The nonlinear dynamics of the heart: chaos and synchronization in networks of cardiac cells

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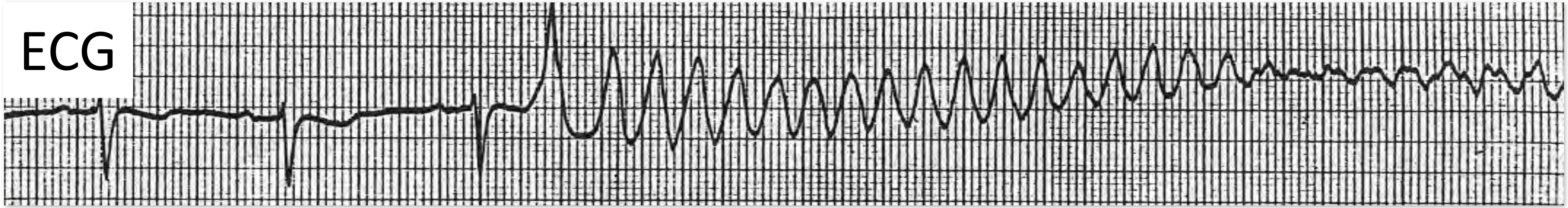
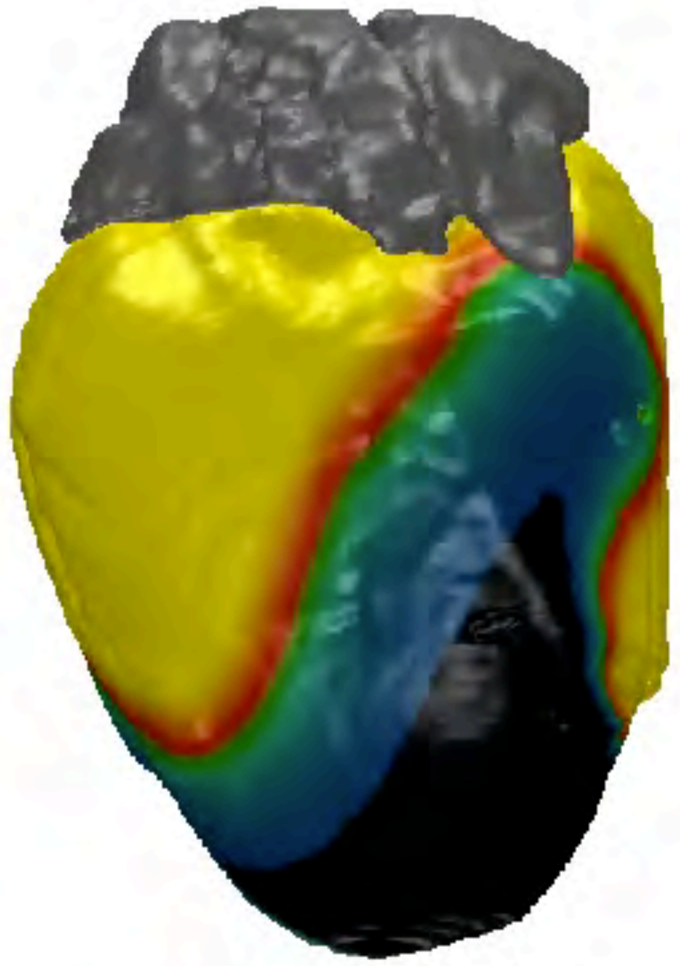
Transitions to Cardiac Arrhythmias

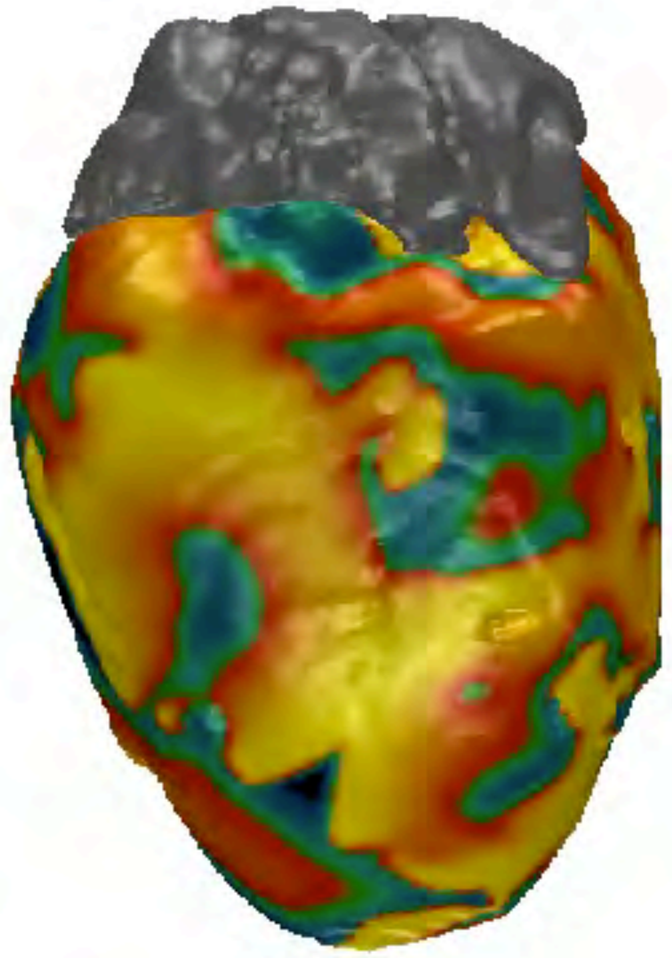
Normal Rhythm → Tachycardia → Fibrillation



electrical excitation waves


plane waves


spiral waves

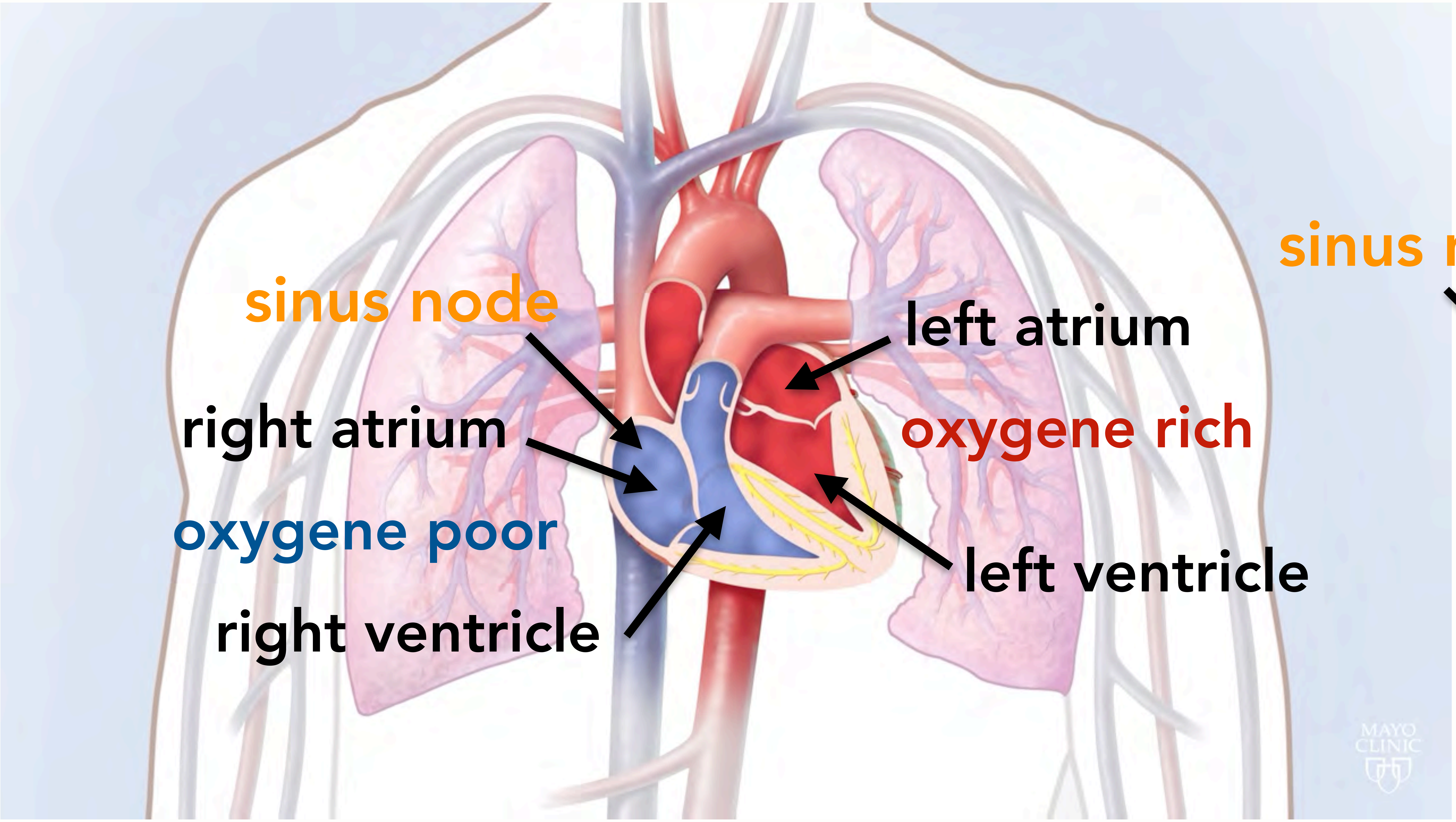

chaos

simulations: P. Bittihn

Outline

- the heart - a network of electrically and mechanically coupled contracting cardiac cells
- excitable media, (chaotic) spiral waves, and phase singularities
- virtual electrodes and low-energy defibrillation
- (transient) chaos and complexity in cardiac arrhythmias

The Heart



sinus node

right atrium

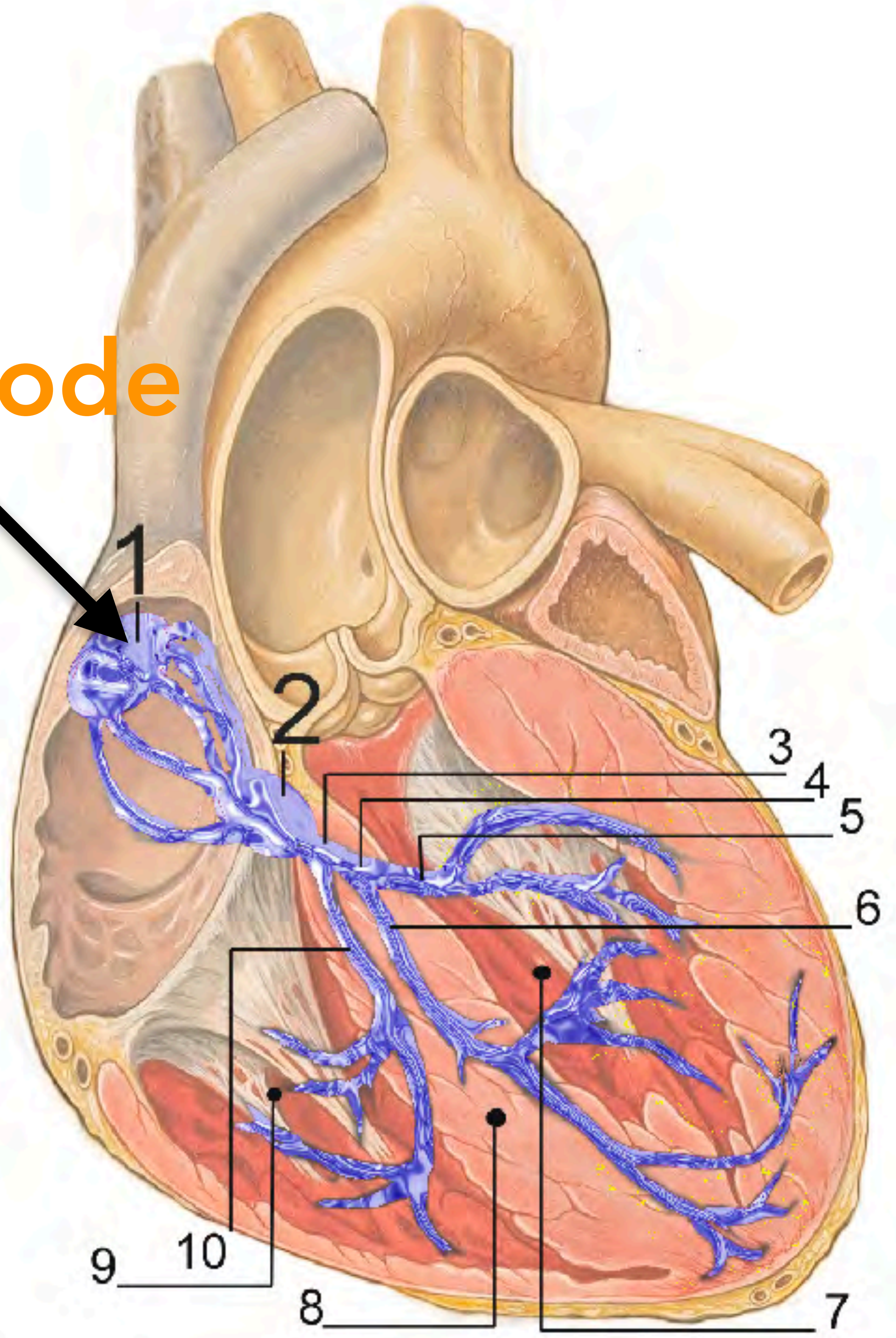
oxygene poor

right ventricle

left atrium

oxygene rich

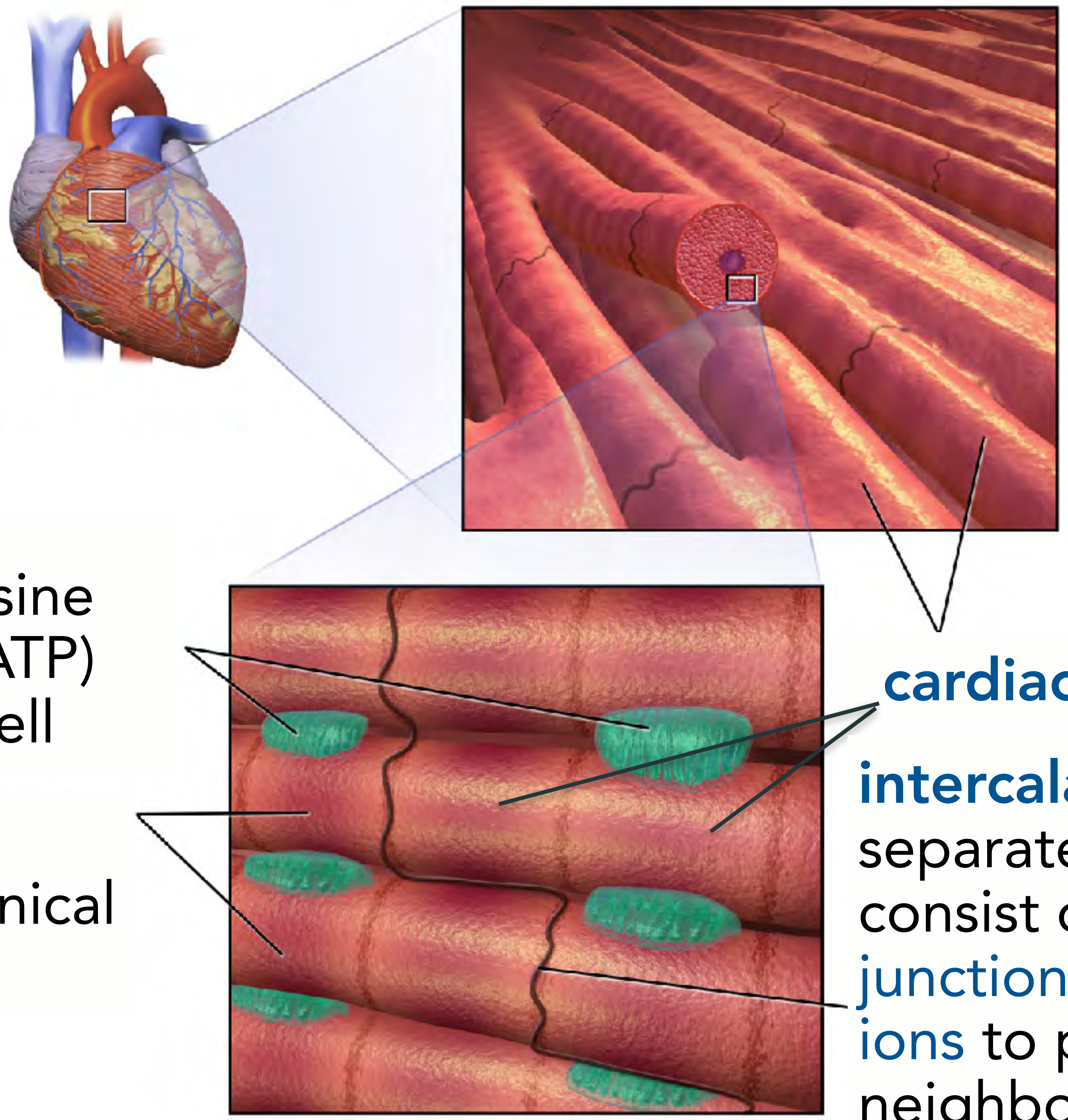
left ventricle



sinus node

https://www.mayoclinic.org/diseases-conditions/heart-disease/multimedia/circulatory-system/vid-20084745
J. Heuser, http://commons.wikimedia.org/wiki/File:RLS_12blauLeg.png

Network of Cardiomyocytes



cardiac muscle

cardiac muscle fibers

BruceBlaus - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=44969447

mitochondria
provide adenosine triphosphate (ATP) supply of the cell

myofibrils
provide mechanical contraction

cardiac muscle cells

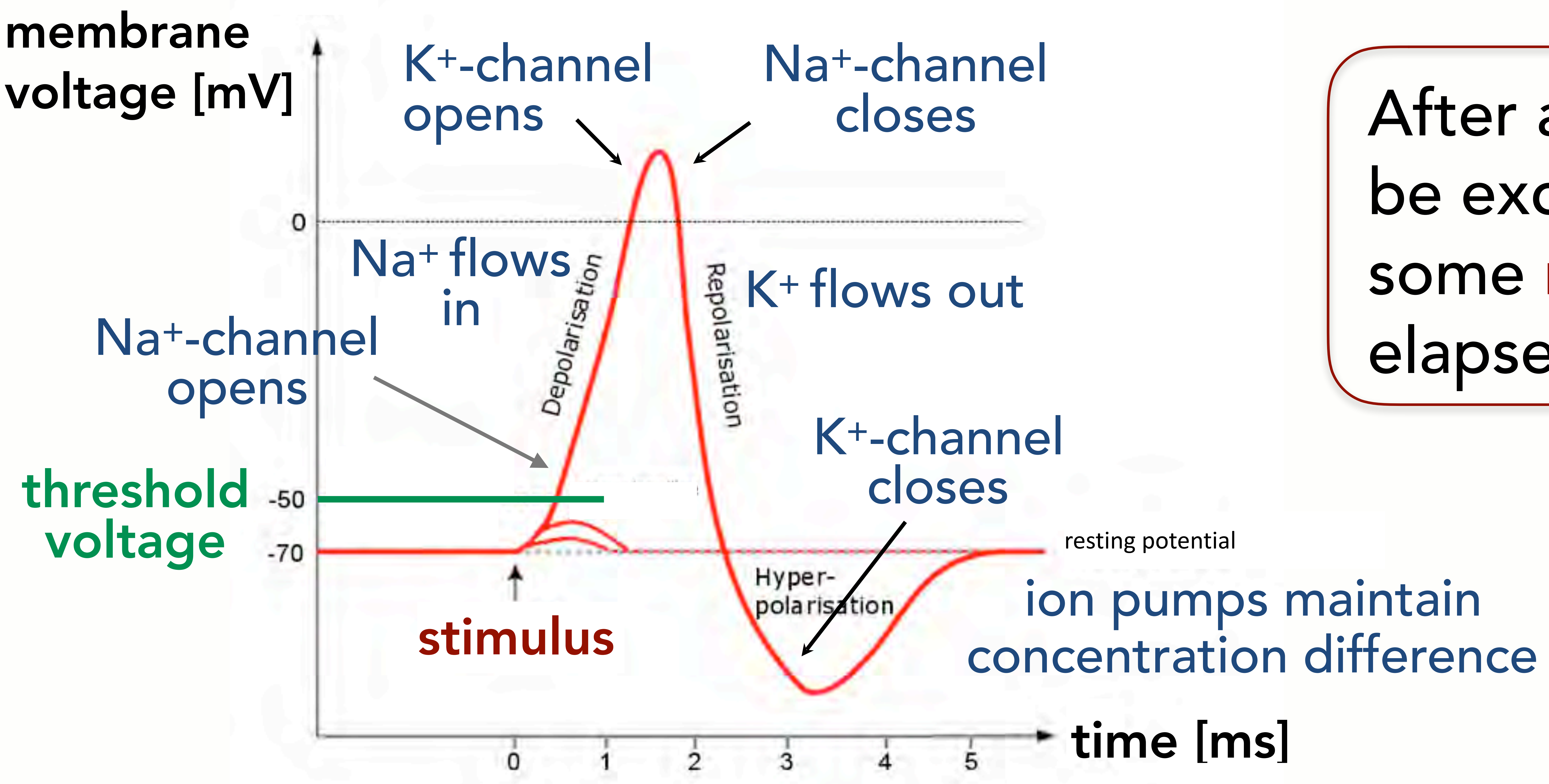
intercalated discs
separate cells and consist of gap junctions that allow ions to propagate to neighbouring cell

Ventricular Cell

~10μm x100μm

© Kornreich & Fenton

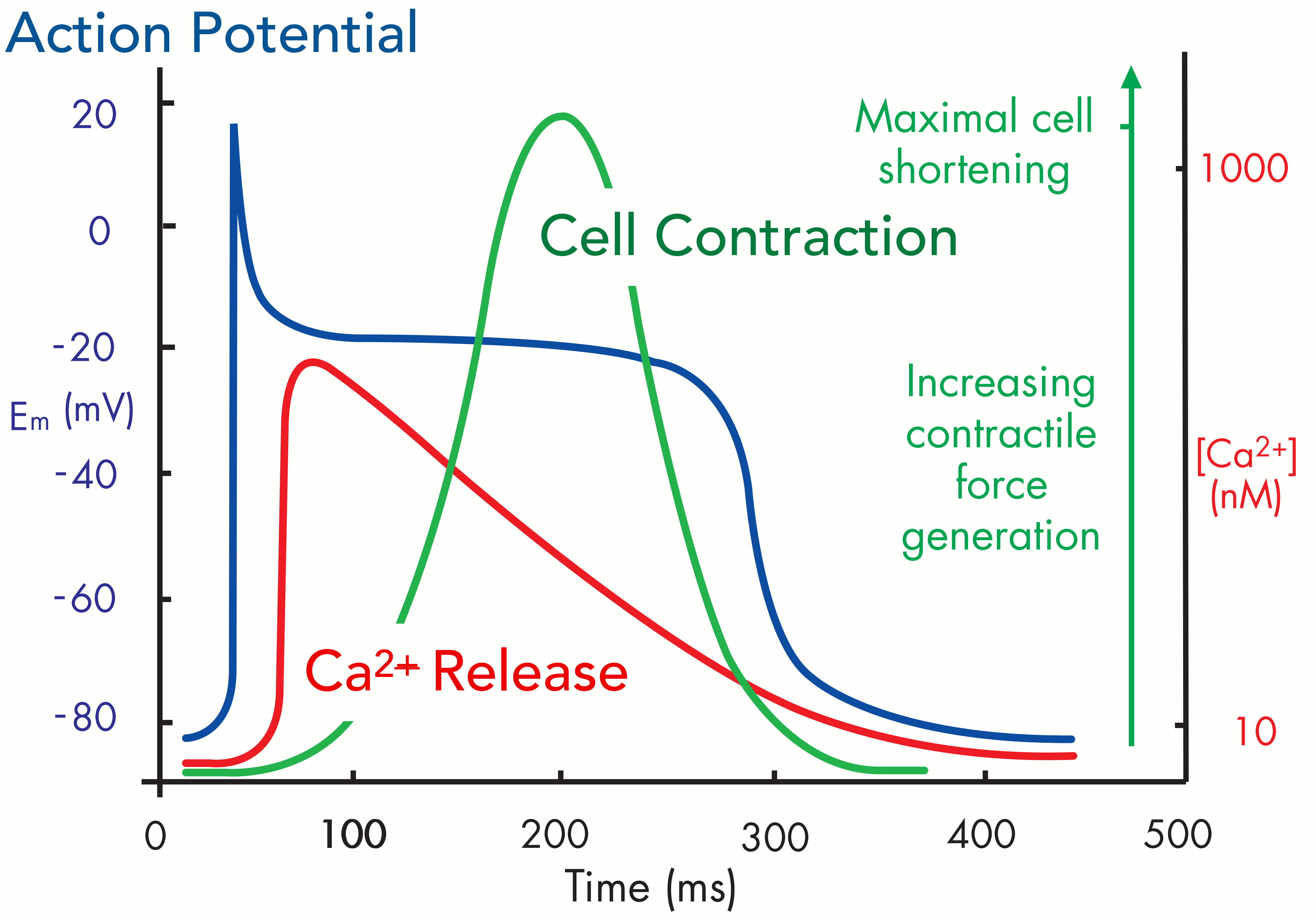
Generation of an Action Potential



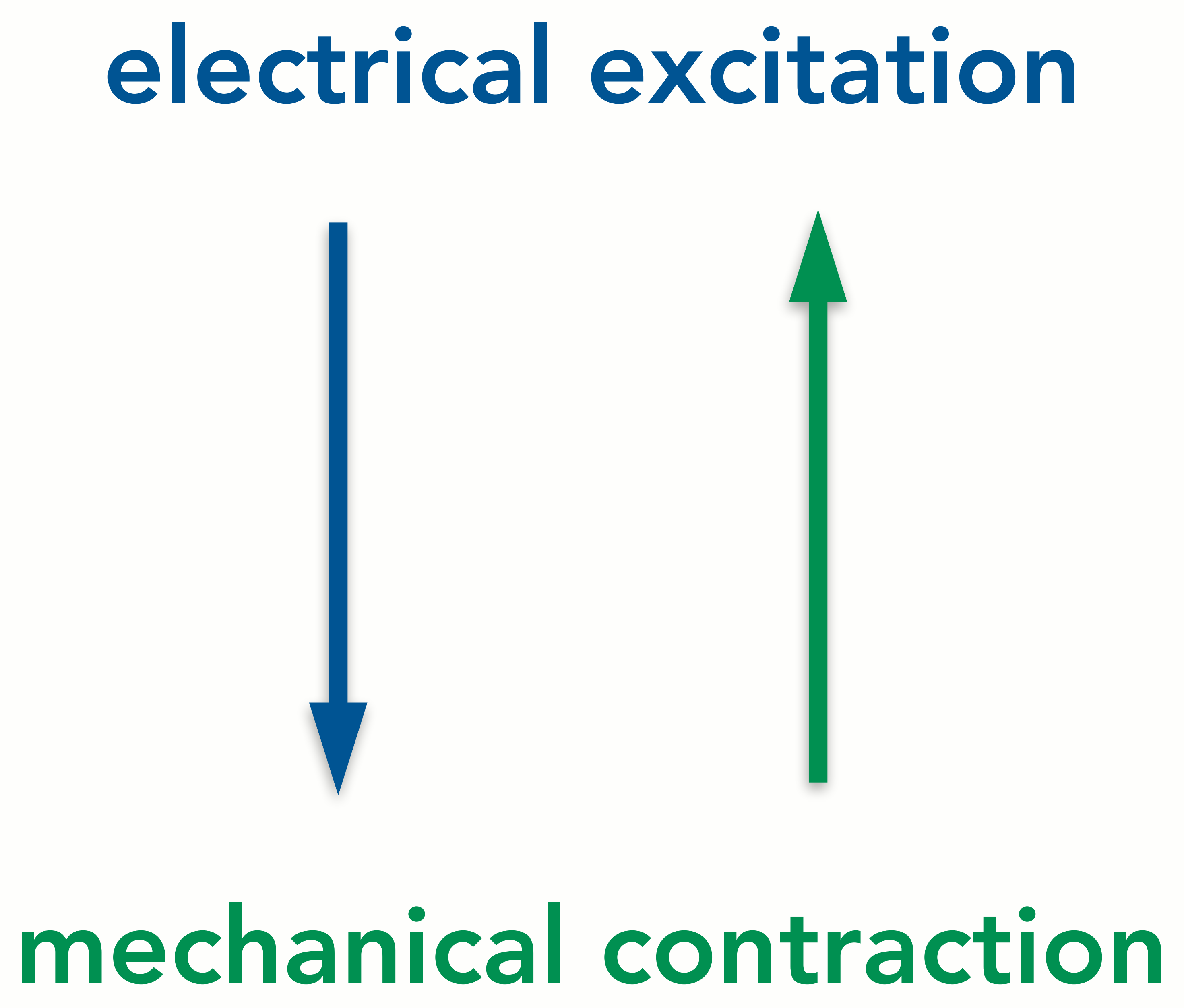
After an excitation the cell can be excited again not before some **refractory phase** has elapsed.

adapted from Wikipedia

Excitation-Contraction Coupling



from: M. Scoote et al., *Heart* 89, 371–376 (2003)



Mechanical perturbation induces electrical stimulation via stretch activated ion channels.

Mathematical Models of Cardiac Dynamics

continuum models averaging electrical behaviour of many cells

detailed ionic models: e.g., Luo-Rudy-II (15), Majahan (27), Bondarenko (44), …

membrane voltage

$$\frac{\partial V_m}{\partial t} = \nabla \cdot \underline{\mathbf{D}} \nabla V_m - I_{\text{ion}}(V_m, \mathbf{h})/C_m$$

$$\frac{\partial \mathbf{h}}{\partial t} = \mathbf{H}(V_m, \mathbf{h})$$

ionic currents

$$I_{\text{ion}}(V_m, \mathbf{h}) = \sum_x I_x(V_m, \mathbf{h}) + I_{\text{injection}}$$

local cell dynamics (15-30 variables, 150 - 300 parameters!)

generic qualitative models: e.g., Fenton-Karma (3), Beeler-Reuter (8), …

simple qualitative models: e.g., Barkley (2), FitzHugh-Nagumo (2), Aliev-Panfilov (2), …

see Scholarpedia article by F. Fenton and E. Cherry discussing 45 models of cardiac cells

Excitable Systems

Simple generic system: The Barkley model

$$\frac{\partial u}{\partial t} = \frac{1}{\varepsilon} u(1-u)\,(u-u_{th})$$

$$u_{th} = \frac{v+b}{a}$$

excitability threshold

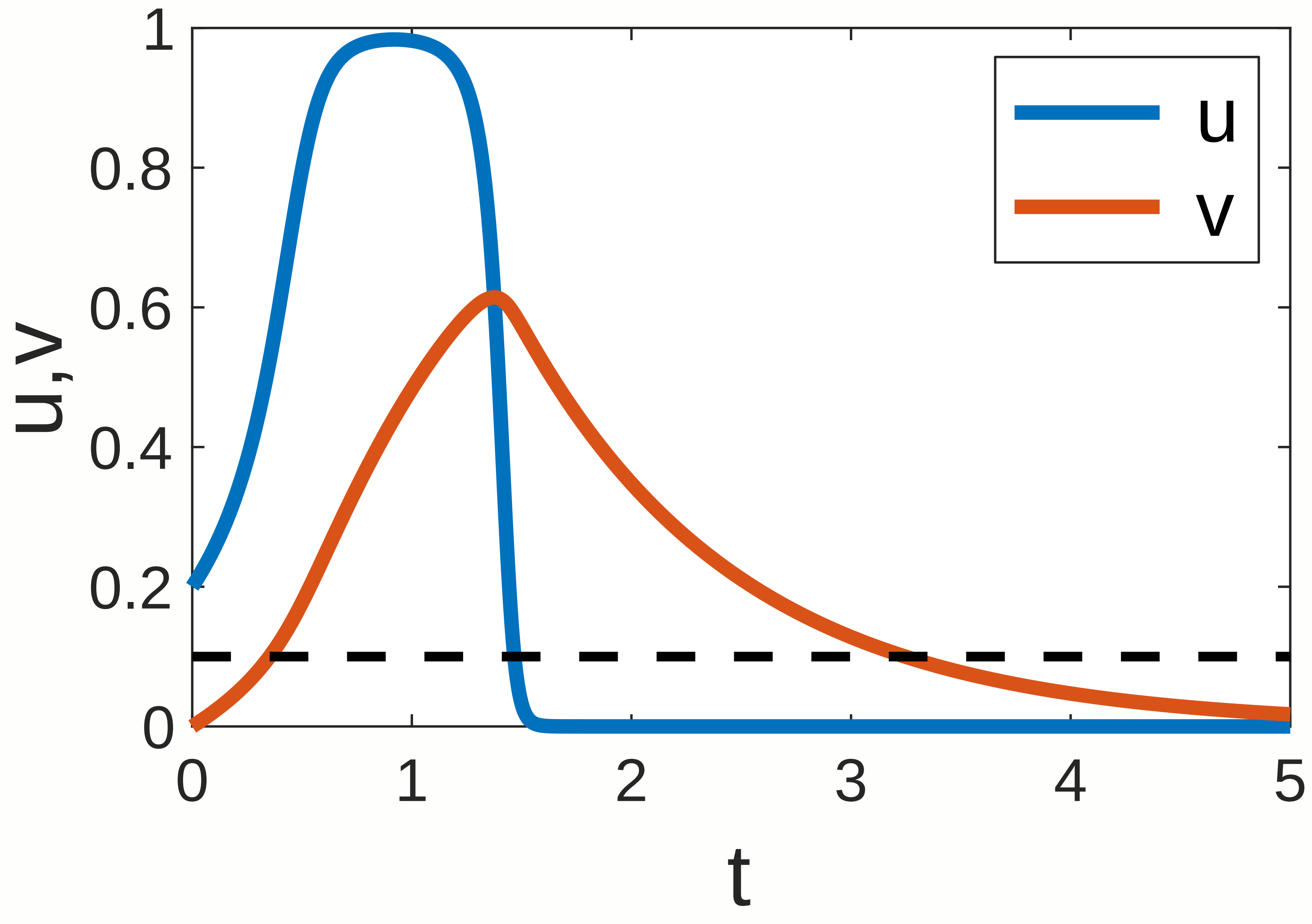
$$\frac{\partial v}{\partial t} = u - v$$

controls excitability threshold

$1/\epsilon$ time scale of the fast variable u

a measure for action potential duration

b/a measure for excitation threshold



D. Barkley et al., Phys. Rev. A 4, 2489 (1990)
D. Barkley, Physica D 49, 6170 (1991)

http://www.scholarpedia.org/article/Barkley_model

The Barkley model

local dynamics

diffusive coupling

$$\frac{\partial u}{\partial t} = \frac{1}{\varepsilon} u(1-u)\,(u-u_{th}) + D \cdot \nabla^2 u$$

$$\frac{\partial v}{\partial t} = u - v$$

with: $u_{th} = \frac{v+b}{a}$

$1/\epsilon$	time scale of the fast variable u
a	measure for action potential duration
b/a	measure for excitation threshold

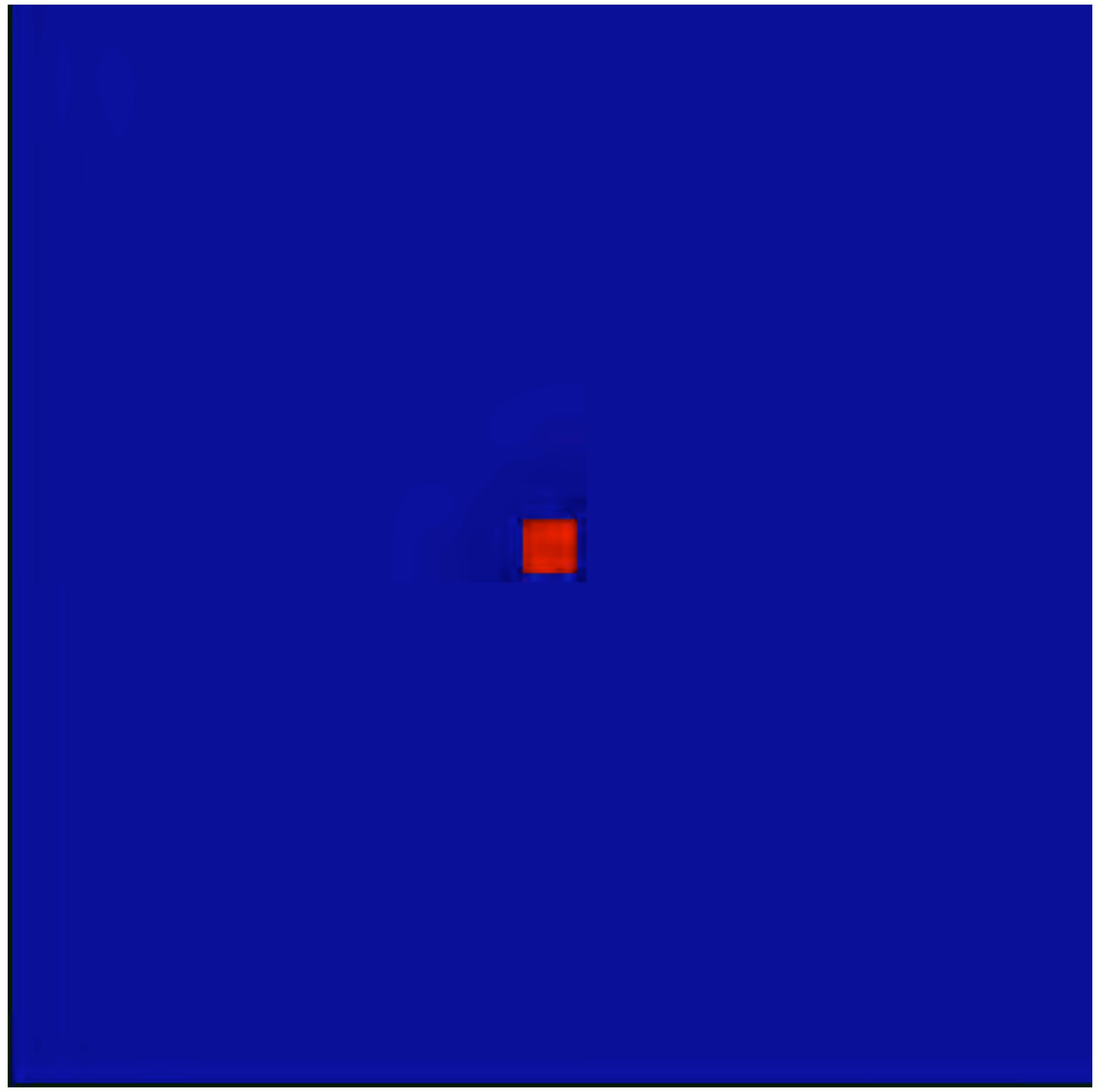
D. Barkley et al., Phys. Rev. A 4, 2489 (1990)
D. Barkley, Physica D 49, 6170 (1991)

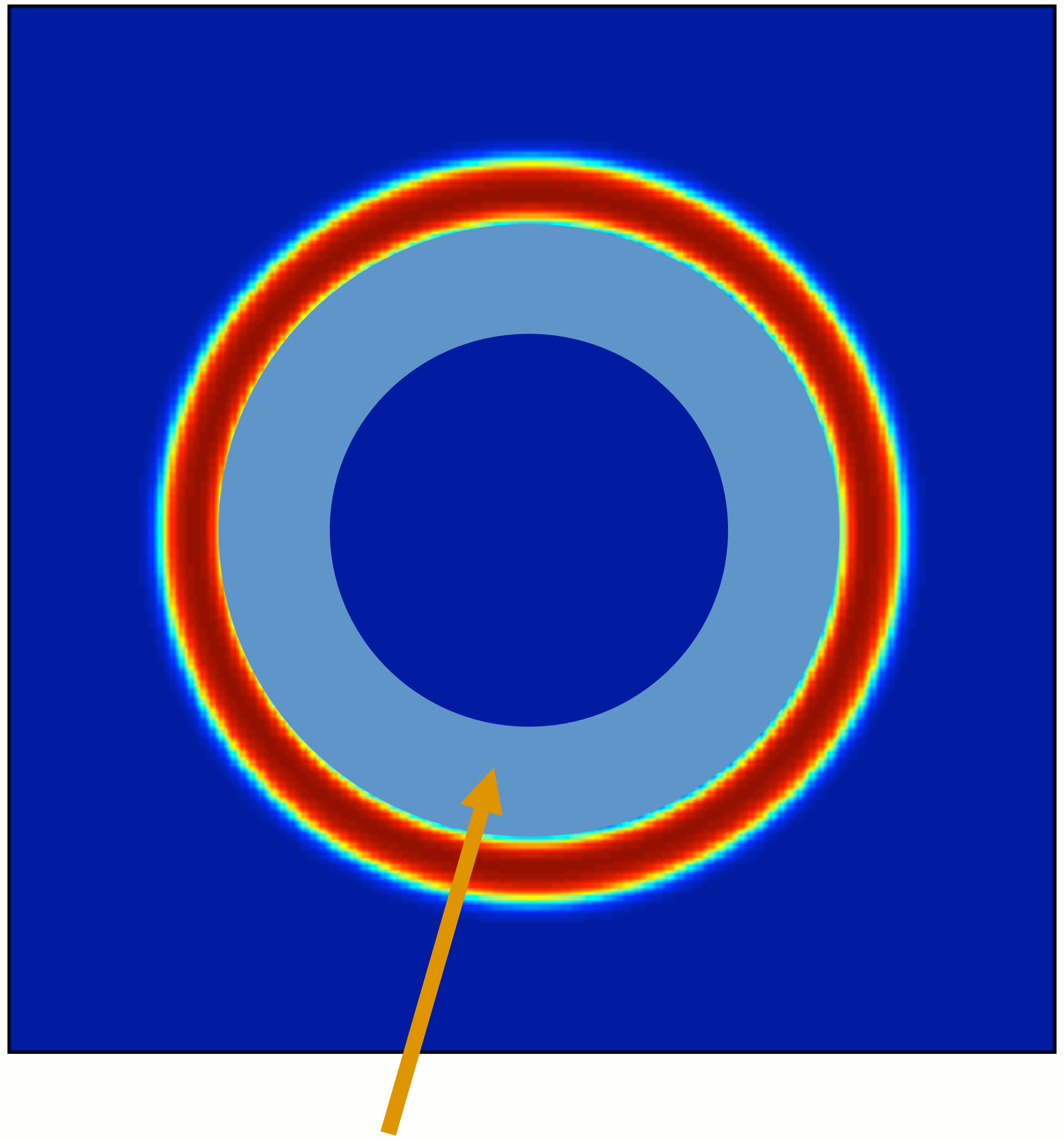
http://www.scholarpedia.org/article/Barkley_model

Excitable Media

Excitation waves (Barkley model)

local stimulation
in the center





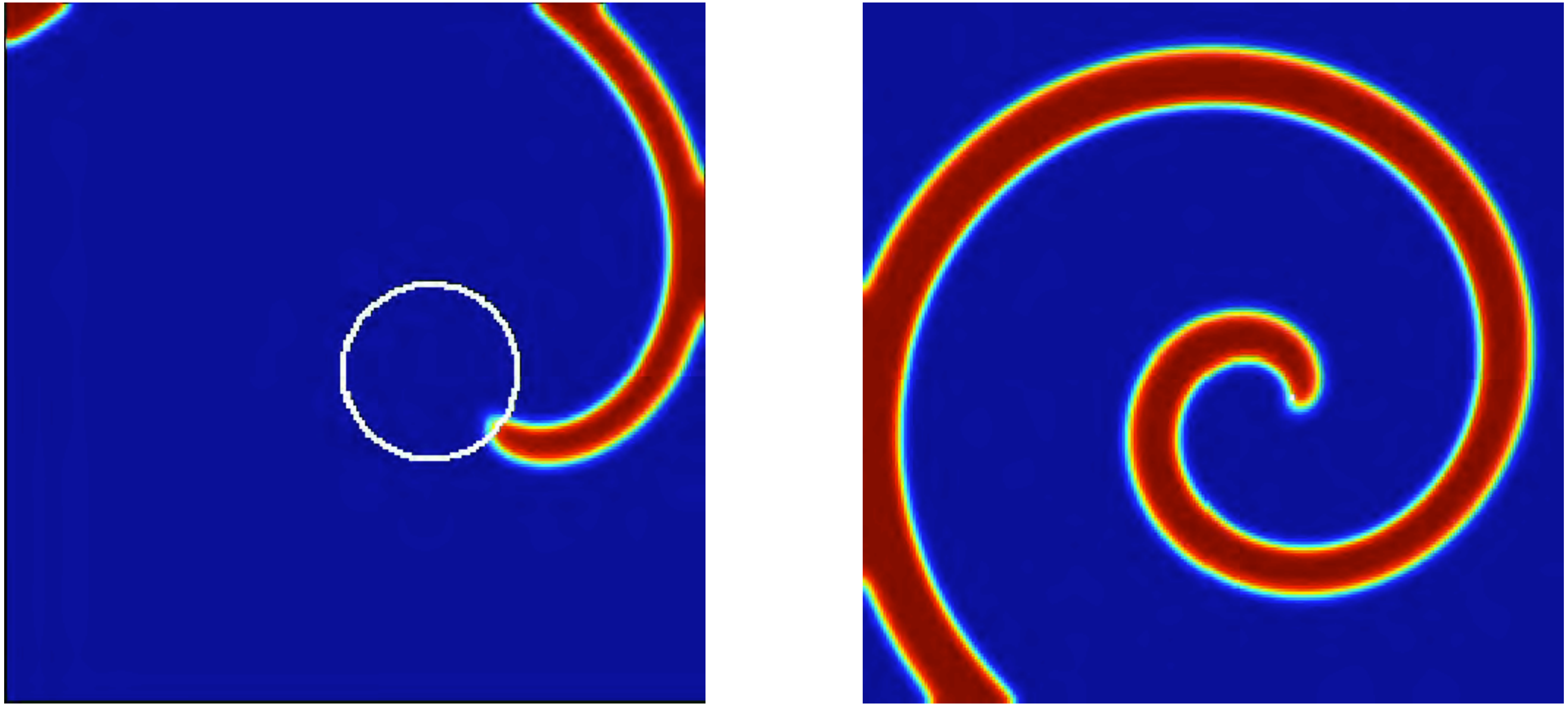
refractory region
(currently not excitable)

no flux boundary conditions

simulations: P. Bittihn

Excitable Media

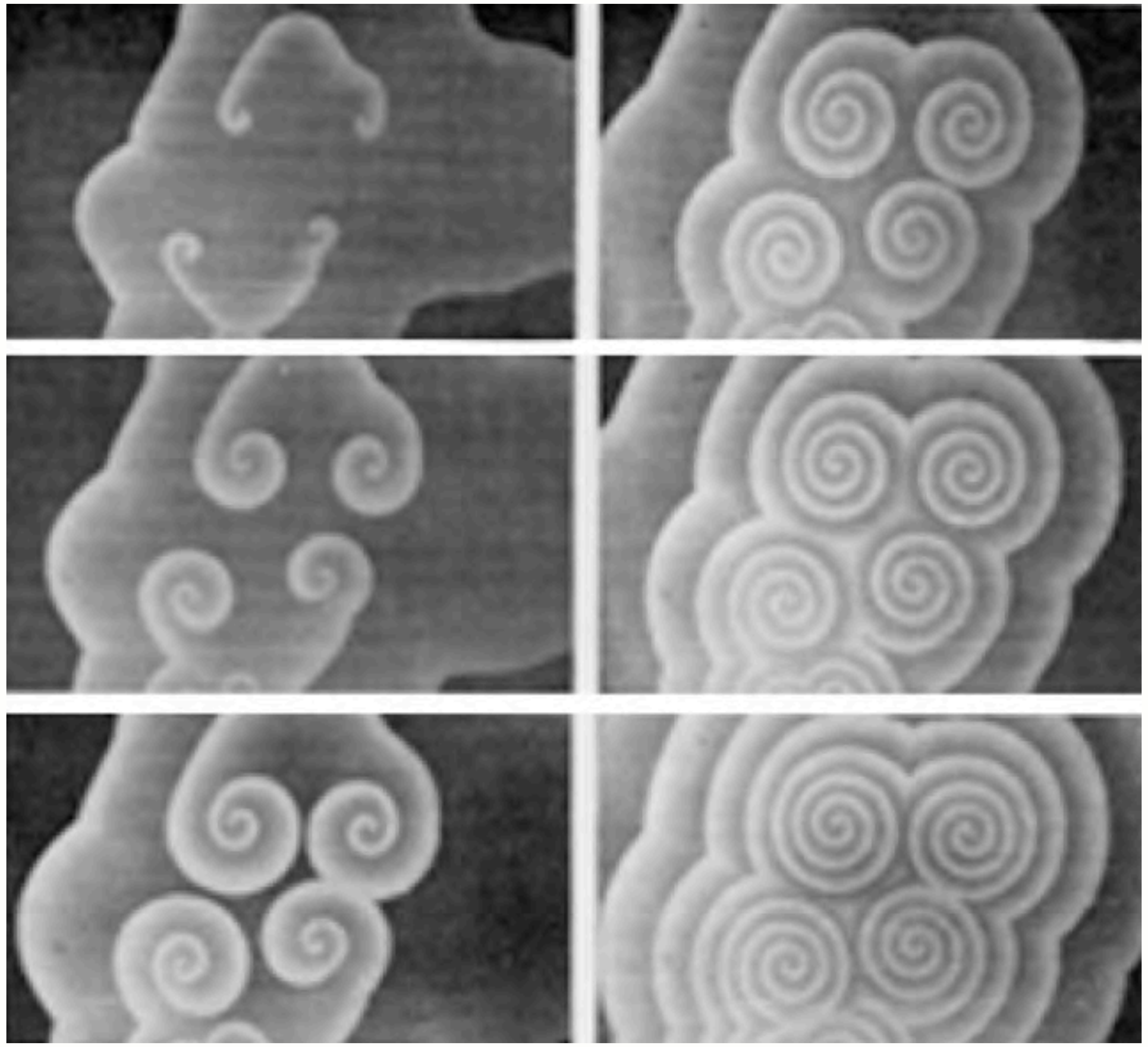
Spiral waves (Barkley model)



simulations: P. Bittihn

Excitable Media

The Belousov-Zhabotinsky (BZ) reaction



Development of spiral waves after hydrodynamic breaking of a concentric wave

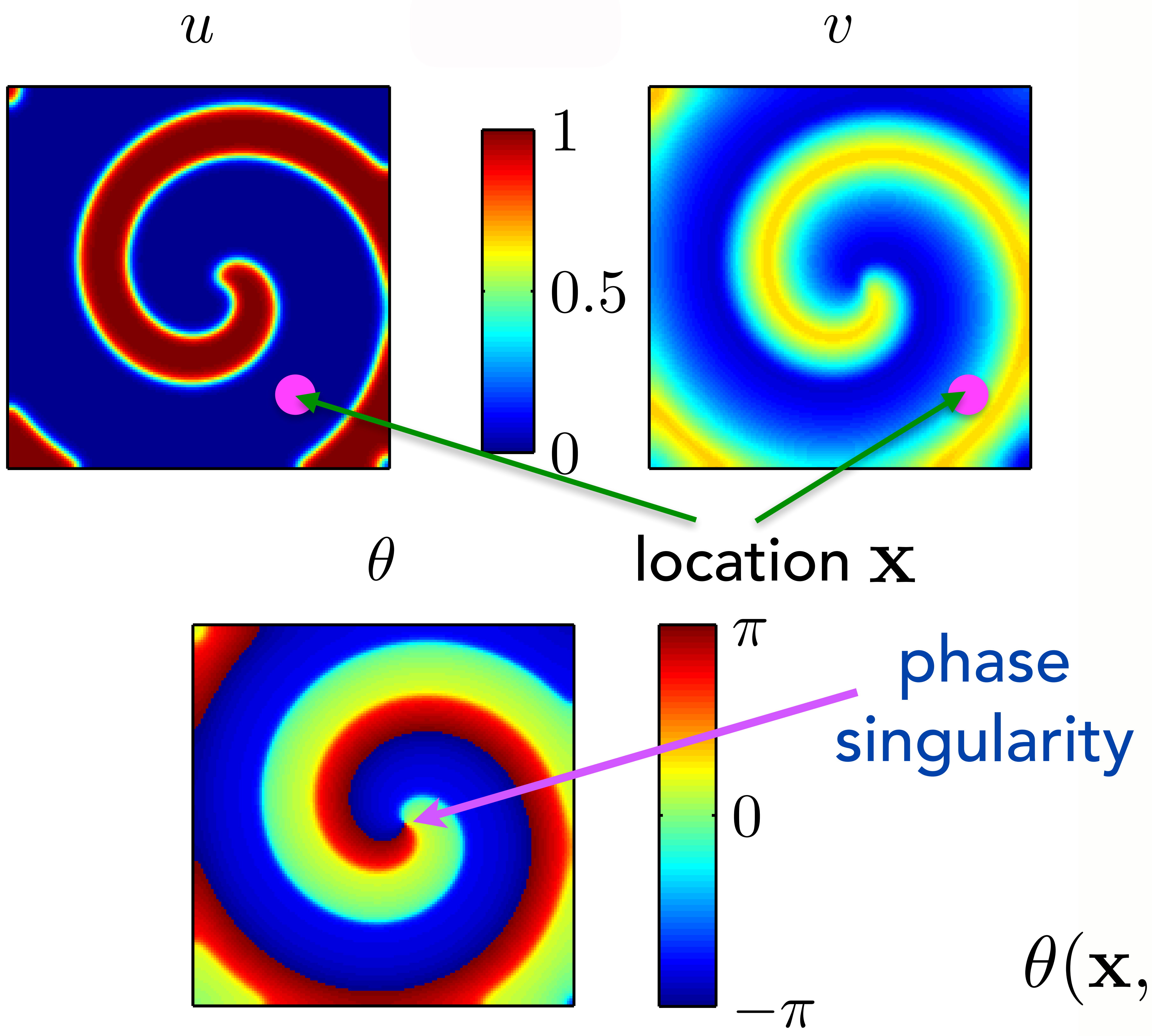
www.scholarpedia.org

Geographic Tongue

inflammatory condition of the mucous membrane of the tongue

By Geographic_tongue.JPG: Martanopuederivative work: Jbarta - This file was derived from: Geographic tongue.JPG:, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=24437119

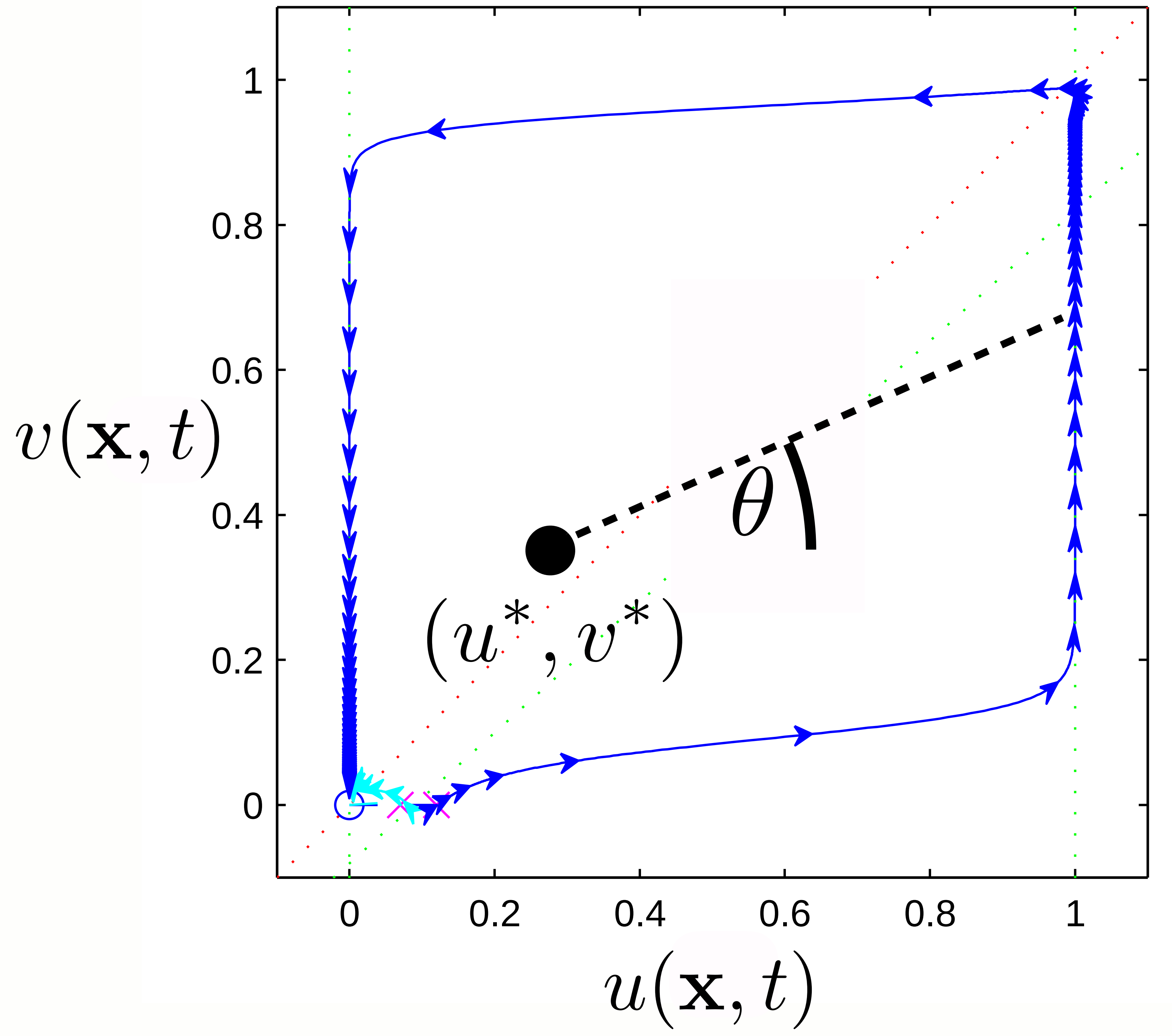
Spiral Tips and Phase Singularities



location $\mathbf{x}$

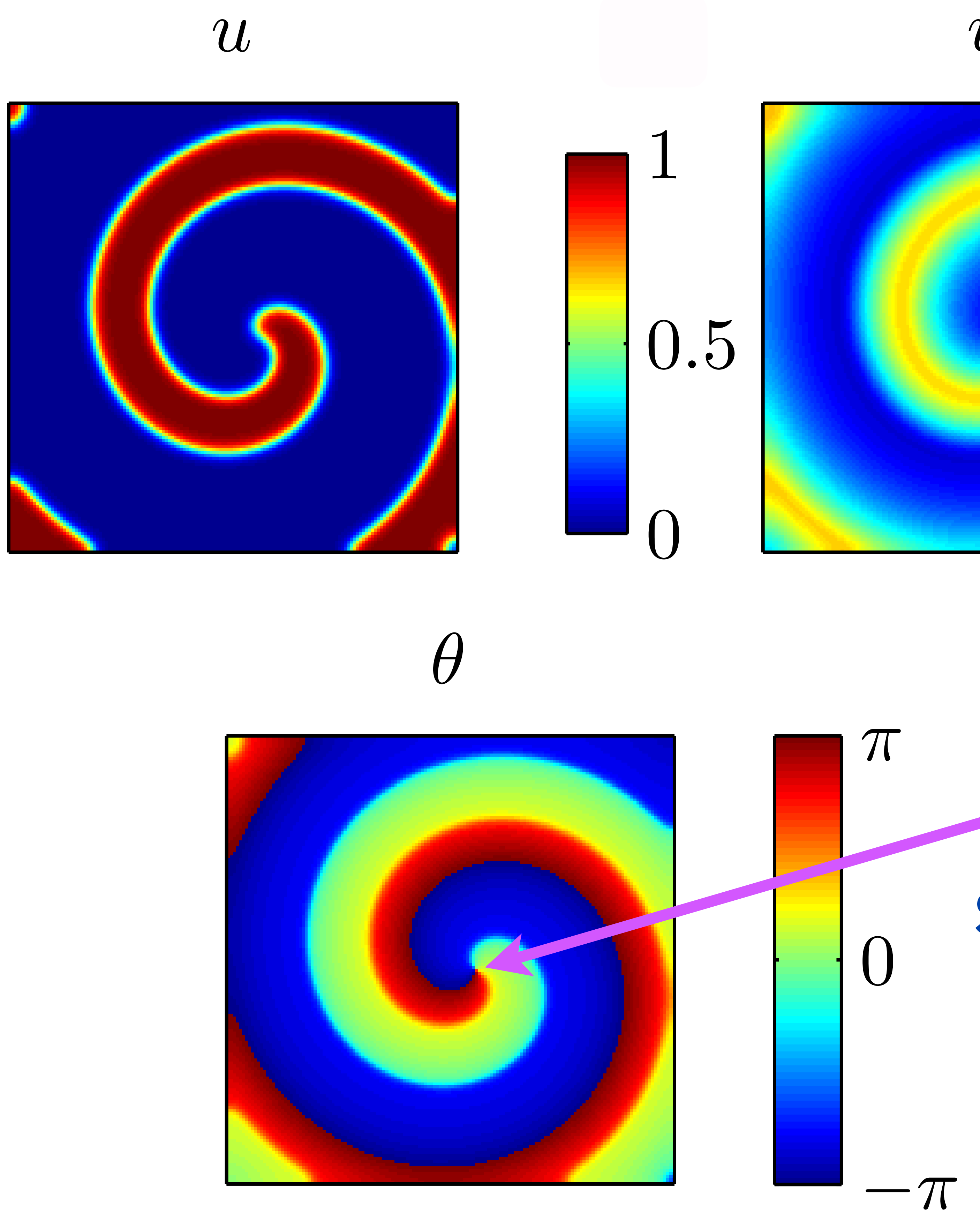
phase singularity

estimate phase at each location $\mathbf{x}$



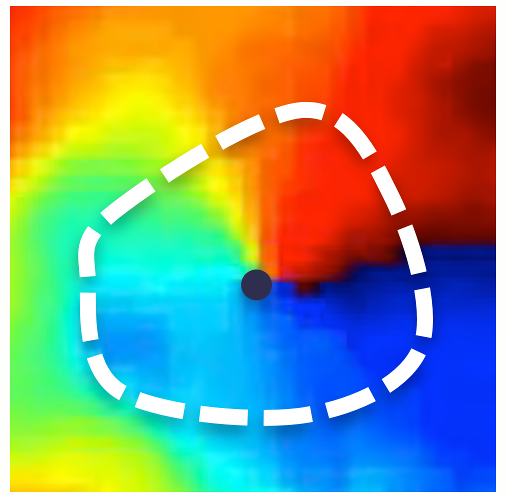
$$\theta(\mathbf{x},t) = \arctan 2(u(\mathbf{x},t) - u^*, v(\mathbf{x},t) - v^*)$$

Spiral Tips and Phase Singularities



phase singularity

sum of the topological charges in a domain $\mathcal{D}$



$$\oint_{\partial\mathcal{D}} \vec{\nabla}\theta \cdot d\vec{l} = 2\pi(n-m)$$

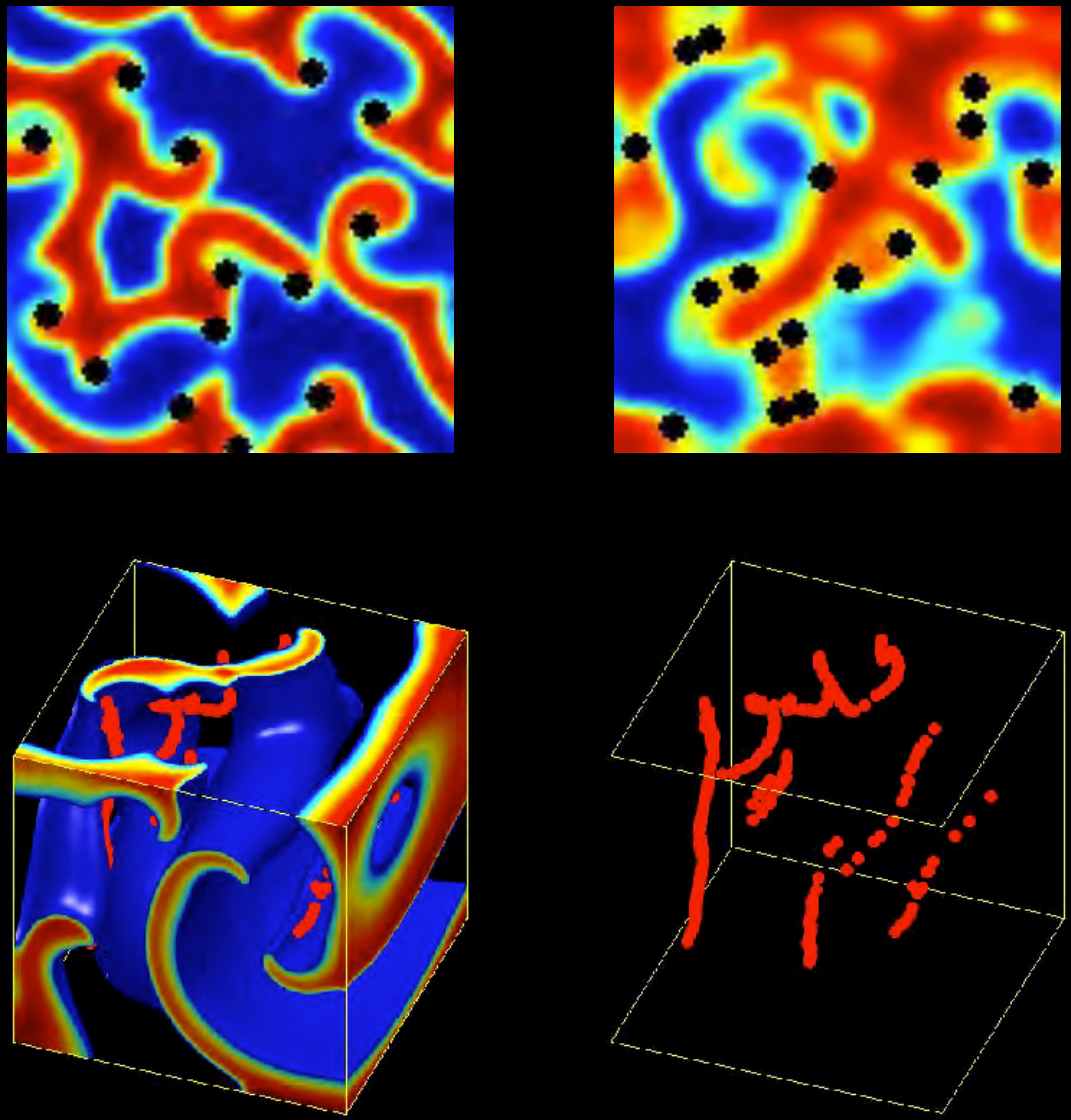
n # clockwise

m # counter clockwise

rotating spirals

alternative approach: D.R. Gurevich and R.O. Grigoriev, *Chaos* 29, 053101 (2019)

Dynamics of Phase Singularities



2D

3D

scroll wave

filaments

F. Fenton, E. Cherry

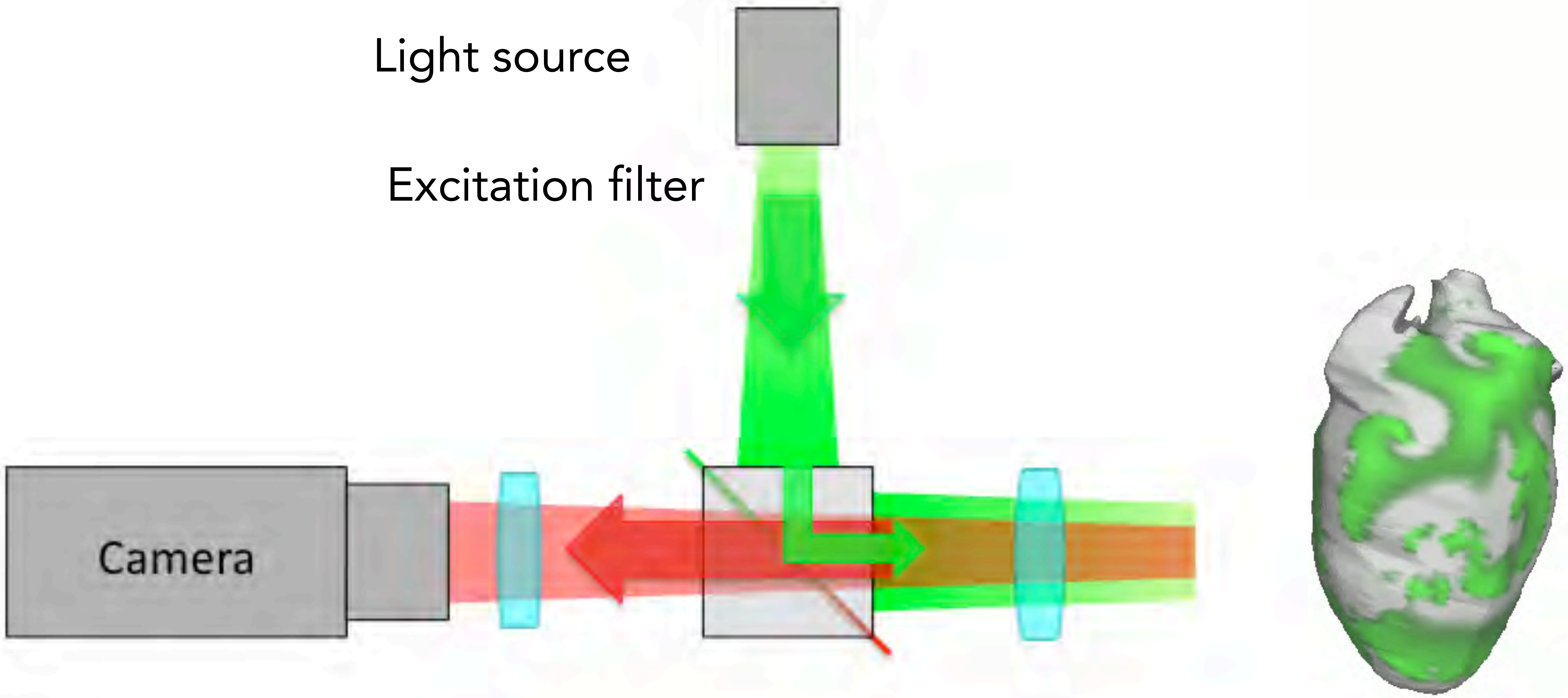
thevirtualheart.org

WebGL simulations

Measuring Cardiac Dynamics

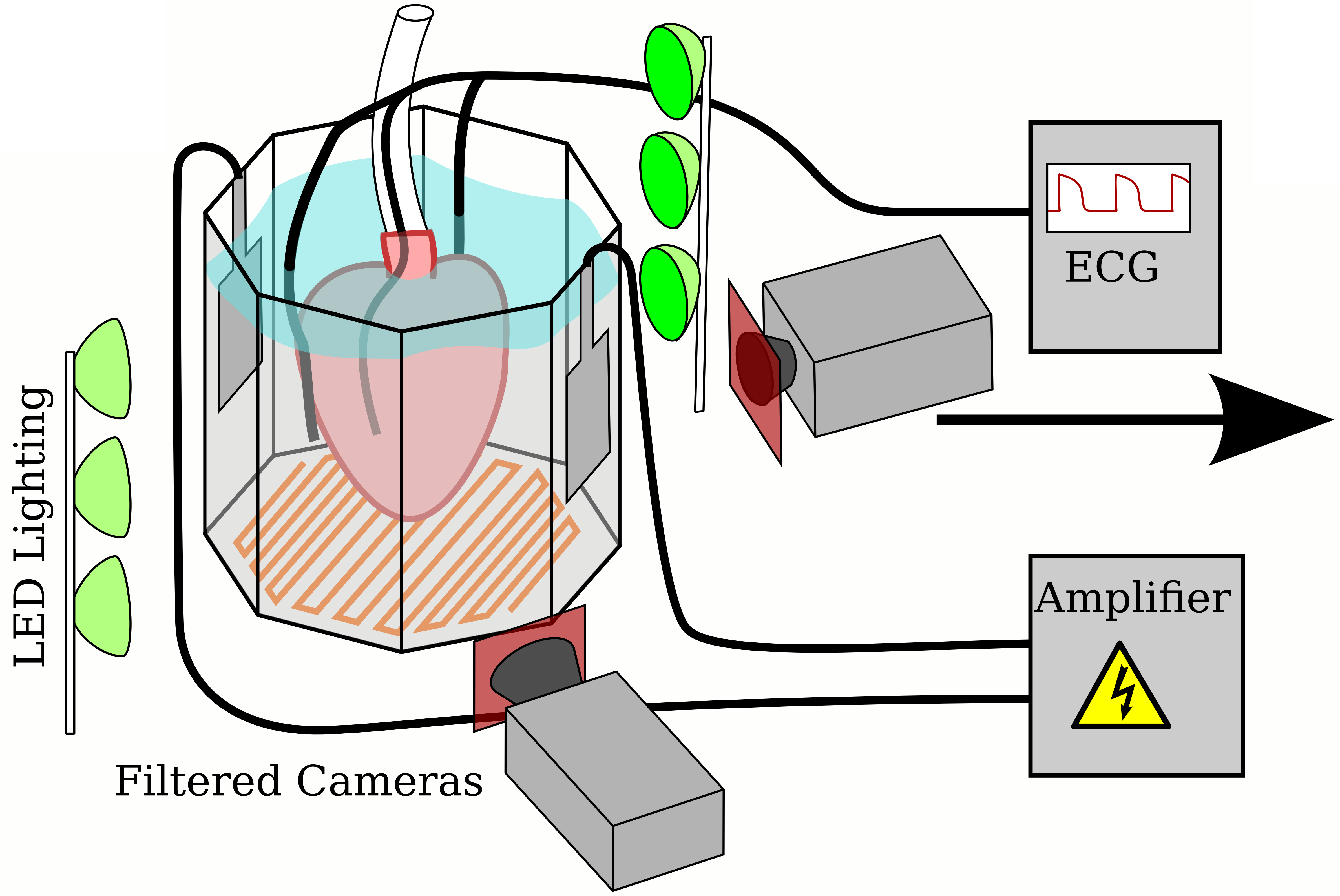
Optical Mapping

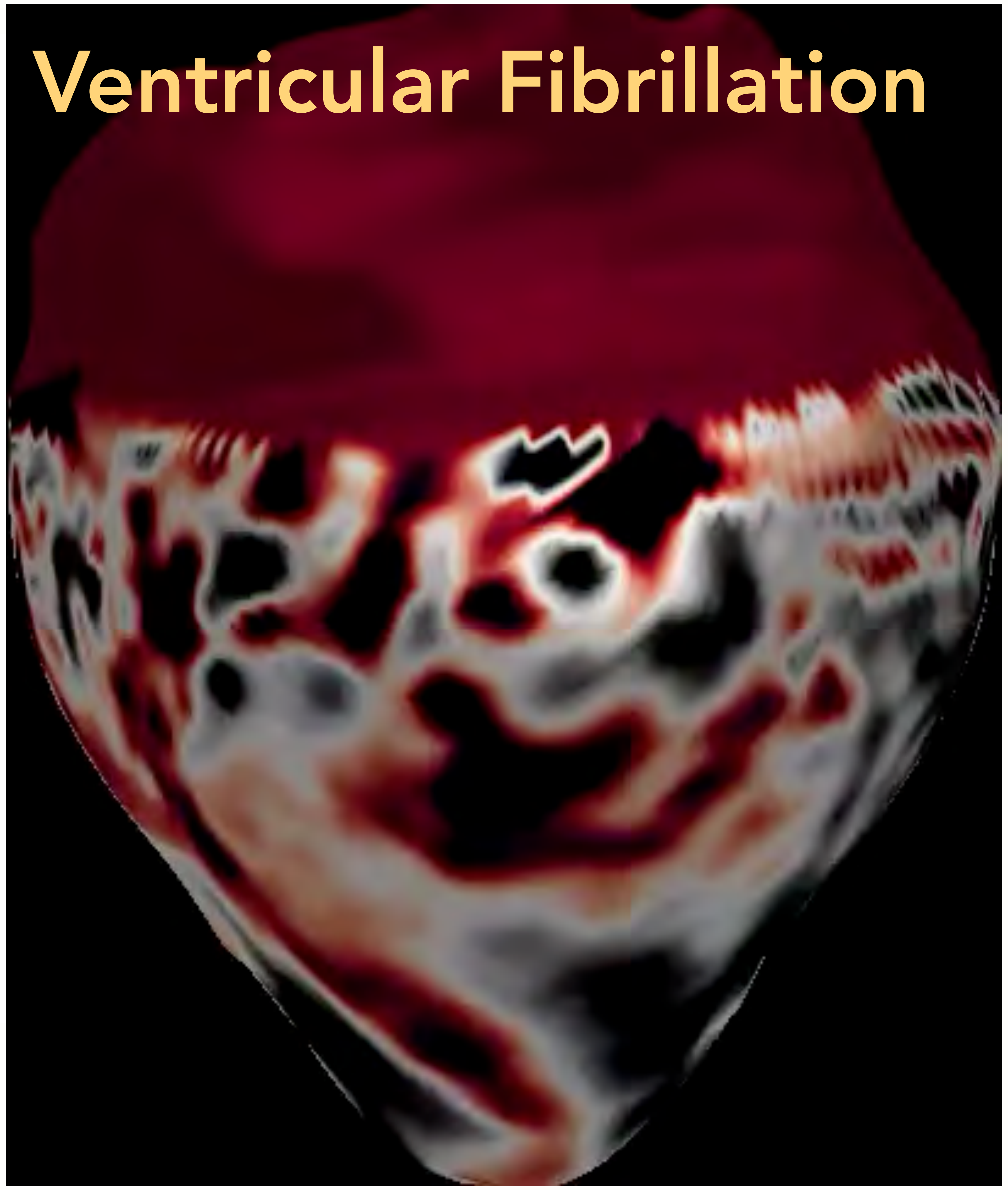
Visualisation of **membrane voltage** and **Ca$^+$ concentration** on the **surface of the heart** using **fluorescent dyes**



Optical mapping in Langendorff perfusion system

using voltage sensitive fluorescent dyes



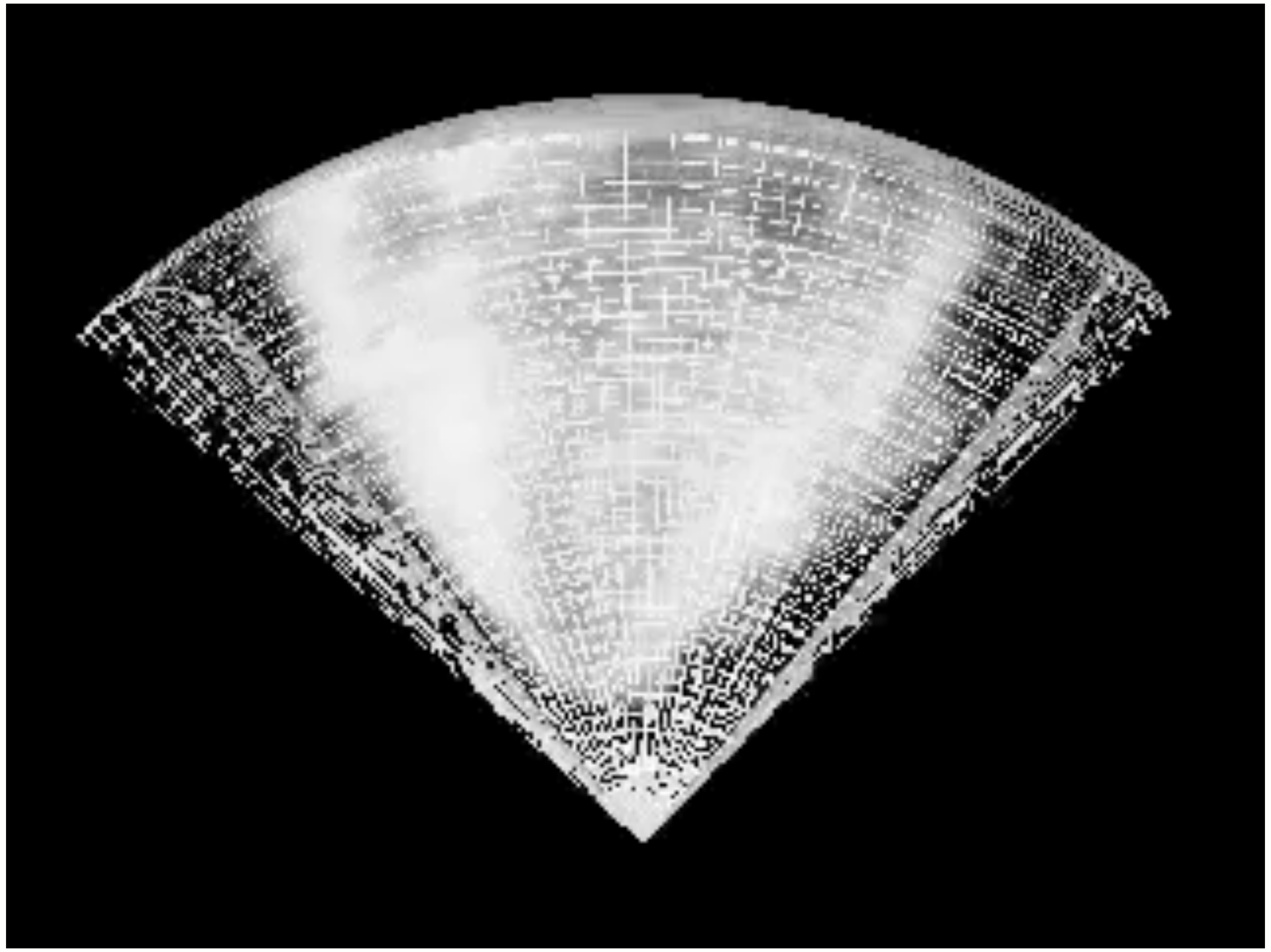


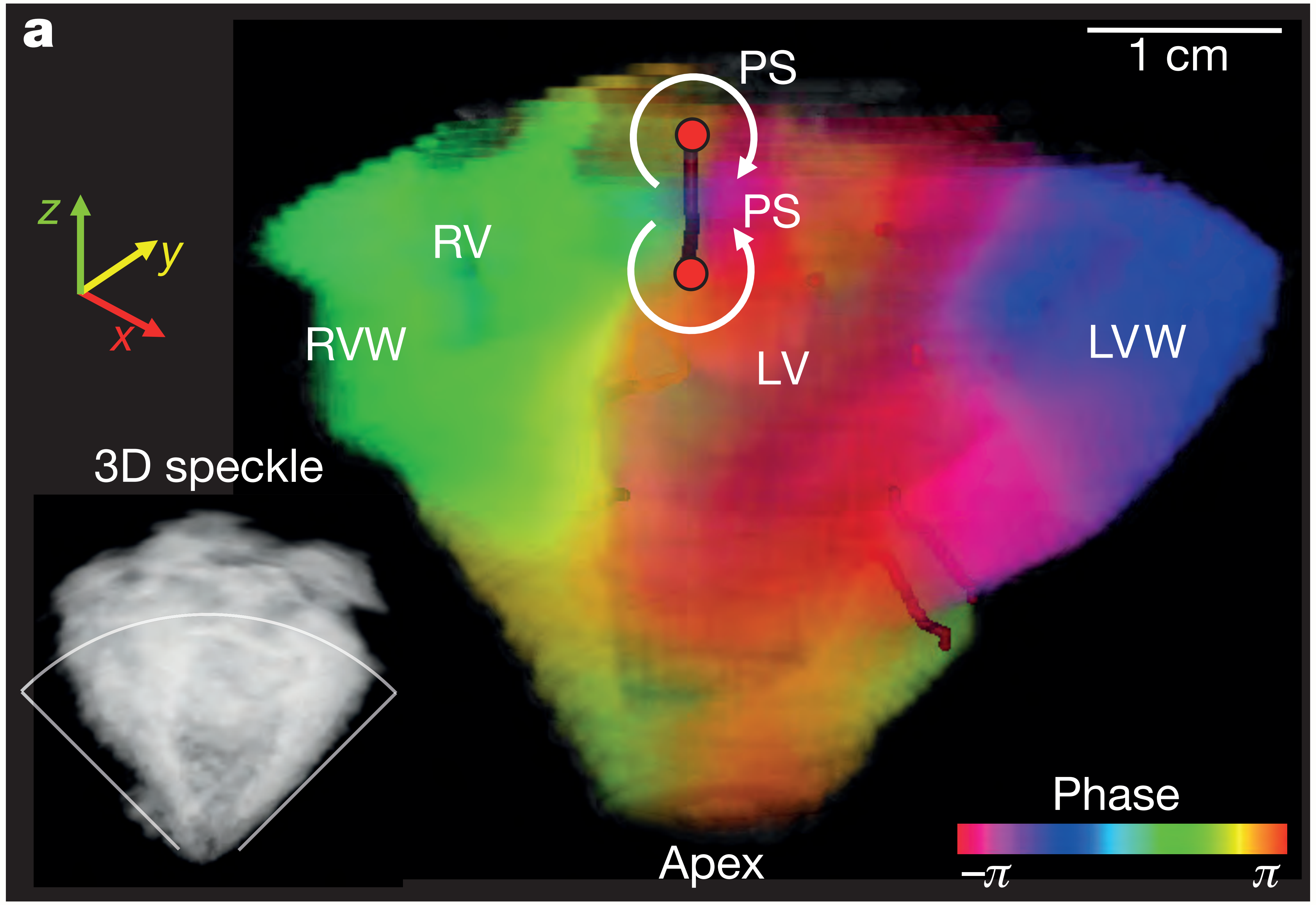
pig heart

100.000 – 200.000 cases of sudden cardiac deaths in Germany per year

J. Schröder-Schetelig

Visualizing mechanical scroll waves within the heart muscle using highspeed ultrasound





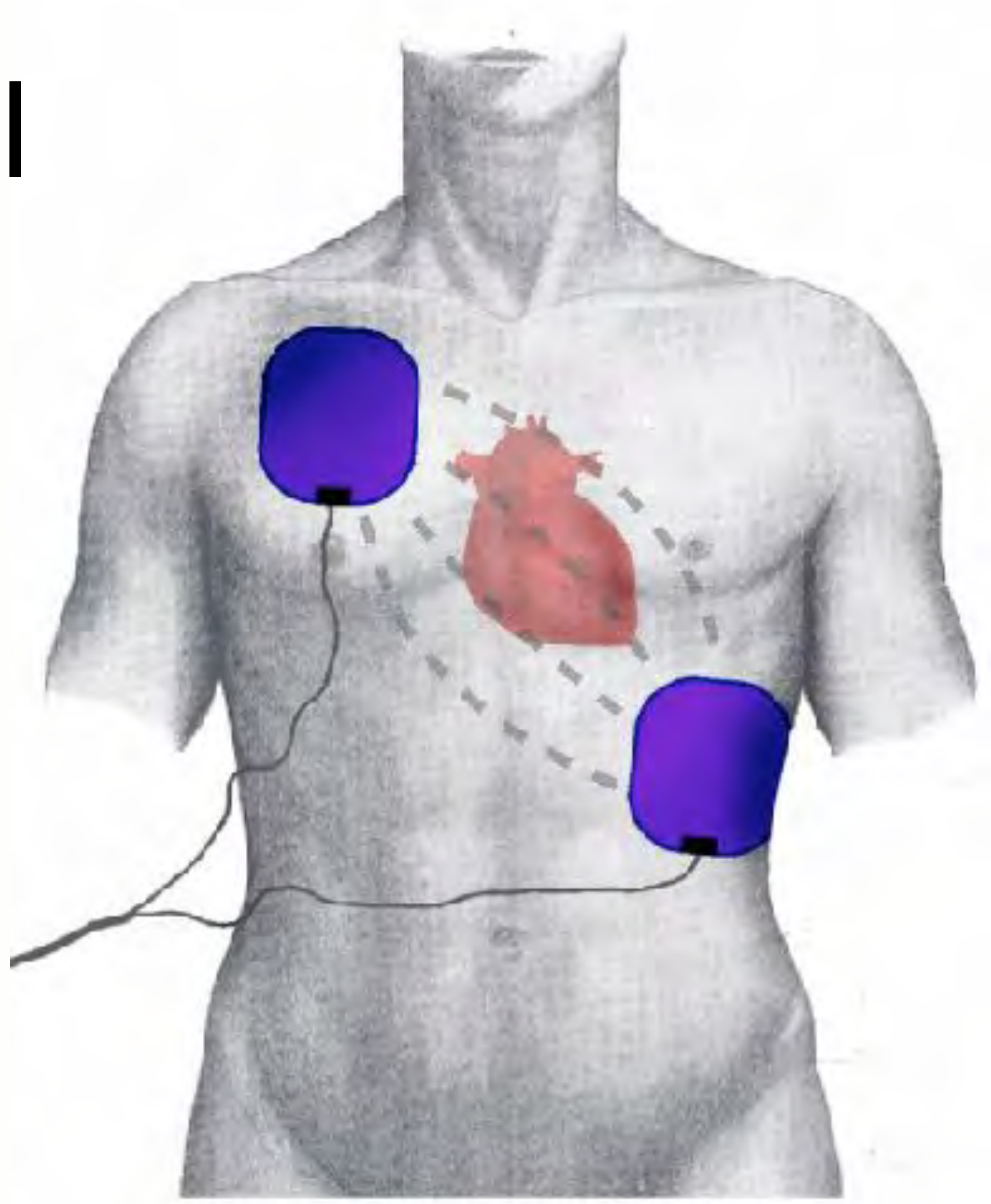
J. Christoph et al., Electromechanical vortex filaments during cardiac fibrillation, Nature 555, 667 (2018)

Terminating Cardiac Arrhythmias

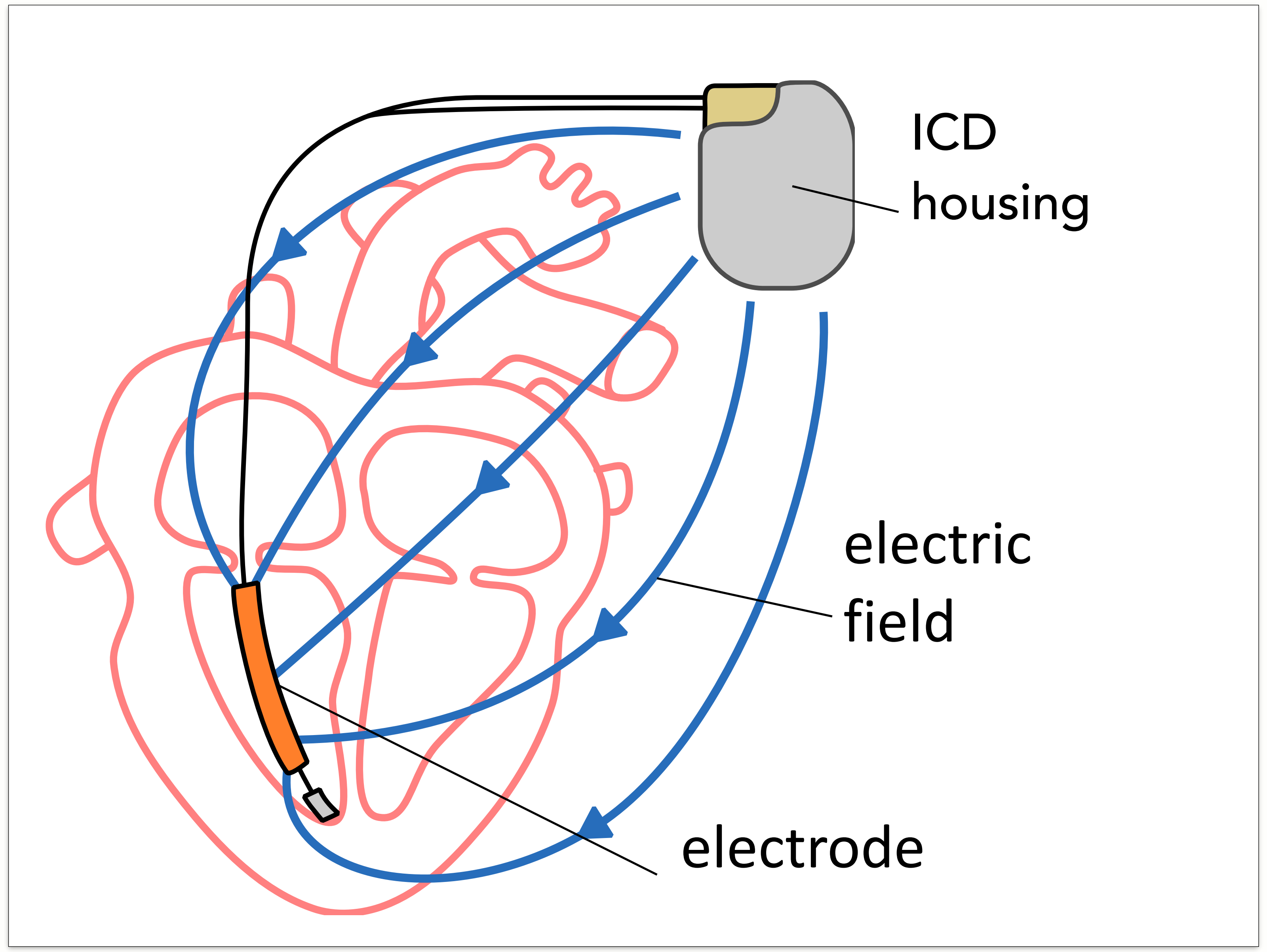
Defibrillation

Principle: Reset electrical activity of all cells by synchronous excitation

external



internal



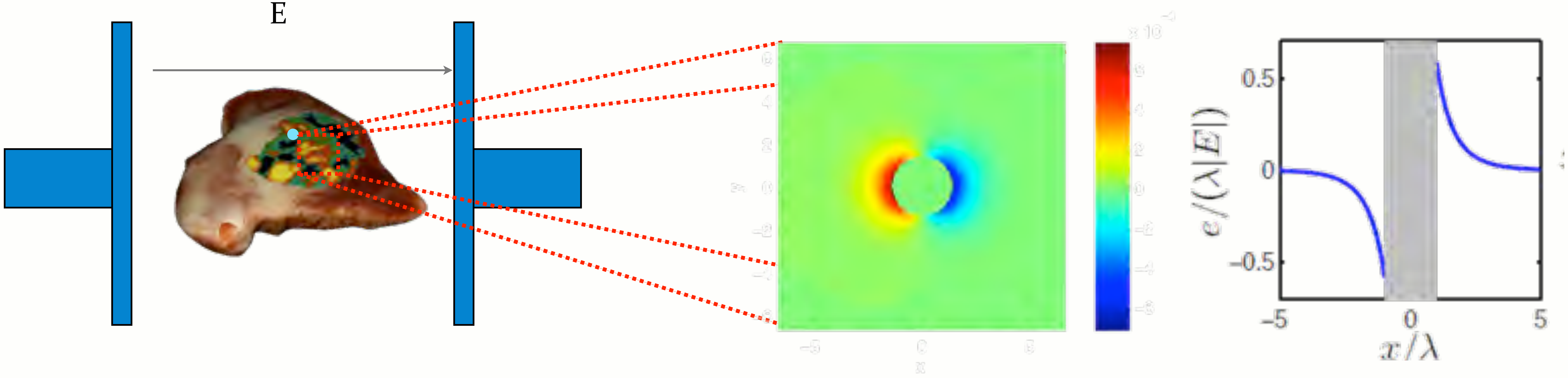
Electric shocks: energy 360J (external) 40 J (internal) 1000 V 30 A 12 ms

Severe side effects: tissue damage - traumatic pain

G.P. Walcott et al., Resuscitation 59, 59-70 (2003)

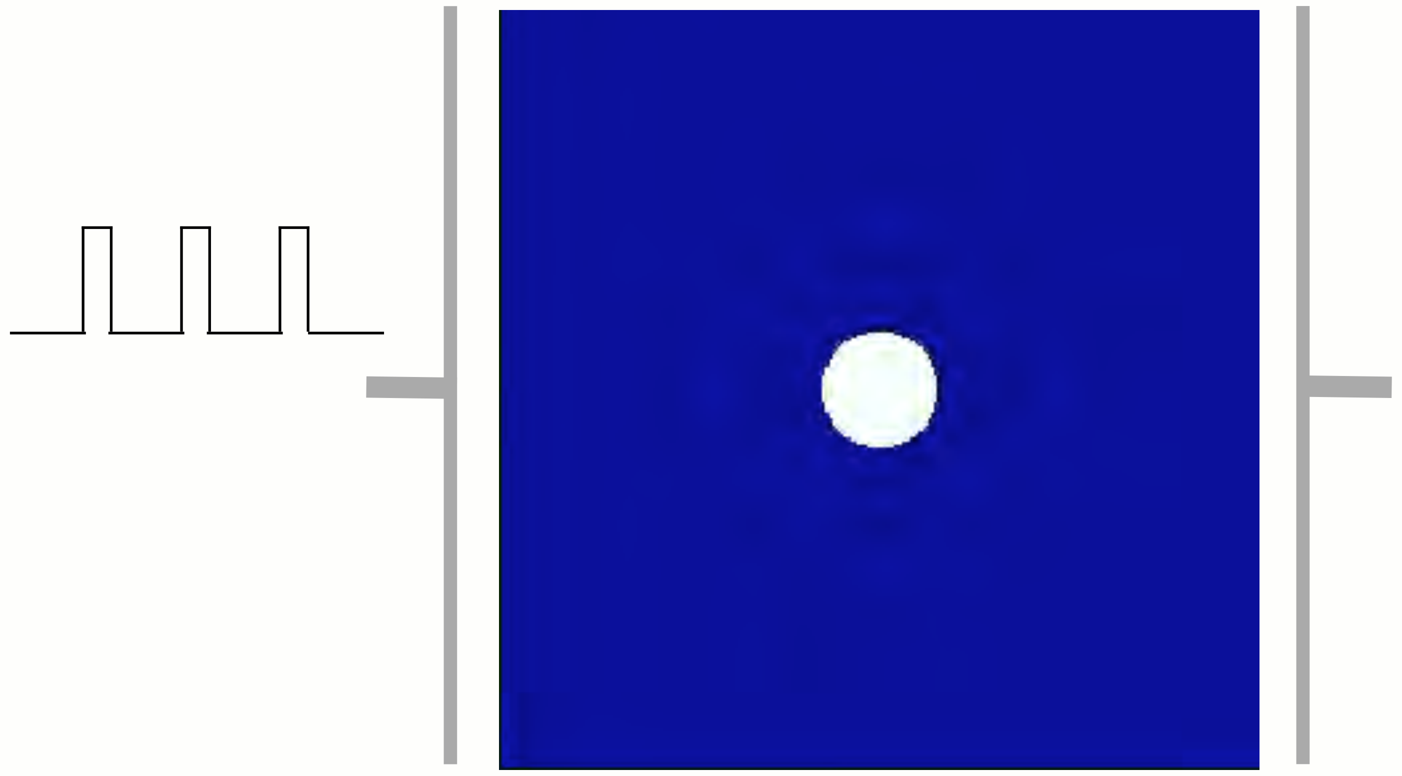
Terminating Cardiac Arrhythmias

Virtual Electrodes



Blood vessels, scars, fatty tissue

- are obstacles to electrical conduction
- may act as virtual electrodes

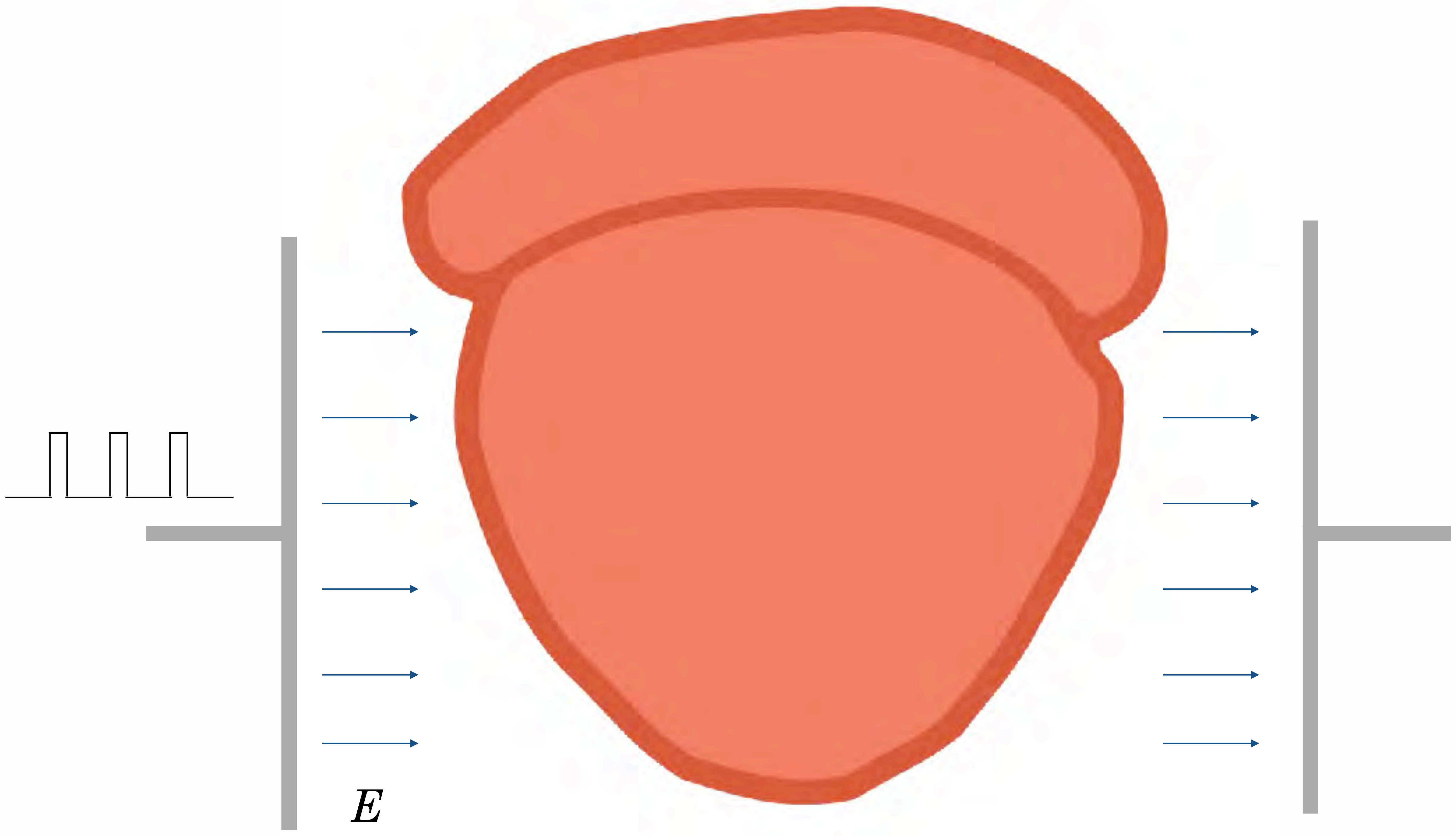


Super-threshold depolarization leads to wave emission if a short rectangular electric field pulse is applied.

A. Pumir and V. Krinsky, J. Theor. Biol. 199, 311 (1999); P. Bittihn et al., Phys. Rev. Lett. 109, 118106 (2012)

Terminating Cardiac Arrhythmias

Recruiting Networks of Virtual Electrodes for Terminating Cardiac Arrhythmias



Animation: T. Lilienkamp

Low-Energy Anti-Fibrillation Pacing (LEAP)

Pulse Generator
Power Amplifier

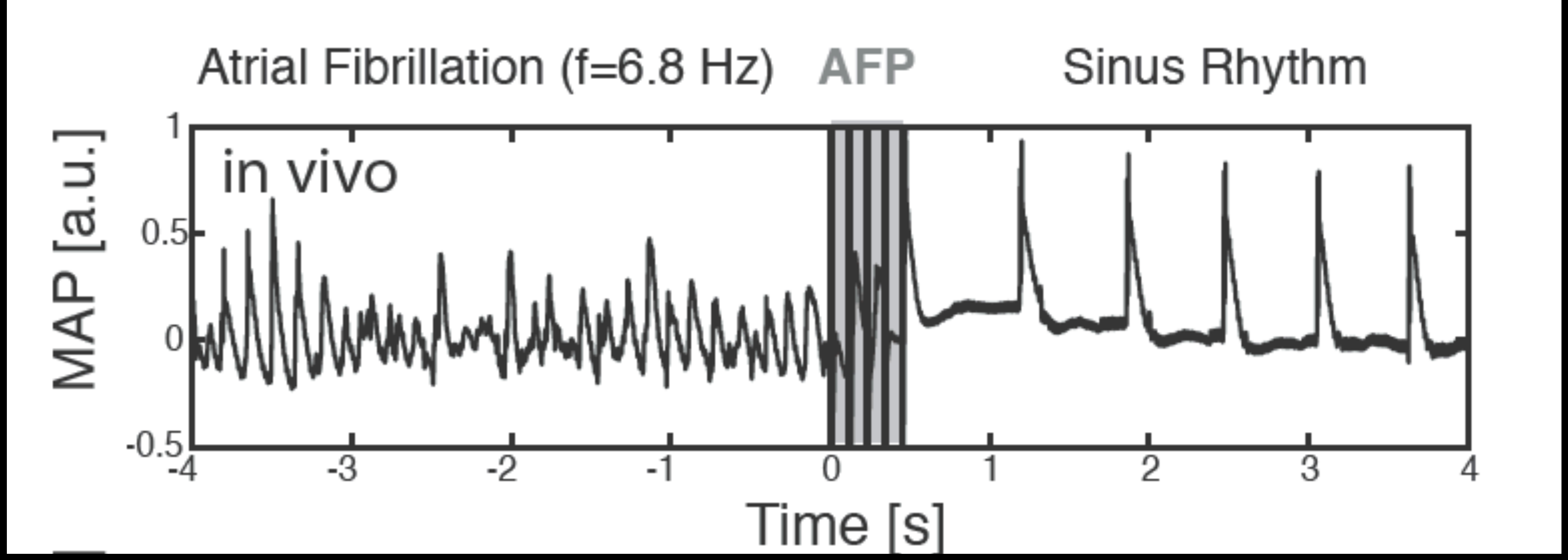
Membrane Potential

20 mV -80

N = 5 low energy pulses

E = 1.4 V/cm

dt = 90 ms

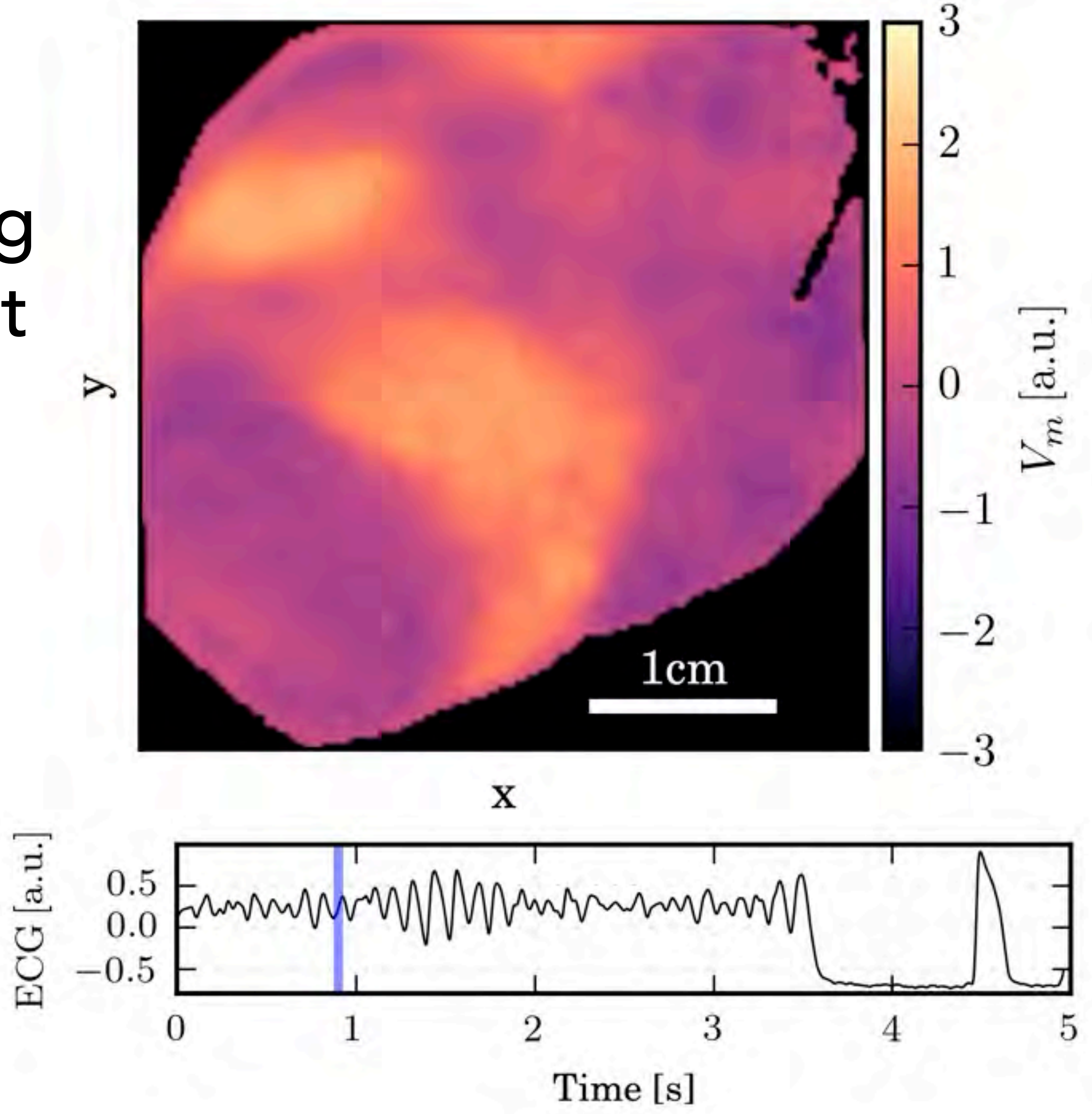


S. Luther et al., Nature 475, 235 (2011)

Transient Scroll Wave Dynamics during Ventricular Fibrillation

Experiment

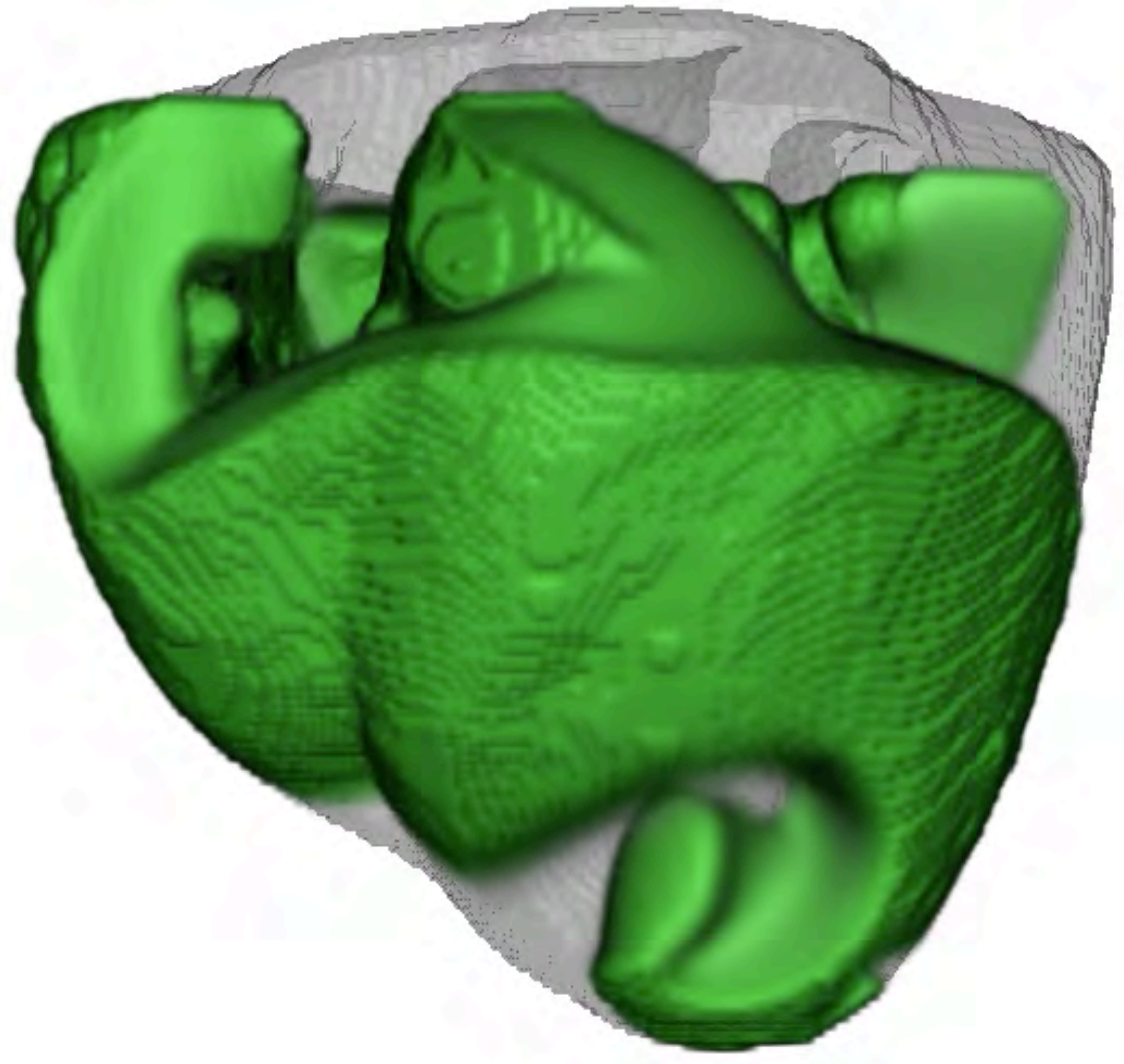
Optical mapping
of a rabbit heart



Sebastian Berg
Daniel Hornung
Marion Kunze

Simulation

in a rabbit heart geometry



Thomas Lilienkamp

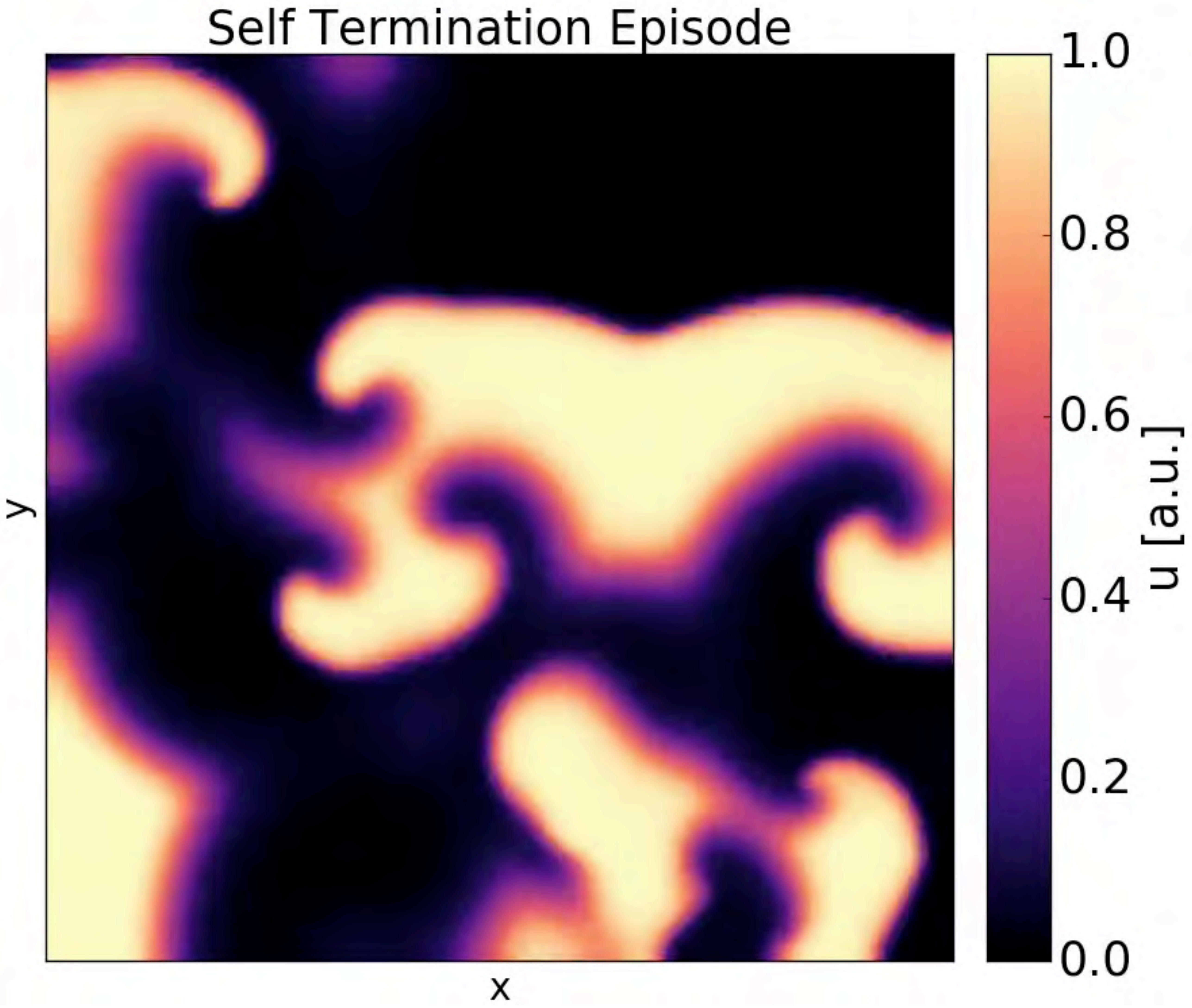
Transient Chaos

Simulation using the Fenton-Karma model

$$\frac{\partial u}{\partial t} = \nabla \cdot \underline{\mathbf{D}} \nabla u - I_{Ion}(u, \mathbf{h})/C_m$$

$$\frac{\partial \mathbf{h}}{\partial t} = \mathbf{g}(u, \mathbf{h})$$

gating variables $\mathbf{h} = (v, w)$

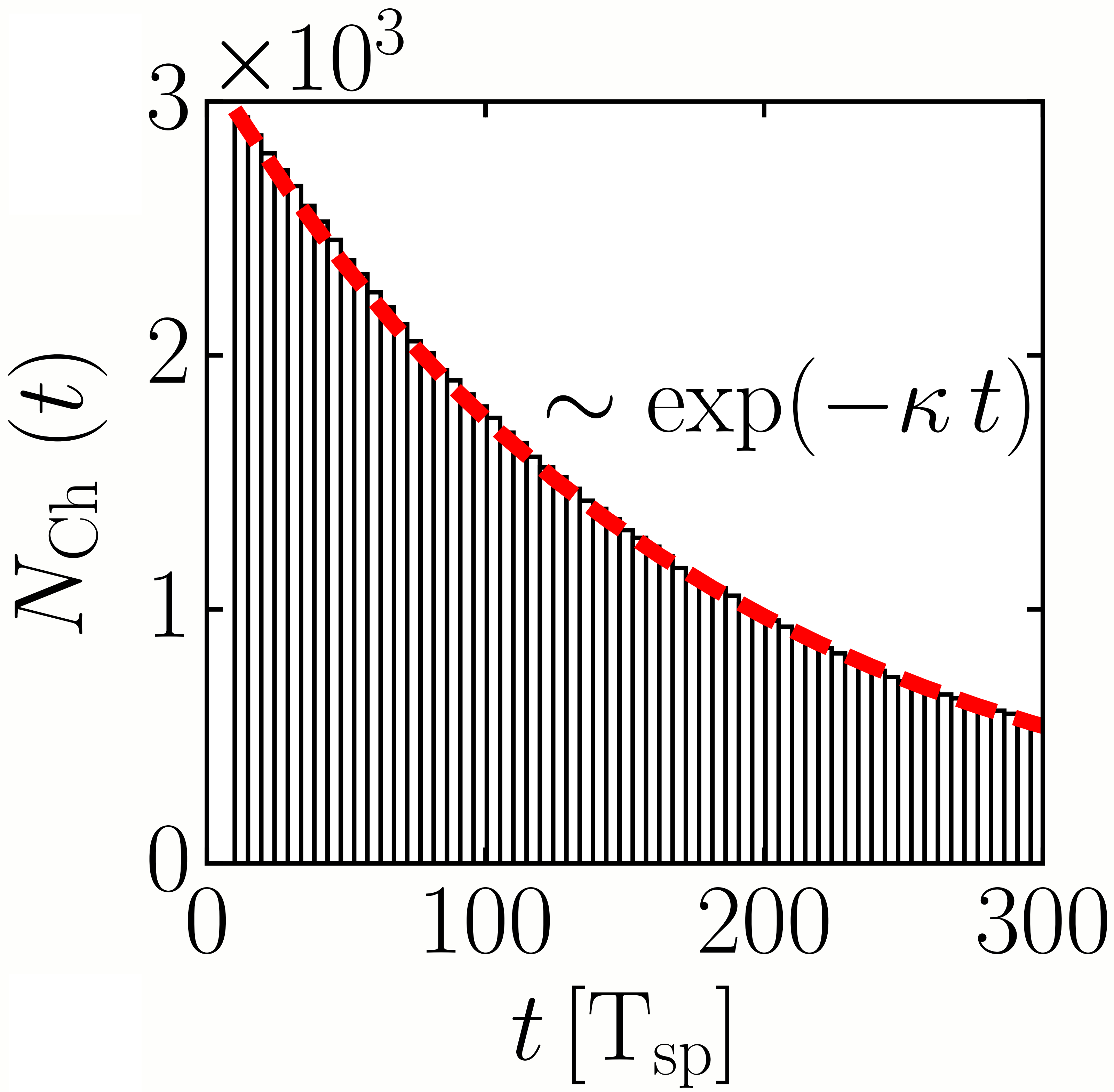


T. Lilienkamp and U. Parlitz, Phys. Rev. Lett. 120, 094101 (2018)

Chaotic transients and the average lifetime in 2D simulations

Fenton-Karma model 3000 initial conditions

fraction of trajectories still showing chaotic dynamics at time *t*



$$N_{Ch}(t) \sim \exp(-\kappa t)$$

escape rate κ

quantifies how fast trajectories from random initial conditions escape the chaotic saddle and reach the final (non-chaotic) state

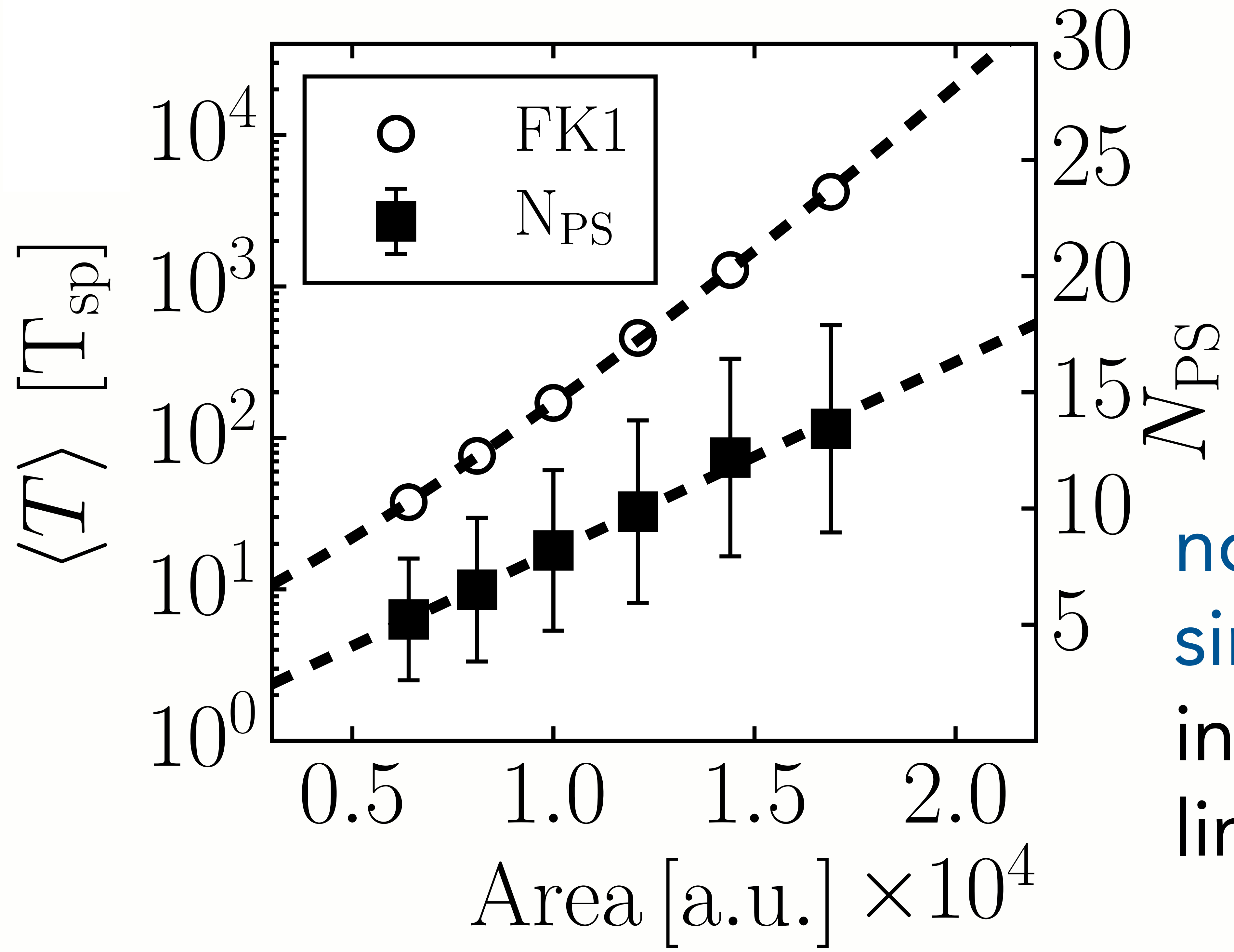
$$\langle T \rangle \approx \frac{1}{\kappa}$$ **average transient lifetime**

T. Lilienkamp et al., Phys. Rev. Lett. 119, 054101 (2017)

Chaotic transients and the average lifetime in 2D simulations

$\langle T \rangle \approx \frac{1}{\kappa}$ **average transient lifetime**

increases exponentially with system size



no. of phase singularities increases linearly

- Larger heart muscle volumes increase the risk of cardiac arrhythmias and related morbidity and mortality.
  - → due to longer transients and more phase singularities (??)
- Impact of (finite) pertubations changes during some period of time prior to the end of the transient.
  - → precursors for end of arrhythmia (??)

T. Lilienkamp and U. Parlitz,
Phys. Rev. Lett. 120, 094101 (2018),
Phys. Rev. E 98, 022215 (2018)

Summary

The heart

- consists of a network of electrically and mechanically coupled excitable elements
- forming an excitable medium that supports plane waves, spiral waves, and
- (life-threatening) **spatio-temporal chaos** (e.g., ventricular fibrillation)
- that can be transient and exhibits complexity fluctuations and
- provides an ambitious target for (low-energy) control methods (defibrillation)

Outlook: Interaction with other organs, in particular heart & brain

→ Network Physiology

Acknowledgement

Stefan Luther and all members of the Research Group Biomedical Physics at the Max Planck Institute for Dynamics and Self-Organization, Göttingen

European Commission

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Federal Ministry
of Education
and Research

Else
Kröner
Fresenius
Stiftung
Forschung fördern. Menschen helfen.

Thank you!