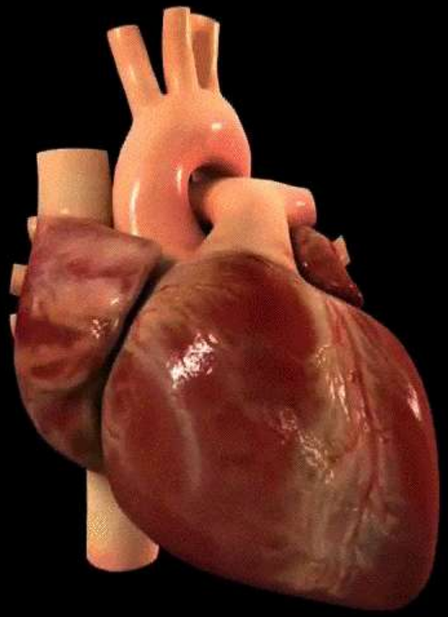
Challenge Problem III: Atrial Fibrillation part I



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NSF 51585
Expeditions
in computing

MCAI 2.0

CMU, Pittsburgh
March 5, 2010

Carnegie Mellon
University of Maryland
Cornell University Founded A.D. 1865
NASA
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NYU New York University
University of Pittsburgh
Lehman College

Outline

- Introduction. The heart (anatomy and function)
- Motivation.
- Description of the problem (atrial arrhythmias)
- Model abstraction and simplified models
- Project overview (link with others)
- Progress to date

The Heart is a…

- Self-assembling,
- Biochemically powered,
- Electrically activated,
- Electrically nonlinear,
- Pressure- and volume-regulated,
- Two-stage,
- Mechanical pump
- With a mean time-to-failure of approximately two to three billion cycles.

The Heart

- The adult human heart is about the size of two clenched fists.
- In an average life time, the heart pumps 1 million barrels of blood.
- In one year, the heart beats about 30 million times.
- The electrical signal produced by the sinus node travels through the entire heart in about ¼ of a second.
- The heart pumps 5 quarts of blood every minute though a network of vessels that, laid end to end, is 60,000 miles long.

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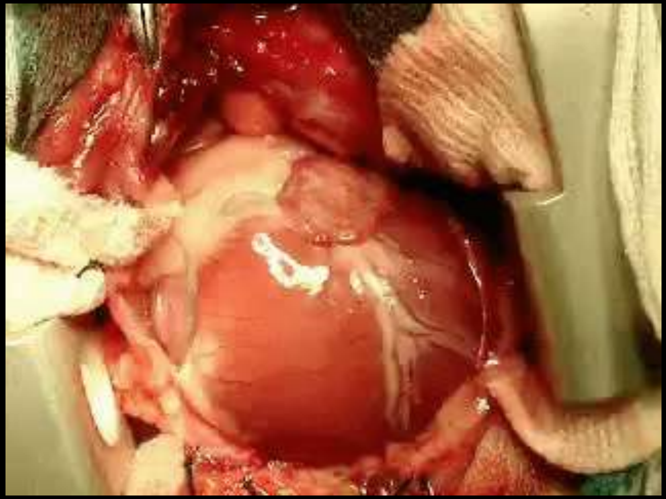

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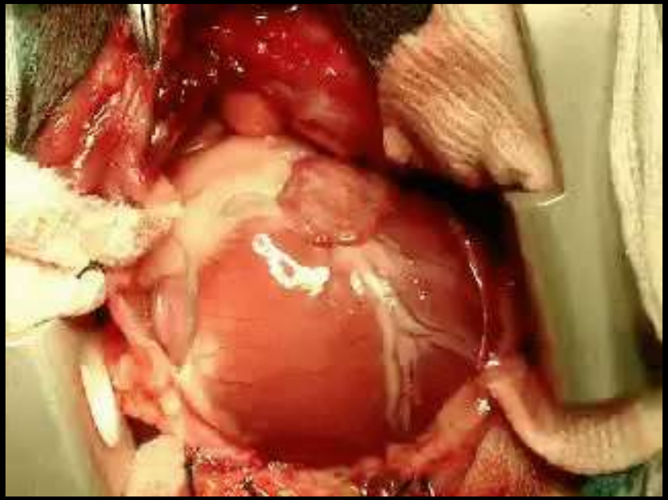

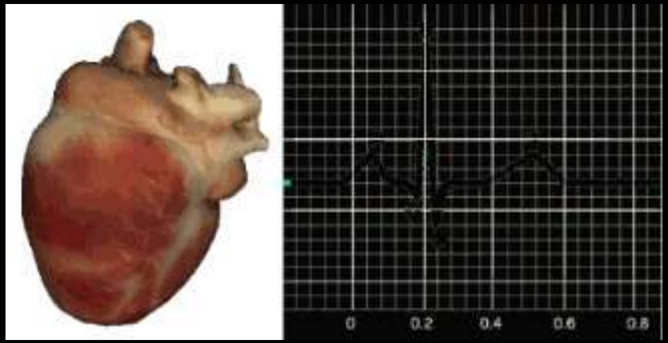

Motivation

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Heart disease is one of the leading causes of death in the world.

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Ranks number one in industrialized countries.

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In the USA alone:

- 1/3 of total deaths are due to heart disease.
- 1 in 5 have some form of heart disease.
- 4.5 million do not die but are hospitalized every year.
- Economic impact: $214 billion a year.

CDC/ Statistics

National Vital Statistics Report, Vol.49, No.11, October 12, 2006

Deaths and percent of total deaths for the 10 leading causes of death: United States

Rank	Cause of death	Total Deaths	Percentage
	All causes	2,391,399	100.0
1	**Diseases of heart**	**725,192**	**30.3**
2	Malignant neoplasms	549,838	23.0
3	Cerebrovascular diseases	167,366	7.0
4	Chronic lower respiratory diseases	124,181	5.2
5	Accidents (unintentional injuries)	97,860	4.1
6	Diabetes mellitus	68,399	2.9
7	Influenza and pneumonia	63,730	2.7
8	Alzheimer's disease	44,536	1.9
9	Nephritis, nephrotic syndrome and nephrosis	35,525	1.5
10	Septicemia	30,680	1.3
	All other causes	484,092	20.2

http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf

Main Types of Heart Disease

- Heart Disease is a broad term that includes:
  - Coronary heart disease (arteries to heart blocked → heart attack).
  - Stroke (arteries to brain blocked or burst).
  - Congestive heart failure (weakened pumping).
  - High blood pressure → all of the above.
  - Arrhythmias (disorders of regular rhythmic beating).

Types of Arrhythmias

- Can occur in upper chambers (atria) or lower chambers (ventricles) or both.
- Heart rate may be increased or decreased.
- May result from pacemaker dysfunction or breakdown of electrical activity (reentry).
- Some are genetic.
- May be asymptomatic or immediately life-threatening.

Atrial fibrillation:

Not immediately life-threatening.
Responsible for 15-20% of all strokes (clotting).

- **Most commonly diagnosed cardiac arrhythmia (~2 million affected)**
- **Risk increases with age: >20% for people over 80 years old**
- **10 million projected to have AF by 2050. Lifetime risks for development of AF would be 1 in 4.**
- **AF is responsible for 15-20% of all strokes**
- **Physician office visits: 2,312,000 (NHLB1 1999)**
- **Hospitalizations: 384,000**

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Mortality Statistics > Atrial fibrillation and flutter (most recent) by country

VIEW DATA: Totals | Per capita   Definition | Source | Printable version

Bar Graph | Pie Chart | Map

Showing latest available data.

Rank	Countries	Amount
# 1	United States:	8,736 deaths
# 2	Germany:	6,194 deaths
# 3	Japan:	4,899 deaths
# 4	Spain:	2,353 deaths
# 5	Sweden:	1,293 deaths
# 6	Netherlands:	1,250 deaths
# 7	Canada:	1,214 deaths
# 8	Poland:	925 deaths
# 9	Brazil:	859 deaths
# 10	Australia:	772 deaths
# 11	Norway:	674 deaths
# 12	Denmark:	529 deaths
# 13	Mexico:	461 deaths
# 14	Austria:	413 deaths
# 15	Argentina:	393 deaths

Internet | Protected Mode: On

What is Atrial Fibrillation?

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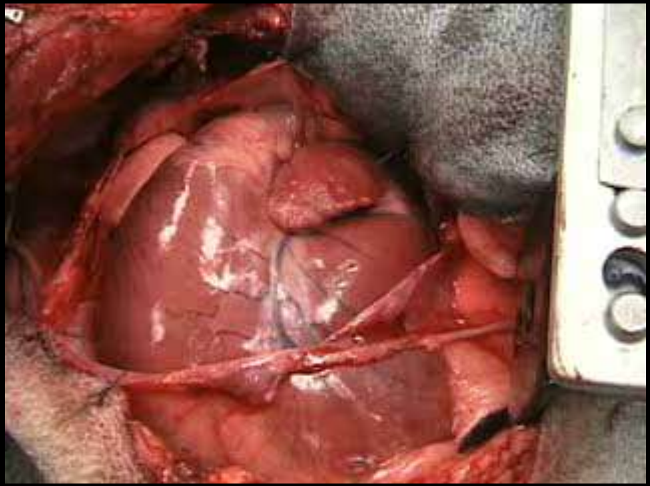

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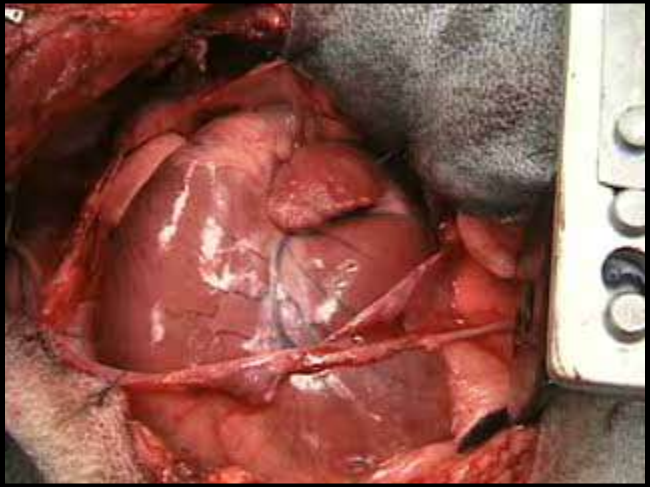

A better understanding of AF → a better treatments and preventions.

Problems studying AF

Problems studying AF

- Complicated structure

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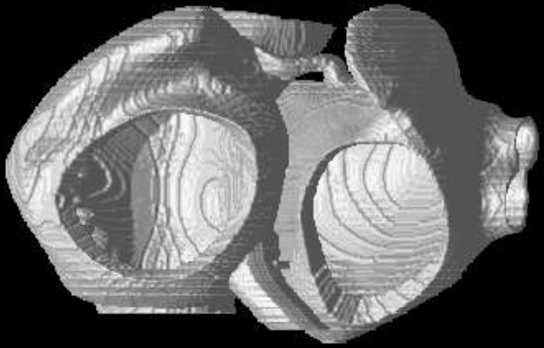


Harrild and Henriquez, 2000
+ coronary sinus

Pulmonary Veins
Superior Vena Cava
Left Atrial Appendage
Left Atrium
Right Atrium
Coronary Sinus
Bachmann's Bundle

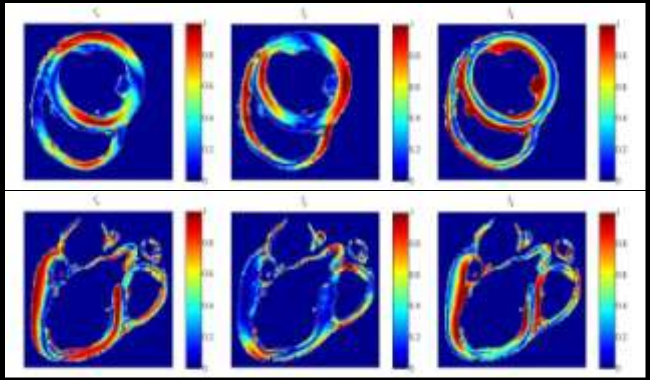
Dimensions:
7.5cm x 7cm x 5.5cm
2.5 million nodes

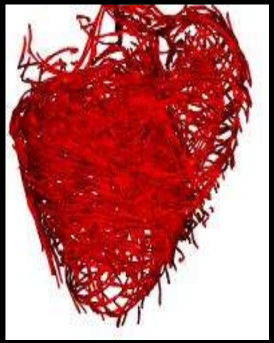
Problems studying AF

- Complicated structure

Canine heart (MRI @120 microns resolution)

Canine heart (DTMRI @ 250 microns resolution)





Pittsburgh NMR Center for Biomedical Research

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- A few complex ionic cell models for atria dynamics. They can be simulated in super computers

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Atrial Tachycardia

Atrial Fibrillation

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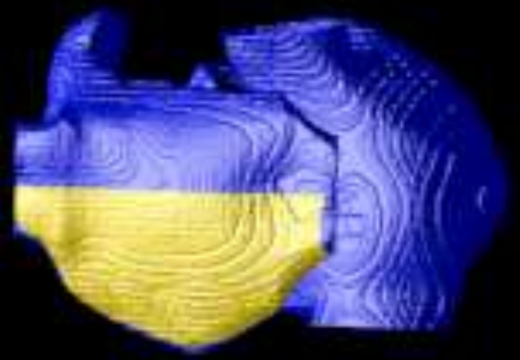
Atrial Tachycardia

Atrial Fibrillation



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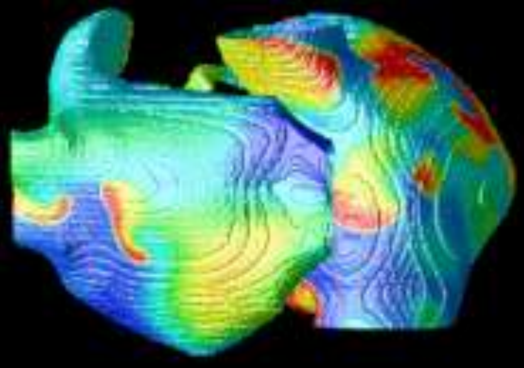
- A few complex ionic cell models for atria dynamics. They can be simulated in super computers

Atrial Tachycardia

Atrial Fibrillation



Problems studying AF

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- A few complex ionic cell models for atria dynamics.

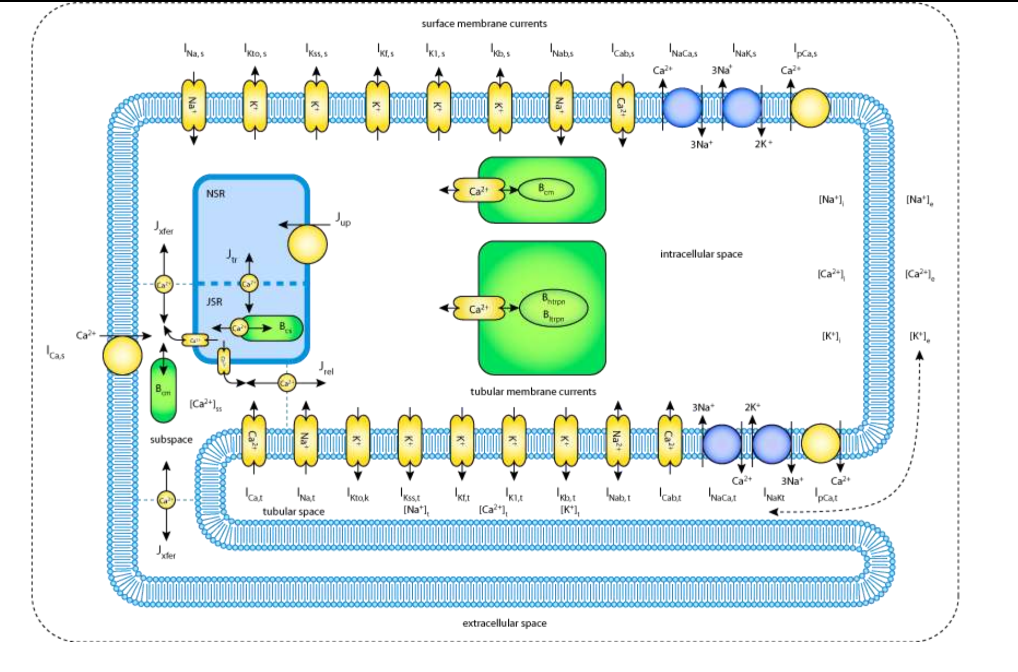
They can be simulated in super computers

Too complex to extract useful information.

TABLE 4 Initial conditions (pacing protocol)

State	Symbol	0.25 Hz
Membrane potential, mV	V	$-9.121\ E^{+01}$
Intracellular sodium, mM	$[Na^+]_i$	$8.006\ E^{+00}$
Intracellular potassium, mM	$[K^+]_i$	$1.274\ E^{+02}$
Intracellular calcium, mM	$[Ca^{2+}]_i$	$4.414\ E^{-05}$
NSR calcium, mM	$[Ca^{2+}]_{NSR}$	$1.741\ E^{-01}$
SS calcium, mM	$[Ca^{2+}]_{SS}$	$4.803\ E^{-05}$
JSR calcium, mM	$[Ca^{2+}]_{JSR}$	$1.741\ E^{-01}$
RyR state C_1	P_{C1}	$9.366\ E^{-01}$
RyR state O_1	P_{O1}	$7.516\ E^{-05}$
RyR state C_2	P_{C2}	$6.337\ E^{-02}$
RyR state O_2	P_{O2}	$1.749\ E^{-11}$
L-type state C_0	C_{0L}	$9.861\ E^{-01}$
L-type state C_1	C_{1L}	$1.251\ E^{-02}$
L-type state C_2	C_{2L}	$5.955\ E^{-05}$
L-type state C_3	C_{3L}	$1.260\ E^{-07}$
L-type state C_4	C_{4L}	$9.990\ E^{-11}$
L-type state O	O_L	$7.493\ E^{-12}$
L-type state C_{ca0}	C_{Ca0L}	$1.210\ E^{-03}$
L-type state C_{ca1}	C_{Ca1L}	$6.140\ E^{-05}$
L-type state C_{ca2}	C_{Ca2L}	$1.169\ E^{-06}$
L-type state C_{ca3}	C_{Ca3L}	$9.889\ E^{-09}$
L-type state C_{ca4}	C_{Ca4L}	$3.137\ E^{-11}$
L-type inactivation variable	y	$9.997\ E^{-01}$
High affinity troponin bound fraction	$HTRPN_{Ca}$	$9.359\ E^{-01}$
Low affinity troponin bound fraction	$LTRPN_{Ca}$	$4.233\ E^{-02}$
$Kv4.3$ state C_1	C_{1Kvf}	$9.527\ E^{-01}$
$Kv4.3$ state C_2	C_{2Kvf}	$2.563\ E^{-02}$
$Kv4.3$ state C_3	C_{3Kvf}	$2.586\ E^{-04}$
$Kv4.3$ state C_4	C_{4Kvf}	$1.159\ E^{-06}$
$Kv4.3$ state O	O_{Kvf}	$1.949\ E^{-09}$
$Kv4.3$ state CI_1	CI_{1Kvf}	$1.514\ E^{-02}$
$Kv4.3$ state CI_2	CI_{2Kvf}	$5.225\ E^{-03}$
$Kv4.3$ state CI_3	CI_{3Kvf}	$9.131\ E^{-04}$
$Kv4.3$ state CI_4	CI_{4Kvf}	$8.401\ E^{-05}$
$Kv4.3$ state I	OI_{1Kvf}	$2.323\ E^{-06}$
$Kv1.4$ state C_1	C_{1Kvs}	$7.630\ E^{-01}$
$Kv1.4$ state C_2	C_{2Kvs}	$2.108\ E^{-01}$
$Kv1.4$ state C_3	C_{3Kvs}	$2.184\ E^{-02}$
$Kv1.4$ state C_4	C_{4Kvs}	$1.006\ E^{-03}$
$Kv1.4$ state O	O_{Kvs}	$1.737\ E^{-05}$
$Kv1.4$ state CI_1	CI_{1Kvs}	$6.505\ E^{-04}$
$Kv1.4$ state CI_2	CI_{2Kvs}	$9.517\ E^{-05}$
$Kv1.4$ state CI_3	CI_{3Kvs}	$3.820\ E^{-04}$
$Kv1.4$ state CI_4	CI_{4Kvs}	$5.143\ E^{-04}$
Kv1.4 state I	OI_{1Kvs}	$1.719\ E^{-03}$
I_{Kr} state C_1	C_{1Kr}	$9.967\ E^{-01}$
I_{Kr} state C_2	C_{2Kr}	$4.163\ E^{-04}$
I_{Kr} state C_3	C_{3Kr}	$7.321\ E^{-05}$
I_{Kr} state O	O_{Kr}	$8.847\ E^{-06}$
I_{Kr} state I	I_{Kr}	$1.387\ E^{-06}$
I_{Ks} state C_0	C_{0Ks}	$9.646\ E^{-01}$
I_{Ks} state C_1	C_{1Ks}	$3.543\ E^{-02}$
I_{Ks} state O_1	O_{1Ks}	$2.294\ E^{-07}$
I_{Ks} state O_2	O_{2Ks}	$4.680\ E^{-11}$
I_{Na} state C_0	C_{0Na}	$1.474\ E^{-01}$
I_{Na} state C_1	C_{1Na}	$4.051\ E^{-02}$
I_{Na} state C_2	C_{2Na}	$4.175\ E^{-03}$
I_{Na} state C_3	C_{3Na}	$1.913\ E^{-04}$
I_{Na} state C_4	C_{4Na}	$3.286\ E^{-06}$
I_{Na} state O_1	O_{1Na}	$1.196\ E^{-08}$
I_{Na} state O_2	O_{2Na}	$2.160\ E^{-09}$
I_{Na} state CI_0	CI_{0Na}	$4.869\ E^{-01}$
I_{Na} state CI_1	CI_{1Na}	$2.625\ E^{-01}$
I_{Na} state CI_2	CI_{2Na}	$5.306\ E^{-02}$
I_{Na} state CI_3	CI_{3Na}	$4.768\ E^{-03}$
I_{Na} state CI_4	CI_{4Na}	$1.606\ E^{-04}$
I_{Na} state I	I_{Na}	$3.097\ E^{-04}$

Iyer et al
Human
cell model
(67 Variables)



For fine tuning of the optimal parameter set, the output of the annealing algorithm is fed into a Neldar-Mead simplex search algorithm (in which only downhill moves are accepted). This approach has been shown to be superior in finding the absolute minimum of functions of several variables (Goffe, 1994).

Model equations and parameters

All rate constants are expressed in units of ms^{-1} unless otherwise noted. Similarly, all concentrations are expressed in mM unless otherwise noted.

Constants

See Tables 1–4.

Membrane currents

See Table 5.

Sodium current I_{Na}

$$I_{Na} = \bar{G}_{Na}(O_{1Na} + O_{2Na})(V - E_{Na}). \quad (1)$$

$$E_{Na} = \frac{RT}{F}\ln\left(\frac{[Na^+]_o}{[Na^+]_i}\right). \quad (2)$$

$$\frac{dC_{0Na}}{dt} = -(4\alpha + c_n)(C_{0Na}) + (\beta)(C_{1Na}) + (c_f)(CI_{0Na}). \quad (3)$$

$$\frac{dC_{1Na}}{dt} = -(\beta + c_n \cdot a + 3\alpha)(C_{1Na}) + (4\alpha)(C_{0Na}) + (2\beta)(C_{2Na}) + (c_f/a)(CI_{1Na}). \quad (4)$$

$$\frac{dC_{2Na}}{dt} = -(2\beta + c_n \cdot a^2 + 2\alpha)(C_{2Na}) + (3\alpha)(C_{1Na}) + (3\beta)(C_{3Na}) + (c_f/a^2)(CI_{2Na}). \quad (5)$$

$$\frac{dC_{3Na}}{dt} = -(3\beta + c_n \cdot a^3 + \alpha)(C_{3Na}) + (2\alpha)(C_{2Na}) + (4\beta)(C_{4Na}) + (c_f/a^3)(CI_{3Na}). \quad (6)$$

$$\frac{dC_{4Na}}{dt} = -(4\beta + c_n \cdot a^4 + \gamma + \eta)(C_{4Na}) + (\alpha)(C_{3Na}) + (\delta)(O_{1Na}) + (\nu)(O_{2Na}) + (c_f/a^4)(CI_{4Na}). \quad (7)$$

$$\frac{dO_{1Na}}{dt} = -(\delta + \varepsilon + o_n)(O_{1Na}) + (\gamma)(C_{4Na}) + (\omega)(O_{2Na}) + (o_f)(I_{Na}). \quad (8)$$

TABLE 1 Physical constants

Constant	Symbol	Value
Faraday's constant	F	96.5°C/mmol
Temperature	T	310 K
Gas constant	R	8.315 J/mol −K
Boltzmann's constant	K	1.381 E^{-23} J/K
Planck's constant	H	6.626 E^{-31} J/ms

TABLE 2 Cell geometry constants

Constant	Symbol	Value
Cell capacitance	A_{cap}	153.4 pF
Myoplasm volume	V_{myo}	25.84 E^{-6} μL
Junctional SR volume	V_{JSR}	0.16 E^{-6} μL
Network SR volume	V_{NSR}	2.1 E^{-6} μL
Subspace volume	V_{ss}	1.2 E^{-9} μL

$$\frac{dO_{2Na}}{dt} = -(\omega + \nu)(O_{2Na}) + (\varepsilon)(O_{1Na}) + (\eta)(C_{4Na}). \quad (9)$$

$$\frac{dCI_{0Na}}{dt} = -(c_f + 4\alpha a)(C_{3Na}) + (\beta/a)(CI_{1Na}) + (c_n)(C_{0Na}). \quad (10)$$

$$\frac{dCI_{1Na}}{dt} = -(\beta/a + 3\alpha a + c_f/a)(CI_{1Na}) + (4\alpha a)(CI_{0Na}) + (2\beta/a)(CI_{2Na}) + (c_n a)(C_{1Na}). \quad (11)$$

$$\frac{dCI_{2Na}}{dt} = -(2\beta/a + 2\alpha a + c_f/a^2)(CI_{2Na}) + (3\alpha a)(CI_{1Na}) + (3\beta/a)(CI_{3Na}) + (c_n a^2)(C_{2Na}). \quad (12)$$

$$\frac{dCI_{3Na}}{dt} = -(3\beta/a + \alpha a + c_f/a^3)(CI_{3Na}) + (2\alpha a)(CI_{2Na}) + (4\beta/a)(CI_{4Na}) + (c_n a^3)(C_{3Na}). \quad (13)$$

$$\frac{dCI_{4Na}}{dt} = -(4\beta/a + \gamma\gamma + c_f/a^4)(CI_{4Na}) + (\alpha a)(CI_{3Na}) + (\delta\delta)(I_{Na}) + (c_n a^4)(C_{4Na}). \quad (14)$$

$$\frac{dI_{Na}}{dt} = -(\delta\delta + o_f)(I_{Na}) + (\gamma\gamma)(CI_{4Na}) + (o_n)(O_{1Na}). \quad (15)$$

See Table 6.

Rapidly-activating delayed rectifier K^+ current I_{Kr}

$$I_{Kr} = \bar{G}_{Kr} f([K^+]_o)(O_{Kr})(V - E_K). \quad (16)$$

$$E_K = \frac{RT}{F}\ln\left(\frac{[K^+]_o}{[K^+]_i}\right). \quad (17)$$

$$f([K^+]_o) = \sqrt{\left(\frac{[K^+]_o}{4}\right)}. \quad (18)$$

$$\frac{dC_{1Kr}}{dt} = -(\alpha_0)(C_{1Kr}) + (\beta_0)(C_{2Kr}). \quad (19)$$

$$\frac{dC_{2Kr}}{dt} = -(\beta_0 + k_f)(C_{2Kr}) + (\alpha_0)(C_{1Kr}) + (k_b)(C_{3Kr}). \quad (20)$$

TABLE 3 Standard ionic concentrations

Permeant ion	Symbol	Value
Sodium	$[Na^+]_o$	138 mM
Potassium	$[K^+]_o$	4 mM
Calcium	$[Ca^{2+}]_o$	2 mM

$$\frac{dO_{Kr}}{dt} = -(\beta_1 + \alpha_i)(O_{Kr}) + (\alpha_1)(C_{3Kr}) + (\beta_i)(I_{Kr}). \quad (21)$$

$$\frac{dO_{Kr}}{dt} = -(\beta_1 + \alpha_i)(O_{Kr}) + (\alpha_1)(C_{3Kr}) + (\beta_i)(I_{Kr}). \quad (22)$$

$$\frac{dI_{Kr}}{dt} = -(\psi + \beta_i)(I_{Kr}) + (\alpha_{i3})(C_{3Kr}) + (\alpha_i)(O_{Kr}). \quad (23)$$

$$\psi = \frac{(\beta_1 \cdot \beta_i \cdot \alpha_{i3})}{(\alpha_1 \cdot \alpha_i)}. \quad (24)$$

See Table 7.

Slowly-activating delayed rectifier K^+ current I_{Ks}

$$I_{Ks} = \bar{G}_{Ks}(O_{1Ks} + O_{2Ks})(V - E_K). \quad (25)$$

$$E_K = \frac{RT}{F}\ln\left(\frac{[K^+]_o}{[K^+]_i}\right). \quad (26)$$

$$\frac{dC_{0Ks}}{dt} = -(\alpha)(C_{0Ks}) + (\beta)(C_{1Ks}). \quad (27)$$

$$\frac{dC_{1Ks}}{dt} = -(\beta + \gamma)(C_{1Ks}) + (\alpha)(C_{0Ks}) + (\delta)(O_{1Ks}). \quad (28)$$

$$\frac{dO_{1Ks}}{dt} = -(\delta + \varepsilon)(O_{1Ks}) + (\gamma)(C_{1Ks}) + (\omega)(O_{2Ks}). \quad (29)$$

$$\frac{dO_{2Ks}}{dt} = -(\omega)(O_{2Ks}) + (\varepsilon)(O_{1Ks}). \quad (30)$$

See Table 8.

Transient outward K^+ current I_{to1}

Fast recovering component, Kv4.3

$$I_{Kv4.3} = \bar{G}_{Kv4.3}(O_{Kvf})(V - E_K). \quad (31)$$

$$E_K = \frac{RT}{F}\ln\left(\frac{[K^+]_o}{[K^+]_i}\right). \quad (32)$$

TABLE 5 Time-dependent current densities

Current	Symbol	Density
Sodium current	G_{Na}	56.32 mS/μF
Delayed rectifier, rapid component	G_{Kr}	0.0186 mS/μF
Delayed rectifier, slow component	G_{Ks}	0.0035 mS/μF
Transient outward current, fast recovery	$G_{Kv4.3}$	0.0775 mS/μF
Transient outward current, slow recovery	$P_{Kv1.4}$	4.161 d^{-8} cm/s

$$\frac{dC_{0Kvf}}{dt} = -(4\alpha_a + \beta_i)(C_{0Kvf}) + (\beta_a)(C_{1Kvf}) + (\alpha_i)(CI_{0Kvf}). \quad (33)$$

$$\frac{dC_{1Kvf}}{dt} = -(\beta_a + 3\alpha_a + f_1\beta_i)(C_{1Kvf}) + (4\alpha_a)(C_{0Kvf}) + (2\beta_a)(C_{2Kvf}) + (\alpha_i/b_1)(CI_{1Kvf}). \quad (34)$$

$$\frac{dC_{2Kvf}}{dt} = -(2\beta_a + 2\alpha_a + f_2\beta_i)(C_{2Kvf}) + (3\alpha_a)(C_{1Kvf}) + (3\beta_a)(C_{3Kvf}) + (\alpha_i/b_2)(CI_{2Kvf}). \quad (35)$$

$$\frac{dC_{3Kvf}}{dt} = -(3\beta_a + \alpha_a + f_3\beta_i)(C_{3Kvf}) + (2\alpha_a)(C_{2Kvf}) + (4\beta_a)(C_{4Kvf}) + (\alpha_i/b_3)(CI_{3Kvf}). \quad (36)$$

$$\frac{dO_{Kvf}}{dt} = -(4\beta_a + f_4\beta_i)(O_{Kvf}) + (\alpha_a)(C_{3Kvf}) + (\alpha_i/b_4)(OI_{Kvf}). \quad (37)$$

$$\frac{dCI_{0Kvf}}{dt} = -(b_1 4\alpha_a + a_i)(CI_{0Kvf}) + (\beta_a/f_1)(CI_{1Kvf}) + (\beta_i)(C_{0Kvf}). \quad (38)$$

TABLE 6 I_{Na} rate constants

	$\lambda = Q\frac{kT}{h}\exp\left(\frac{-\Delta H_\lambda}{RT} + \frac{\Delta S_\lambda}{R} + \frac{z_\lambda FV}{RT}\right)$ parameters		
Rate constant	ΔH, J/mol	ΔS, J/mol −K	z
α	114,007	224.114	0.2864
β	272,470	708.146	−2.2853
γ	196,337	529.952	2.7808
δ	133,690	229.205	−1.5580
O_n	62,123	39.295	0.2888
O_f	97,658	1.510	0.0685
$\gamma\gamma$	−116,431	−578.317	0.7641
$\delta\delta$	55,701	−130.639	−3.6498
ε	85,800	70.078	0
ω	121,955	225.175	0
η	147,814	338.915	2.1360
ν	121,322	193.265	−1.7429
C_n	287,913	786.217	0
C_f	59,565	0.00711	0
Scaling a	1.4004		
Q	1.389		

TABLE 7 I_{Kr} **rate constants**

Rate constant	Value
α_o	$0.0171 \cdot \exp(0.0330\ V)\ ms^{-1}$
β_o	$0.0397 \cdot \exp(-0.0431\ V)\ ms^{-1}$
α_1	$0.0206 \cdot \exp(0.0262\ V)\ ms^{-1}$
β_1	$0.0013 \cdot \exp(-0.0269\ V)\ ms^{-1}$
α_i	$0.1067 \cdot \exp(0.0057\ V)\ ms^{-1}$
β_i	$0.0065 \cdot \exp(-0.0454\ V)\ ms^{-1}$
α_{i3}	$8.04\ E^{-5} \cdot \exp(6.98\ E^{-7}\ V)\ ms^{-1}$
k_f	$0.0261\ ms^{-1}$
k_b	$0.1483\ ms^{-1}$

$$\frac{dCI_{1Kvf}}{dt} = -(\beta_a/f_1 + b_2 3\alpha_a/b_1 + \alpha_i/b_1)(CI_{1Kvf}) + (b_1 4\alpha_a)(CI_{0Kvf}) + (f_1 2\beta_a/f_2)(CI_{2Kvf}) + (f_1\beta_i)(C_{1Kvf}). \quad (39)$$

$$\frac{dCI_{2Kvf}}{dt} = -(f_1 2\beta_a/f_2 + b_3 2\alpha_a/b_2 + \alpha_i/b_2)(CI_{2Kvf}) + (b_2 3\alpha_a/b_1)(CI_{1Kvf}) + (f_2 3\beta_a/f_3)(CI_{3Kvf}) + (f_2\beta_i)(C_{2Kvf}). \quad (40)$$

$$\frac{dCI_{3Kvf}}{dt} = -(f_2 3\beta_a/f_3 + b_4\alpha_a/b_3 + \alpha_i/b_3)(CI_{3Kvf}) + (b_3 2\alpha_a/b_2)(CI_{2Kvf}) + (f_3 4\beta_a/f_4)(OI_{Kvf}) + (f_3\beta_i)(C_{3Kvf}). \quad (41)$$

$$\frac{dOI_{Kvf}}{dt} = -(f_3 4\beta_a/f_4 + \alpha_i/b_4)(OI_{Kvf}) + (b_4\alpha_a/b_3) \times (CI_{3Kvf}) + (f_4\beta_i)(O_{Kvf}). \quad (42)$$

Slowly recovering component, Kv *1.4*

$$I_{Kv1.4} = P_{Kv1.4} O_{Kvs} \frac{4VF^2}{RT} \frac{[K^+]_i \exp\left(\frac{VF}{RT}\right) - [K^+]_o}{\exp\left(\frac{VF}{RT}\right) - 1} + I_{Kv1.4,Na}. \quad (43)$$

$$I_{Kv1.4,Na} = 0.02 \cdot P_{Kv1.4} O_{Kvs} \frac{4VF^2}{RT} \frac{[Na^+]_i \exp\left(\frac{VF}{RT}\right) - [Na^+]_o}{\exp\left(\frac{VF}{RT}\right) - 1}. \quad (44)$$

TABLE 8 I_{Ks} **rate constants**

Rate constant	Value
α	$7.956\ E^{-3}\ ms^{-1}$
β	$2.16\ E^{-1} \cdot \exp(-0.00002\ V)\ ms^{-1}$
γ	$3.97\ E^{-2}\ ms^{-1}$
δ	$7\ E^{-3} \cdot \exp(-0.15\ V)\ ms^{-1}$
ε	$7.67\ E^{-3} \cdot \exp(0.087\ V)\ ms^{-1}$
ω	$3.80\ E^{-3} \cdot \exp(-0.014\ V)\ ms^{-1}$

$$\frac{dC_{0Kvs}}{dt} = -(4\alpha_a + \beta_i)(C_{0Kvs}) + (\beta_a)(C_{1Kvs}) + (\alpha_i)(CI_{0Kvs}). \quad (45)$$

$$\frac{dC_{1Kvs}}{dt} = -(\beta_a + 3\alpha_a + f_1\beta_i)(C_{1Kvs}) + (4\alpha_a)(C_{0Kvs}) + (2\beta_a)(C_{2Kvs}) + (\alpha_i/b_1)(CI_{1Kvs}). \quad (46)$$

$$\frac{dC_{2Kvs}}{dt} = -(2\beta_a + 2\alpha_a + f_2\beta_i)(C_{2Kvs}) + (3\alpha_a)(C_{1Kvs}) + (3\beta_a)(C_{3Kvs}) + (\alpha_i/b_2)(CI_{2Kvs}). \quad (47)$$

$$\frac{dC_{3Kvs}}{dt} = -(3\beta_a + \alpha_a + f_3\beta_i)(C_{3Kvs}) + (2\alpha_a)(C_{2Kvs}) + (4\beta_a)(C_{4Kvs}) + (\alpha_i/b_3)(CI_{3Kvs}). \quad (48)$$

$$\frac{dO_{Kvs}}{dt} = -(4\beta_a + f_4\beta_i)(O_{Kvs}) + (\alpha_a)(C_{3Kvs}) + (\alpha_i/b_4)(OI_{Kvs}). \quad (49)$$

$$\frac{dCI_{0Kvs}}{dt} = -(b_1 4\alpha_a + a_i)(CI_{0Kvs}) + (\beta_a/f_1)(CI_{1Kvs}) + (\beta_i)(C_{0Kvs}). \quad (50)$$

$$\frac{dCI_{1Kvs}}{dt} = -(\beta_a/f_1 + b_2 3\alpha_a/b_1 + \alpha_i/b_1)(CI_{1Kvs}) + (b_1 4\alpha_a)(CI_{0Kvs}) + (f_1 2\beta_a/f_2)(CI_{2Kvs}) + (f_1\beta_i)(C_{1Kvs}). \quad (51)$$

$$\frac{dCI_{2Kvs}}{dt} = -(f_1 2\beta_a/f_2 + b_3 2\alpha_a/b_2 + \alpha_i/b_2)(CI_{2Kvs}) + (b_2 3\alpha_a/b_1)(CI_{1Kvs}) + (f_2 3\beta_a/f_3)(CI_{3Kvs}) + (f_2\beta_i)(C_{2Kvs}). \quad (52)$$

$$\frac{dCI_{3Kvs}}{dt} = -(f_2 3\beta_a/f_3 + b_4\alpha_a/b_3 + \alpha_i/b_3)(CI_{3Kvs}) + (b_3 2\alpha_a/b_2)(CI_{2Kvs}) + (f_3 4\beta_a/f_4)(OI_{Kvs}) + (f_3\beta_i)(C_{3Kvs}). \quad (53)$$

$$\frac{dOI_{Kvs}}{dt} = -(f_3 4\beta_a/f_4 + \alpha_i/b_4)(OI_{Kvs}) + (b_4\alpha_a/b_3)(CI_{3Kvs}) + (f_4\beta_i)(O_{Kvs}). \quad (54)$$

See Table 9.

Time-independent K^+ current I_{K1}

$$I_{K1} = \bar{G}_{K1} K_1^{\infty}(V)\left(\sqrt{[K^+]_o}\right)(V - E_K). \quad (55)$$

TABLE 9 I_{to1} **rate constants**

Rate constant	$Kv4.3$ current, ms^{-1}	$Kv1.4$ current, ms^{-1}
α_a	$0.675,425 \cdot \exp(0.0255\ V)$	$1.840024 \cdot \exp(0.0077\ V)$
β_a	$0.088269 \cdot \exp(-0.0883\ V)$	$0.010817 \cdot \exp(-0.0779\ V)$
α_i	0.109566	0.003058
β_i	$3.03334\ E^{-4}$	$2.4936\ E^{-6}$
f_1	1.66120	0.52465
f_2	22.2463	17.5188
f_3	195.978	938.587
f_4	181.609	54749.1
b_1	0.72246	1.00947
b_2	0.47656	1.17100
b_3	7.77537	0.63902
b_4	318.232	2.12035

$$K_1^{\infty}(V) = \frac{1}{0.94 + \exp\left(\frac{1.26}{RT/F}(V - EK)\right)}. \quad (56)$$

$$E_K = \frac{RT}{F}\ln\left(\frac{[K^+]_o}{[K^+]_i}\right). \quad (57)$$

$$\bar{G}_{K1} = 0.125 \frac{mS}{\mu F \cdot mM^{1/2}}. \quad (58)$$

Sodium handling mechanisms

NCX current I_{NaCa}

$$I_{NaCa} = k_{NaCa} \frac{1}{K_{m,Na}^3 + [Na^+]_o^3} \frac{1}{K_{m,Ca} + [Ca^{2+}]_o} \frac{1}{1 + k_{sat} e^{(\eta-1)\frac{VF}{RT}}} \times \left(e^{\frac{\eta VF}{RT}}[Na^+]_i^3[Ca^{2+}]_o - e^{\frac{(\eta-1)VF}{RT}}[Na^+]_o^3[Ca^{2+}]_i\right). \quad (59)$$

Na^+ background current $I_{Na,b}$

$$I_{Na,b} = \bar{G}_{Na,b}(V - E_{Na}). \quad (60)$$

Na^+-K^+ pump current I_{NaK}

$$I_{NaK} = k_{NaK} f_{NaK} \frac{1}{1 + \left(\frac{K_{m,Nai}}{[Na^+]_i}\right)^{1.5}} \frac{[K^+]_o}{[K^+]_o + K_{m,Ko}}. \quad (61)$$

$$f_{NaK} = \frac{1}{1 + 0.1245 e^{-0.1\frac{VF}{RT}} + 0.0365 \sigma e^{-1.33\frac{VF}{RT}}}. \quad (62)$$

$$\sigma = \frac{1}{7}\left(e^{\frac{[Na^+]_o}{67.3}} - 1\right). \quad (63)$$

See Table 10.

TABLE 10 Sodium handling parameters

Parameter	Value
$G_{Na,b}$	0.001 mS/μF
$K_{m,Na}$	87.5 mM
$K_{m,Ca}$	1.38 mM
k_{sat}	0.2
η	0.35
k_{NaK}	2.387 μA/μF
$K_{m,Nai}$	20 mM
$K_{m,Ko}$	1.5 mM

Calcium handling mechanisms

Sarcolemmal Ca^{2+} pump current $I_{p(Ca)}$

$$I_{p(Ca)} = \bar{I}_{p(Ca)} \frac{[Ca^{2+}]_i}{K_{m,p(Ca)} + [Ca^{2+}]_i}. \quad (64)$$

Ca^{2+} background current $I_{Ca,b}$

$$I_{Ca,b} = \bar{G}_{Ca,b}(V - E_{Ca}). \quad (65)$$

$$E_{Ca} = \frac{RT}{2F}\ln\left(\frac{[Ca^{2+}]_o}{[Ca^{2+}]_i}\right). \quad (66)$$

See Table 11.

L-type Ca^{2+} current I_{Ca}

$$\alpha = 1.997 e^{0.012(V-35)}. \quad (67)$$

$$\beta = 0.0882 e^{-0.065(V-22)}. \quad (68)$$

$$\alpha' = \alpha a. \quad (69)$$

$$\beta' = \frac{\beta}{b}. \quad (70)$$

$$\gamma = 0.0554[Ca^{2+}]_{ss}. \quad (71)$$

$$\frac{dC_{0L}}{dt} = -(4\alpha + \gamma)C_{0L} + \beta C_{1L} + \omega C_{Ca0L}. \quad (72)$$

$$\frac{dC_{1L}}{dt} = -(3\alpha + \beta + \gamma a)C_{1L} + 4\alpha C_{0L} + 2\beta C_{2L} + \frac{\omega}{b} C_{Ca1L}. \quad (73)$$

$$\frac{dC_{2L}}{dt} = -(2\alpha + 2\beta + \gamma a^2)C_{2L} + 3\alpha C_{1L} + 3\beta C_{3L} + \frac{\omega}{b^2} C_{Ca2L}. \quad (74)$$

$$\frac{dC_{3L}}{dt} = -(\alpha + 3\beta + \gamma a^3)C_{3L} + 2\alpha C_{2L} + 4\beta C_{4L} + \frac{\omega}{b^3} C_{Ca3L}. \quad (75)$$

$$\frac{dC_{4L}}{dt} = -(f + 4\beta + \gamma a^4)C_{4L} + \alpha C_{3L} + g O_L + \frac{\omega}{b^4} C_{Ca4L}. \quad (76)$$

TABLE 11 Membrane calcium exchangers, background current

Parameter	Value
$\bar{I}_{p(Ca)}$	0.05 pA/pF
$K_{m,p(Ca)}$	0.0005 mM
$\bar{G}_{Ca,b}$	7.684 d^{-5} ms/μF

$$\frac{dO_L}{dt} = -gO_L + fC_{4L}. \tag{77}$$

$$\frac{dC_{Ca0L}}{dt} = -(4\alpha' + \omega)C_{Ca0L} + \beta' C_{Ca1L} + \gamma C_{0L}. \tag{78}$$

$$\frac{dC_{Ca1L}}{dt} = -\left(3\alpha' + \beta' + \frac{\omega}{b}\right)C_{Ca1L} + 4\alpha' C_{Ca0L} + 2\beta' C_{Ca2L} + \gamma a C_{1L}. \tag{79}$$

$$\frac{dC_{Ca2L}}{dt} = -\left(2\alpha' + 2\beta' + \frac{\omega}{b^2}\right)C_{Ca2L} + 3\alpha' C_{Ca1L} + 3\beta' C_{Ca3L} + \gamma a^2 C_{2L}. \tag{80}$$

$$\frac{dC_{Ca3L}}{dt} = -\left(\alpha' + 3\beta' + \frac{\omega}{b^3}\right)C_{Ca3L} + 2\alpha' C_{Ca2L} + 4\beta' C_{Ca4L} + \gamma a^3 C_{3L}. \tag{81}$$

$$\frac{dC_{Ca4L}}{dt} = -\left(4\beta' + \frac{\omega}{b^4}\right)C_{Ca4L} + \alpha' C_{Ca3L} + \gamma a^4 C_{4L}. \tag{82}$$

$$\frac{dy_{Ca}}{dt} = \frac{y_\infty - y}{\tau_y}. \tag{83}$$

$$y_\infty = \frac{0.82}{1 + e^{\frac{V+28.5}{7.8}}} + 0.18. \tag{84}$$

$$\tau_y = \frac{1}{\frac{0.00653}{0.5 + e^{-V/7.1}} + 0.00512 e^{-V/39.8}} \tag{85}$$

$$\bar{I}_{Ca} = \frac{\bar{P}_{Ca}}{C_{sc}} \frac{4VF^2}{RT} \frac{0.001 e^{2VF/RT} - 0.341[Ca^{2+}]_o}{e^{2VF/RT} - 1}. \tag{86}$$

$$I_{Ca} = \bar{I}_{Ca} y O_L \tag{87}$$

$$I_{Ca,K} = \frac{P'_K}{C_{SC}} y O_L \left(\frac{VF^2}{RT} \frac{[K^+]_i e^{\frac{VF}{RT}} - [K^+]_o}{e^{\frac{VF}{RT}} - 1}\right). \tag{88}$$

$$P'_K = \frac{\bar{P}_K}{1 + \frac{\bar{I}_{Ca}}{I_{Ca,half}}} \tag{89}$$

See Table 12.

RyR channel

$$\frac{dP_{C1}}{dt} = -k_a^+ [Ca^{2+}]_{ss}^n P_{C1} + k_a^- P_{O1}. \tag{90}$$

TABLE 12 I_{Ca} parameters

Parameter	Value
f	0.3 ms^{-1}
g	4 ms^{-1}
a	2
b	2
ω	2.5 d^{-3} ms^{-1} mm^{-1}
P_{Ca}	1.7283 d^{-3} cm/s
P_K	3.2018 d^{-6} cm/s
$I_{Ca,half}$	−0.265 pA/pF

$$\frac{dP_{O1}}{dt} = k_a^+ [Ca^{2+}]_{ss}^n P_{C1} - k_a^- P_{O1} - k_b^+ [Ca^{2+}]_{ss}^m P_{O1} + k_b^- P_{O2} - k_c^+ P_{O1} + k_c^- P_{C2}. \tag{91}$$

$$\frac{dP_{O2}}{dt} = k_b^+ [Ca^{2+}]_{ss}^m P_{O1} - k_b^- P_{O2}. \tag{92}$$

$$\frac{dP_{C2}}{dt} = k_c^+ P_{O1} - k_c^- P_{C2}. \tag{93}$$

$$J_{rel} = v_1 (P_{O1} + P_{O2})([Ca^{2+}]_{JSR} - [Ca^{2+}]_{SS}). \tag{94}$$

SERCA2a pump

$$f_b = \left(\frac{[Ca^{2+}]_i}{K_{fb}}\right)^{N_{fb}}. \tag{95}$$

$$r_b = \left(\frac{[Ca^{2+}]_{NSR}}{K_{rb}}\right)^{N_{rb}}. \tag{96}$$

$$J_{up} = K_{SR}\left(\frac{v_{maxf} f_b - v_{maxr} r_b}{1 + f_b + r_b}\right). \tag{97}$$

See Table 13.

Intracellular Ca^{2+} fluxes

$$J_{tr} = \frac{[Ca^{2+}]_{NSR} - [Ca^{2+}]_{JSR}}{\tau_{tr}}. \tag{98}$$

TABLE 13 *SR* parameters

Parameter	Value
K_a^+	0.01215 μM^{-4} ms^{-1}
K_a^-	0.576 ms^{-1}
K_b^+	0.00405 μM^{-3} ms^{-1}
K_b^-	1.93 ms^{-1}
K_c^+	0.3 ms^{-1}
K_c^-	0.0009 ms^{-1}
v_1	1.8 ms^{-1}
K_{fb}	0.000168 mM
N_{fb}	1.2
K_{rb}	3.29 mM
N_{rb}	1
v_{maxf}	0.0748 d^{-3} mM/ms
v_{maxr}	0.03748 d^{-3} mM/ms
K_{SR}	1.2

$$J_{xfer} = \frac{[Ca^{2+}]_{ss} - [Ca^{2+}]_i}{\tau_{xfer}}. \tag{99}$$

$$J_{trpn} = \frac{d[HTRPN_{Ca}]}{dt} + \frac{d[LTRPN_{Ca}]}{dt}. \tag{100}$$

$$\frac{d[HTRPN_{Ca}]}{dt} = k_{htrpn}^+ [Ca^{2+}]_i ([HTRPN]_{tot} - [HTRPN_{Ca}]) - k_{htrpn}^- [HTRPN_{Ca}]. \tag{101}$$

$$\frac{d[LTRPN_{Ca}]}{dt} = k_{ltrpn}^+ [Ca^{2+}]_i ([LTRPN]_{tot} - [LTRPN_{Ca}]) - k_{ltrpn}^- [LTRPN_{Ca}]. \tag{102}$$

See Table 14.

Intracellular ion concentrations and membrane potential

$$\frac{d[Na^+]_i}{dt} = -(I_{Na} + I_{Na,b} + 3I_{NaCa} + 3I_{NaK} + I_{Kv1.4,Na}) \frac{A_{cap} C_{sc}}{V_{myo} F}. \tag{103}$$

$$\frac{d[K^+]_i}{dt} = -(I_{Kr} + I_{Ks} + I_{Kv4.3} + I_{Kv1.4,K} + I_{K1} + I_{Ca,K} - 2I_{NaK} + I_{stim}) \frac{A_{cap} C_{sc}}{V_{myo} F}. \tag{104}$$

$$\frac{d[Ca^{2+}]_i}{dt} = \beta_i \left(J_{xfer} - J_{up} - J_{trpn} - (I_{Ca,b} - 2I_{NaCa} + I_{p(Ca)}) \times \frac{A_{cap} C_{sc}}{2V_{myo} F}\right). \tag{105}$$

$$\beta_i = \left(1 + \frac{[CMDN]_{tot} K_m^{CMDN}}{(K_m^{CMDN} + [Ca^{2+}]_i)^2} + \frac{[EGTA]_{tot} K_m^{EGTA}}{(K_m^{EGTA} + [Ca^{2+}]_i)^2}\right). \tag{106}$$

$$\beta_{ss} = \left(1 + \frac{[CMDN]_{tot} K_m^{CMDN}}{(K_m^{CMDN} + [Ca^{2+}]_{ss})^2} + \frac{[EGTA]_{tot} K_m^{EGTA}}{(K_m^{EGTA} + [Ca^{2+}]_{ss})^2}\right). \tag{107}$$

TABLE 14 Calcium buffering and diffusion

Parameter	Value
τ_{tr}	0.5747 ms
τ_{xfer}	26.7 ms
$HTRPN_{tot}$	140 d^{-3} mM
$LTRPN_{tot}$	70 d^{-3} mM
K_{HTRPN}^+	20 mM^{-1} ms^{-1}
K_{HTRPN}^-	0.066 d^{-3} ms^{-1}
K_{LTRPN}^+	40 mM^{-1} ms^{-1}
K_{LTRPN}^-	40 d^{-3} ms^{-1}
K_m^{CMDN}	2.38 d^{-3} mM
K_m^{CSQN}	0.8 mM
K_m^{EGTA}	1.5 d^{-4} mM
$EGTA_{tot}$	0 mM

$$\beta_{JSR} = \left(1 + \frac{[CSQN]_{tot} K_m^{CSQN}}{(K_m^{CSQN} + [Ca^{2+}]_{JSR})^2}\right)^{-1}. \tag{108}$$

$$\frac{d[Ca^{2+}]_{ss}}{dt} = \beta_{ss}\left(J_{rel}\frac{V_{JSR}}{V_{ss}} - J_{xfer}\frac{V_{myo}}{V_{ss}} - (I_{Ca})\frac{A_{cap} C_{sc}}{2V_{ss} F}\right). \tag{109}$$

$$\frac{d[Ca^{2+}]_{JSR}}{dt} = \beta_{JSR}(J_{tr} - J_{rel}). \tag{110}$$

$$\frac{d[Ca^{2+}]_{NSR}}{dt} = J_{up}\frac{V_{myo}}{V_{NSR}} - J_{tr}\frac{V_{JSR}}{V_{NSR}}. \tag{111}$$

$$\frac{dV}{dt} = -(I_{Na} + I_{Ca} + I_{Ca,K} + I_{Kr} + I_{Ks} + I_{K1} + I_{NaCa} + I_{NaK} + I_{Kv1.4} + I_{Kv4.3} + I_{p(Ca)} + I_{Ca,b} + I_{Na,b} + I_{stim}). \tag{112}$$

$$I_{stim} = -100\,pA/pF. \tag{113}$$

Problems studying AF

Complicated structure

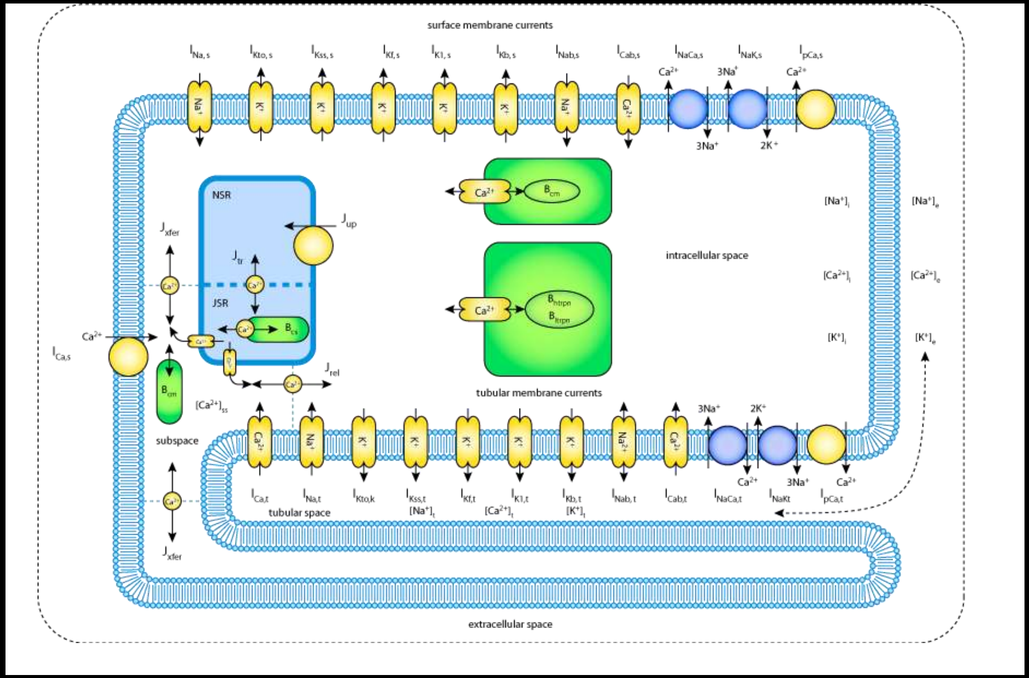
Problems studying AF

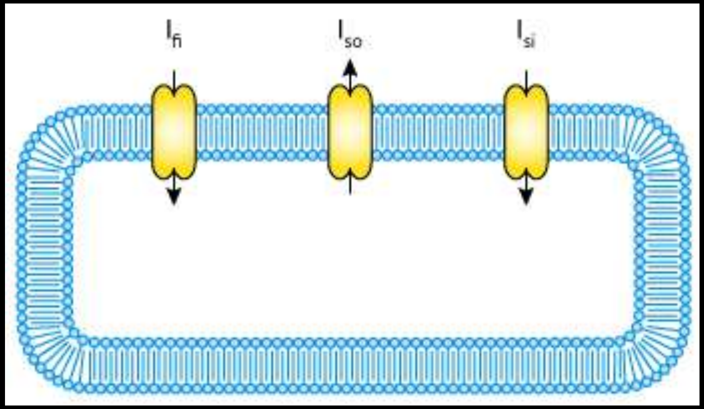
Complicated structure

A few complex ionic cell models for atria dynamics.
They can be simulated in super computers
Too complex to extract useful information.
Not correct when simulated in tissue.

Model reduction

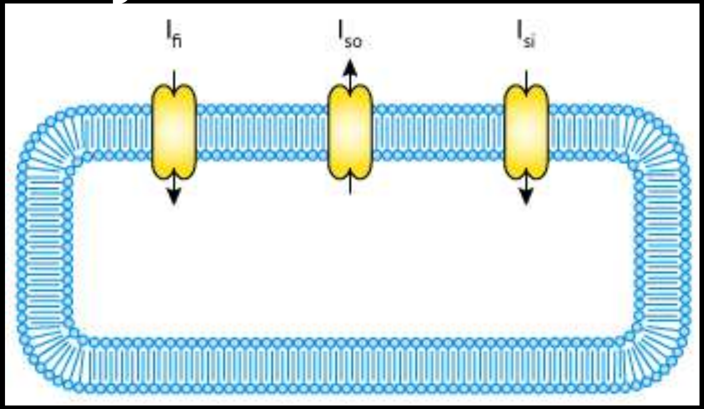
Adiabatic elimination
Asymptotic methods (Tikhonov, embedding)
Abstraction





Abstraction and model reduction

3 total currents have enough structure to reproduce AP morphology and dynamics



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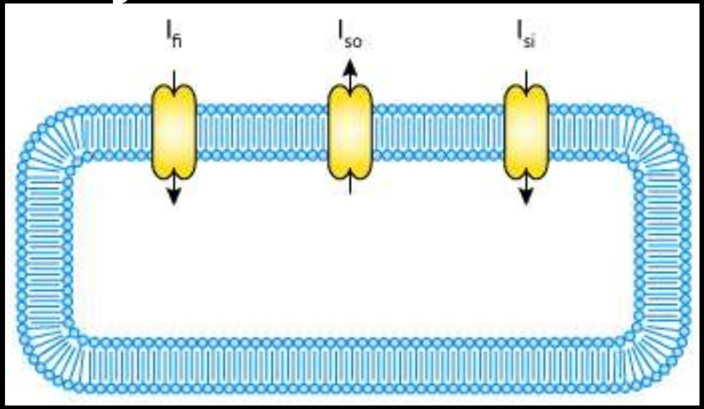

However it has limitations

Cell Model Equations

Cell Model Equations

Example: A simple 3 current phenomenological model

Cell Model Equations

Example: A simple 3 current phenomenological model

The model consists of 3 variables: V the membrane voltage, v a fast ionic gate and w a slow ionic gate and 14 parameters.

They are used to produce 3 independent phenomenological ionic currents.

Cell Model Equations

Example: A simple 3 current phenomenological model

The model consists of 3 variables: V the membrane voltage, v a fast ionic gate and w a slow ionic gate and 14 parameters.

They are used to produce 3 independent phenomenological ionic currents.

$$
\begin{aligned}
I_{fi}(V;\mathbf{v}) &= -\mathbf{v}\, p\,(V - V_c)(V - V_m)/\tau_d \\
I_{so}(V) &= (V - V_o)\,(1 - p)/\tau_o + p/\tau_r \\
I_{si}(V;\mathbf{w}) &= -\mathbf{w}\,\left(1 + \tanh\left[k\,(V - V_c^{si})\right]\right)/(2\tau_{si})
\end{aligned}
$$

Cell Model Equations

The equations for the 3 variables are:

$$\begin{aligned}
\partial_t V(\vec{x}, t) &= \nabla \cdot (\tilde{D} \nabla V) - I_{\mathrm{ion}} \\
\partial_t \mathbf{v}(t) &= (1-p)\,(1-\mathbf{v})/\tau_{\mathbf{v}}^{-}(V) - p\,\mathbf{v}/\tau_{\mathbf{v}}^{+} \\
\partial_t \mathbf{w}(t) &= (1-p)\,(1-\mathbf{w})/\tau_{\mathbf{w}}^{-} - p\,\mathbf{w}/\tau_{\mathbf{w}}^{+}
\end{aligned}$$

where $\tau_{\mathbf{v}}^{-}(V) = (1-q)\,\tau_{\mathbf{v1}}^{-} + q\,\tau_{\mathbf{v2}}^{-}$

$$p = \begin{cases} 1 & \text{if } V \geq V_c \\ 0 & \text{if } V < V_c \end{cases} \quad \text{and} \quad q = \begin{cases} 1 & \text{if } V \geq V_{\mathbf{v}} \\ 0 & \text{if } V < V_{\mathbf{v}} \end{cases}$$

Cell Model Equations

The equations for the 3 variables are:

$$\begin{aligned}
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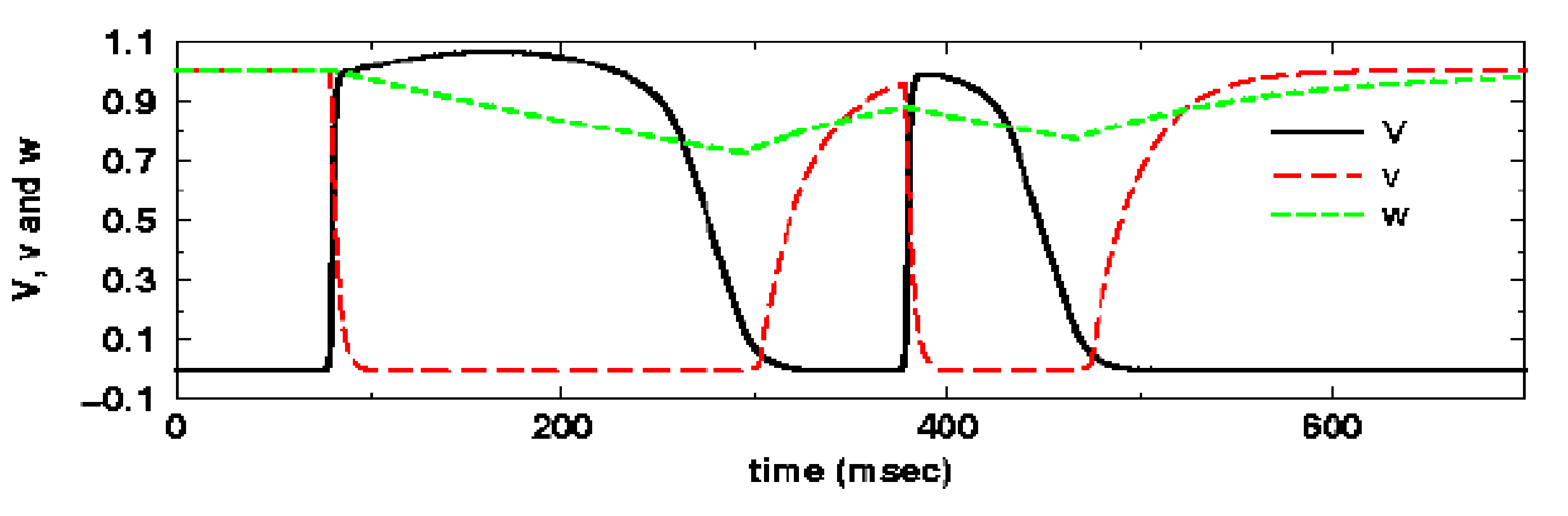
\partial_t \mathbf{w}(t) &= (1-p)\,(1-\mathbf{w})/\tau_{\mathbf{w}}^{-} \; - \; p\,\mathbf{w}/\tau_{\mathbf{w}}^{+}
\end{aligned}$$

where $\tau_{\mathbf{v}}^{-}(V) = (1-q)\,\tau_{\mathbf{v}1}^{-} + q\,\tau_{\mathbf{v}2}^{-}$

$$p = \begin{cases} 1 & \text{if } V \geq V_c \\ 0 & \text{if } V < V_c \end{cases} \quad \text{and} \quad q = \begin{cases} 1 & \text{if } V \geq V_{\mathbf{v}} \\ 0 & \text{if } V < V_{\mathbf{v}} \end{cases}$$



Cell Model Equations

The equations for the 3 variables are:

$$\partial_t V(\vec{x}, t) = \nabla \cdot (\tilde{D} \nabla V) - I_{\text{ion}}$$

$$\partial_t \mathbf{v}(t) = (1-p)\,(1-\mathbf{v})/\tau_{\mathbf{v}}^-(V) - p\,\mathbf{v}/\tau_{\mathbf{v}}^+$$

$$\partial_t \mathbf{w}(t) = (1-p)\,(1-\mathbf{w})/\tau_{\mathbf{w}}^- - p\,\mathbf{w}/\tau_{\mathbf{w}}^+$$

$$\ldots) = (1-q)\,\tau_{\mathbf{v}1}^- + q\,\tau_{\mathbf{v}2}^-$$

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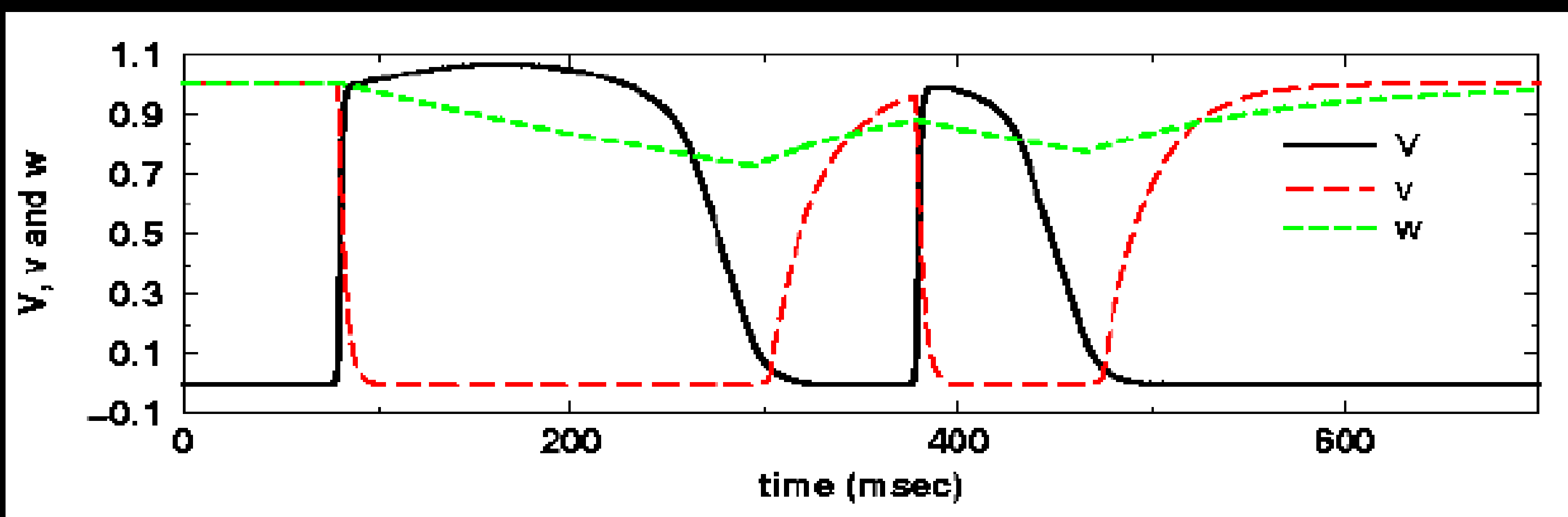
Can reproduce adaptation to pacing



Comparison to other models

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where $\tau_{\mathbf{v}}^{-}(V) = (1-q)\,\tau_{\mathbf{v1}}^{-} + q\,\tau_{\mathbf{v2}}^{-}$

$$p = \begin{cases} 1 & \text{if } V \geq V_c \\ 0 & \text{if } V < V_c \end{cases} \quad \text{and} \quad q = \begin{cases} 1 & \text{if } V \geq V_{\mathbf{v}} \\ 0 & \text{if } V < V_{\mathbf{v}} \end{cases}$$

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A 4V version can be fitted to other more complex models and experimental data

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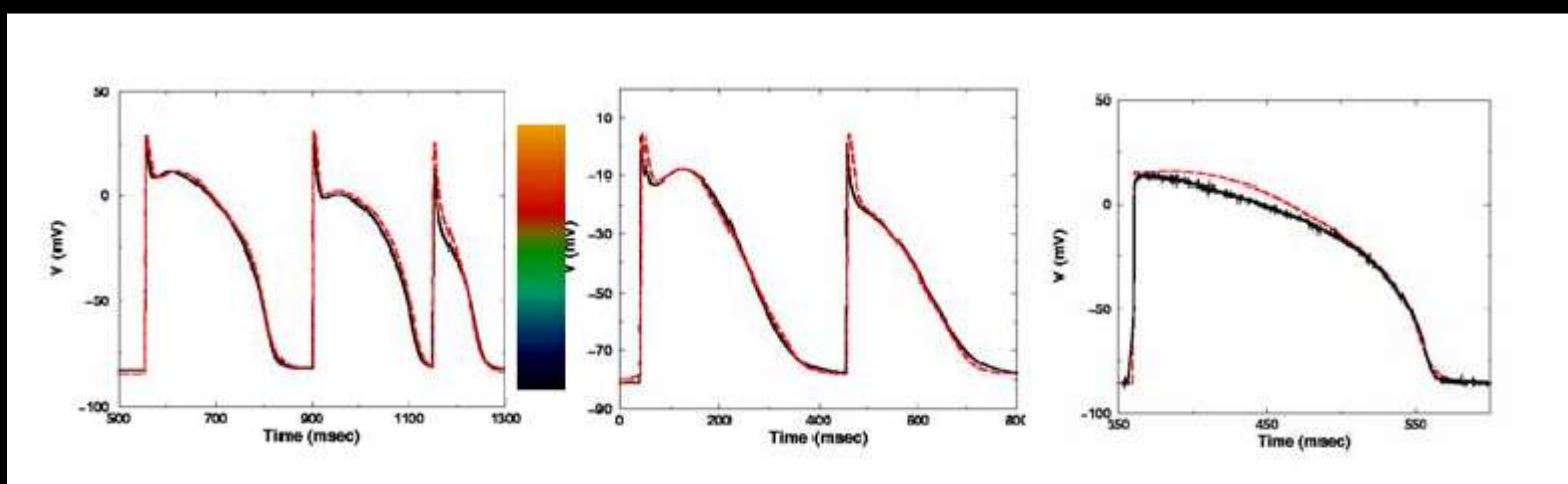
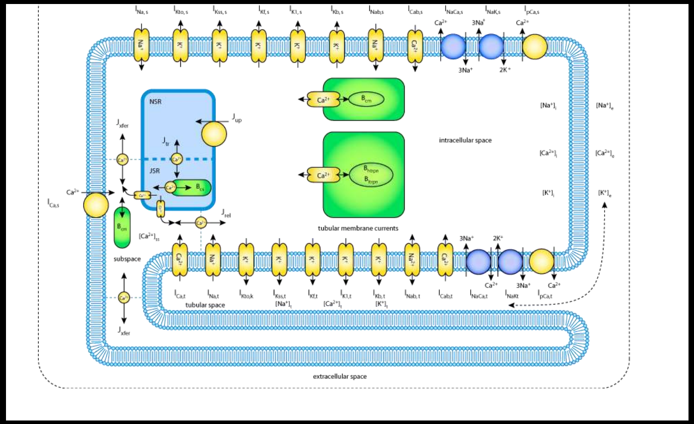
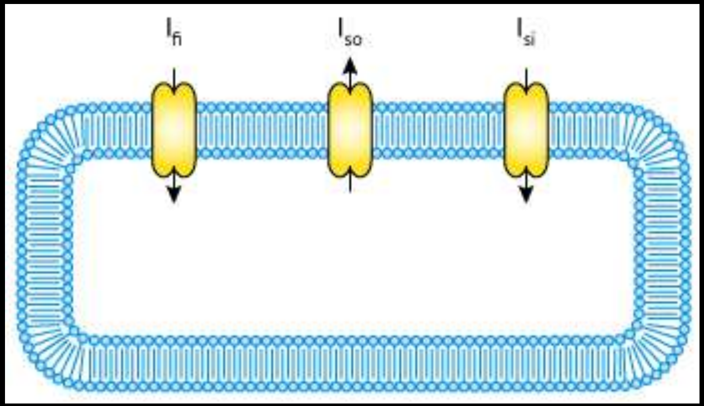


Beeler-Reuter Courtemanche Rabbit exp.

Abstraction and model reduction



Time ratio
8084:1
Variables:
67 Vs 4



Overview of Project

model reduction, hybretization and linearization

Atrial detail models ←→ Minimal models ←→ Hybrid automata

Experimental data (normal and disease)

Characteristics with model checking

Specific Criteria:

Single cell:

- Threshold for excitation
- dV/dt_max (upstroke)
- Resting membrane potential
- APD_min and DI_min
- Adaptation to changes in Cycle length (APD and CV restitution)
- AP Shape at all cycle lengths

Tissue:

- Wave length
- # of singularities
- Dominant frequency
- Life time of singularities

Overview of Project

Year 1-2

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Year 1-2

SBU+Cornell (Wiki)

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SBU+Cornell + Lehman

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SBU+Cornell + Lehman

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Specific Criteria:

Single cell:

SBU+Cornell+CMU+NYU+Pitt

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Overview of Project

Year 3-4

•Quantification of AF initiation and of differences between Normal and disease models.

•Parameter optimization for low voltage FF-AFP

Overview of Project

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Carnegie Mellon

UNIVERSITY OF MARYLAND

CORNELL UNIVERSITY FOUNDED A.D. 1865

NASA

STONY BROOK STATE UNIVERSITY OF NEW YORK

University of Pittsburgh

NYU New York University

LEHMAN COLLEGE

Progress to date

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- Obtained structural data
- Obtained electrophysiological data (normal and disease)
- Analyzing the electrophysiological data
- Fitting mathematical models to data
- Created a hybrid model from the minimal model
- Curvature and curl calculations

  (Cornell: 1 Grad student and two undergrads)

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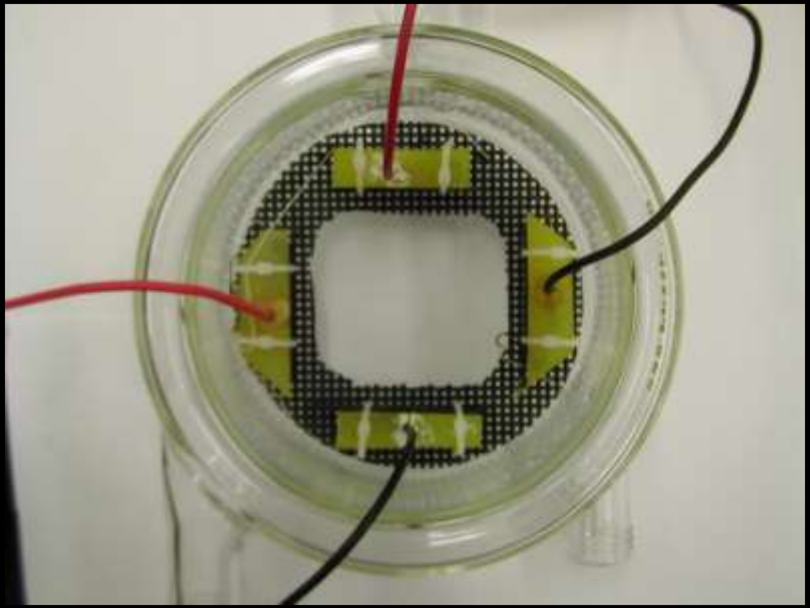
Experimental data

Optical Mapping



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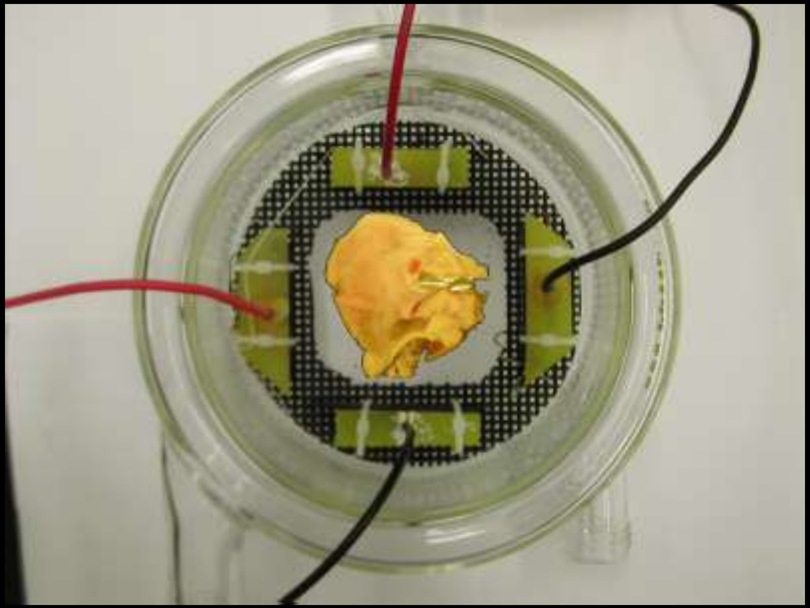

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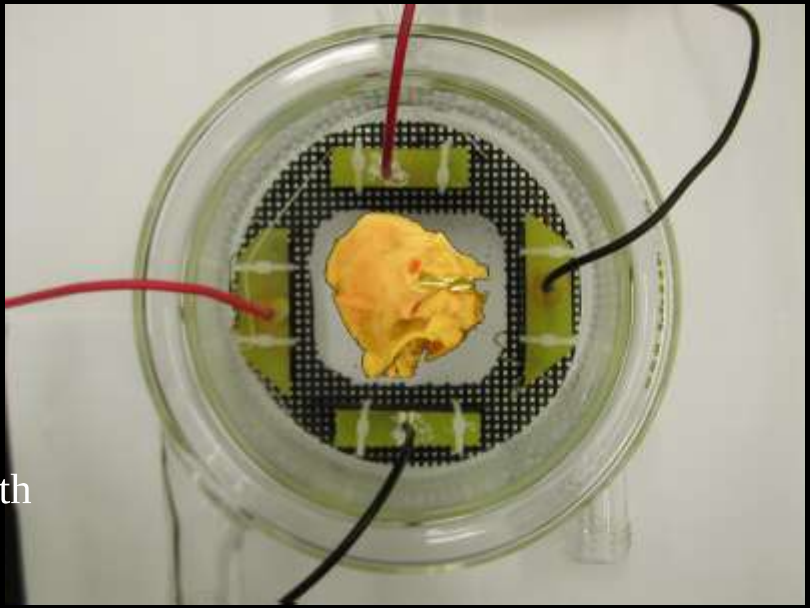

Tissue bath

Experimental data

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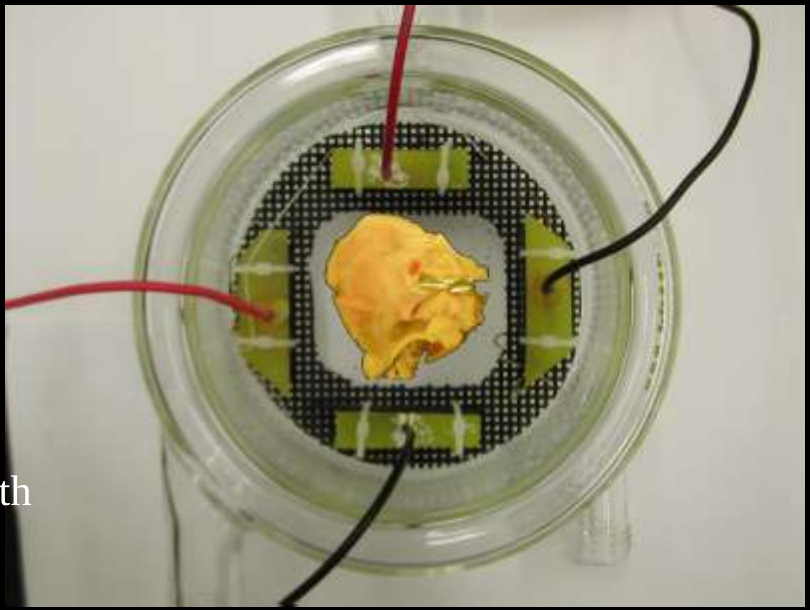

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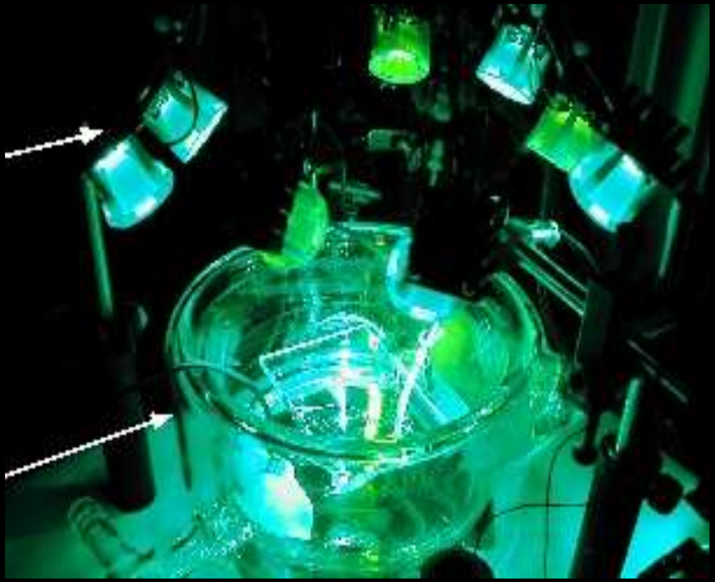
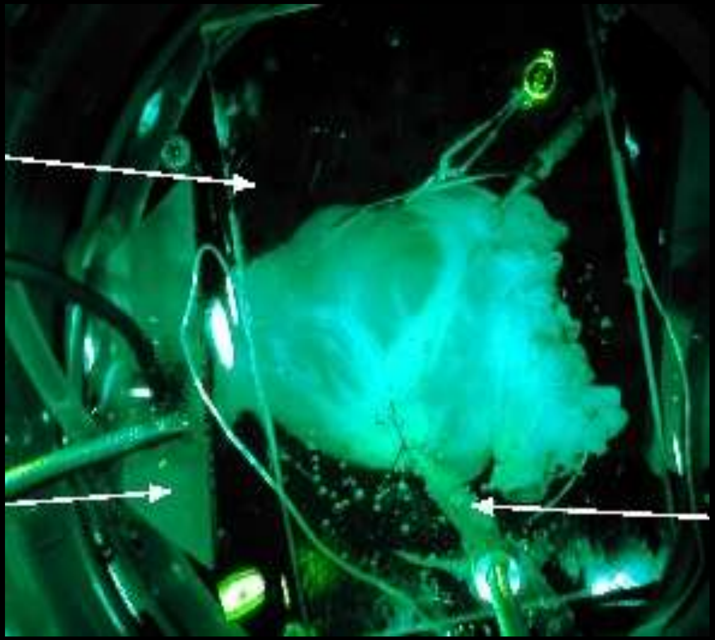
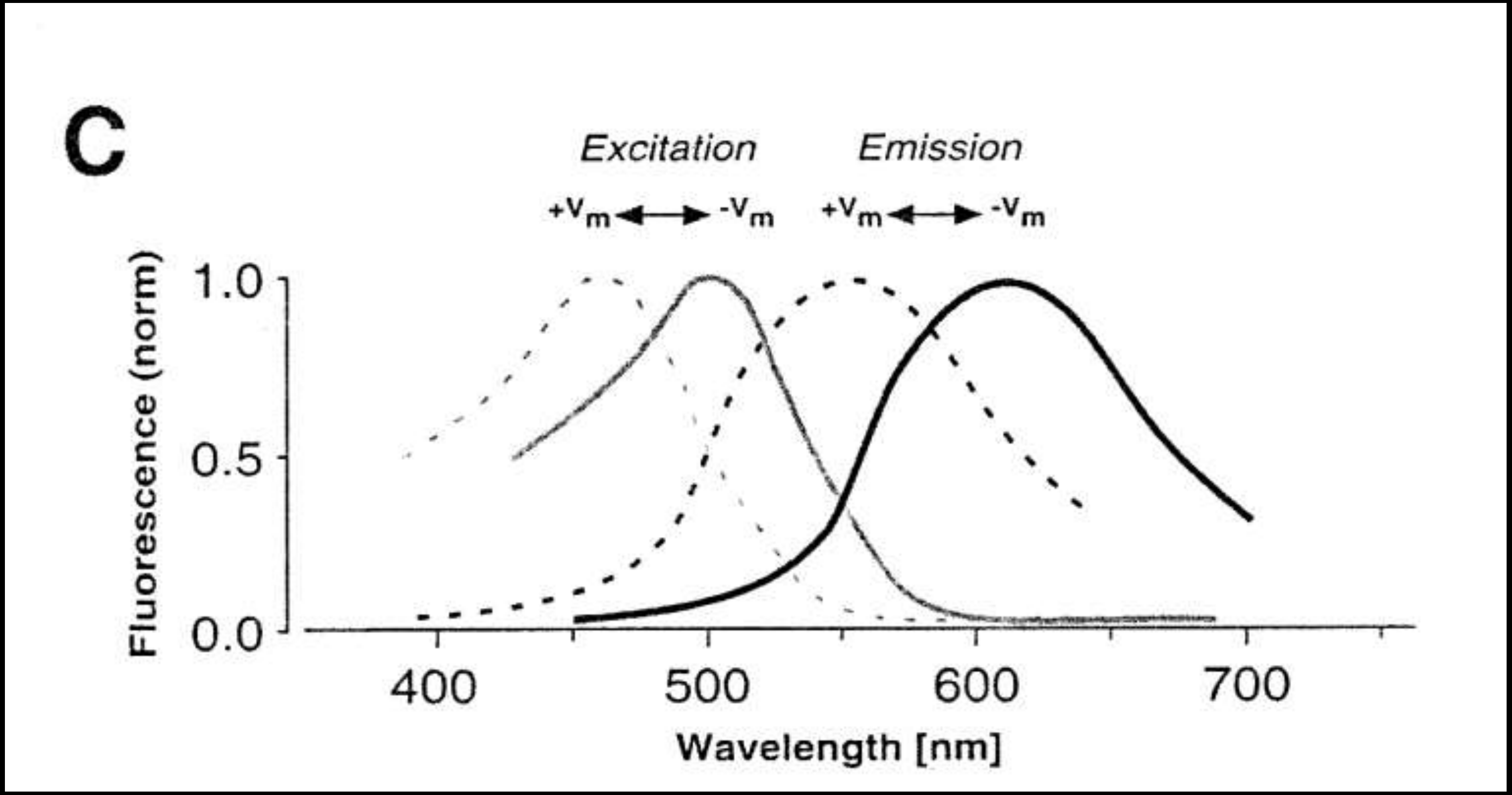




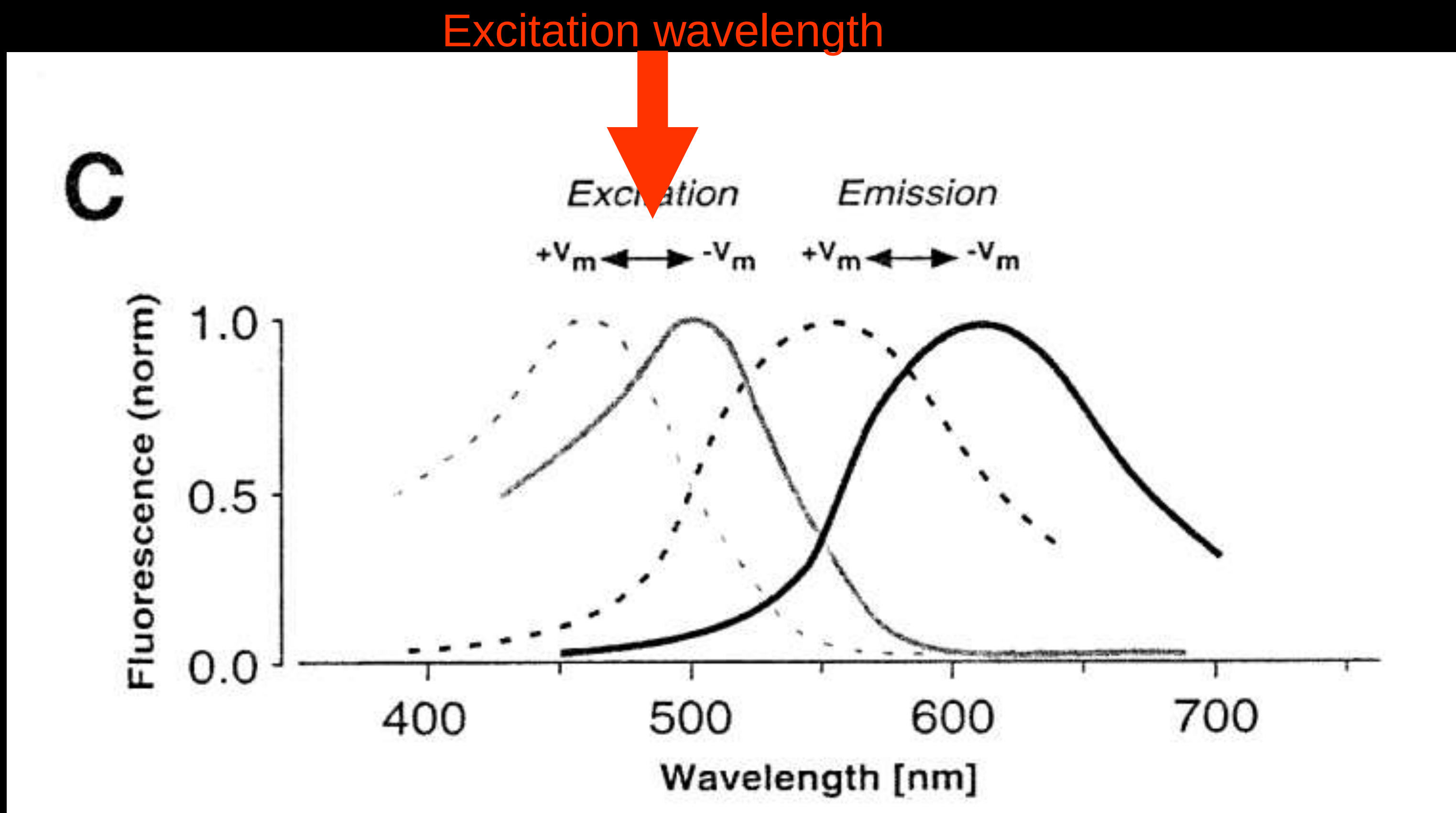
- Di-4-ANEPPS (voltage sensitive dye)
- Diodes 530 nm wavelength
- Cascade cameras at 511 Hz
- 128x128 window view

Fluorescence Imaging with di-4-anneps



Intensity AND maximum of spectrum change with membrane potential

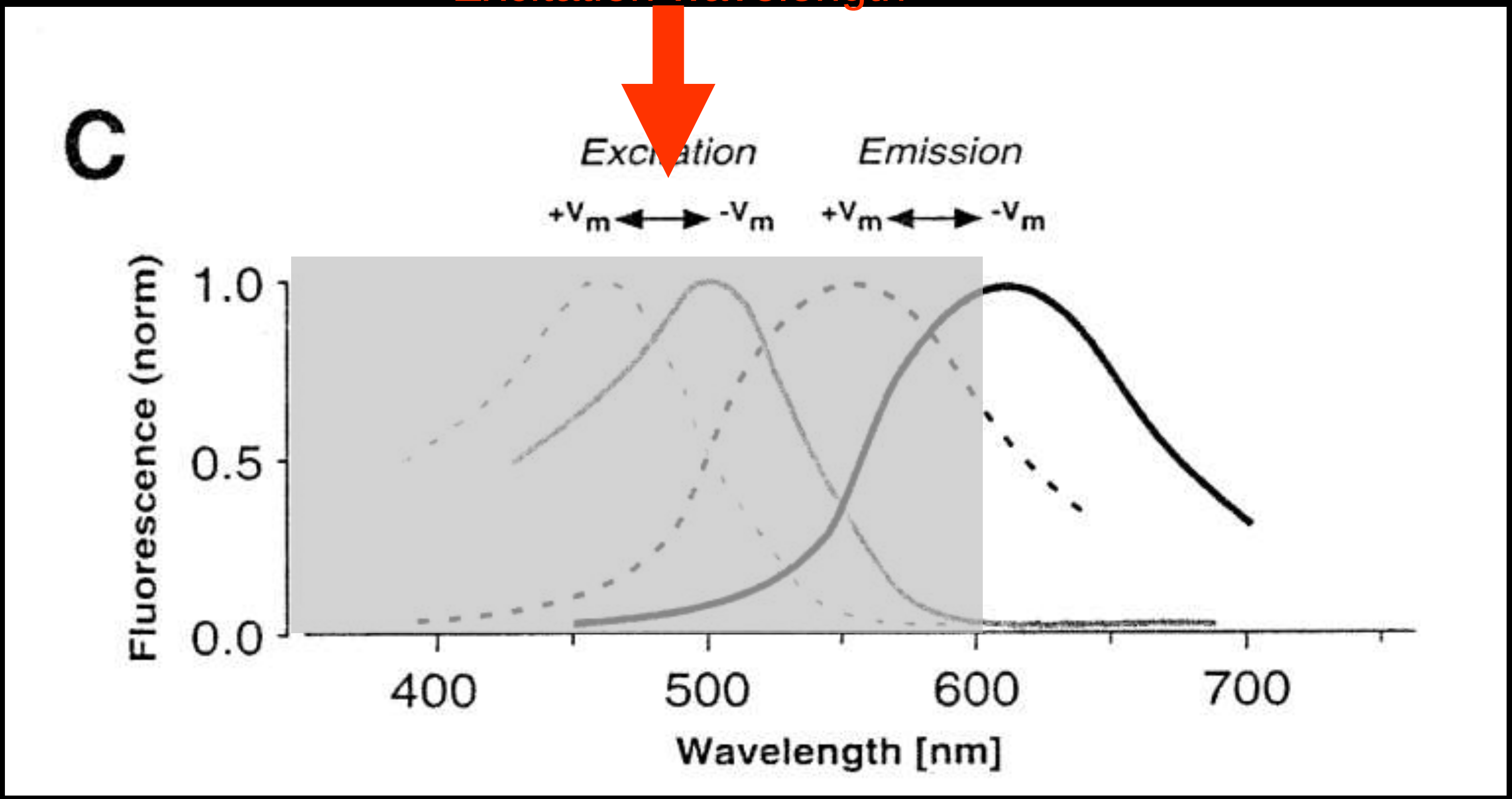
Fluorescence Imaging with di-4-anneps



Intensity AND maximum of spectrum change with membrane potential

Fluorescence Imaging with di-4-anneps

Excitation wavelength



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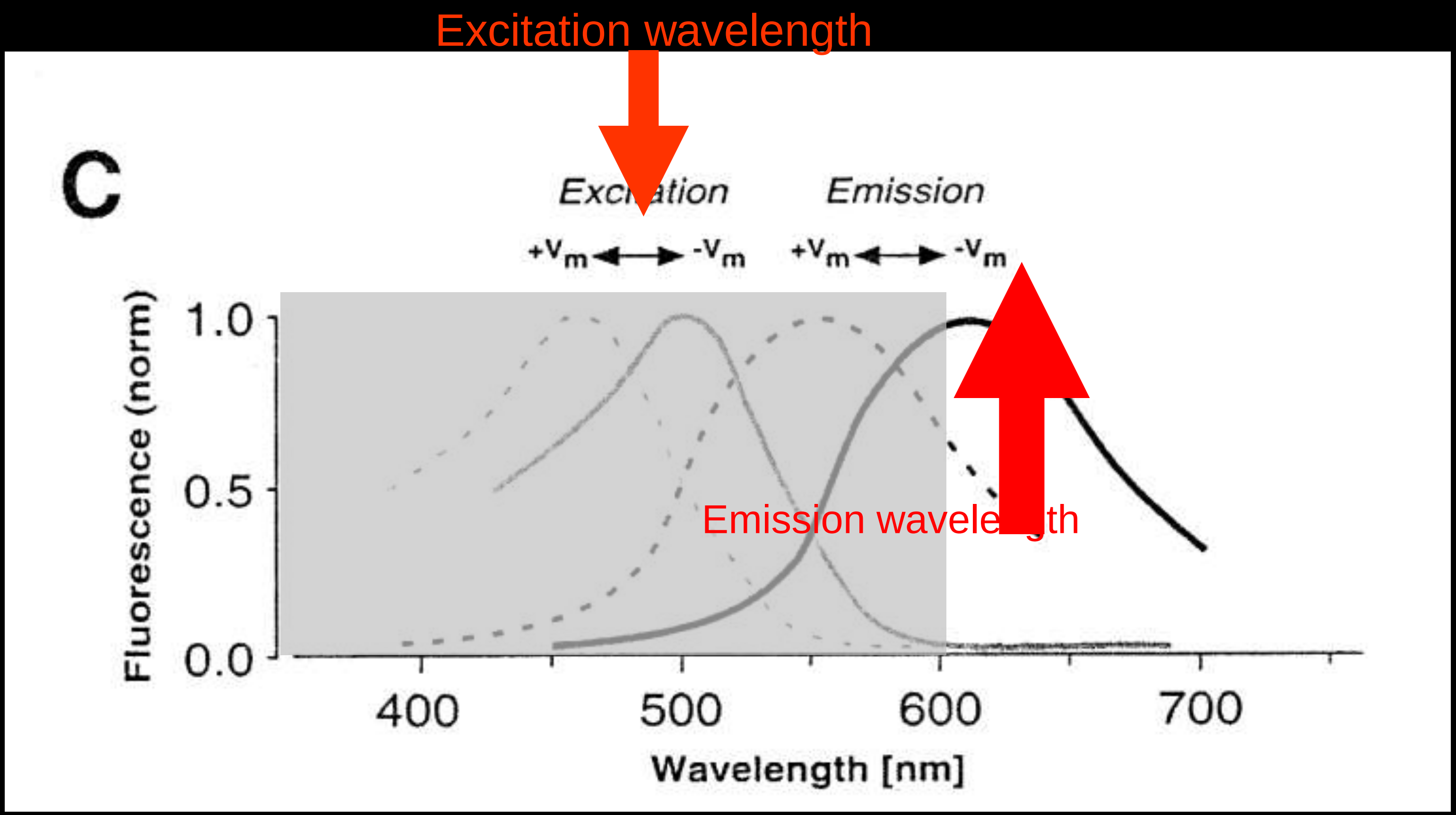

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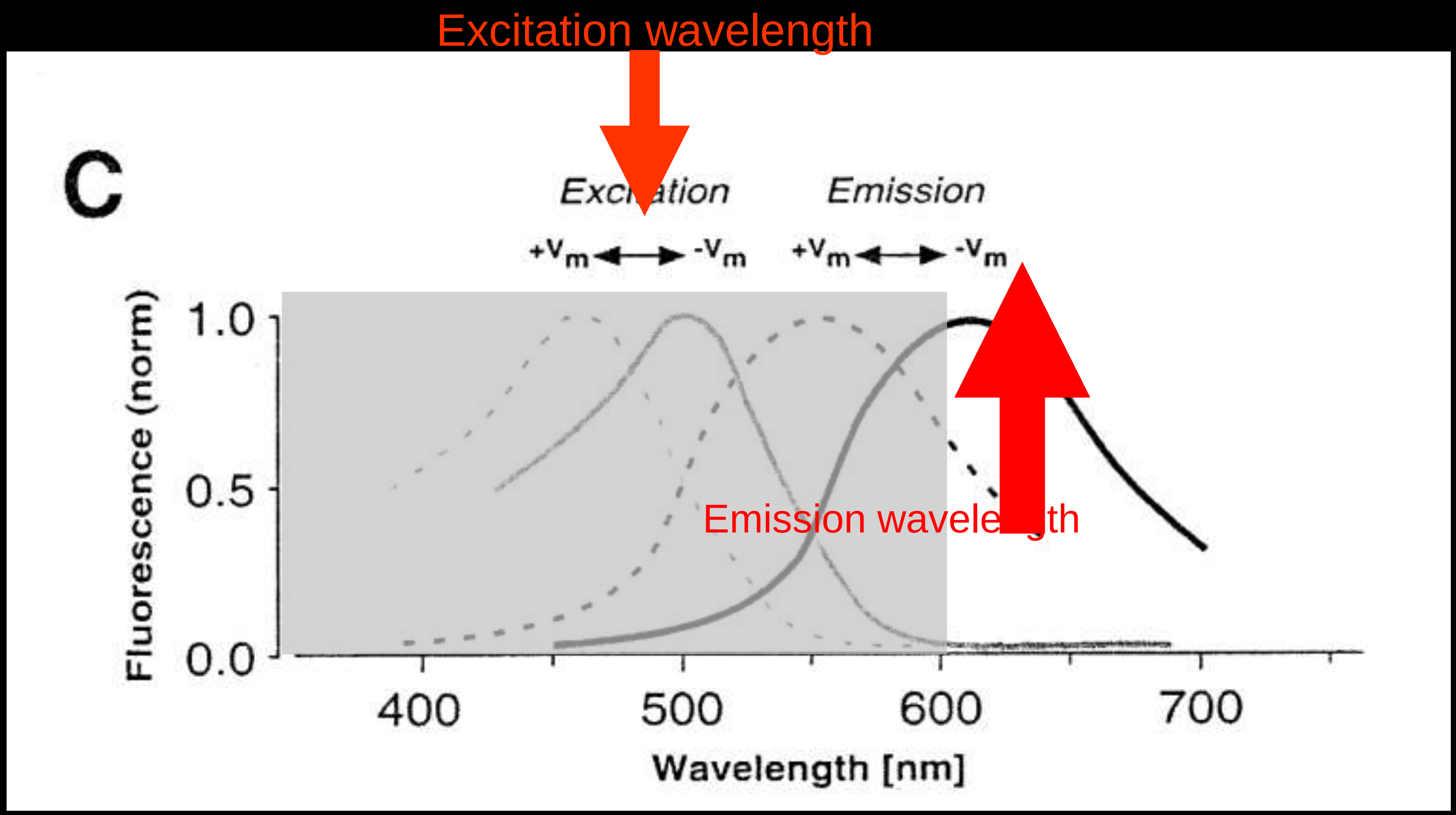
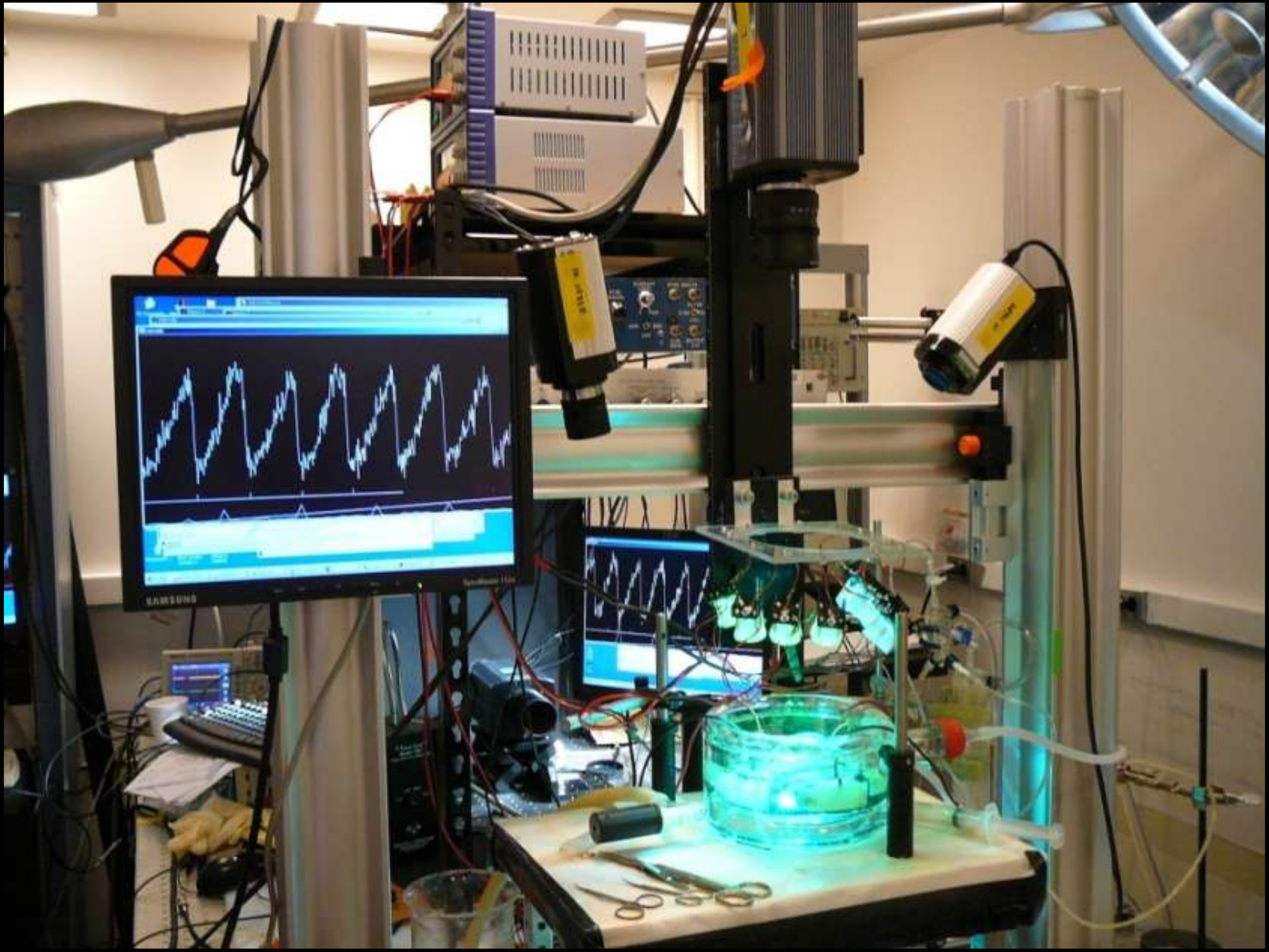


Intensity AND maximum of spectrum change with membrane potential

Fractional intensity change 1-10% (for a filter cut-off of λ = 600 nm)

Optical Mapping Setup

Optical Mapping Setup



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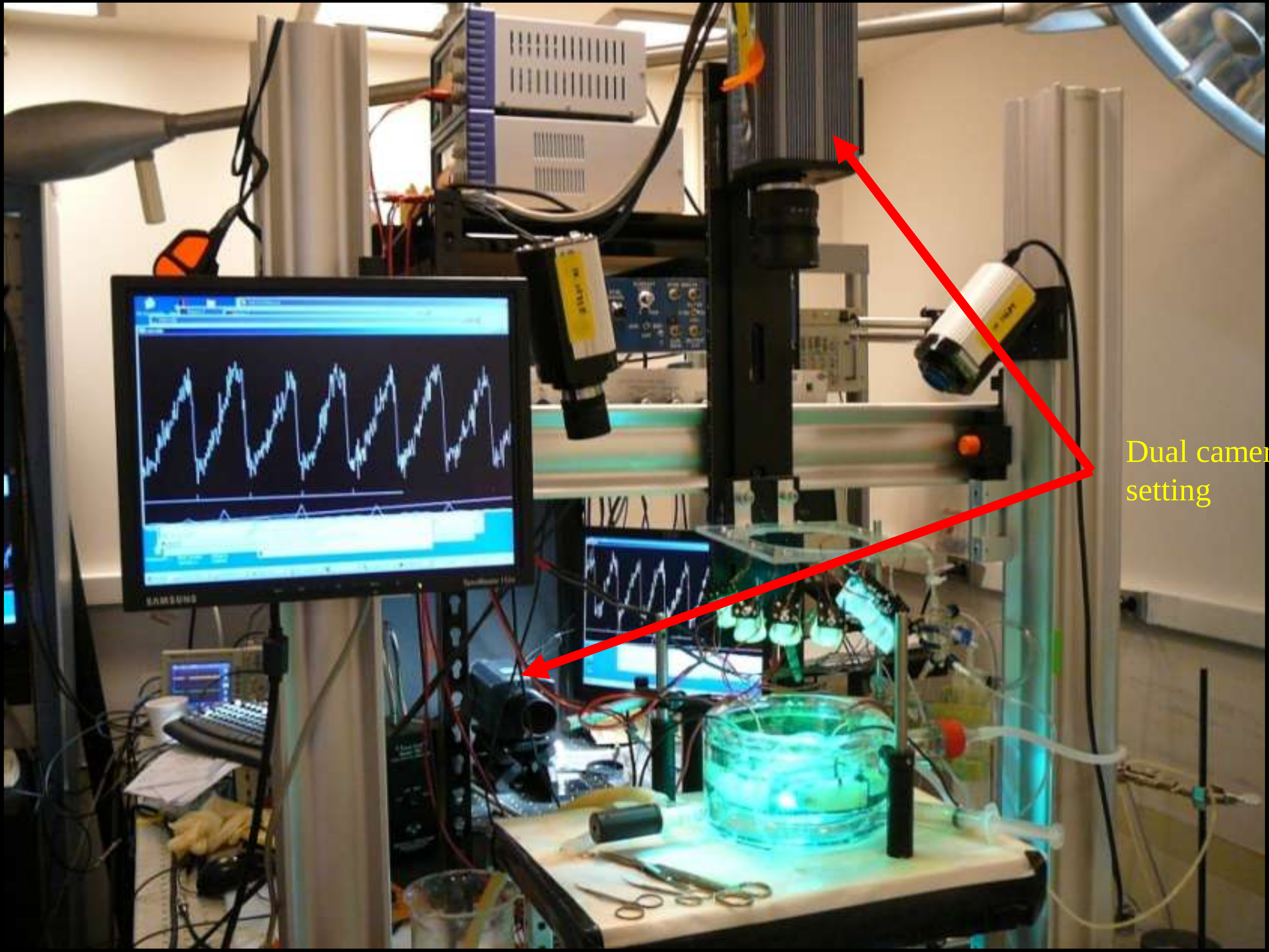
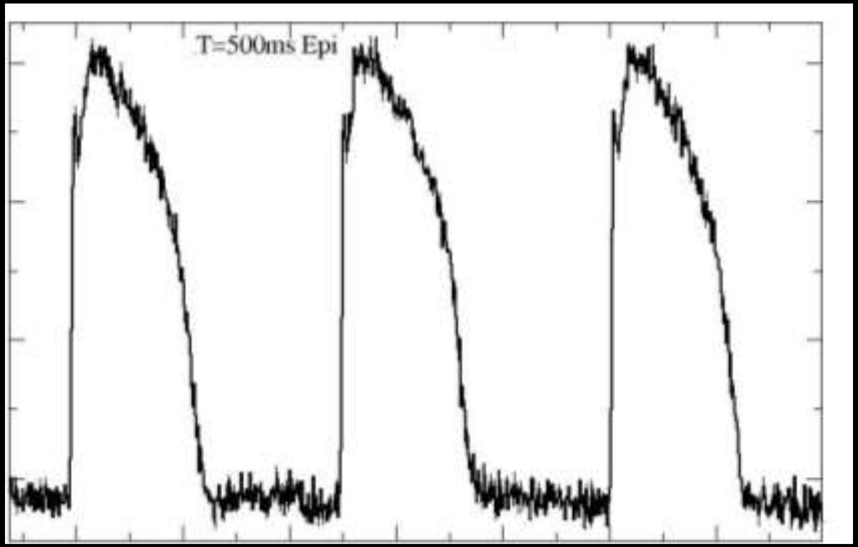


Dual camera setting

Example of AP Recordings in Ventricular Tissue

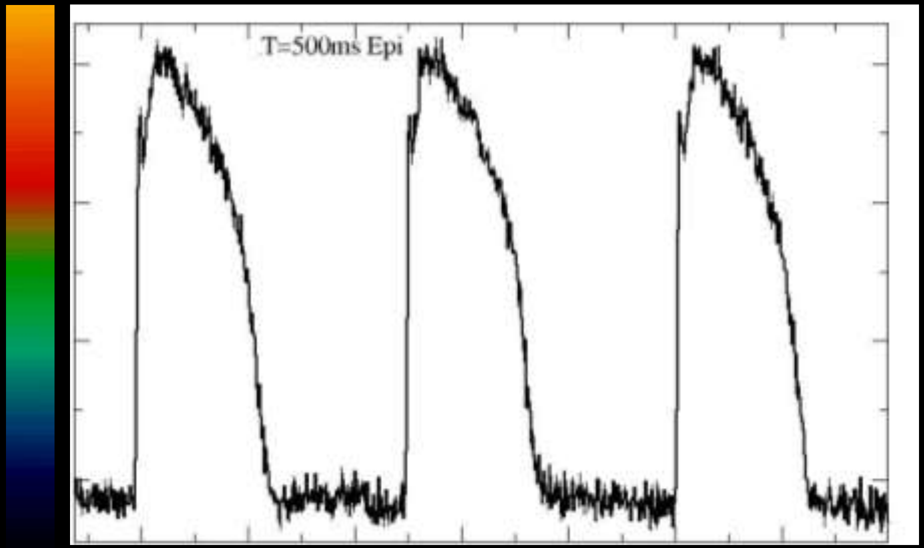


Optical mapping

Example of AP Recordings in Ventricular Tissue

20mV

-85mV



Optical mapping

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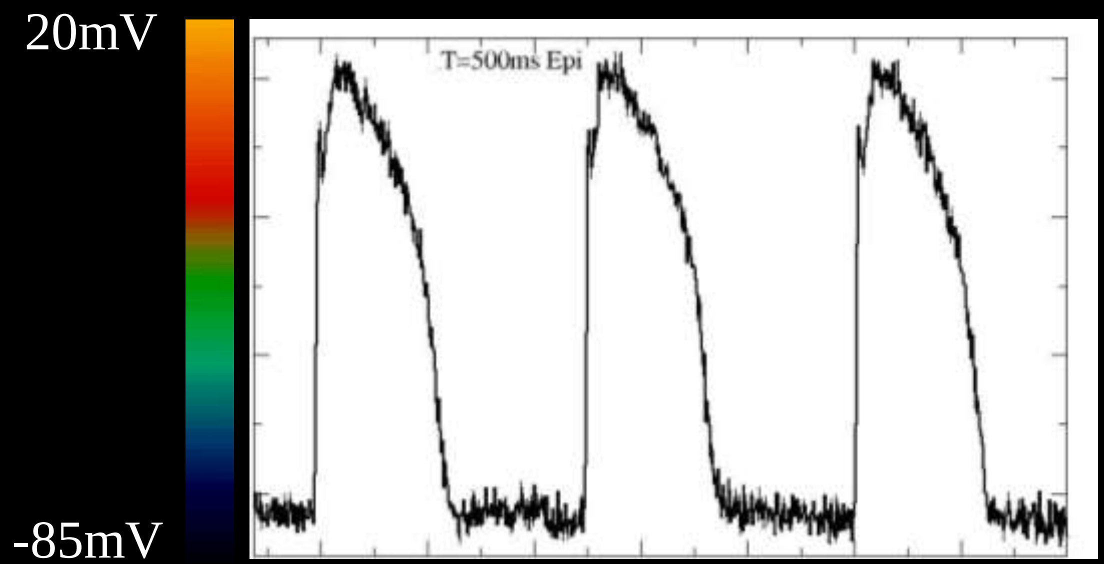

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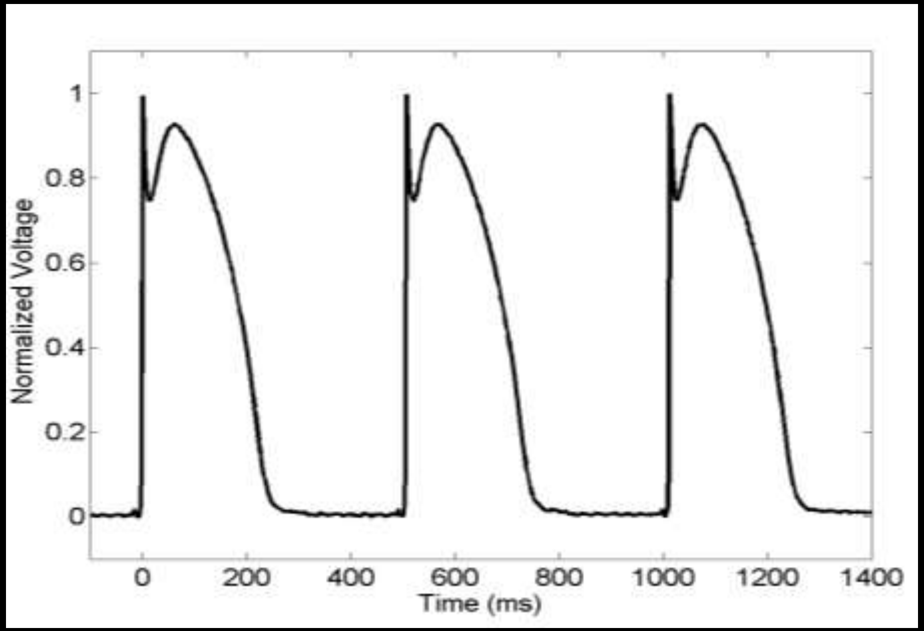
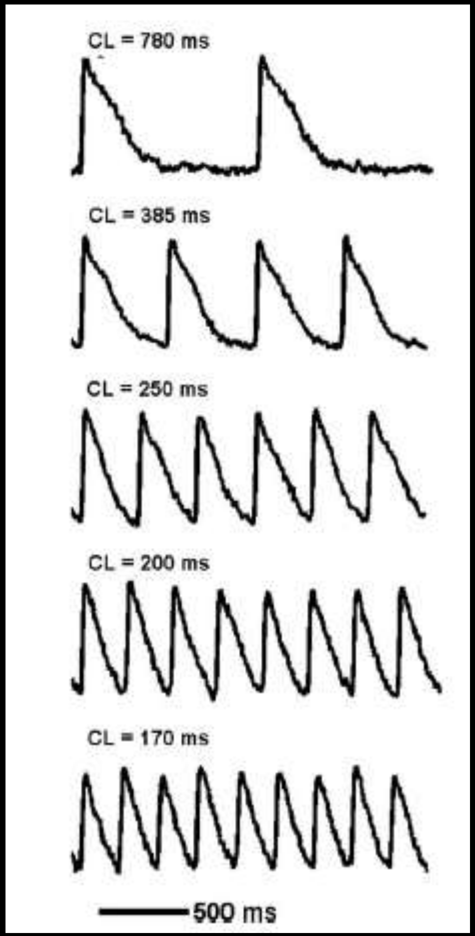
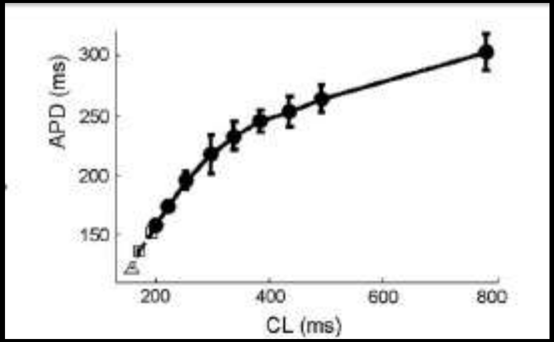


Microelectrode recordings.
Better signal/noise
Discontinuous in space
Not for long times

Obtain spatio-temporal AP signals at different pacing cycle lengths

Electrical activity in the atria





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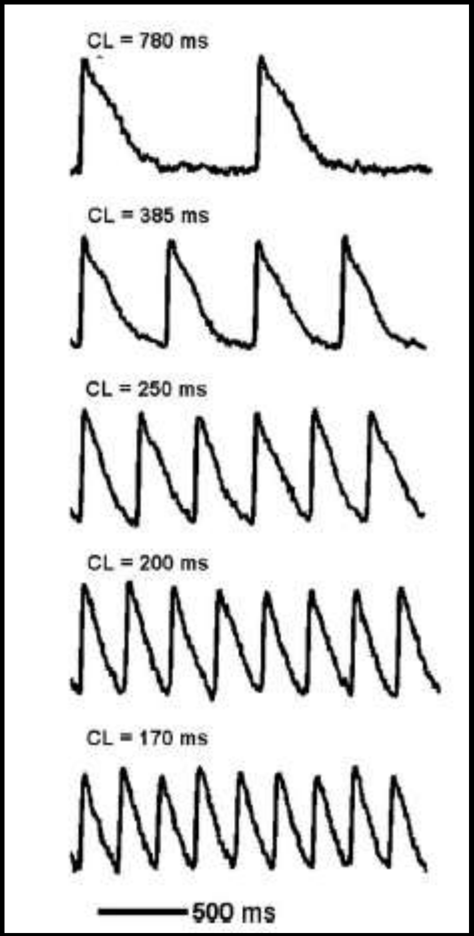

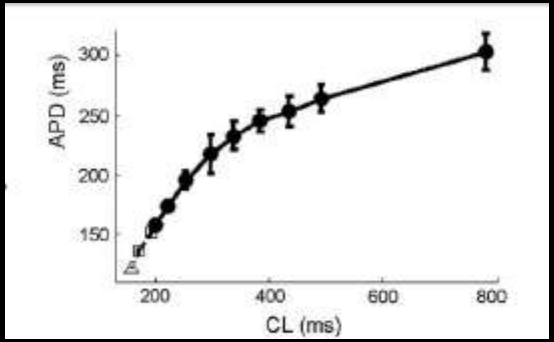

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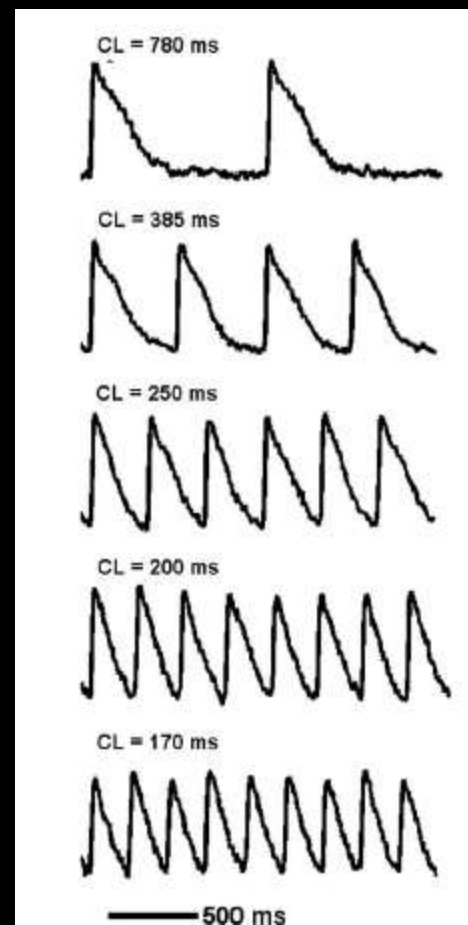

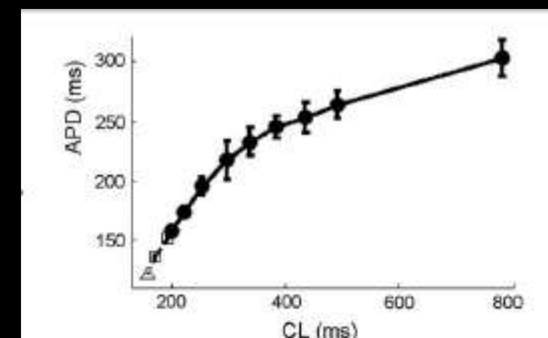

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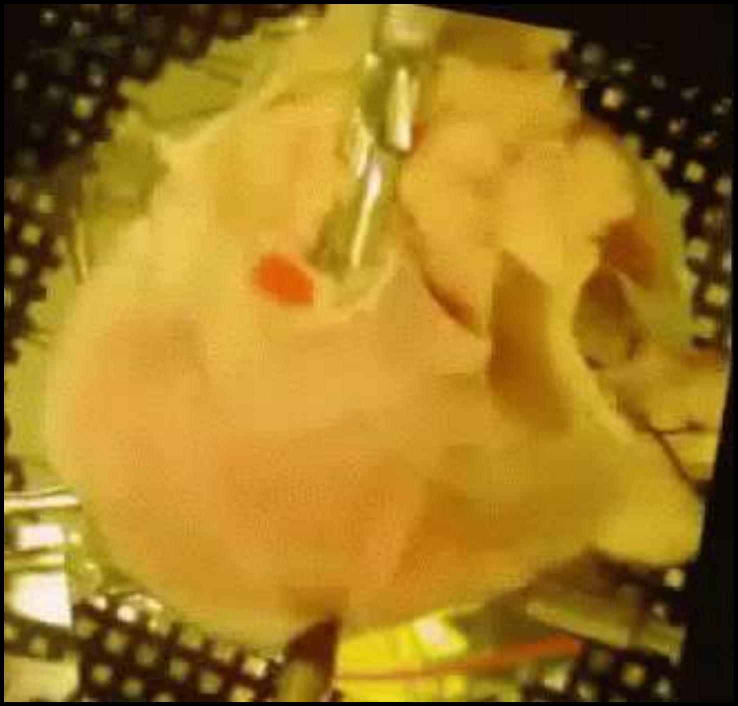

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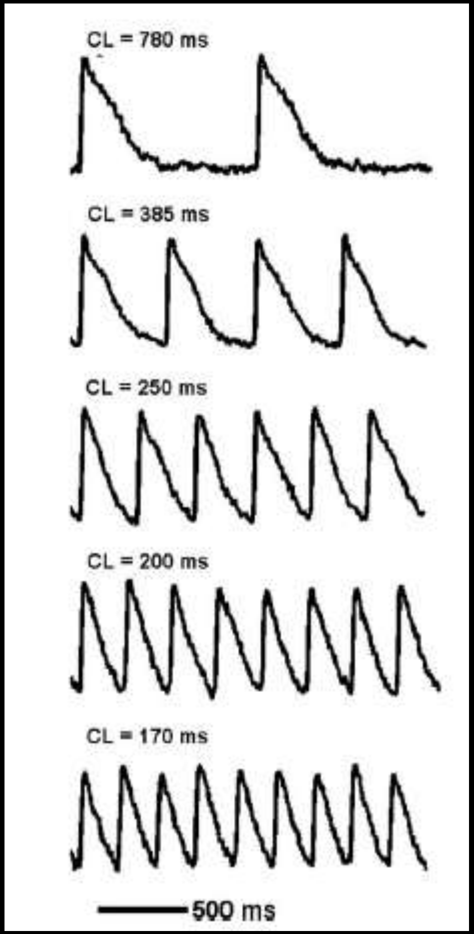

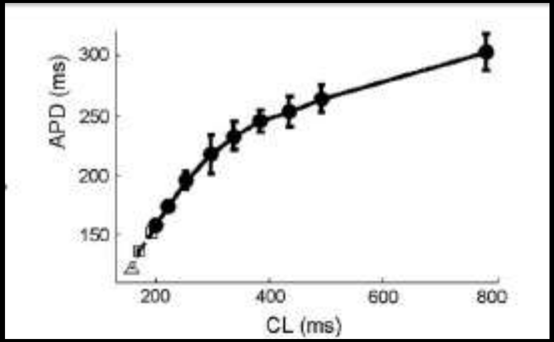

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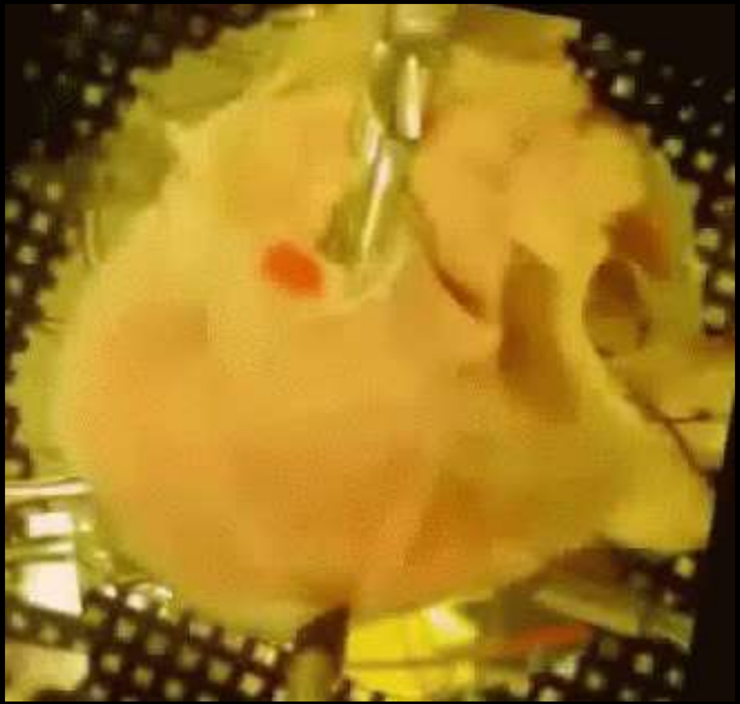

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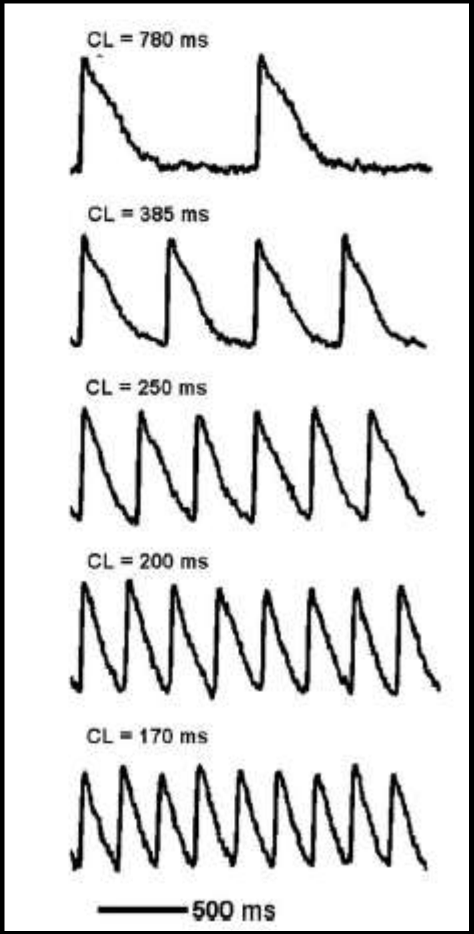
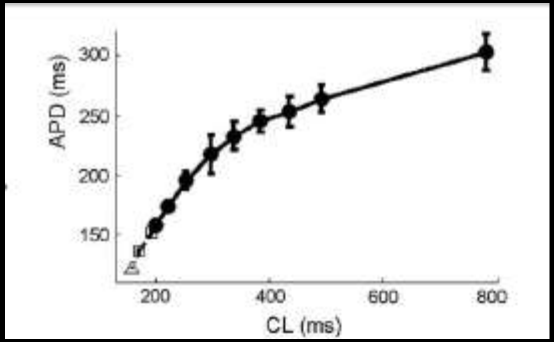
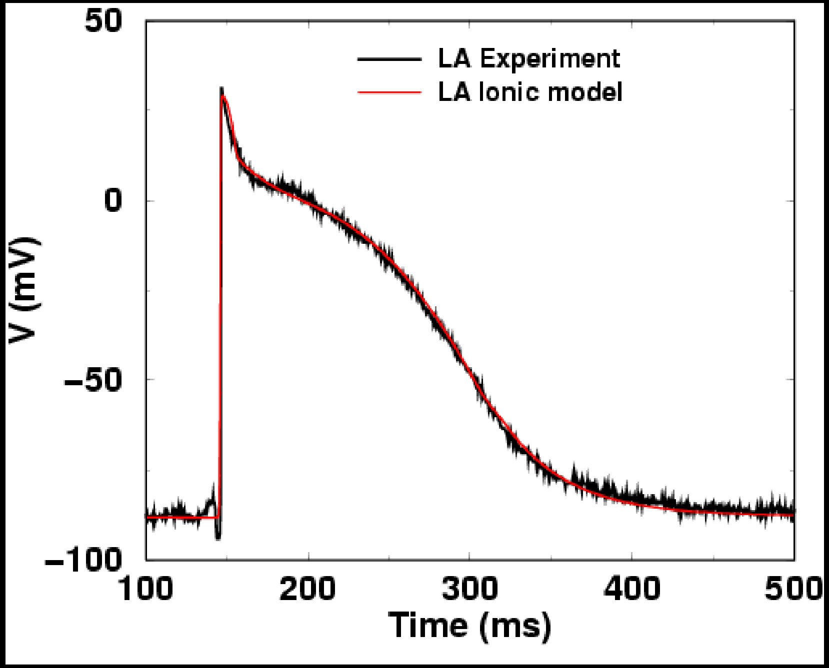
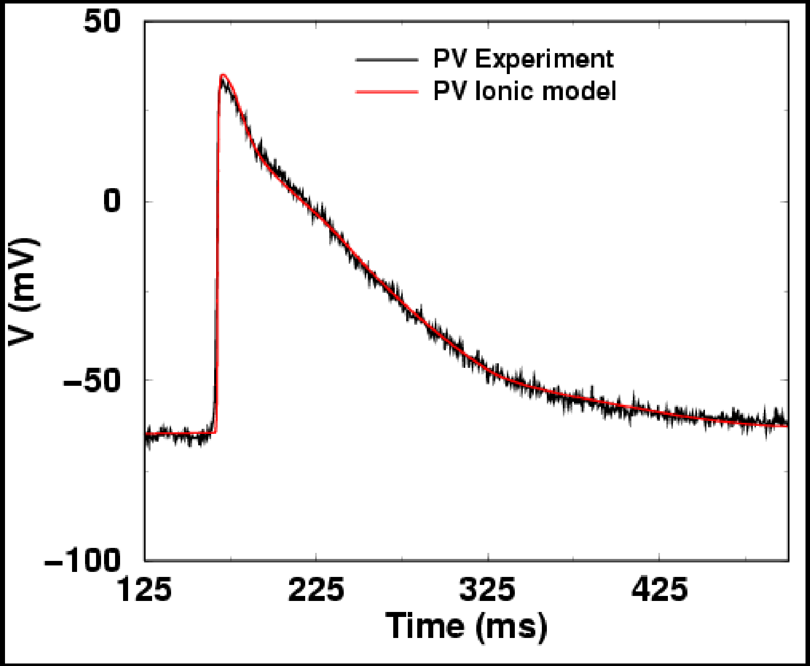


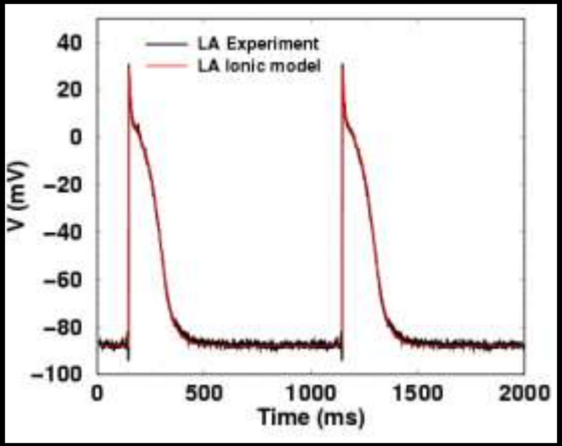


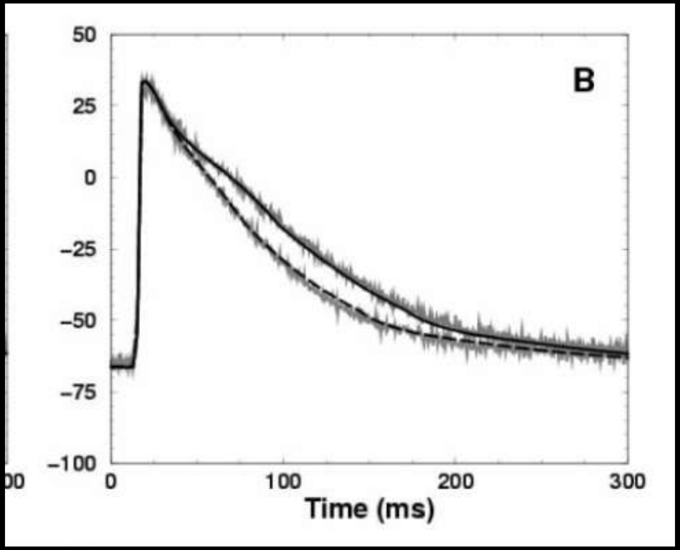
Model fitted to experimental data

4V model

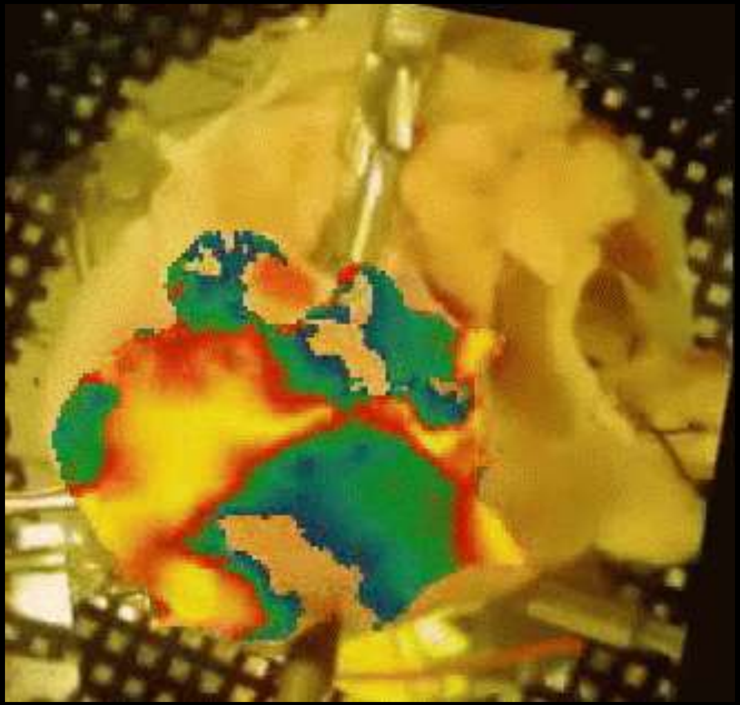


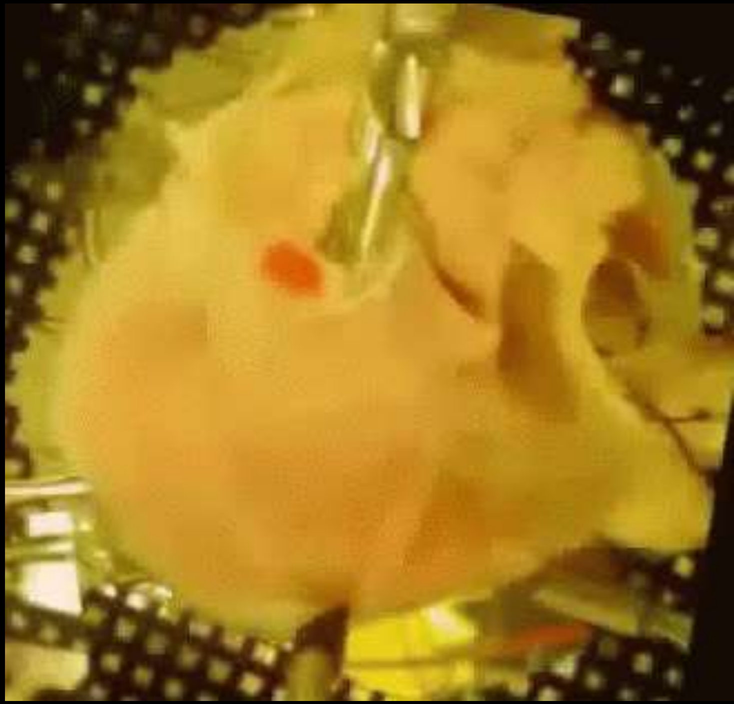






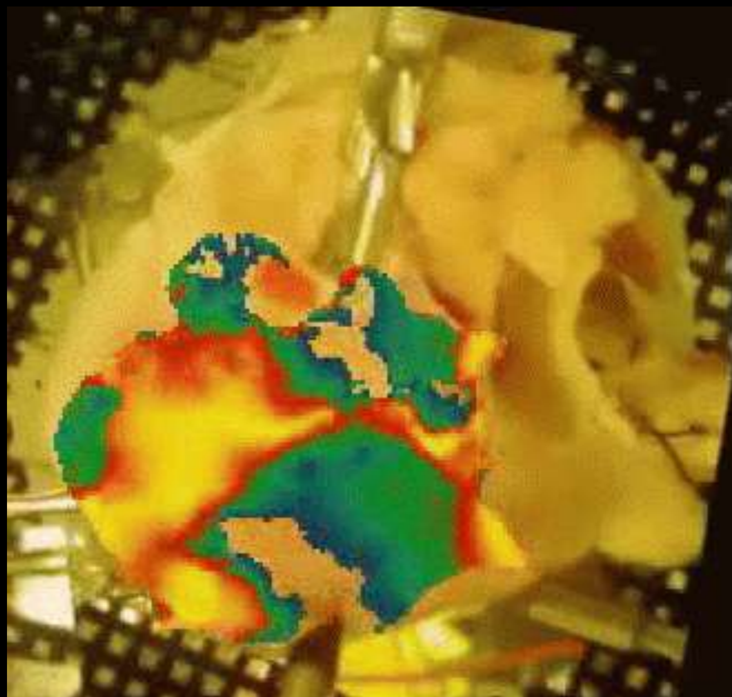
Spiral Wave Instabilities

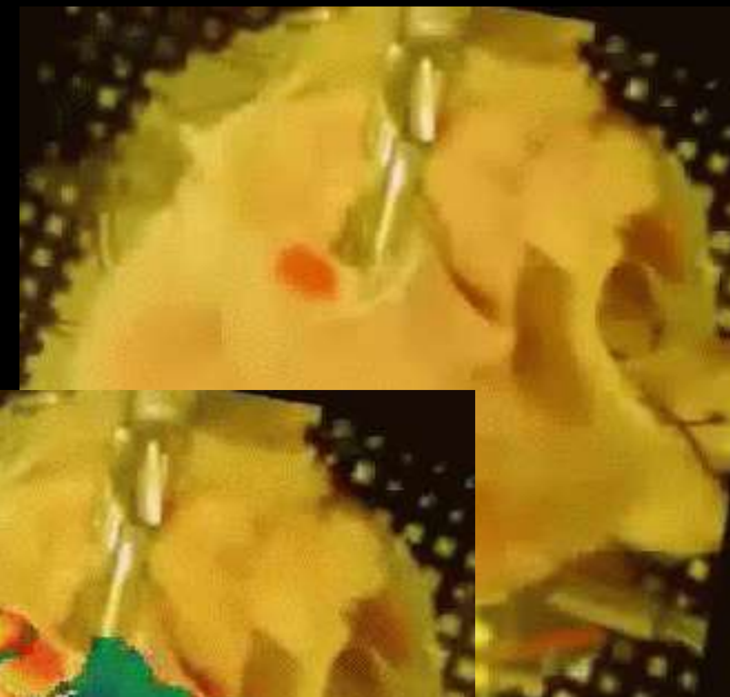


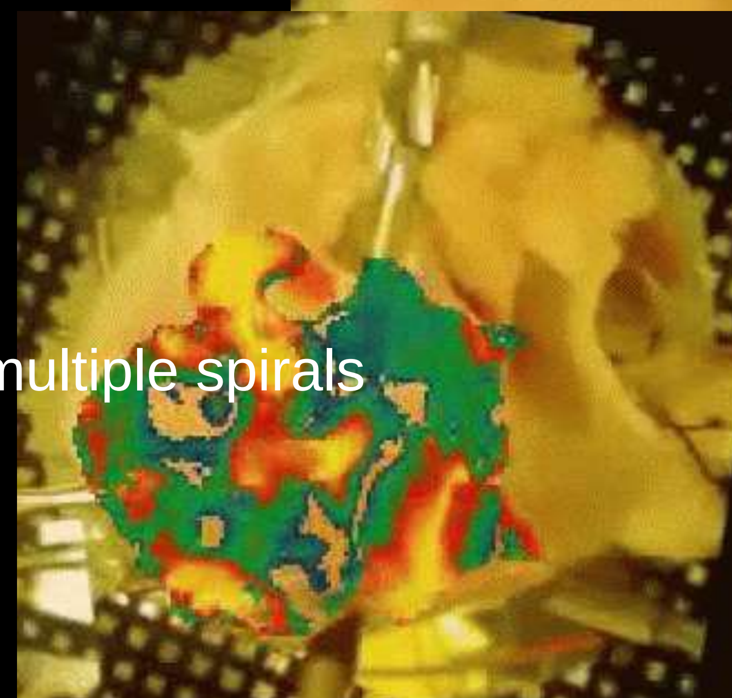


From one spiral to multiple spirals

Spiral Wave Instabilities

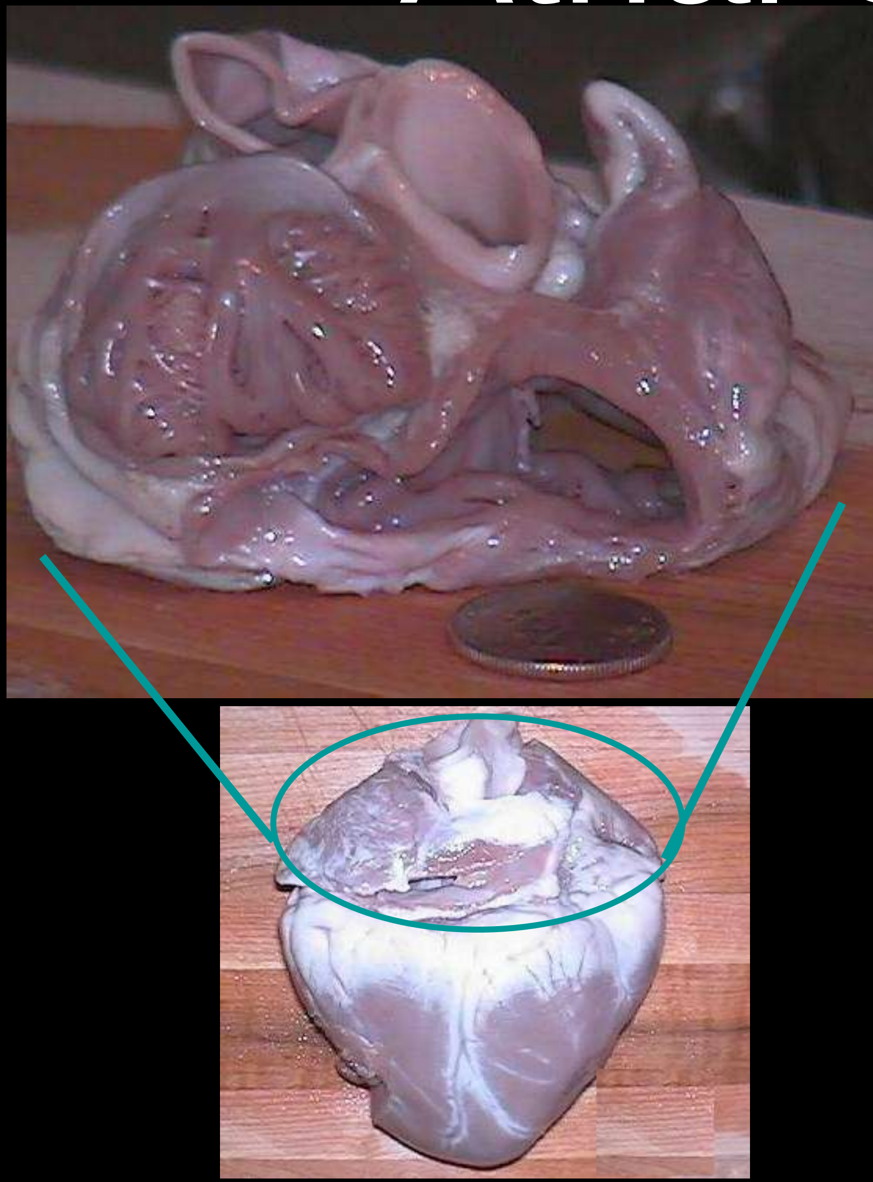


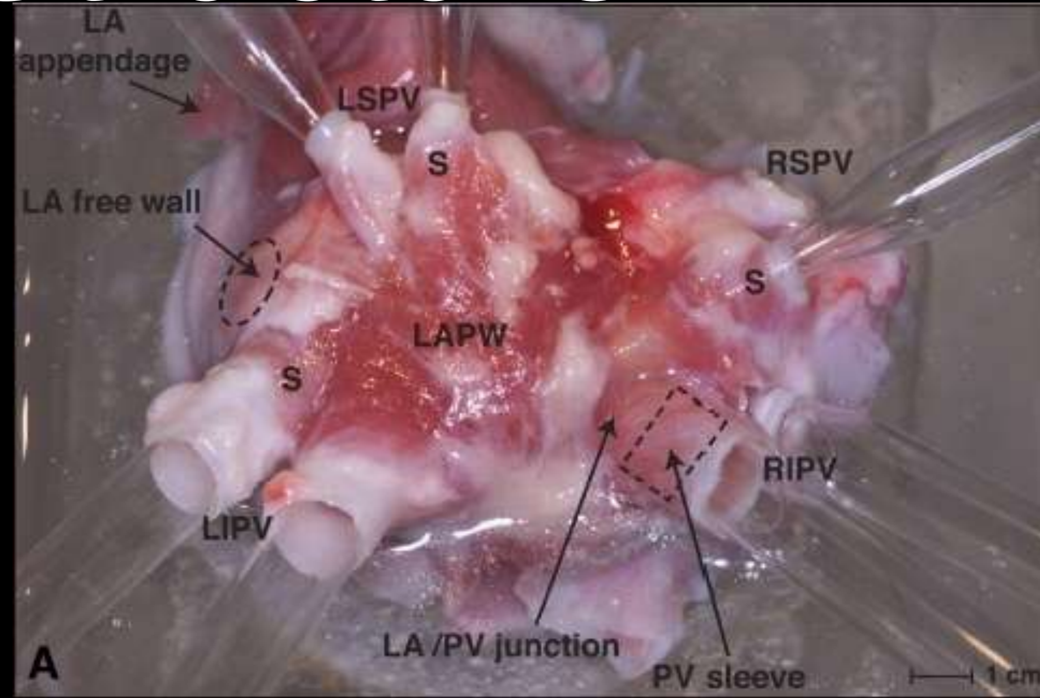




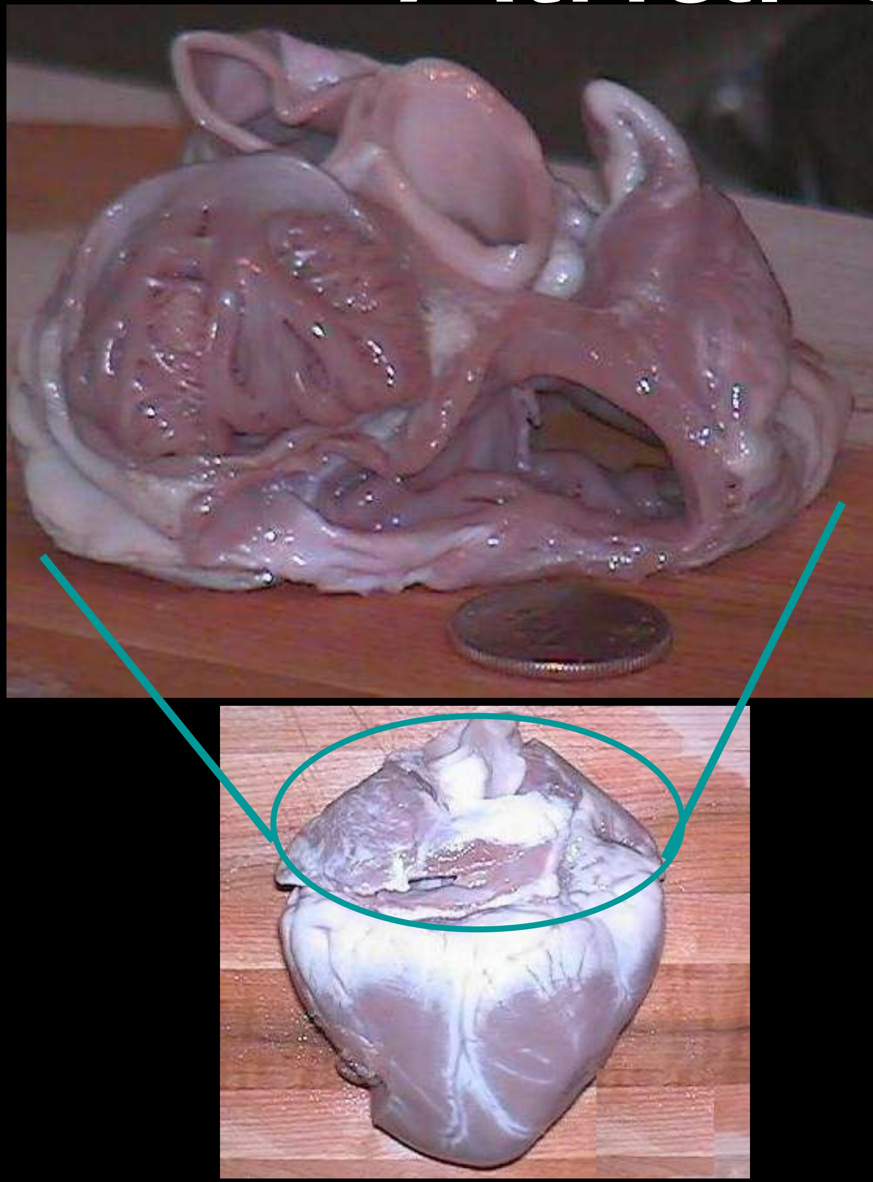
From one spiral to multiple spirals

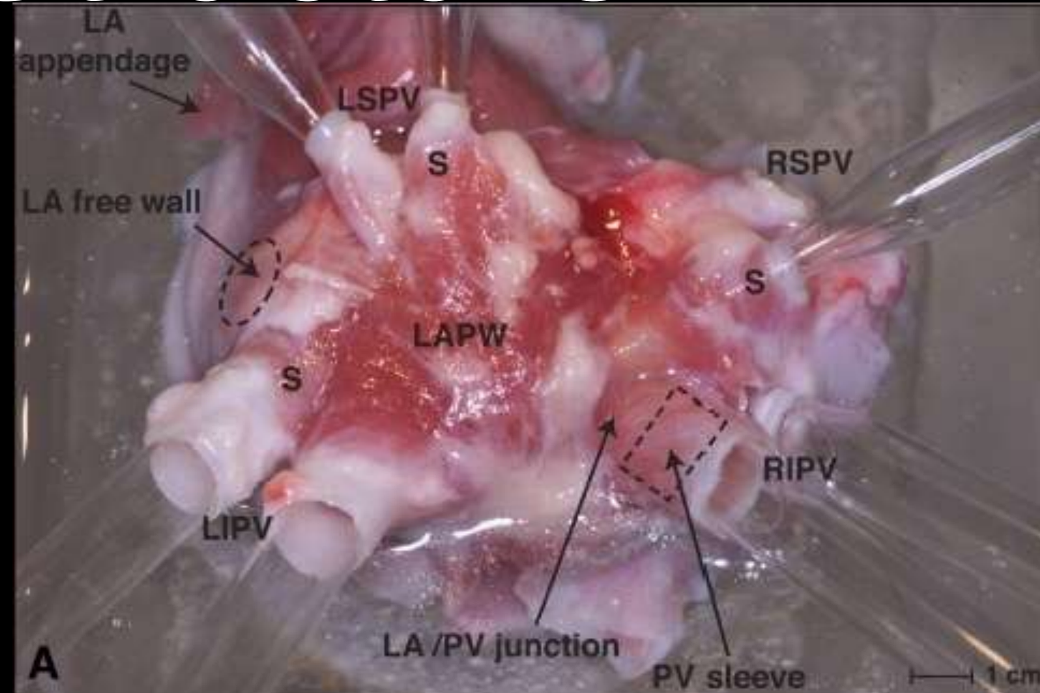
Atrial Structure

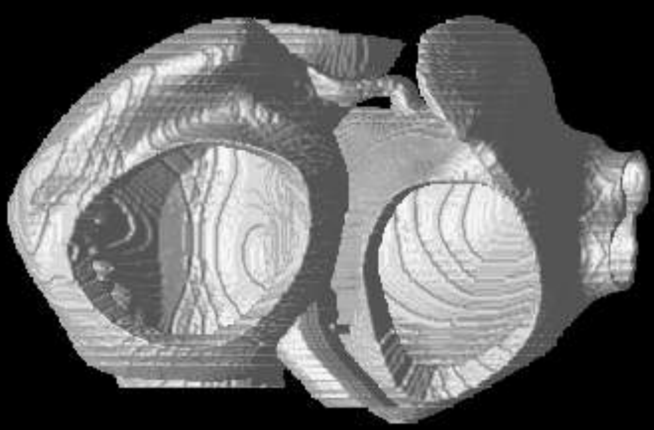




Atrial Structure







Visualization of Electrical Activity in the Heart

Visualizing Electrical Activity

- Computer simulations.
  - Mathematical models of cellular electrophysiology.
- Optical mapping.
  - Fluorescence recordings using voltage-sensitive dyes.
  - Intensity proportional to membrane potential.

Normal Sinus Rhythm
Plane Waves (Optical Mapping)

Electrical activity in the atria

Normal Sinus Rhythm
Plane Waves (Optical Mapping)

Electrical activity in the atria

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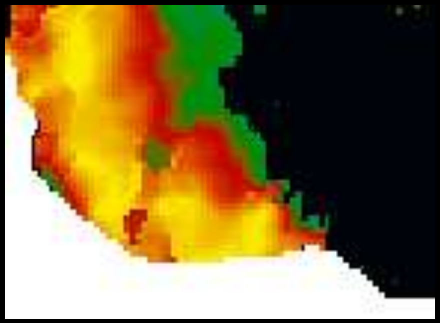
Normal Sinus Rhythm Plane Waves (Optical Mapping)

Electrical activity in the atria

Electrical activity in the ventricle

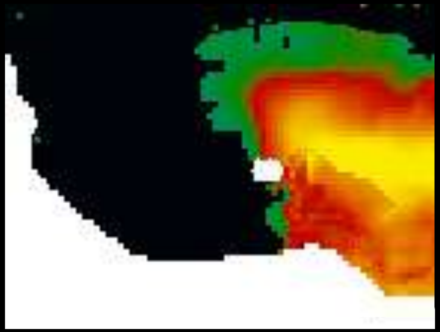
Experimental spiral waves



Circular core
Spiral wave

Cherry EM, Fenton FH. New Journal of Physics 2008; 10: 125016

Experimental spiral waves



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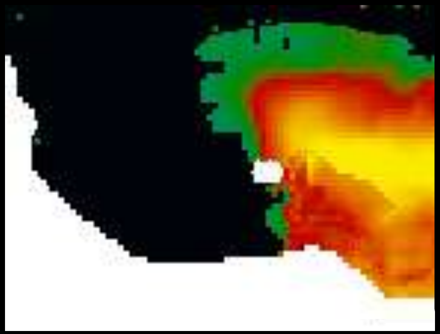

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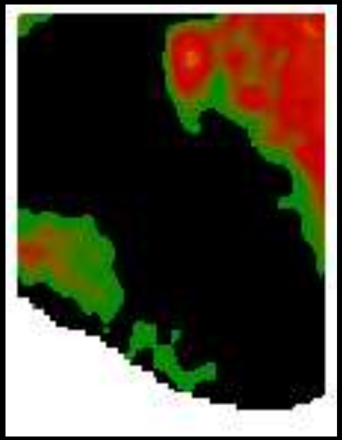

Linear core
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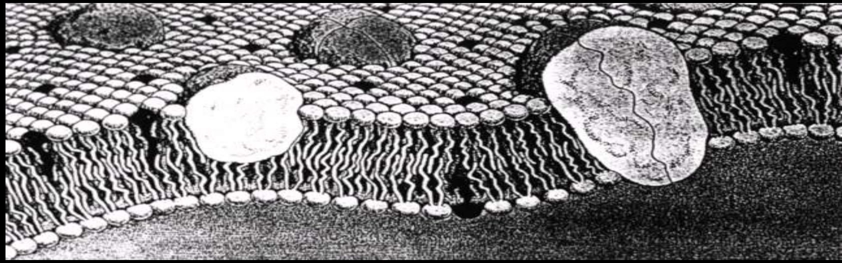
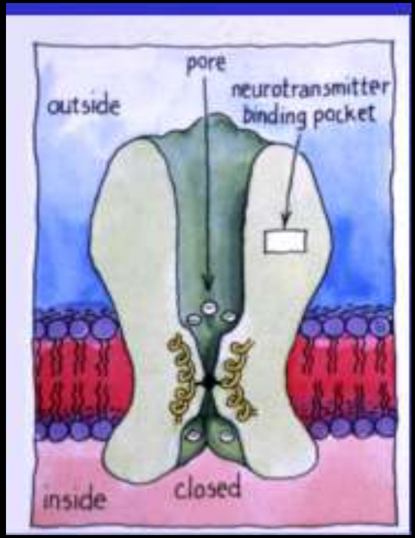
Cherry EM, Fenton FH. New Journal of Physics 2008; 10: 125016

- Cardiac cells are about 100-150 μm in length, 10-20 μm in diameter.
- The cell membrane: lipid bi-layer 10 nm thick, impermeable to ions except through specialized proteins (ion channels).
- Ion concentration gradient and voltage drop across membrane.
- Movement of ions across the membrane produces an action potential.
- Active transport through pumps and exchangers in the membrane restores original concentrations.





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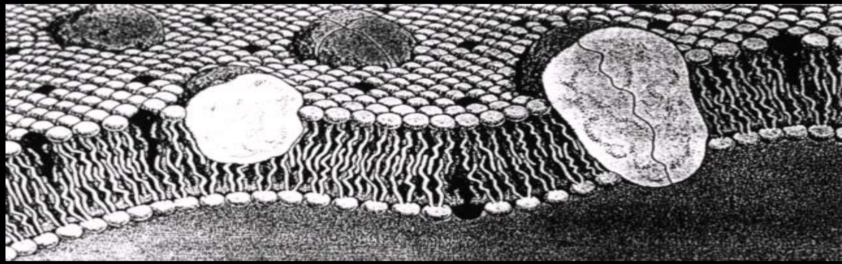
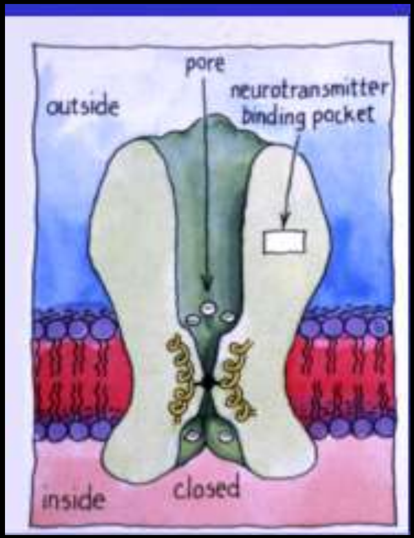
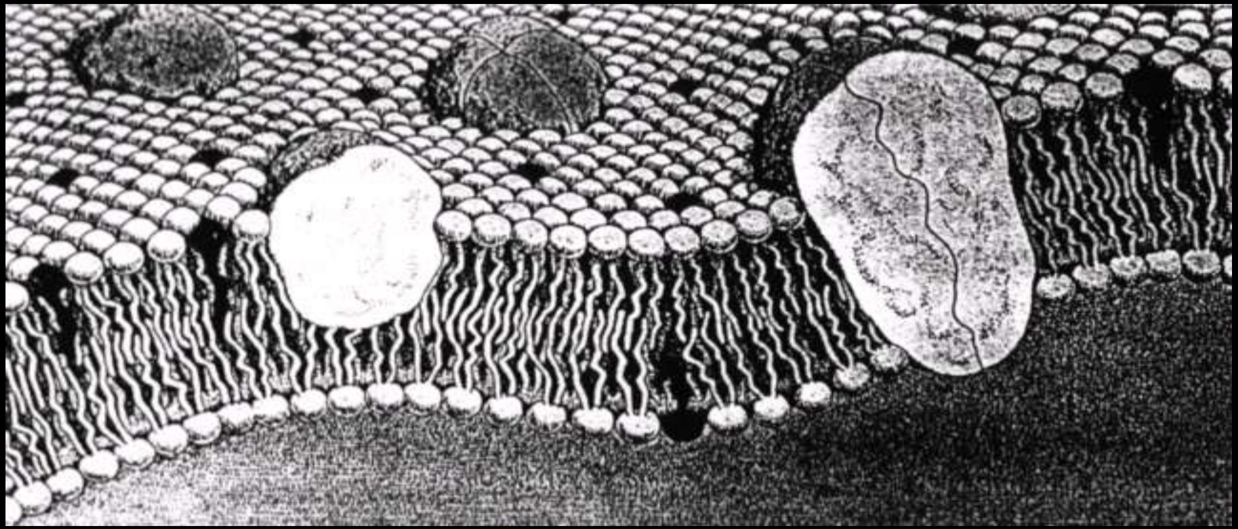
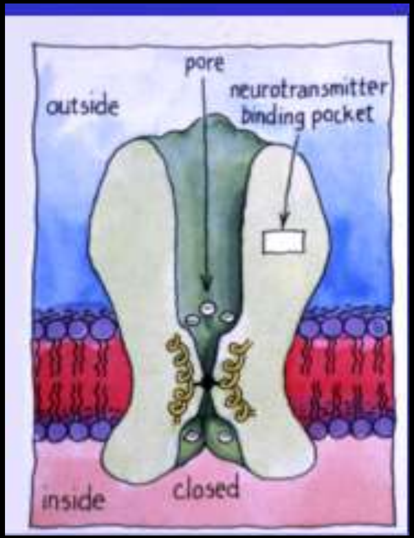




Cellular Electrophysiology

Ca^{2+}, Na^{+}, K^{+}





Electrical-Contraction Coupling

Cellular action potential triggers contraction through calcium processes.

Increased calcium current stimulates release of intracellular store.

Transiently increased calcium binds to contraction proteins.

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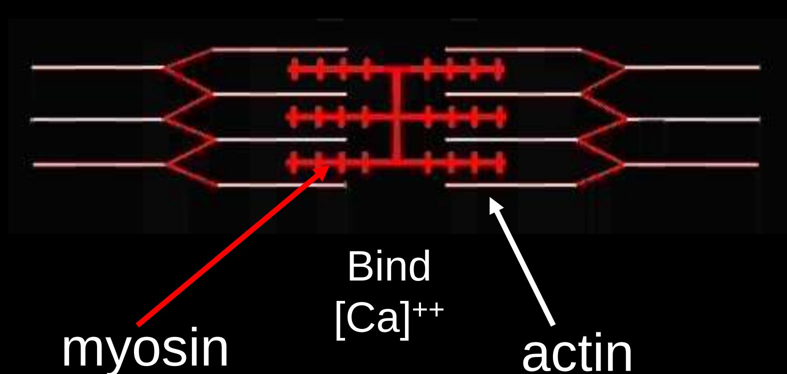

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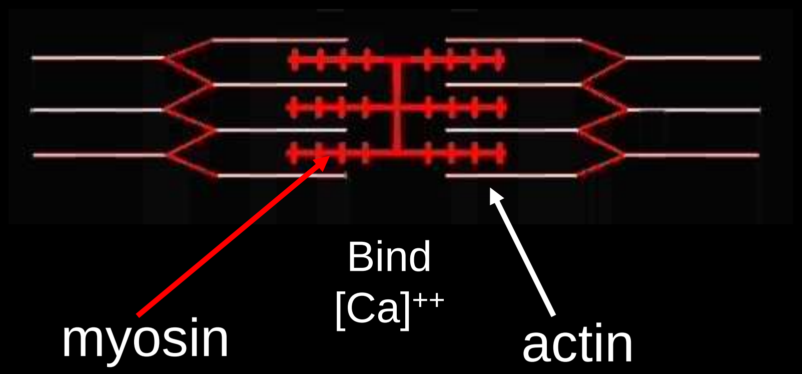
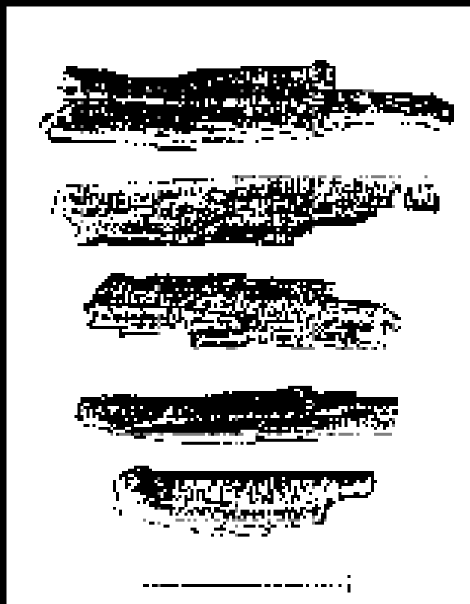
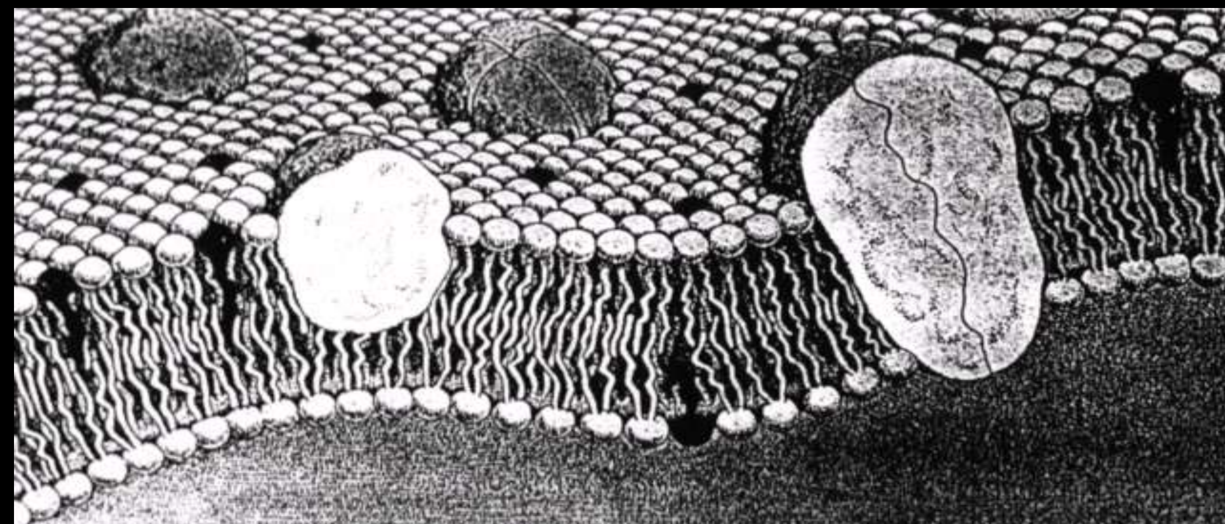


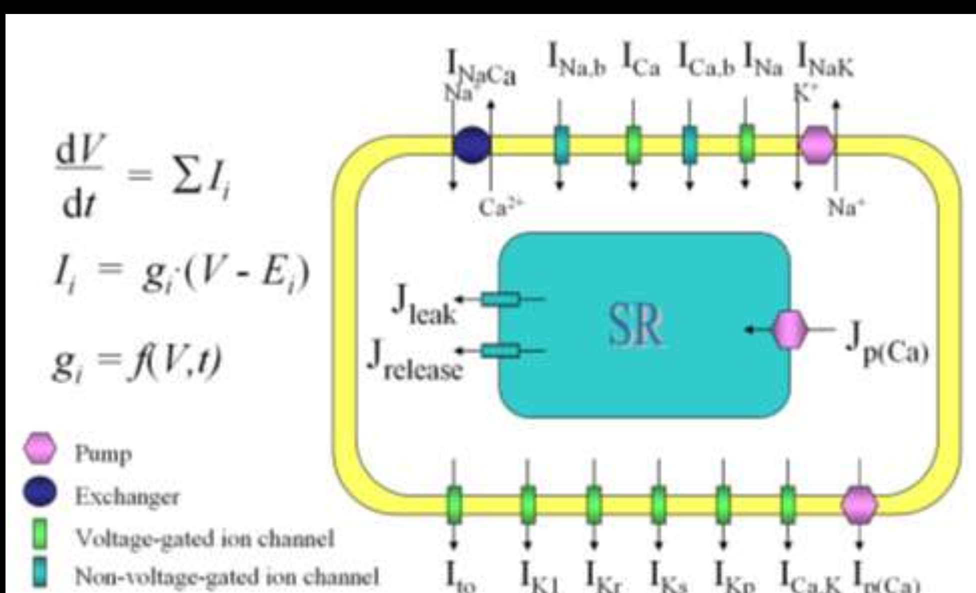
Modeling Cell Electrophysiology



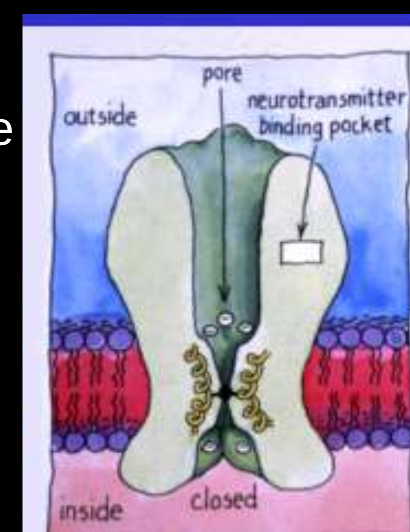
100 microns

Cell membrane thickness: 10 nanometers

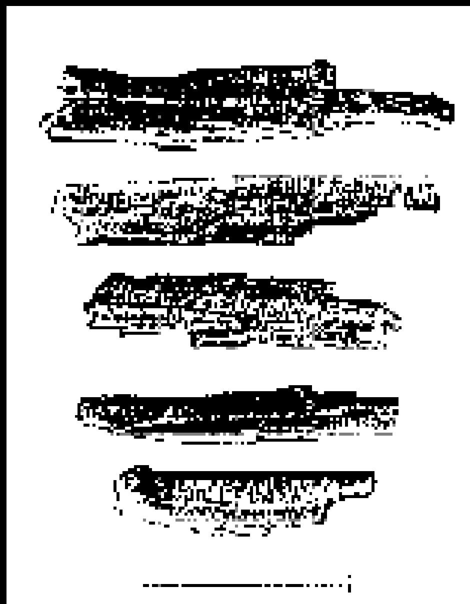


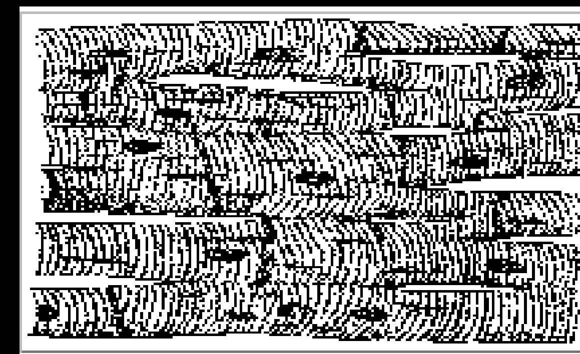


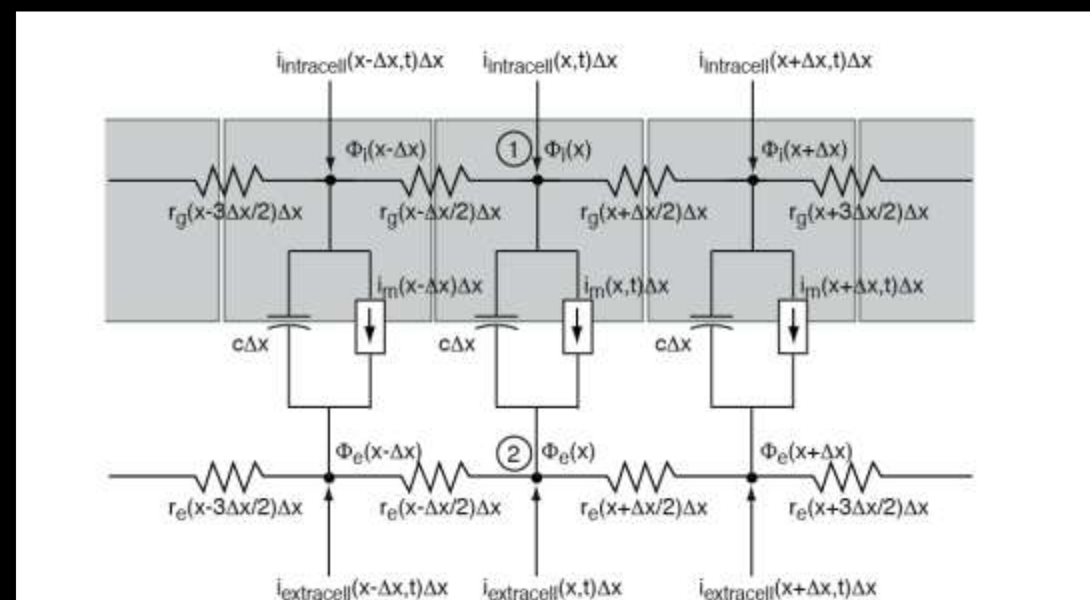
The cell membrane is a lipid bilayer impermeable to ions except through specialized structures.

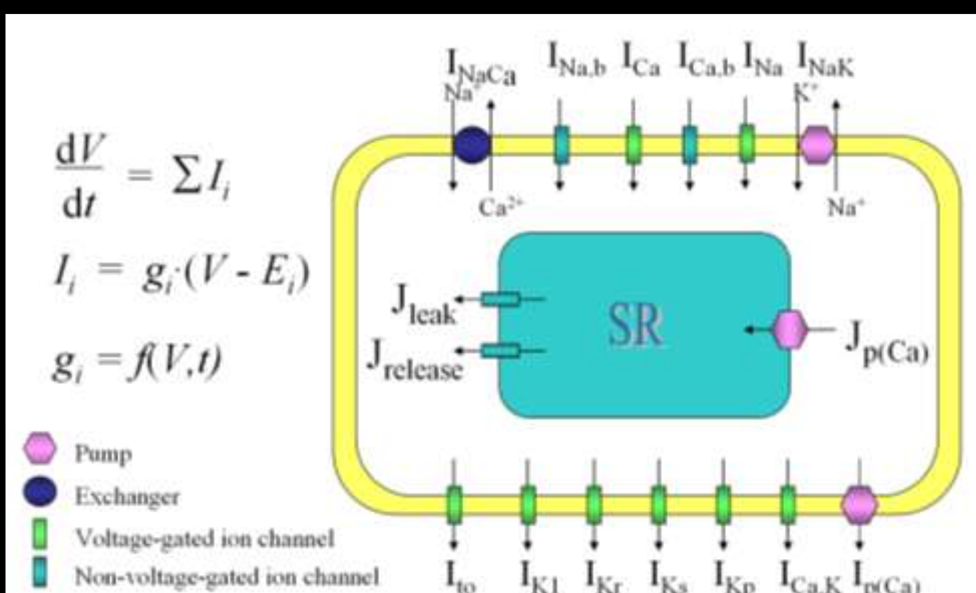


Cell Electrophysiology and Waves in Tissue

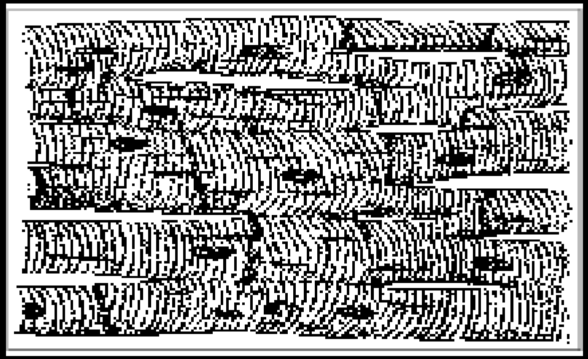


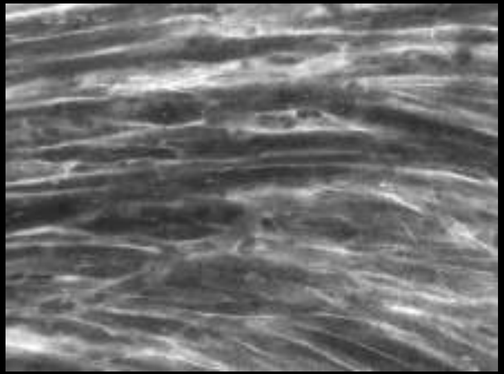


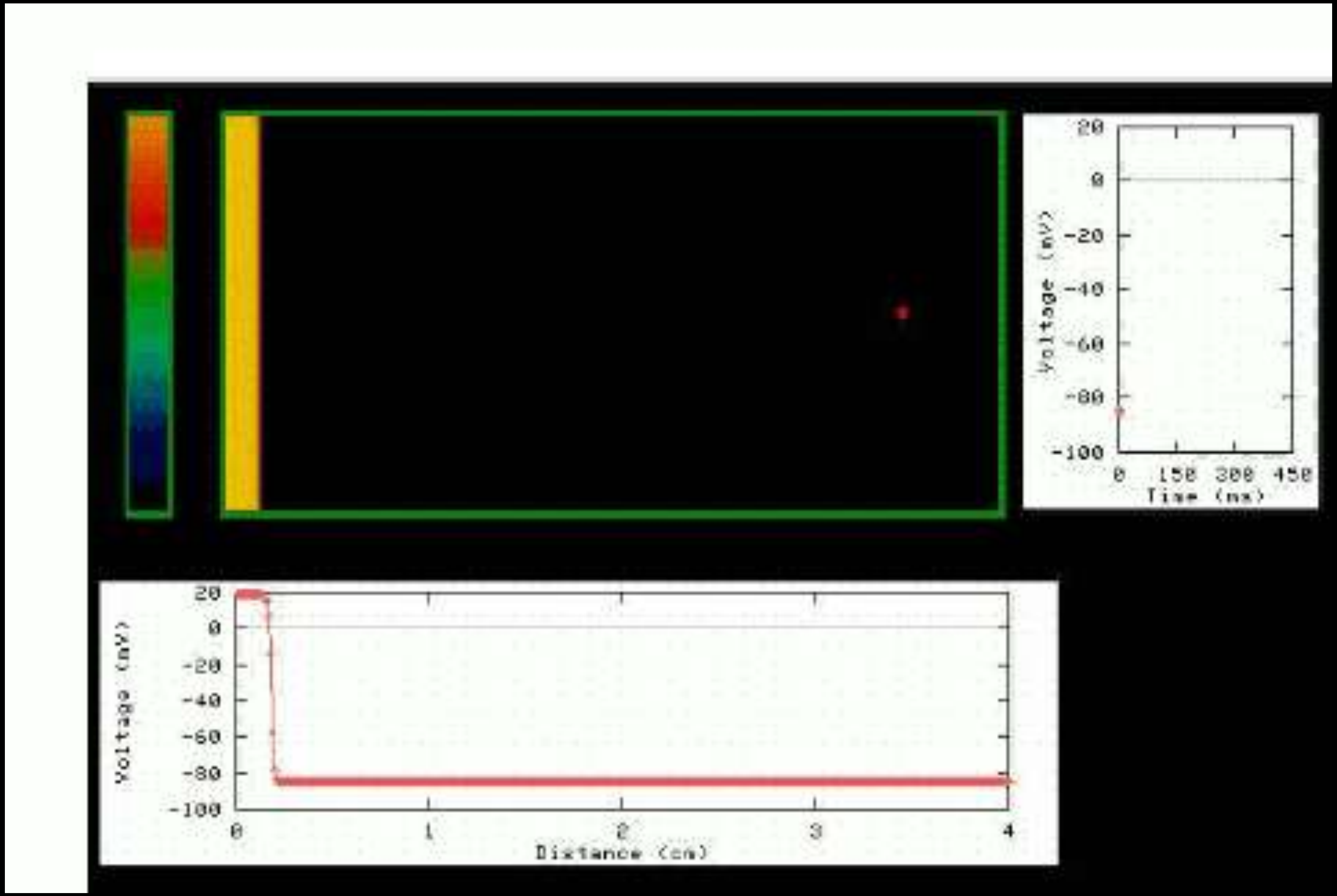




Cells connected
in a 2D preparation







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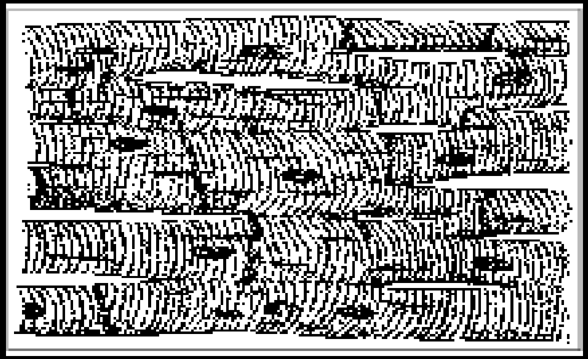
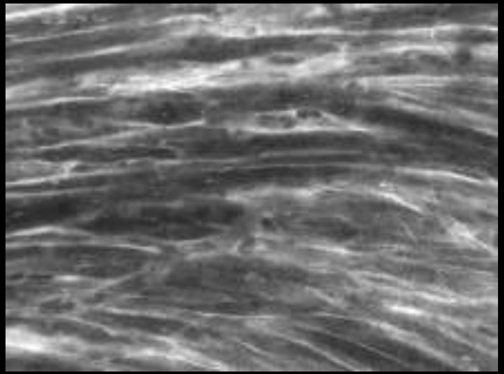
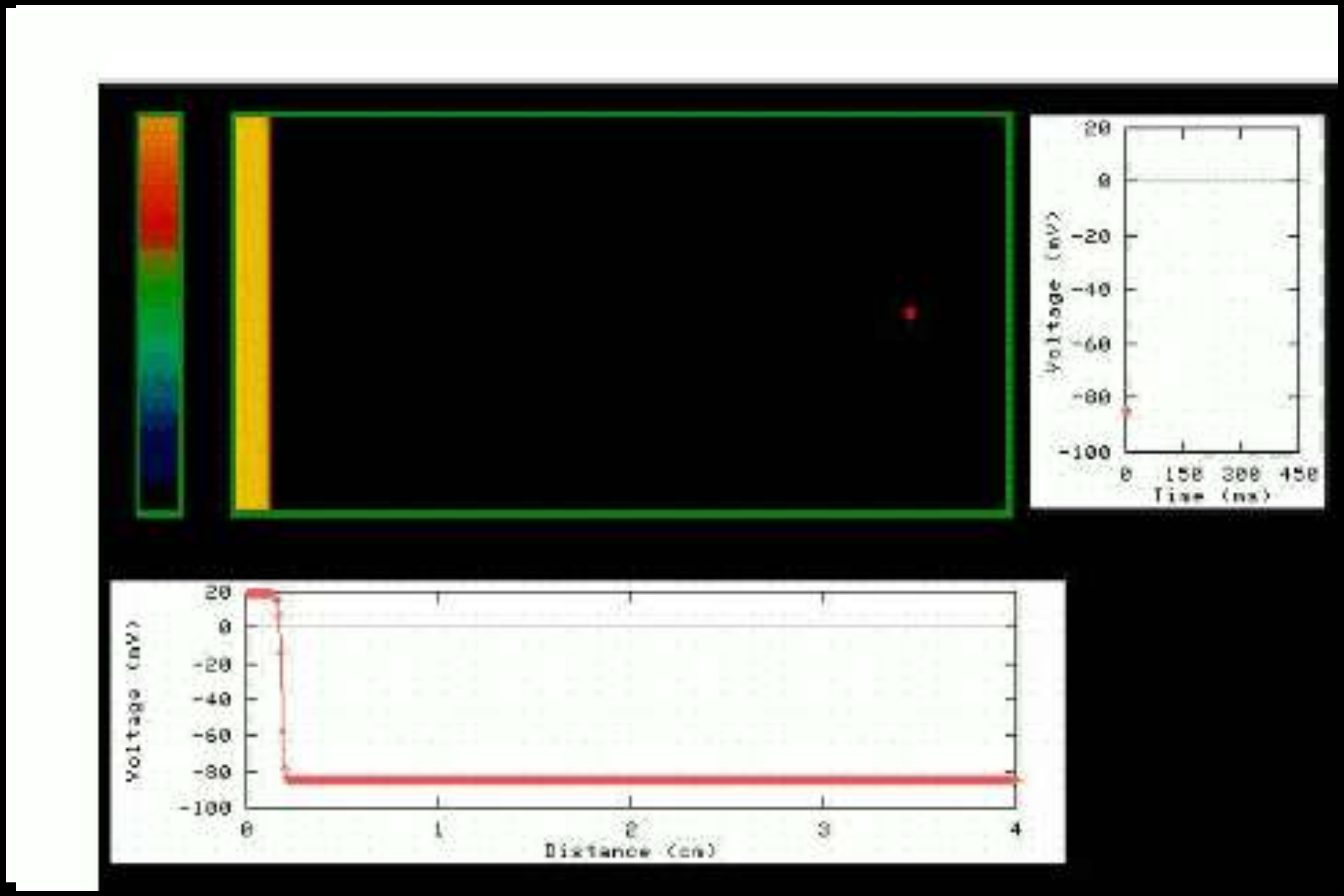
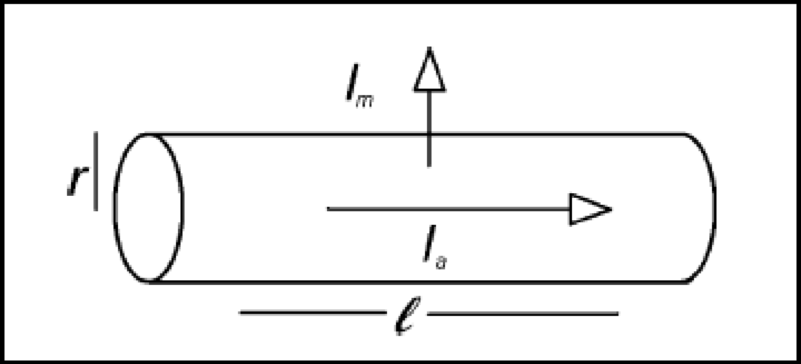






Nonlinear parabolic reaction-diffusion equations

The cable equation for cardiac tissue



Consider cylindrical cells where current flows along and across the membrane

Nonlinear parabolic reaction-diffusion equations

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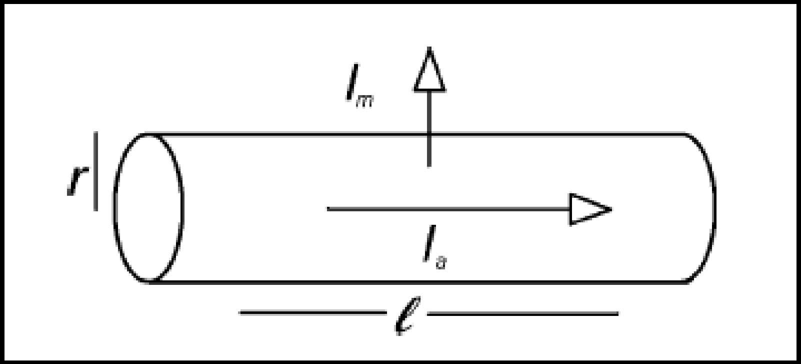

Consider cylindrical cells where current flows along and across the membrane

Charge conservation: membrane current = change in axial current

$$I_{\mathrm{m}} 2\pi r l = [I_{\mathrm{a}}(x+l) - I_{\mathrm{a}}(x)]\pi r^2 \approx -\left(\frac{\partial i_{\mathrm{a}}}{\partial x}\right)\pi l r^2 \qquad (1)$$

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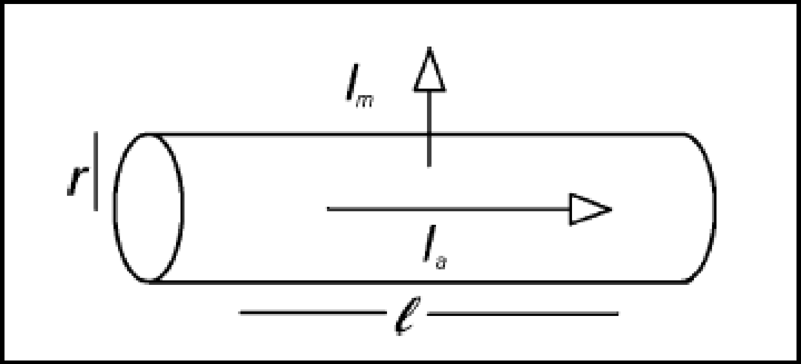

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The flow of current along the cable
Is proportional to the voltage gradient
(Ohm's law)

$$\left(\frac{\partial V_{\mathrm{m}}}{\partial x}\right) = -\rho i_{\mathrm{a}} \qquad (2)$$

Nonlinear parabolic reaction-diffusion equations

The cable equation for cardiac tissue

Nonlinear parabolic reaction-diffusion equations

The cable equation for cardiac tissue

I_m includes: the currents from the flux of ions thought the membrane and a capacitive current I_c from the dielectric membrane

$$I_{\mathrm{m}} = I_{\mathrm{c}} + I_{\mathrm{ion}} = C_{\mathrm{m}}\left(\frac{\partial V_{\mathrm{m}}}{\partial t}\right) + I_{\mathrm{ion}} \qquad (3)$$

Nonlinear parabolic reaction-diffusion equations

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Combining Eq. 1-3 we obtain the equation used to describe voltage Propagation along a 1D cable.

$$\left(\frac{\partial V_{\mathrm{m}}}{\partial t}\right) = r\left(\frac{\partial^2 V_{\mathrm{m}}/\partial x^2}{2\rho C_{\mathrm{m}}}\right) - \frac{I_{\mathrm{ion}}}{C_{\mathrm{m}}} = D\left(\frac{\partial^2 V_{\mathrm{m}}}{\partial x^2}\right) - \frac{I_{\mathrm{ion}}}{C_{\mathrm{m}}} \tag{4}$$

Nonlinear parabolic reaction-diffusion equations

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Continuum Mathematical Model

Nonlinear parabolic reaction-diffusion equations:

$$C_{\mathrm{m}}\partial_t V(t,\mathbf{x}) = \nabla\cdot(D(\mathbf{x})\nabla V) - I_{\mathrm{ion}}(V,\mathbf{m}) - I_{\mathrm{stim}}(t,\mathbf{x})$$

$$\partial_t \mathbf{m}(t,\mathbf{x}) = \mathbf{f}(V,\mathbf{m})$$

$V(t,\mathbf{x})$ membrane potential

$\mathbf{m}(t,\mathbf{x})$ gating variables, ionic concentrations

C_{m} membrane capacitance

$D(\mathbf{x})$ conductivity tensor

$I_{\mathbf{ion}}$ total ionic current across the membrane of the cell

$I_{\mathbf{stim}}$ external stimulus current

Neumann boundary conditions on potential V:

$$n\cdot\nabla V=0$$

Continuum Mathematical Model

Nonlinear parabolic reaction-diffusion equations:

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Examples:

Ventricular:

- Luo-Rudy d (LRd) 20v
- Fox et al. 13v

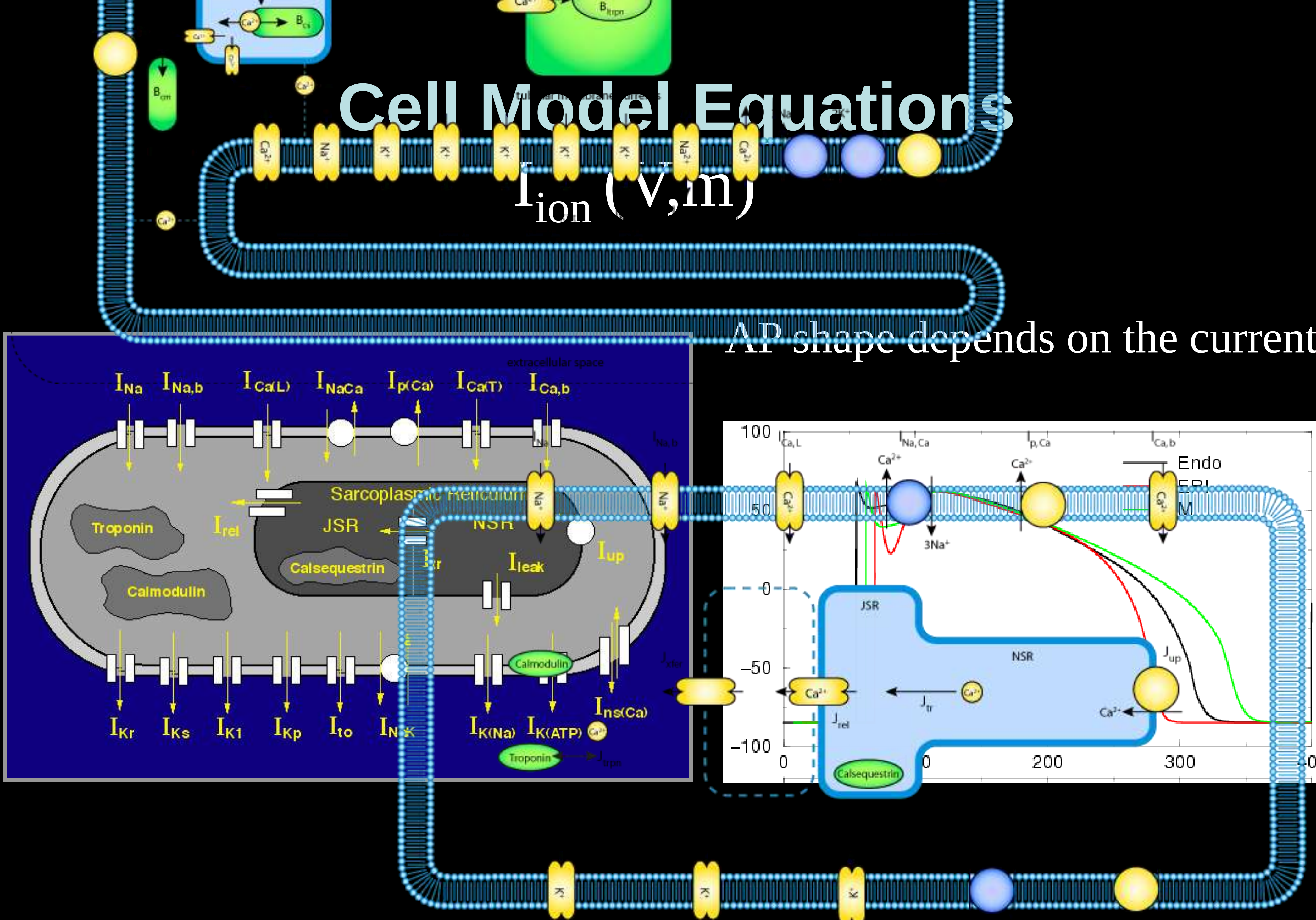
Atrial:

- Courtemanche. 19v
- Nygren. 29v

Cell Model Equations

$I_{ion}(V, m)$

AP shape depends on the currents



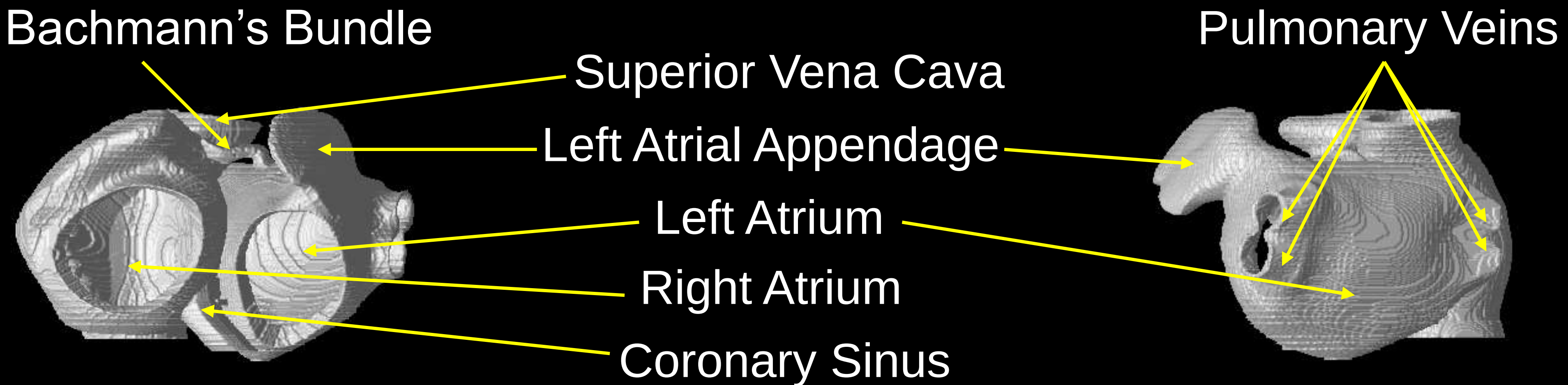
Anatomically Realistic Model of Human Atria

Dimensions:

7.5cm x 7cm x 5.5cm

2.5 million nodes

Harrild and Henriquez, 2000
+ coronary sinus



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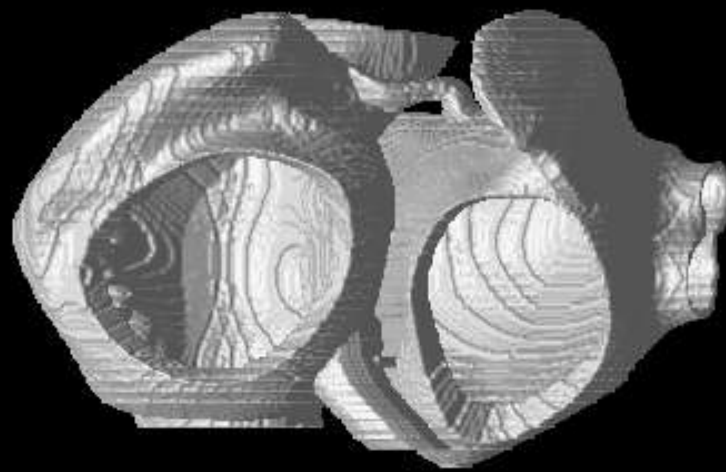

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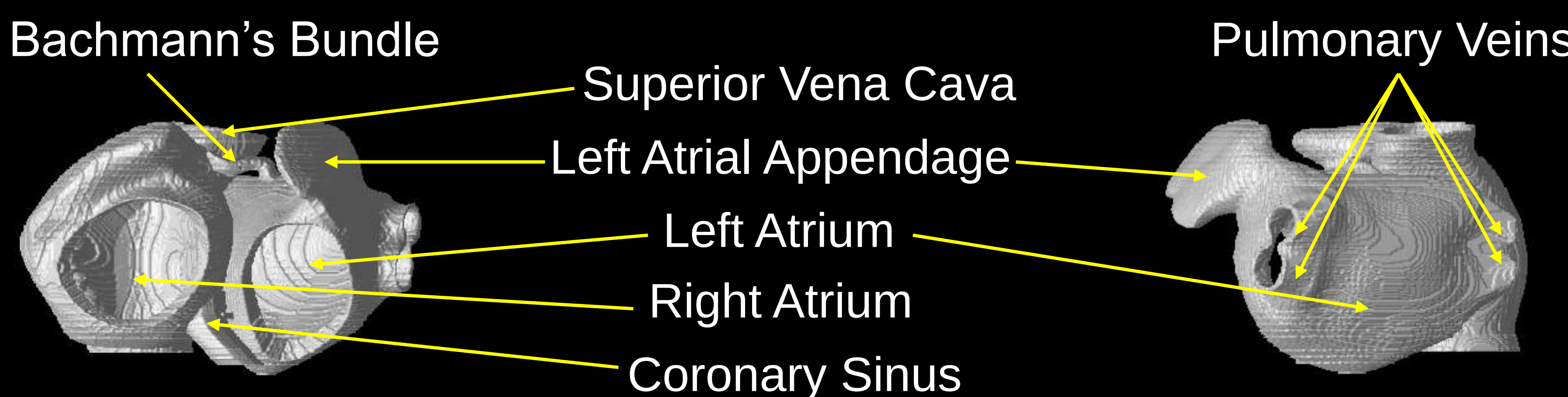


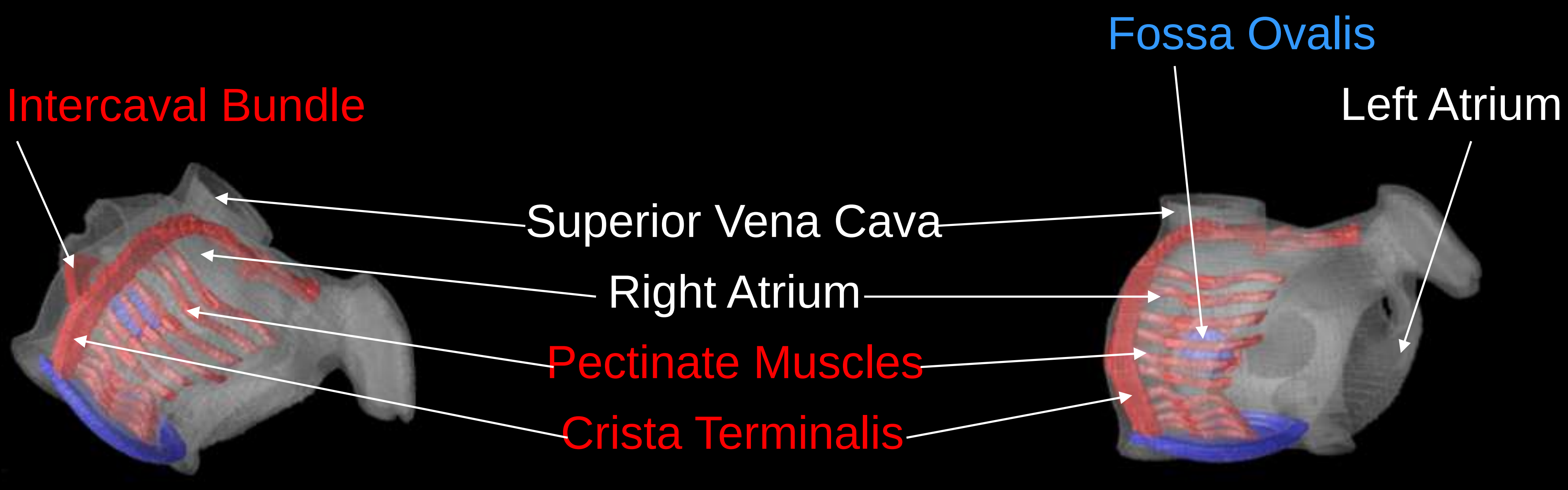
Bundle Conductivities

Healthy atria

Fast CV: 150 cm/s

Bulk CV: 60 cm/s

Slow CV: 35 cm/s



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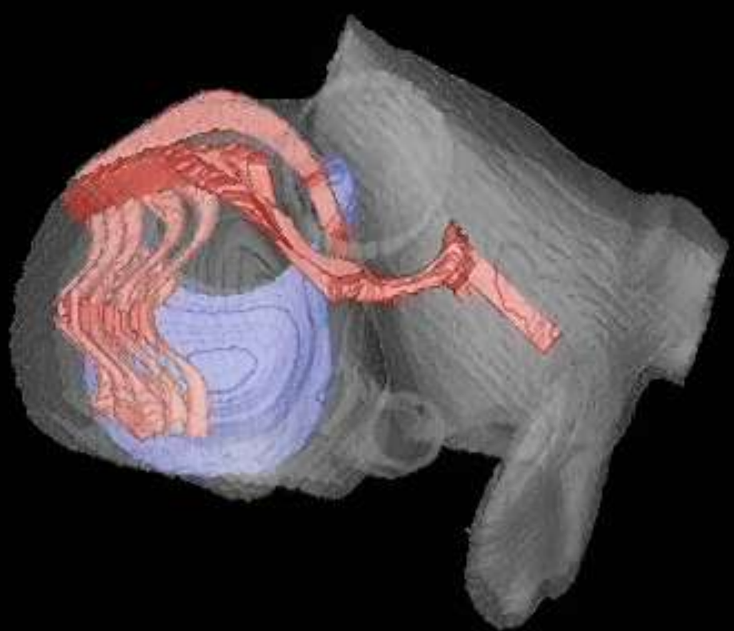
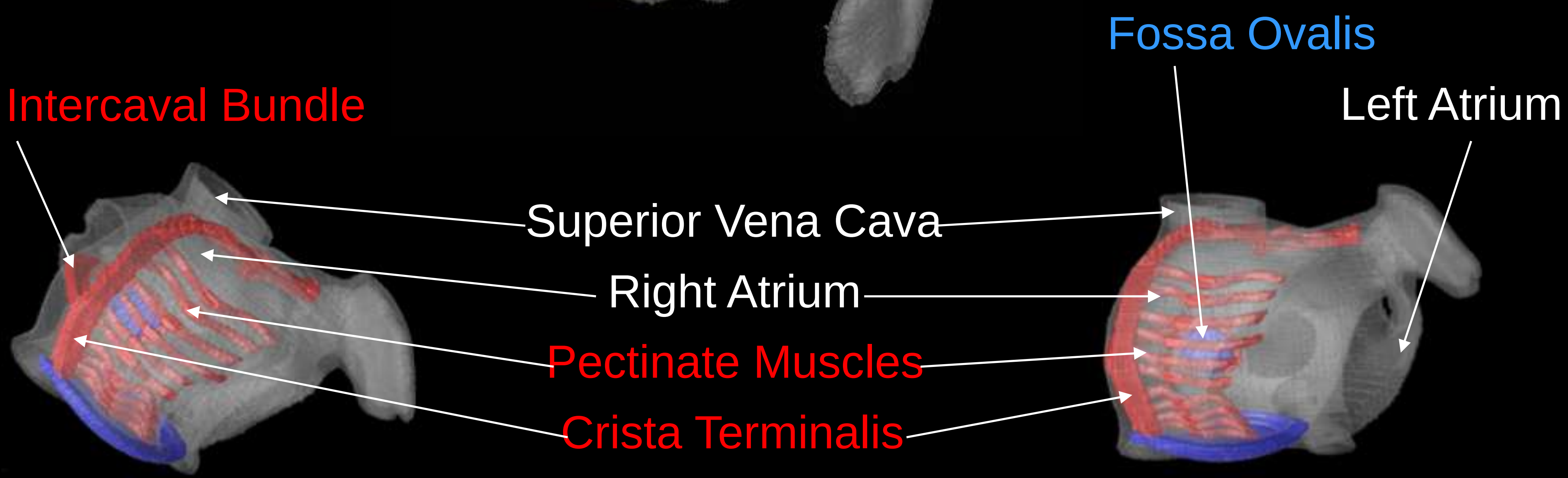




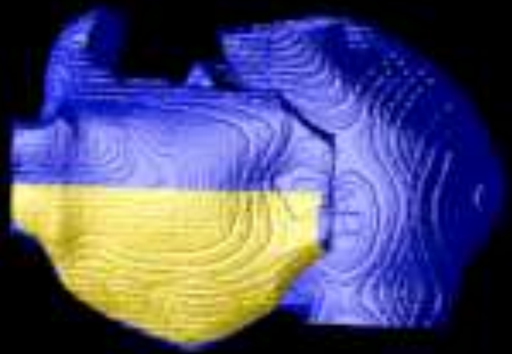
Reentry in the Atrial Model

Atrial Tachycardia

Atrial Fibrillation

Reentry in the Atrial Model

Atrial Tachycardia



Atrial Fibrillation

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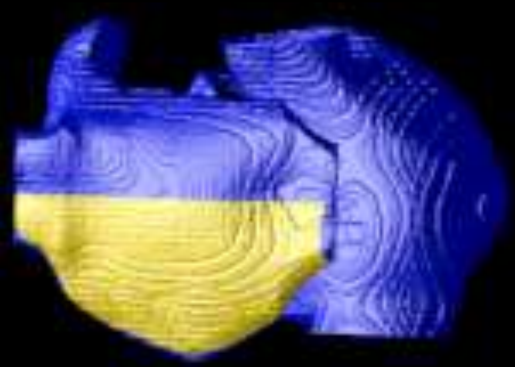

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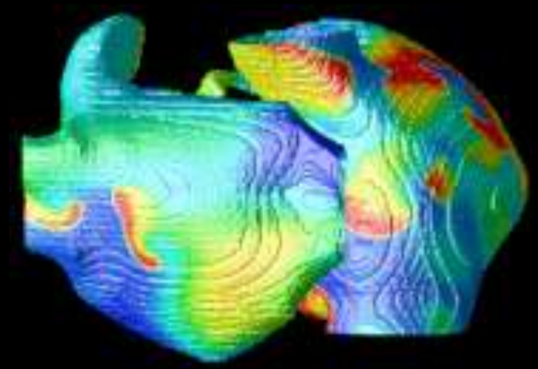

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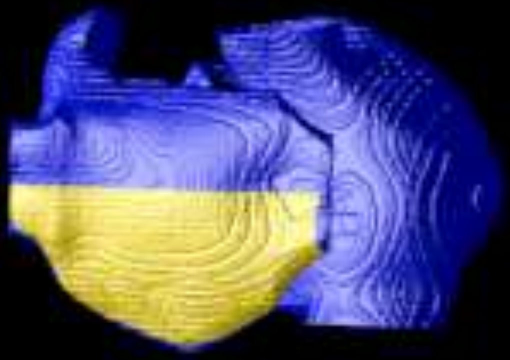

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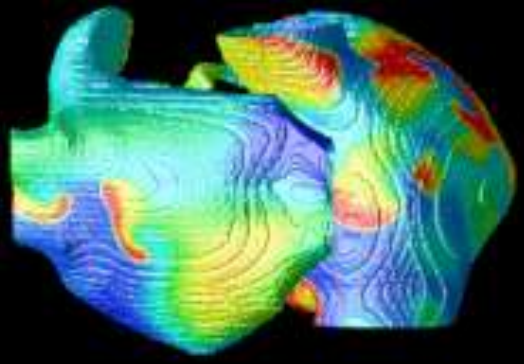


How to terminate reentrant arrhythmias?

Modeling AF Ablation

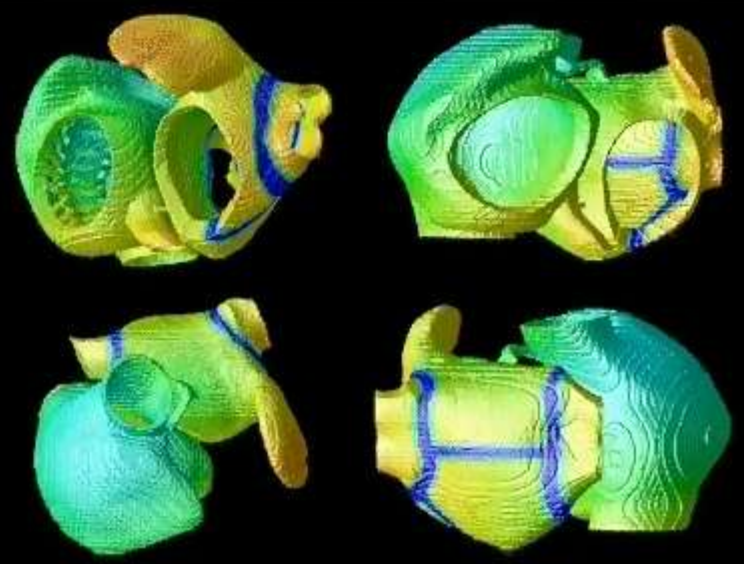
Left atrial lines only

Left + right lines

Modeling AF Ablation

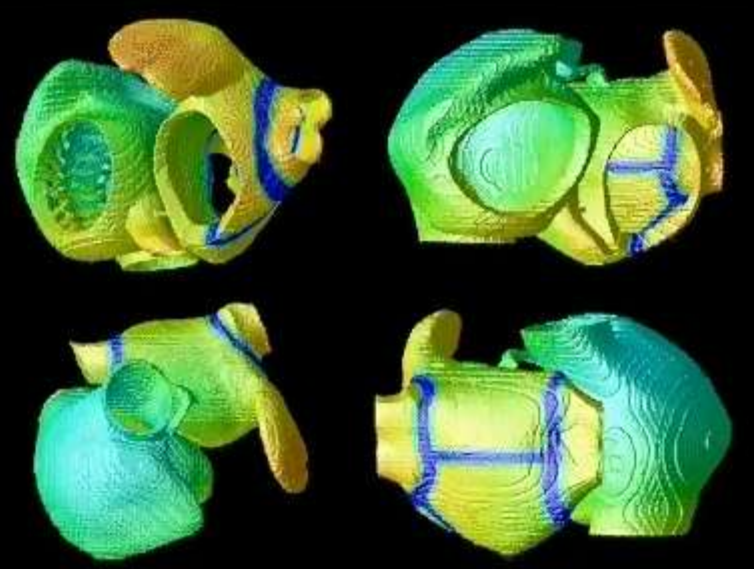
Left atrial lines only

Left + right lines



Modeling AF Ablation

Left atrial lines only



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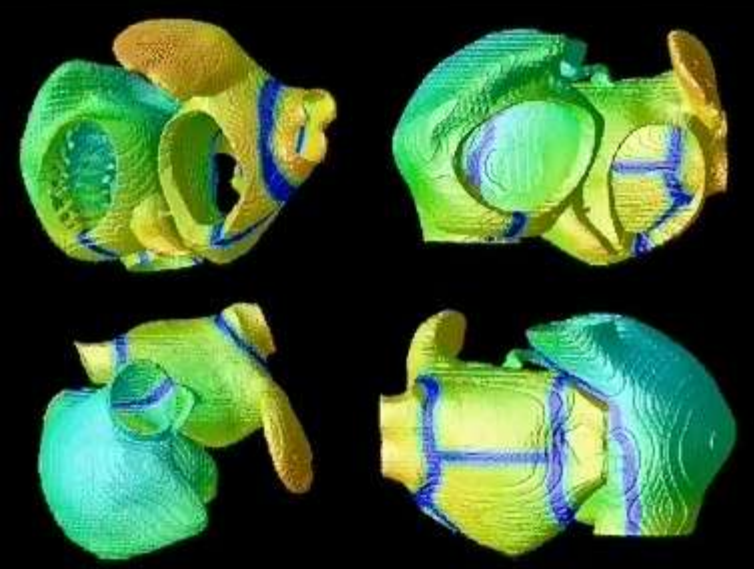
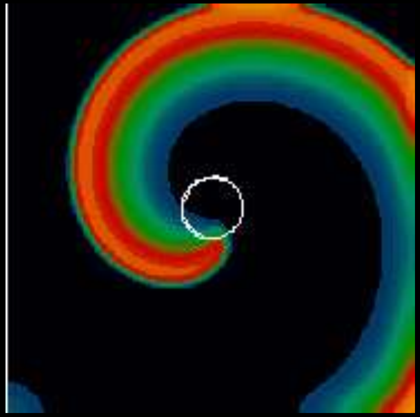


Spiral waves
simulation and optical mapping

Cherry EM, Fenton FH. New Journal of Physics 2008; 10: 125016

Spiral waves
simulation and optical mapping



Circular core Spiral wave

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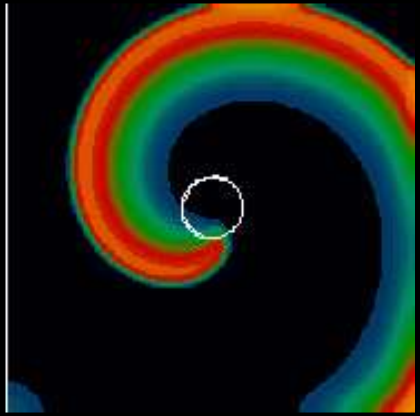

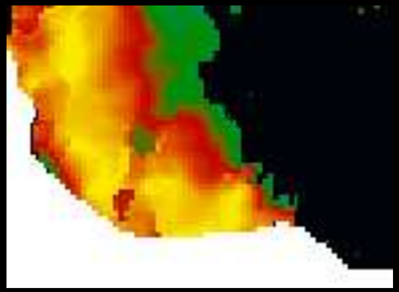

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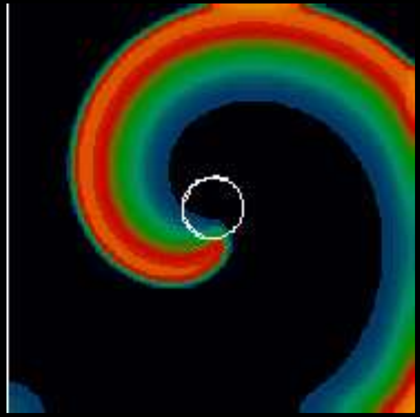

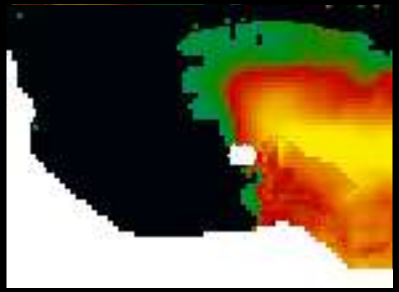

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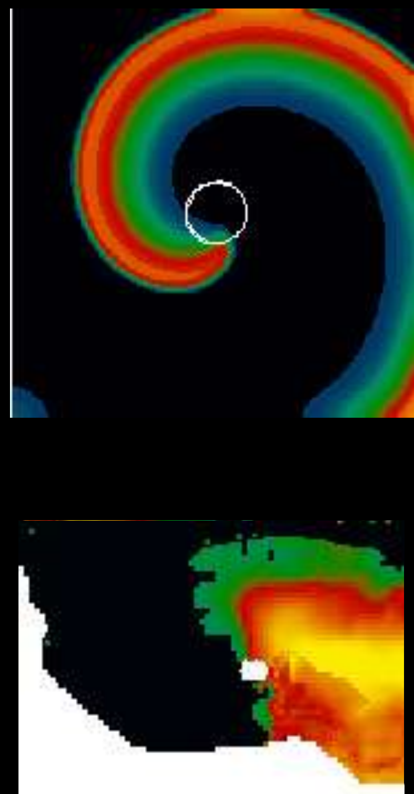
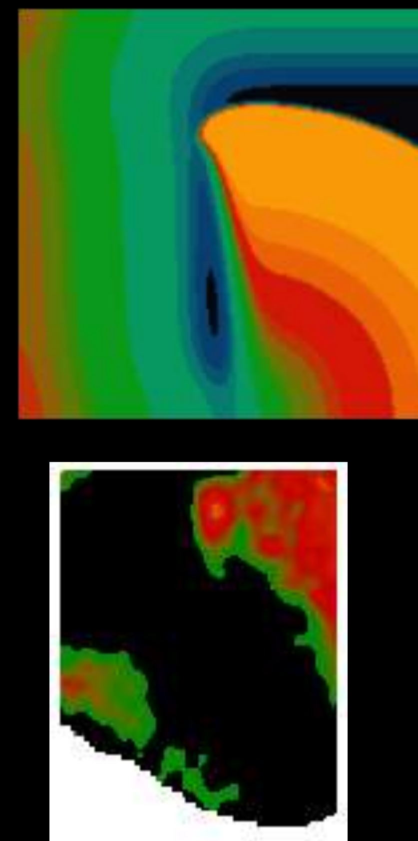


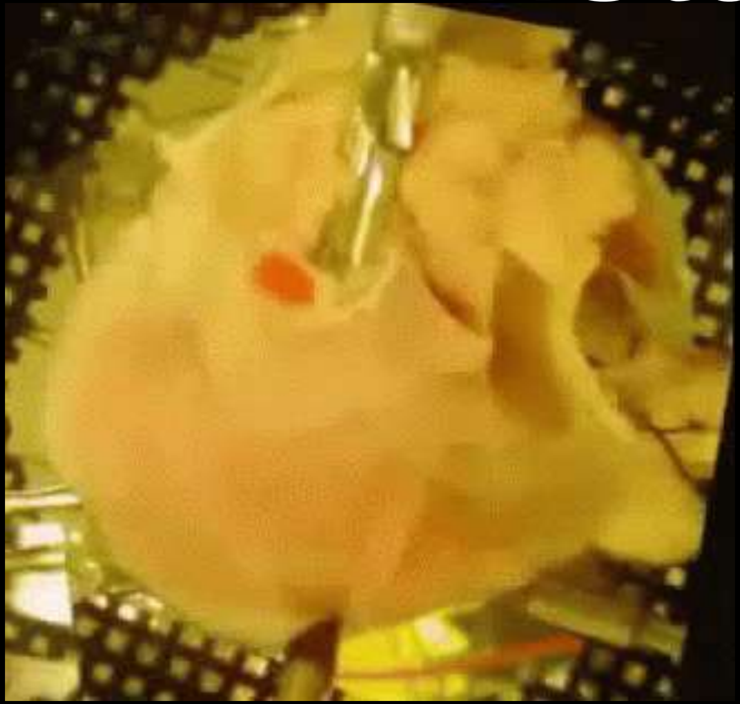
Circular core Spiral wave



Linear core Spiral wave

Cherry EM, Fenton FH. New Journal of Physics 2008; 10: 125016

Spiral Wave Instabilities



Modeling AF defibrillation

- Electrical therapies

1 Ideker RE, Zhou X, Knisley SB.
Pacing Clin Electrophysiol 1995;18:512-525.
2 Santini et al. J Interv Card Electrophysiol 1999;3:45-51.
3 Koster et al. Am Heart J 2004;147:e20-e26.

Modeling AF defibrillation

- Electrical therapies
  - ATP (effective only for slow tachycardias)
  - Electrical cardioversion (requires >5V/cm)[1]

    External ~ 100J - 280J up to 360J (1000V, 30-45 A)[3]

    Internal ~7J (350V, 4 A)[2]

1 Ideker RE, Zhou X, Knisley SB.
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Modeling AF defibrillation

- Electrical therapies
  - ATP (effective only for slow tachycardias)
  - Electrical cardioversion (requires >5V/cm)[1]

    External ~ 100J - 280J up to 360J (1000V, 30-45 A)[3]

    Internal ~7J (350V, 4 A)[2]

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Overview of Project

S Smolka, R Grosu, J. Glimm, R. Gilmour, F. Fenton

- Model Checking and abstraction
- Atrial detail models ←→ Minimal models ←→ Hybrid automata models
- Experimental data (normal and disease)
  Characteristics with model checking

Specific Criteria:

Single cell:

- Threshold for excitation
- dV/dt_max (upstroke)
- Resting membrane potential
- APD_min and DI_min
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- AP Shape at all cycle lengths

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- Wave length
- # of singularities
- Dominant frequency
- Life time of singularities

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Overview of Project

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Year 3-4

- Quantification of AF initiation and of differences between Normal and disease models.

- Parameter optimization for low voltage FF-AFP

Future Directions

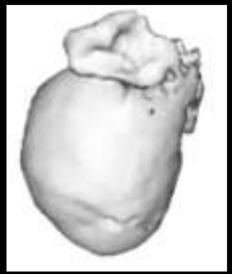
- Apply our expertise in cell modeling to incorporate spatial variability in human ventricular and atrial electrophysiology.

Future Directions

- Use our knowledge and experience in reconstructing three-dimensional tissue structure to develop anatomical models of the human ventricles and atria.

canine

mouse



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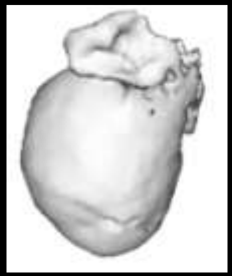
canine

Canine heart (MRI @120 microns resolution)

mouse



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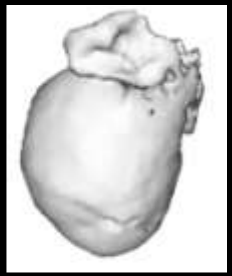

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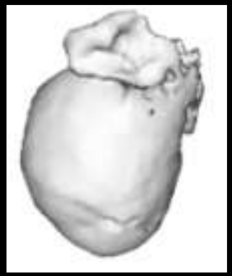

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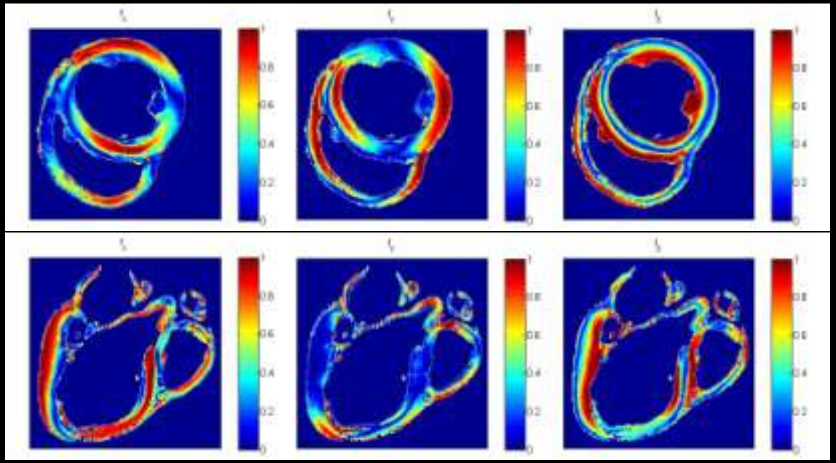

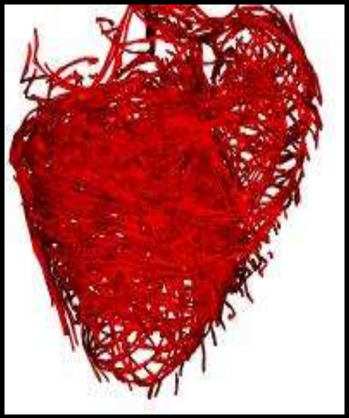

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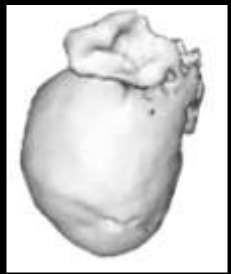

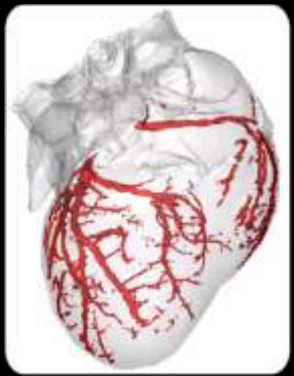

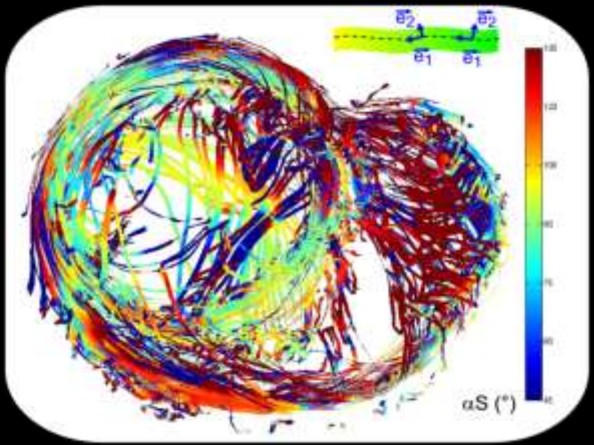

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Collaborators

Robert F. Gilmour, Jr.
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http://TheVirtualHeart.org

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