Challenges of state and parameter estimation in cardiac dynamics nonlinear dynamics of the heart

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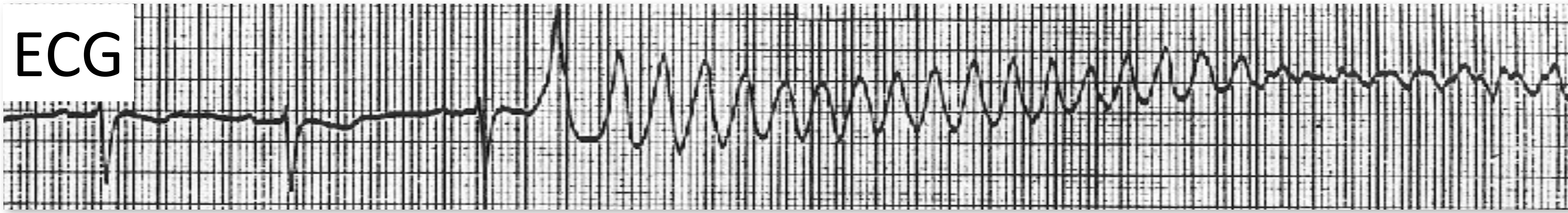
Outline

Towards data assimilation in cardiac dynamics

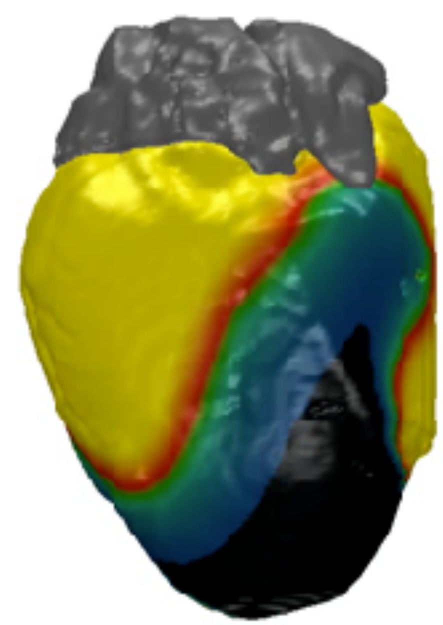
- cardiac tissue is an excitable medium
- measuring cardiac dynamics
- mathematical models of cardiac dynamics
- simulating cardiac arrhythmias and novel defibrillation methods
- parameter estimation and data assimilation tasks
- synchronization based state and parameter estimation
- estimability analysis of state variables and parameters based on the delay coordinates map

Normal Rhythm → Tachycardia → Fibrillation

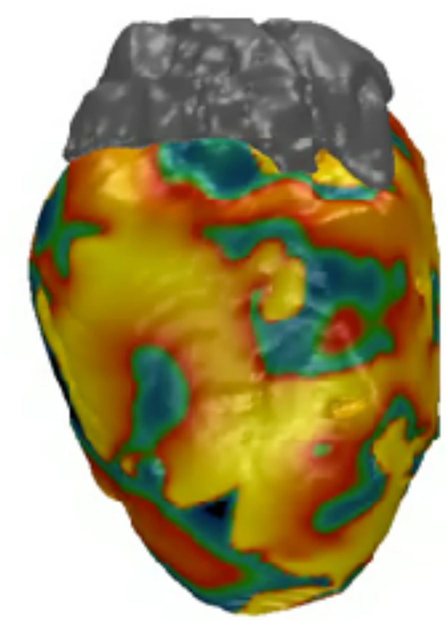


electrical excitation waves

plane waves



spiral waves



chaos

simulations: P. Bittihn

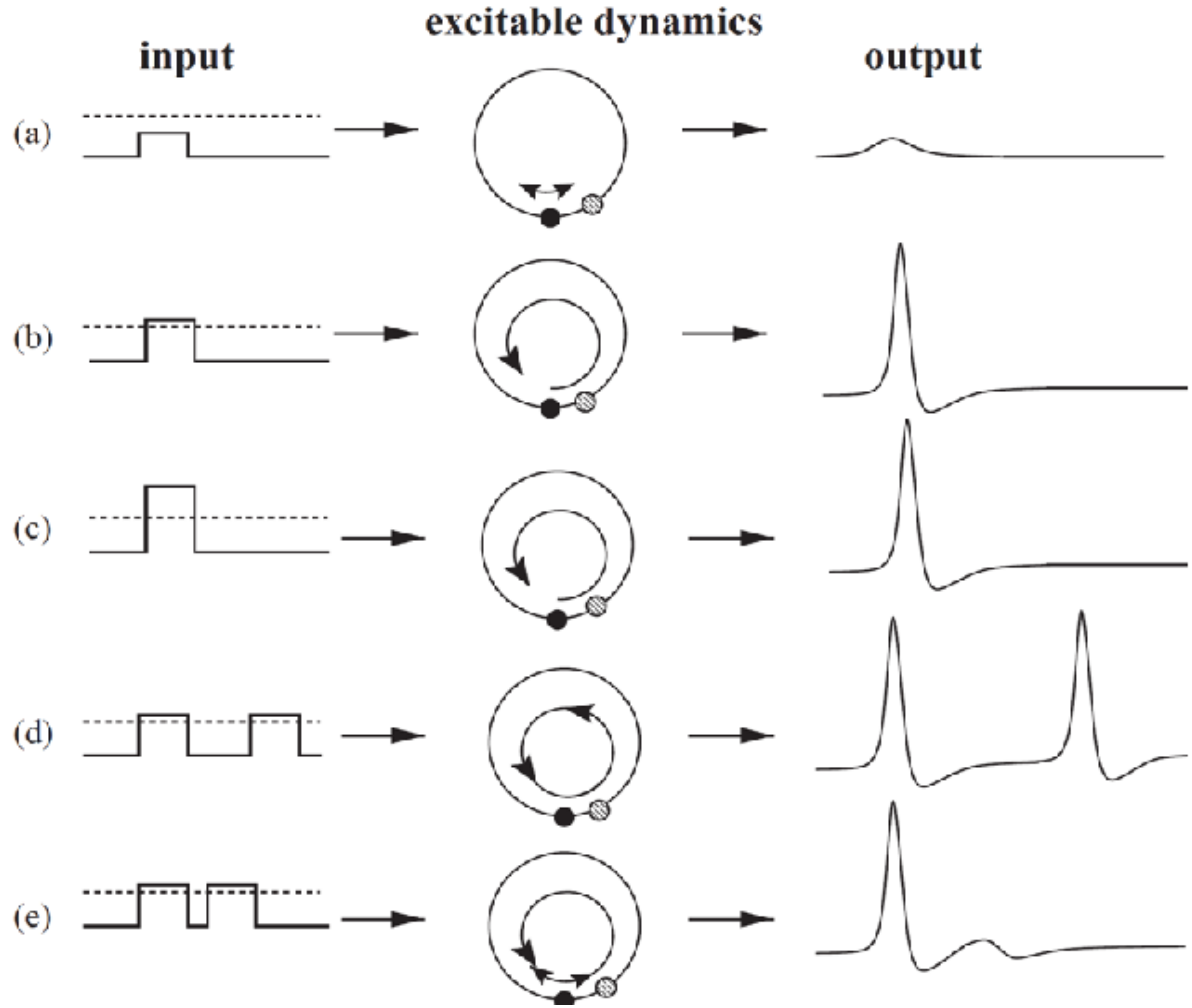
Response of an excitable system to different stimuli

sub-threshold perturbation
→ **small response**

super-threshold perturbation
→ **loop**

repeated excitation with well **separated perturbations**

no excitation by a second pulse during **refractory phase**



B. Lindner et al. , Physics Reports 392 (2004) 321–424

Mathematical Models of Excitable Media

Simple generic system: 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: $u_{th} = \dfrac{v+b}{a}$

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

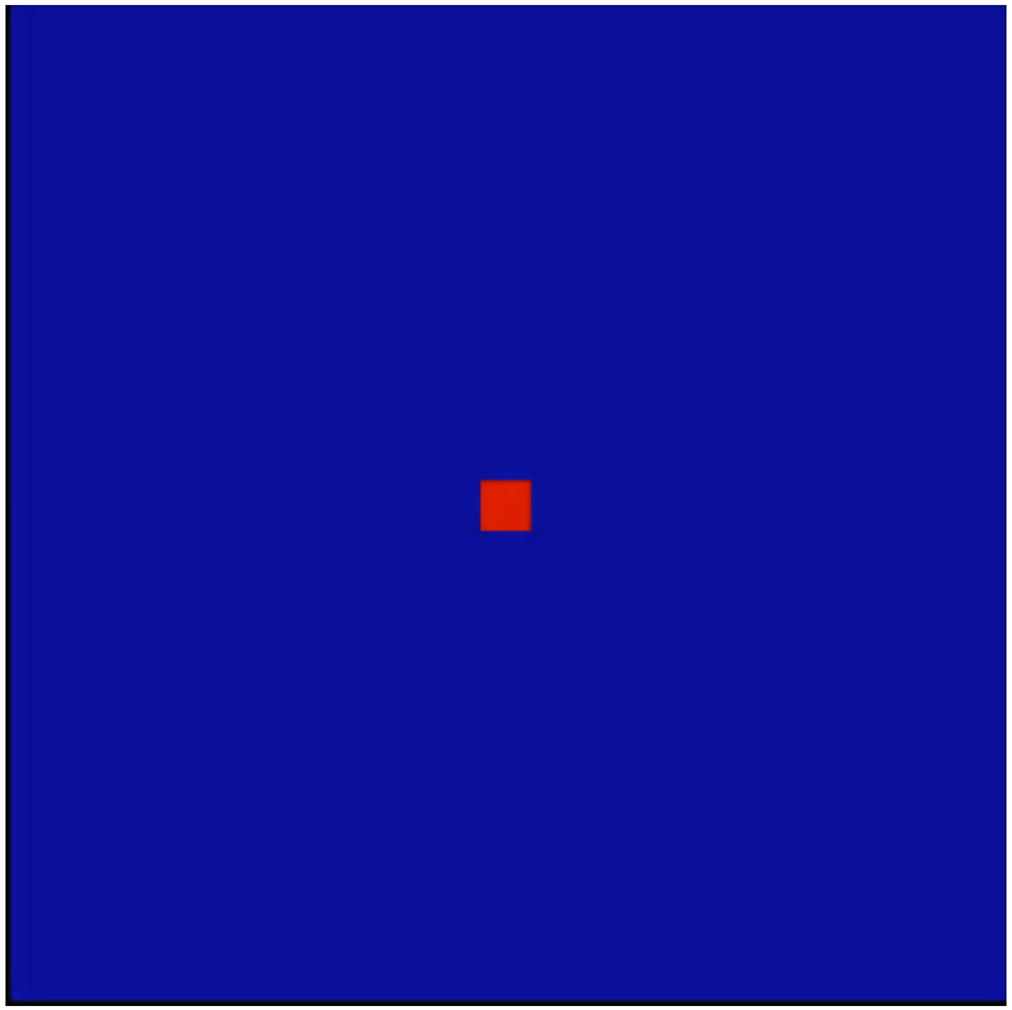
a measure for action potential duration

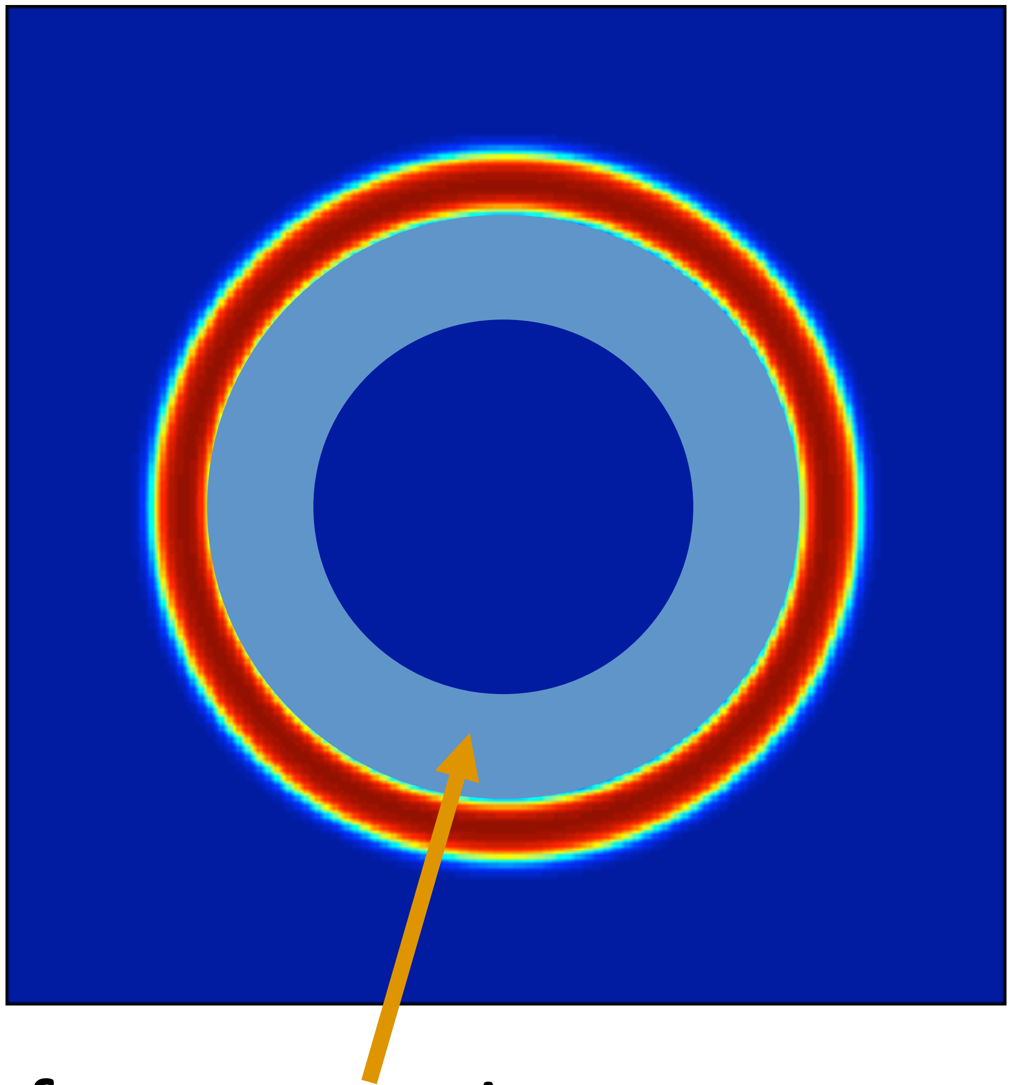
b/a measure for excitation threshold

D. Barkley, M. Kness, and L. S. Tuckerman, Phys. Rev. A 4, 2489 (1990)
D. Barkley, Physica D 49, 6170 (1991)

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

Excitation waves (Barkley model)

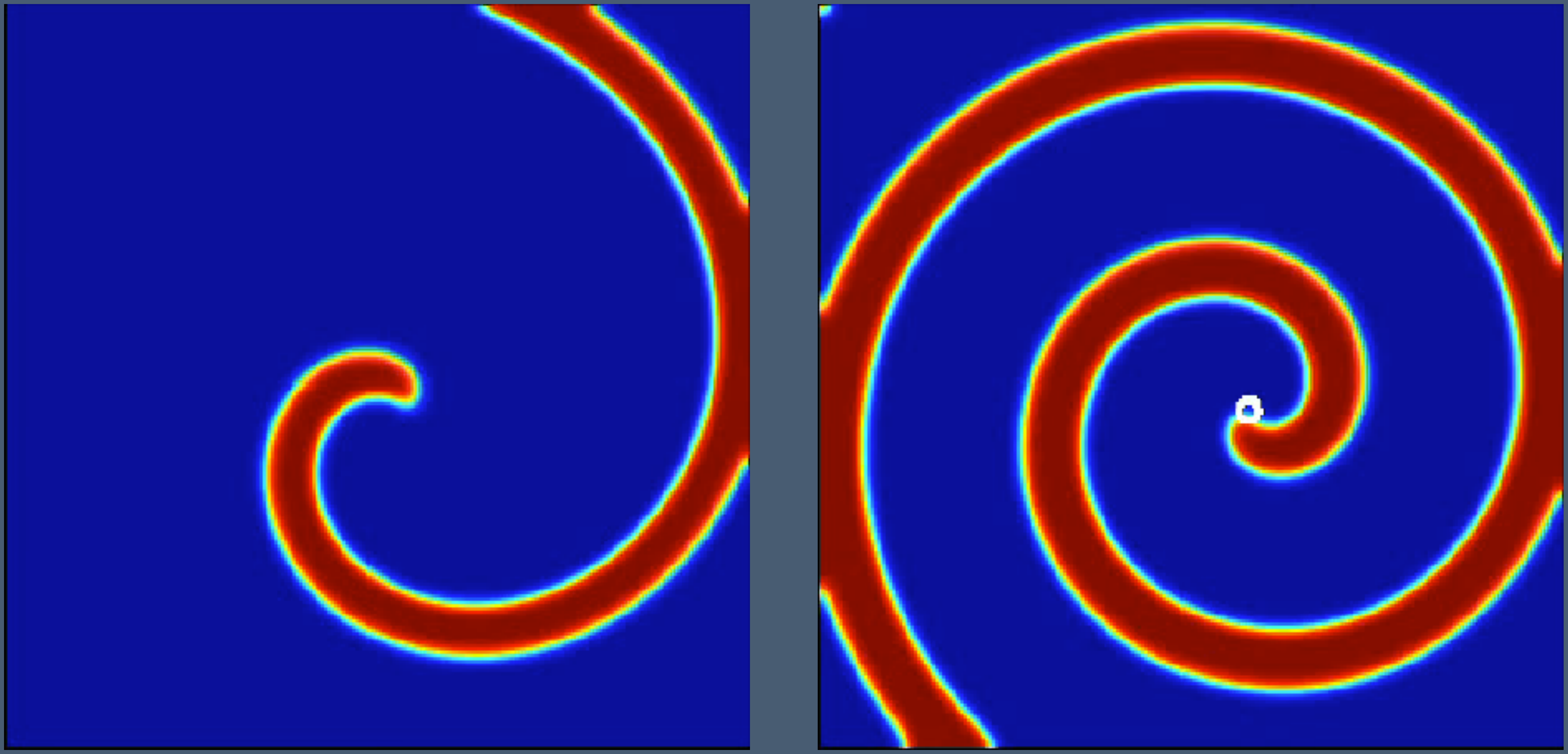




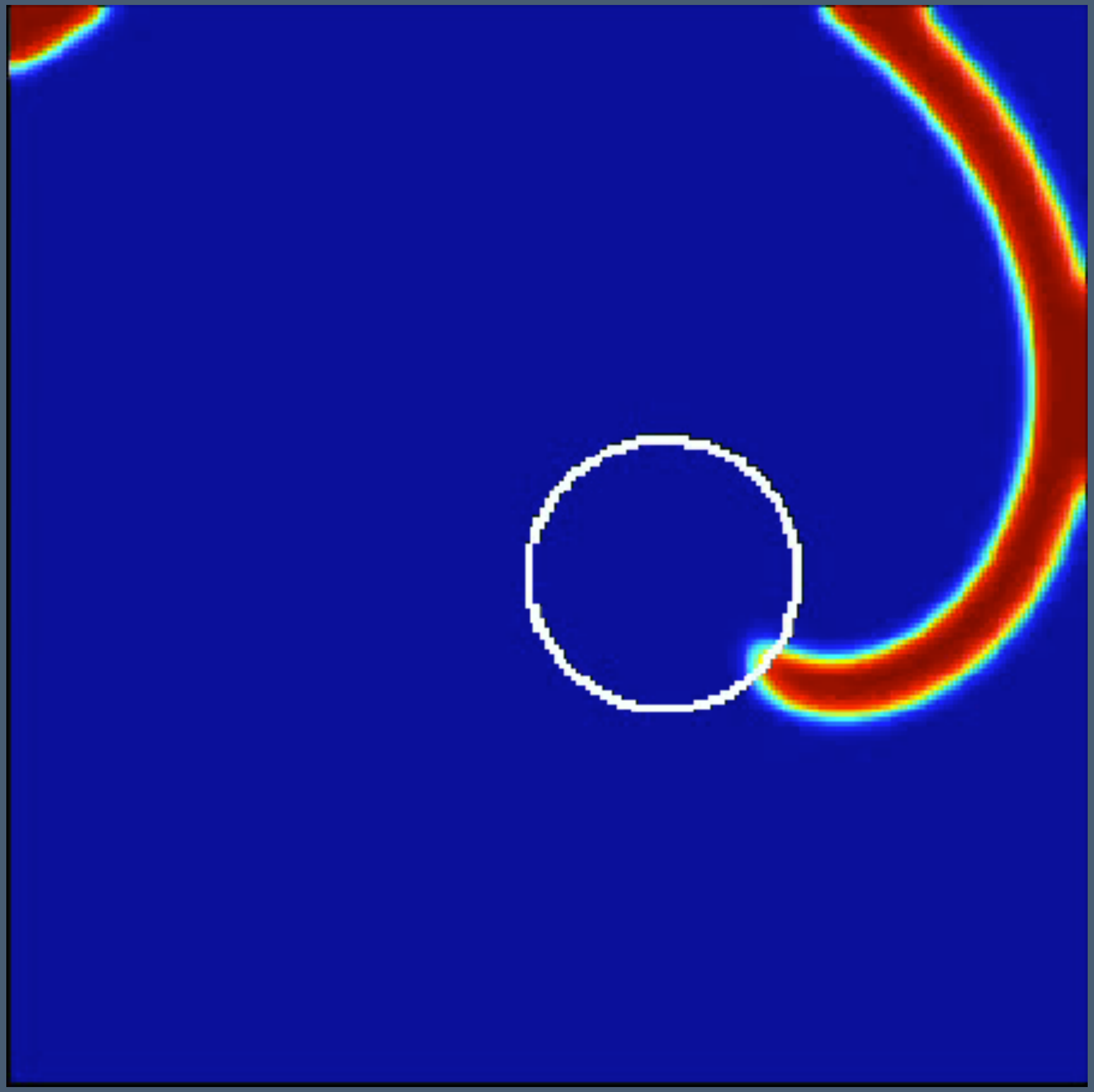
simulations: P. Bittihn

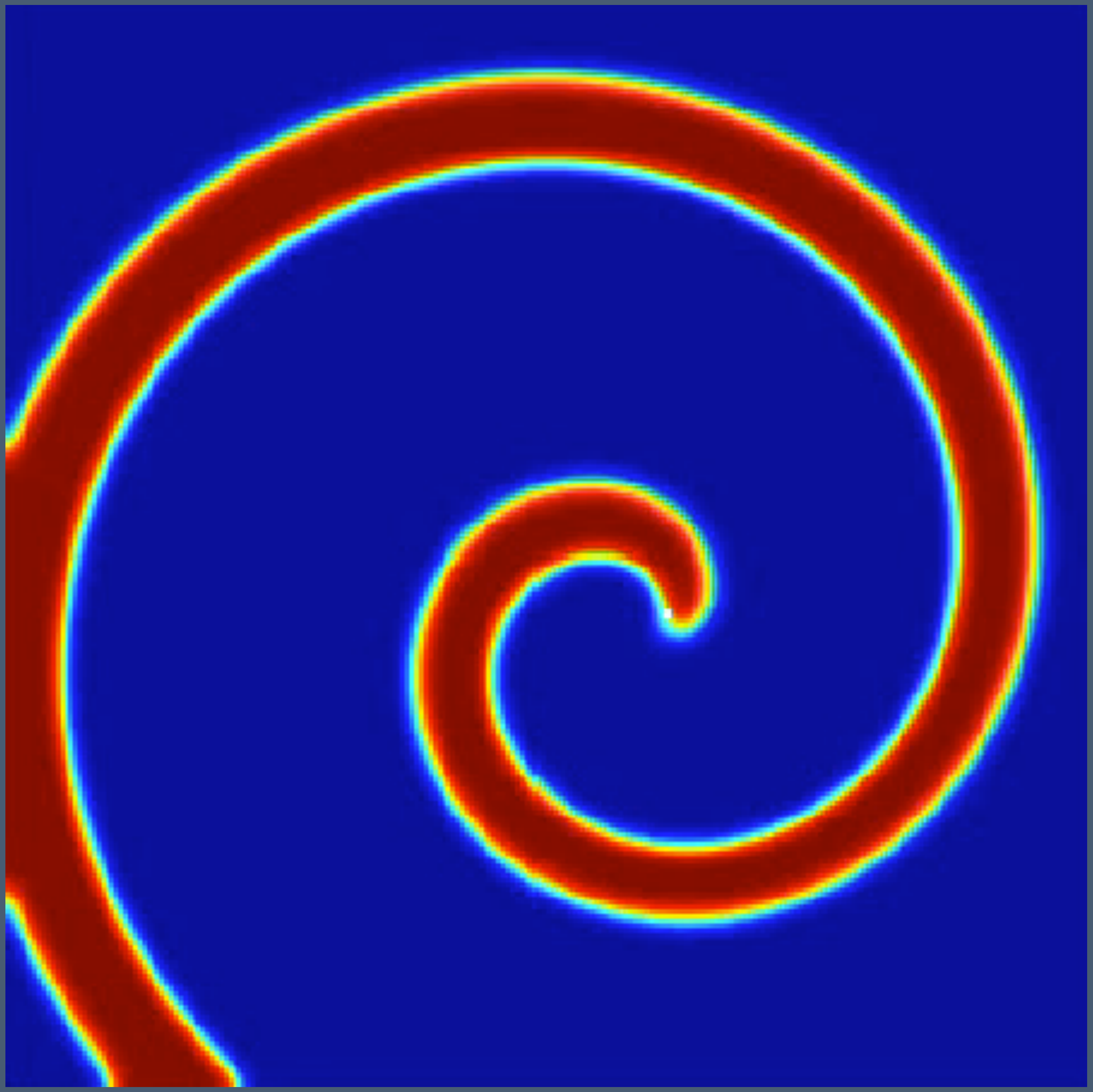
refractory region
(currently not excitable)

Spiral waves (Barkley model)



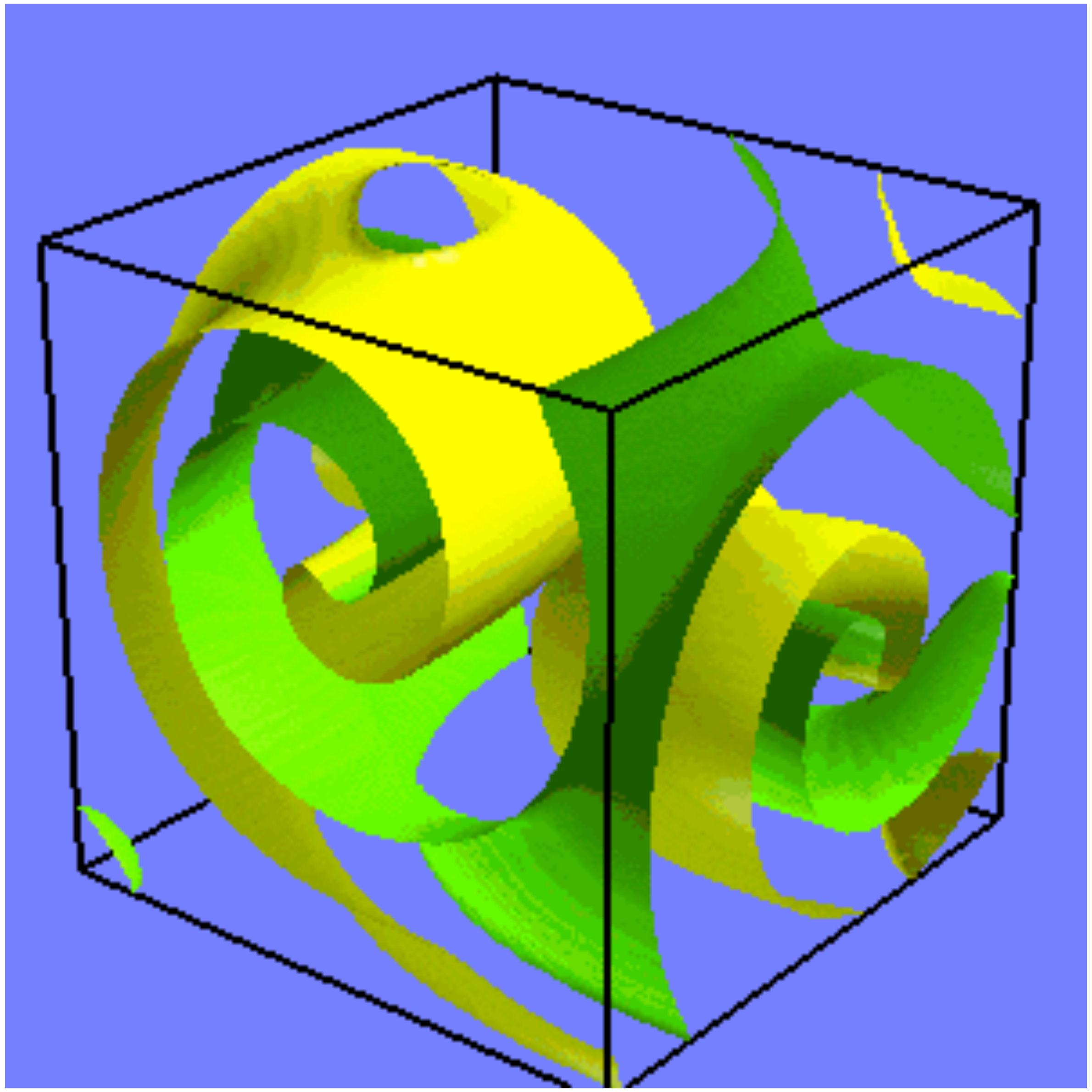
Spiral waves (Barkley model)





The Barkley Model in 3D

scroll waves

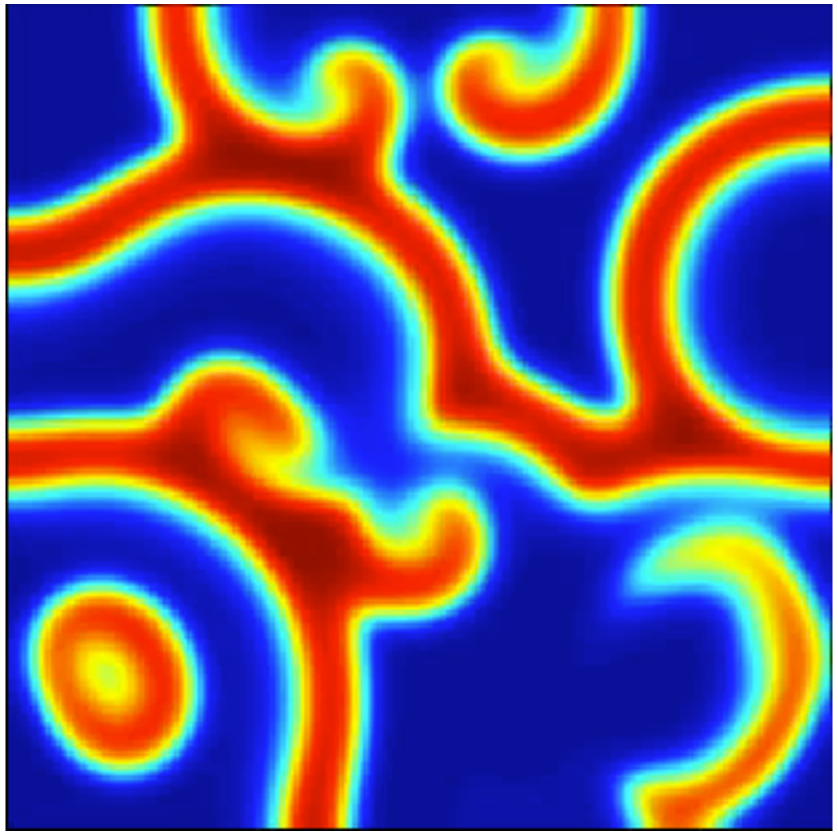


http://www.scholarpedia.org/article/Barkley_model

Cubic Barkley Model

$$\frac{\partial u}{\partial t} = \frac{1}{\varepsilon} u(1-u)\left(u - \frac{v+b}{a}\right) + D \cdot \nabla^2 u$$

$$\frac{\partial v}{\partial t} = u^3 - v$$



exhibits spiral break up and
spatio-temporal chaos

Many excitable media exhibit **transient chaos**:

- lifetime of chaotic transients increases exponentially with system size
- Kaplan-Yorke dimension of the chaotic saddle increases linearly with system size and with number of phase singularities

Measuring Cardiac Dynamics

isolated hearts (in a perfusion system)

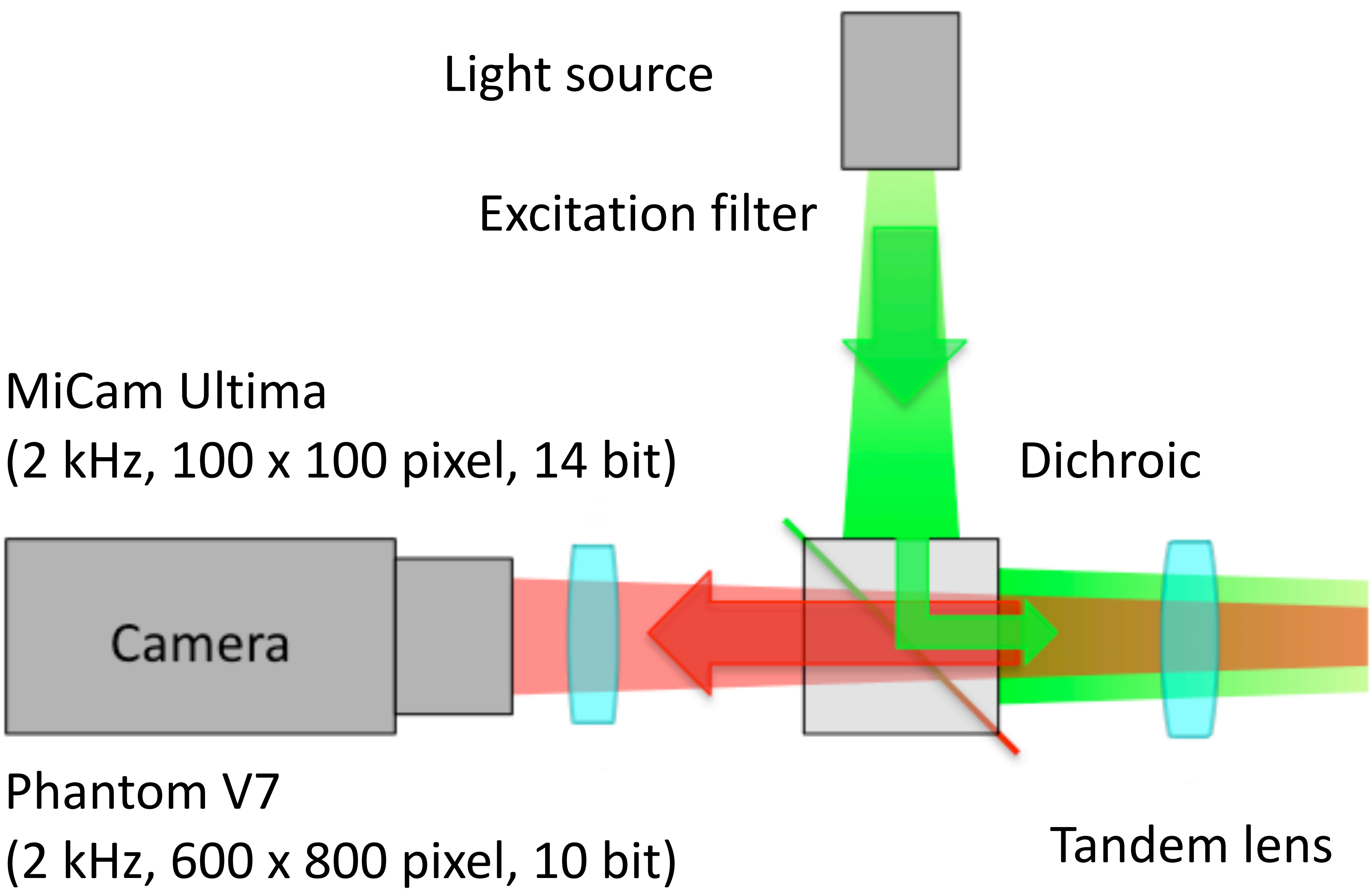
- Membrane potential and Calcium concentration on the surface using fluorescent dyes (optical mapping)
- Shape reconstruction based on 3 or more camera projections
- Electrical signals from local electrodes (ECG like)
- CT scans for determining the geometry of the heart
- Ultrasound measurements of mechanical activity and deformation

intact hearts (within the body)

- Electrical signals from the body surface (ECG imaging; inverse problem)
- CT scans for determining the geometry of the heart
- Ultrasound measurements of mechanical activity and deformation

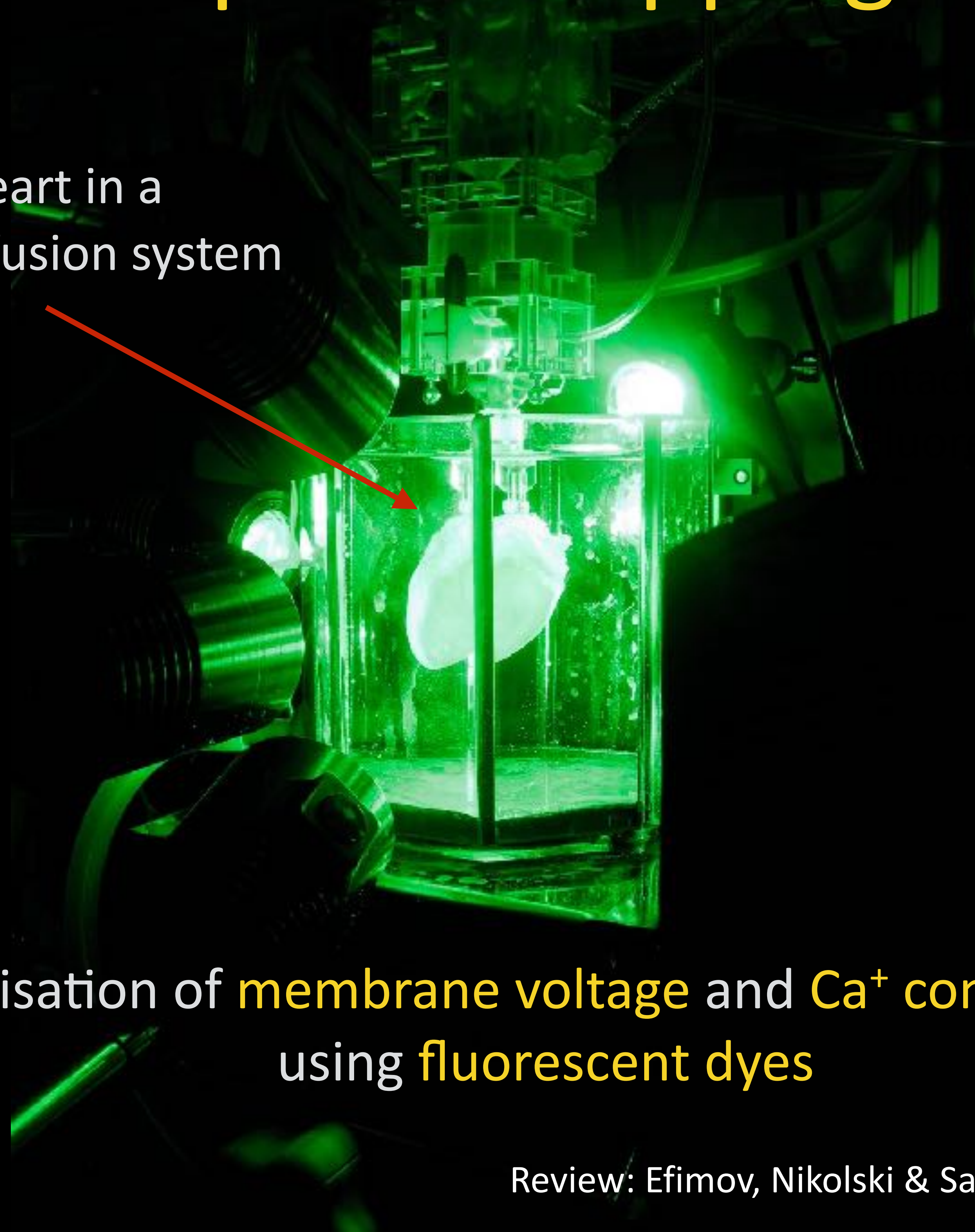
Optical Mapping

Visualisation of membrane voltage and Ca^+ concentration using fluorescent dyes



Optical Mapping

Isolated heart in a
Langendorf perfusion system



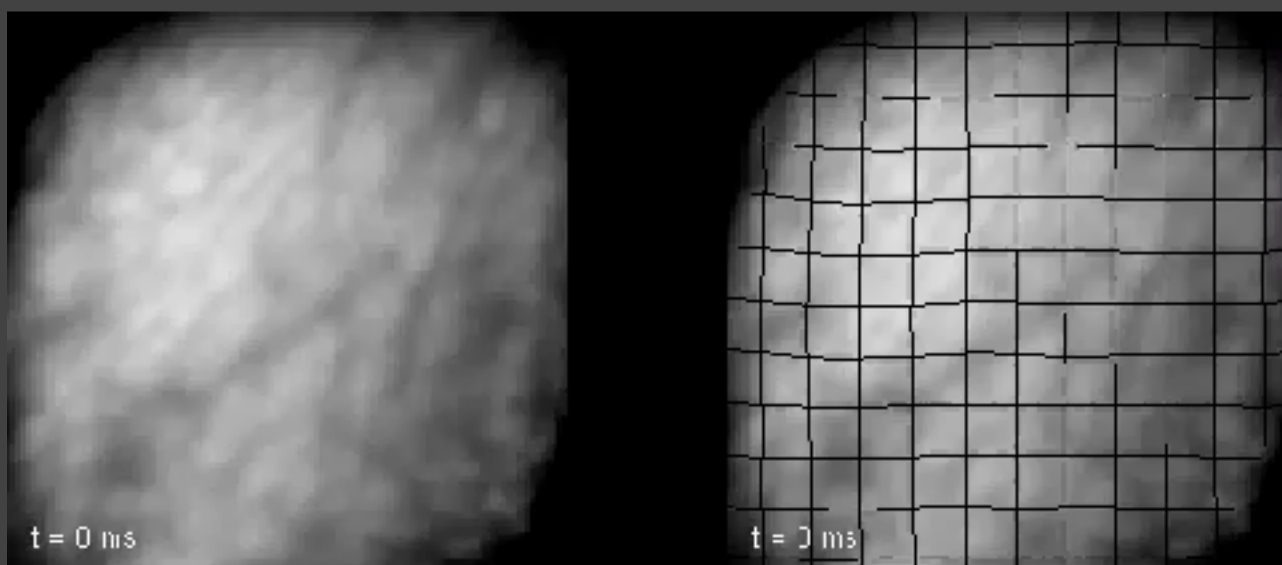
Visualisation of membrane voltage and Ca^{+} concentration
using fluorescent dyes

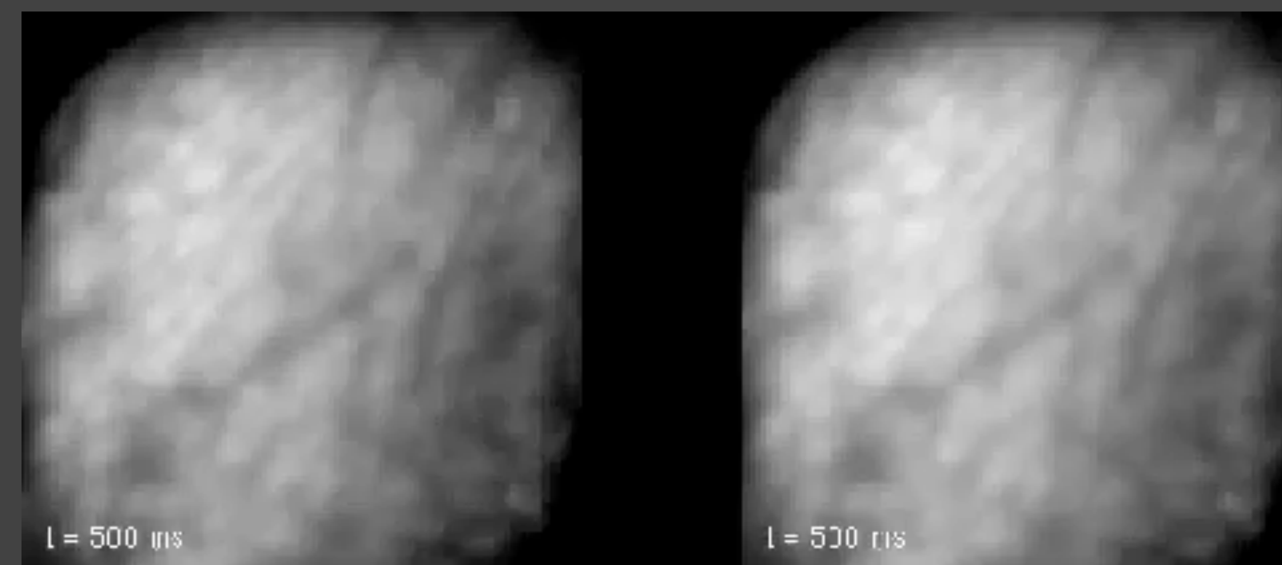
Review: Efimov, Nikolski & Salama, Circ. Res. (2004)

Motion Artifact Reduction

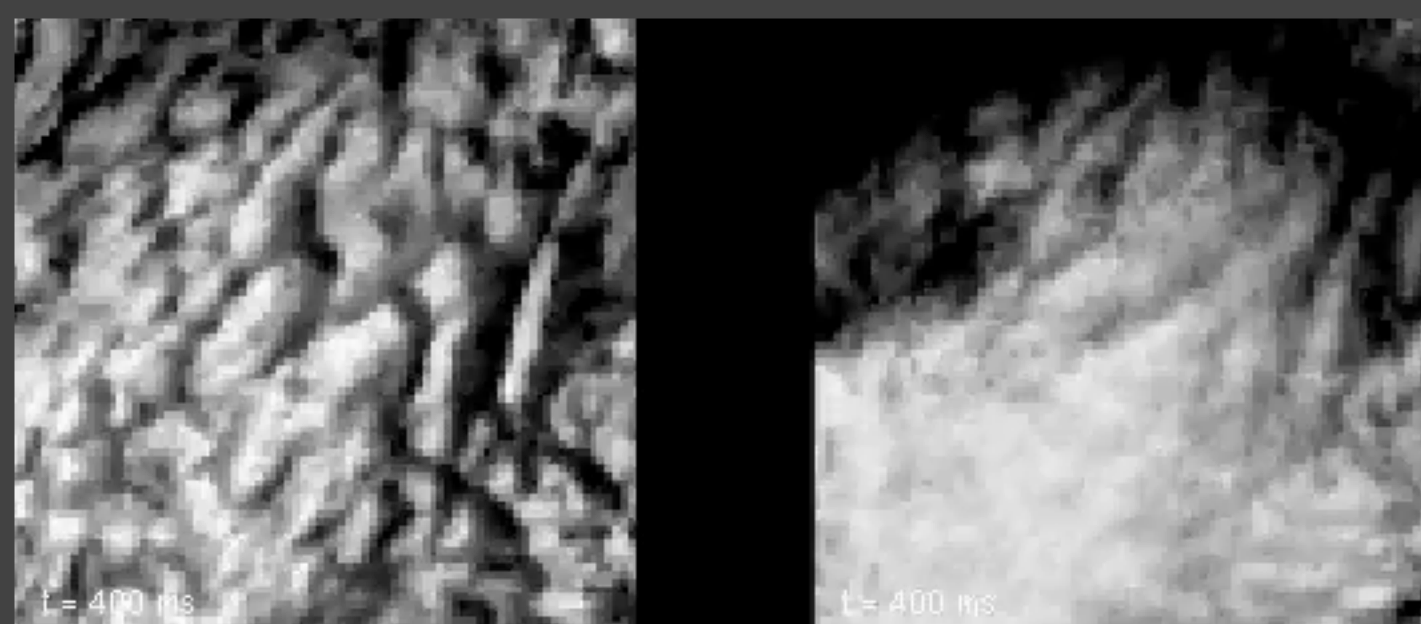
Use motion tracking for separating electrical wave pattern from mechanical motion

Raw data | Motion tracking | Raw data | Stabilized data





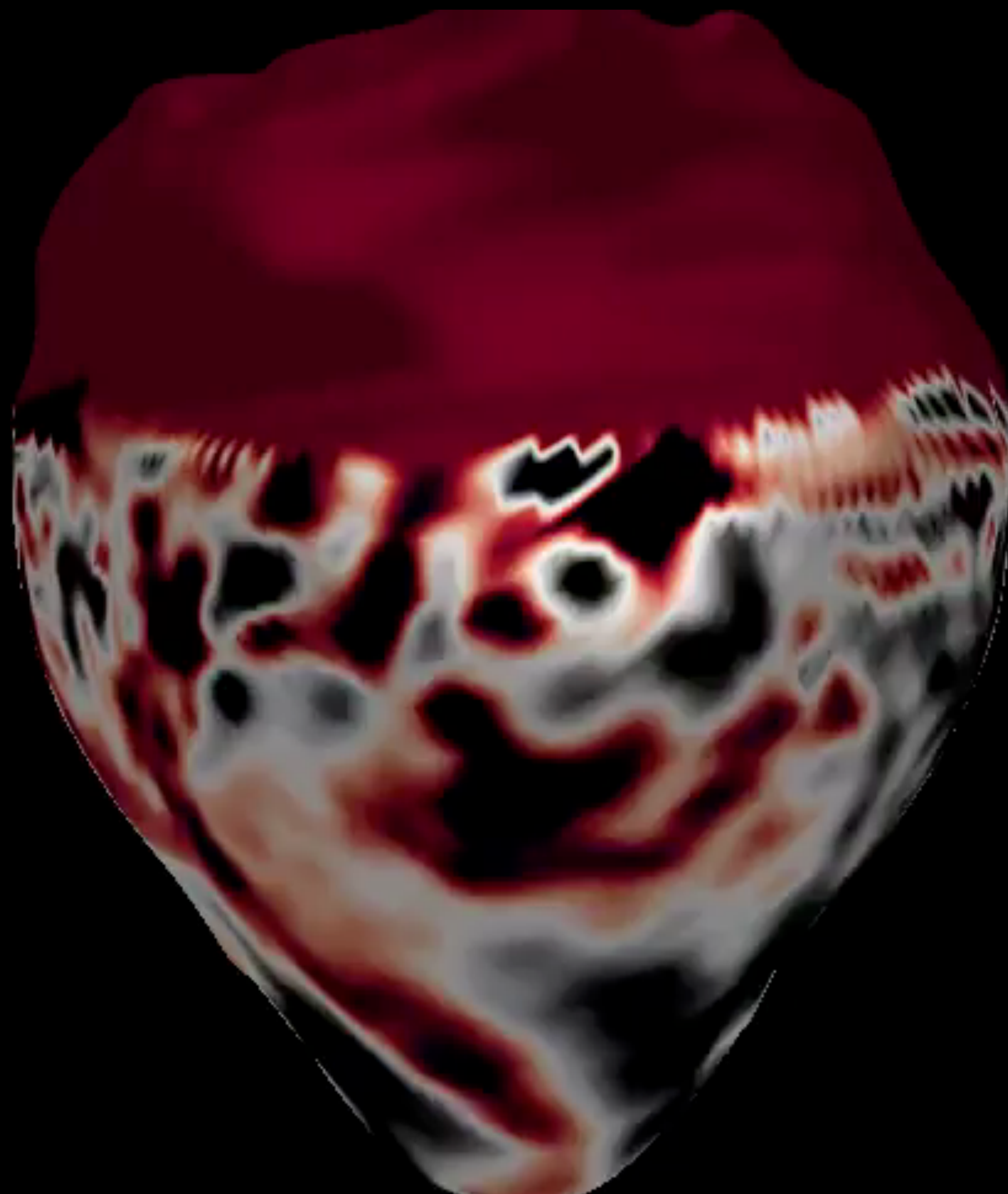
Ventricular Tachycardia



Electrical Excitation Waves

J. Christoph, J. Schröder-Schetelig

Ventricular Fibrillation in a Pig Heart



membrane voltage
(di-4-ANEPPS)

3D panoramic view using
4 cameras (128x128 px @ 500Hz)

J. Schröder-Schetelig

Mathematical Models of Cardiac Dynamics

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

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

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

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

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

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

ionic currents

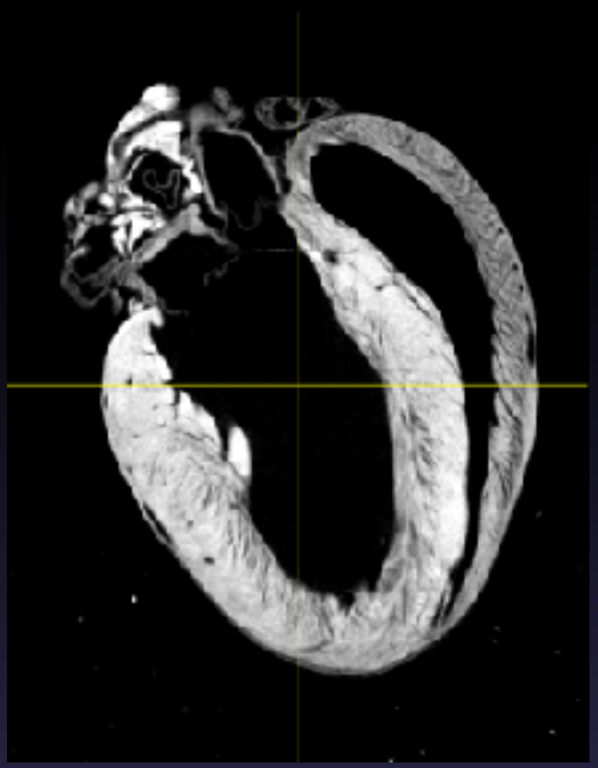
$$I_{\mathrm{ion}}(V_m, \mathbf{h}) = \sum_x I_x(V_m, \mathbf{h}) + I_{\mathrm{injection}}$$

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

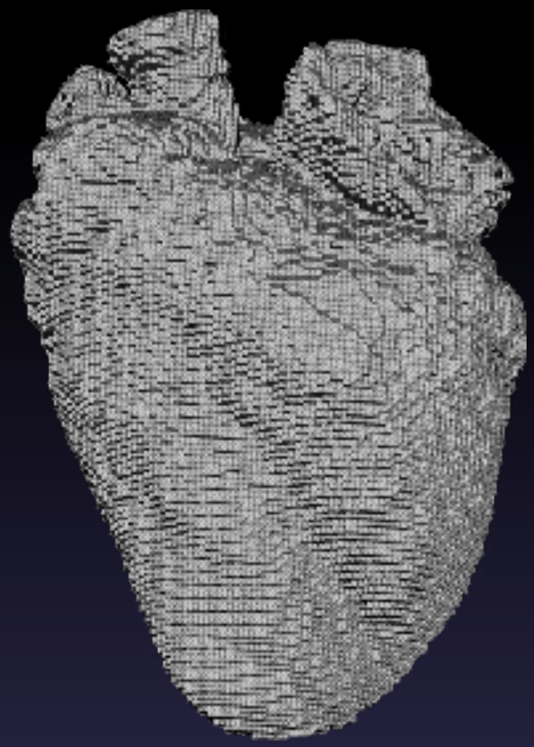
Very detailed models may suffer from “overfitting” and are not very robust.

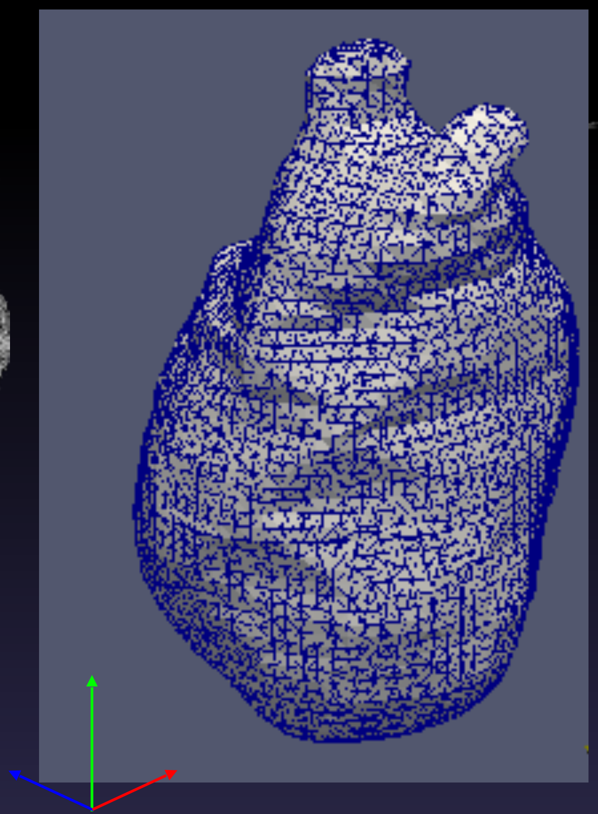
→ S.Otte et al., Commun. Nonlin. Sci. Numer. Simulat. 37, 265 (2016)

Electro-mechanical Modeling

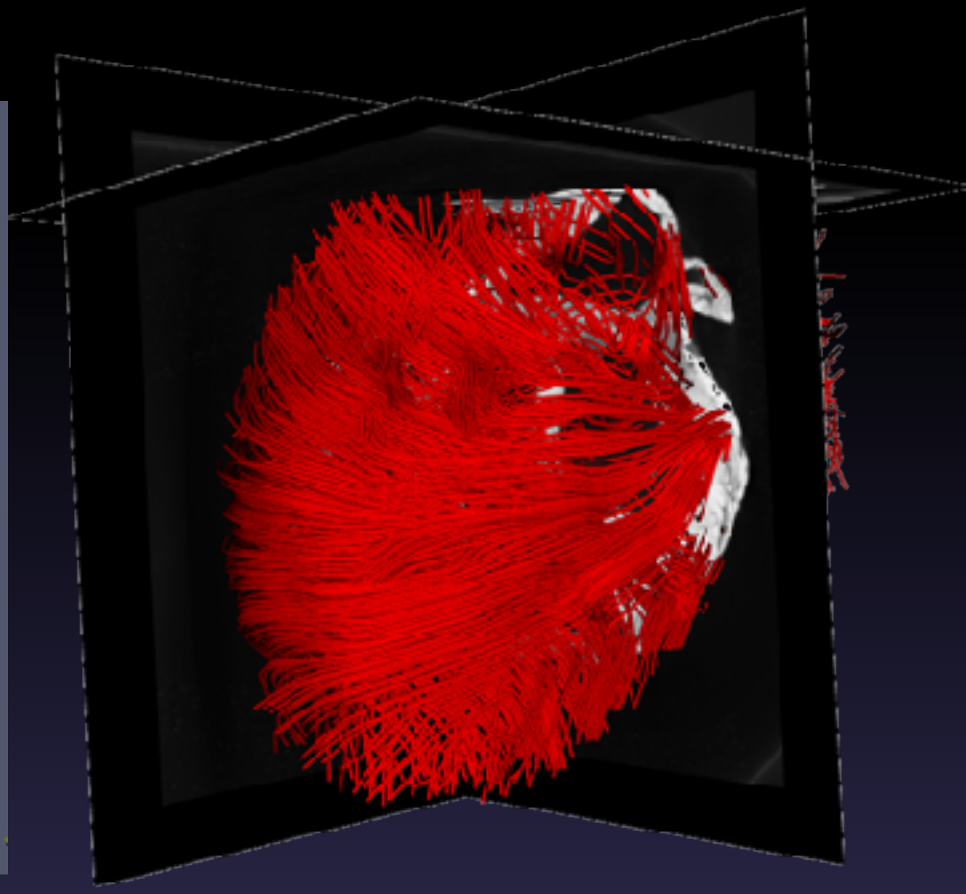


µCT





Segmentation & discretization



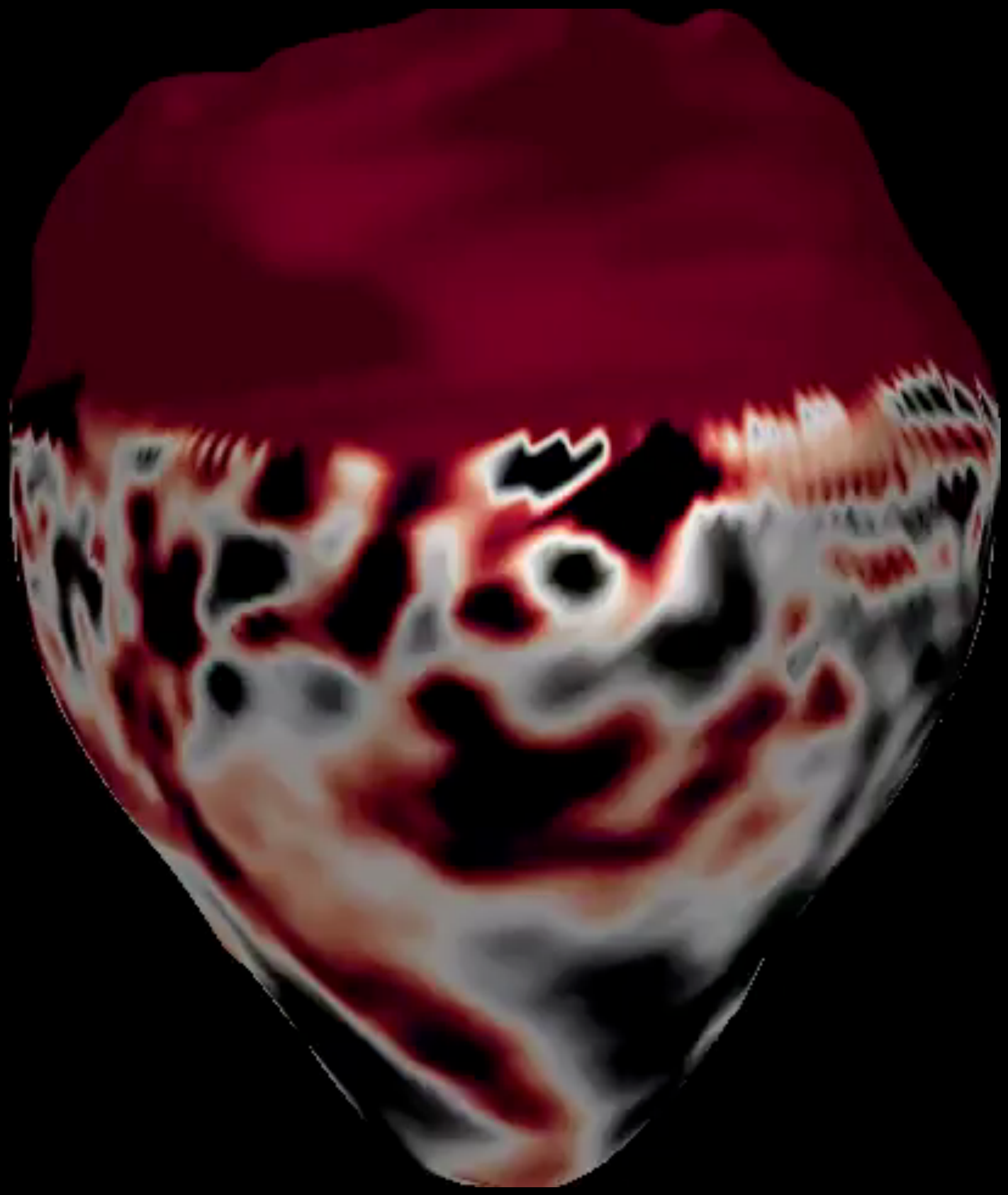
Local fiber orientation, vasculature, etc.

- Deformable Reaction-Diffusion System
- Electrophysiology (Fenton-Karma, detailed ionic model)
- Tissue mechanics (FEM, discrete particle model)
- Parameter estimation & model validation

Simulating Cardiac Arrhythmias

for Developing Novel Diagnostic and Defibrillation Approaches

Ventricular Fibrillation (VF)



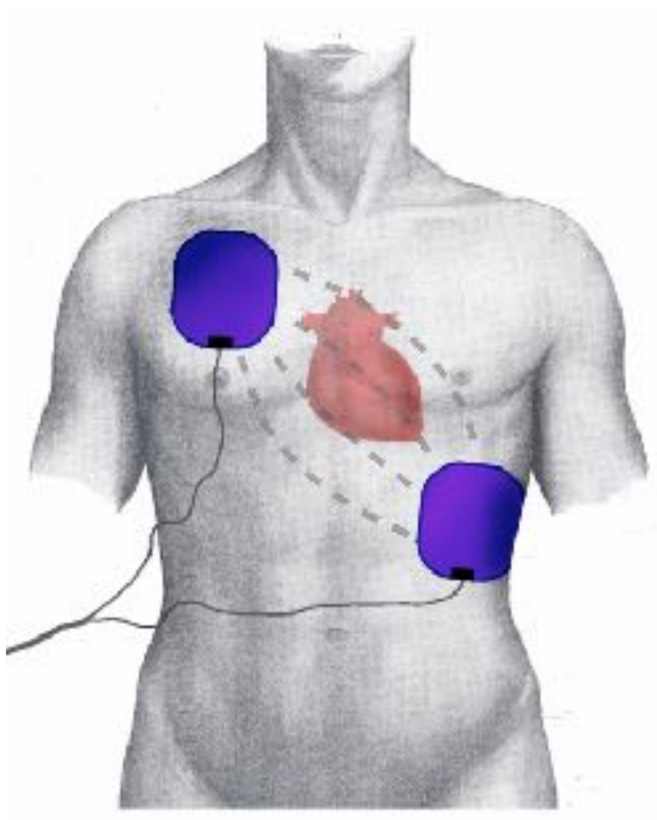
- Most common deadly manifestation of cardiac disease
- 100.000 – 200.000 sudden cardiac deaths (SCD) in Germany per year
- Requires immediate defibrillation using high-energy shock

J. Schröder-Schetelig

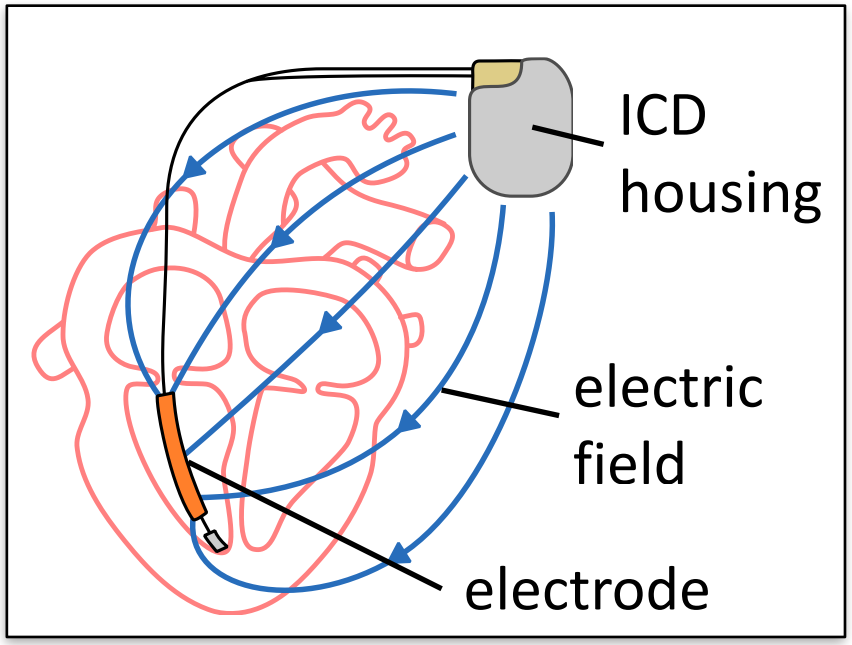
Defibrillation

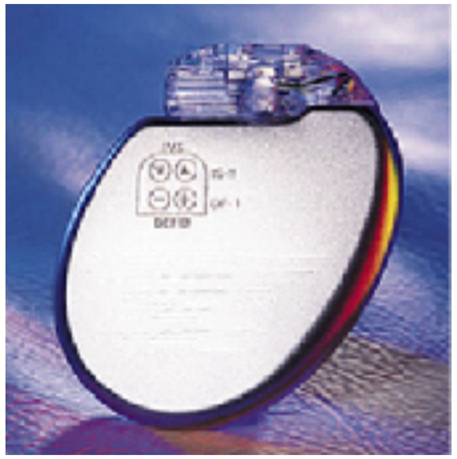
Principle: Reset electrical activity

external



internal





Electric shocks: energy 360J (external) 40 J (internal)

1000 V 30 A 12 ms

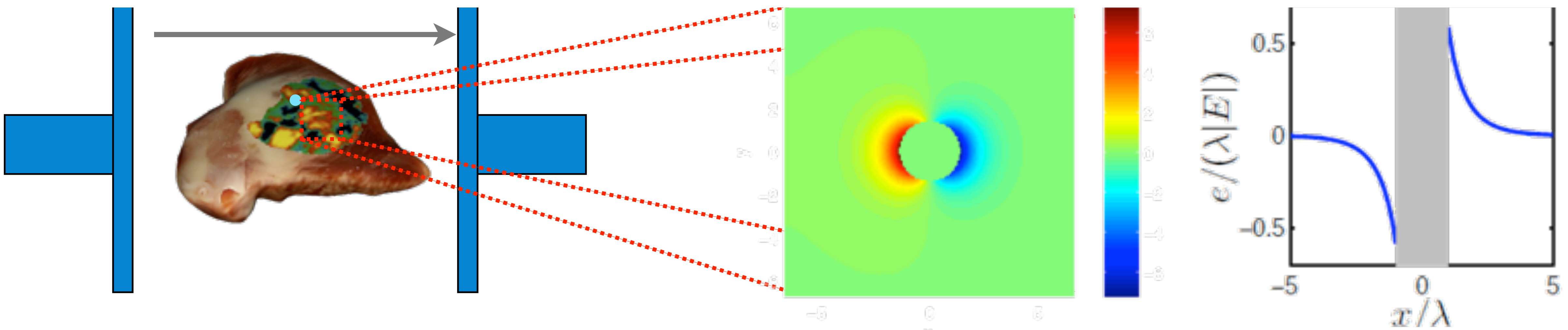
Severe side effects: tissue damage - traumatic pain

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

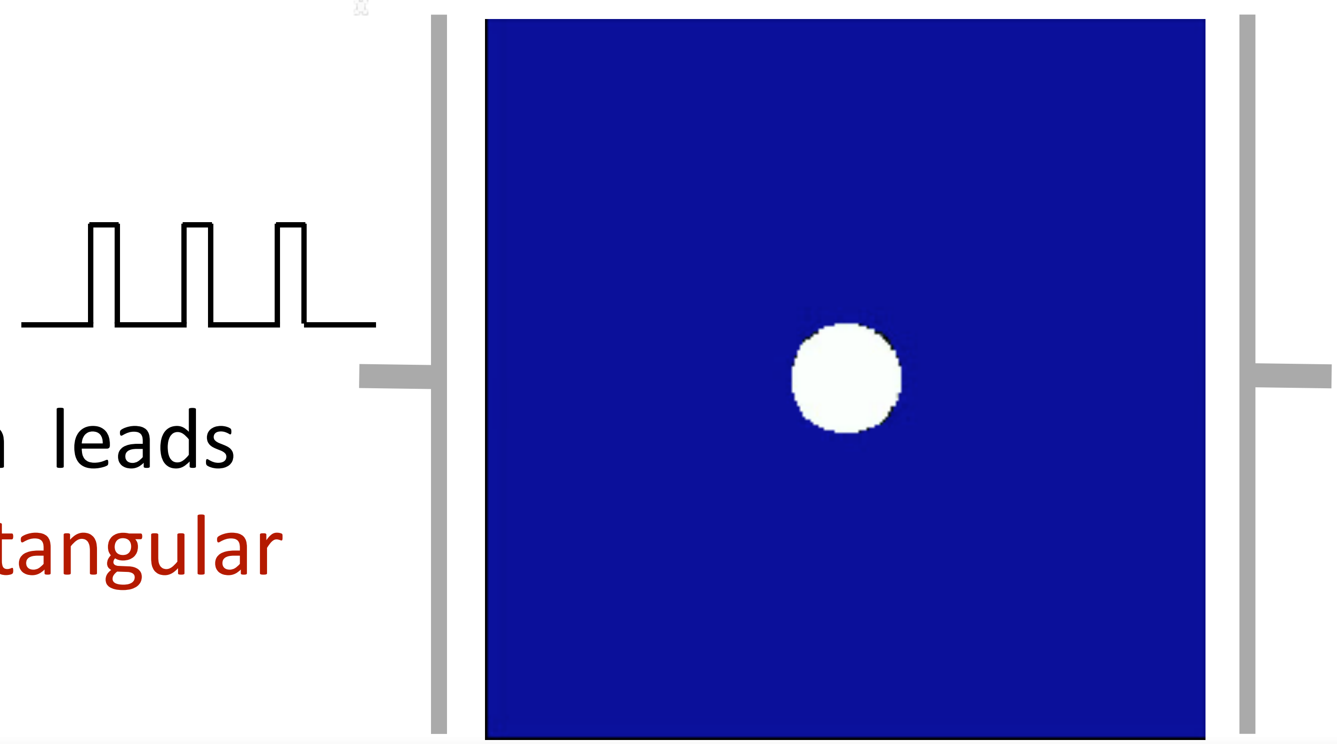
Virtual Electrodes

Blood vessels, scars, fatty tissue

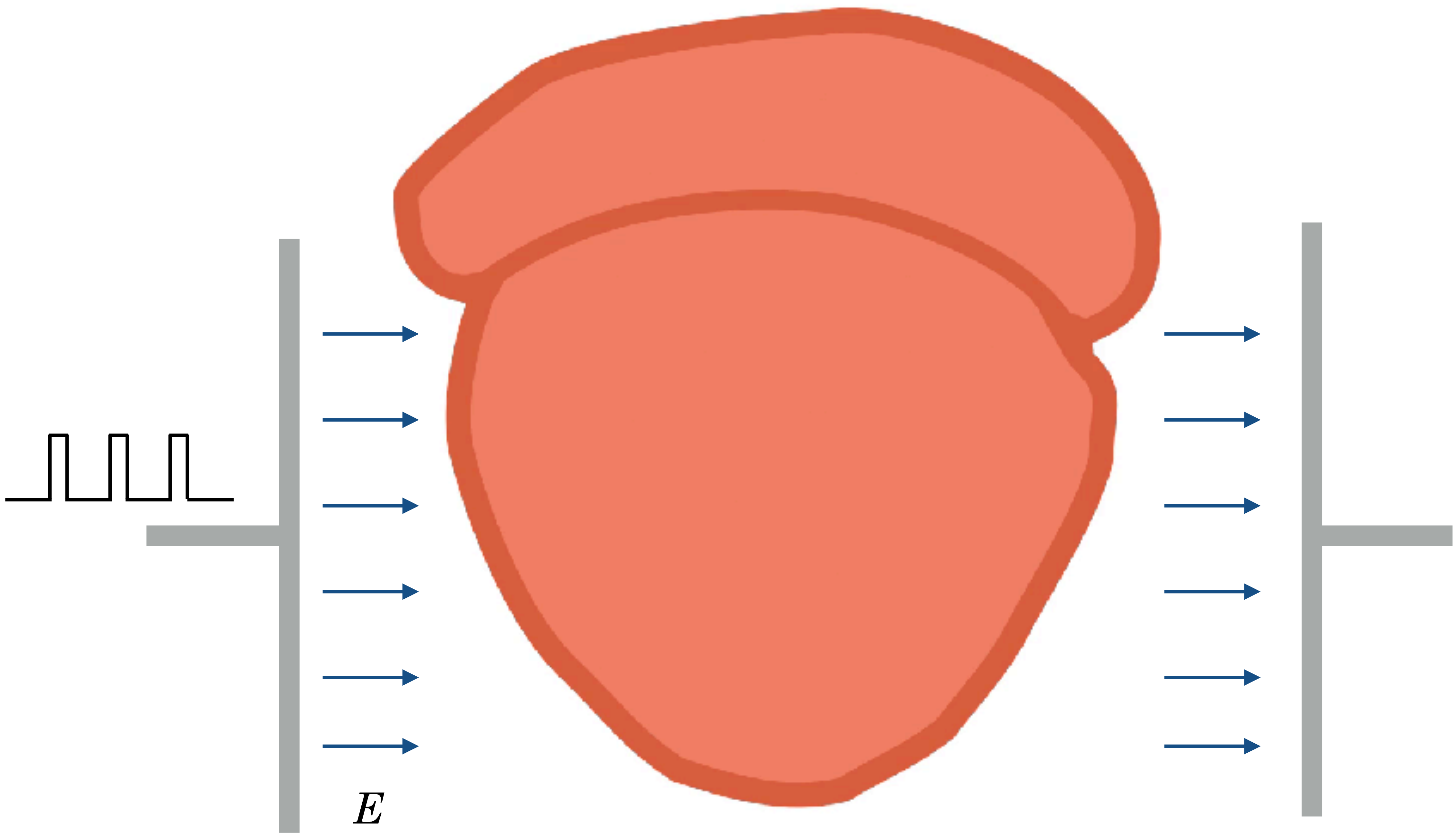
- are obstacles to electrical conduction
- may act as virtual electrodes (Pumir&Krinsky, J. Theor. Biol. 199, 311 (1999))



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

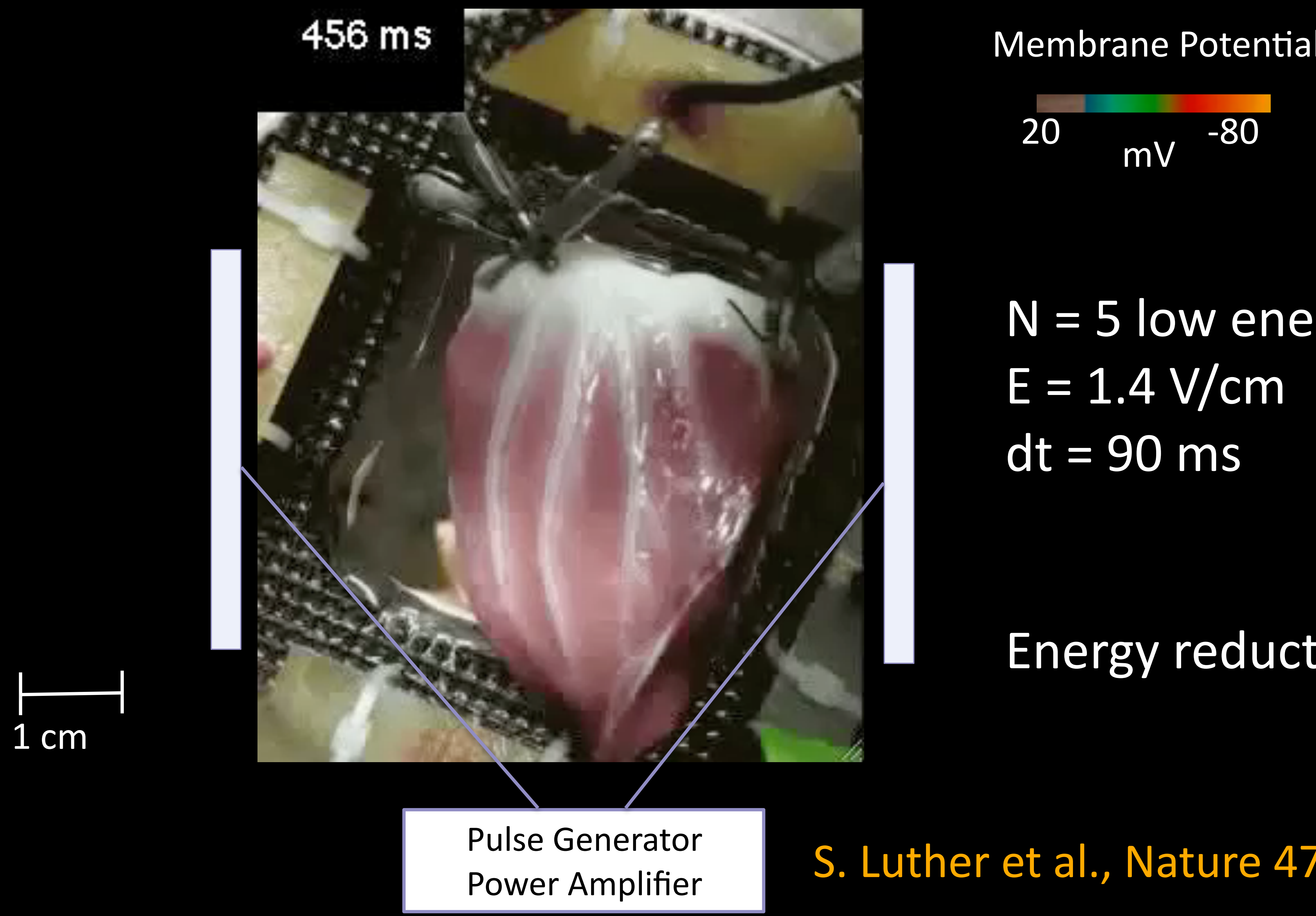


Recruiting Virtual Electrodes for Terminating Cardiac Arrhythmias



Animation: T. Lilienkamp

Low-Energy Anti-Fibrillation Pacing (LEAP)

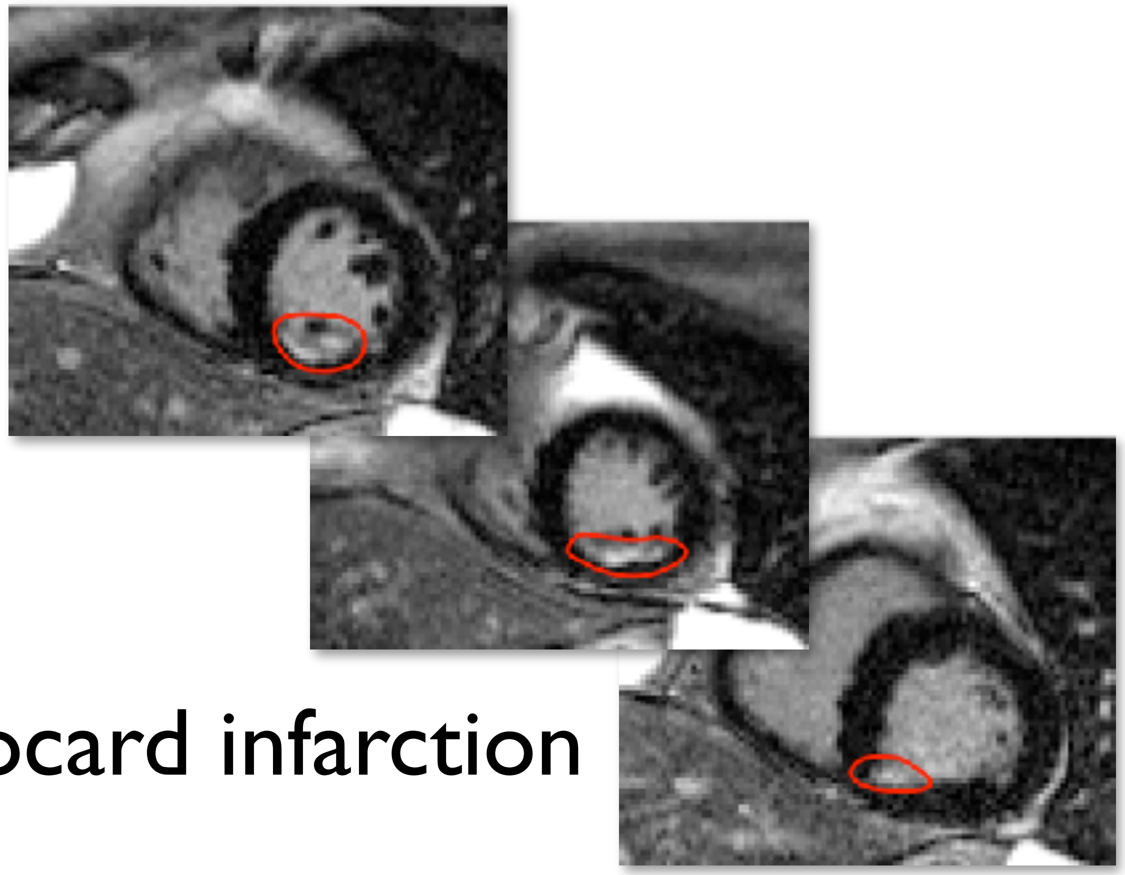


N = 5 low energy pulses
E = 1.4 V/cm
dt = 90 ms

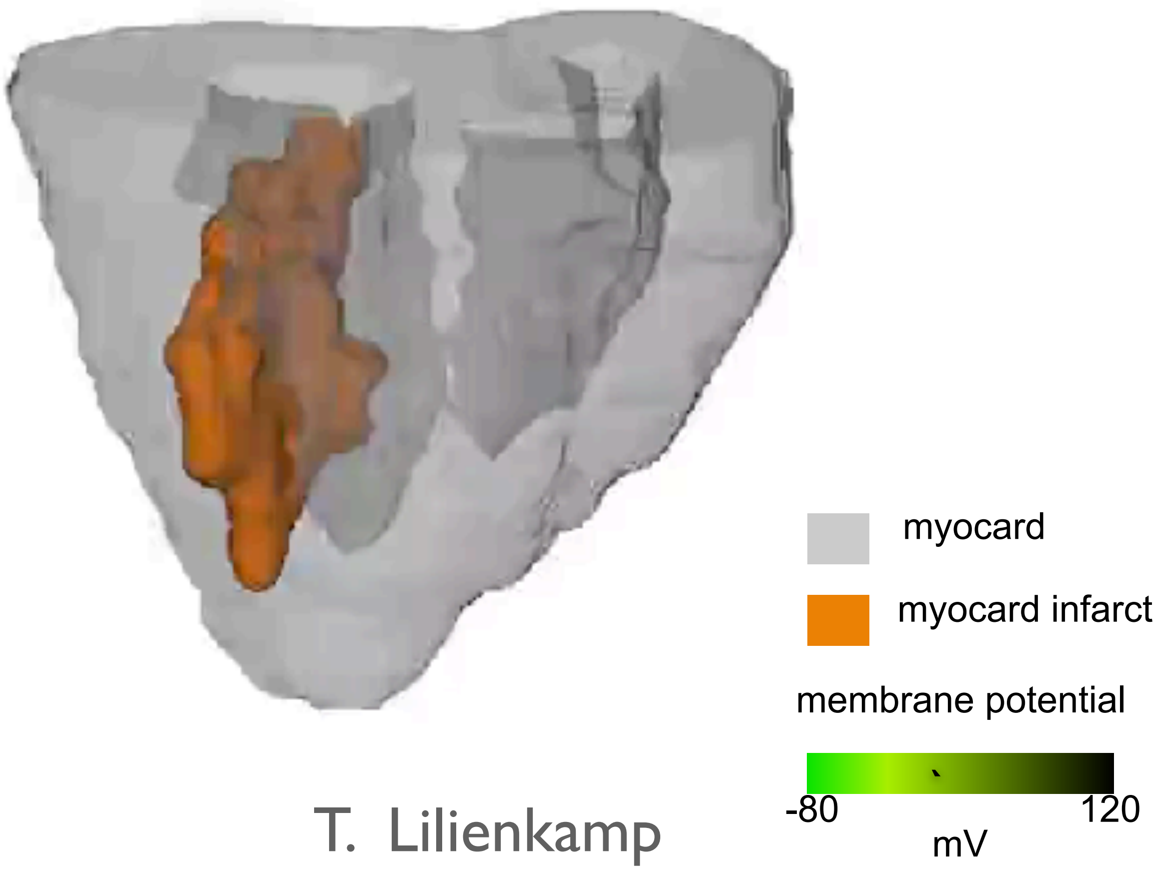
Energy reduction: 82 %

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

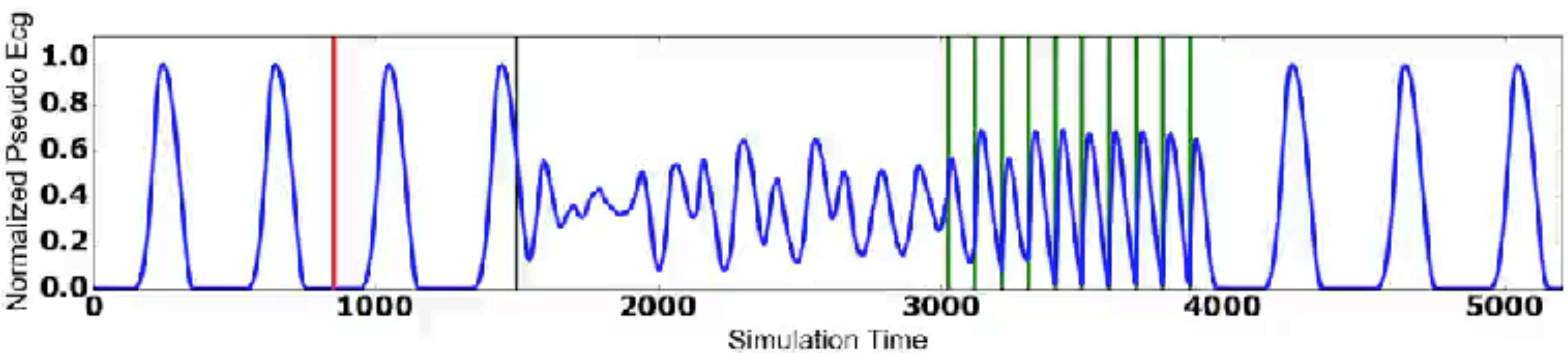
Simulation using a MRT-based heart model



myocard infarction



T. Lilienkamp



Parameter Estimation and Data Assimilation Tasks

- for **isolated hearts** in a Langendorf perfusion system

  reconstruct intramural dynamics (inside the heart) from

  - surface information employing fluorescent dyes (voltage, Ca+, mechanical stress and strain)
  - ultrasound imaging

- for **intact hearts** (inside the body)

  reconstruct dynamics of the heart

  - electrical wave pattern using extra corporal electrodes (on the surface of the body) → ECG imaging (Y. Rudy, 1999)
  - mechanical deformation and motion from ultrasound imaging

- for **improving simulation models**
  - parameter estimation for cardiac cell models
  - model evaluation

Synchronization based state and parameter estimation

- drive the model with the time series using a suitable coupling term
- minimize synchronization error by adjusting parameters

Experiment or Model

$$\dot{x} = f(x, p)$$

$$s = h(x) \longrightarrow$$

(Computer) Model

$$\dot{y} = f(y, q) + c(s - h(y))$$

$$q \to p \quad \Rightarrow \lim_{t \to \infty} \|x(t) - y(t)\| = 0$$

U. Parlitz *et al.*, Phys. Rev. E 54, 6253 (1996)
U. Parlitz, Phys. Rev. Lett. 76, 1232 (1996)

D. Rey et al. Phys. Lett. A 378, 869 (2014)
D. Rey et al. Phys. Rev. E 90, 062916 (2014)

Example: Excitable Media

cubic Barkley model

$a = 0.75 \quad b = 0.08 \quad \varepsilon = \frac{1}{12}$

chaotic

$$\frac{\partial u}{\partial t} = \frac{1}{\varepsilon} u(1-u)\left(u - \frac{v+b}{a}\right) + D \cdot \nabla^2 u$$

$$\frac{\partial v}{\partial t} = u^3 - v$$

- no-flux boundary conditions
- implementation of the PDE integration scheme on a graphics processing unit (GPU) resulting in a speed up of a factor 50-100

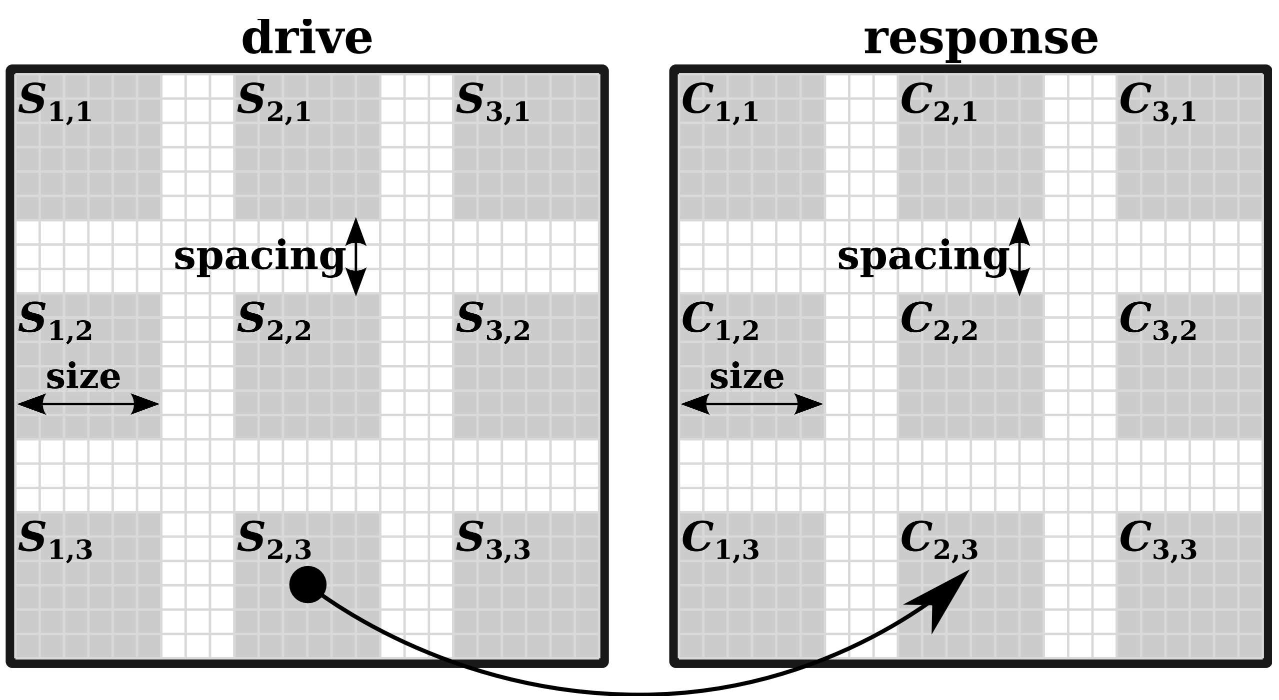
Uni-directional local coupling

"experiment" → "model"

using sensors and controllers

S. Berg et al., Chaos 21, 033104 (2011)

M.J. Hoffman et al., Chaos 26, 013107 (2016)



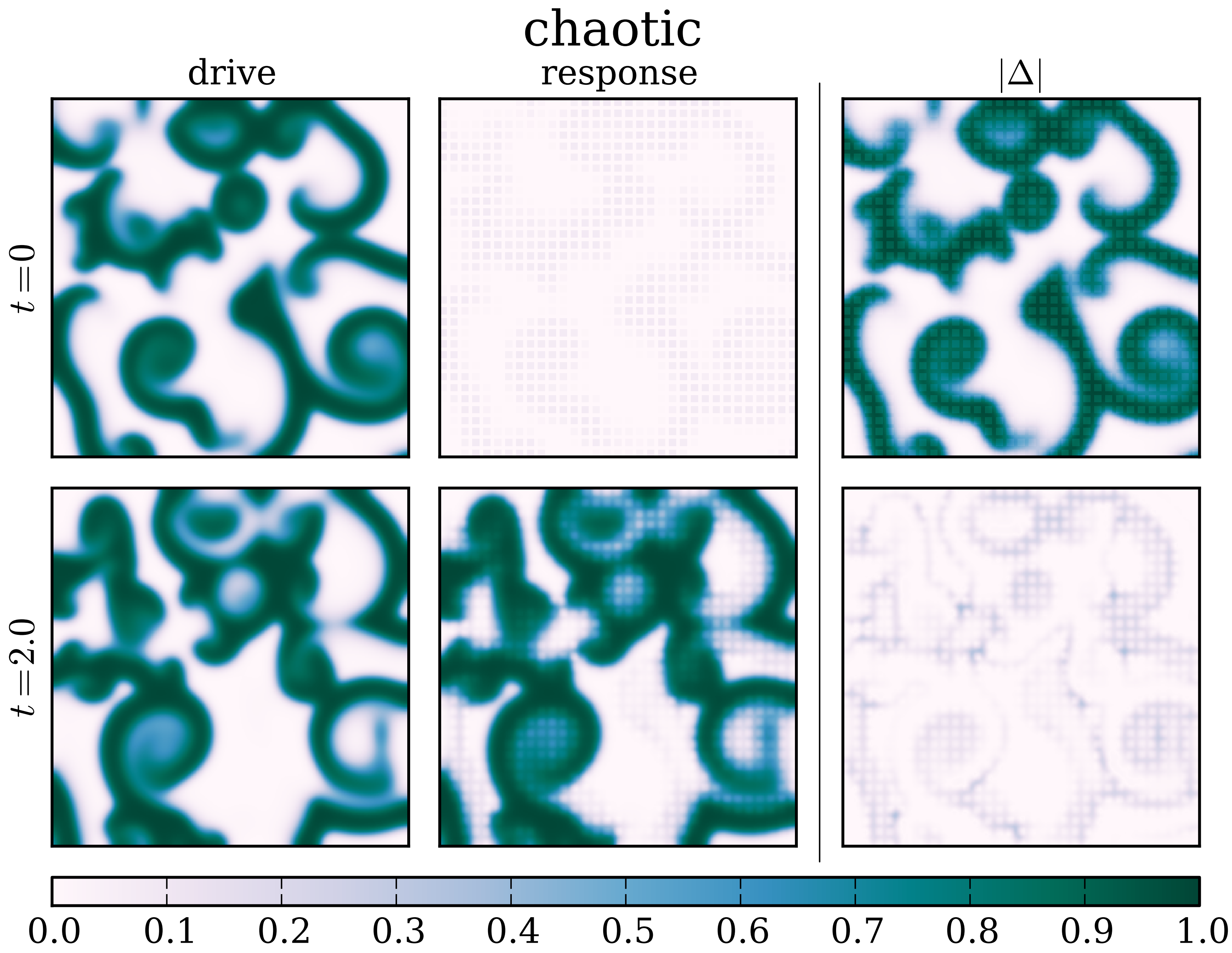
Synchronization Based State and Parameter Estimation

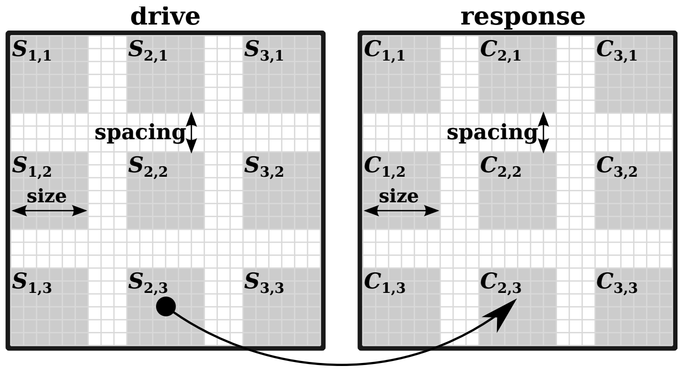
freely running   driven   difference

Cubic Barkley model

t=0

t=2

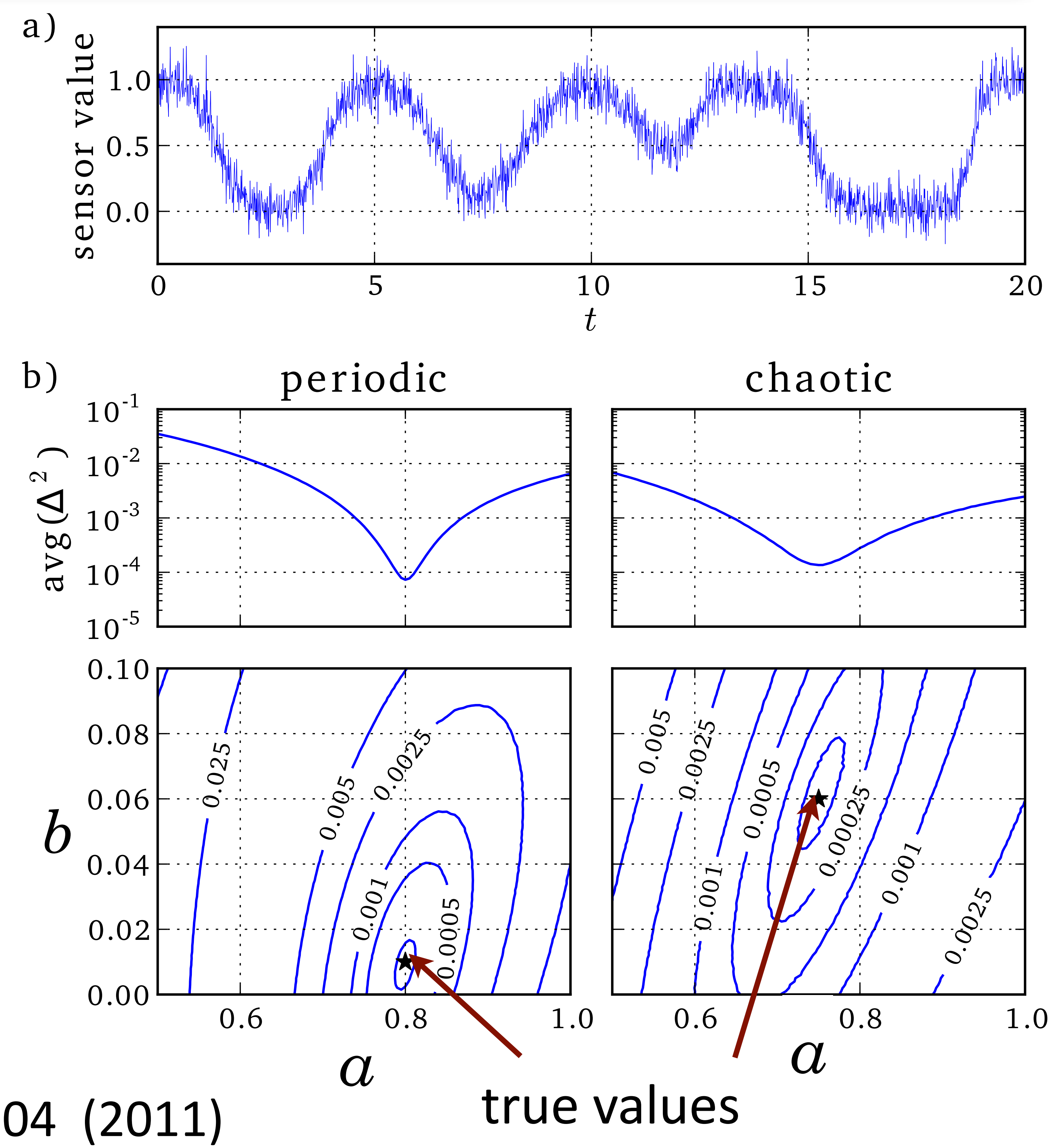




grid of size: 294×294 - sensor sizes: 6×6 grid points - sensor spacing 3 grid points

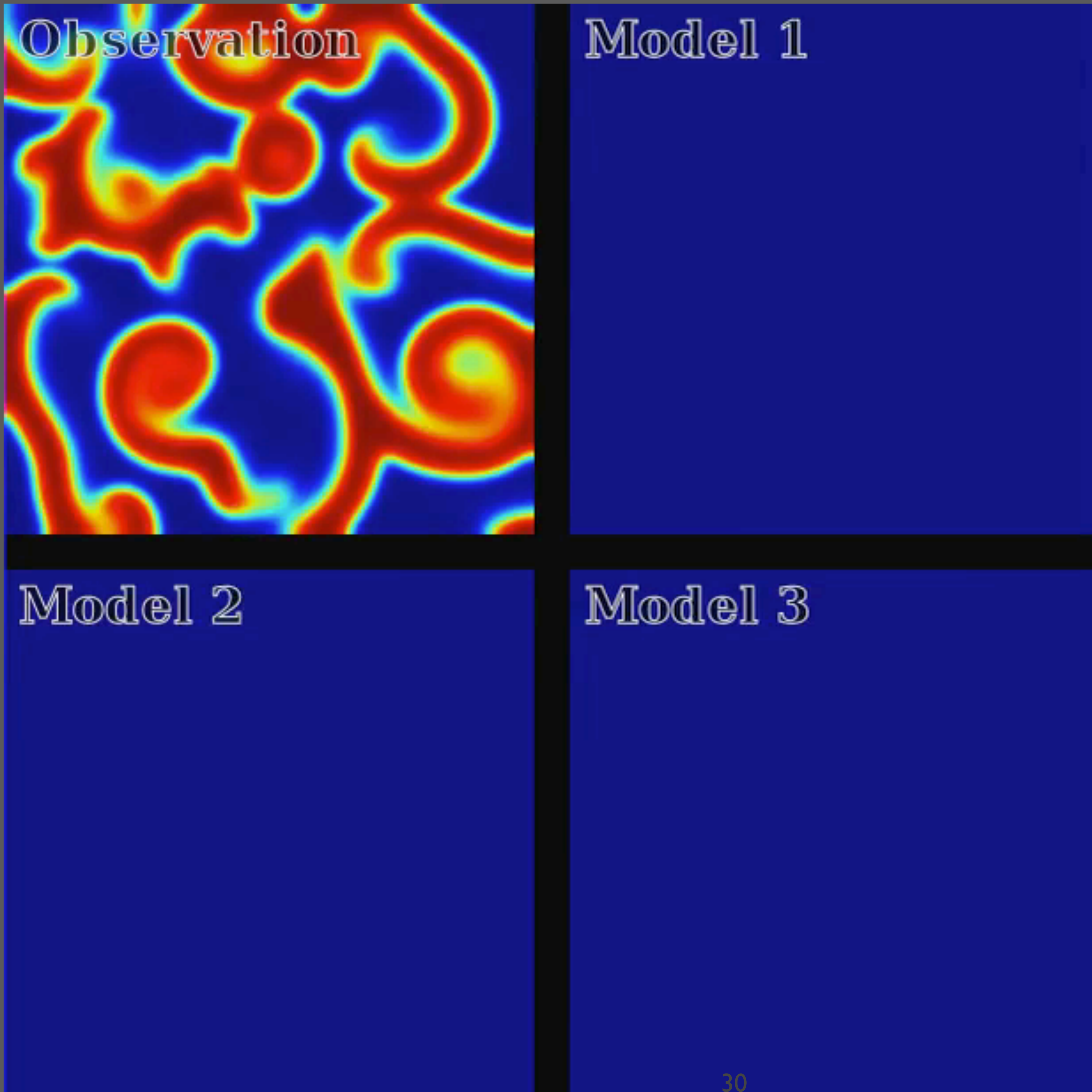
Synchronization Based State and Parameter Estimation

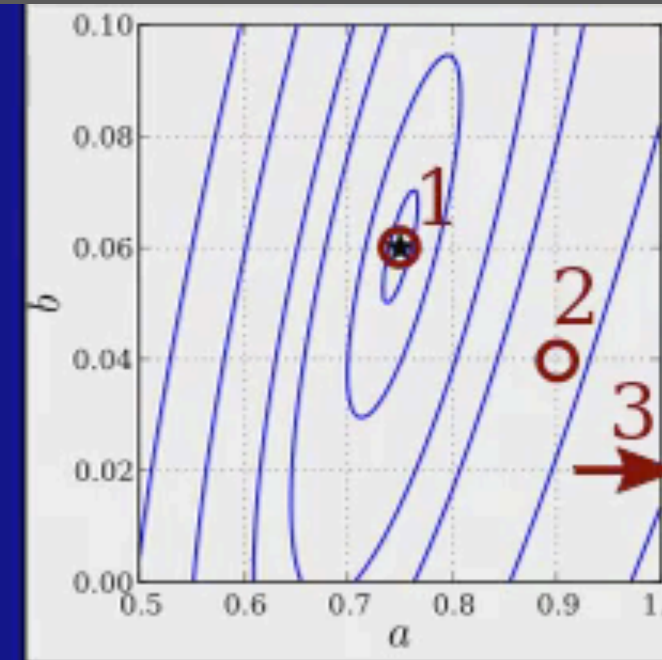
Typical noisy chaotic sensor signal (SNR= 12dB)



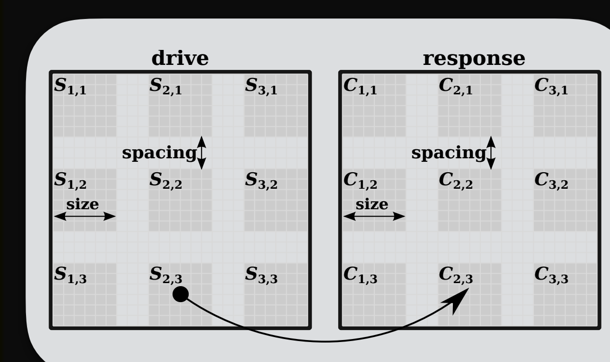
Parameter space of the response Barkley system with contour curves showing the averaged synchronization error

S. Berg *et al.*, Chaos **21**(3), 033104 (2011)

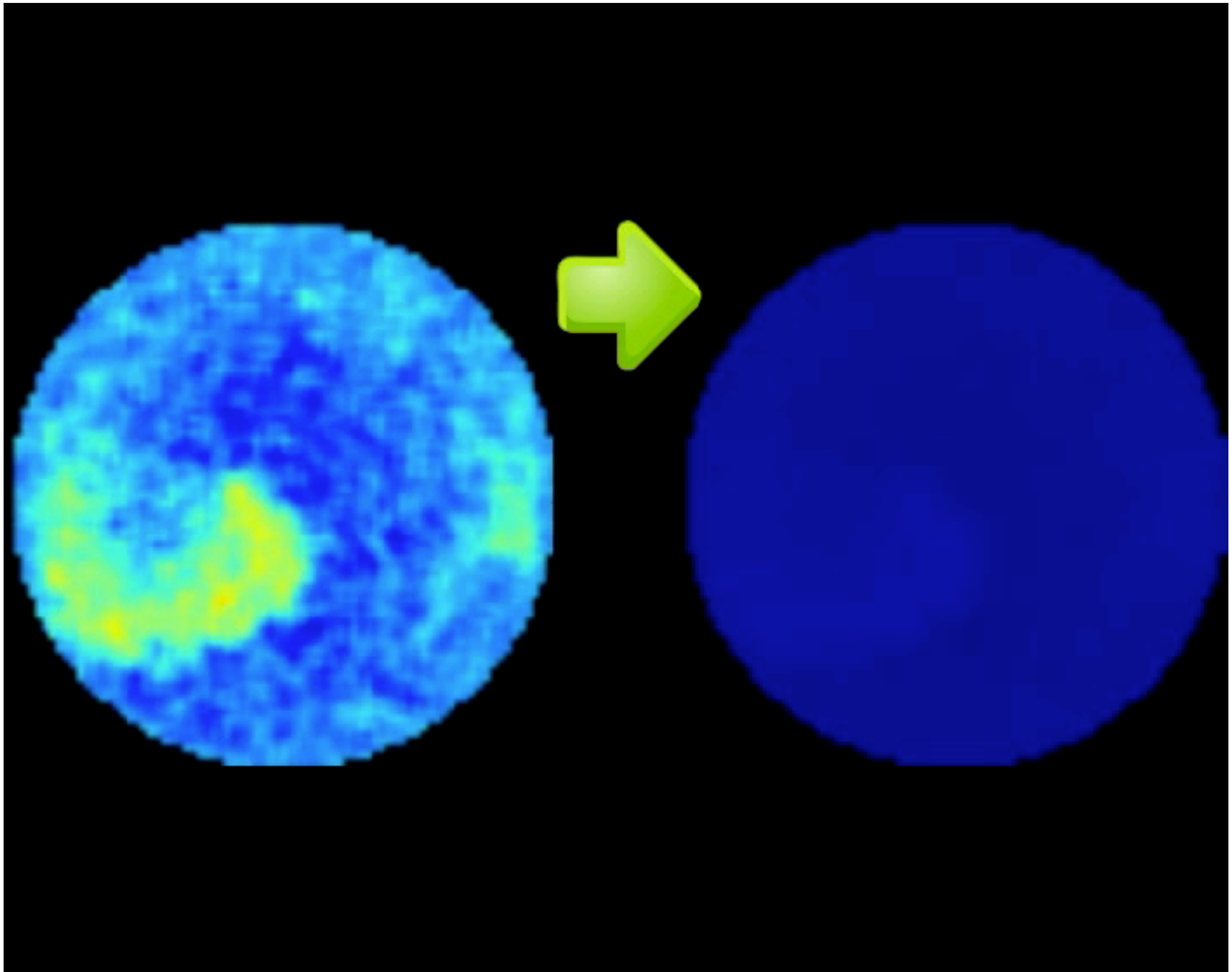




model parameter space with contour lines of the synchronization error



Cardiac Cell Culture Experiment drives Barkley Model



T.K. Shajahan
S. Berg

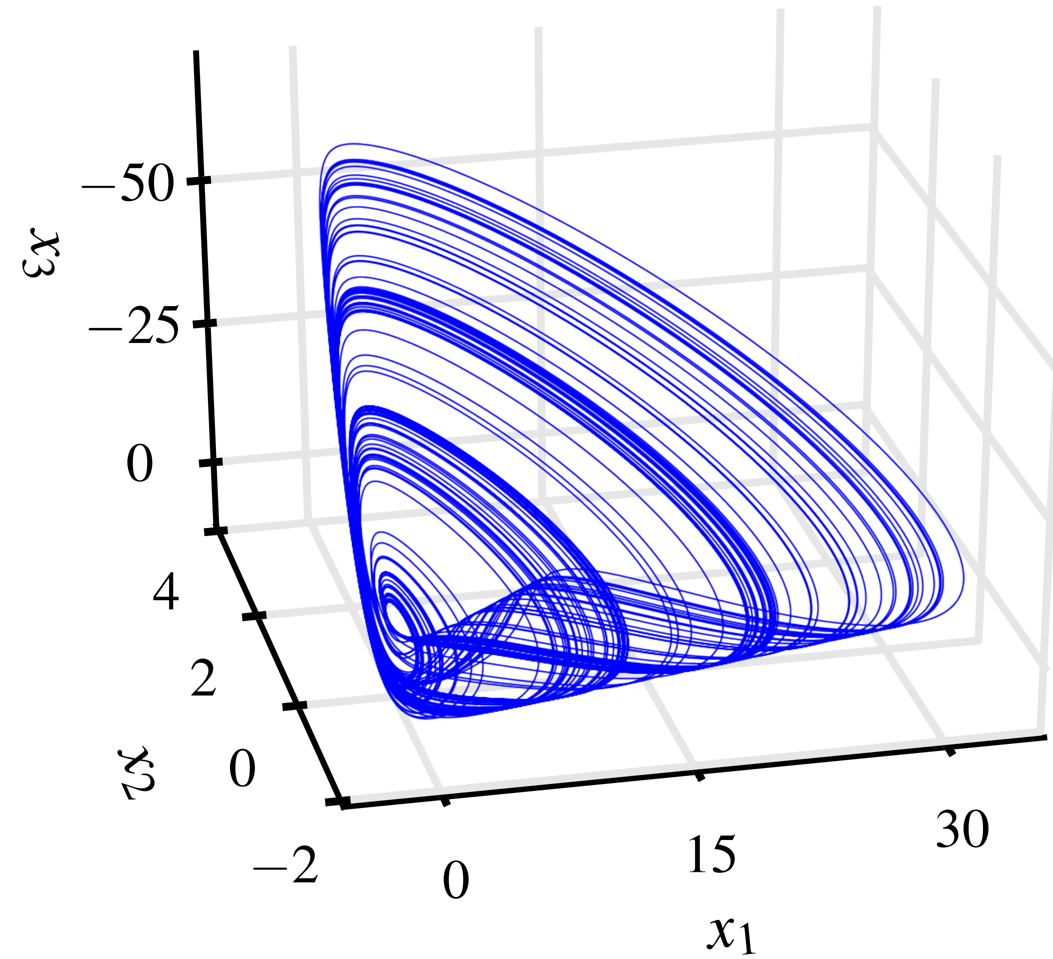
Estimability analysis of state variables and parameters based on delay coordinates map

Example: Colpitts Oscillator

nonlinear electronic oscillator

model equations

$$\dot{x}_1 = p_1 x_2$$
$$\dot{x}_2 = -p_2(x_1 + x_3) - p_3 x_2$$
$$\dot{x}_3 = p_4 \left(x_2 + 1 - e^{-x_1}\right)$$



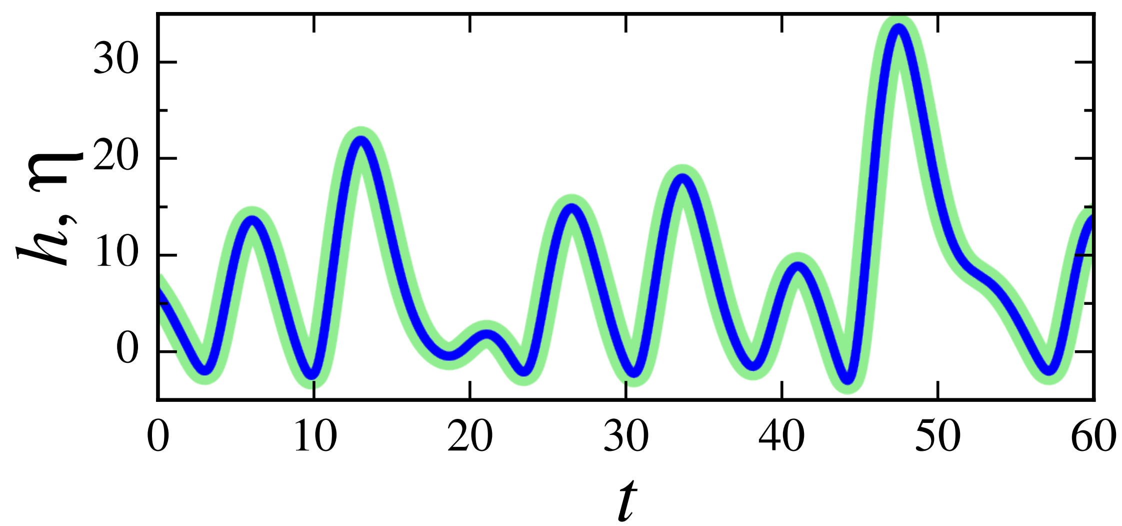
twin-experiment: simulated data (first model variable)

measurement function $h(\mathbf{x}) = x_1$

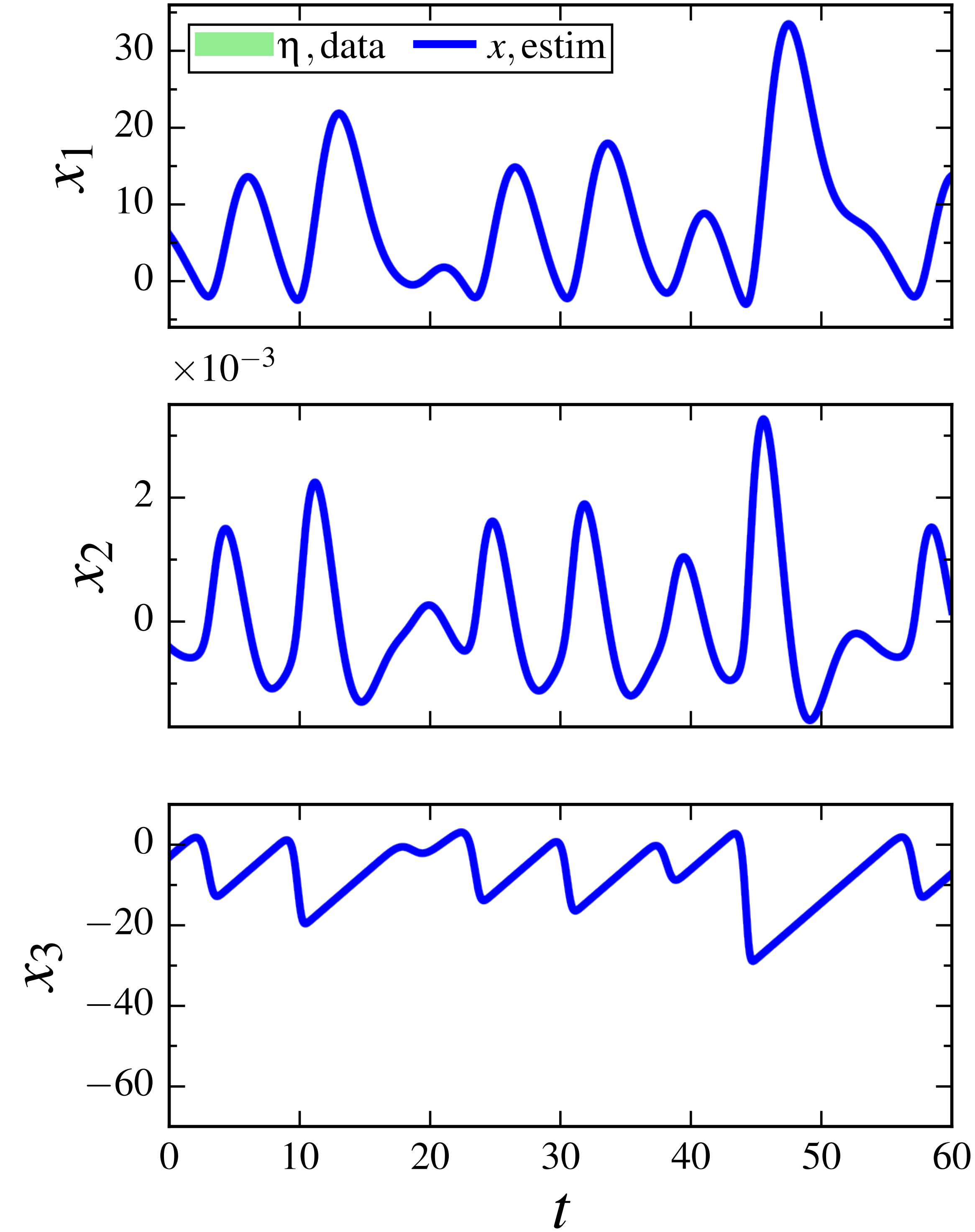
optimization (4D-Var)

J. Schumann-Bischoff and U. Parlitz, Phys. Rev. E 84, 056214 (2011)

Example: Colpitts Oscillator



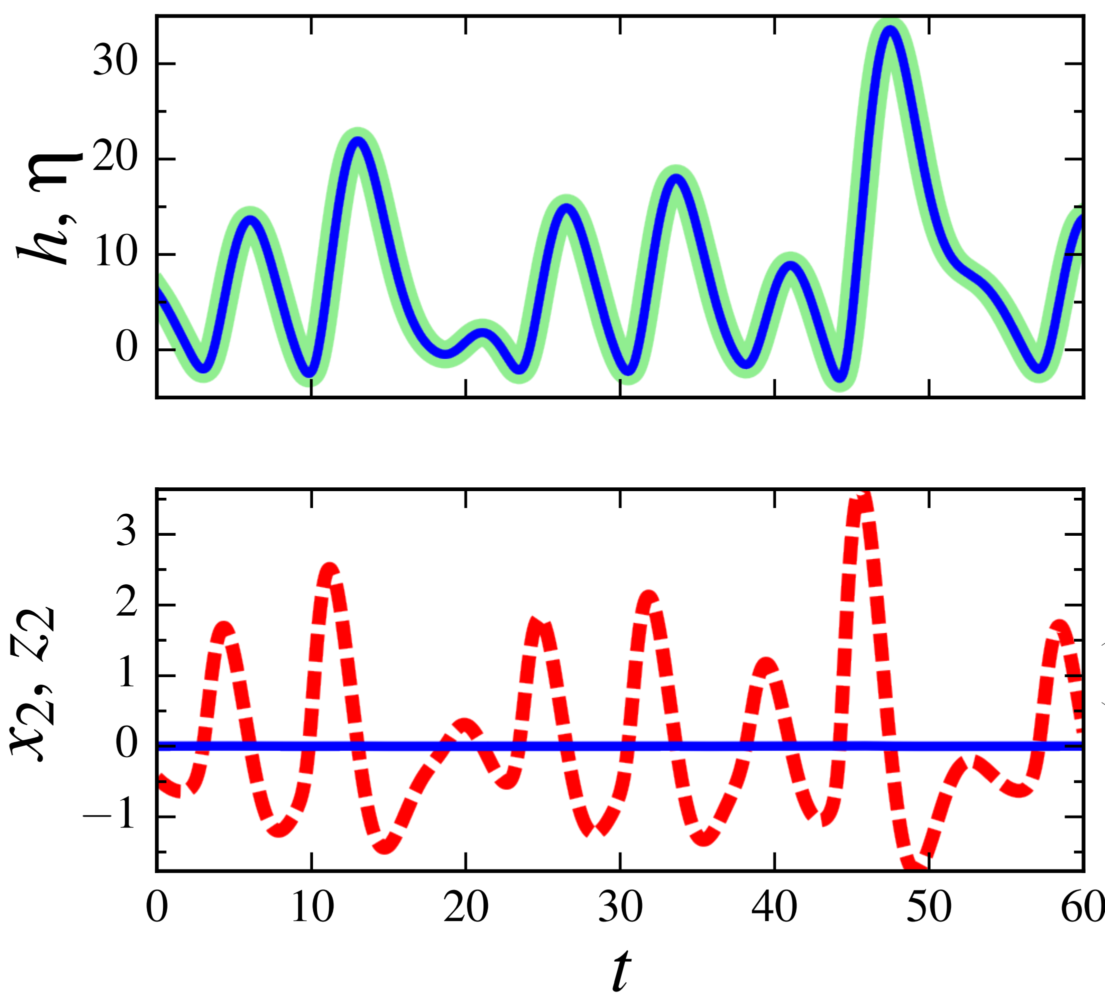
result of estimation



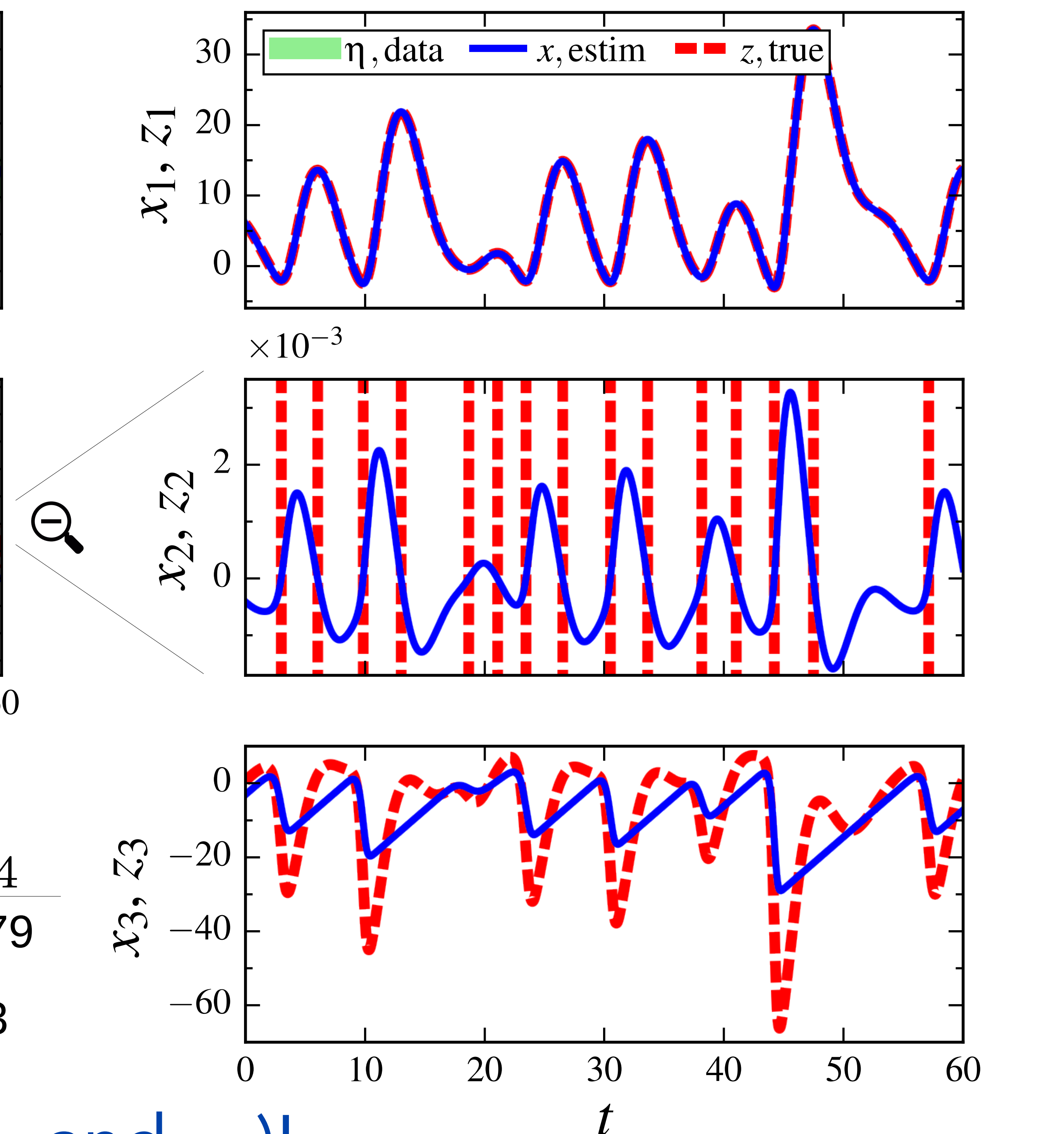
measured time series is successfully reproduced

	p_1	p_2	p_3	p_4
estim.	5573	0.00016	0.700	2.79
data				

Example: Colpitts Oscillator



comparison with the true solution



	p_1	p_2	p_3	p_4
estim.	5573	0.00016	0.700	2.79
data	5	0.08	0.7	6.3

Estimation fails (except for x_1 and p_3)!

Estimability

Success in parameter and state variable estimation depends on

- measured variable (observable)
- particular variable or parameter to be estimated

Which variables or parameters of a given model can be estimated using a given time series (observable) ?

→ Observability / Identifiability / Estimability

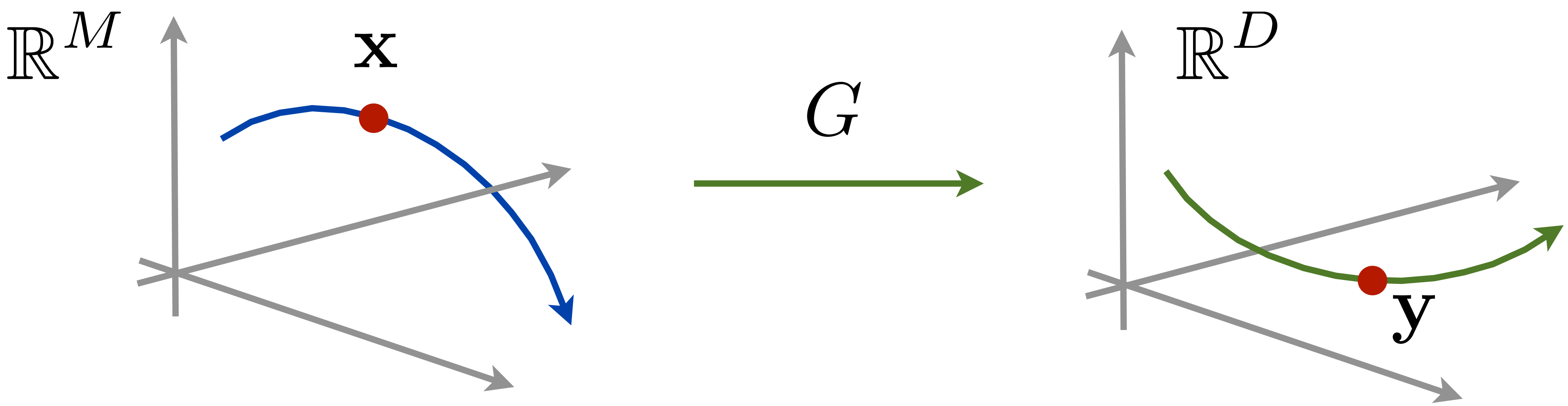
Investigating Estimability Using Delay Coordinates

M-dimensional discrete system $\mathbf{x}(n+1) = \mathbf{g}(\mathbf{x}(n))$

times series $\{s(n)\}$ with $s(n) = h(\mathbf{x}(n))$ $(n = 1, \ldots, N)$

D-dimensional delay coordinates

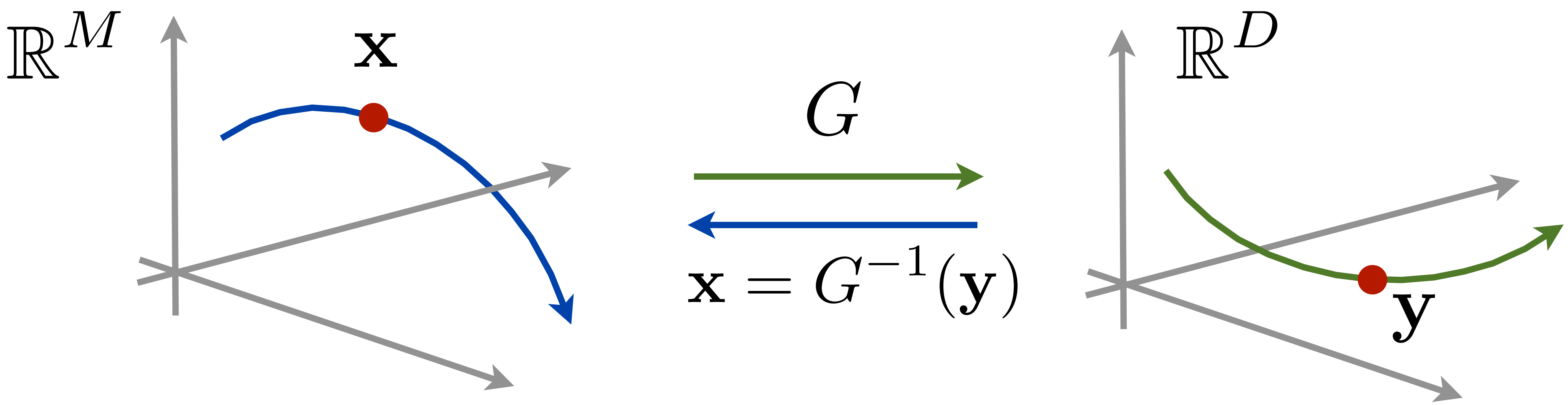
$$\mathbf{y} = (s(n), s(n+1), ..., s(n+D-1)) = G(\mathbf{x}) \in \mathbb{R}^D$$



delay coordinates map $G : \mathbb{R}^M \to \mathbb{R}^D$

Estimability

delay coordinates map $G : \mathbb{R}^M \to \mathbb{R}^D$



State variables x_i can be recovered from the observed time series s if the delay coordinates map G can be locally inverted, i.e. if the

Jacobian matrix $DG(\mathbf{x})$ of G has full rank

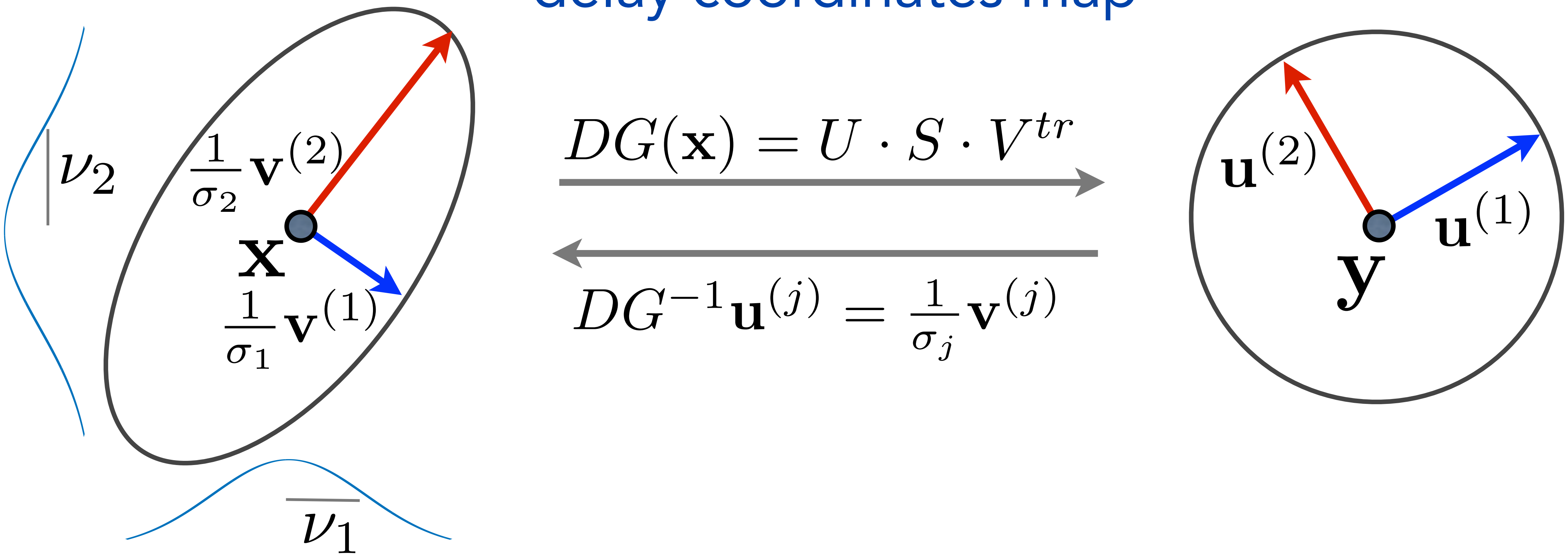
i.e., if its null space (kernel) is zero dimensional.

U. Parlitz et al., Phys. Rev. E 89, 050902(R) (2014); Chaos 24, 024411 (2014)

Estimability

state space ⟶ reconstruction space

delay coordinates map



$DG^{-1}(\mathbf{y})$ maps perturbations of $\mathbf{y}$ in delay reconstruction space to deviations from the state $\mathbf{x}$

uncertainty of variable x_m

$$\nu_m = \sqrt{[DG^{tr} \cdot DG]^{-1}_{mm}} = \sqrt{[V \cdot S^{-2} \cdot V^{tr}]_{mm}}$$

Detecting estimable and redundant parameters

unknown quantities $\mathbf{w} = (\mathbf{x}, \mathbf{p})$

delay coordinates map

$$\mathbf{g} = G[\mathbf{w}] = \left[x_1(t), \quad x_1(t+\tau), \quad \ldots, \quad x_1(t+(K-1)\tau)\right]^{tr}$$

transformation of perturbations $\mathrm{D}G\,\Delta\mathbf{w} = \Delta\mathbf{g}$

perturbations of $\mathrm{w} = (\mathrm{x},\mathrm{p})$ within the null space of $\mathrm{D}G$ have no impact on the observations

$$\mathrm{D}G\Delta\mathbf{w} = 0$$

Vanishing components of basis vectors of the null space indicate estimable parameters and (groups of) redundant parameters and variables.

Schumann-Bischoff et al., Phys. Rev. E 94, 032221 (2016)

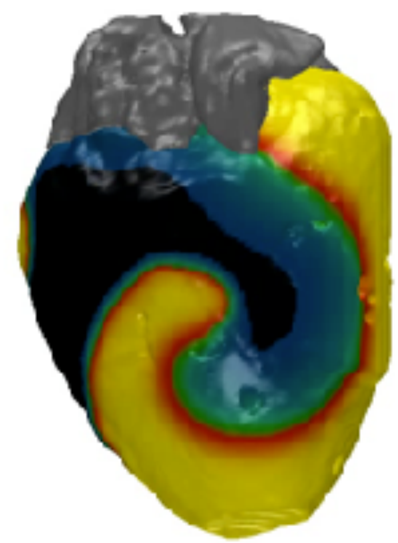
Summary

Data Assimilation and Parameter Estimation in Cardiac Dynamics

excitable medium

CT scan
↓
geometry

ultrasound
↓
mechanical motion



fluorescent dyes
↓
voltage, Ca+, mechanics
isolated heart, surface only

electrical sensors
↓
electrical wave pattern
ECG imaging

↓

mathematical model

parameter estimation
model evaluation

local cell dynamics + diffusion
electro-mechanical coupling
mechanical motion

synchronization
estimability

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Thank You !