Modelling cardiac propagation in two, three dimensions and in anatomically accurate models of the heart

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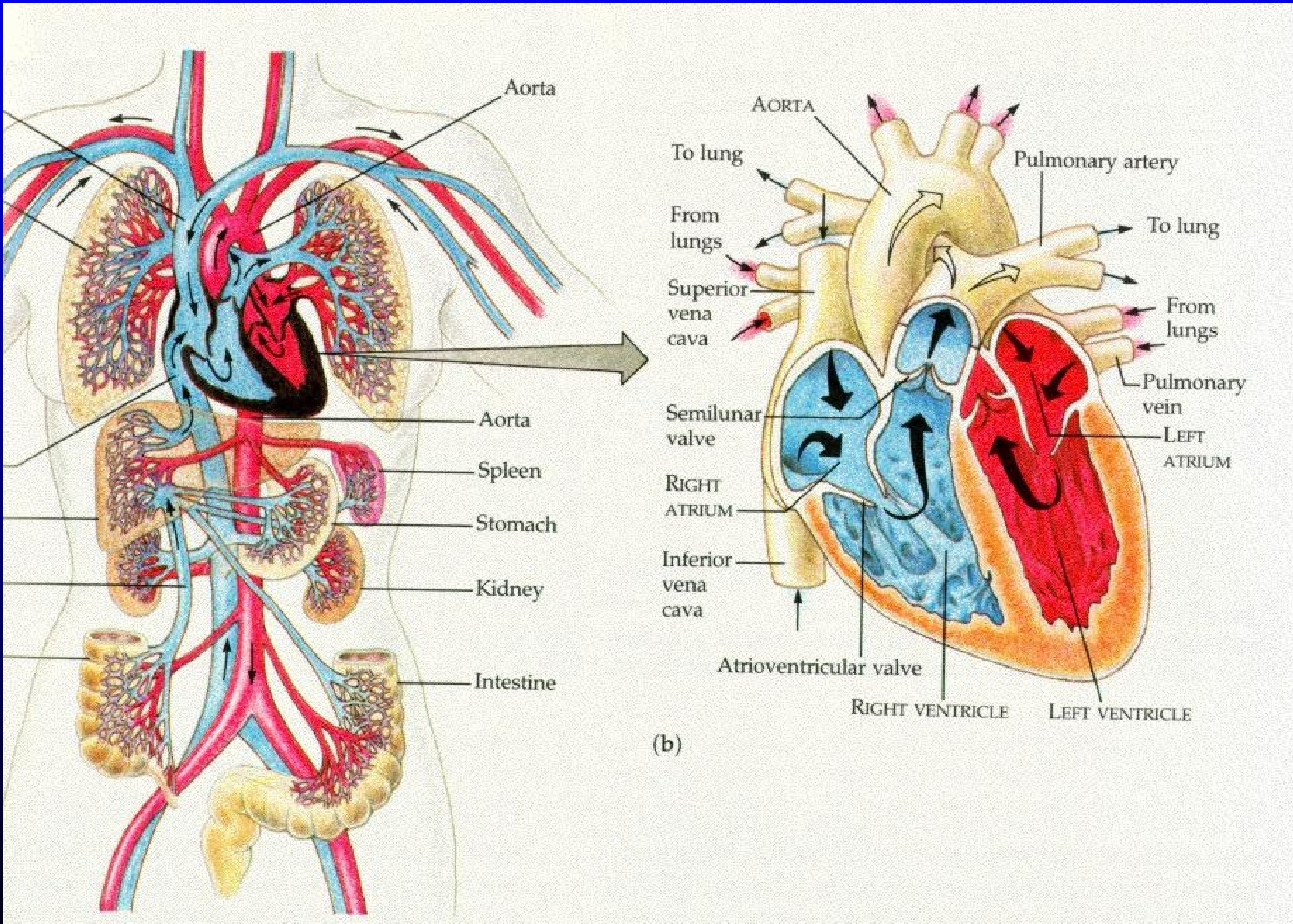
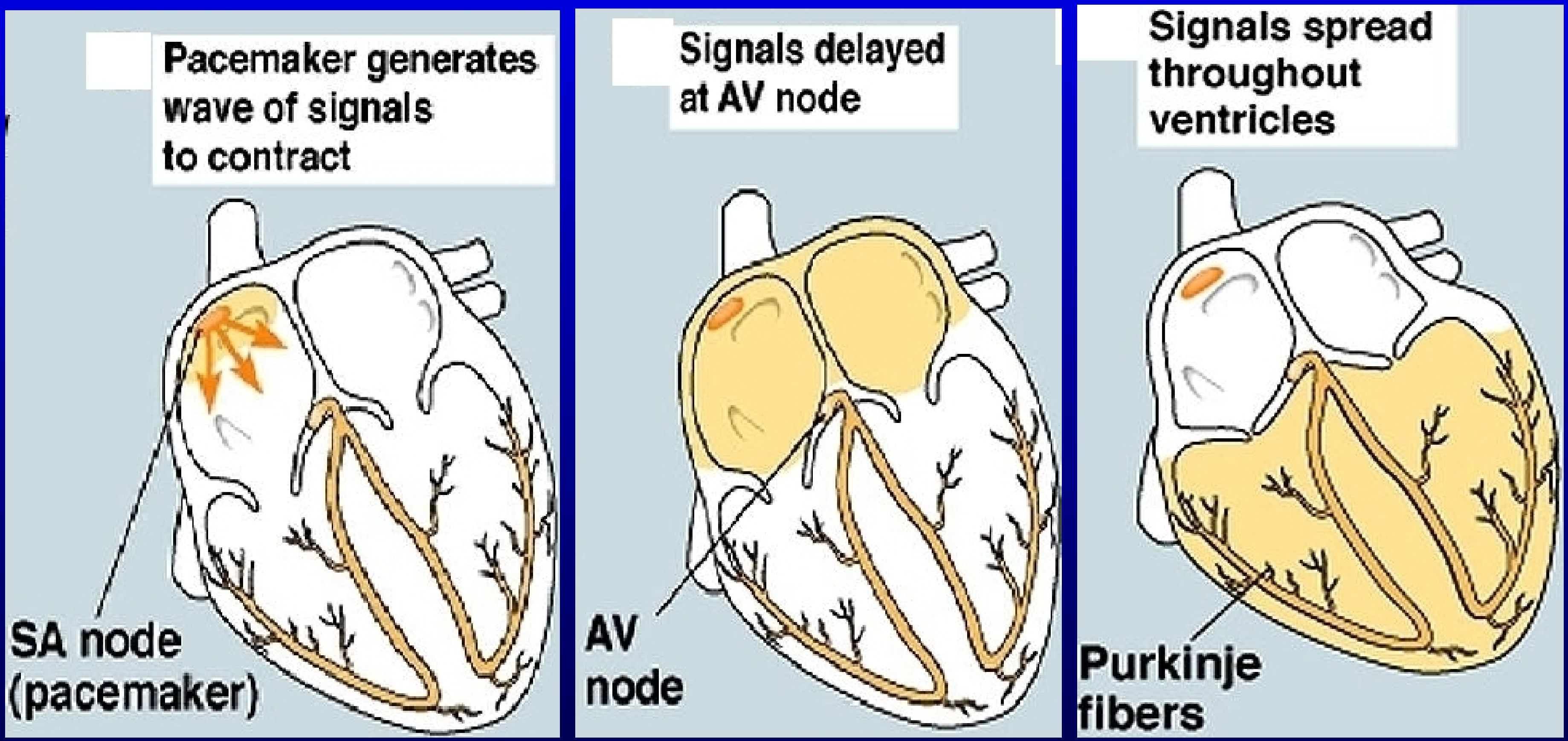


Aorta
Aorta
Spleen
Stomach
Kidney
Intestine
Aorta
To lung
From lungs
Superior vena cava
Pulmonary artery
To lung
From lungs
Pulmonary vein
Semilunar valve
Left atrium
Right atrium
Inferior vena cava
Atrioventricular valve
Right ventricle
Left ventricle
(b)

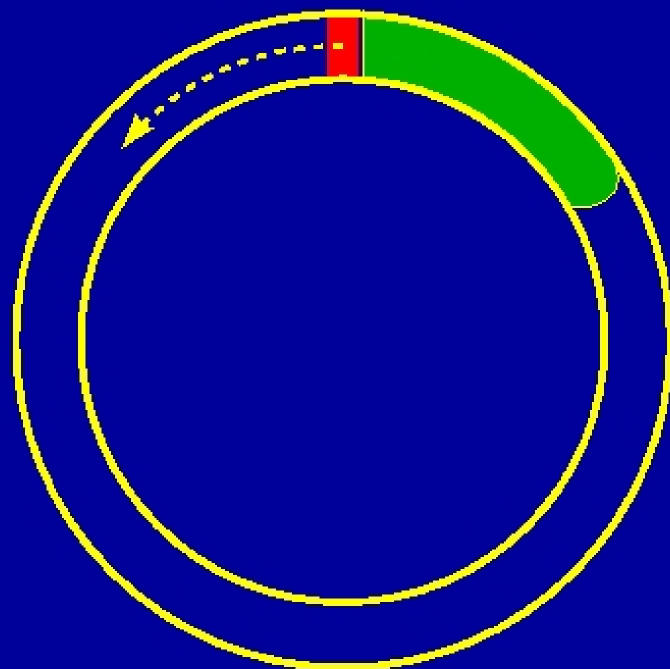
Normal excitation of the heart



Some types of arrhythmias?

- Ectopic beats. The heart has an extra beat. Treatment usually is not needed.
- Paroxysmal atrial tachycardia. The heart has episodes when it beats fast, but regularly. This type of arrhythmia may be unpleasant but is usually not dangerous.
- Atrial fibrillation. The heart beats too fast and irregularly. This type of arrhythmia requires treatment and can increase your risk of stroke.
- Ventricular tachycardia and ventricular fibrillation. The heart beats too fast and may not pump enough blood. These types of arrhythmias are very dangerous and need immediate treatment.

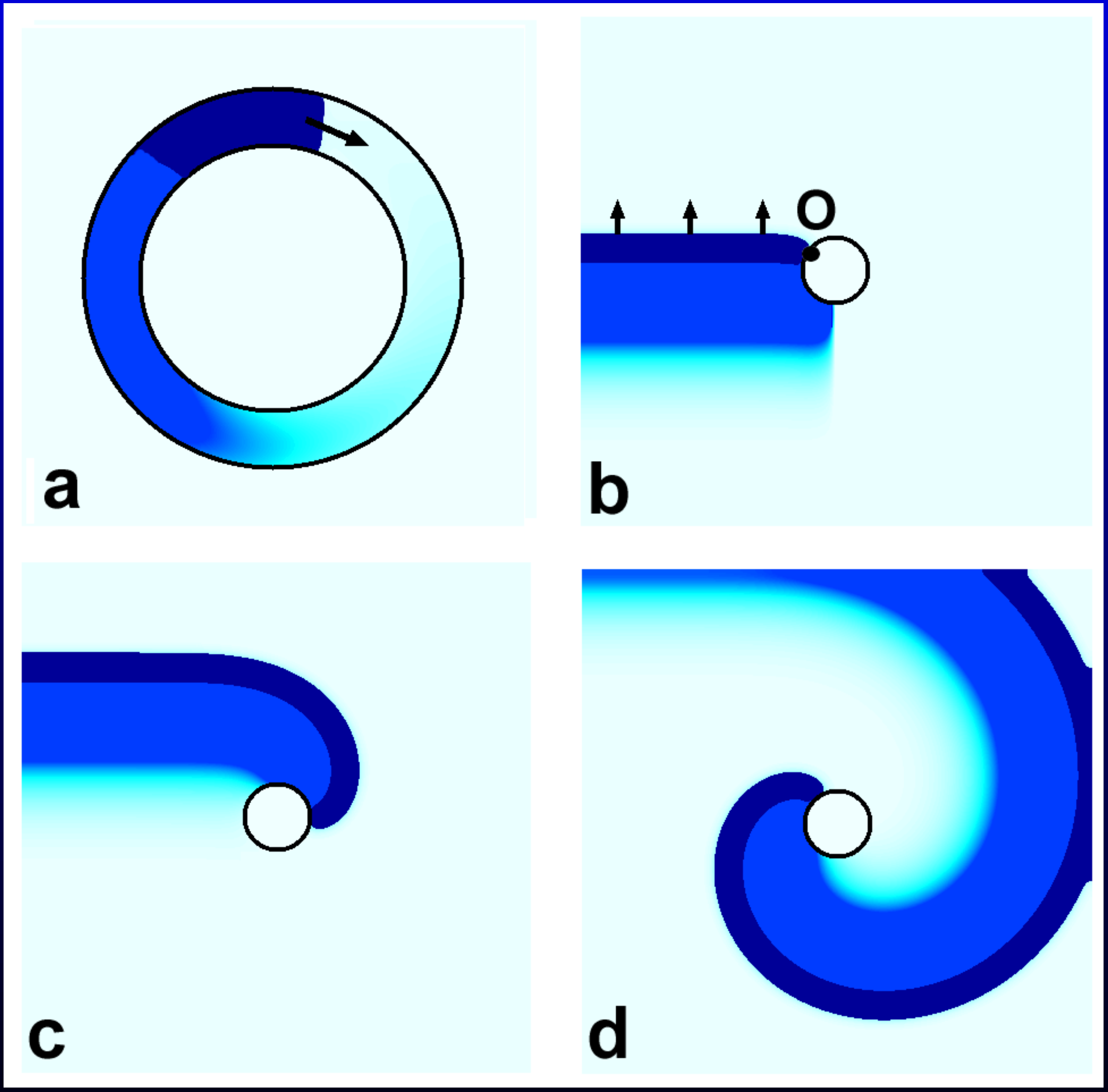
Rotation of excitation in a thin ring of excitable tissue



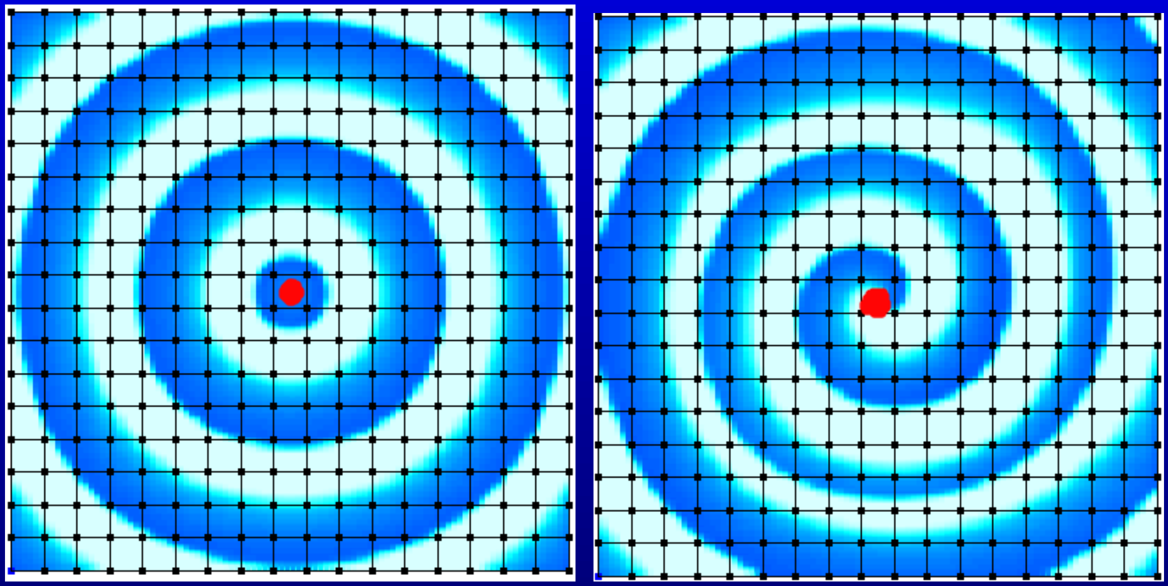
Rotation is possible if the length of a ring (L) is longer than the product the refractory period and the velocity of the wave:

$$L>R*v$$

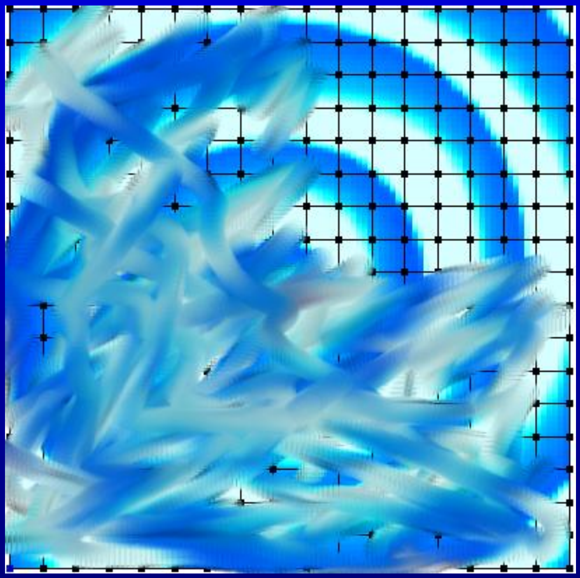
Spiral waves

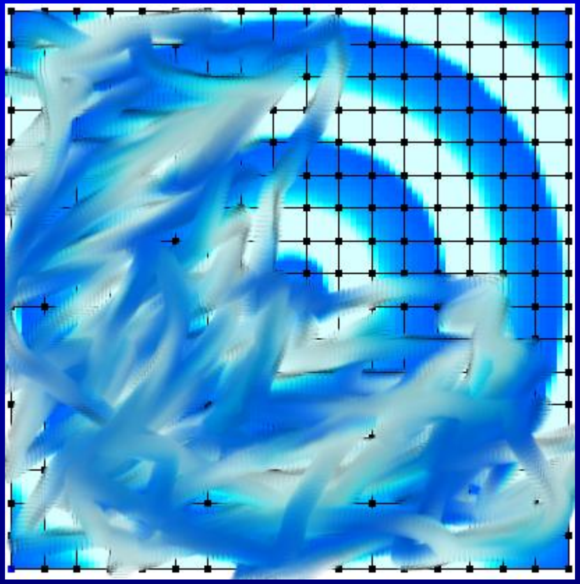


Spiral wave is an excitation source



Spiral wave is an excitation source

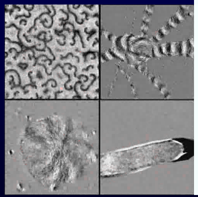


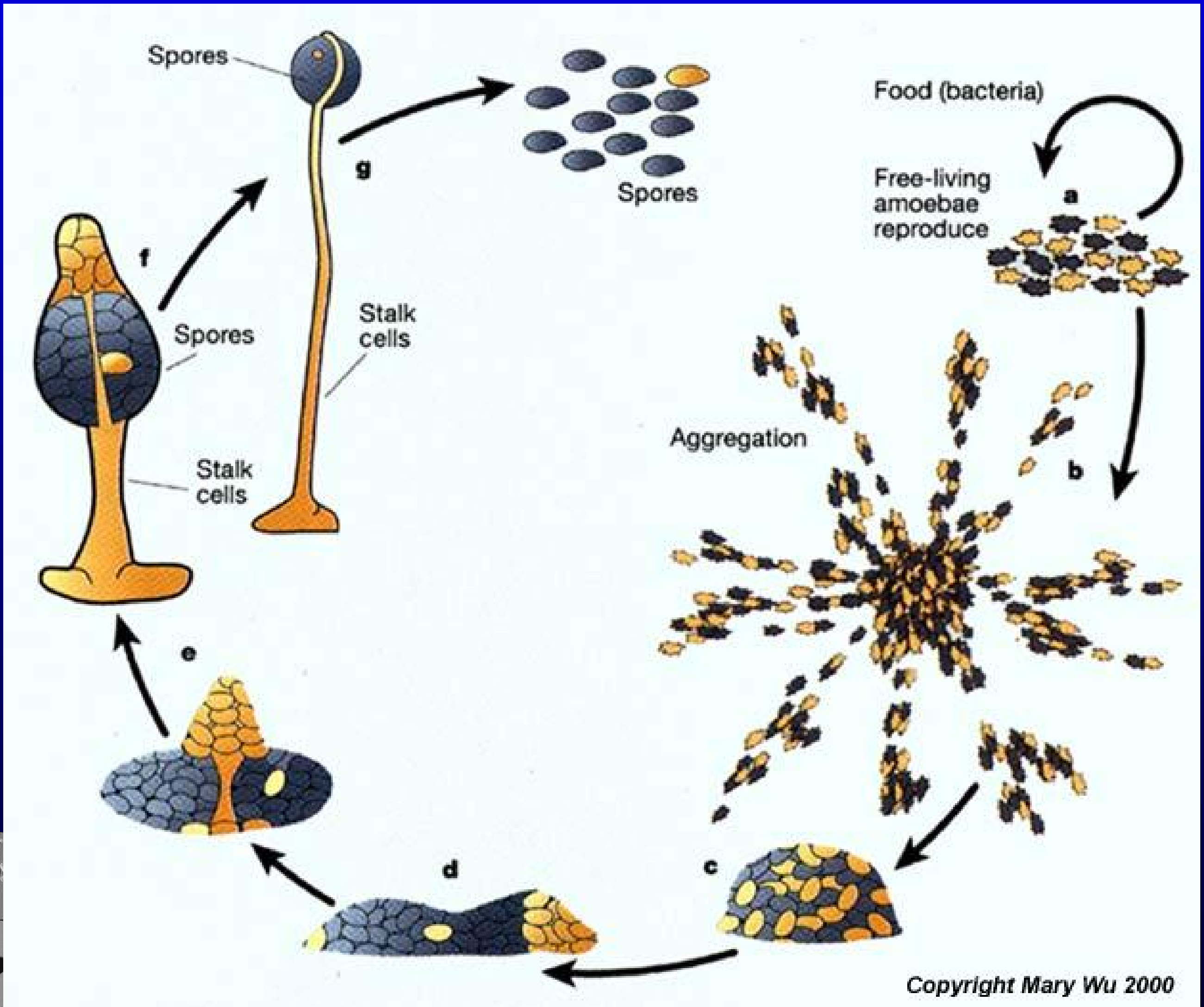


Rotating spiral waves were found in the following systems

- Belousov Zhabotinsky reaction
- Heart tissue
- Morphogenesis of *Dictyostelium discoideum* amoebae
- Retina of a chicken
- *Xenopus* oocytes
- Heterogeneous catalysis

Spiral waves during Dd morphogenesis



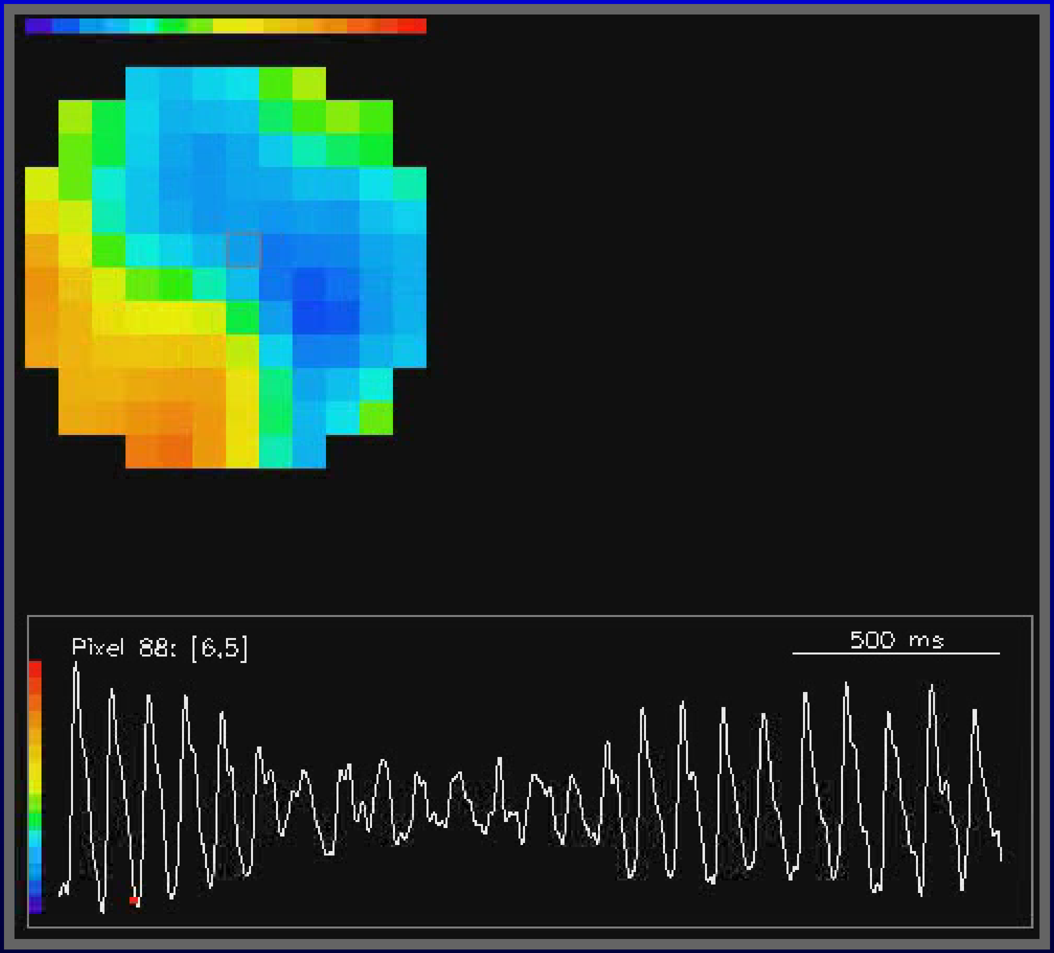


(from lab of C.Weijer, Univ. of Dundee,UK)

Spiral waves of CICR in Xenopus Oocyte

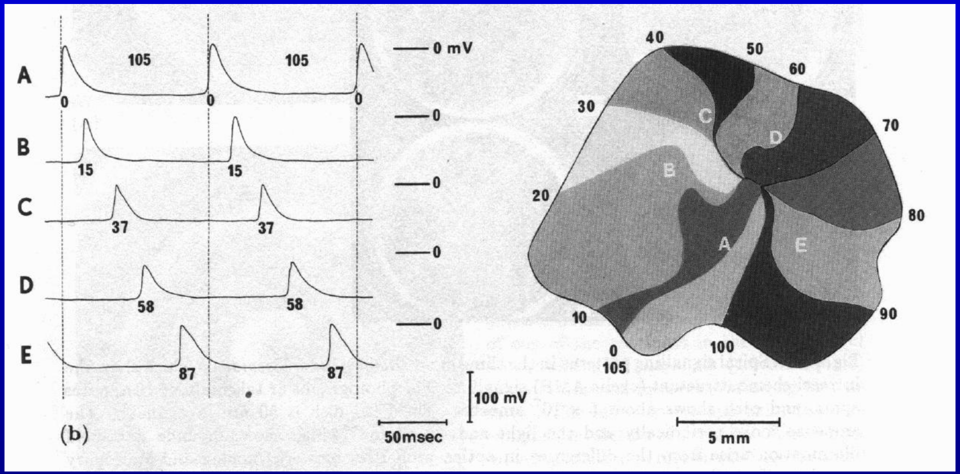
(from lab of James D. Lechleiter, Univ. of Texas at San Antonio)

Spiral waves in Mammalian Neocortex

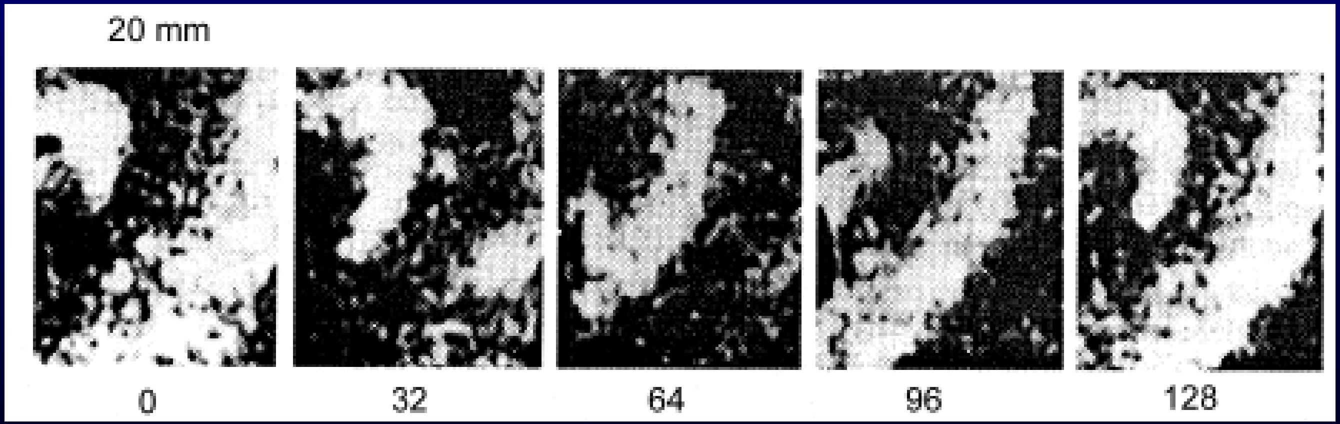


(Huang et al. J. Neurosci., v.24,p. 9897-9902,2004)

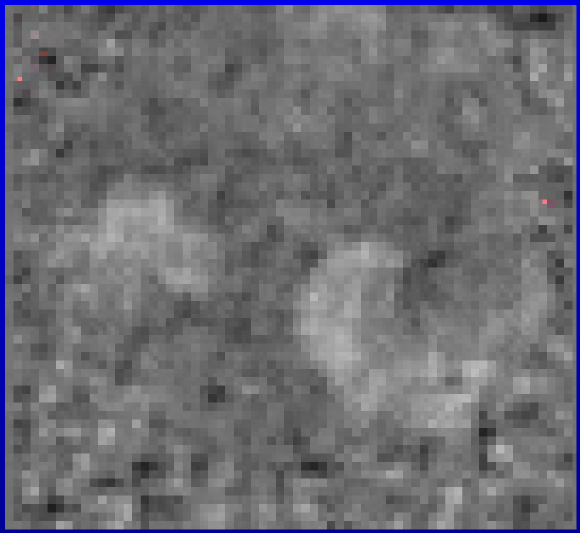
Spiral waves in the heart



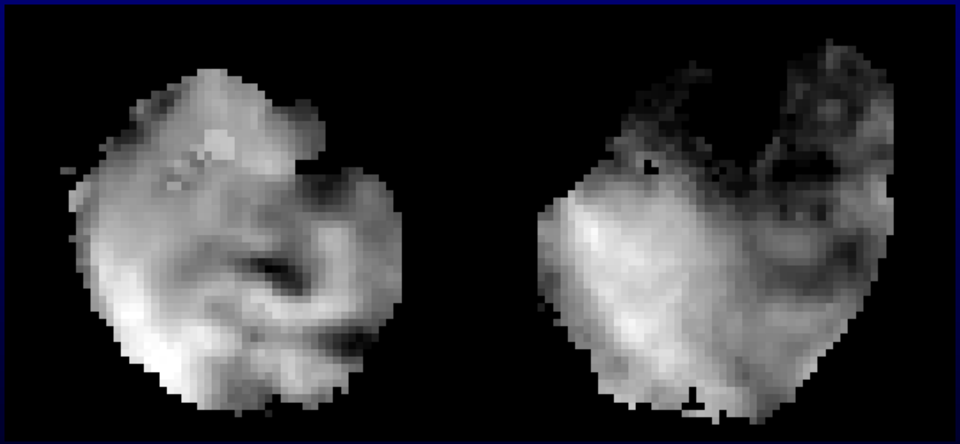
(Allessie et al., 1973)



(Davidenko et al., 1991)



Spiral waves in the culture of cardiac cells (from L. Glass lab)

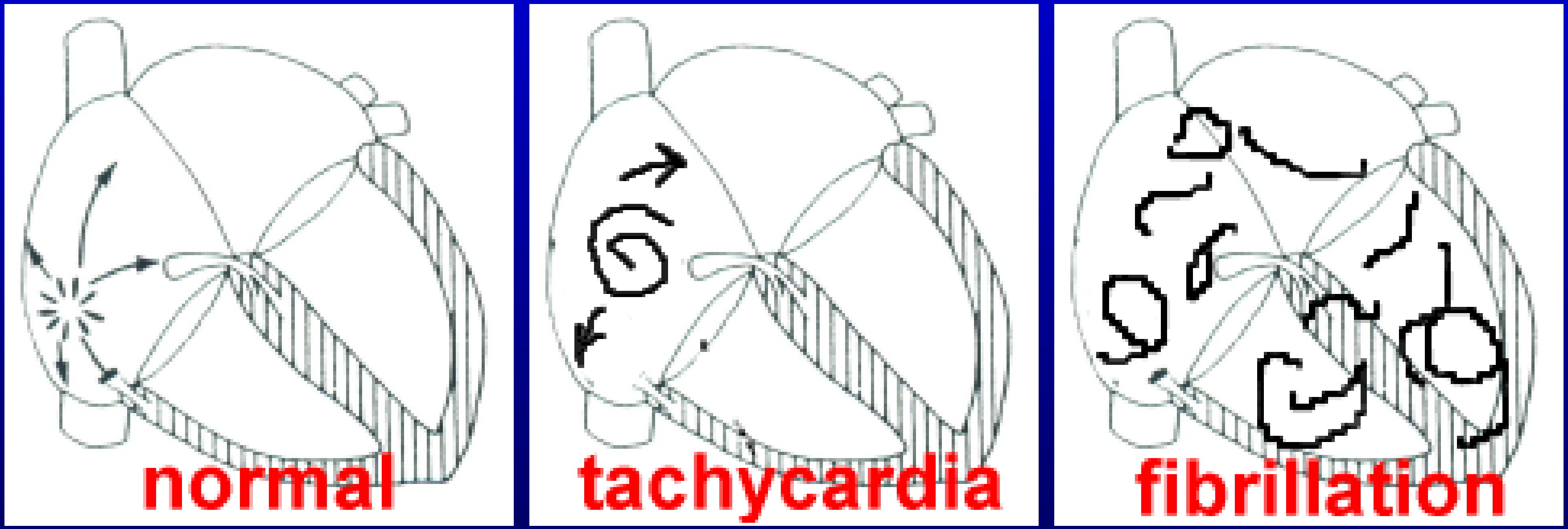


VF in a guinea pig heart (from J.Jalife lab)

Reentry (recirculation of excitation) in the heart

- In normal conditions cardiac rhythm is determined by a period of a pacemaker in *sinus node*.
- Period of reentry is 2-3 times shorter than the period of pacemaker.
- reentry suppresses pacemaker and the heart contracts with the period of the reentry, i.e. 2-3 times faster than normal.

Sources of an arrhythmia and fibrillation



Cardiac arrhythmias → millions of cells

Virtual heart

Cell $\longrightarrow$ Tissue $\longrightarrow$ Organ

allows us to

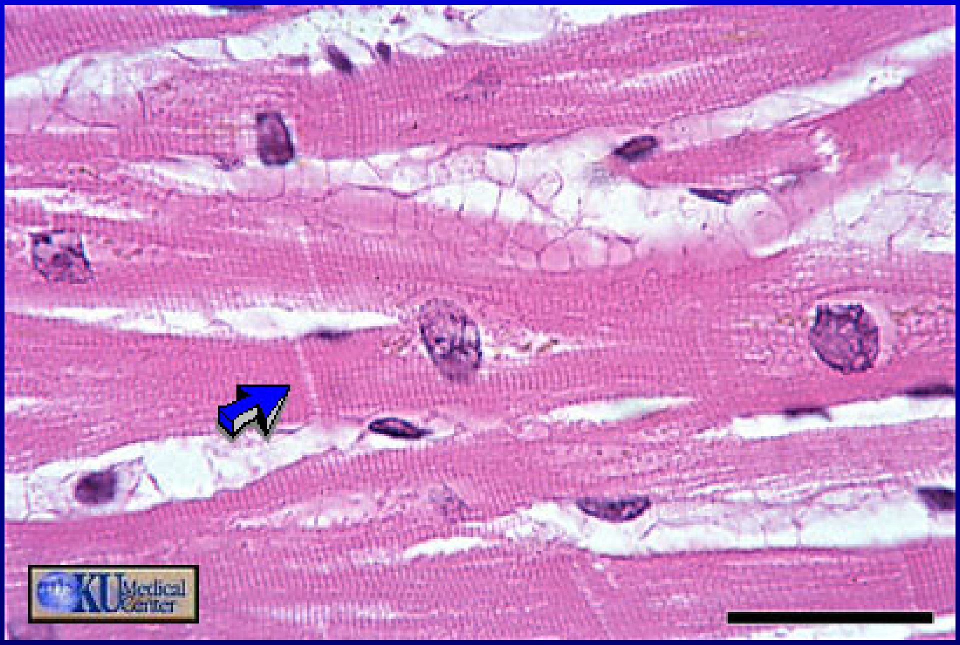
- extend one cell $\longrightarrow$ whole organ
- study excitation in 3D
- study arrhythmias in human heart

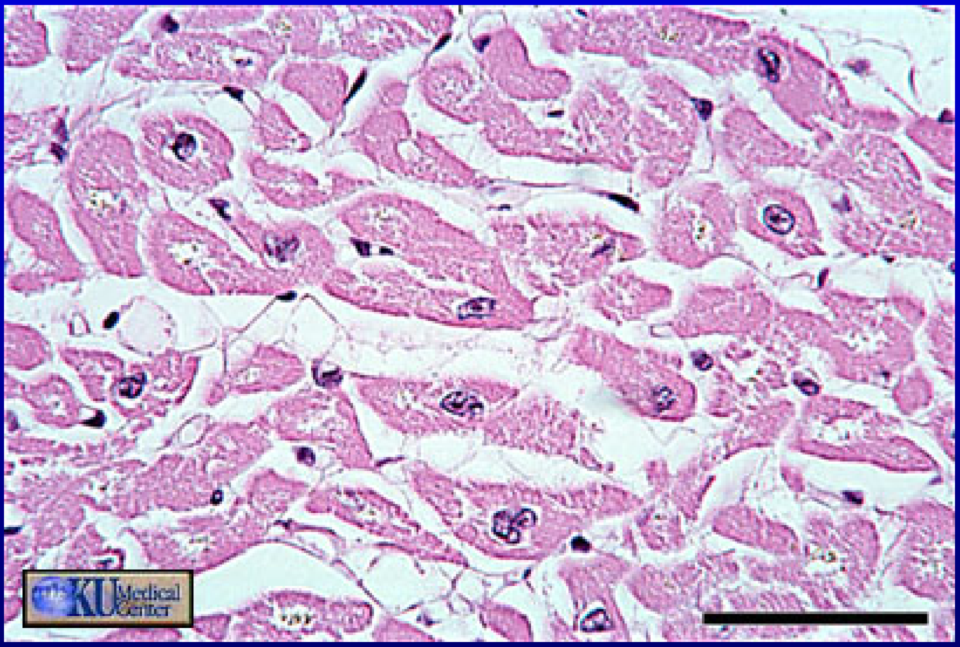
Normal 2D propagation

Basic 2D effects:

- anostropy
- curvature

Cardiac cell structure (anistropy)



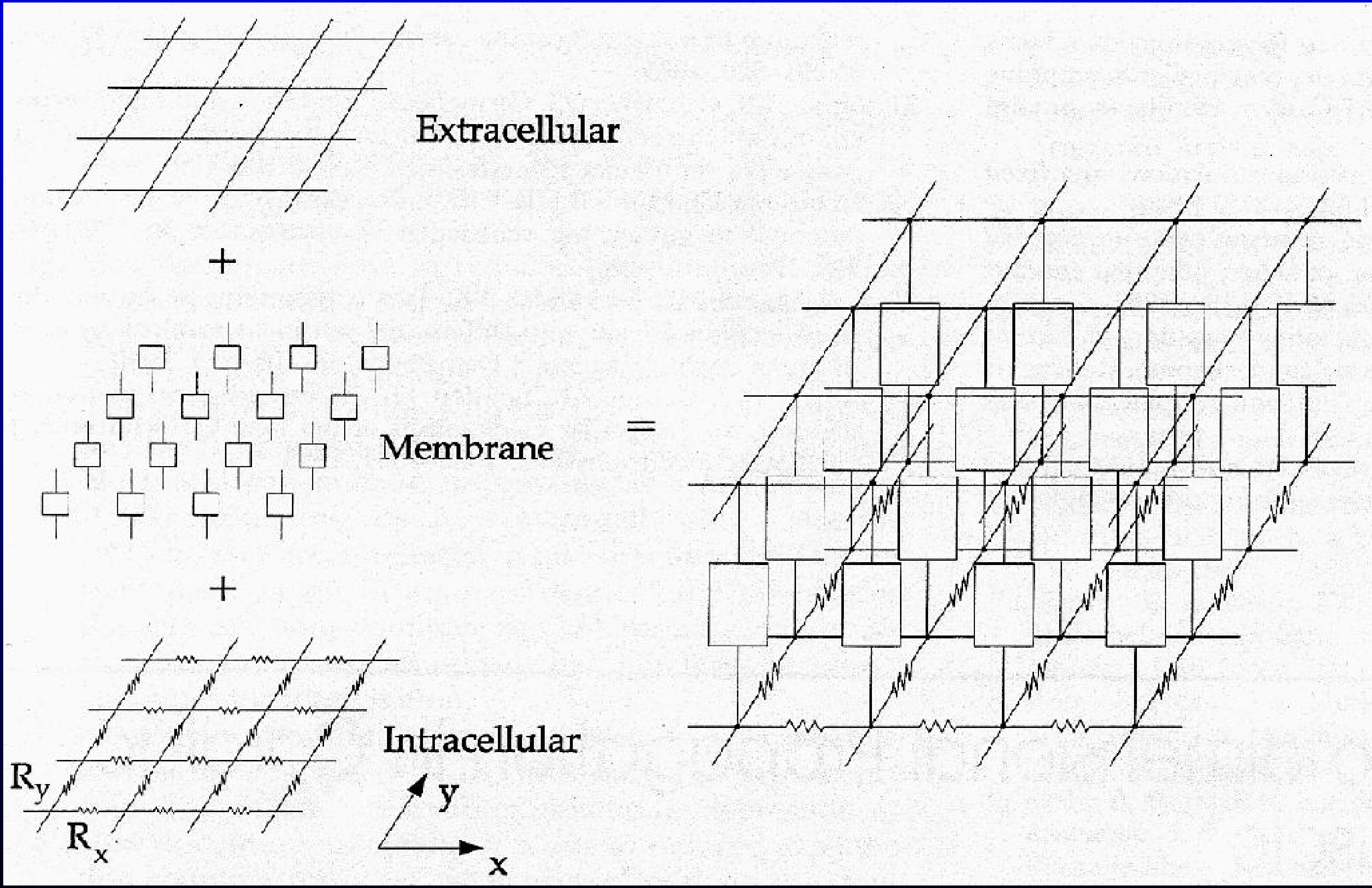


Cardiac muscle:

a-longitudinal section. Bar is 30 microns;

b-transverse section. Bar is 50 microns.

Cardiac tissue, monodomain models



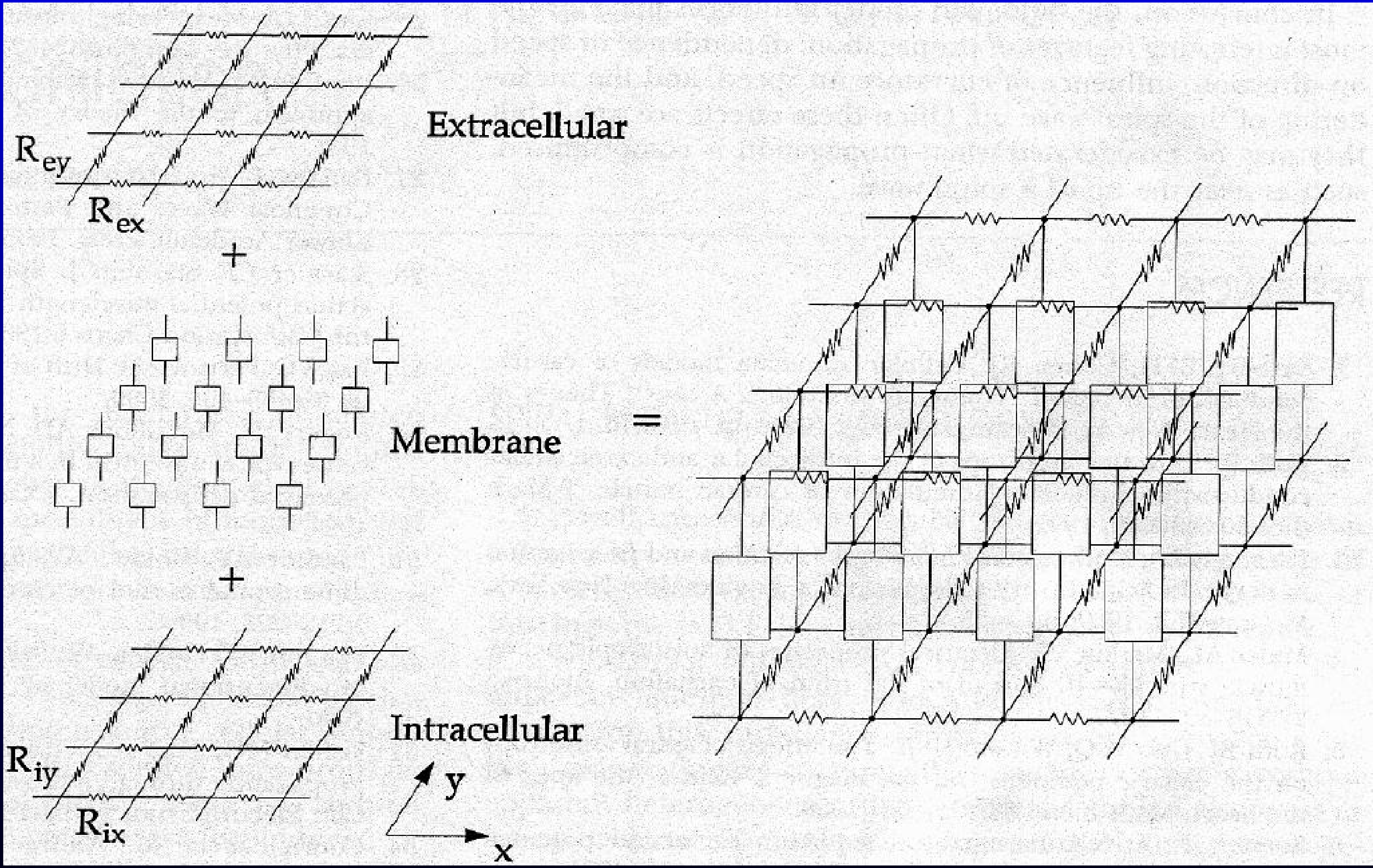
Monodomain model.Equations

$$\frac{\partial V_m}{\partial t} = div d grad V_m + I_{ion}(V_m, g_i)$$

$$\frac{\partial g_i}{\partial t} = (\phi(V_m) - g_i)/\tau(V_m)$$

$$d = \begin{pmatrix} d_{11} & d_{12} \\ d_{21} & d_{22} \end{pmatrix}$$

Cardiac tissue, bidomain models



Bidomain model. Equations

$$\frac{\partial V_m}{\partial t} = div d_e grad V_e + I_{ion}(V_m, g_i)$$

$$div d_e grad V_e + div d_i grad V_i = 0$$

$$\frac{\partial g_i}{\partial t} = (\phi(V_m) - g_i)/\tau(V_m)$$

$$V_m = V_i - V_e$$

Anistropy tensor can be found from fiber orientation vector $\vec{\alpha}$

Transformation matrix: $A = (\vec{\alpha}, \vec{\beta})$

$$D = A^T * d * A; \qquad or \qquad d = A * D * A^T$$

where d is a matrix in our coordinate system.

From (1) we get:

$$d = D_1 \vec{\alpha}\vec{\alpha}^T + D_2 \vec{\beta}\vec{\beta}^T$$

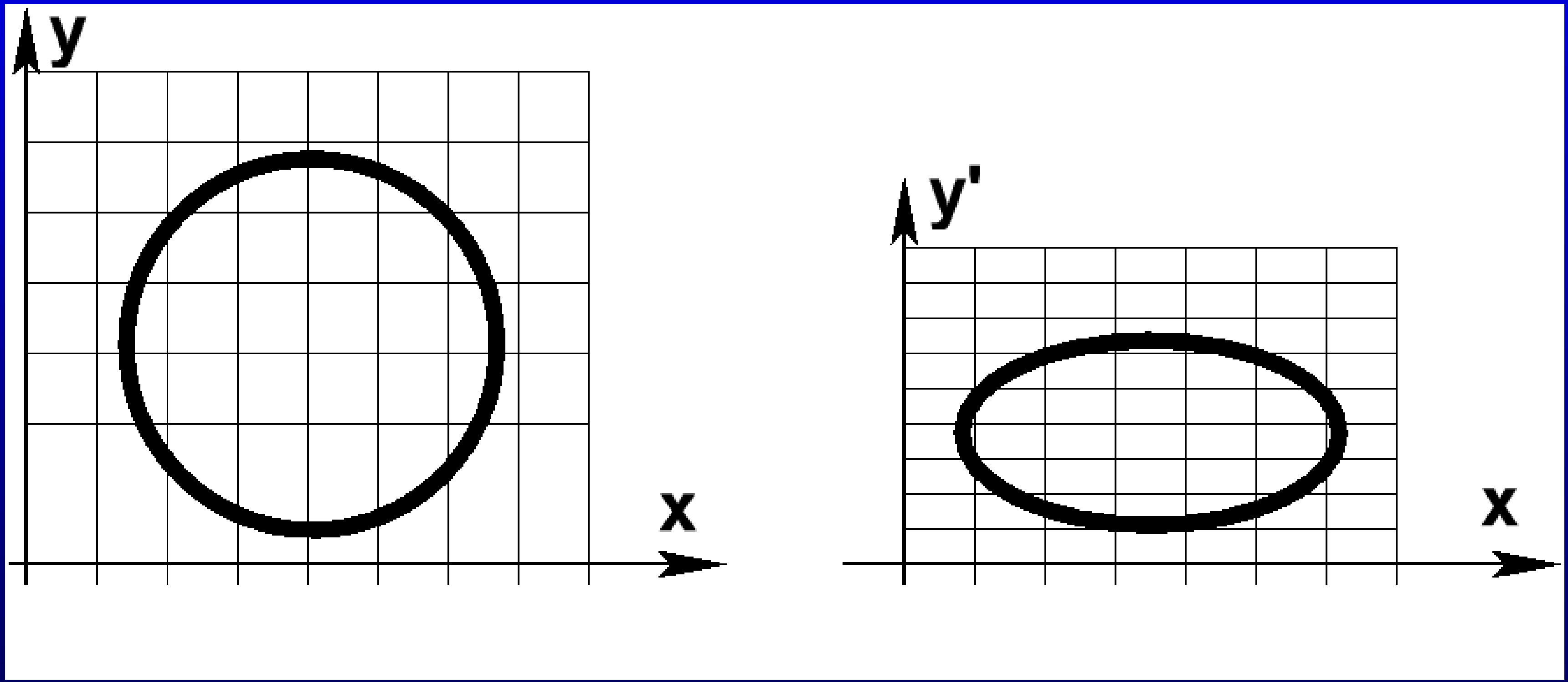
A is an orthogonal matrix:

$$\vec{\alpha}\vec{\alpha}^T + \vec{\beta}\vec{\beta}^T = I$$

thus:

$$d = D_2 I + (D_1 - D_2)\vec{\alpha}\vec{\alpha}^T$$

Anisotropy is just a rescaling

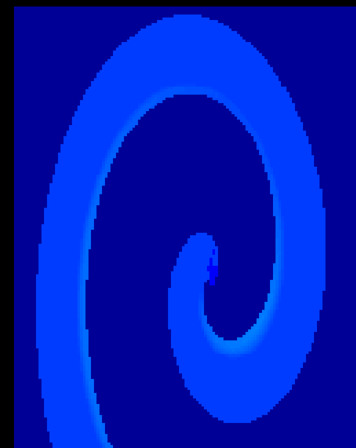


$$y' = y/2$$

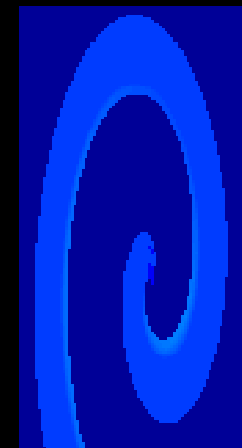
$$D = \begin{pmatrix} 1 & 0 \\ 0 & \frac{1}{4} \end{pmatrix}$$

Anisotropy is just a rescaling

1:1



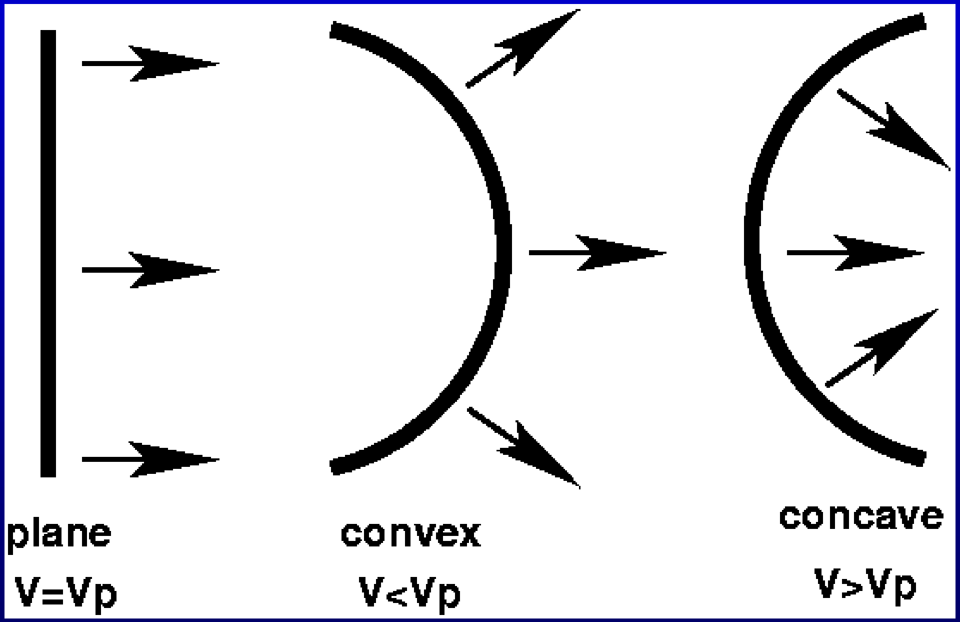
0.5:1



0.33:1

$$D_1 = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \quad D_2 = \begin{pmatrix} 1 & 0 \\ 0 & \frac{1}{4} \end{pmatrix} \quad D_3 = \begin{pmatrix} 1 & 0 \\ 0 & \frac{1}{9} \end{pmatrix}$$

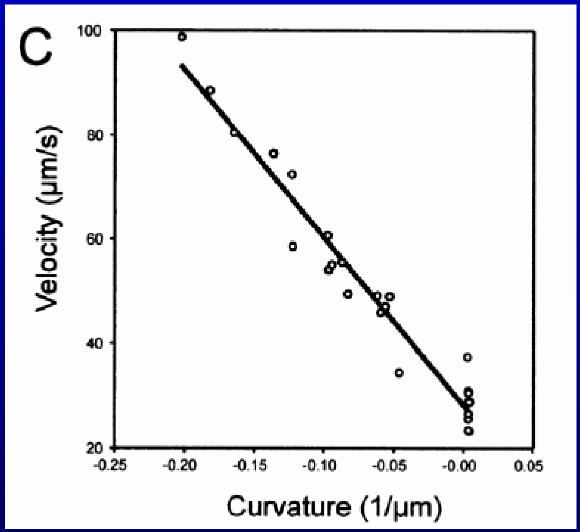
Basic 2D effects: curvature



$$\Delta = \frac{\partial^2 V_m}{\partial x^2} + \frac{\partial^2 V_m}{\partial y^2} = \frac{\partial^2 V_m}{\partial r^2} + \frac{1}{r}\frac{\partial V_m}{\partial r}$$

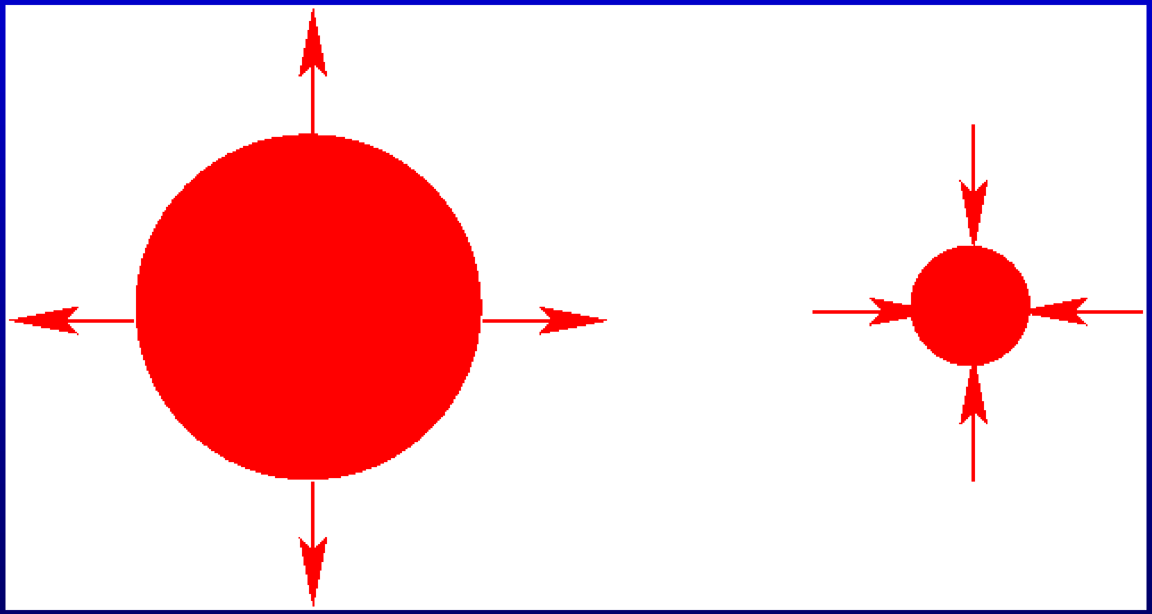
Basic 2D effects

- velocity- curvature relation $V = V_0 - D * k$

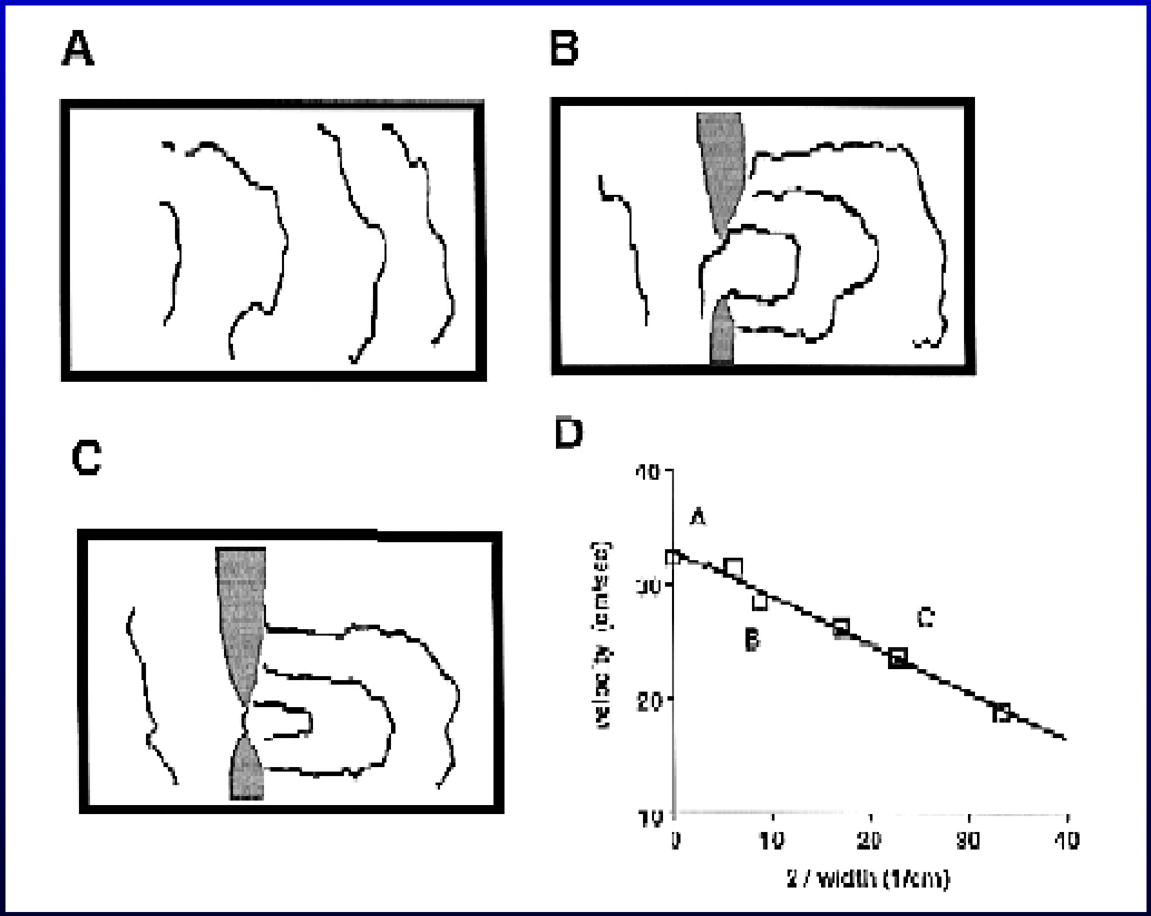


the velocity curvature relationship from single and colliding calcium waves in excitable medium of agarose gel with homogeneously distributed vesicles of skeletal sarcoplasmic reticulum. From Wussling et al., Biophysical Journal,v.80, p. 2658-2666, 2001.

- critical curvature $V = V_0 - D * k_{crit} = 0 \quad k_{crit} = V_0/D$

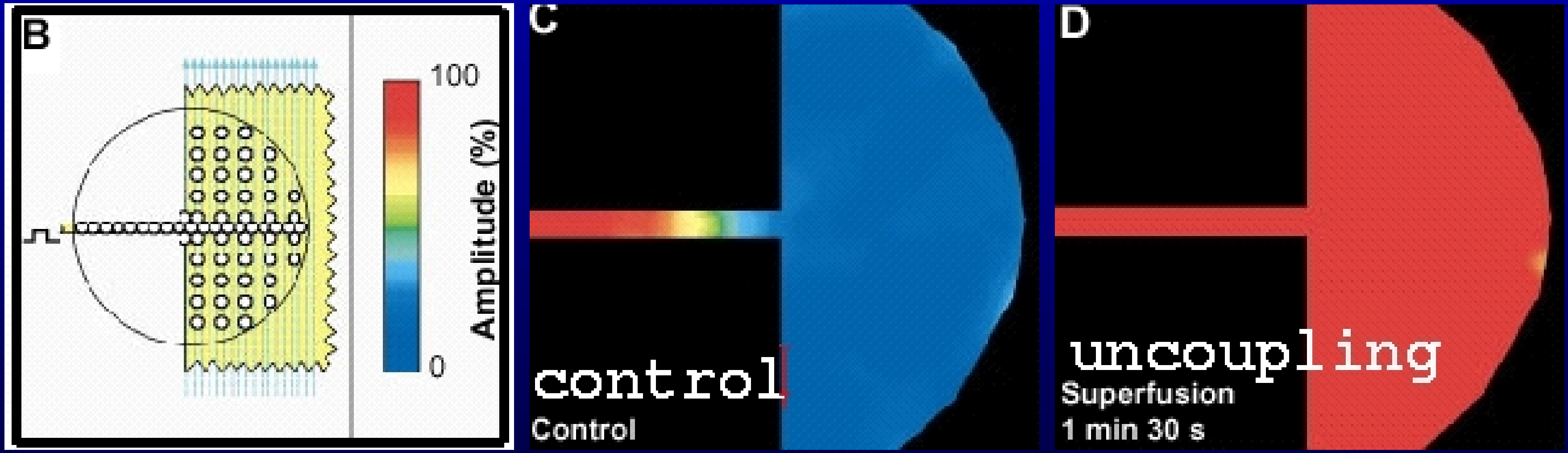


Wave propagation across a narrow tissue isthmus



(from Cabo et al., Circ.Res,v.75,1014-1028,1994)

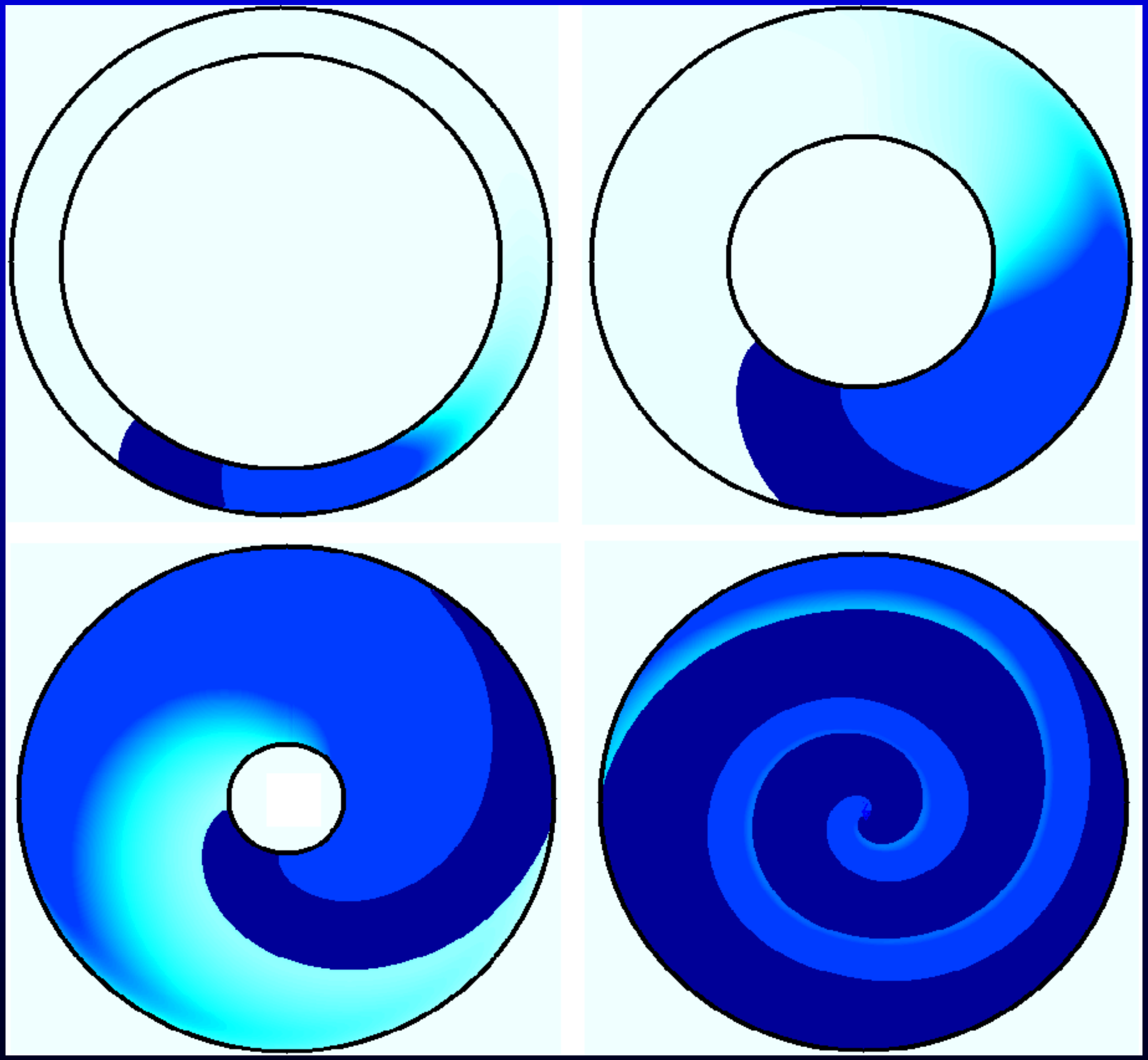
Paradoxical improvement of impulse conduction by cellular uncoupling



(from Rohr et al., Science,275,841-844,1997)

Abnormal 2D propagation (spiral waves)

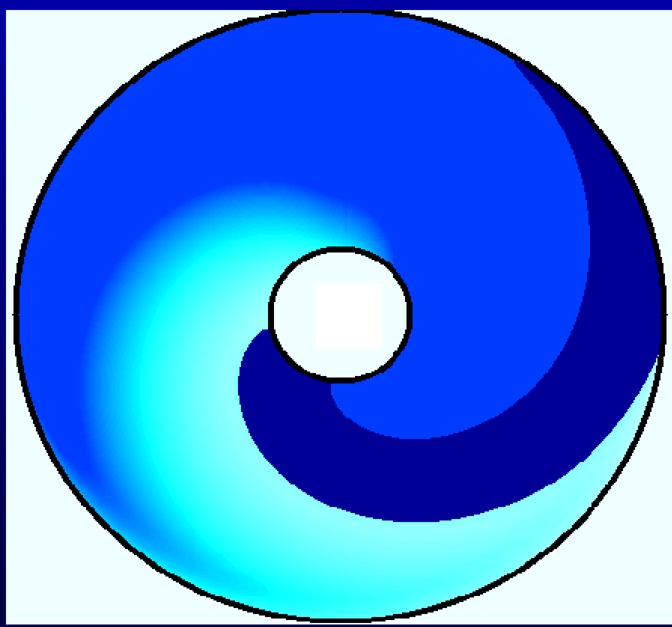
Spiral shape → just geometry



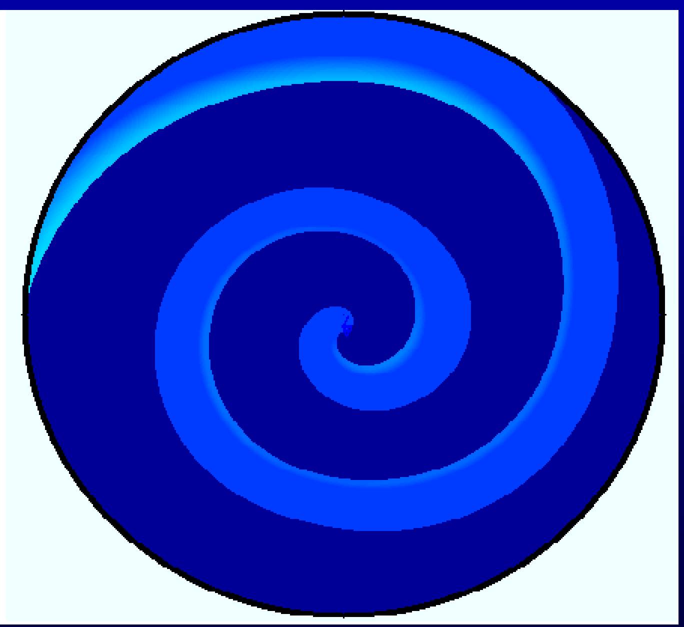
Types of spiral waves

anatomical

(around obstacle)

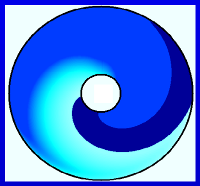


functional



What are dynamics of the spiral wave reentry?

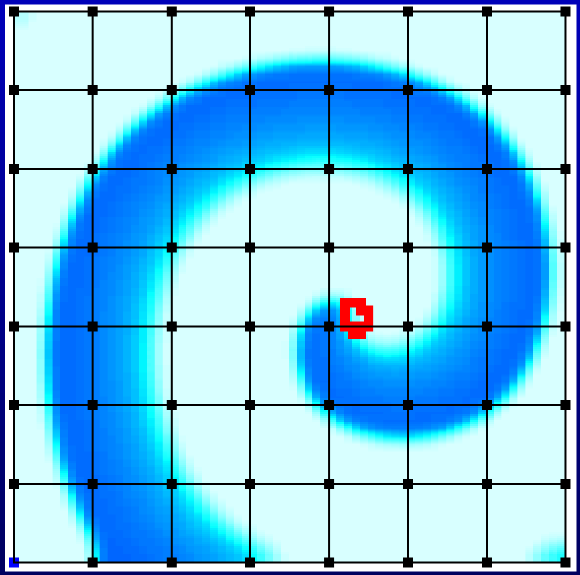
Anatomical spiral wave



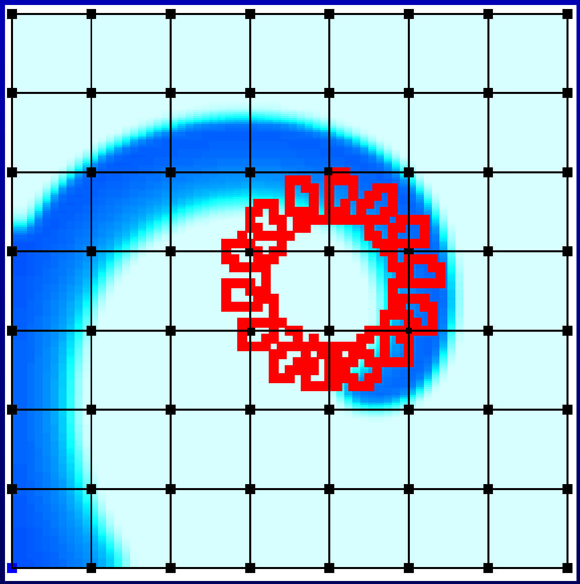
- Dynamics: (normally) stationary rotation
- ECG manifestation: periodic-monomorphic tachycardias

Spiral waves dynamics

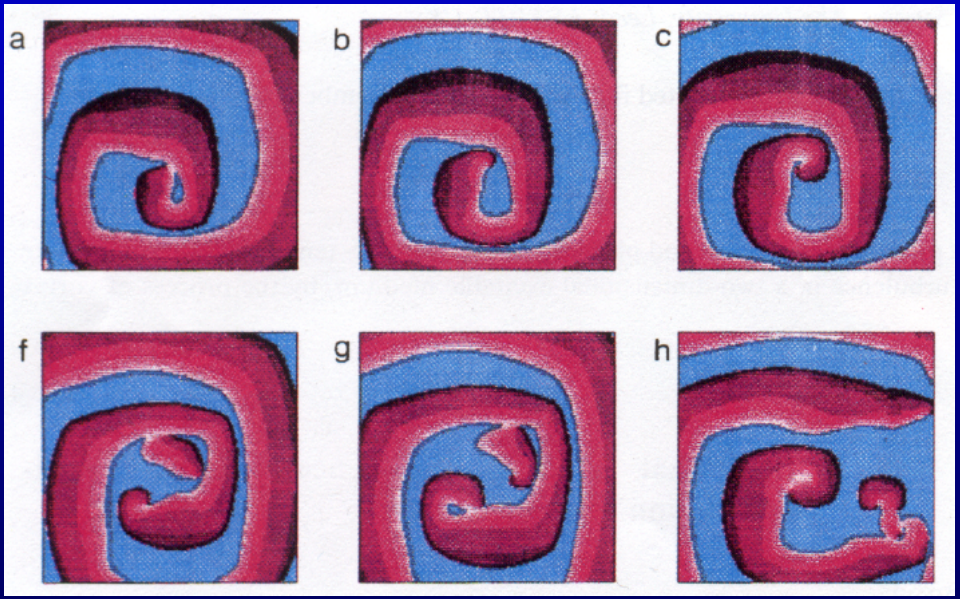
Stable rotation



Meandering

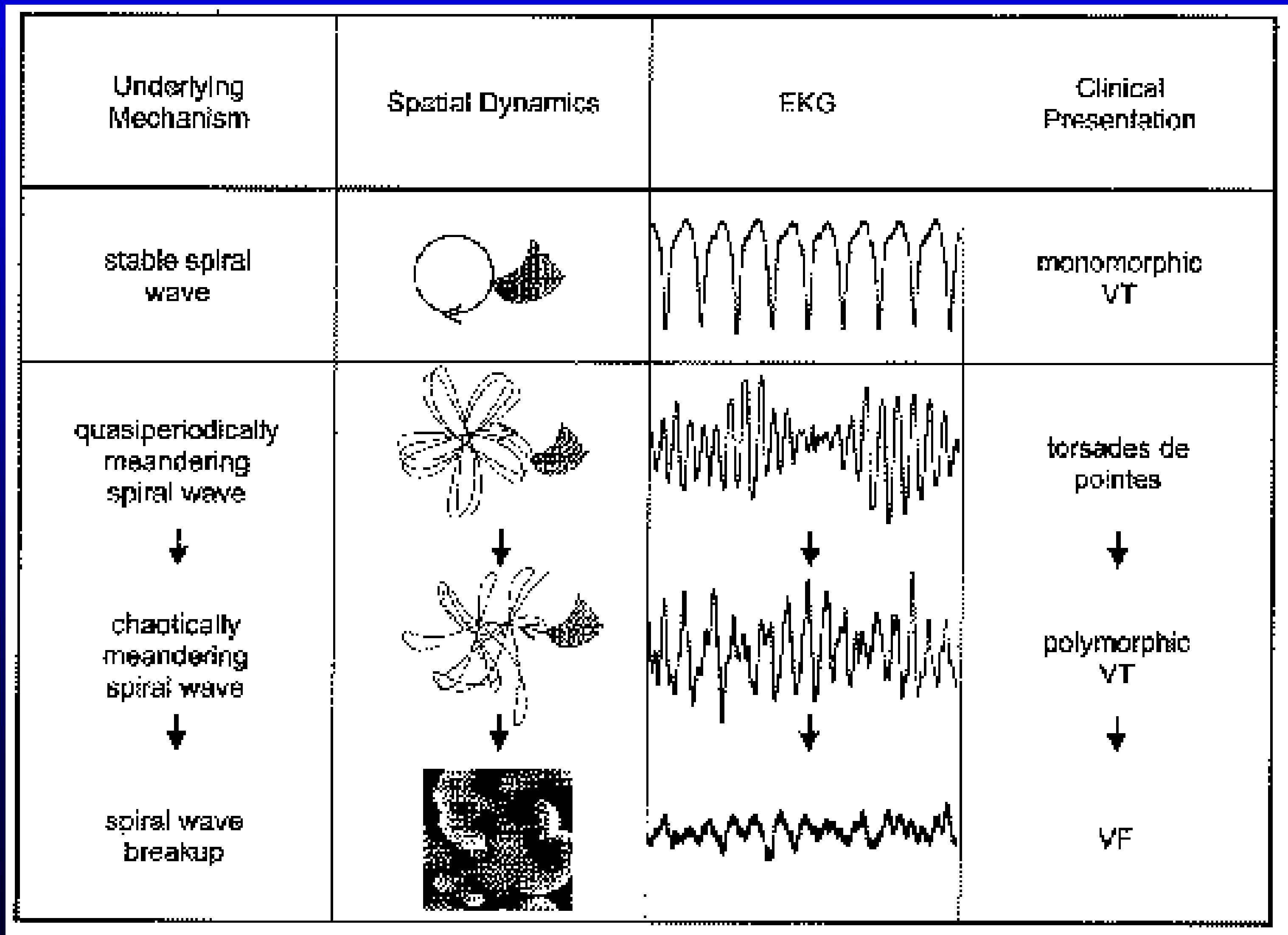


Breakup



Spiral breakup in N 1962 model *from (Panfilov,Holden, Physics Letters A, v.151,23-26, 1990)*.

Spiral wave dynamics and arrhythmia type

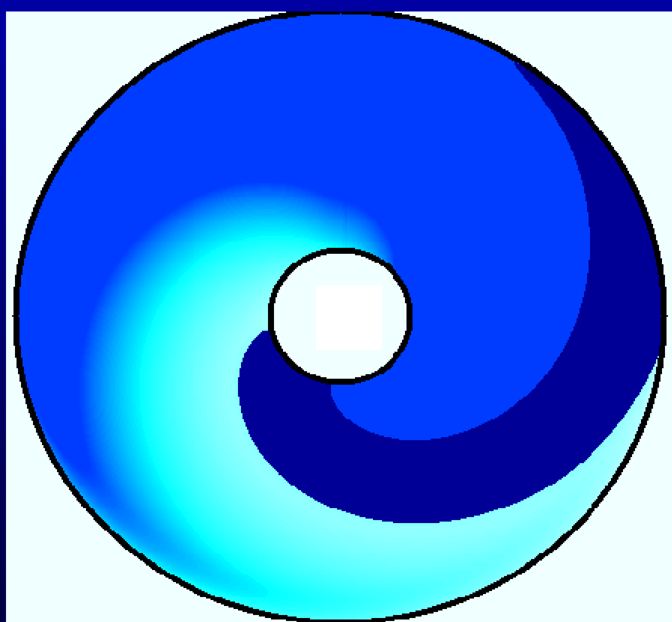


Possible ECG manifestations:

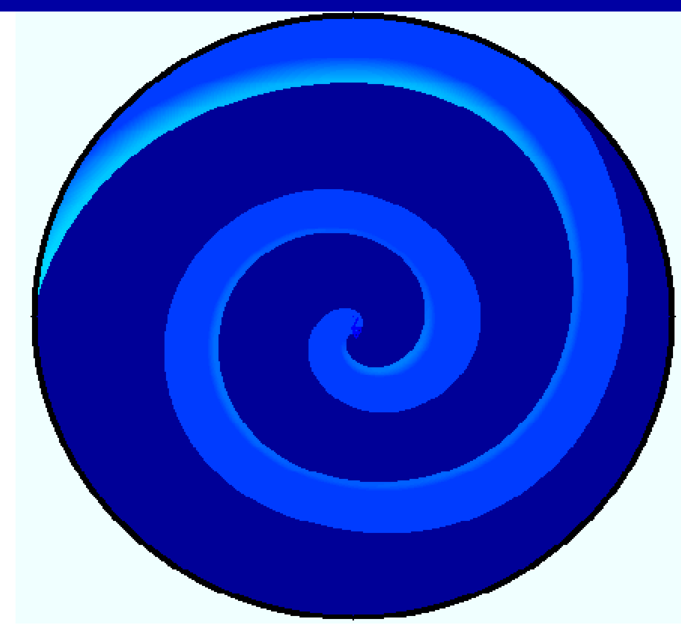
- periodic: monomorphic tachycardias
- meandering, drift: polymorphic tachycardias (TdP)
- breakup: fibrillation

Types of spiral waves

anatomical
(around obstacle)



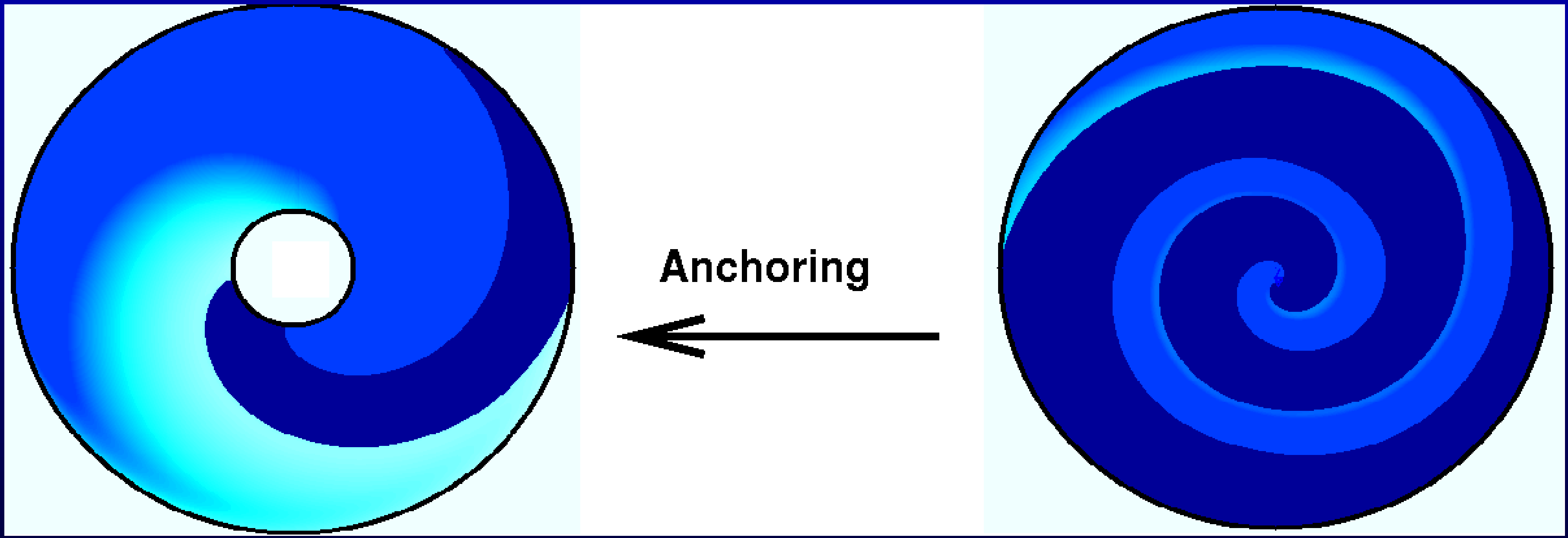
functional



Types of spiral waves

anatomical (around obstacle)

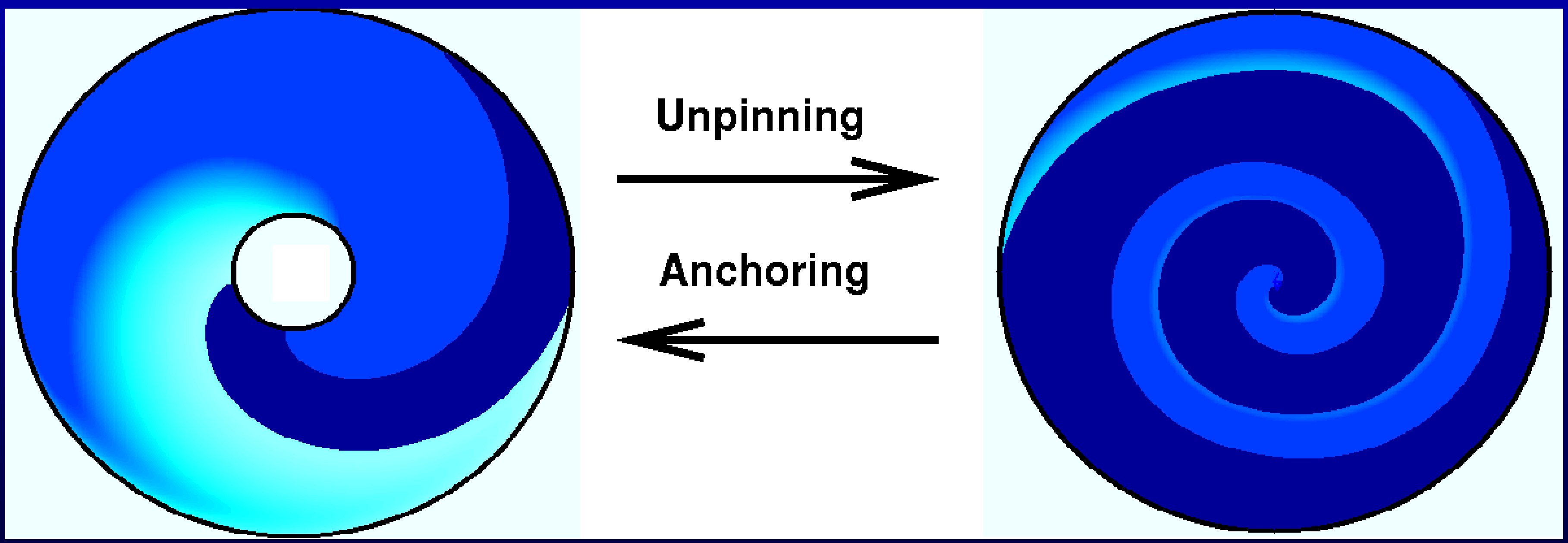
functional



Types of spiral waves

anatomical
(around obstacle)

functional

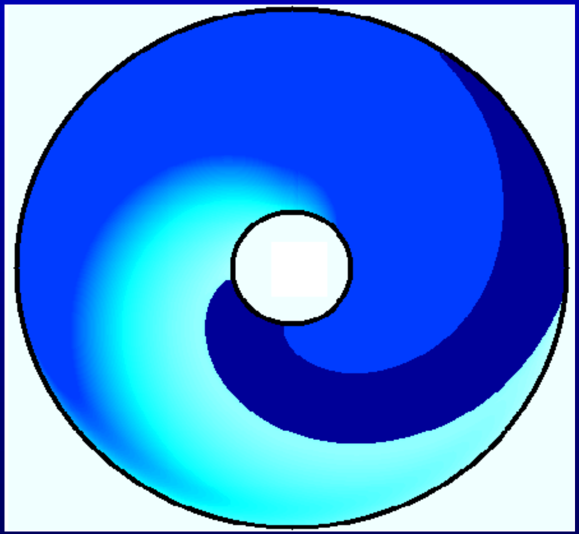


Spiral wave dynamics and change of arrhythmia type

PVT → anchoring → MVT

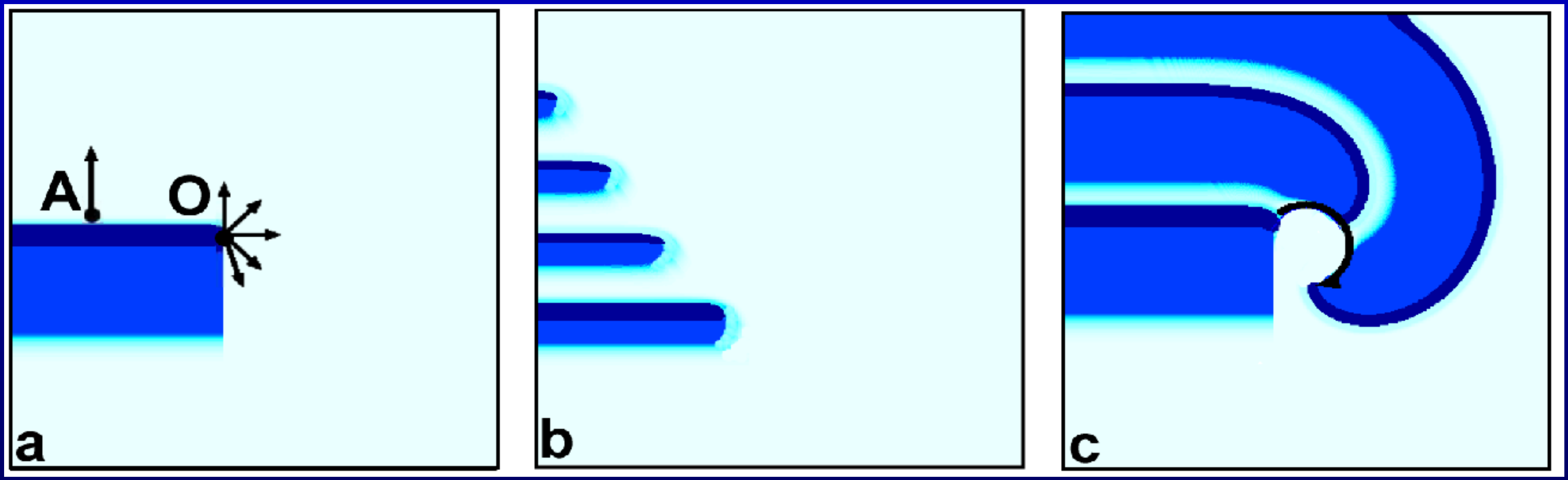
Pertsov, Jalife, Fast 1990s

What determines dynamics of anatomical spiral wave reentry?



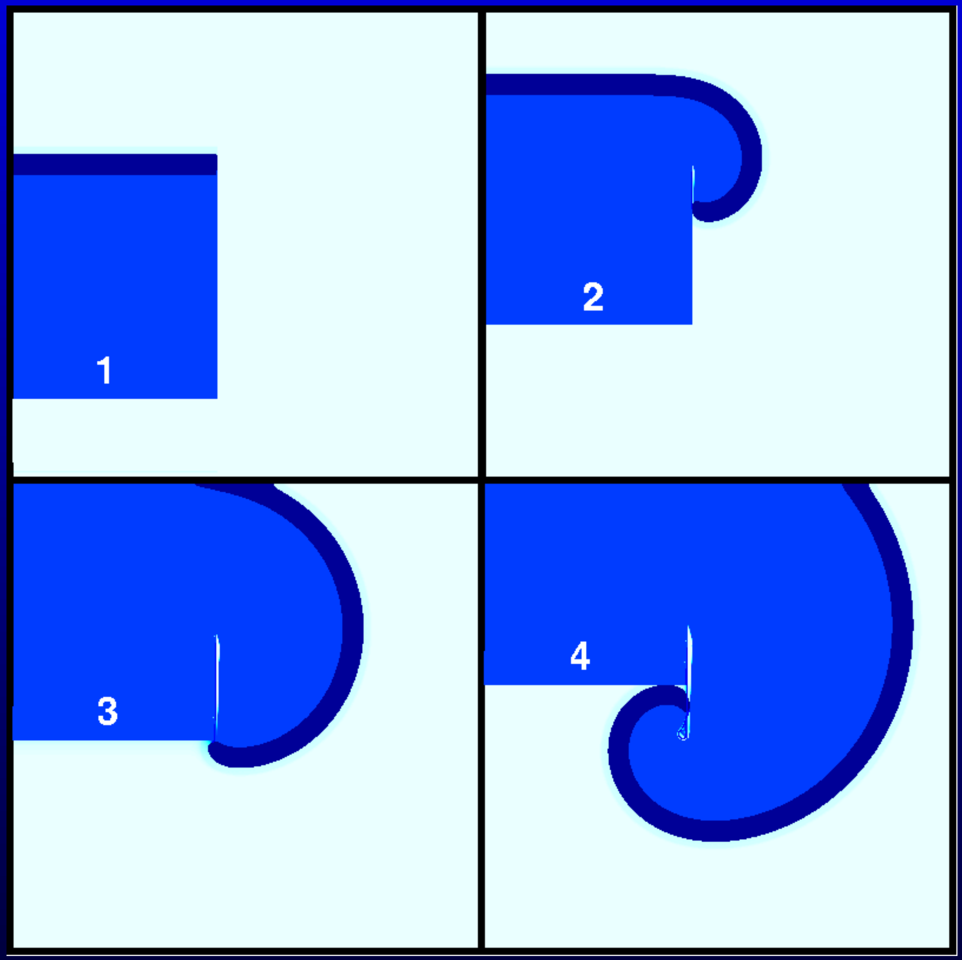
$T_{spiral} \approx L/v$ (anatomically pre-defined)

What determines dynamics of the (functional) spiral wave?



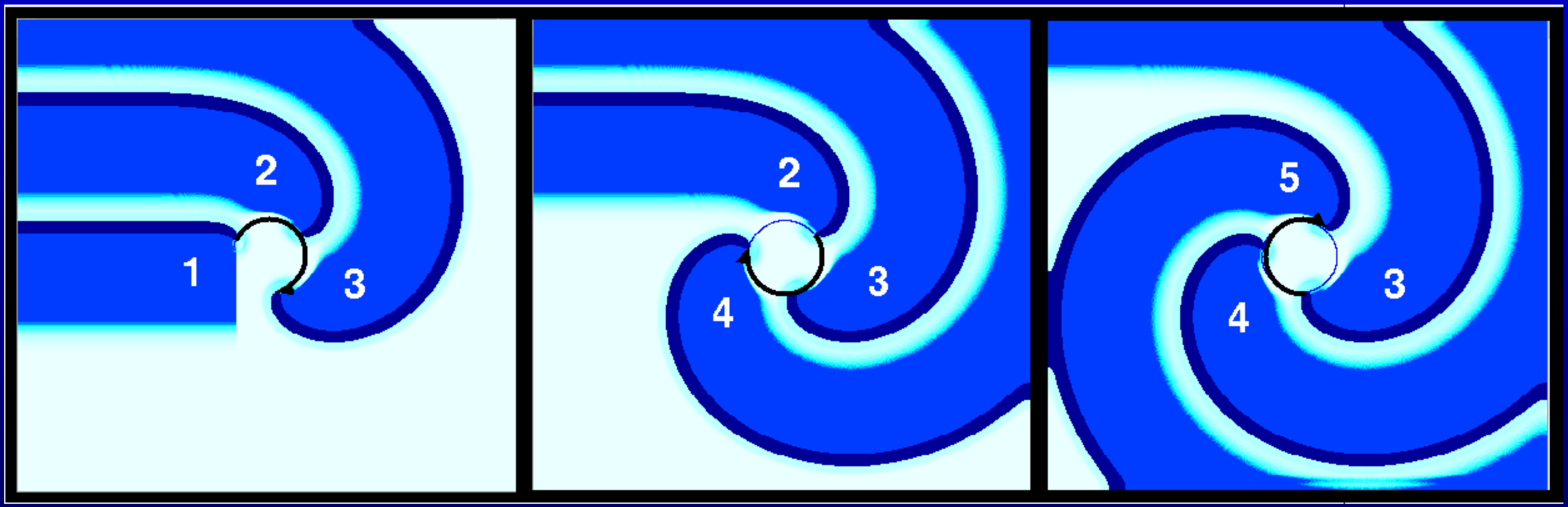
from A.V.Panfilov,in ” Cardiac Electrophysiology: From Cell to Bedside, 5th Edition”,Ed.D.P. Zipes and J. Jalife,p.329-337, (2009)

Instantaneous rotation (high excitability)



Period close to the reforactory period, small excitable gap

Circular rotation (lower excitability)



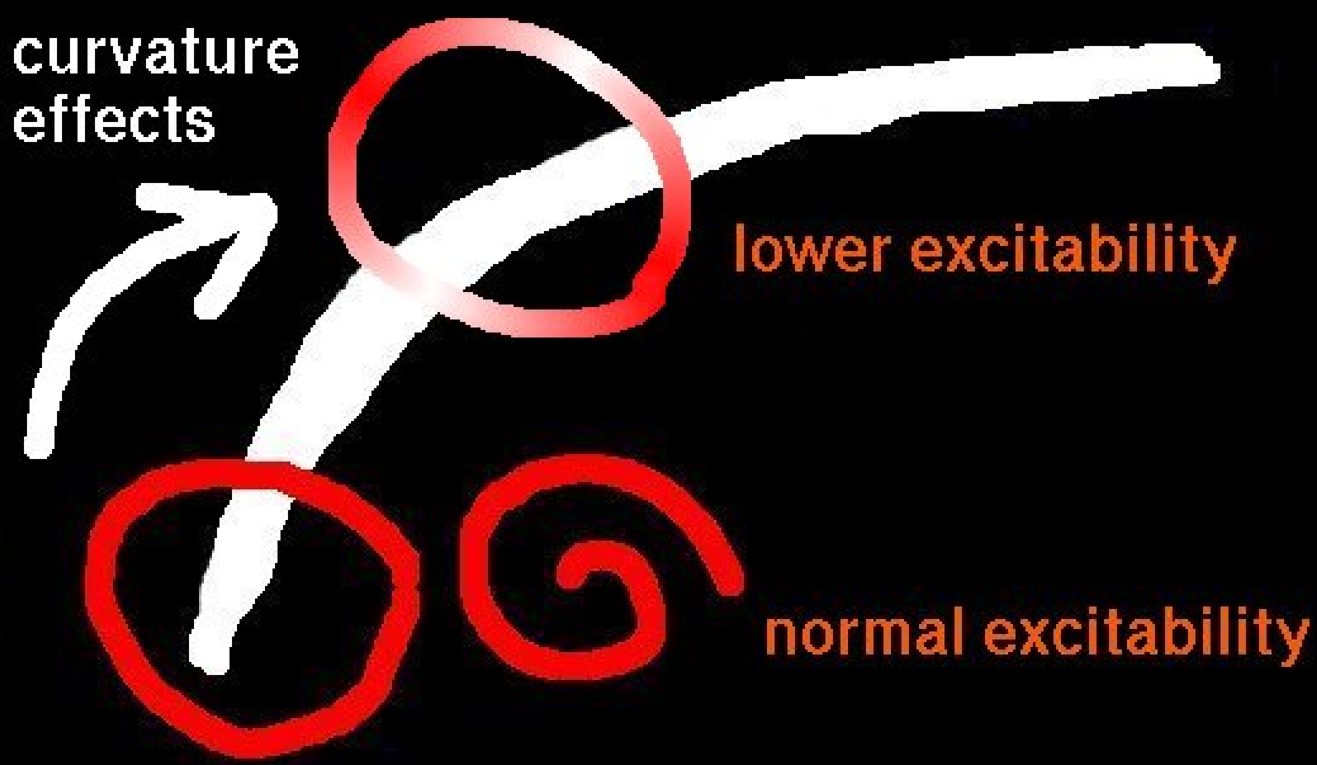
Period longer than the reforactory period, substantial excitable gap

Period on the APD restitution curve

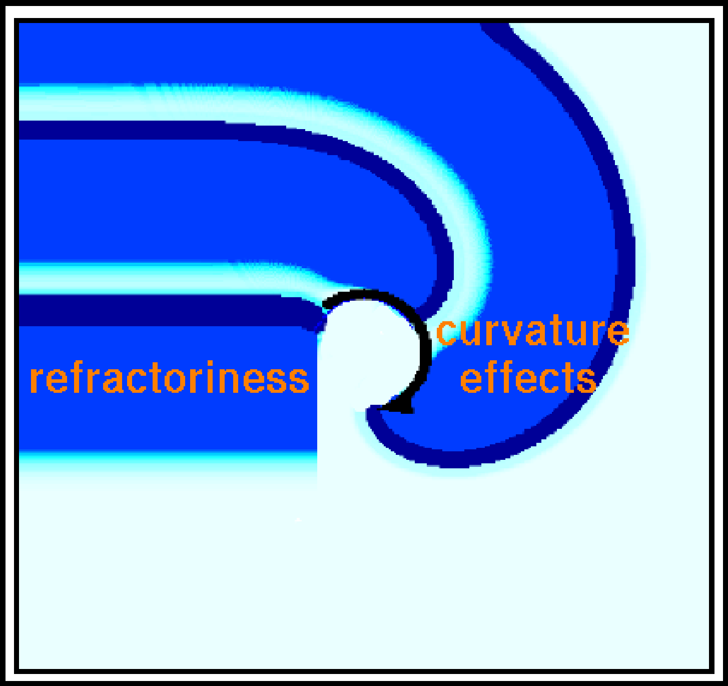
normal/high excitability

Period on the APD restitution curve

high → low excitability



Period of spiral wave

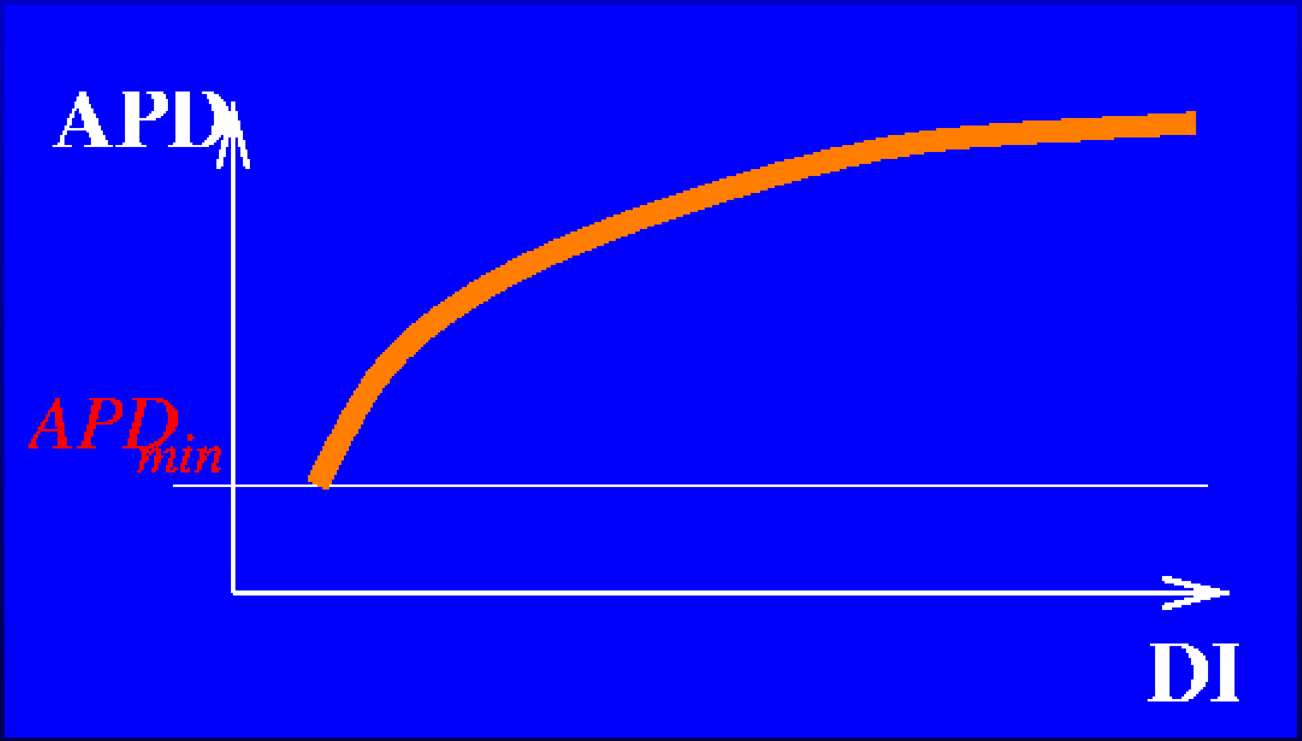


PERIOD

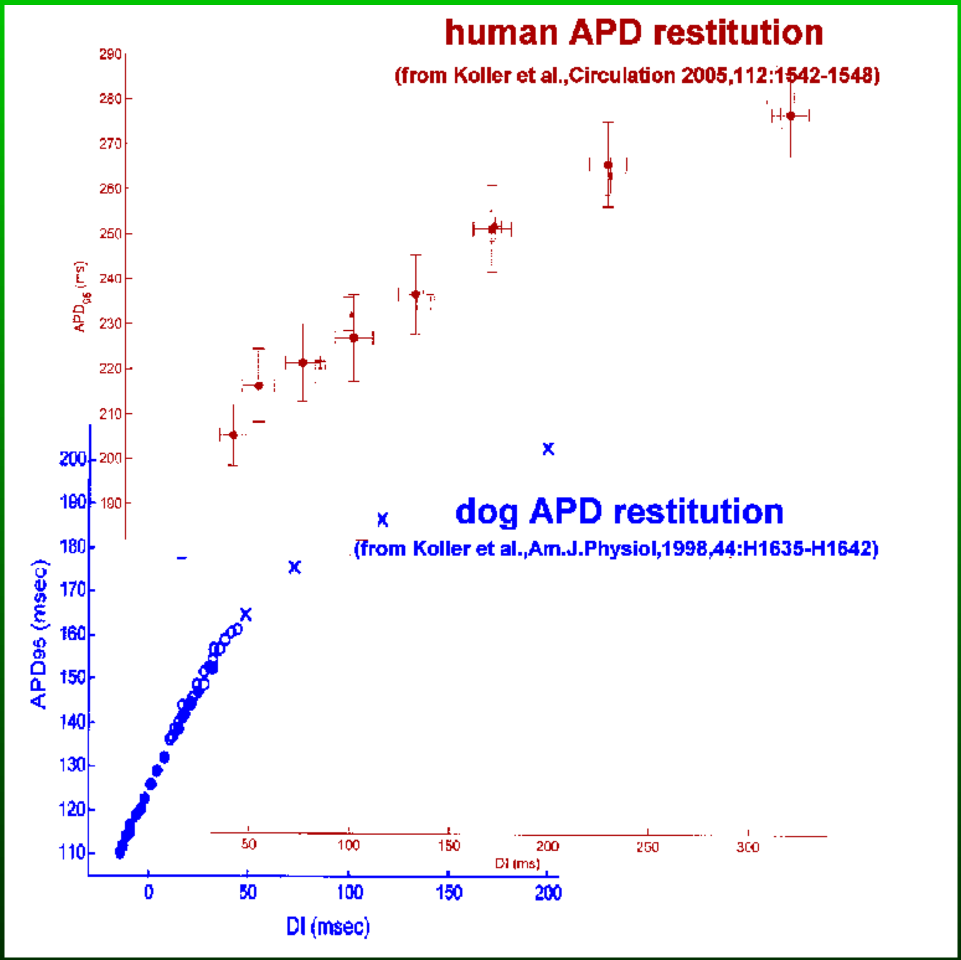
refractory period + curvature effects

curvature effects decrease
with increase of excitability

Role of APD_{min} on wave patterns

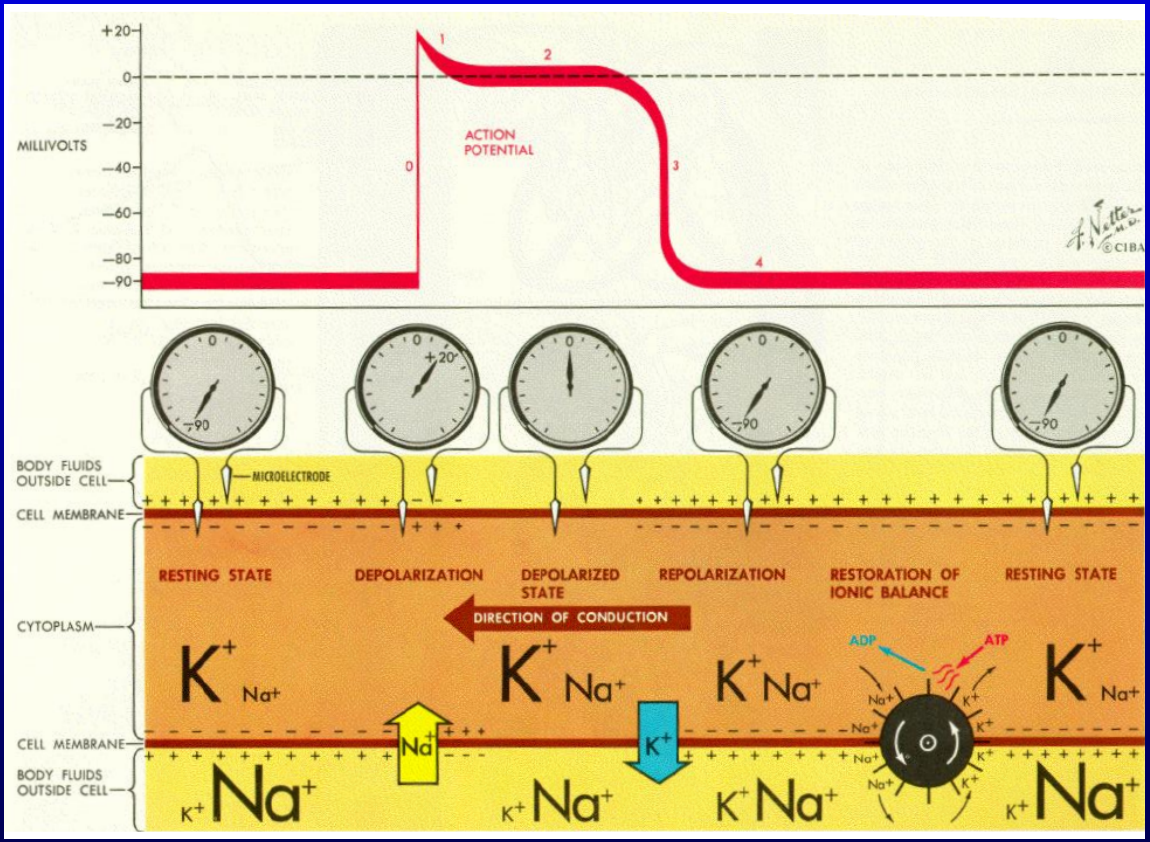


In human heart APD_{min} is substantially longer than in dog heart

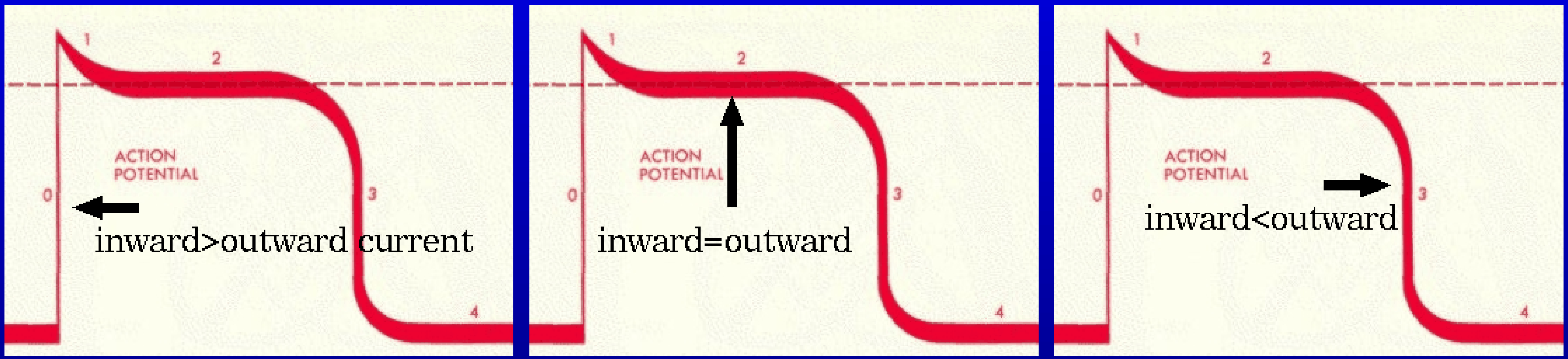


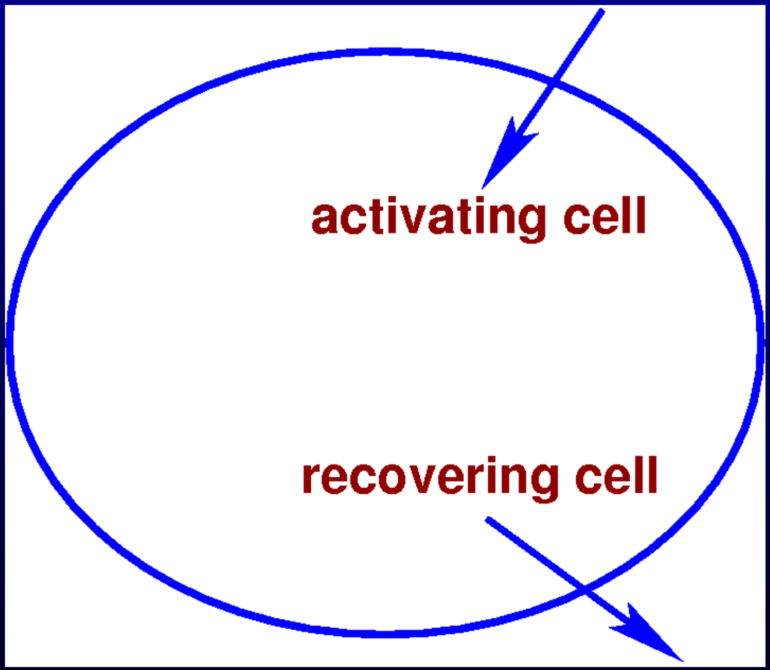
How to change period of spiral wave

Excitation at cellular level

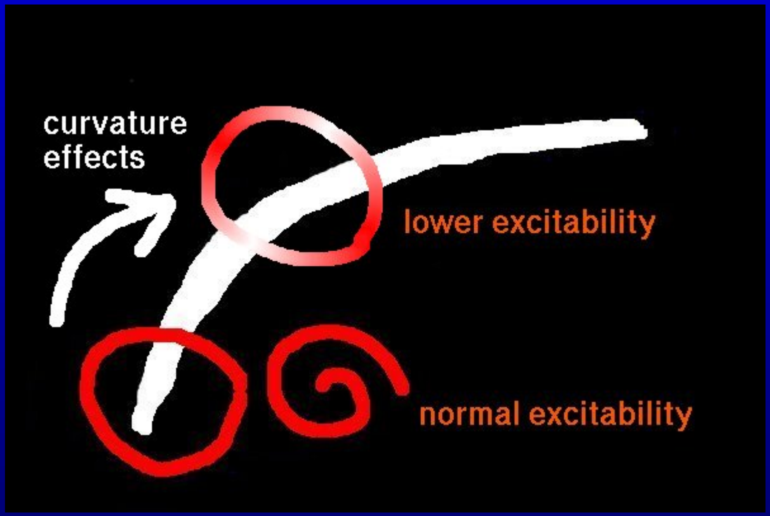


Balance of currents during action potential





How to change period of spiral wave

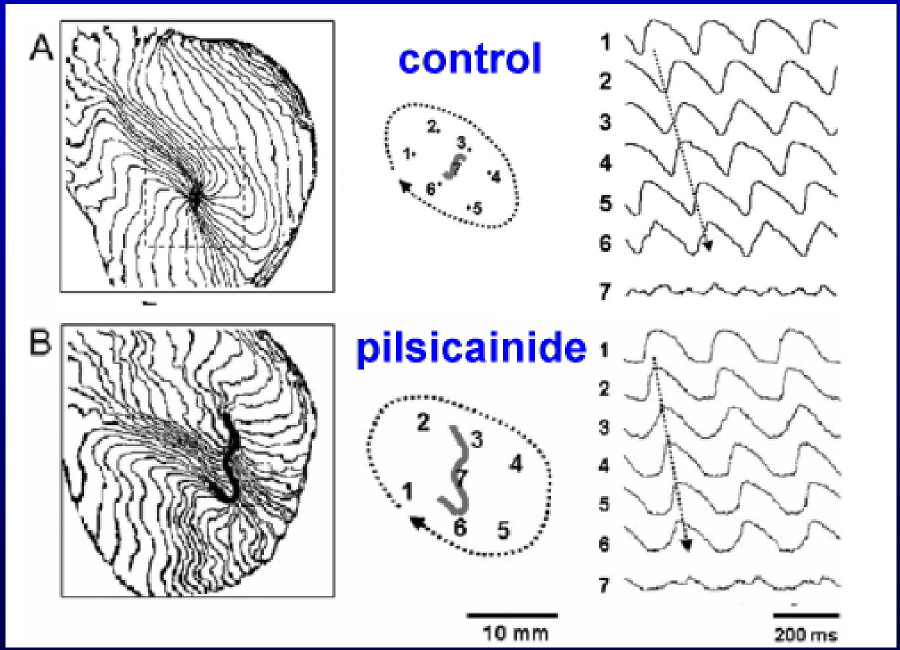


- To decrease refractory period one needs to increase the outwards (K^+) currents, or decrease I_{Ca}.
- To increase curvature effects one needs to decrease I_{Na}

I_{Na}

Sodium channel blockers (pilsicainide,disopyramide, cibenzoline):

- increase the period
- increase excitable gap
- increase size of the core
- make rotation more stable



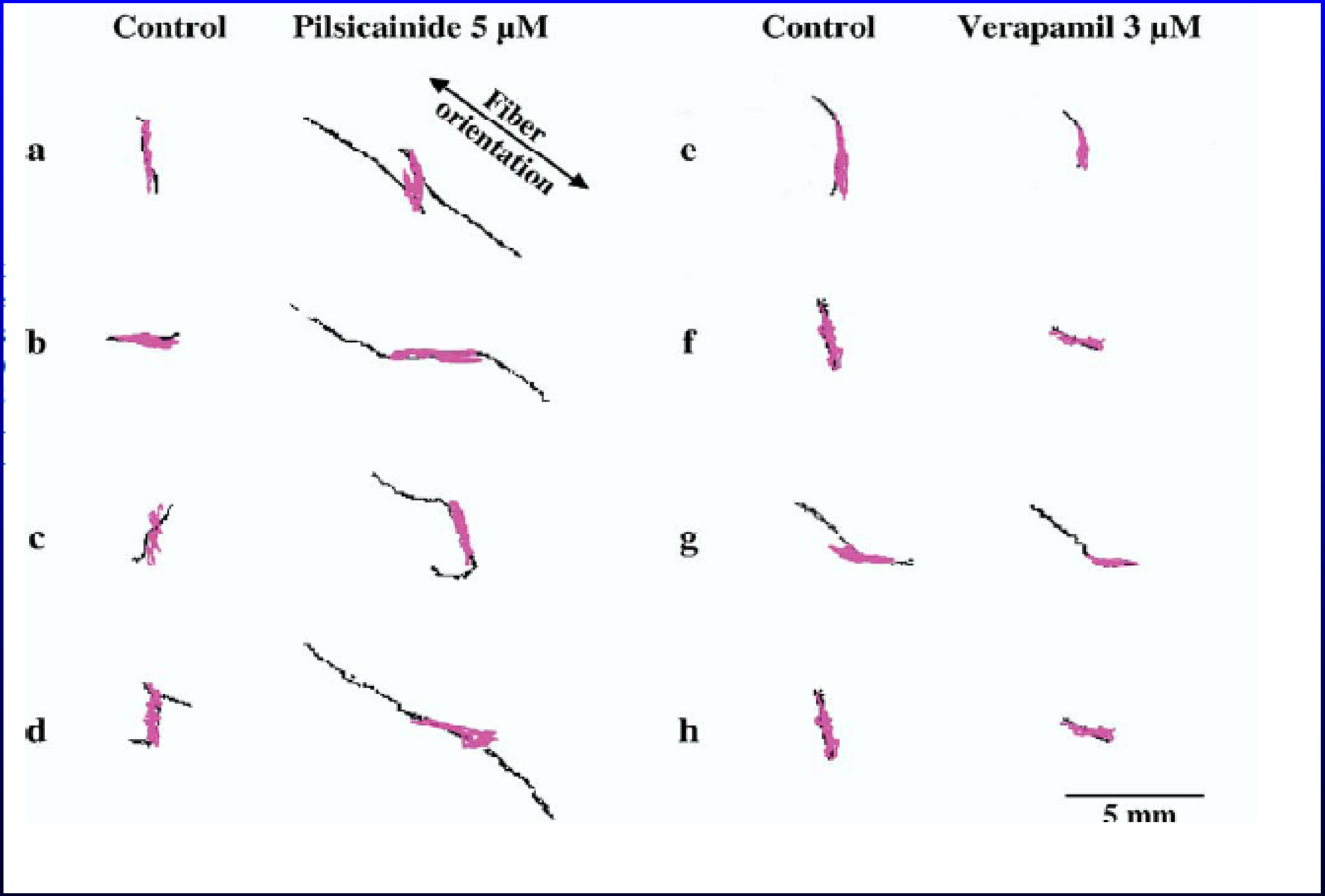
(Kodama et al., J. Electrocardiol.2005,38;126-130.)

I_{Ca}

Ca channel blocker (Verapamil 3μM):

- decrease size of the core
- decrease the period (141 to 109 ms)

(Ishiguro et al., Heart Rhythm .2009,6;684-692)

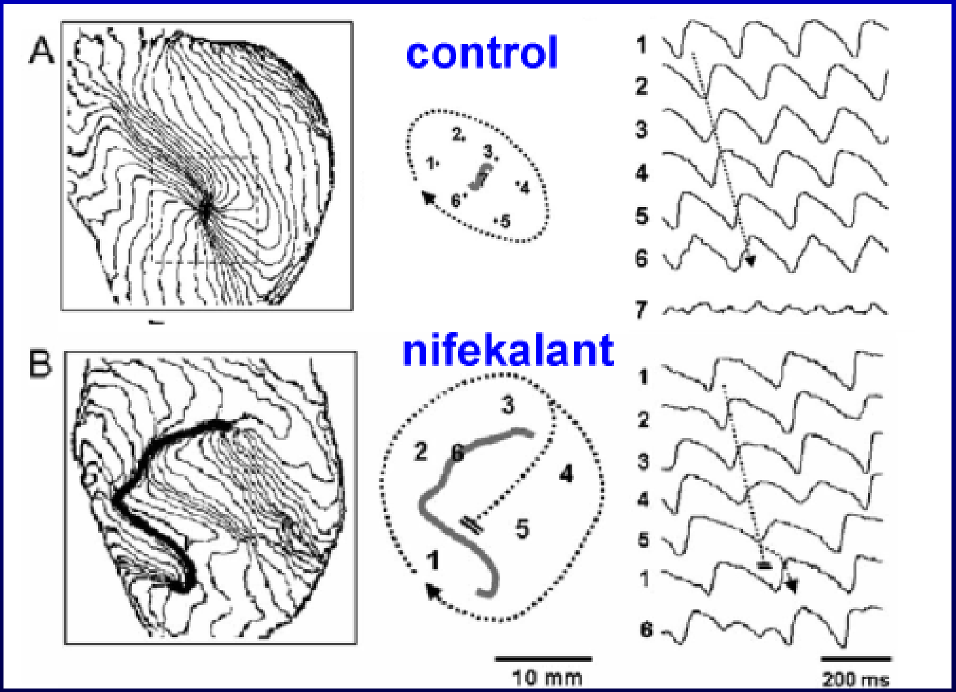


(Ishiguro et al., Heart Rhythm, 2009,6;684-692)

I_{Kr}

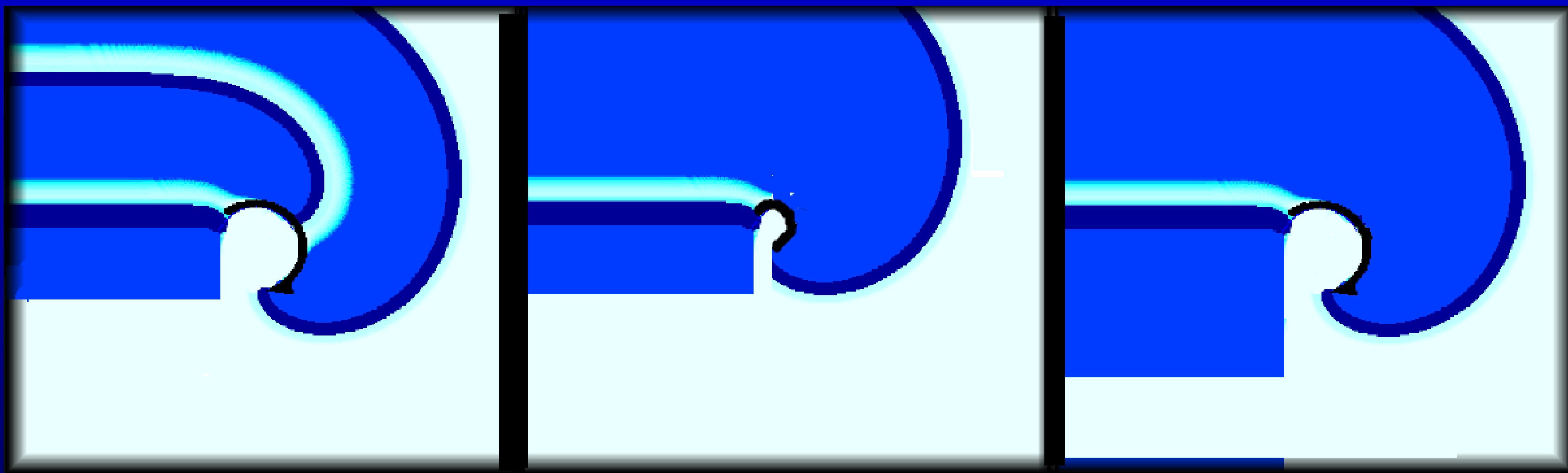
I_{Kr} blocker nifekalant:

- increase the period
- increase size of the core
- make rotation less stable



(Kodama et al., J. Electrocardiol.2005,38;126-130.)

Meandering of spiral waves

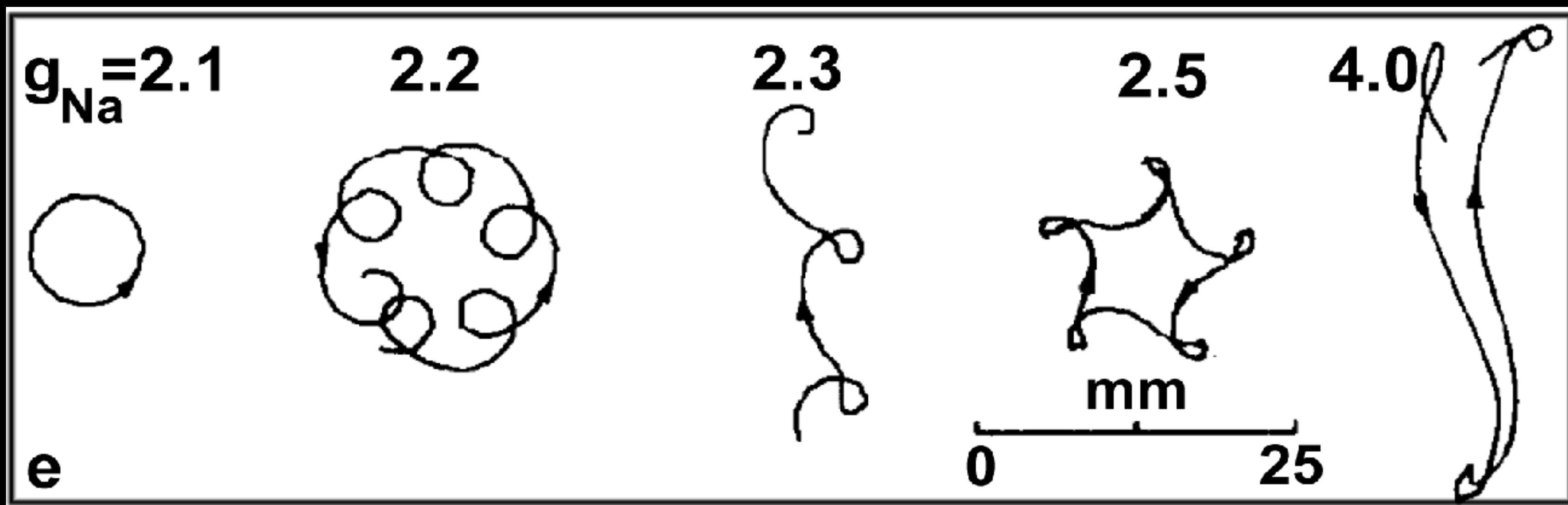


circular

meadering
higher 'I_{Na}'

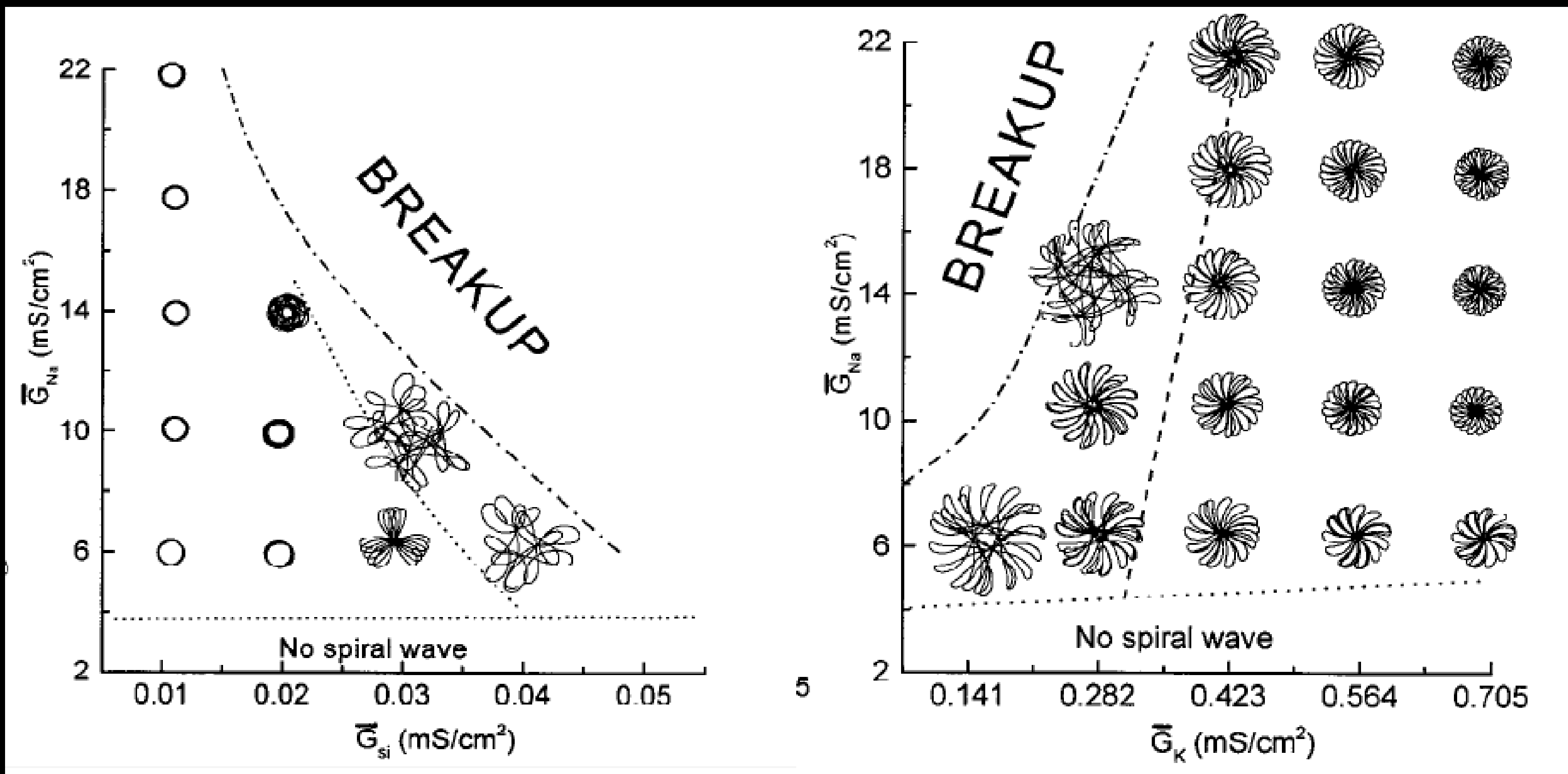
meandering
lower 'I_K'

Meandering and I_{Na}



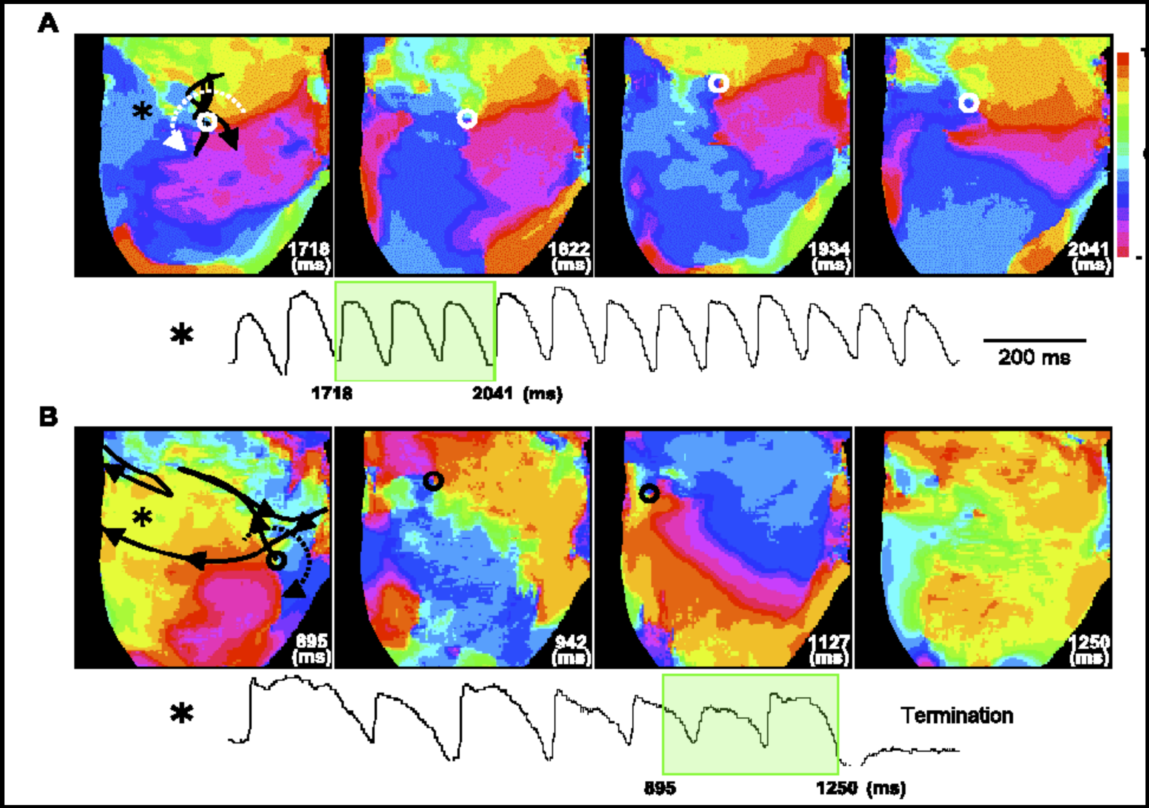
(from Efimov, Krinsky, Jalife,Chaos,1995,5;513-526.)

Meandering in LR1 model



(from Qu et al., Ann. Biomed. Eng.,200;28;755-771.)

Meandering and nifekalant (class III)



(from Yamazaki et al., AJP,2007,292;H539-H548.)

Meandering and I_{K1}

J Physiol 578.1 (2007) pp 315–326

Up-regulation of the inward rectifier K^+ current (I_{K1}) in the mouse heart accelerates and stabilizes rotors

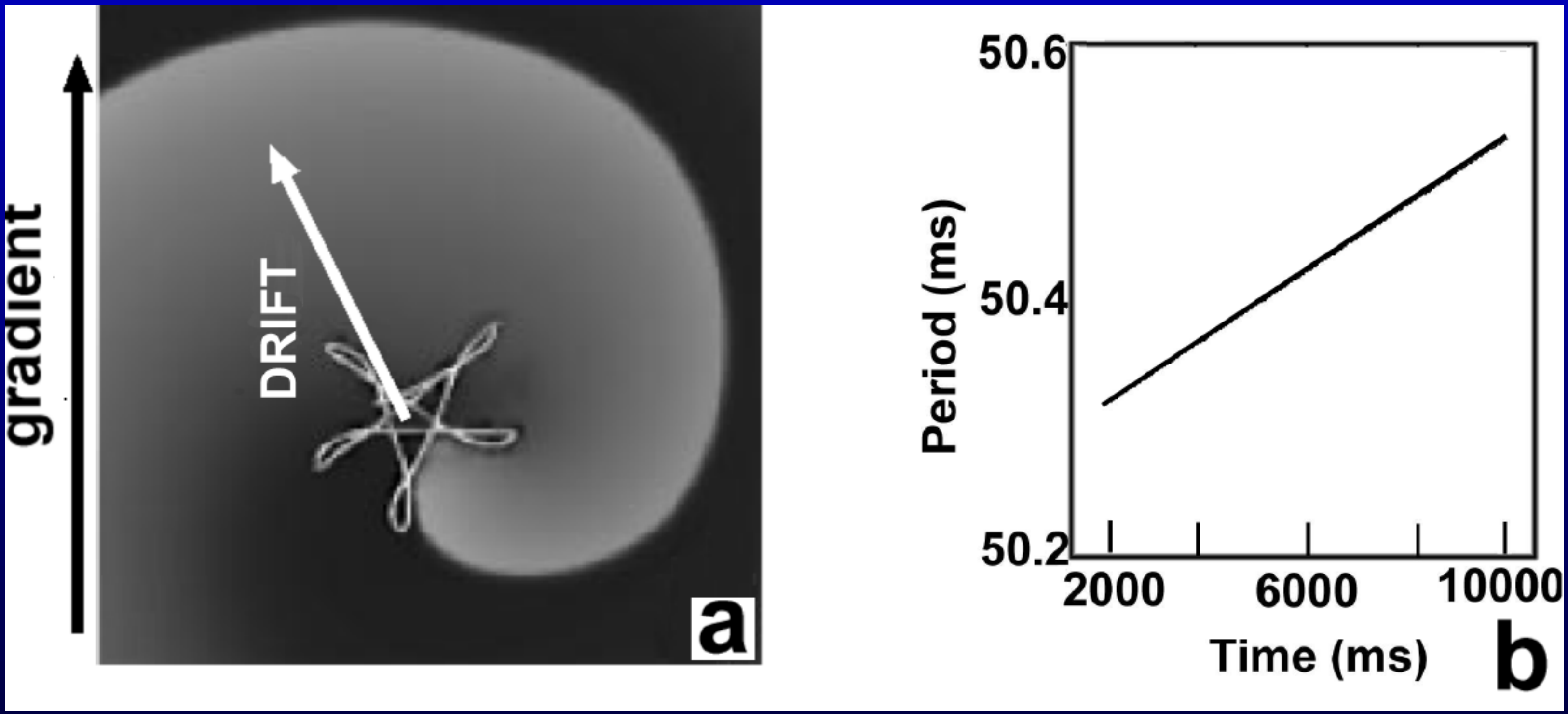
Sami F. Noujaim[1]*, Sandeep V. Pandit[1]*, Omer Berenfeld[1], Karen Vikstrom[1], Marina Cerrone[1], Sergey Mironov[1], Michelle Zugermayr[1], Anatoli N. Lopatin[2] and José Jalife[1]

[1]*Institute for Cardiovascular Research and Department of Pharmacology, SUNY Upstate Medical University, Syracuse, NY, USA*
[2]*Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI, USA*

Previous studies have suggested an important role for the inward rectifier K^+ current (I_{K1}) in stabilizing rotors responsible for ventricular tachycardia (VT) and fibrillation (VF). To test this hypothesis, we used a line of transgenic mice (TG) overexpressing Kir 2.1–green fluorescent protein (GFP) fusion protein in a cardiac-specific manner. Optical mapping of the epicardial surface in ventricles showed that the Langendorff-perfused TG hearts were able to sustain stable VT/VF for 350 ± 1181 s at a very high dominant frequency (DF) of 44.6 ± 4.3 Hz. In contrast, tachyarrhythmias in wild-type hearts (WT) were short-lived (3 ± 9 s), and the DF was 26.3 ± 5.2 Hz. The stable, high frequency, reentrant activity in TG hearts slowed down, and eventually terminated in the presence of 10 μM Ba^{2+}, suggesting an important role for I_{K1}. Moreover, by increasing I_{K1} density in a two-dimensional computer model having realistic mouse ionic and action potential properties, a highly stable, fast rotor (≈45 Hz) could be induced. Simulations suggested that the TG hearts allowed such a fast and stable rotor because of both greater outward conductance at the core and shortened action potential duration in the core vicinity, as well as increased excitability, in part due to faster recovery of Na^+ current. The latter resulted in a larger rate of increase in the local conduction velocity as a function of the distance from the core in TG compared to WT hearts, in both simulations and experiments. Finally, simulations showed that rotor frequencies were more sensitive to changes (doubling) in I_{K1}, compared to other K^+ currents. In combination, these results provide the first direct evidence

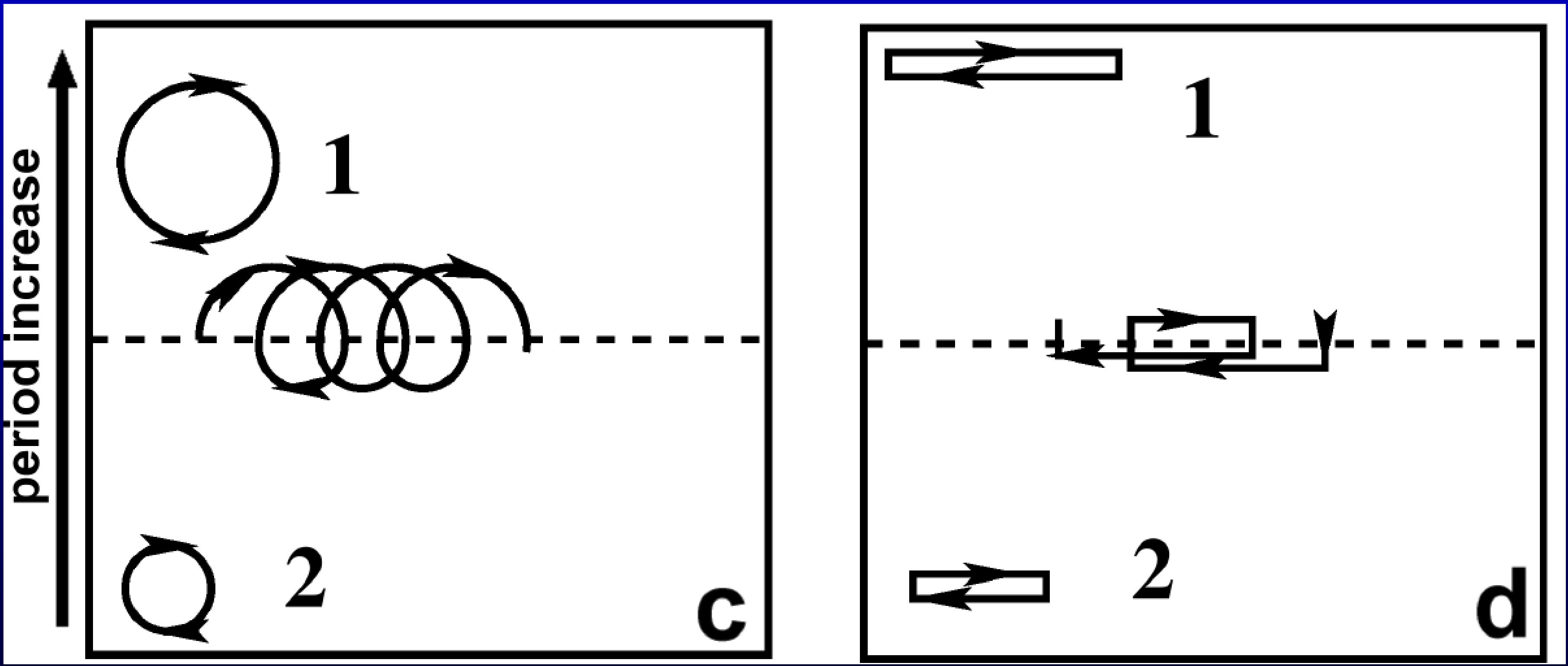
Spirals in heterogeneous medium

spiral wave drift in a gradient heterogeneity

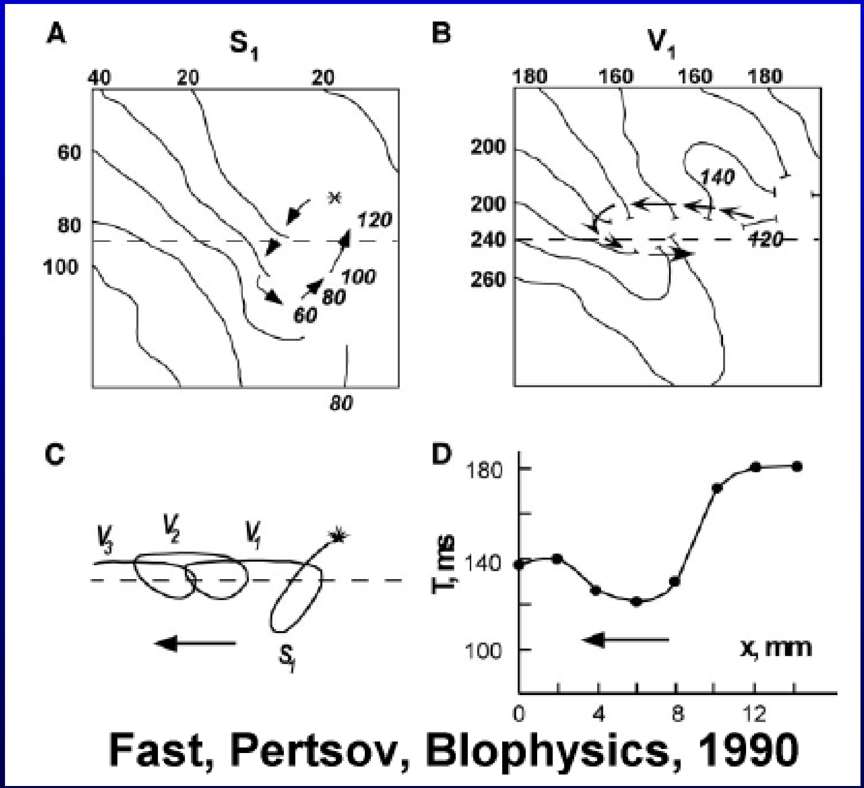


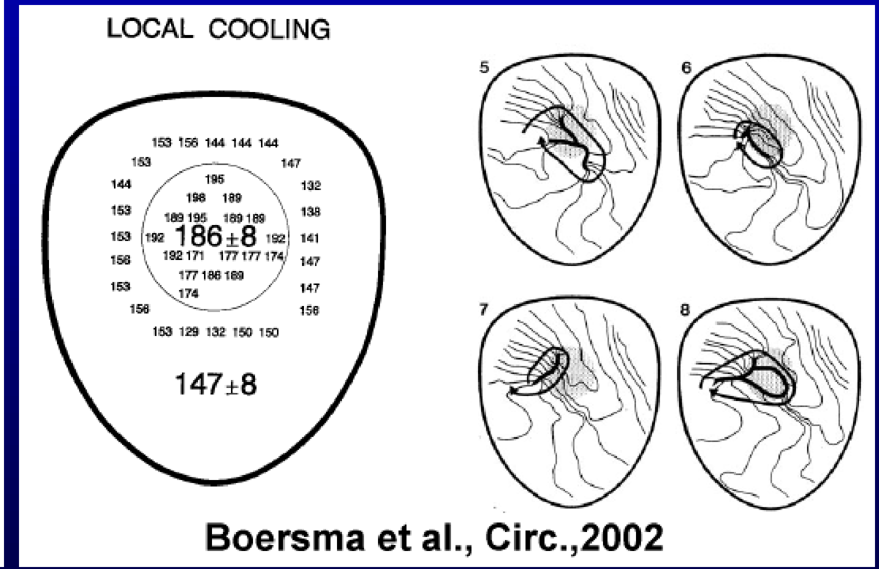
Ten Tusscher Panfilov, AJP, 2003

the transversal component of spiral wave drift



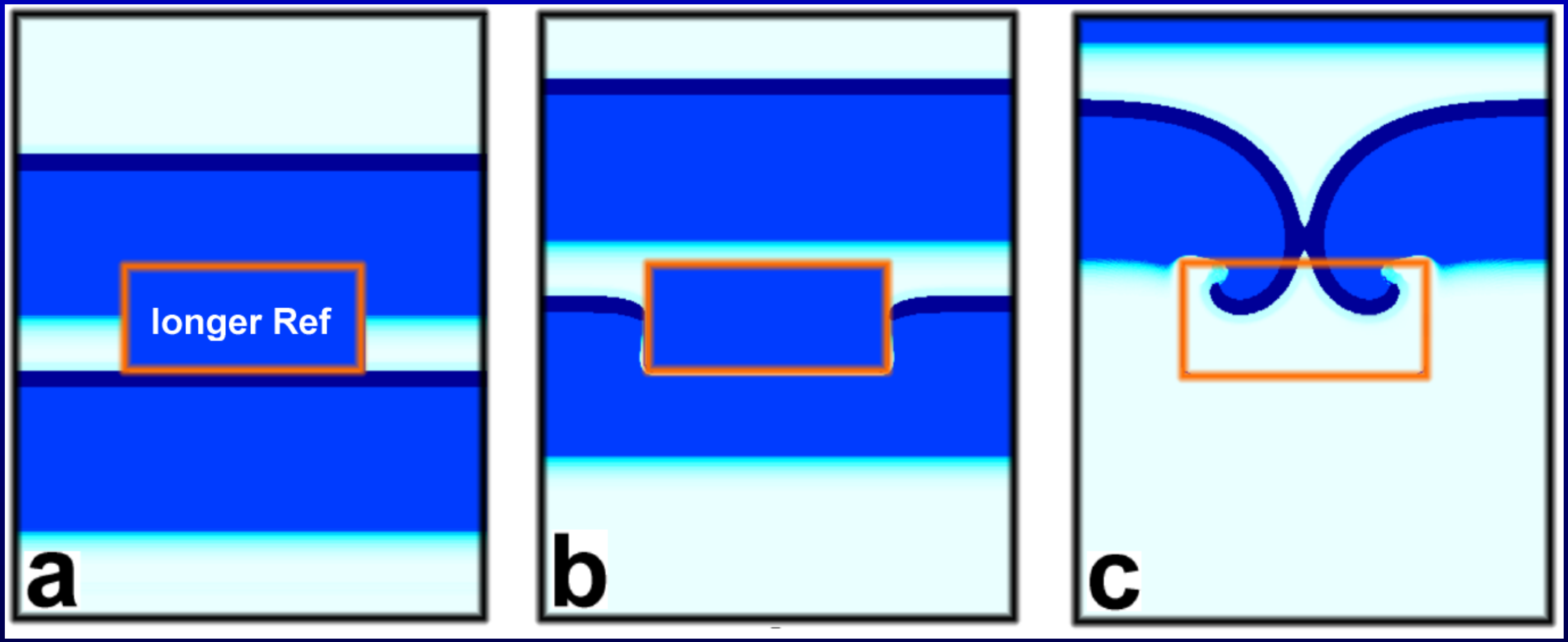
drift in experiement





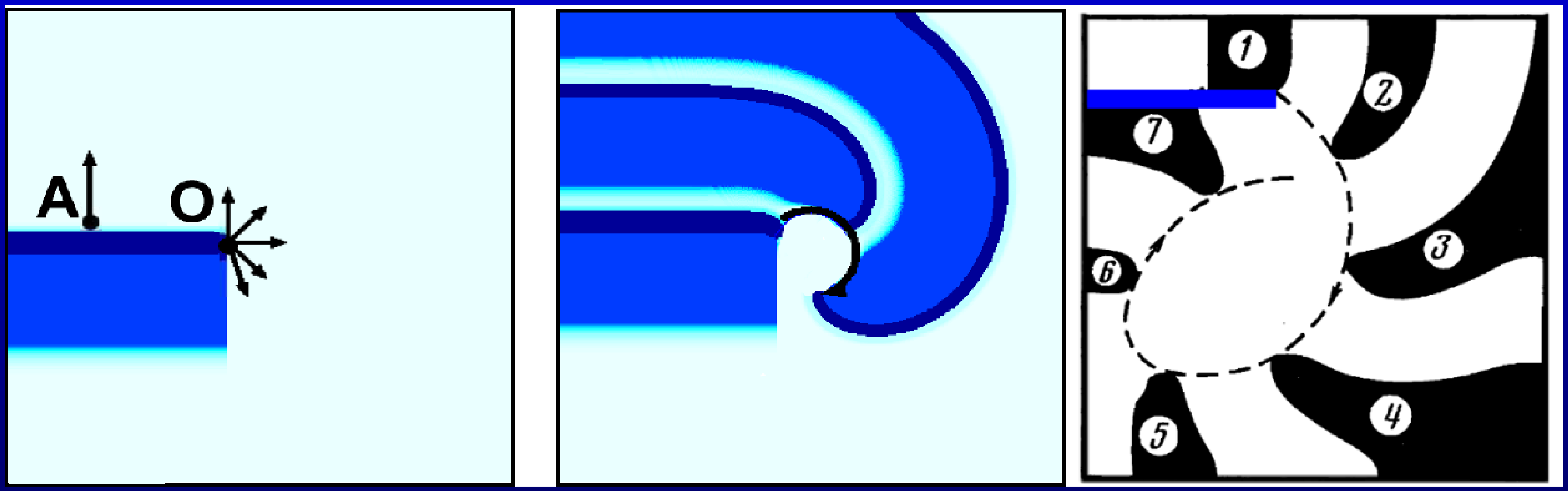
Initiation of spiral waves

spiral waves created by heterogeneity



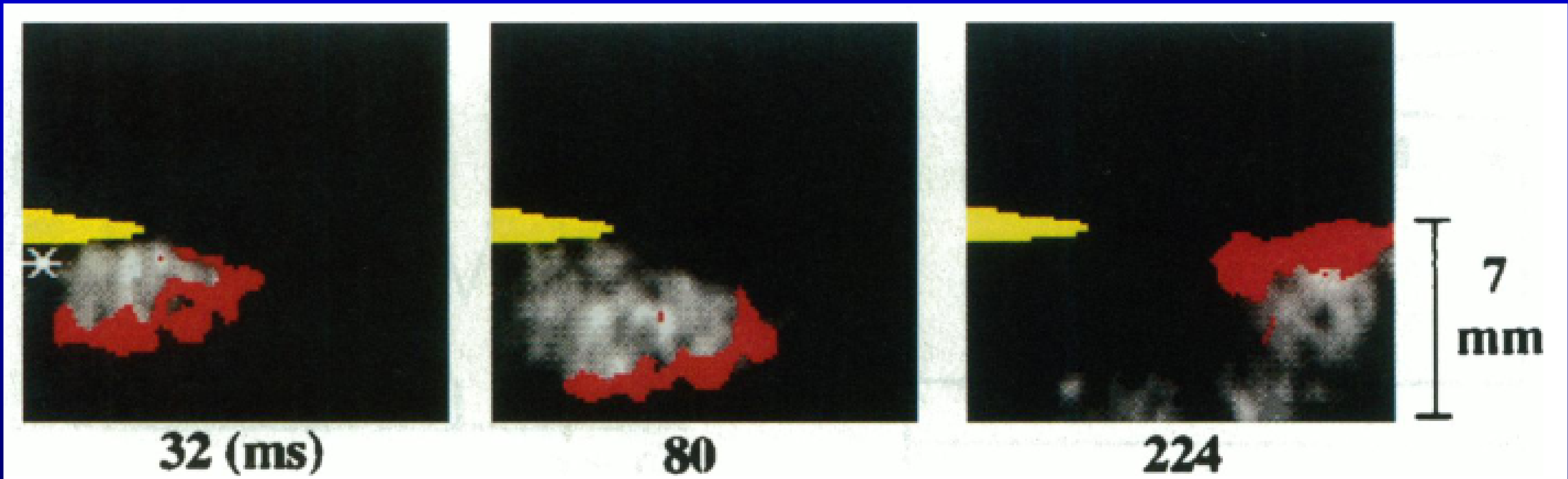
Krinsky, Biophysics 1966

spiral waves created by geometry



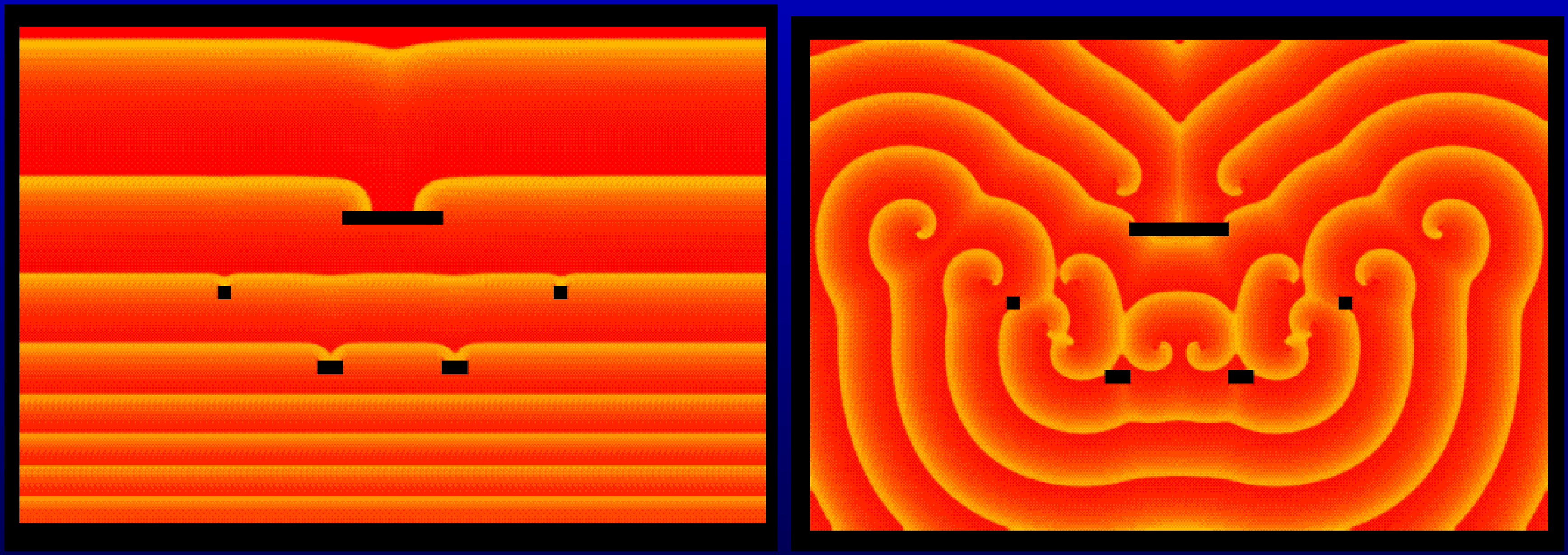
Panfilov and Pertsov, Biophysics, 1982

spiral waves created by geometry



Cabo et al., BJ, 1996

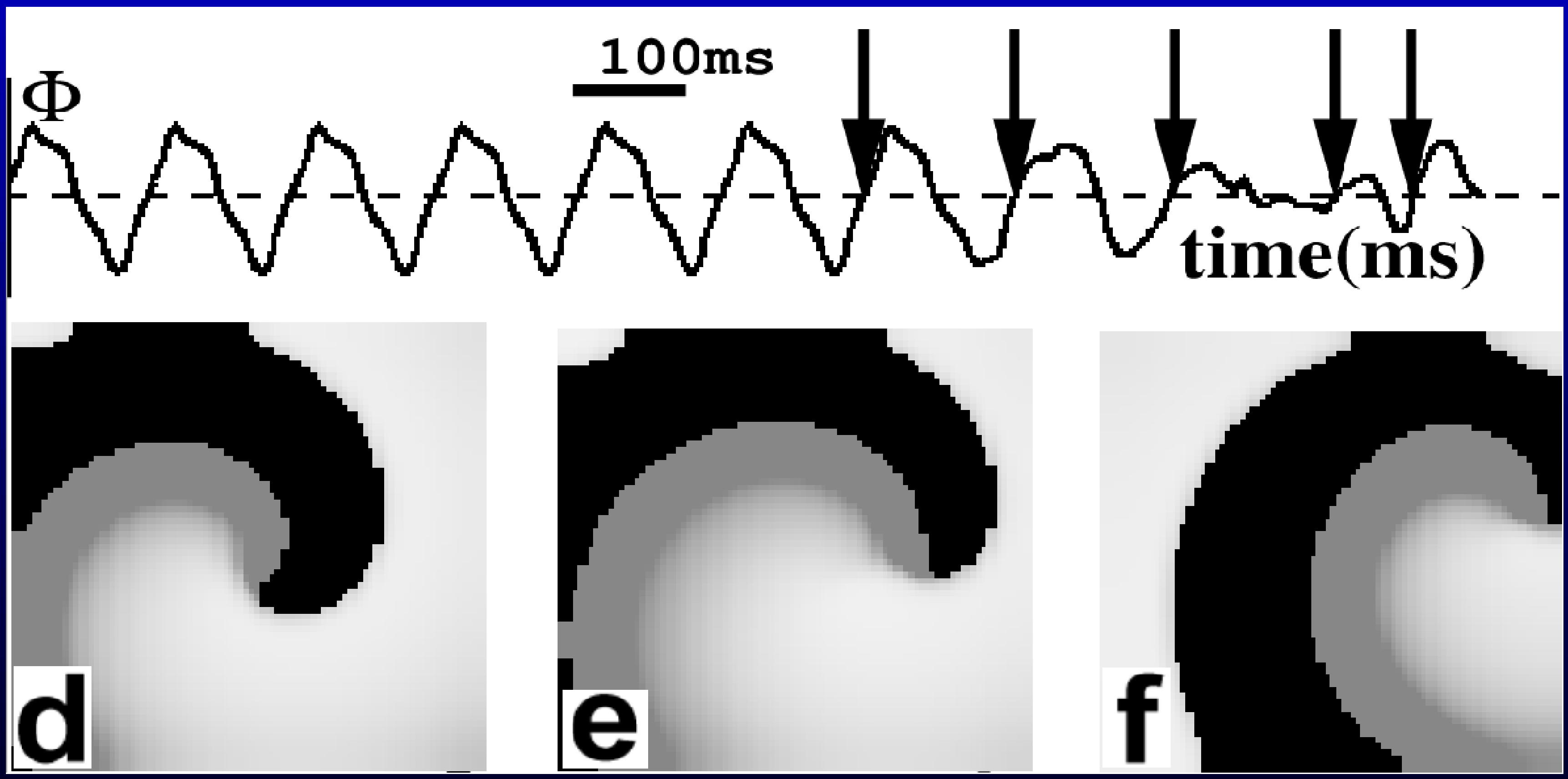
spiral waves created by geometry (effect of frequency of stimulation)



(from K. Agladze, J. Keener, S.C. Müller and A. Panfilov, *Science*, v.264, 1746-1748, (1994).)

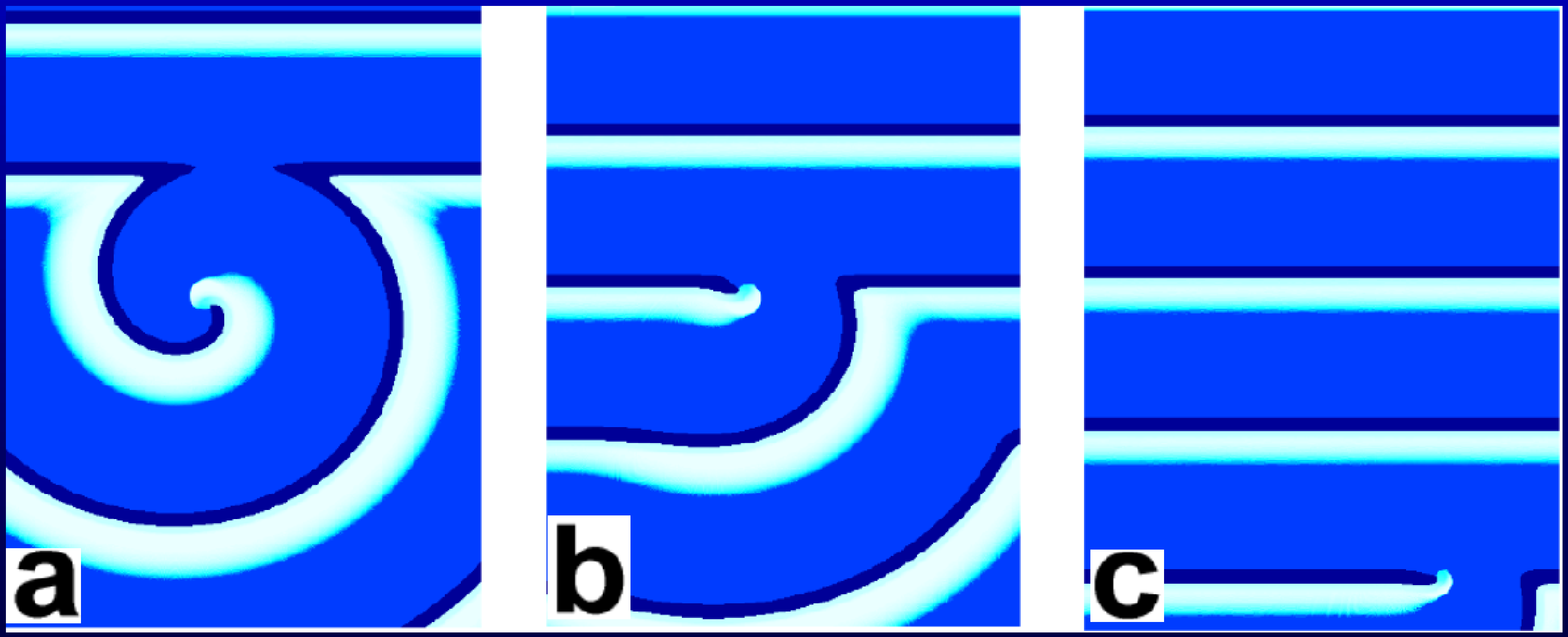
Non-pharmacological ways to remove spiral waves

Resonant drift of spiral waves



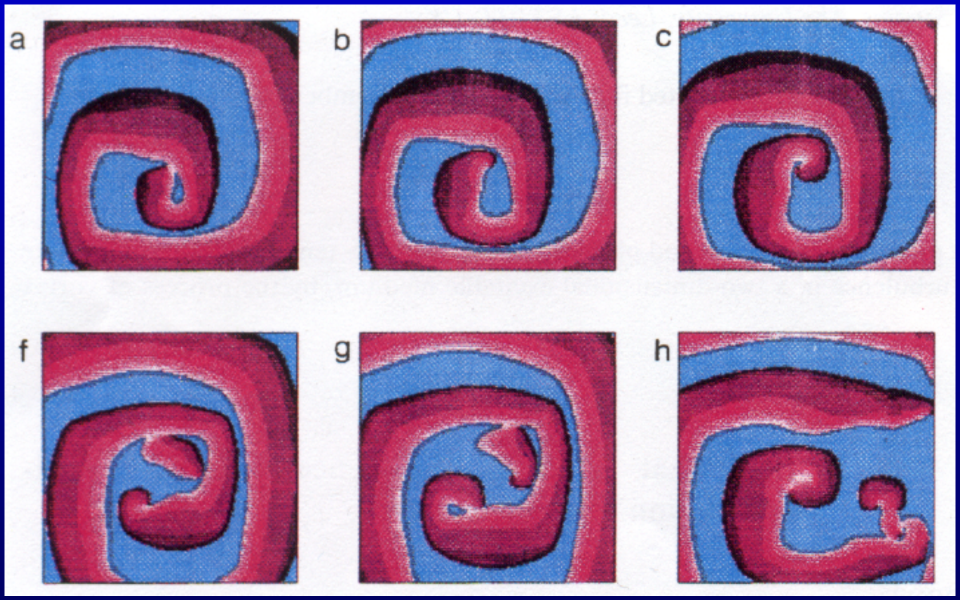
Davydov 1982

Overdrive pacing of spiral waves



Krinsky and Agladze, Physica D 1983

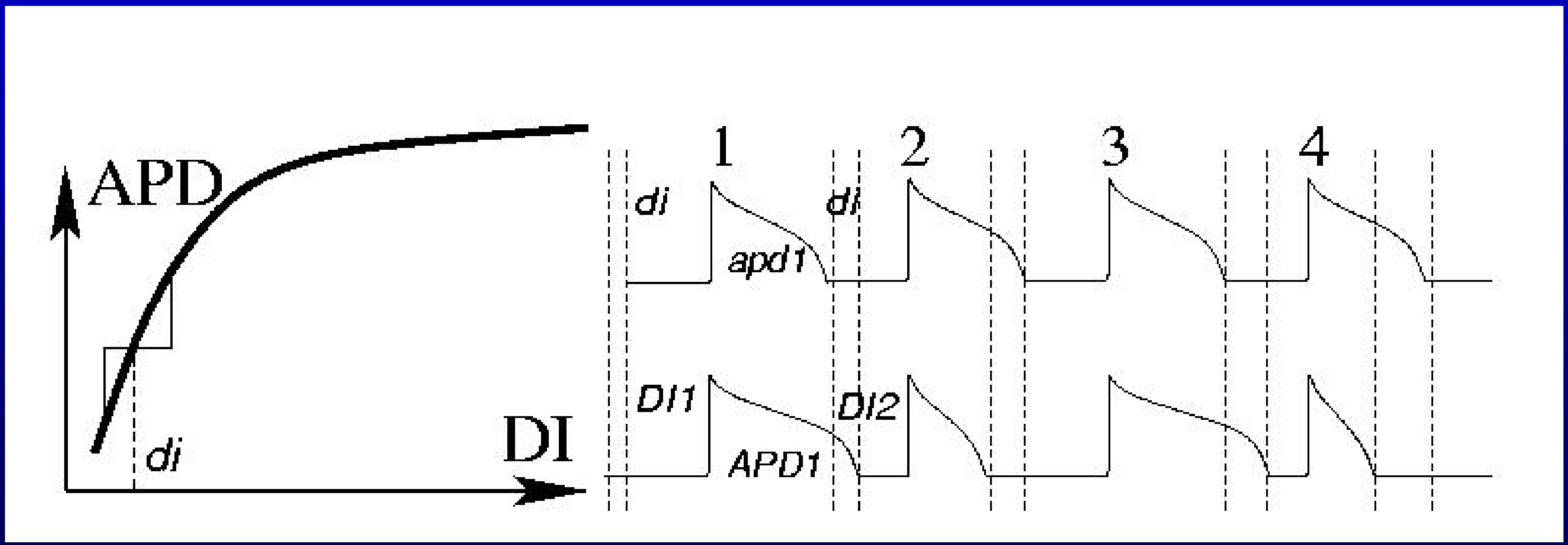
Breakup

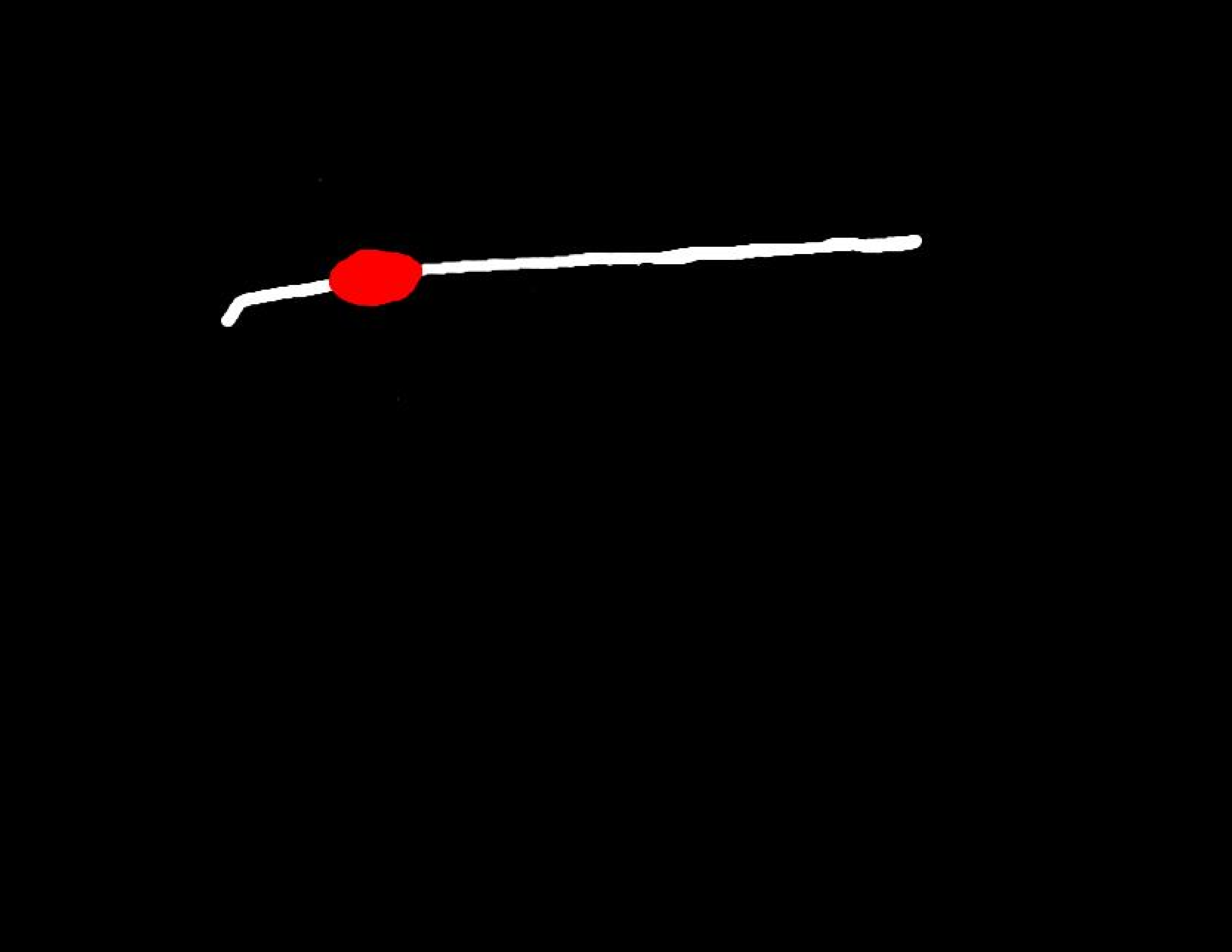


Spiral breakup in N 1962 model *from (Panfilov,Holden, Physics Letters A, v.151,23-26, 1990)*.

Breakup occurs if the slope of the APD restitution curve is greater than 1

(Nolasco & Dahlen 1964, Guevara et al., 1984, Karma 1994)





Restitution and VF

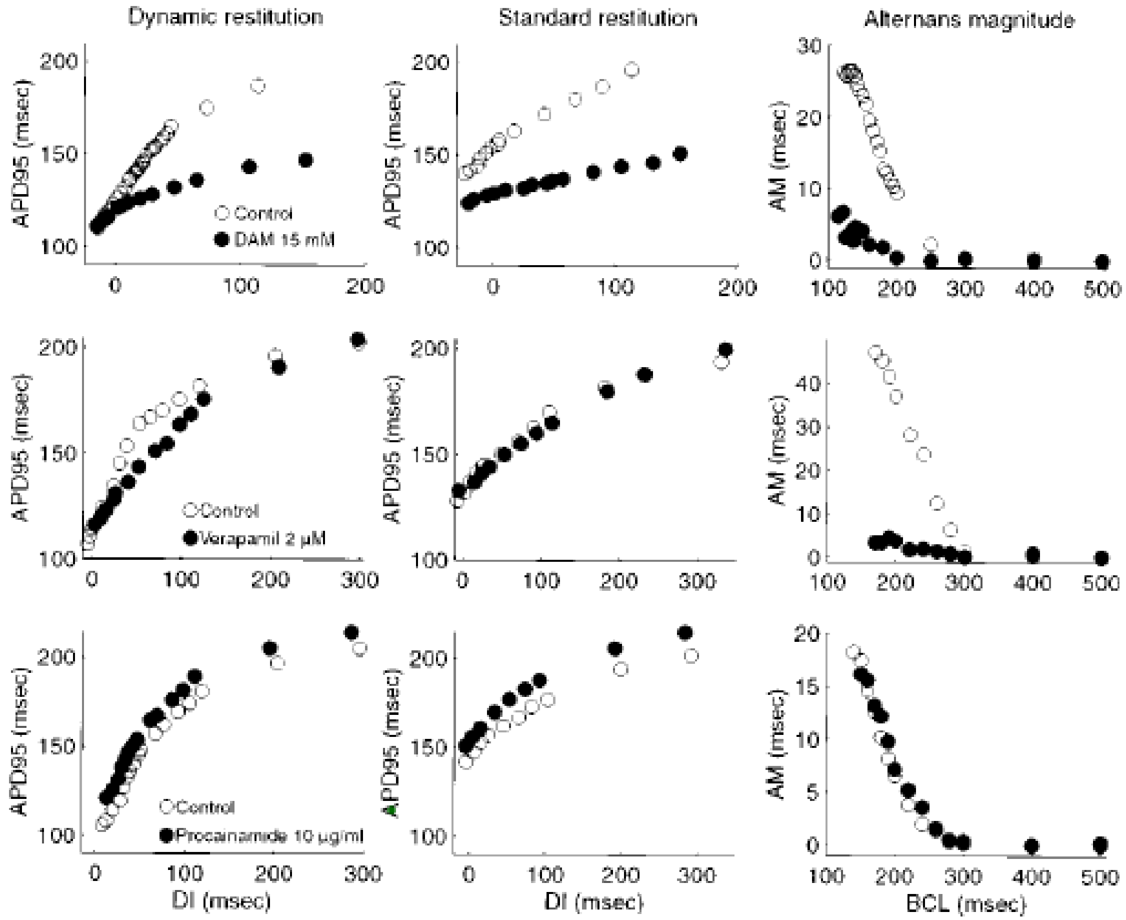


Figure 1. Effects of drugs on dynamic restitution, standard restitution, and magnitude of APD alternans in canine endocardium. Results are shown for DAM (15 mmol/L, top panels), verapamil (2 μmol/L, middle panels), and procainamide (10 μg/mL; bottom panels).

Effects of drugs on dynamic restitution (from: Ricco et al., 1999)

Restitution and VF

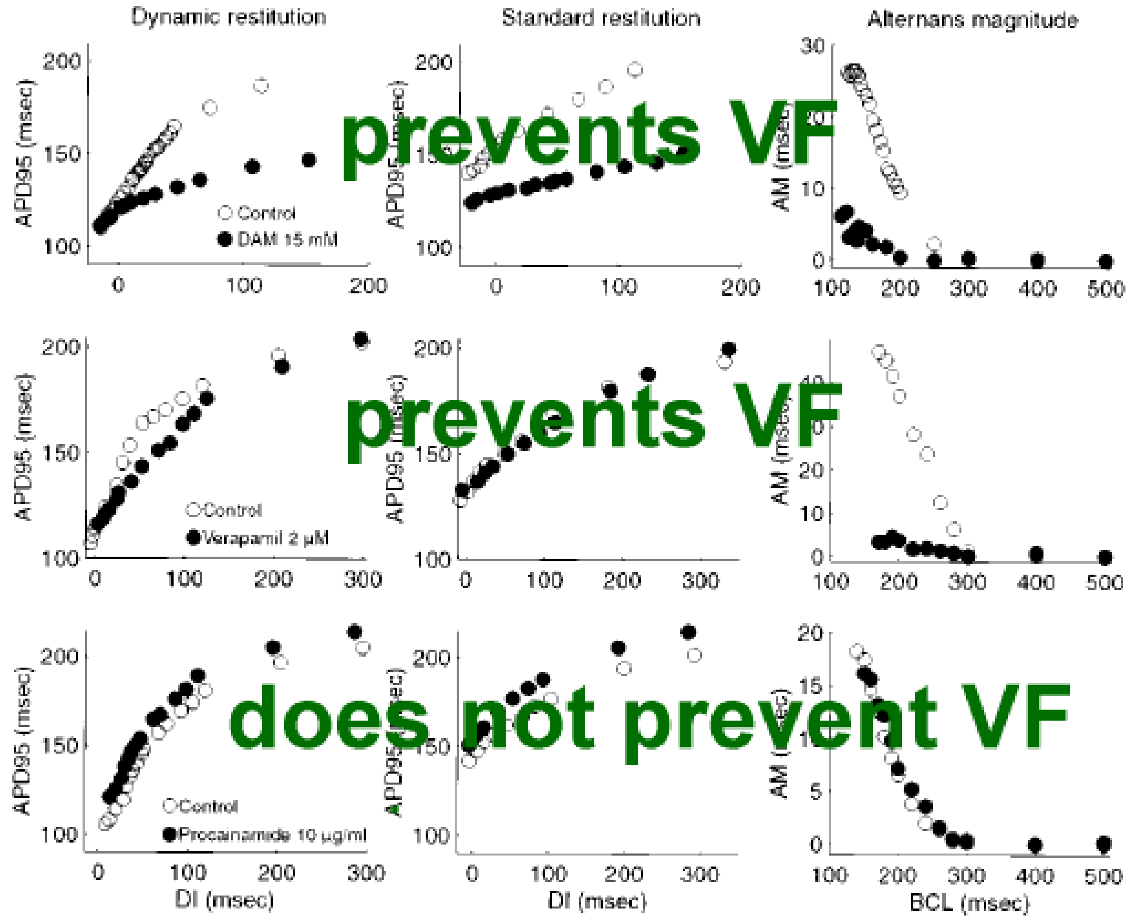


Figure 1. Effects of drugs on dynamic restitution, standard restitution, and magnitude of APD alternans in canine endocardium. Results are shown for DAM (15 mmol/L, top panels), verapamil (2 μmol/L, middle panels), and procainamide (10 μg/mL; bottom panels).

Effects of drugs on dynamic restitution (from: Ricco et al., 1999)

3D propagation

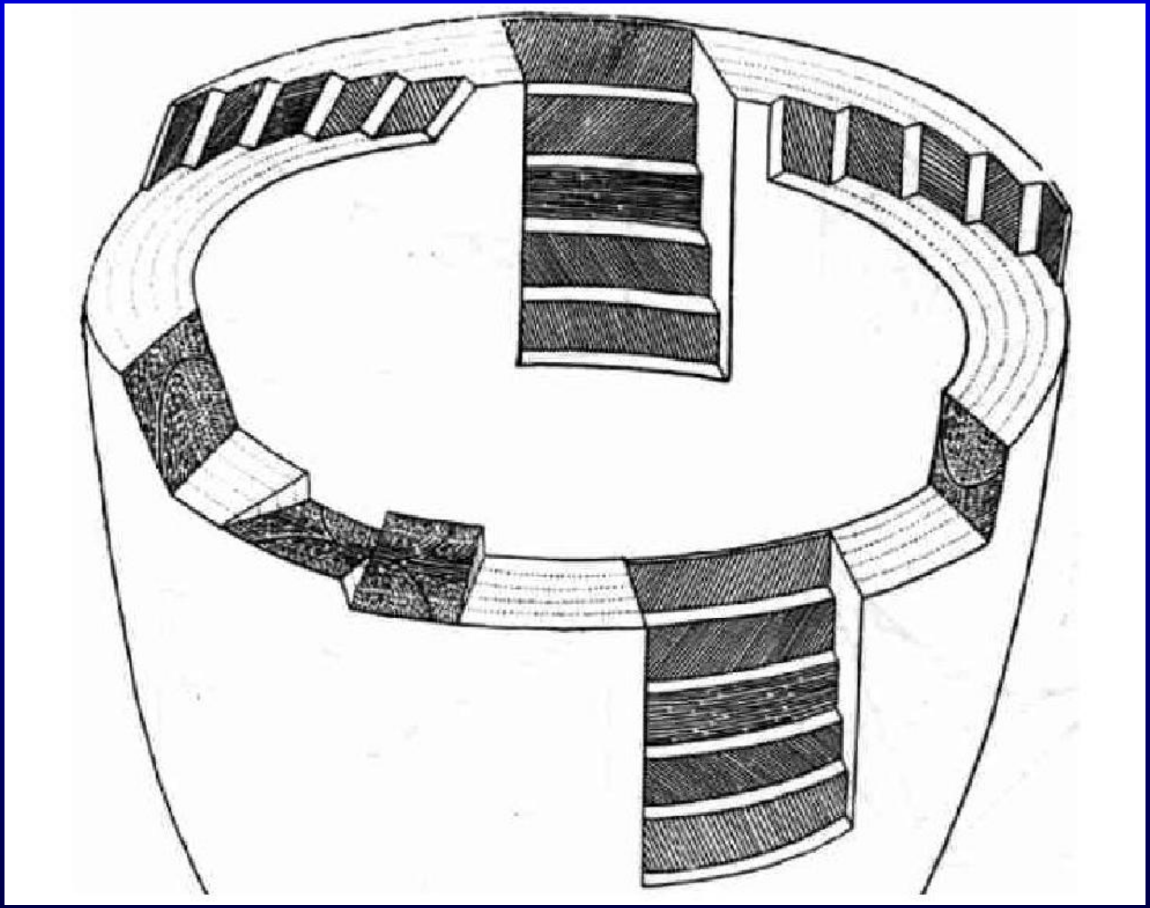
3D propagation

$$\frac{\partial V_m}{\partial t} = div\, d\, grad V_m + I_{ion}(V_m, g_i)$$

$$\frac{\partial g_i}{\partial t} = (\phi(V_m) - g_i)/\tau(V_m)$$

$$d = \begin{pmatrix} d_{11} & d_{12} & d_{13} \\ d_{21} & d_{22} & d_{23} \\ d_{31} & d_{32} & d_{33} \end{pmatrix}$$

3D anistropy

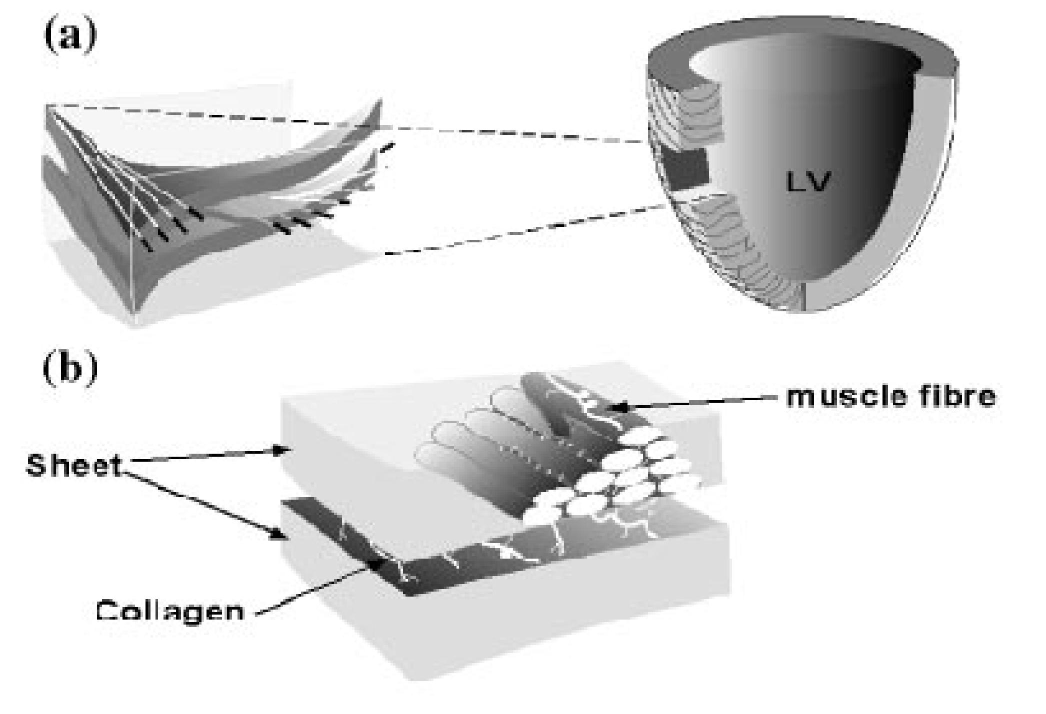


(Feneis H, Morphol Jahrb,v.89:371-406,1943)

Conduction tensor

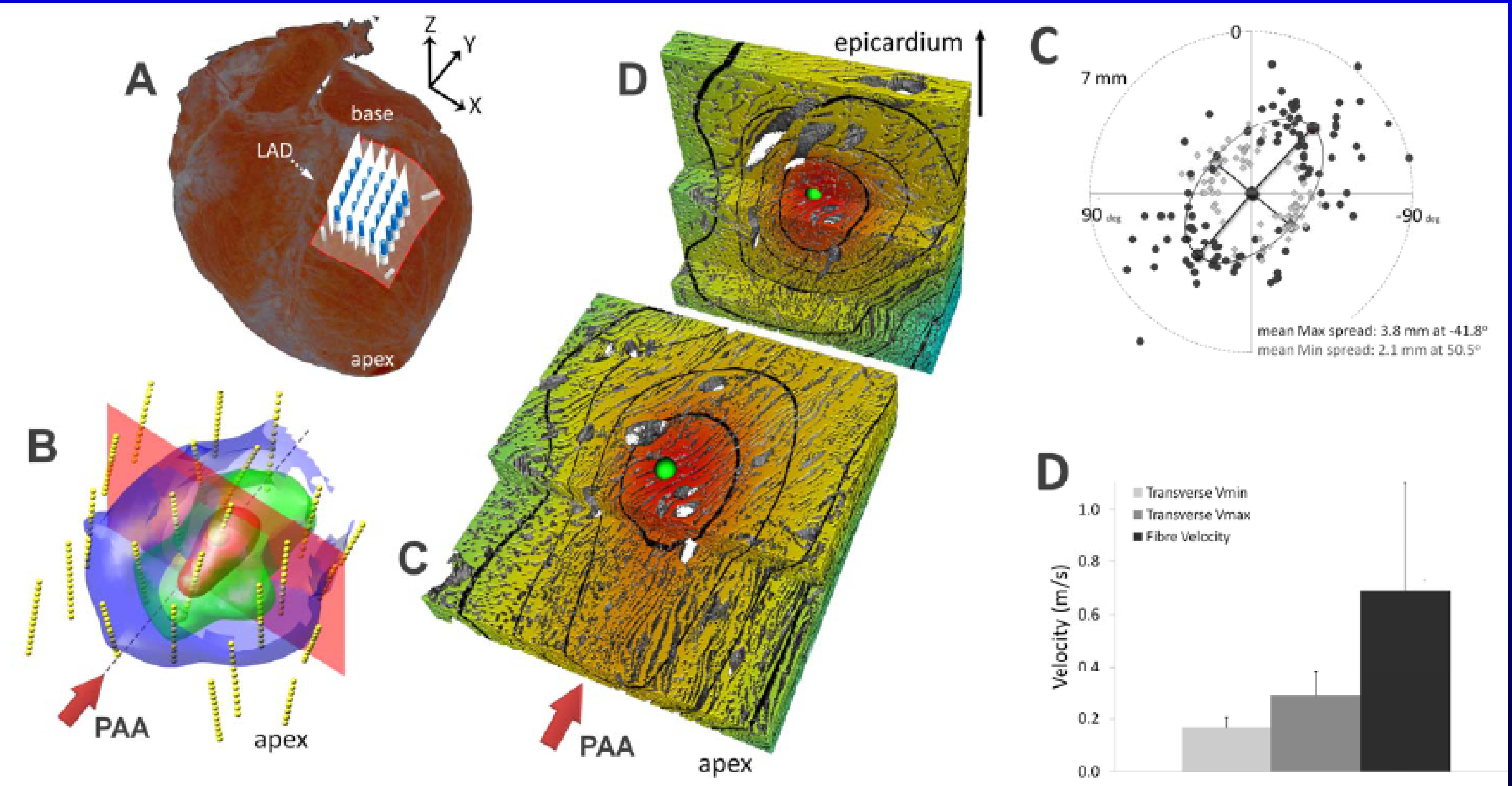
$$\frac{\partial V}{\partial t} = \frac{\partial}{\partial x_i}(d_{ij}\frac{\partial V}{\partial x_j}) + I_{ion}$$

...



(LeGrice,Smaill,Chai,Edgar,Gavin,Hunter,AJP 1995)

Orthotropic anisotropy



Caldwell, Trew, Sands, Hooks, LeGrice, Smaill, Circ. 2009

Conduction tensor

In the principle coordinate system:

$$D_{ij} = \begin{pmatrix} D_1 & 0 & 0 \\ 0 & D_2 & 0 \\ 0 & 0 & D_3 \end{pmatrix}$$

D_1, D_2, and D_3 the coupling in the three principle (orthogonal) directions:
$\vec{\alpha}, \vec{\beta}, \vec{\gamma}$

Transformation into lab coordinate system

Transformation matrix:

$$A = (\vec{\alpha}, \vec{\beta}, \vec{\gamma}),$$

$$D = A^T * d * A; \qquad or \qquad d = A * D * A^T$$

where d is a matrix in our coordinate system.

From (1) we get:

$$d = D_1 \vec{\alpha}\vec{\alpha}^T + D_2 \vec{\beta}\vec{\beta}^T + D_3 \vec{\gamma}\vec{\gamma}^T$$

A is an orthogonal matrix, thus:

$$\vec{\alpha}\vec{\alpha}^T + \vec{\beta}\vec{\beta}^T + \vec{\gamma}\vec{\gamma}^T = I$$

Case $D_2 = D_3$

$$d = D_1 \vec{\alpha}\vec{\alpha}^T + D_2 \vec{\beta}\vec{\beta}^T + D_3 \vec{\gamma}\vec{\gamma}^T =$$
$$D_1 \vec{\alpha}\vec{\alpha}^T + D_2 (\vec{\beta}\vec{\beta}^T + \vec{\gamma}\vec{\gamma}^T) =$$
$$D_1 \vec{\alpha}\vec{\alpha}^T + D_2 (I - \vec{\alpha}\vec{\alpha}^T)$$

Finally:

$$d = D_2 I + (D_1 - D_2)\vec{\alpha}\vec{\alpha}^T$$

or

$$d_{i,j} = D_2 \delta_{i,j} + (D_1 - D_2)\alpha_i \alpha_j$$

Orthotropic anistropy

$$d = D_1\vec{\alpha}\vec{\alpha}^T + D_2\vec{\beta}\vec{\beta}^T + D_3\vec{\gamma}\vec{\gamma}^T =$$

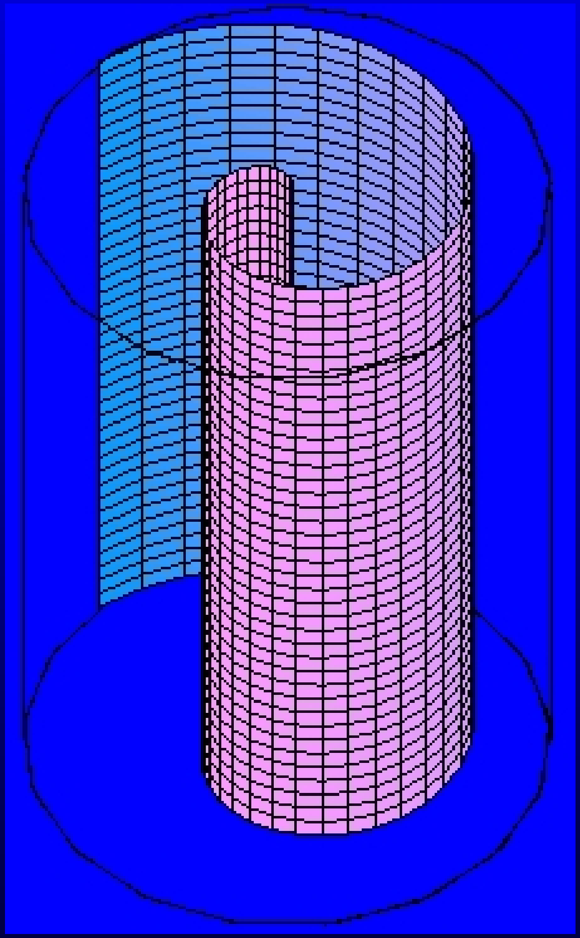
$$D_1\vec{\alpha}\vec{\alpha}^T + D_2\vec{\beta}\vec{\beta}^T + D_3(I - \vec{\alpha}\vec{\alpha}^T - \vec{\beta}\vec{\beta}^T) =$$

$$D_3 I + (D_1 - D_3)\vec{\alpha}\vec{\alpha}^T + (D_2 - D_3)\vec{\beta}\vec{\beta}^T$$

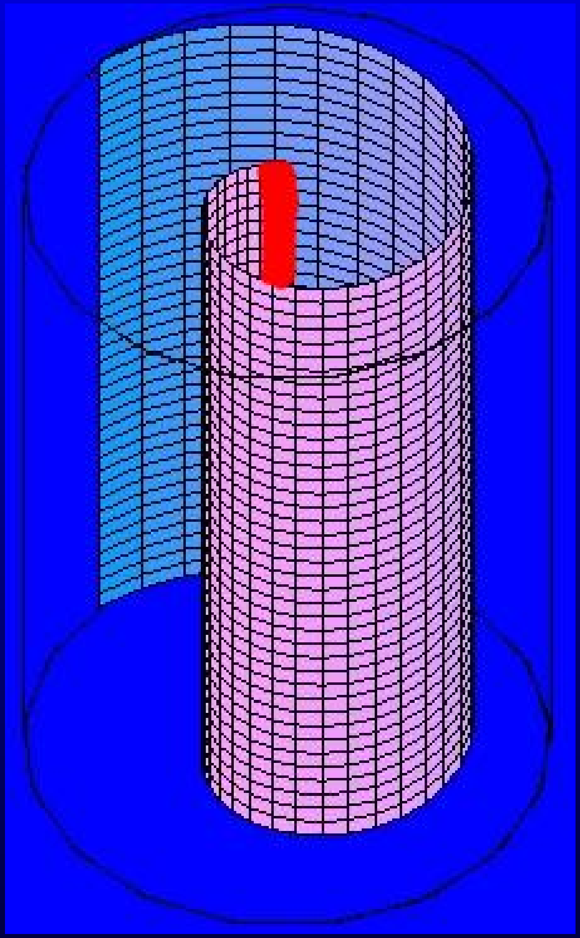
or

$$d_{ij} = D_3\delta_{i,j} + (D_1 - D_3)\alpha_i\alpha_j + (D_2 - D_3)\beta_i\beta_j$$

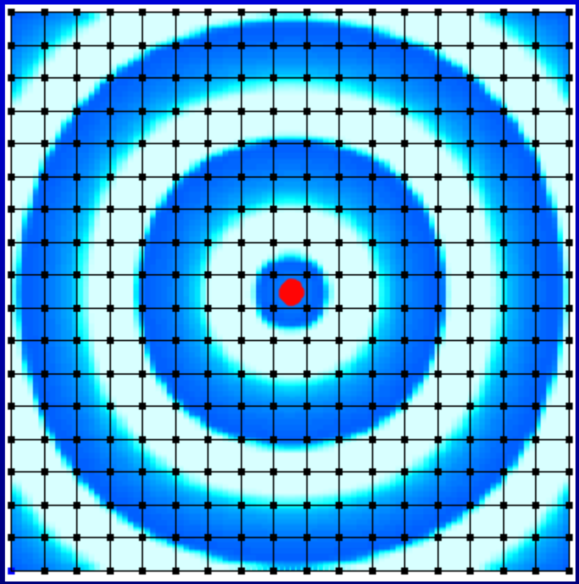
Scroll wave in 3 dimensions

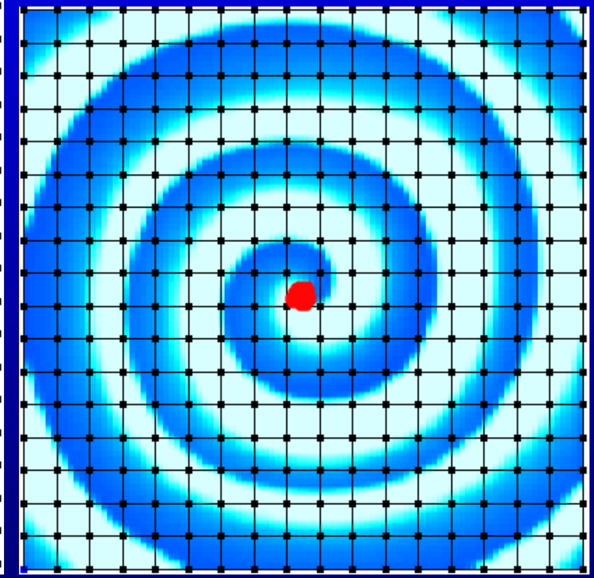


Scroll wave filament

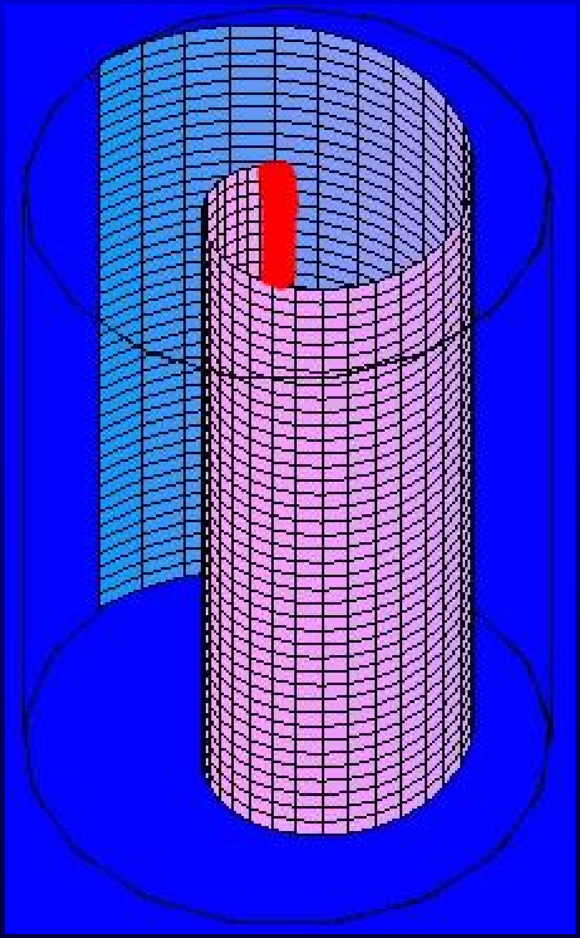


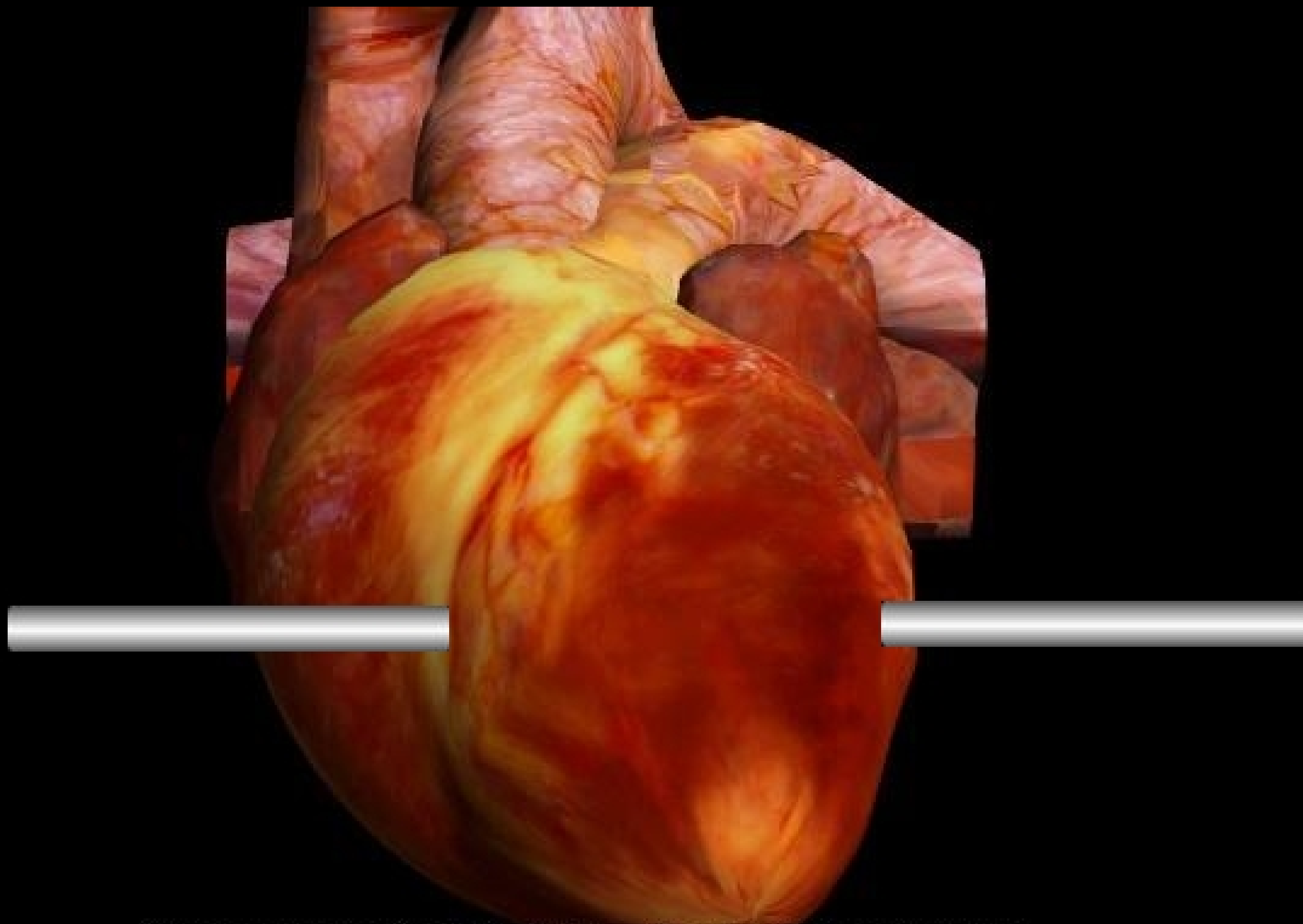
Spiral wave is an excitation source



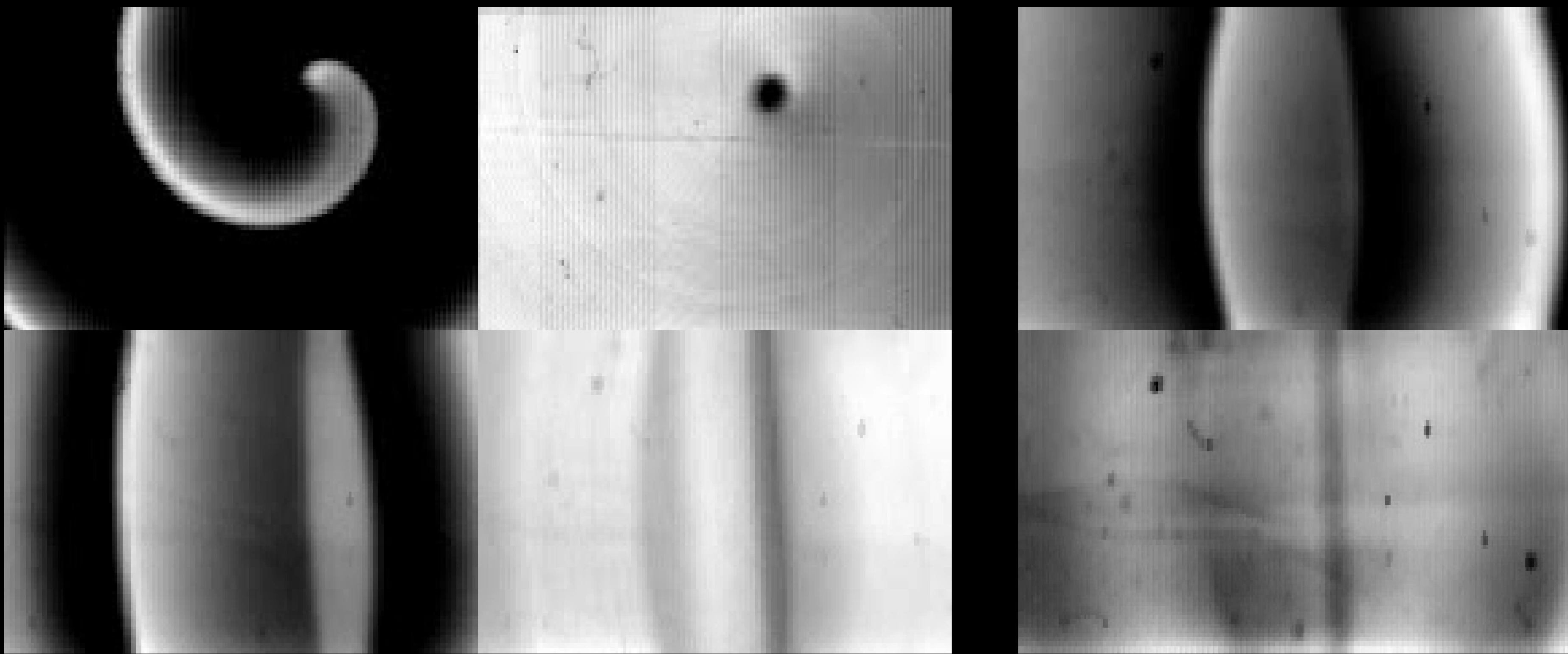


Scroll wave filament



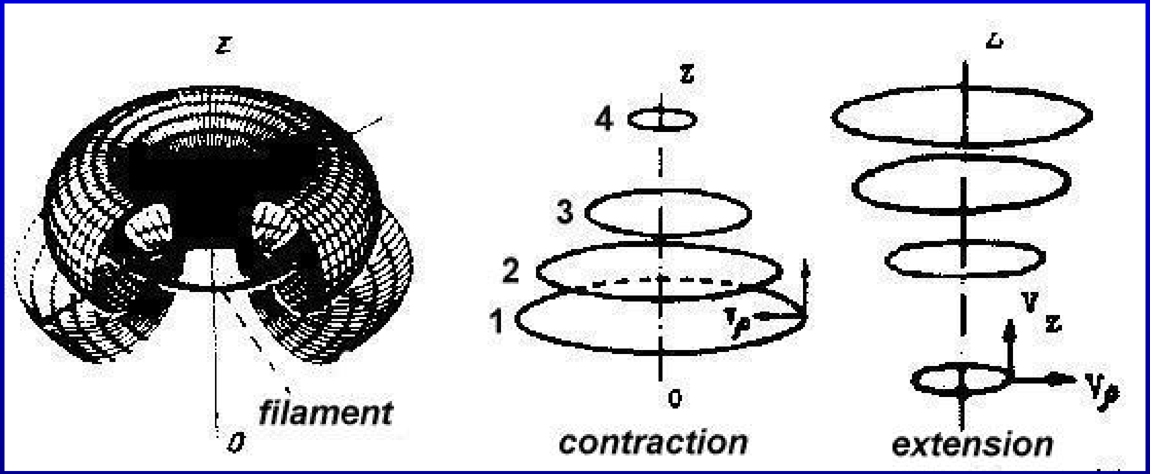


Scroll waves and filament sproing in the BZ reaction



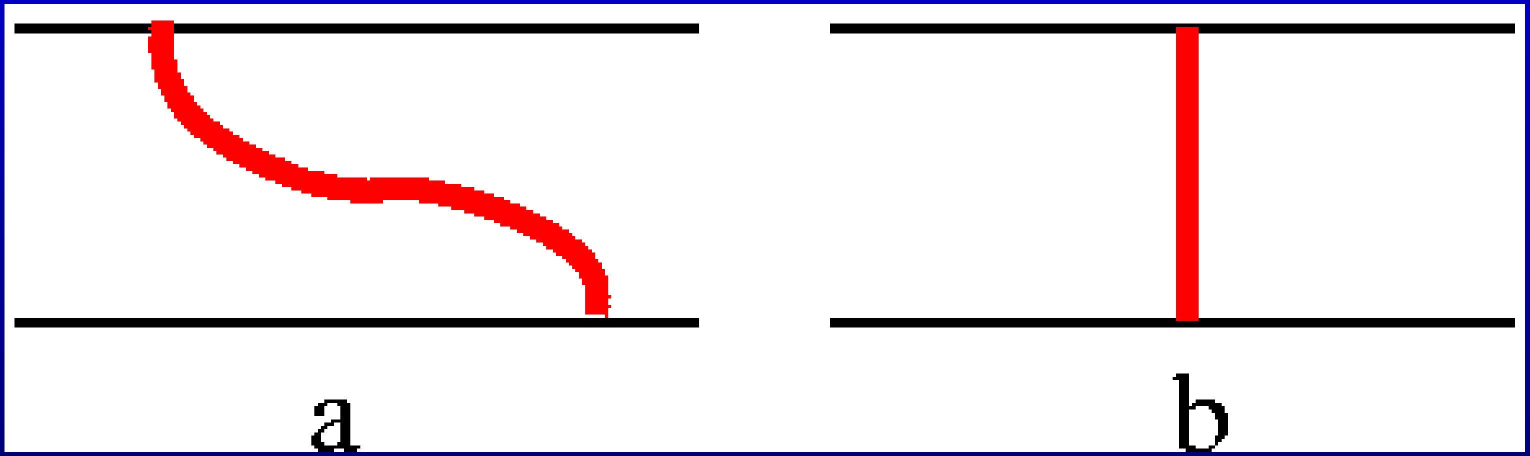
(experiments from lab of A.Pertsov, SUNY, USA).

Curvature induced drift of the filament



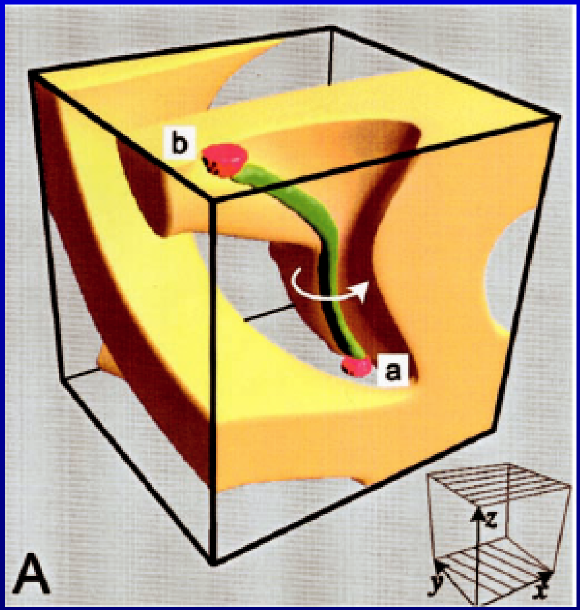
(Panfilov A.V. and Rudenko A.N. Physica D, v.28,p.215-218, 1987)

Filaments with positive tension in a slab of cardiac tissue



left- initial position; right-stationary configuration (minimal length)

Filaments in medium with anisotropic diffusion



$$\ddot{x}_i = g_{il}^{-1}(-g_{jl,k} + \frac{1}{2}g_{jk,l})\dot{x}_j\dot{x}_k \quad g_{ij} = D_{ij}^{-1}$$

(M. Wellner, O. Berenfeld, J. Jalife, and A. Pertsov, Proc. Natl. Acad. Sci. USA **99**, 8015 (2002)).

Filaments in medium with anisotropic diffusion

$$T(\vec{X}) = \frac{1}{v_0}\int_{\vec{x_0}}^{\vec{X}} (g_{ij}\dot{x}_i\dot{x}_j)^{1/2} dt = \int_{\vec{x_0}}^{\vec{X}} F(\vec{x},\dot{\vec{x}})dt,$$

$$dt = \frac{1}{v_0}(g_{ij}dx_i dx_j)^{1/2}$$

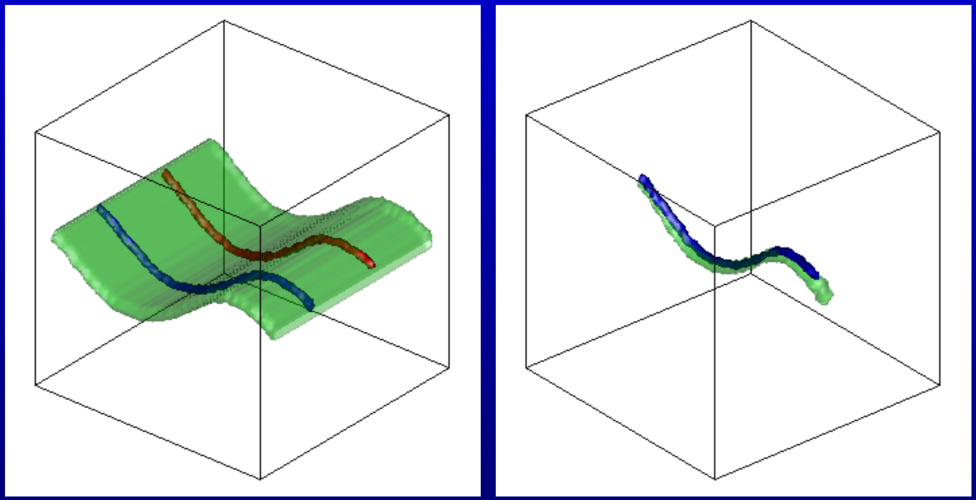
$$\hat{D}_{ij}\frac{\partial T}{\partial x_i}\frac{\partial T}{\partial x_j} \equiv g_{ij}^{-1}\frac{\partial T}{\partial x_i}\frac{\partial T}{\partial x_j} = \frac{1}{v_0^2}\frac{g_{ij}\dot{x}_i\dot{x}_j}{g_{kl}\dot{x}_k\dot{x}_l} = \frac{1}{v_0^2} \quad (2)$$

Eq.(2) is an eikonal equation for wave propagation in RD system:

$$\frac{\partial u}{\partial t} = \frac{\partial}{\partial x_i}D_{ij}\frac{\partial u}{\partial x_j} + \Phi(u,\vec{v}); \qquad \frac{\partial \vec{v}}{\partial t} = \vec{\Psi}(u,\vec{v})$$

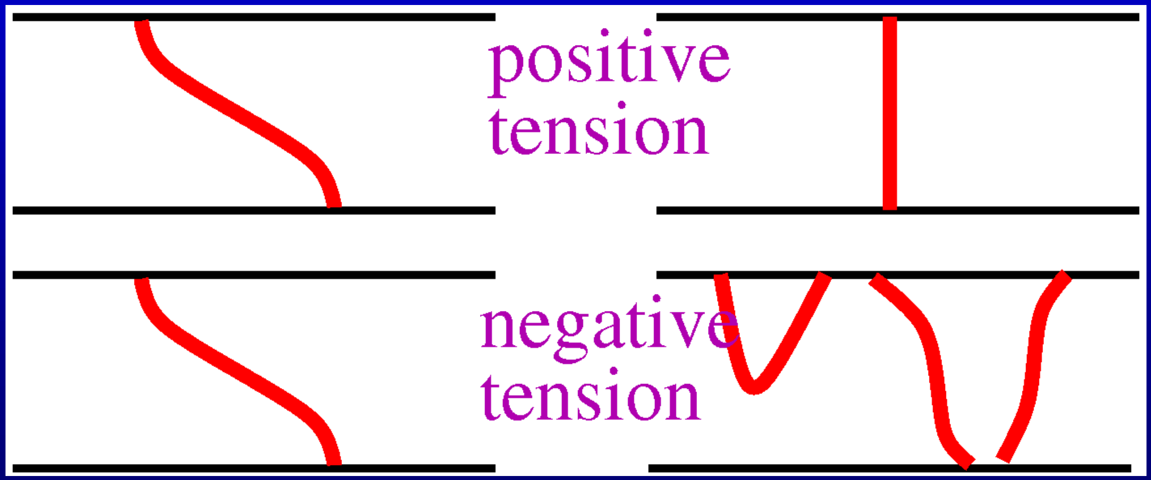
(Ten Tusscher KHWJ, Panfilov, A. V.,Phys. Rev. Lett,v.93,108106,(2004)).

Filament drift in the medium with anisotropic diffusion



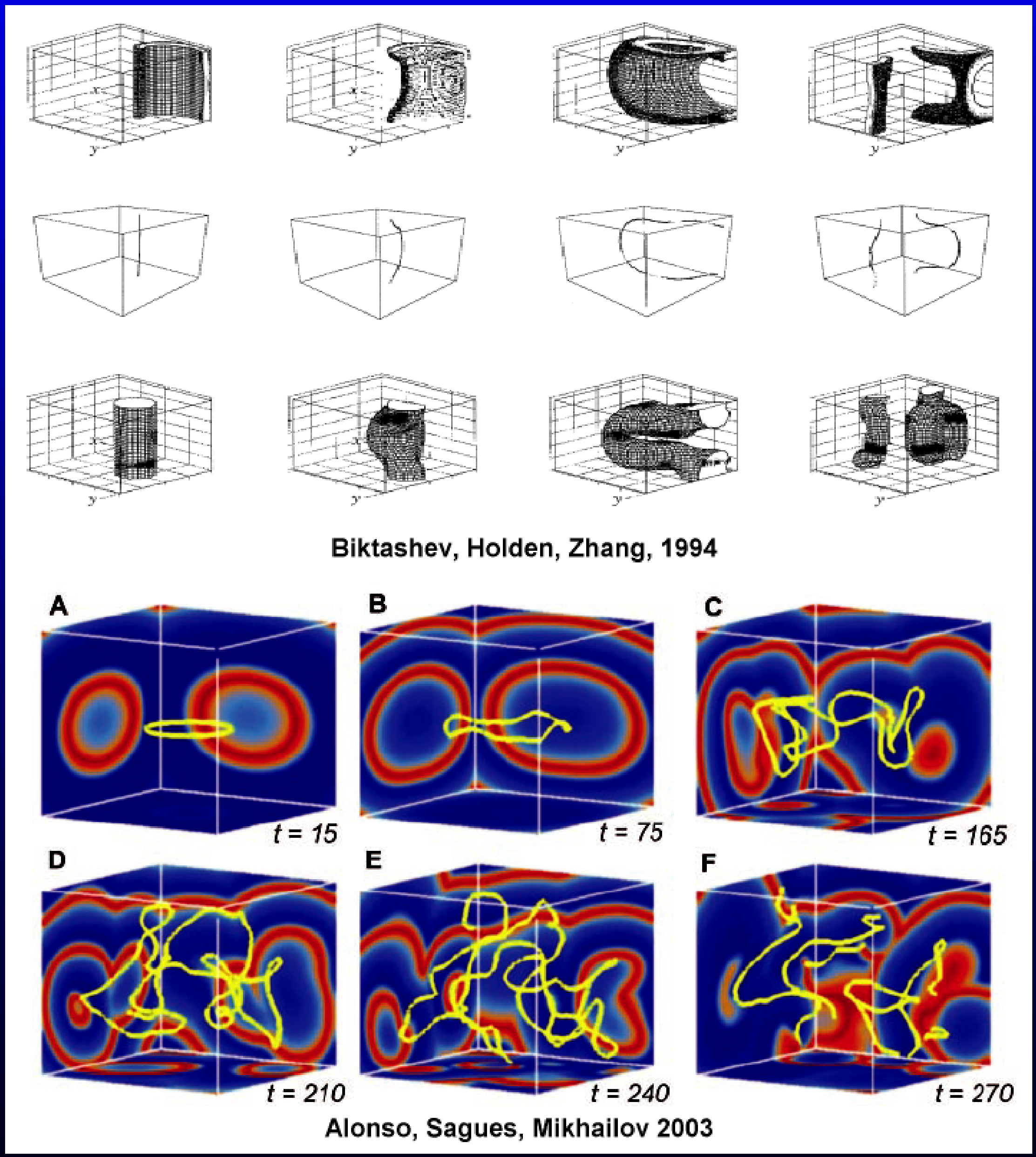
Filament drift in anisotropic medium. In green are the theoretical predictions. (Ten Tusscher KHWJ, Panfilov, A. V.,Phys. Rev. Lett,v.93,108106,(2004)).

Filaments with negatve tension in a slab of cardiac tissue

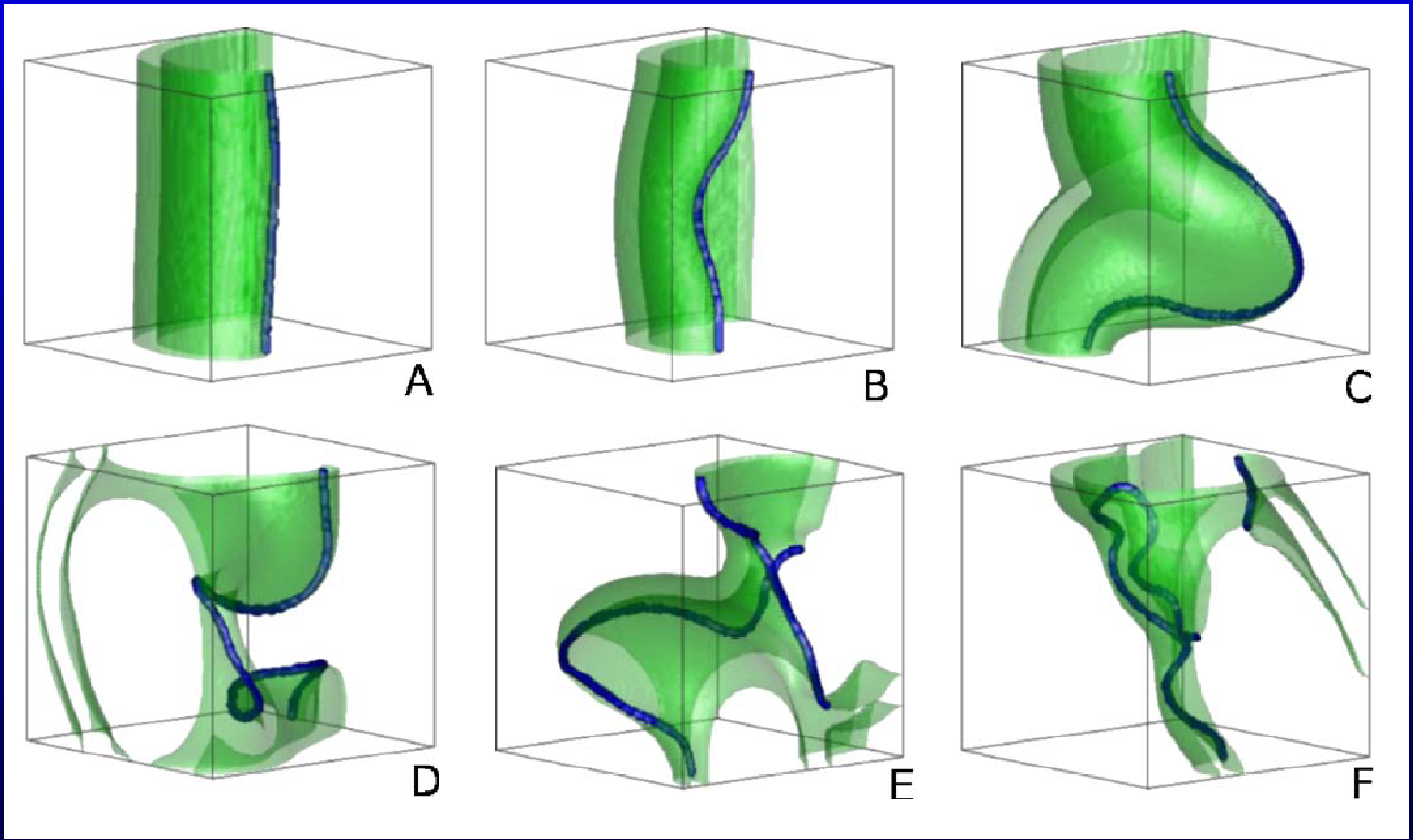


left- initial position; right-after some time

Turbulence due to negative filament tension



Filaments with negative tension in the LR1 model



(from: Alonso S., Panfilov AV., ”Negative filament tension in the Luo-Rudy model of cardiac tissue”, Chaos, v.17, 015102, (2007))

Non-trivial relations between different spiral wave dynamics