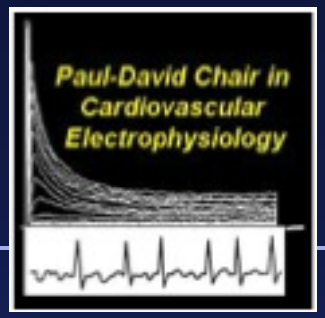

The Atrial Remodeling Determinants of Rotor Dynamics in AF

Stanley Nattel, MD

Montreal Heart Institute

Outline

- What are rotors?
- How does the rotor concept differ from the leading circle paradigm?
- What happens with atrial remodeling?

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Belousov-Zhabotinsky Reaction and Fibrillation

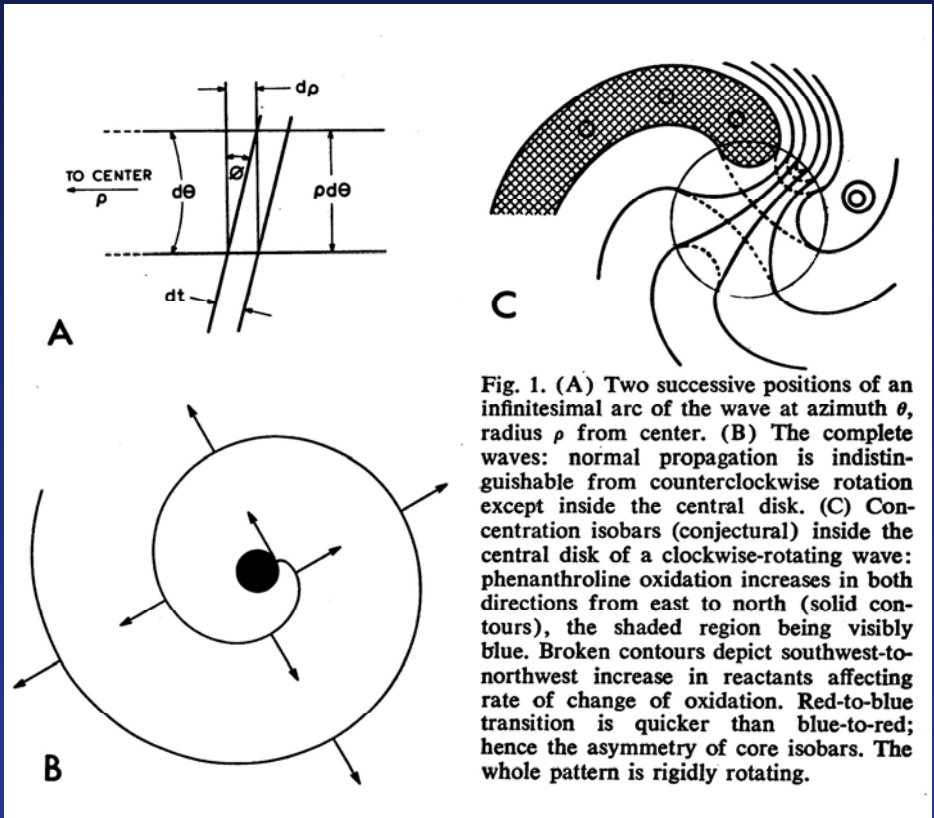


Fig. 1. (A) Two successive positions of an infinitesimal arc of the wave at azimuth θ, radius ρ from center. (B) The complete waves: normal propagation is indistinguishable from counterclockwise rotation except inside the central disk. (C) Concentration isobars (conjectural) inside the central disk of a clockwise-rotating wave: phenanthroline oxidation increases in both directions from east to north (solid contours), the shaded region being visibly blue. Broken contours depict southwest-to-northwest increase in reactants affecting rate of change of oxidation. Red-to-blue transition is quicker than blue-to-red; hence the asymmetry of core isobars. The whole pattern is rigidly rotating.

Winfree AT, Science *1972;175:63-6.*

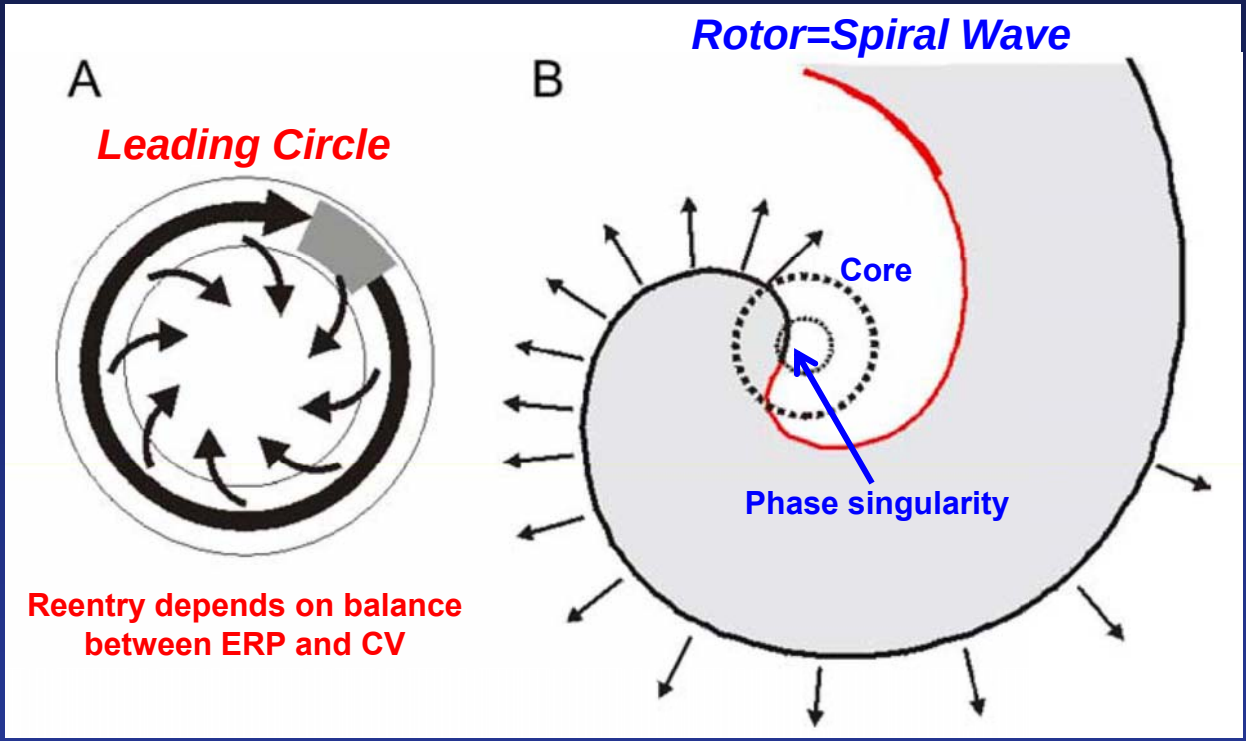
Sudden Cardiac Death: A Problem in Topology

Many sudden deaths are the result of fibrillation: a disruption of the coordinated contraction of heart muscle fibers. The cause may lie in a state of affairs described by a mathematical theorem

Arthur T. Winfree | May 1, 1983 |

Winfree AT, Scientific American *1983;248:144-9.*

So, what really is a rotor?

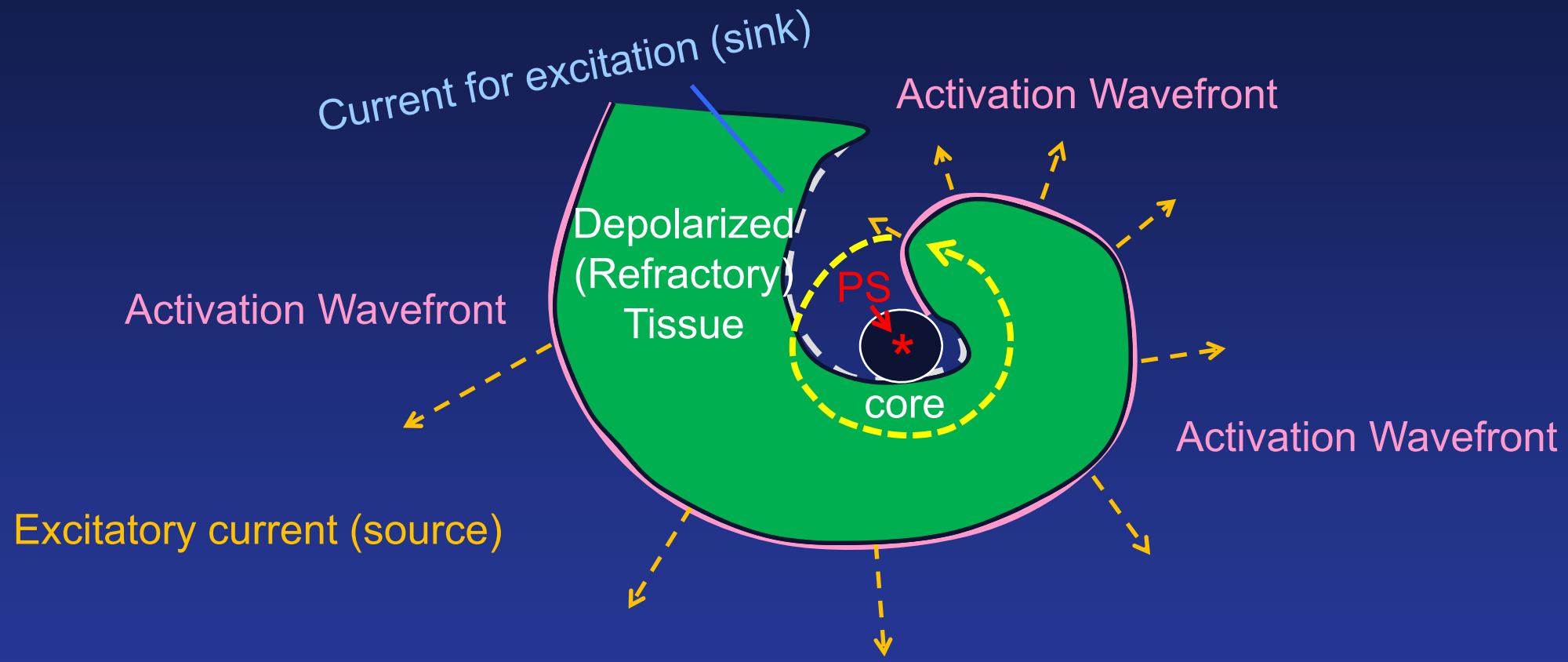


Rotors (spiral waves) as mechanism of reentry
Differences from leading circle:

- Core is not kept refractory by centripetal waves; excitable but unexcited
- No role for “excitable gap”
- Maintenance and properties depend on excitability (determined by propagation strength and refractoriness), not balance between conduction velocity and refractory period

Comtois P et al, Europace *2005;7 S2:10-20.*

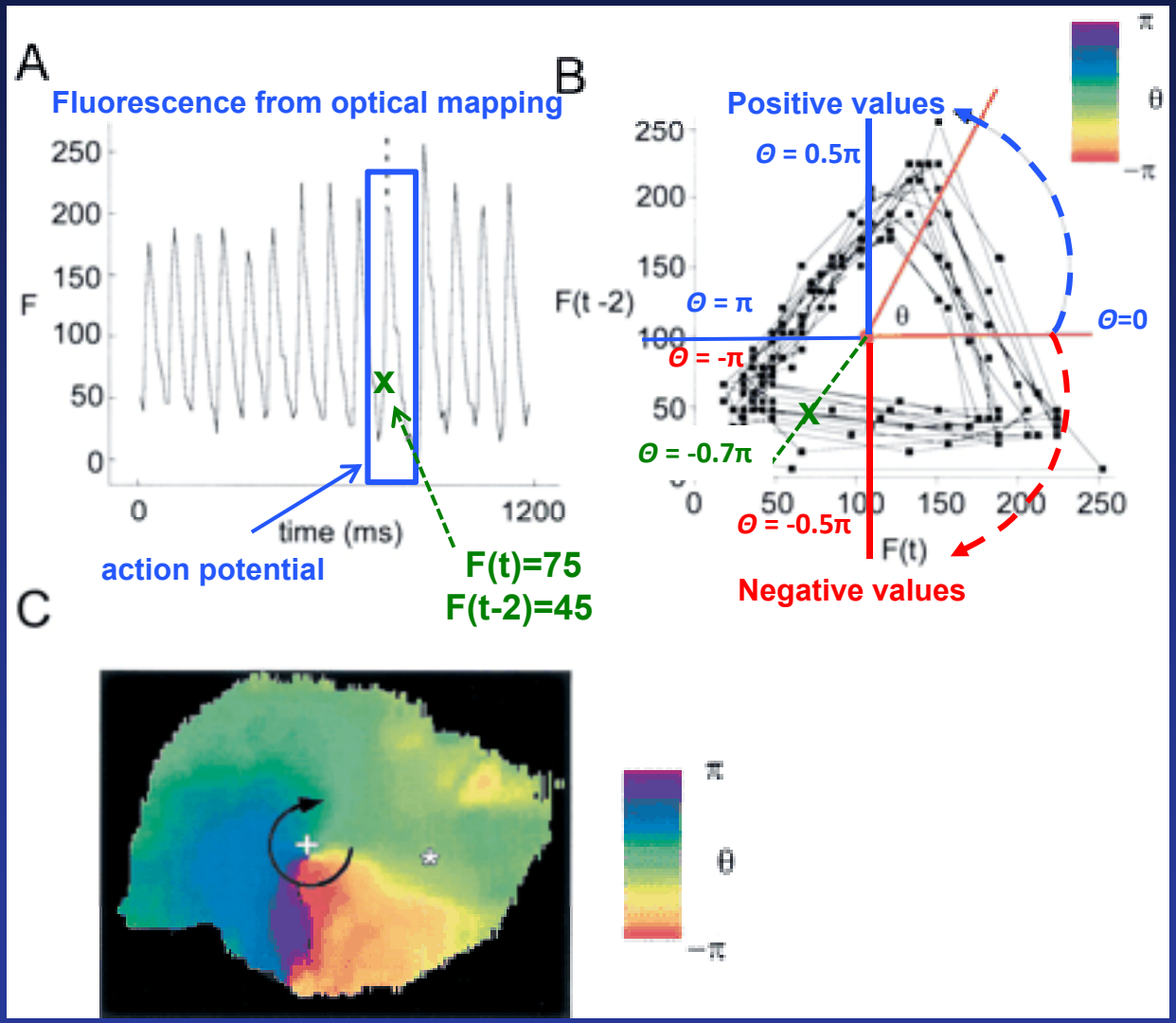
Functional determinants of rotor-based reeentry



Perpetuation depends on ability of wavefront to continuously activate tissue, which depends on:

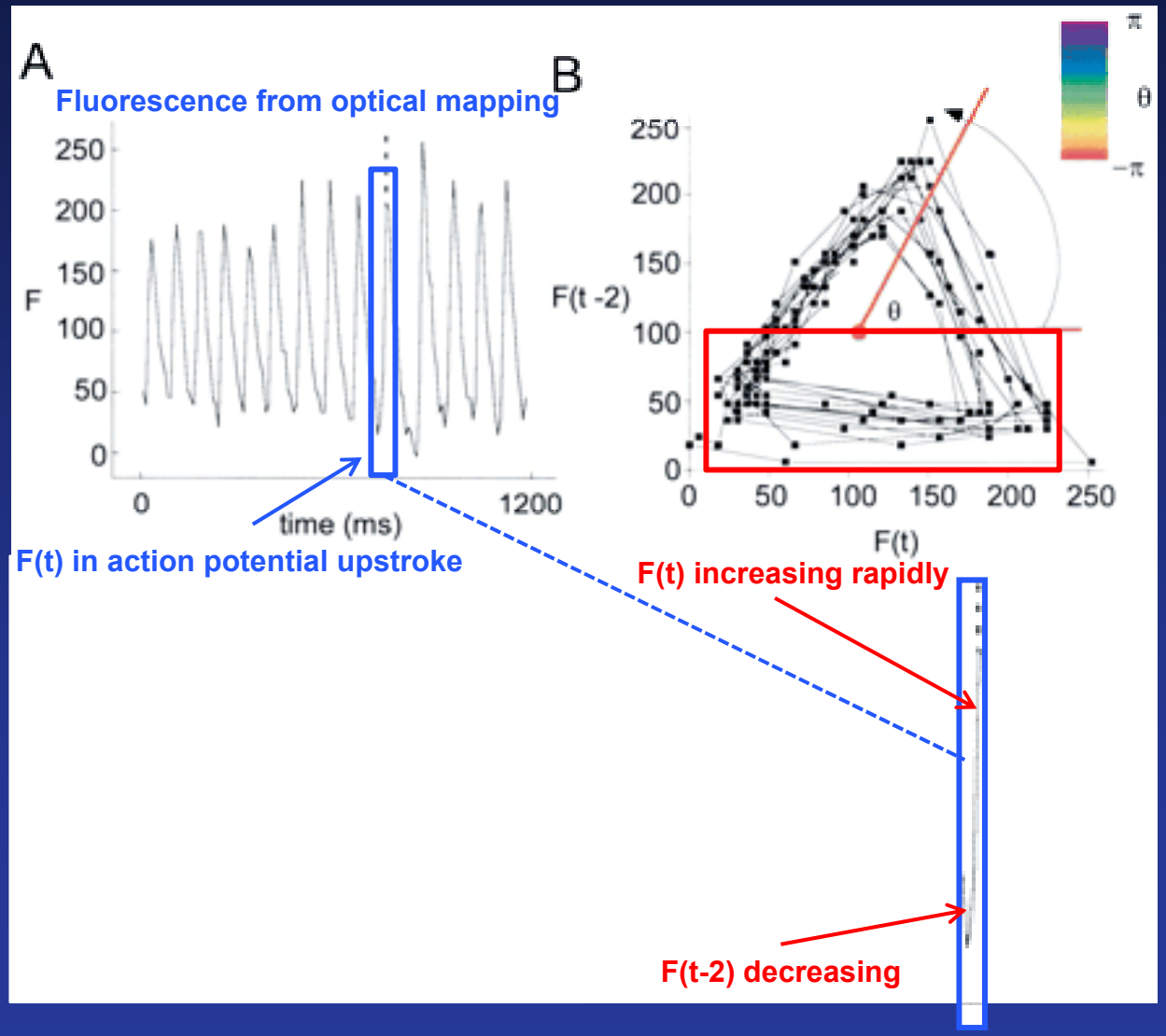
- Strength of excitatory source
- Magnitude of current sink

Phase-mapping and rotors: Concept of phase singularity (PS)

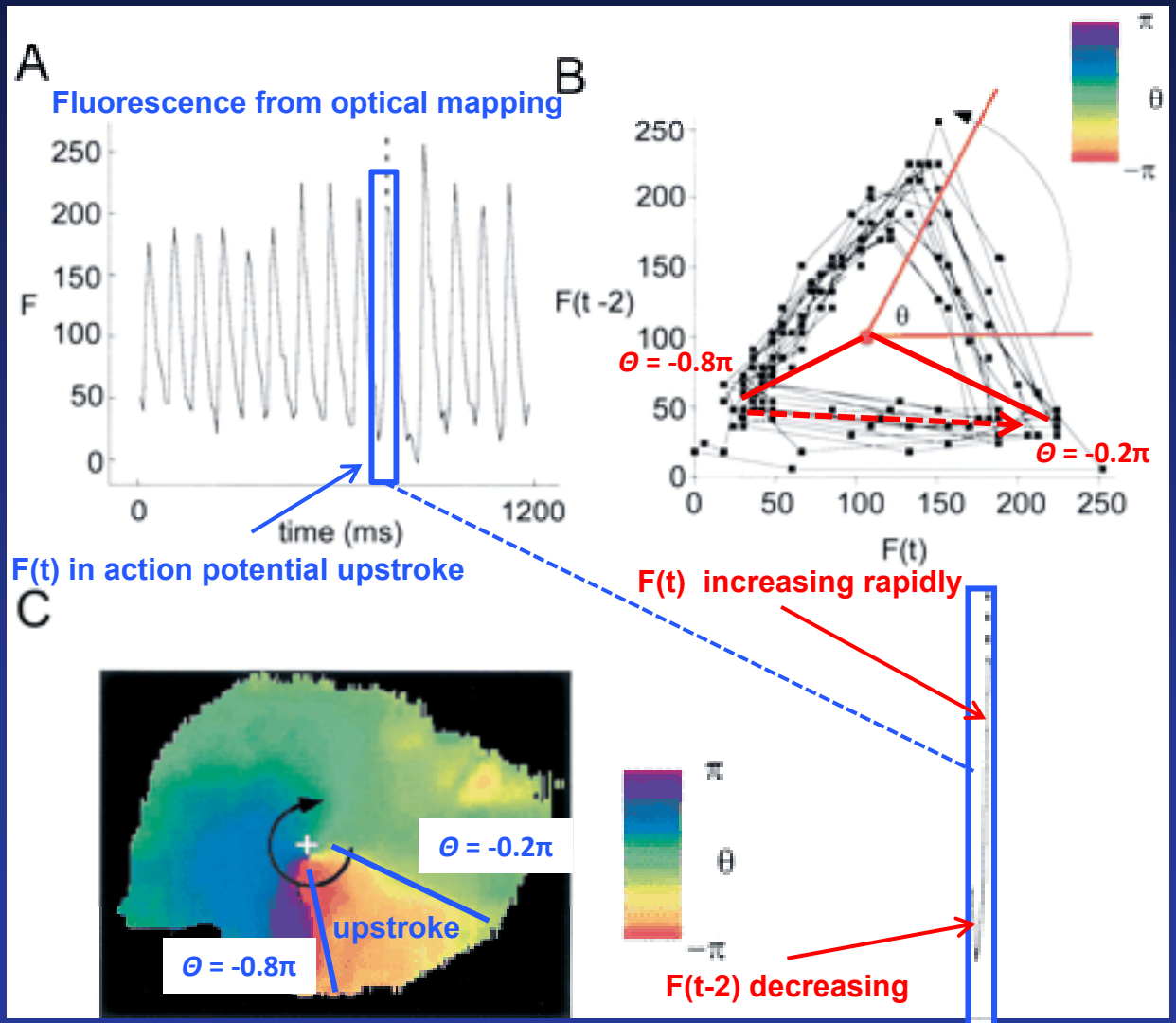


Chen J et al, Cardiovasc Res 2000.

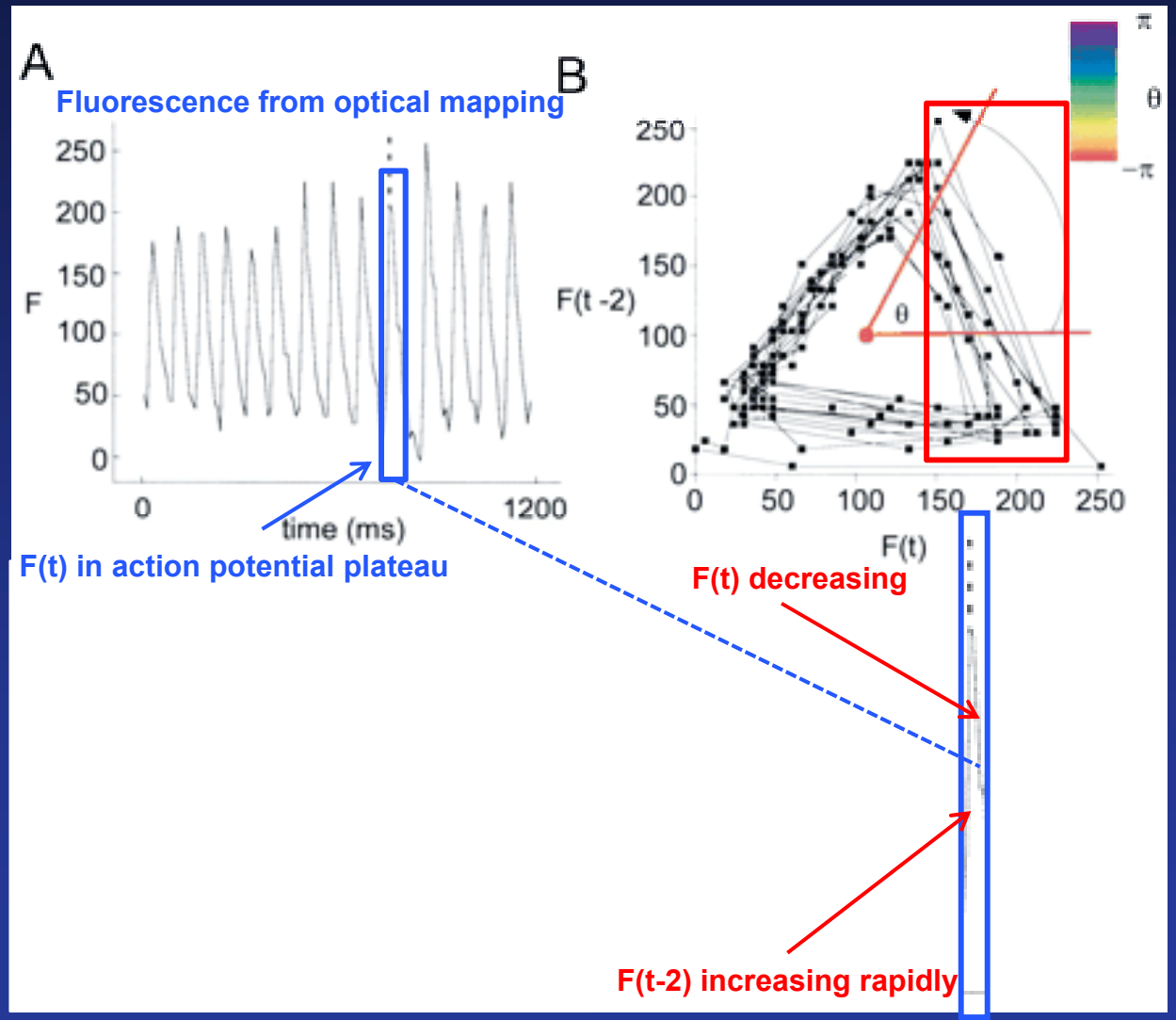
Phase-mapping and rotors



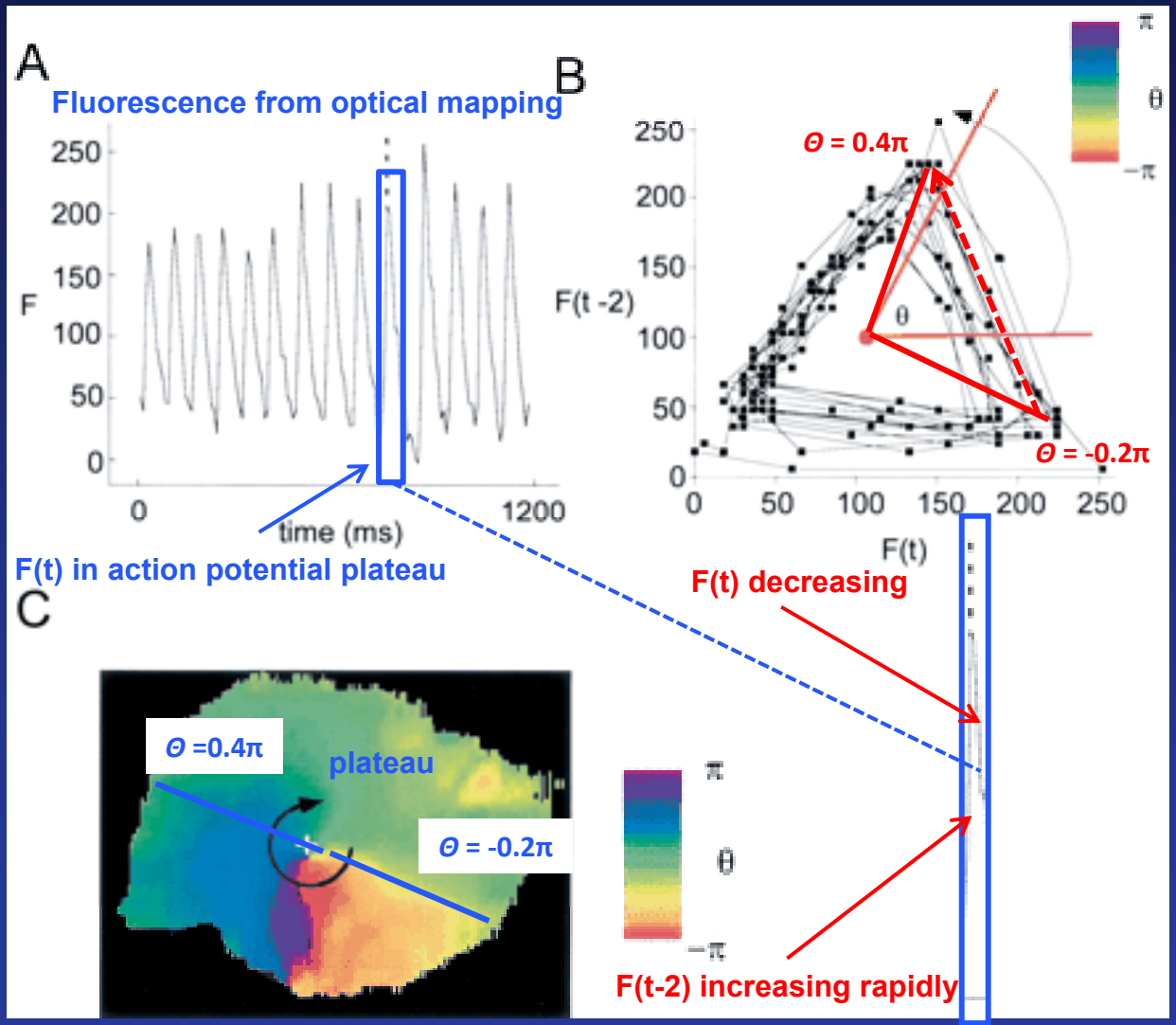
Phase-mapping and rotors



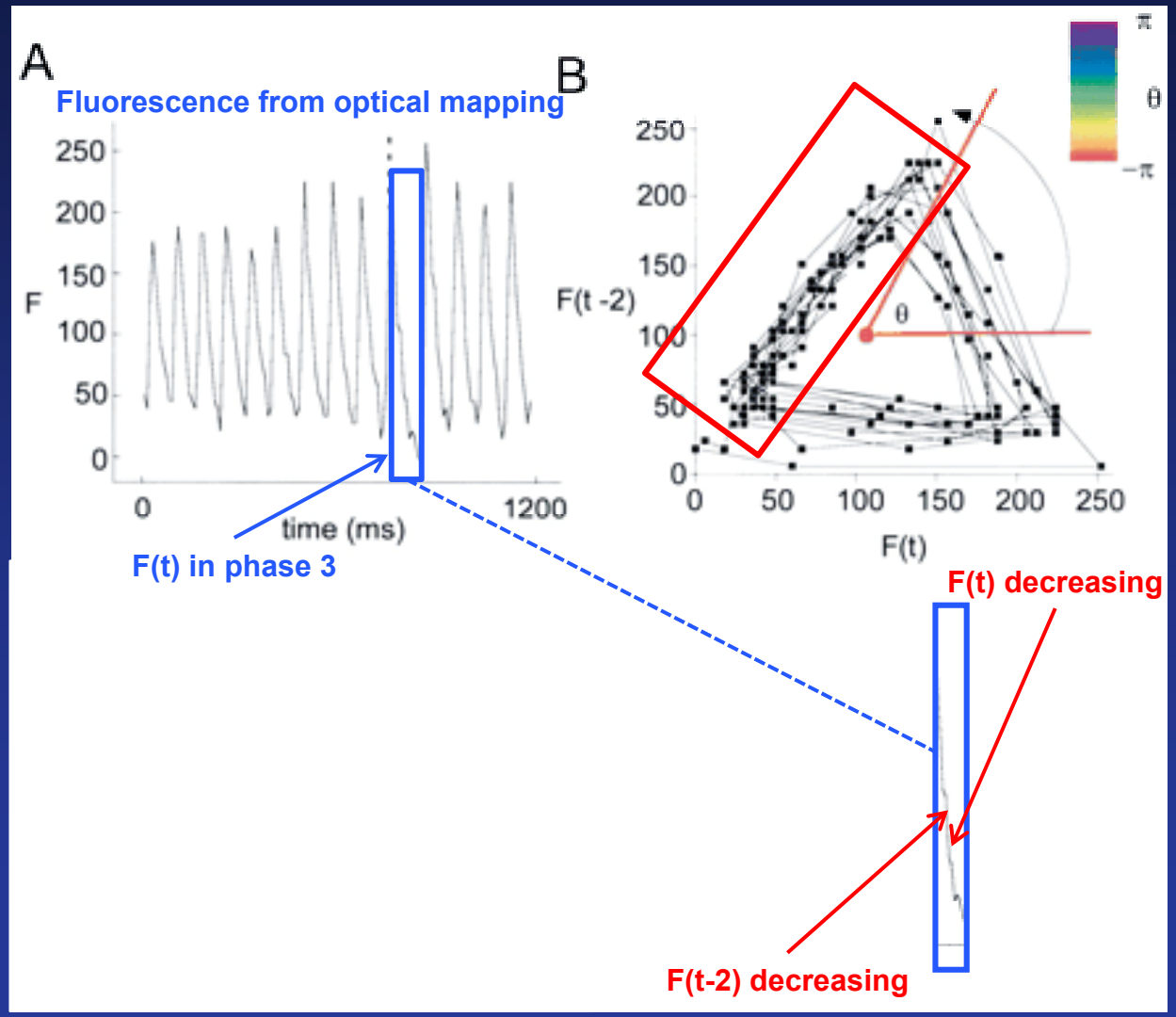
Phase-mapping and rotors



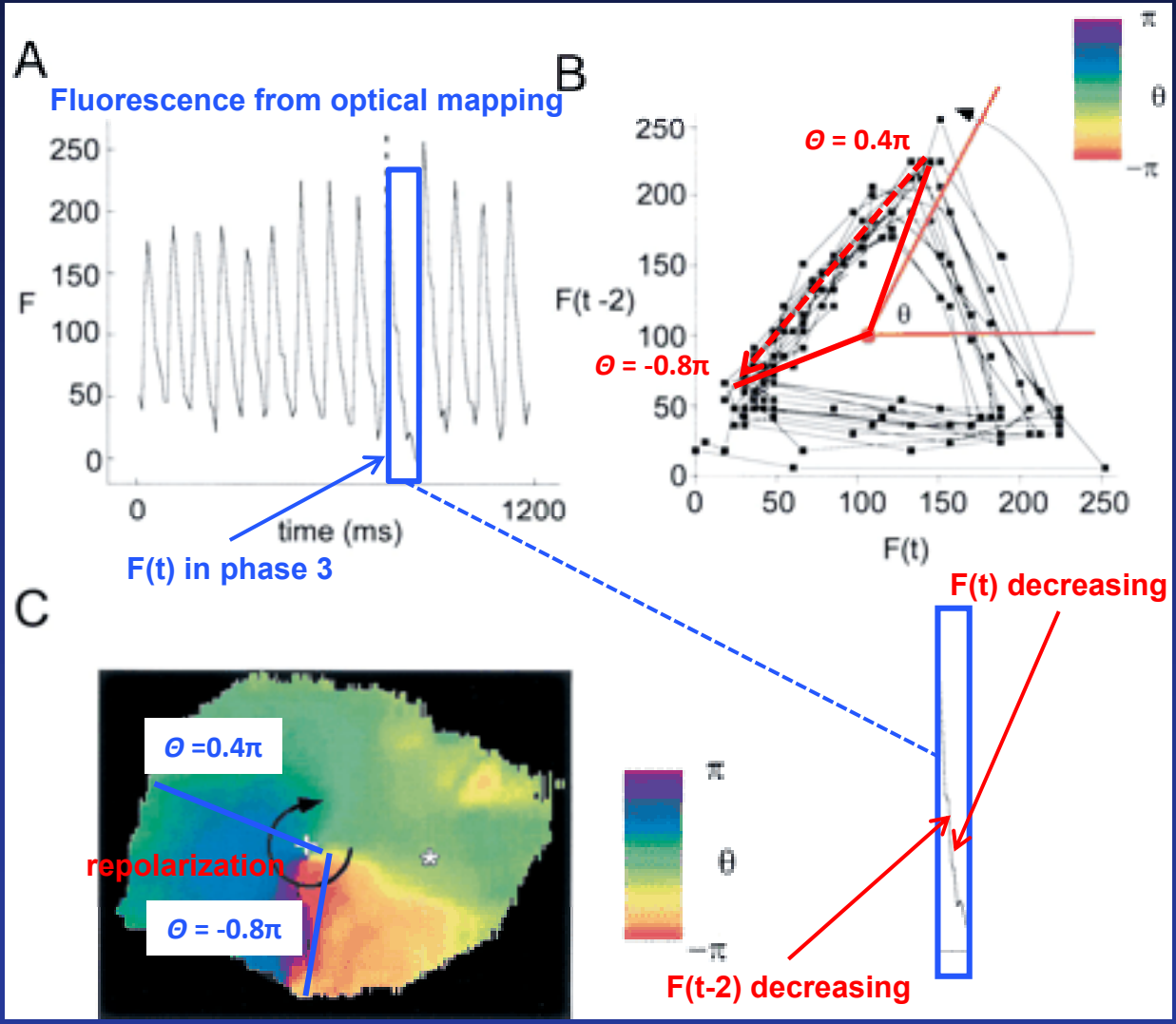
Phase-mapping and rotors



Phase-mapping and rotors



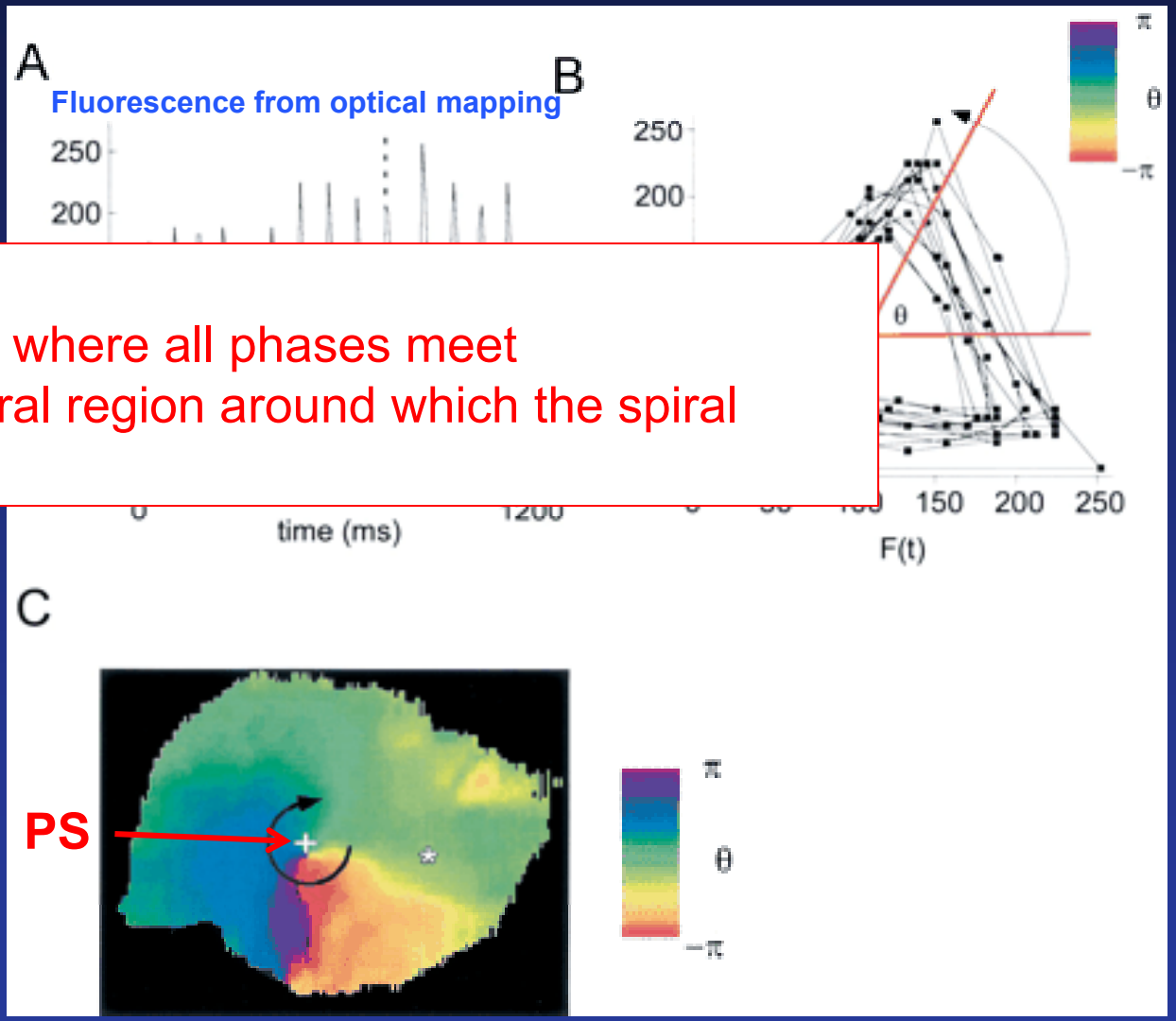
Phase-mapping and rotors



Phase-mapping and rotors concept of phase singularity (PS)

PS:

- A region of undefined phase where all phases meet
- Can be used to identify central region around which the spiral wave rotates



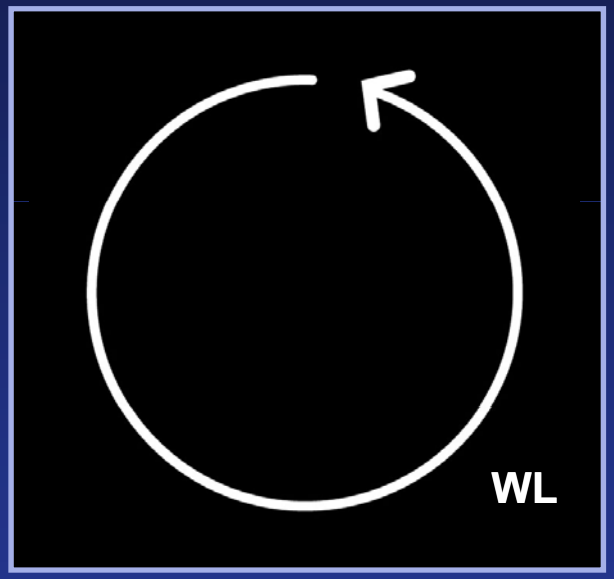
Chen J et al, Cardiovasc Res 2000.

Outline

- What are rotors?
- How does the rotor concept differ from the leading circle paradigm?
- What happens with atrial remodeling?

Classical Concepts Based on Leading Circle:

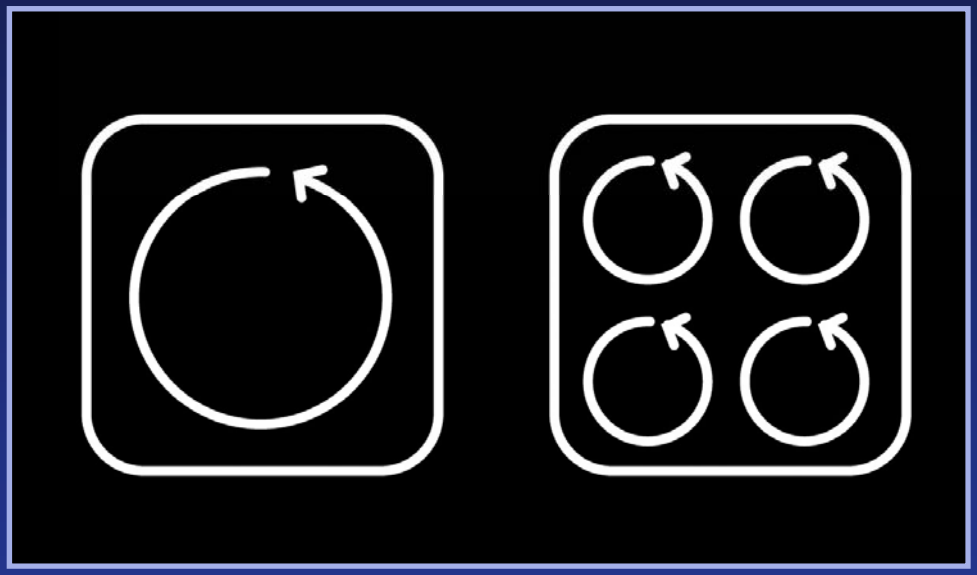
A



Wavelength (WL) =
refractory period x conduction velocity

- minimal path length for reentry
- size of functional reentry circuits

B



Normal atrial size
Normal WL

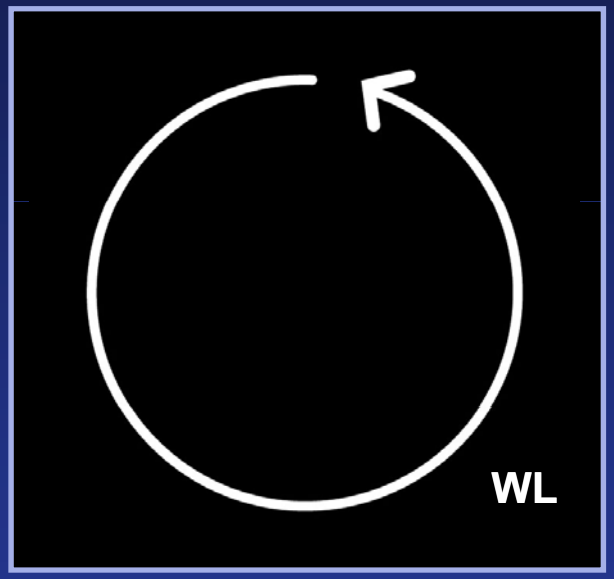
- AF not sustained

Normal atrial size
Short WL

- AF sustained

Classical Concepts Based on Leading Circle: Expected effect of I_{Na} inhibition

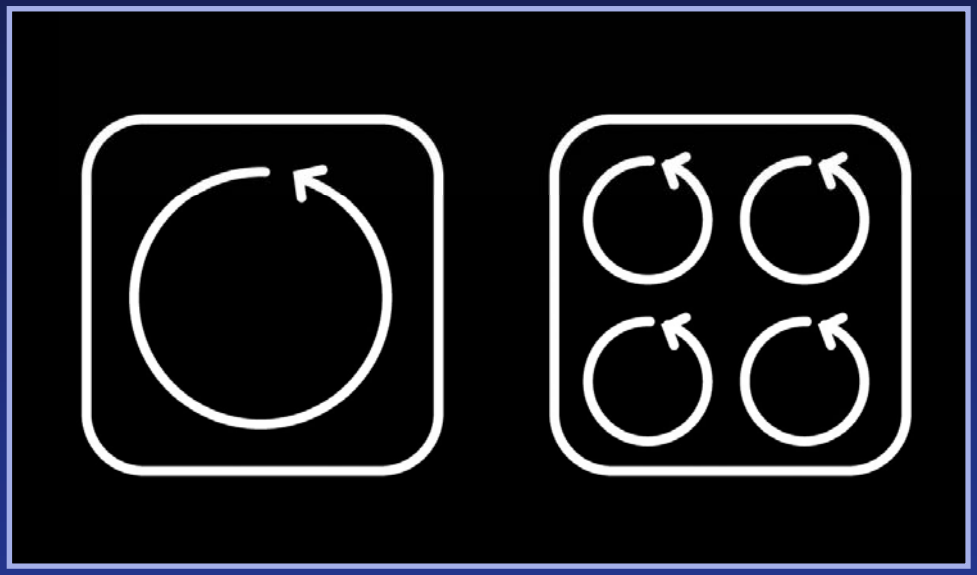
A



Wavelength (WL) ↓ =
refractory period x conduction velocity ↓

- minimal path length for reentry
- size of functional reentry circuits

B



Normal atrial size
Normal WL

- AF not sustained

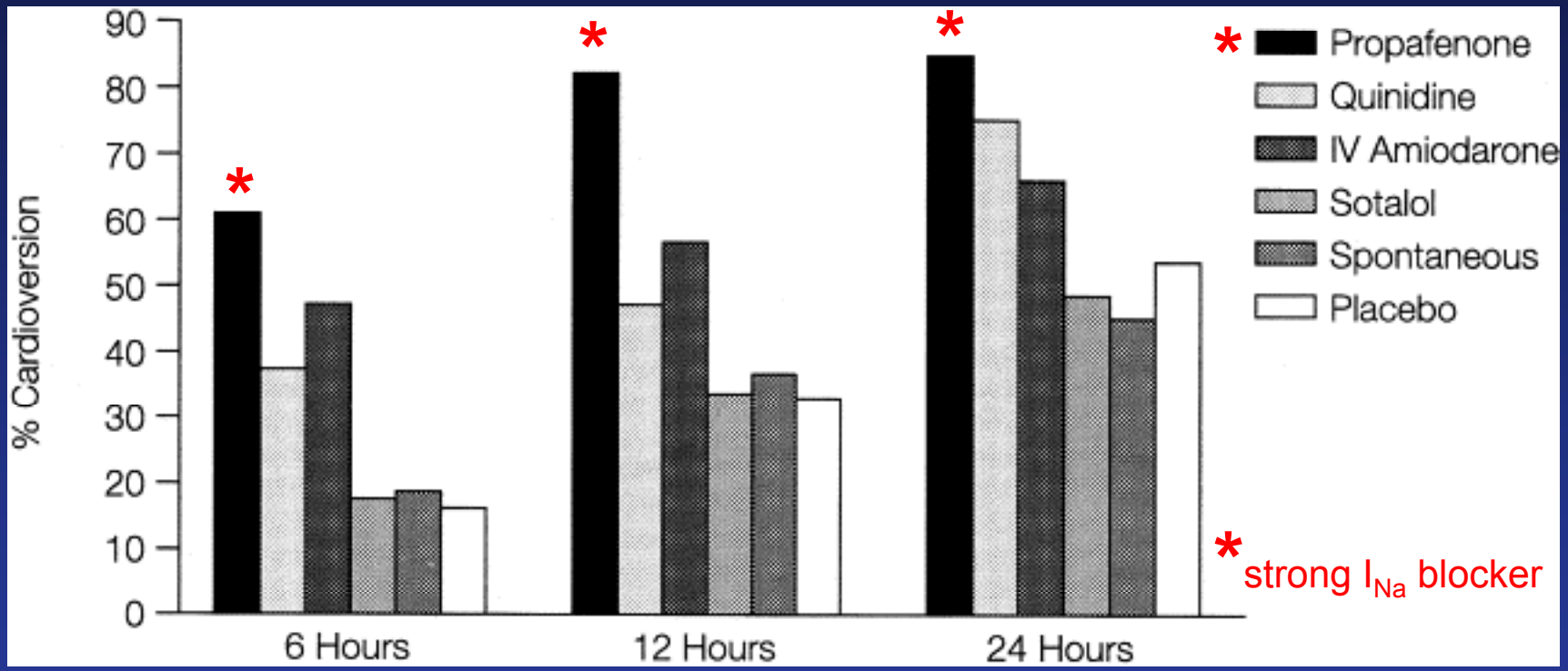
Normal atrial size
Short WL

- AF sustained

Expected effect of I_{Na} block

Wavelength concept predicts enhanced AF with Na^+ channel blockade- what happens clinically?

Comparative efficacy of antiarrhythmics for AF termination



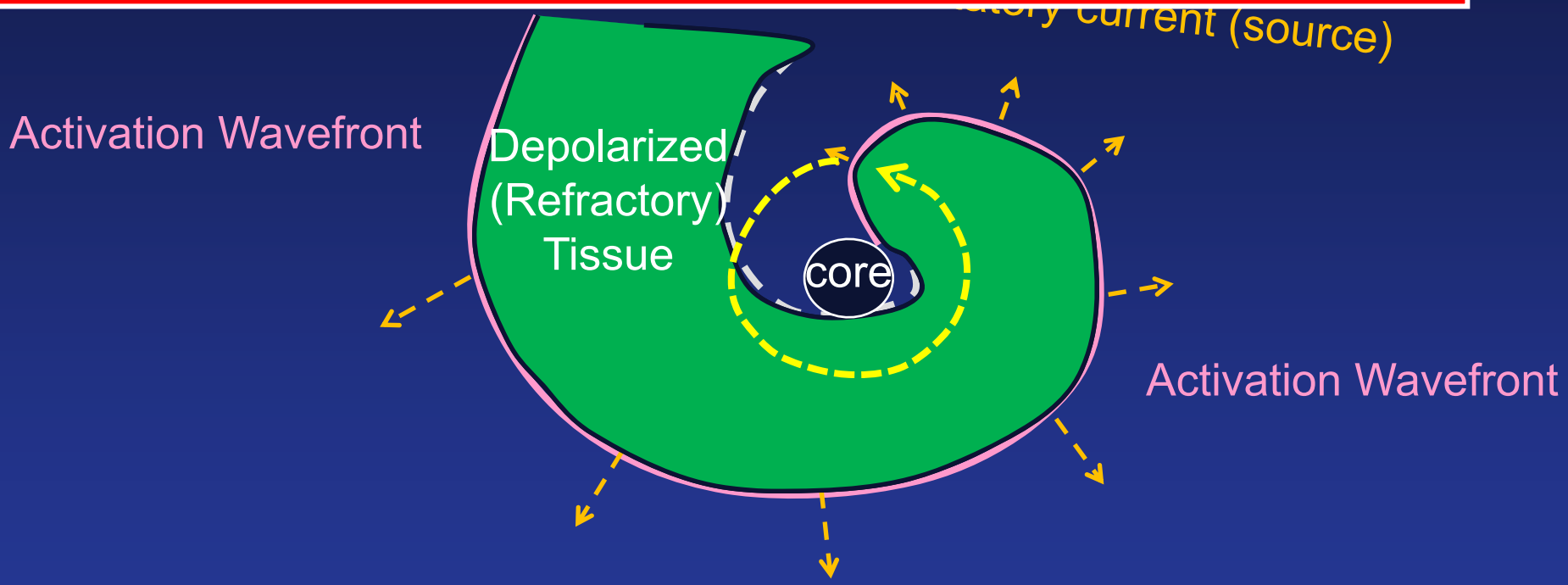
Similar data for:

- Flecainide
- Ranolazine
- Vernakalant

Naccarelli GV et al, Am J Cardiol *2003;91:15D-26D.*

Effect of decreased Na^+ current on rotor maintenance

- **Decreased excitatory current causes reentry to terminate when current at excitatory wavefront destabilizes the rotor.**
- **This explains effcicacy of I_{Na} blockade in AF**

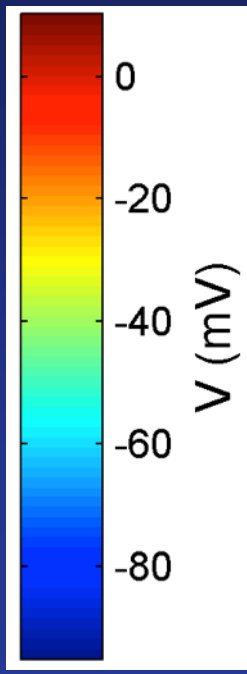


Activity depends on ability of wavefront to continuously activate tissue, which depends on:

- Strength of excitatory source (smaller Na^+ current decreases source strength)
- Magnitude of current sink

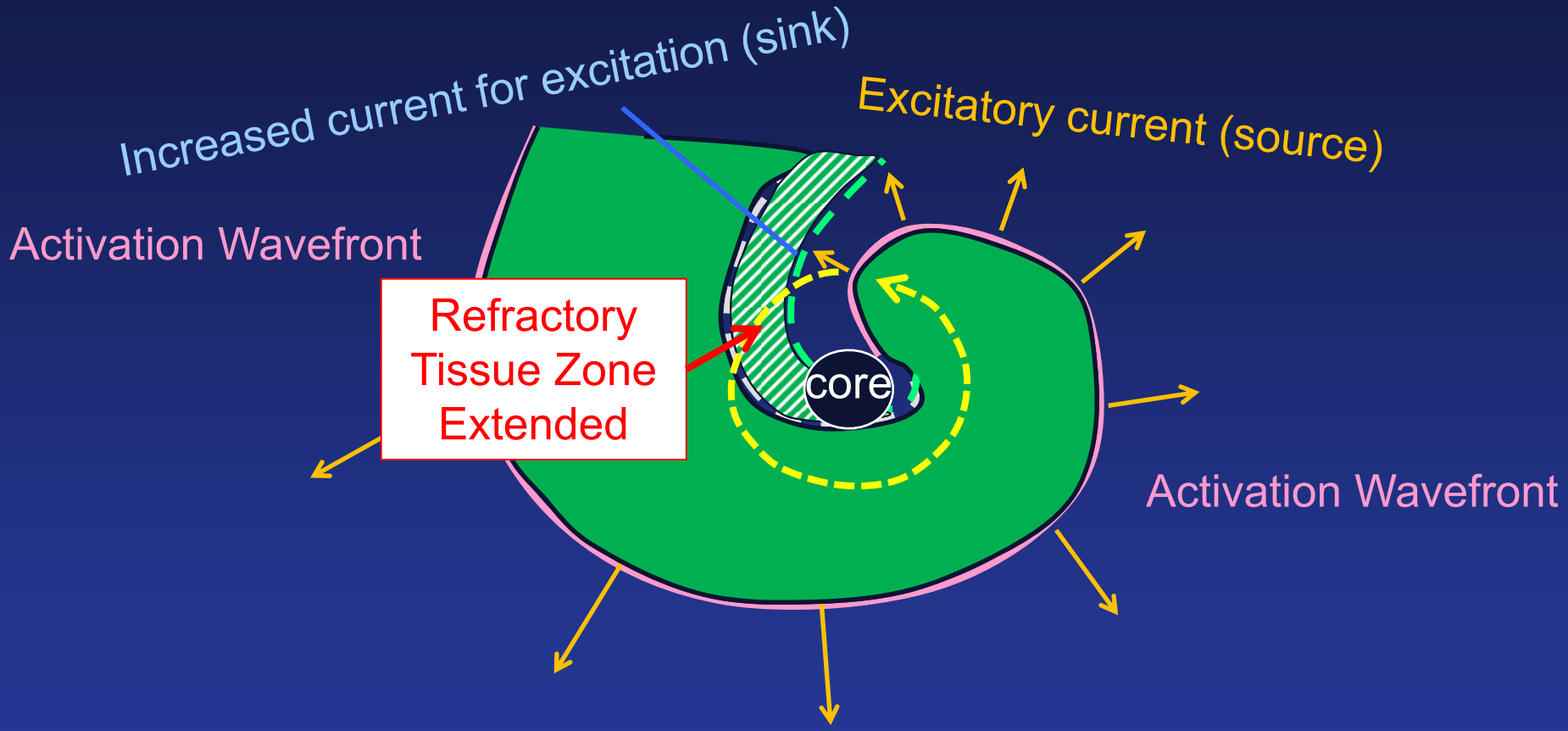
Effect of decreased Na^+ current

- Decreased excitatory current can cause reentry to terminate when current at excitatory wavefront destabilizes the rotor.



Eff ck)

- **Increased refractoriness terminates reentry because current at excitatory wavefront becomes insufficient.**
- **This explains efficacy of I_K blockade in AF**



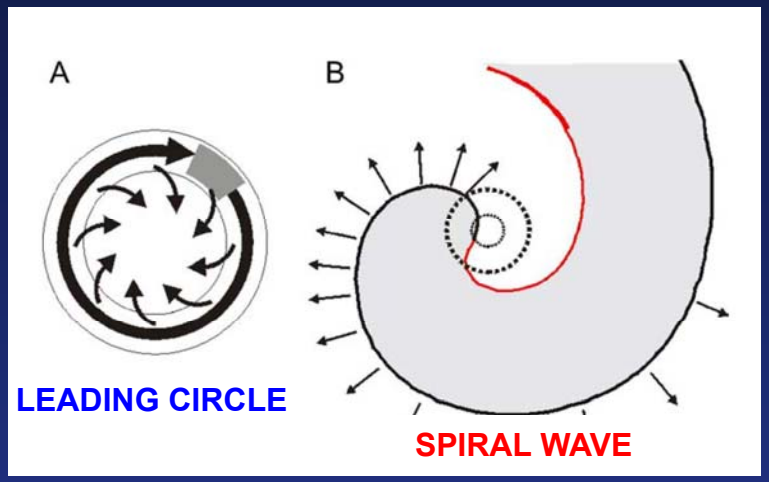
Activity depends on ability of wavefront to continuously activate tissue, which depends on:

- Strength of excitatory source
- Magnitude of current sink increased

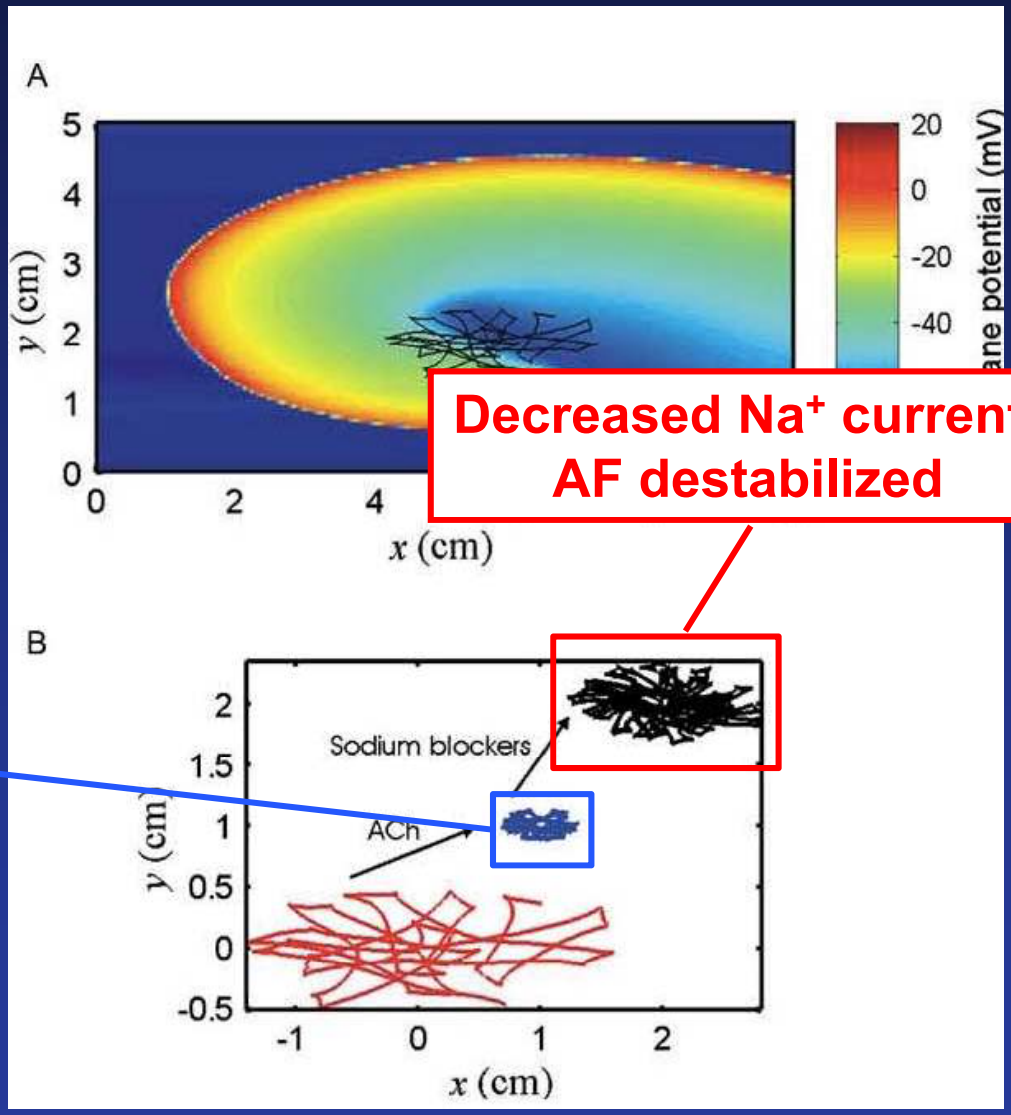
Outline

- What are rotors?
- How does the rotor concept differ from the leading circle paradigm?
- What happens with atrial remodeling?

Ionic determinants of rotor maintenance and effects of increased inward rectifier current or reduced I_{Na}



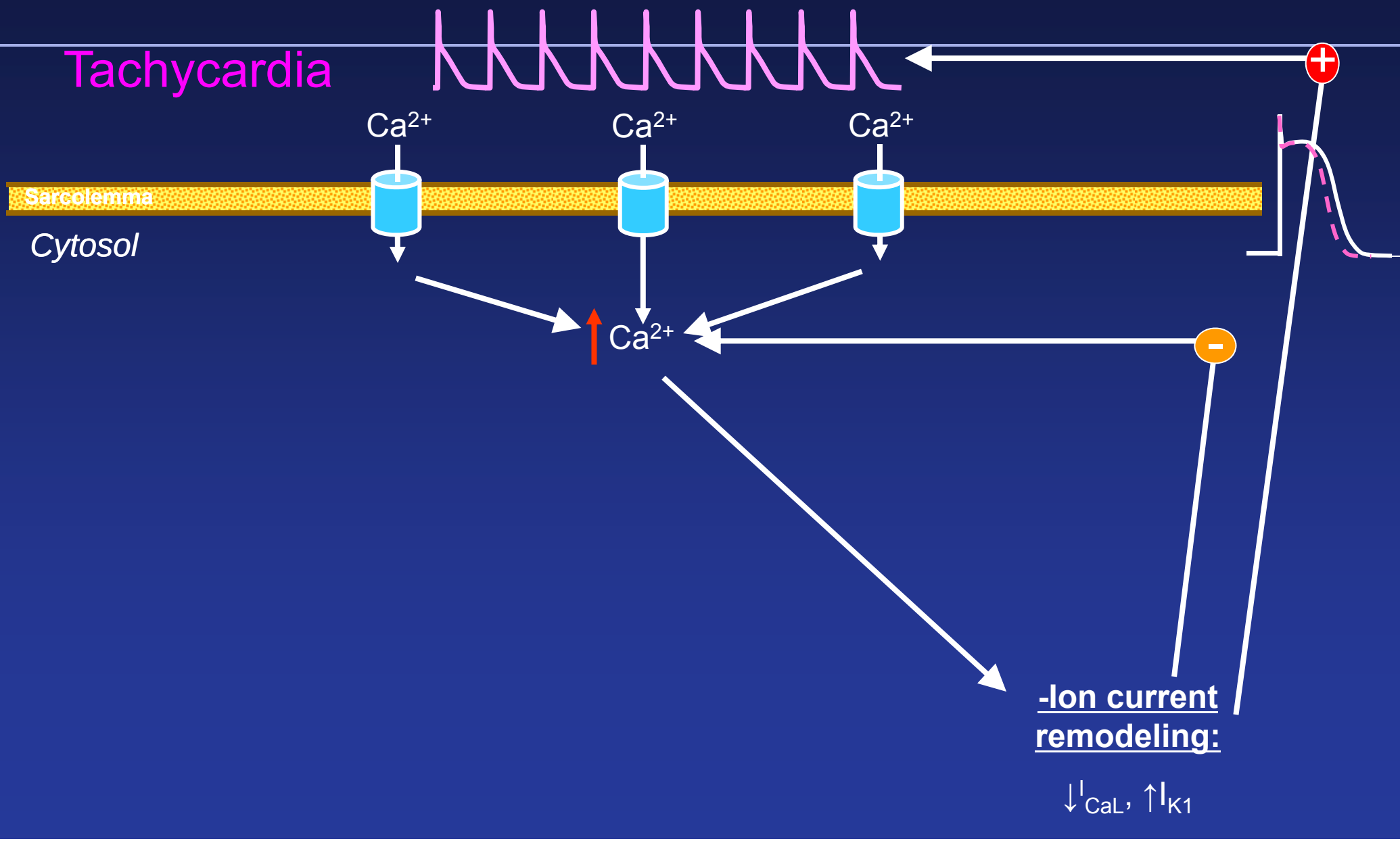
Increased K^+ current: AF promoted



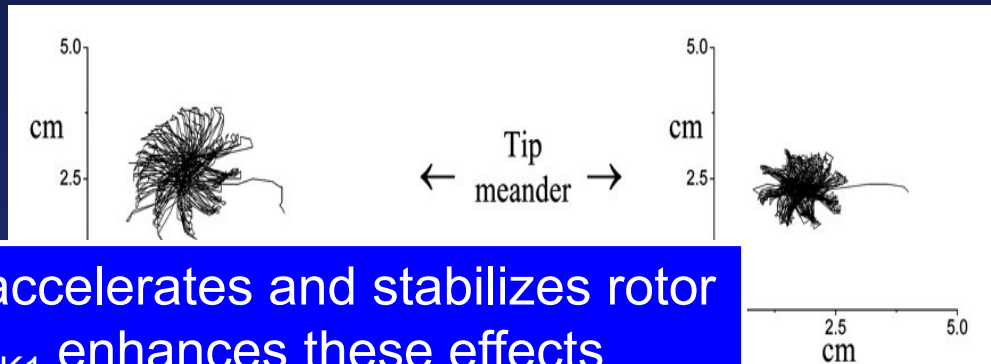
Decreased Na^+ current: AF destabilized

Comtois P et al, Europace 2005;7:510-20.

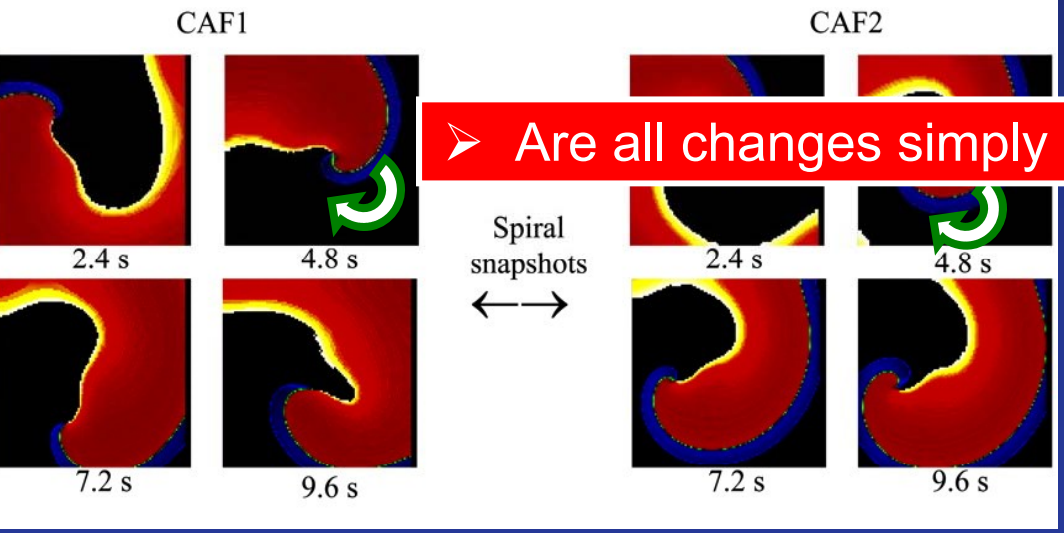
Electrical remodeling response to AF:



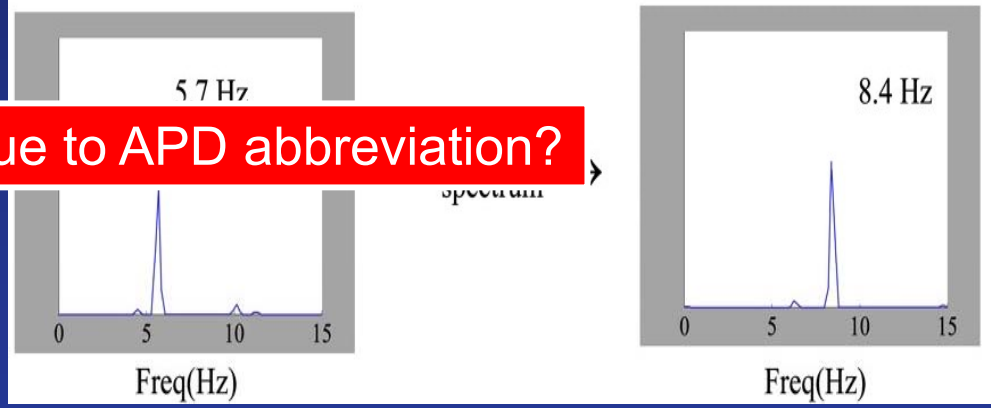
AF dynamics: Role of Ca^{2+} current downregulation and inward rectifier K^+ current upregulation in AF stability



- Downregulation of I_{CaL} (CAF1) accelerates and stabilizes rotor
- Additional upregulation of I_{K1} enhances these effects



- Are all changes simply due to APD abbreviation?

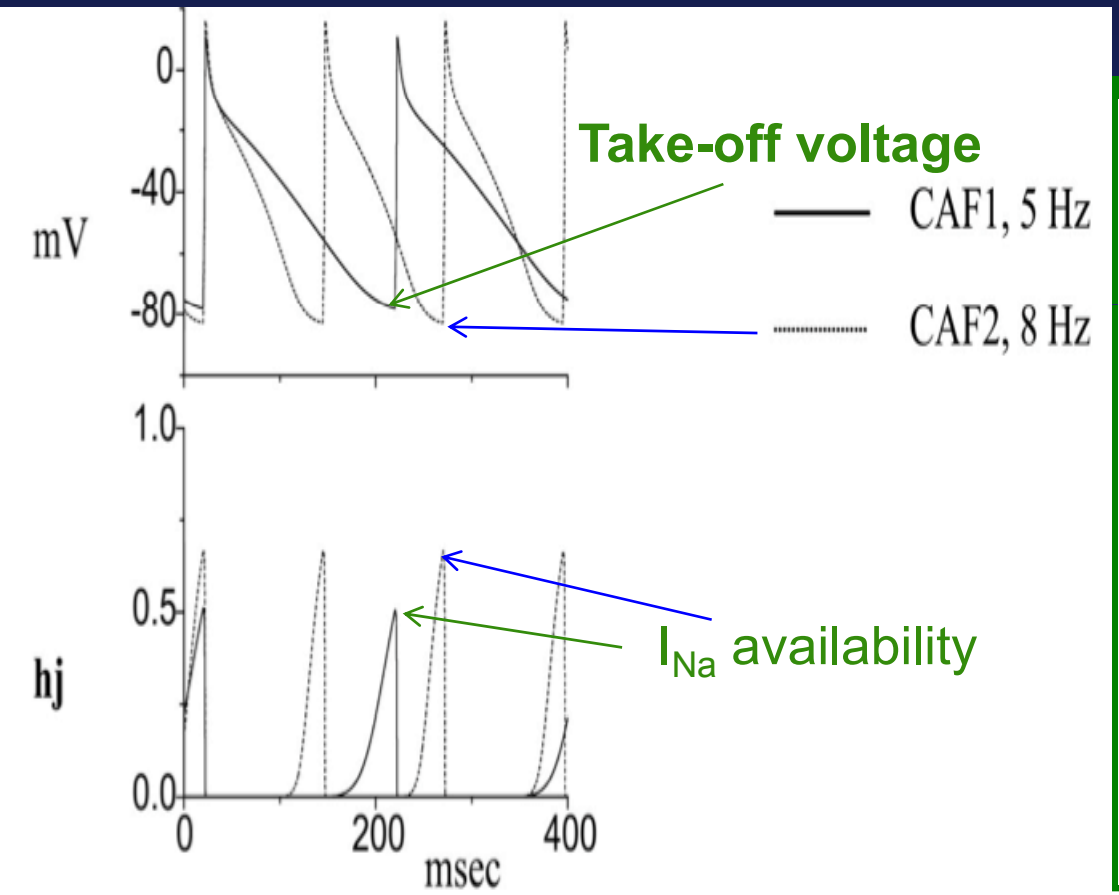


CAF1
Changes in I_{CaL}

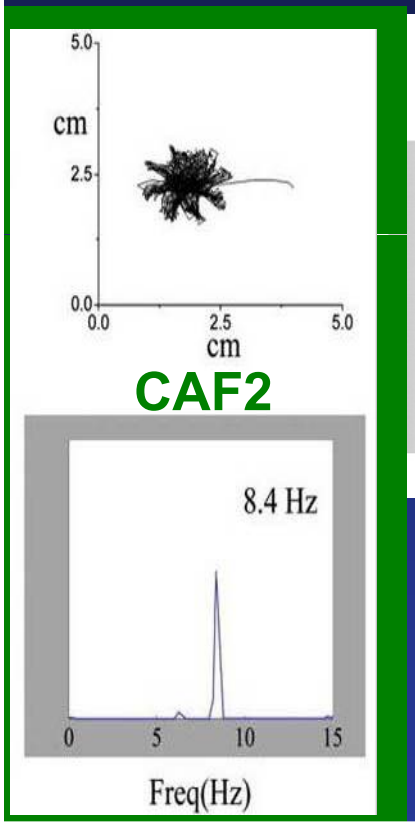
CAF1
Changes in ICaL
Plus increased I_{K1}

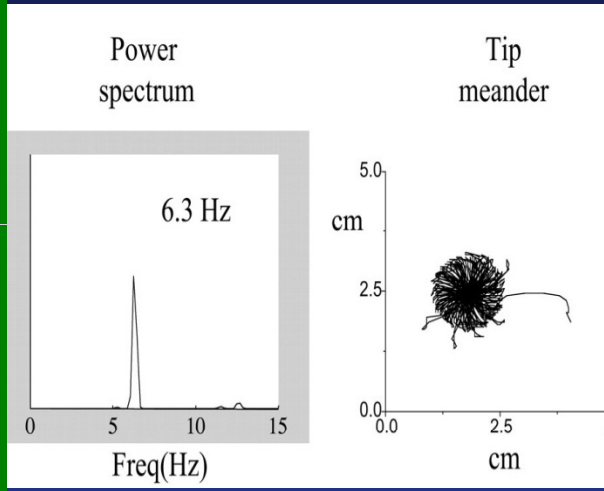
Pandit SV et al, *Biophys J. 2005;88:3806-21.*

AF dynamics: Why is the rotor faster with inward rectifier K^+ current upregulation?



APD of CAF1 reduced to match CAF2 by $\downarrow I_{CaL}$

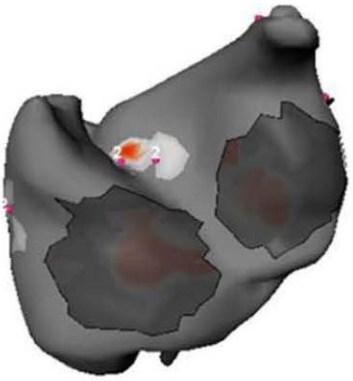


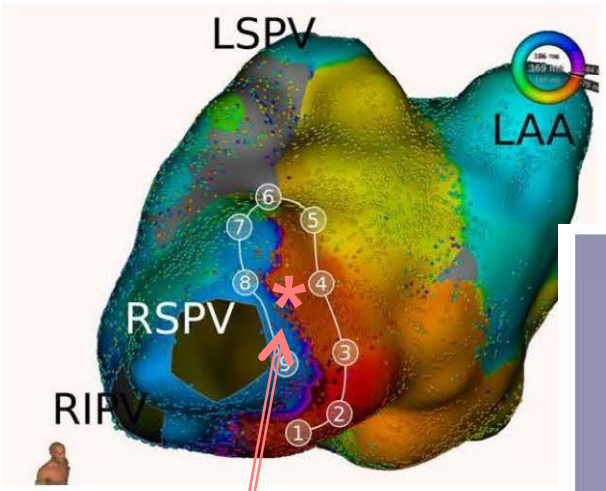


Therefore, hyperpolarization caused by increased inward-rectifier K+ current contributes importantly to rotor acceleration

Pandit SV et al, *Biophys J. 2005;88:3806-21.*

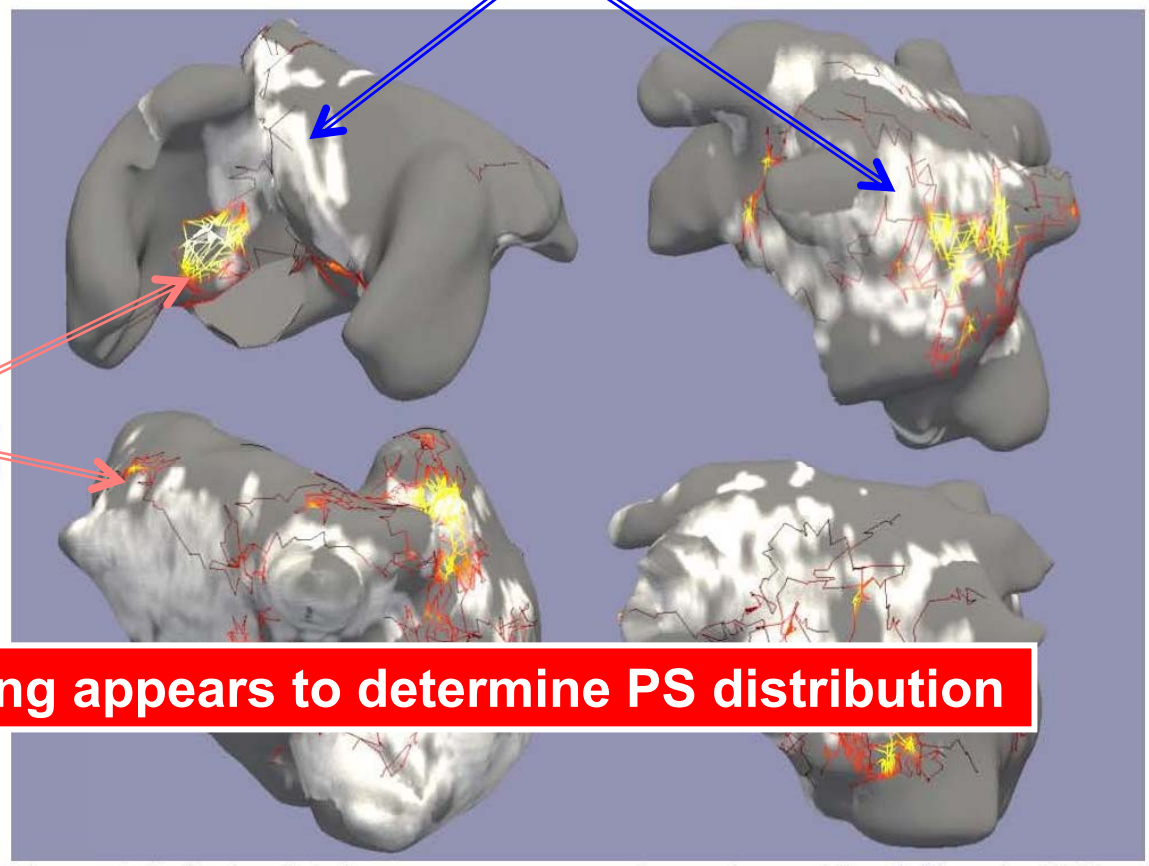
ECGi mapping with MRI imaging of fibrosis (LGE MRI)





Fibrotic zones

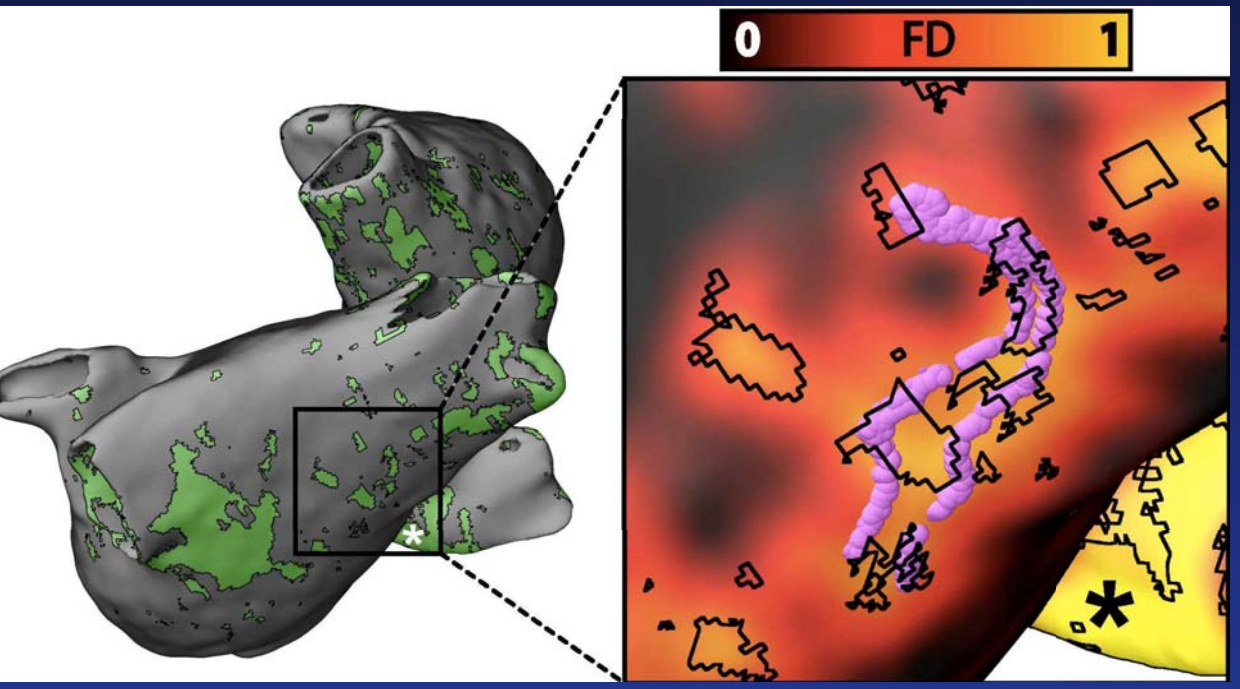
PSs of Reentrant Rotors

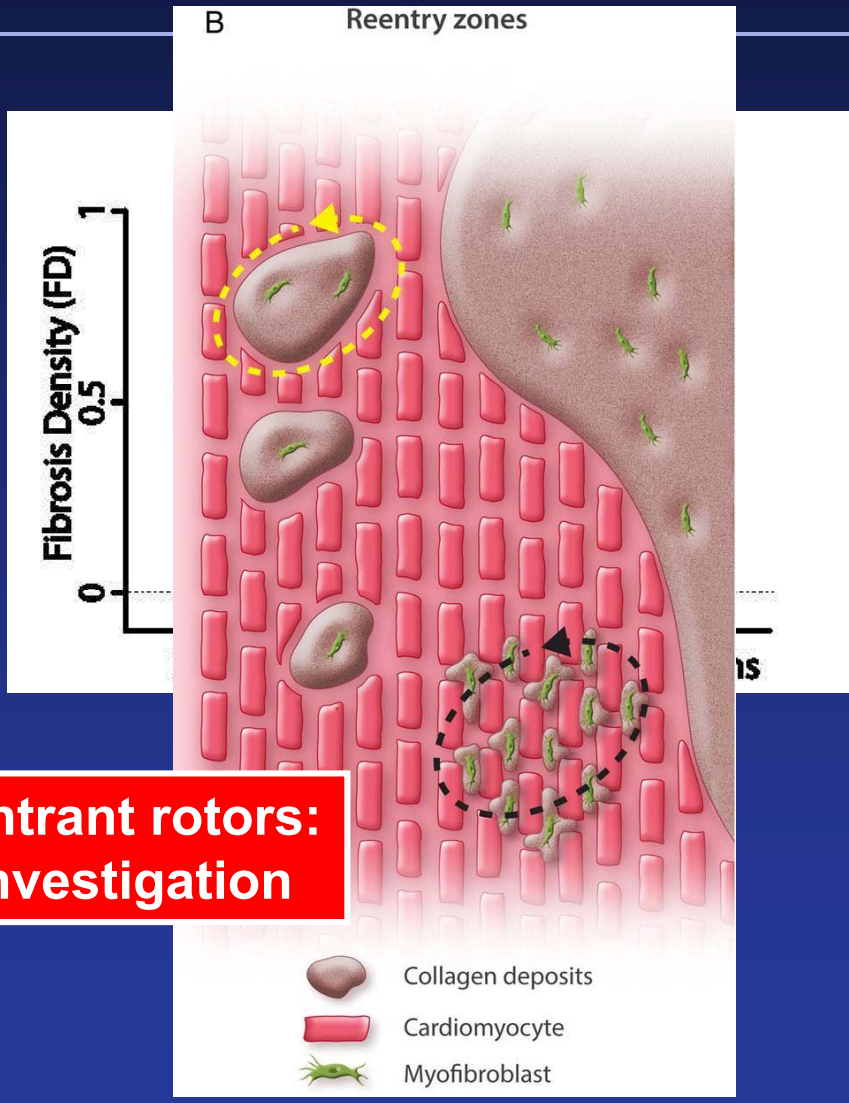


The location of fibrotic remodeling appears to determine PS distribution

Haissaguerre J Physiol in press

Reentrant drivers and fibrosis (LGE MRI) in math model





Tissue fibrosis stabilizes reentrant rotors: Mechanisms require more investigation

Zahid S Cardiovasc Res in press

Nattel Cardiovasc Res in press

Conclusions

- The rotor concept is a biophysically accurate way to understand reentry and accounts for a variety of clinical phenomena
- AF-related ionic remodeling promotes rotor stability, frequency and maintenance
- AF-related structural remodeling promotes rotor formation and localization
- Much work remains to be done to fully understand the clinical implications of the rotor concept and to exploit it therapeutically

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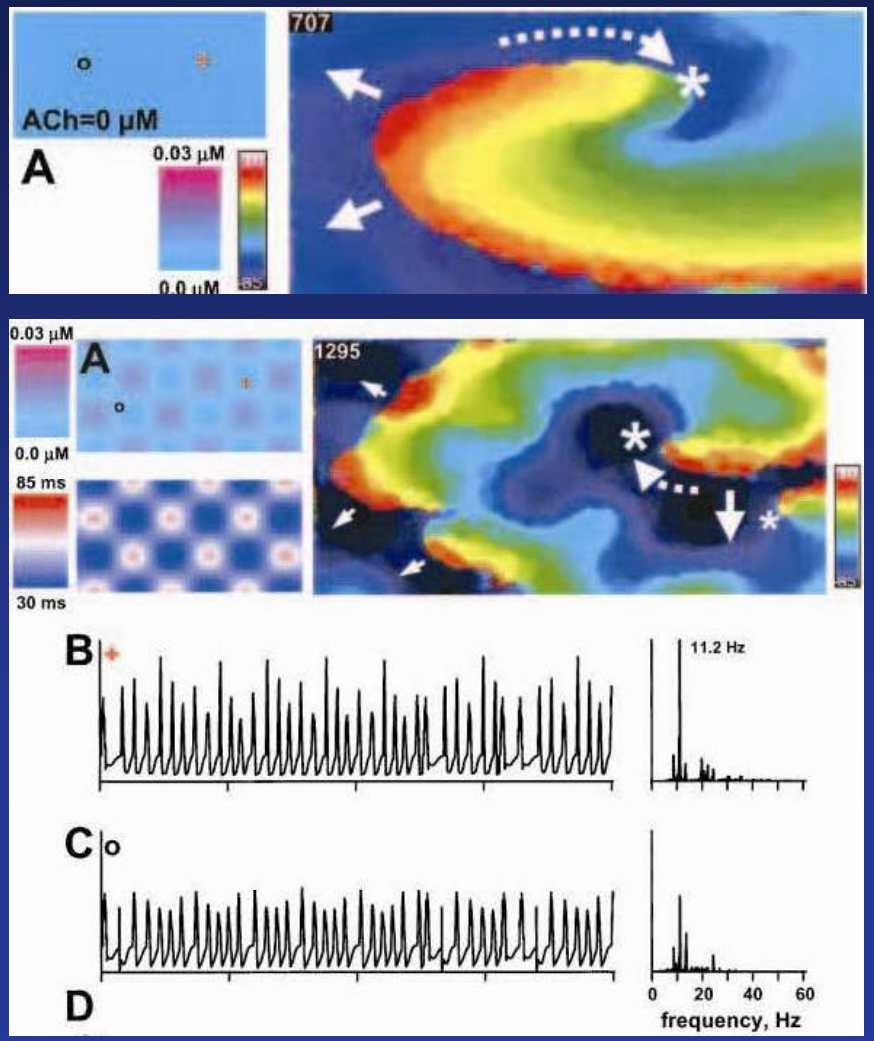
Thank you!

UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE L'UNIVERSITÉ D'OTTAWA

Emerging Pathways in Cardiovascular Disease

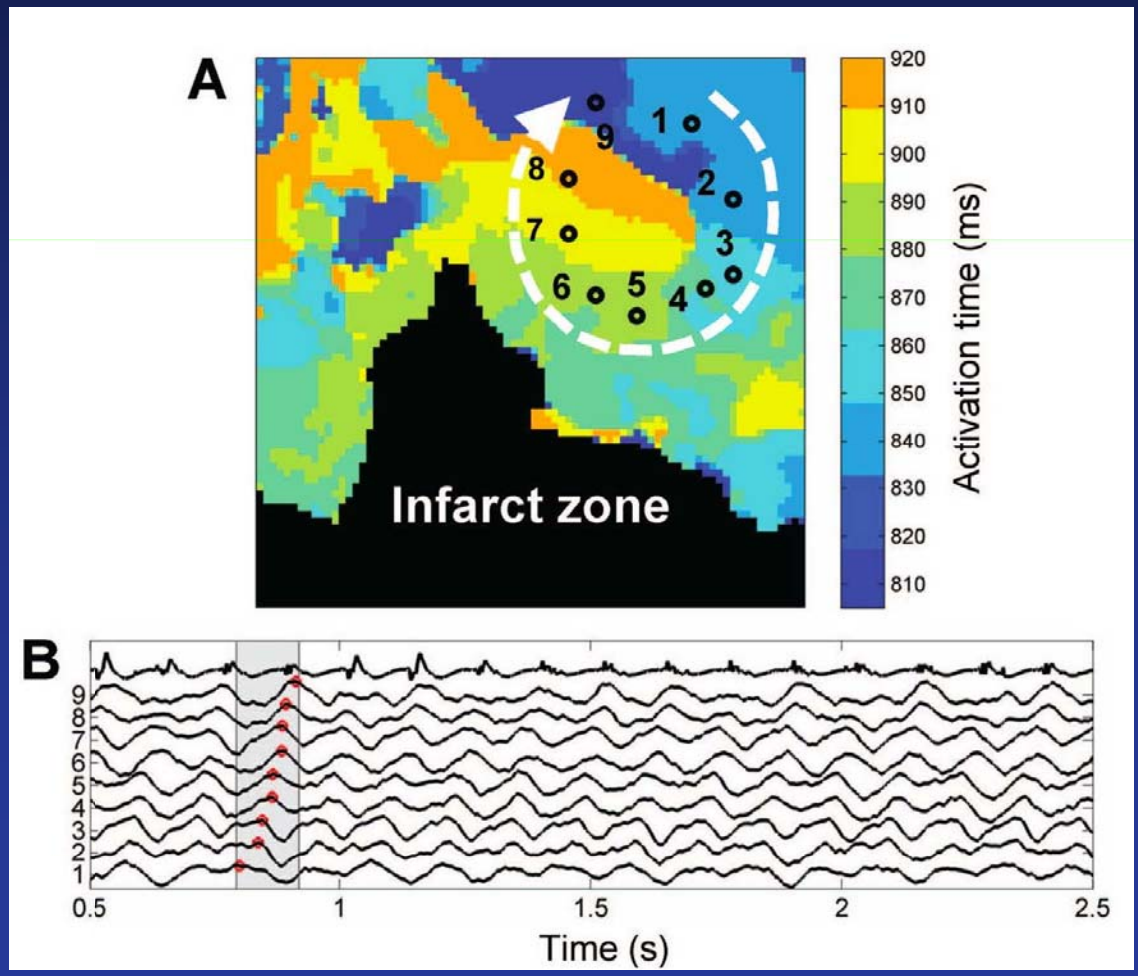
What do you actually see when you induce reentry?

In a realistic mathematical model



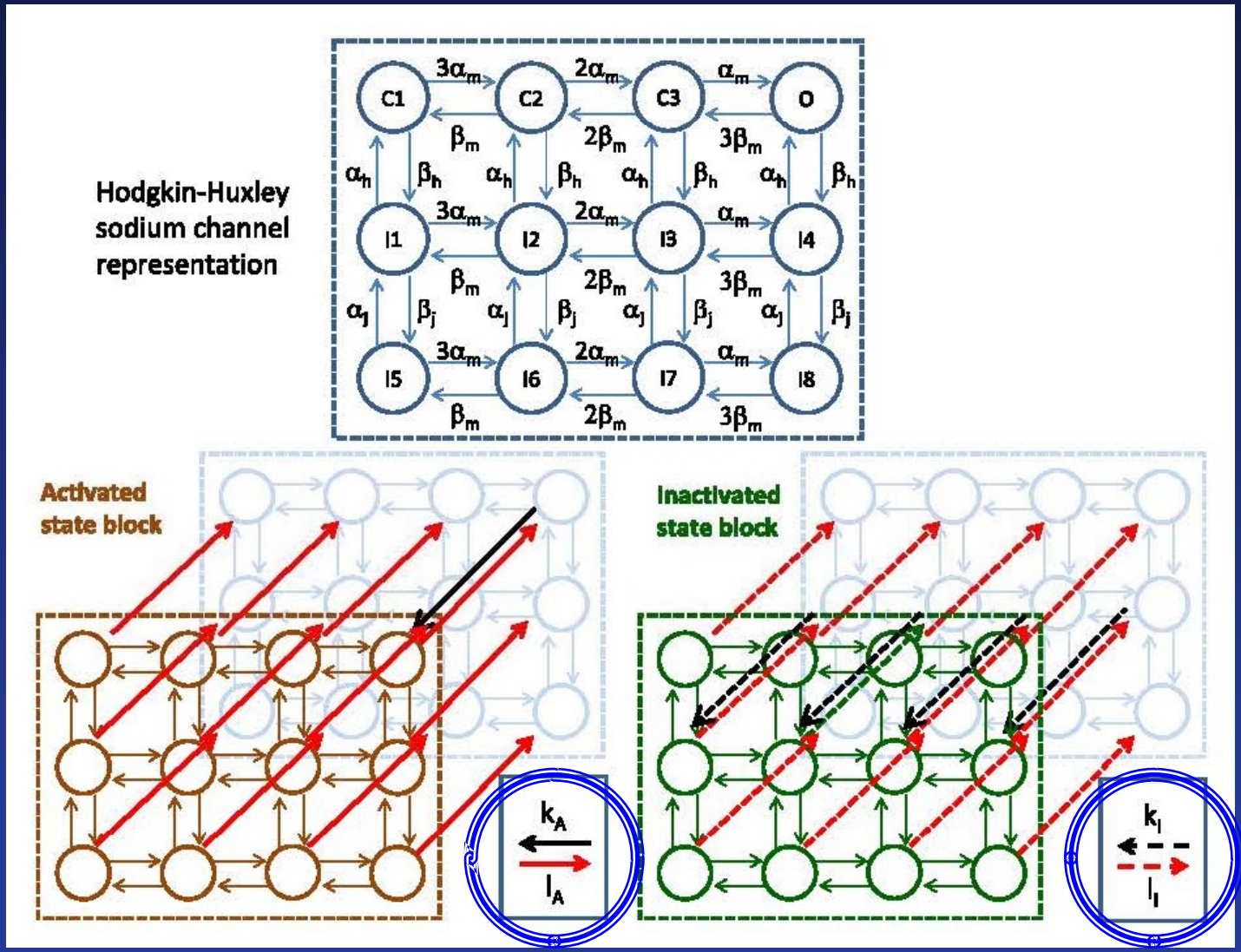
Kneller J et al, Circ Res 2002;90:E73-87.

In an experimental prep (atrial MI)



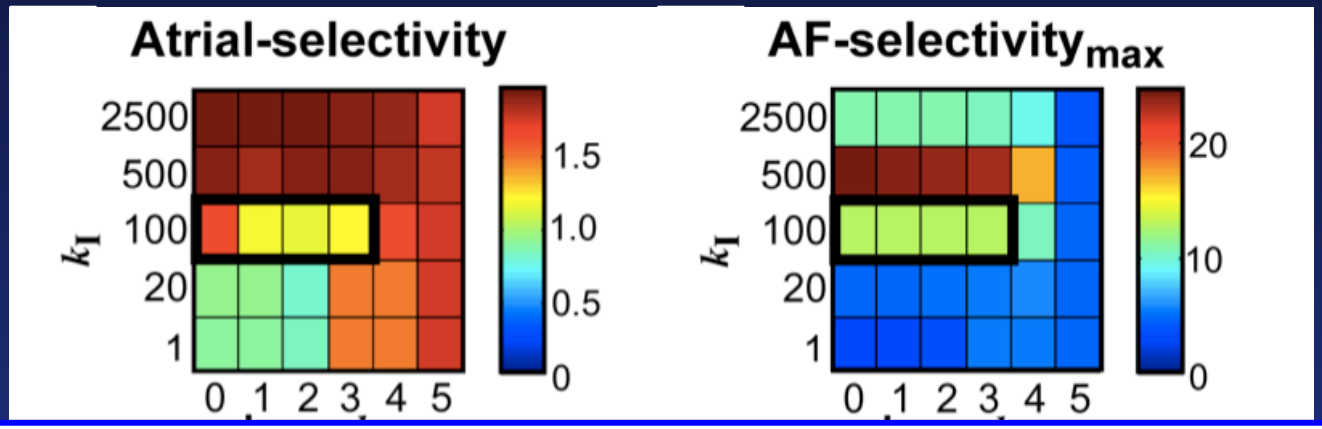
Nishida K et al, Circulation 2011;123:137-146.

Optimizing I_{Na} inhibition for AF-selectivity

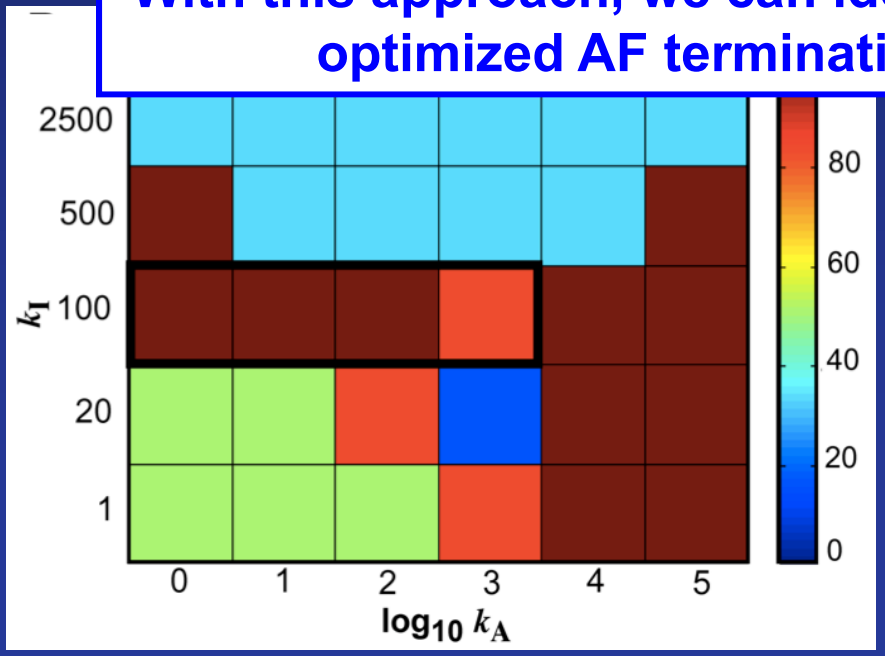


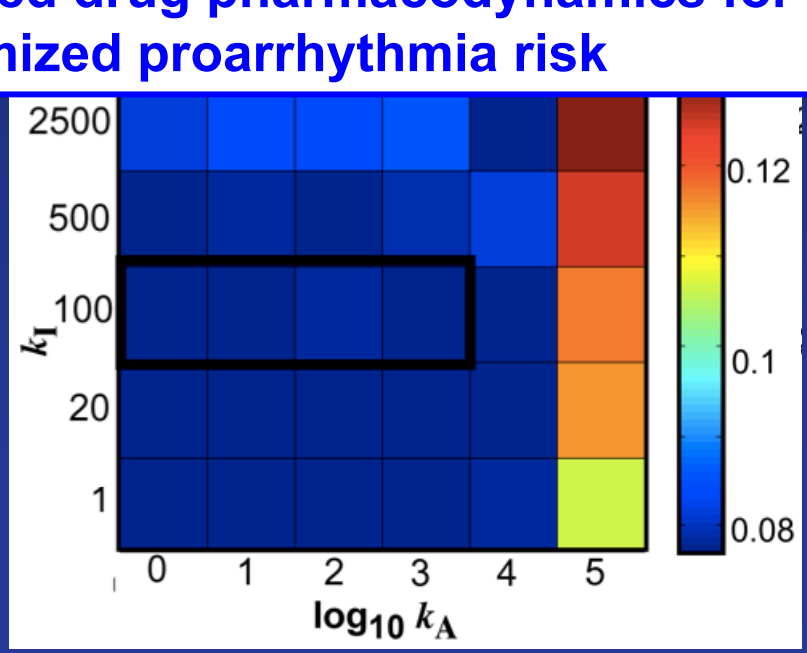
AGUILAR-SHARDONOFSKY et al, Biophys J. 2012;102:951-60

Optimizing I_{Na} inhibition for AF-selectivity

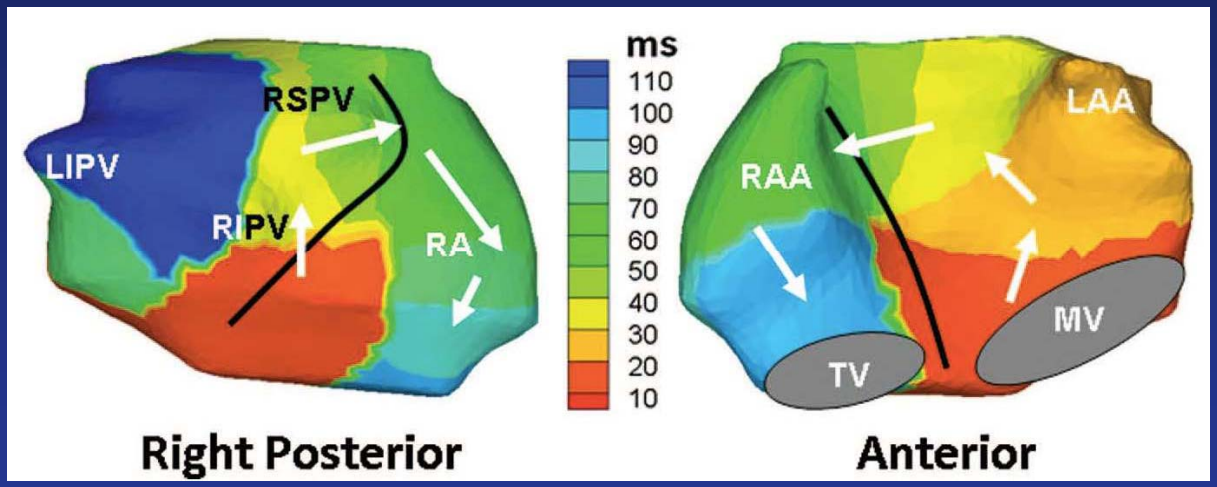


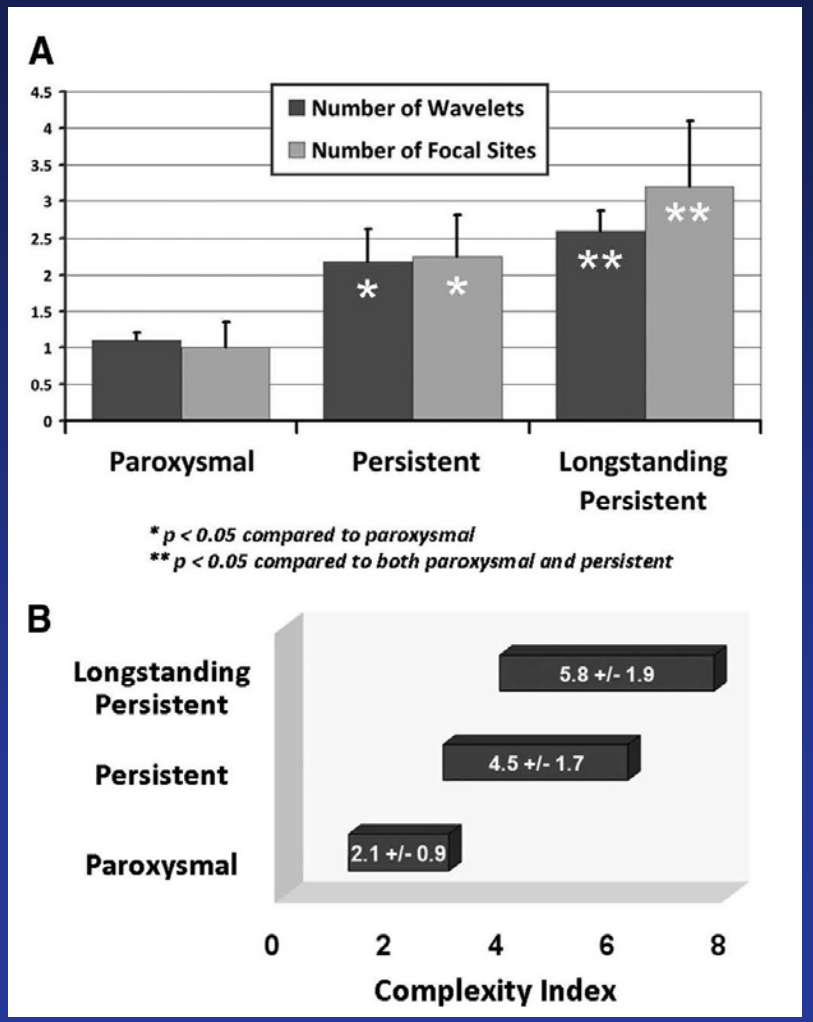
With this approach, we can identify optimized drug pharmacodynamics for optimized AF termination with minimized proarrhythmia risk





Evidence for AF-maintaining rotors in man: Body-surface mapping ECGi approach

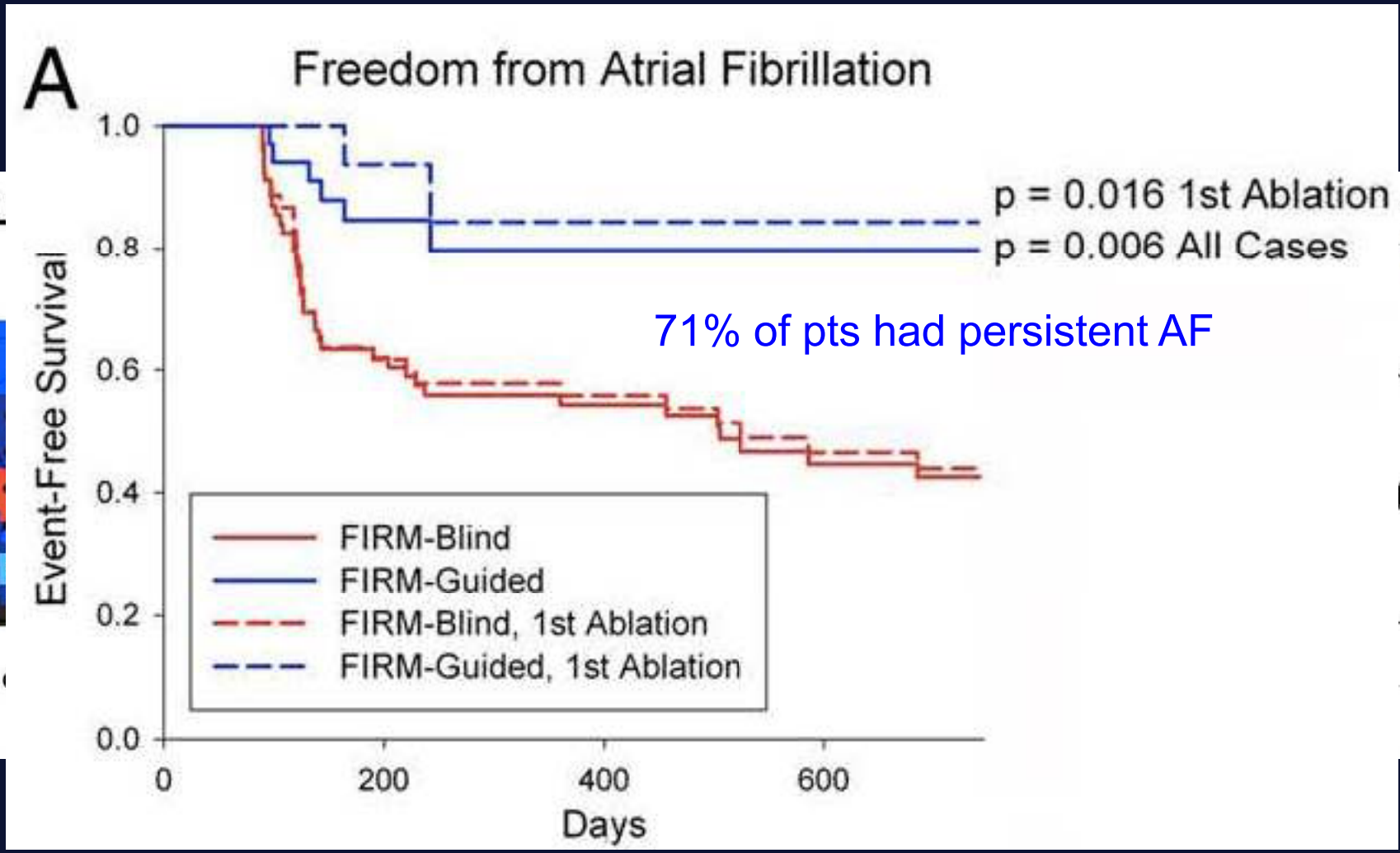




CUCULICH PS et al, *Circulation. 2010;122:1364-1372.*

Results of Rotor ablation

Rotor ablation is a promising new approach for ablation of persistent AF.



NARAYAN SM et al, *J Am Coll Cardiol. 2012;60:628-36.*

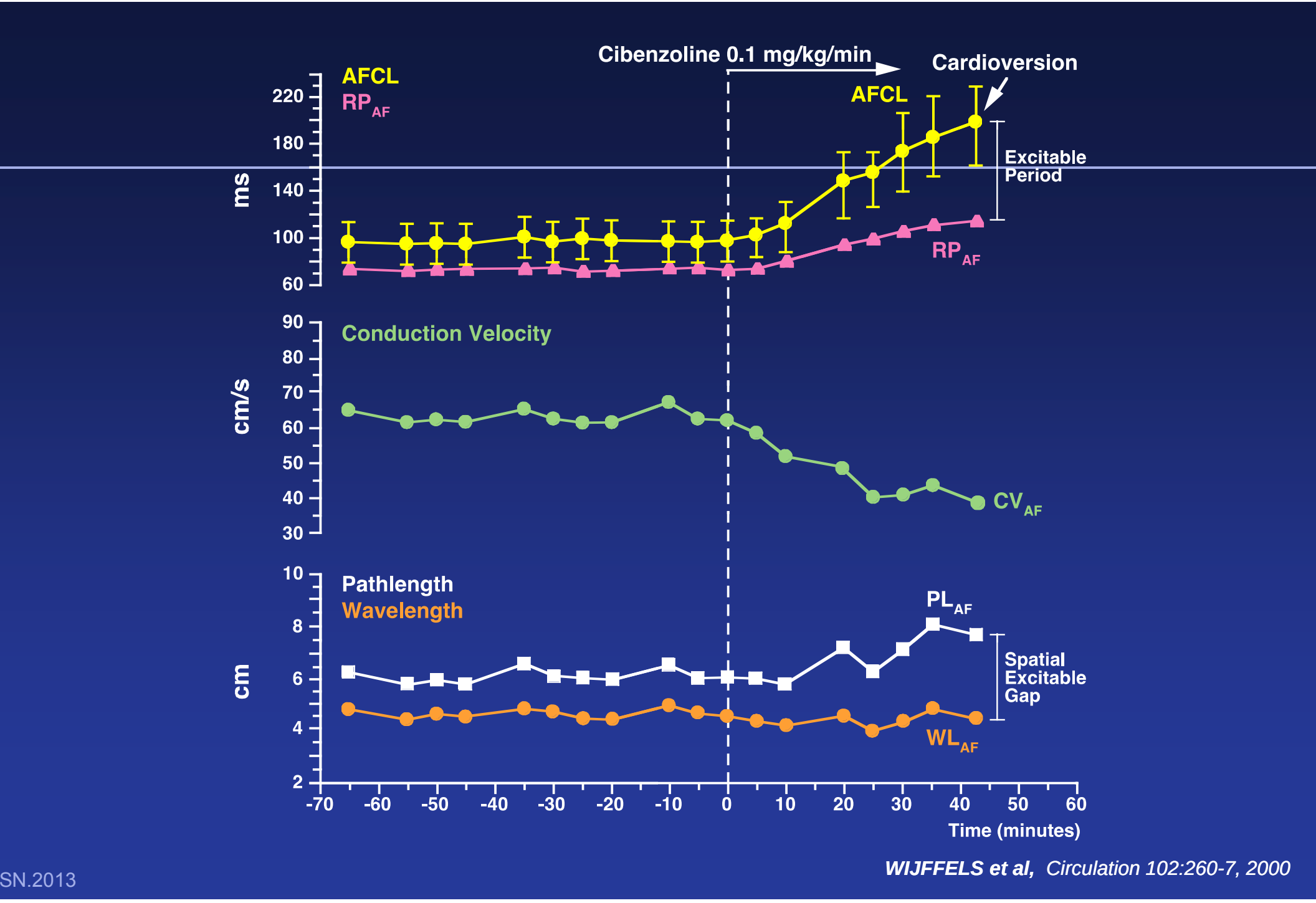
Tropical storm

Hurricane starts in Caribbean

Strong winds, high velocity, storm is small in size and very stable.

Hurricane moves to northeast

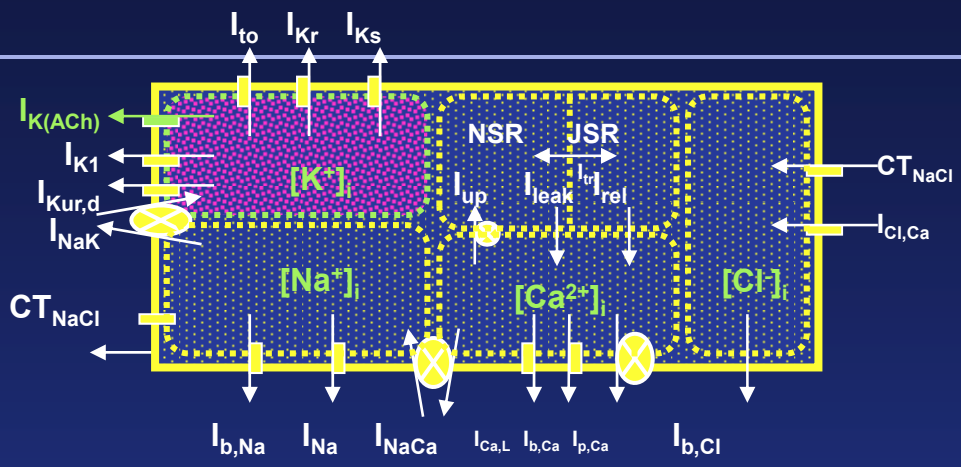
Winds slow, storm enlarges, becomes unstable and dies out.



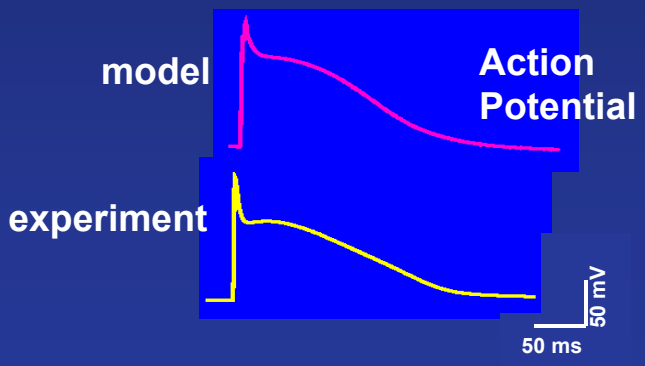
WIJFFELS et al, *Circulation 102:260-7, 2000*

SN.2013

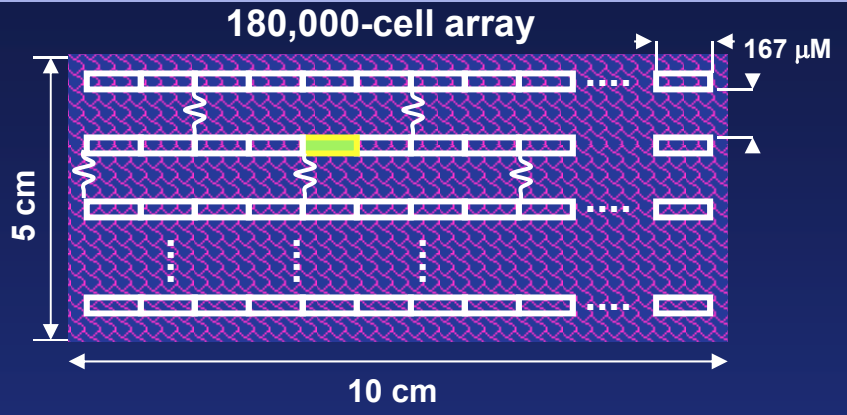
Cell Model[1,2]



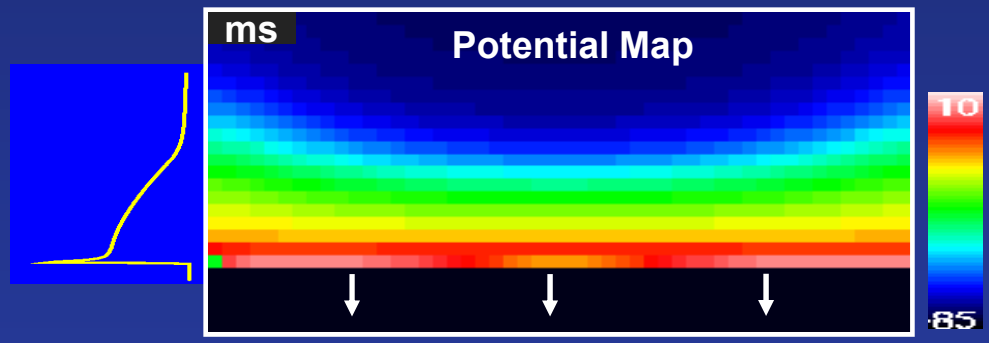
$$\frac{dV}{dt} = -\frac{(I_{ion} + I_{stim})}{C_m}$$



Tissue Model[3,4]

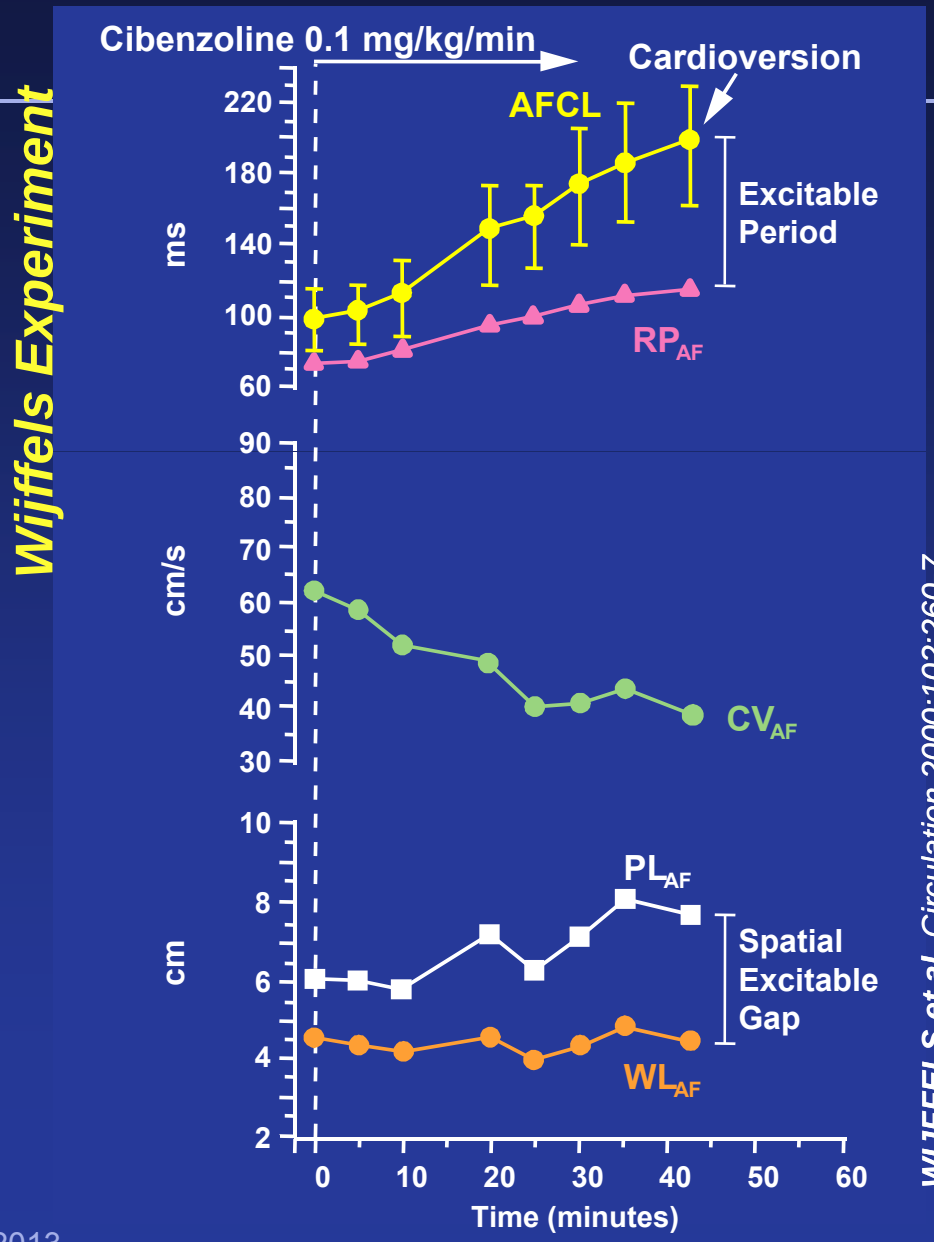


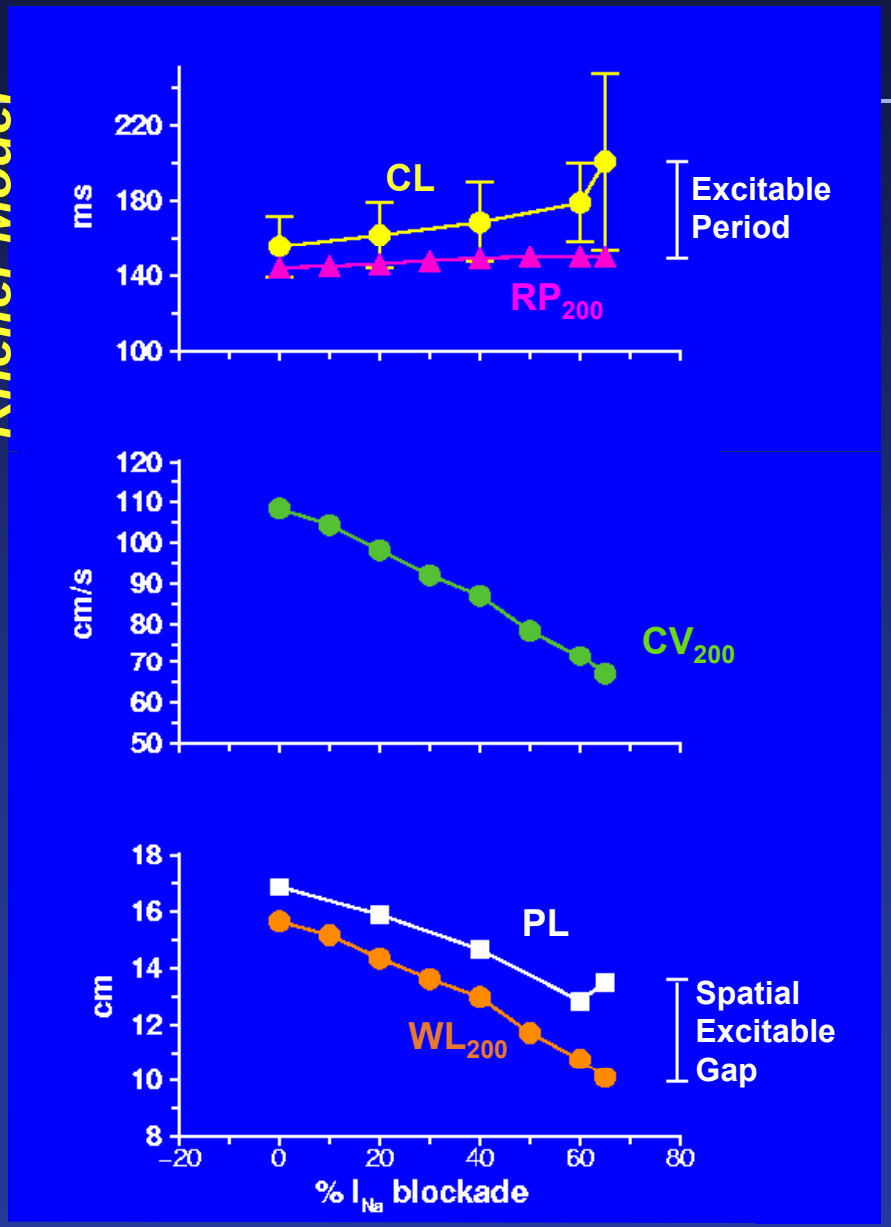
$$\frac{\partial^2 V}{\partial x^2} = C_m \frac{\partial V(x)}{\partial t} + I_{ion}(V, x)$$



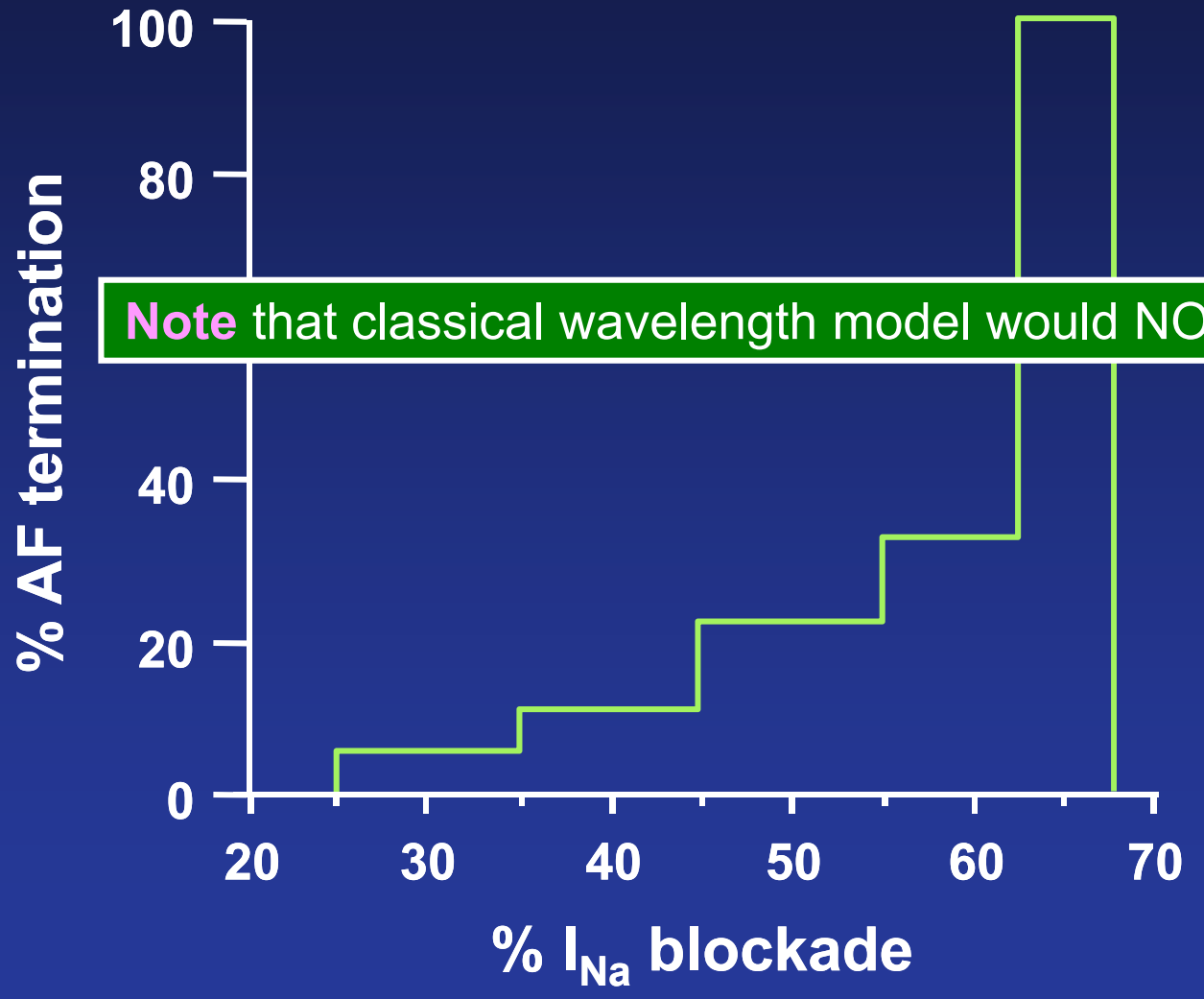
1. Ramirez *et al*. Am J Physiol. 2000.
2. Kneller *et al.* Am. J. Physiol. 2002.
3. Kneller *et al*. Circ. Res. 2002.
4. Vigmond *et al*. Ann Biomed Eng. 1999.

Effects of I_{Na} Inhibition on Atrial EP Properties

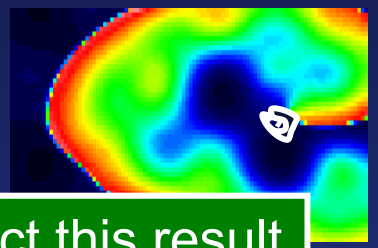


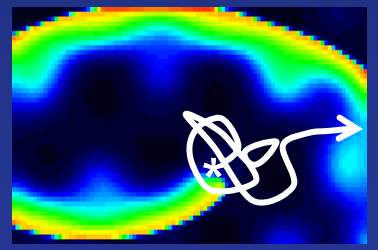


Relation between intensity of I_{Na} inhibition and AF termination; termination mechanism



Note that classical wavelength model would NOT predict this result



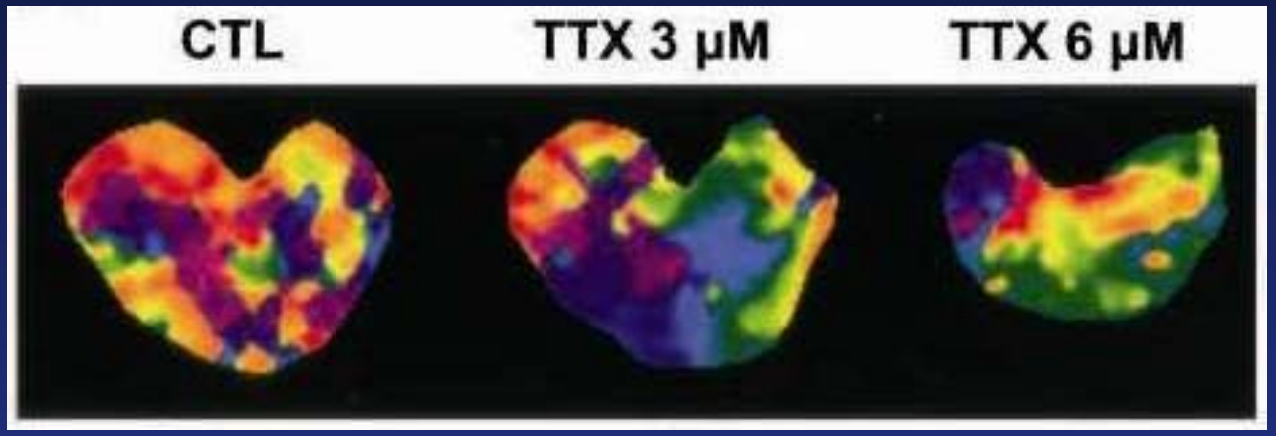


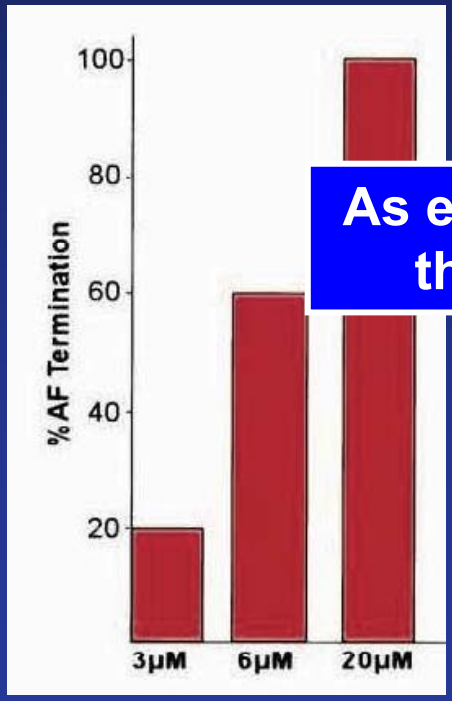
Spiral waves enlarge, slow, meander and terminate

KNELLER et al, *Circ Res 96: e48-e57, 2005*

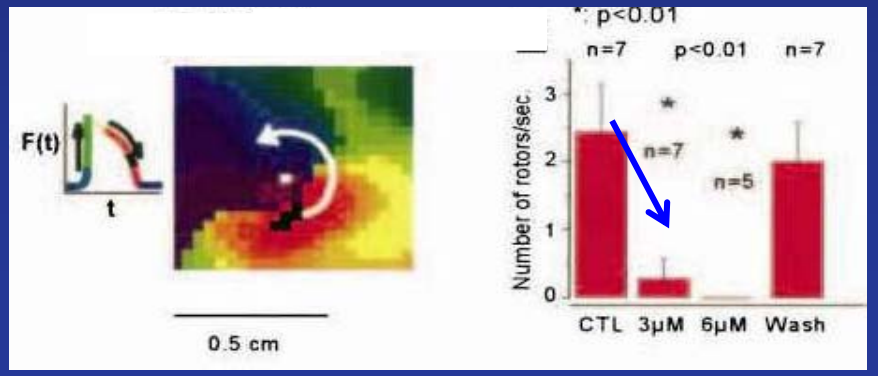
SN.2010

What happens experimentally: TTX administration during cholinergic AF





As expected, TTX terminates AF while decreasing the number of rotors and destabilizing them



KNELLER et al, *Circ Res 96: e48-e57, 2005*

Dreidel (top) concept

Phase-mapping and rotors