Twist and Buckle: Spatiotemporal Patterns in the Heart

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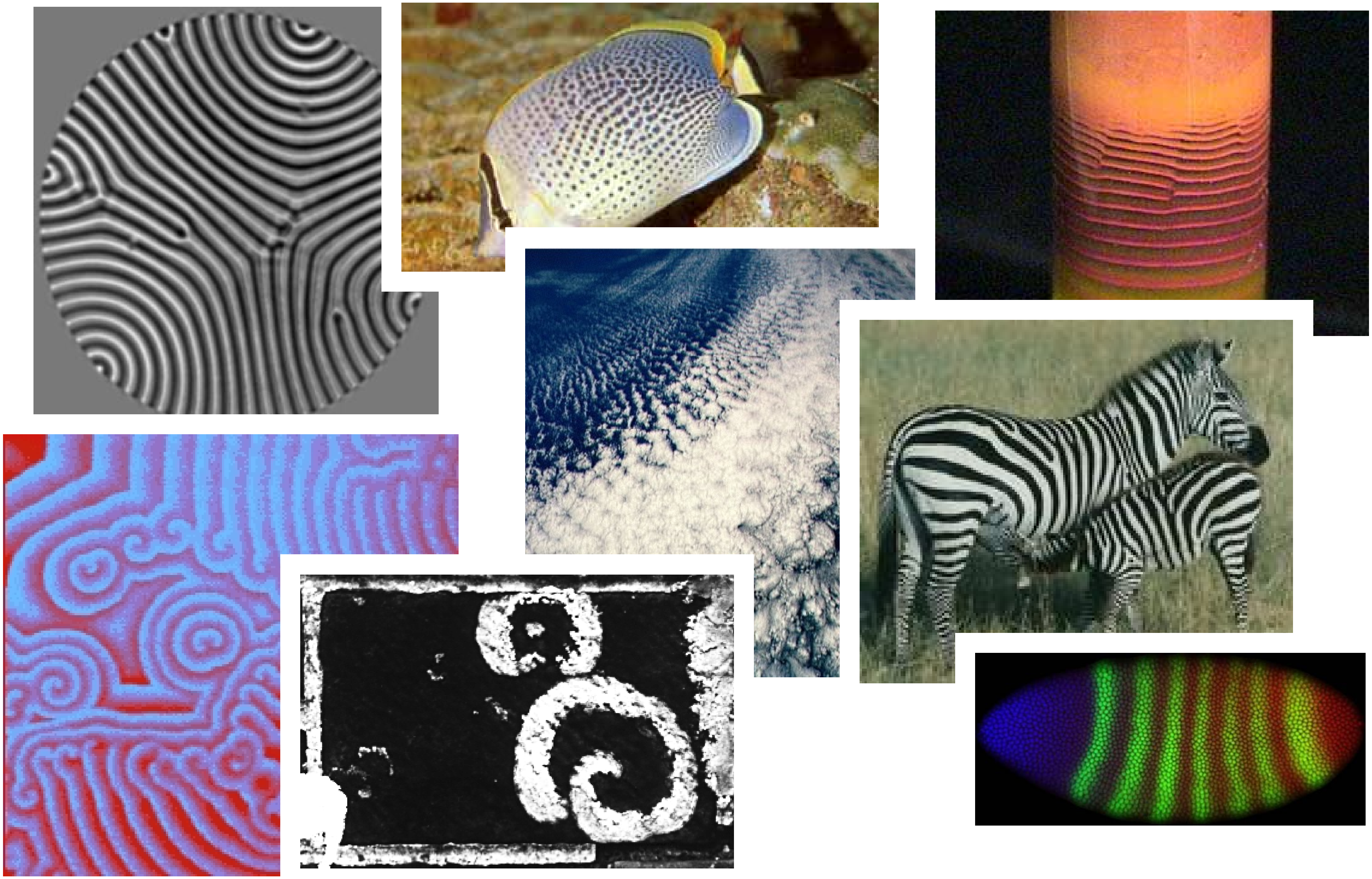
Stripes, Spots and Scrolls

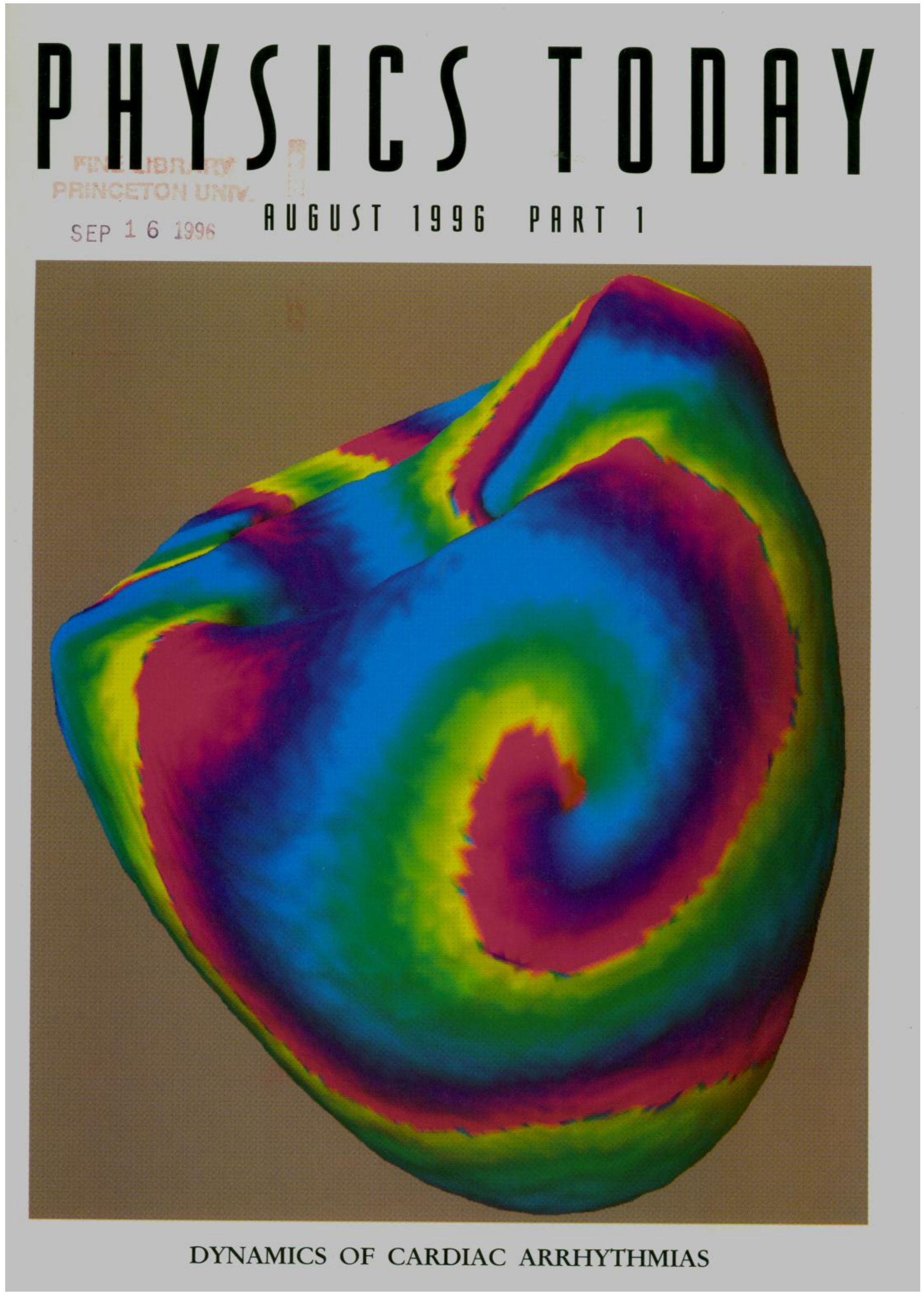


Overview

- Common processes underlying natural patterns give rise to model equations capturing generic features of pattern-forming systems

- Theoretical approaches accessible near onset, but must resort to numerical tools and experiments far from onset

- Need for high-fidelity scientific computation to describe realistic physical systems as a bridge between theory and experiment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AUGUST 1996 PART 1
DYNAMICS OF CARDIAC ARRHYTHMIAS

The Heart as a Physical System

- Sudden cardiac failure is the leading cause of death in industrialized nations.

1000 deaths/day in North America

- Growing experimental evidence that self-sustained patterns of electrical activity in cardiac tissue are related to fatal arrhythmias.

- Goal is to use analytical and numerical tools to study the dynamics of reentrant waves in the heart on physiologically realistic domains.

And ...

- The heart is an interesting arena for applying the ideas of pattern formation.

Credits

Collaborators

- *Andrew Bernoff*,
  Mathematics Department, Harvey Mudd College

Acknowledgements

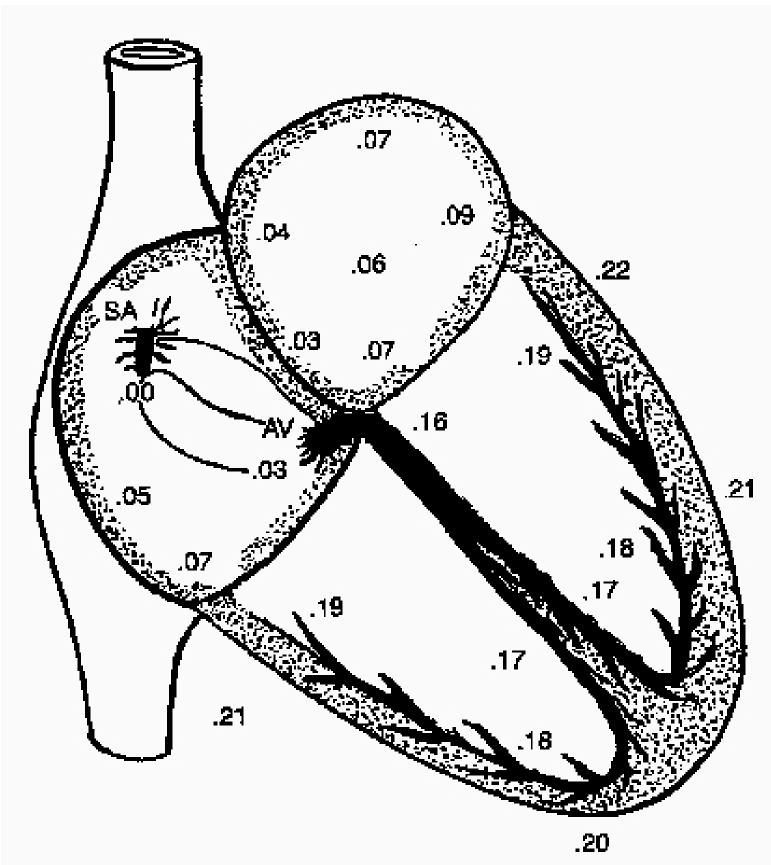
- *Herb Keller*,
  Applied Mathematics Department, Caltech
- *Alain Karma*,
  Physics Department, Northeastern University

Scroll Waves in Anisotropic Excitable Media with Application to the Heart

with Prof. Andrew Bernoff, Harvey Mudd College

Heart Physiology

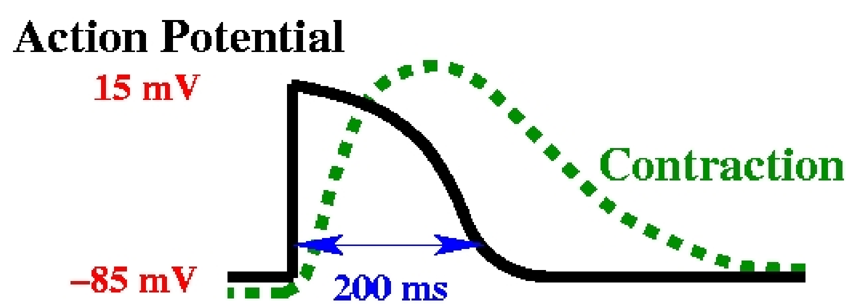
Electrical Activity $\Longrightarrow$ Mechanical Function



From Textbook of Medical Physiology,
by Guyton and Hall

Seconds

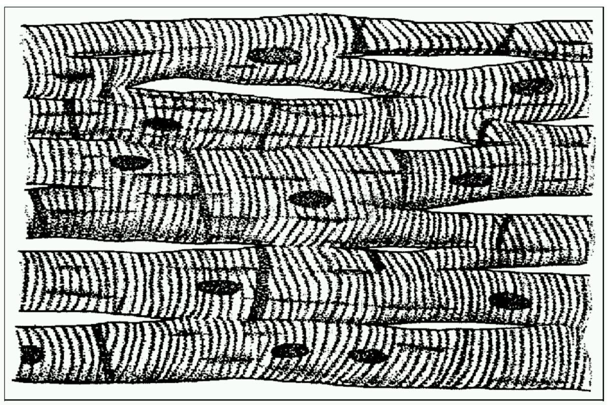
Sinus Node (0.0)
↓
Atria (0.09)
↓
AV Node (0.03)
↓
Purkinje Fibers (0.19)
↓
Ventricles (0.22)



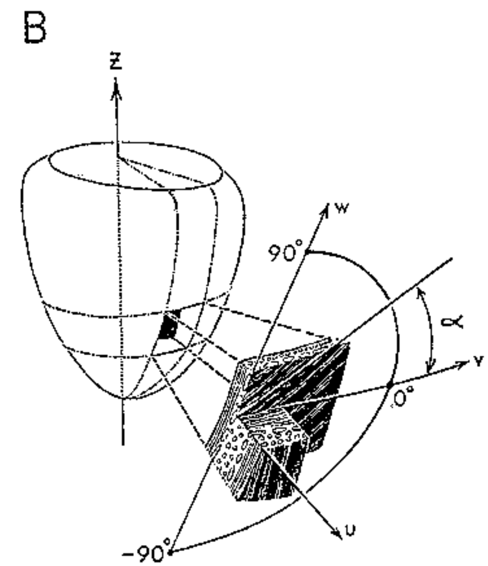
Heart Physiology (cont'd)

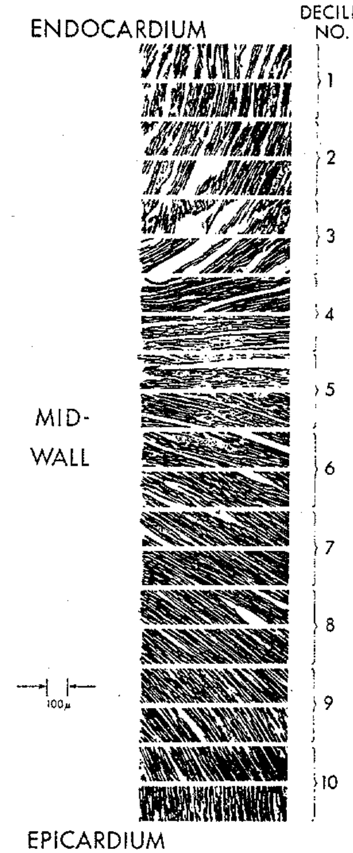
Tissue structure:

- $3d$ conduction pathway with uniaxial anisotropy
- Propagation speeds:
  $c_{\|} = 0.5$ m/s,
  $c_{\perp} = 0.17$ m/s



From *Textbook of Medical Physiology*,
by Guyton and Hall



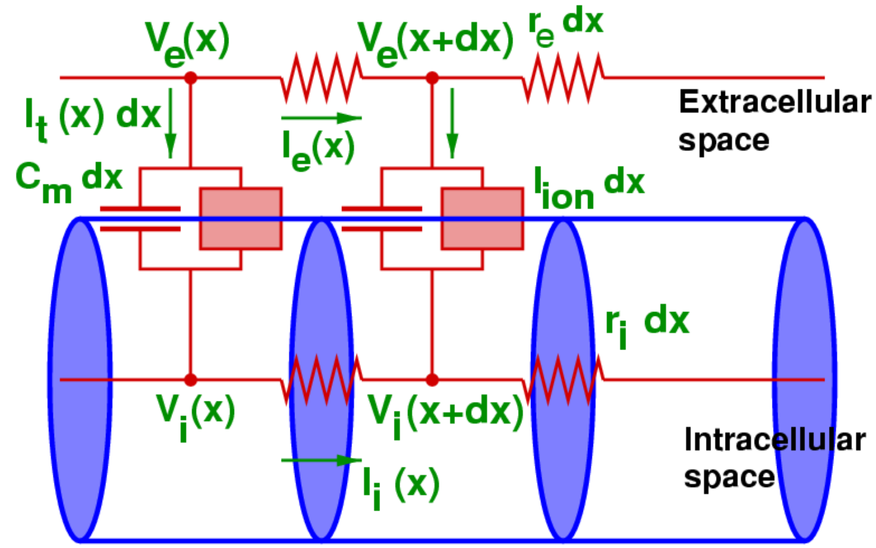


From Streeter, *et al.*, Circ. Res. **24**, p. 339 (1969).

Cable Theory

Electric potential propagation in a neuronal cable: Hodgkin and Rushton (1946), Rall (1957,...)

$$\tau_m \partial V/\partial t + R_m I_{ion} = \lambda_m^2 \partial^2 V/\partial x^2$$



Adapted from Mathematical Physiology, by Keener & Sneyd (1998).

$$\begin{aligned}
Axial\ current &: I_a = I_i + I_e \\
Transmembrane\ current &: I_t = I_{ionic} + I_{capacitive} + I_{applied} \\
Transmembrane\ potential &: V = V_i - V_e \\
Physical\ properties &: C_m, R_m, r_i, r_e, p, d
\end{aligned}$$

- Kirchoff's law: $I_i(x+dx) - I_i(x) = I_e(x) - I_e(x+dx) = -I_t dx$
- Conservation of charge: $\partial I_a/\partial x = 0$
- Ohmic axial currents: $V_{i,e}(x+dx) - V_{i,e}(x) = -I_{i,e}(x) r_{i,e} dx$

Extension to the Heart

3d Cardiac Tissue

- Continuous approximation
  - *Bidomain: Intra/extracellular conductivities* $\boldsymbol{\sigma}_i, \boldsymbol{\sigma}_e$
  - *Monodomain:* $\boldsymbol{\sigma}_i = \alpha \; \boldsymbol{\sigma}_e$

Ionic Modeling: $I_{Na^+}(V), I_{K^+}(V), I_{Ca^{++}}(V), \ldots$

- Quantitative modeling
  - *Hodgkin-Huxley (1952): Squid giant axon*
  - *Noble (1960), Beeler-Reuter (1977), Luo-Rudy (1991, 1994), ...*
- Reduced models: FitzHugh-Nagumo (1960), ...

Equations:

$$\begin{aligned} \frac{\partial u}{\partial t} &= \varepsilon^{-1} f(u,v) + D\nabla^2 u \\ \frac{\partial v}{\partial t} &= g(u,v) \\ f(u,v) &= 3u - u^3 - v \\ g(u,v) &= u - \delta \end{aligned}$$

Notation:

$$\begin{aligned} Potential\ , V &\rightarrow u \\ I_{ion} &\rightarrow f(u,v) \\ Gating\ variables &\rightarrow v \end{aligned}$$

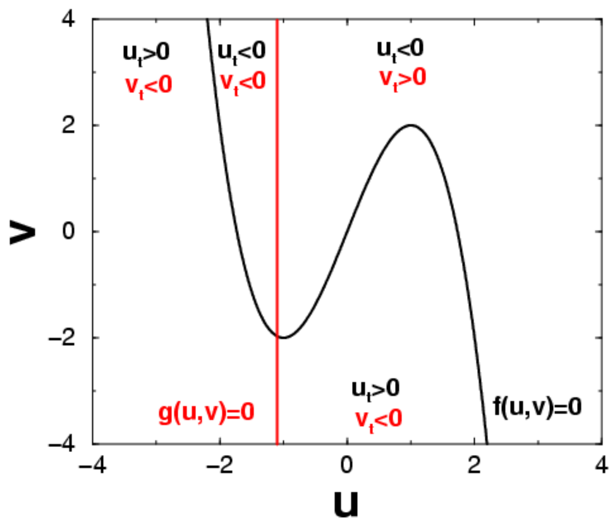
Physical parameters:

- ε: excitability
- δ: excitable/oscillatory

Excitable Dynamics

Nullclines

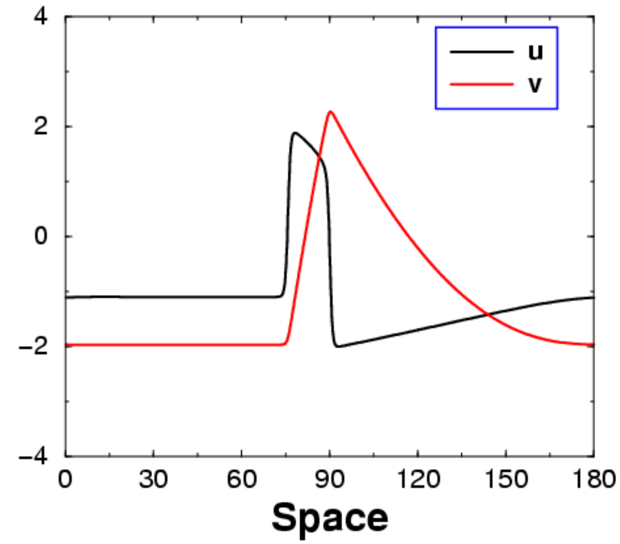
$$u_t = \varepsilon^{-1} f(u,v) + D\nabla^2 u$$
$$v_t = g(u,v)$$

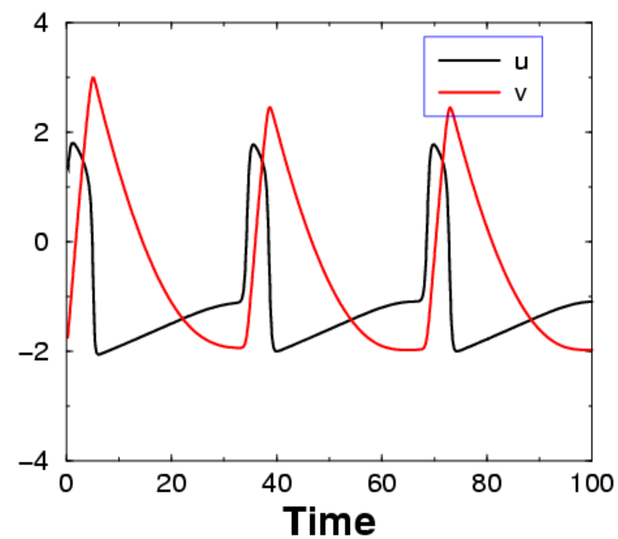


Characterized by:

- Shape of nullclines (knees)
- Difference in time scales: $\varepsilon \ll 1$
- 4 stages: upstroke, excited, refractory, recovering

Propagating pulse: 1d





Birth of Spirals

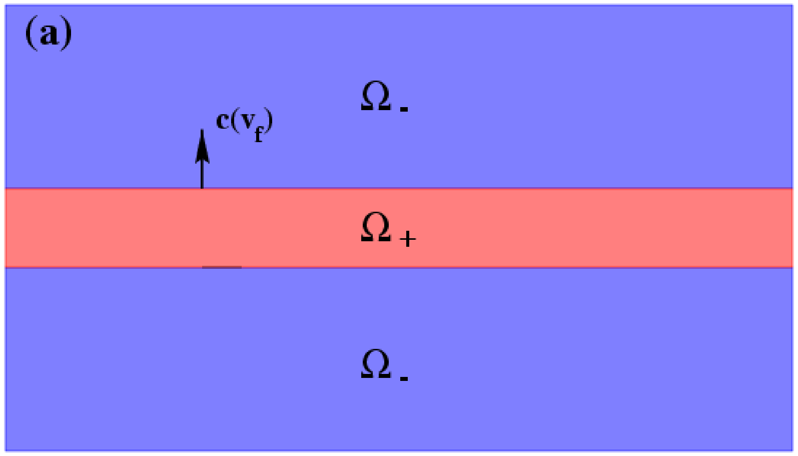
(a) Propagating band

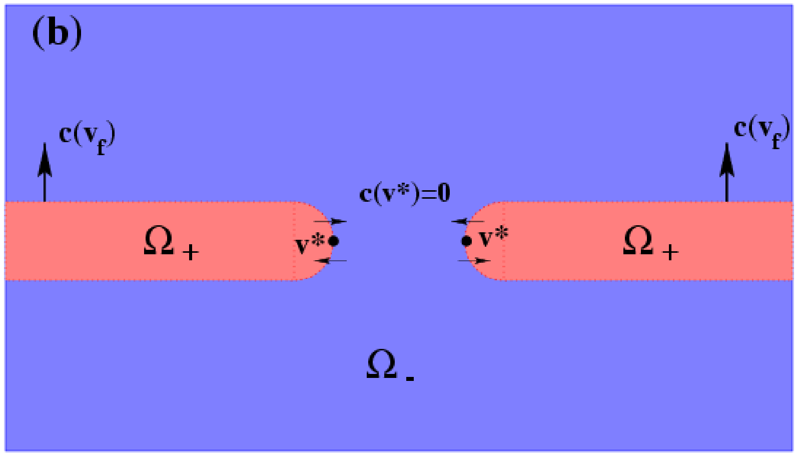
$$\Omega_+ \quad : \quad \textit{Excited}$$
$$\Omega_- \quad : \quad \textit{Rest}$$

- speed $c = c(v)$
- $c(v_f) = -c(v_b)$

(b) Disturbance (inhomogeneity):

- $c(v)$ varies continuously through zero: $c(v_f) > 0$ and $c(v_b) < 0$
- Existence of pivot point: $c(v^*) = 0$





Click for animation.

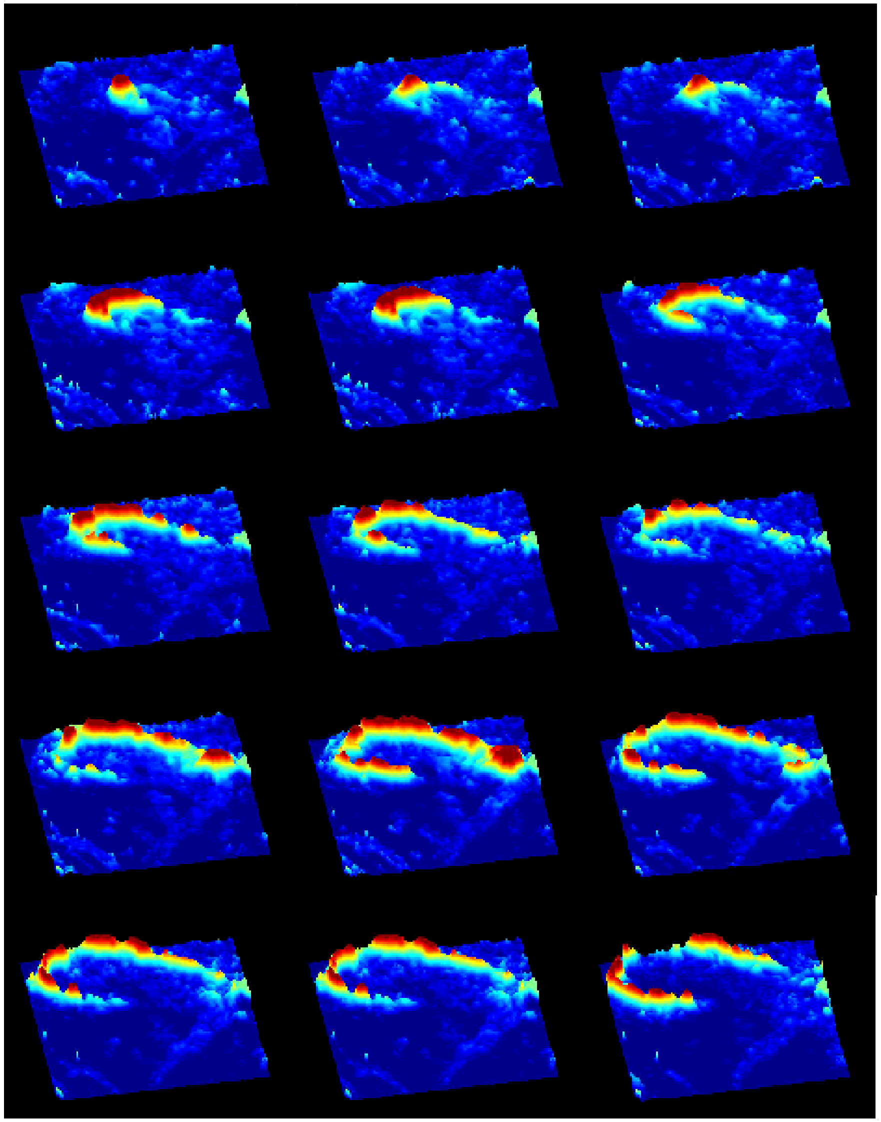
Reviews: Fife (1984), Keener and Tyson (1988), Cross and Hohenberg (1993)

Birth of Spirals: Experiment

From W. F. Witkowski, et al., Nature **392**, p. 78.

- Time spacing between frames $\sim$ 5 ms
- Image size $\sim$ 5 cm

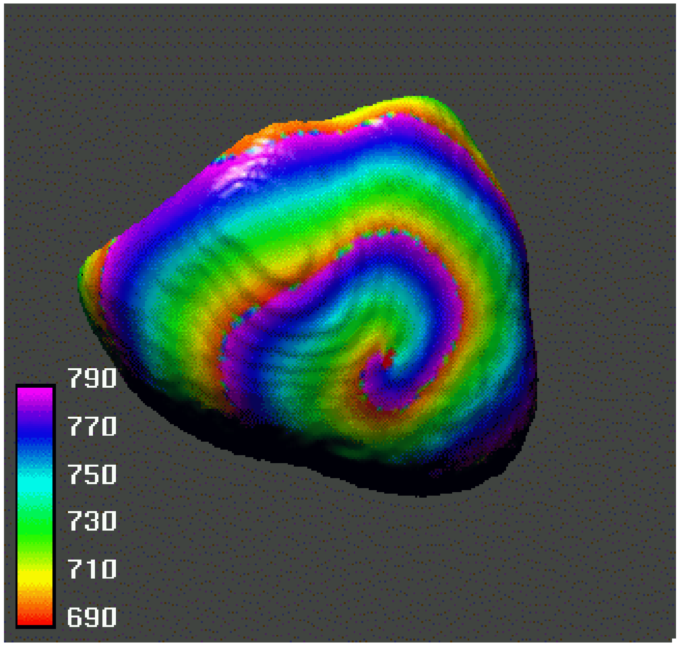
Click for animation.



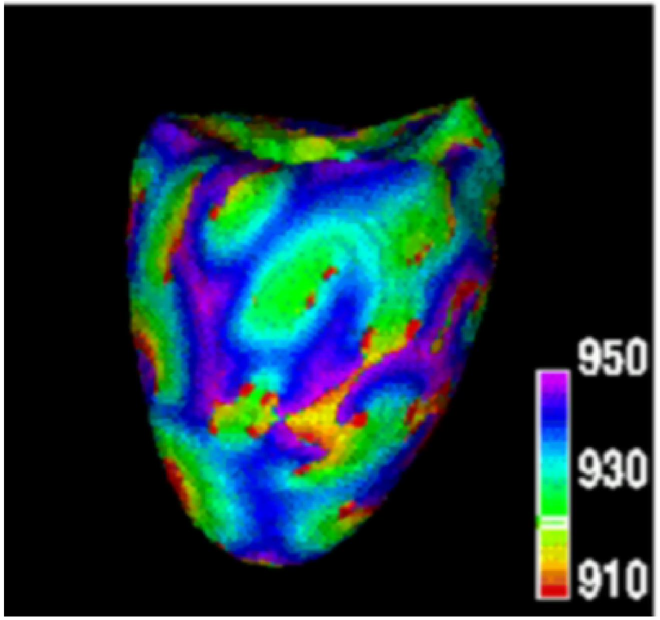
Big Picture

What is the mechanism of transition from ventricular *tachychardia* to *fibrillation*? How can we control it?

Tachycardia:



Fibrillation:



Courtesy of Sasha Panfilov, University of Utrecht

Click for animation.

Cartoon: Breakdown of single spiral to disordered state resulting from various mechanisms of spiral instability.

Focus

What is the role of geometry and anisotropy inherent in the fiber architecture of the heart on scroll wave dynamics?

Previous Work:

A. T. Winfree, in *Progress in Biophysics and Molecular Biology, D. Noble et al. eds., (1997).*

Numerical "experiments"

In rectangular slab geometries:

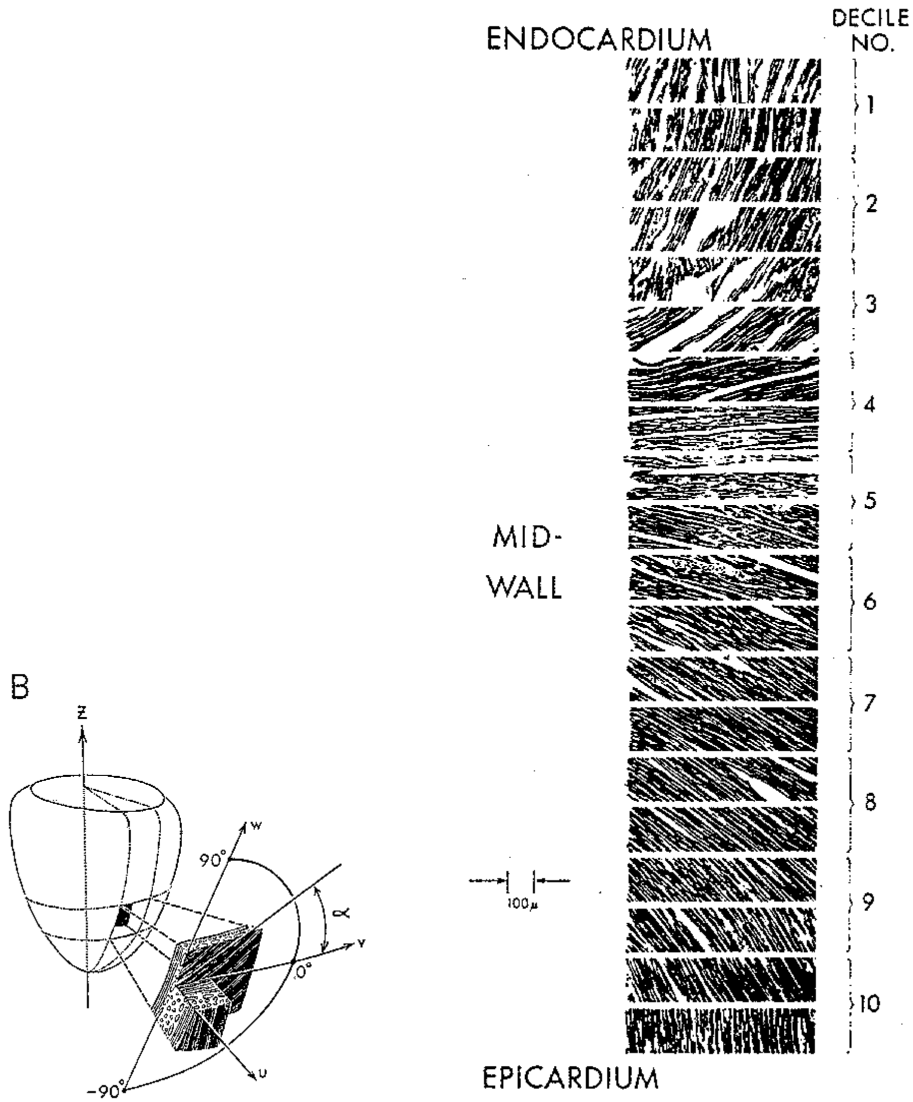
- Panfilov, A. V. and Keener, J. P., Physica D **84**, 545 (1995): *Scroll wave breakup due to rotating anisotropy.*
- *Fenton, F. and Karma, A., Chaos* **8**, *20 (1998): Rotating anisotropy leading to "twistons", eventually destabilizing scroll filament.*

Analytical work

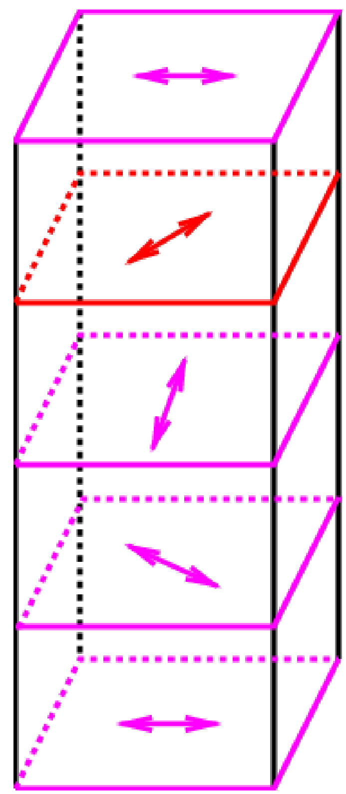
Dynamics of scroll waves in isotropic excitable media, beginning with:

- Keener, J. P., Physica D **31**, 269 (1988).
- Biktashev, V. N., Physica D **36**, 167 (1989).

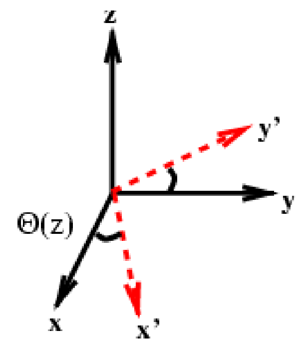
Rotating anisotropy



from Streeter, *et al.*, Circ. Res. **24**, p. 339 (1969).



$$\begin{pmatrix} D_{\perp_1} & 0 & 0 \\ 0 & D_{\|} & 0 \\ 0 & 0 & D_{\perp_2} \end{pmatrix}$$



$$\begin{pmatrix} D_{\|} & 0 & 0 \\ 0 & D_{\perp_1} & 0 \\ 0 & 0 & D_{\perp_2} \end{pmatrix}$$

Diffusion constants:

$$D_{\|} > D_{\perp_1} \sim D_{\perp_2}$$

Coordinate System

Natural coordinate system defined by fiber direction:

$$\underbrace{\begin{pmatrix} \tilde{x} \\ \tilde{y} \\ \tilde{z} \end{pmatrix}}_{\text{'new'}} = \underbrace{\begin{pmatrix} 1 & 0 & 0 \\ 0 & \alpha & 0 \\ 0 & 0 & 1 \end{pmatrix}}_{S} \underbrace{\begin{pmatrix} \cos\Theta(z) & \sin\Theta(z) & 0 \\ -\sin\Theta(z) & \cos\Theta(z) & 0 \\ 0 & 0 & 1 \end{pmatrix}}_{R} \underbrace{\begin{pmatrix} x \\ y \\ z \end{pmatrix}}_{\text{'old'}}$$

S : rescaling, according to 2d anisotropy $\alpha \equiv (D_{\perp_1}/D_{\|})^{1/2}$
R : rotation, according to fiber direction $\Theta(z)$

Governing Equations

Governing reaction-diffusion equation in new coordinates:

$$
\begin{aligned}
\vec{u}_t \quad = \quad & \vec{f}(\vec{u}) + \boldsymbol{D}_{\|} \cdot \Delta_2 \vec{u} + \boldsymbol{D}_{\perp_2} \cdot \vec{u}_{zz} \\
& + \boldsymbol{D}_{\perp_2} \cdot \left\{ \Theta'^2 \left[\frac{\partial^2}{\partial \theta^2} + (\alpha^2 - 1) x^2 \frac{\partial^2}{\partial y^2} + \left(\frac{1}{\alpha^2} - 1 \right) y^2 \frac{\partial^2}{\partial x^2} \right] \vec{u} \right. \\
& \qquad - 2\Theta' \left[\frac{\partial}{\partial \theta} + (\alpha - 1) x \frac{\partial}{\partial y} - \left(\frac{1}{\alpha} - 1 \right) y \frac{\partial}{\partial x} \right] \frac{\partial \vec{u}}{\partial z} \\
& \qquad \left. - \Theta'' \left[\frac{\partial}{\partial \theta} + (\alpha - 1) x \frac{\partial}{\partial y} - \left(\frac{1}{\alpha} - 1 \right) y \frac{\partial}{\partial x} \right] \vec{u} \right\},
\end{aligned}
$$

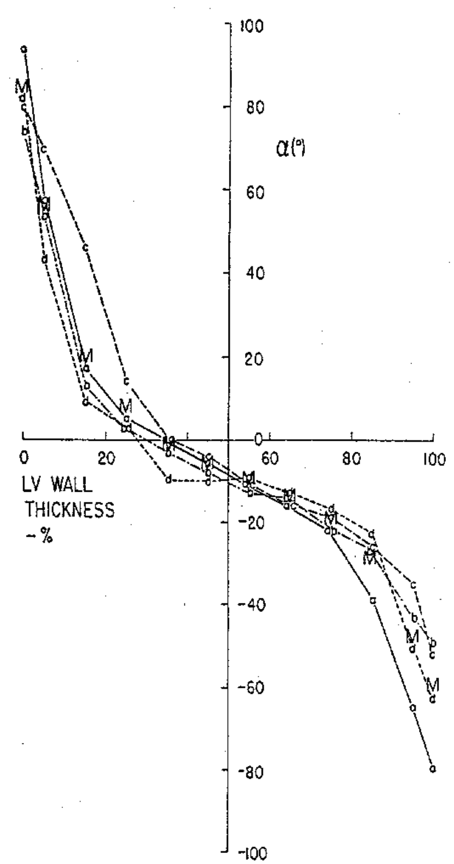
Only depends on fiber rotation rate, Θ' (no explicit dependence on $\Theta(z)$).

For FitzHugh-Naguomo (FHN) kinetics:

$$
\vec{u} = \begin{pmatrix} u \\ v \end{pmatrix}, \qquad \vec{f} = \begin{pmatrix} -u^3 + 3u - v \\ \epsilon(u - \delta) \end{pmatrix}, \qquad \boldsymbol{D}_{\|} = \begin{pmatrix} D_{\|} & 0 \\ 0 & 0 \end{pmatrix}, \qquad etc \ldots
$$

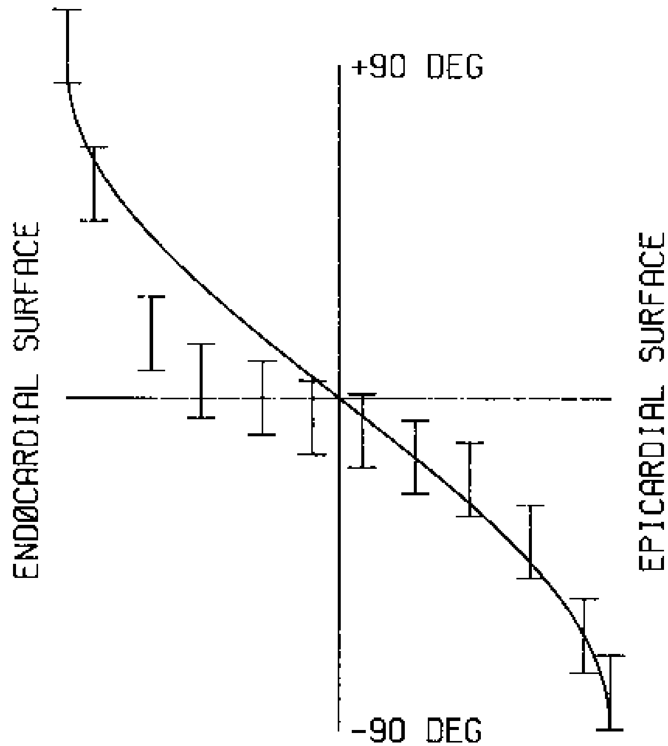
Peskin Fiber Distribution Profile

Measured



from Streeter, *et al.*, Circ. Res. **24**, p. 339 (1969)

Derived



from Peskin, *et al.*, Comm. on Pure and Appl. Math **42**, p. 79 (1989)

$$\Theta(z) = \sin^{-1}(z/rL)$$

$r =$ cutoff parameter
$2L =$ thickness of ventricular wall

Perturbation Analysis

Consider the limit of 'small rotating anisotropy' :

- Non-dimensional small parameter:

$$\epsilon^2 = \frac{D_{\perp_2}}{\omega_0 L^2} \frac{1}{r^2 - 1} \left(\frac{\gamma^2}{4} - 1 \right)$$

$\left(\frac{D_{\perp_2}}{\omega_0}\right)^{1/2}$: transverse diffusion length, ℓ

$2L$: thickness of ventricular wall

r : cutoff parameter

$\gamma = \alpha + 1/\alpha$: 'anisotropy'

- Seek a solution in the form of:

$$\vec{u} = \vec{U}_0(r, \theta - \omega_0 t + \Theta(z) + \phi(z, t)) + \epsilon^2 \vec{u}_2,$$

where $\vec{U}_0(r, \theta - \omega_0 t)$ satisfies:

$$\mathcal{O}(1) : \quad \frac{\partial \vec{U}_0}{\partial t} = \vec{f}(\vec{U}_0) + D_{\parallel} \cdot \Delta_2 \vec{U}_0$$

- Scaling assumptions: $\vec{u}_2 \sim \mathcal{O}(1), \quad \phi_z \sim \mathcal{O}(\epsilon), \quad \phi_t \sim \mathcal{O}(\epsilon^2).$

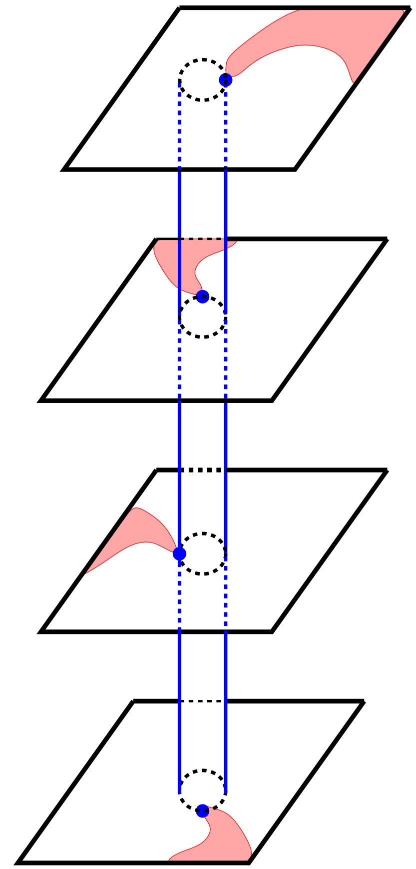
Validity of Perturbation Analysis?

Q: **What is the value of the small parameter for the human ventricle?**

Parameter	Value
$D_{\|}$	$1.0\ cm^2\, s^{-1}$
$D_{\perp}$	$0.1\ cm^2\, s^{-1}$
ω_0	$12.6\ s^{-1}$
$\Delta\Theta$	180°
$2L$	$1.0\ cm$
r	1.5

$$\epsilon^2 \sim 0.45$$

Scroll Twist



For a straight scroll:

$$w(z,t) = \left(\frac{\partial \hat{N}}{\partial z} \times \hat{N}\right) \cdot \hat{z}$$

$\hat{N} = \vec{\nabla} u / |\vec{\nabla} u|$
normal to tip trajectory at t

In new coordinates:

$$w(z,t) = \phi_z(z,t) + \Theta'(z).$$

In old coordinates:

$$w(\tilde{z},t) = \Theta'(\tilde{z}) - \frac{2\alpha\left(\phi_{\tilde{z}}(\tilde{z},t) + \Theta'(\tilde{z})\right)}{(\alpha^2-1)\ \cos\left[2\ (\omega_0 t - \phi(\tilde{z},t) - \Theta(\tilde{z}))\right] + (1+\alpha^2)}.$$

Phase Equation

At $\mathcal{O}(\epsilon^2)$, introducing $\Phi(z,t) \equiv \left(\frac{c_1}{c_2}\right) \left[\phi(z,t) - \left(\frac{\gamma}{2} - 1\right)\Theta(z)\right]$:

$$\Phi_t - \Phi_z^2 - \Phi_{zz} = A(\gamma, r)\, F(z; r), \qquad -1 < z < 1$$

Burgers' equation, with forcing given by fiber rotation:

- $F(z;r) = \frac{1-1/r^2}{1-(z/r)^2}, \qquad A(\gamma, r) = \tilde{A}\left(\frac{\gamma^2}{4} - 1\right)\frac{1}{r^2-1}, \qquad \tilde{A} = \left(\frac{c_1}{c_2}\right)^2 \left(\frac{4a_1}{c_1} - 1\right)$
- (a_i, c_i) given by inner products from the solvability condition

Seek asymptotic and numerical solutions, using constant frequency-shift ansatz:

$$\Phi(z,t) = \int_{-1}^{z} k(z')dz' + \lambda t + \Phi_0$$

Twist-dominated Regime: $\Phi_{zz} \ll \Phi_z^2$

Formally valid for: $|A| \gg 1$

Cole-Hopf transformation: $k(z) = \psi_z(z)/\psi(z)$,

$$d^2\psi/dz^2 + [-\lambda - V(z)]\psi = 0, \qquad V(z) = \mp A(\gamma, r)F(z; r).$$

Ground state (smallest $|\lambda|$) determined by potential in the vicinity of its minimum:

Negative forcing: $A < 0$
1d harmonic oscillator equation, λ determined by behaviour at the origin:

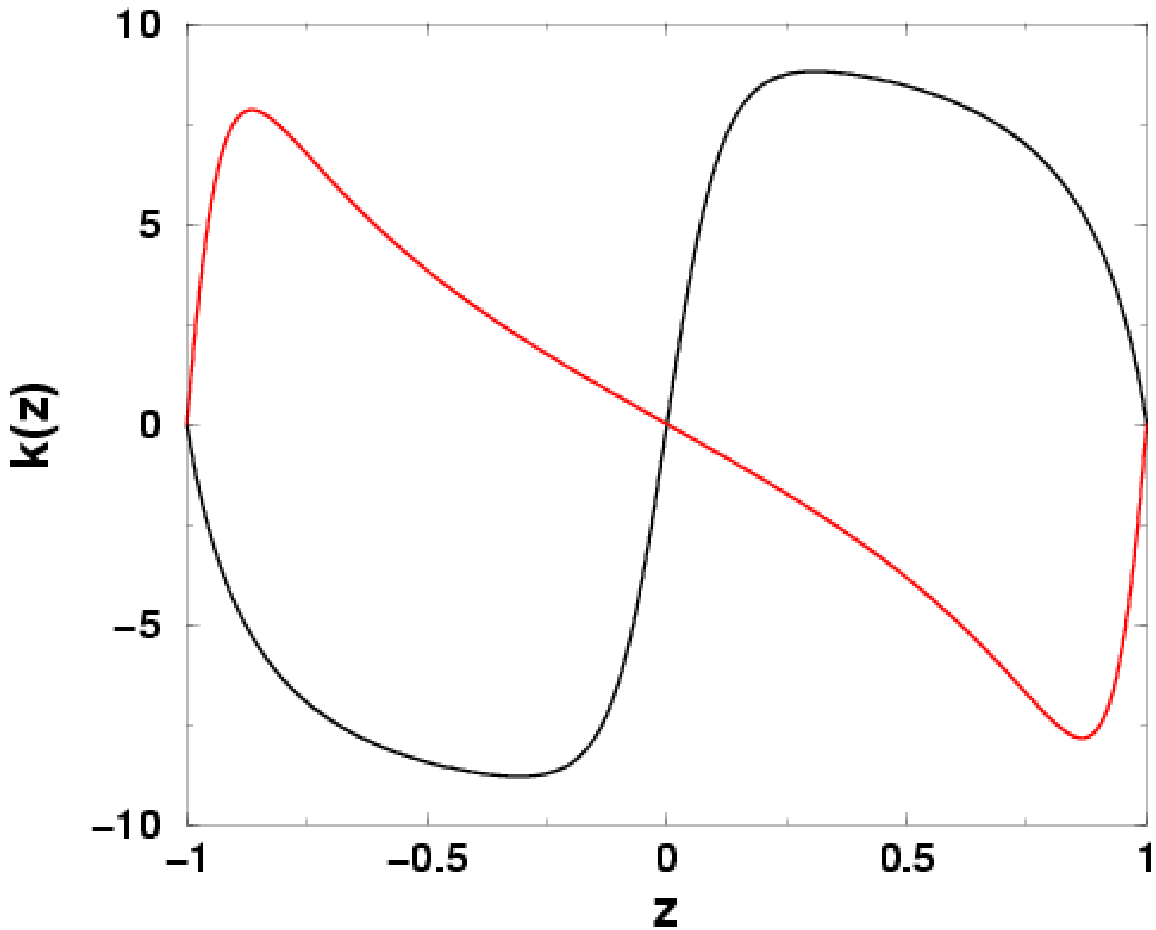
$$\lambda_0 = -\bar{A}/r^2, \qquad \lambda_1 = -\bar{A}^{1/2}/r^2 \qquad \bar{A} = \tilde{A}\left(\gamma^2/4 - 1\right)$$

Positive forcing: $A > 0$
Airy equation, λ determined by behaviour at boundaries:

$$\lambda_0 = \bar{A}/(r^2 - 1), \qquad \lambda_1 = \eta\left(2\bar{A}\right)^{2/3}/(r^2 - 1)^{4/3}$$

where η is the first zero of $Ai'(z)$.

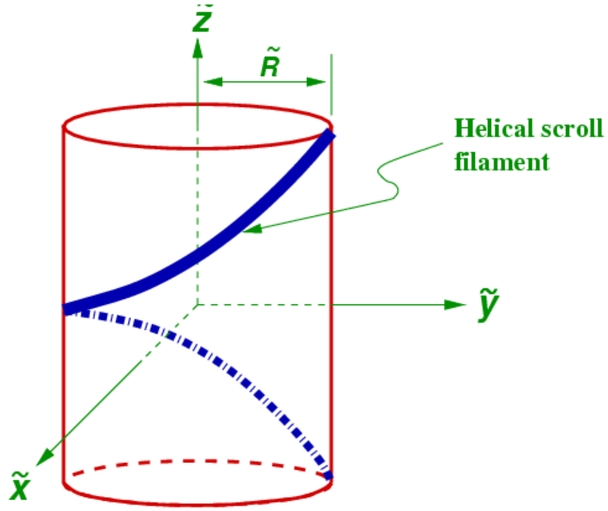
Twist-dominated Regime: $\Phi_{zz} \ll \Phi_z^2$ (cont'd)



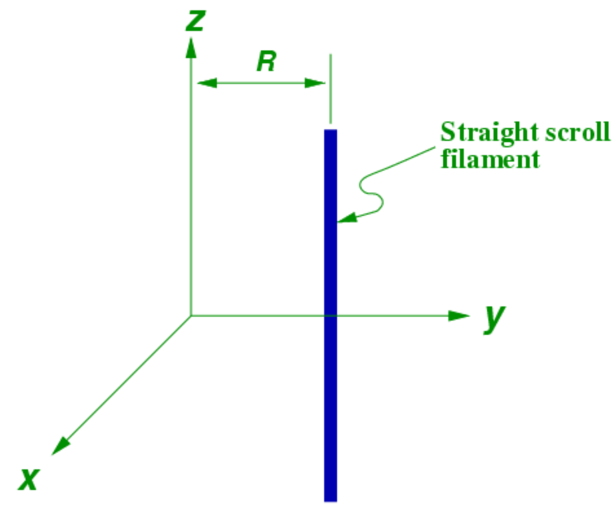
$A > 0$: Formation of large twist in boundary layer in bulk
$A < 0$: Expulsion of large twist from bulk to boundaries

Old versus New: Filaments

Old Coordinates:



New Coordinates:



Assuming:

- Constant fiber rotation rate: $\Theta' =$ constant
- Simple (straight, untwisted) scroll as initial conditions in new coordinates
- No-flux or periodic at vertical boundaries at vertical boundaries

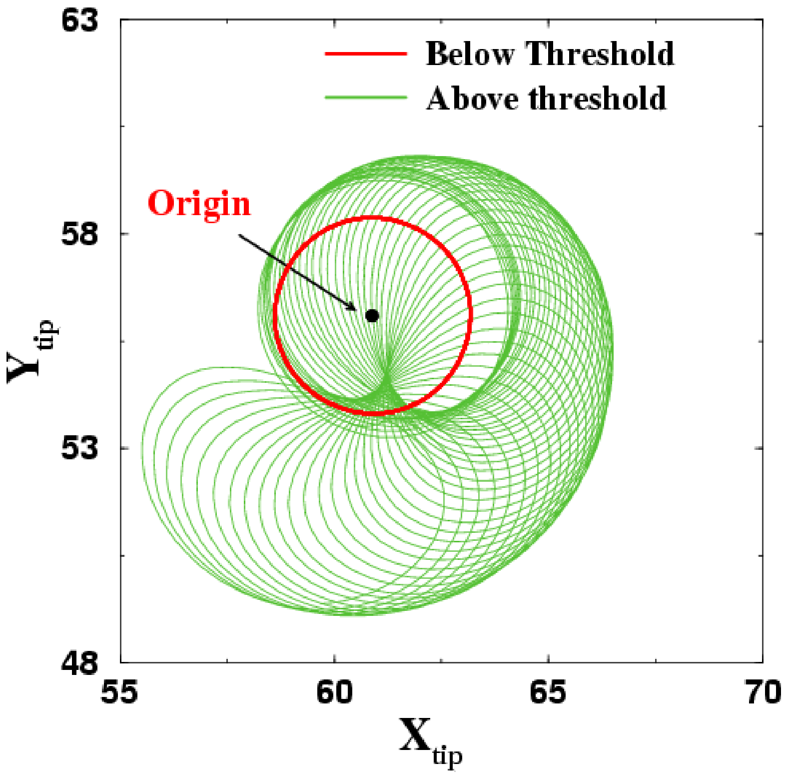
Dynamics reduces to two dimensions:
Helical buckling $\longleftrightarrow$ Motion of spiral center.

Relevance?

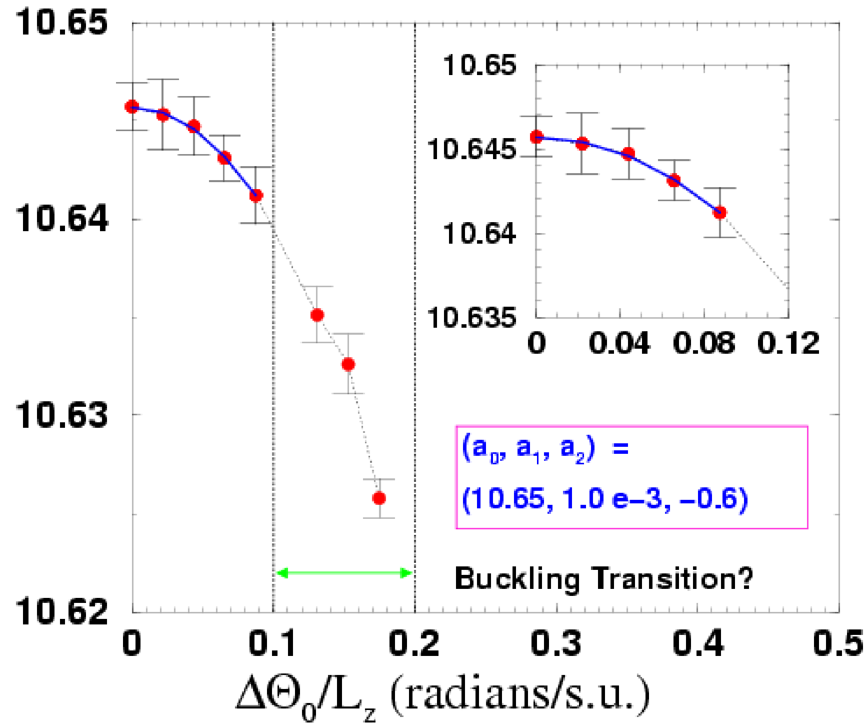
Henzi, et al. Can. J. Phys. **68**, 683 (1990):

$\alpha = 1$: Helical buckling ("sproing instability") for $twist > twist^*$

Tip Trajectory



Scroll Period



What about $\alpha \neq 1$???

Filament motion

Additional coordinate transformation:

$$x \rightarrow x - X_c(t),$$
$$y \rightarrow y - Y_c(t),$$
$$\frac{\partial}{\partial t} \rightarrow \frac{\partial}{\partial t} + \frac{dX_c}{dt}\frac{\partial}{\partial x} + \frac{dY_c}{dt}\frac{\partial}{\partial y},$$

Phase equation:

$$\phi_T = \Theta_Z^2 \left[c_3(\alpha) + r_1 \left(\frac{1}{\alpha^2} Y_c^2 + \alpha^2 X_c^2 \right) \right]$$

Dynamics of the center:

$$\frac{d}{dT}\begin{pmatrix} X_c \\ Y_c \end{pmatrix} = \Theta_Z^2 \underbrace{\begin{pmatrix} \mu_1 & \mu_2 \\ \mu_3 & \mu_4 \end{pmatrix}}_{\mathbf{M}} \begin{pmatrix} X_c \\ Y_c \end{pmatrix}$$

where $\mu_i = \mu_i(\alpha)$:

$$\mu_1(1) = \mu_4(1) = t_1$$
$$\mu_2(1) = -\mu_3(1) = t_2.$$

with:

$$t_1 = \left\langle \vec{\tilde{Y}}_x, \boldsymbol{D}_{\perp_2} \cdot x\vec{U}_{0_x} \right\rangle$$
$$= \left\langle \vec{\tilde{Y}}_y, \boldsymbol{D}_{\perp_2} \cdot y\vec{U}_{0_y} \right\rangle, \; etc.$$
$$r_1 = \left\langle \vec{\tilde{Y}}_0, \boldsymbol{D}_{\perp_2} \cdot \vec{U}_{0_{xx}} \right\rangle$$
$$= \left\langle \vec{\tilde{Y}}_0, \boldsymbol{D}_{\perp_2} \cdot \vec{U}_{0_{yy}} \right\rangle$$

Notes:

- Symmetry: $\alpha \Longleftrightarrow 1/\alpha$
- At $\mathcal{O}(\epsilon^2)$ with $\phi_z = 0$: Motion of center is decoupled from dynamics of phase.

Motion of center/Helical buckling

Dynamics of spiral center governed by eigenvalues of M:

$$\vec{R}_c(T) = C_+ \vec{v}_+ e^{\lambda_+ T} + C_- \vec{v}_- e^{\lambda_- T}$$

No anisotropy: $\alpha = 1$

$$\lambda_\pm = t_1 \pm i t_2$$

- Stability is determined by t_1, depends on reaction kinetics only.
- At $\mathcal{O}(\epsilon^2)$, Θ_z determines only the scaling of filament dynamics.

Weak anisotropy: $\alpha - 1 \equiv \delta$, $|\delta| \ll 1$

$$\lambda_\pm \approx t_1 \pm \sqrt{-t_2^2 + 4\delta^2 \left(B^2 - A^2\right)}$$

- Rotating anisotropy can lead to change in stability! (Necessary condition: $B > A$.)

Dependence on reaction kinetics of
- **$\alpha = 1$: Existence of a finite twist threshold to buckling**
- **$\alpha \neq 1$: Destabilizing or restabilizing role of rotating anisotropy**

Summary

The heart is an important physiological system that is amenable to physical analysis.

What has been done:

- Extension of asymptotics of scroll waves to anisotropic media, verified by numerics:
  - ▷ *Forced Burgers' equation for phase dynamics* [a]
  - ▷ *Stationary twist solutions for realistic fiber distribution profile* [a]

Rotating anisotropy generates twist: Destabilizing ("sproing instability") or restabilizing role of cardiac tissue structure on dynamics of scrolls depends on electrophysiology. [b]

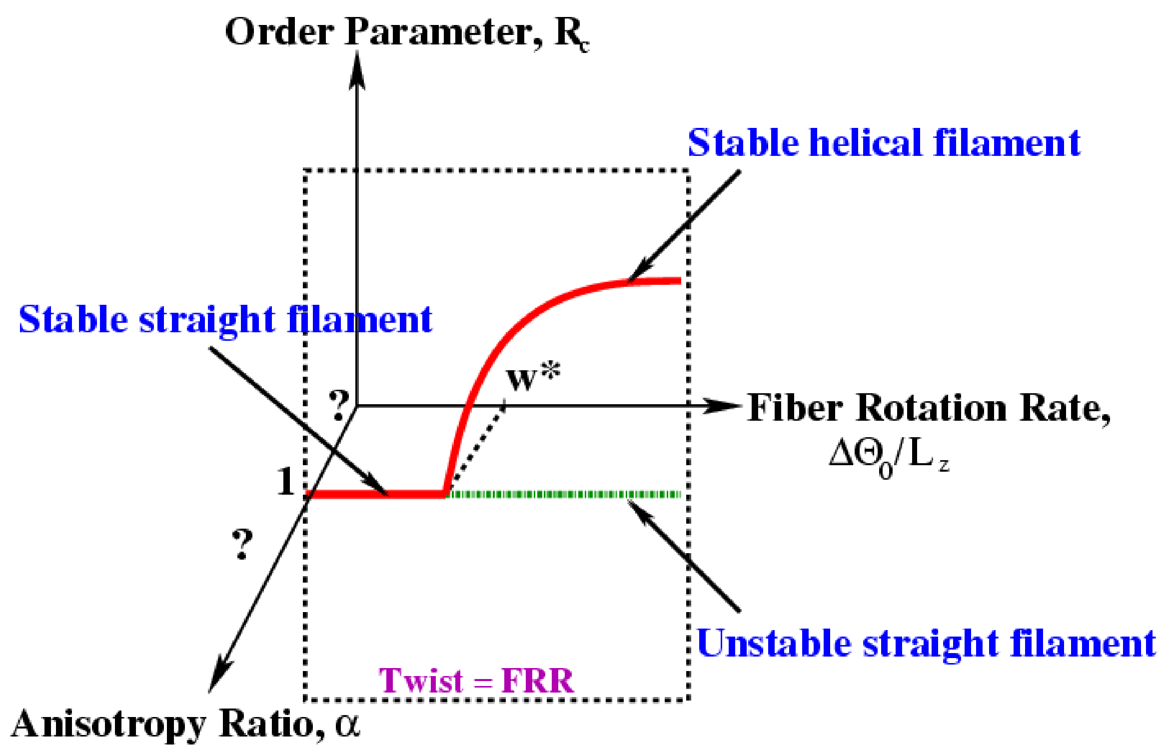
Extensions:

- Numerical verification of change in stability of scroll filament due to rotating anisotropy
- Extension to bidomain description

a : Setayeshgar and Bernoff, Phys. Rev. Lett. **88**, 2002. b : Setayeshgar and Bernoff, in preparation.

Summary (cont'd)

- Numerical sproing bifurcation diagram with rotating anisotropy

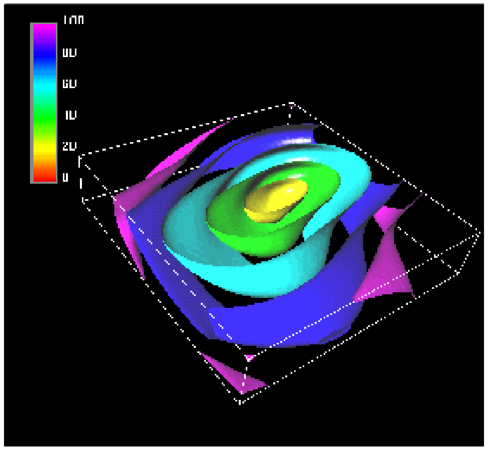


Numerical Simulation of 3d Propagation in Myocardium

with Xiujiang Li, graduate student in Chemical Engineering, Princeton University

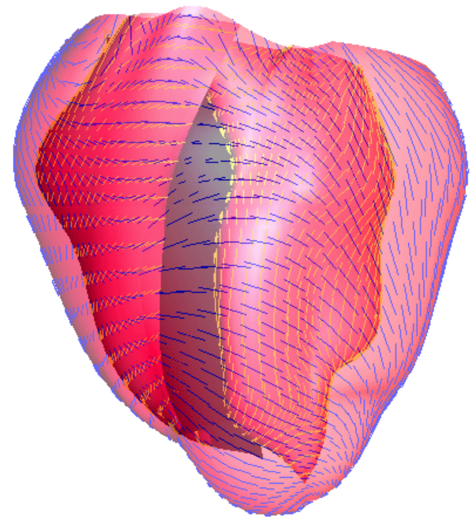
From Toy to Fully Realistic Ventricular Modeling

Rectangular slab



From J.P. Keener, et al., in Cadiac Electrophysiology, eds. D.P. Zipes et al., (1995).

Intact ventricles, using physiological data



Courtesy of UCSD Cardiac Mechanics Group

- Complement experiments
- Systematic studies of electrophysiology on physiologically realistic domains
- Better defibrillation protocols, drug therapy

Fiber Architecture Modeling: Dissection Results

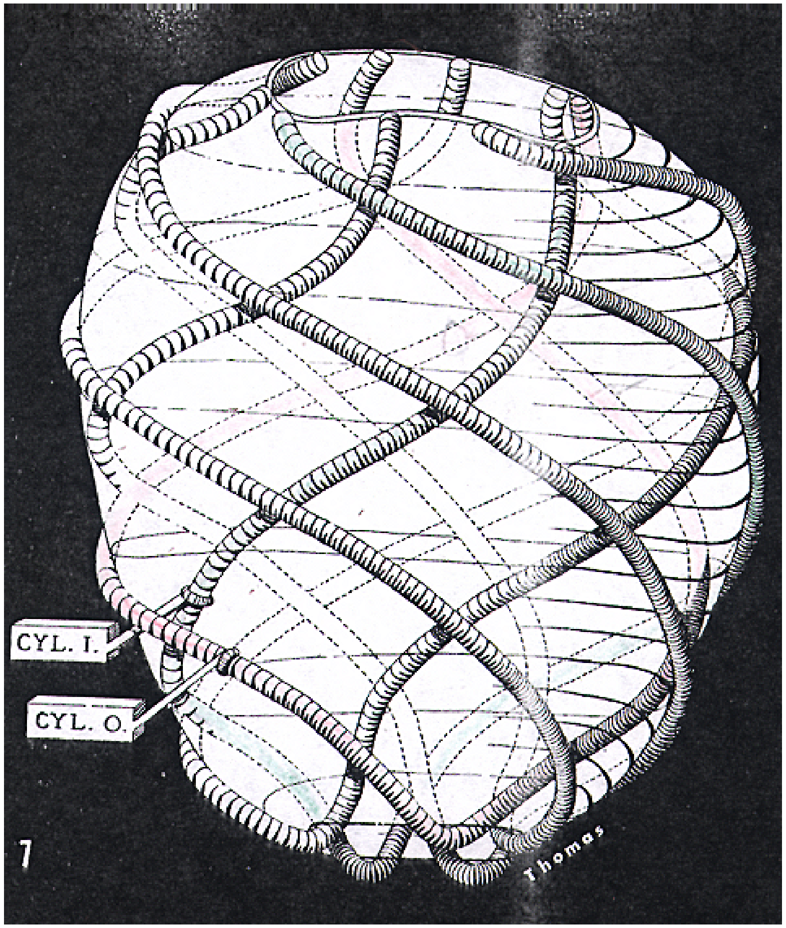
C. E. Thomas (1957)

- ▷ *Nested, layered fiber surfaces*
- ▷ *Complete, qualitative description*
- ▷ *Beautifully hand-illustrated!*

D. Streeter *et al.* **(1969, 1978)**

- ▷ *Measurement of fiber angle distribution*
- ▷ *Fiber trajectories = geodesics!*

''Cylinder'' of the Left Ventricle

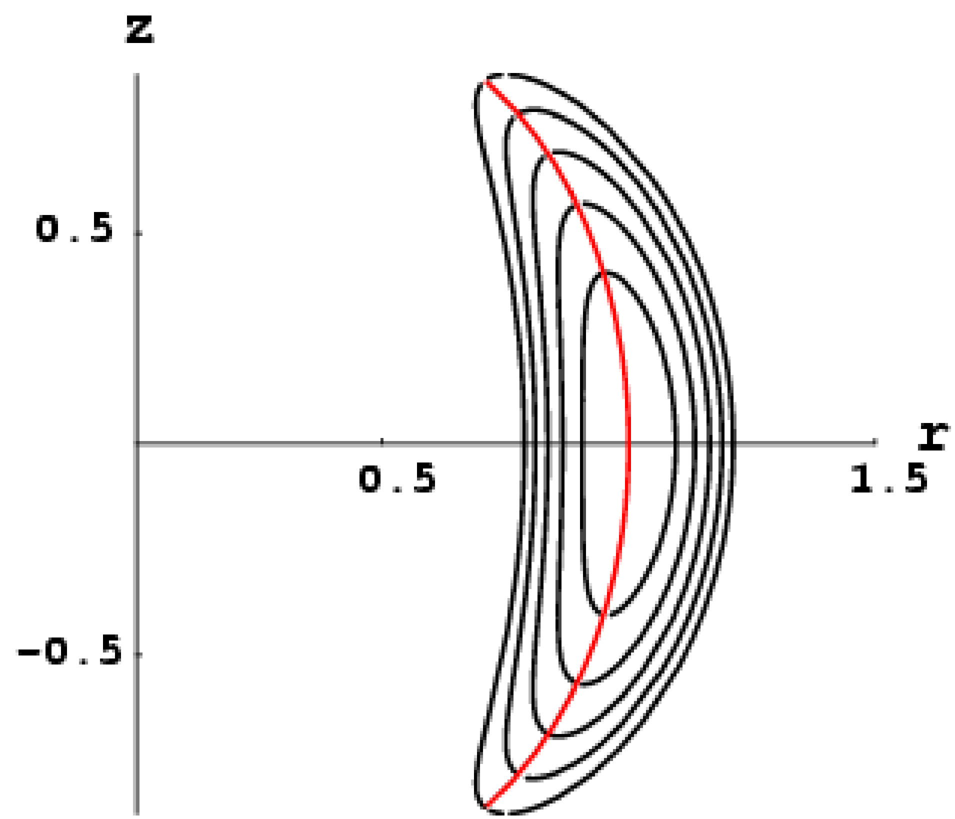


From C. E. Thomas, Am. J. of Anatomy (1957).

Fiber Architecture Modeling: Peskin derived model

C. S. Peskin: Comm. on Pure and Appl. Math **42**, p. 79 (1989)

Fiber Surfaces



What goes in:

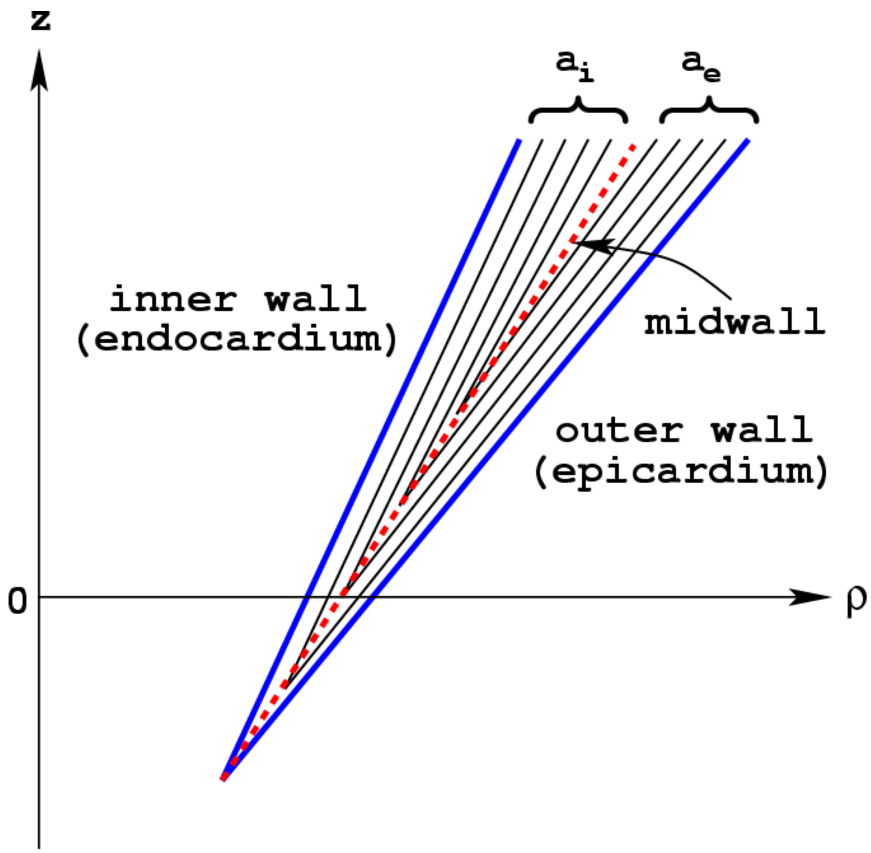
- Stress: $\sigma_{ij} = -p\delta_{ij} + T\tau_i\tau_j$
- (Near) mechanical equilibrium: $\partial\sigma_{ij}/\partial x_j = 0$
- Design criterion: $\vec{\nabla} \cdot \vec{\tau} = 0$

What comes out:

- Fiber surfaces: nested ''toroids''
- Fiber paths: approximate geodesics
- Fiber angle distribution: in good agreement with dissection results!

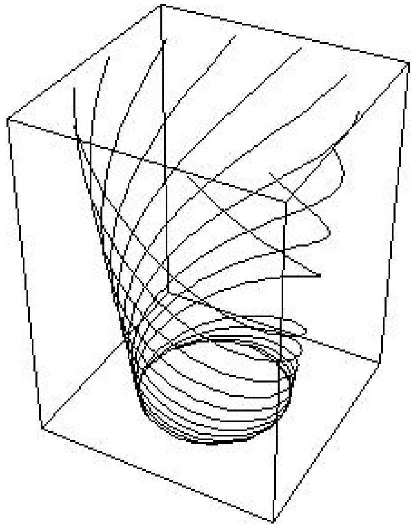
Minimally realistic fiber architecture

Nested cone geometry

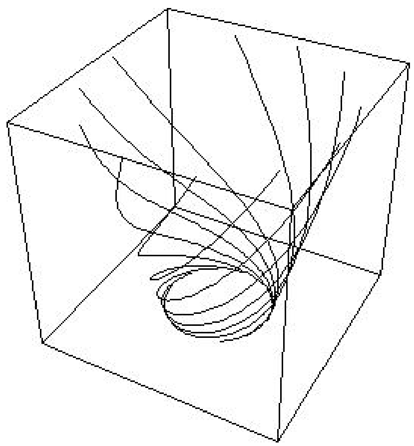


Computation is reduced to that in a rectangular box by working in spherical polar coordinates.

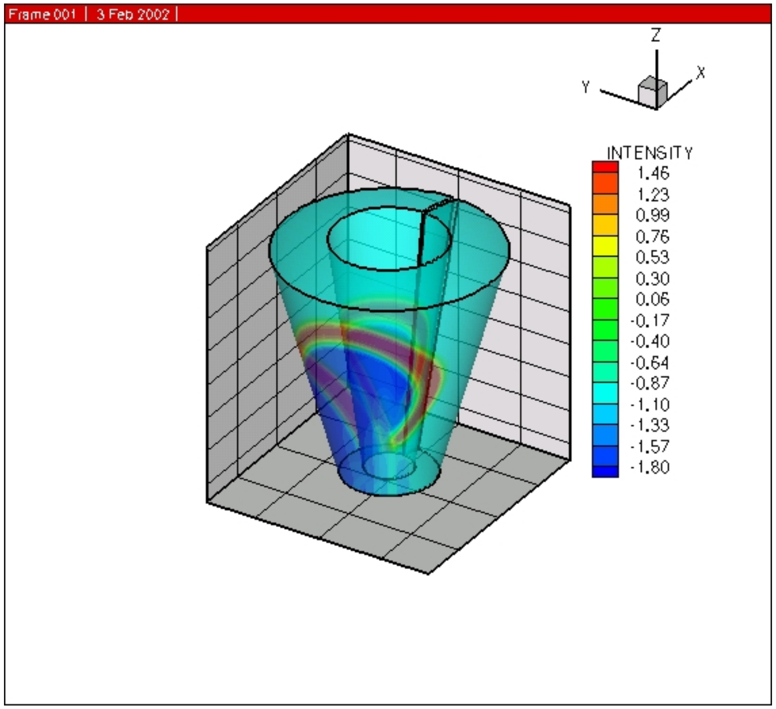
Fibers in



Fibers out



Preliminary Results



This approach motivated by:

- Numerical simulation severely restricted by sharpness of action potential
- Need for high fidelity numerical experiments
- Systematic parameter studies
- Dynamics of scrolls on spheres, see
  - ▷ *Chavez, F., et al., Chaos* **11**, *757 (2001).*