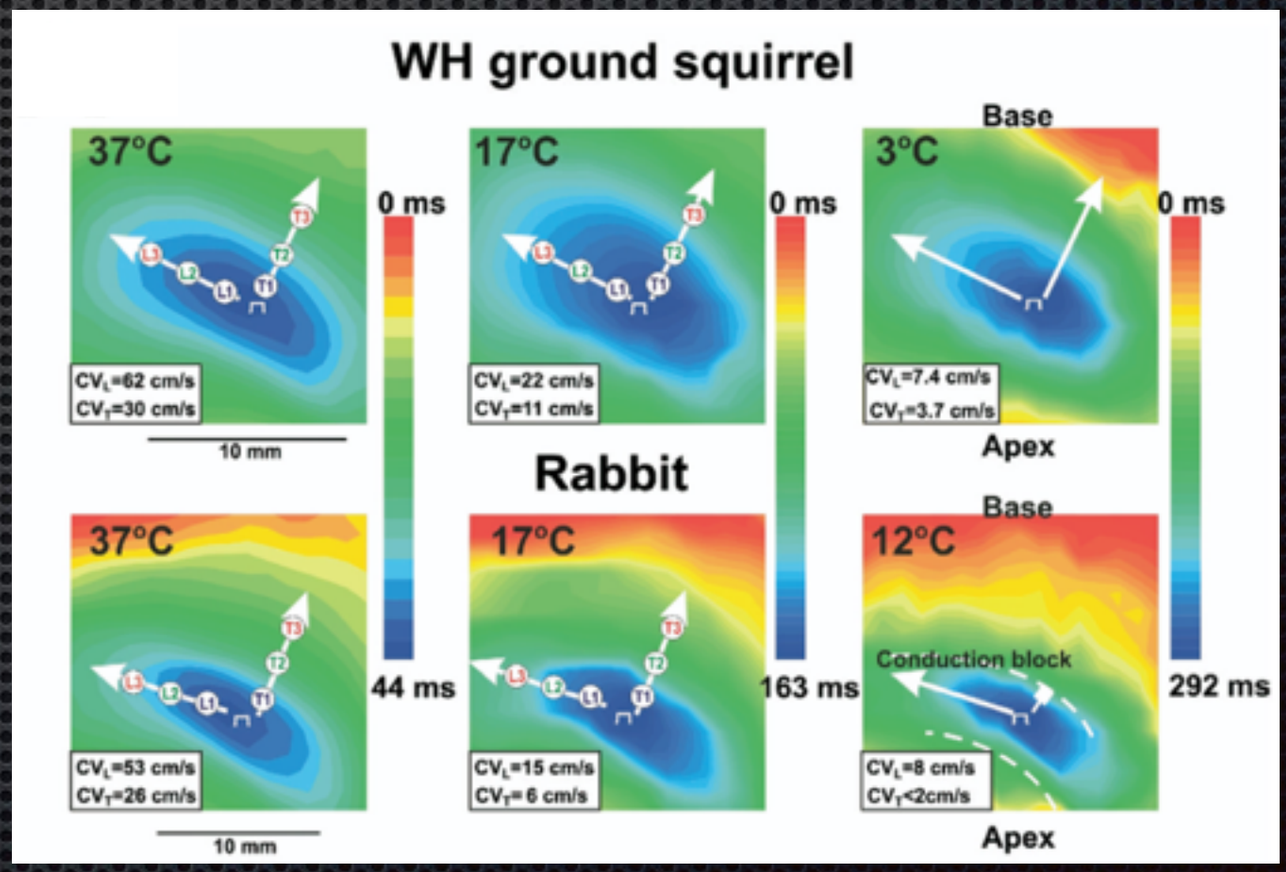




Hodgkin, A. L., & Katz, B. (1949). *The Journal of physiology*, *109*(1-2), 240.

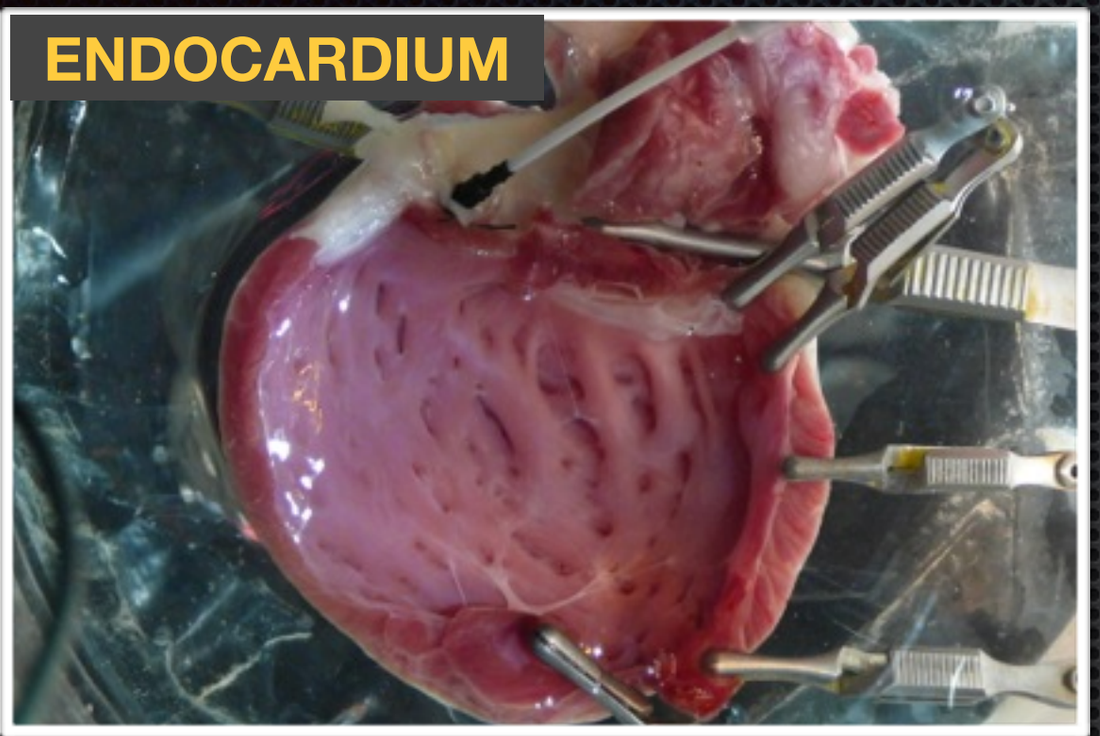
Effects of Temperature

- APD duration
- Frequency
- Excitability threshold
- Spatio-Temporal behaviours…



Fedorov, V. V., Glukhov, A. V., Sudharshan, S., Egorov, Y., Rosenshtraukh, L. V., & Efimov, I. R. (2008). *Heart Rhythm*, *5*(11), 1587-1596.

Experimental Setup



PROTOCOL

- Canine heart excised, right ventricle isolation and cannulation
- Tyrode solution with Voltage-Sensitive Dye (Di-4-ANEPPS) equilibration (37°C)
- Blebbistatin
- Selected light emission (530 nm)
- Endocardial stimulation
- Endo-Epi synchronous recording (2 ms/frame, 128x128 pixels, 600 µm/pixel)

Cornell University
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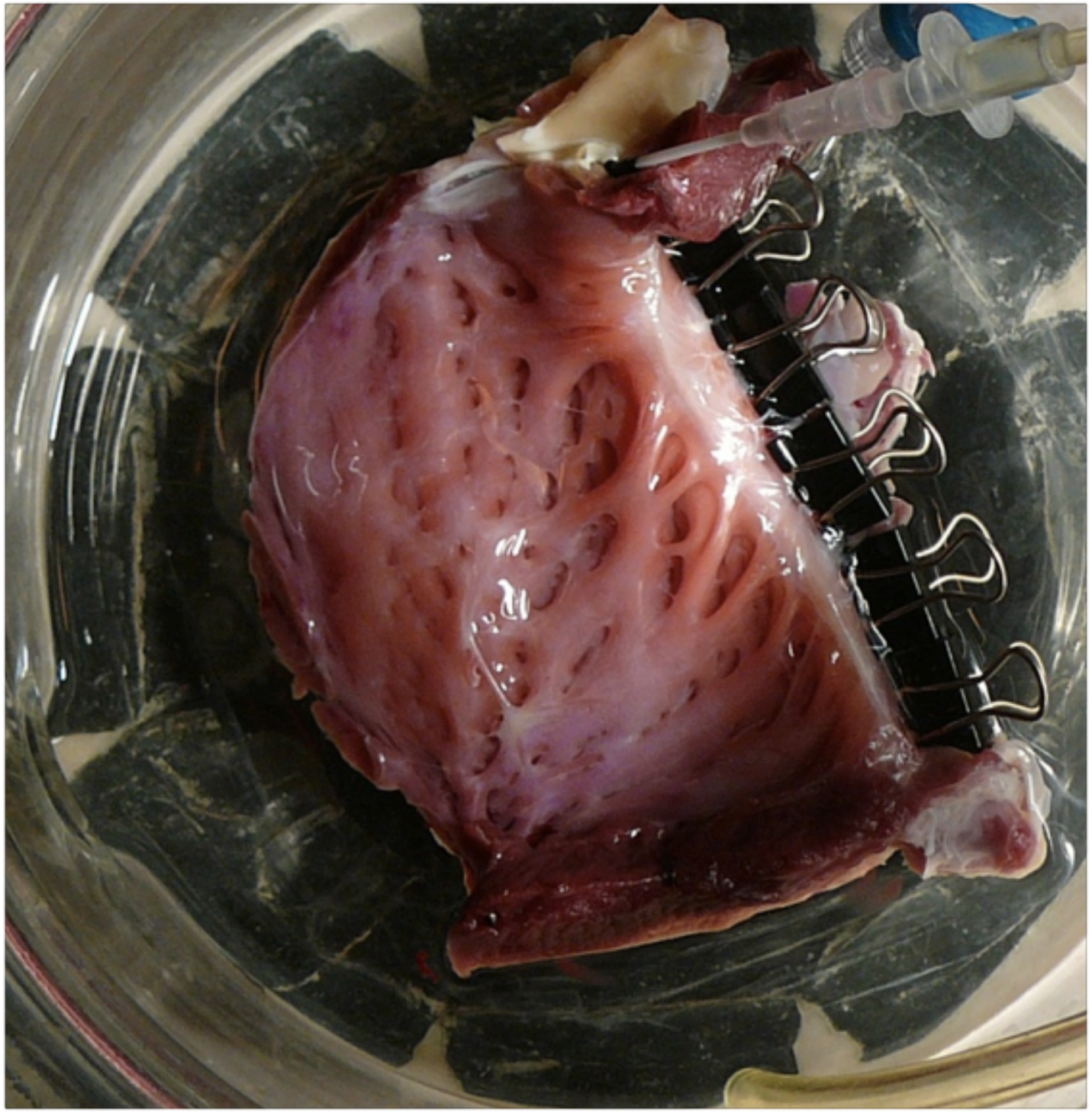
Experimental Setup

- **IN VITRO OPTICAL MAPPING RECORDINGS**



Original Tissue

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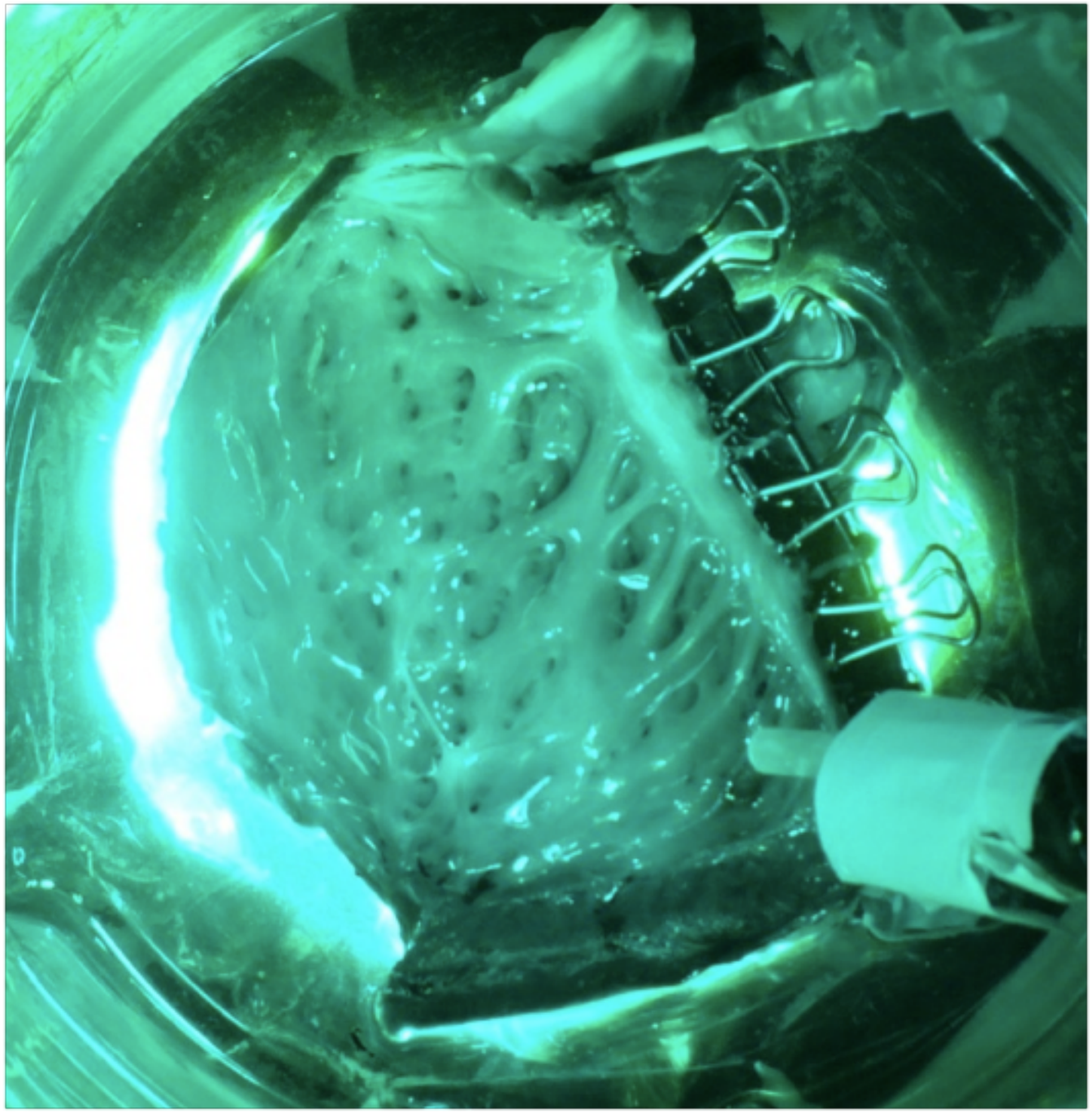
Experimental Setup

- **IN VITRO OPTICAL MAPPING RECORDINGS**



Original Tissue

Illuminated Tissue

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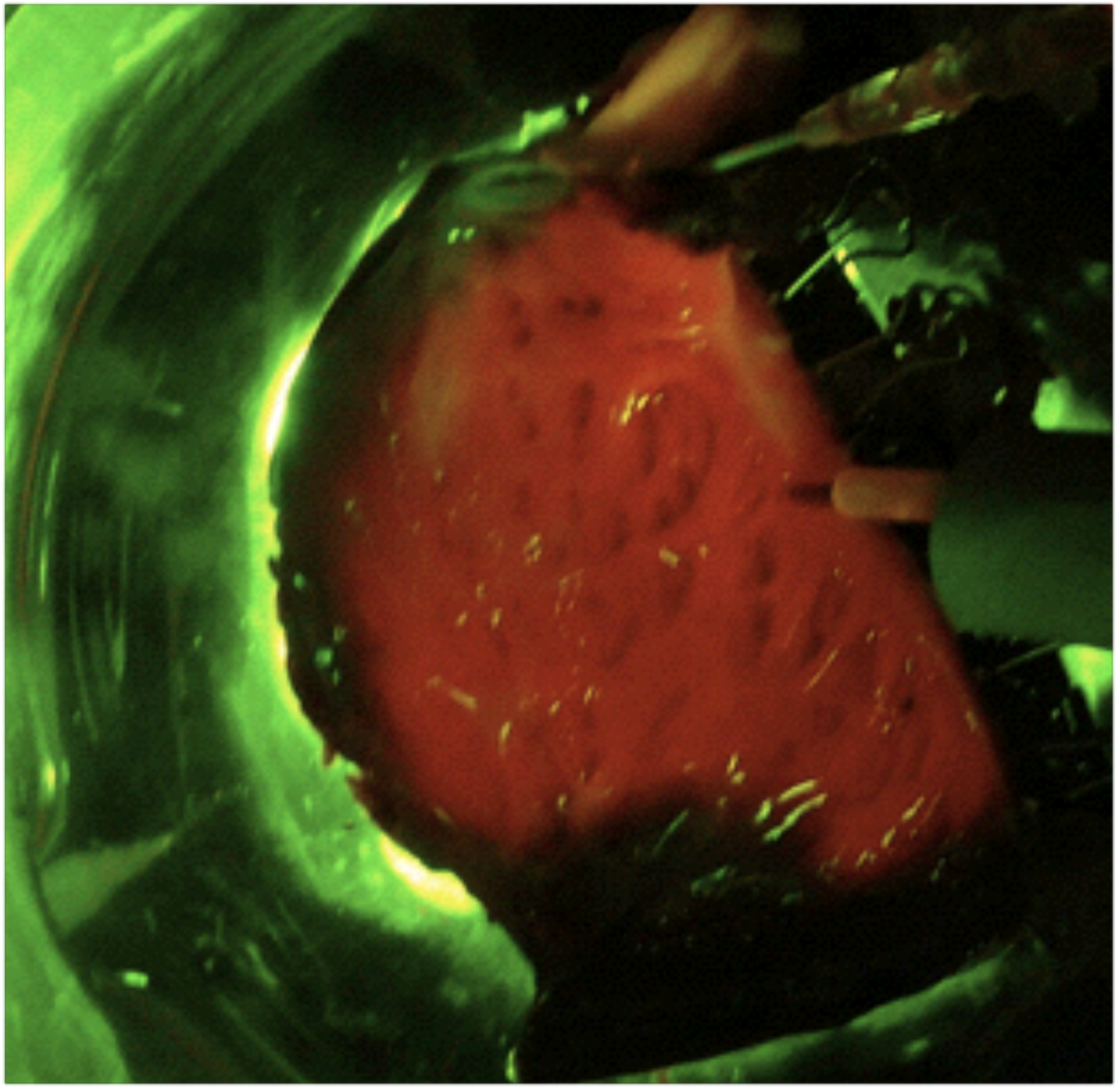
Experimental Setup

- **IN VITRO OPTICAL MAPPING RECORDINGS**



Original Tissue

Illuminated Tissue

Fluorescent Signal

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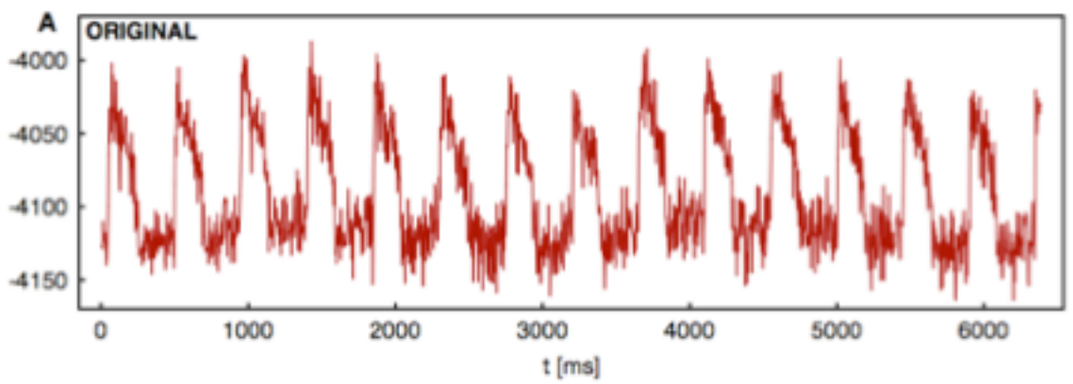
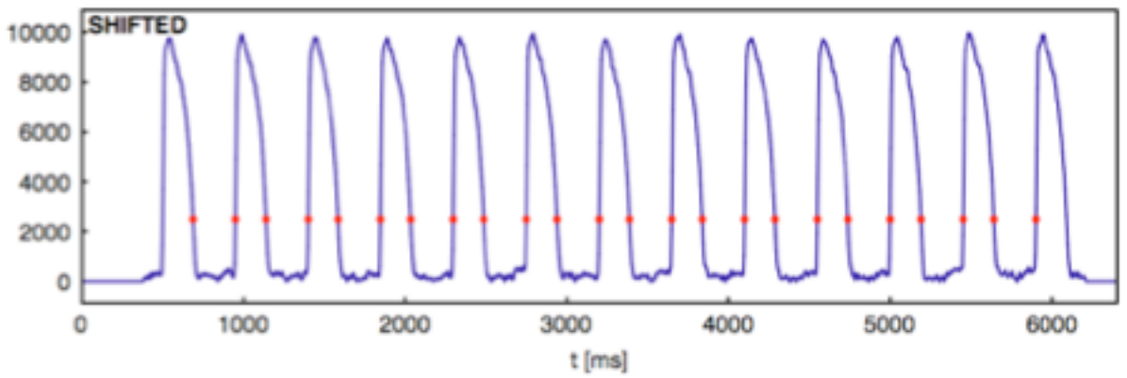
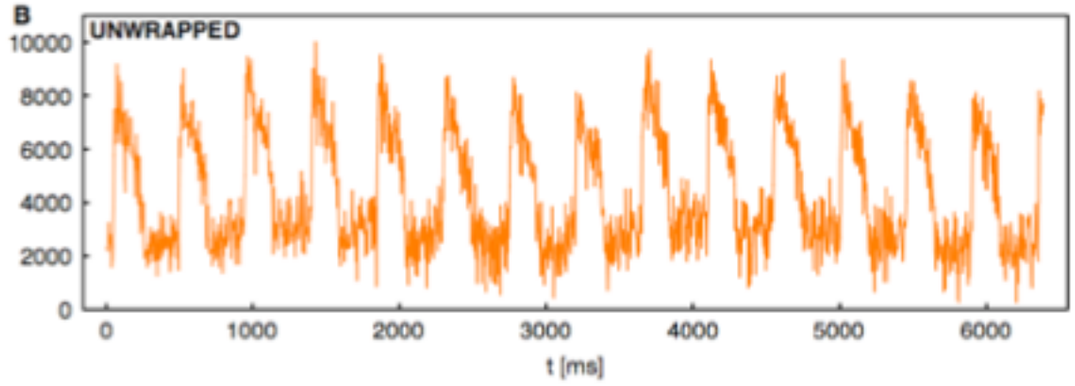
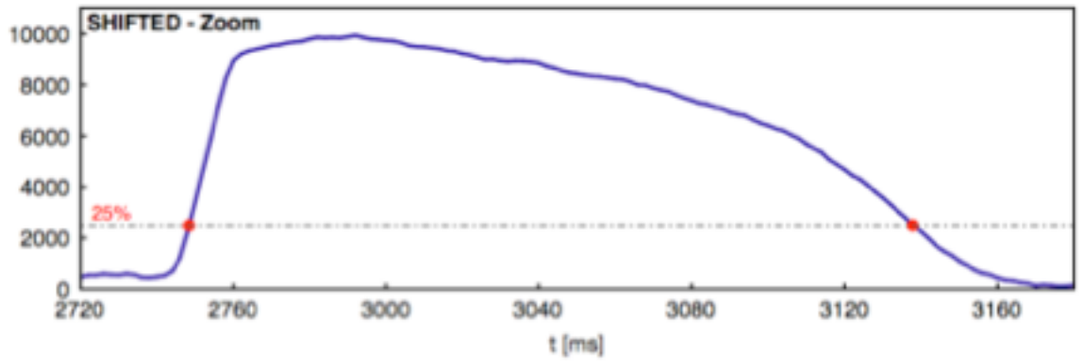
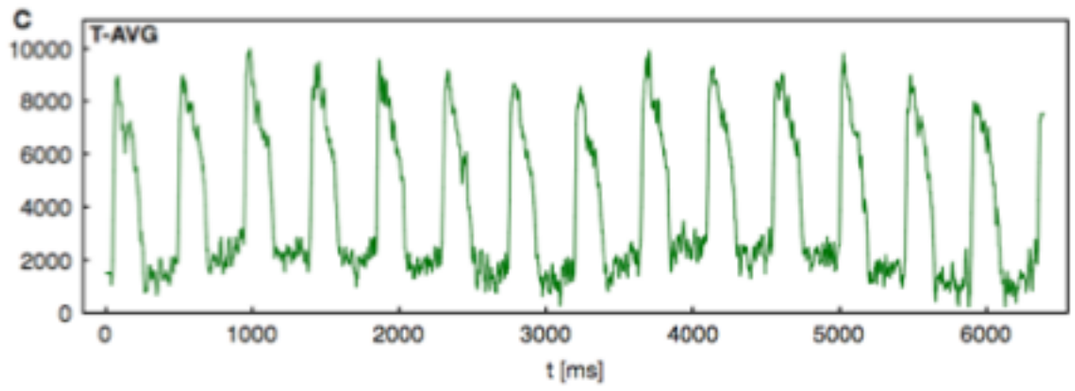
Experimental Data Analysis

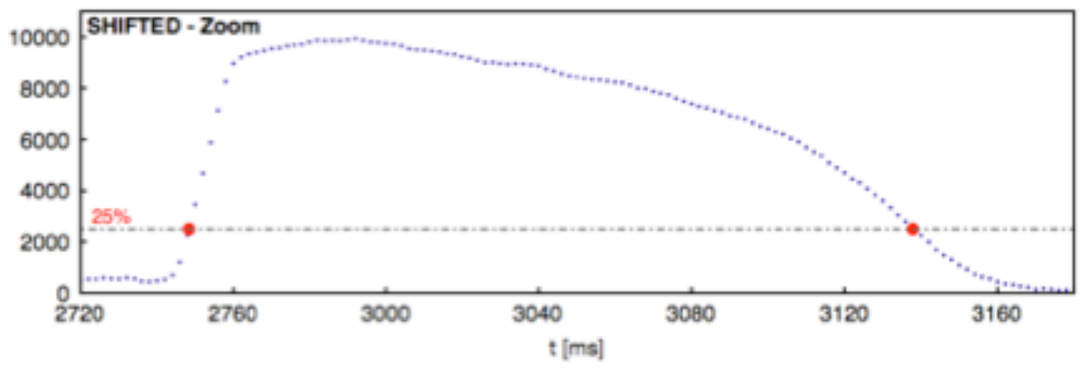


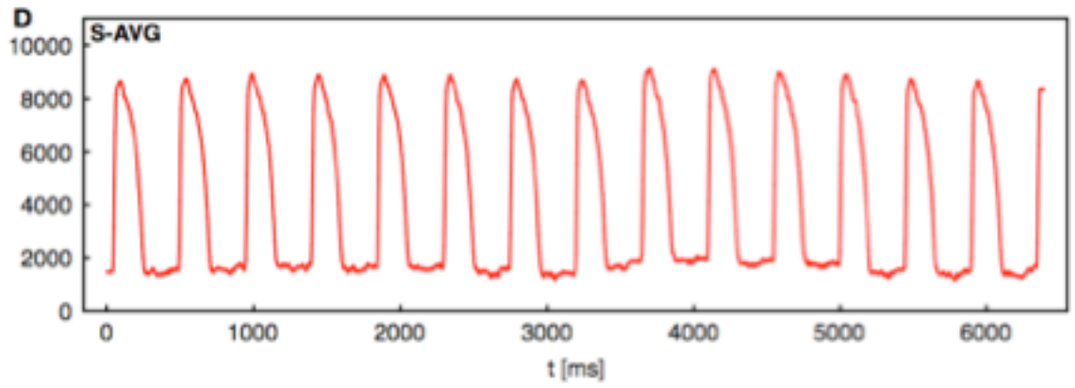


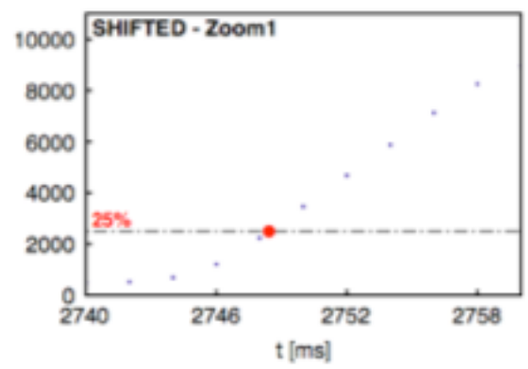


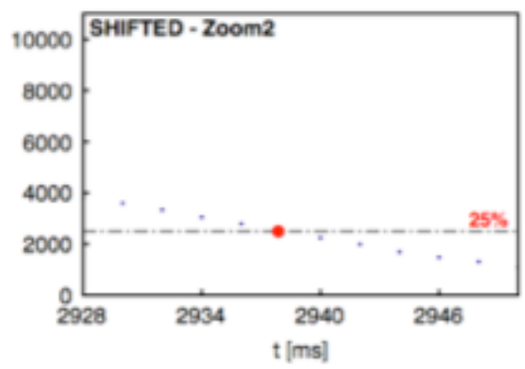








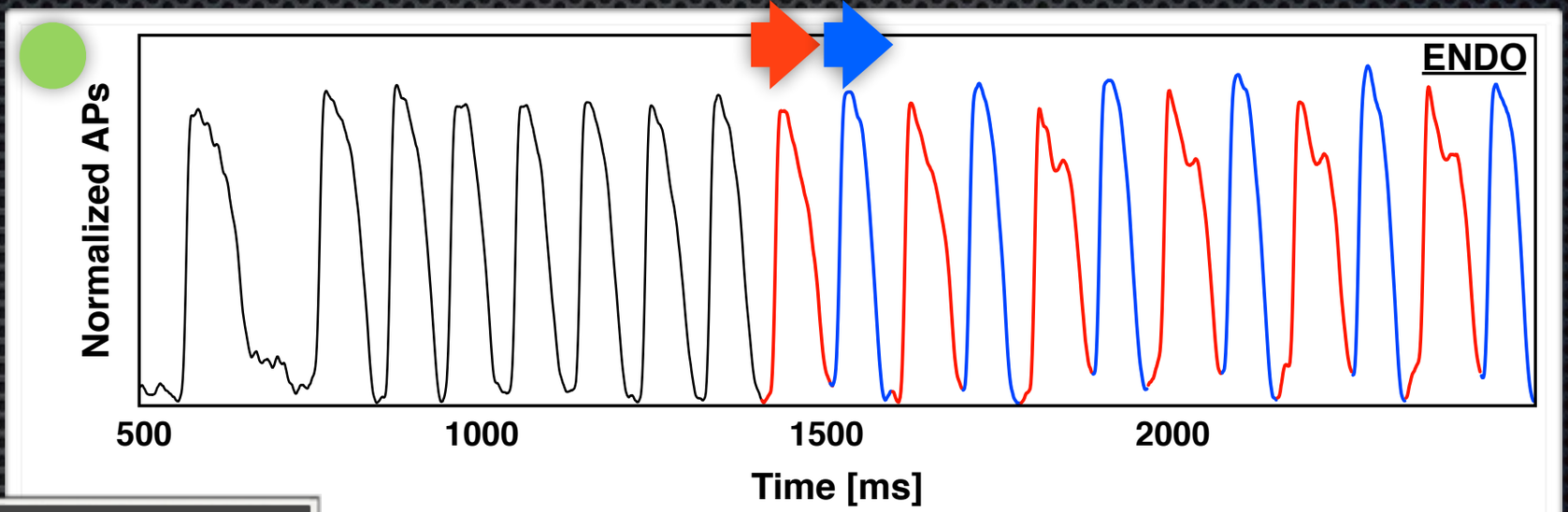


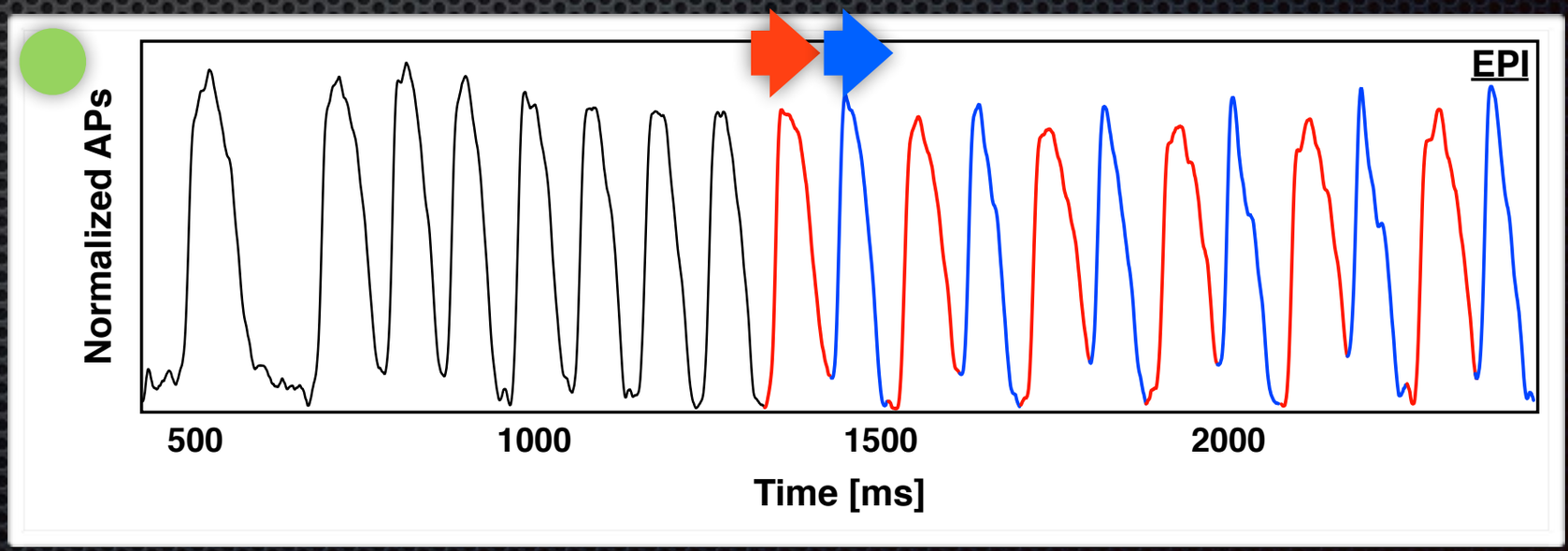


Experimental Data Analysis

- **Development**: constant pacing Cycle Lenght (CL=160ms)

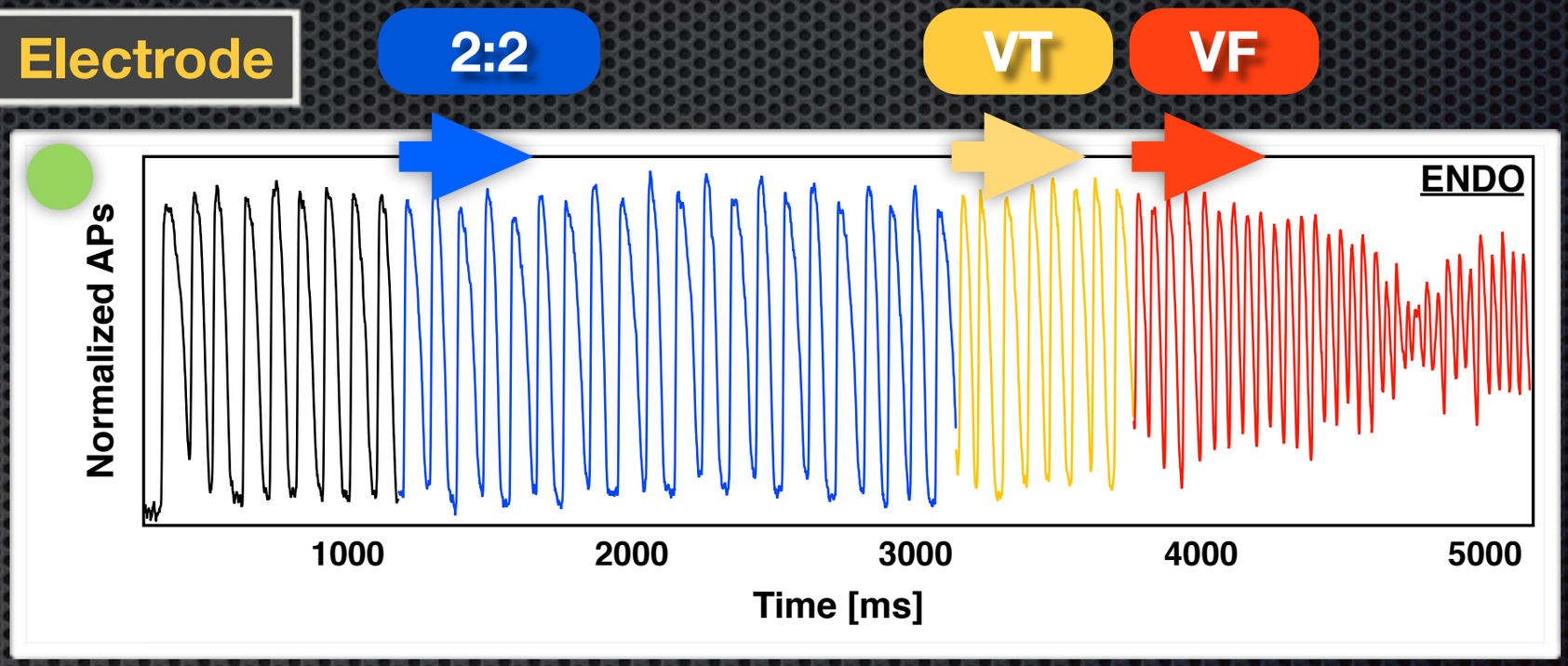
Pacing Electrode

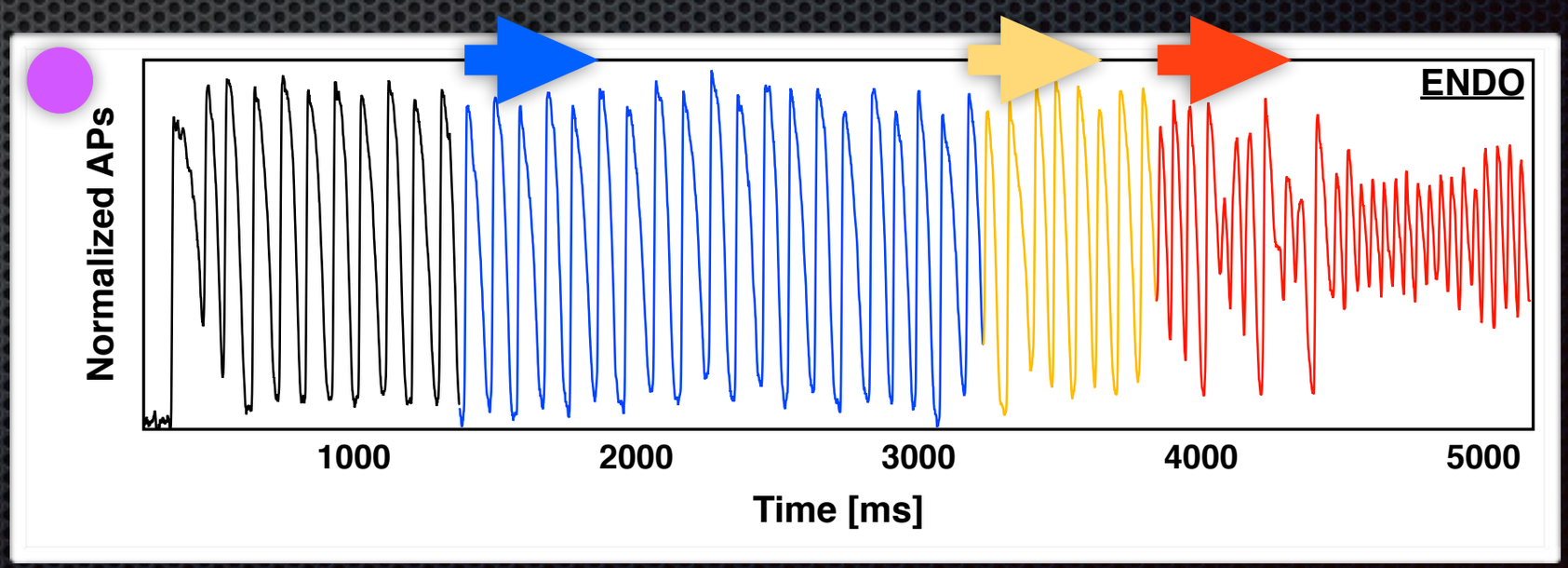




Experimental Data Analysis

- Development into VF with a transition in VT (CL=160ms)





Mathematical Model

Phenomenological Minimal Model for Human Action Potential (Bueno-Orovio et al. 2008)

$$\partial_t u = D\nabla^2 u - (J_{fi} + J_{so} + J_{si}), \quad (1)$$

$$\partial_t v = \phi_v(T)\left[[1 - H(u-\theta_v)]\frac{(v_\infty - v)}{\tau_v^-} - \frac{H(u-\theta_v)v}{\tau_v^+}\right], \quad (2)$$

$$\partial_t w = \phi_w(T)\left[[1 - H(u-\theta_w)]\frac{(w_\infty - w)}{\tau_w^-} - \frac{H(u-\theta_w)w}{\tau_w^+}\right], \quad (3)$$

$$\partial_t s = \phi_s(T)\left[\frac{\{1+\tanh[k_s(u-u_s)]\}/2 - s}{\tau_s}\right], \quad (4)$$

$$J_{fi} = \eta_{fi}(T)\left[-H(u-\theta_v)(u-\theta_v)(u_u - u)\frac{v}{\tau_{fi}}\right], \quad (5)$$

$$J_{so} = \eta_{so}(T)\left[[1 - H(u-\theta_w)]\frac{(u-u_o)}{\tau_o} + \frac{H(u-\theta_w)}{\tau_{so}}\right], \quad (6)$$

$$J_{si} = \eta_{si}(T)\left[-H(u-\theta_w)\frac{ws}{\tau_{si}}\right], \quad (7)$$

$$\tau_v^-(u) = [1 - H(u-\theta_v^-)]\tau_{v1}^- + H(u-\theta_v^-)\tau_{v2}^-, \quad (8)$$

$$\tau_w^+(u) = \tau_{w1}^+ + (\tau_{w2}^+ - \tau_{w1}^+)\frac{\tanh[k_w^+(u-u_w^+)]+1}{2}, \quad (9)$$

$$\tau_w^-(u) = \tau_{w1}^- + (\tau_{w2}^- - \tau_{w1}^-)\frac{\tanh[k_w^-(u-u_w^-)]+1}{2}, \quad (10)$$

$$\tau_{so}(u) = \tau_{so1} + (\tau_{so2} - \tau_{so1})\frac{\tanh[k_{so}(u-u_{so})]+1}{2}, \quad (11)$$

$$\tau_s(u) = [1 - H(u-\theta_w)]\tau_{s1} + H(u-\theta_w)\tau_{s2}, \quad (12)$$

$$\tau_o(u) = [1 - H(u-\theta_o)]\tau_{o1} + H(u-\theta_o)\tau_{o2}. \quad (13)$$

$$v_\infty = \begin{cases} 1, & u < \theta_v^- \\ 0, & u \geqslant \theta_v^- \end{cases} \quad (14)$$

$$w_\infty = [1 - H(u-\theta_o)]\left(1 - \frac{u}{\tau_{w\infty}}\right) + H(u-\theta_o)w_\infty^*, \quad (15)$$

PHYSICAL REVIEW E **87**, 042717 (2013)

Role of temperature on nonlinear cardiac dynamics

Flavio H. Fenton,[1] Alessio Gizzi,[2,3] Christian Cherubini,[2,4] Nicola Pomella,[2,3] and Simonetta Filippi[2,4]

$$\phi(T) = Q_{10}^{(T-T_a)/10},$$

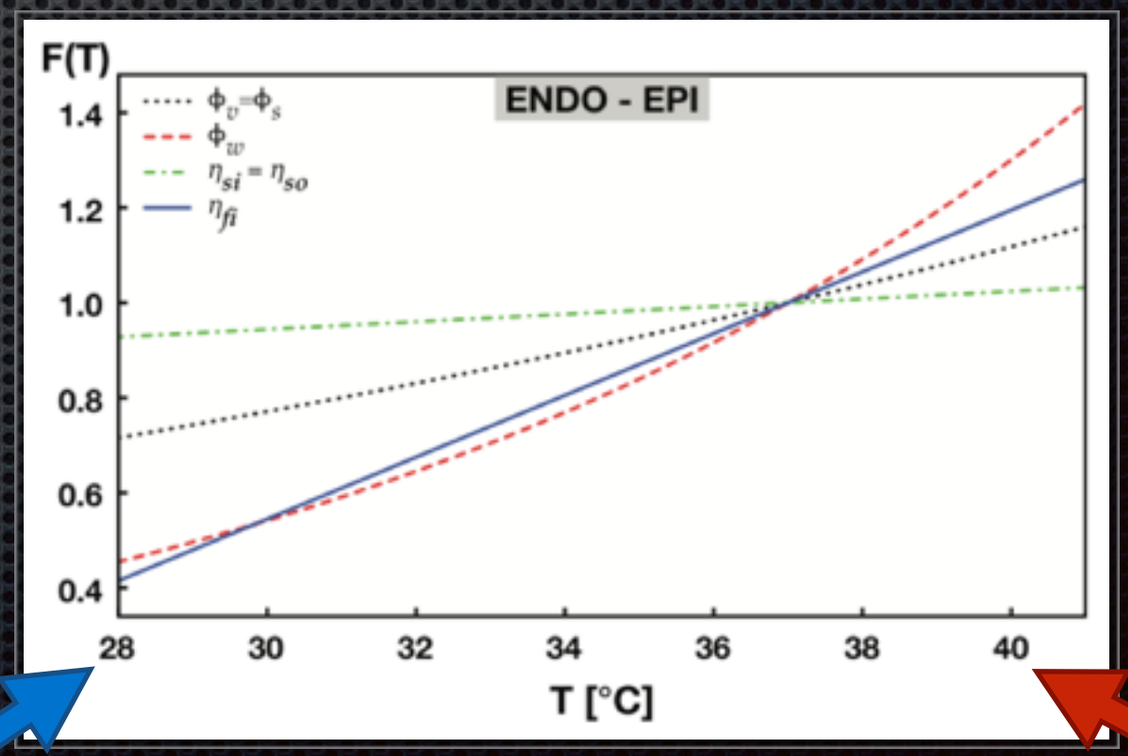
$$\eta(T) = A[1 + B\,(T - T_a)].$$

Arrhenius

Moore

Changes on the Time Constants

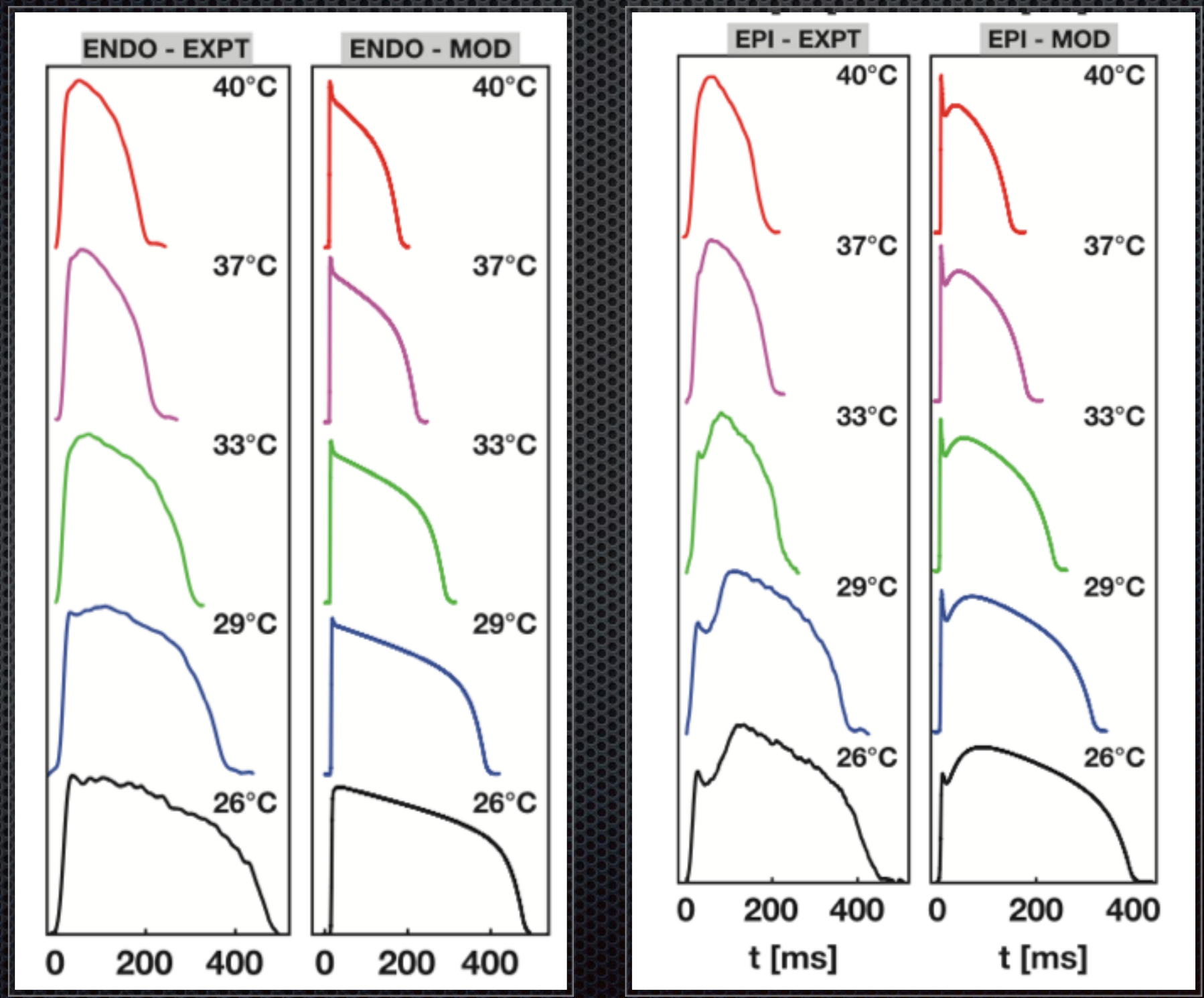
Motivated on Experimental Setup



Model Tuning

Action Potential Shape Fitting

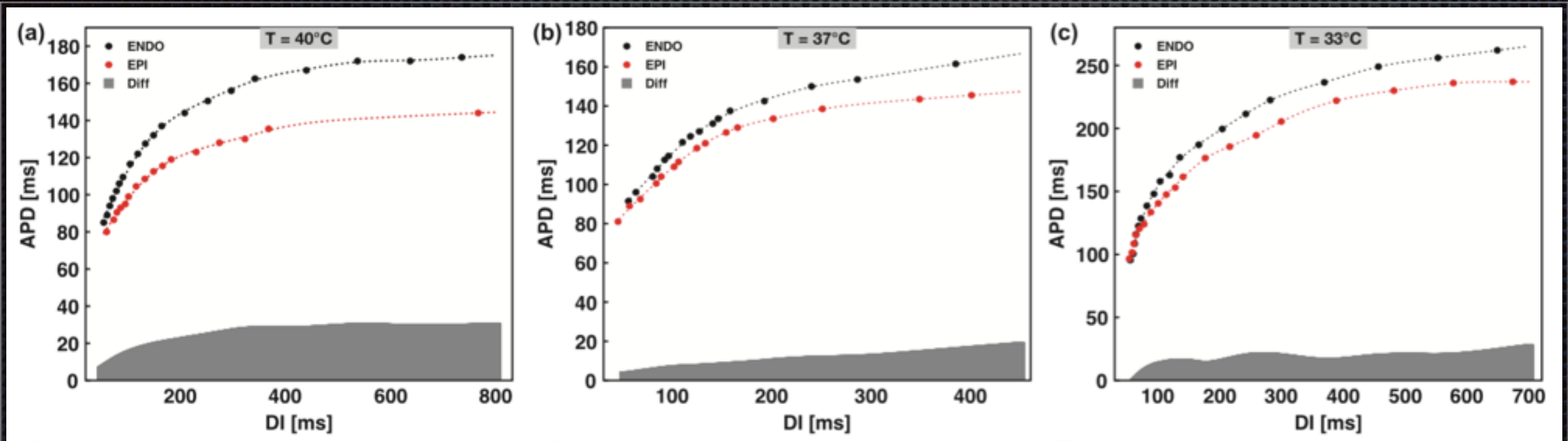
Qualitative Matching

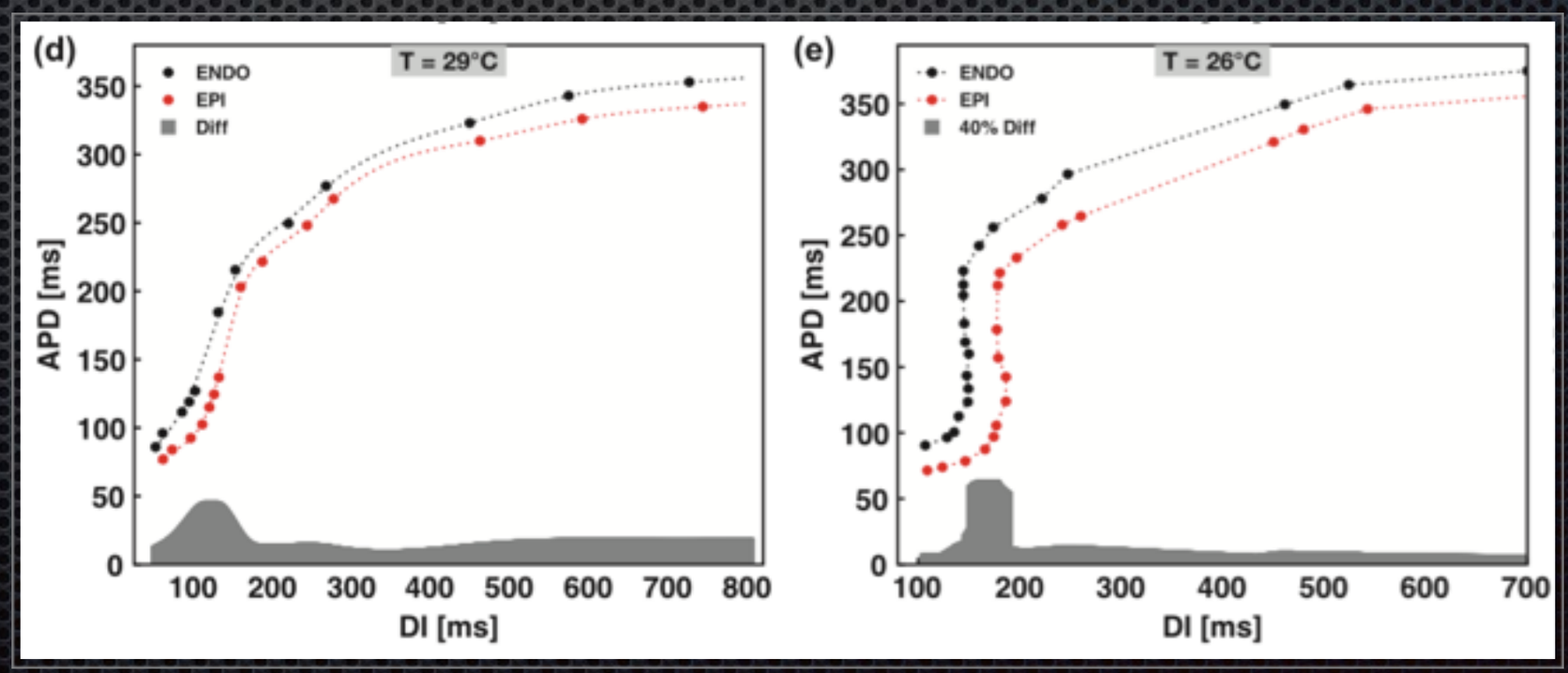


Model Tuning

Restitution Curve Fitting

★ Intramural dispersion

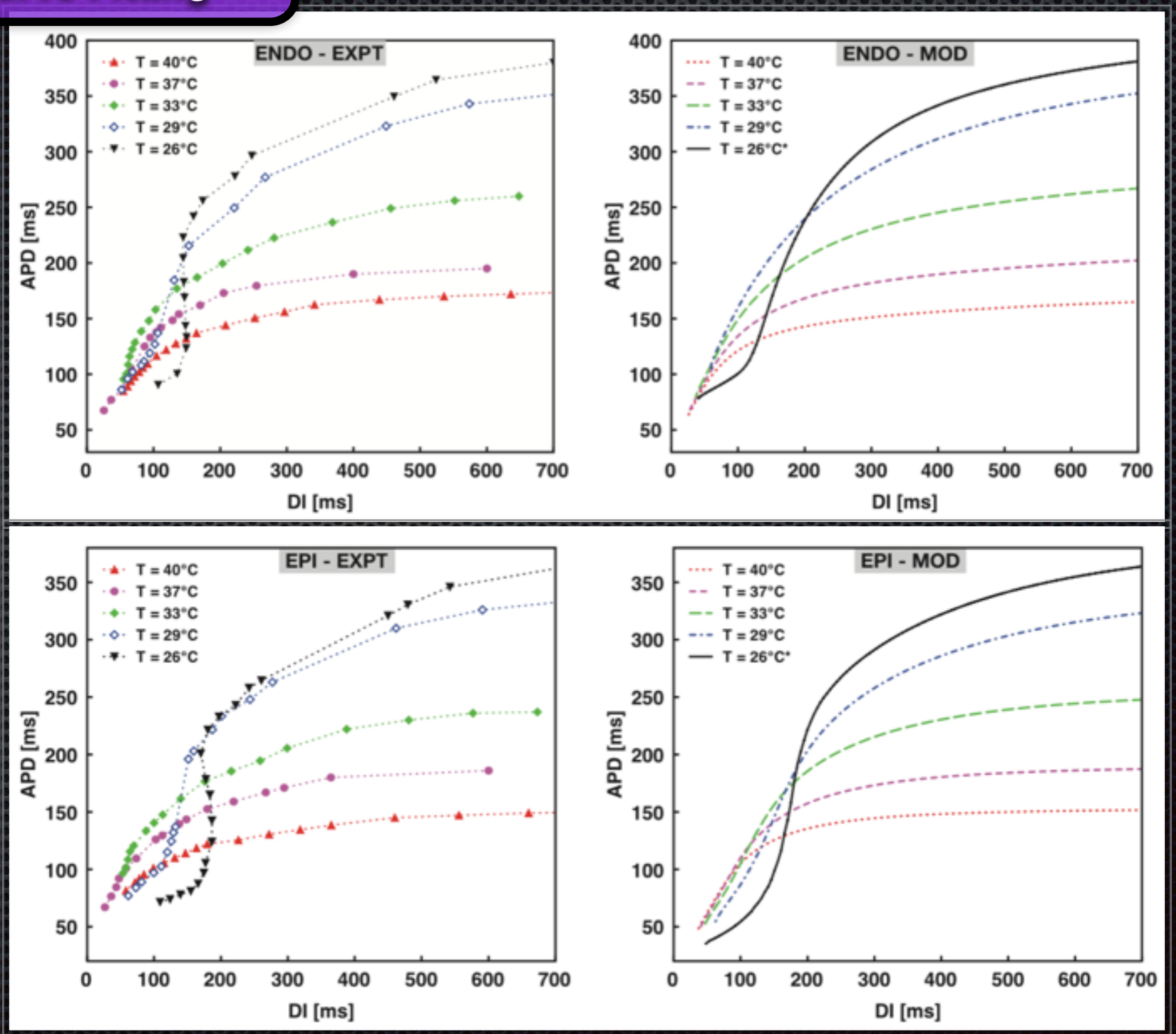




Different time constants

Model Tuning

Restitution Curve Fitting

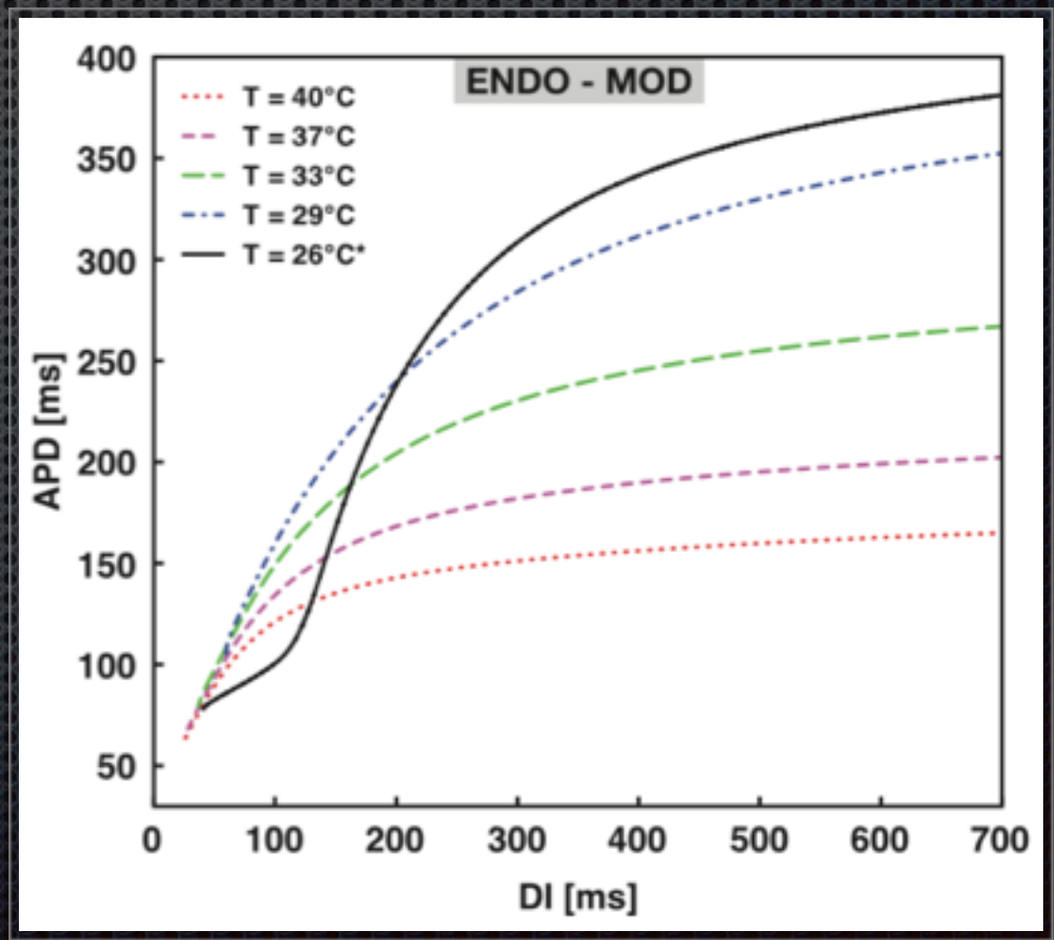


Model Tuning

EPI_{29-40}	$ENDO_{29-40}$	EPI_{26}	$ENDO_{26}$
$u_o = 0$	0	0	0
$u_u = 1.55$	1.56	1.55	1.56
$\theta_v = 0.3$	0.3	0.3	0.3
$\theta_w = 0.13$	0.13	0.13	0.13
$\theta_v^- = 0.006$	0.2	0.006	0.2
$\theta_o = 0.006$	0.006	0.006	0.006
$\tau_v^+ = 1.4506$	1.4506	1.4506	1.4506
$\tau_{v1}^- = 20$	55	10	15
$\tau_{v2}^- = 1150$	40	1150	40
$\tau_{w1}^- = 120$	40	75	40
$\tau_{w2}^- = 300$	115	90	165
$\tau_{w1}^+ = 120$	175	90	175
$\tau_{w2}^+ = 140$	230	140	150
$k_w^- = 65$	20	65	8000
$u_w^- = 0.03$	0.00615	0.02	0.005
$k_w^+ = 5.7$	8	6.5	8
$u_w^+ = 0.15$	0.0005	0.8	0.0005
$\tau_{fi} = 0.11$	0.10	0.11	0.10
$\tau_{o1} = 400$	470	400	470
$\tau_{o2} = 6$	6	6	6
$\tau_{so1} = 30.0181$	40	30.0181	40
$\tau_{so2} = 0.9957$	1.2	0.9957	1.2
$k_{so} = 2.0458$	2	2.0458	2
$u_{so} = 0.65$	0.65	0.65	0.65
$\tau_{s1} = 2.7342$	2.7342	2.7342	2.7342
$\tau_{s2} = 16$	2	16	2
$k_s = 2.0994$	2.0994	2.0994	2.0994
$u_s = 0.9087$	0.9087	0.9087	0.9087
$\tau_{si} = 1.8875$	2.9013	1.8875	2.9013
$\tau_{w\infty} = 0.07$	0.0273	0.07	0.0273
$w_\infty^* = 0.94$	0.78	0.94	0.78
$Q_{10,v} = 1.5$	1.5	0.9	1.5
$Q_{10,w} = 2.45$	2.45	3	2.5
$Q_{10,s} = 1.5$	1.5	1.35	1.5
$A_{fi} = 1$	1	2	1.5
$B_{fi} = 0.065$	0.065	0.065	0.065
$A_{so} = 1$	1	1.4	1
$B_{so} = 0.008$	0.008	0.008	0.008
$A_{si} = 1$	1	1.4	1
$B_{si} = 0.008$	0.008	0.008	0.008

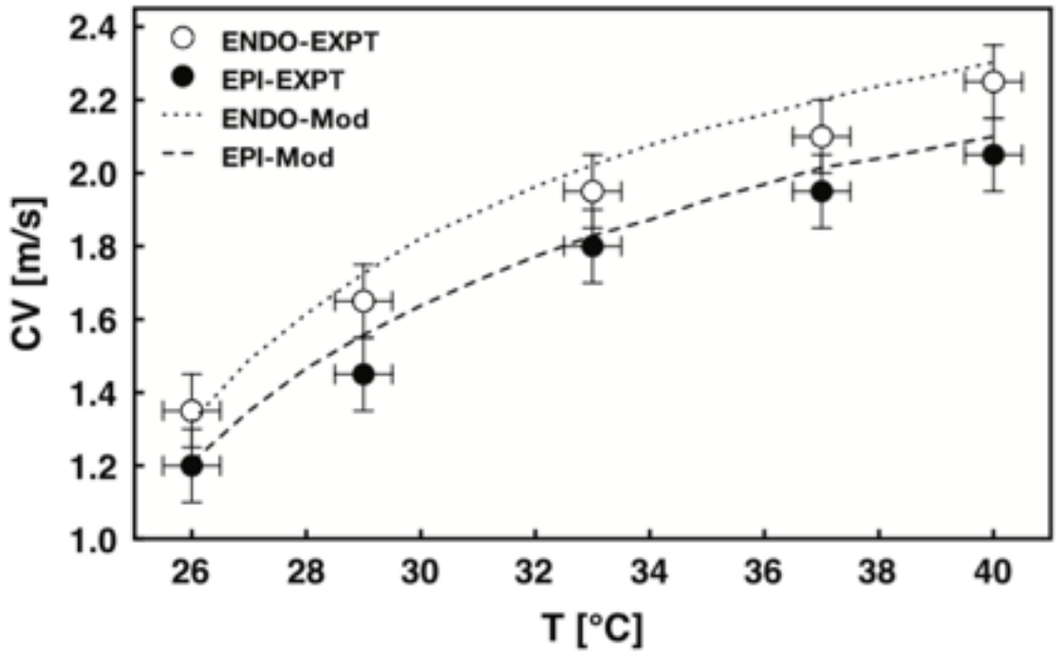
Optimal Set of Parameters

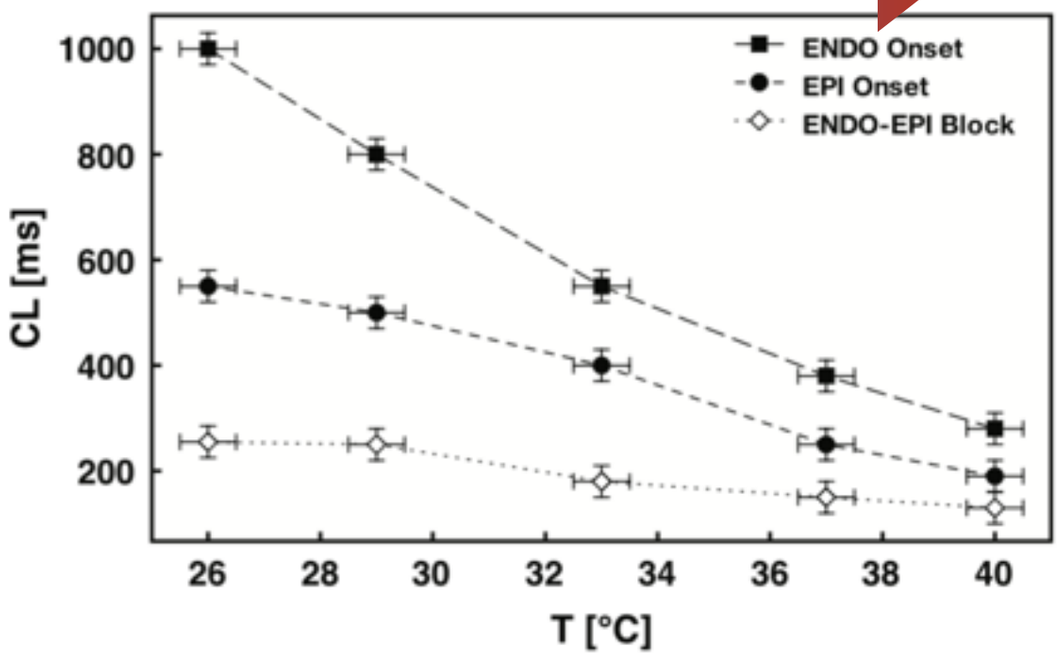
Curve	p	R square
$ENDO_{29}$	2.3730462×10^{-5}	0,9991
$ENDO_{33}$	4.7727621×10^{-4}	0,9987
EPI_{29}	1.1400597×10^{-4}	0,9956
EPI_{33}	4.2275630×10^{-4}	0,9989
EPI_{40}	1.6385054×10^{-4}	0,9988

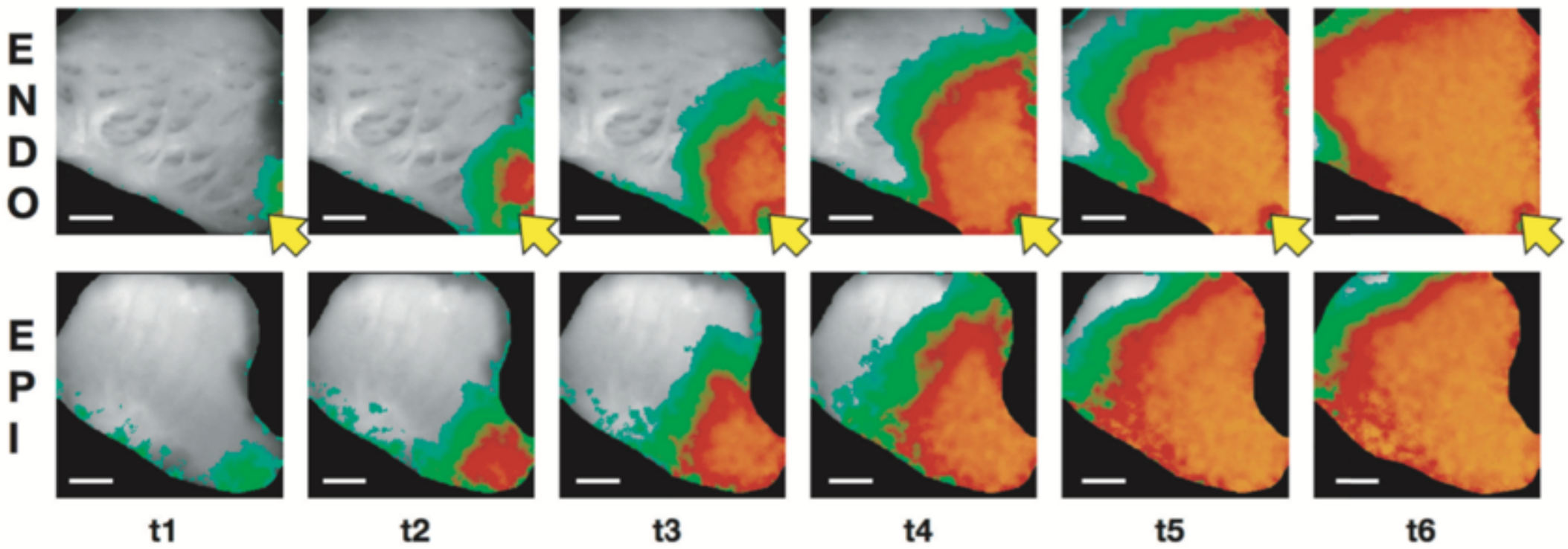


Model Tuning

Spatio-Temporal Features

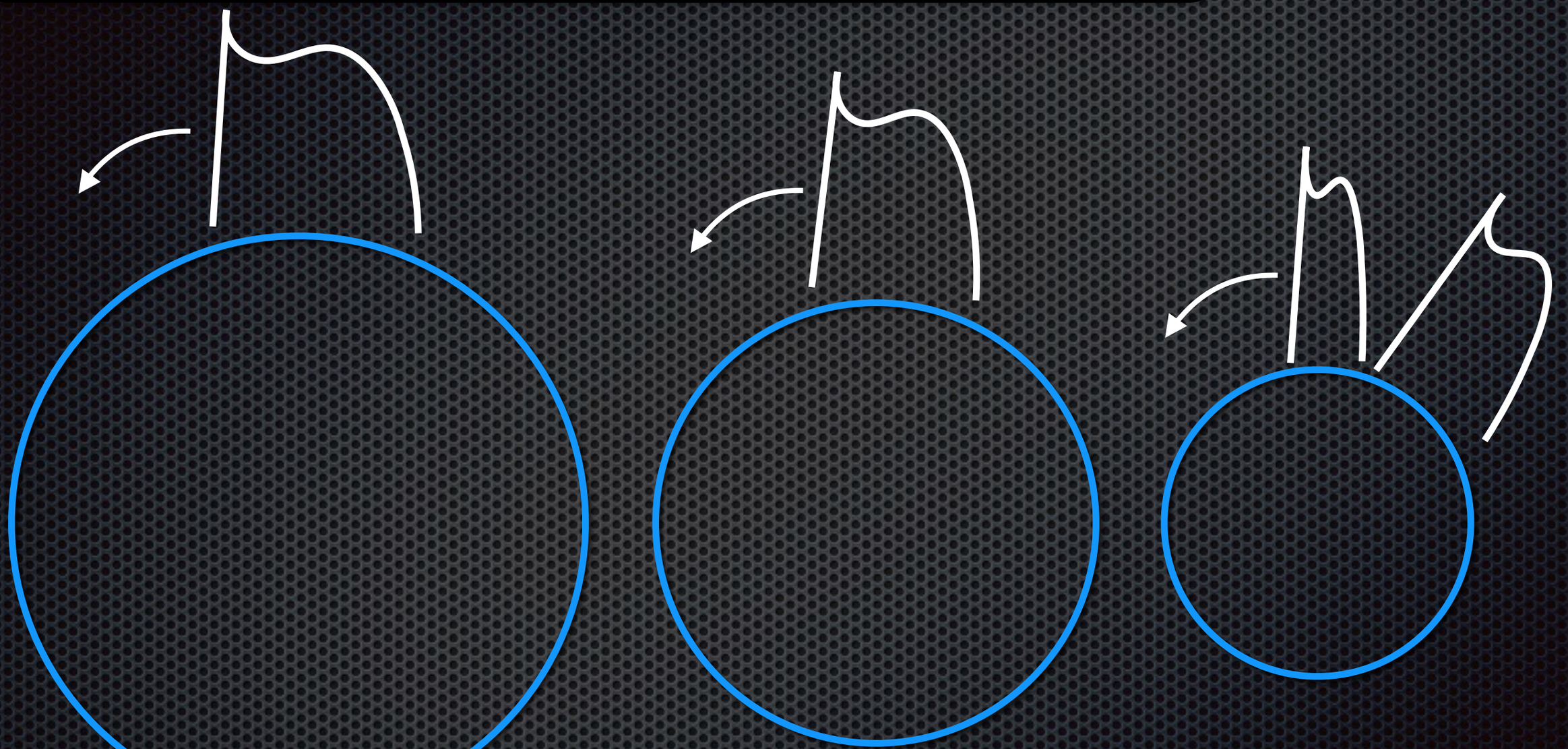






Bifurcation Analysis

Idea: circuit length reduction during single AP propagation

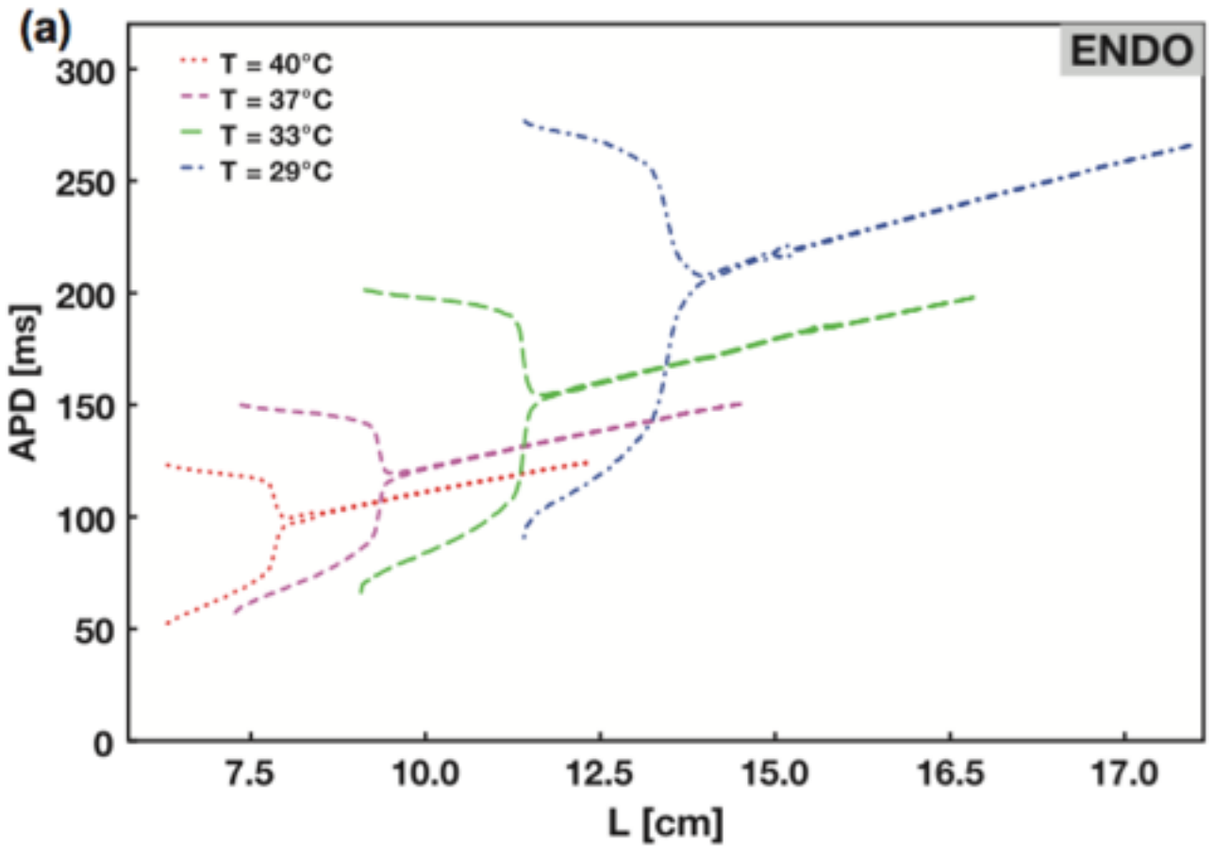


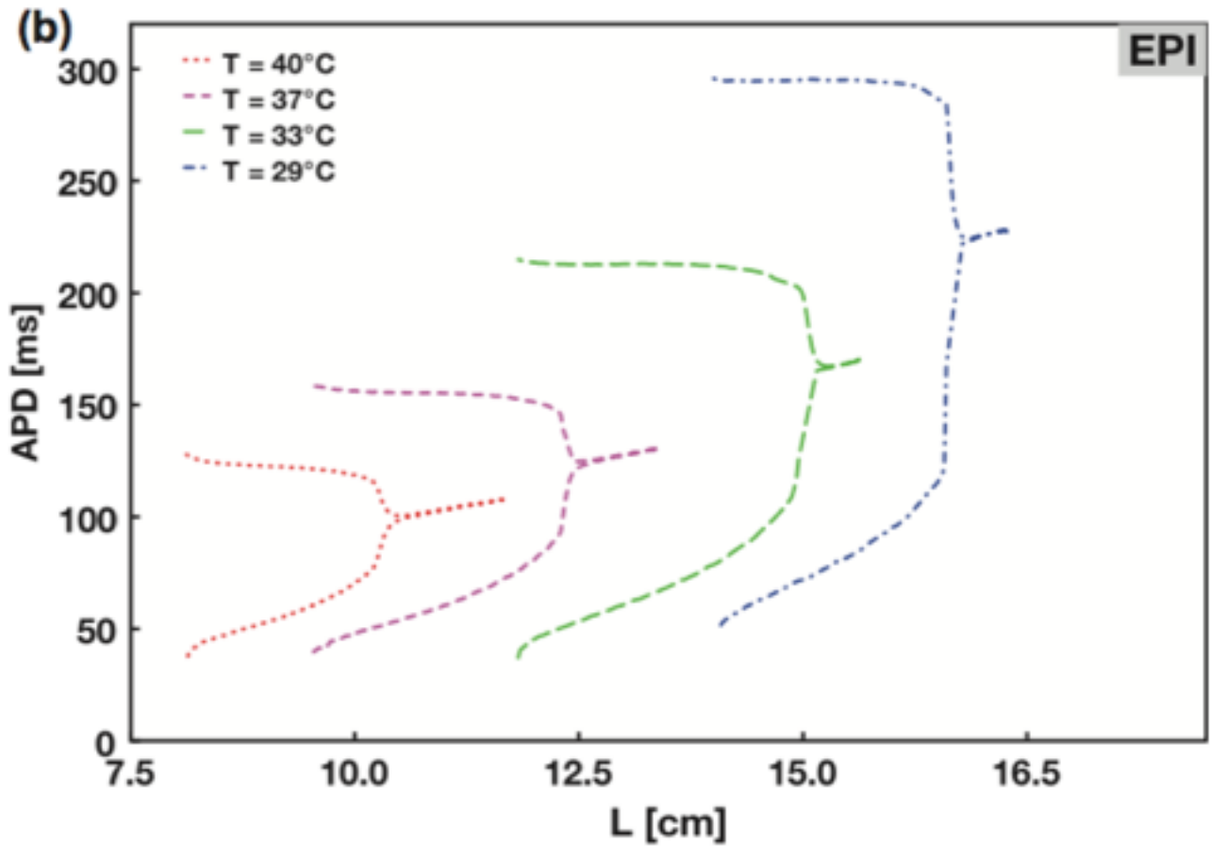
Induction of Alternans

Sun, J., Amellal, F., Glass, L., & Billette, J. (1995). *Journal of theoretical biology*, *173*(1), 79-91.

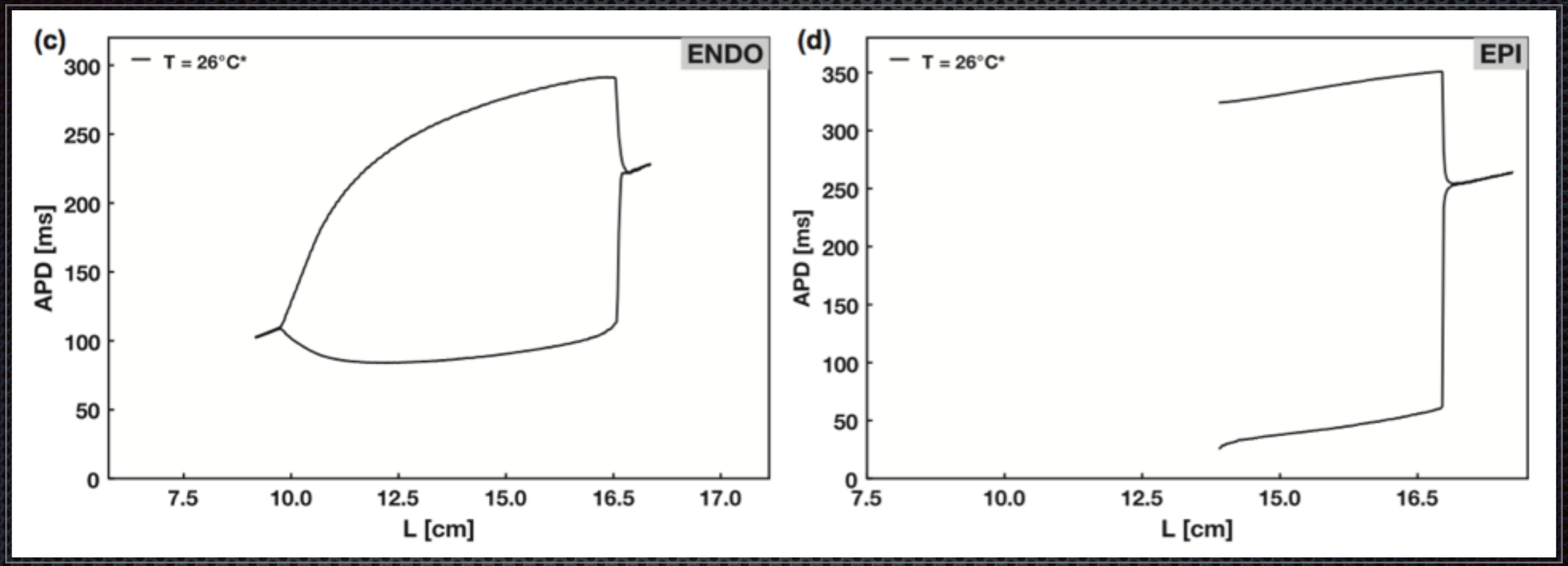
Winfree, Arthur T. *The geometry of biological time*. Vol. 12. Springer Science & Business Media, 2001.

Bifurcation Analysis



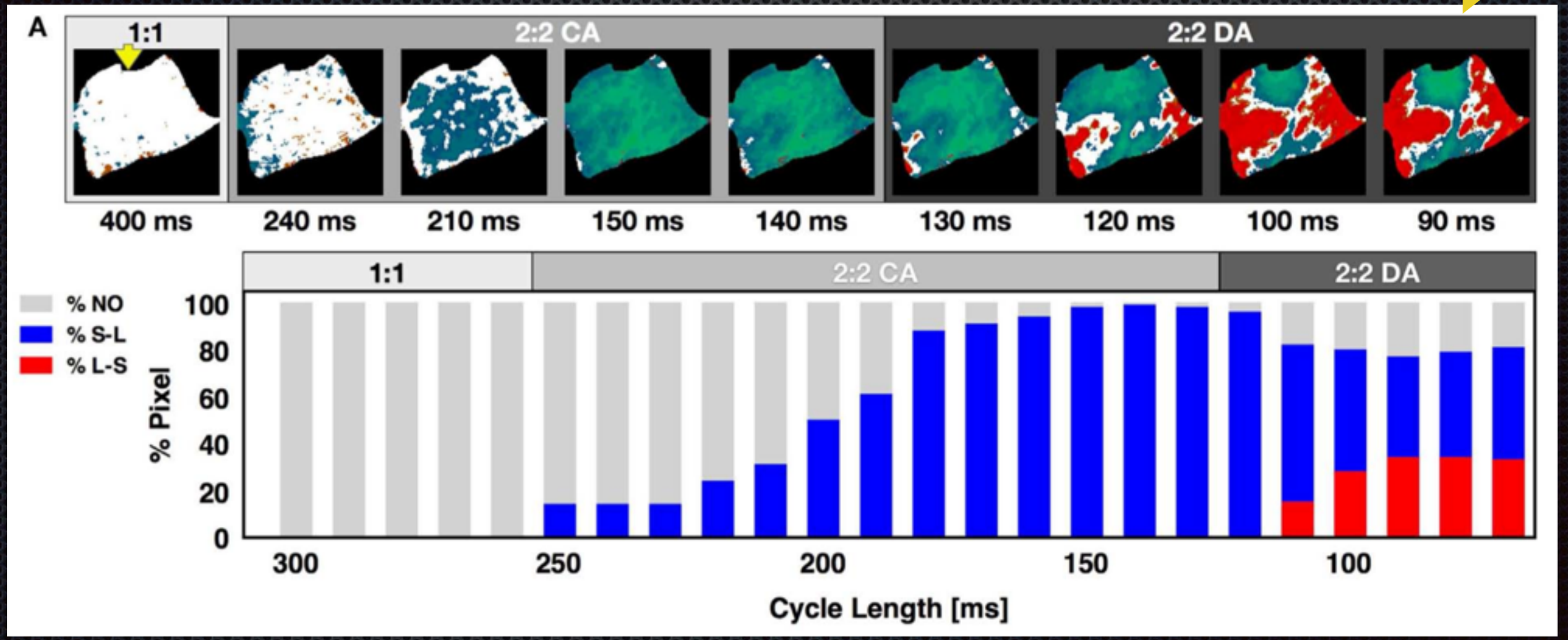


Bifurcation Analysis



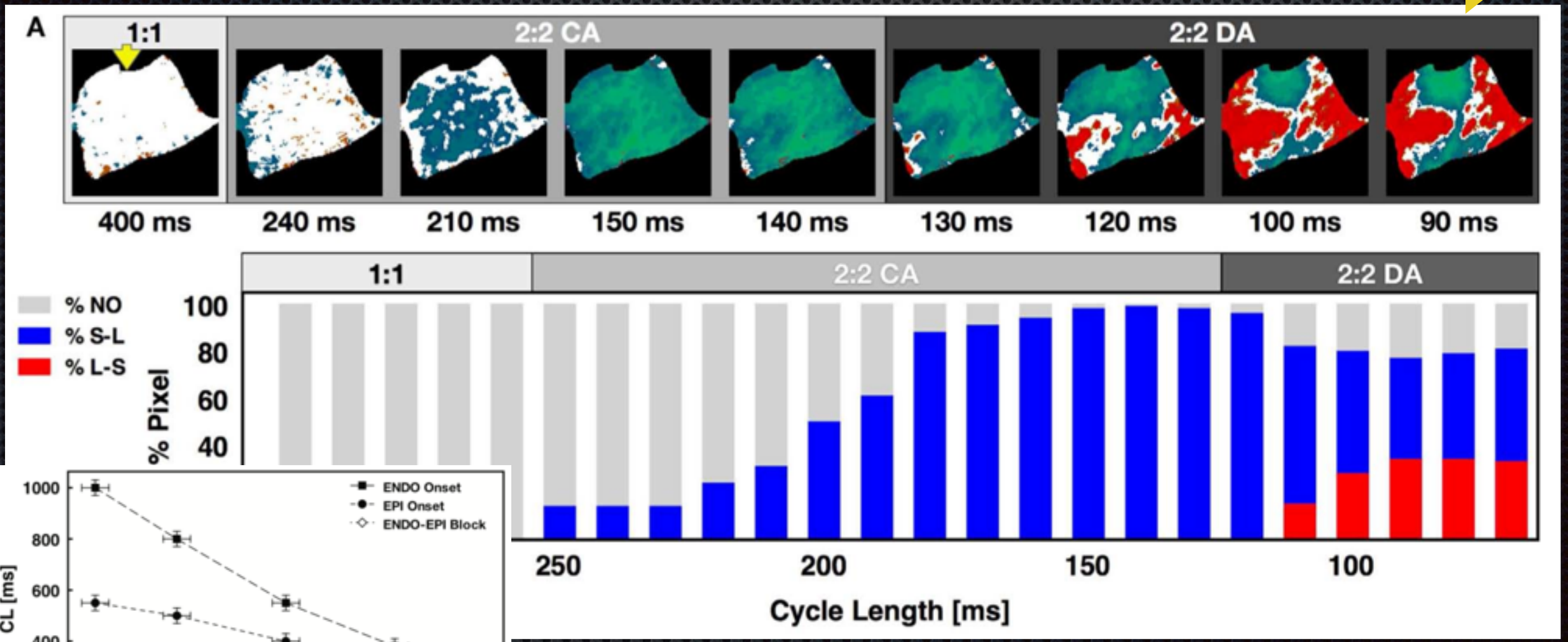
Spatio-Temporal Bifurcation

Alternans Patterns Onset and Development



Spatio-Temporal Bifurcation

Alternans Patterns Onset and Development



Size Effect Analysis

Effect of the domain size on the sustenance of arrhythmias (spirals)

Tissue model	40°C	37°C	34°C	31°C	29°C
EPI 2.5 × 2.5 cm^2	NS	NS	NS	NS	NS
EPI 3.2 × 3.2 cm^2	NS	NS	NS	NS	NS
EPI 6.4 × 6.4 cm^2	S	S	S	NS	NS
EPI 12.8 × 12.8 cm^2	S	S	S	S	S
ENDO EPI 2.5 × 2.5 cm^2	S	NS	NS	NS	NS
ENDO 3.2 × 3.2 cm^2	S	S	NS	NS	NS
ENDO 6.4 × 6.4 cm^2	S	S	S	NS	NS
ENDO 12.8 × 12.8 cm^2	S	S	S	S	S

GPU - WebGL

Europace (2014) 16, 424–434
doi:10.1093/europace/eut031

FOCUSED ISSUE: ORIGINAL RESEARCH

Mechanistic insights into hypothermic ventricular fibrillation: the role of temperature and tissue size

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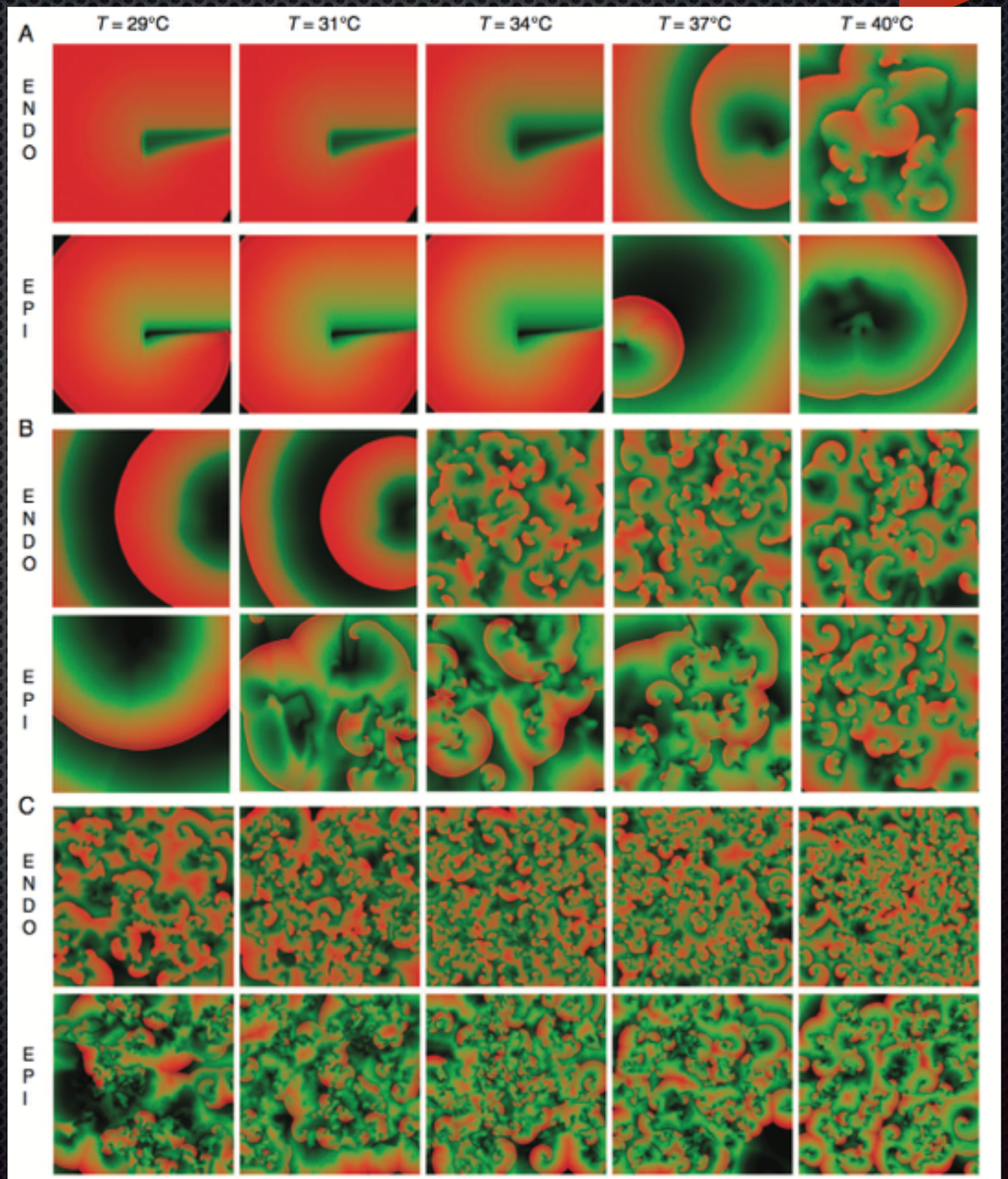
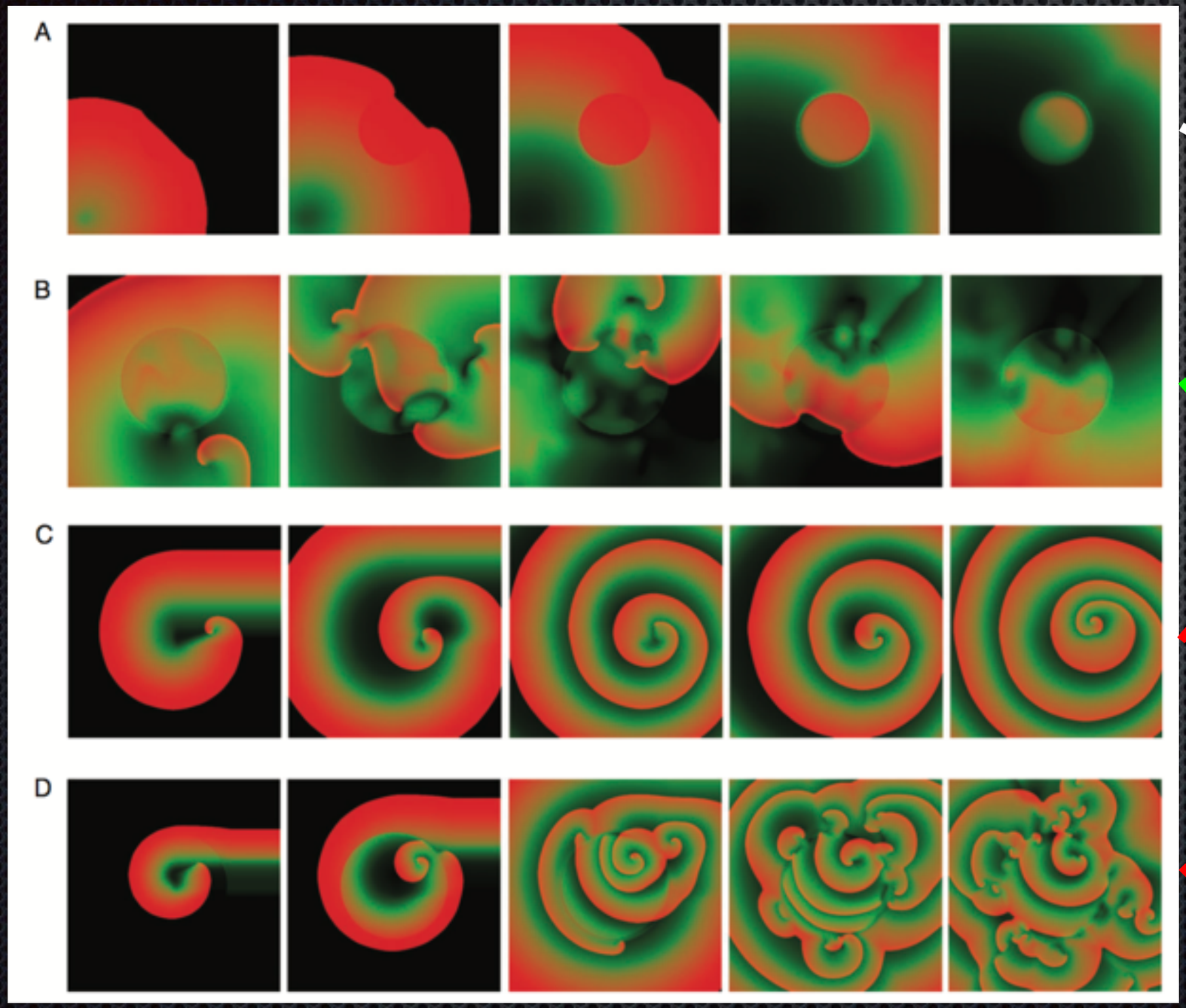


Regional Cooling

time



Tissue 37°C - Disc 29°C
Disc radius: 0.4 cm
Domain: 2.5 cm x 2.5 cm

Tissue 37°C - Disc 29°C
Disc radius: 0.8 cm
Domain: 3.2 cm x 3.2 cm

Tissue 40°C - No Cooling
Domain: 6.4 cm x 6.4 cm

Tissue 40°C - Disc 29°C
Disc radius: 1.6 cm
Domain: 6.4 cm x 6.4 cm

Conclusions

- **Temporal dynamics:** temperature affects significantly action potential shape and restitution curves.
- **Spatio-temporal dynamics:** alternans onset (affected by conduction velocity and pacing frequency) depends on temperature.
- **Tissue and temperature effects:** sustenance of arrhythmias is clearly affected by the mixed effects of tissue size and temperature.
- **Thermal treatment:** localised hypothermic treatment affects fibrillation sustenance…

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Thank You for Your Attention

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