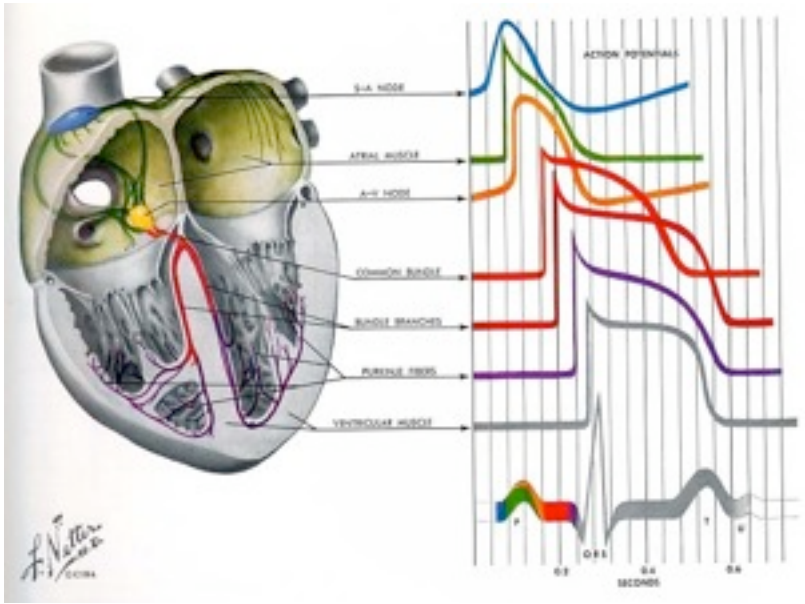
Multiscale computational modeling of cardiac arrhythmogenesis

Trine Krogh-Madsen
Dept. Medicine (Cardiology) *and*
Institute for Computational Biology

Cardiac arrhythmias

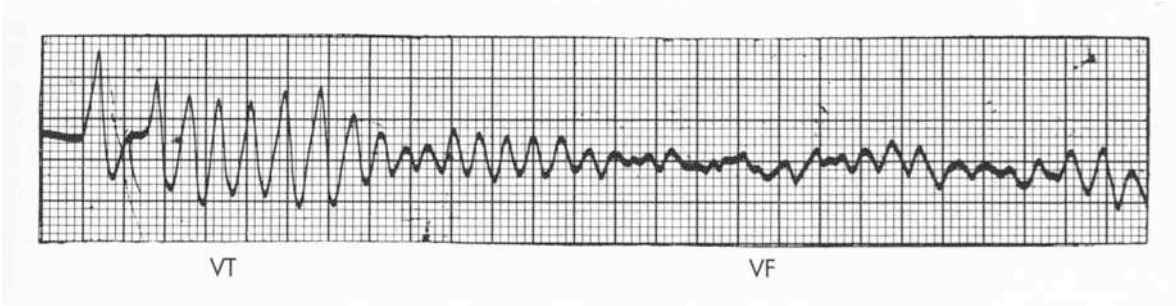


Sudden cardiac death:
~300,000 deaths/year

Ventricular tachycardia
- Rapid activation
- May impair pumping
- May degenerate to VF

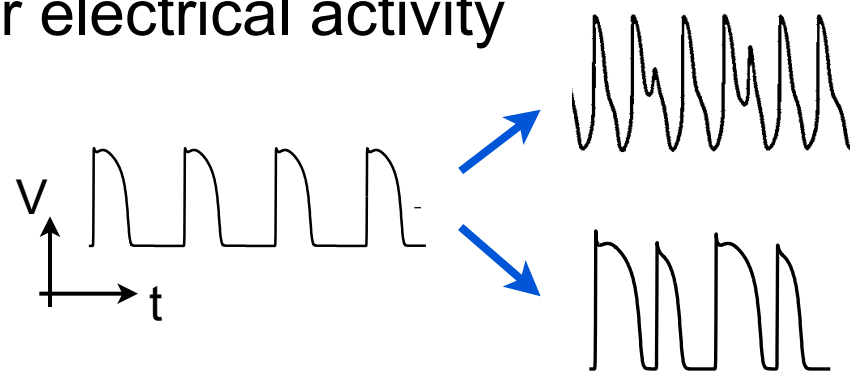
Ventricular fibrillation
- Loss of synchronous activation
- Syncope, death

- How do cardiac arrhythmias initiate?
- How are they sustained?
- What can we do to prevent their occurrence?
- How can we terminate them?

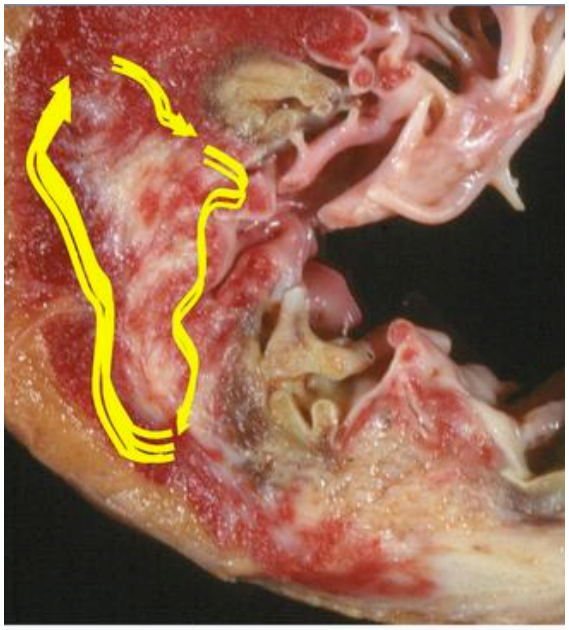


Initiation

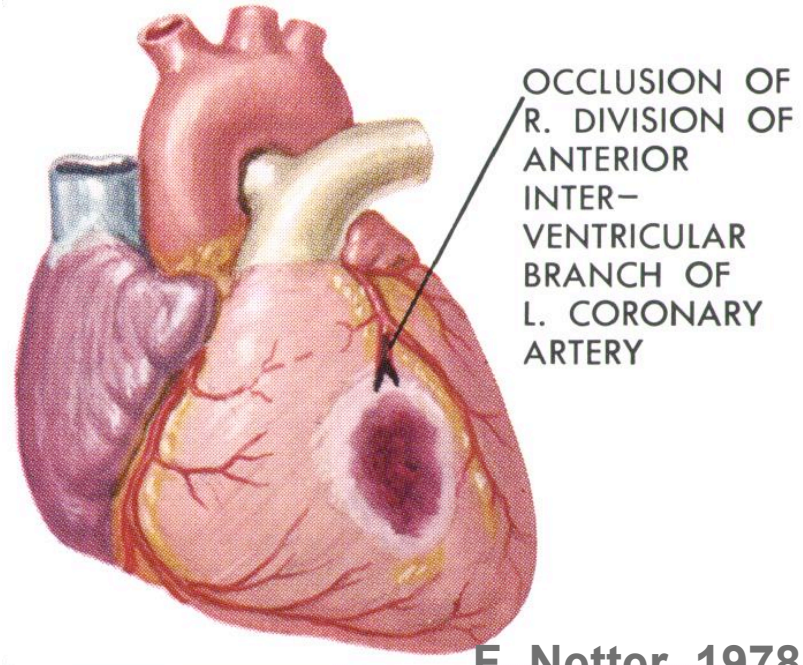
Abnormal cellular electrical activity



Structural heterogeneity

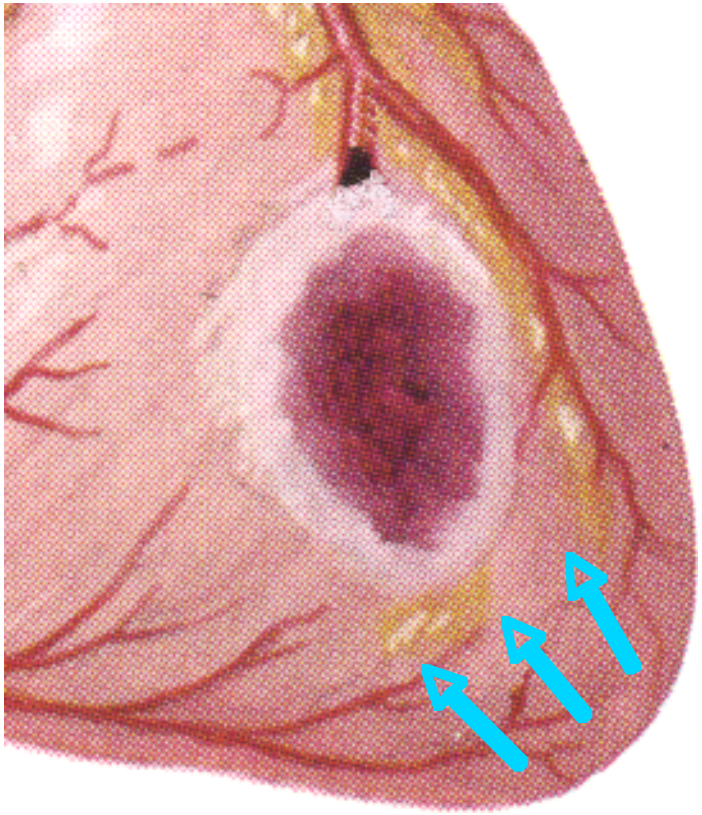


Bill Stevenson, KITP seminar, 2006.

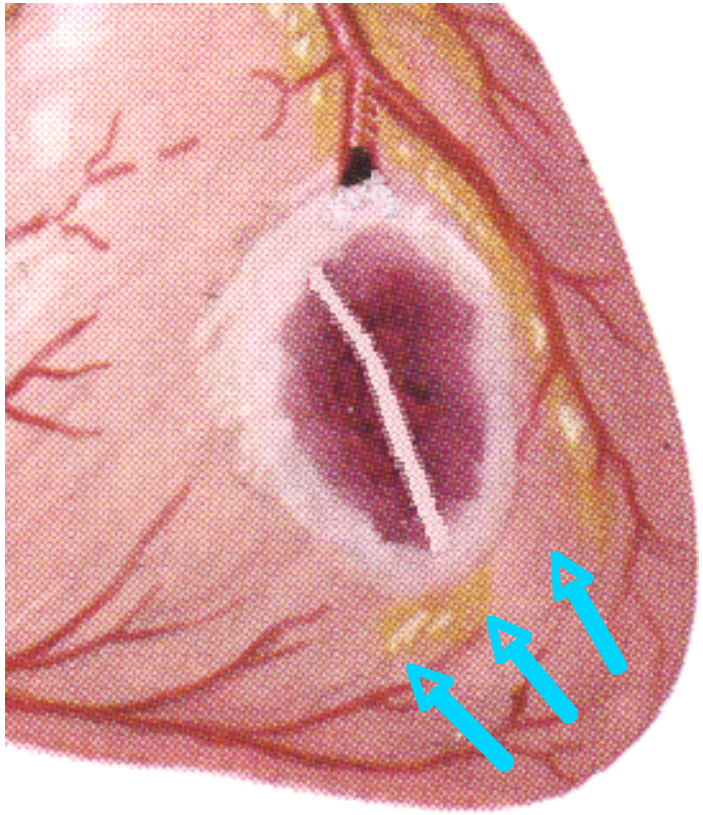


F. Netter, 1978

Example: how can scar tissue initiate arrhythmias?

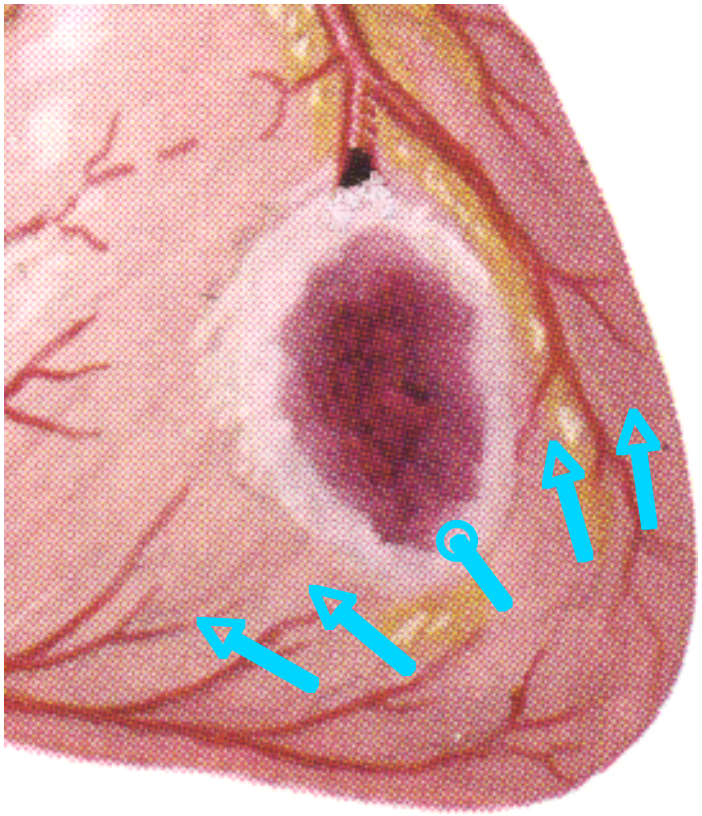


Wave propagating in presence of dense scar

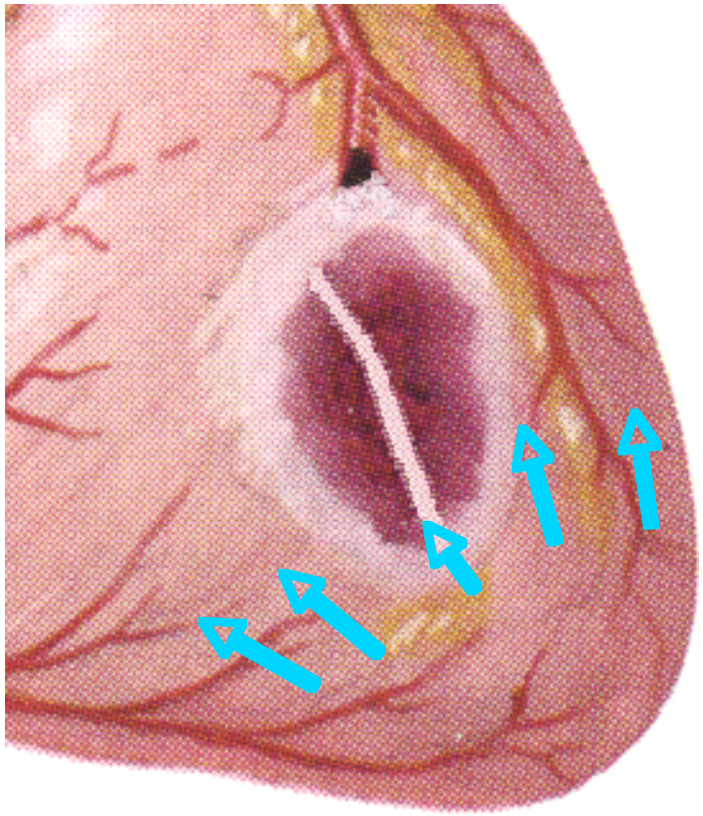


Wave propagating in presence of scar with viable, but damaged, tissue within scar

Example: how can scar tissue initiate arrhythmias?



Wave propagates around, but not into, scar



Wave propagates around, and into, scar

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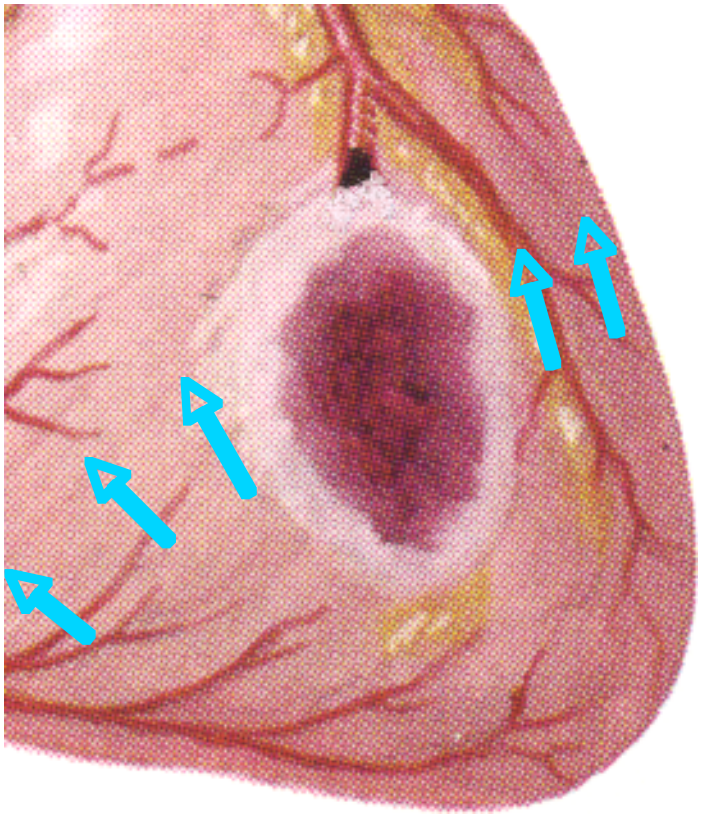
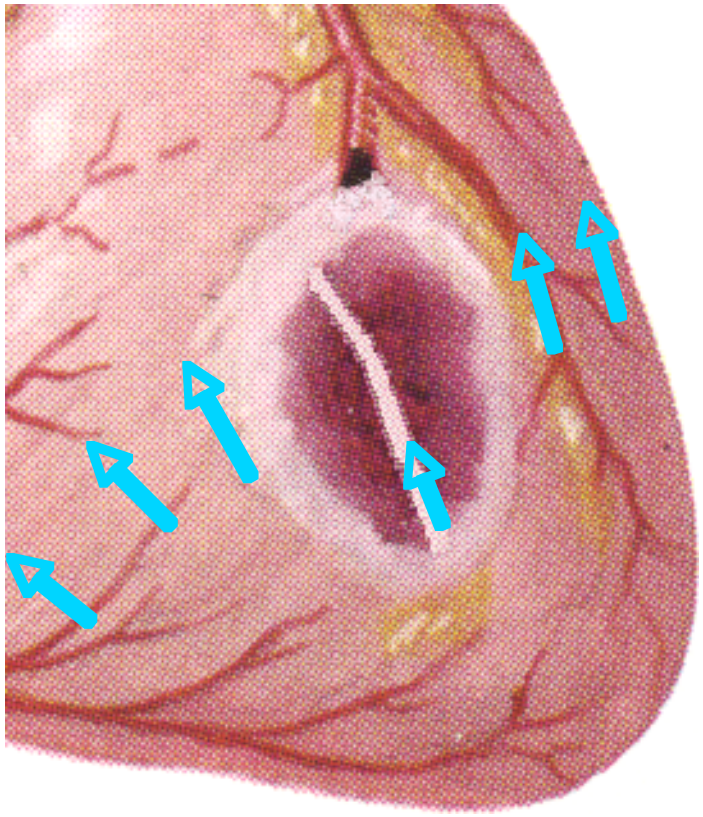
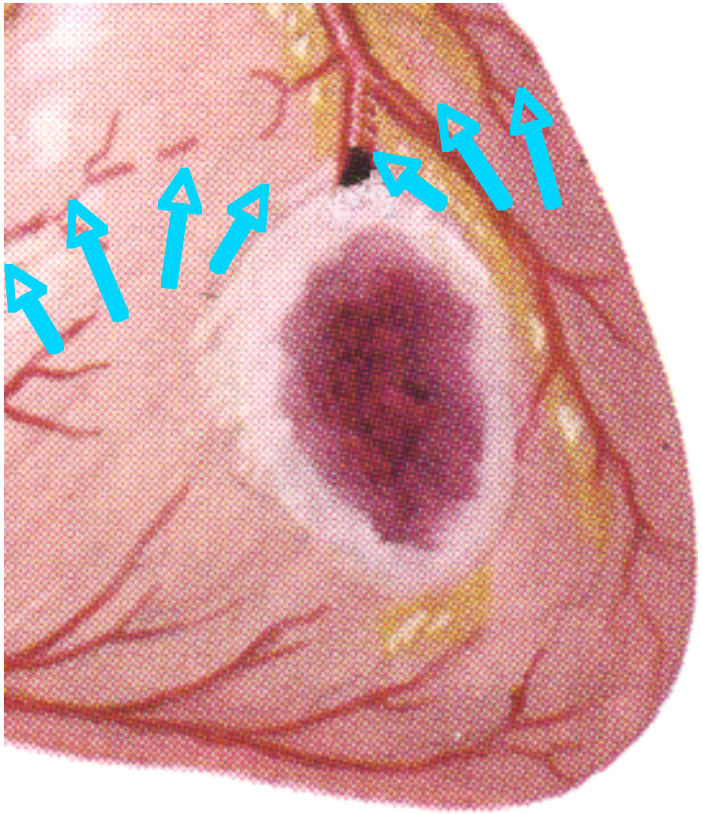
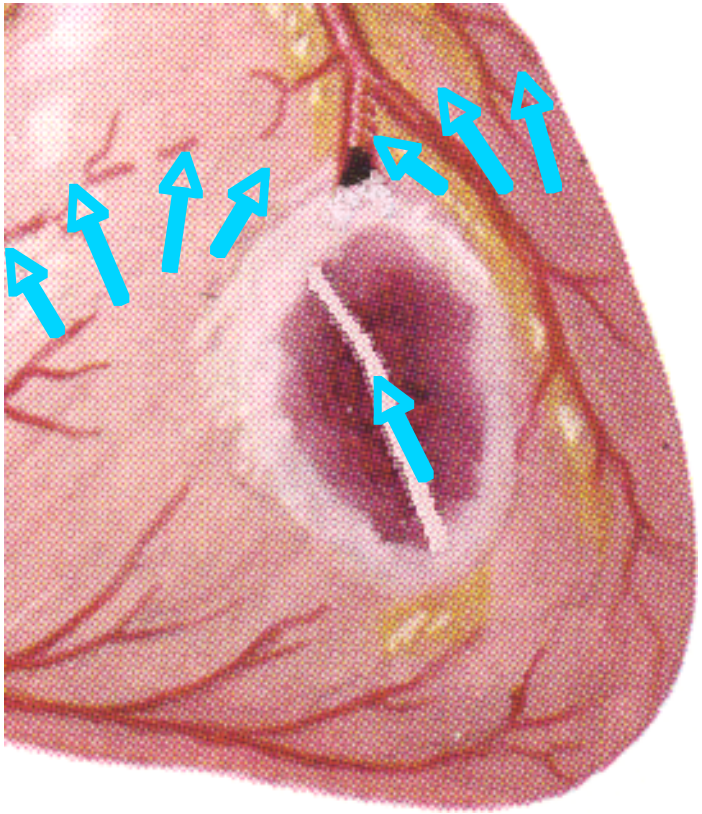




Wave propagates through scar slowly because the tissue is poorly coupled

Example: how can scar tissue initiate arrhythmias?





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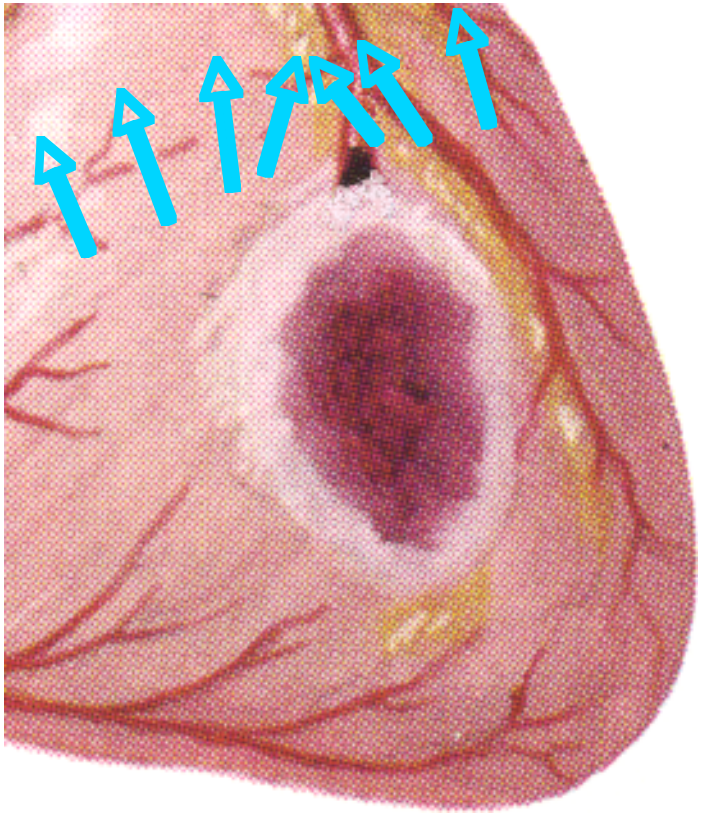
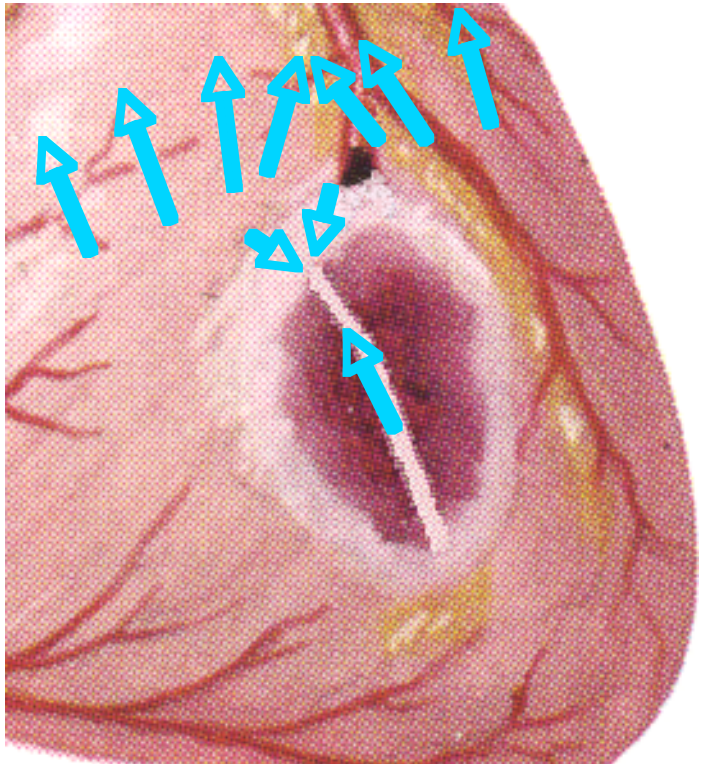
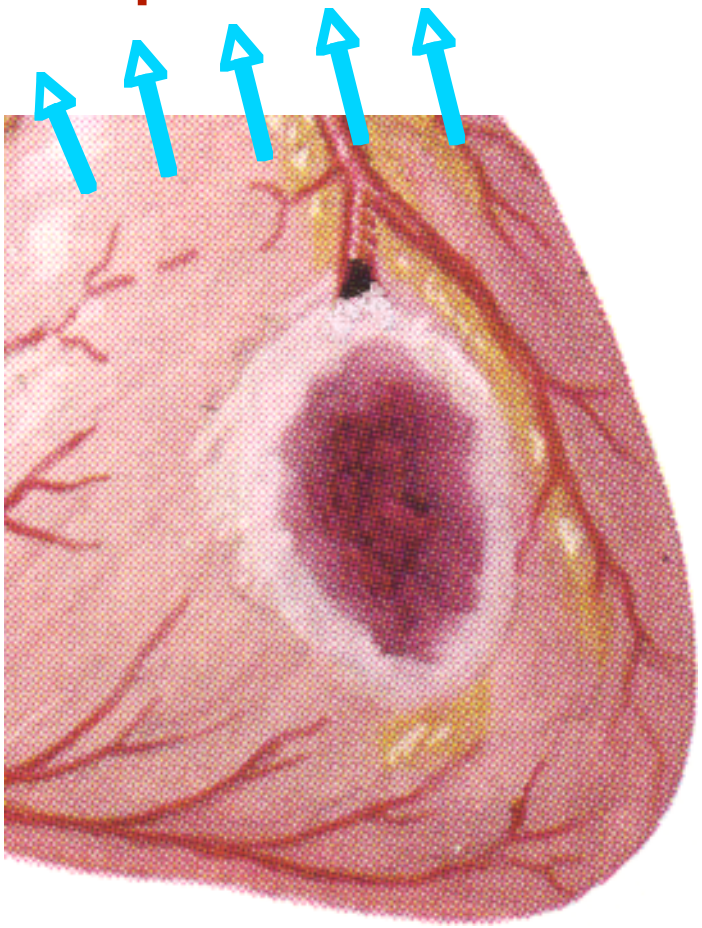


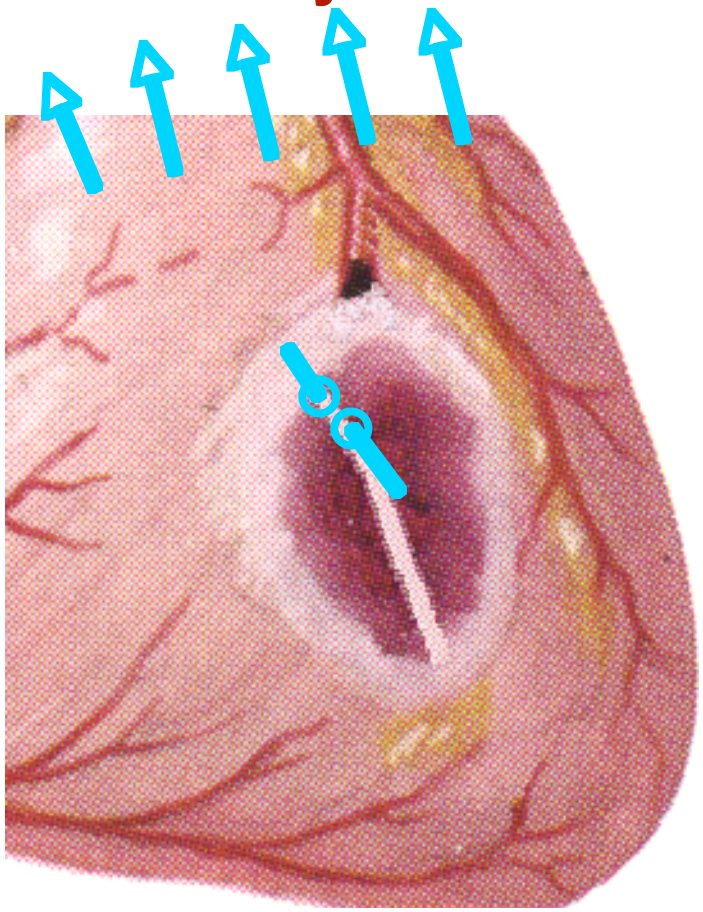
Waves from either side of the scar merge and propagate beyond scar



Waves from either side of the scar merge and propagate back into scar (excitable waves propagate into any tissue that is viable and non-refractory)

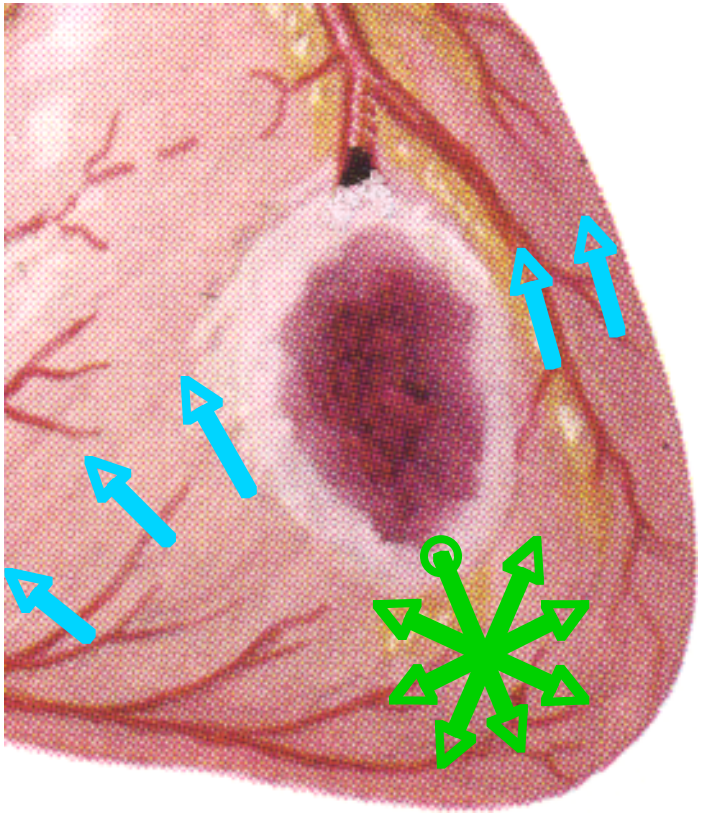
Example: how can scar tissue initiate arrhythmias?

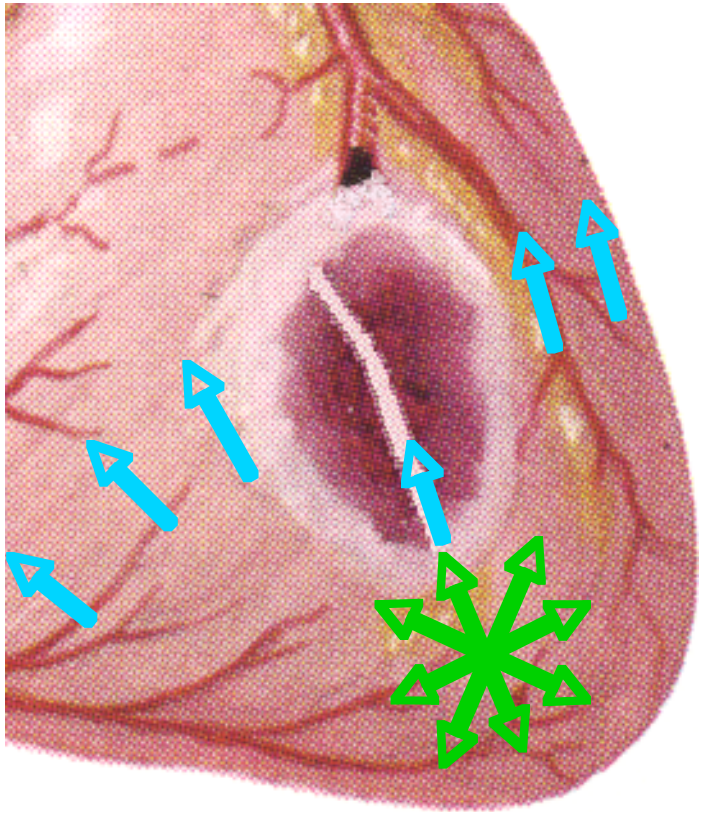




The two intra-scar waves, flowing in opposite directions, annihilate one another. No reentrant rhythm occurs.

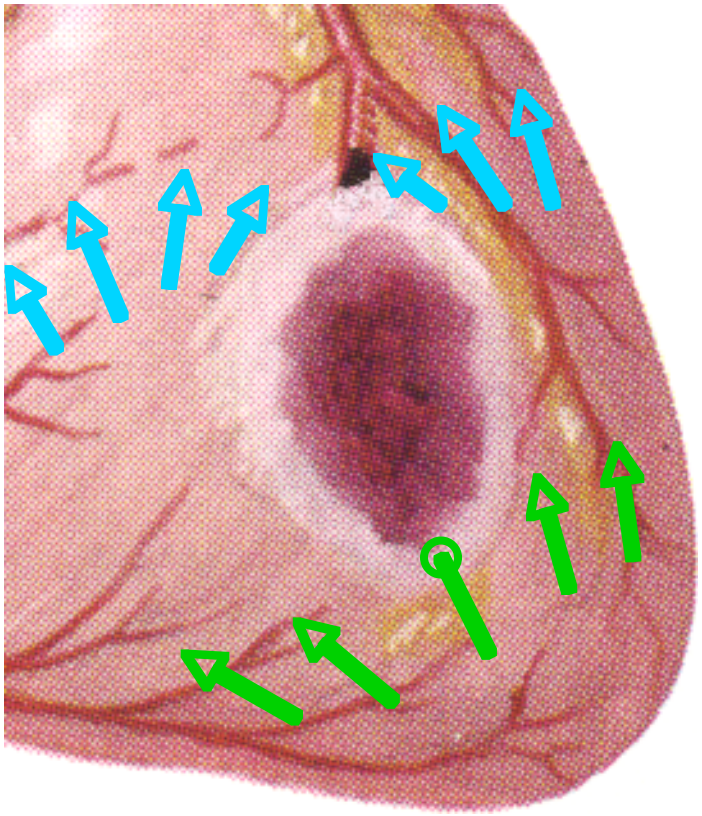
Example: how can scar tissue initiate arrhythmias?

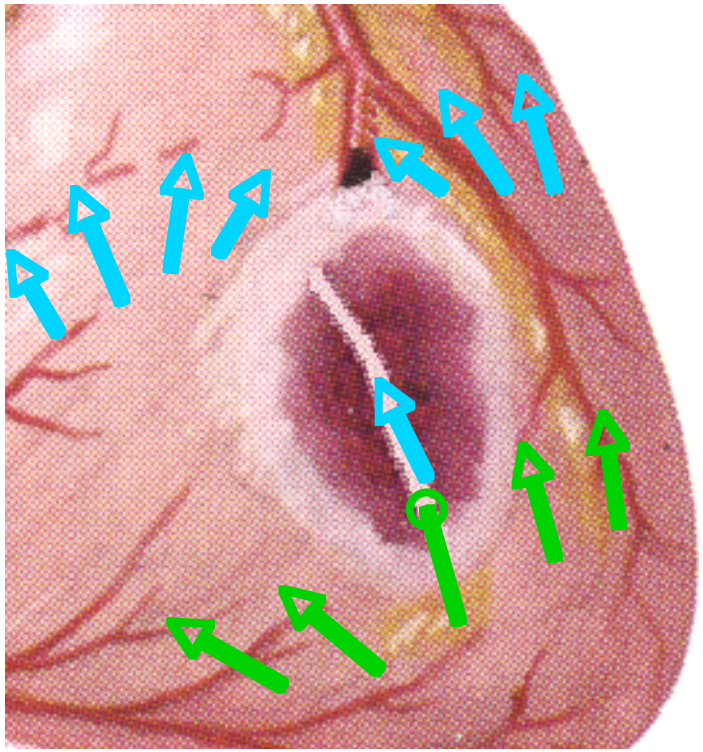




Now let's examine what can happen when an *ectopic beat* occurs at the "wrong place and wrong time".

Example: how can scar tissue initiate arrhythmias?





Because the slow conduction zone can also lengthen refractory period, the ectopic wave can block by running into the tail of the preceding wave

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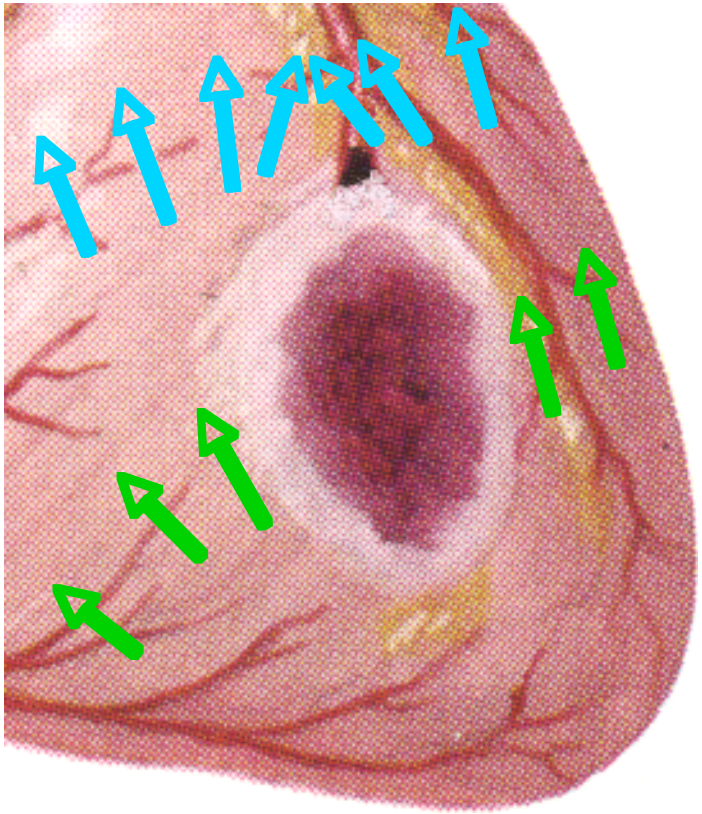

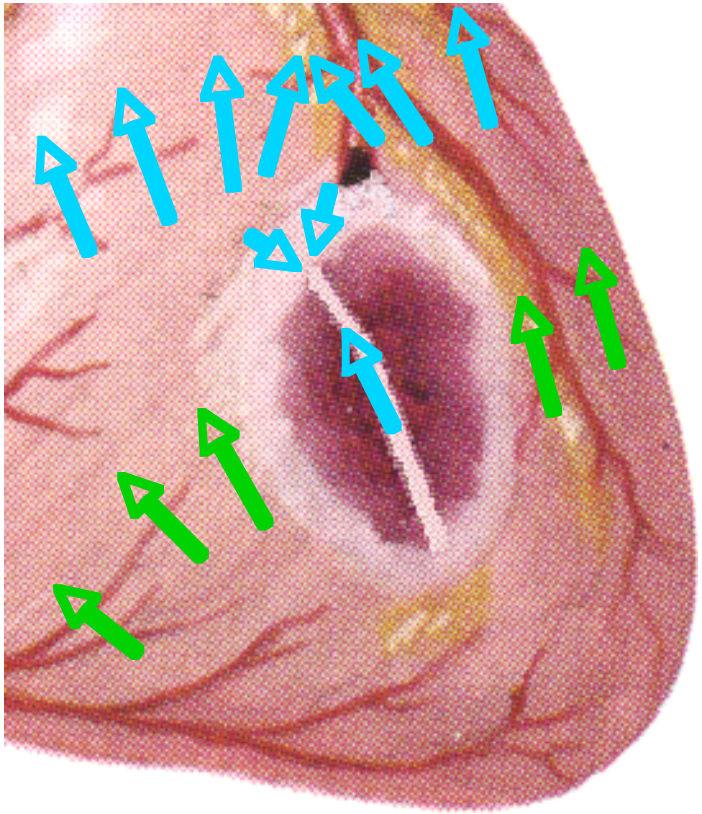

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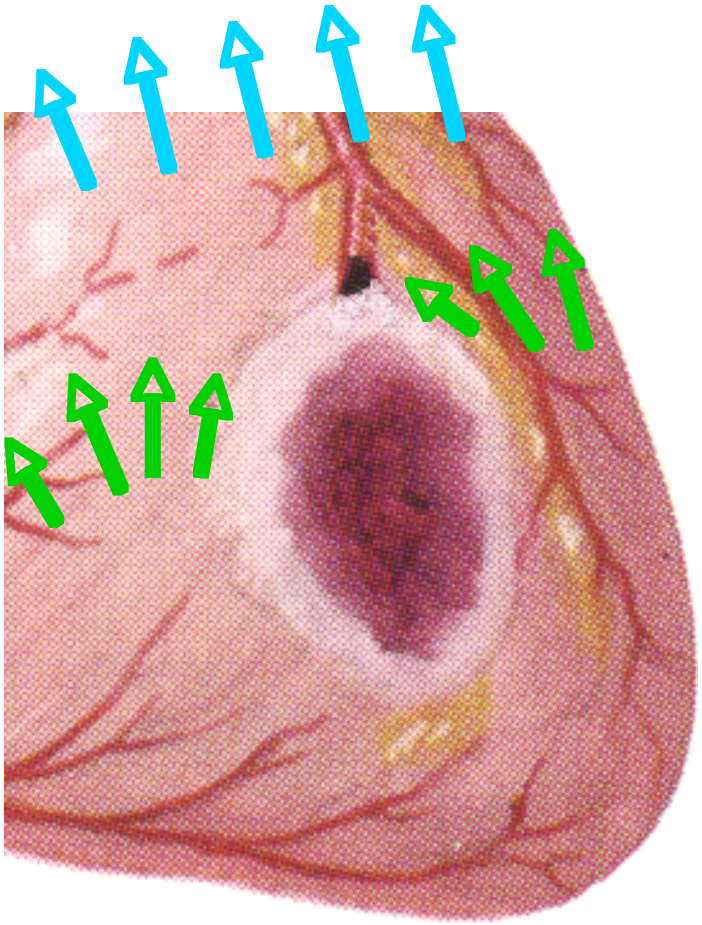

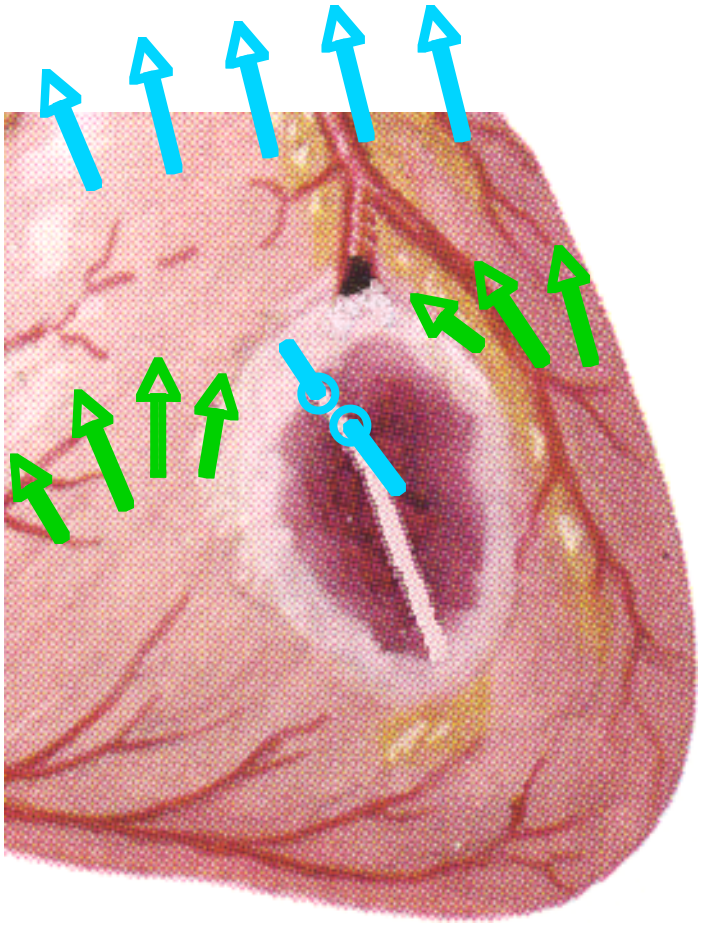

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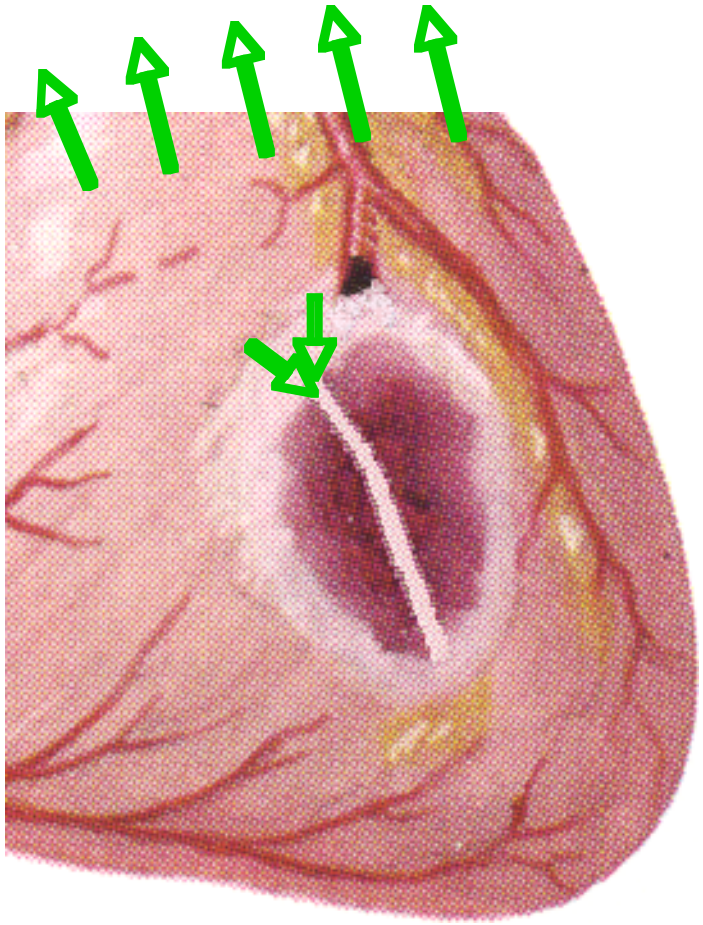

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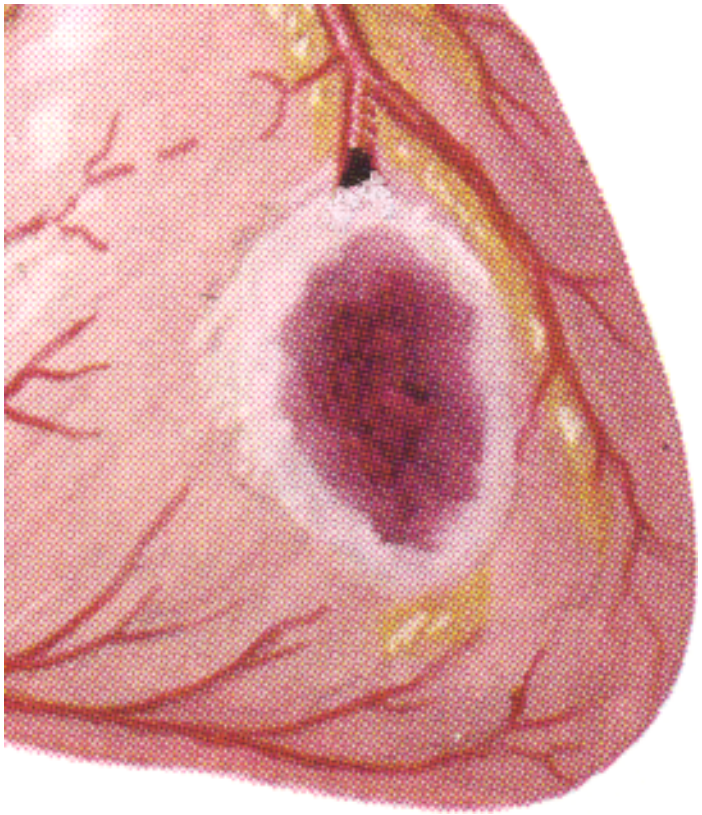

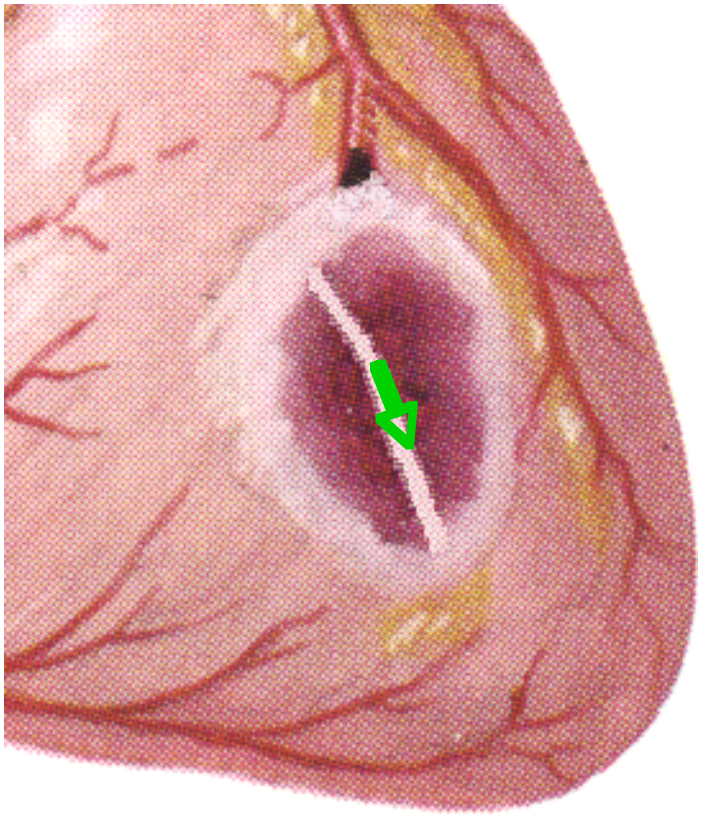

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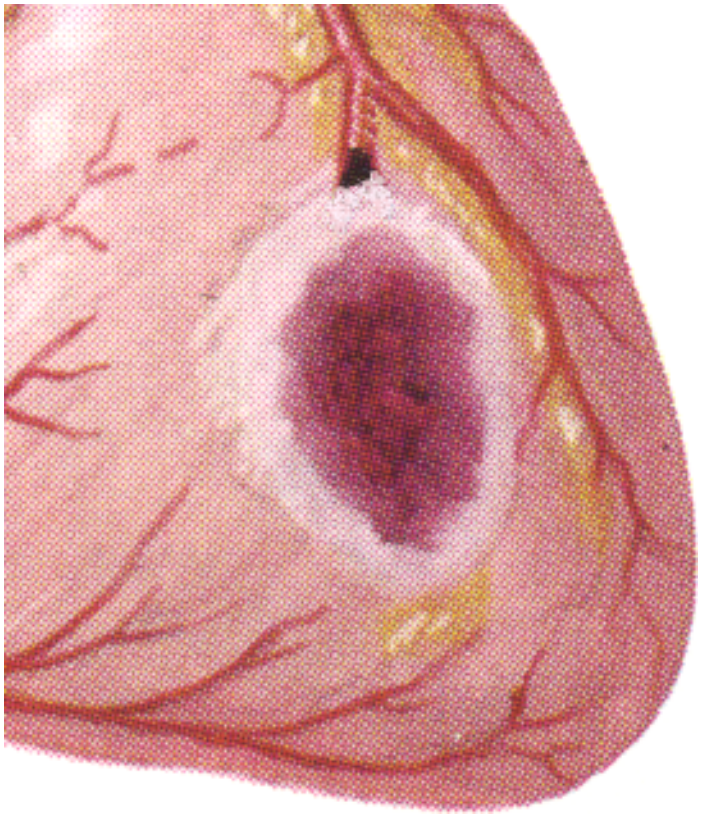

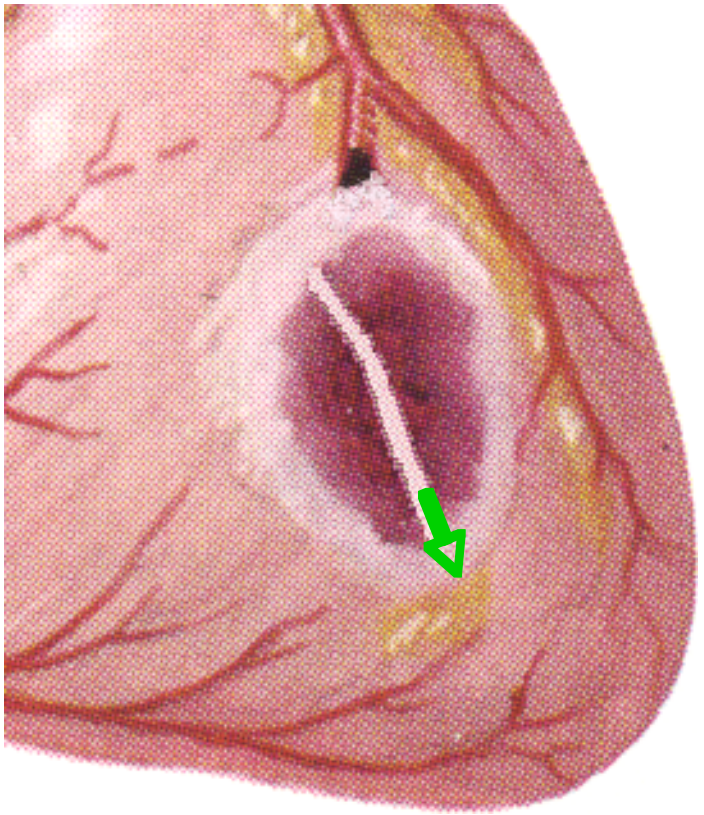

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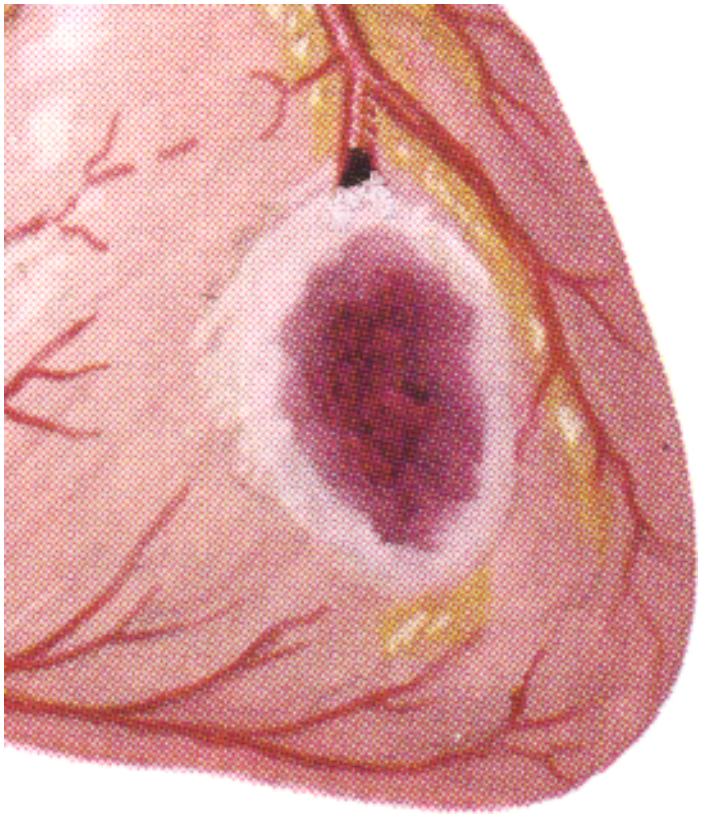

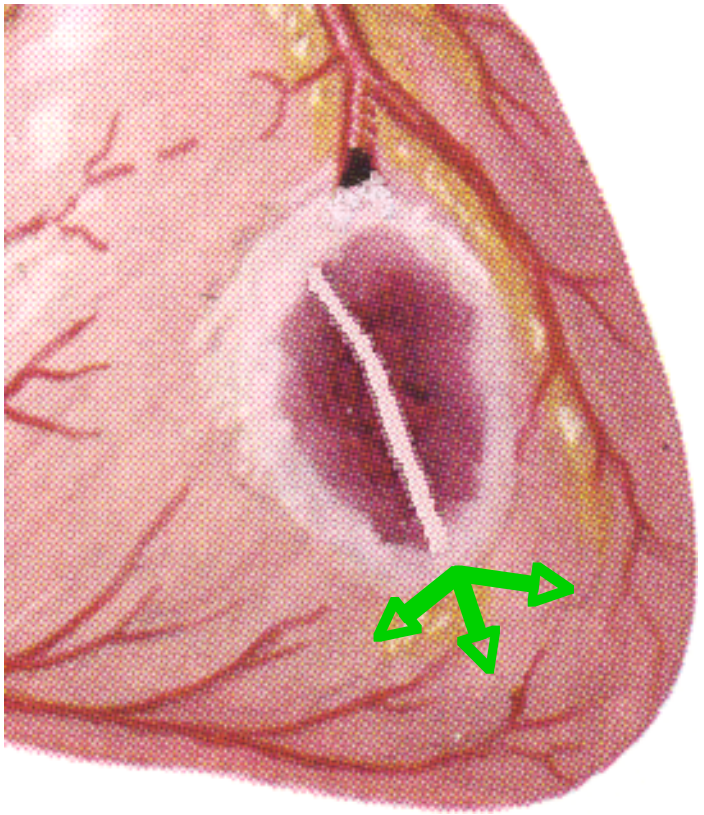

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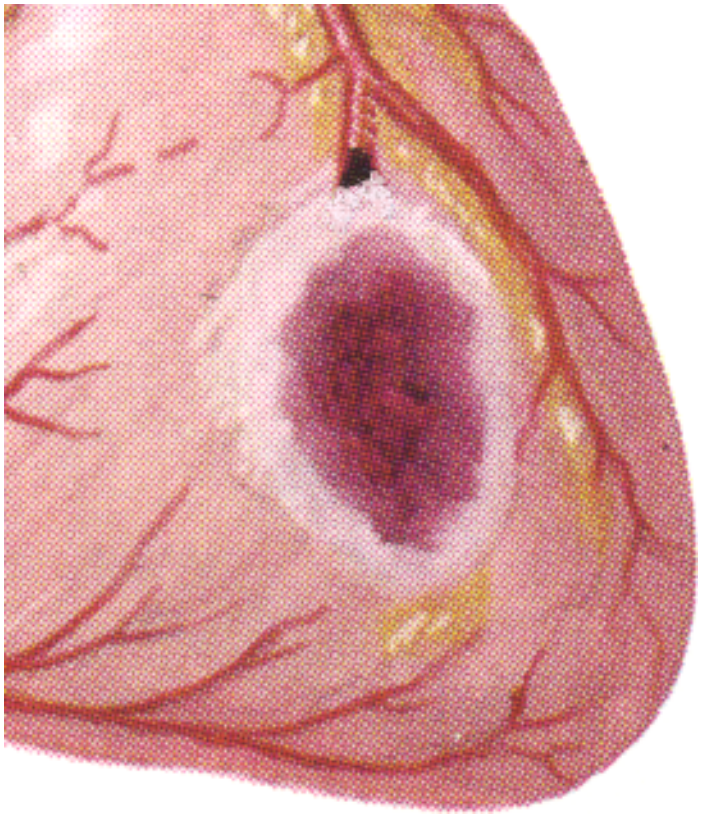

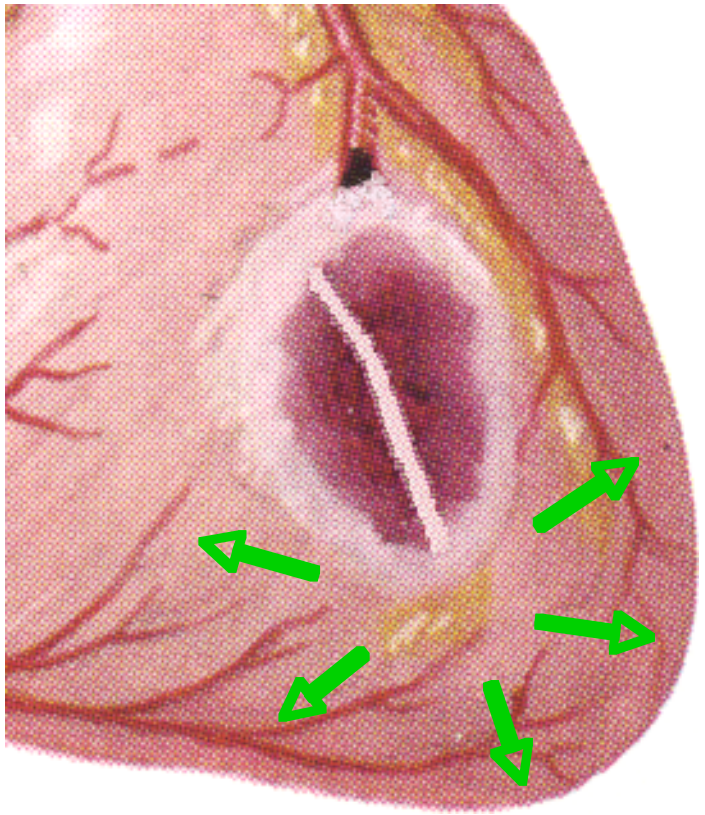

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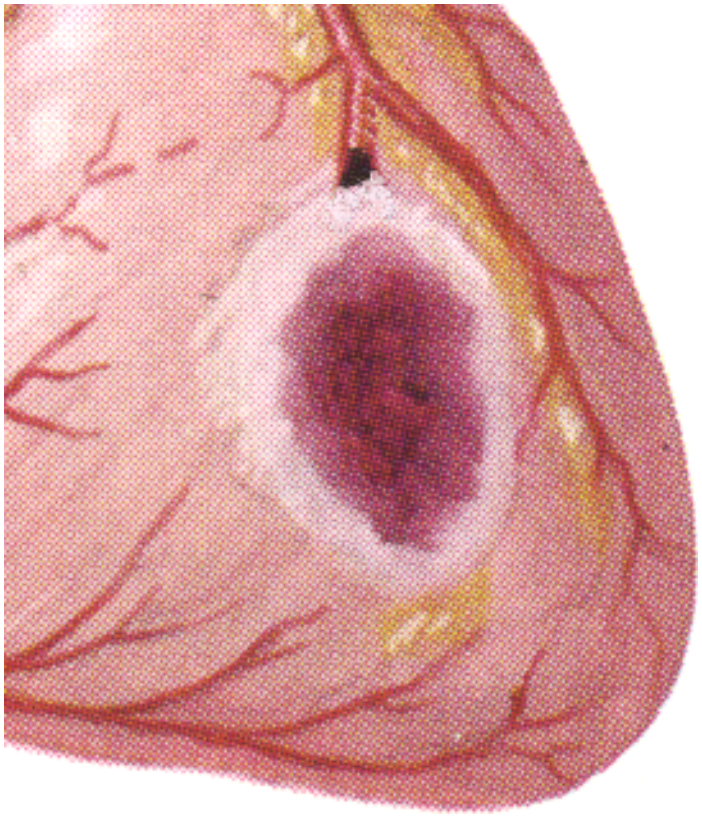

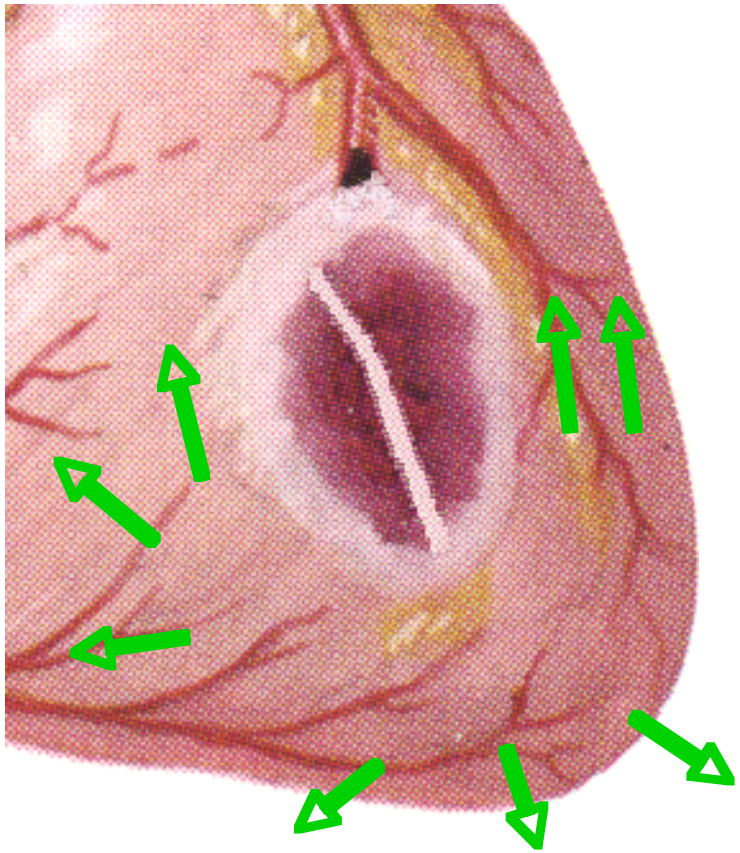

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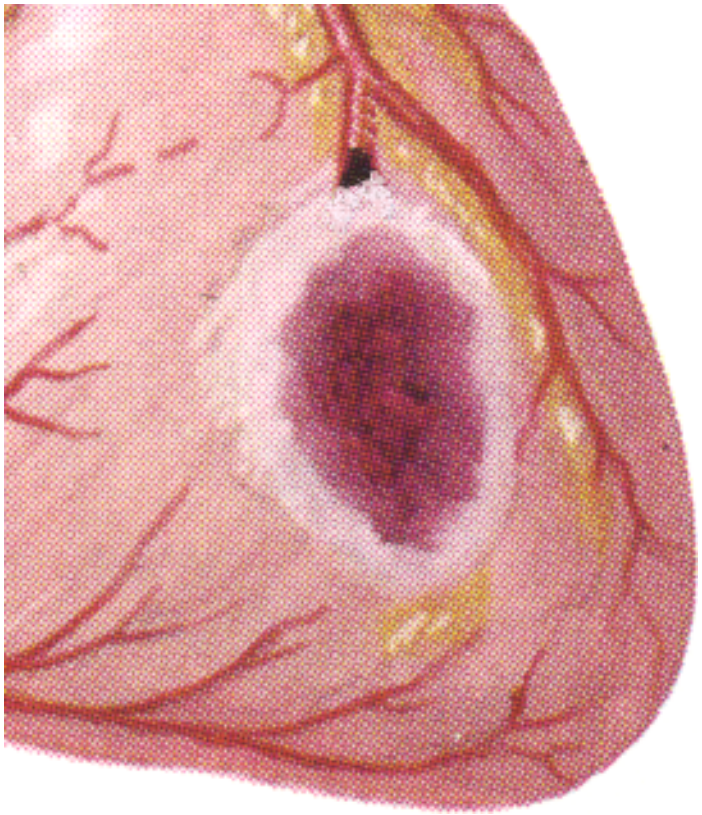

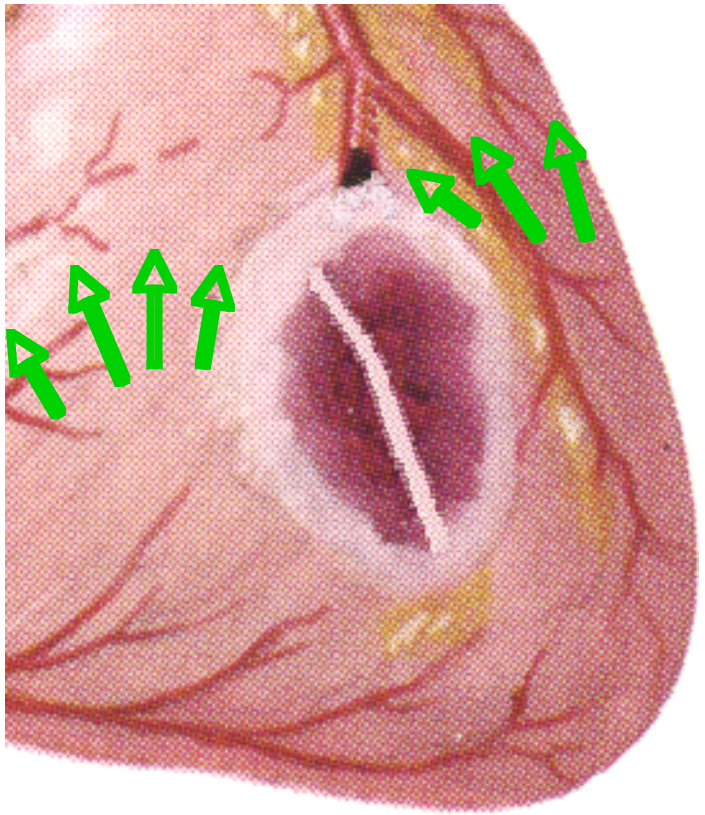

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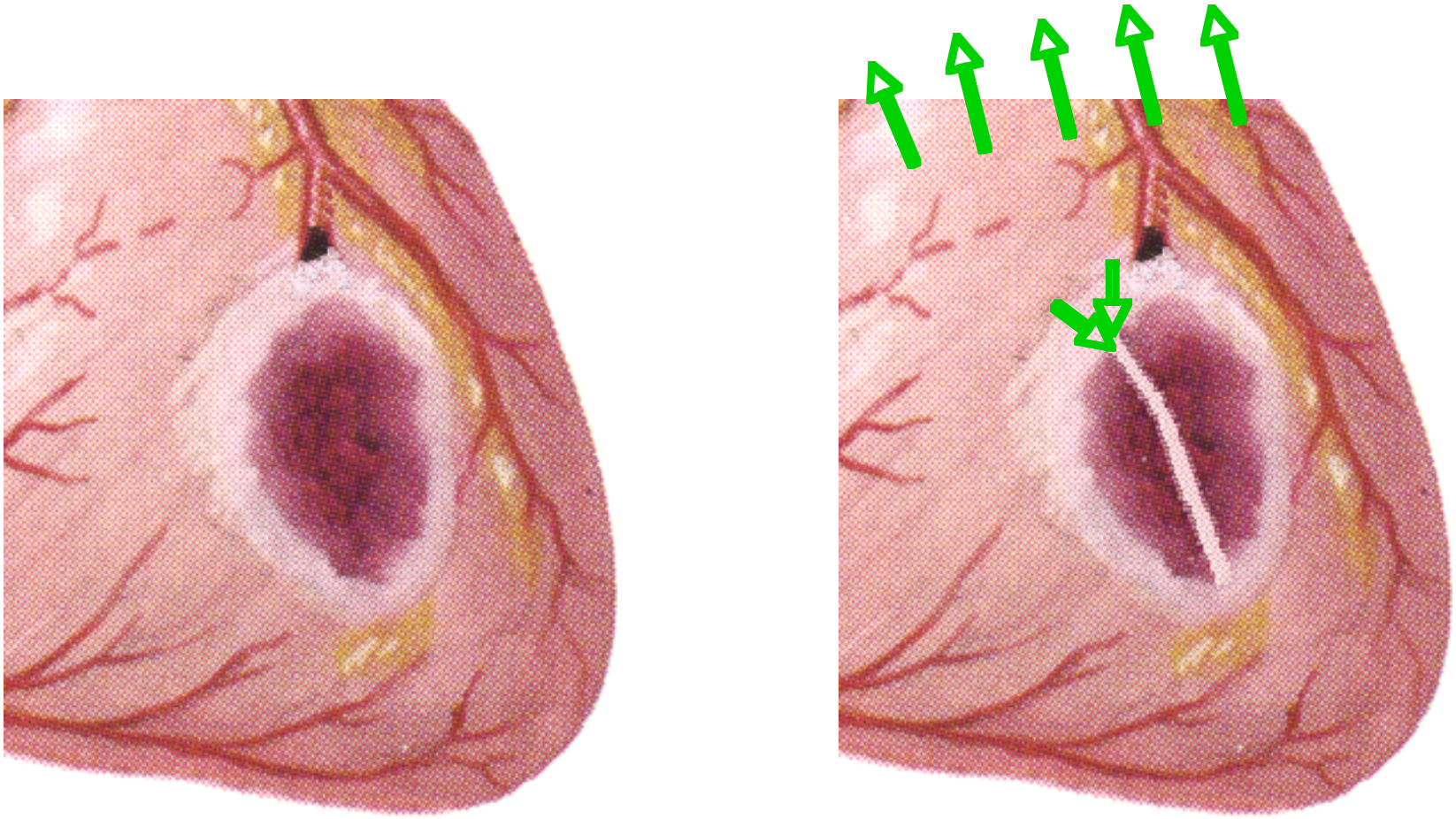
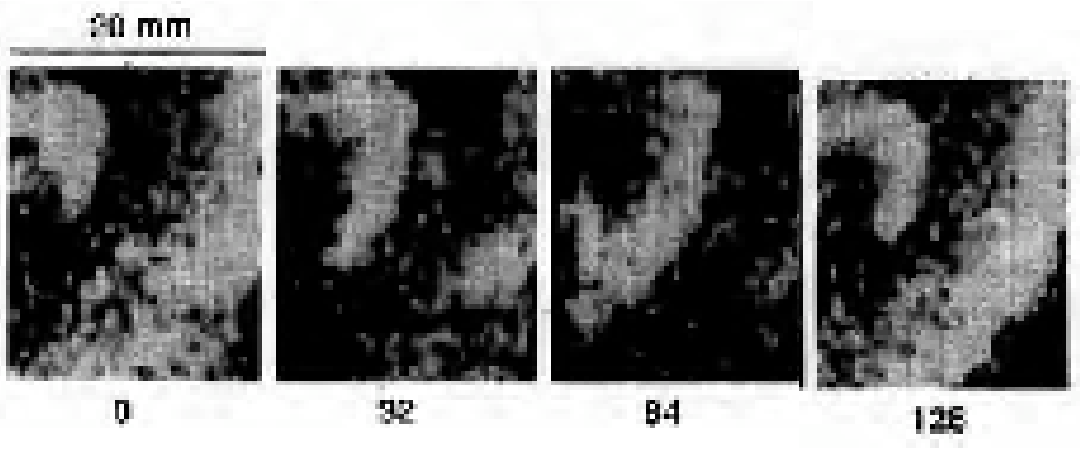


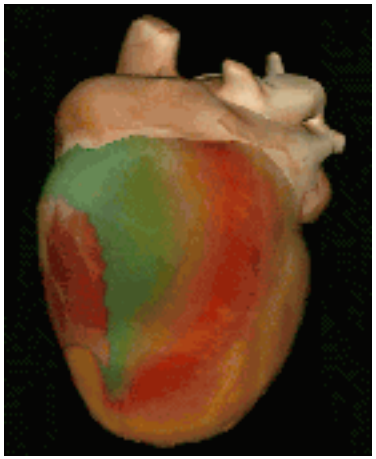
Maintenance

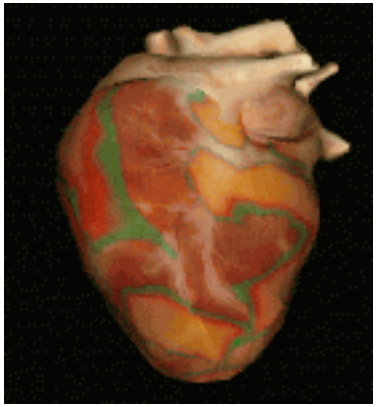
Reentry: anatomical or functional



Davidenko et al.,
Nature, 1992.

Break-up: tachycardia to fibrillation

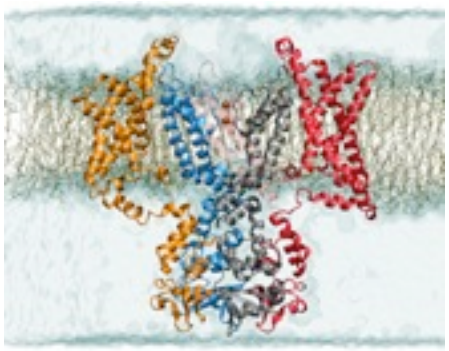


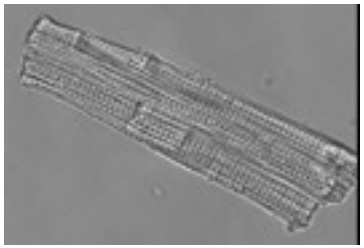


thevirtualheart.org

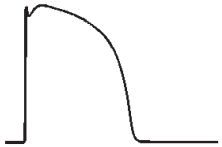
Multiscale phenomena

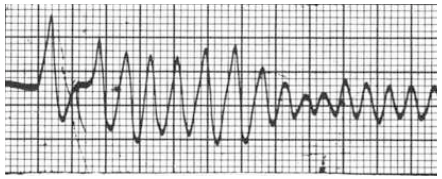
single channel → single cell → tissue, organ





1 Å | 1 nm | 10 nm | 100 nm | 1 µm | 10 µm | 100 µm | 1 mm | 1 cm | 10 cm





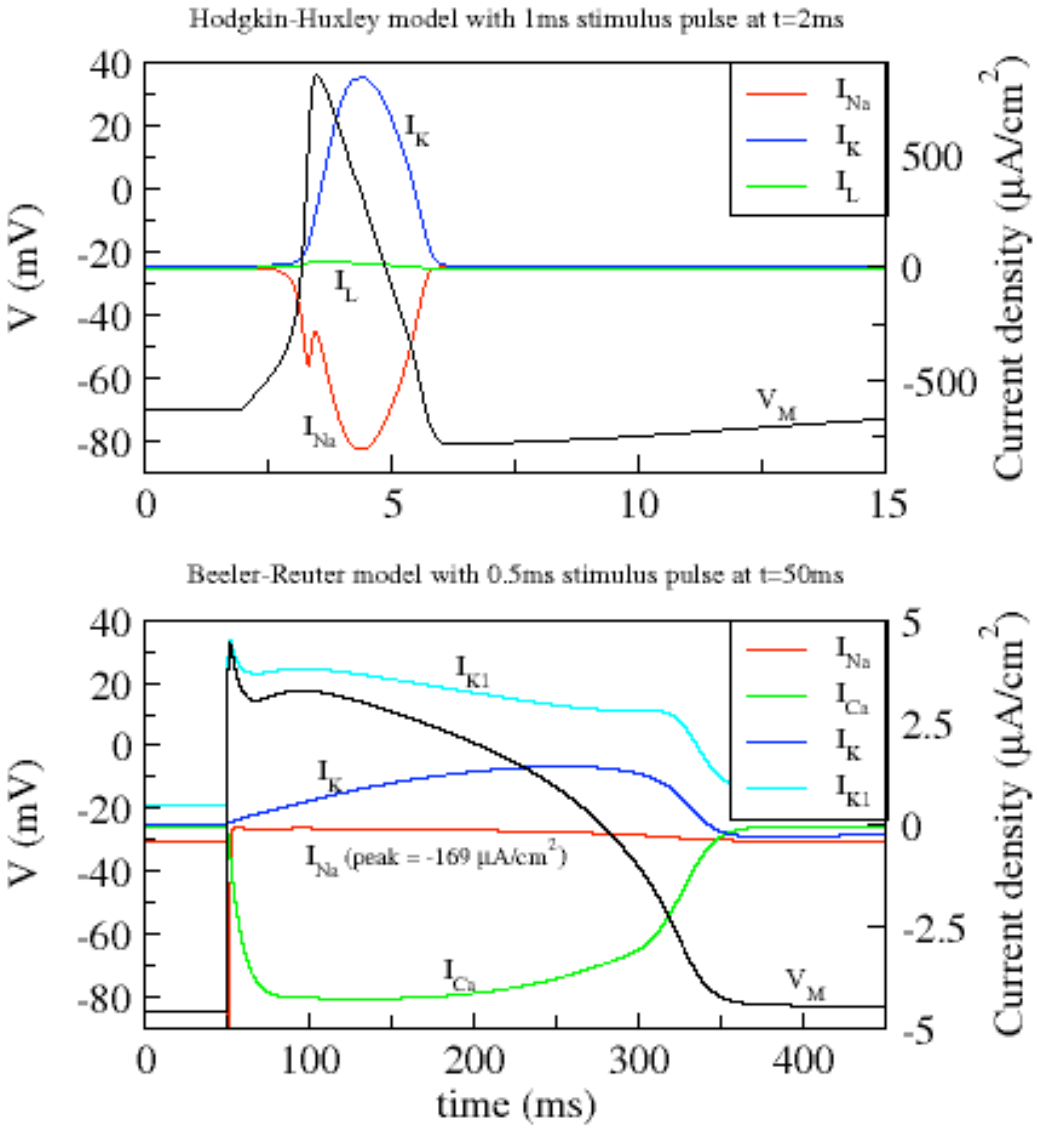
10 µs | 100 µs | 1 ms | 10 ms | 100 ms | 1 s | 10 s | 100 s

Action potential generation

Java

Cardiac action potentials

- Upstroke of ventricular AP is Na^+ mediated.
- At the peak, Ca^{2+} channels open, causing an inward current that prolongs AP (plateau).
- Ca^{2+} influx triggers additional Ca^{2+} release from the sarcoplasmic reticulum..
- Cytoplasmic Ca^{2+} produces muscle contraction.
- Cardiac cells have many different types of K^+ channels.



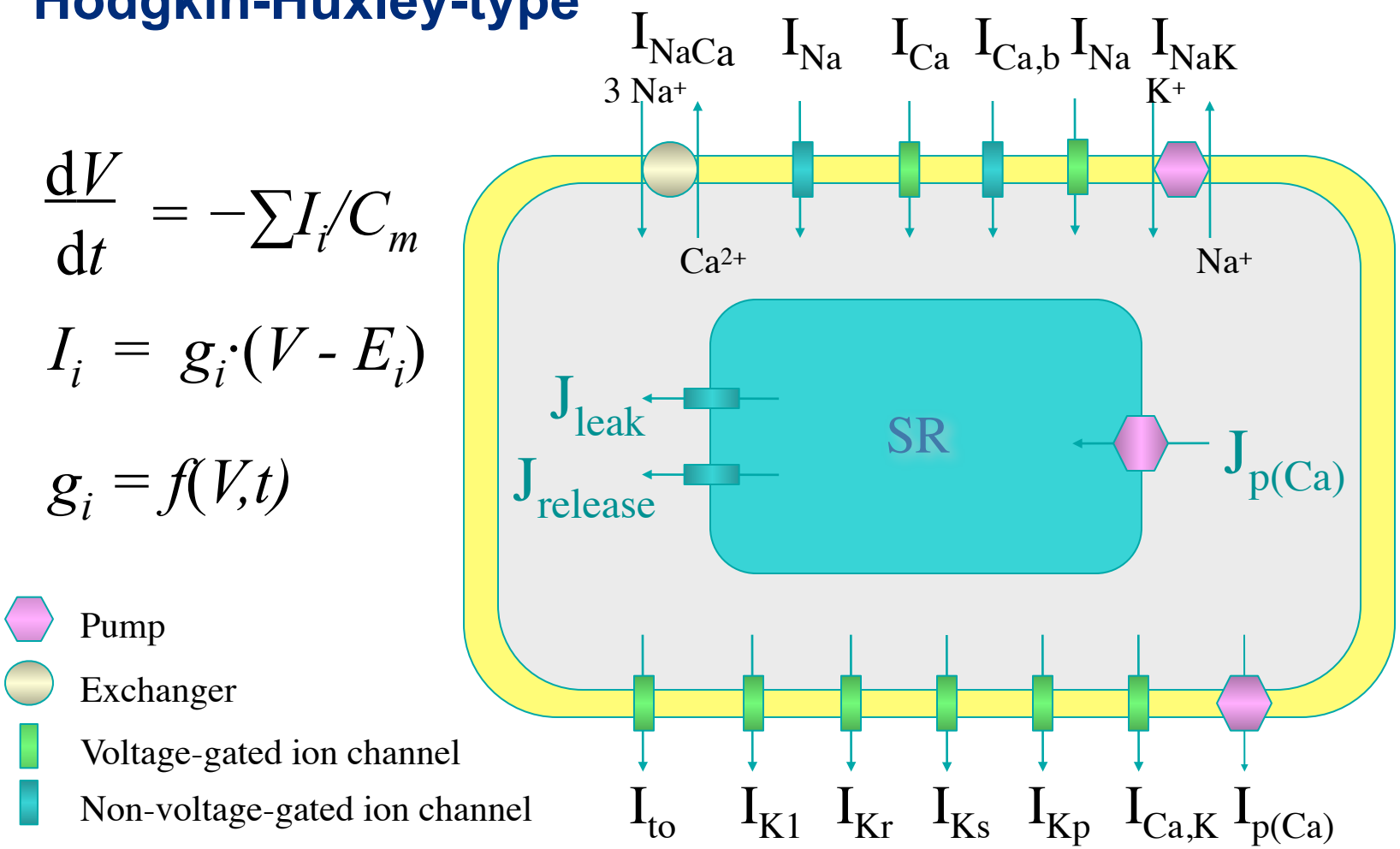
Computational modeling at the single cell level

Hodgkin-Huxley-type

$$\frac{dV}{dt} = -\sum I_i / C_m$$

$$I_i = g_i \cdot (V - E_i)$$

$$g_i = f(V,t)$$



CVM model of the canine ventricular myocyte
13 state variables and ~60 parameters

courtesy of R. Gilmour

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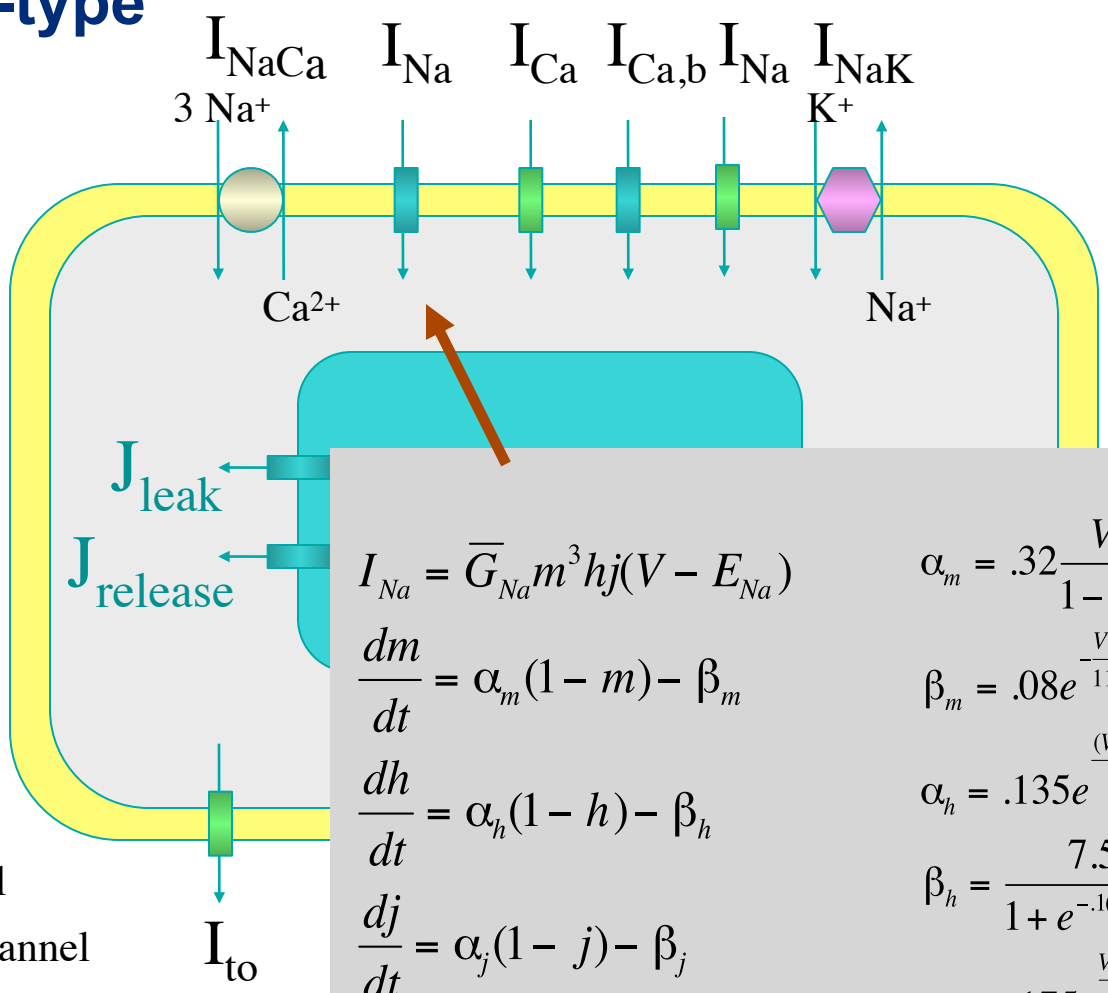


Pump

Exchanger

Voltage-gated ion channel

Non-voltage-gated ion channel

$$I_{Na} = \bar{G}_{Na} m^3 hj (V - E_{Na})$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h$$

$$\frac{dj}{dt} = \alpha_j (1 - j) - \beta_j$$

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

$$\alpha_m = .32 \frac{V + 47.13}{1 - e^{-.1(V+47.13)}}$$

$$\beta_m = .08 e^{-\frac{V}{11}}$$

$$\alpha_h = .135 e^{\frac{(V+80)}{-6.8}}$$

$$\beta_h = \frac{7.5}{1 + e^{-.1(V+11)}}$$

$$\alpha_j = \frac{.175 e^{\frac{V+100}{-23}}}{1 + e^{.15(V+79)}}$$

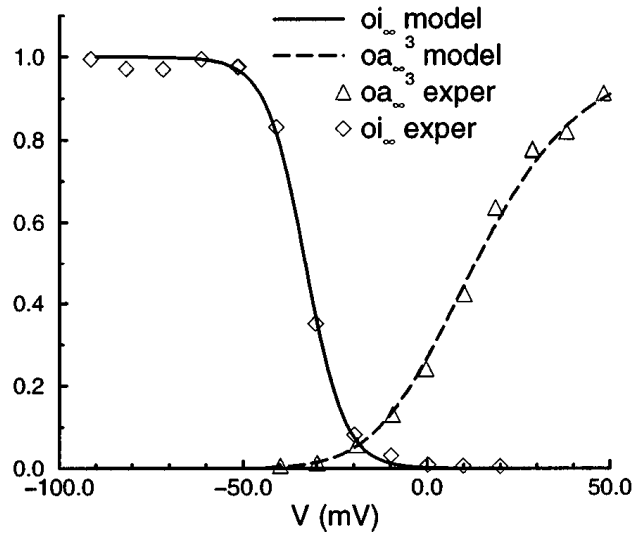
$$\beta_j = \frac{.3}{1 + e^{-.1(V+32)}}$$

CVM mod
~13 state

Computational modeling at the single cell level

Activation and inactivation

$$x \underset{\alpha(V)}{\overset{\beta(V)}{\rightleftharpoons}} 1-x$$

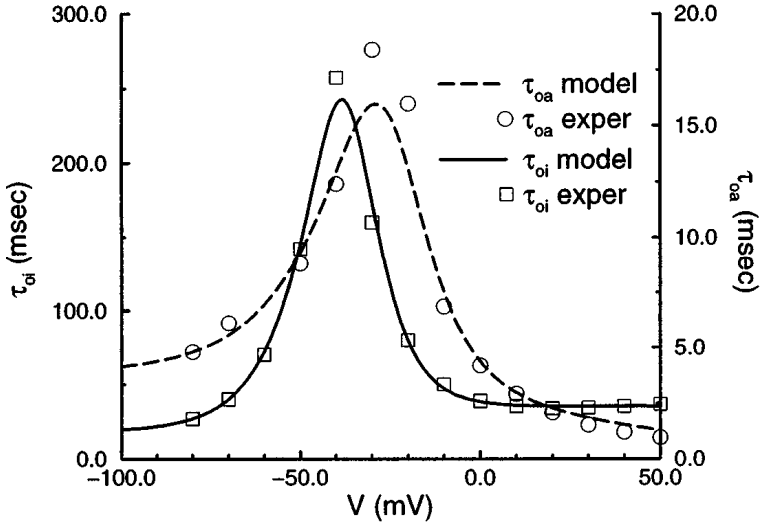


ODE for gating variable

$$dx/dt = \alpha_x(1-x) - \beta_x x$$
$$= -(\alpha_x + \beta_x)x + \alpha_x$$
$$= (x_\infty - x)/\tau_x$$

where

$$x_\infty = \alpha_x/(\alpha_x + \beta_x)$$
$$\tau_x = 1/(\alpha_x + \beta_x).$$



Computational modeling at the single cell level

Solution for constant V: (think voltage clamp)

$$dx/dt = (x_\infty - x)/\tau_x$$

$$1/(x_\infty - x)dx = 1/\tau_x dt$$

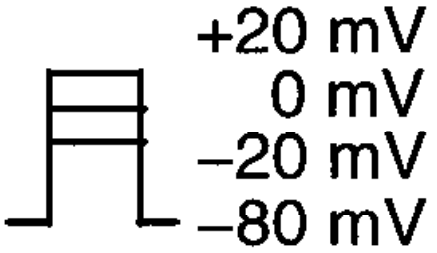
$$\int_{x_0}^{x} 1/(x_\infty - x')dx' = \int_{0}^{t} 1/\tau_x dt'$$

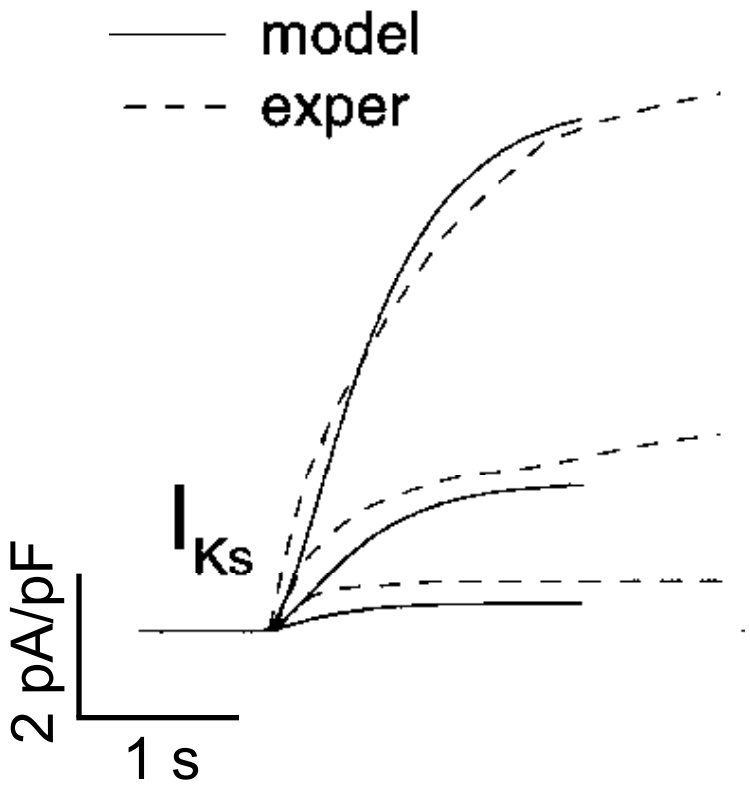
$$\left[-\ln(x_\infty - x')\right]_{x_0}^{x} = t/\tau_x$$

$$\ln\frac{x_\infty - x}{x_\infty - x_0} = -t/\tau_x$$

$$\frac{x_\infty - x}{x_\infty - x_0} = \exp(-t/\tau_x)$$

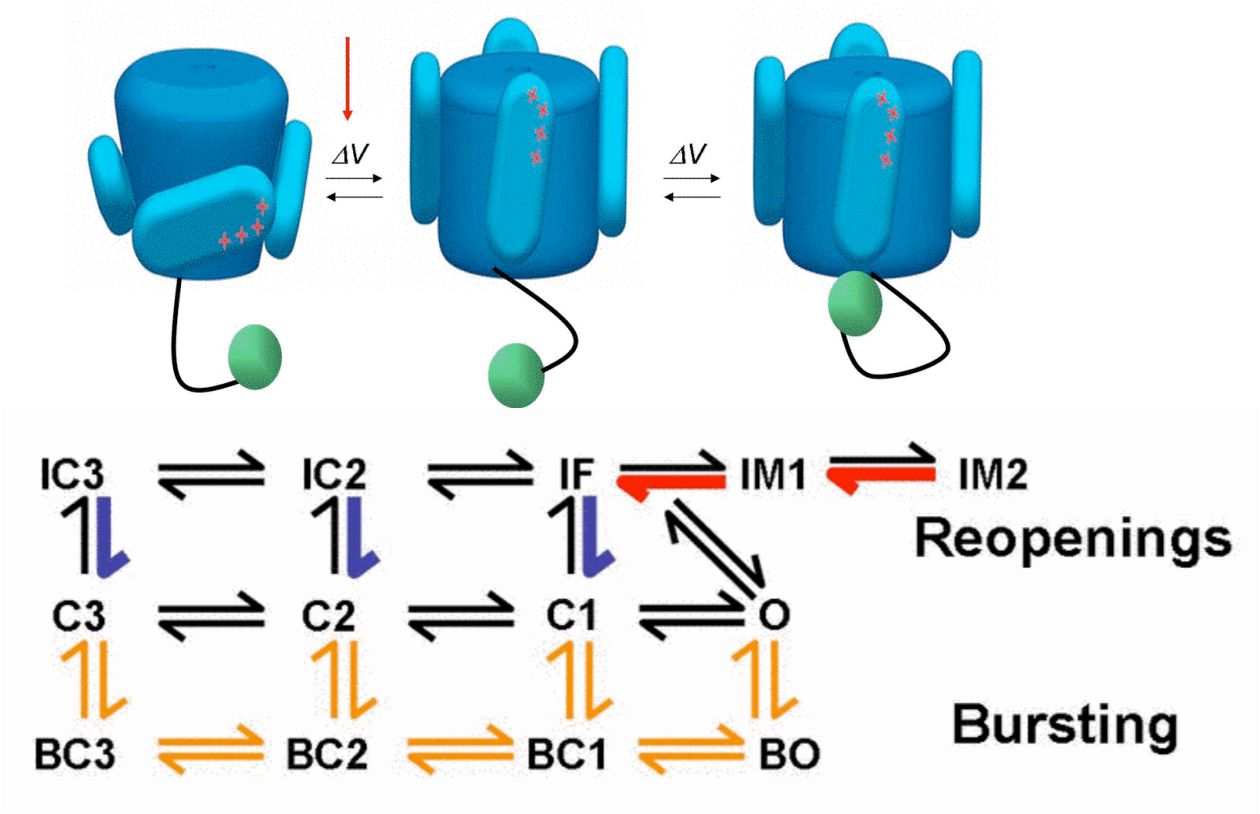
$$x = x_\infty - (x_\infty - x_0)\exp(-t/\tau_x)$$





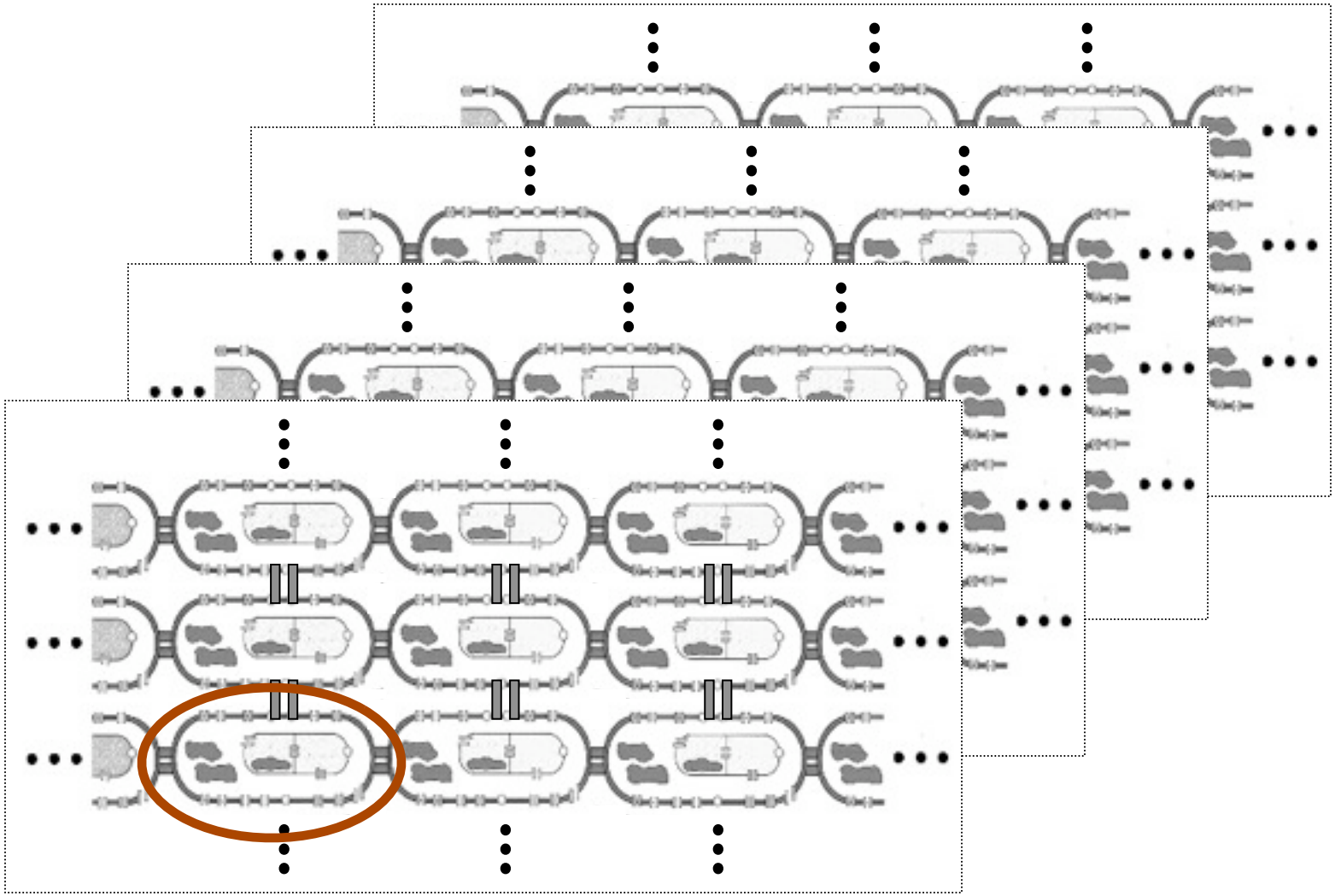
Single-channel modeling: Markov model

Beyond Hodgkin-Huxley



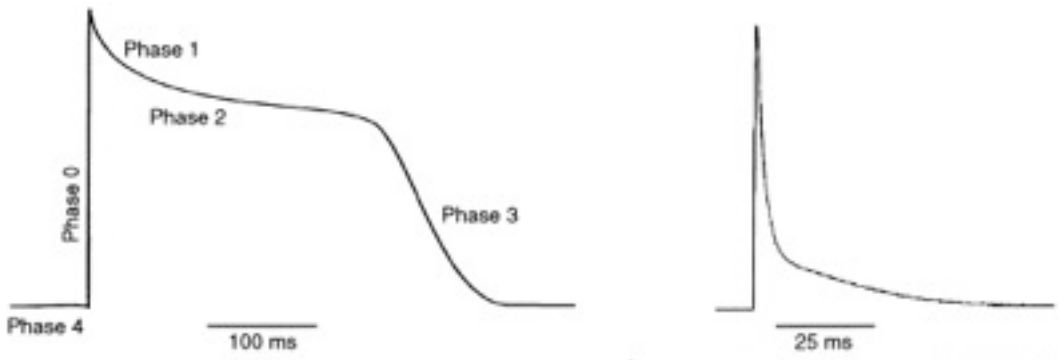
- May be based on channel structure
- Gates not necessarily independent
- May reproduce experimental data better than HH

Three-dimensional virtual cardiac tissue



Why use computational modeling for cardiac electrophysiology?

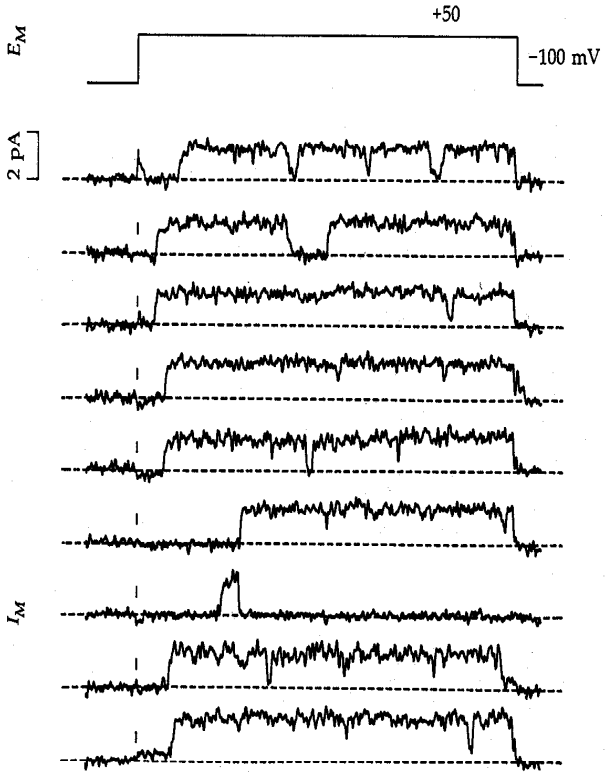
- Rodent cardiac myocytes have fundamentally different channel expression levels (especially repolarizing currents). Therefore, transgenic models are not appropriate.
- Modeling allows one to monitor each component simultaneously – not possible in experiments.
- Dynamics can be observed at resolutions that are unattainable experimentally or clinically.
- It is often faster and cheaper to do so.

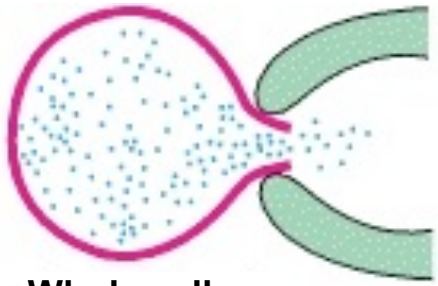


Nerbonne.
Trends Cardiovasc. Med.
2004.

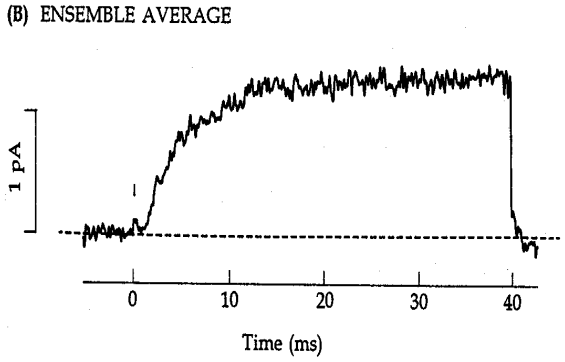
Multiscale modeling example: single-channel noise

Excised patch





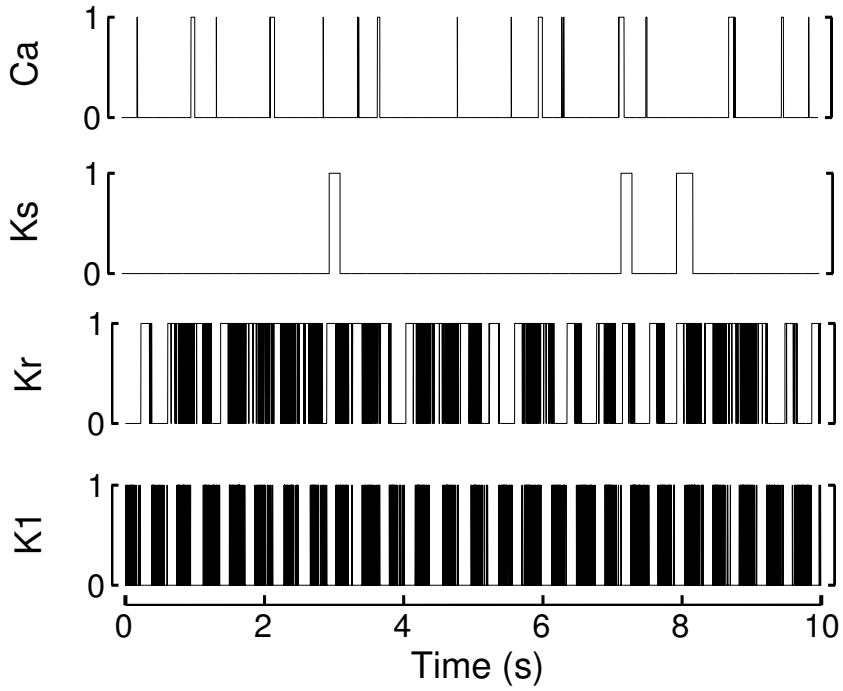
Whole cell

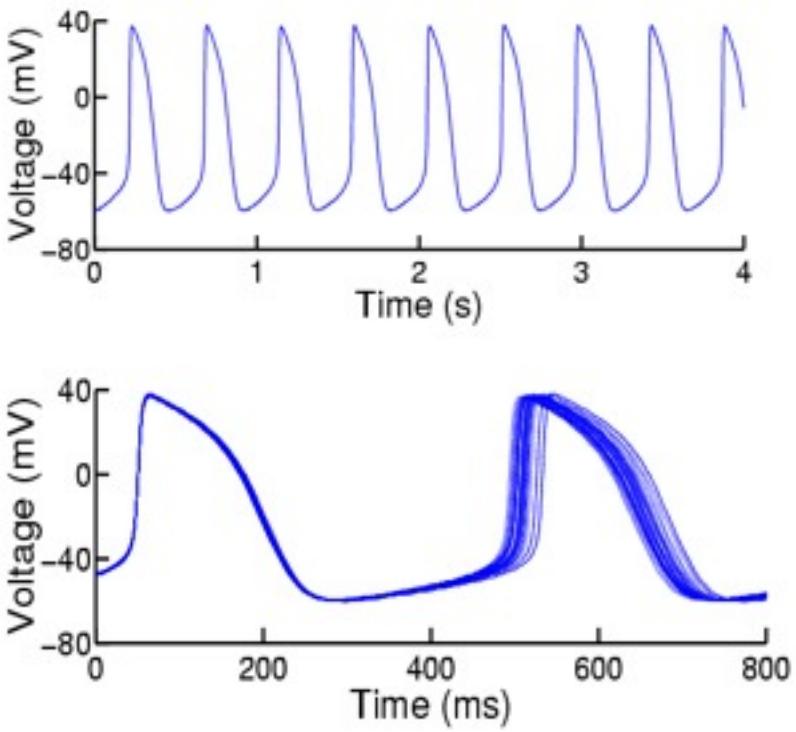


Unitary events add up to give the macroscopic current.

Multiscale modeling example: single-channel noise

Single channel noise → irregularity of beating





Multiscale modeling example: AF maintenance

Atrial fibrillation:

- 2.3 million sufferers in the U.S.
- 1/3 of all strokes over age 65
- doubled mortality rate

Multiscale modeling example: AF maintenance

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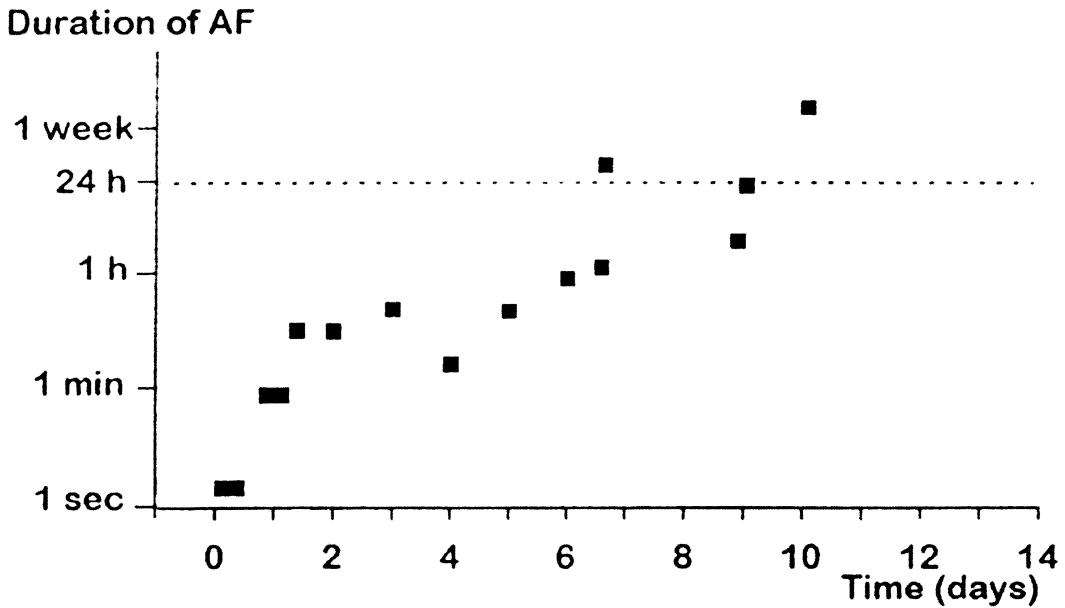
Clinical/exp observations:

- “AF begets AF”



Wijffels et al., Circulation, 1995.

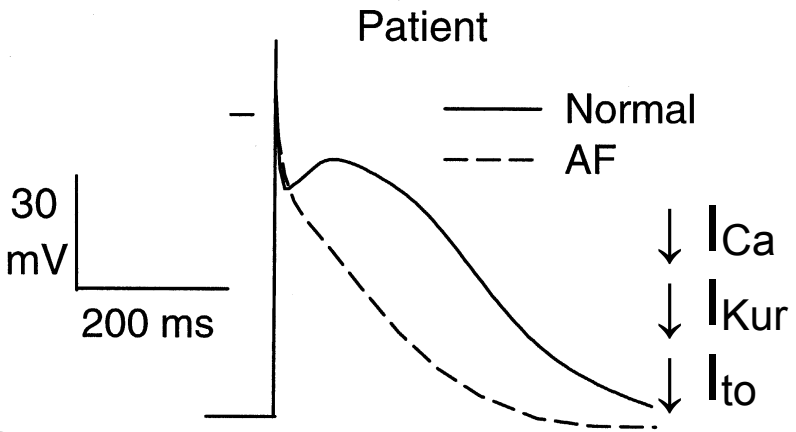
Multiscale modeling example: AF maintenance

Atrial fibrillation:

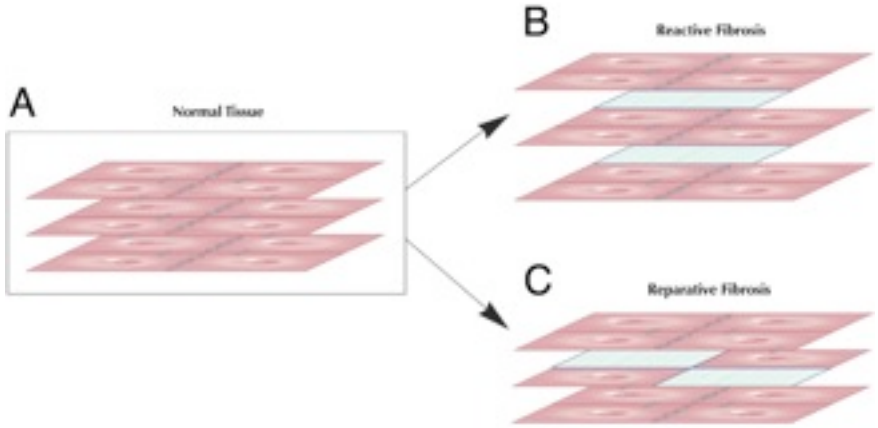
- 2.3 million sufferers in the U.S.
- 1/3 of all strokes over age 65
- doubled mortality rate

Clinical/exp observations:

- “AF begets AF”
- electrical and structural remodeling

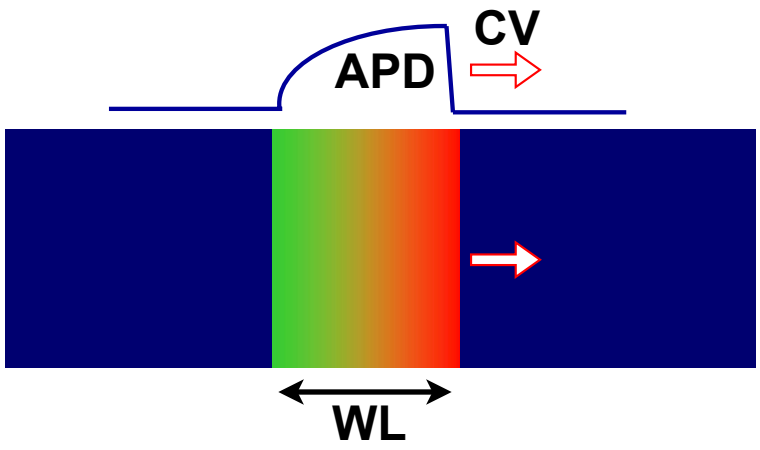


Courtemanche et al.,
Cardiovascular Research, 1999.



Burstein & Nattel,
J. American College of Cardiology, 2005.

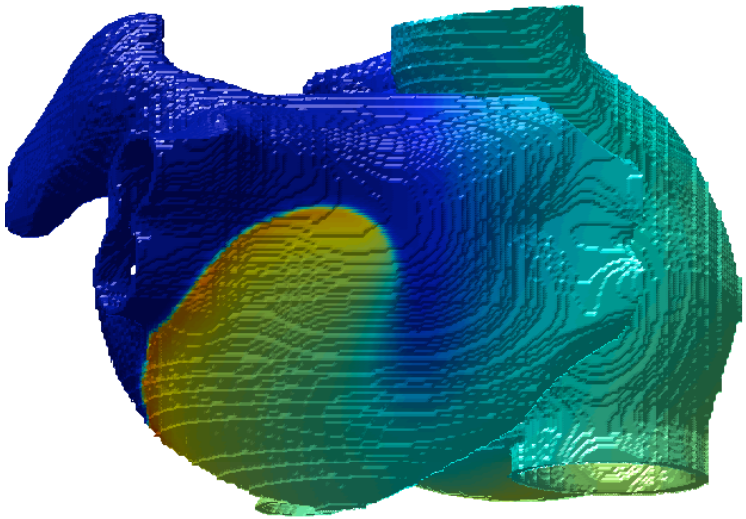
Multiscale modeling example: AF maintenance

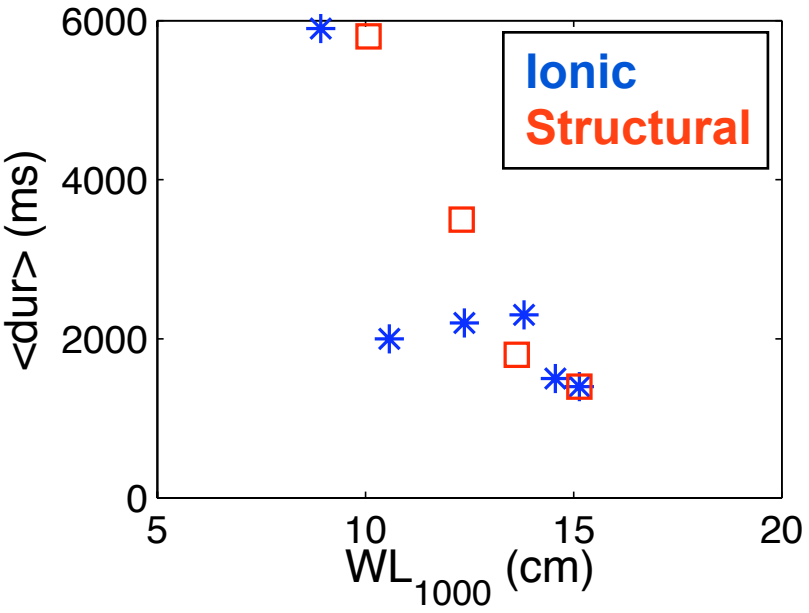


Wave length: WL = CV · APD

↓ CV
↓ APD ⇨ **↓ WL** ⇨ **multiple waves can fit in the atria**

Model: can separate ionic vs. structural remodeling

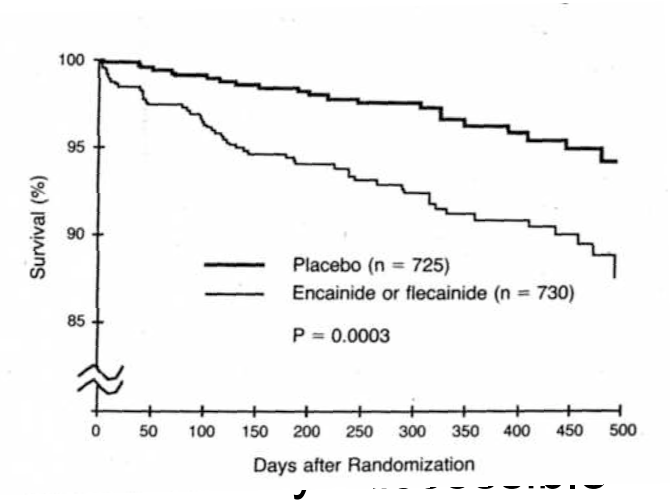




Sudden cardiac death: Treatment, prevention, termination

Pharmacological treatment (prevention)

- β-blockers
- ion channel blockers have *increased* mortality in some trials



CAST: Echt et al.
New England J. Medicine, 1991

Treatment, prevention, termination

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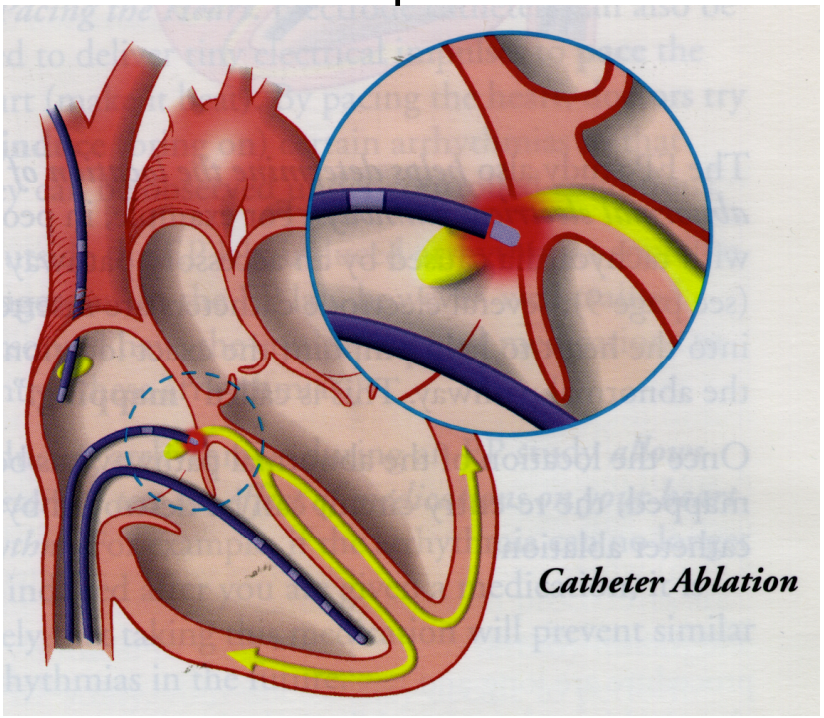
Ablation therapy (cure)

- doesn't work well in ventricles
- only if a localized, abnormal region of tissue is responsible



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External defibrillation

- not always accessible

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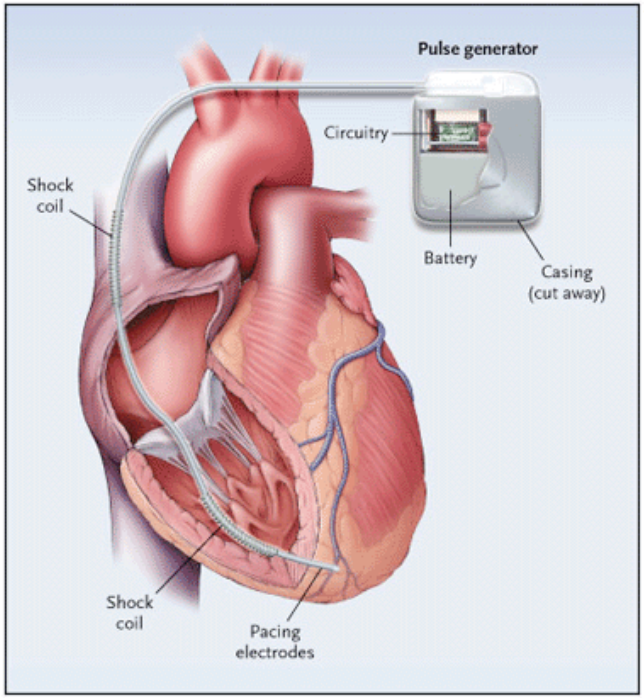
External defibrillation

- not always accessible

Implantable cardioverter defibrillator

- therapy of choice for many patients
- expensive



Alternans and its control

repolarization alternans

⇩

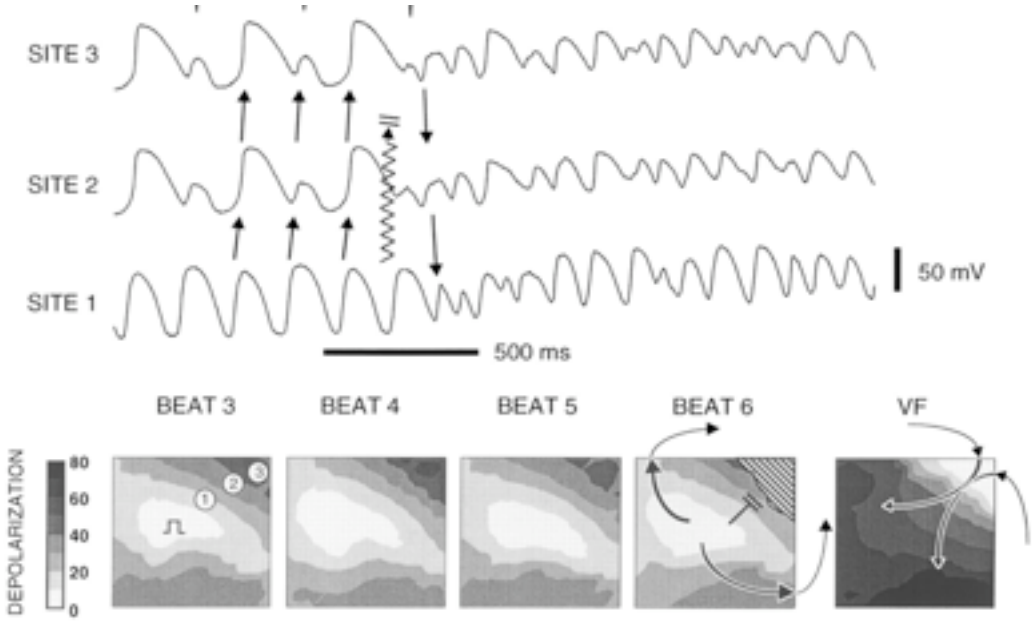
repolarization gradients

⇩

conduction block

⇩

tachyarrhythmias



Pastore et al., Circulation, 1999

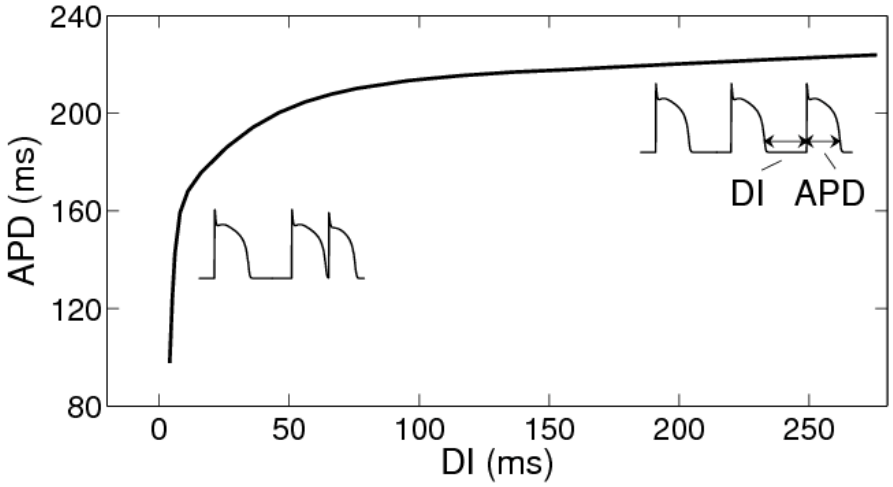
Alternans control

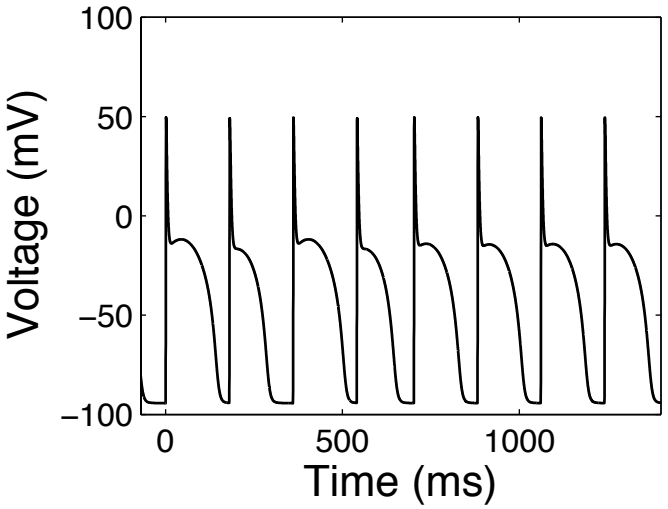
Basic concept: eliminate alternans by applying (small) electrical stimuli at well-timed intervals

$$\mathrm{BCL}_{n+1} = \begin{cases} \mathrm{BCL}^{\star} & \text{for} \quad \Delta\mathrm{BCL}_{n+1} > 0, \\ \mathrm{BCL}^{\star} + \Delta\mathrm{BCL}_{n+1} & \text{for} \quad \Delta\mathrm{BCL}_{n+1} \leq 0, \end{cases}$$

with

$$\Delta\mathrm{BCL}_{n+1} = \frac{\gamma}{2}(\mathrm{APD}_{n+1} - \mathrm{APD}_{n}),$$





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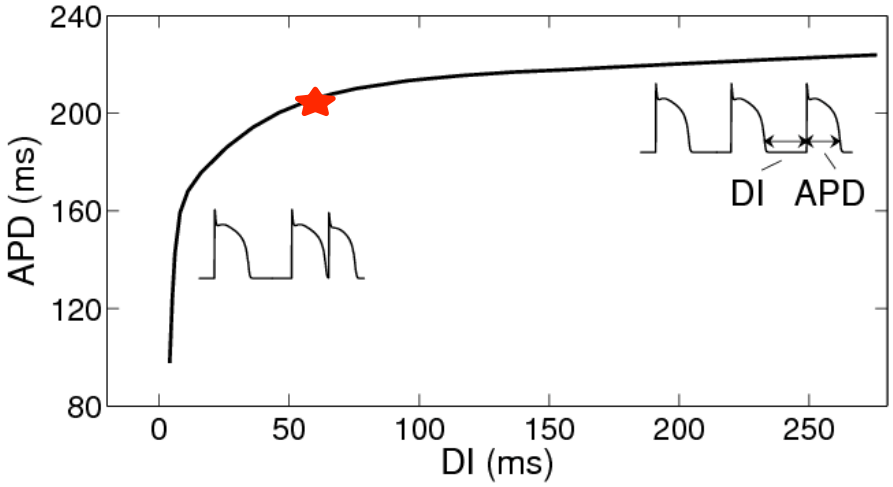

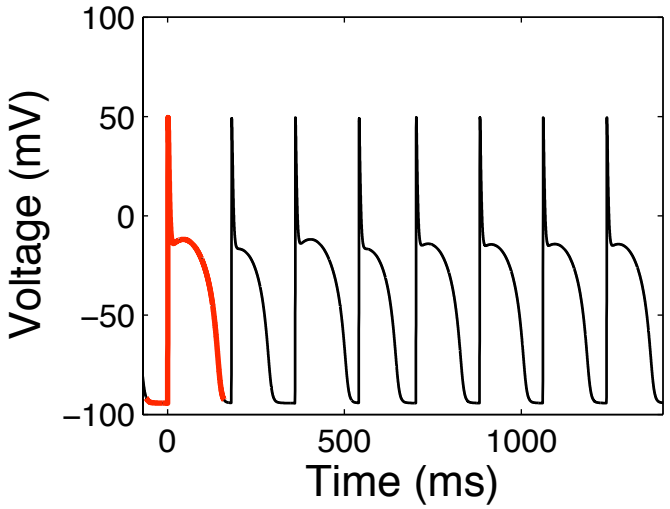

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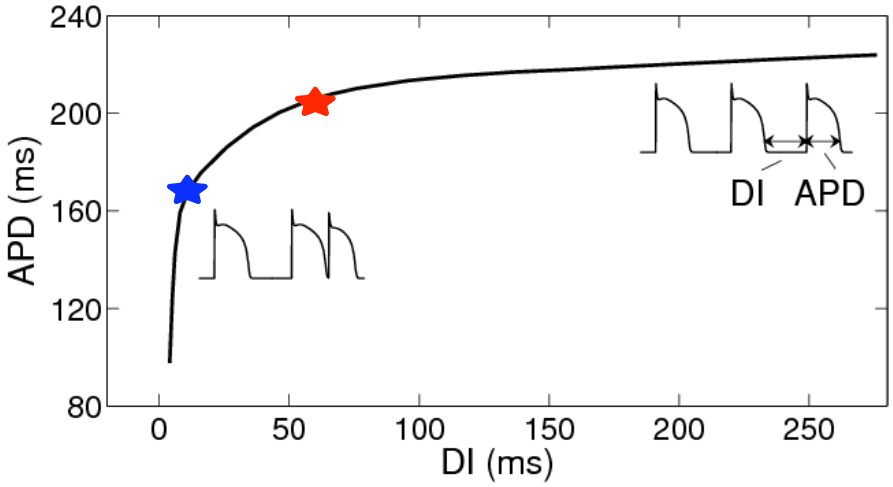

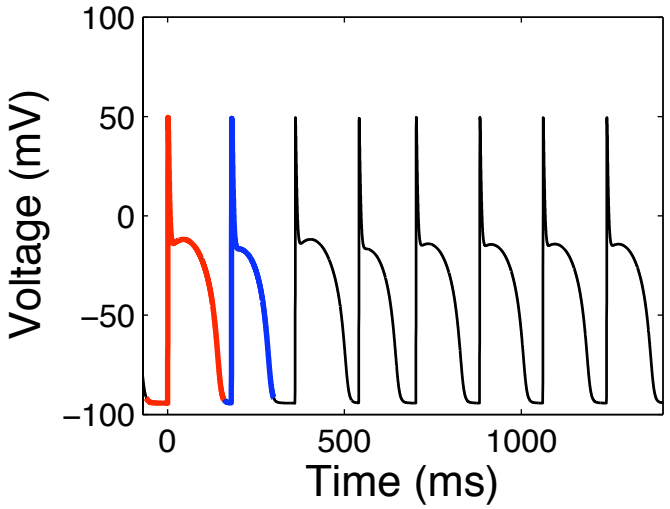

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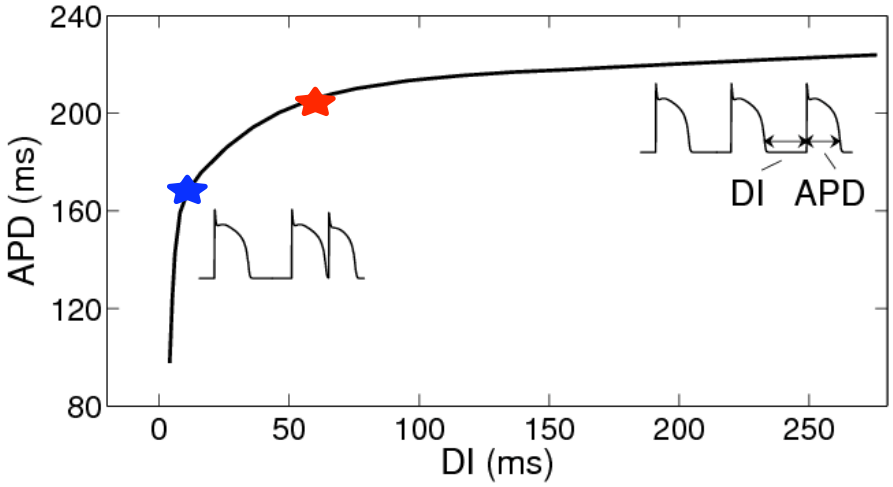

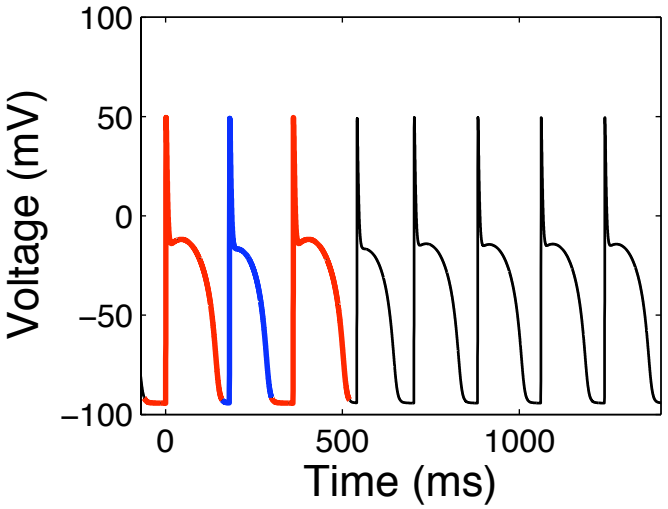

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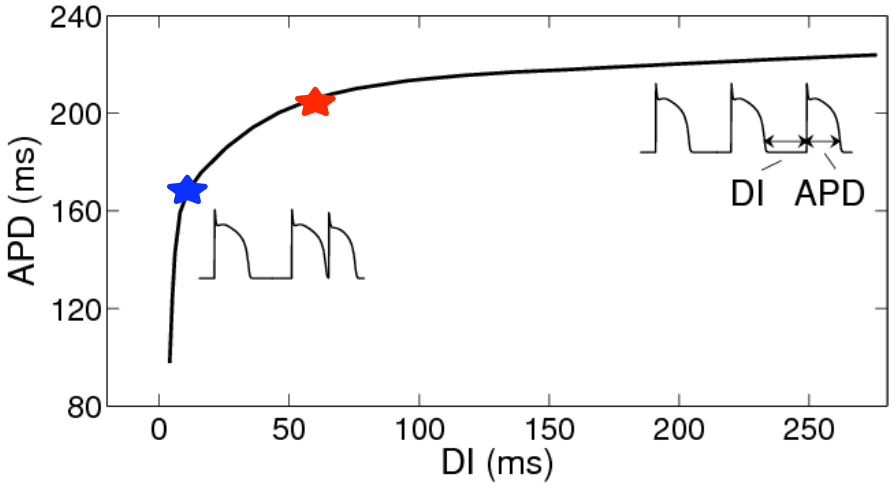

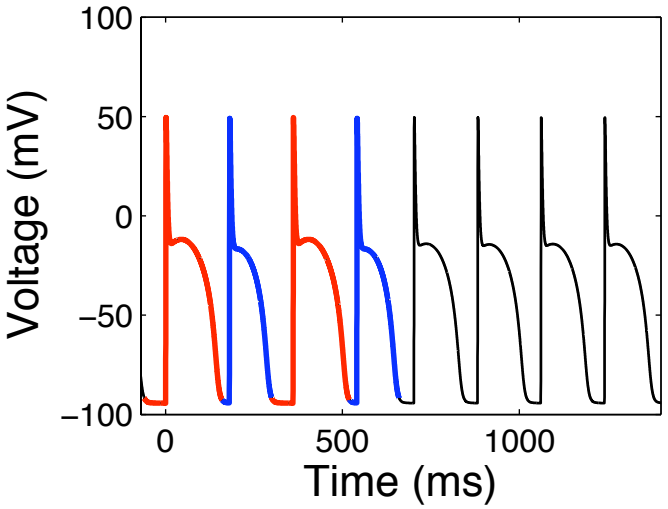

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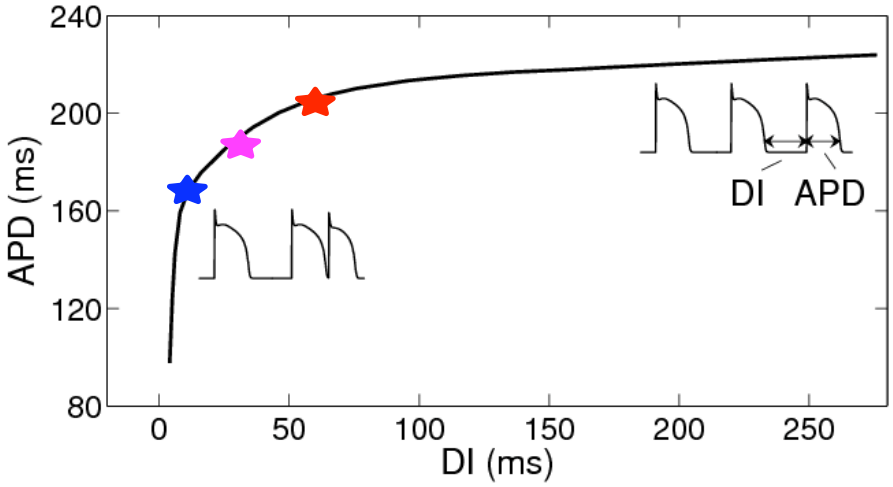
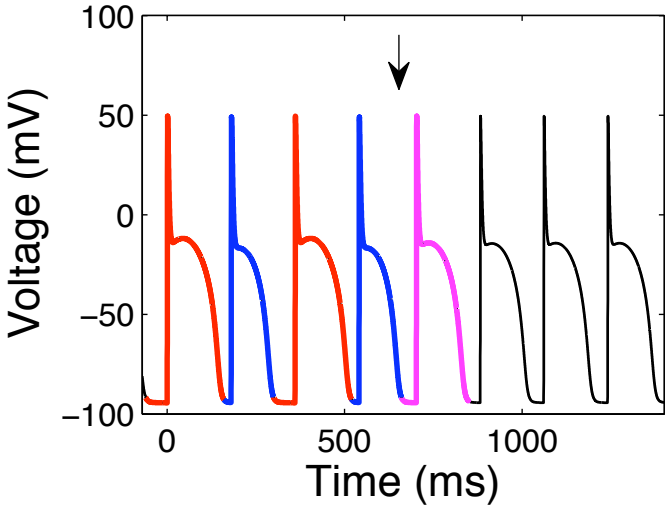
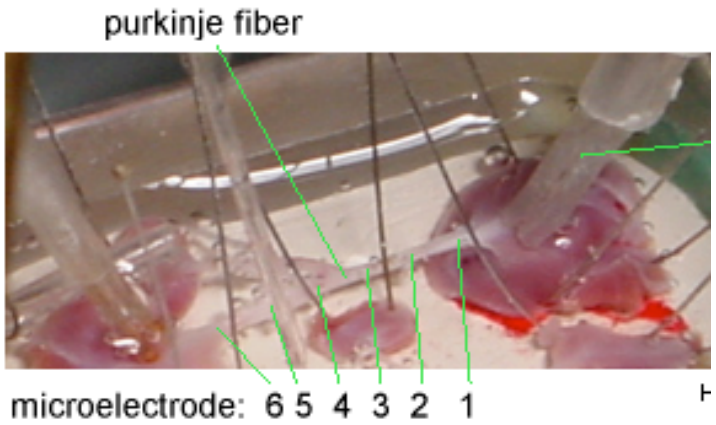
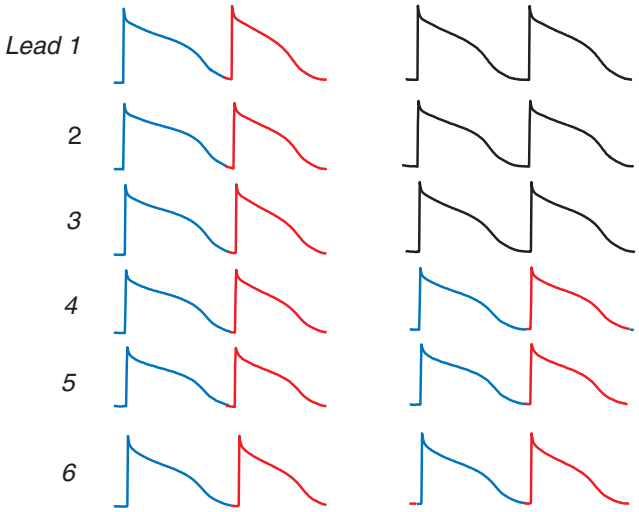
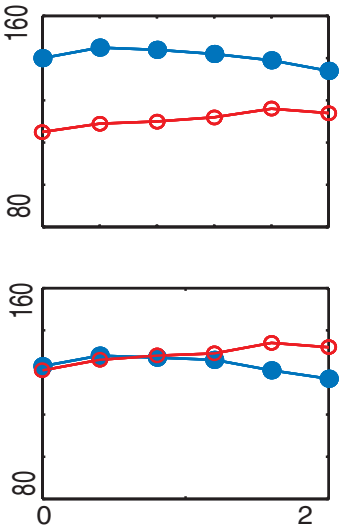




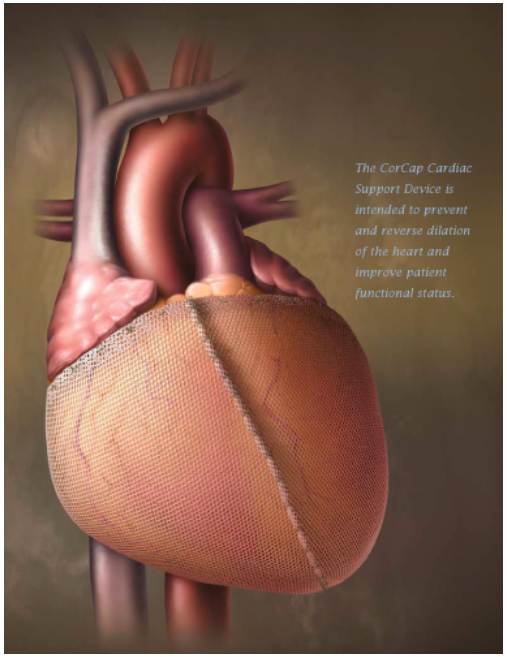
Alternans control works well is single cells but is only effective over ~1 cm in tissue.





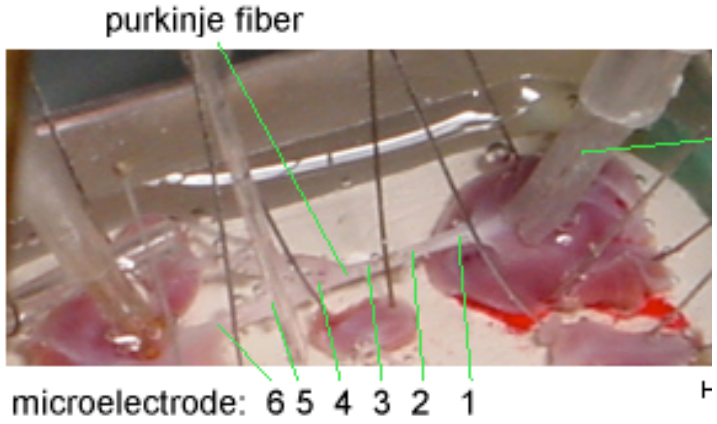


Christini et al., Physical Review Letters, 2006



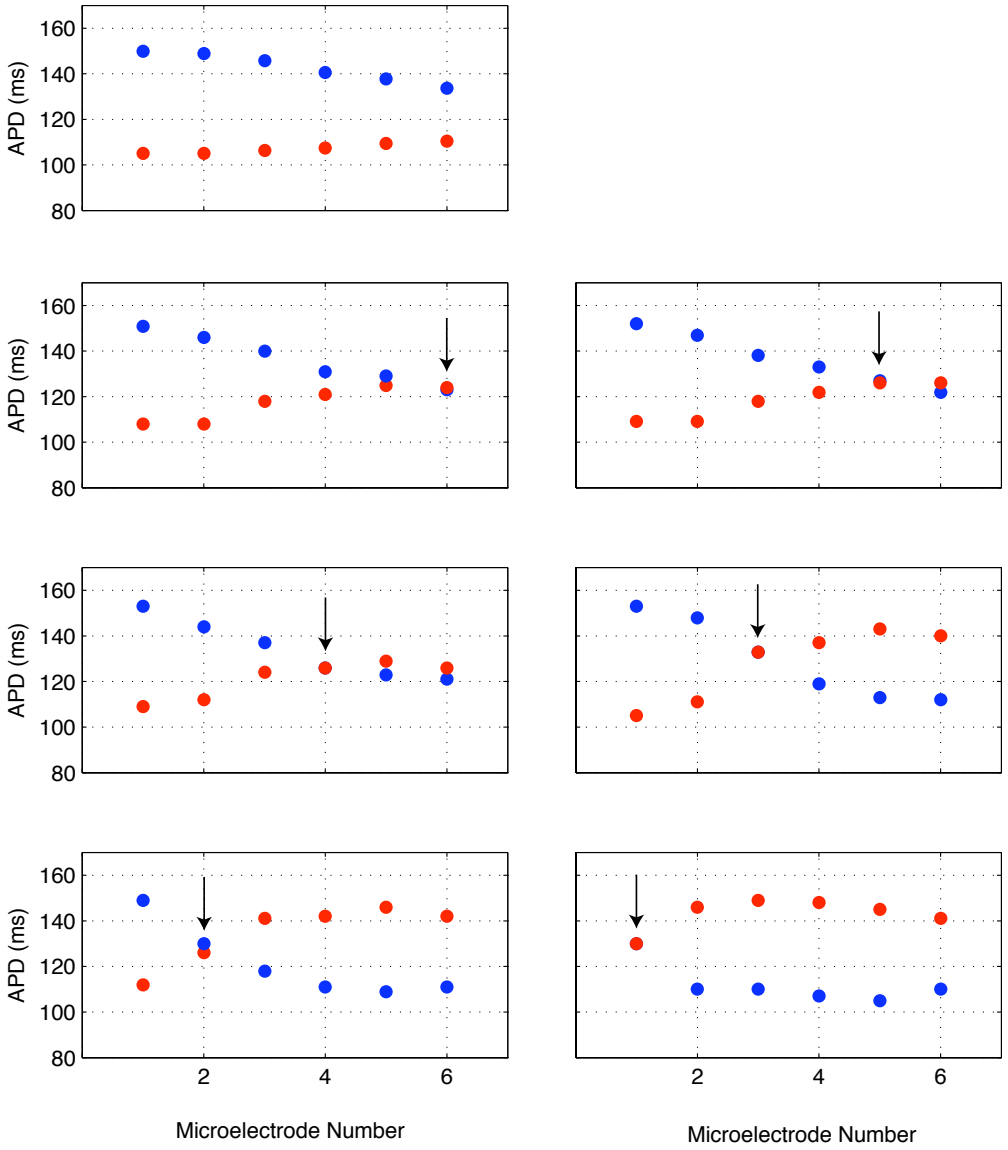
CorCap Cardiac Support Device: prevent and reverse dilation; add electrode grid?

Off-site alternans control

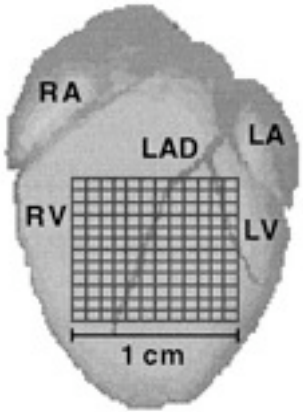


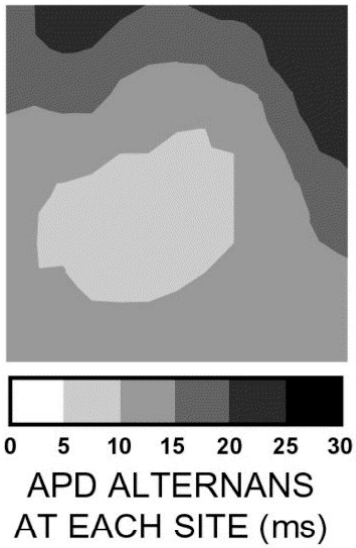
Use data from remote site to control alternans there

Krogh-Madsen et al., Physical Review E, 2010

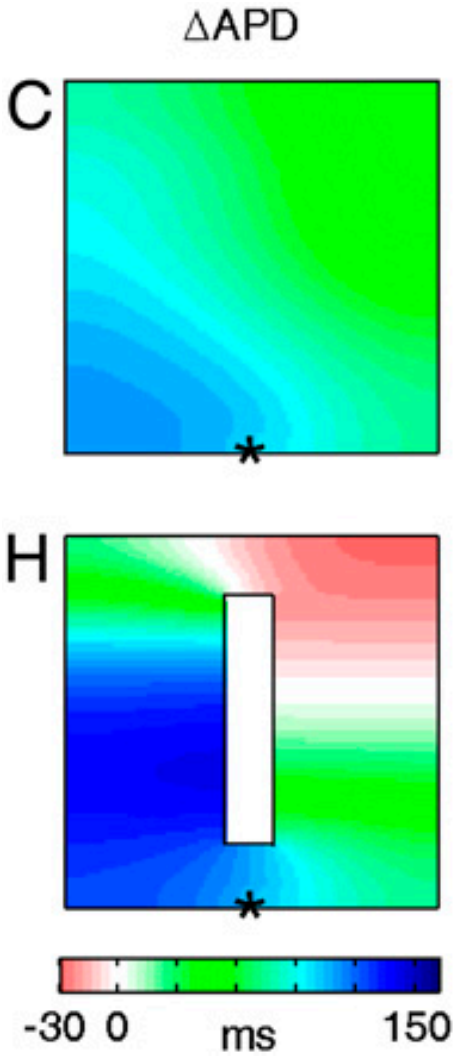


Use off-site control to eliminate alternans where it's amplitude is large?





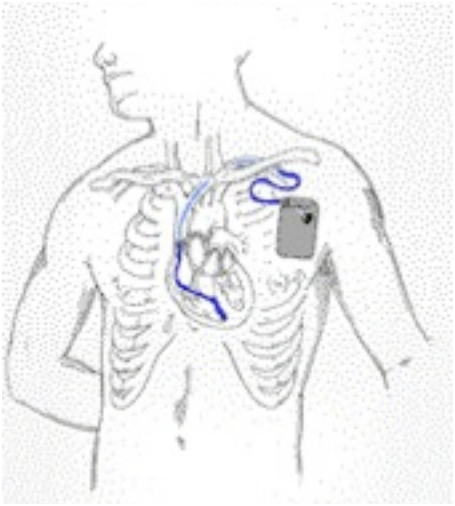
Pastore et al.,
Heart Rhythm Journal, 2006



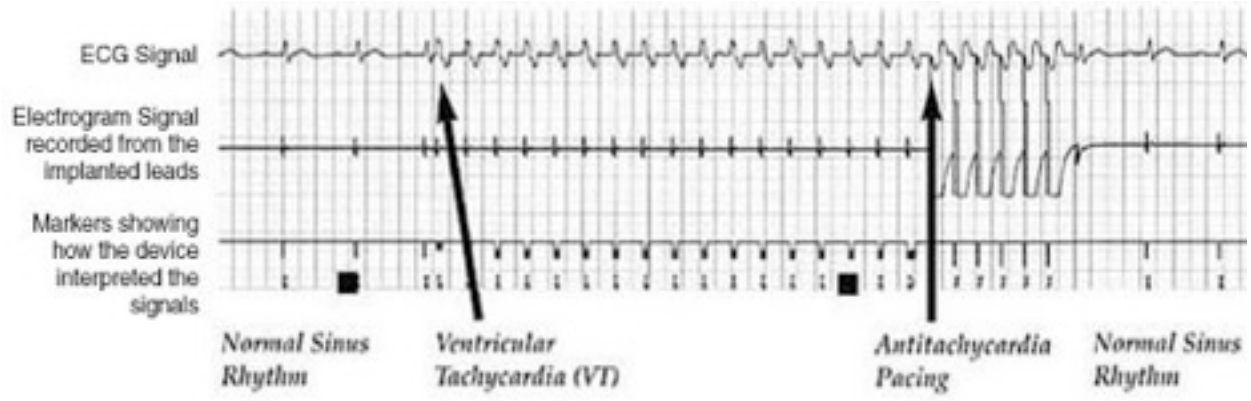
Krogh-Madsen & Christini,
Biophysical Journal, 2007

Pacing-induced termination of reentry

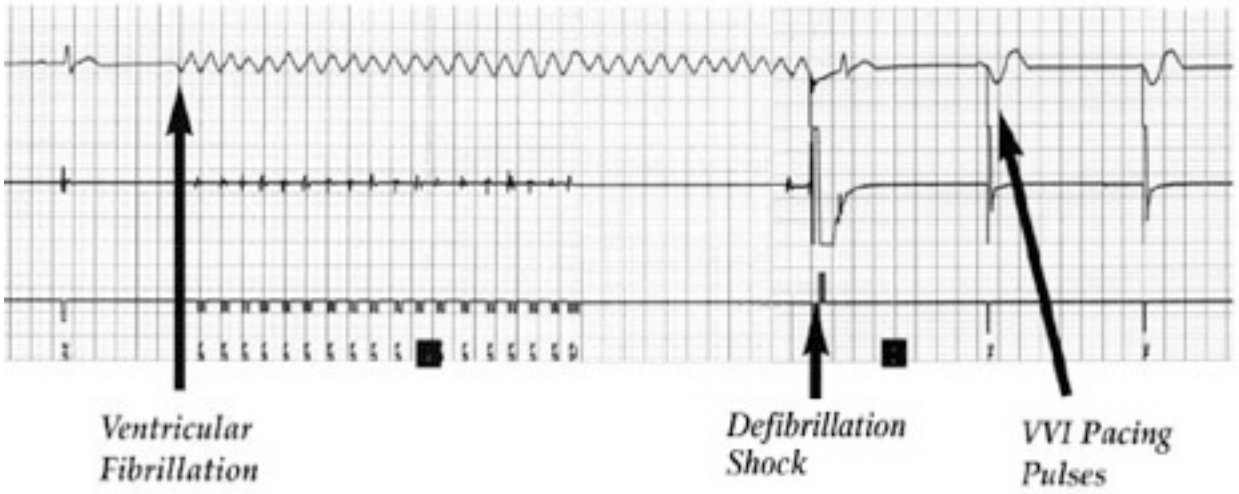
Implantable Cardioverter Defibrillator (ICD)



Antitachycardia pacing therapy



Defibrillation therapy



ICDs - engineering advances

- Size reduction; longevity increase.
- Arrhythmia detection improvement – reduction in false shocks, reducing pain and chronic anxiety.

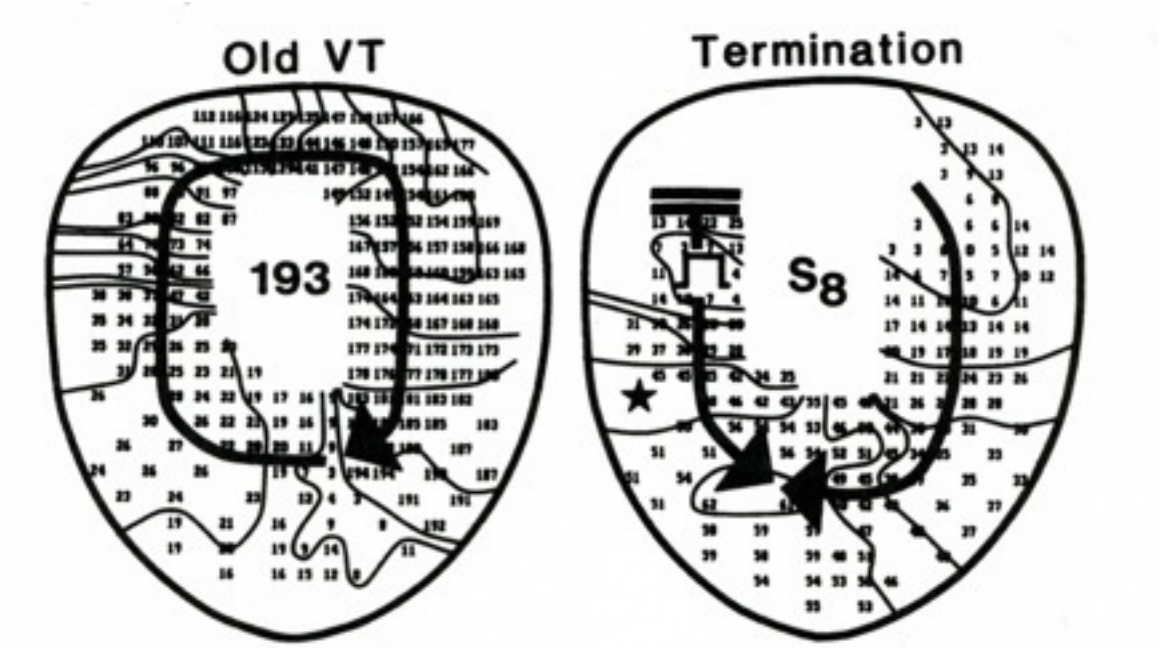
ICDs - arrhythmia termination improvement

Works in 85-90% of attempted trials

Incorporation of understanding of arrhythmia nonlinear dynamics into termination strategies:

- Can we come up with better pacing algorithms for ATP?
- *Even a small improvement would positively effect tens of thousands*

Unidirectional block



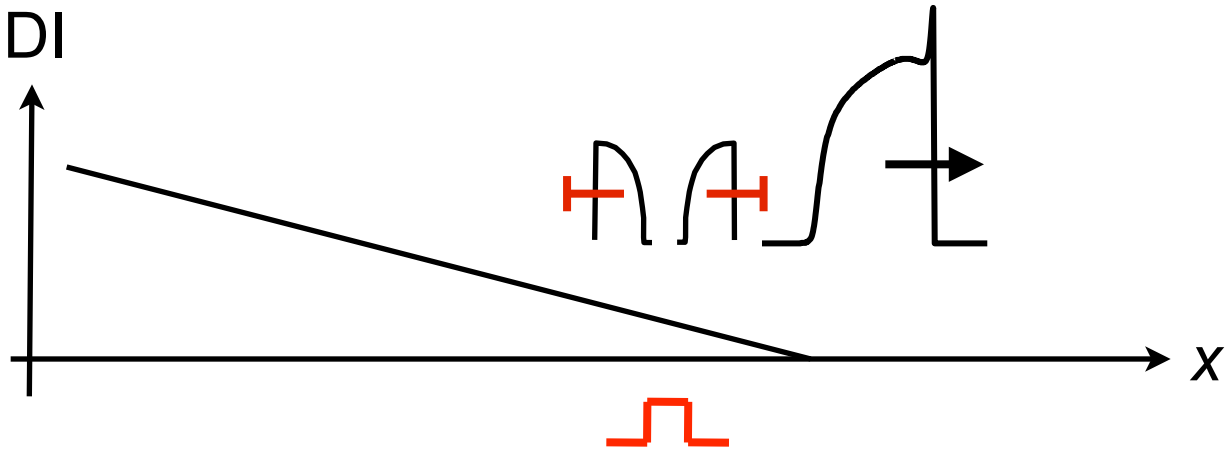
Boersma et al.,
Circulation, 1993

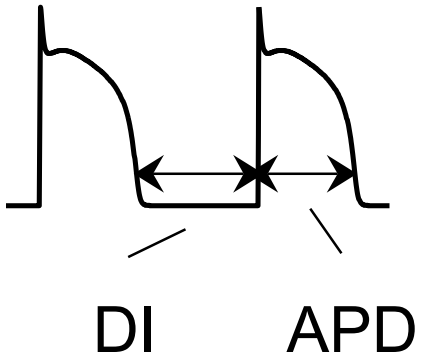
Why do more stimuli work better than one?

Dynamical instability?

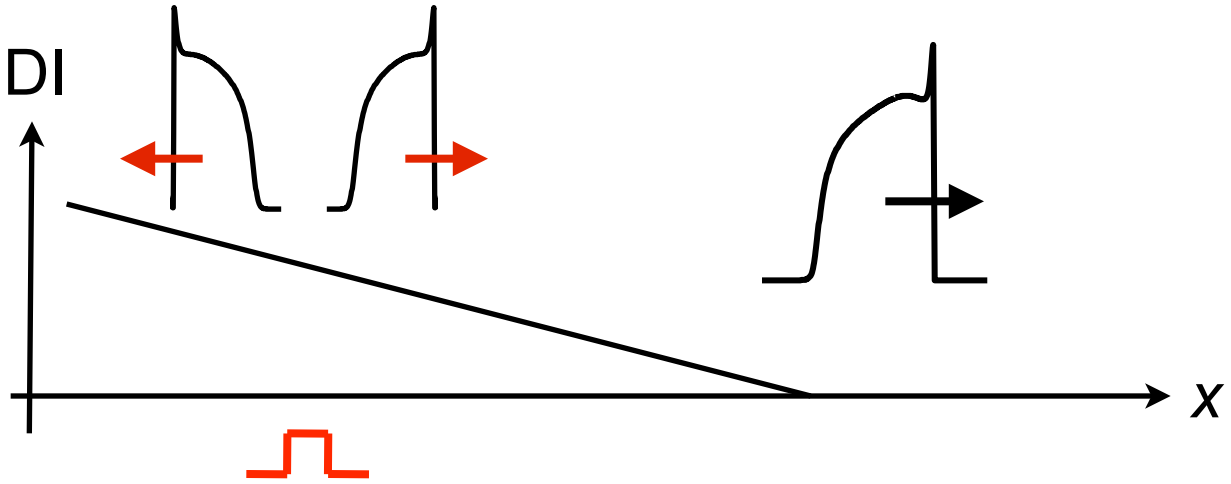
By exploiting such instability can we increase efficacy of pacing-induced termination?

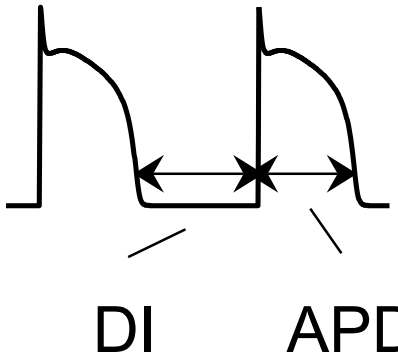
Spatial gradient in recovery time (DI) causes unidirectional block



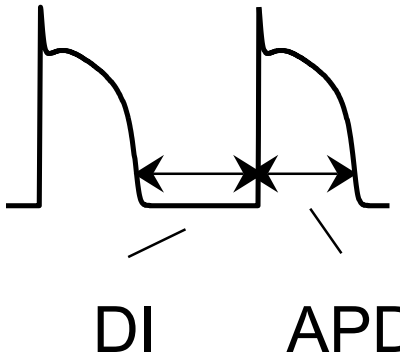


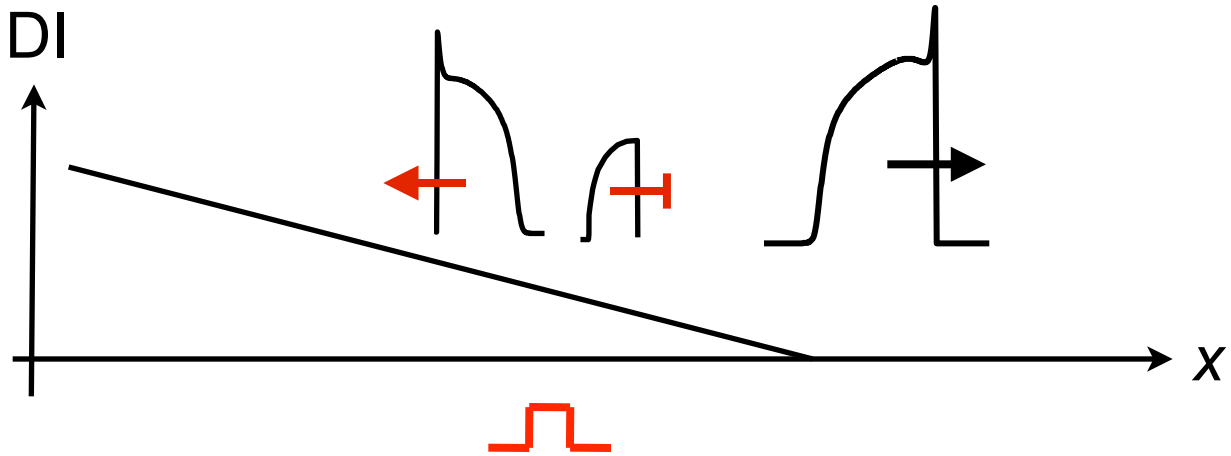
Spatial gradient in recovery time (DI) causes unidirectional block





Spatial gradient in recovery time (DI) causes unidirectional block





Vulnerable window for unidirectional block (1-2 ms)

$\partial DI/\partial x < 0$ ⇨ block in the anterograde direction

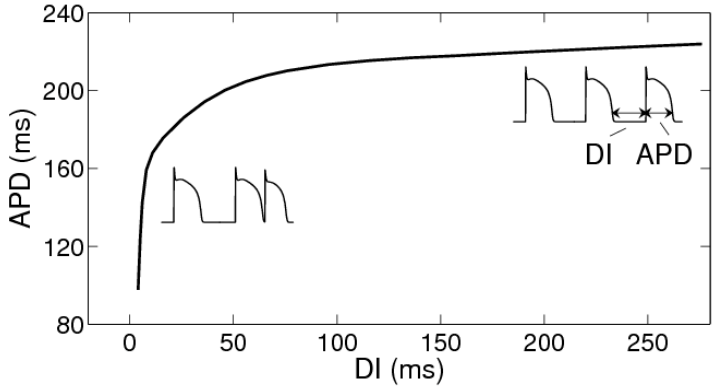
$\partial DI/\partial x > 0$ ⇨ block in the retrograde direction

Analytical approach

Map model: APD and CV are functions of previous DI

$$\frac{\partial \mathrm{DI}_1}{\partial x} = -1/\mathrm{CV_F} = -22\ \mathrm{ms/cm}$$

$$\frac{\partial \mathrm{DI}_i}{\partial x} = -\frac{da(\mathrm{DI}_{i-1})}{d\mathrm{DI}}\frac{\partial \mathrm{DI}_{i-1}}{\partial x} - \frac{1}{\mathrm{CV}_{i-1}} + \frac{1}{\mathrm{CV}_i}$$



Predictions

- the direction in which block occurs may alternate
- ∂DI/∂*x* may be amplified for short coupling intervals
- the window of unidirectional block may increase for short coupling intervals

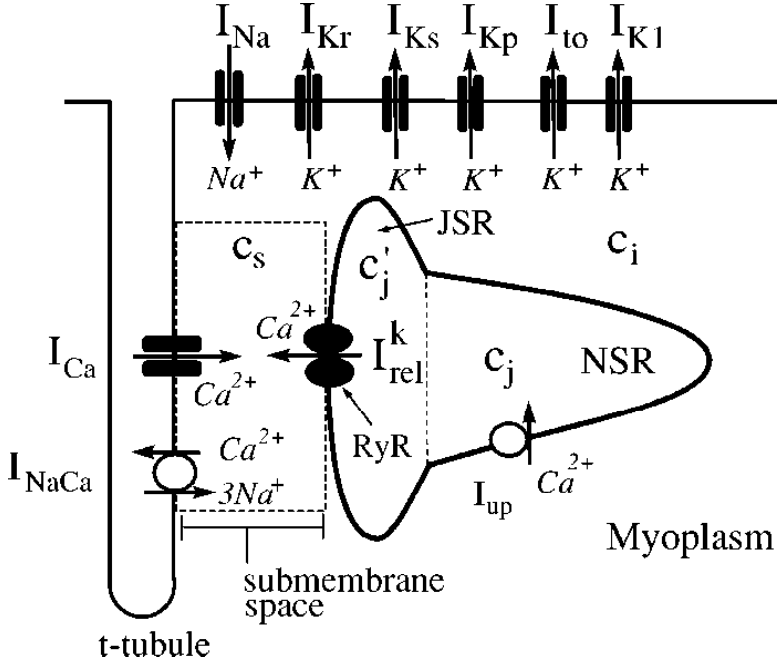
Krogh-Madsen & Christini, Physical Review E, 2009

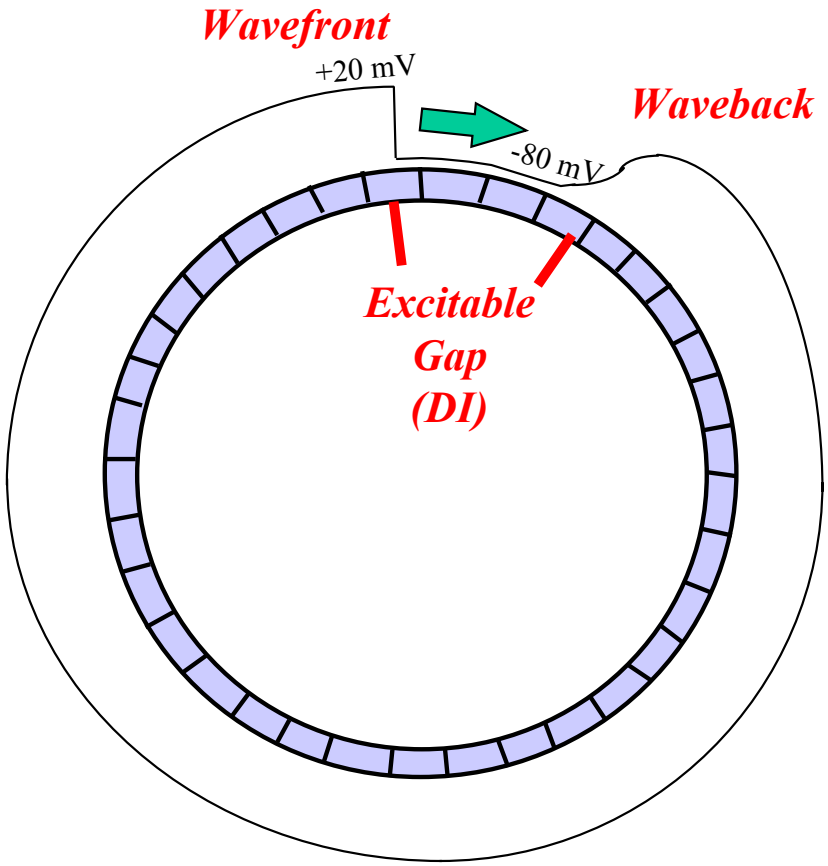
Numerical approach

Cable equation with periodic boundary conditions

$$\frac{\partial V}{\partial t} = D\frac{\partial^2 V}{\partial x^2} - I_{ion}/C_m$$

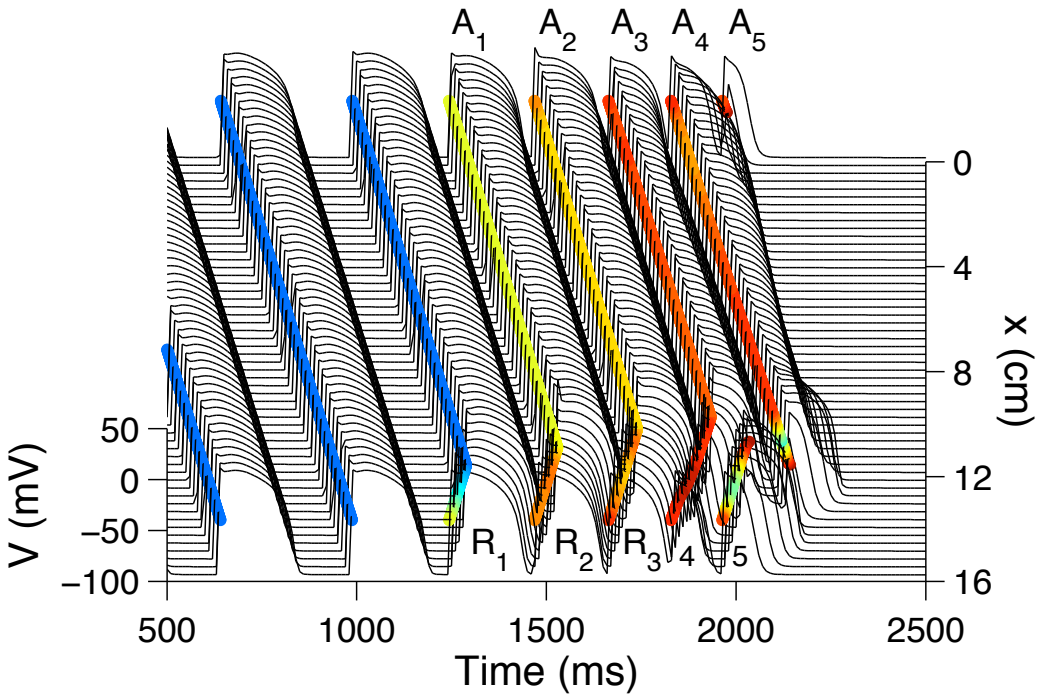
I_{ion} described by coupled ODEs

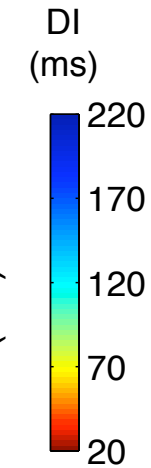


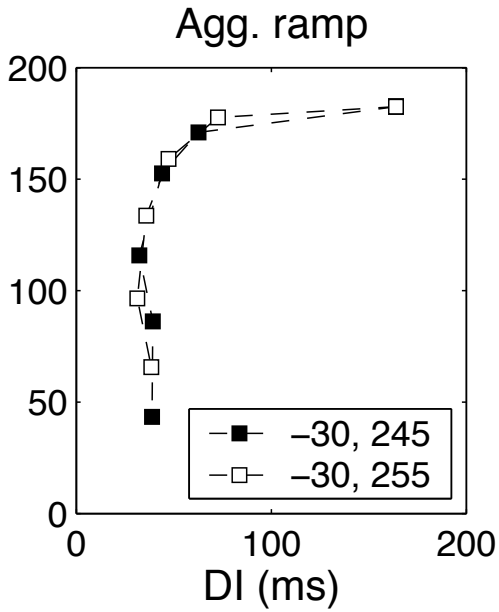


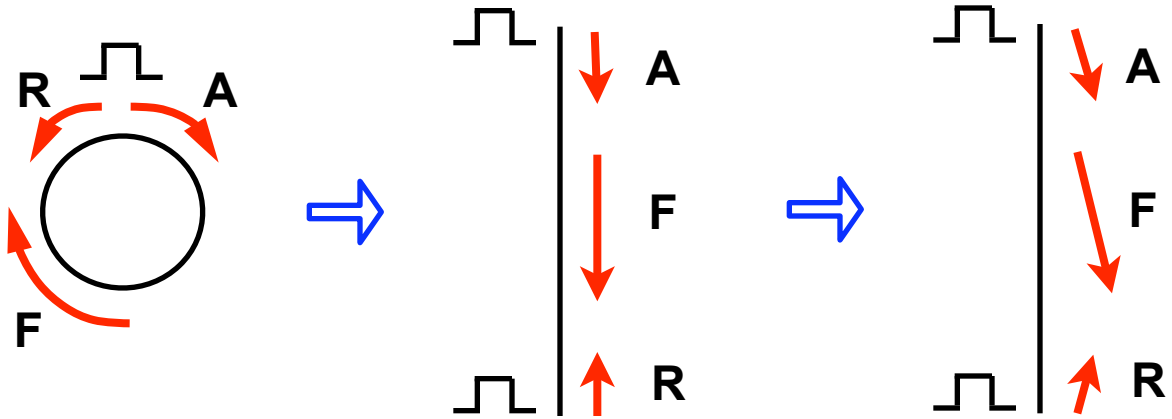
Shiferaw et al., Physical Review E, 2005.

Aggressive ramp pacing

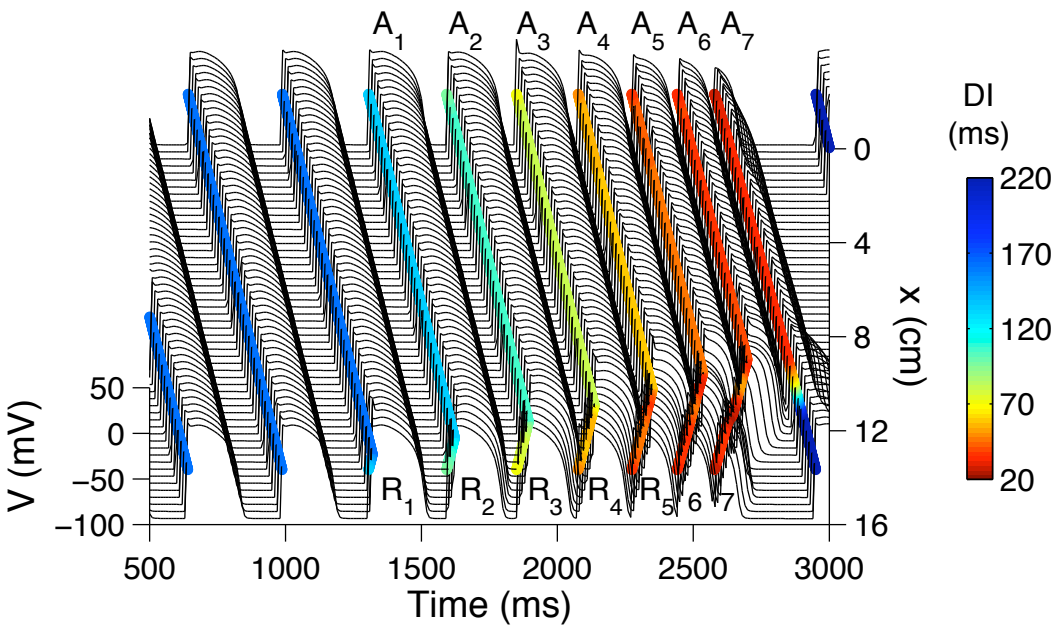


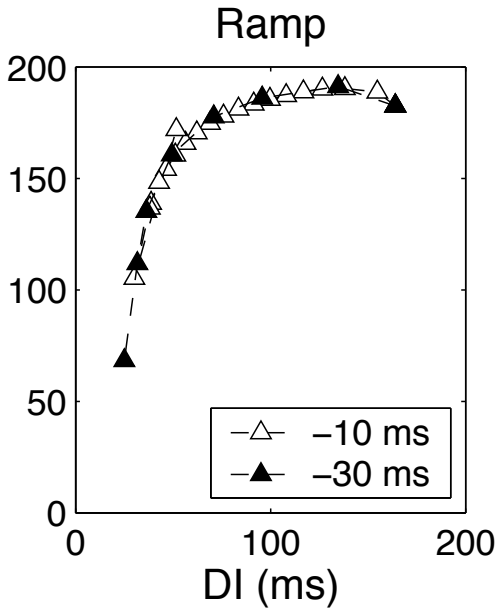




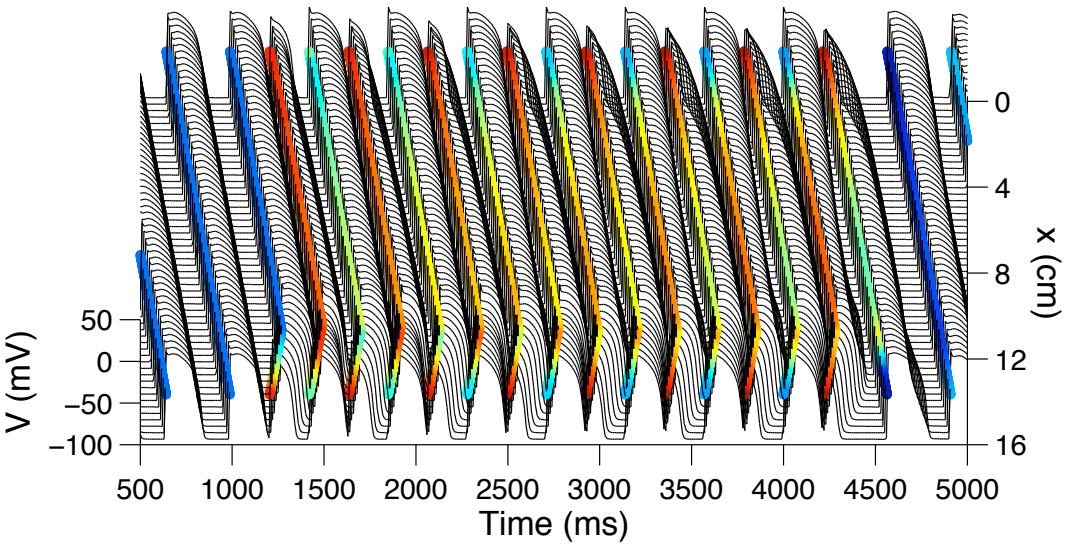


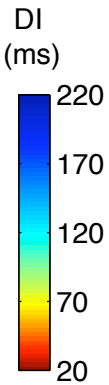
Ramp pacing

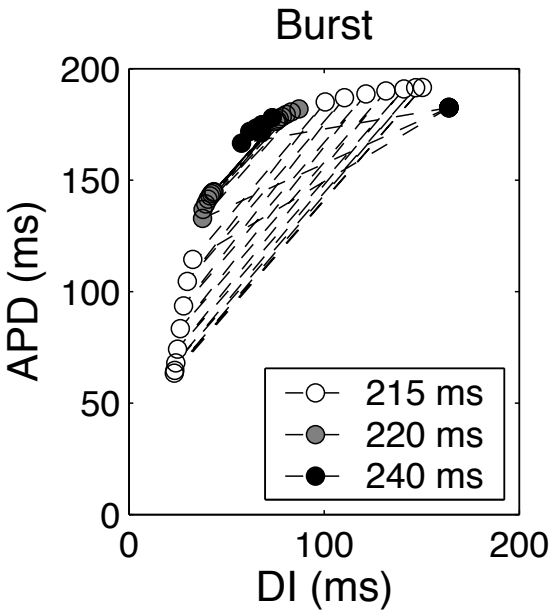

A1
A2
A3
A4
A5
A6
A7
R1
R2
R3
R4
R5
6
7
V (mV)
50
0
−50
−100
500
1000
1500
2000
2500
3000
Time (ms)
0
4
8
12
16
x (cm)
DI
(ms)
220
170
120
70
20


Ramp
200
150
100
50
0
0
100
200
DI (ms)
−10 ms
−30 ms

Burst pacing







Take-home message

Cardiac modeling is fun and worthwhile and useful for studying many types of problems using different models ranging from very simple (e.g., threshold dynamics) to highly complex (e.g., 3D anatomical).