Bioeng 6460
Electrophysiology and Bioelectricity

Fundamentals of Arrhythmias

(Part 2)

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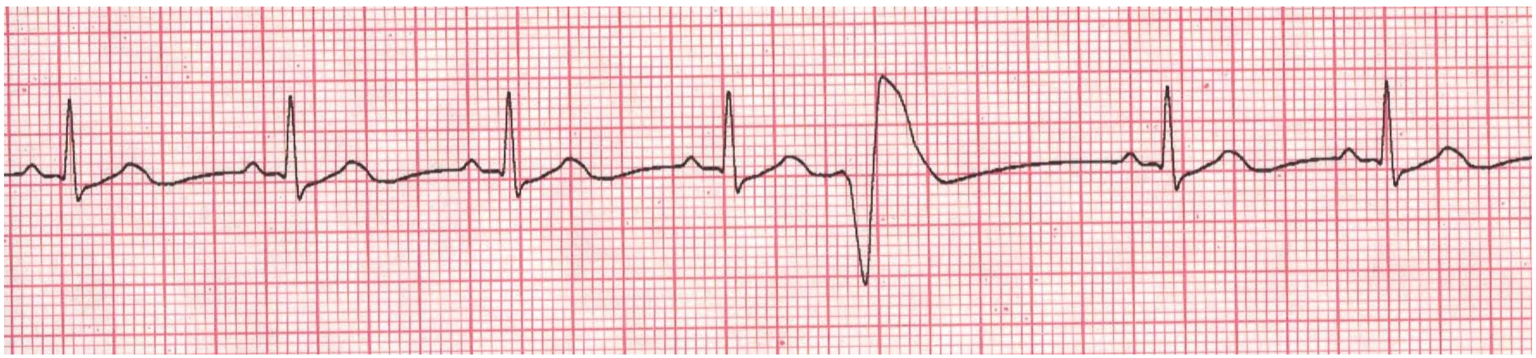
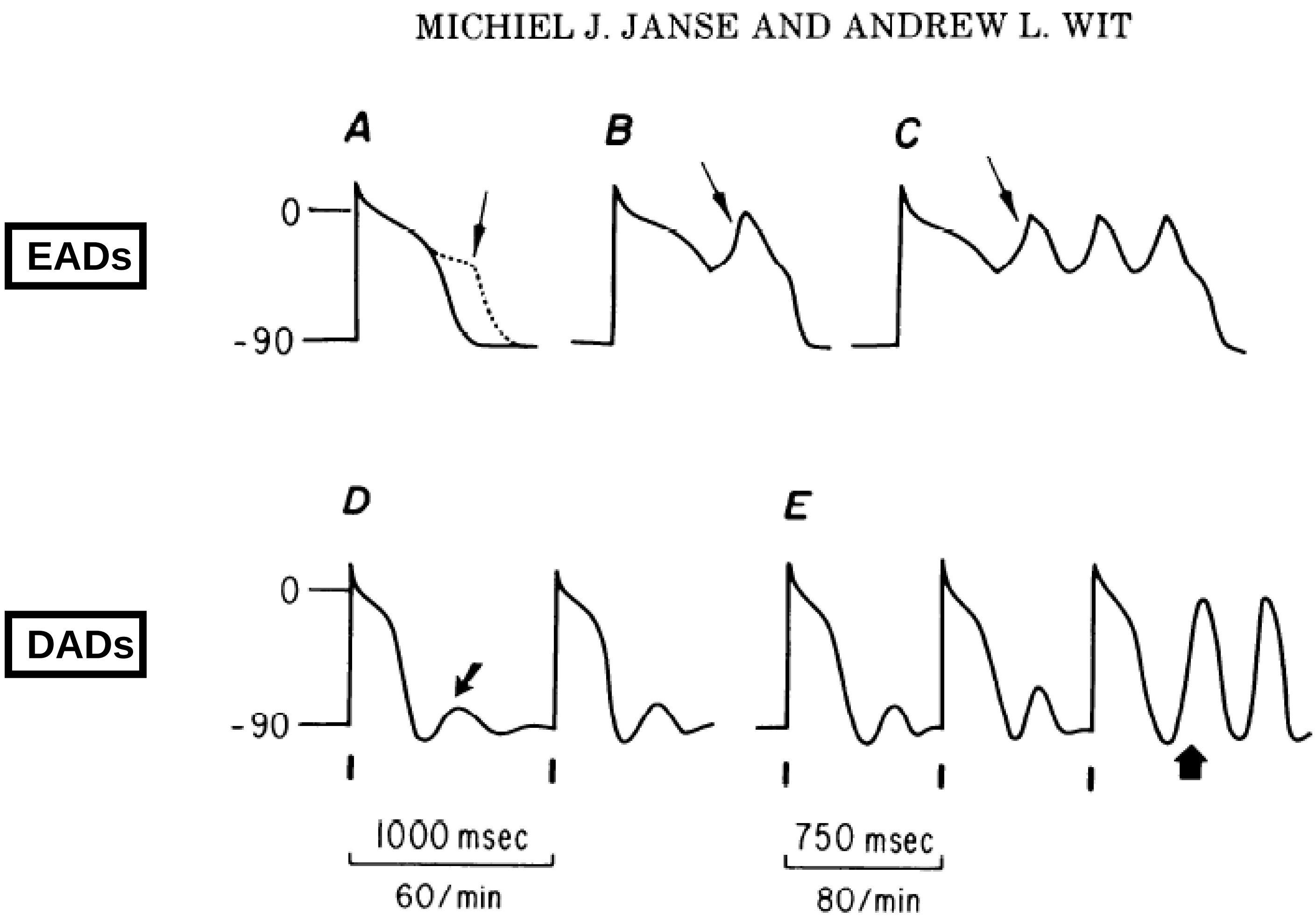
Group work

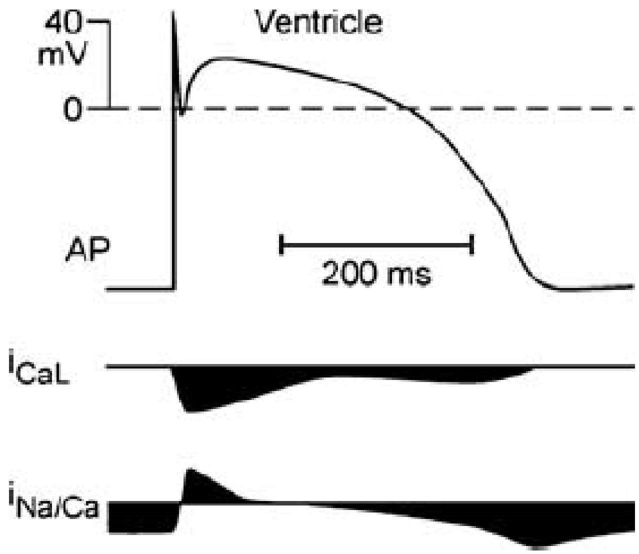
Why do we care at all to understand the mechanisms of arrhythmia?

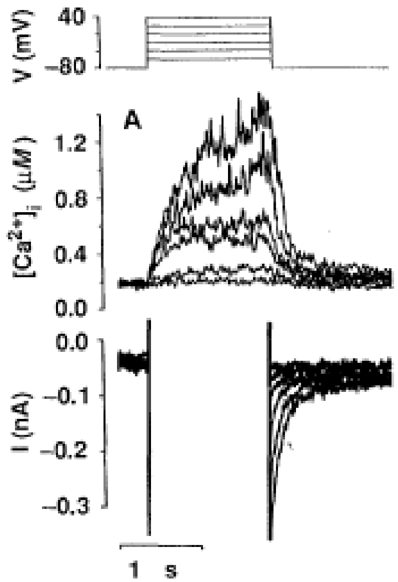


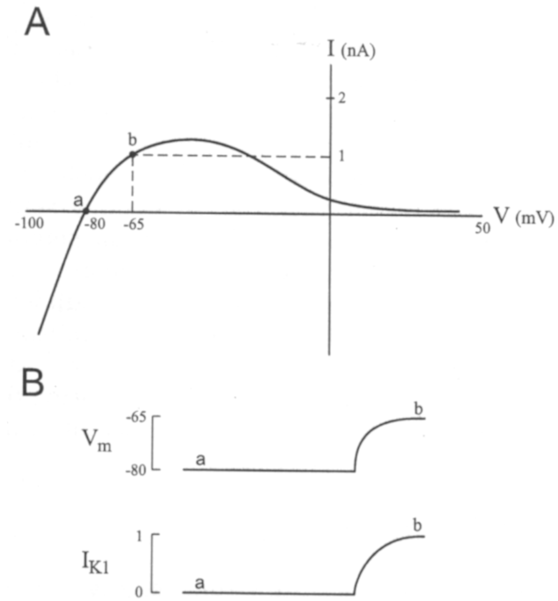
EADs and DADs



Janse and Wit Physiol Rev 1989


40
mV
0
Ventricle
AP
200 ms
iCaL
iNa/Ca

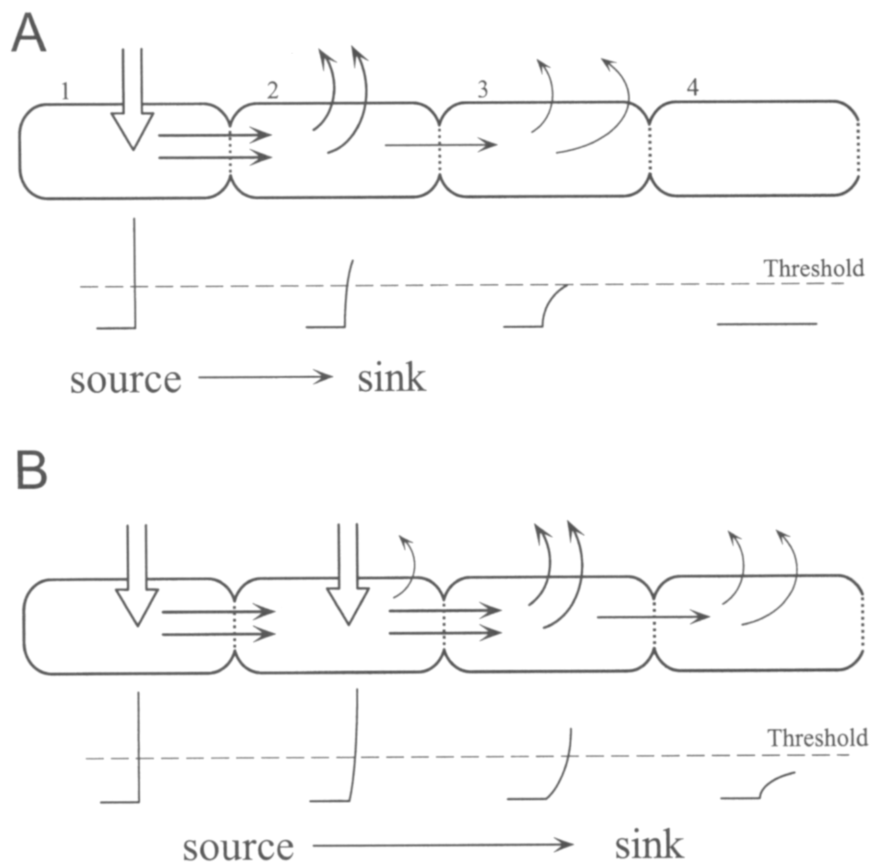

V (mV)
40
−80
A
[Ca2+]i (μM)
1.2
0.8
0.4
0.0
I (nA)
0.0
−0.1
−0.2
−0.3
1 s


A
I (nA)
2
1
b
a
-100
-80
-65
50
V (mV)
B
Vm
-65
-80
a
b
IK1
1
0
a
b

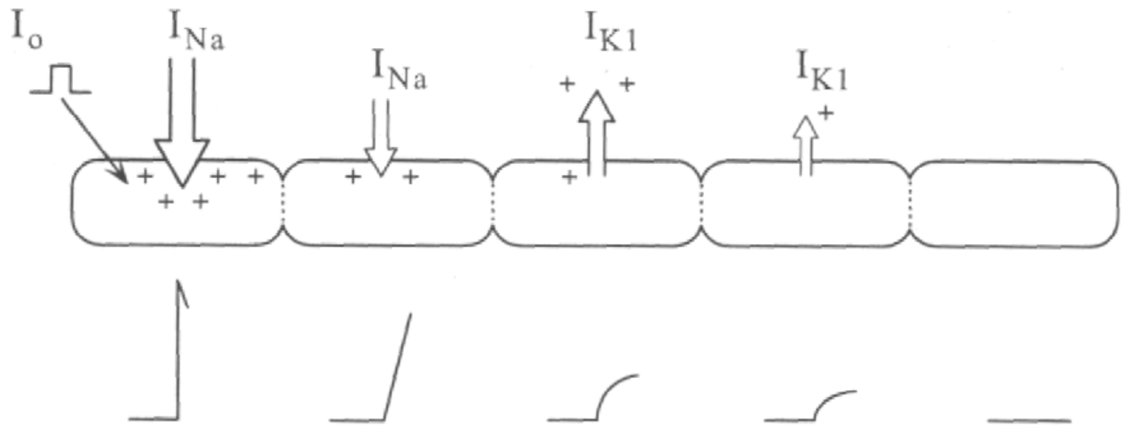
Overview

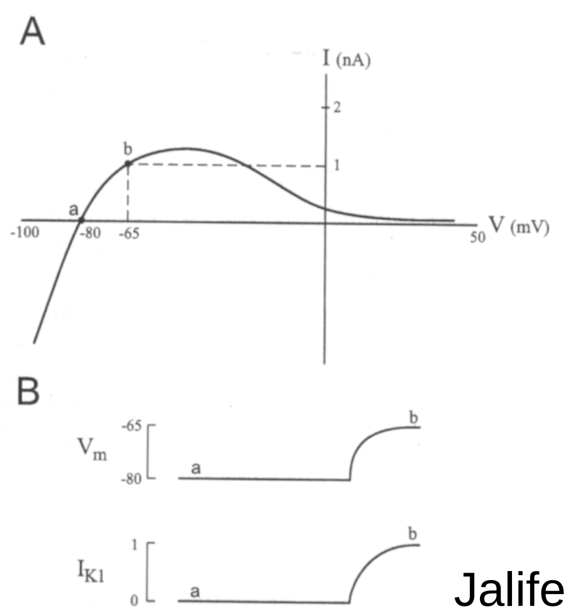
- Basic concepts (review) related to the success of conduction in 1-D and 2-D
- Arrhythmic mechanisms related to abnormal conduction
  - Reflection
  - Classical reentry
  - Leading circle model of reentry
  - Spiral wave reentry

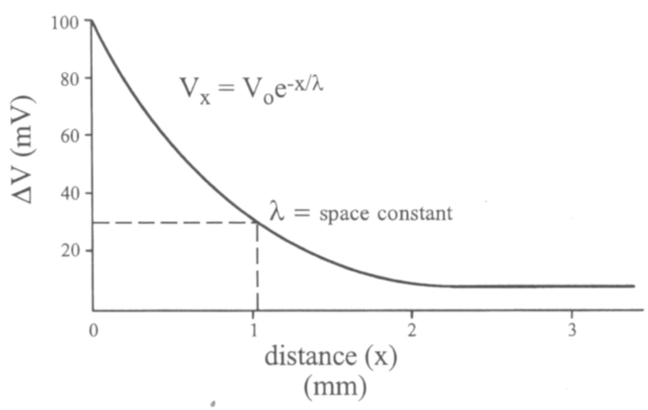
Propagation



Propagation



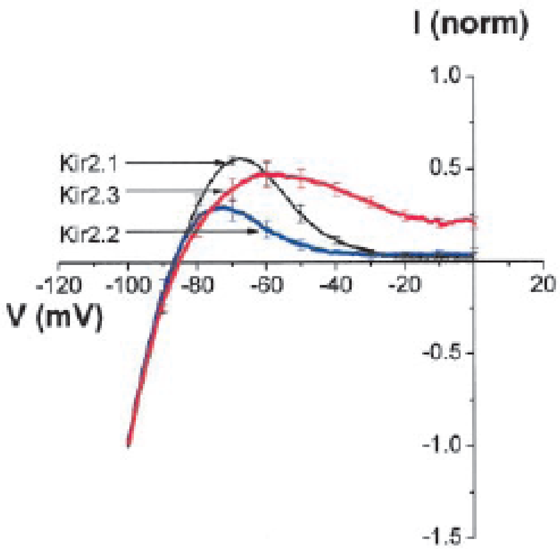




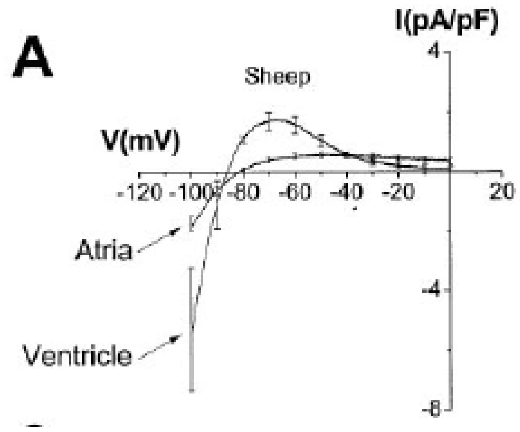
Jalife et al. Futura Publishing Co. 1999

Role of I_{K1} in propagation

Kir 2.x I-V curves



I_{K1} I-V curves

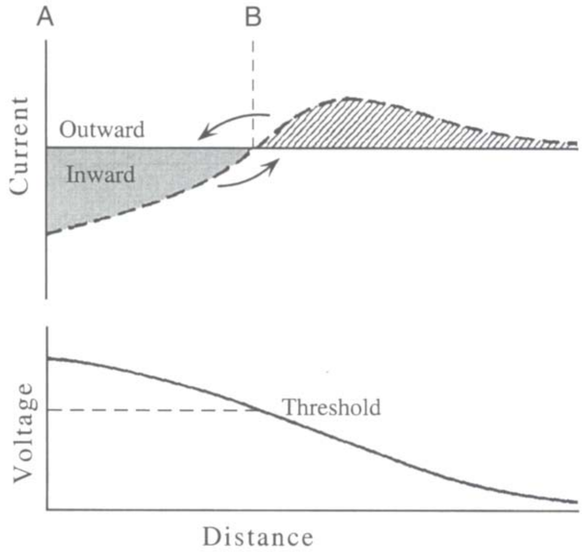


<u>Group Work:</u> Based on the profile of I_{K1} alone, in what tissue type would you expect a faster conduction velocity?

Dhamoon et al. Circ Res 2004

Liminal length

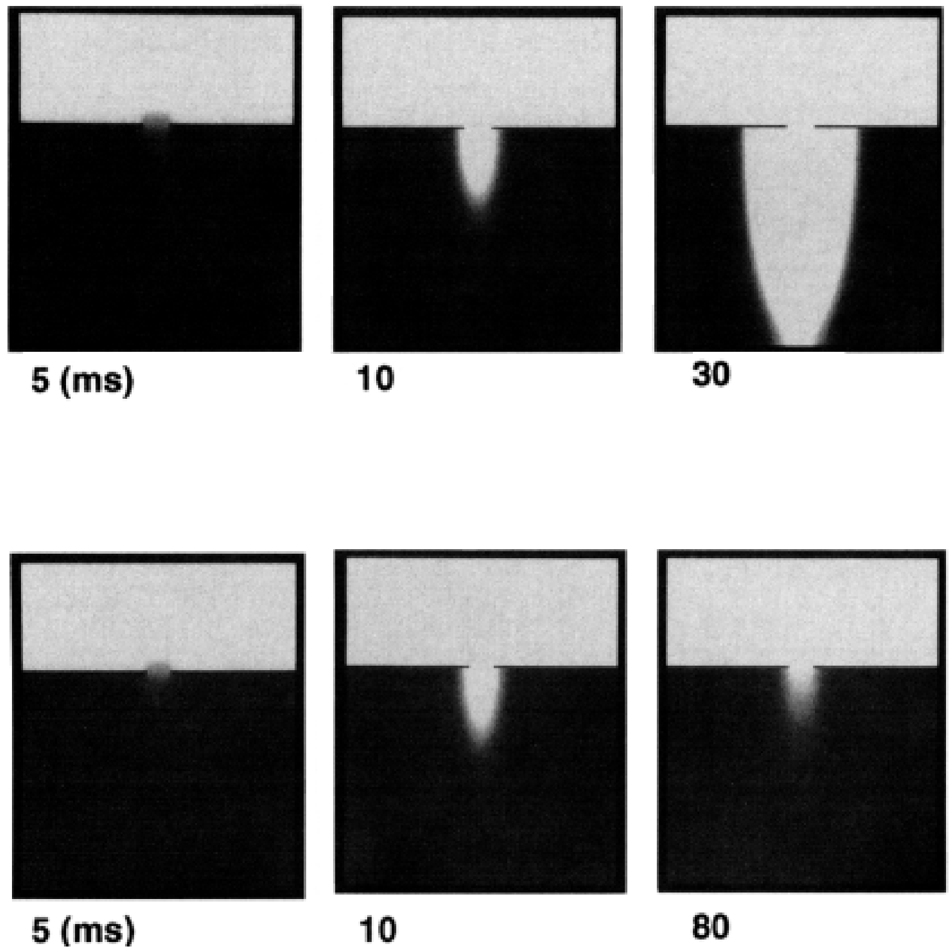
The liminal length concept was developed by Rushton in order to describe analytically the interplay between depolarizing and repolarizing forces in the propagated action potential. In a case of a 1-D fiber, this concept defines the length of fiber that needs to be raised above a threshold so that the depolarizing influence of the currents generated within that length exceed the repolarizing influence of the fiber downstream.



$$\text{L.L.} = \frac{0{\cdot}855 Q_{\text{th}}}{2(\pi)^{\frac{3}{2}} a C_{\text{m}} \lambda_{\text{m}} V_{\text{th}}}.$$

Fozzard and Schoenberg J Physiol 1972

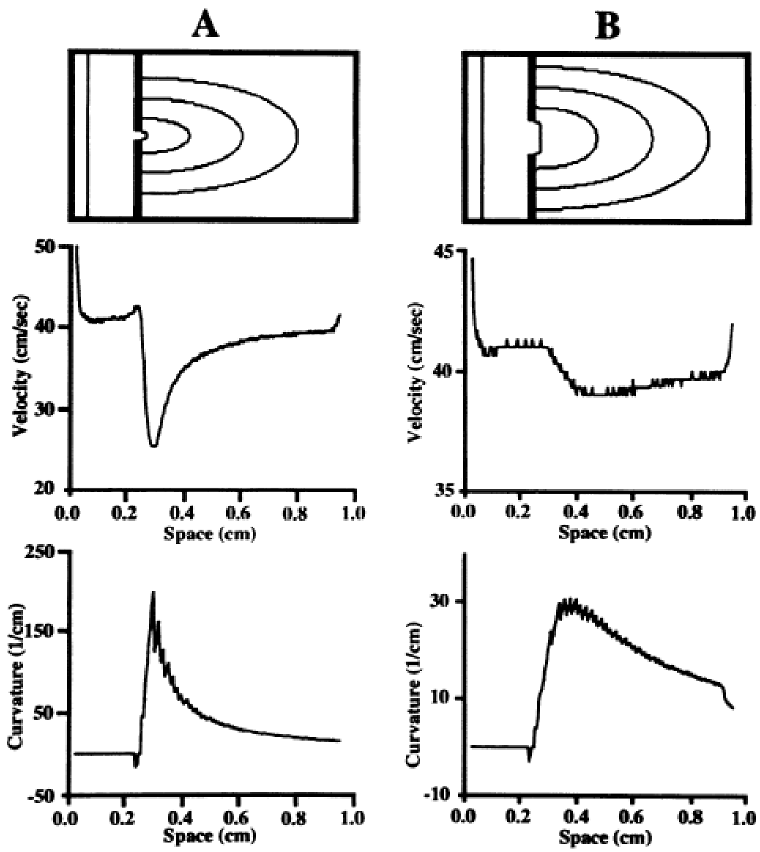
Propagation in 2-D (dependence on the size of isthmus)



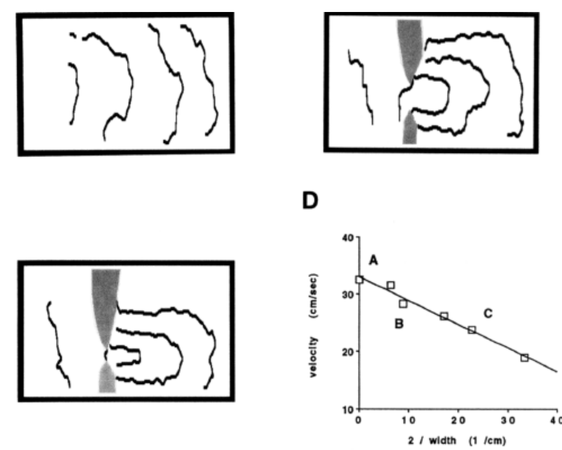
Cabo et al. Circ Res 1994

Propagation in 2-D (dependence on the size of isthmus)

SIMULATION



EXPERIMENT



Isthmuses of different widths diffracted the plane wave to elliptical waves of different curvature. The minimum velocity of propagation occurs after passing the isthmus, when the curvature of the elliptical wave-front is maximum.

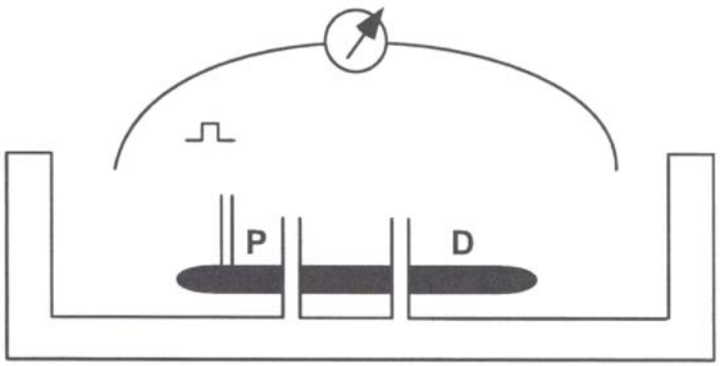
Cabo et al. Circ Res 1994

What would happen if we reduce the size of the isthmus further?

Classification of arrhythmogenic mechanisms

- Abnormal Impulse Formation (Class 1)
- Abnormal impulse conduction (Class 2)
  - Reflection
  - Classical reentry (circus movement reentry)
  - Functional reentry
    - Leading circle type reentry
    - Spiral wave reentry

Reflection (modulation by the shunt resistance)

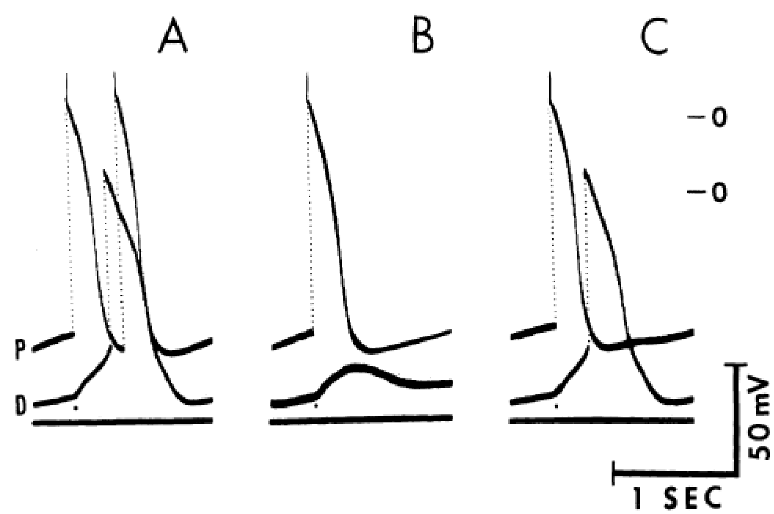


In the excitable gap, propagation is governed by the equations for a passive cable.

$$\lambda^2 = \frac{r_m}{r_i + r_e} \quad \text{and} \quad \tau = r_m c_m$$

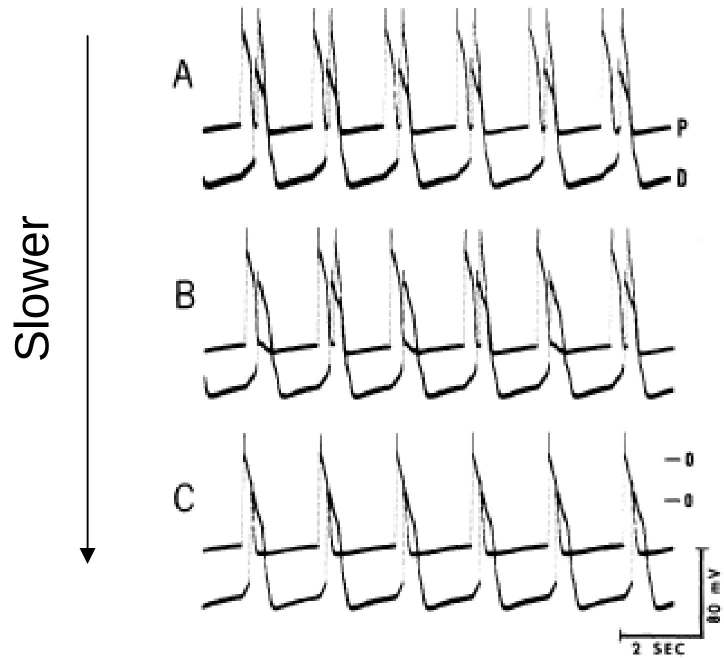
$$\lambda = \sqrt{\frac{r_m}{r_i + r_e}}$$

Sucrose gap preparation: Purkinje fiber in which a central region (approx. 1mm) is made unexcitable but still remains viable and electrically coupled to the Proximal (P) and Distal (D) regions. The P region is paced, whereas the D region is made automatic by reducing K^+ and isoproterenol.



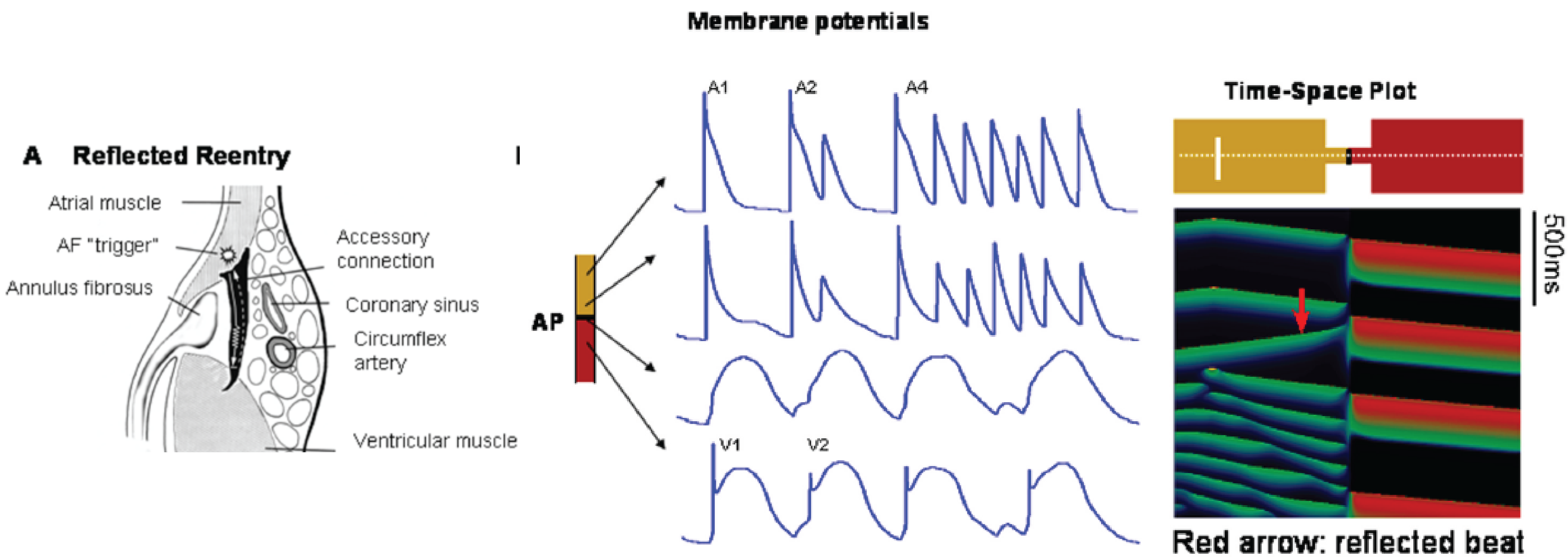
Antzelevitch et al. Circ Res 1980

Reflection (frequency dependence)



Antzelevitch et al. Circ Res 1980

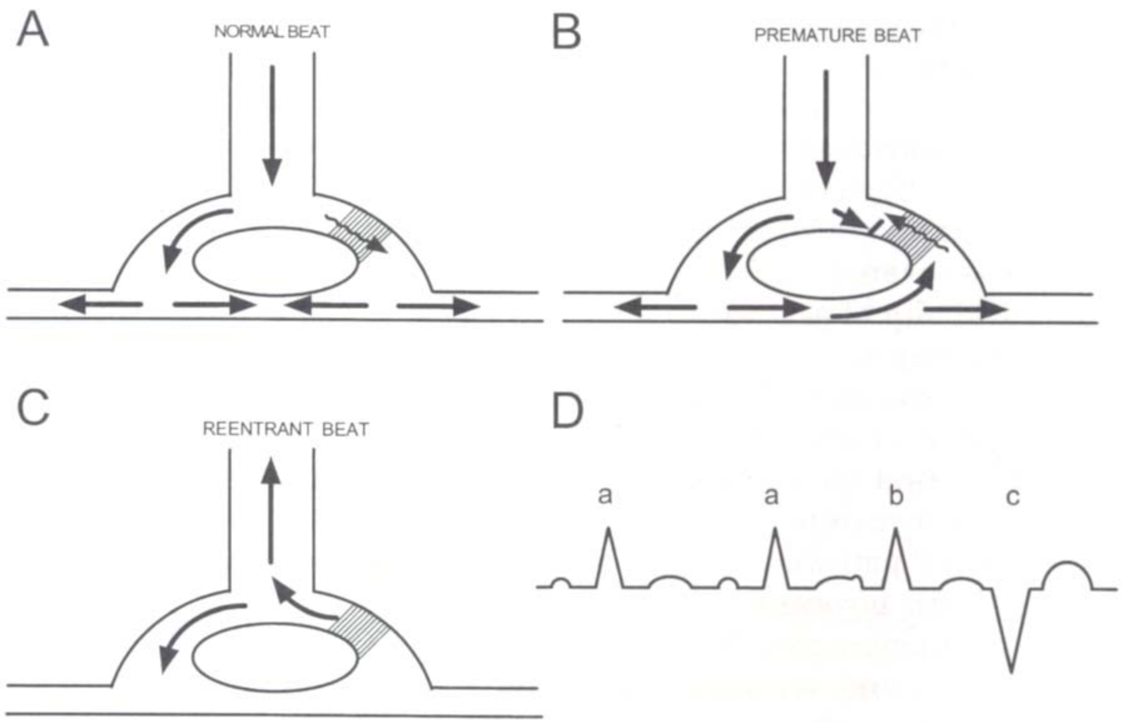
Reflection can trigger arrhtyhmias such as AF



Sucrose gap preparation: In this simulation of an accessory connection between the atria (A) and the ventricle (V), a reflected impulse from A to V and back to A triggered the onset of AF.

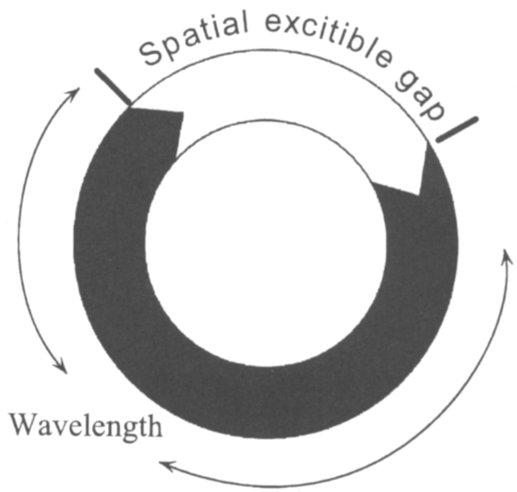
Schwieler et al. Heart Rhythm 2008

Classical reentry (circus movement reentry)



The concept was originally formulated by Mines (1914) and it requires **1)** the presence of a fixed anatomical obstacle or predetermined circuit of 'adequate size', and **2)** unidirectional block. These conditions may bring about the development of a reentrant wave which may perpetuate to form a reentrant tachy-arrhtyhmia. An 'adequate size' involves the set of conditions which allow excess time for the impulse to successfully complete the circuit: a) physical size of the circuit; b) conduction velocity; c) refractory period or duration of the action potential

Wavelength



WL=CV x ERP

WL < Length of circuit

Group work

WL=CV x ERP

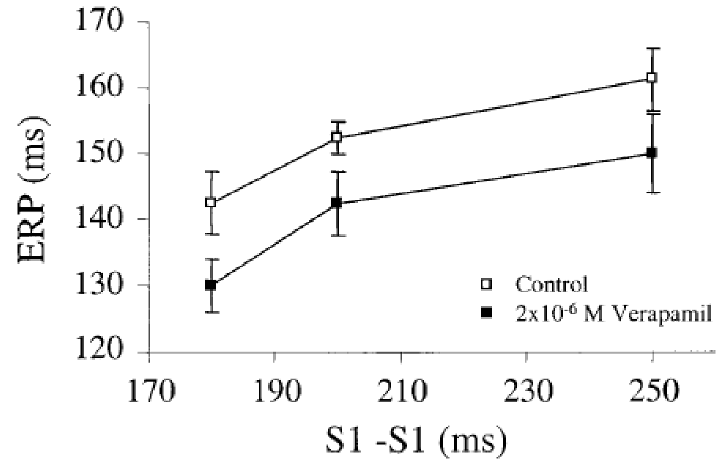
Rabbit

Max and min CV pacing at 300 ms

CVmax = 54.4±2.2 cm/s

CVmin = 35.5±2.1 cm/s

ERP

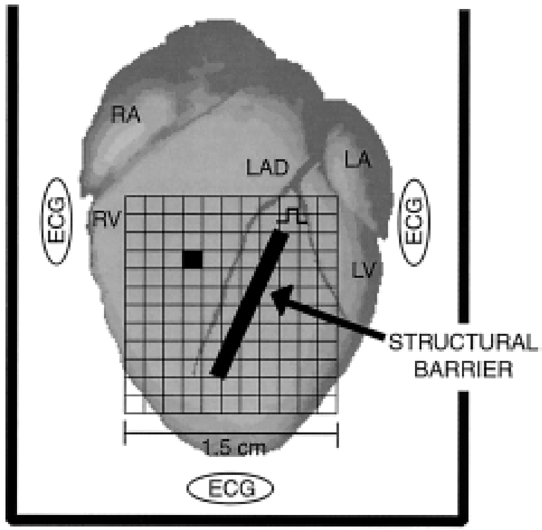


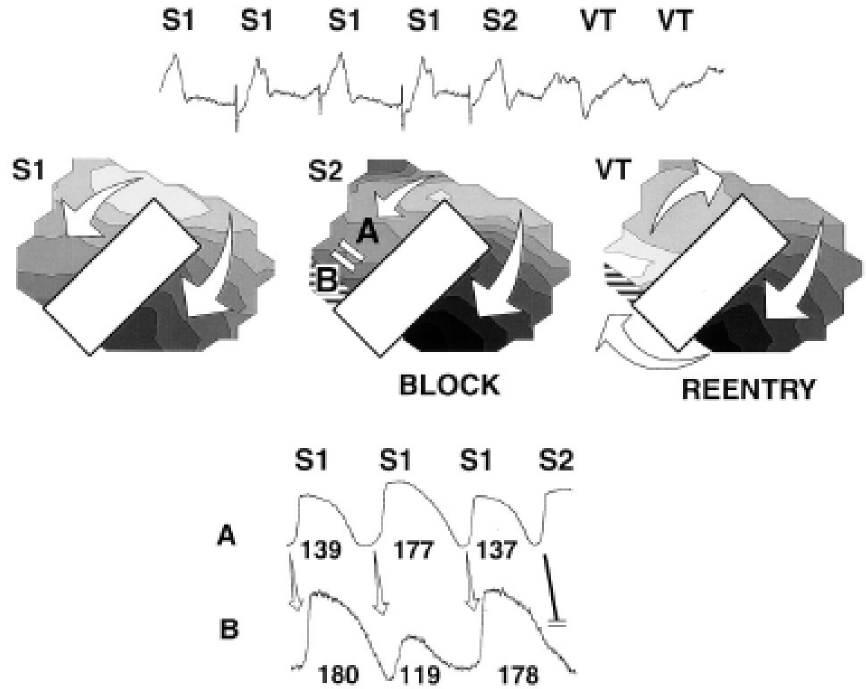
1- Calculate wavelength

2- Given these experimental values of CV and ERP could reentry be maintained in a rabbit heart?

Data from Samie et al. Circ Res 2000

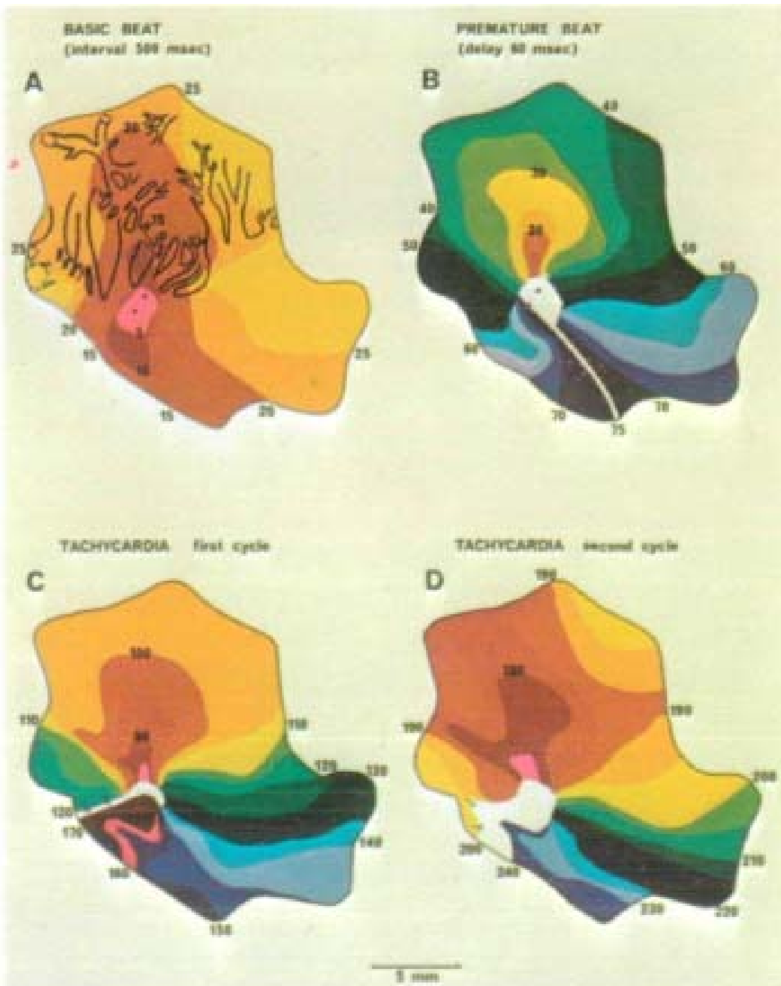
Classical reentry (circus movement reentry)





Pastore and Rosenbaum Circ Res 2000

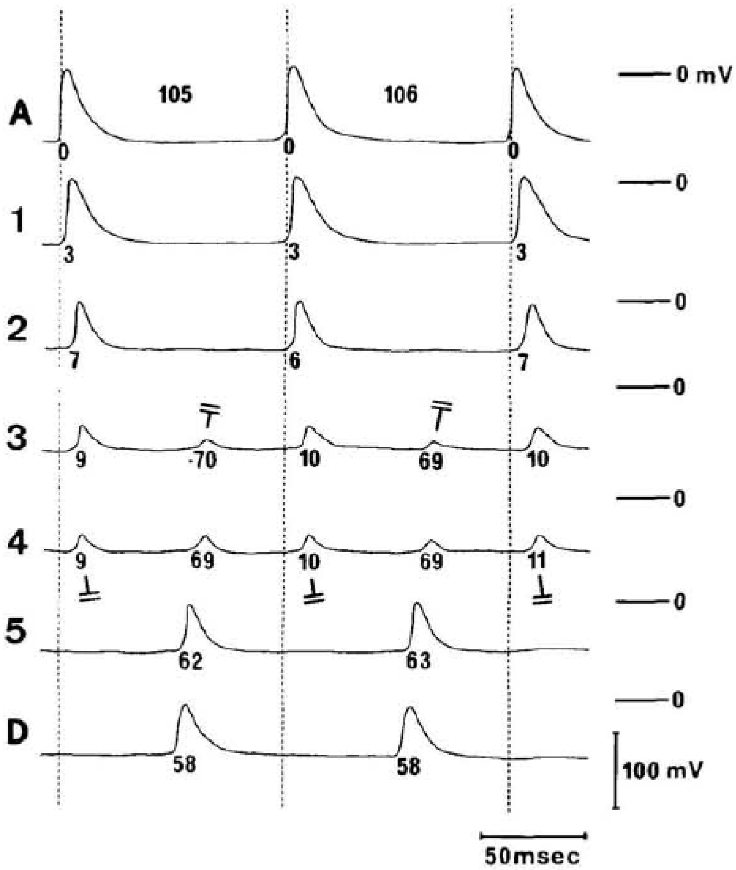
Functional reentry/ the leading circle model

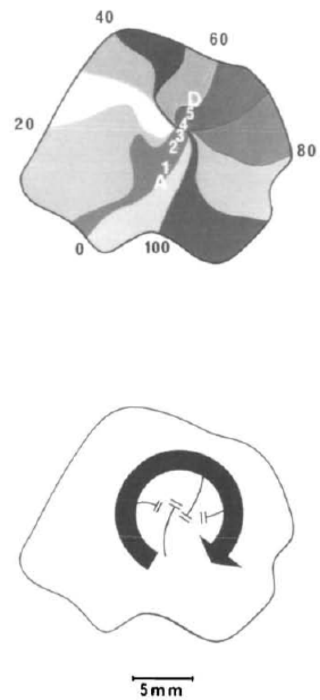


Allessie and co-workers were the first to demonstrate the occurrence of reentry in functionally normal tissue, i.e. in tissue devoid of anatomical obstacles or predetermined circuits that would lend themselves to the formation of reentry as described in the classical model. This type of reentry is called functional reentry. Note from the figure that both during the basic beat and the premature beat all tissue is excited demonstrating the lack anatomical obstacles. Following the premature beat reentry ensues in a stable manner

Allessie et al. Circ Res 1973

Functional reentry/ the leading circle model



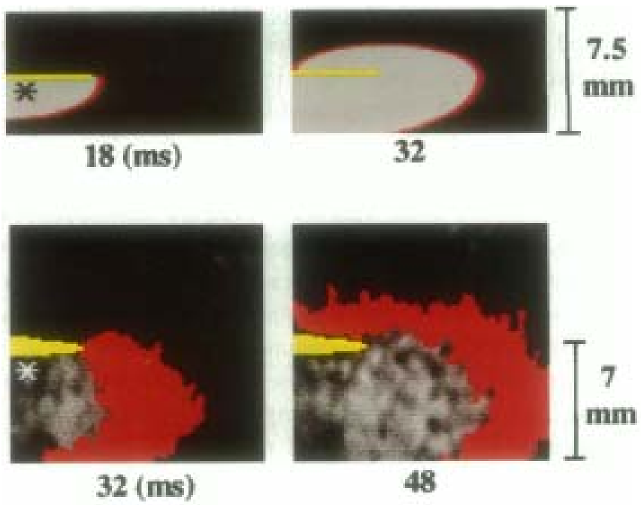


The ***leading circle model*** is a mechanistic explanation for this type of functional reentry. The circulating waves have a centripetal component which, via an electrotonic influence, elevate the transmembrane potential value of cells in the central region ('core') to values above threshold potential, thus effectively rendering this region unexcitable. The unexcitable region effectively prevents circulating wavelets to short-cut the activation, and thus the reentry may be perpetuated.

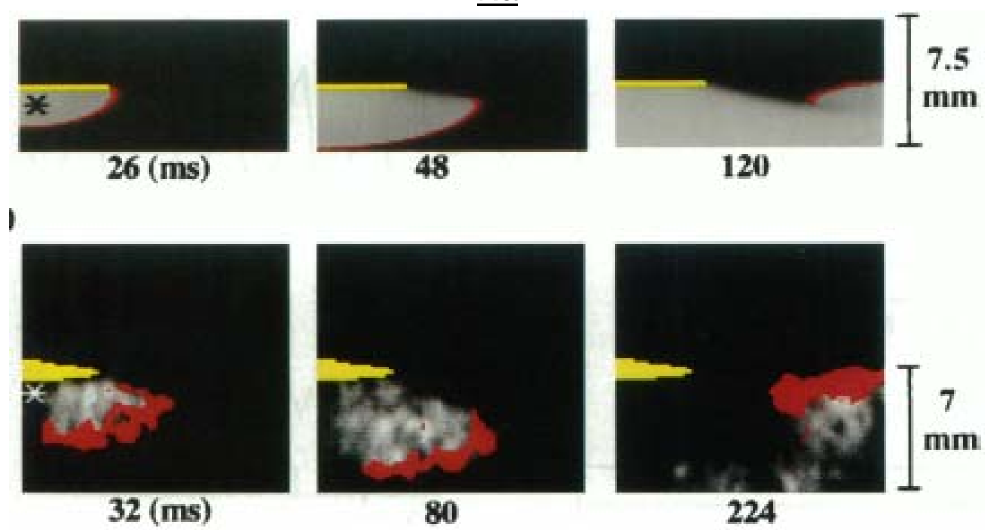
Allessie et al. Circ Res 1973

How to 'brake' a wave

Normal excitability

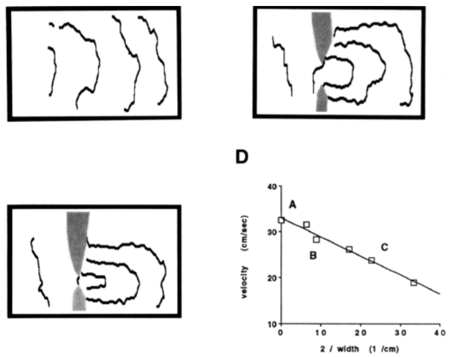


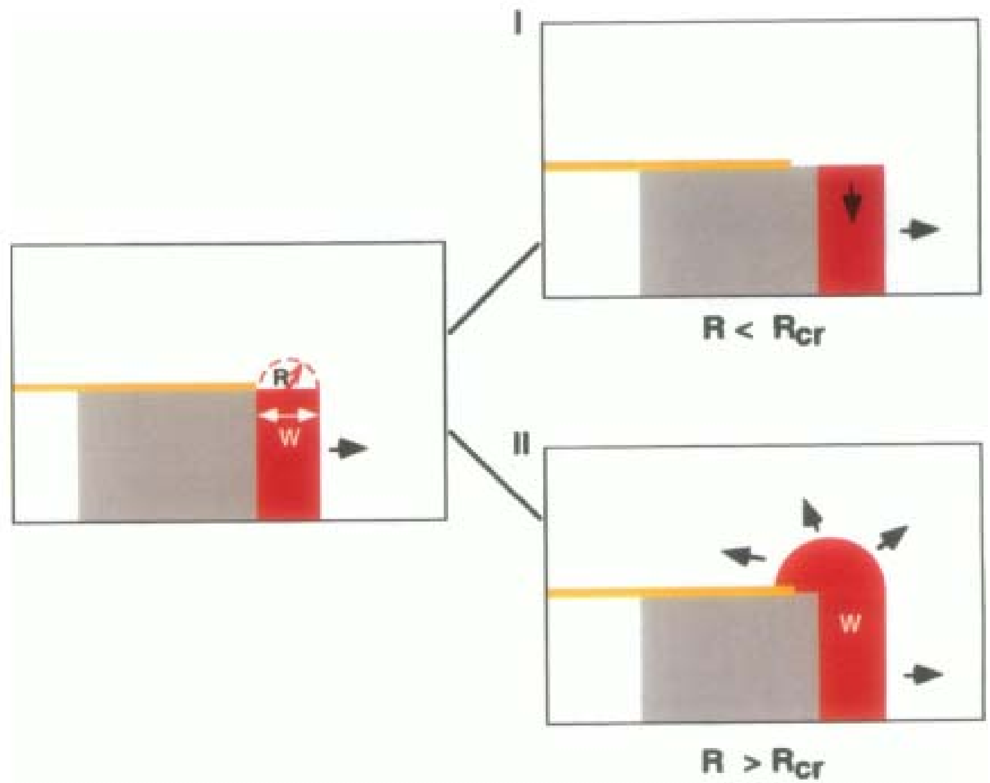
Reduced excitability (I_{Na} block with TTX)



Cabo et al. Biophys J 1996

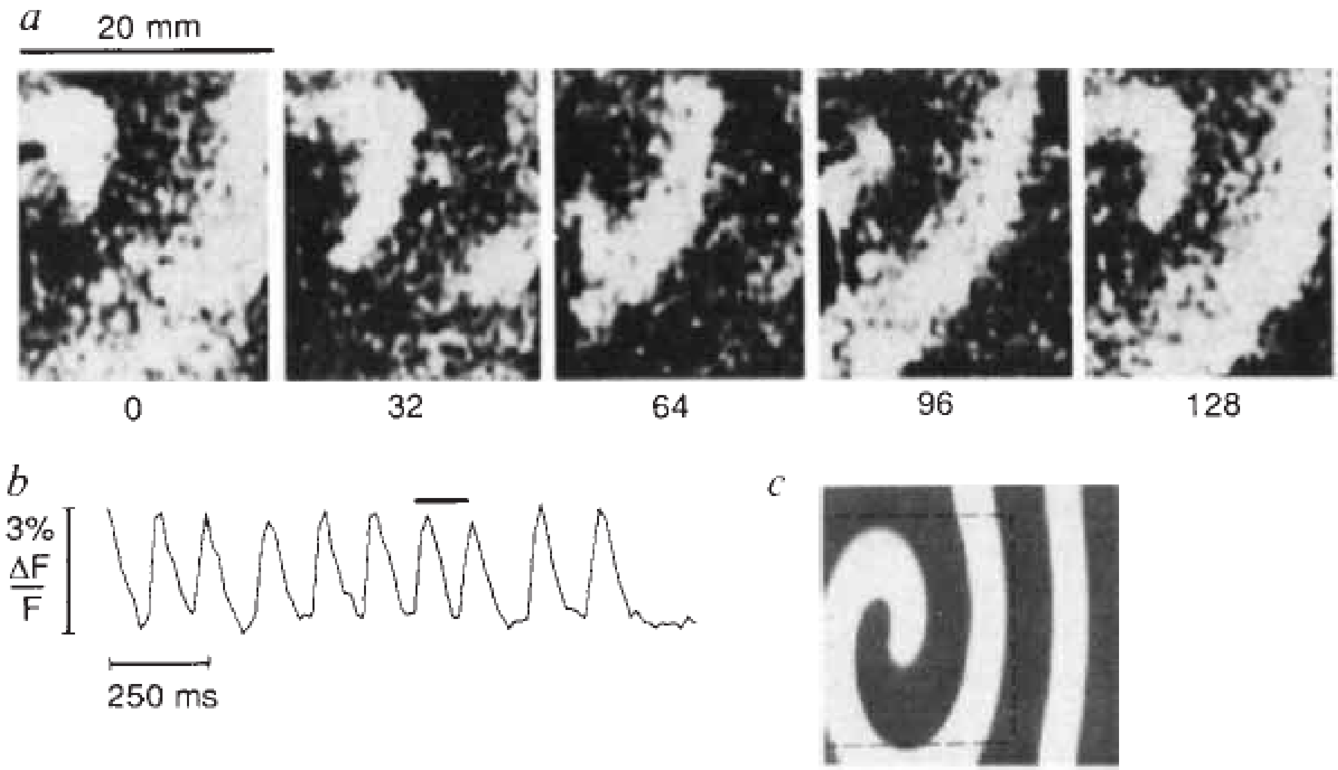
How to ‘brake’ a wave





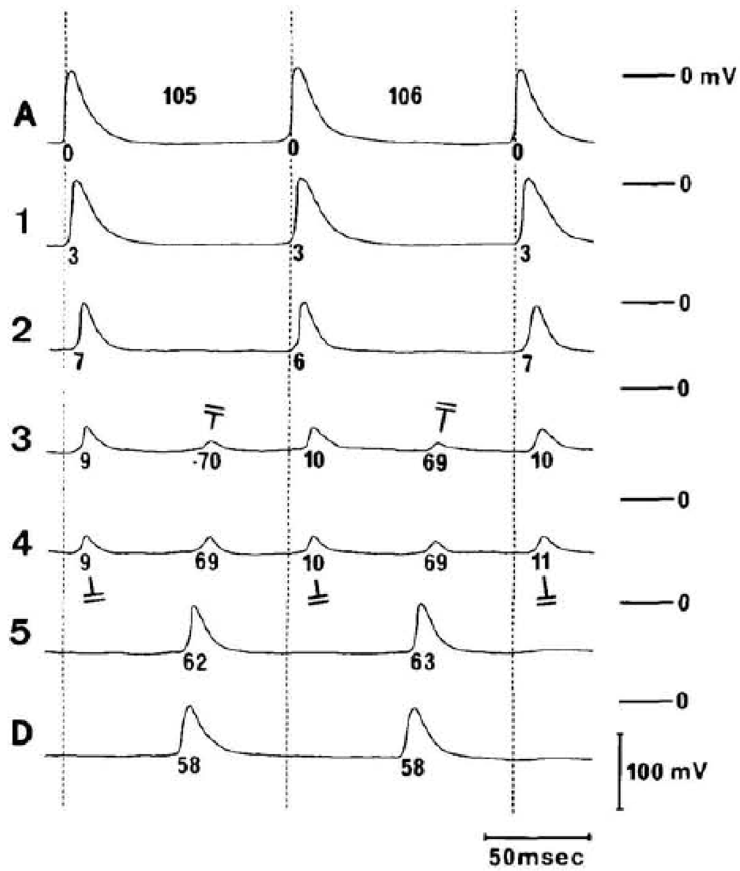
Cabo et al. Biophys J 1996

Spiral waves in cardiac tissue

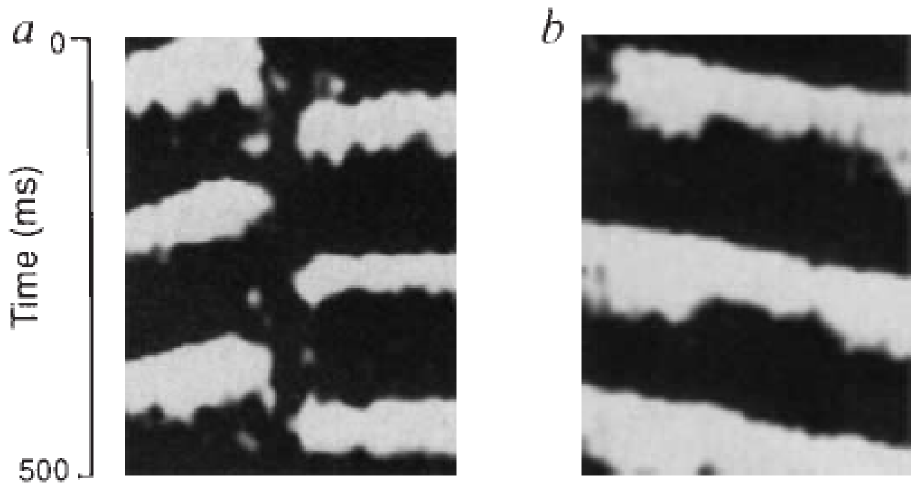


Davidenko et al. Nature 1992

Is there any difference between a spiral wave and a ‘leading circle reentry’?

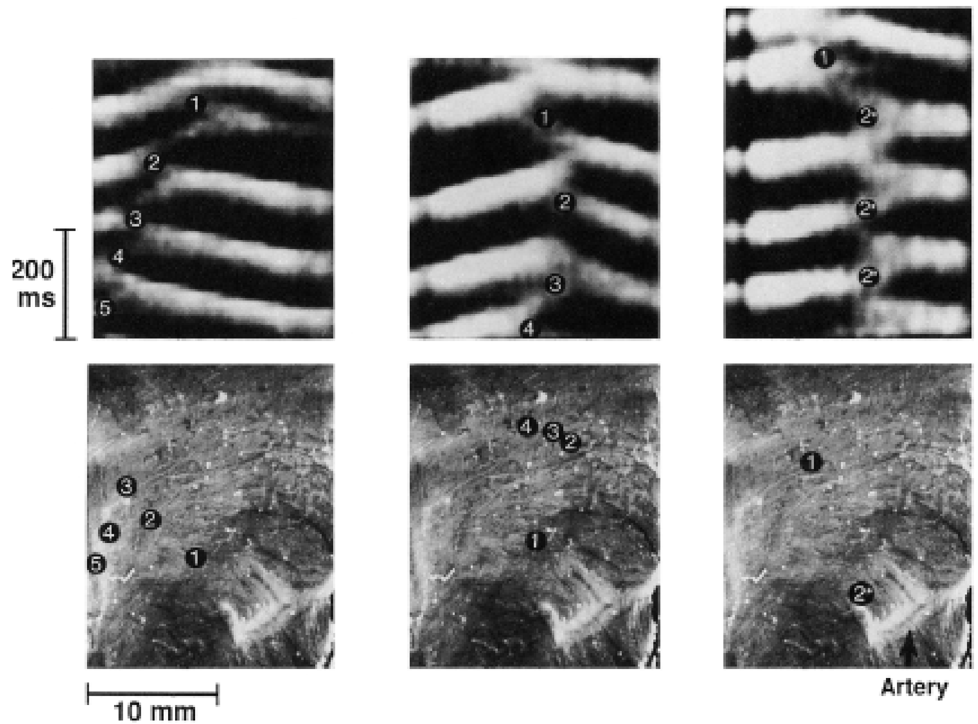

A
1
2
3
4
5
D
105
106
0 mV
0
100 mV
50msec
0
3
7
6
9
-70
10
69
11
62
63
58

Time-space-plots and Christmas tree



Davidenko et al. Nature 1992

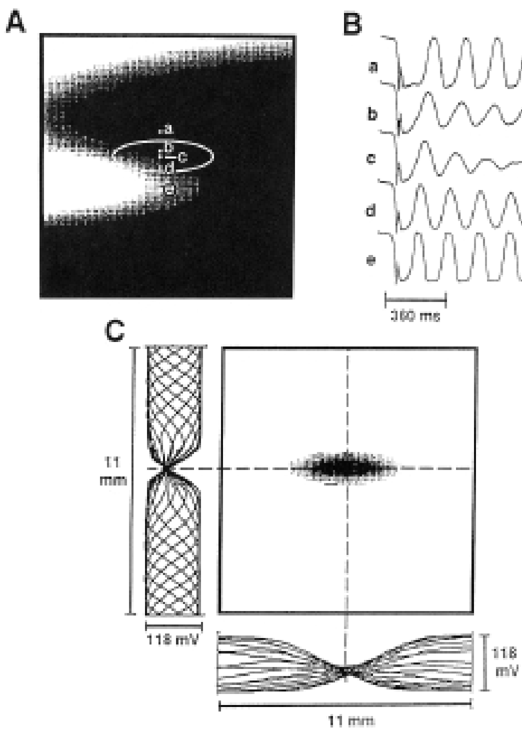
Spiral wave drift vs. anchoring



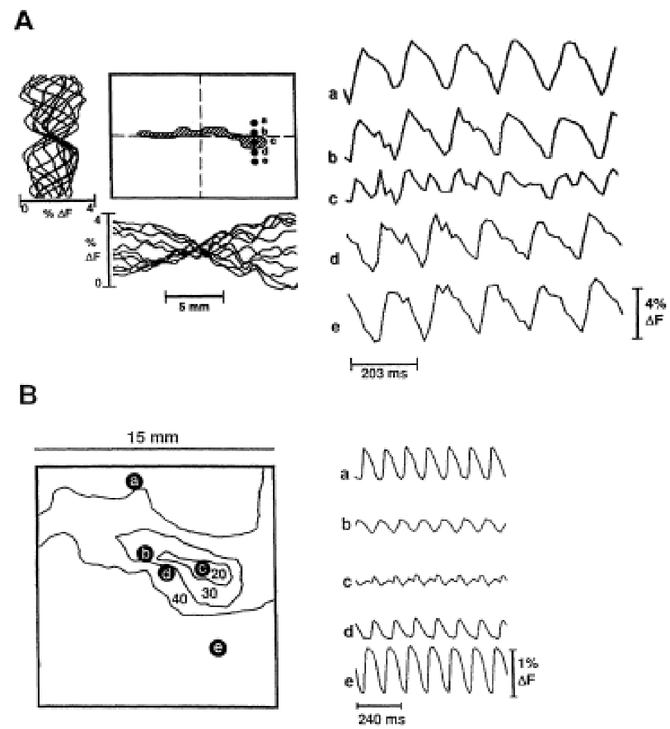
Pertsov et al. Circ Res 1993

The spiral wave 'core'

SIMULATION

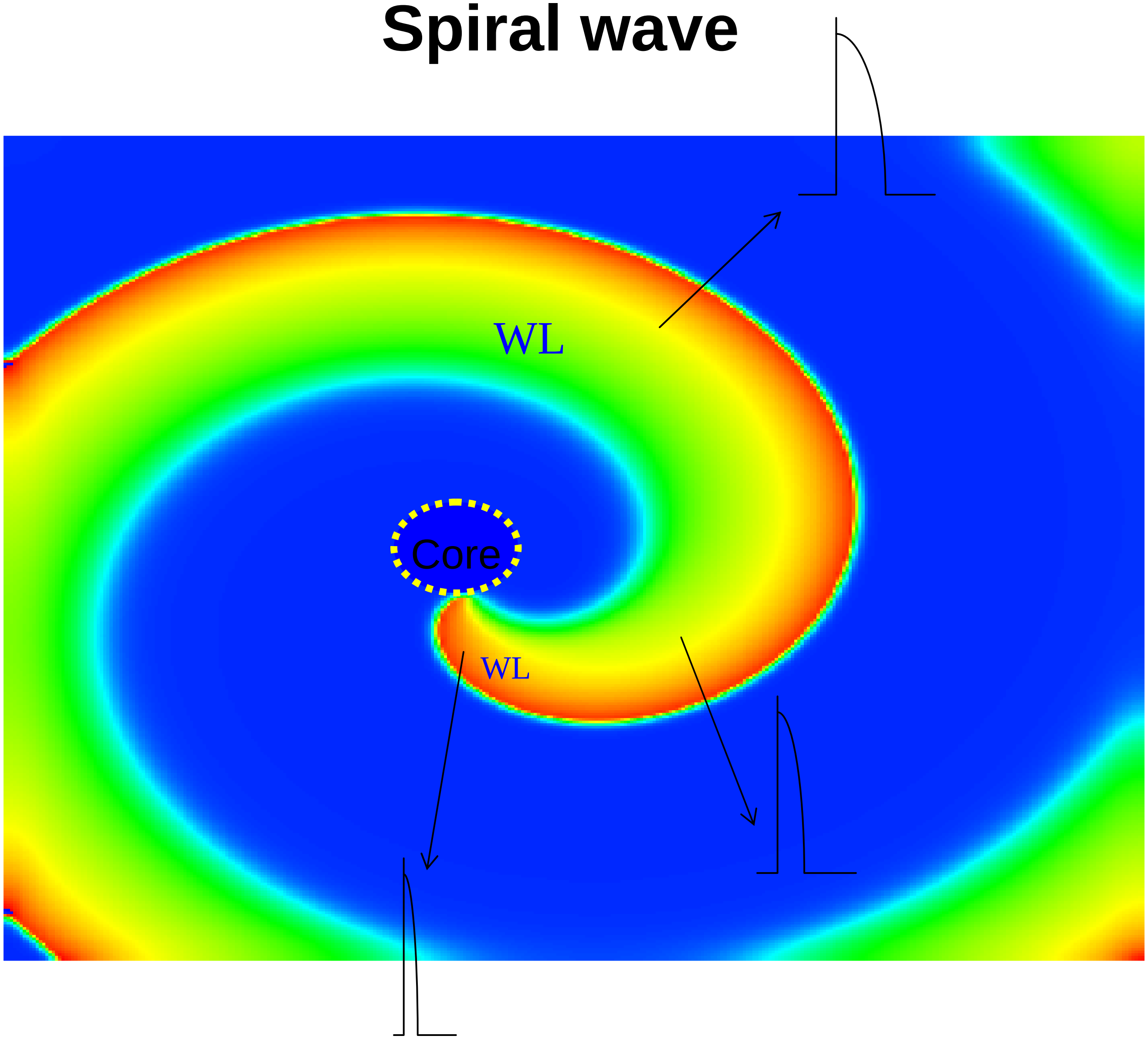


EXPERIMENT

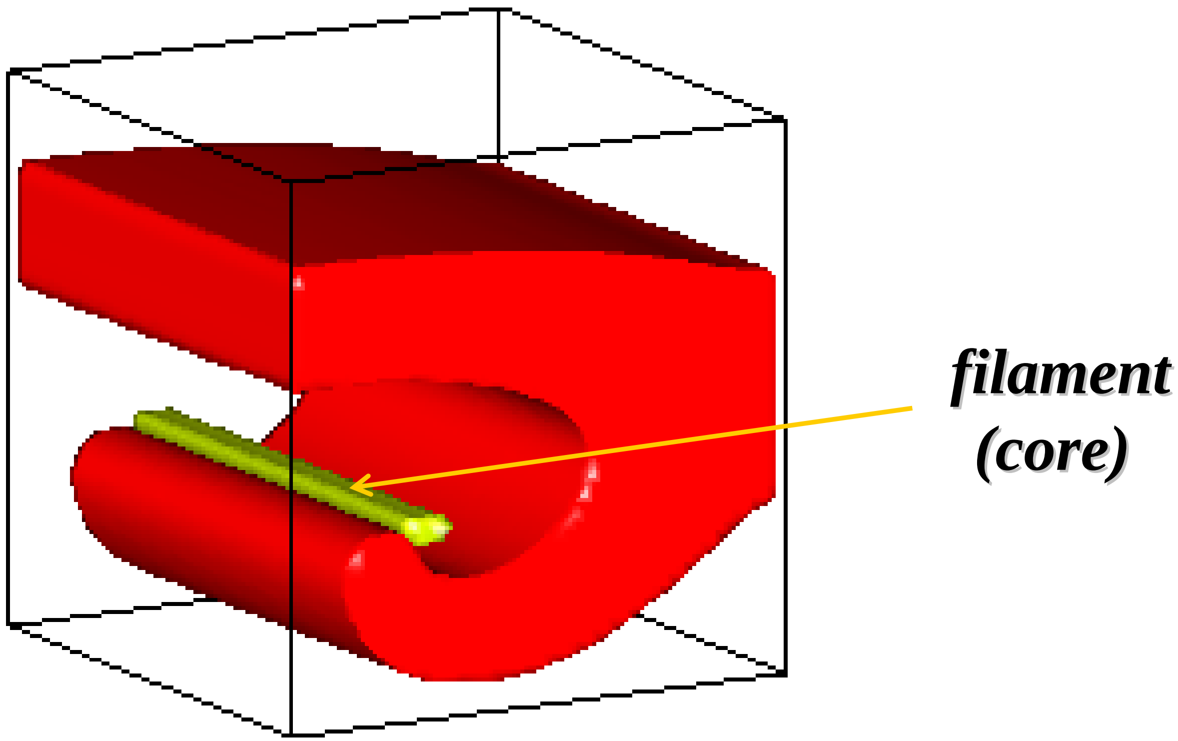


Pertsov et al. Circ Res 1993

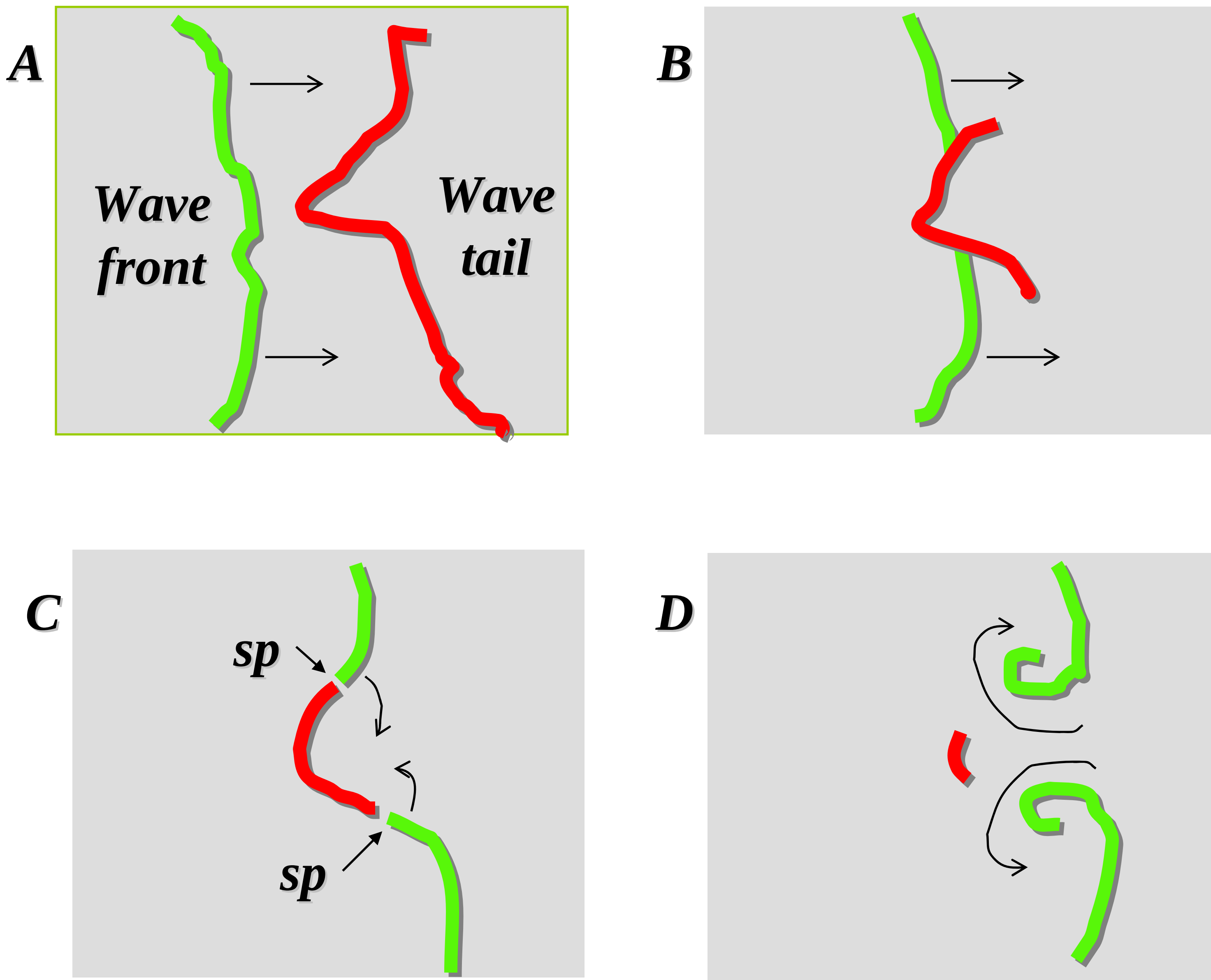
Spiral wave



Three-dimensional rotor (scroll wave)



Berenfeld et al., J Theor Biol. 1999


A
Wave front
Wave tail
B
C
sp
sp
D

END

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