Systems Biology: A Personal View XXVIII. Waves in disordered excitable media: Obstacles, Gradients, & Pinning

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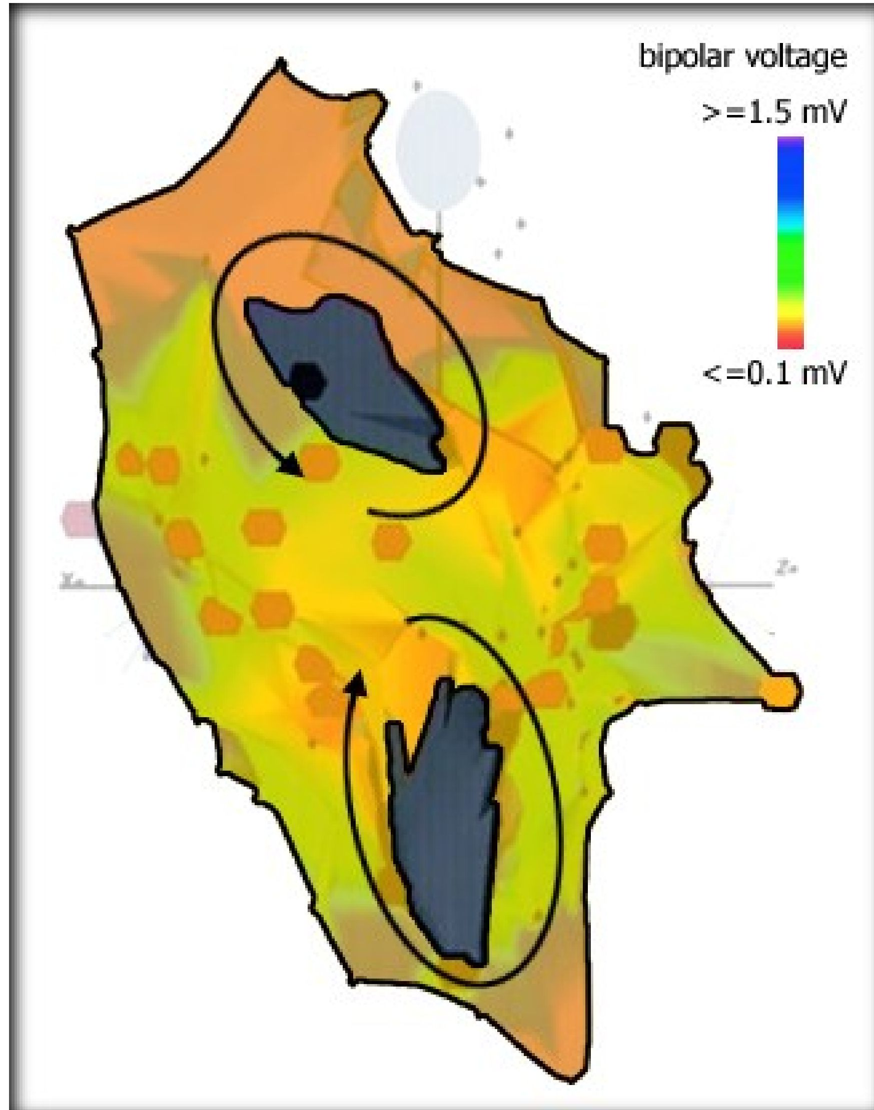
Disorder induces creation of spiral waves

- Sustained tachycardia because of ***reentry*** around pre-existing scar tissue

Reentry: self-sustaining feedback loop of excitation

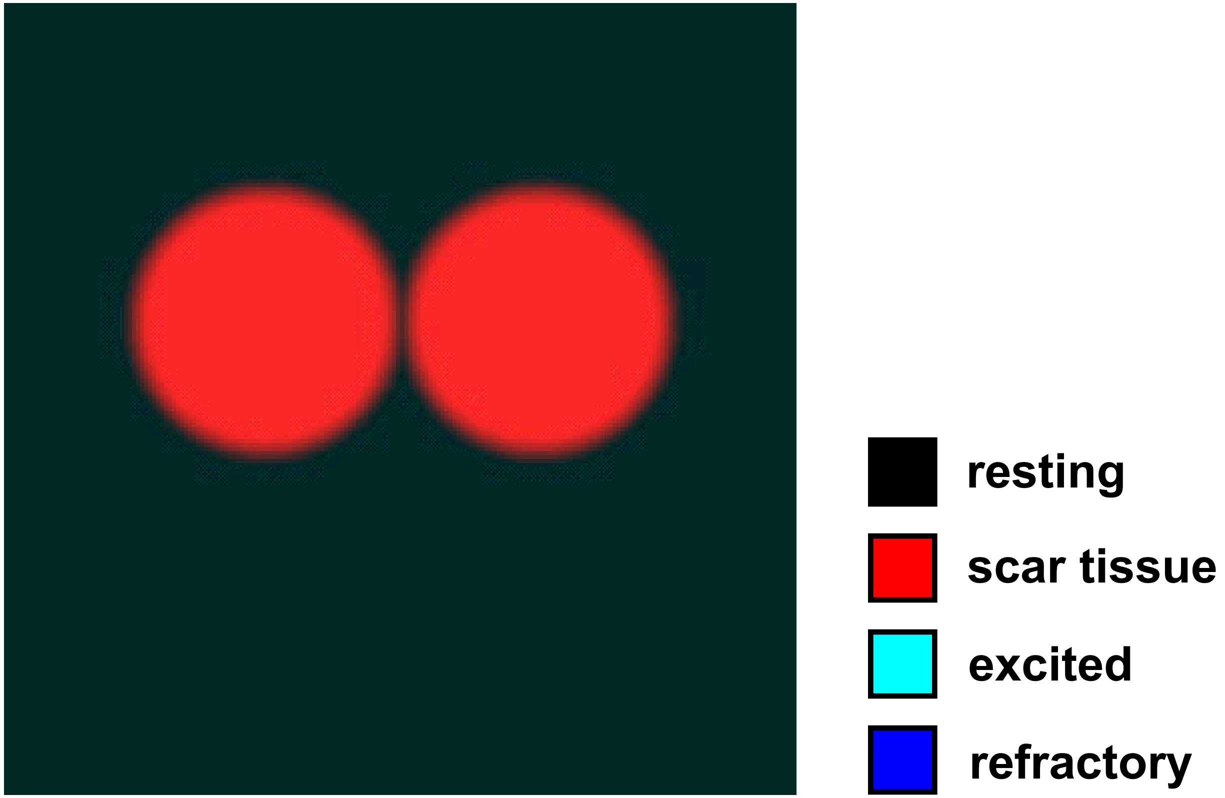
- Clinically manifested as tachycardia

- First exptly shown by G R Mines (1913)



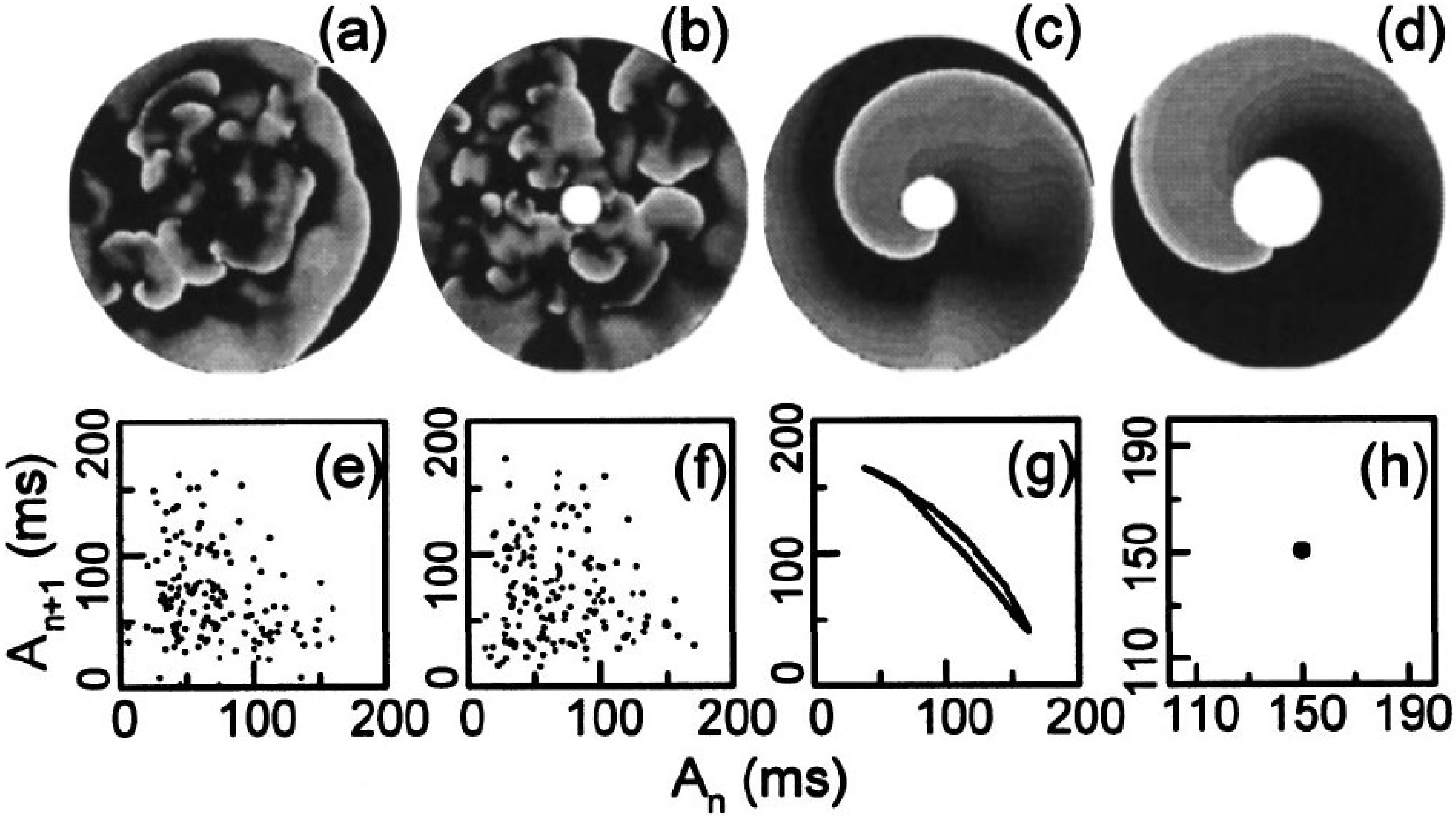
biosense measurement

Creation of pinned reentrant waves around disorder (scar tissue)



Movie: Onset of reentry in Panfilov Model

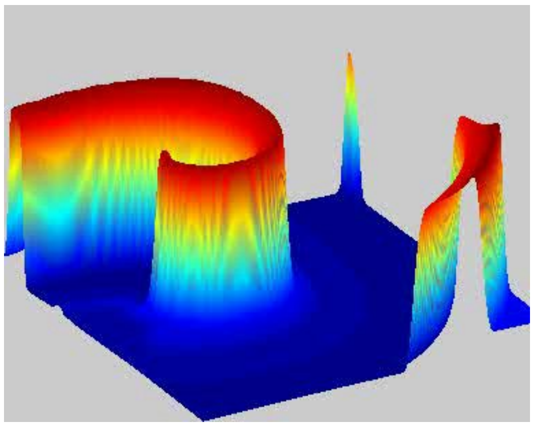
Role of structural disorder: Transition from spatiotemporal chaos to pinned rotating wave

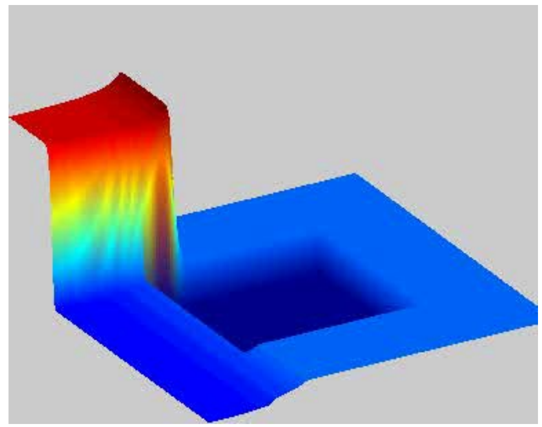


F. Xie, Z. Qu, and A. Garfinkel, Phys. Rev. E **58**, 6355 1998.

Investigating the role of defects on the propagation of electrical activity

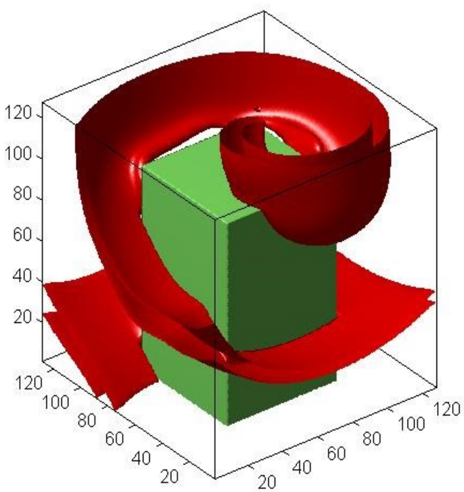
Obstacles may prevent *breakup* of spiral waves…

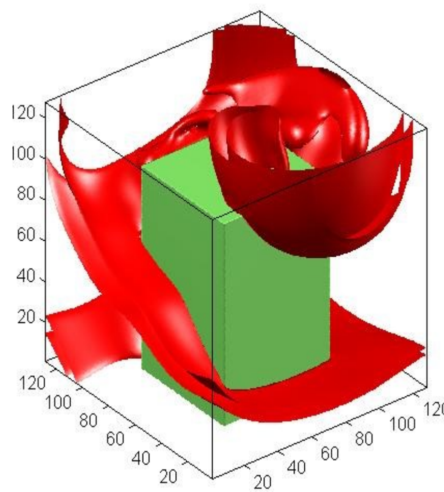


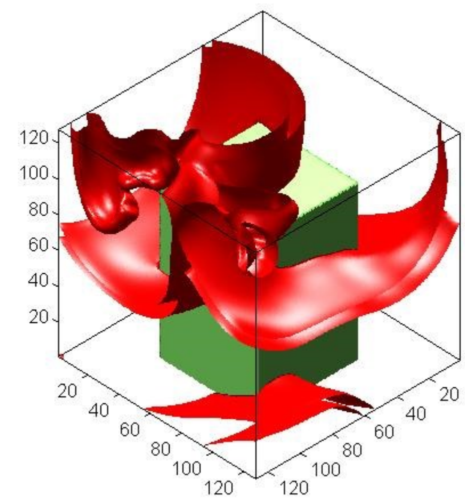


… on the other hand, we have seen *purely* disorder induced breakup of spiral waves in 3-D models of cardiac tissue

[S Sridhar, A Ghosh & SS, *EPL,* 2013]



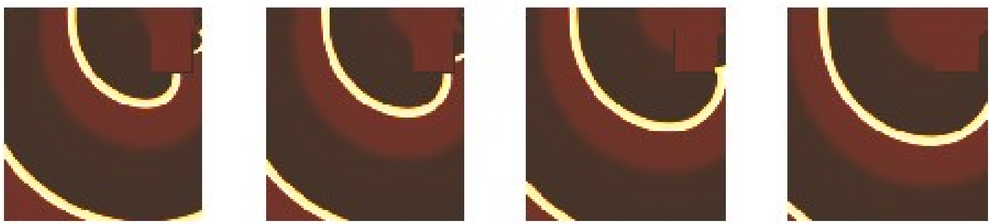




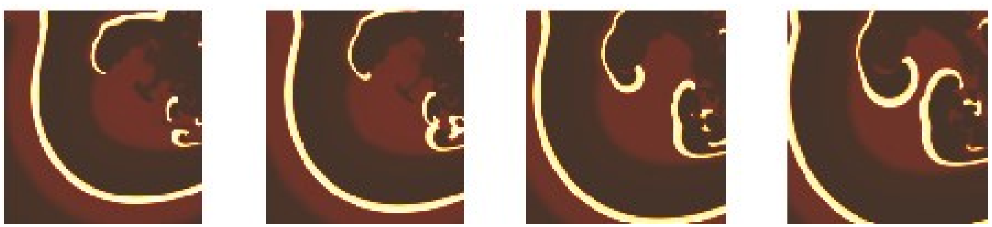
In fact…

Sensitive dependence on position & size of disorder

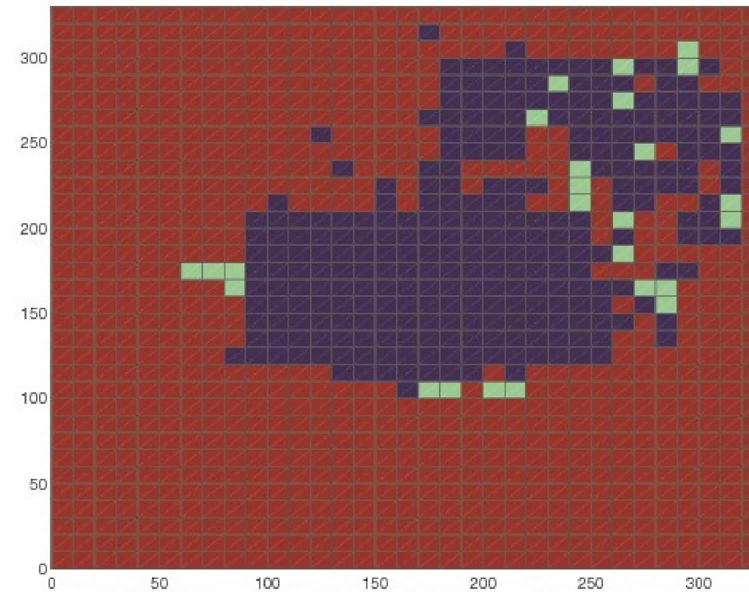
Pinned spiral



Termination of activity



Spatiotemporal chaos



Shajahan, Sinha & Pandit, *Phys Rev E*, 75, 011929 (2007)

Drift of spiral waves in presence of gradient

Excitable media model with heterogeneity gradient

$$\boxed{\begin{array}{c} \partial V/\partial t = \nabla\gamma D\nabla V + \alpha I_{ion}(V, g_i), \\ \\ \partial g_i/\partial t = F(V, g_i). \end{array}}$$

Barkley model:

$$I_{ion} = [V(1-V)(V-((g+b)/a)]/\epsilon$$

$$F(V,g) = V - g$$

gradient in local excitation kinetics: $\alpha(x) = \alpha_0 + \Delta\alpha\ x$

gradient in cellular coupling: $\gamma(x) = \gamma_0 + \Delta\gamma\ x$

$\Delta\alpha$, $\Delta\gamma$: rate of change of along *x*, principal direction of inhomogeneity gradient

Increasing $\alpha, \gamma \Rightarrow$ Increase in excitability $\Rightarrow$ Decrease in spiral wave rotation period

Drift of spiral waves in presence of gradient

First Observation of

Anomalous drift: to region of higher excitability or shorter period

Anomalous drift *Normal drift*

Lower excitability

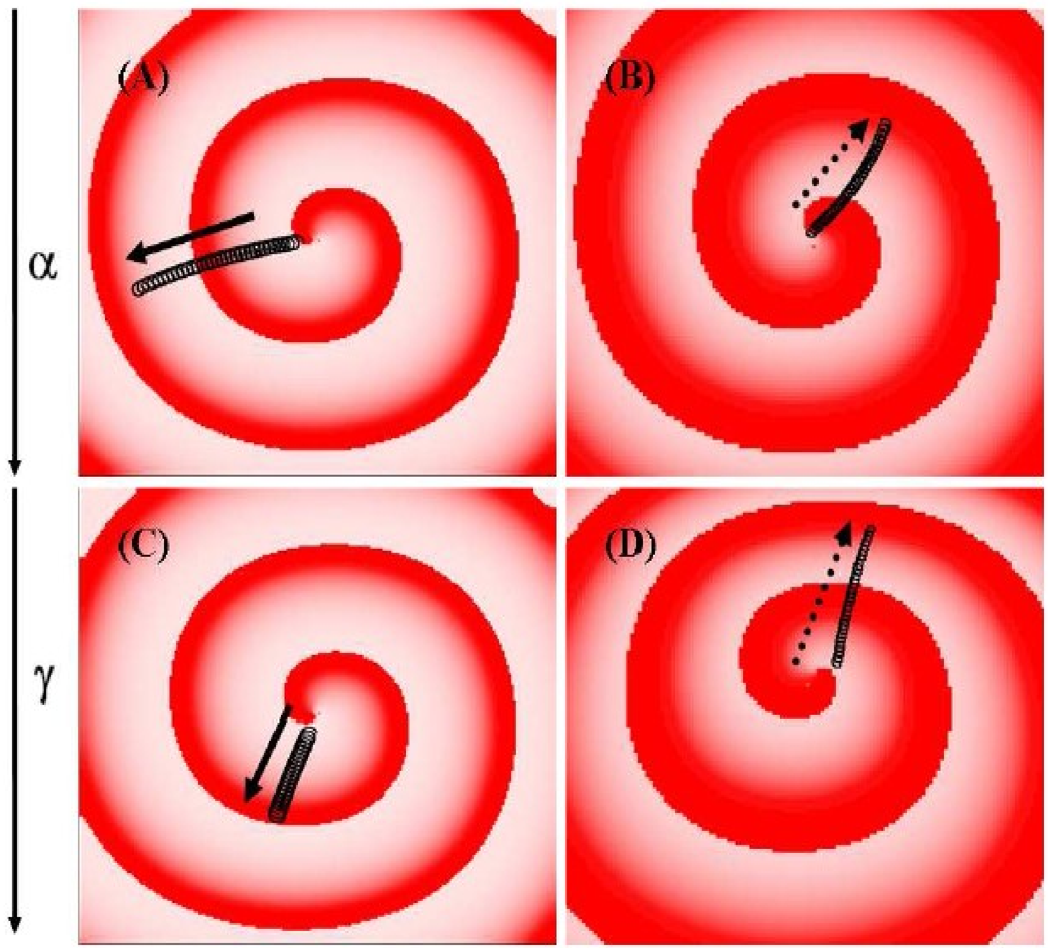
gradient in local excitation kinetics

Higher excitability

Lower excitability

gradient in cellular coupling

Higher excitability



S. Sridhar, SS and A V Panfilov, arXiv:0909.4398

Drift of spiral waves in presence of gradient

Implication of

Anomalous drift: to region of higher excitability or shorter period

The spiral gradually moves towards regions where the spiral wave rotates faster

However, far from the rotating core, in a low excitability region the medium cannot support such high frequency of activity $\Rightarrow$ break-up of wave far from spiral core

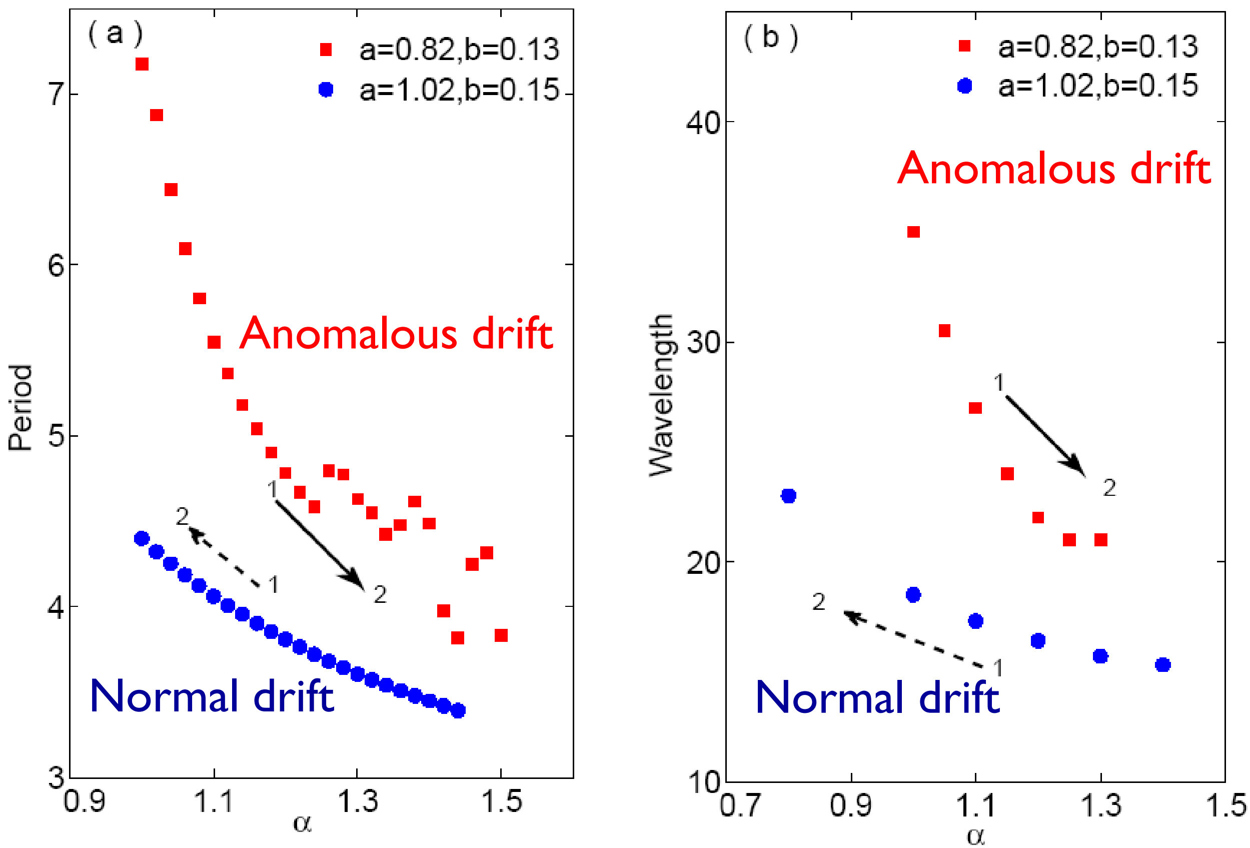
A plausible generative mechanism (?) for

Mother rotor fibrillation: a stationary persistent source of high-frequency excitations with wave-breaks far from the source, resulting in turbulent activity in the heart

Drift of spiral waves in presence of gradient

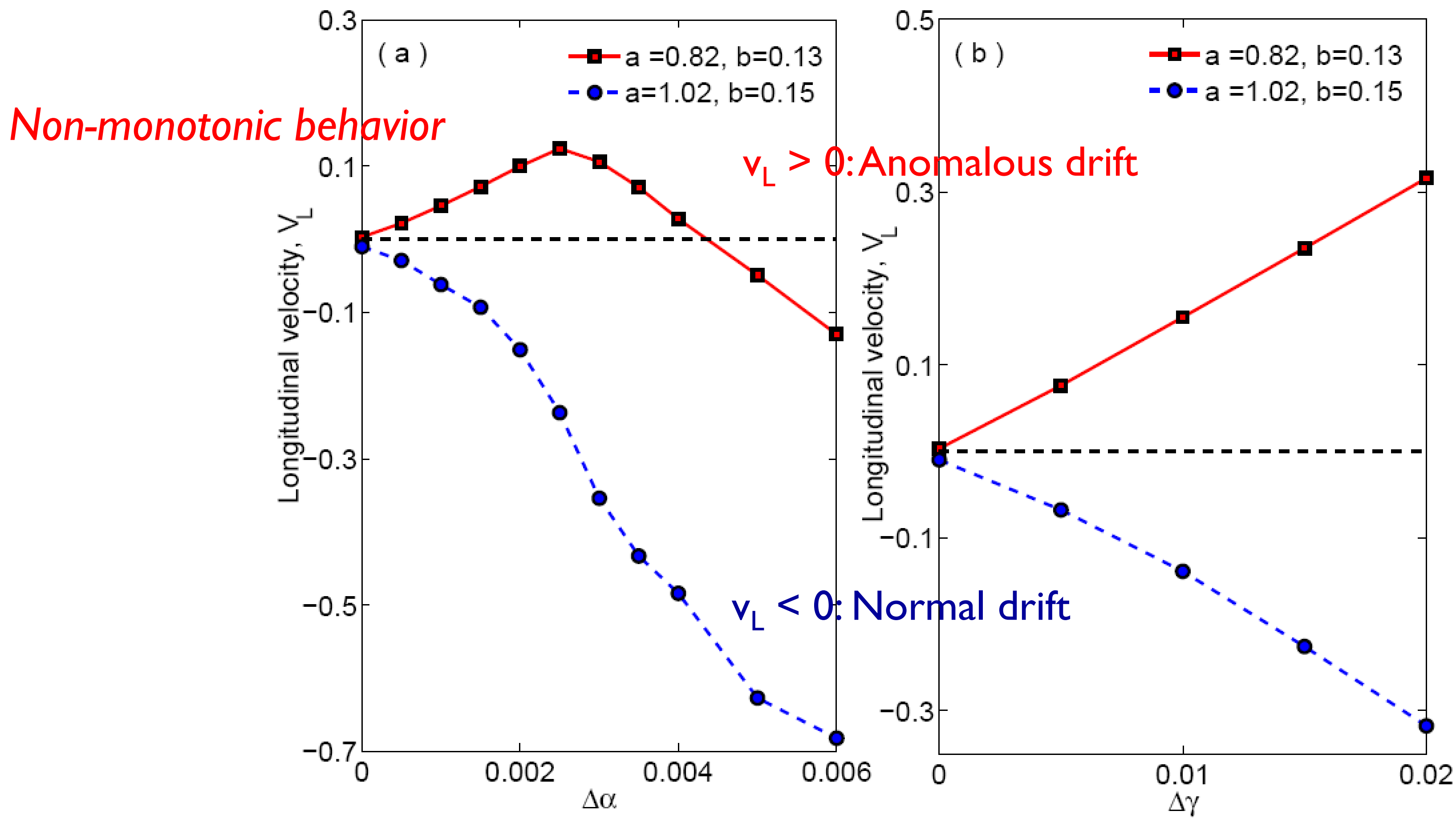
In homogeneous medium, γ only scales D: does not affect spiral period, while, spiral wavelength ~ $\sqrt{\gamma}$

But….how does the local excitation kinetics parameter α affect spiral wave dynamics in a homogeneous medium ?



Drift of spiral waves in presence of gradient

Effect of magnitude of spatial gradient on the longitudinal component of spiral drift velocity v_L, i.e., along the gradient



Drift of spiral waves in presence of gradient

Mechanism of anomalous drift

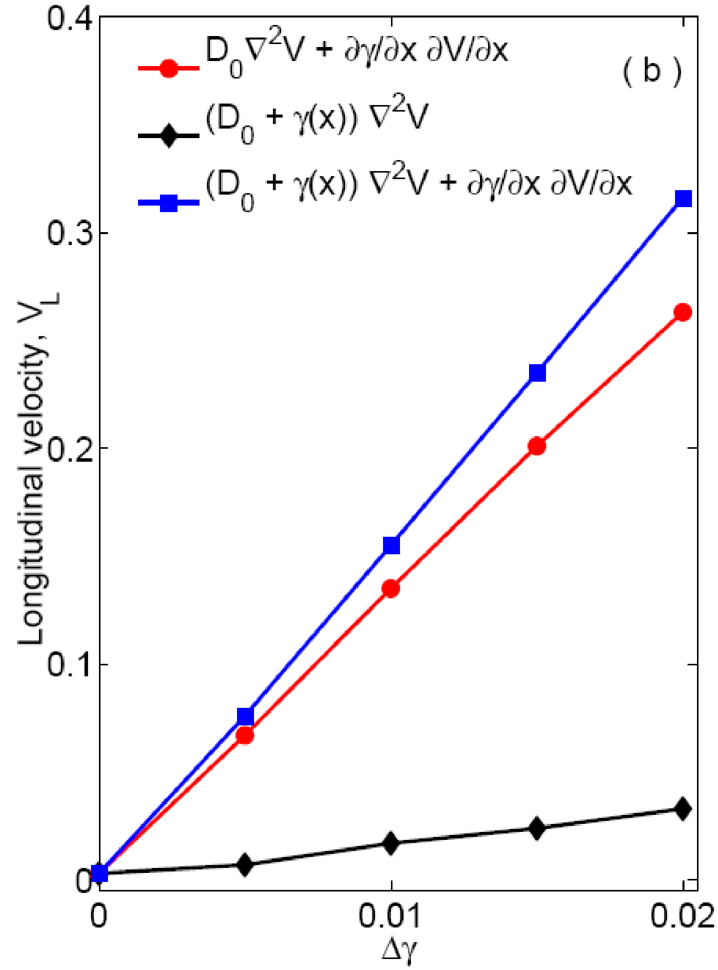
Expanding the Laplacian

$$\nabla\gamma(x)D\nabla V = (D_0 + \gamma(x))\nabla^2 V + \partial\gamma/\partial x\ \partial V/\partial x.$$

2nd order term   gradient term

Principal effect on v_L is due to gradient term

Similar to gradient term determining drift in presence of electric field and drift of scroll wave filaments in 3-dimensions $\Rightarrow$ Anomalous drift is a consequence of long-wavelength instabilities



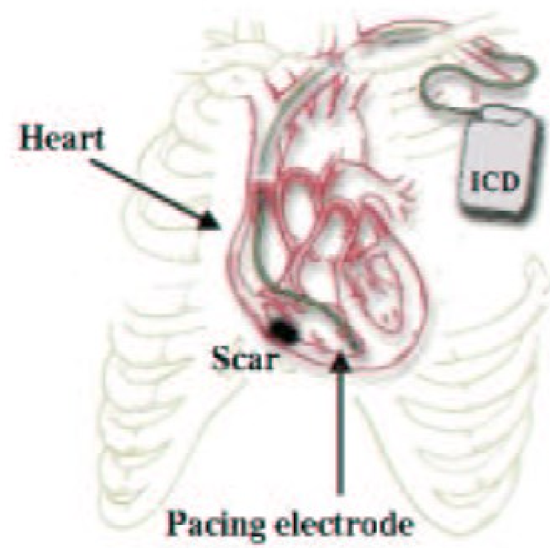
Scroll expansion (3-D) $\Leftrightarrow$ Anomalous drift (2-D)

If spiral wave is drifting $\Rightarrow$ driven to boundary and eventually disappears

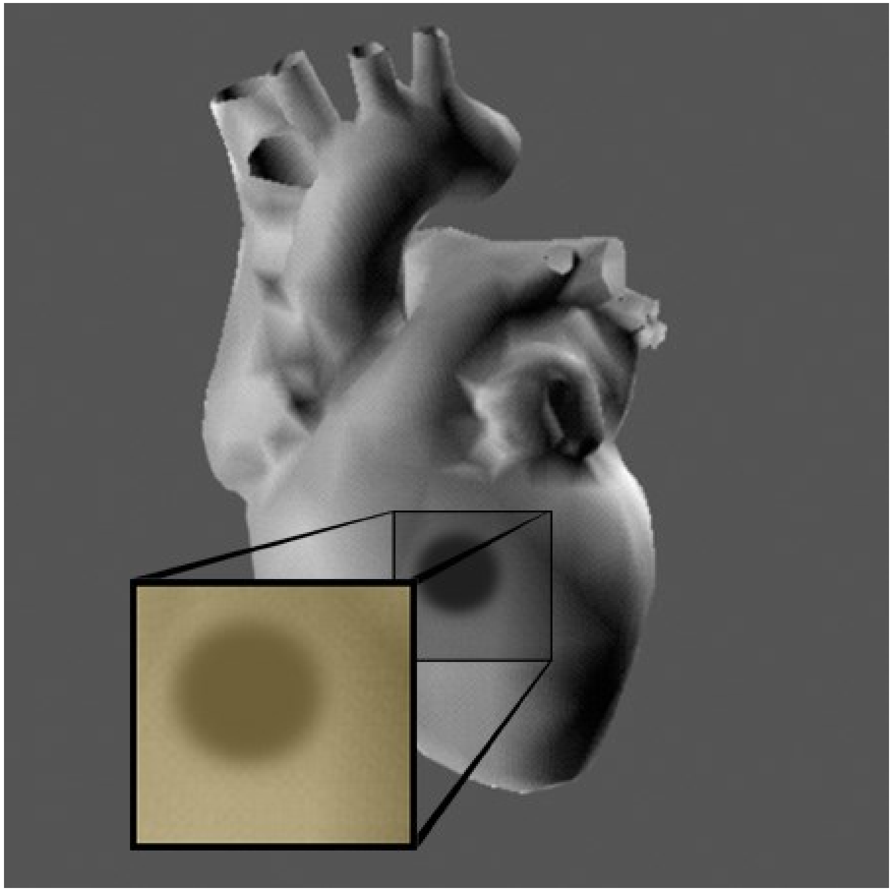
Not possible if spiral wave is rotating around (pinned to) an inexcitable obstacle !

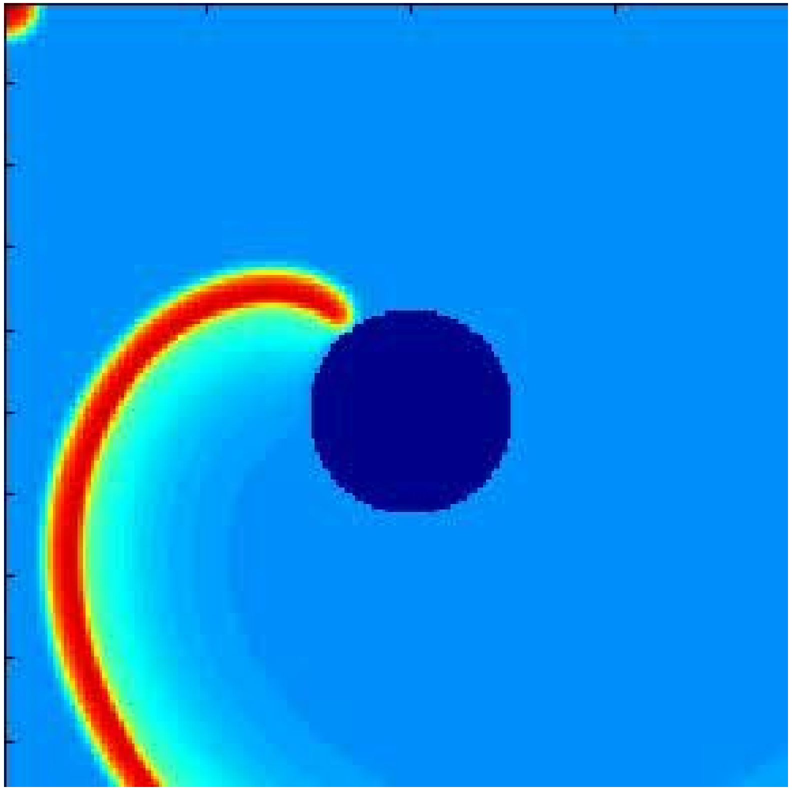
How to terminate persistent tachycardia by removing spiral waves pinned to inexcitable obstacles ?

Pacing from an Implantable Cardioverter-Defibrillator (ICD)



Termination by Rapid Pacing



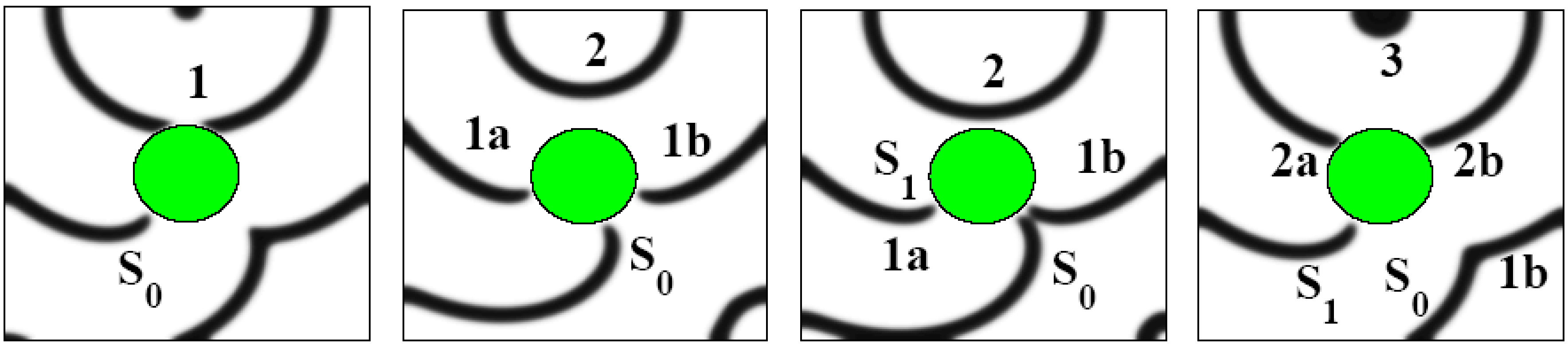


Pacing induced termination of pinned reentry

If spiral wave is drifting $\Rightarrow$ driven to boundary and eventually disappears

Not possible if spiral wave is rotating around (pinned to) an inexcitable obstacle !

A Pumir et al, PRE (2010)



$n^+ = 1$

$n^+ \to n^+ + 1$
$n^- \to n^- + 1$

$n^+ \to n^+ - 1$
$n^- \to n^- - 1$

$n^+ = 1$

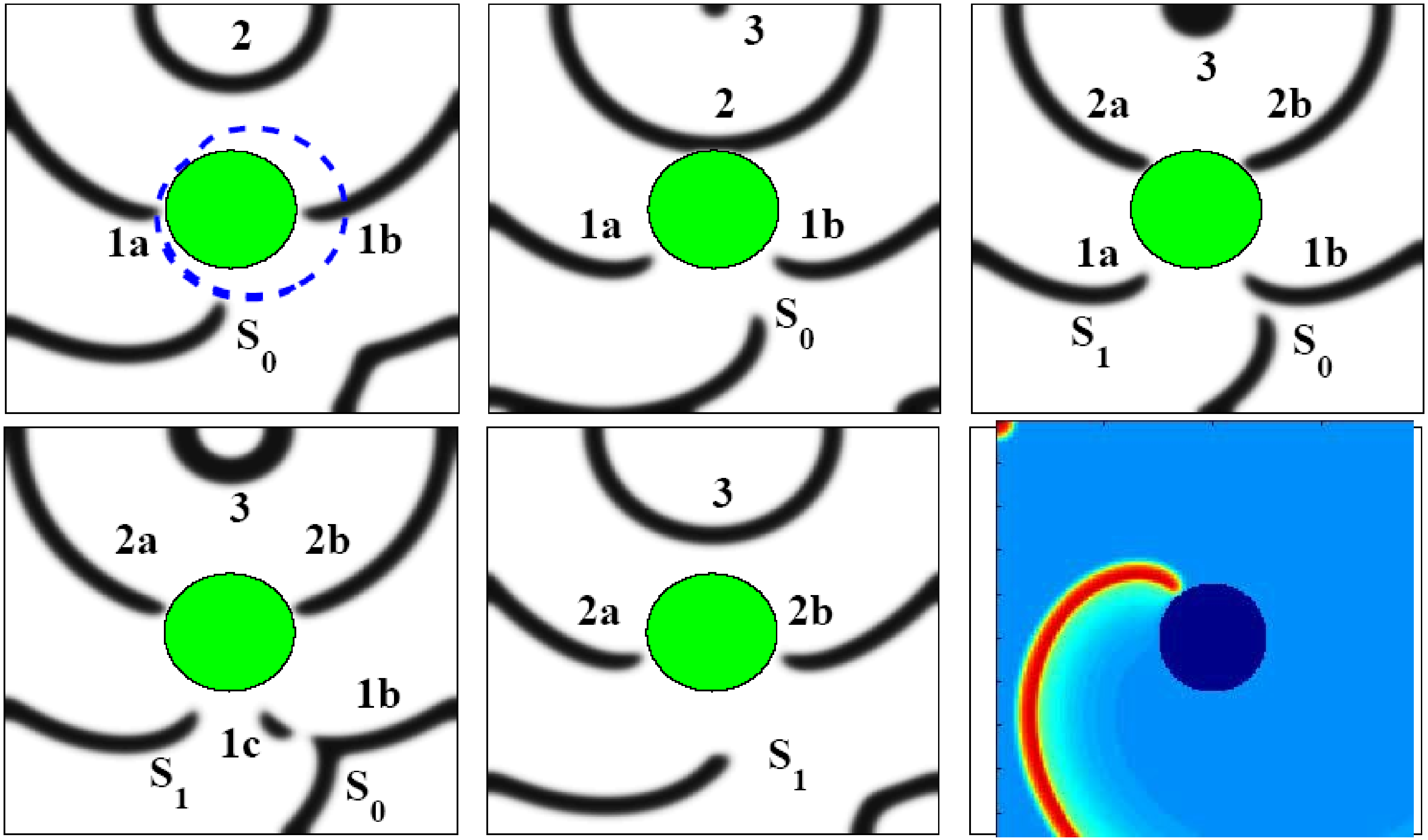
$n^+ \to n^+ + 1$
$n^- \to n^- + 1$

Can one unpin a wave rotating about a large inexcitable obstacle through rapid pacing ?

Classical result of Wiener & Rosenblueth (1946) seems to suggest "NO" based on assumption of *topological charge conservation* (i.e., the net number of counter-clockwise and clockwise rotating spirals, n^+-n^-, is constant)

But…

The WR argument is valid for vortex core < obstacle size

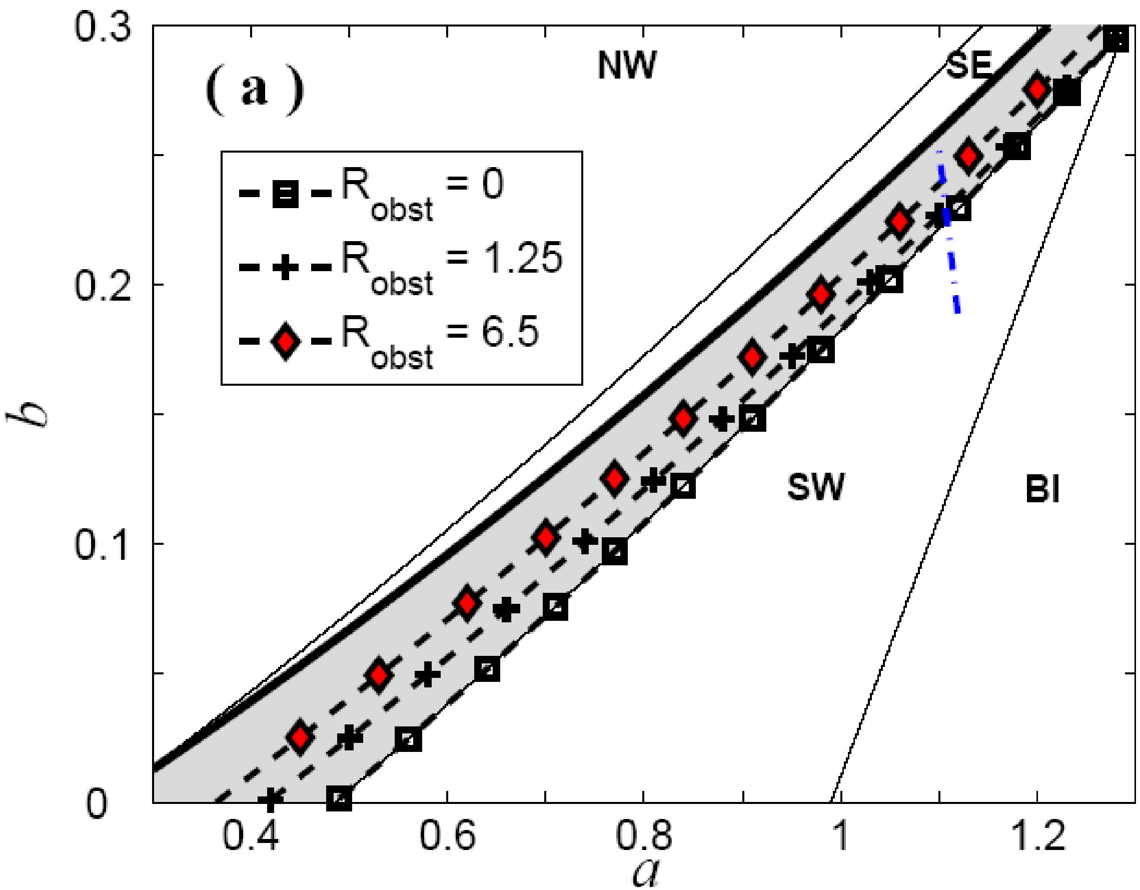


When *vortex core > obstacle (e.g., for lower excitability)*, spiral tip is <u>not</u> physically attached to the obstacle and can be unpinned by rapid pacing

The pacing-induced removal of pinned spiral waves is possible only when the medium is close to the sub-excitable regime

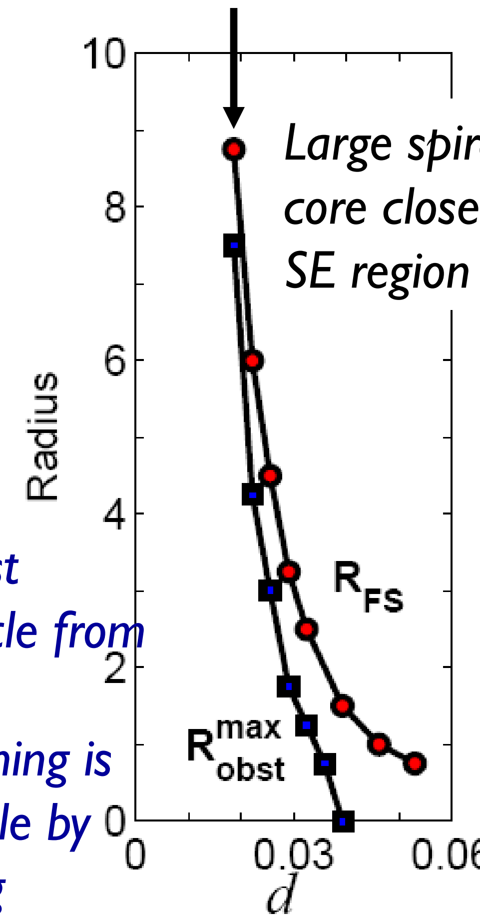
Barkley model:

$$\begin{aligned}\partial_t u &= \frac{1}{\epsilon} u(1-u)[u-(v+\frac{b}{a})] + \nabla^2 u,\\ \partial_t v &= (u-v),\end{aligned}$$

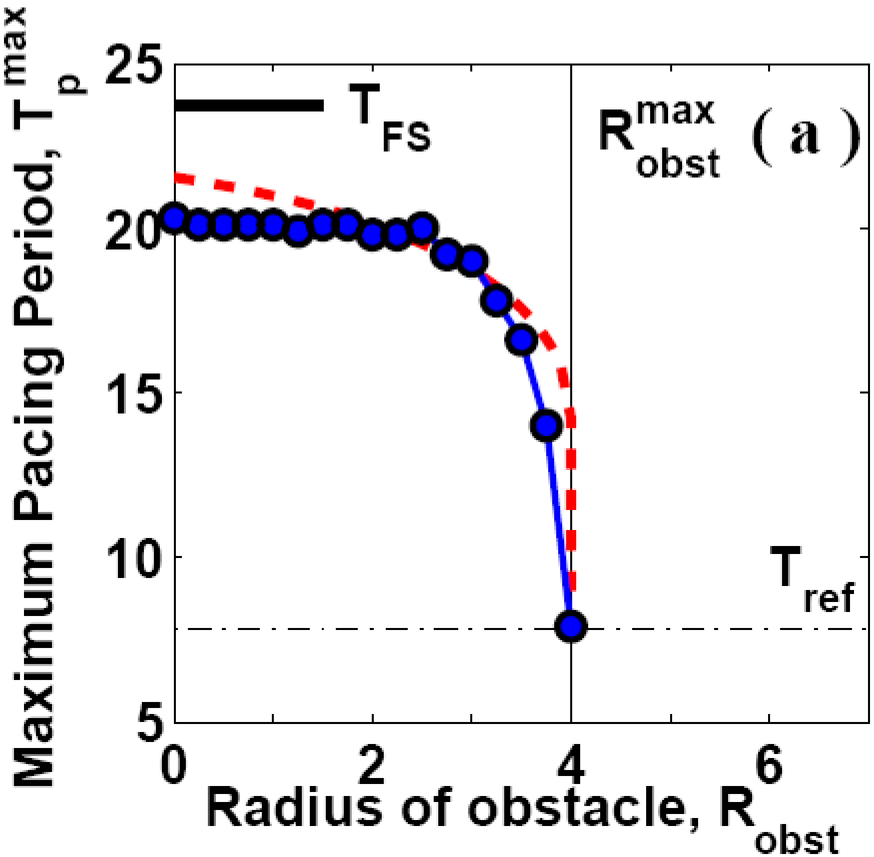


Largest obstacle from which unpinning is possible by pacing

divergence



Large spiral core close to SE region

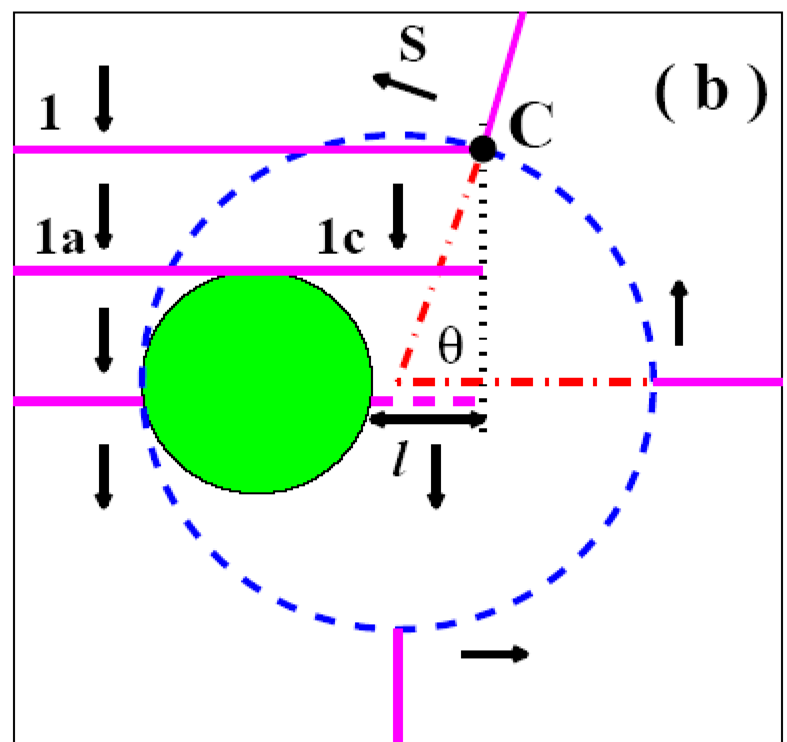


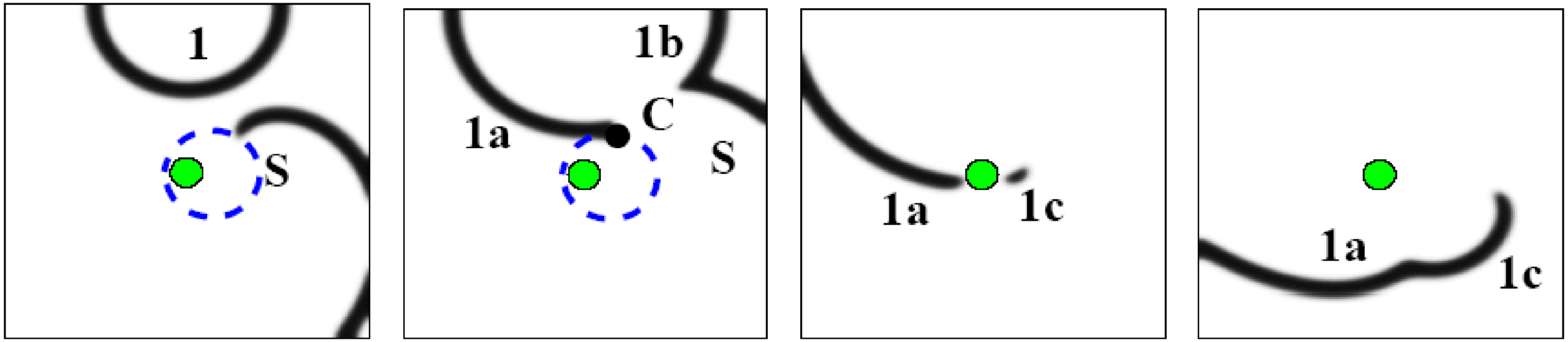
Thus, pacing can unpin only when obstacle smaller than core radius of free spiral

Maximum pacing period necessary for detaching a pinned spiral from an obstacle is a decreasing function of the obstacle size

Can be explained semi-quantitatively by a geometric argument – valid when obstacle size < spiral core

θ: angle made by C (point of collision of spiral and pacing wave) with symmetry axis (joining center of obstacle and spiral core)





The maximum pacing period leading to detachment of spiral from the obstacle is:

$$T_p^{max} = \frac{R_{FS}}{v}(\sin\theta_c - f_R) + \frac{f_R T_{FS}}{4} + \frac{T_{FS}(\theta_c + \pi)}{2\pi}$$

$$\theta_c = \arccos(2f_R - 1 + [l_n/R_{FS}])$$

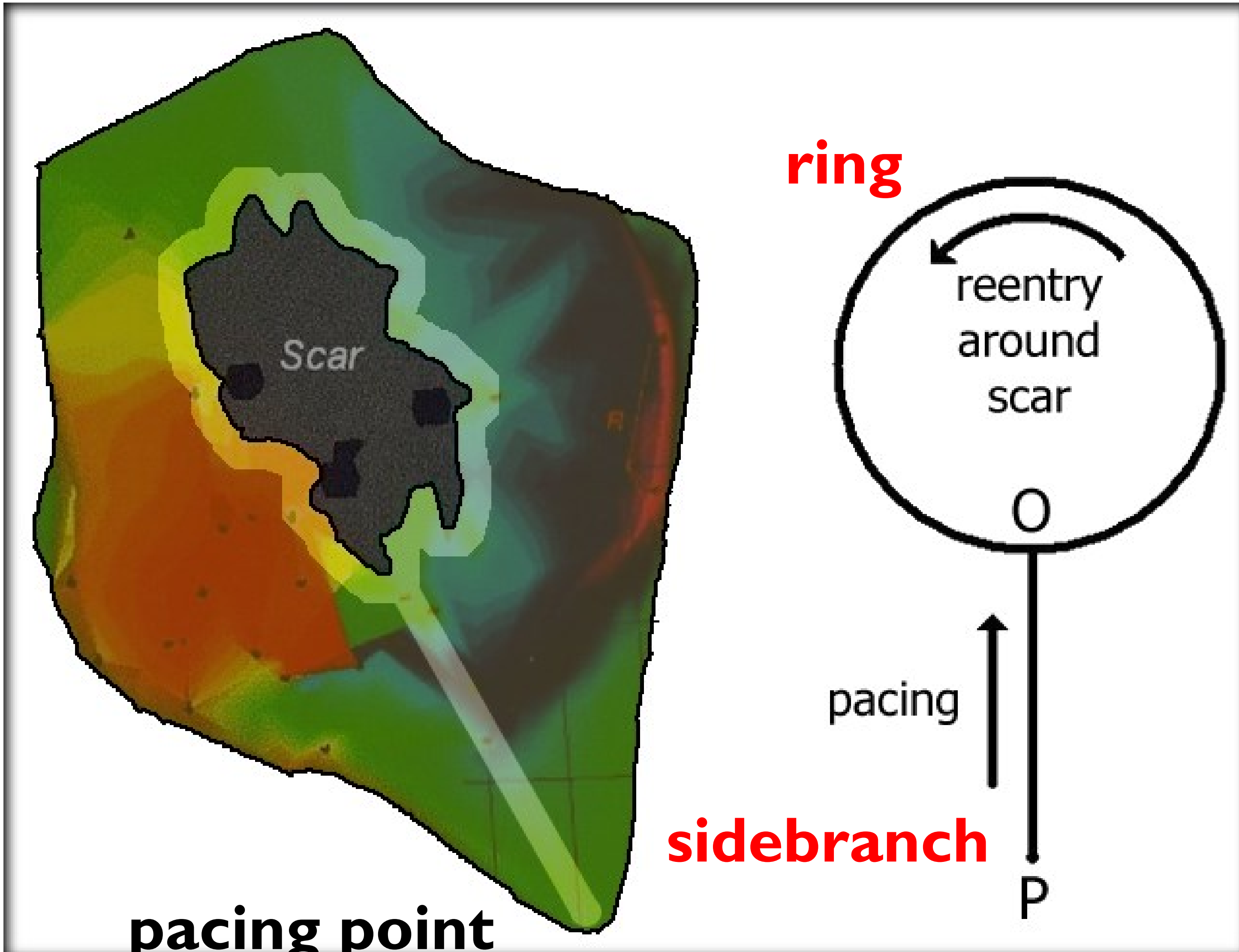
$f_R = R_{obst}/R_{FS}$

l_n is the nucleation length, the size below which a wave fragment shrinks and disappears

When $R_{obst} > R_{obst}^{max} = R_{FS} - (l_n/2)$, T_p^{max} has complex values

$\Rightarrow$ fragment too small to survive when obstacle is larger than a critical value

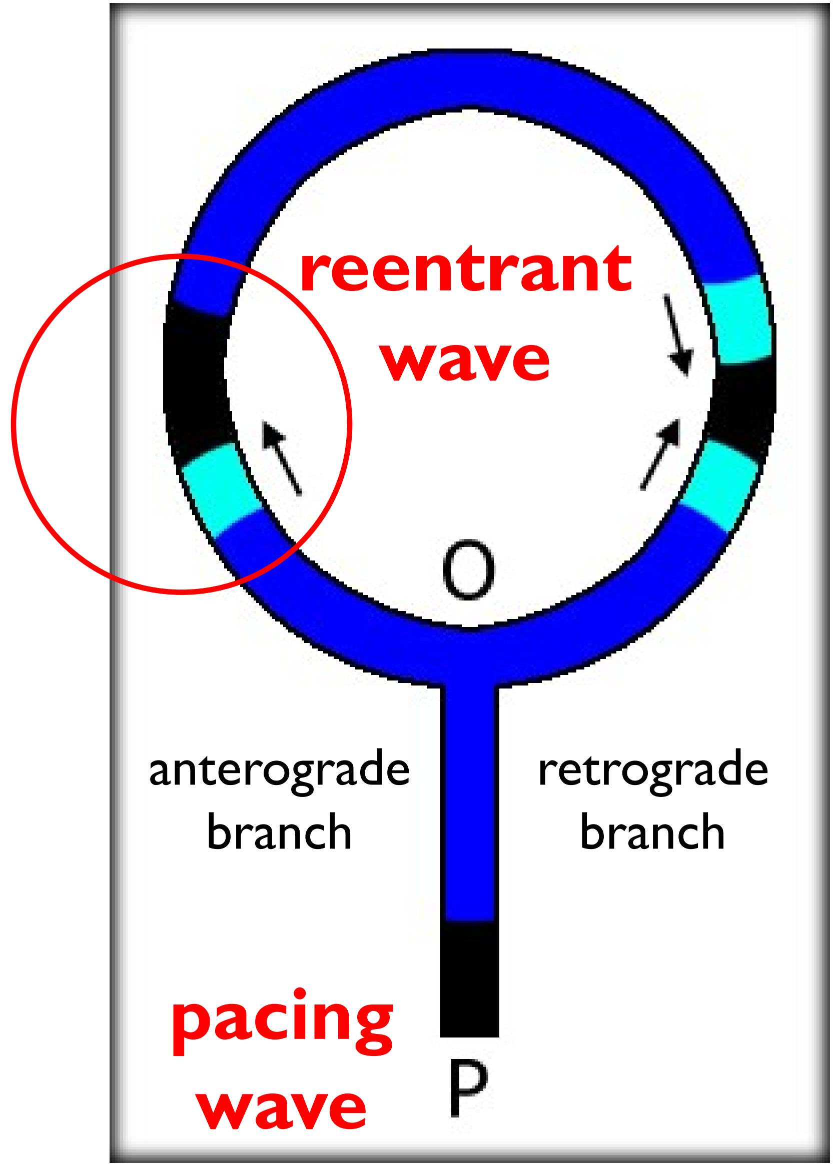
Reentry in a one dimensional ring



Effect of pacing on the reentry

Reentrant wave and pacing wave collide in sidebranch

Anterograde branch forms new reentrant wave



Termination of reentry not possible?

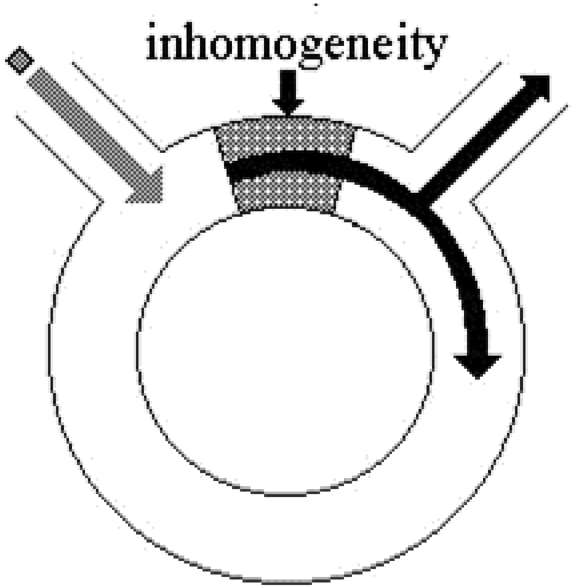
Interaction between wave front and wave back

Termination of reentry occurs by *conduction block in the anterograde branch*

The Critical Role of Disorder

Termination of reentry occurs by
conduction block in the anterograde branch

...requires inhomogeneity in the reentry circuit !



If inhomogeneity exists in circuit waves travel faster or slower depending on location in the circuit.

So, stimulus may encounter a region that is still refractory.

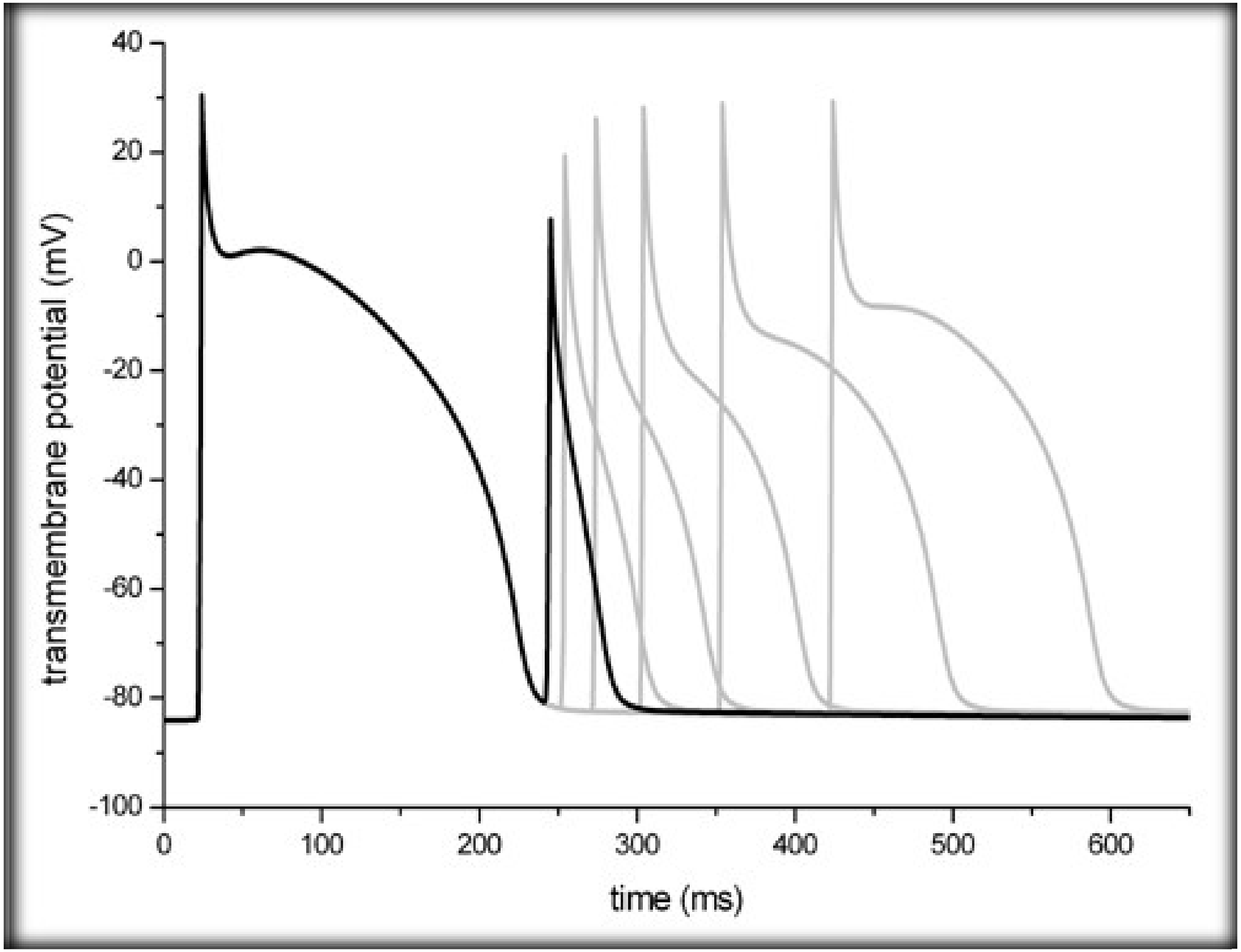
Leads to block of the anterograde branch of the stimulus $\Rightarrow$ *successful termination.*

S S & D J Christini, *PRE* 66 (2002) 061903
SS, K M Stein & D J Christini, *Chaos* 12 (2002) 893

However…

… the nonlinear dynamics of wave propagation in cardiac tissue can spontaneously generate disorder even in a homogeneous medium

The restitution effect

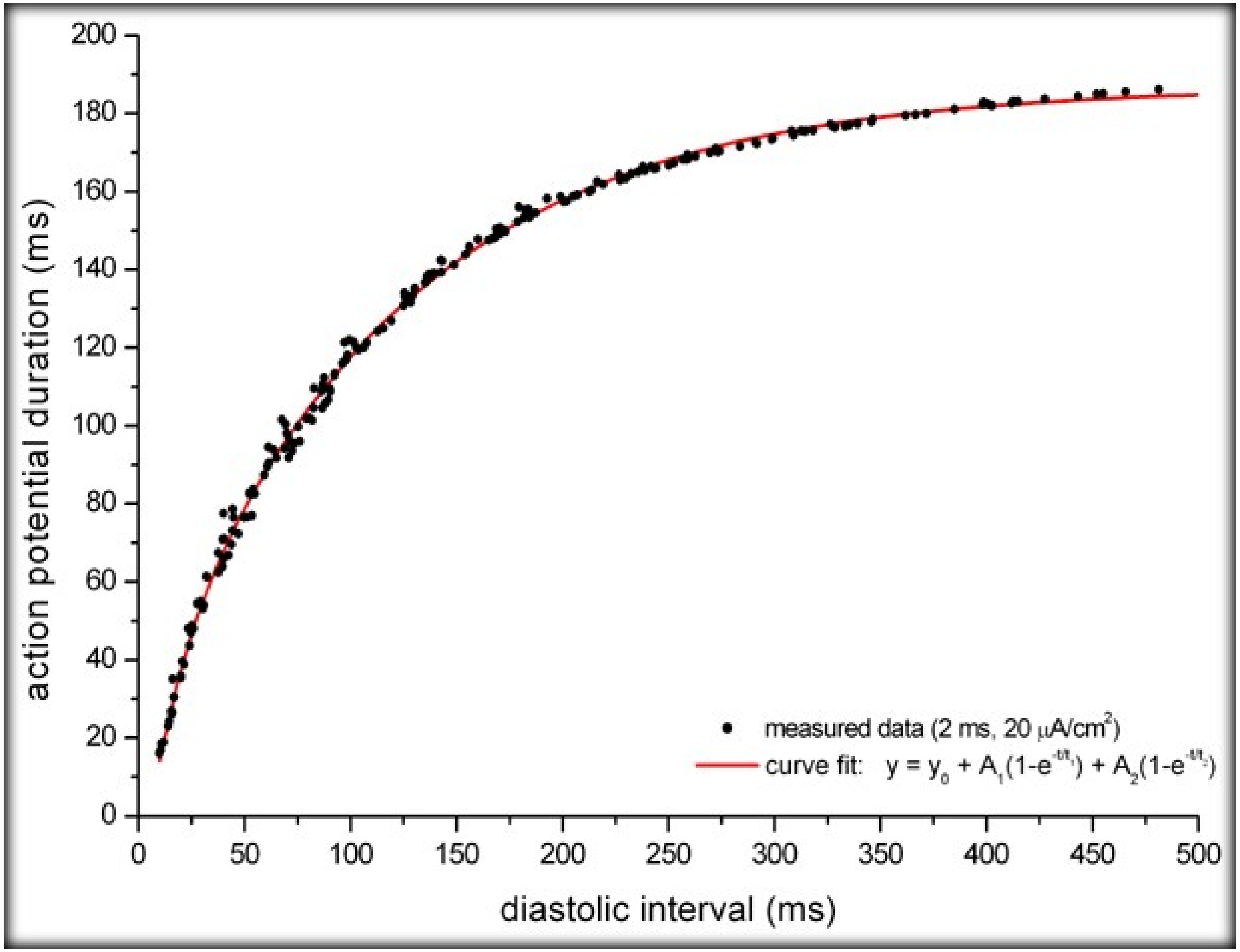


restitution in Luo-Rudy Model

APD is dependent on preceding DI

No excitation if DI below a critical value

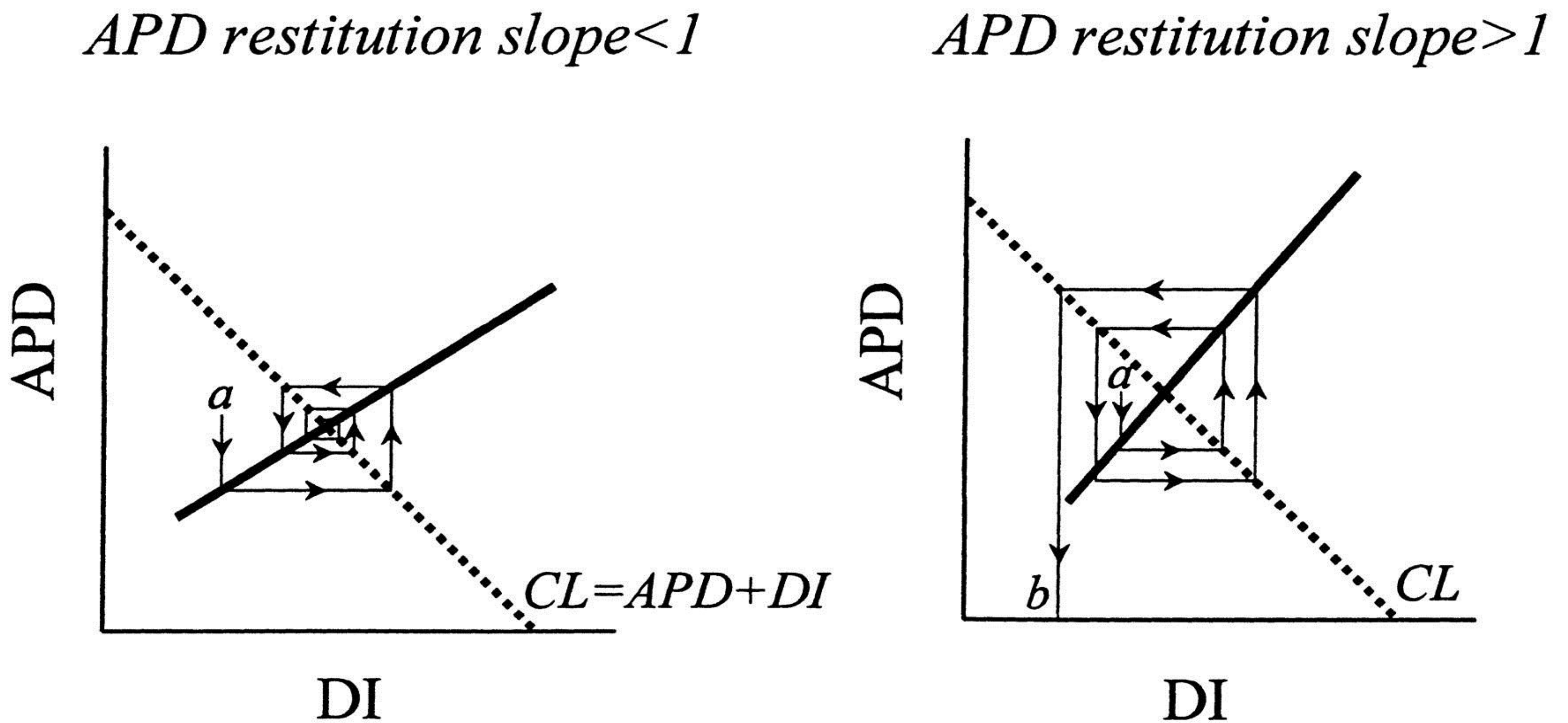
The restitution function



restitution curve in Luo-Rudy Model

$$APD_{n+1} = f\,(DI_n)$$

Alternans



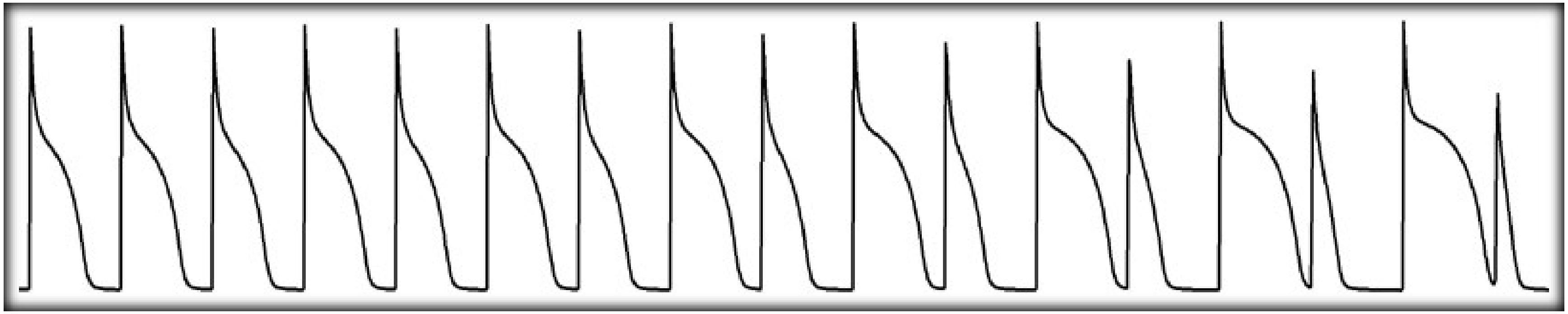
slope depends on CL

Nolasco & Dahlen (1968):

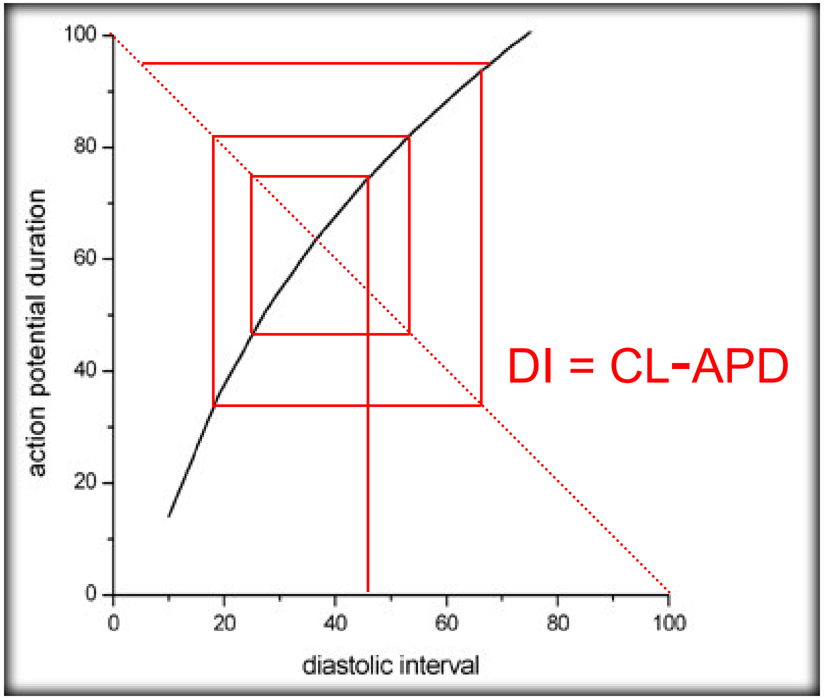
Steepness of the restitution curve → arrhythmia

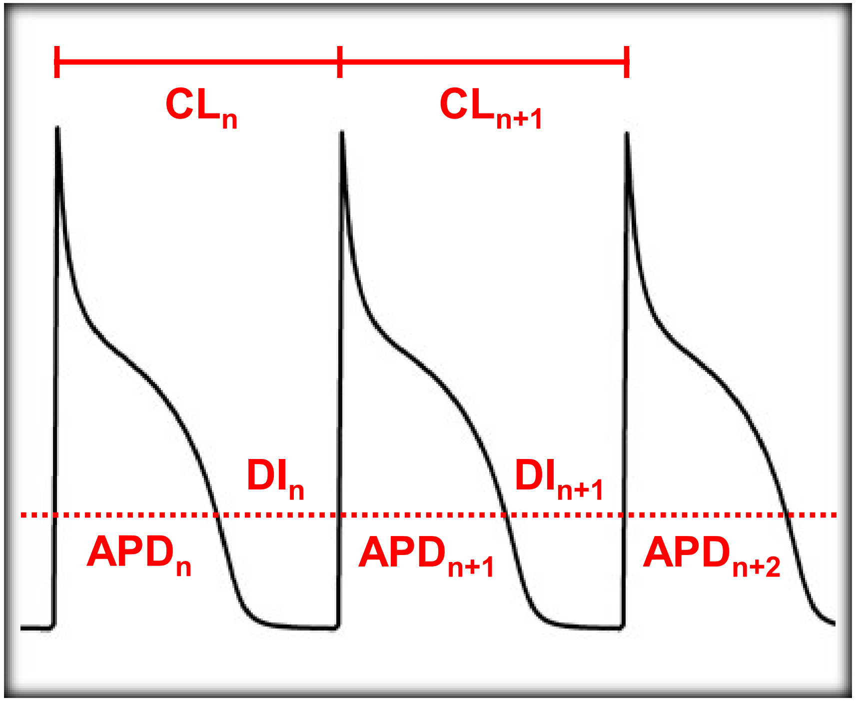
Alternans

- pacing with constant ***cycle length***

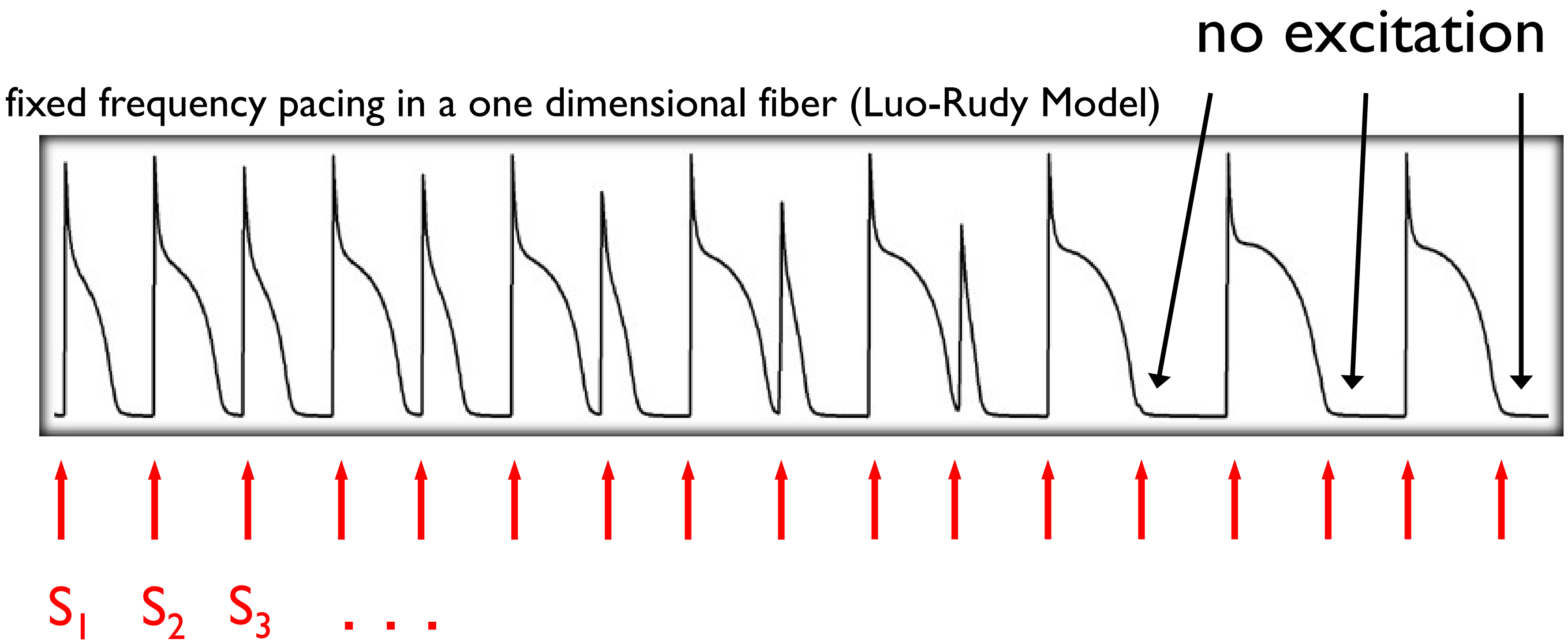


fixed frequency pacing in a one dimensional fiber (Luo-Rudy Model)

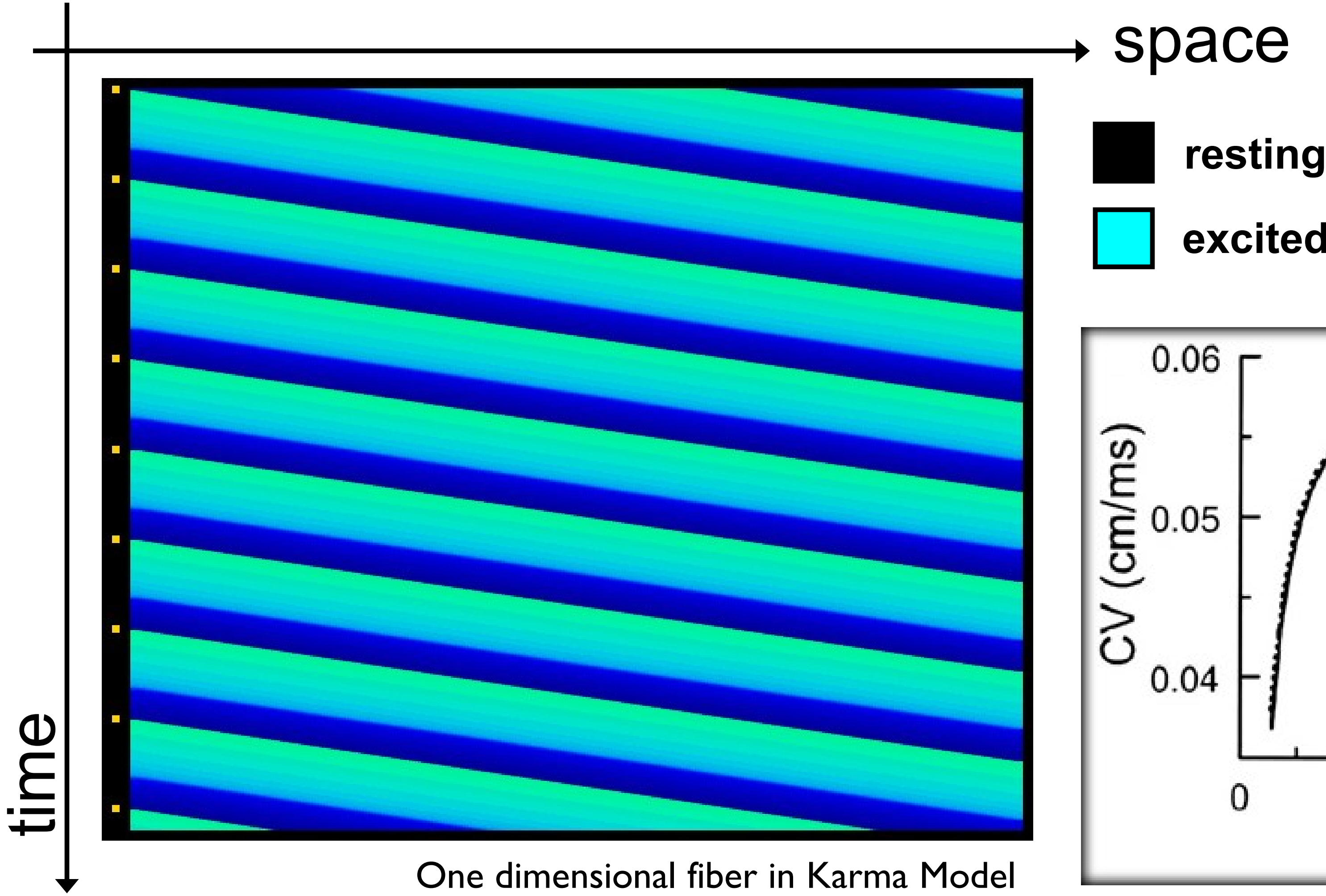




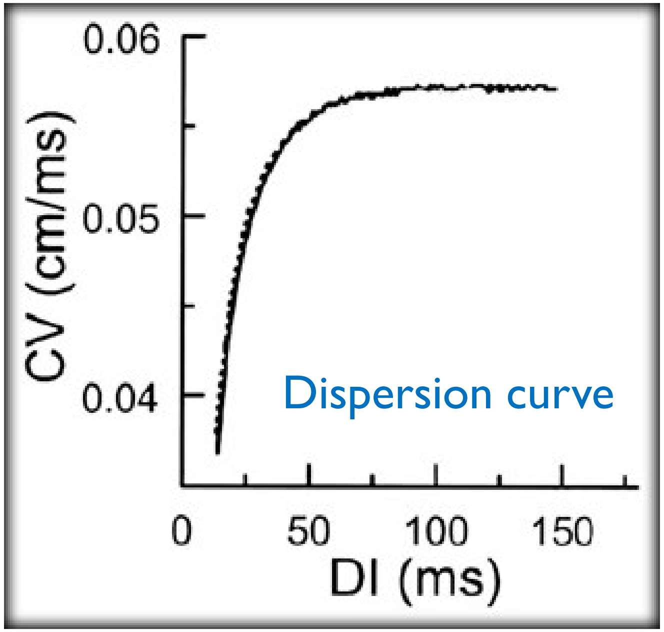
Conduction block after alternans



Wave propagation in 1-dimensional fiber



One dimensional fiber in Karma Model



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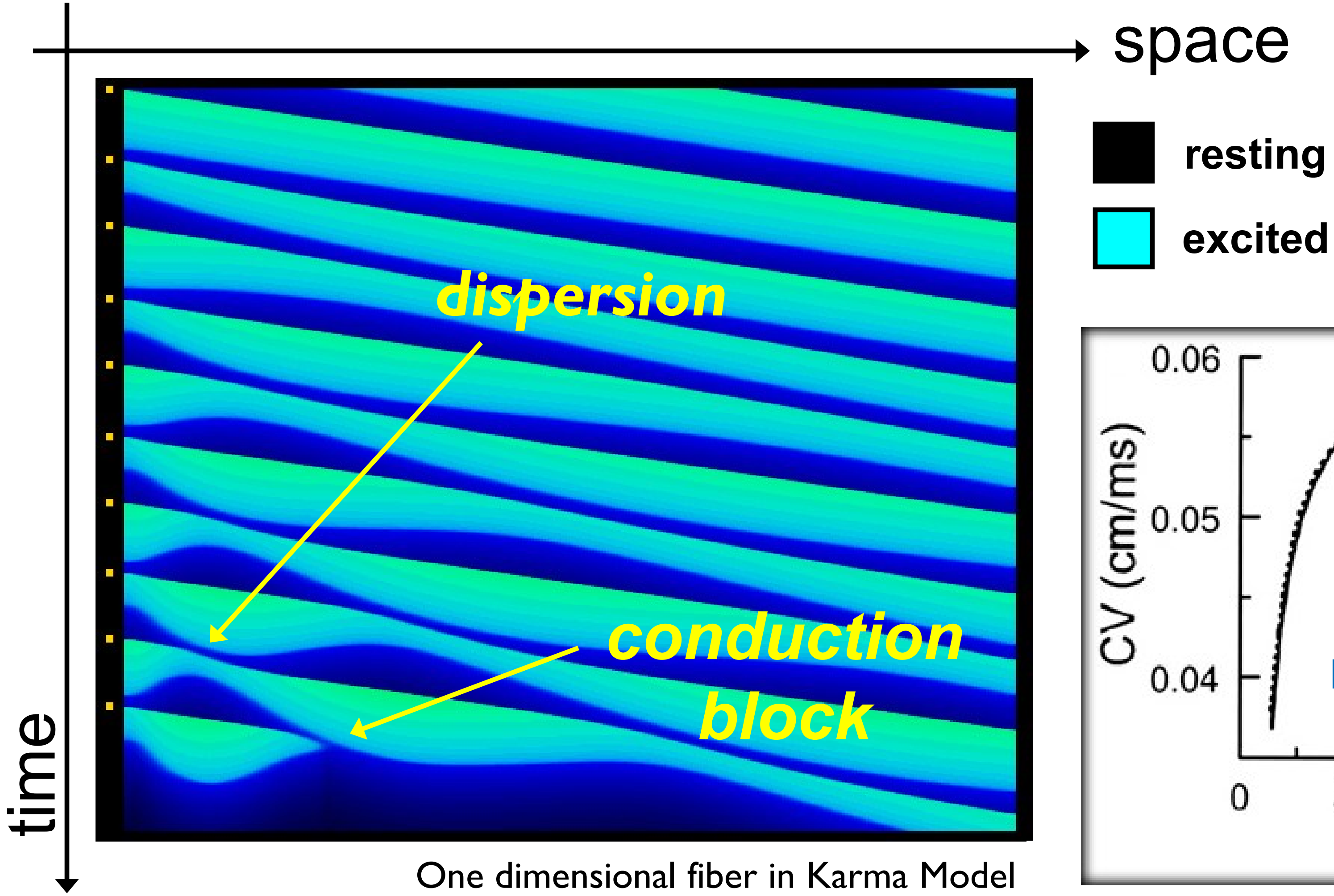

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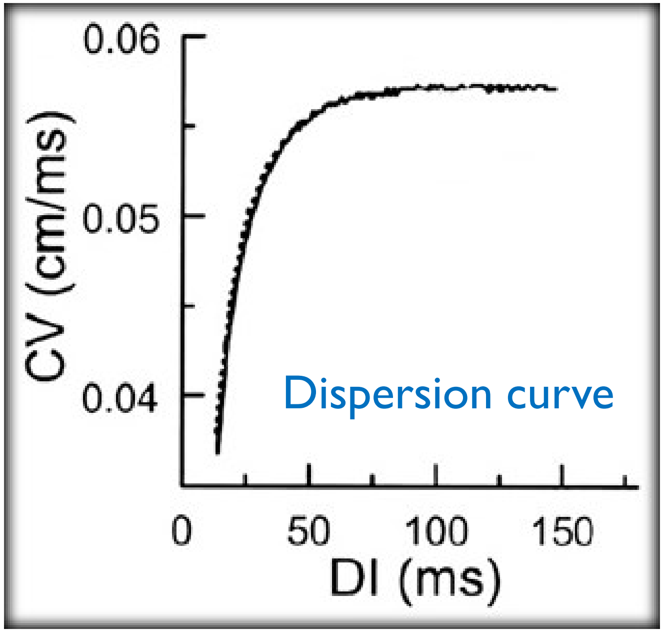
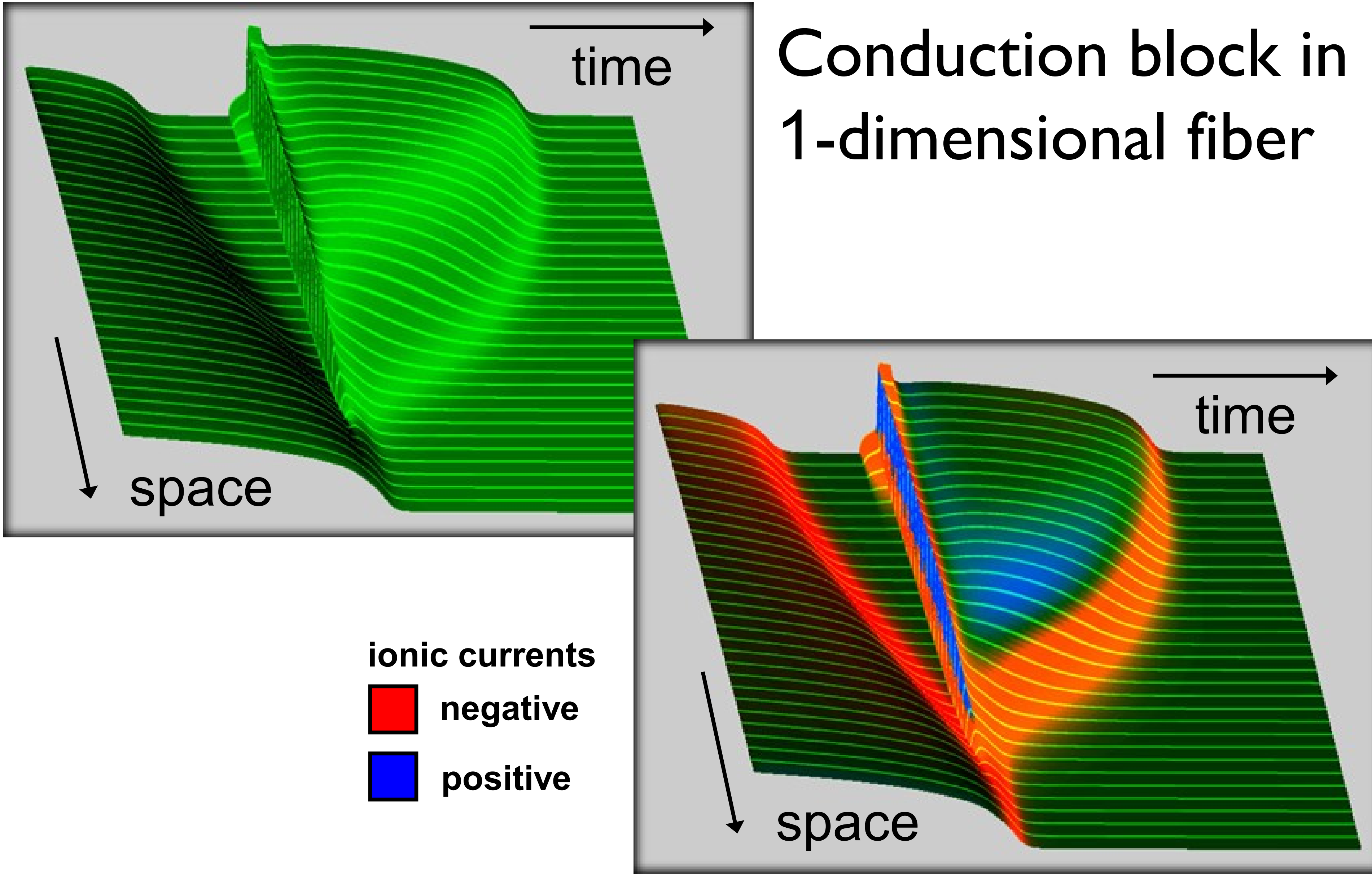


- Decreasing the cycle length leads to modulation of the APD and can lead to ***conduction block***

Conduction block in 1-dimensional fiber



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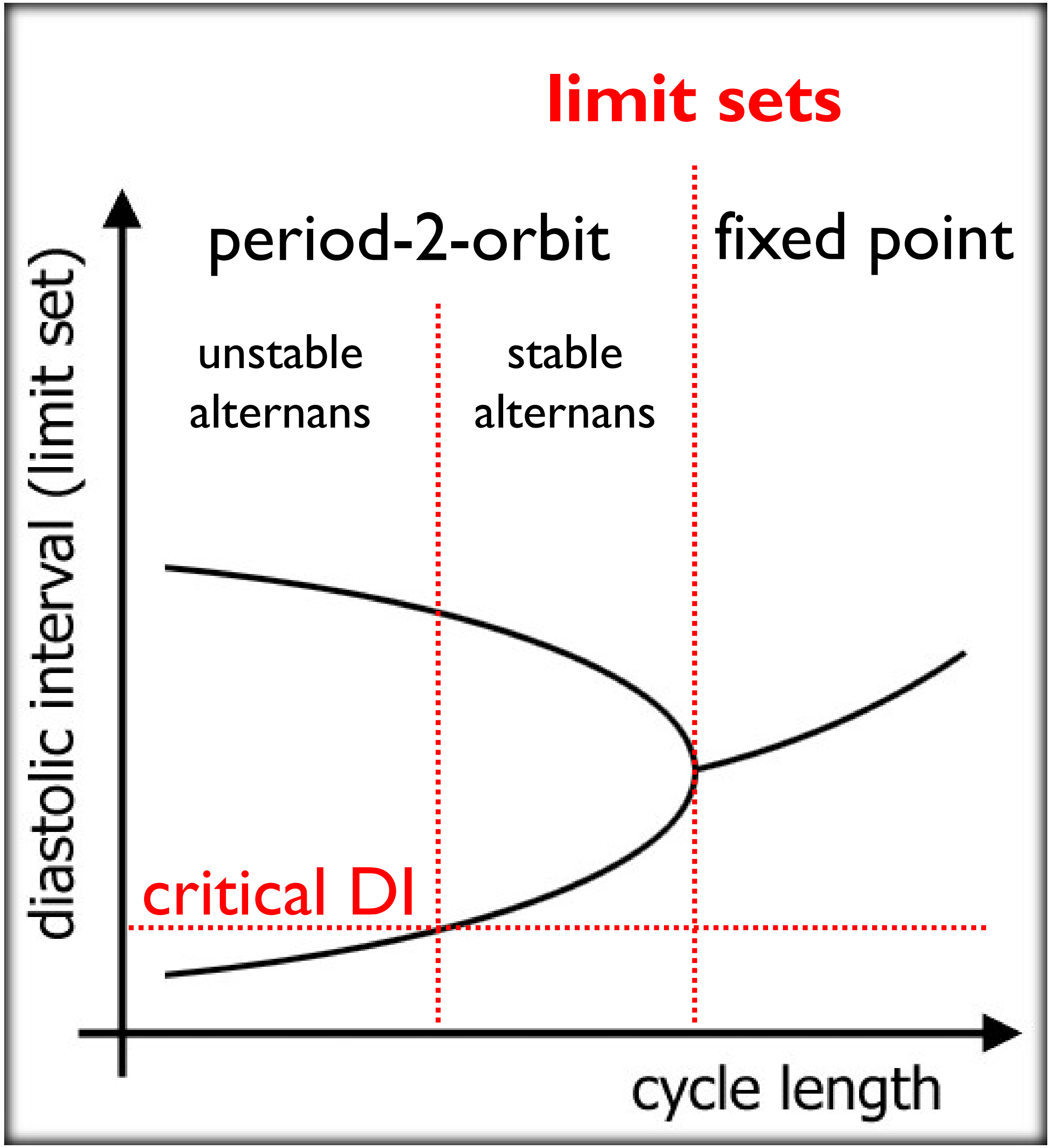
Bifurcation

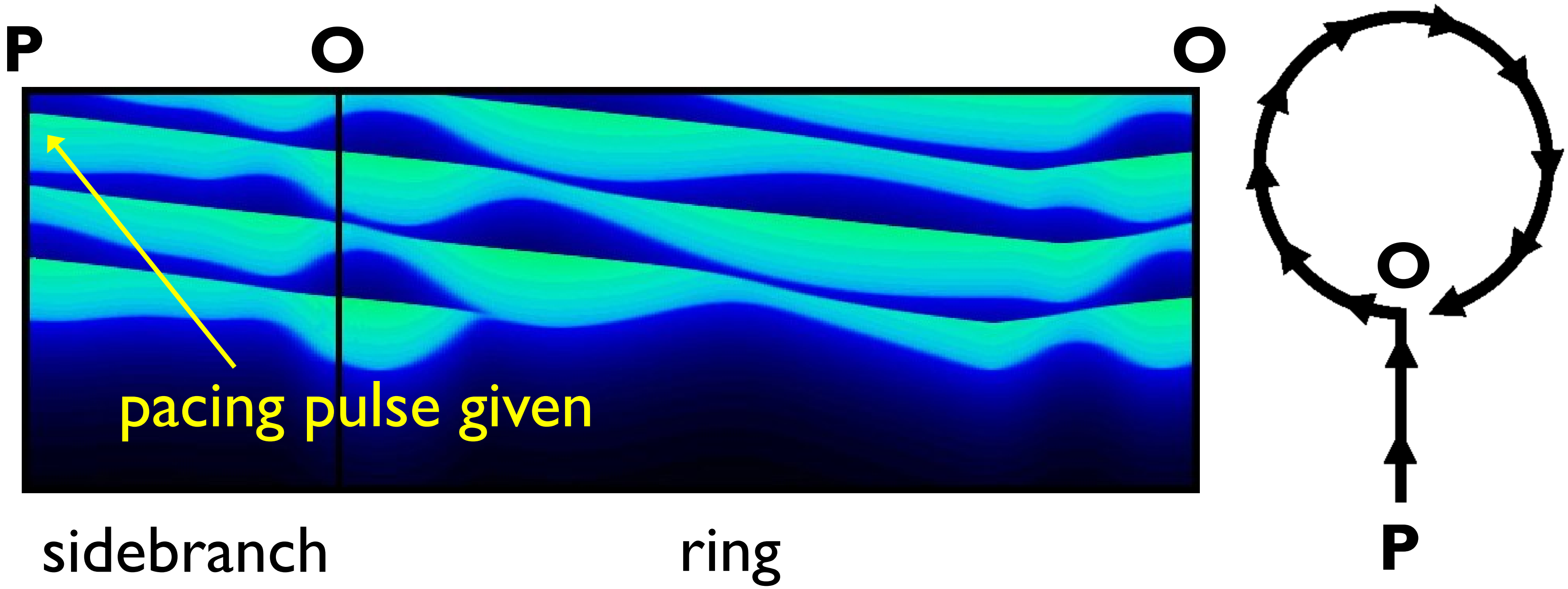


What does that mean for termination of VT?

Cycle length in ring is determined by its size

Pacing decreases the cycle length and creates or enlarges modulations around the ring

If conduction block occurs in the ring (not in the sidebranch) ***VT*** is stopped



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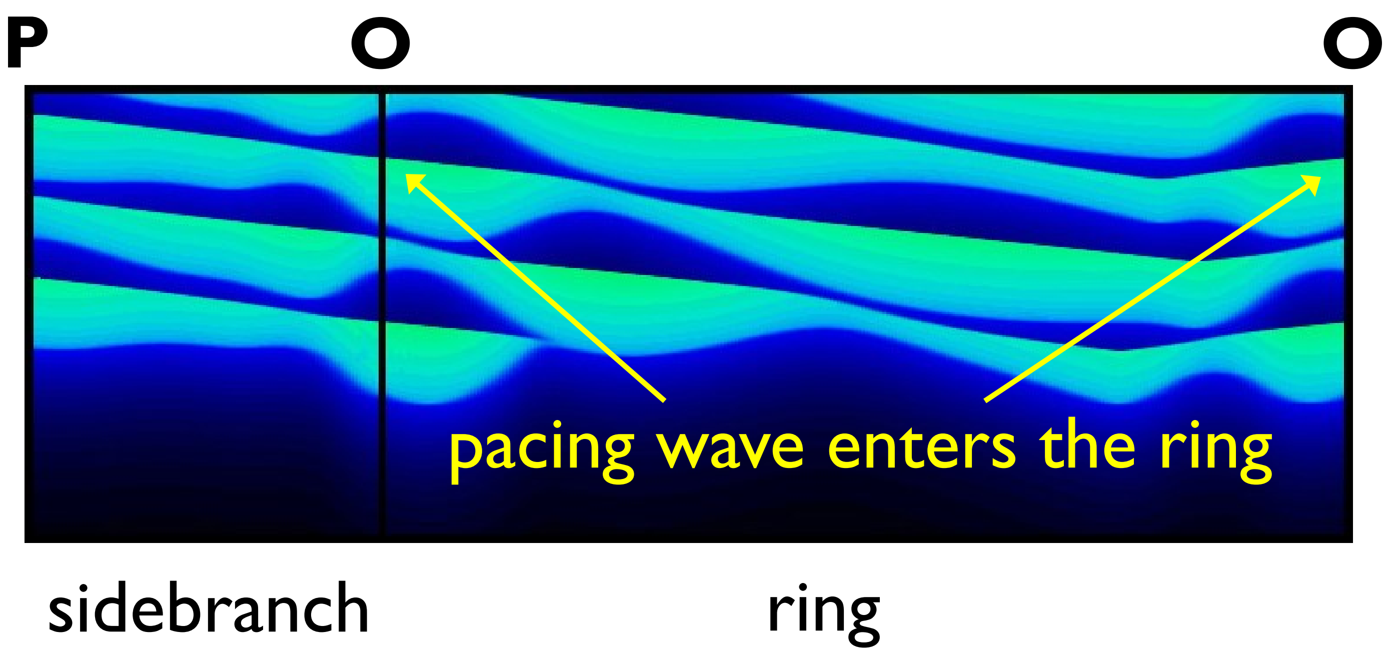

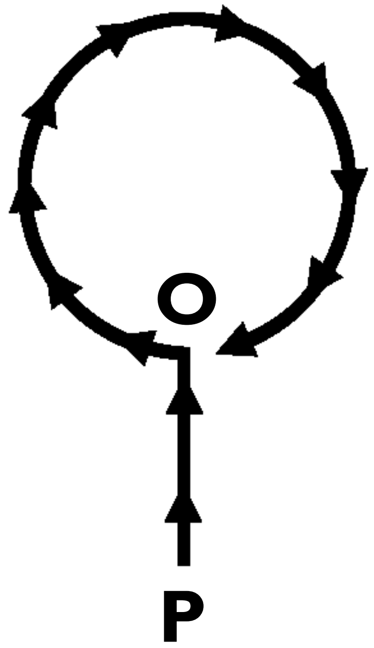

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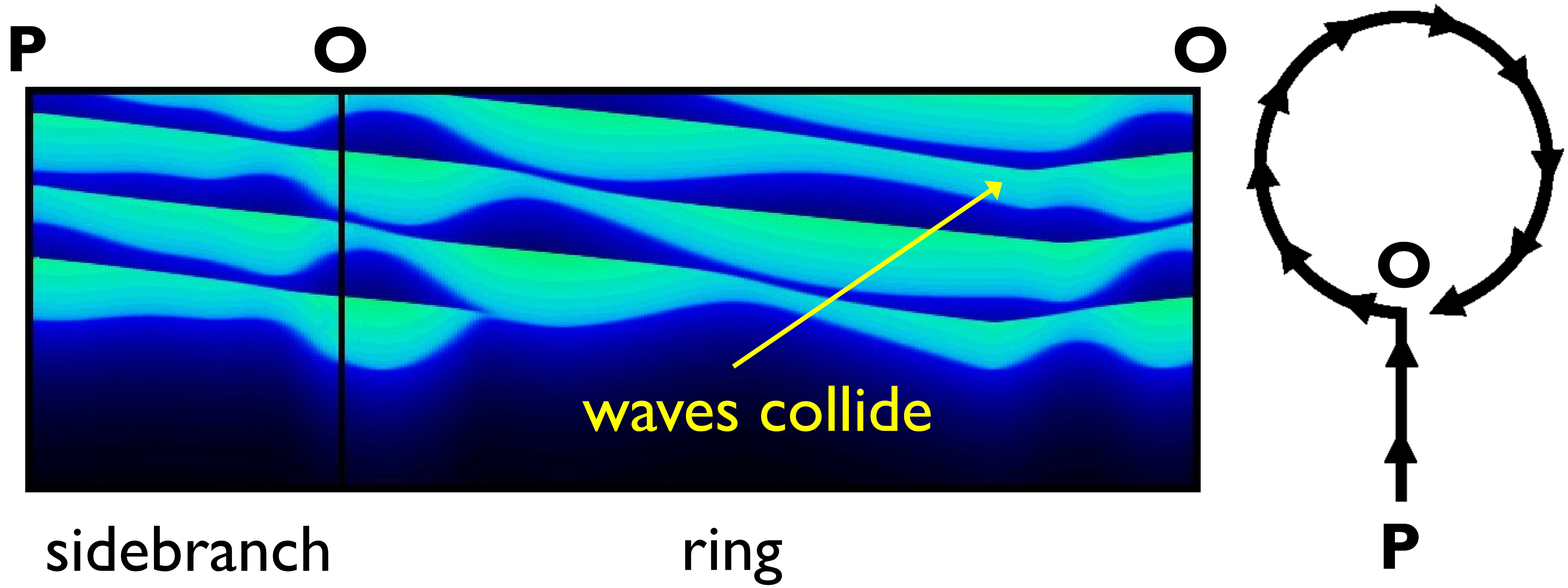

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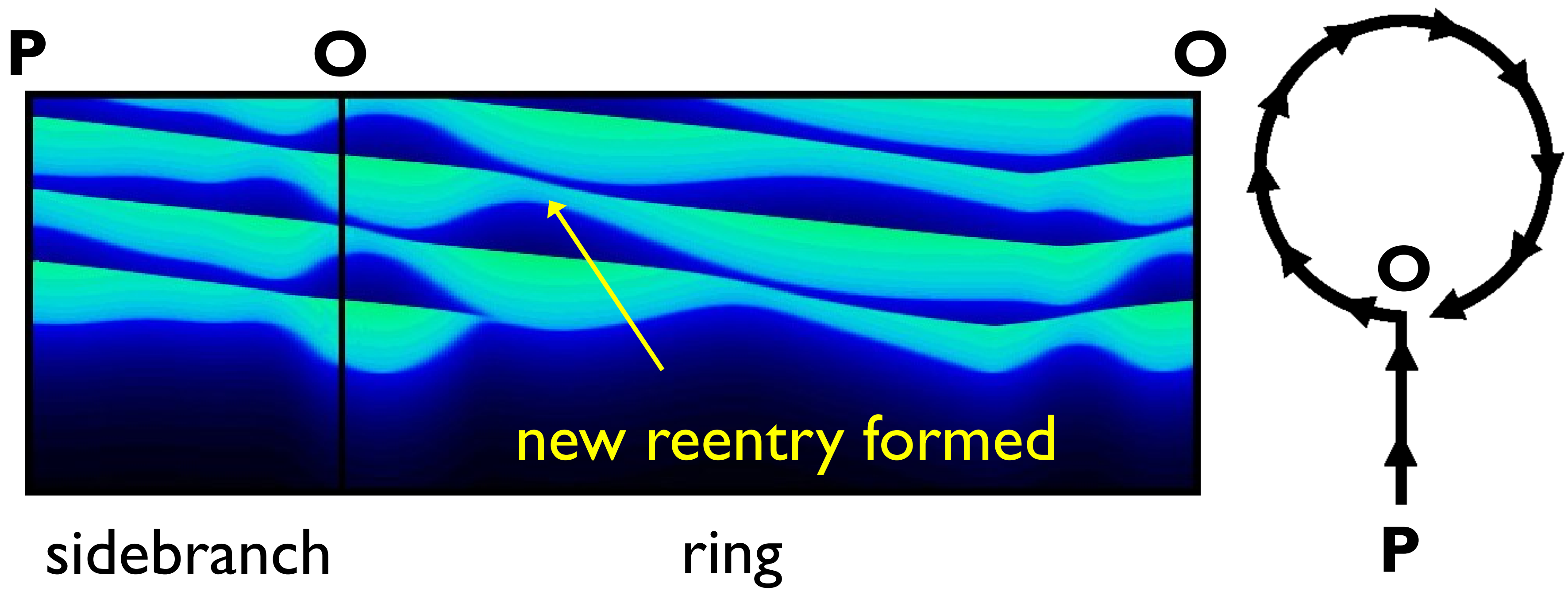

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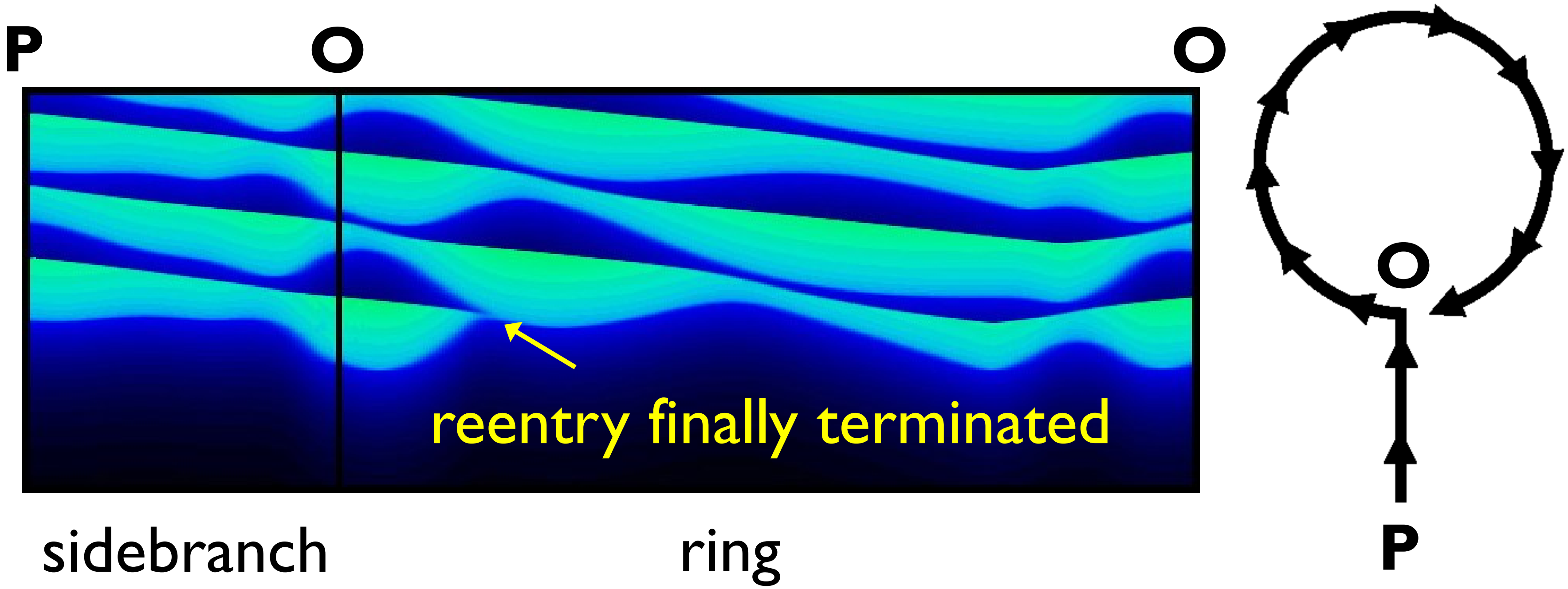
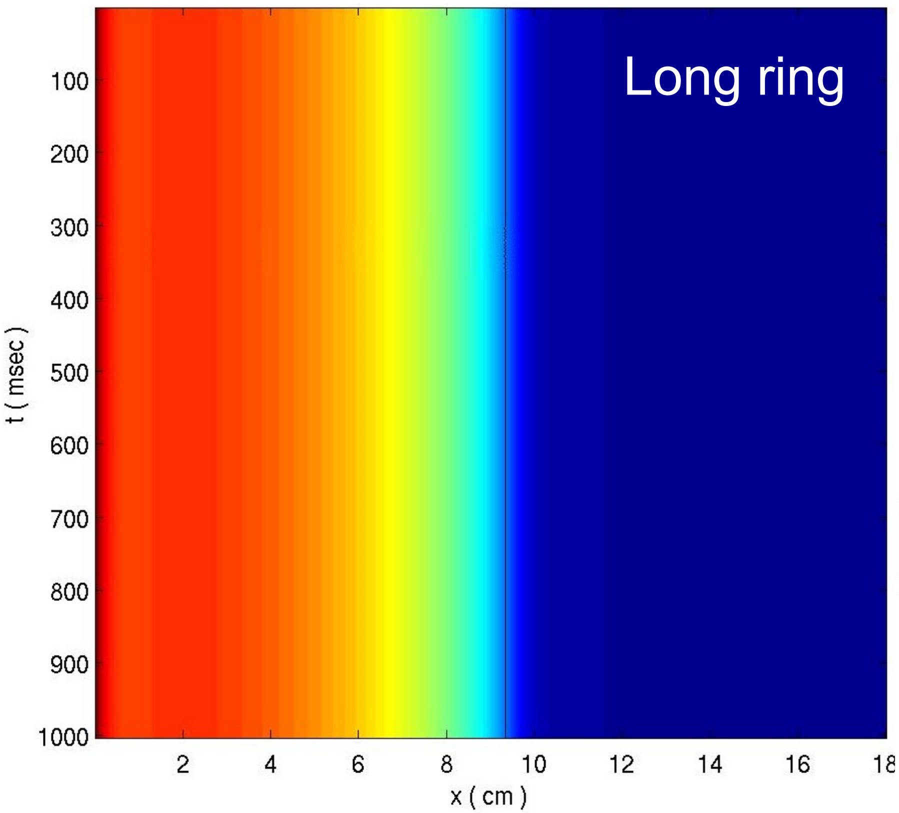
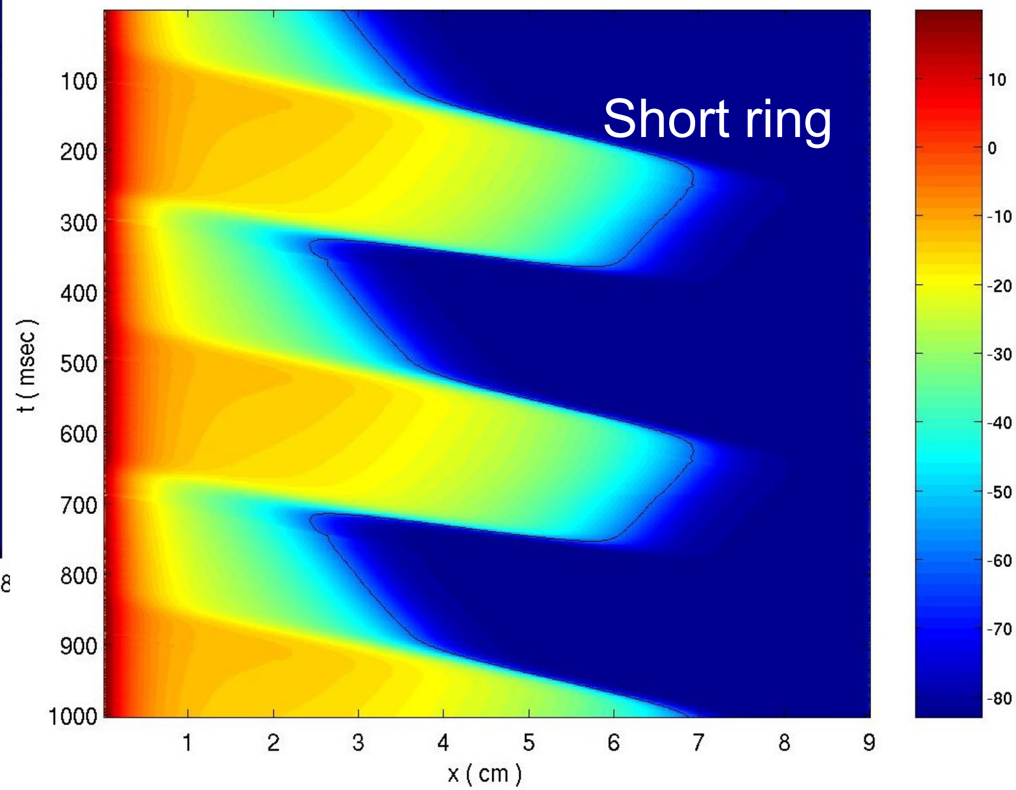


Diffusion + Restitution + Dispersion →
Dynamical disorder through pattern forming instability
(like Turing patterns)





Reference frame fixed with respect to moving wavefront