Challenges of data driven modelling in cardiac dynamics

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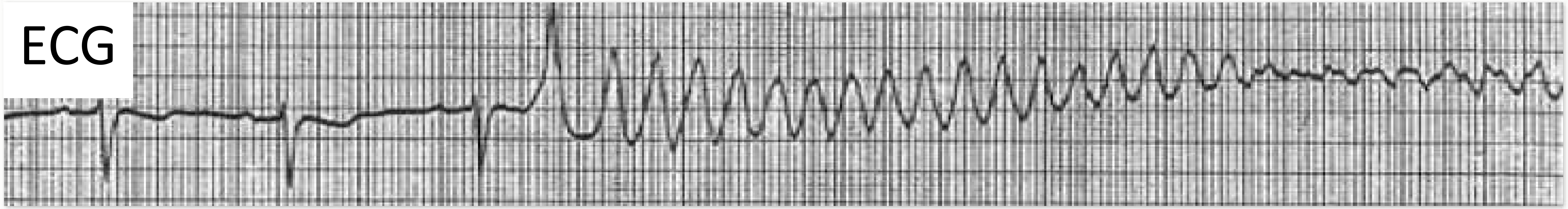
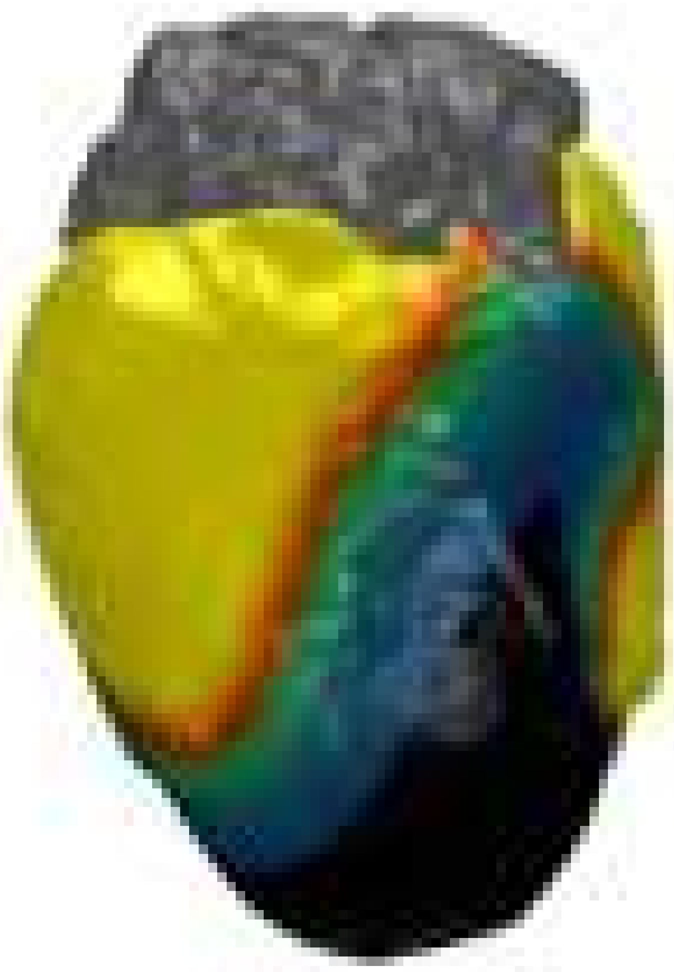
Transitions to Cardiac Arrhythmias

Normal Rhythm → Tachycardia → Fibrillation

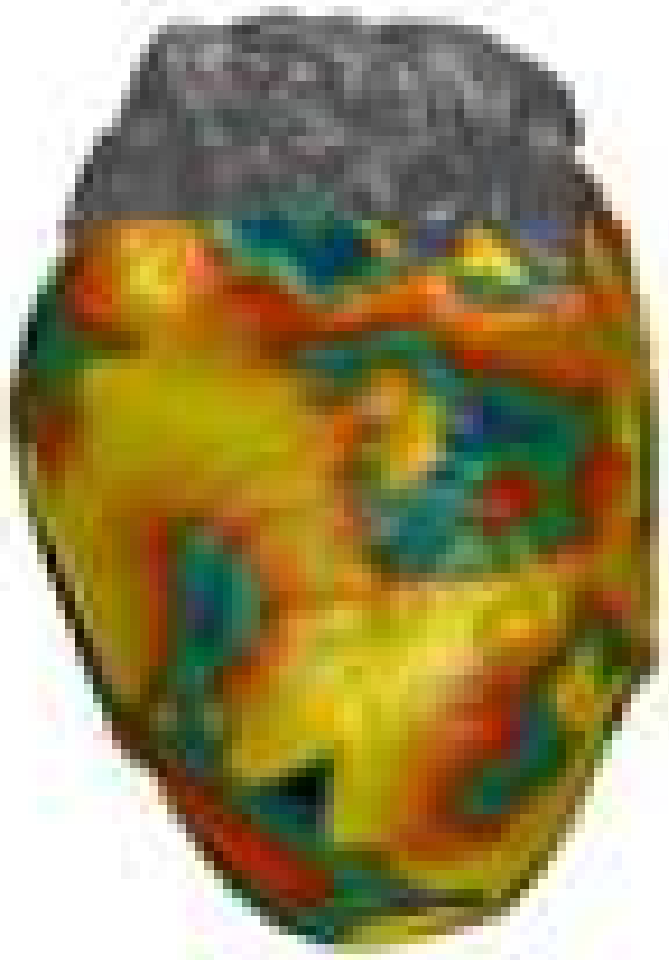


electrical excitation waves

plane waves



spiral waves



chaos

simulations: P. Bittihn

Challenges for diagnosis and therapy

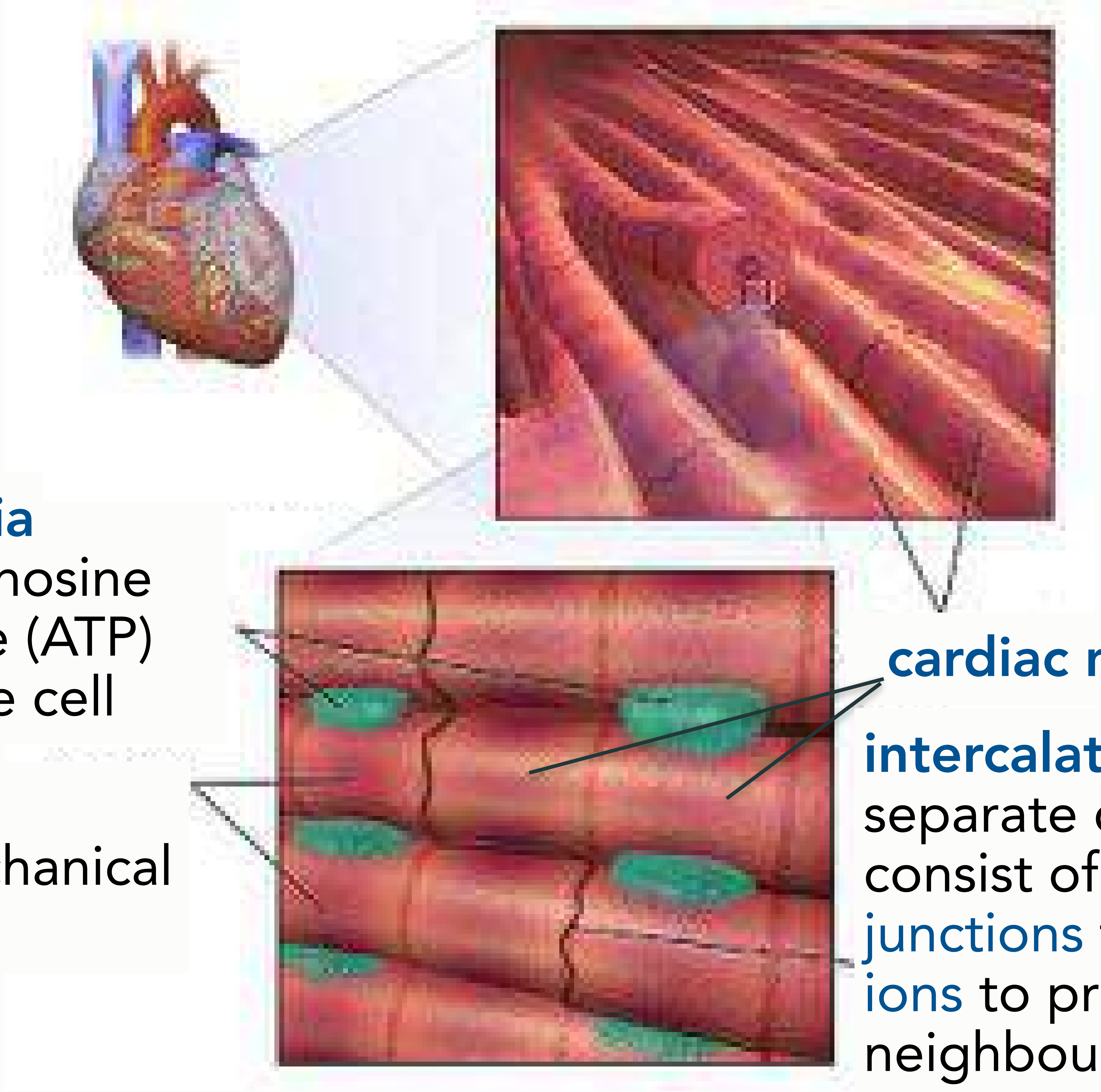
- develop tools for observing the dynamics of arrhythmias (e.g., novel measurement modalities and advanced methods for data analysis)
- understand conditions for the onset of cardiac arrhythmias and characterise their dynamical features
- devise minimal invasive methods for terminating (lethal) states of arrhythmias like ventricular fibrillation (avoiding strong shocks with high local currents)

Potential contributions from dynamical systems theory and data driven modelling?

Characterization of Cardiac Arrhythmias

The heart: A 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

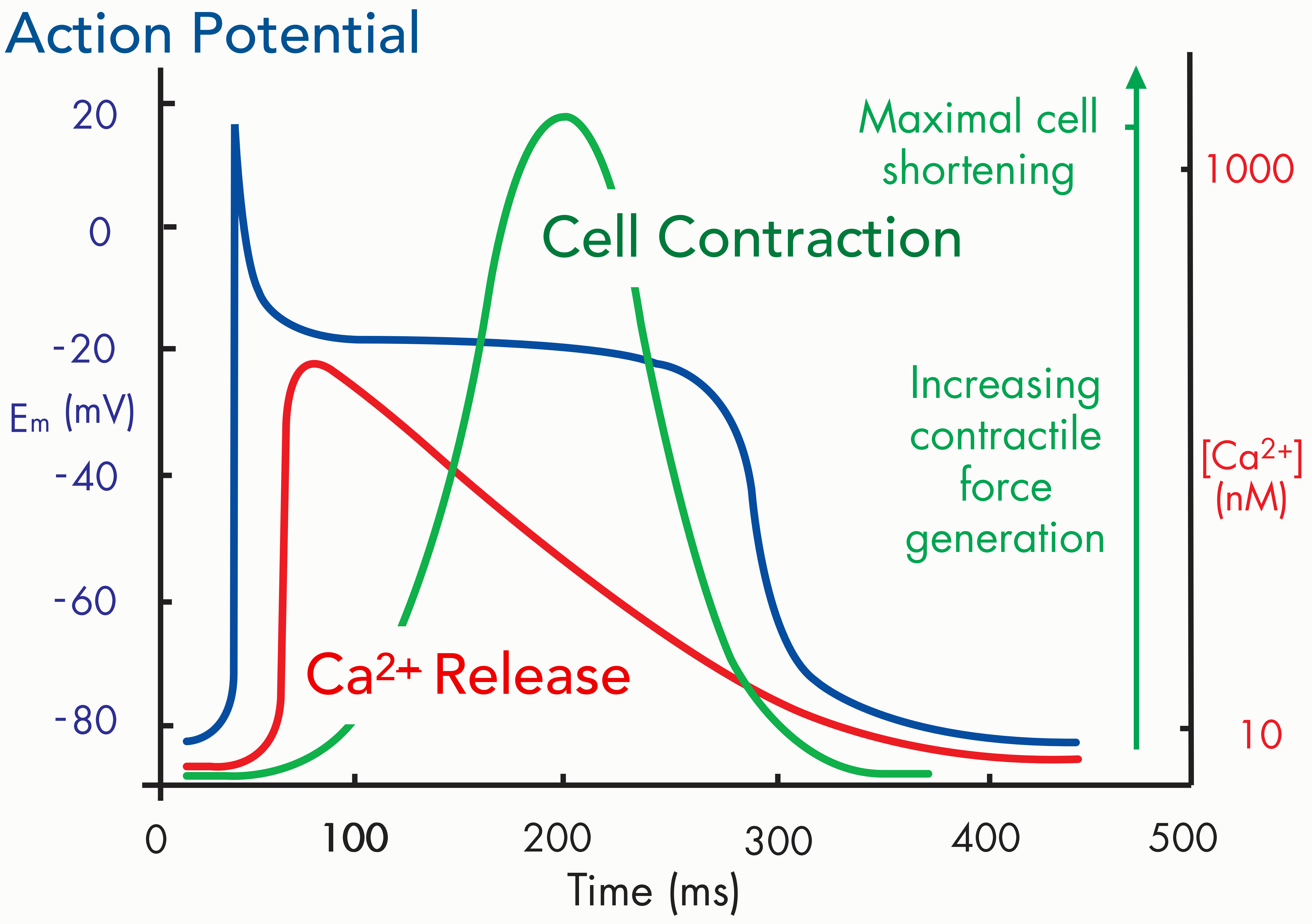
cardiac muscle cells

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

Ventricular Cell

© Kornreich & Fenton

Excitation-Contraction Coupling



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

electrical excitation

mechanical contraction

Mechanical perturbation induces electrical stimulation via stretch activated ion channels.

→ Commotio Cordis

Excitable Media

- An excitable medium
- is a spatially extended nonlinear dynamical system
- which has the capacity to propagate excitation waves,
- and which cannot support the passing of another wave until some time has passed (refractory period/phase)

→ refractory region/zone

The existence of a refractory region means that an excitation wave cannot propagate in any direction but only to the excitable region of the medium.

As a result, rotating waves, also called spiral waves may occur.

The spatiotemporal Fitzhugh-Nagumo model

$$\begin{aligned} \dot{u} &= au(u-b)(1-u) - w + d\Delta u \\ \dot{w} &= \varepsilon(u-w) \end{aligned}$$

fundamental model describing an excitable medium

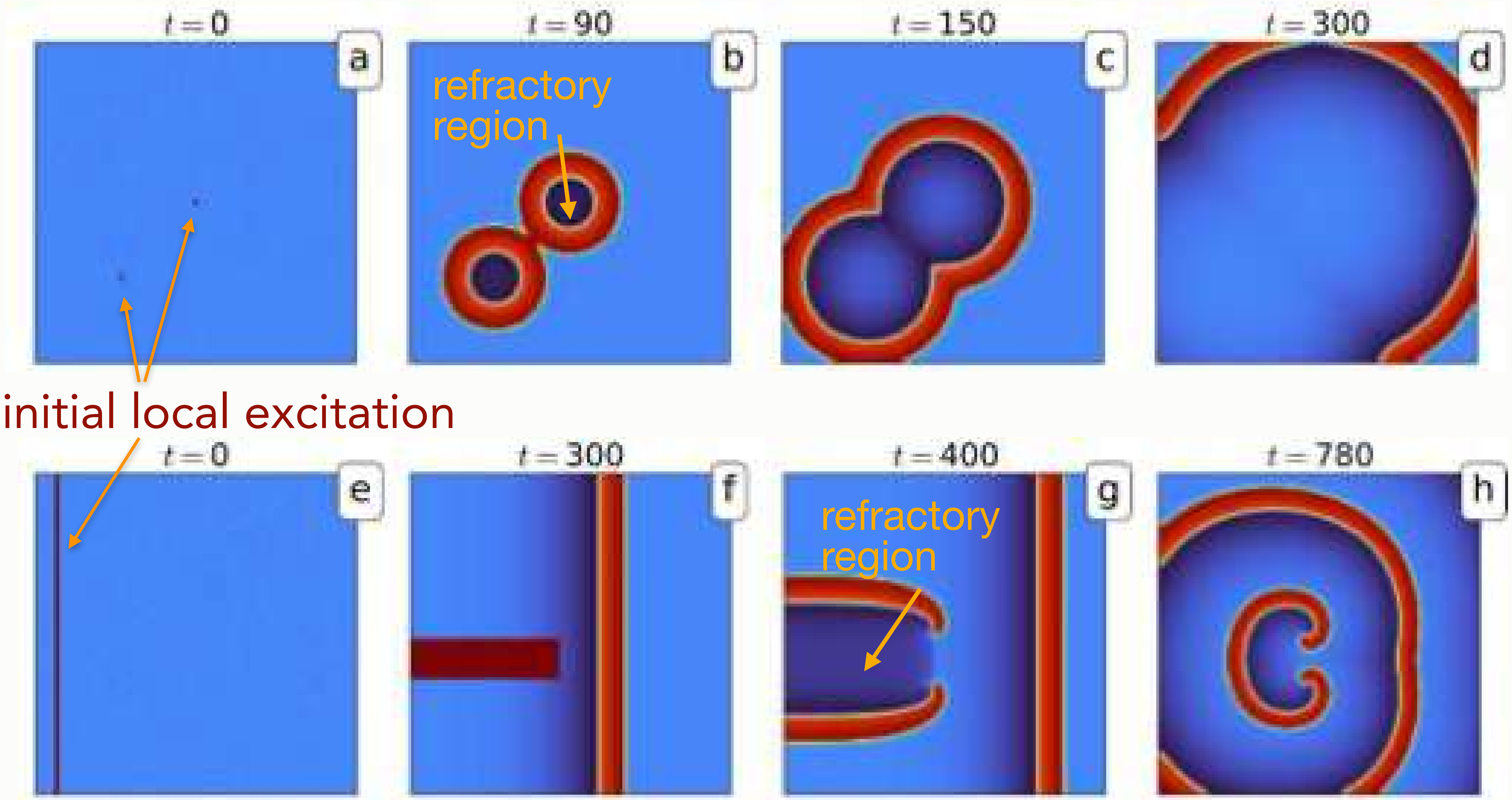
spatial coupling via diffusion term

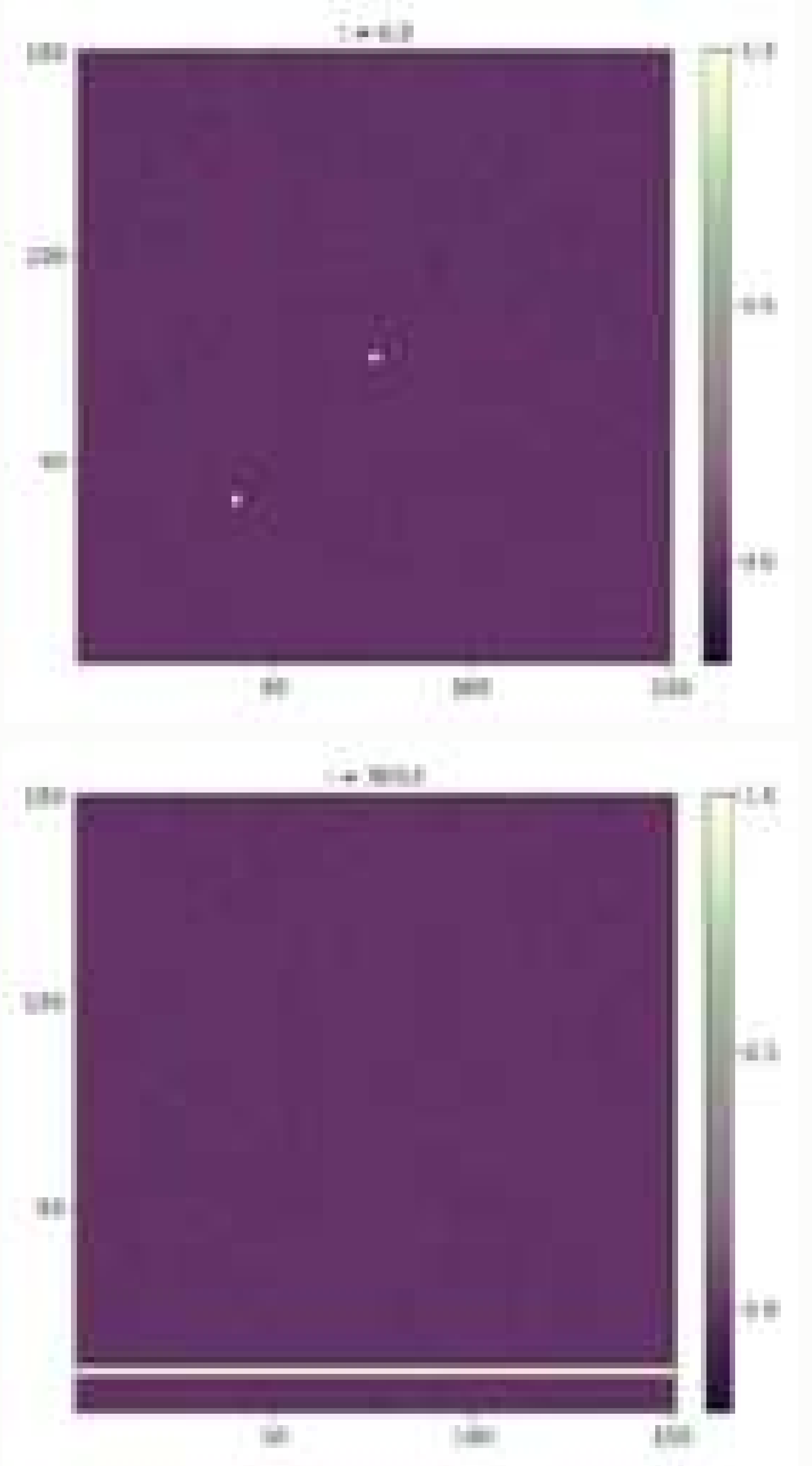
spatial domain with no-flux boundary conditions

Depending on initial conditions and specific perturbations plane waves, concentric waves or spiral waves can be generated.

Excitable Media

Fitzhugh-Nagumo model $a = 3,\ b = 0.2,\ \varepsilon = 0.01,\ d = 1$





G. Datseris and U. Parlitz, Nonlinear Dynamics, Springer 2022

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

Transient Chaos

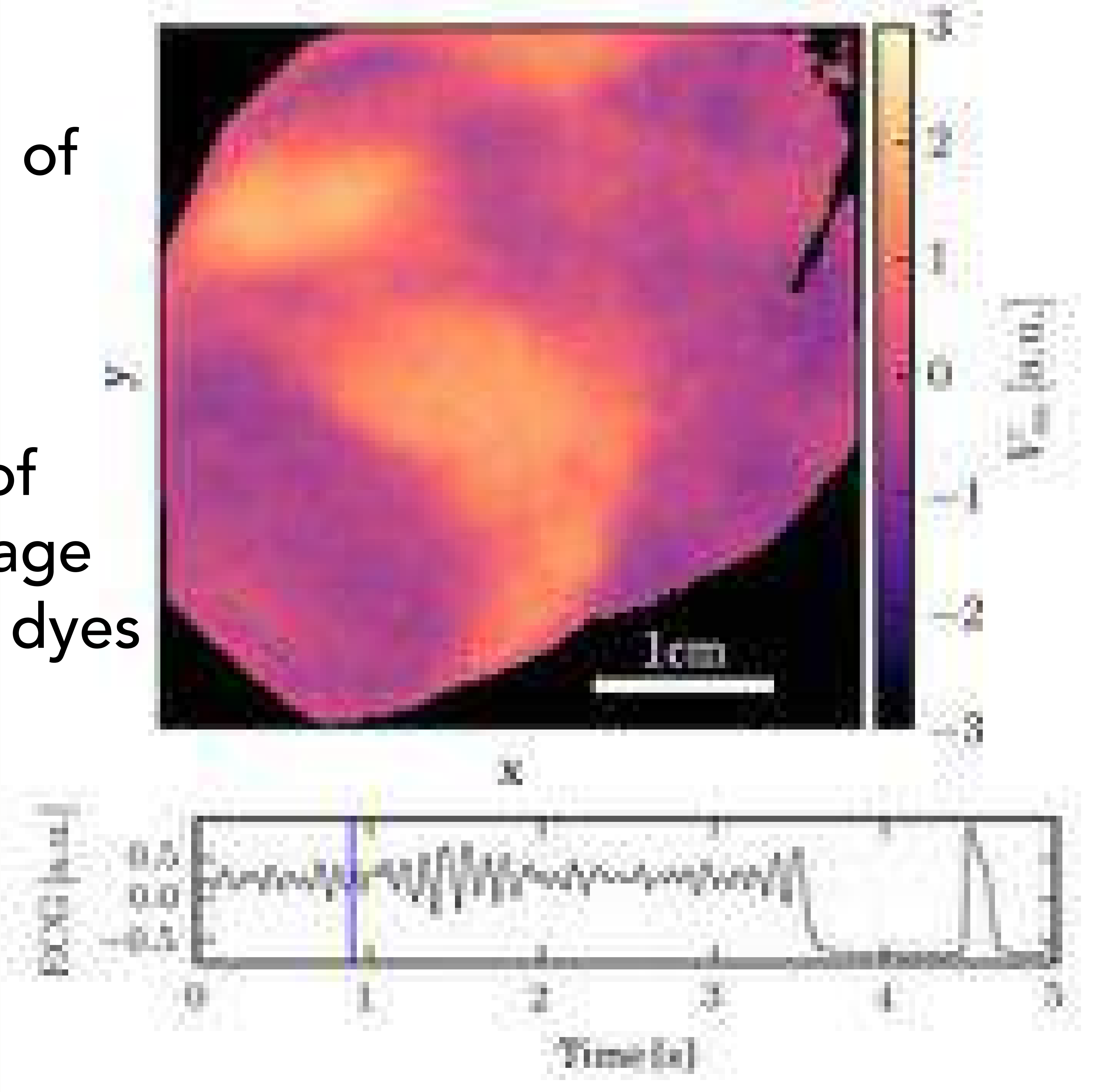
Transient Scroll Wave Dynamics during Ventricular Fibrillation

Experiment

Optical mapping of
a rabbit heart

Visualisation of
membrane voltage
using fluorescent dyes

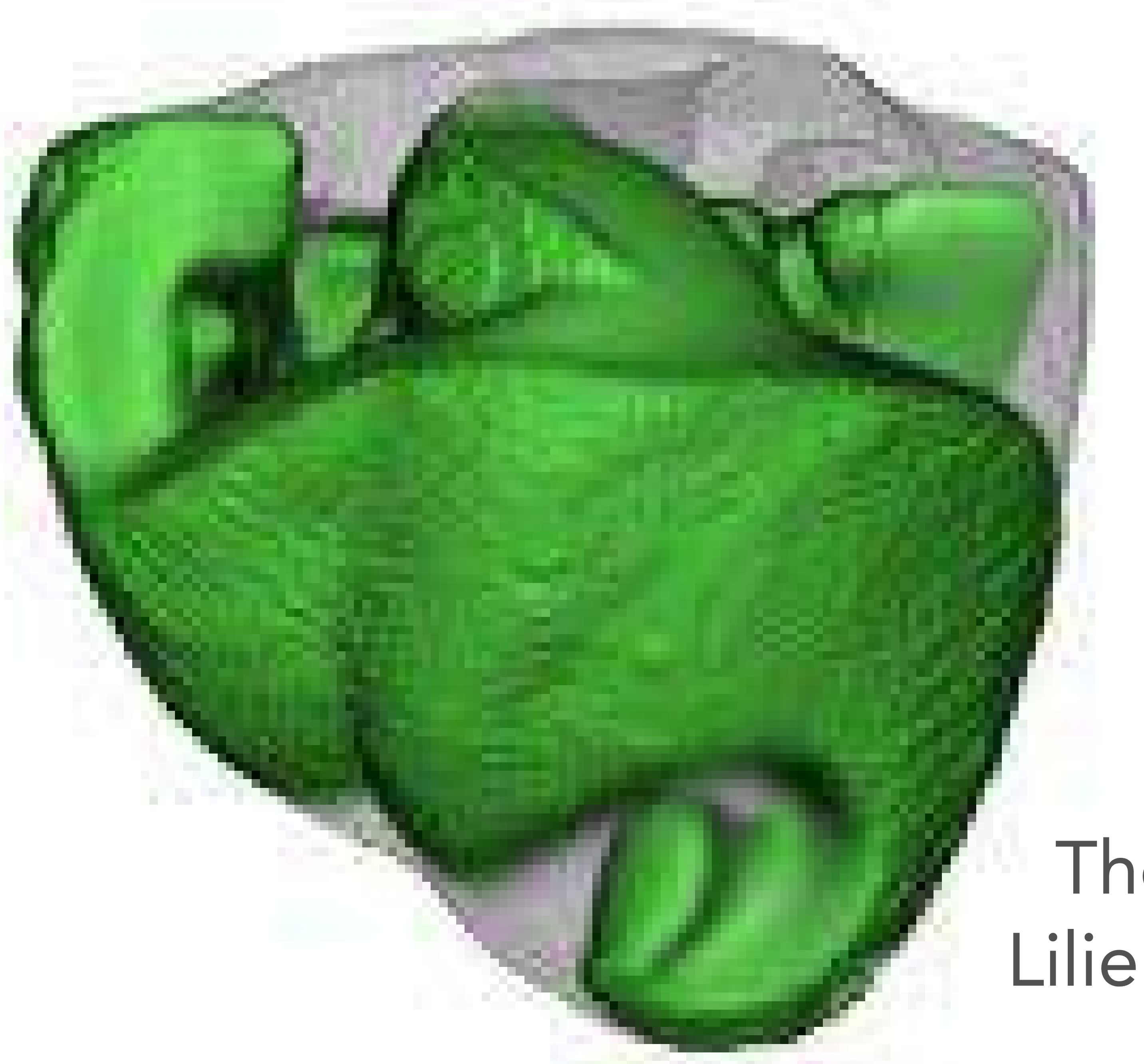
Sebastian Berg
Daniel Hornung
Marion Kunze



Transient events of fibrillation have also been observed with human patients.

Simulation

in a rabbit heart geometry



Thomas Lilienkamp

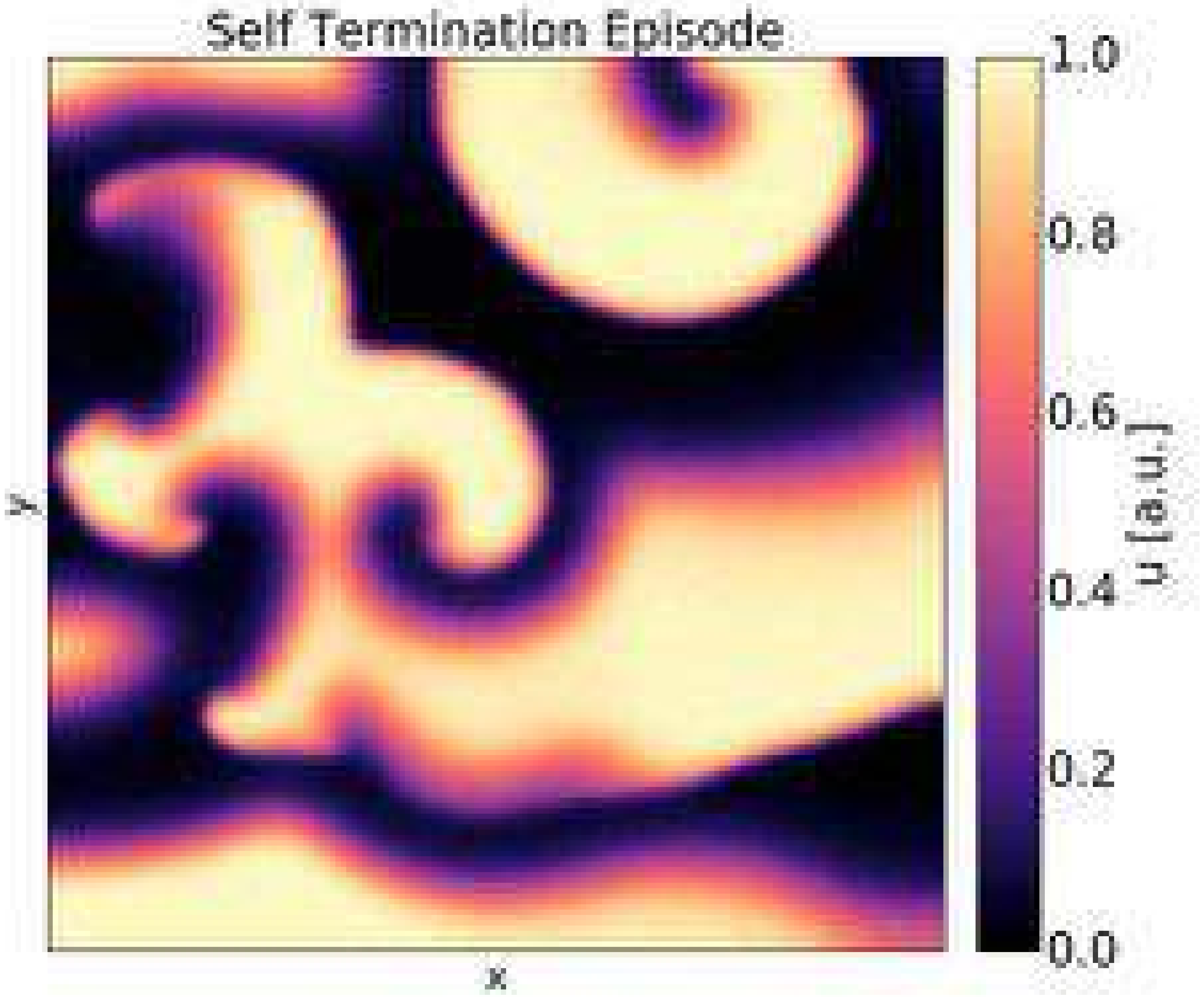
$$T_{\text{transient}} \overset{?}{<} T_{\text{survival}}$$

Transient chaos in 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 $\mathbf{h} = (v, w)$

average transient lifetime increases exponentially with system size



T. Lilienkamp et al., Phys. Rev. Lett. 119 (2017)
T. Lilienkamp and U. Parlitz, Phys. Rev. Lett. 120 (2018)

Can we predict the end of the chaotic transient?

No, not yet :-)

But during a period of time close to the end of the transient the system responds differently to external perturbations. *Prediction possible ??*

T. Lilienkamp and U. Parlitz, PRL 120 (2018); PRE 98 (2018); PRE 102 (2020)

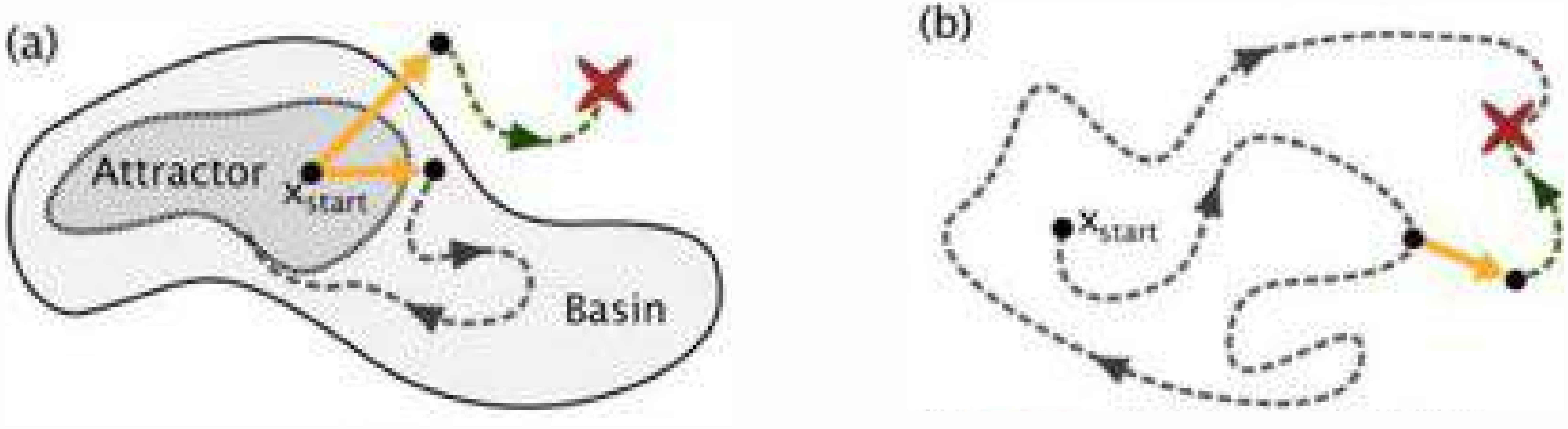
We can, however, predict the average transient lifetime from observable quantities like:

- dominant frequency
- excitable gap
- (pseudo) ECG
- shape of the action-potential- duration (APD) curve
- no. of phase singularities

M. Aron et al., J. Phys. Complex. 2, 035016 (2021)

Potential Implications of Transient Chaos for Defibrillation

Persistent chaos vs. Transient chaos



Desired State: ✖ Perturbations: → Trajectories: --▶--

control: kick state into basin of another attractor | kick state to neighbouring orbit with (much) shorter transient time

minimal perturbation strength required | can be achieved with (very) small perturbations

Terminating spiral wave chaos with few single perturbations

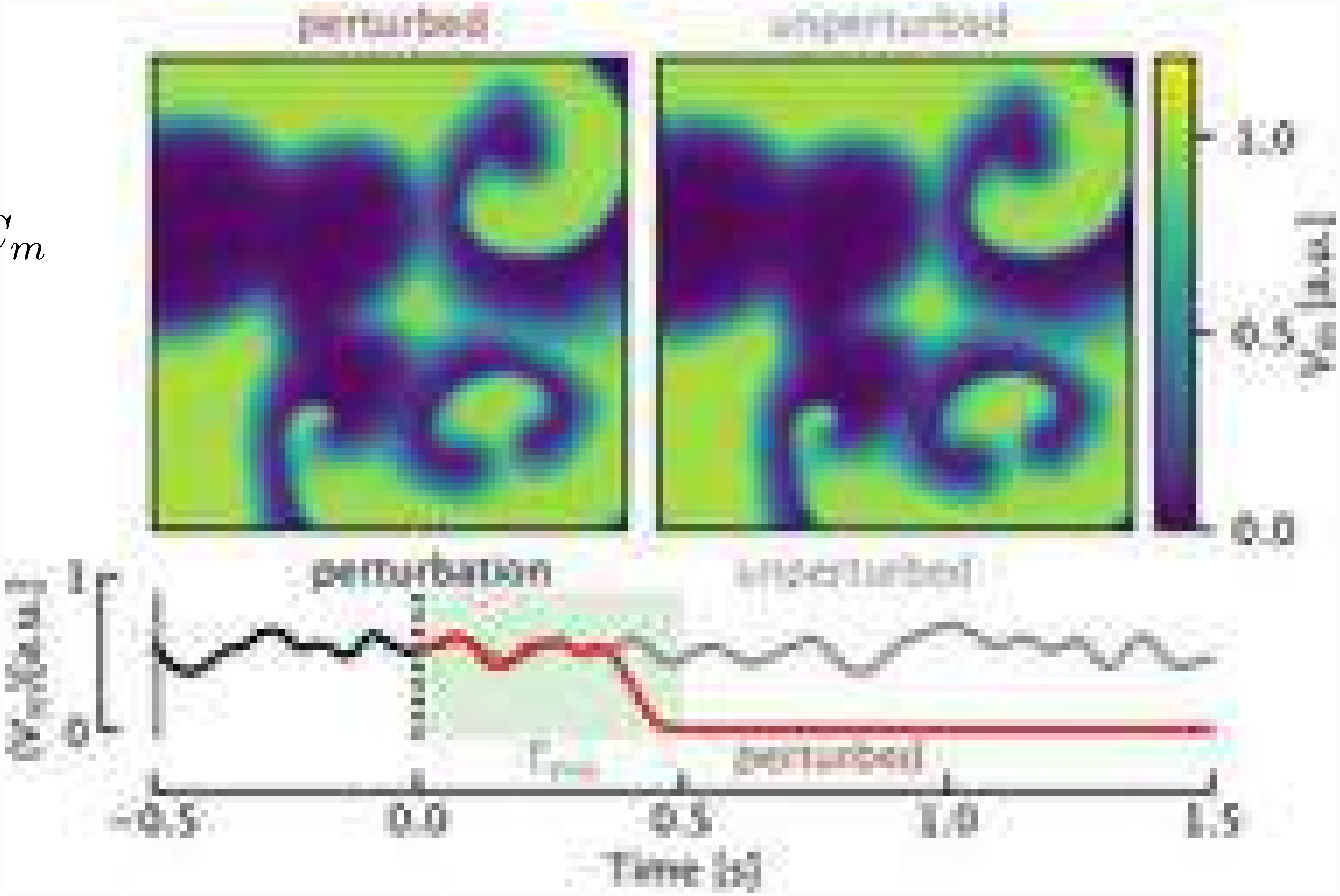
Fenton-Karma model

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

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

T_{evo}= 500 ms

T. Lilienkamp and U. Parlitz,
Chaos 30, 051108 (2020)

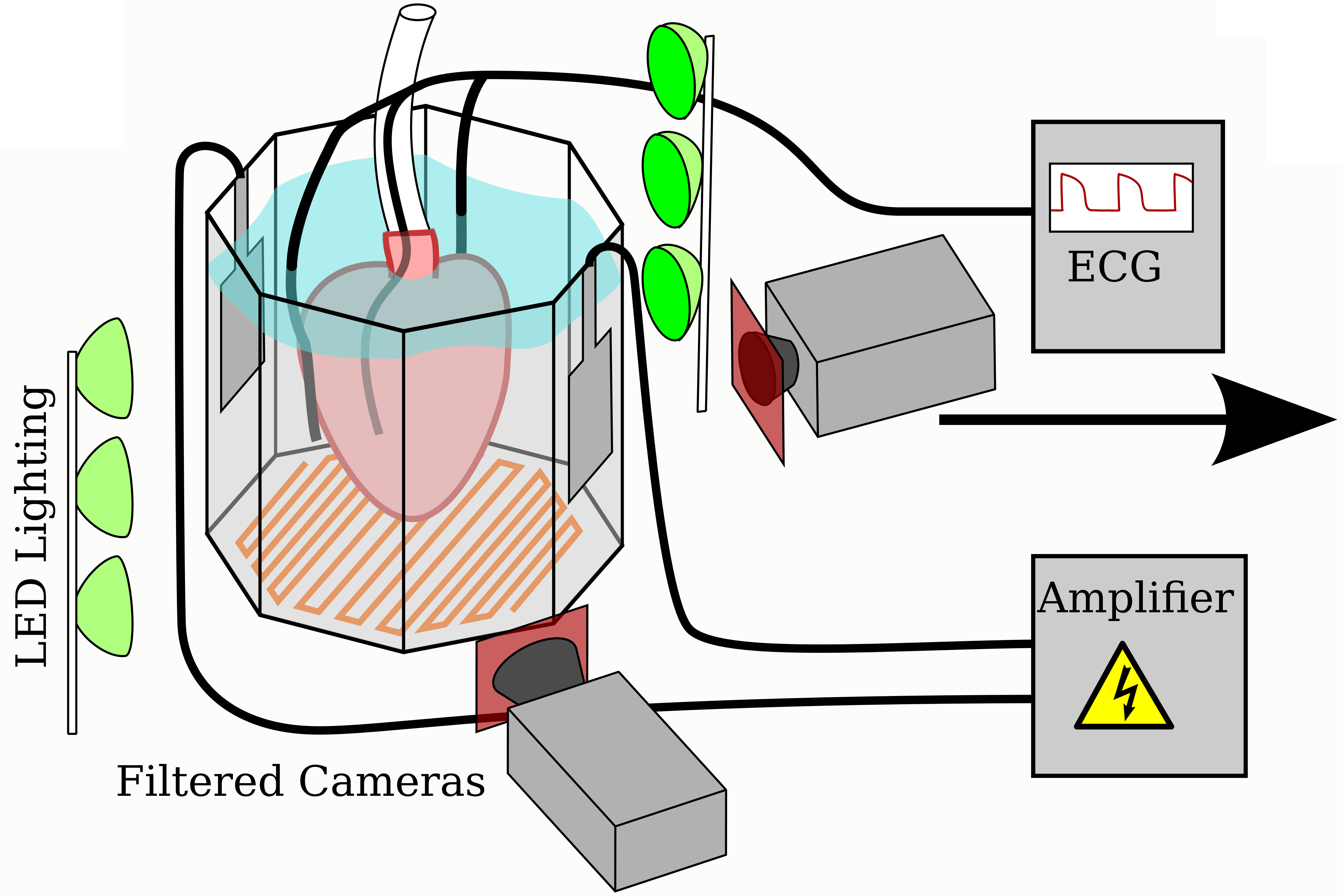


S. P. Cornelius et al., Nat. Commun. 4, 2939 (2013)

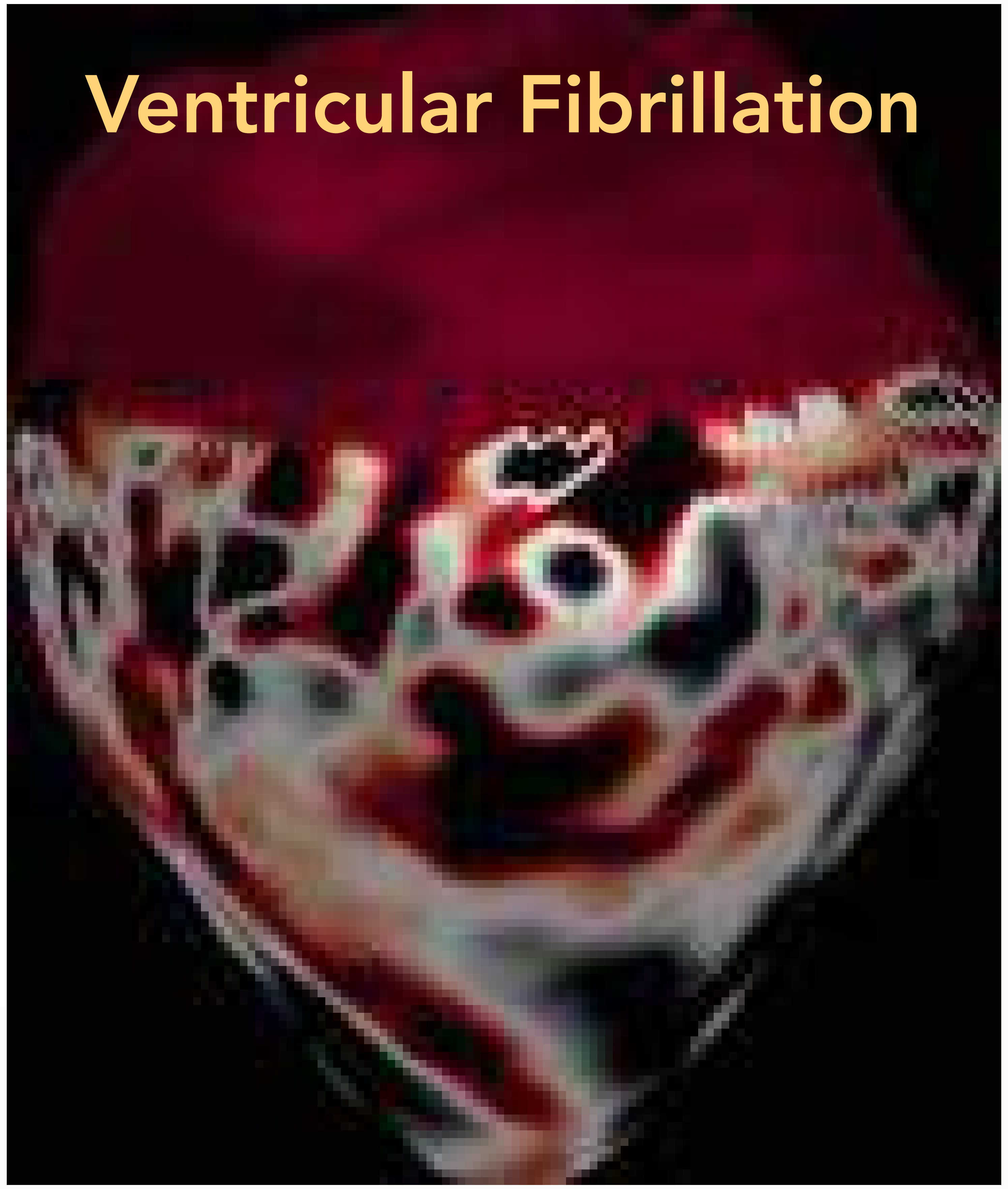
Measurering Cardiac Dynamics

Optical mapping in Langendorff perfusion system

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

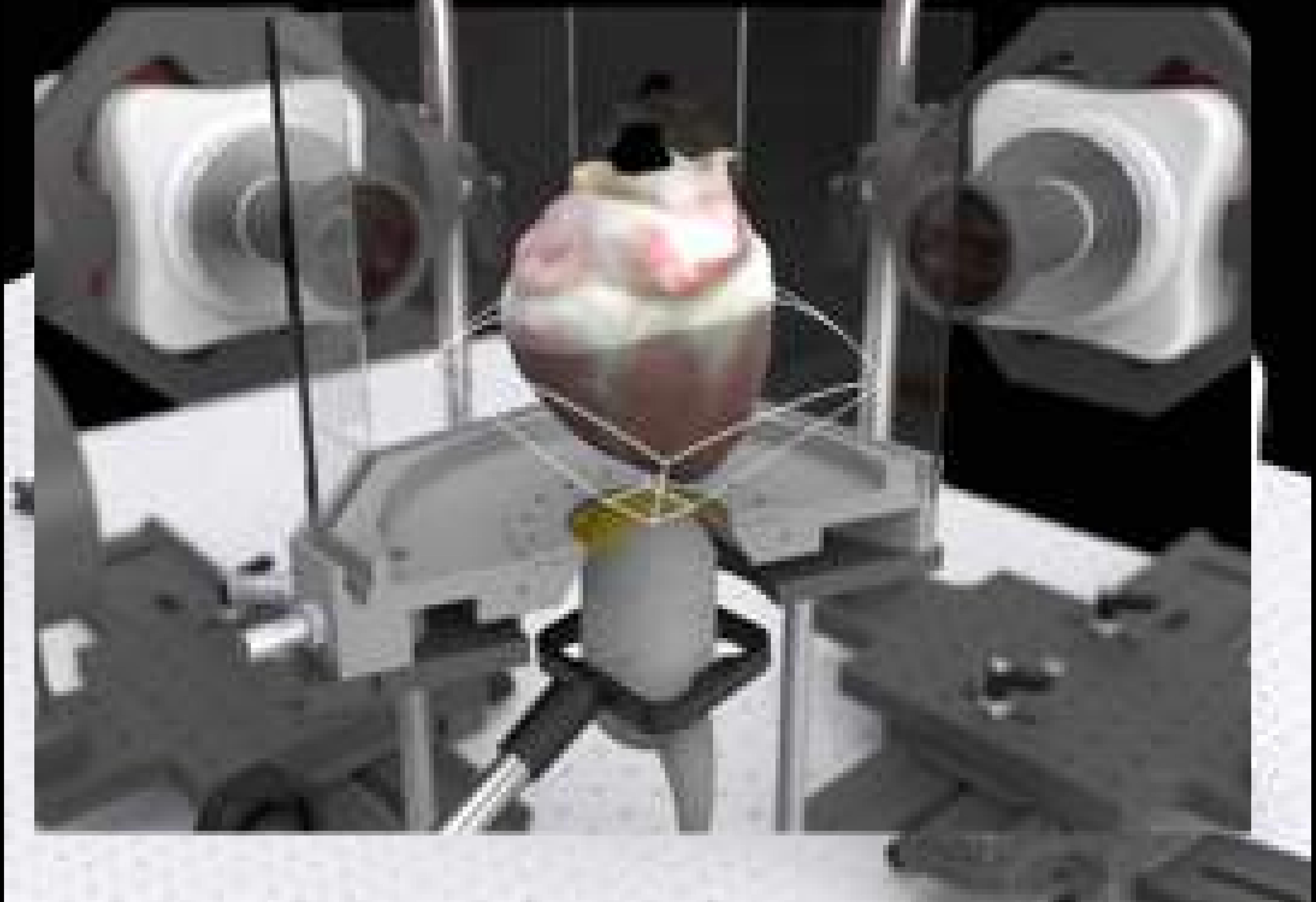


J. Schröder-Schetelig



pig heart

Simultaneous Optical Mapping and 4D Ultrasound



Visualizing mechanical scroll waves within the heart muscle using highspeed ultrasound

Mechanical Filament

Acuson SC2000 (Siemens Inc.), Transducer 4Z1c, 2.8 MHz, 134 vps, 0.5 mm

1 cm

tensile

Strain Rate

contractile

π

Phase

-π

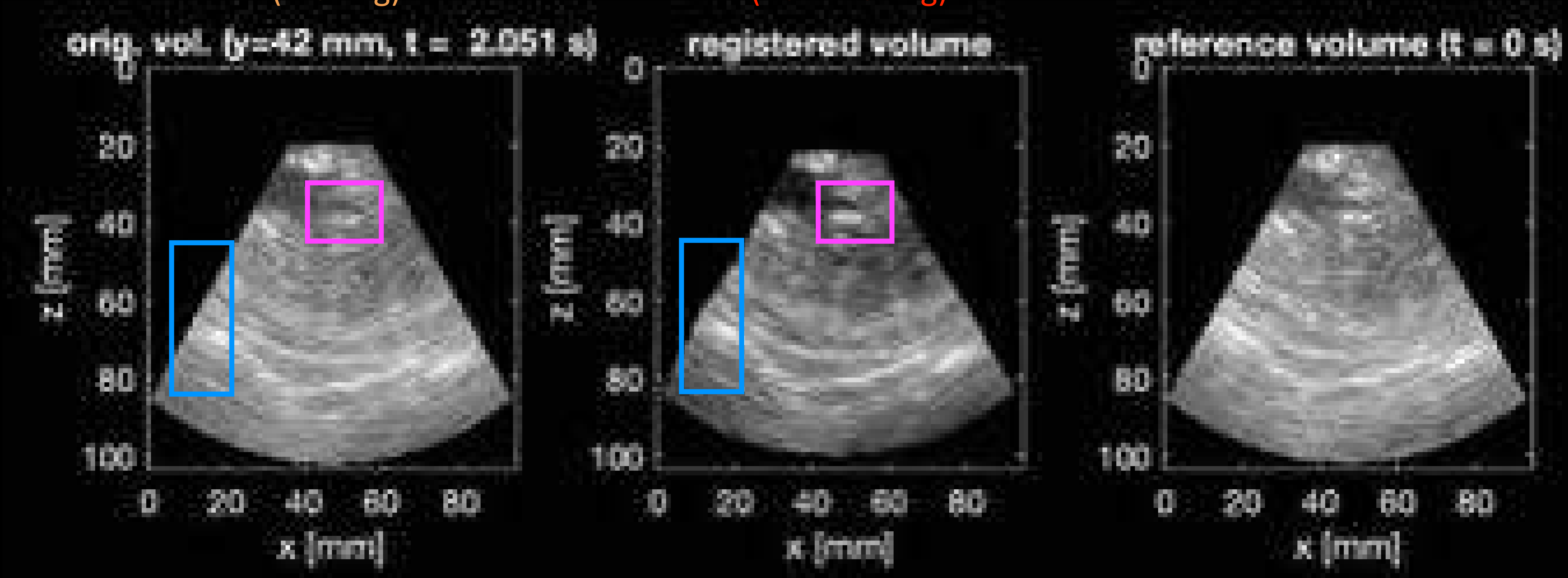
J. Christoph et al. *Nature* (2018)

Ultrasound imaging of a human heart during by-pass surgery

Motion analysis estimates a **3D displacement vector field** that describes the motion of the tissue

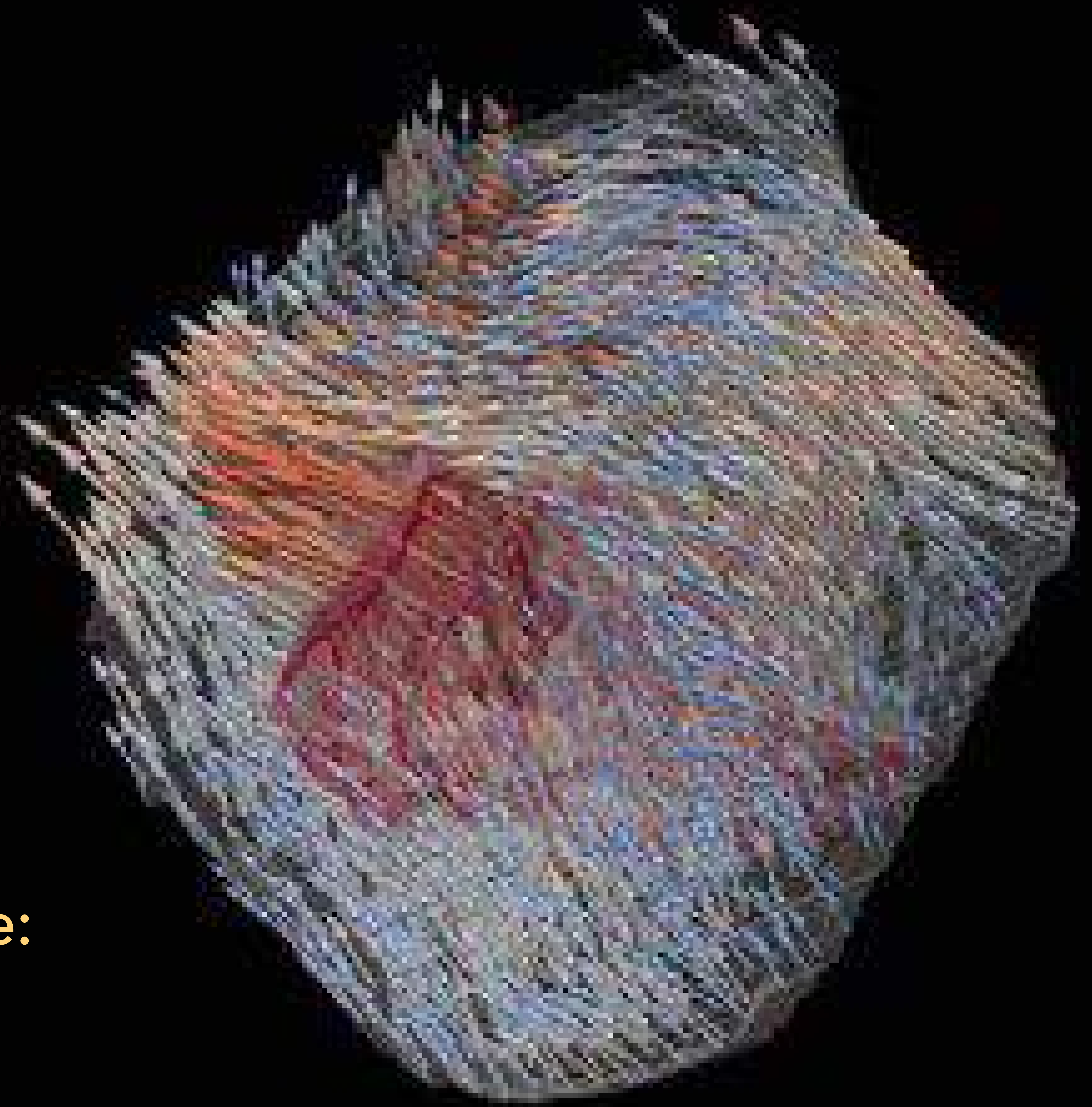
Observed volume
(moving)

Registered volume
(non-moving)



Motion tracking in high-resolution 4D ultrasound resolves mechanical motion during ventricular fibrillation

ultrasound device



First observation of mechanical scroll waves within the heart muscle:
J. Christoph et al. Nature 555 (2018)

Data driven modelling in cardiac research

- prediction of future evolution (e.g., membrane voltages, mechanical motion)
- extraction of relevant features from (noisy) raw data → classification
- cross estimation of observables that are difficult to measure directly (e.g. electrical activity inside the heart muscle)

Methods for spatio-temporal timeseries:

- nearest neighbours prediction using reconstructed local states
  J. Isensee et al., J. of Nonlin. Sci. 30, 713–735 (2020)
- echo state networks (reservoir computing)
  R.S. Zimmermann and U. Parlitz, Chaos 28, 043118 (2018); S. Herzog et al., Frontiers in Appl. Math. and Statistics 6, 616584 (2021)
- convolutional neural networks
  S. Herzog et al., Front. in Appl. Math. and Stat. 4, 60 (2018); Chaos 29, 123116 (2019); R. Stenger et al., (under review)

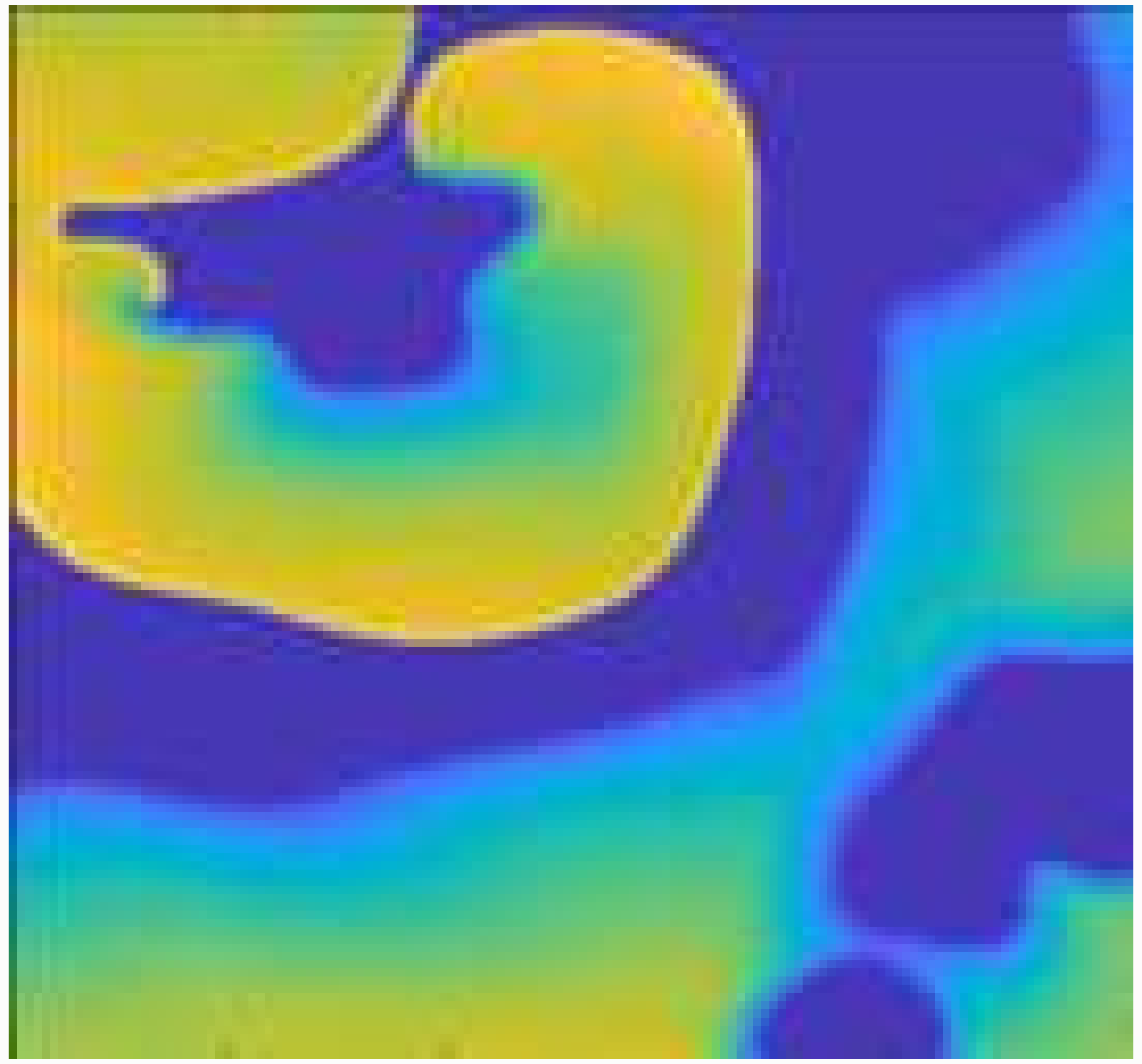
Prediction of future evolution of membrane voltage

Data Driven Modeling of Spatio-Temporal Systems

Model to generate training and test data: The Bueno-Orovio-Cherry-Fenton model

A. Bueno-Orovio et al., J. Theor. Biol. 253 (2008)

PDEs describing electrical excitation waves in cardiac tissue



u membrane potential
to be predicted

$$\boxed{\frac{\partial u}{\partial t} = D \cdot \nabla^2 u - (J_{si} + J_{fi} + J_{so})}$$

$$\frac{\partial v}{\partial t} = \frac{1}{\tau_v^-}(1 - H(u-\theta_v))(v_\infty - v) - \frac{1}{\tau_v^+} H(u-\theta_v) v$$

$$\frac{\partial w}{\partial t} = \frac{1}{\tau_w^-}(1 - H(u-\theta_w))(w_\infty - w) - \frac{1}{\tau_w^+} H(u-\theta_w) w$$

$$\frac{\partial s}{\partial t} = \frac{1}{2\tau_s}((1 + \tanh(k_s(u-u_s))) - 2s)$$

with ionic currents:

$$J_{si} = -\frac{1}{\tau_{si}} H(u-\theta_w) ws$$

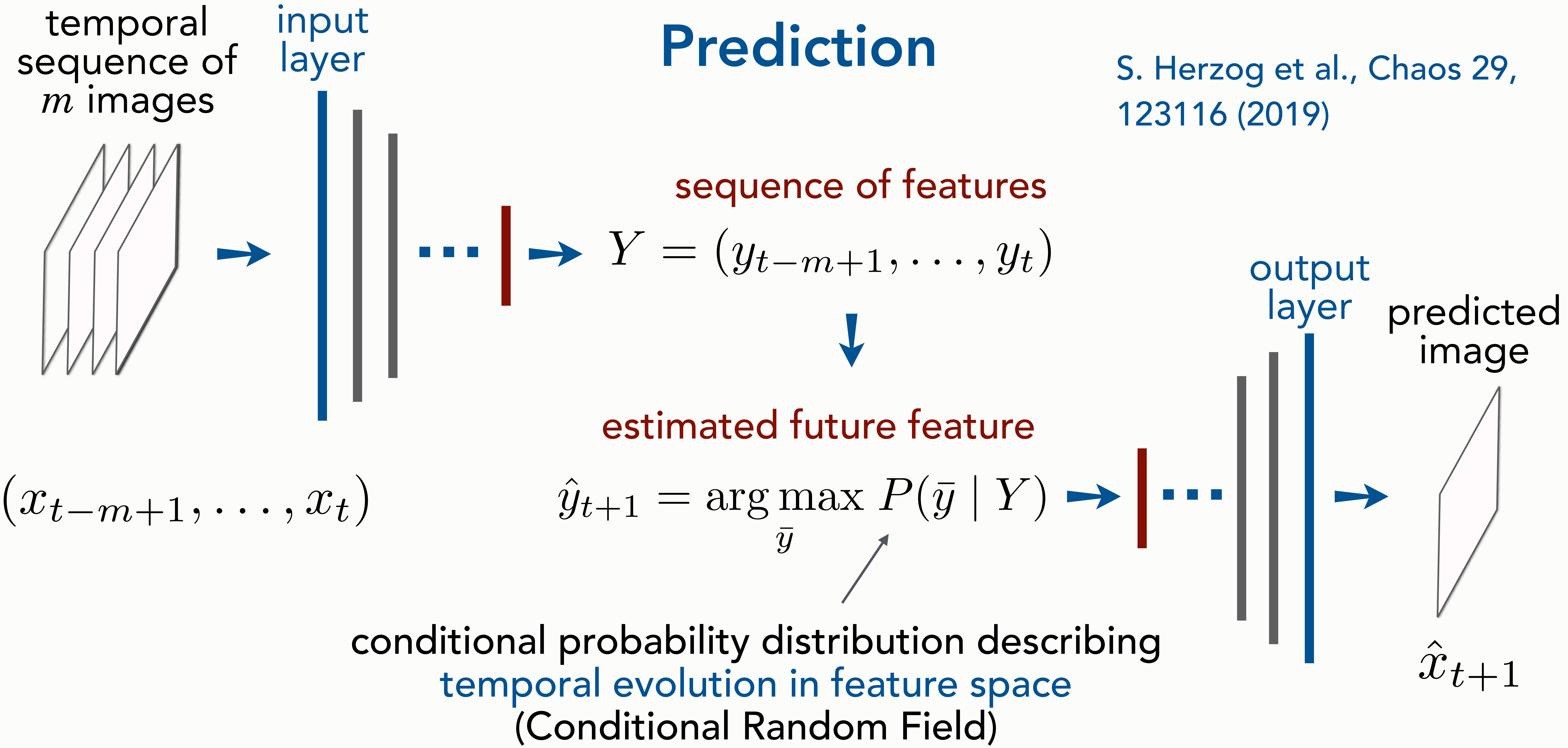
$$J_{fi} = -\frac{1}{\tau_{fi}} vH(u-\theta_v)(u-\theta_v)(u_u - u)$$

$$J_{so} = \frac{1}{\tau_o}(u-u_o)(1 - H(u-\theta_w)) + \frac{1}{\tau_{so}} H(u-\theta_w)$$

Convolutional Auto-Encoder

Prediction

S. Herzog et al., Chaos 29, 123116 (2019)



Iterated Forecasting of $u(t)$

true forecast difference

good for 5 spiral rotations

S. Herzog et al., Frontiers in Appl. Math. and Statistics 4, 60 (2018)

Prediction of Kuramoto-Sivashinsky Dynamics

$$\frac{\partial u}{\partial t} + \frac{\partial^2 u}{\partial x^2} + \frac{\partial^4 u}{\partial x^4} + \left|\frac{\partial u}{\partial x}\right|^2 = \mu \cos\left(\frac{2\pi x}{\lambda}\right)$$

$$\mu = 0.01$$

largest Lyapunov exponent

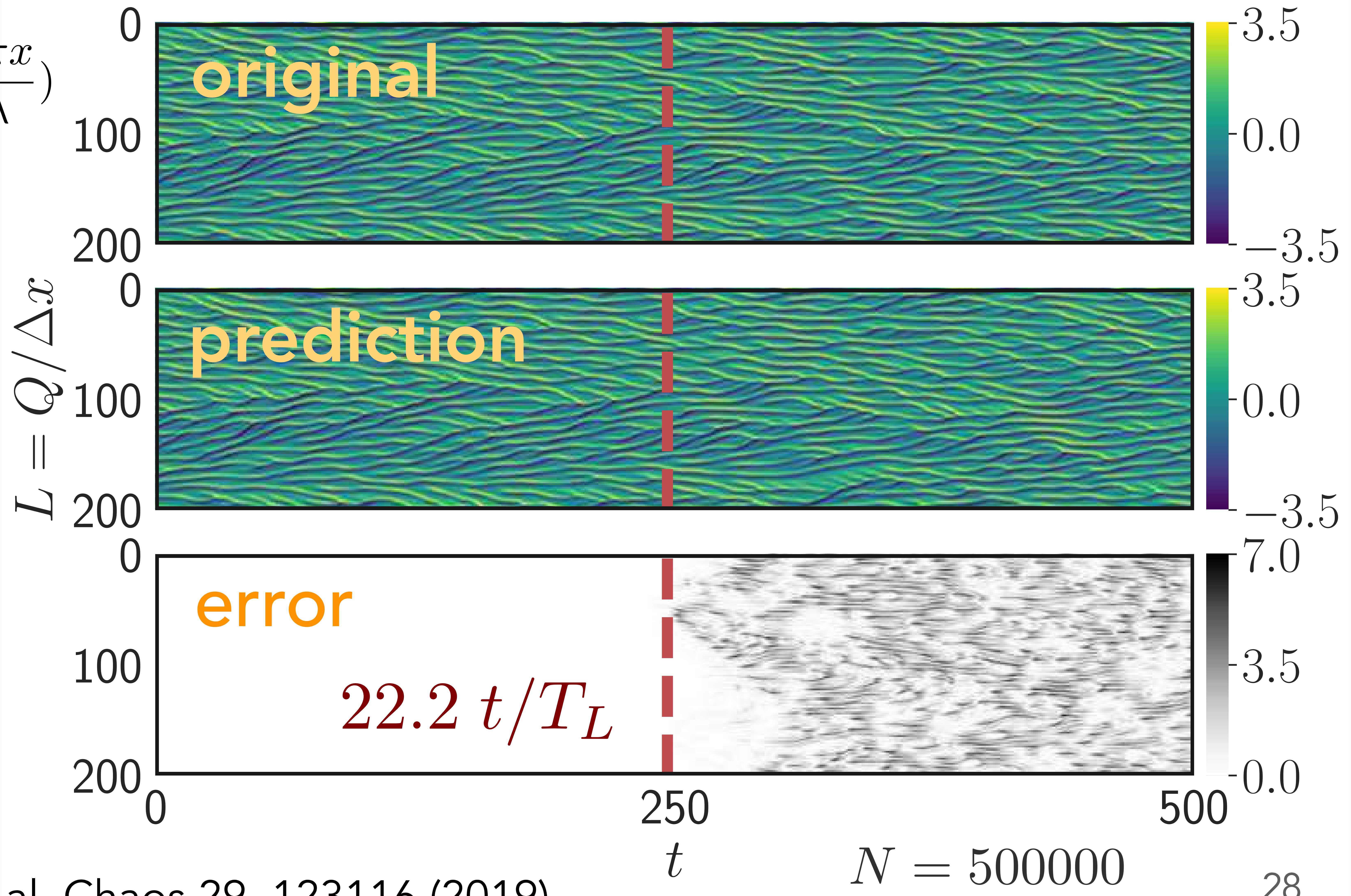
$$\Lambda_{max} = 0.09$$

Lyapunov time

$$T_L = \frac{1}{\Lambda_{max}} = 11.1$$

J. Pathak et al.,
Phys. Rev. Lett. 120 (2018)

$L = 120 : \approx 4\Lambda t$



S. Herzog et al. Chaos 29, 123116 (2019)

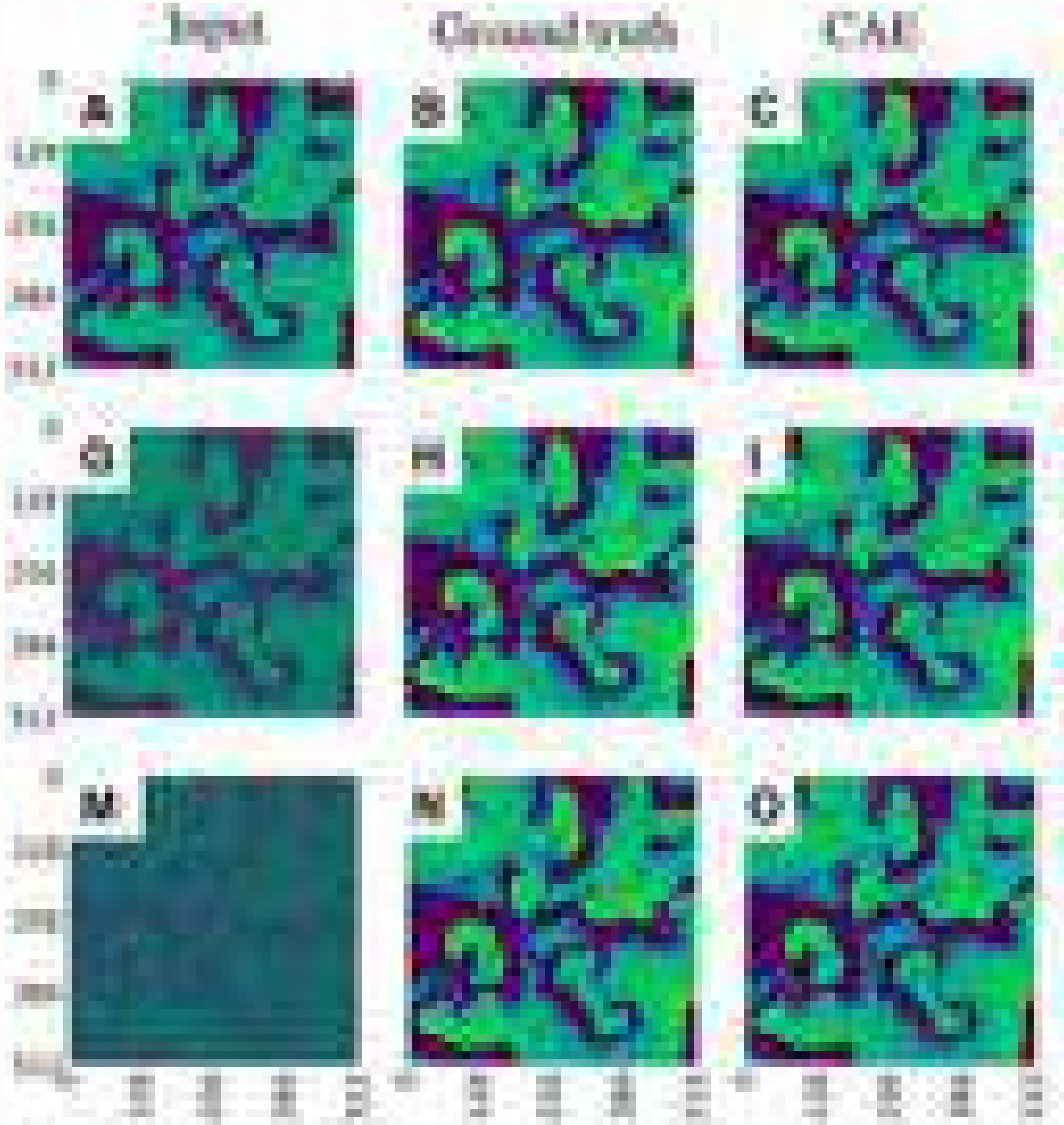
Cross estimation tasks:

- recovering complex wave patterns from impaired observations (e.g. noise)
- cross-predicting electrical excitation from mechanical contraction
- predicting electrical excitation waves ***inside*** the heart muscle from observations on the ***surface***

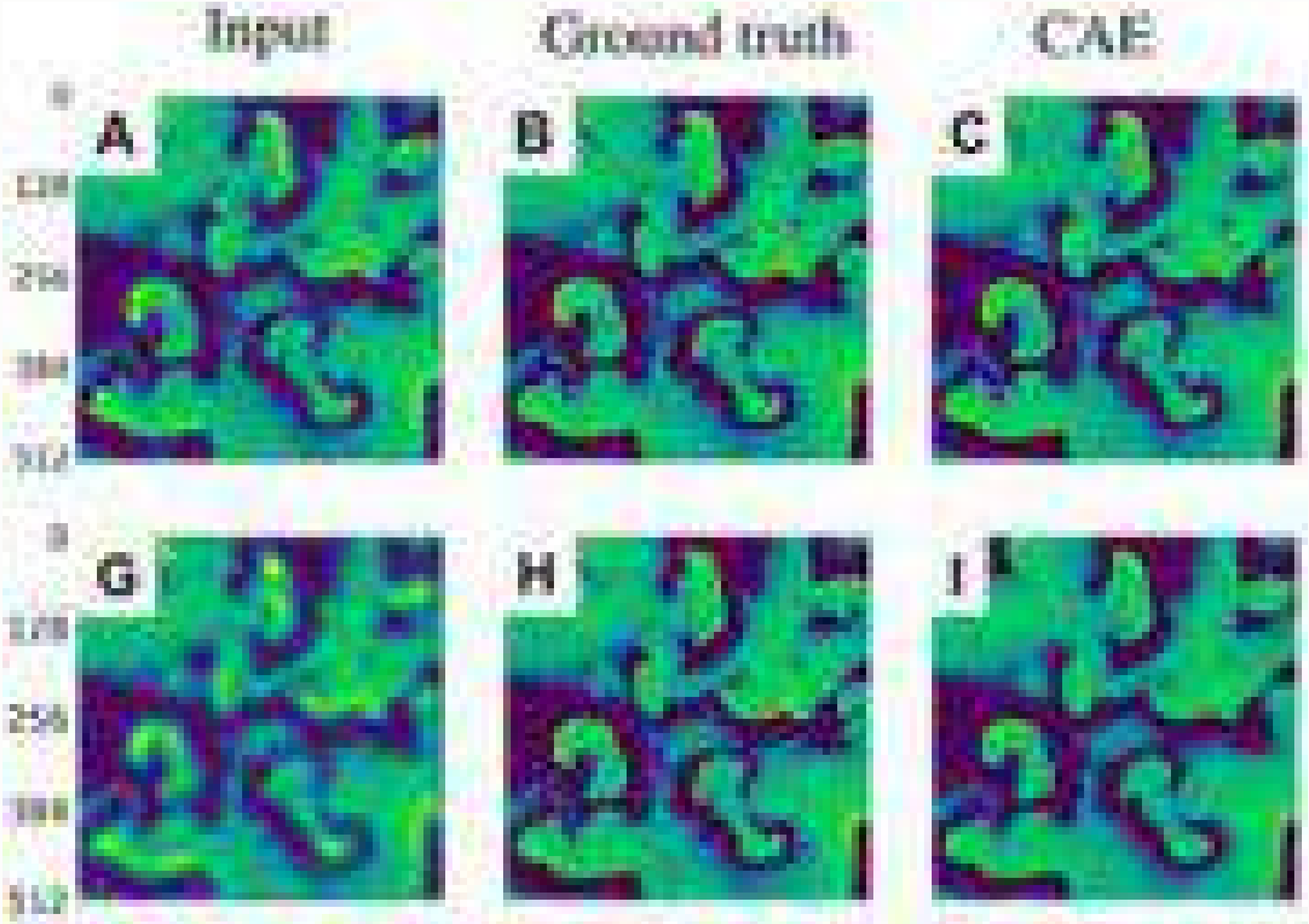
Recovering Complex Wave Patterns From Impaired Observations

Reconstruct original data from noisy, blurred or undersampled data.

noisy:



blurred:



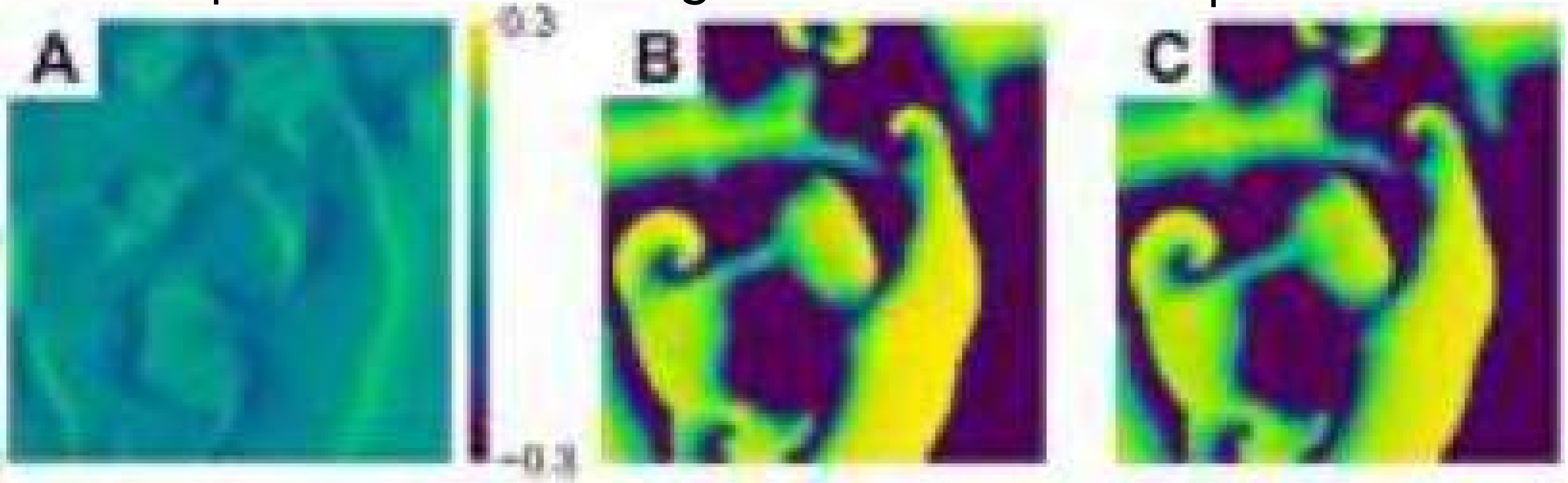
CAE = convolutional autoencoder

S. Herzog et al., Frontiers in Appl. Math. and Statistics 6, 616584 (2021)

Electrical excitation from mechanical deformation

mechanical deformation → **electrical excitation**

input ground truth prediction



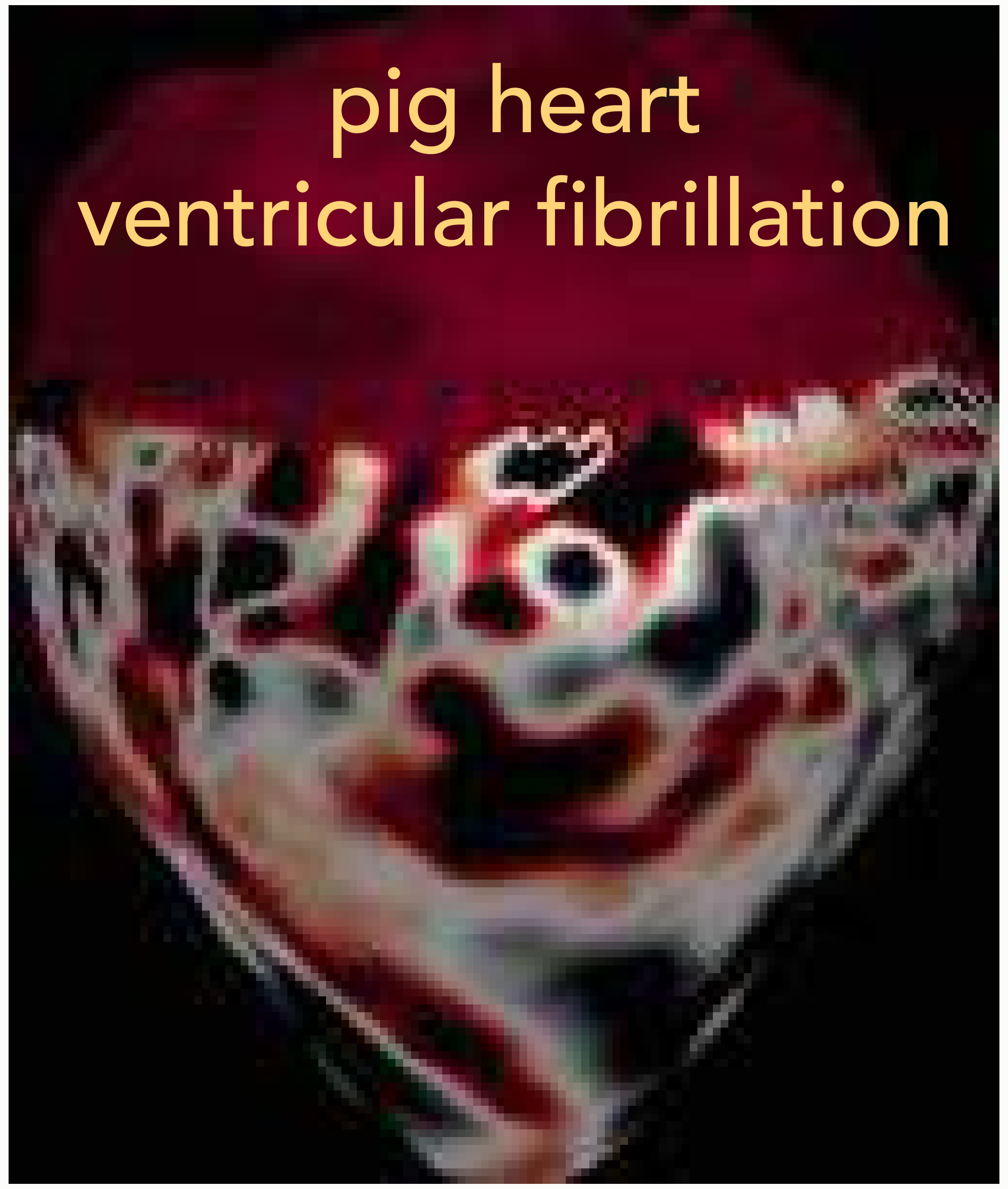
Data generated by a conceptual electro-mechanical model (BOCF model driving a mass-spring system)
Convolutional Auto-encoder; Reservoir Computing

S. Herzog et al., Frontiers Appl. Math. Stat. 6 (2021) ; J. Christoph and J. Lebert, Chaos 30 (2020)

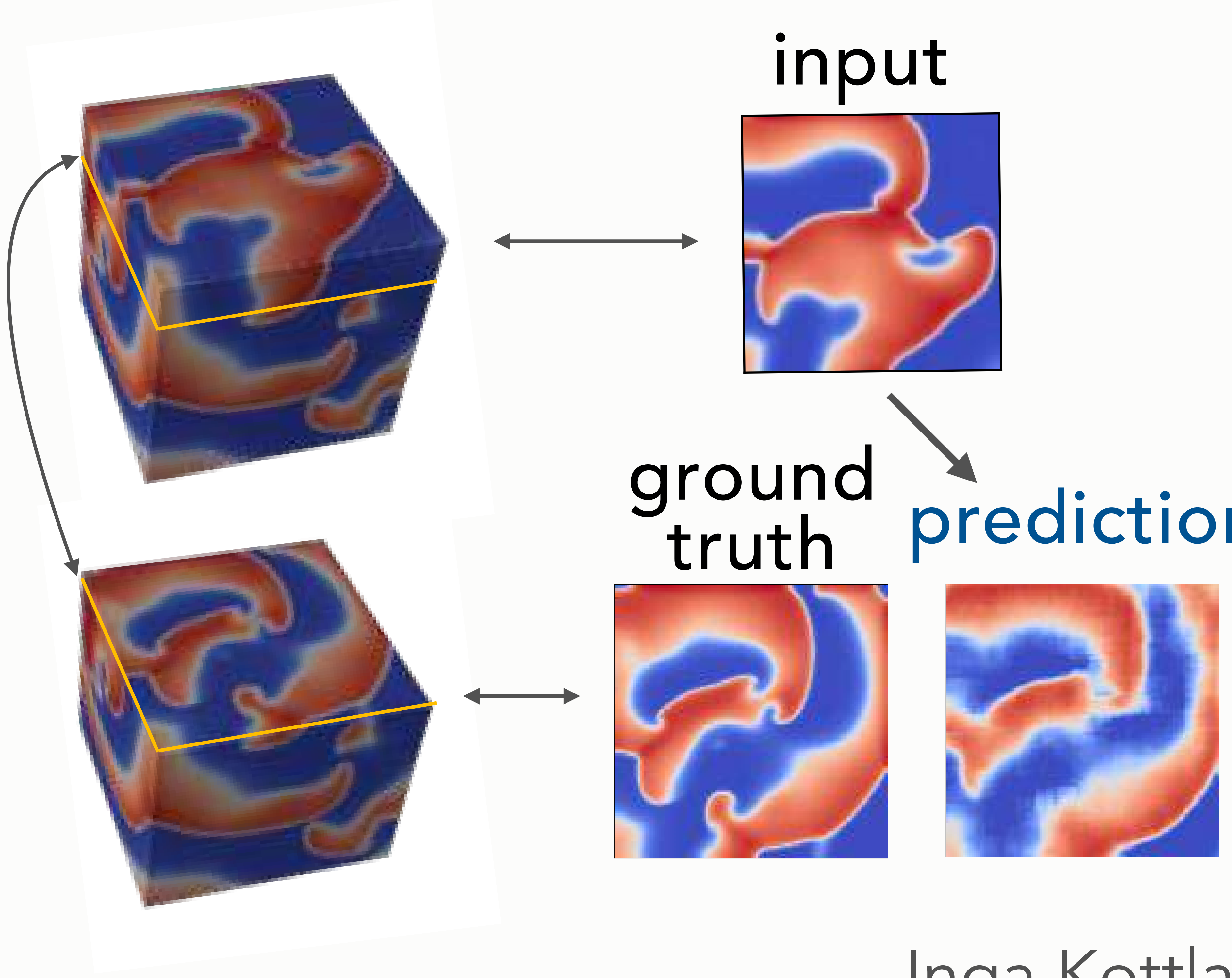
From the surface into the depth

optical mapping using voltage sensitive dyes provides electrical excitation waves only on the surface of the heart

predict activity in deeper layers using Convolutional Neural Network



simulation of a 3D excitable medium



Inga Kottlarz

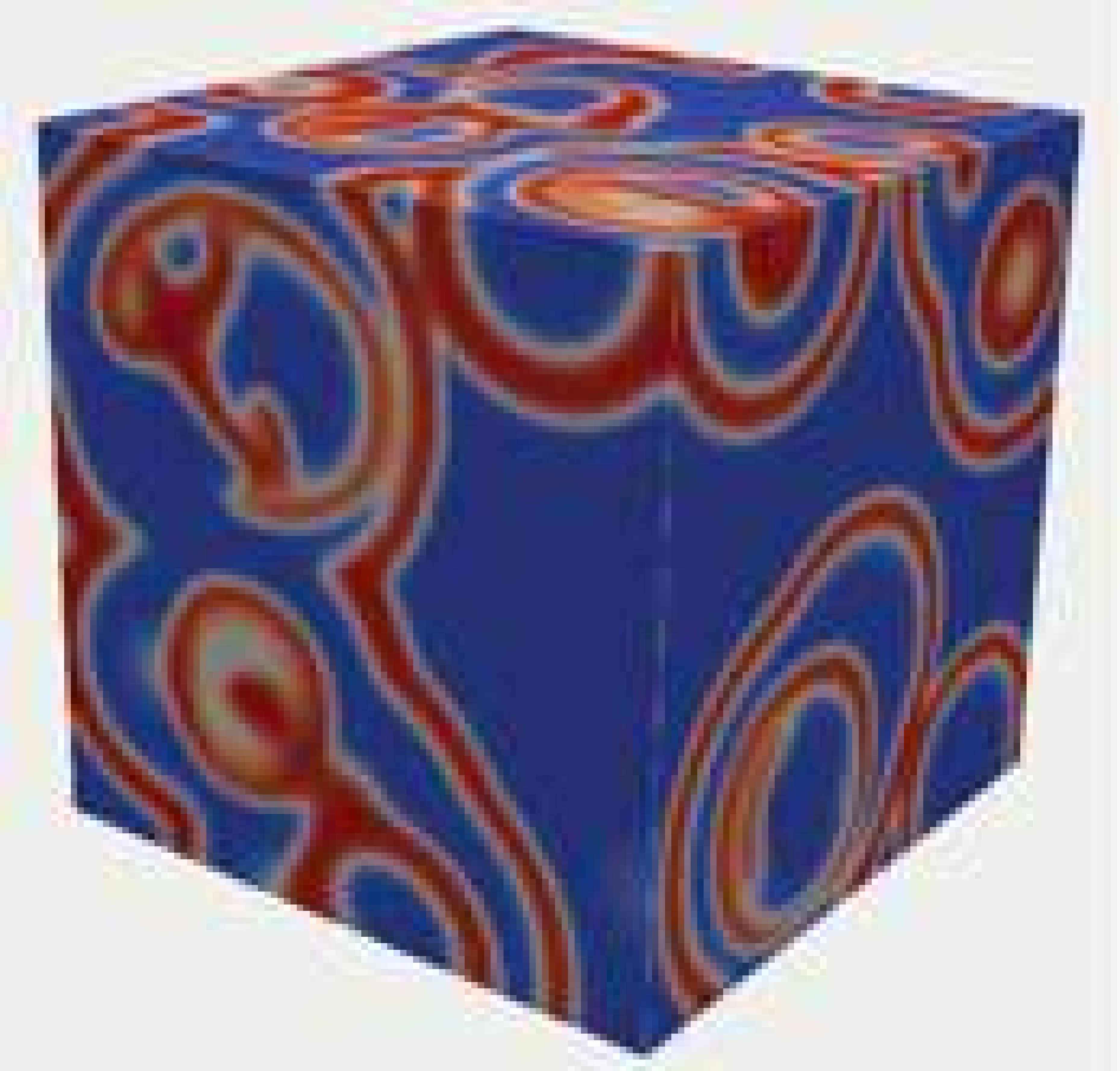
From Surface To Depth

3D Barkley model

$$\frac{du}{dt} = D\nabla^2 u + \frac{1}{\varepsilon} u(1-u)\left(u - \frac{v+b}{a}\right)$$
$$\frac{dv}{dt} = u^3 - v$$

$a = 0.75$ $\quad b = 0.06$ $\quad \varepsilon = 0.08$ $\quad D = 0.02$

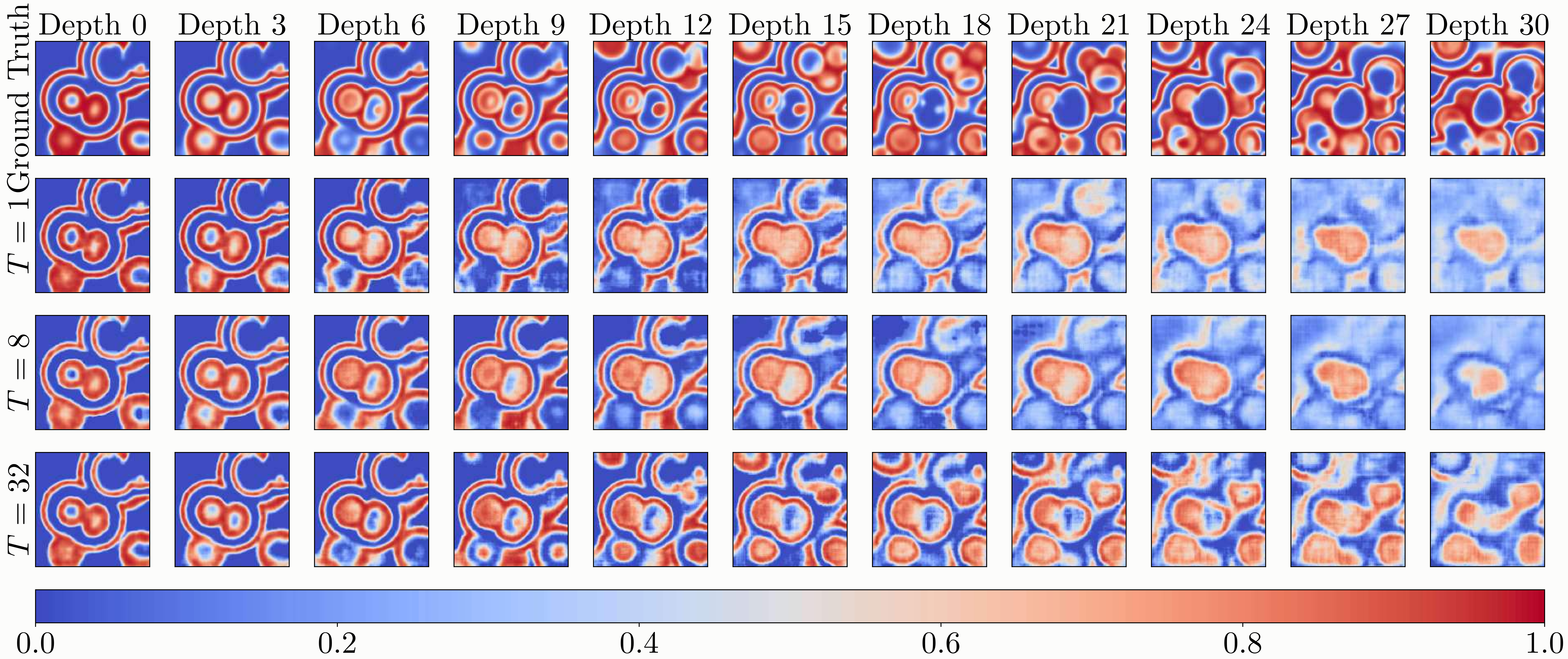
grid: $120 \times 120 \times 120$



predict deeper layers from data at surface
using convolutional neural networks:

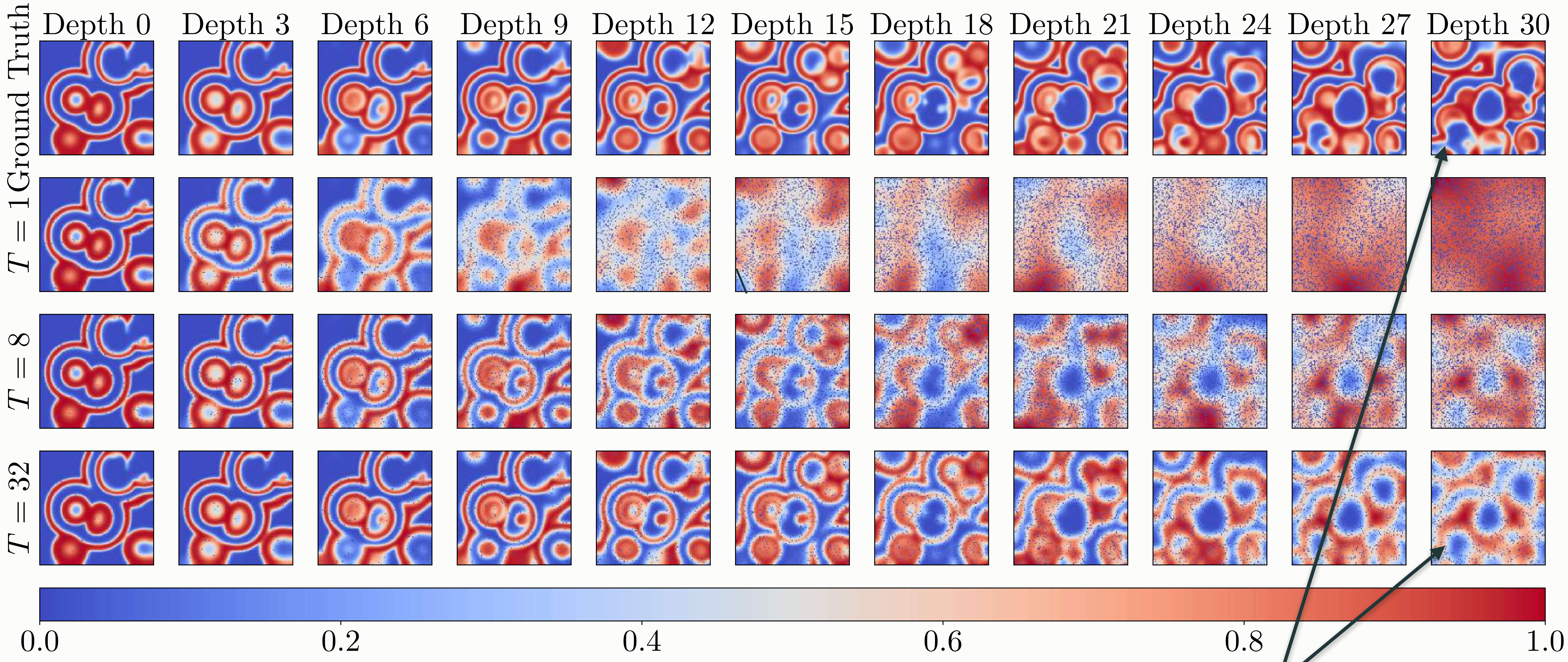
Auto-Encoder, Spatio-Temporal LSTM, Diffusion Model

Reconstruction using Autoencoder with different input lengths T ∈ {1, 8, 32}



R. Stenger et al., (under review, Chaos, 2022)

Reconstruction using diffusion model with different input lengths of T ∈ {1, 8, 32}



qualitative agreement

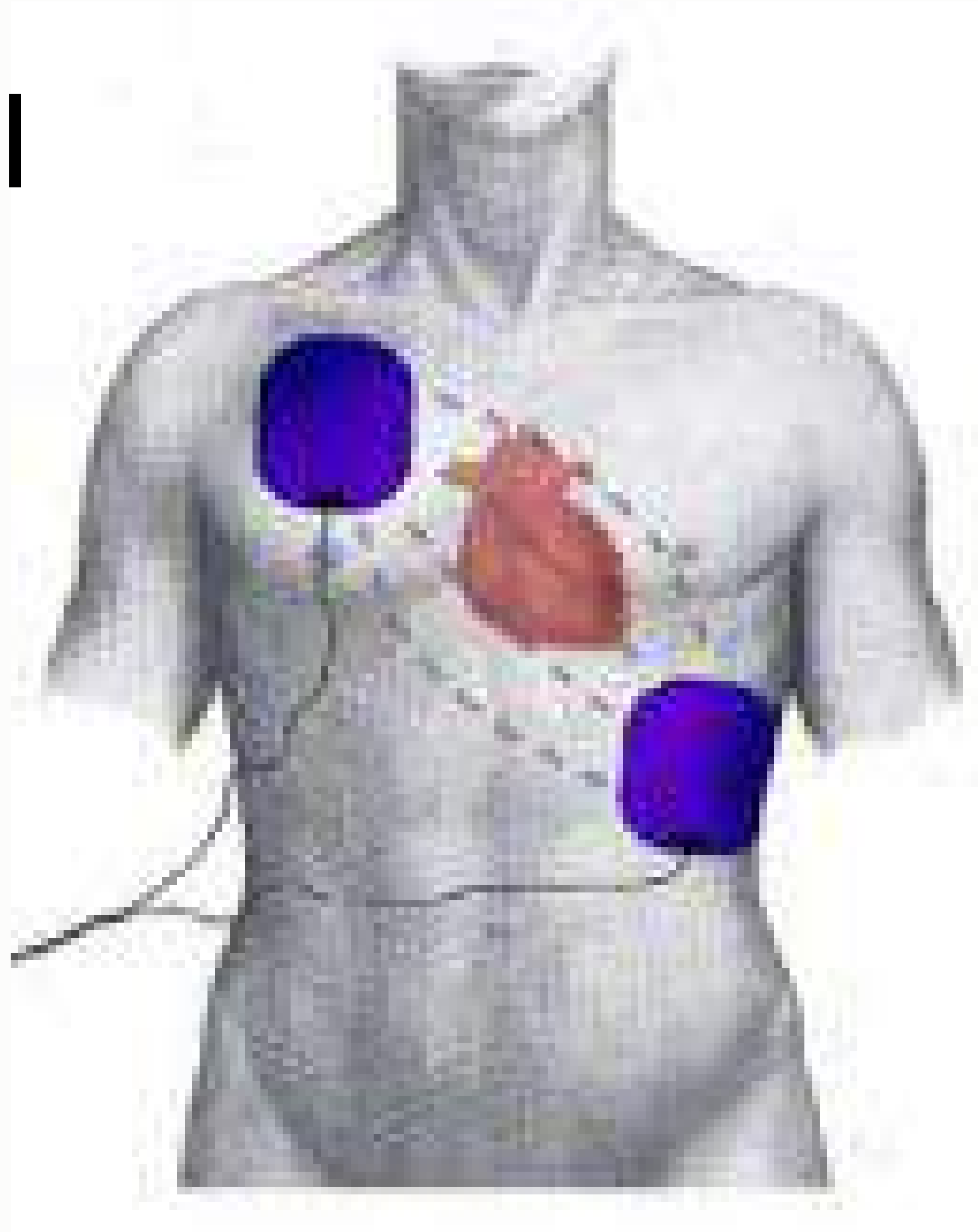
R. Stenger et al., (under review, Chaos, 2022)

Terminating cardiac arrhythmias

Defibrillation

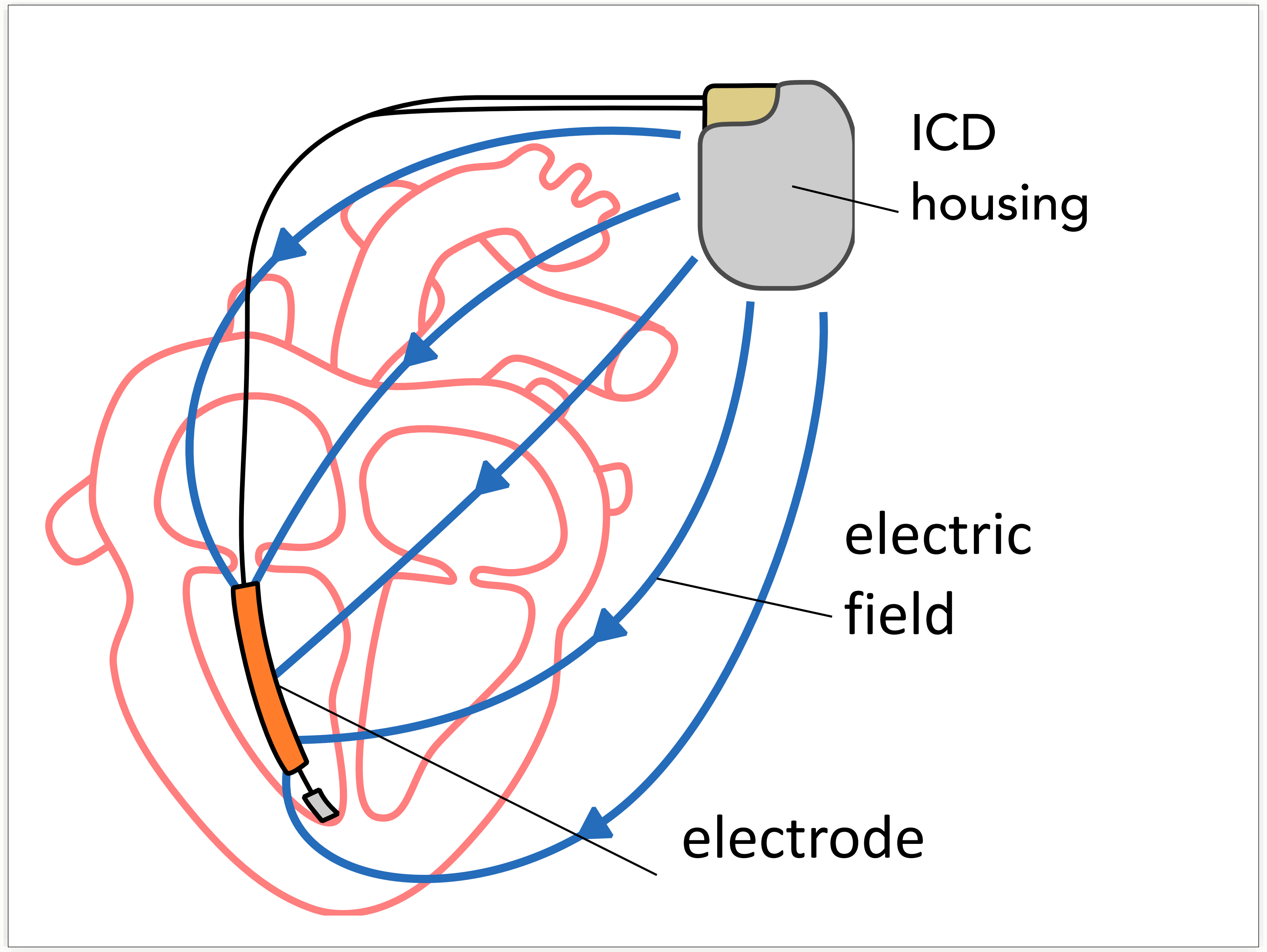
Principle: Reset electrical activity of all cells by synchronous excitation

external



PhilippN
wikimedia.org

internal



1000 V 20 A 12ms → 240 J

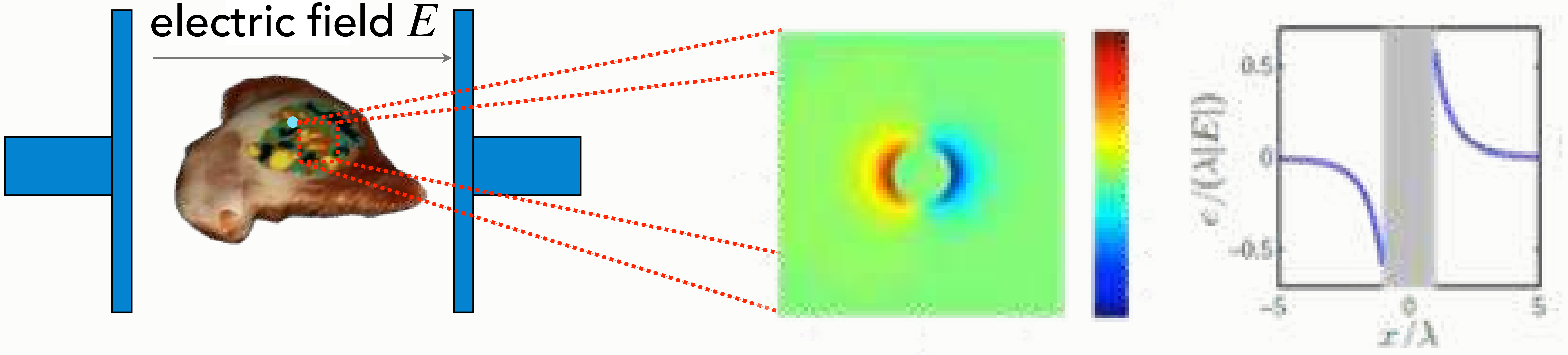
400 V 8 A 12 ms → 40J

Severe side effects: tissue damage - traumatic pain

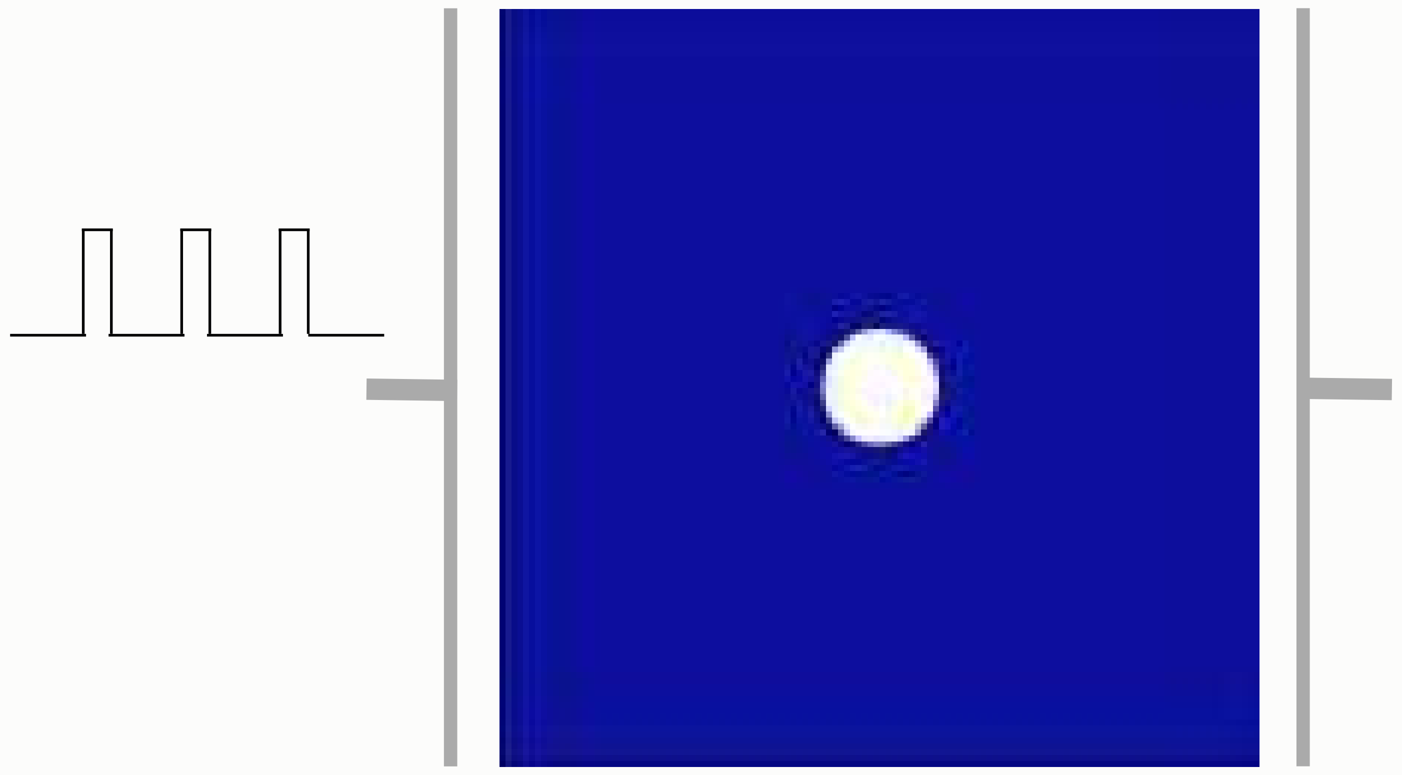
G.P. Walcott et al., Resuscitation 59 (2003)

Conduction heterogeneities act as virtual electrodes

blood vessels, scars, fatty tissue, …



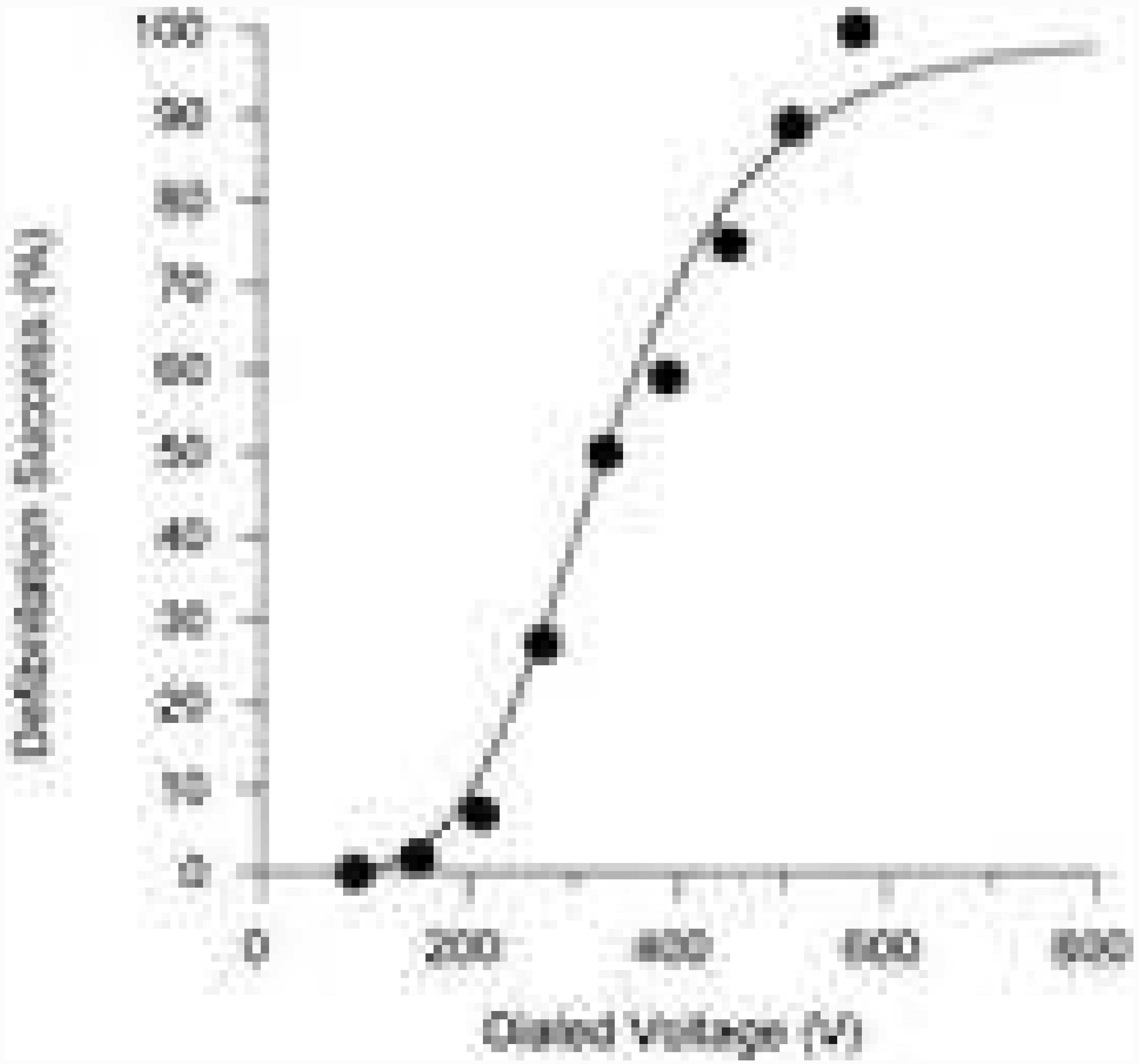
Super-threshold depolarization leads to wave emission if a short rectangular electric field pulse is applied.



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

Conventional defibrillation: termination with a single electrical pulse

Defibrillation success versus shock voltage for 273 shocks in 23 hearts



sigmoid dose-response curve

from: K.F. Kwaku and S.M. Dillon, Circulation Research 79, 957–973 (1996)

Pulse timing matters

Strong temporal fluctuations in termination success rate

J. Steyer et al., to appear in: Frontiers in Network Physiology (2022)

Predictable ??

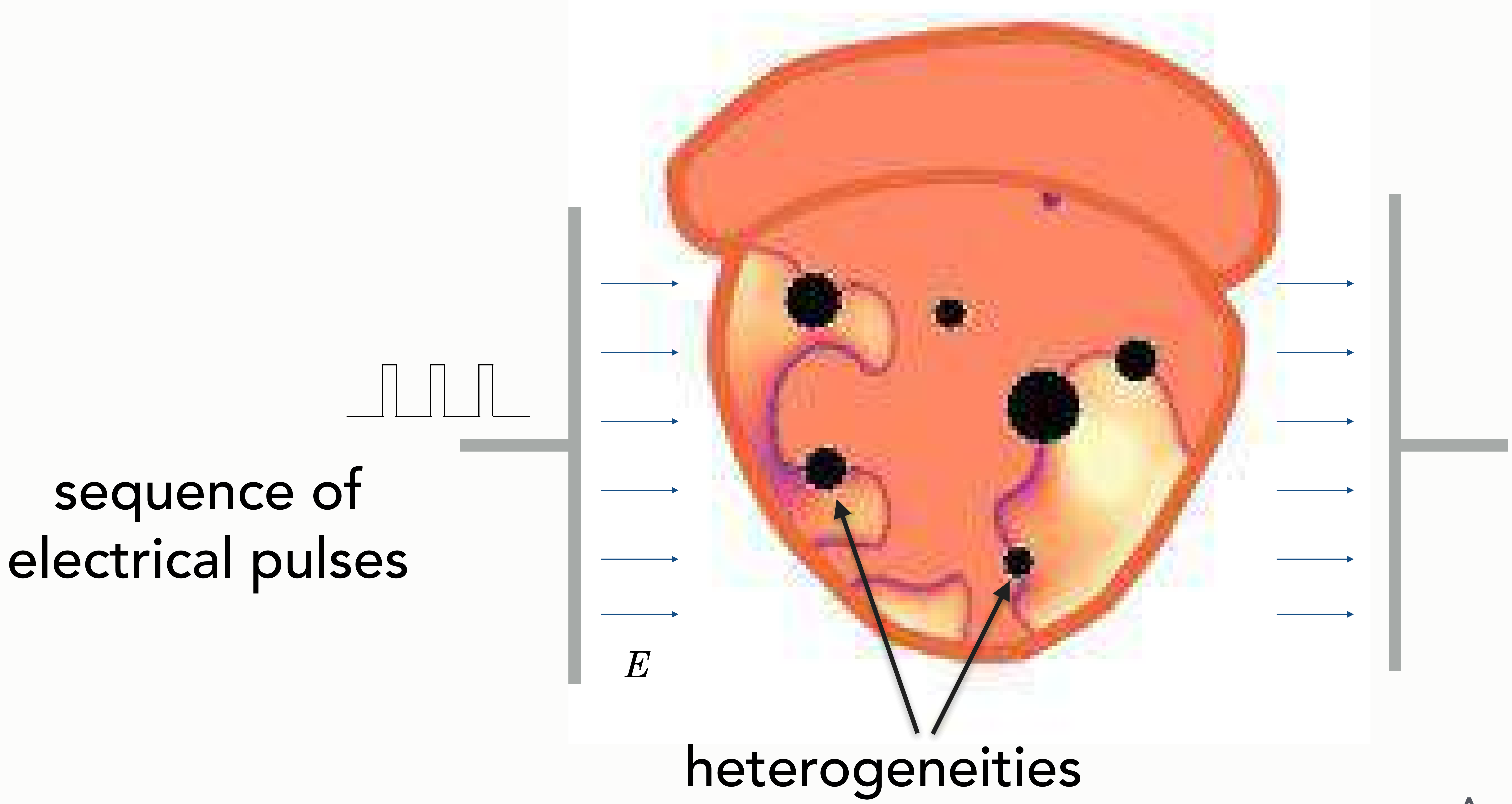
Terminating Cardiac Arrhythmias (Defibrillation) avoiding strong shocks

Sequences of weak pulses (LEAP)

Experiments:
S. Luther, F. Fenton et al., Nature 475 (2011)
H. Janardhan et al., J. of the American College of Cardiology 63 (2014),

Simulations:
P. Buran et al., Chaos 27 (2017)
….

Recruiting Virtual Electrodes for Terminating Cardiac Arrhythmias



Animation: T. Lilienkamp

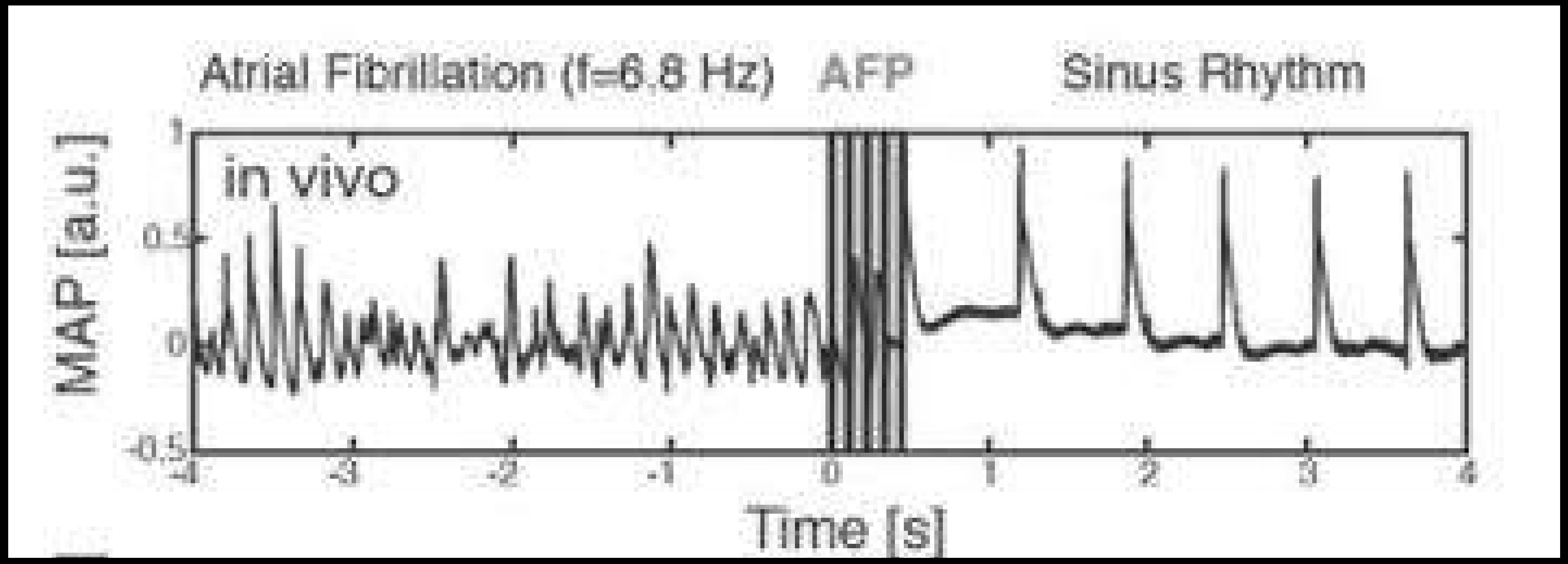
Low-Energy Anti-Fibrillation Pacing (LEAP)

Membrane Potential

N = 5 low energy pulses

E = 1.4 V/cm

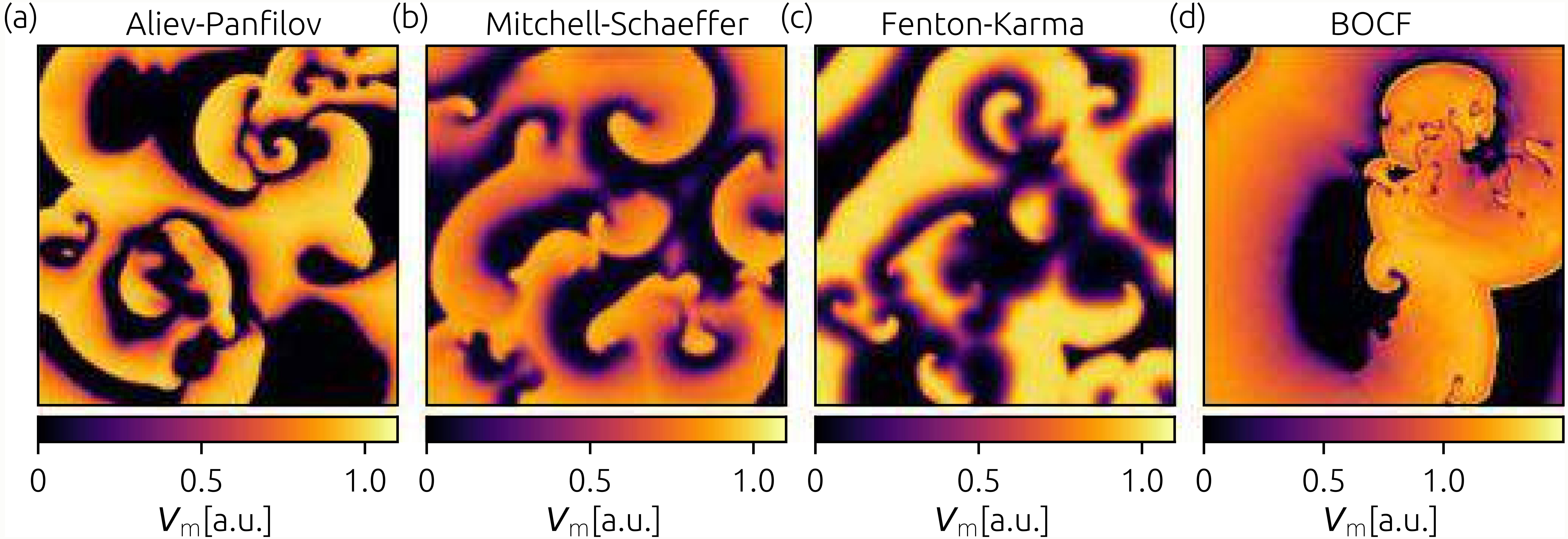
dt = 90 ms



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

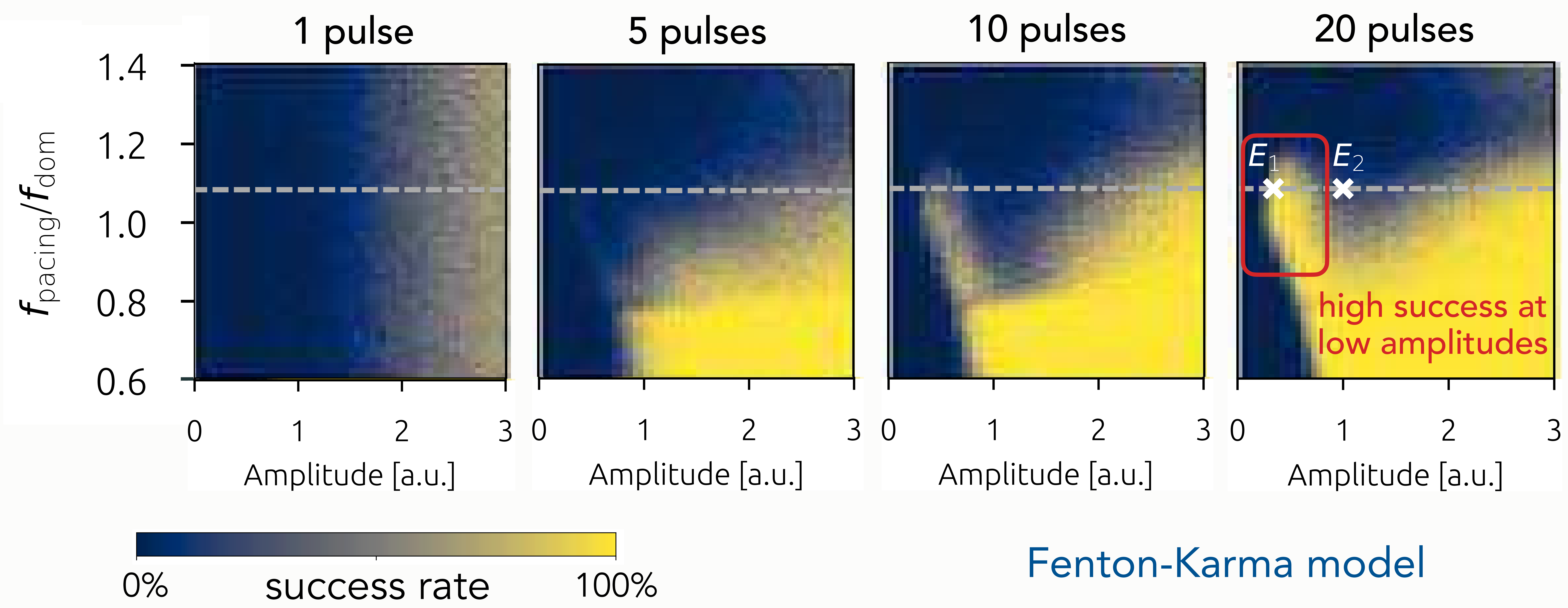
What does the dose-response curve look like for sequences of pulses?

Four model systems investigated



T. Lilienkamp et al., Scientific Reports 12 (2022)

Termination success rate *vs.* pacing amplitude and pacing frequency



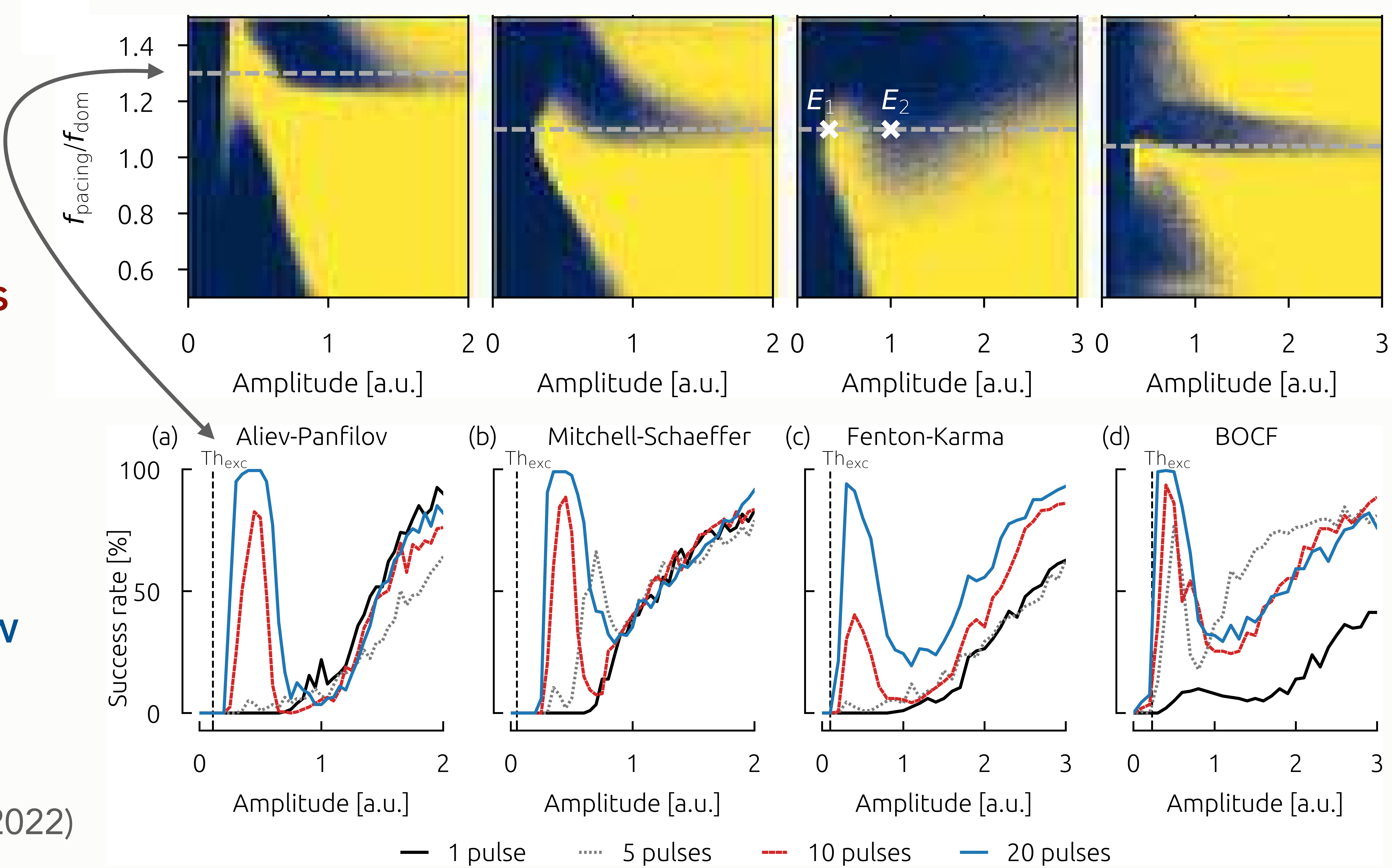
Fenton-Karma model

Non-monotonous Dose-Response Curve

Sequences of pulses result in

non-monotonous dose-response curves

with a peak of high termination probability at low pacing energy

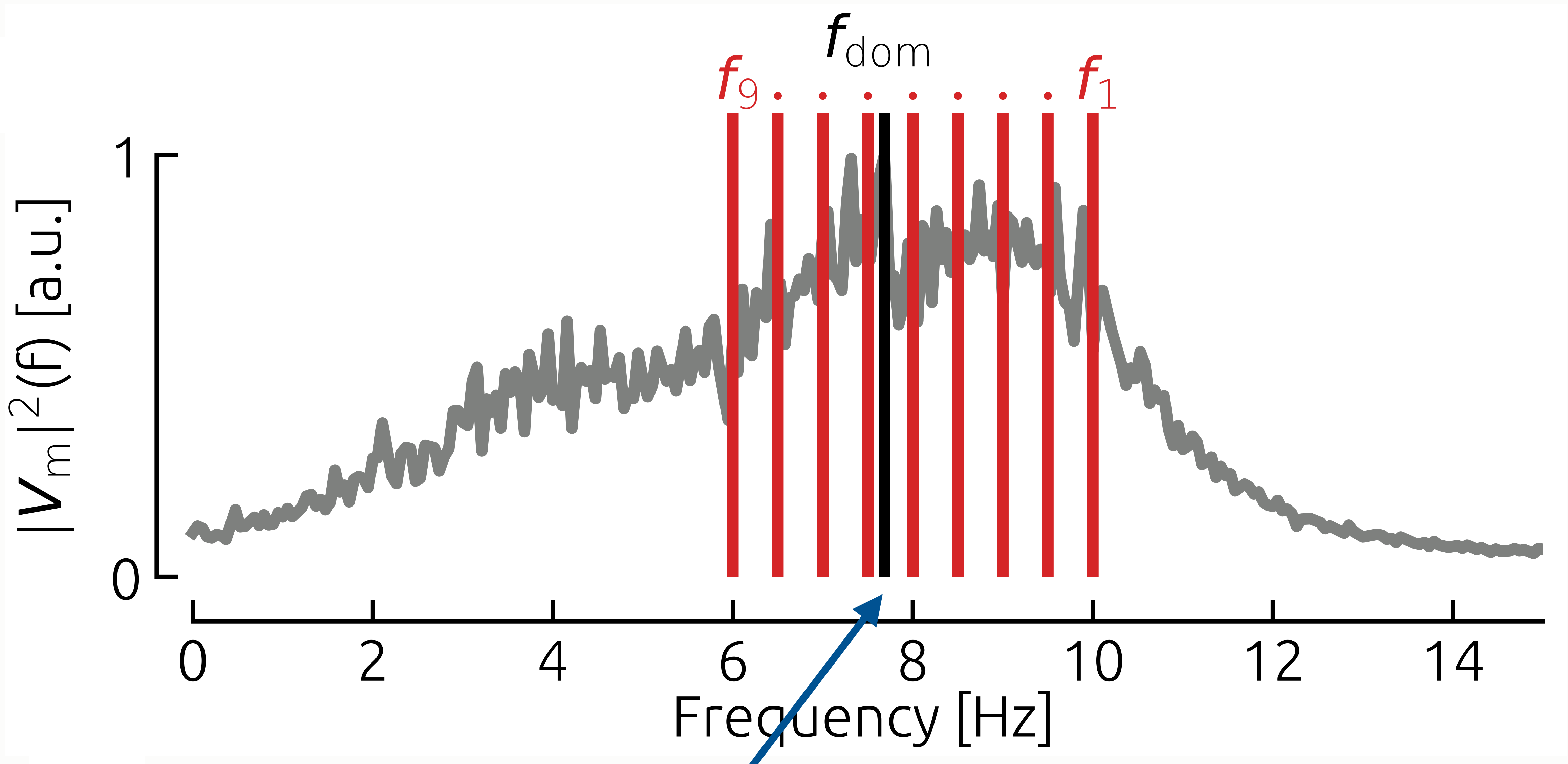


T. Lilienkamp et al., Scientific Reports 12 (2022)

Proper choice of pacing parameters is crucial

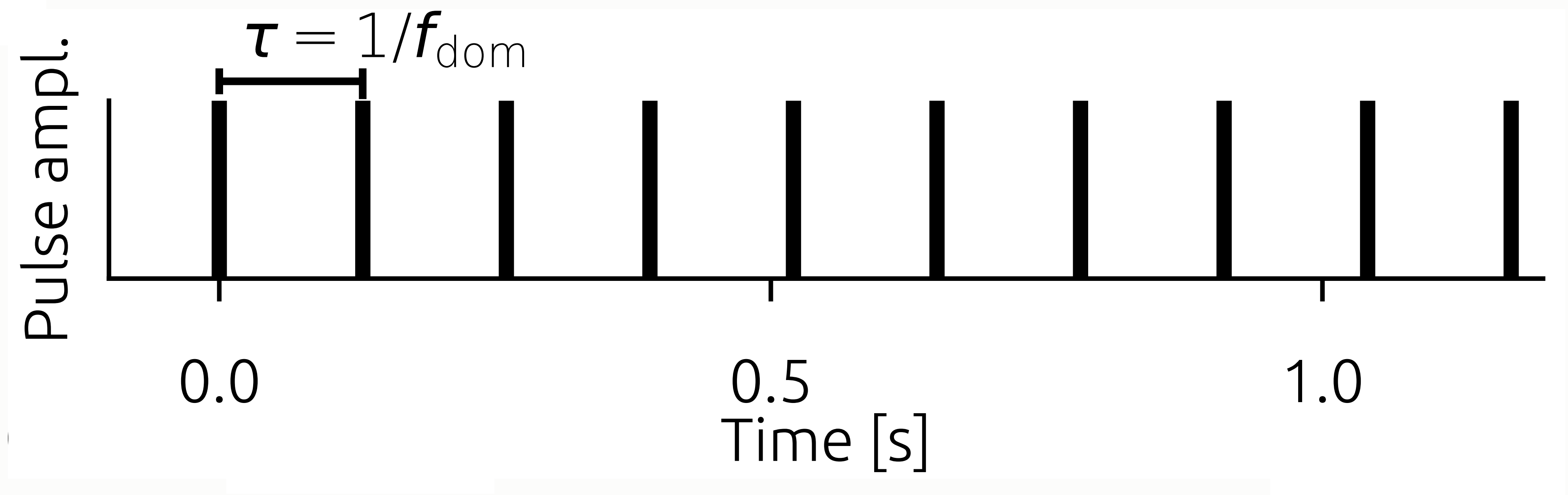
Use non-equidistant pulse sequences to cover a frequency range

power spectrum (e.g., ECG)

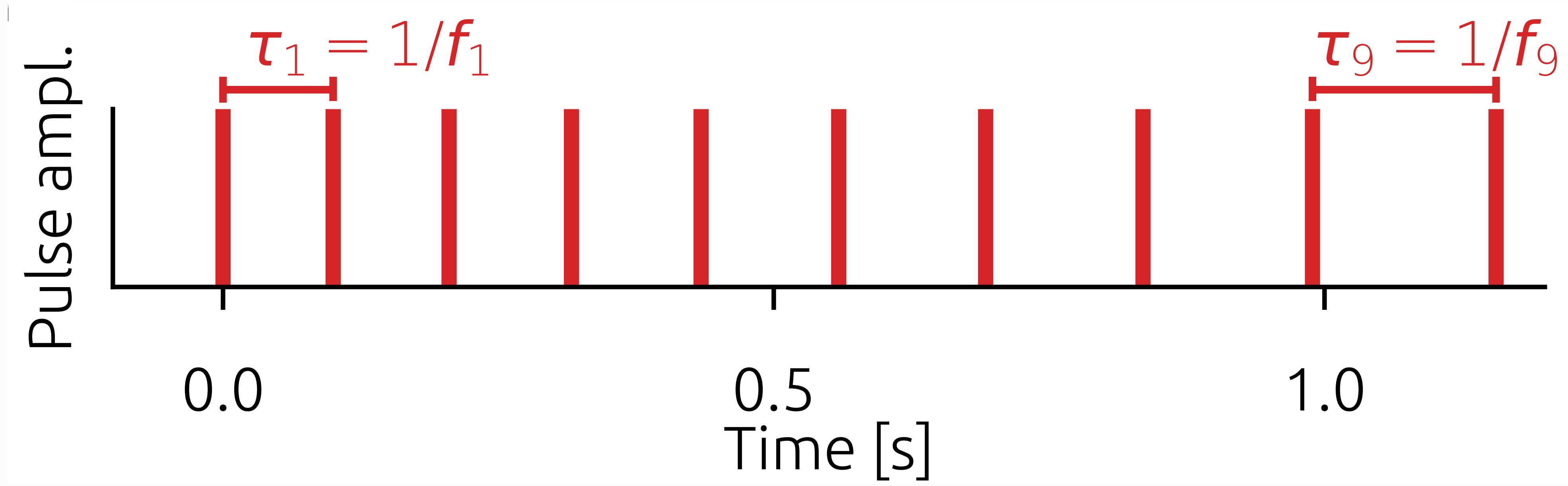


dominant frequency f_{dom}

equidistant pulses: $\tau = 1/f_{dom}$



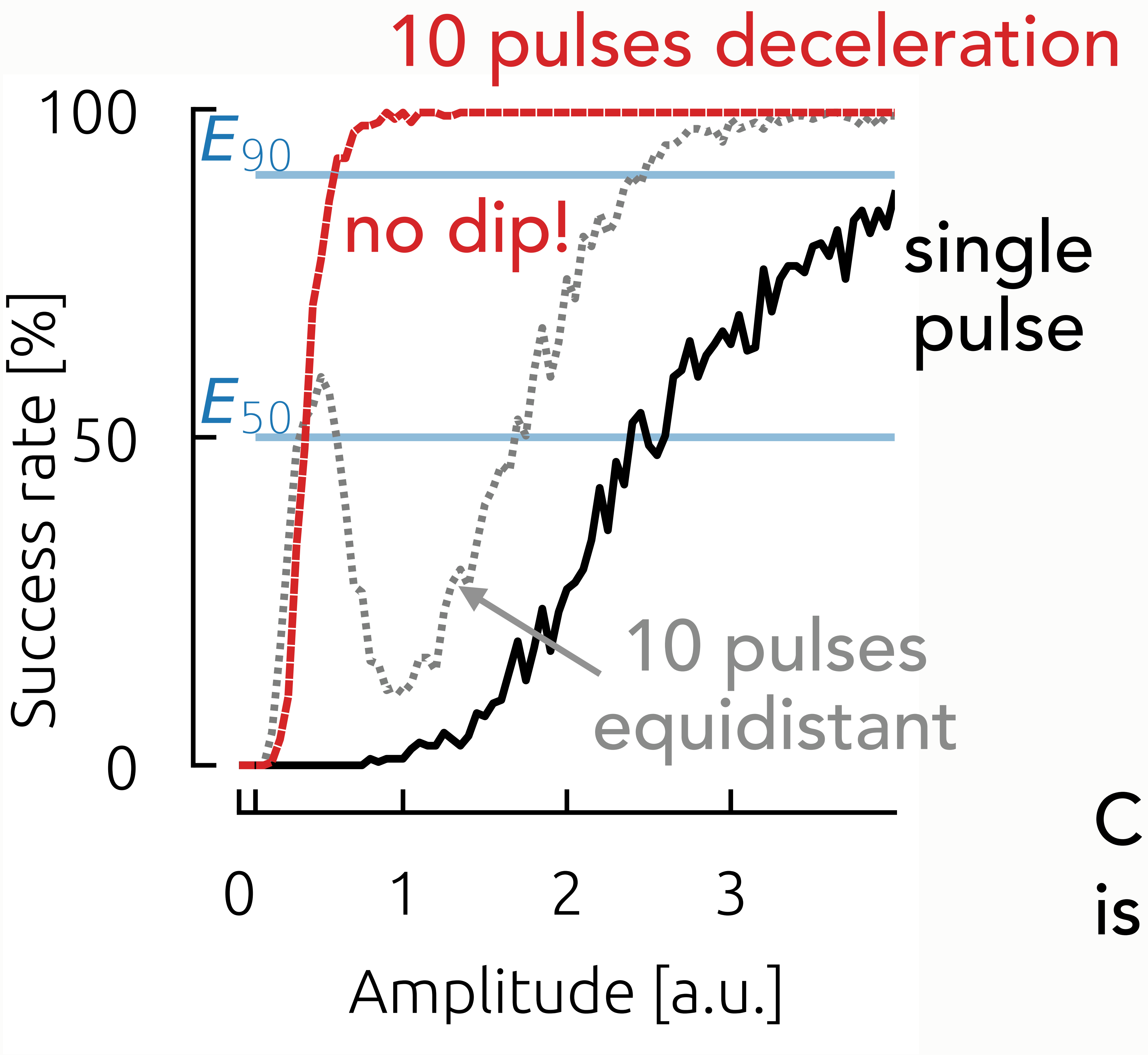
non-equidistant pulses: $\tau_k = 1/f_k$



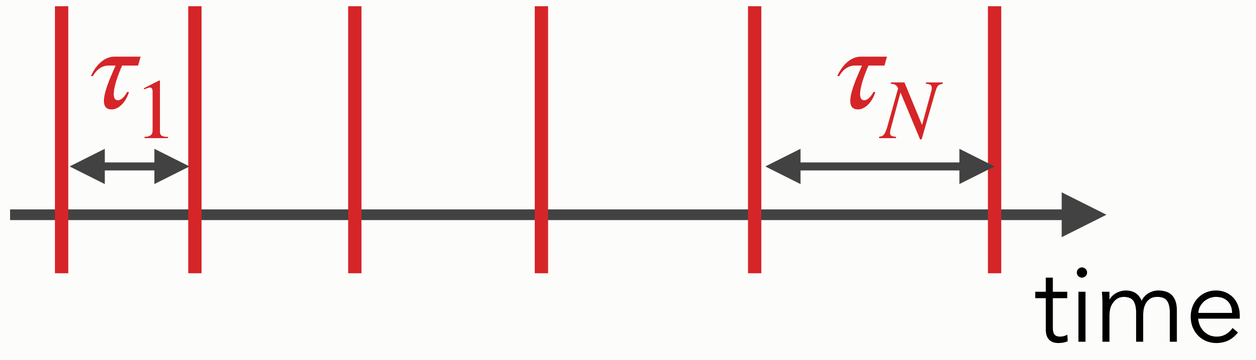
➞ deceleration pacing

Dose-response curves

Fenton-Karma model



linear increase of inter-pulse intervals

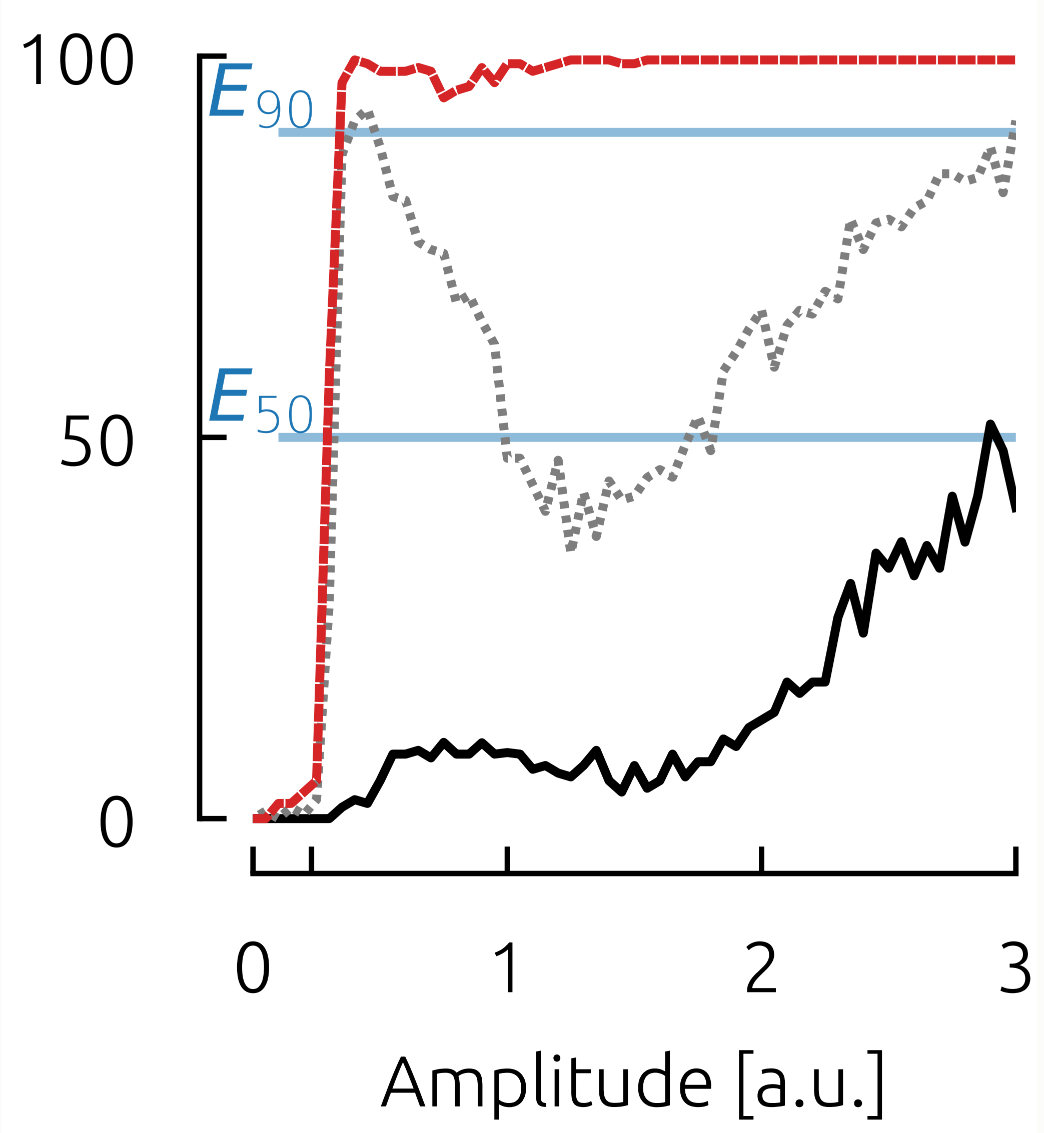


$$\tau_k = \tau_1 + \frac{k-1}{N-1}(\tau_N - \tau_1)$$

Choice of start τ_1 and end value τ_N is crucial and depends on model.

similar results for other models

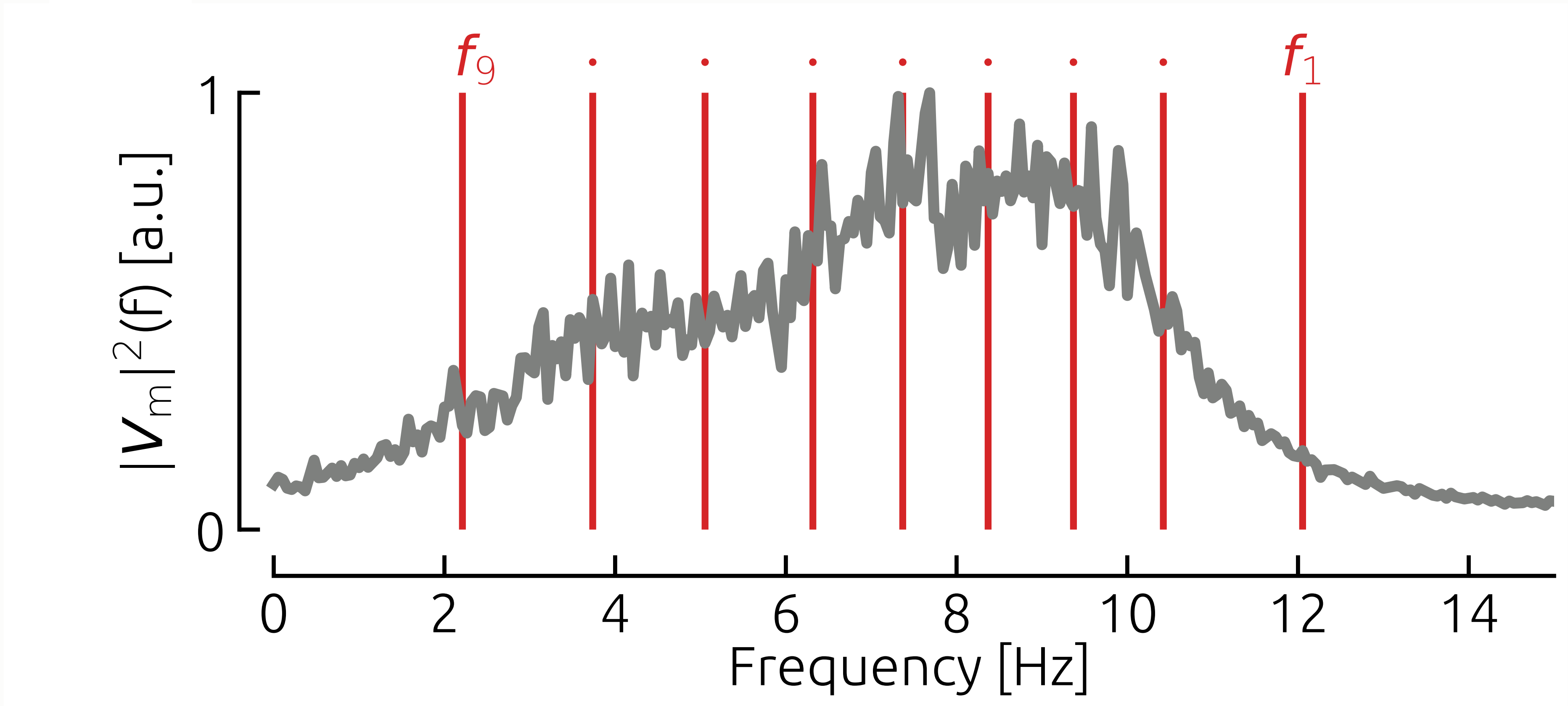
BOCF



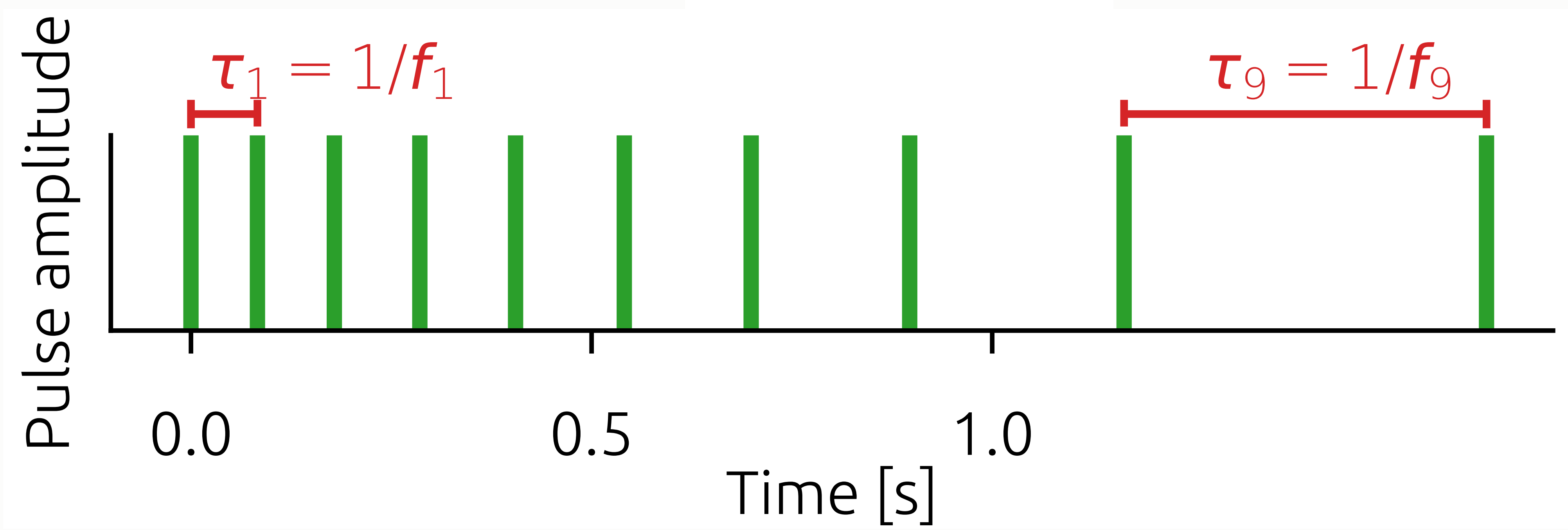
→ Need for a robust, model-independent protocol that is practical to use

Adaptive deceleration pacing (ADP)

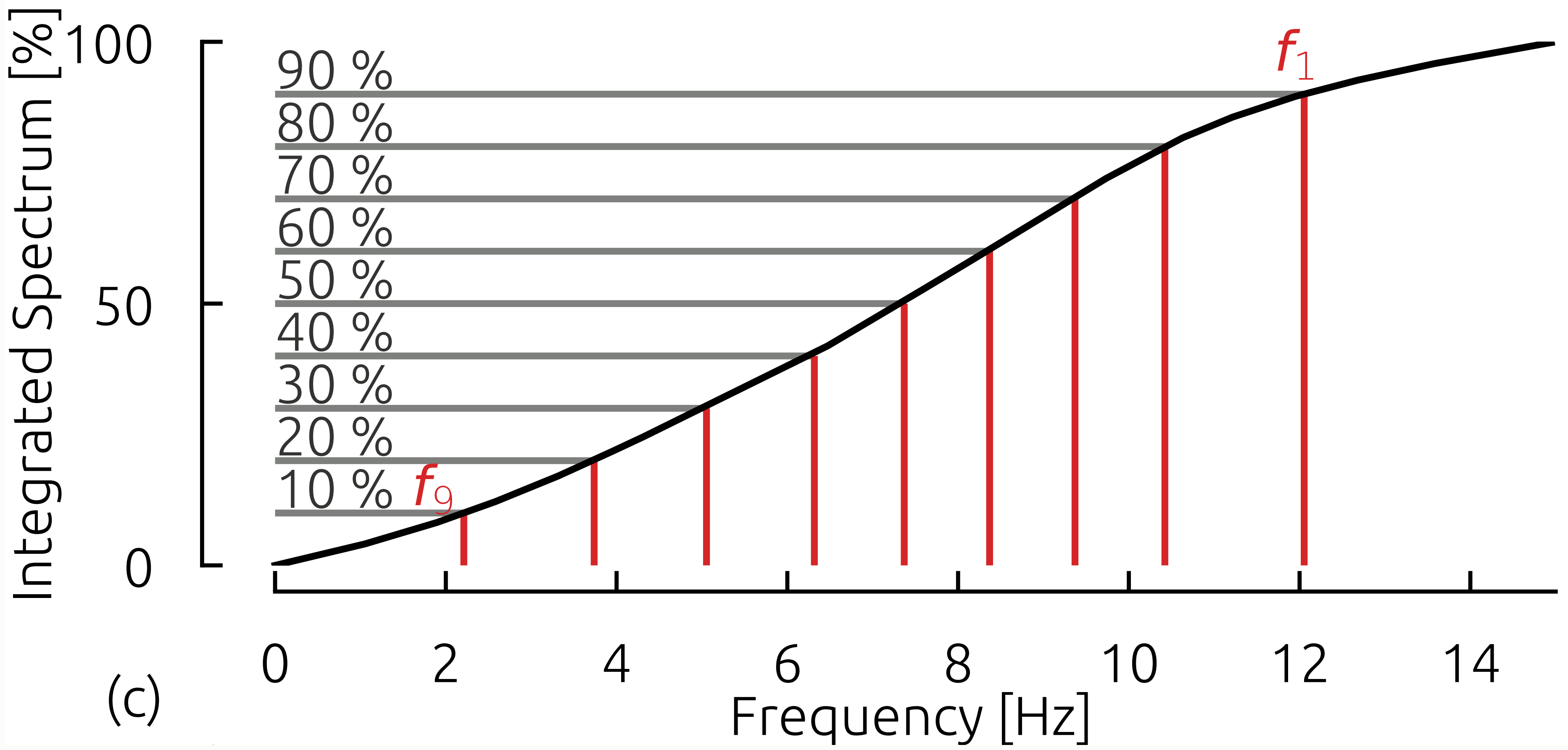
Fourier spectrum (e.g., ECG)



frequencies f_k ➙ pulse intervals $\tau_k = 1/f_k$



Integral: equidistant levels ➙ f_k



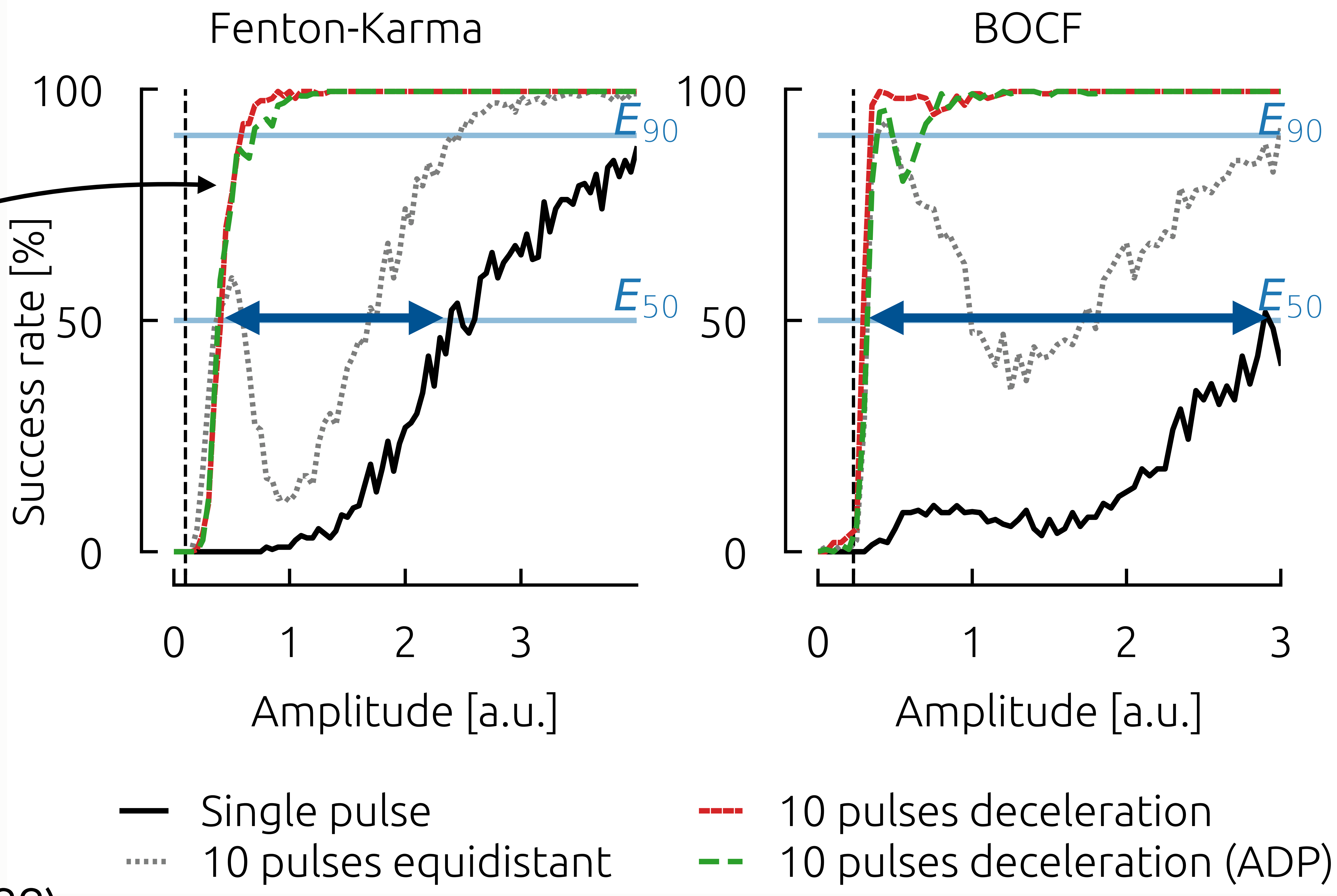
- ADP pacing sequences are highly adaptable to the specific characteristics of the dynamics
- only two free parameters: cut-off frequency & no. of pulses
- easy to implement experimentally

Adaptive deceleration pacing (ADP)

dose-response curves

ADP almost as good as linear deceleration with carefully selected start and end frequencies

significant reduction of required pulse amplitude



T. Lilienkamp et al., Chaos (2022)

Summary

- Ventricular fibrillation (VF) is a lethal state which requires immediate treatment: defibrillation using strong electrical shocks with side effects
- VF is closely connected to spiral wave chaos in excitable media
- data driven modelling is a promising approach to predict excitable cardiac dynamics and to reconstruct quantities that are difficult observe directly
- complex dynamics in excitable media can be governed by transient chaos with immediate consequence for its controllability
- pulse sequences of low energy may provide an alternative for defibrillation avoiding strong shocks with adverse side effects
- a novel and very promising approach employs adaptive deceleration pacing where pacing is slowed down in a systematic manner

Summary

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