Nonlinear Dynamics of the Heart (I)

Ulrich Parlitz

Max Planck Research Group for Biomedical Physics

Max Planck Institute for Dynamics and Self-Organization

Institute for Nonlinear Dynamics

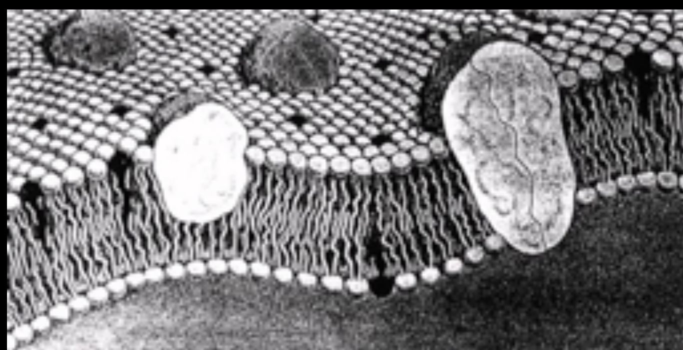
Georg-August-Universität Göttingen

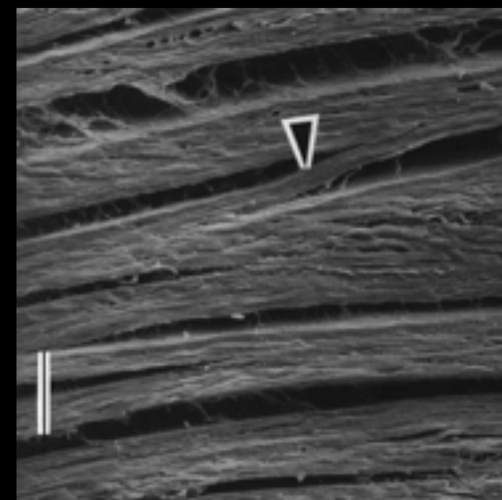
Göttingen, Germany

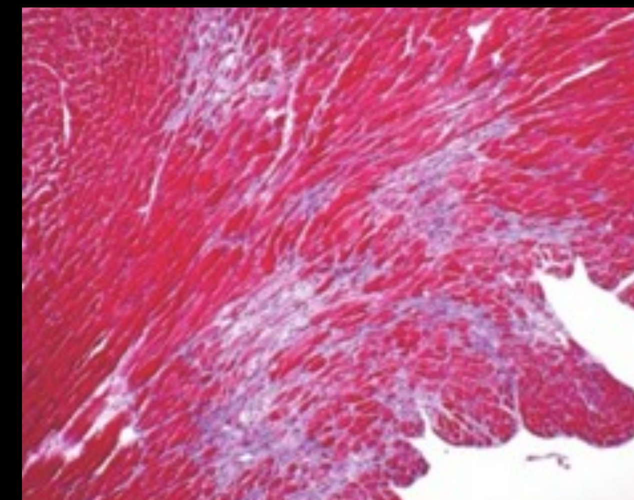
The Heart

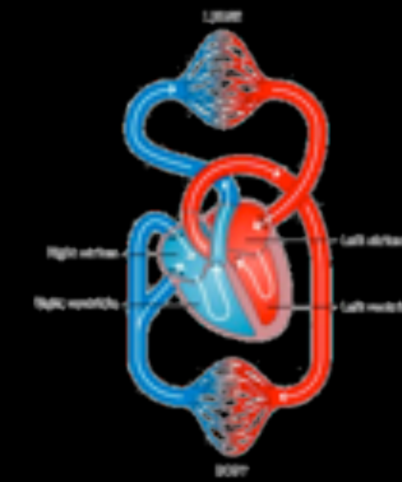
Visualization F.H. Fenton

From Molecule to Organ







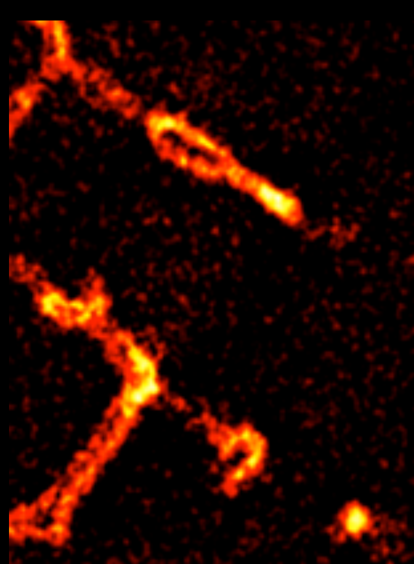


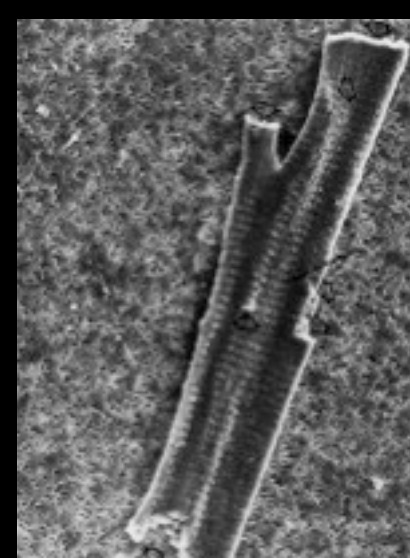
subcellullar tissue system

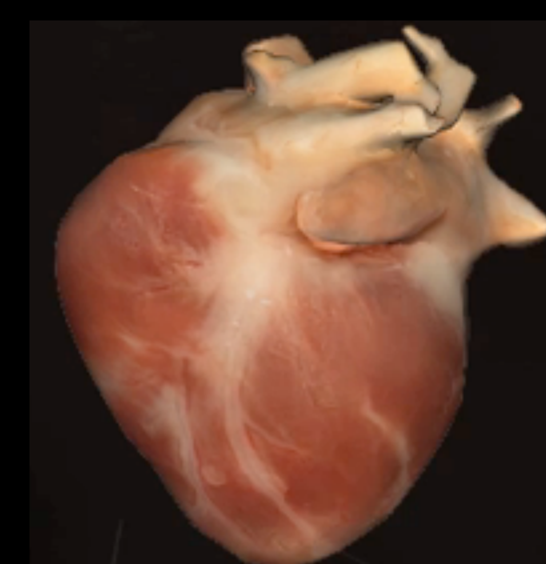
10^{-9} 10^{-4} 10^{-1}

10^{-8} 10^{-3} m

cell organ





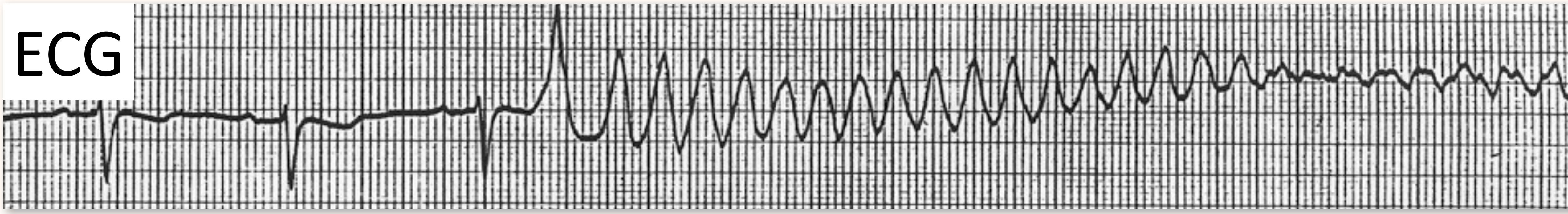


Outline

- Dynamical States of the Heart
- Excitable Systems
- Experimental Techniques
- State and Parameter Estimation

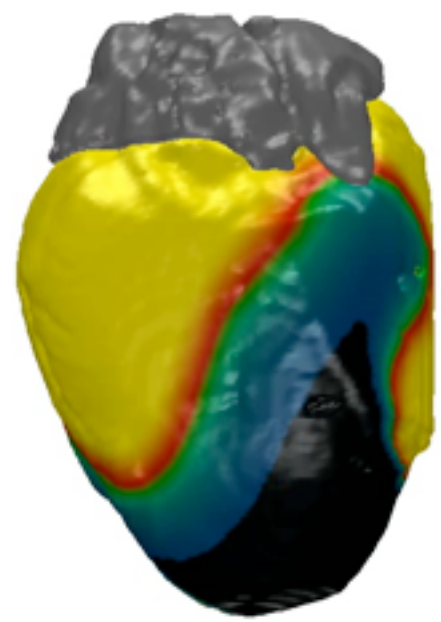
The Nonlinear Dynamics of the Heart

Normal Rhythm → Tachycardia → Fibrillation

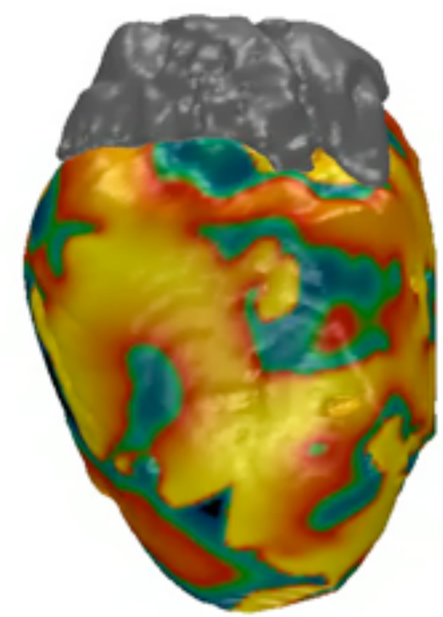


electrical excitation waves

plane waves



spiral waves



chaos

simulations: P. Bittihn

Cardiac Tissue is an Excitable Medium

An **excitable medium**

- is a nonlinear dynamical system
- which has the capacity to propagate some particular waves,
- and which cannot support the passing of another wave until a certain amount of time has passed (refractory time)

A **forest** may be considered as an **excitable medium**:

If a wildfire burns through the forest (wave), no fire can return to a burnt spot until the vegetation has gone through its refractory period and regrown.

Example: **The Belousov-Zhabotinsky (BZ) reaction**

- oscillating chemical reaction (in a homogeneous medium)
- transition-metal ions catalyze oxidation of various, usually organic, reductants by bromic acid in acidic water solution
- convenient human temporal and spatial scale (seconds and millimeters)
- several thousand oscillatory cycles in a closed system

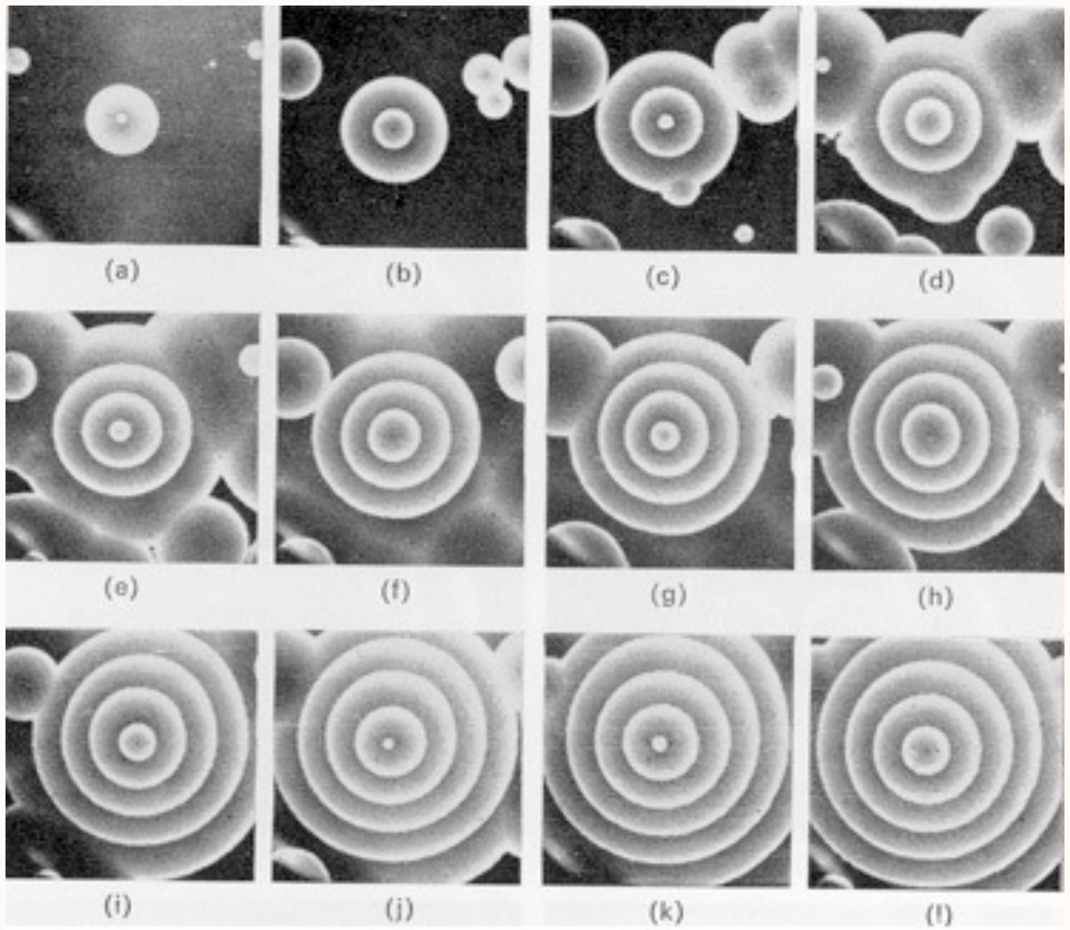
Analogy *BZR – Cardiac Fibrillation*

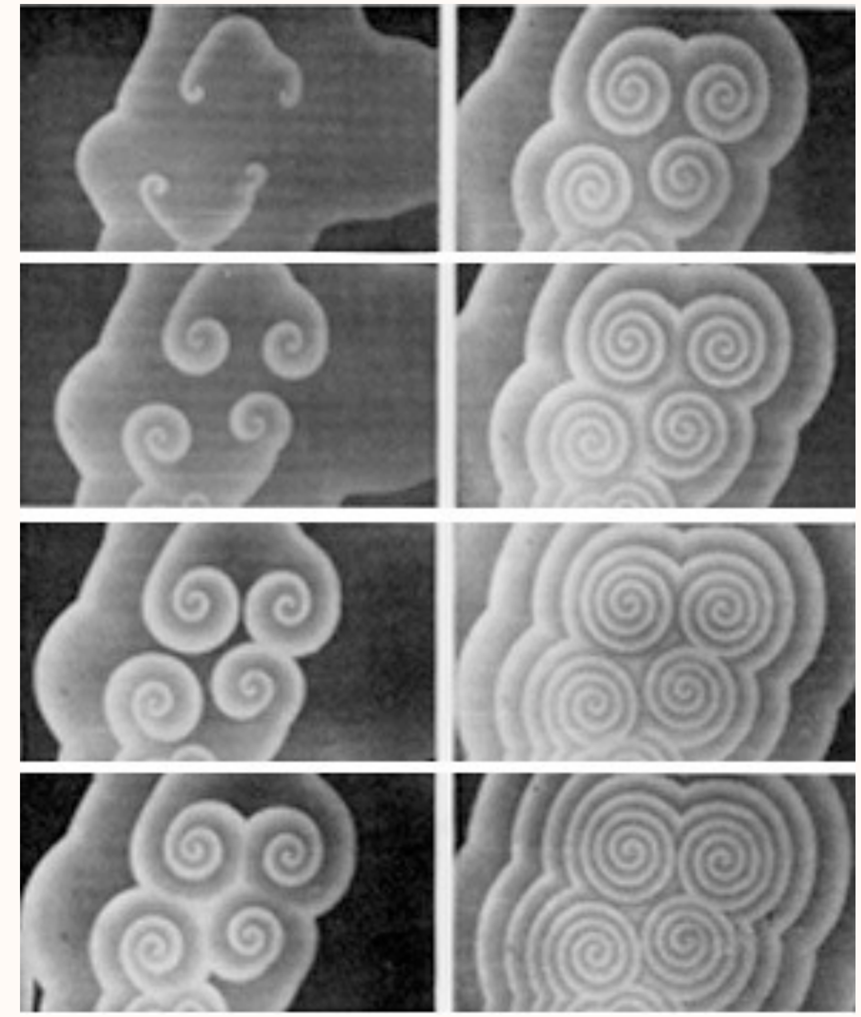
V.I. Krinskii, Biophysics 11, 776 (1966)

Concept of *dynamical disease*

M.C. Mackey, L. Glass, Science 197, 287(1977)

The Belousov-Zhabotinsky (BZ) reaction





Generation of concentric waves by pacemakers and entrainment by the fastest pacemaker resulting in a single target pattern in the BZ reaction-diffusion system

Development of spiral waves after hydrodynamic breaking of a concentric wave

www.scholarpedia.org

The Belousov-Zhabotinsky (BZ) Reaction

http://www.youtube.com/watch?v=3JAqrRnKFHo&feature=related

Example: **Dictyostelium discoideum** (slime mold)

Spiral waves

Spiral geometry of a signal transmitter in an amoeba population (*Dictyostelium discoideum*) leads to chemotactic movements of cells in direction of the spiral core.

from: http://www.uni-magdeburg.de/abp/picturegallery.htm

Excitable Media

Another example: **„La Ola"** (the Mexican Wave)

http://angel.elte.hu/wave

Excitable media can be modeled using both partial differential equations or cellular automata.

Excitable media often consist of or are modeled as coupled **excitable systems** (not extended in space)

Excitable Systems

General concept

- dynamical system with a stable fixed point
- small perturbations (or stimuli) from the fixed point decay
- large perturbation (exceeding a certain threshold) result in a large excursion in phase space finally re-approaching the stable fixed point
- form and duration of the excitation do not depend on the exact form of the perturbation
- new perturbation affects system only if it is close to fixed point, again → **refractory time**

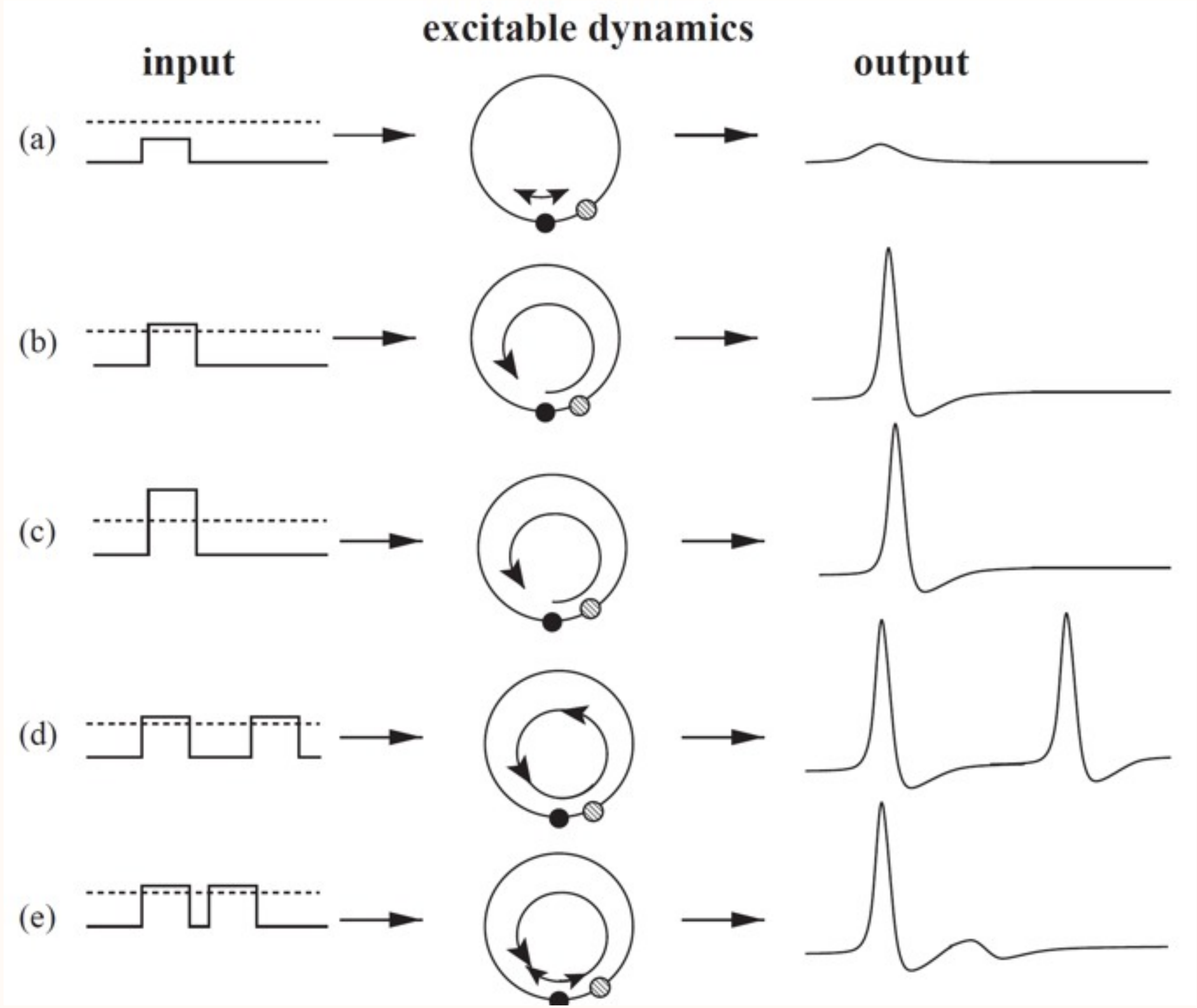
Response of an excitable system to different stimuli

sub-threshold perturbation
→ **small response**

super-threshold perturbation
→ **loop**

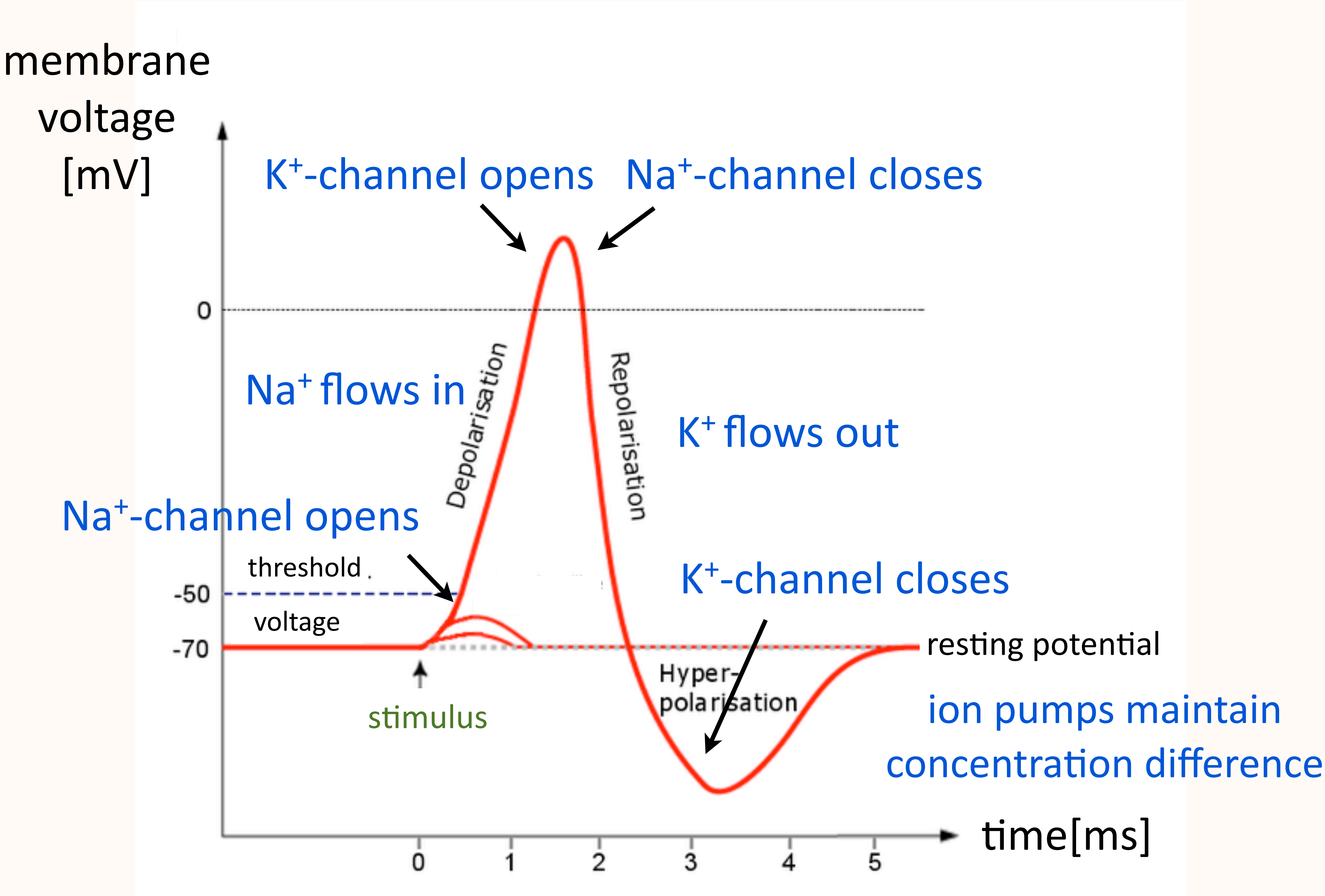
repeated excitation with well **separated perturbations**

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



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

Generation of an action potential



adapted from Wikipedia

The FitzHugh-Nagumo (FHN) system

- originally derived from the Hodgkin-Huxley model for the giant nerve fiber of a squid
- now "the" archetype model for excitable systems

$$
\begin{aligned}
\frac{du}{dt} &= \frac{1}{\varepsilon}\left(u - au^3 - v\right) \\
\frac{dv}{dt} &= \gamma u - v + b
\end{aligned}
$$

ε , a, and b are real, positive parameters

ε is chosen small in order to guarantee a clear timescale separation between the fast u variable (activator) and the slow v variable (inhibitor)

http://www.scholarpedia.org/article/FitzHugh-Nagumo_model

The FitzHugh-Nagumo (FHN) system

nullclines:

$$0 = \frac{du}{dt} \quad = \quad \frac{1}{\varepsilon}\left(u - au^3 - v\right)$$

$$0 = \frac{dv}{dt} \quad = \quad \gamma u - v + b$$

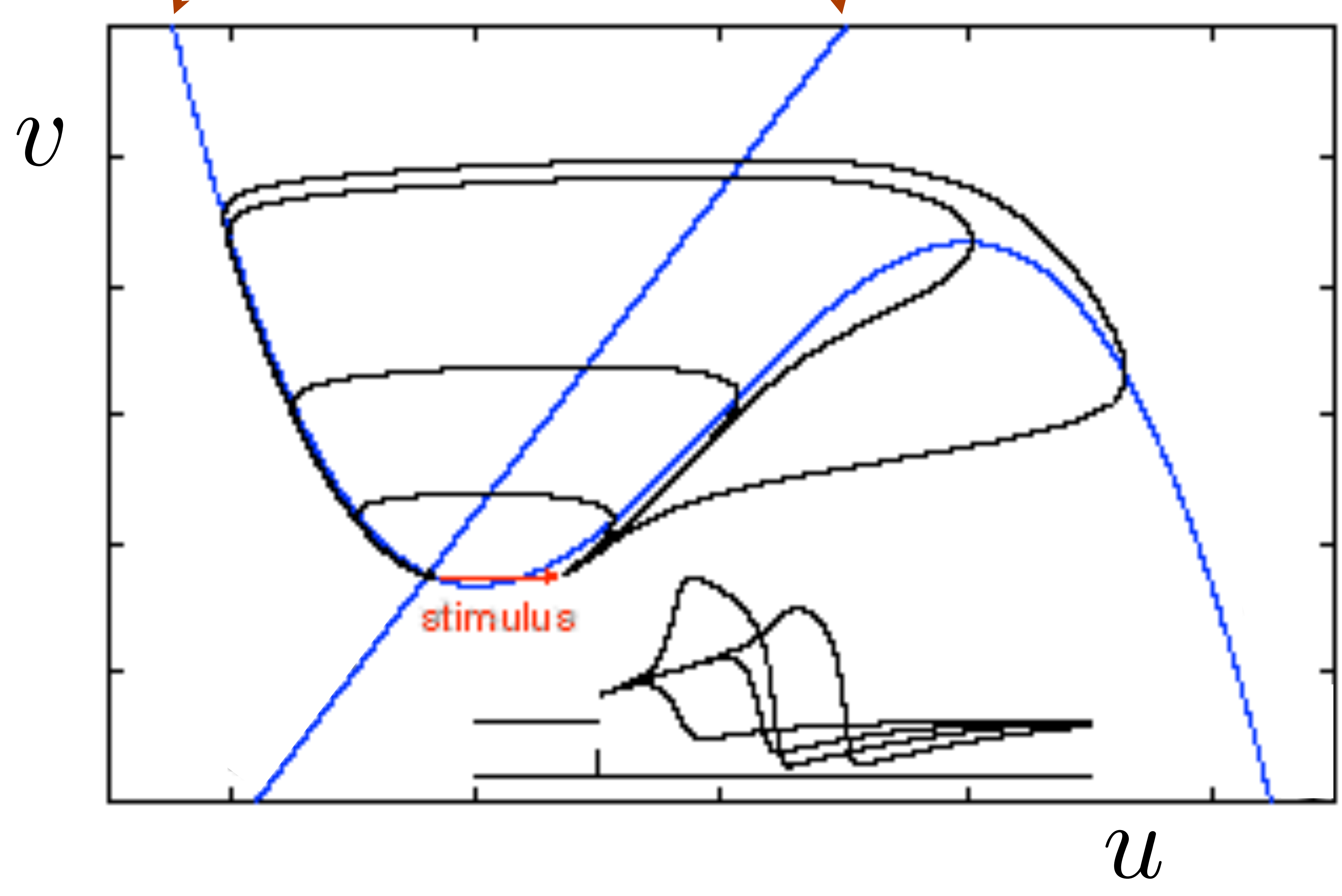
$$\Rightarrow v = f(u) = u - au^3$$

$$\Rightarrow v = g(u) = u + b$$

The FitzHugh-Nagumo (FHN) system

$$\dot{u} = 0 :$$
$$v = f(u) = u - au^3$$

$$\dot{v} = 0 :$$
$$v = g(u) = u + b$$



Mathematical Models of Excitable Media

Another 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)

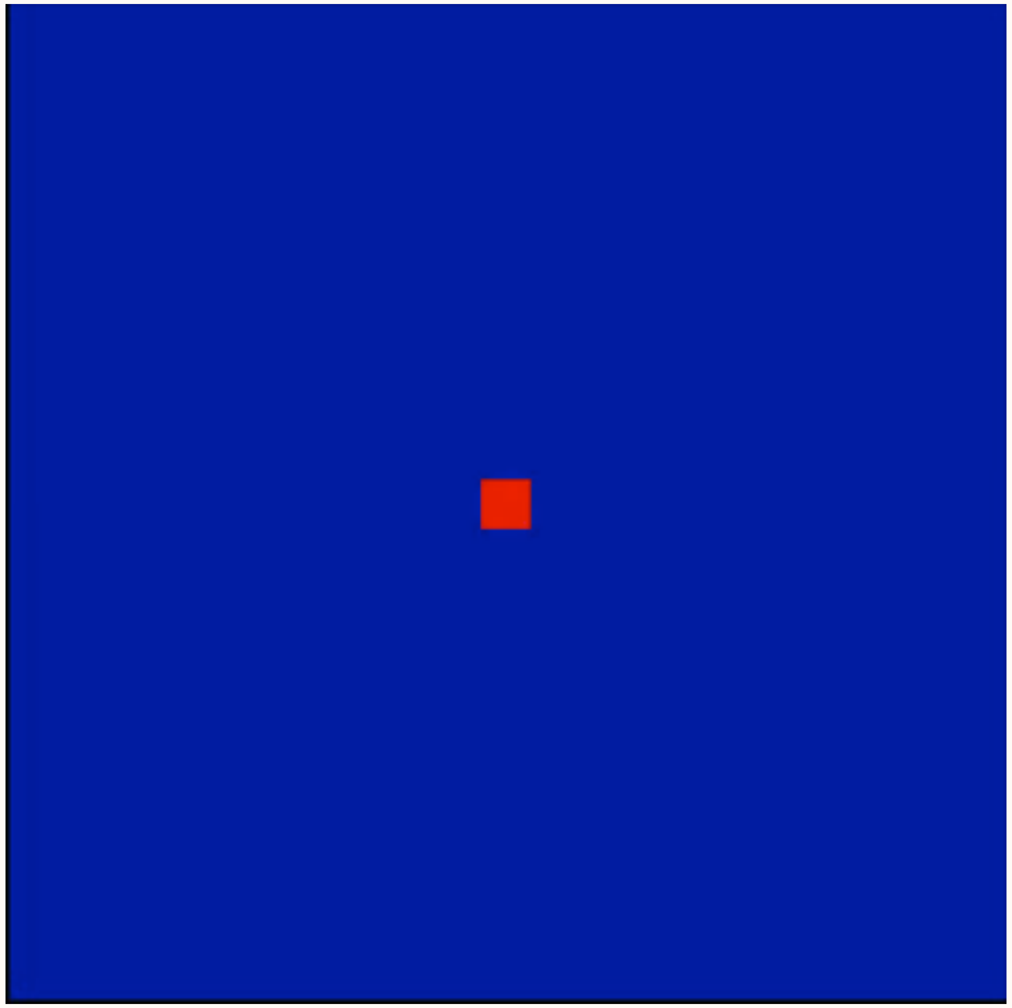
D. Barkley, Physica D 49, 6170 (1991)

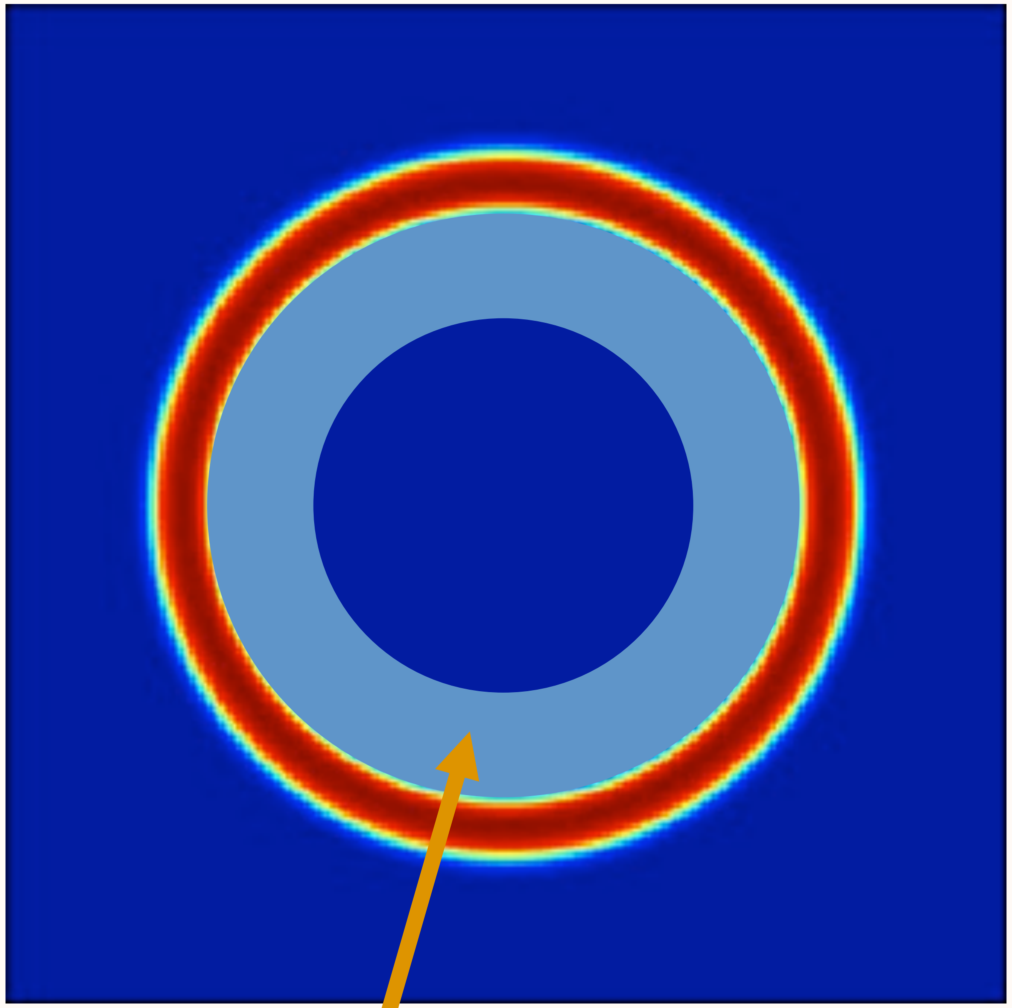
http://www.scholarpedia.org/article/Barkley_model

Excitable Media

Spatially extended, excitable systems (e.g. heart tissue)

Excitation waves (Barkley model)

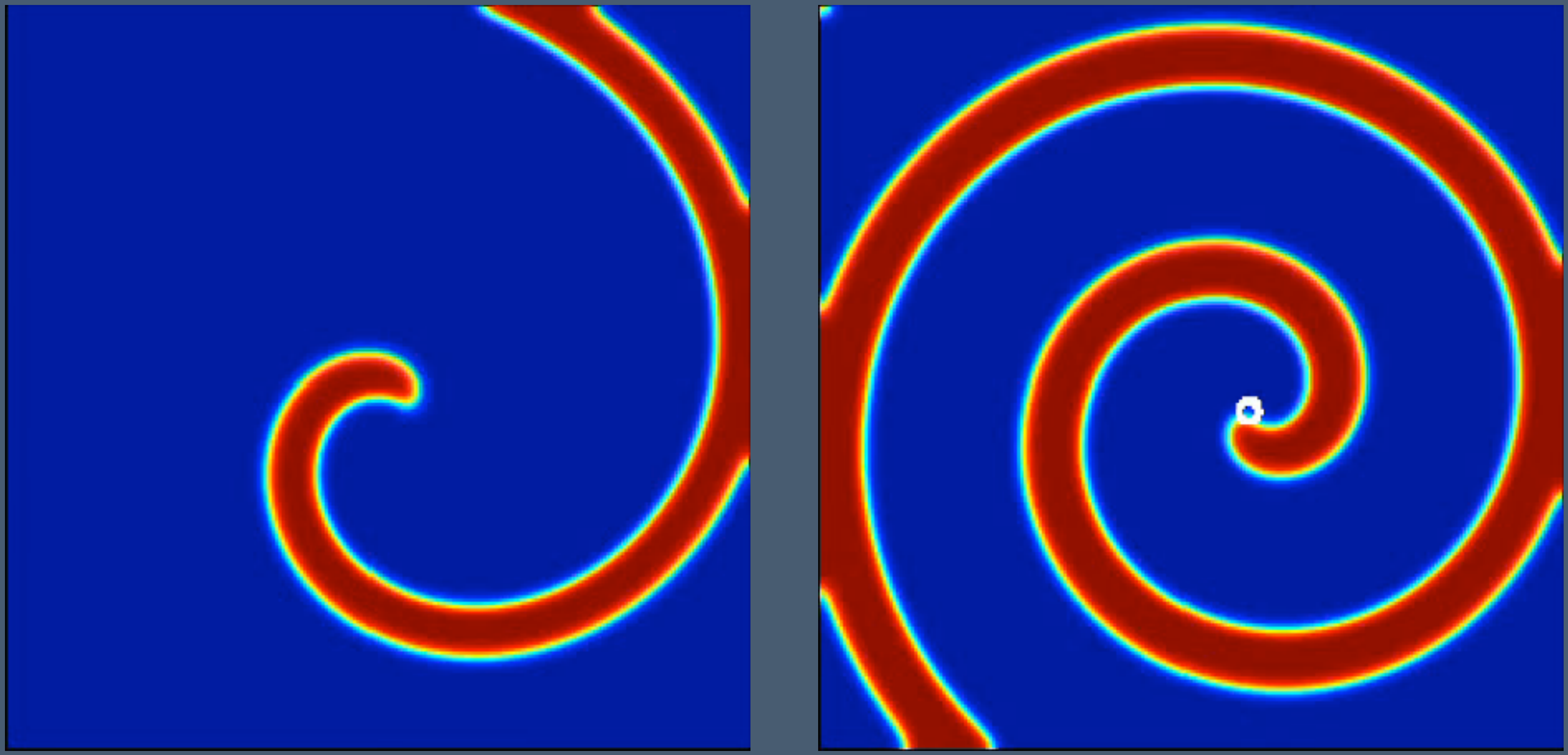




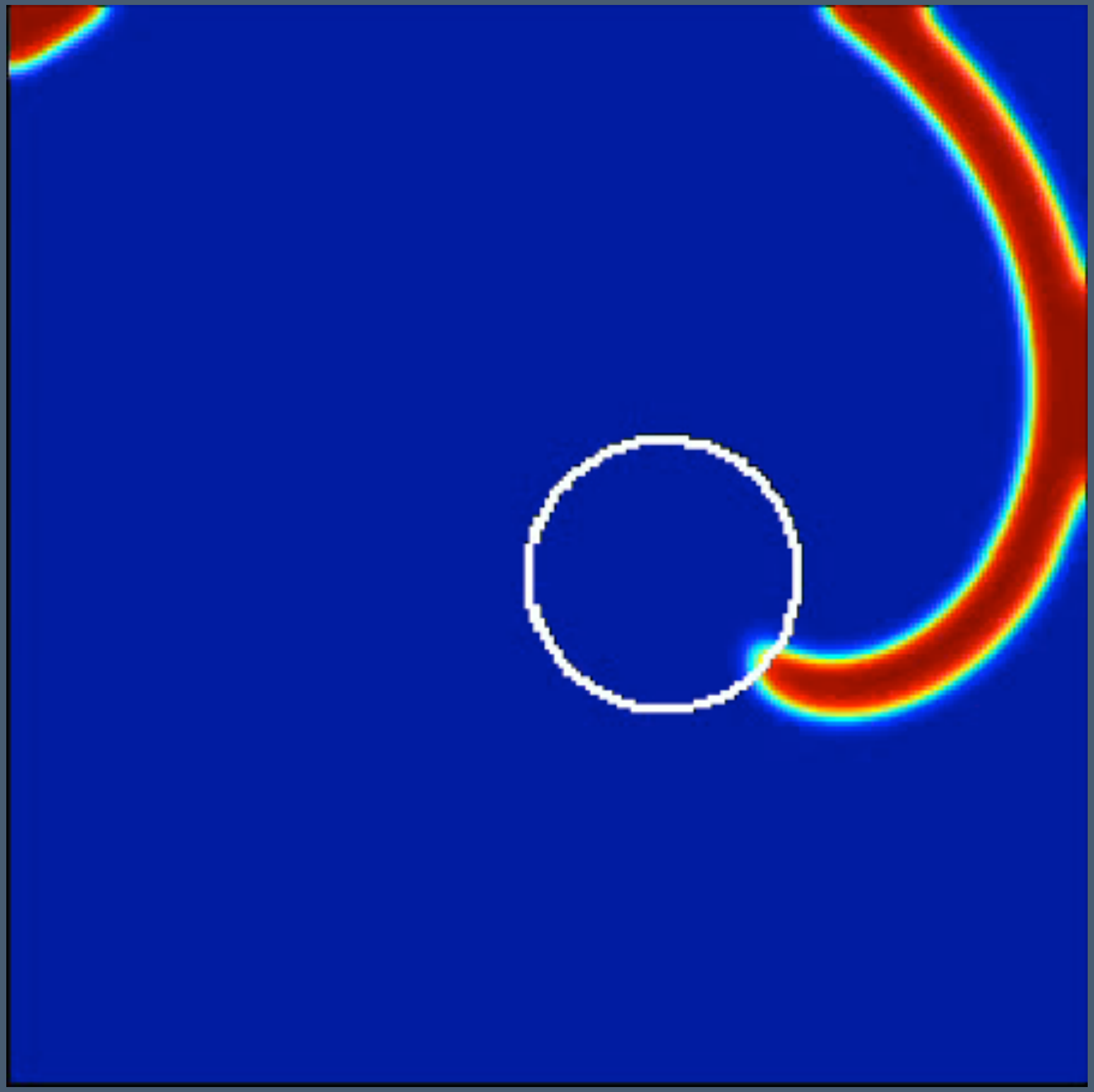
simulations: P. Bittihn

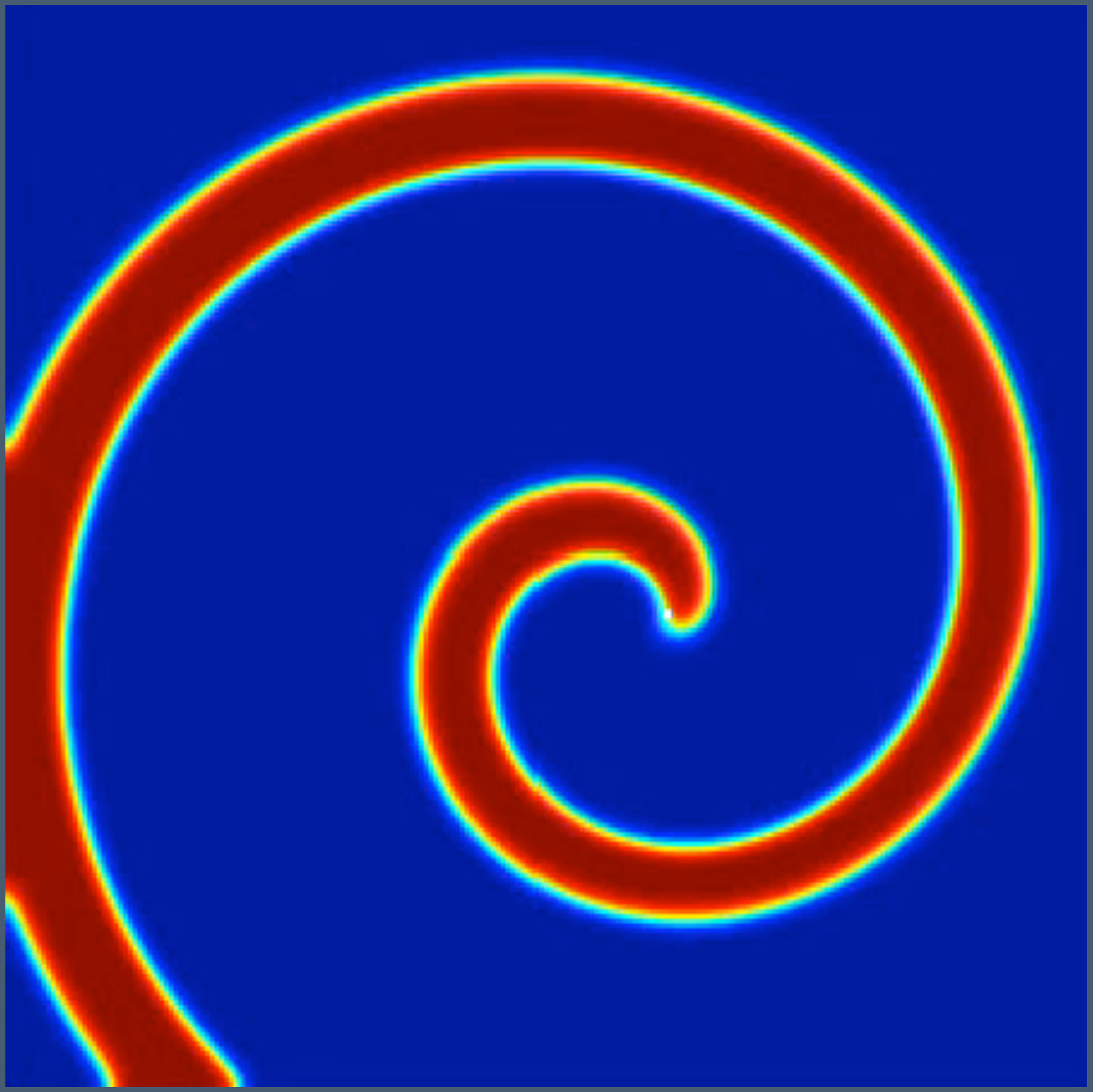
refractory region
(currently not excitable)

Spiral waves (Barkley model)

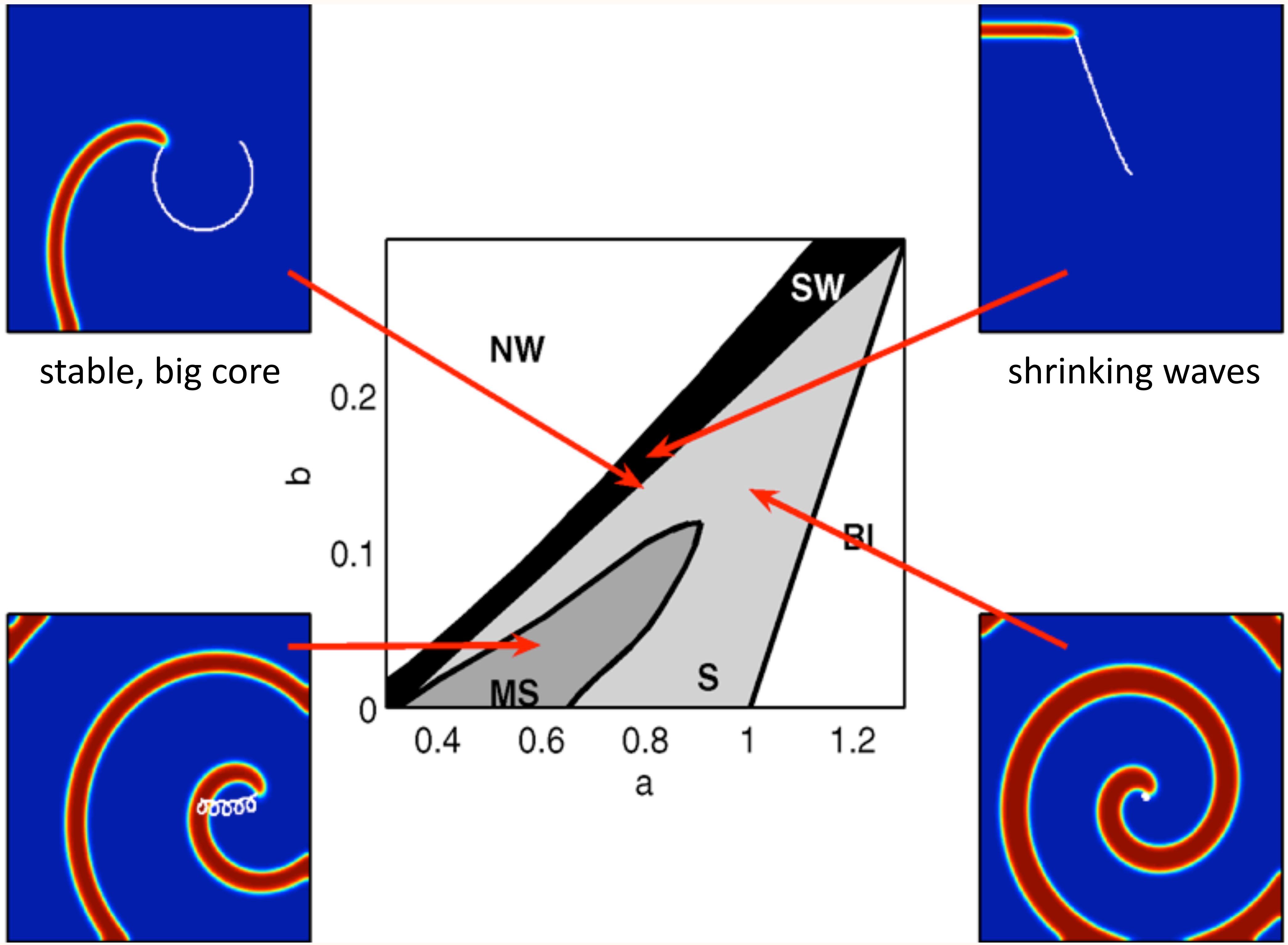


Spiral waves (Barkley model)





Barkley Model – Parameter Space



stable, big core

shrinking waves

meandering spirals

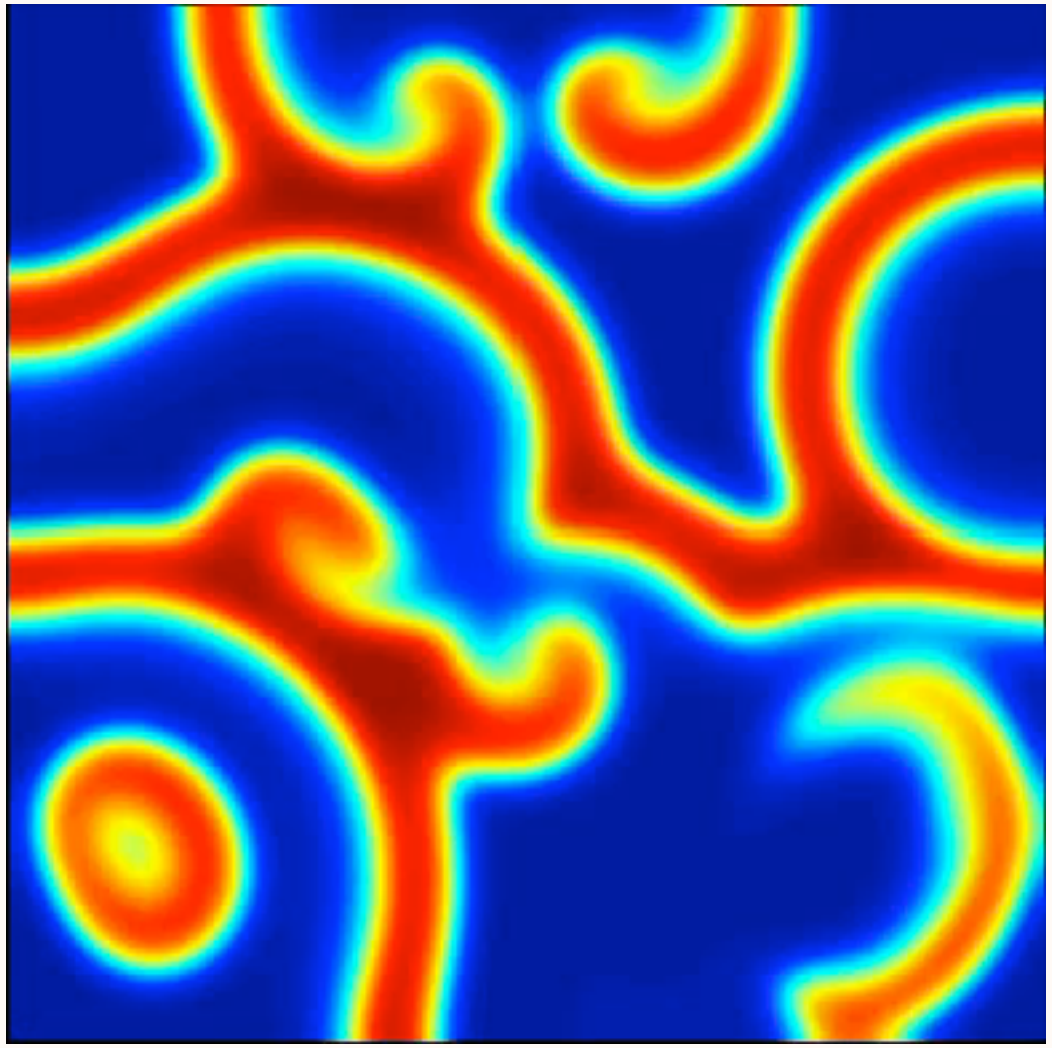
stable, small core

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

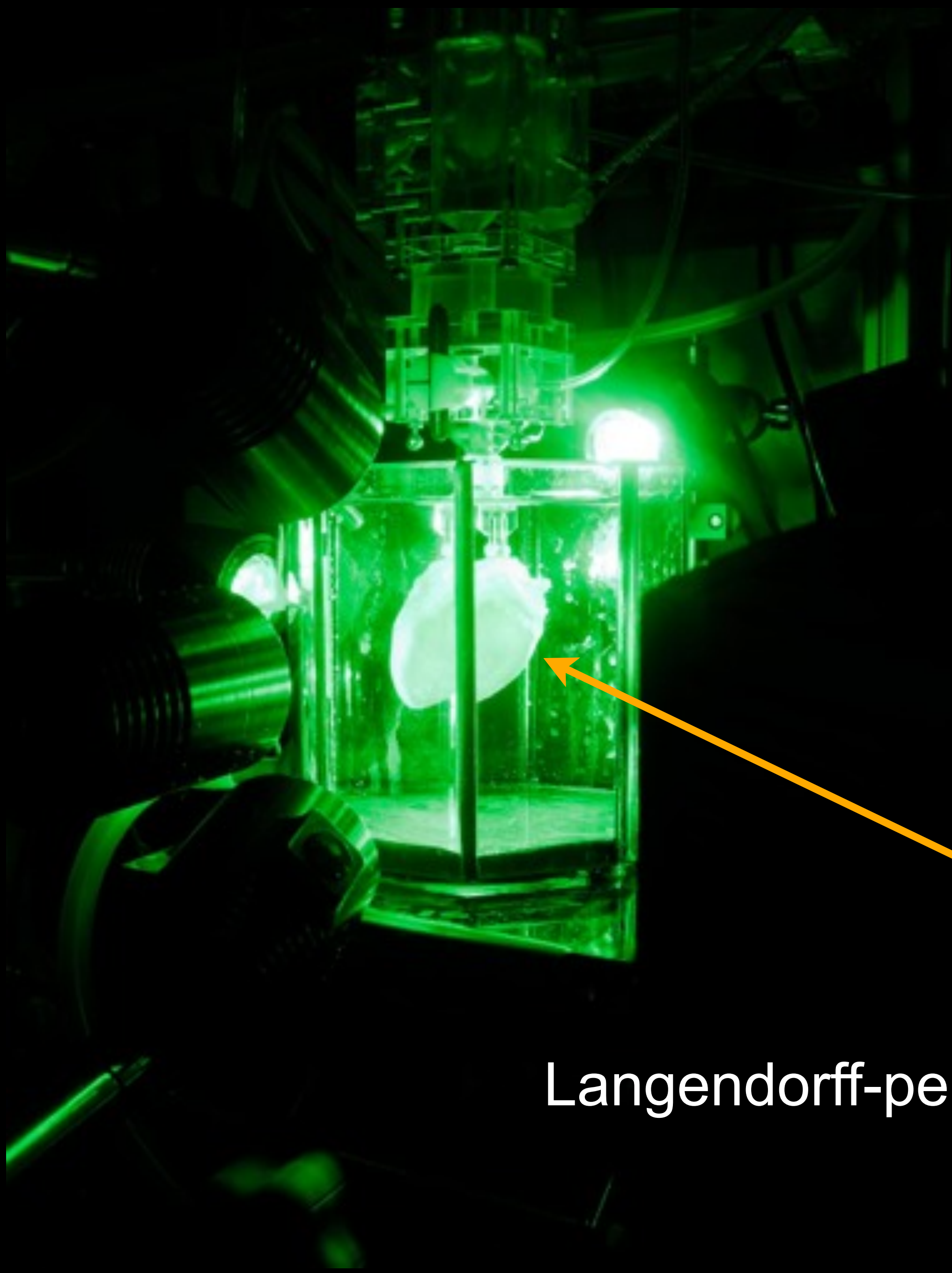


http://www.scholarpedia.org/article/Barkley_model

Experimental Techniques

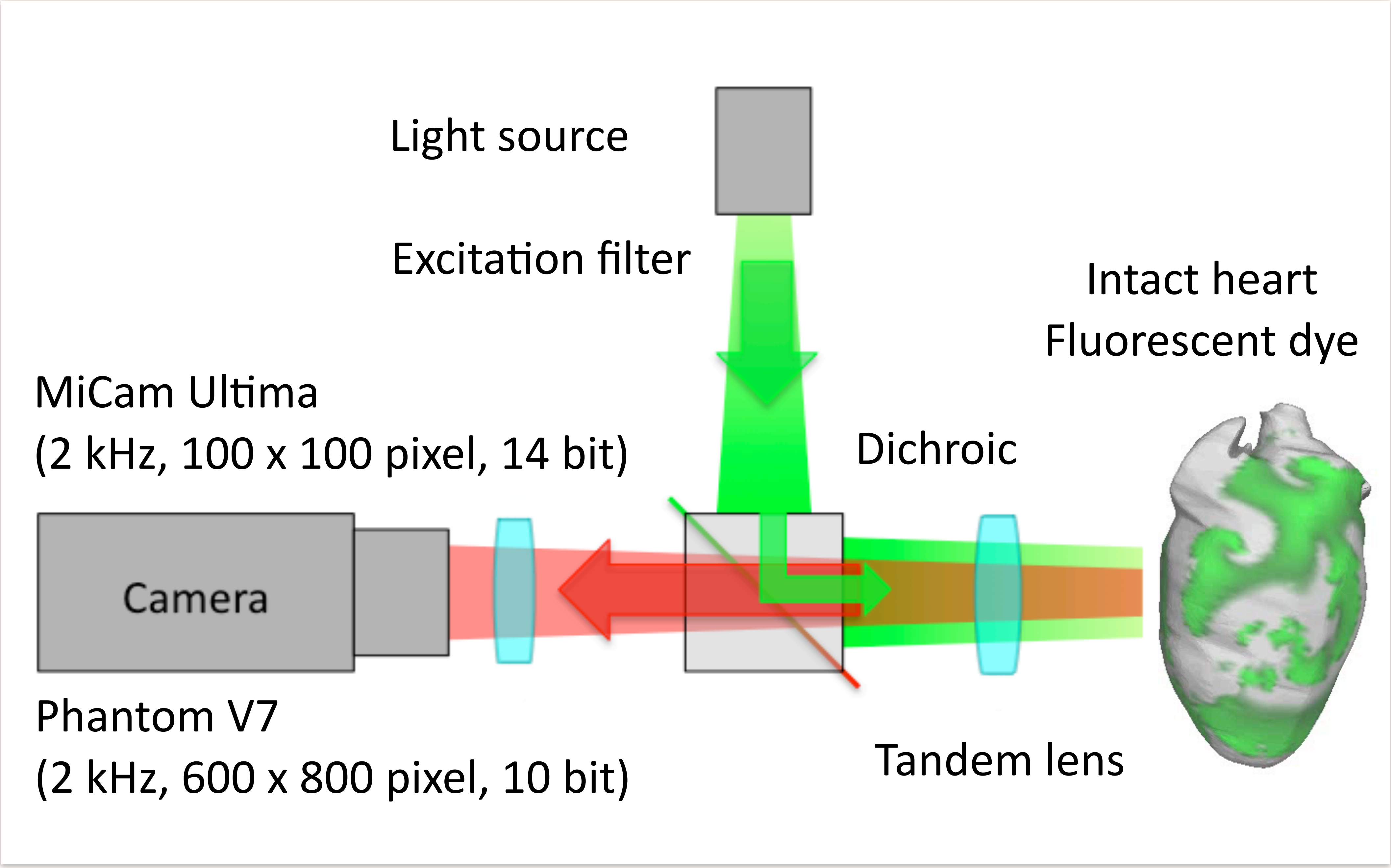
How to visualize electrical excitation in experiments

Optical Mapping



Langendorff-perfused intact rabbit heart

Optical Mapping using Fluorescent Dyes

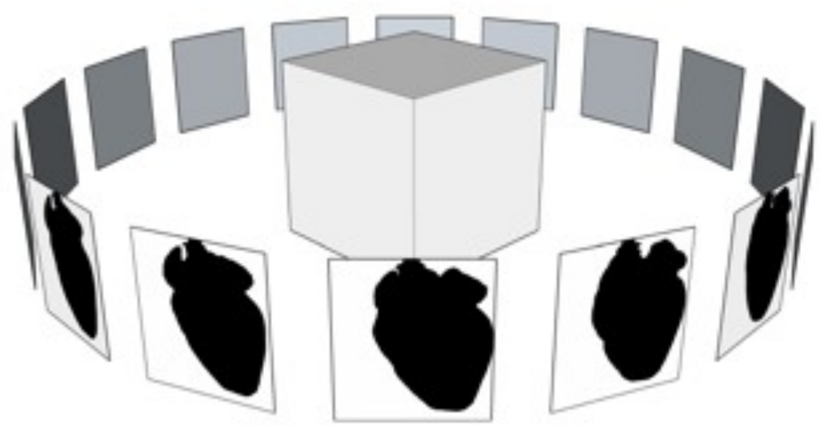


Spectral intensity of emitted light (here: red) depends on membrane voltage and/or Calcium concentration.

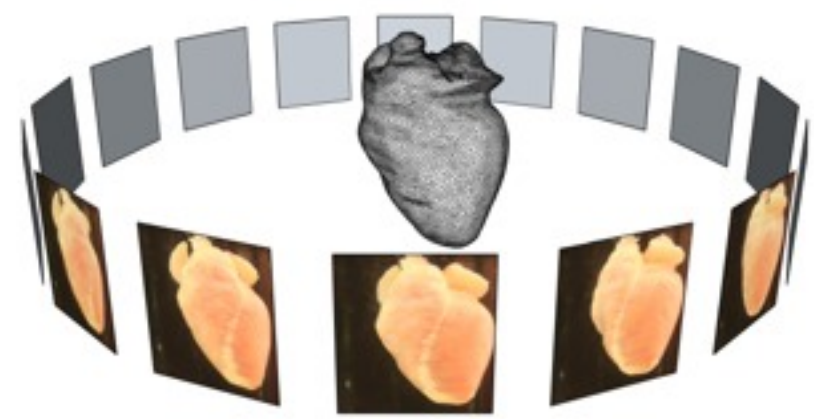
3D Surface Reconstruction

1. Image acquisition with calibrated camera

2. Intersect projected silhouettes with 3d volume.

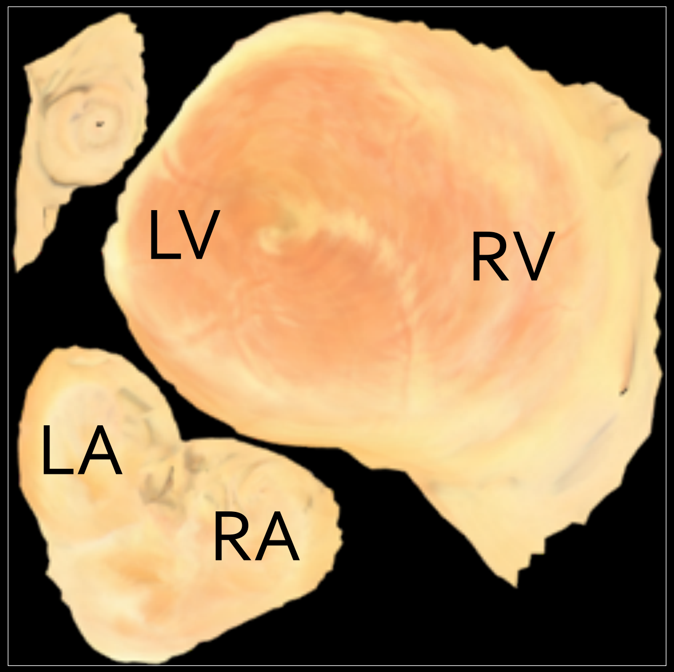


3. Project images onto reconstructed mesh.



Final textured mesh:

Texture map:



State and Parameter Estimation

Experiment or Model — **Time Series** → **Model of Interest**
parameters & variables unknown

Task: Estimate model states and parameters from observed time series.

Methods: Synchronization, Optimization, Kalman Filter, Particle Filters, ...

G. Evensen, *Data assimilation: The Ensemble Kalman Filter.* (Springer, Berlin, 2006)

H. U. Voss, J. Timmer, and J. Kurths, Int. J. Bif. Chaos 14, 1905 (2004)

P. J. van Leeuwen,Q. J. R. Meteorol. Soc. 136, 1991 (2010)

and many others ...

Synchronization based state and parameter estimation

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

Synchronization Based State and Parameter Estimation

Example: Excitable Media

cubic Barkley model

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

chaotic

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

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

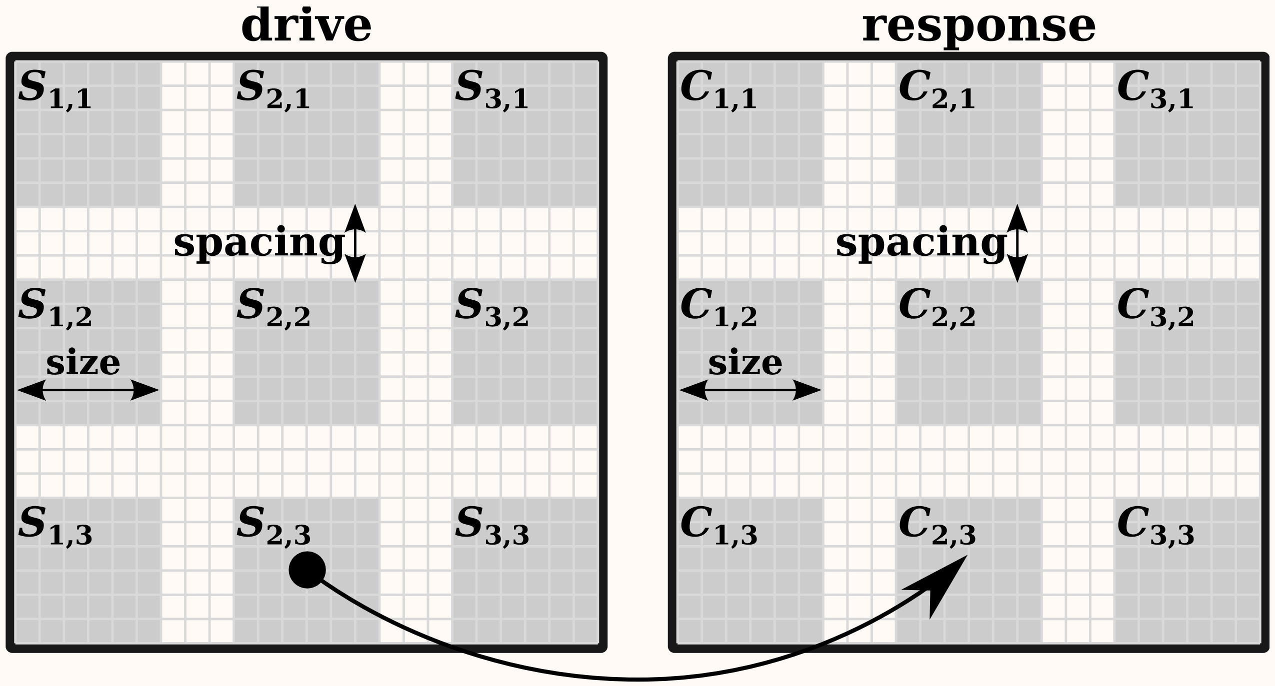
- no-flux boundary conditions
- implementation of the PDE integration scheme on a graphics processing unit (GPU) resulting in a speed up of a factor 50-100

Uni-directional local coupling

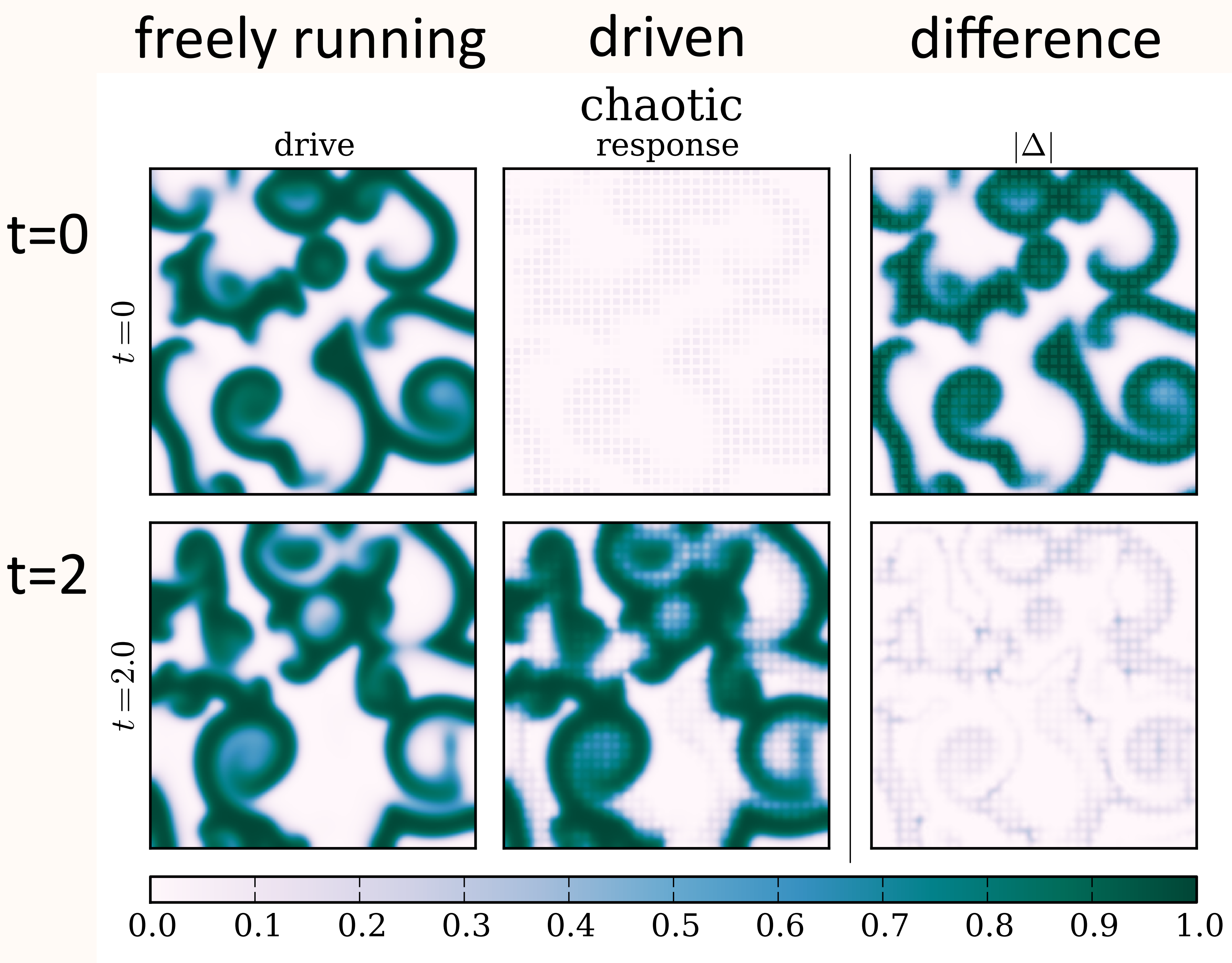
"experiment" → "model"

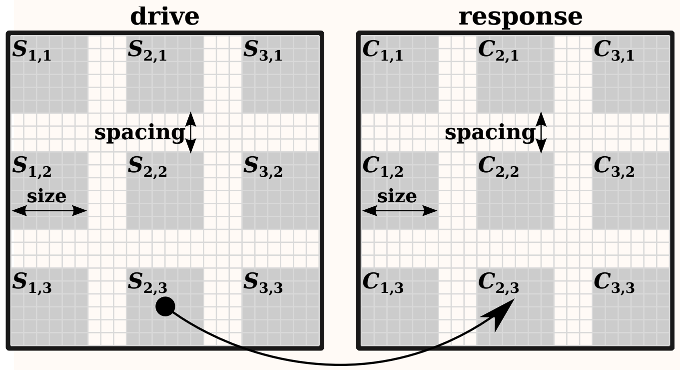
using Sensors and Controllers

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



Cubic Barkley model



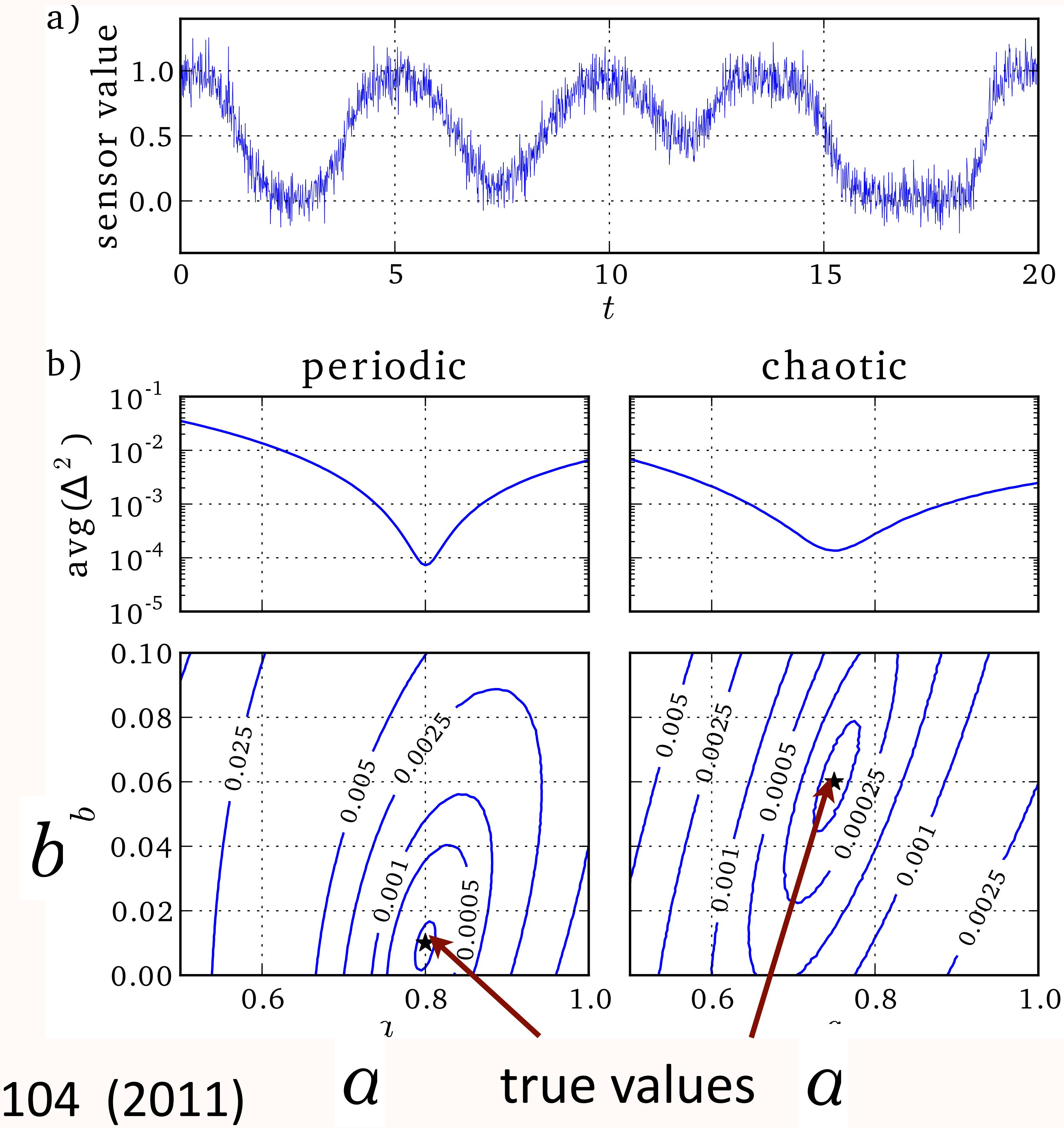


grid of size: 294×294 - sensor sizes: 6×6 grid points - sensor spacing 3 grid points

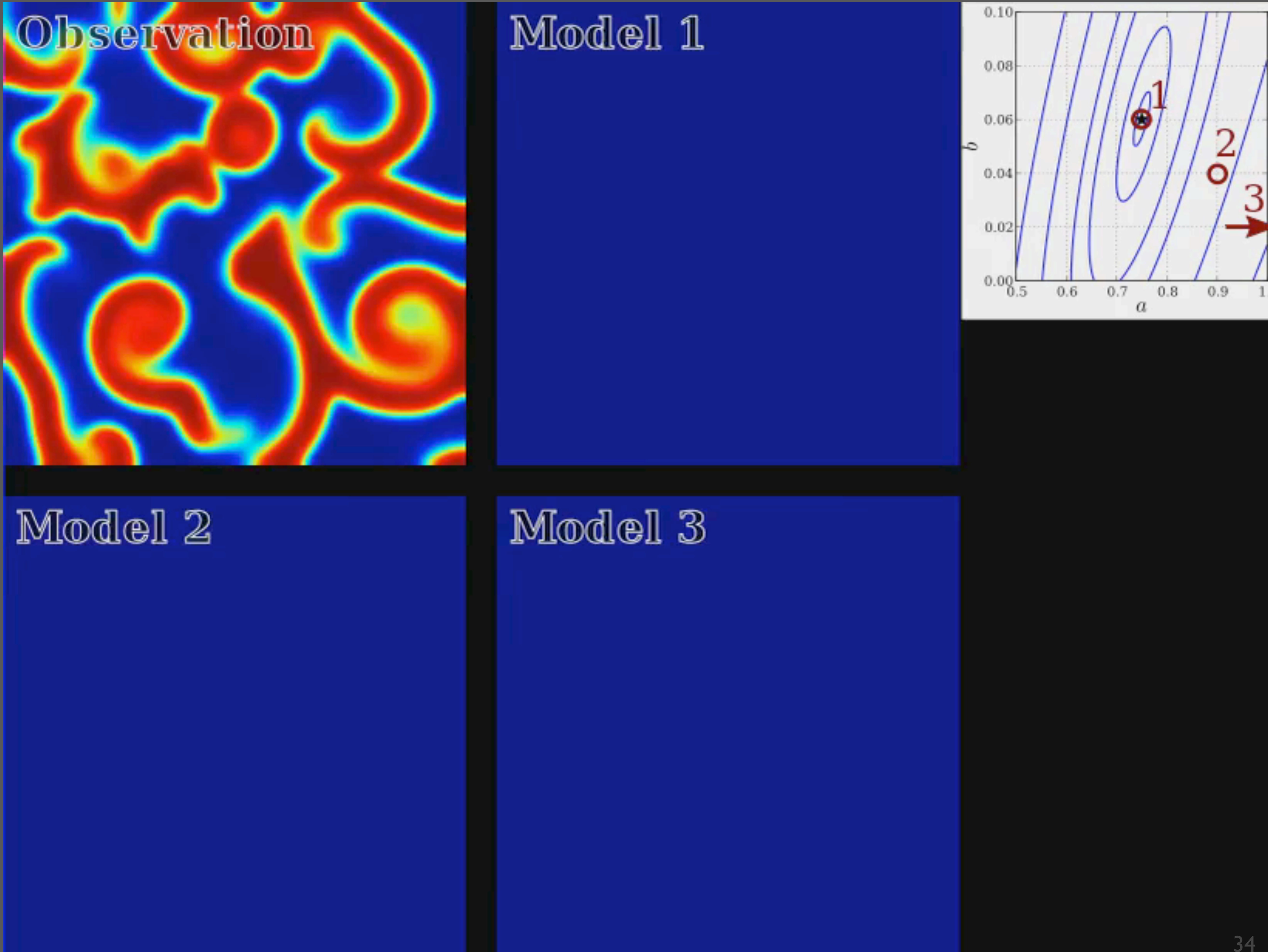
Parameter Estimation

Typical noisy chaotic sensor signal (SNR= 12dB)

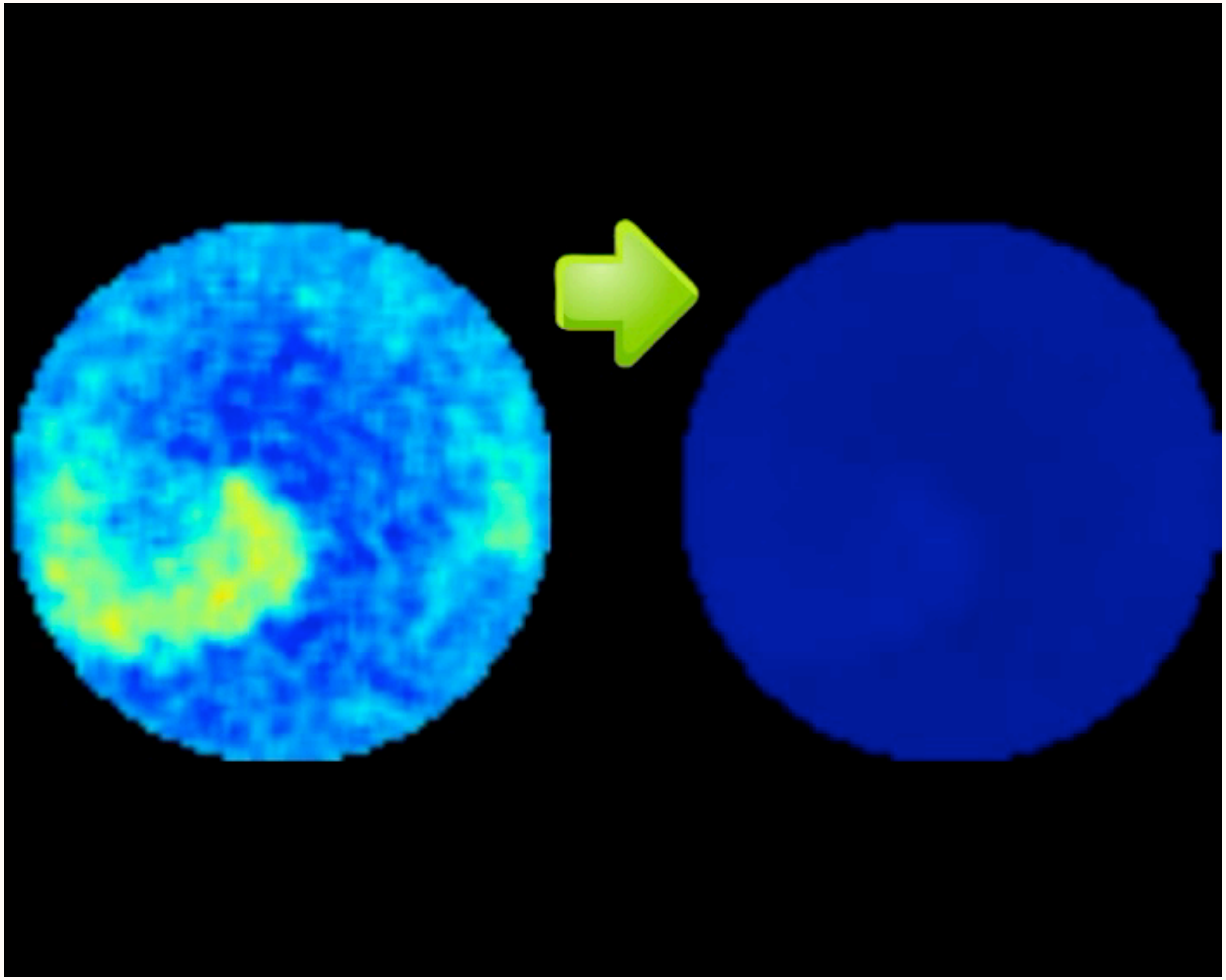
Parameter space of the response Barkley system with contour curves showing the averaged synchronization error



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


Observation
Model 1
Model 2
Model 3
0.10
0.08
0.06
0.04
0.02
0.00
b
0.5
0.6
0.7
0.8
0.9
1.0
a
1
2
3

Cell Culture Experiment drives Barkley Model



T.K. Shajahan
S. Berg

Exploiting delay coordinates for synchronization

Accurate state and parameter estimation in nonlinear systems with sparse observations

Daniel Rey, Michael Eldridge, Mark Kostuk, Henry D.I. Abarbanel, Jan Schumann-Bischoff, UP

Physics Letters A 378 (2014) 869–873

Exploiting delay coordinates for synchronization

D - dimensional system generating the time series: $$\frac{d\mathbf{y}}{dt} = \mathbf{F}(\mathbf{y}, \mathbf{p})$$

scalar time series: $\{y_1(t)\}$

M - dimensional delay coordinates map H

$$\mathbf{r}(t) = \mathbf{H}(\mathbf{y}(t)) = \{y_1(t), y_1(t+\tau), ..., y_1(t+(D_M-1)\tau)\}$$

model: $$\frac{d\mathbf{x}}{dt} = \mathbf{F}(\mathbf{x}, \mathbf{p})$$ $\rightarrow$ time series: $\{x_1(t)\}$

generates *M* - dimensional delay vector:

$$\mathbf{s}(t) = \mathbf{H}(\mathbf{x}(t)) = \{x_1(t), x_1(t+\tau), ..., x_1(t+(D_M-1)\tau)\}$$

Exploiting delay coordinates for synchronization

diffusive coupling exploiting delay reconstruction:

$$
\begin{aligned}
g\left[\mathbf{y}(t) - \mathbf{x}(t)\right] &= g\left[\mathbf{H}^{-1}(\mathbf{r}(t)) - \mathbf{H}^{-1}(\mathbf{s}(t))\right] \\
&\approx gD\mathbf{H}^{-1}(\mathbf{r}(t) - \mathbf{s}(t))
\end{aligned}
$$

implemented in the original state space via inverse Jacobian matrix $D\mathbf{H}^{-1}$ of the delay coordinates map H:

coupling switched on at discrete times, only

$$
\frac{d\mathbf{x}(t)}{dt} = \mathbf{F}(\mathbf{x}(t)) + \sum_{n=0}^{N} g\delta(t - t_n)\, D\mathbf{H}^{-1}\big(\mathbf{r}(t) - \mathbf{s}(t)\big)
$$

parameter estimation:

consider parameter as additional variable $x_{D+1} = p$ with $\dfrac{dx_{D+1}}{dt} = 0$

Exploiting delay coordinates for synchronization

Example: Lorenz-96 model

ring of D oscillators (introduced by E. Lorenz in 1996) here: D = 20, 10

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = x_{i-1}(t) \cdot (x_{i+1}(t) - x_{i-2}(t)) - x_i(t) + f$$

forcing parameter: $f = 8.17$

$$i = D: \;\; i+1 = 1$$
$$i = 1: \;\; i-1 = D$$

scalar time series: $\{x_1(t_n)\}$

sampled at times: $t_n = n \cdot 0.01, \quad n = 0, \ldots, N = 10001$

model: $$\frac{\mathrm{d}y_i}{\mathrm{d}t} = y_{i-1}(t) \cdot (y_{i+1}(t) - y_{i-2}(t)) - y_i(t) + p$$

Exploiting delay coordinates for synchronization

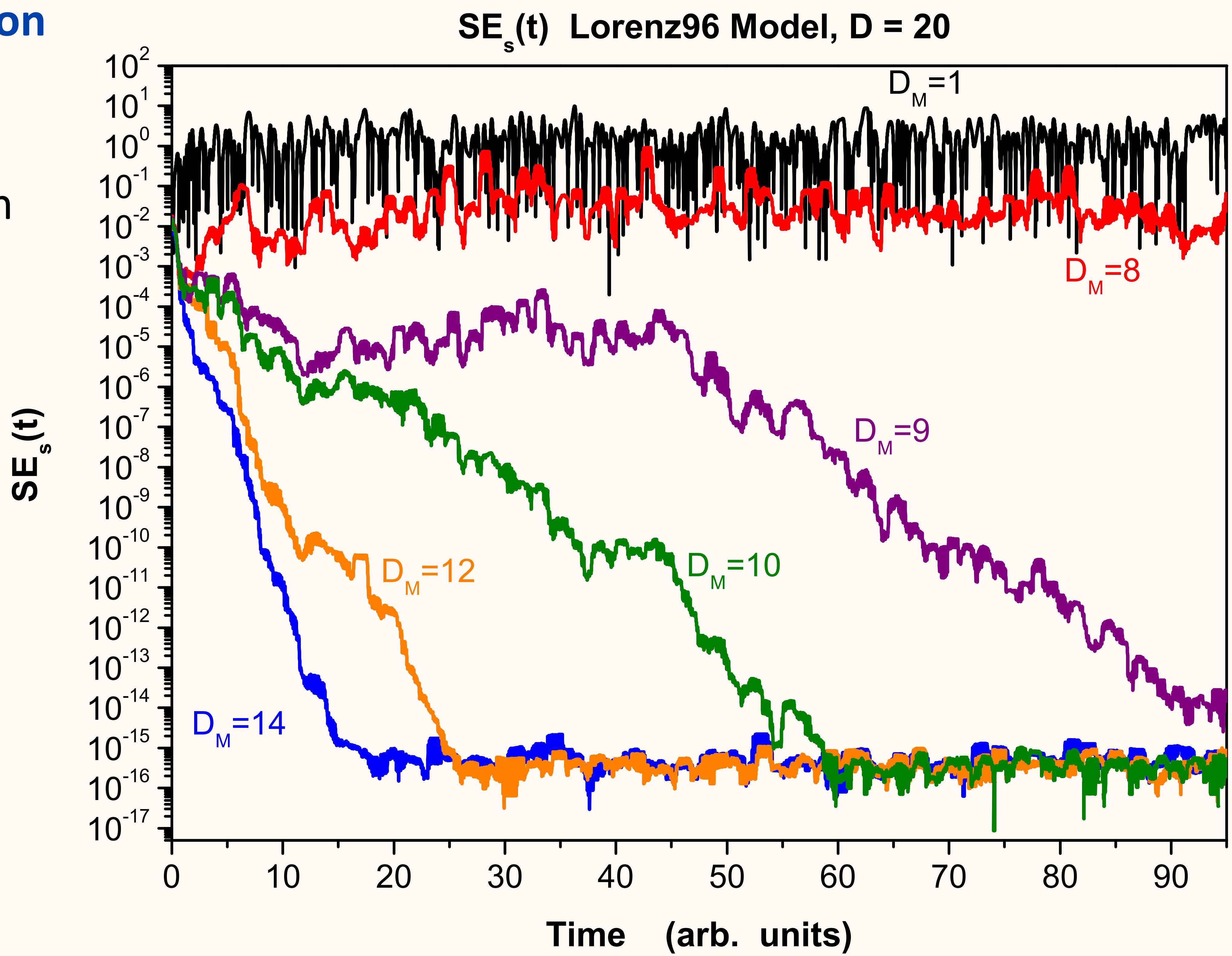
Synchronization Error

synchronization occurs for reconstruction dimension

$$D_M > 8$$

attractor dimension

$$D_A \approx 12$$



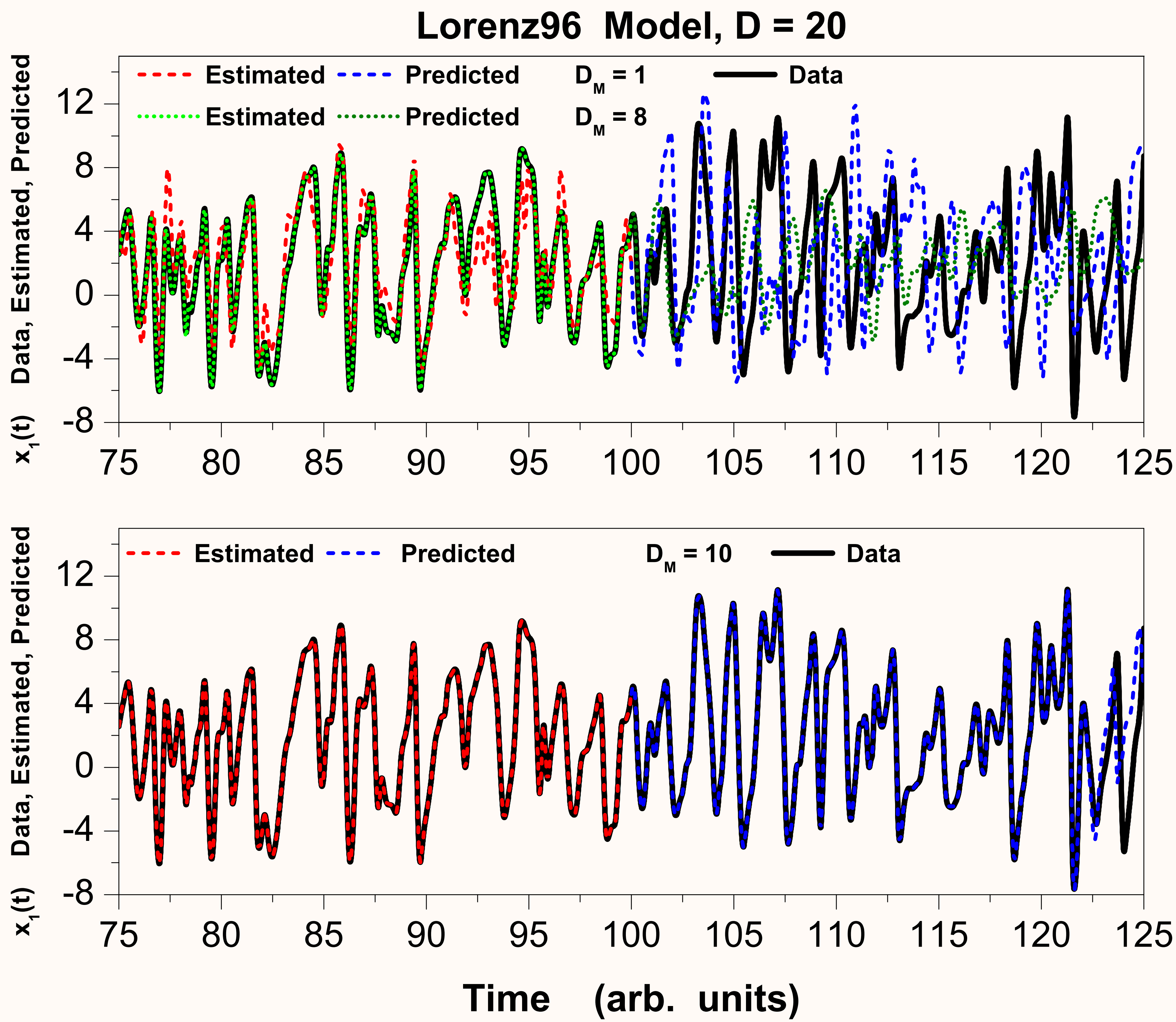
Exploiting delay coordinates for synchronization

Estimation and Prediction

not successful for

$$D_M = 1$$

$$D_M = 8$$

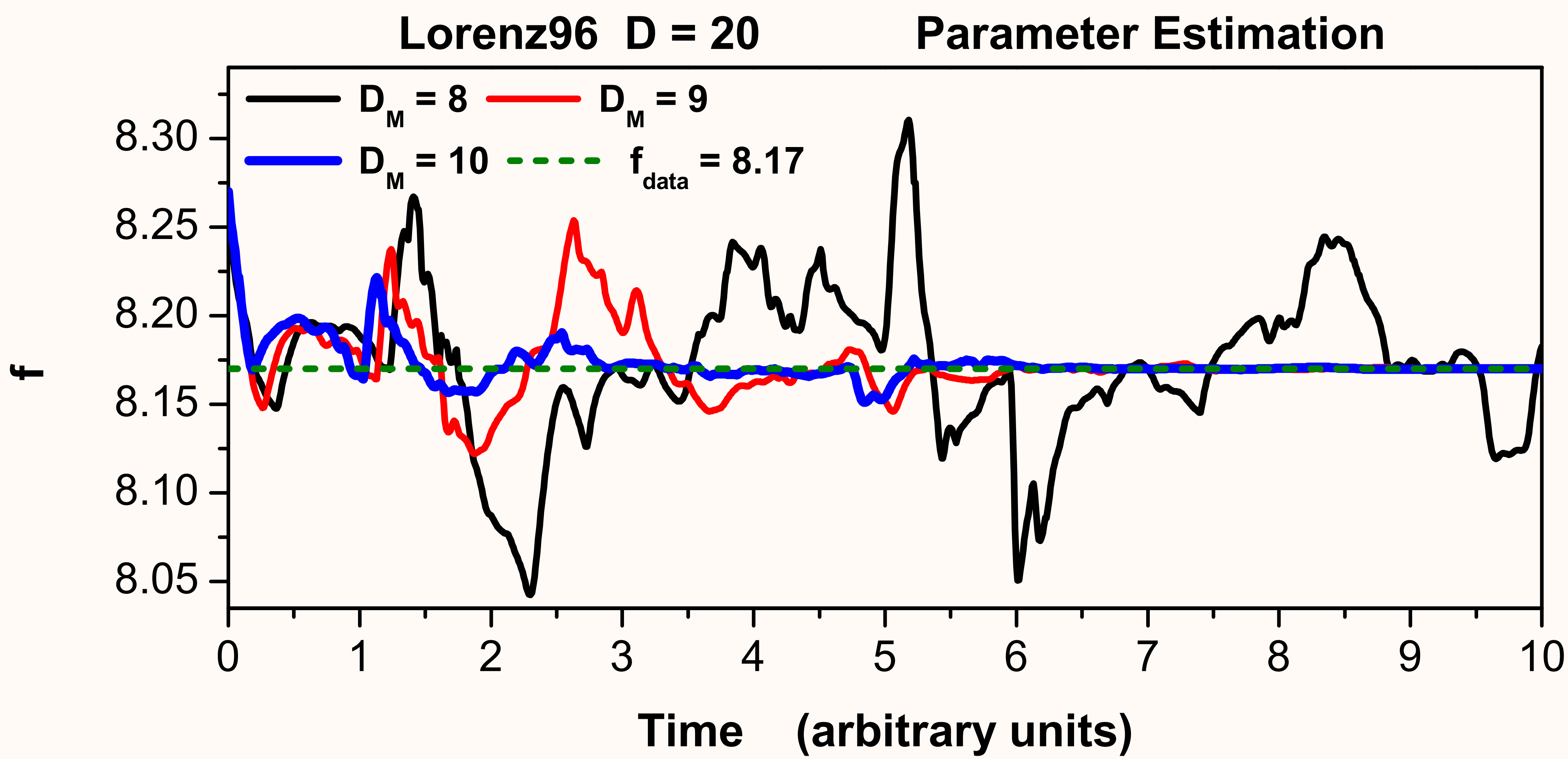


successful for

$$D_M = 10$$

Exploiting delay coordinates for synchronization

Parameter Estimation

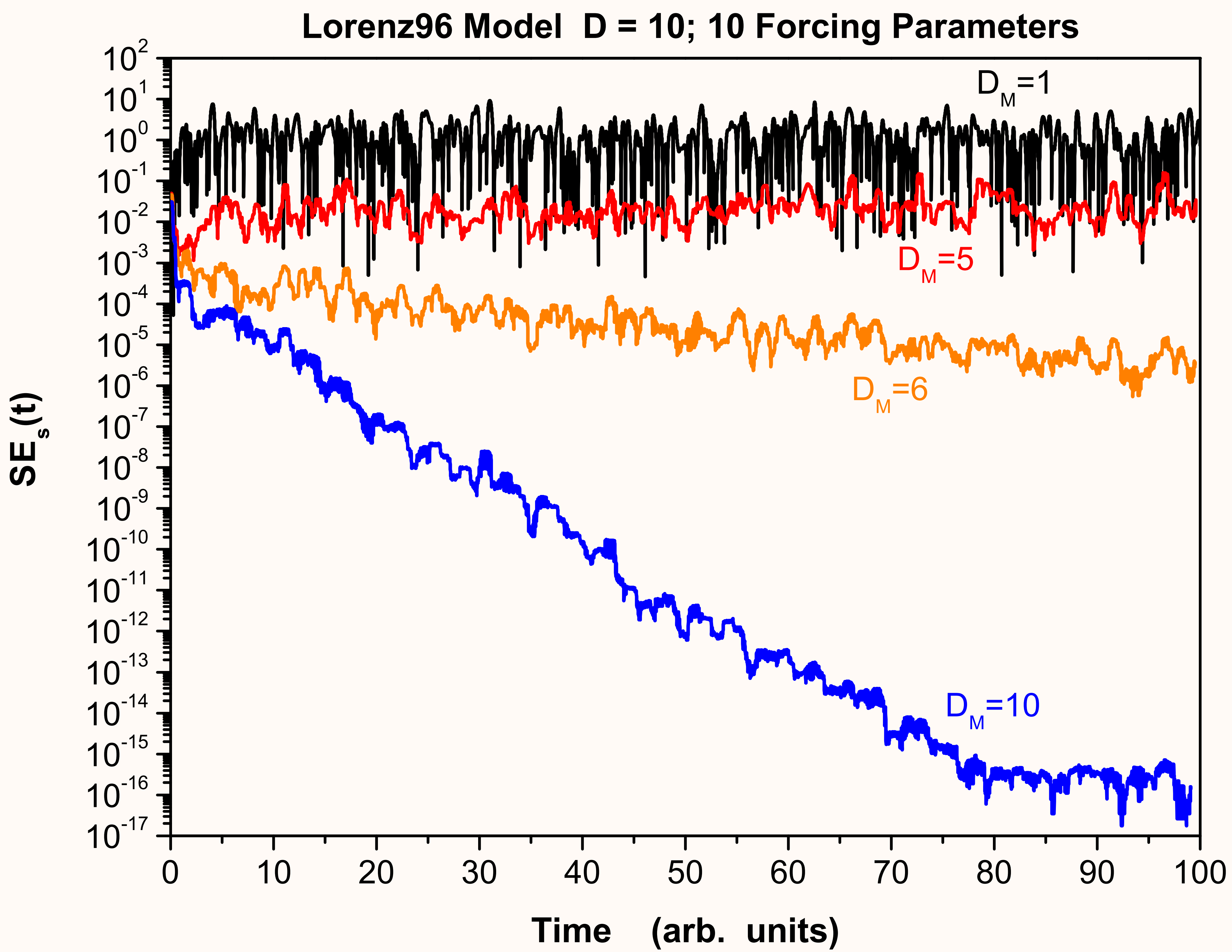


Exploiting delay coordinates for synchronization

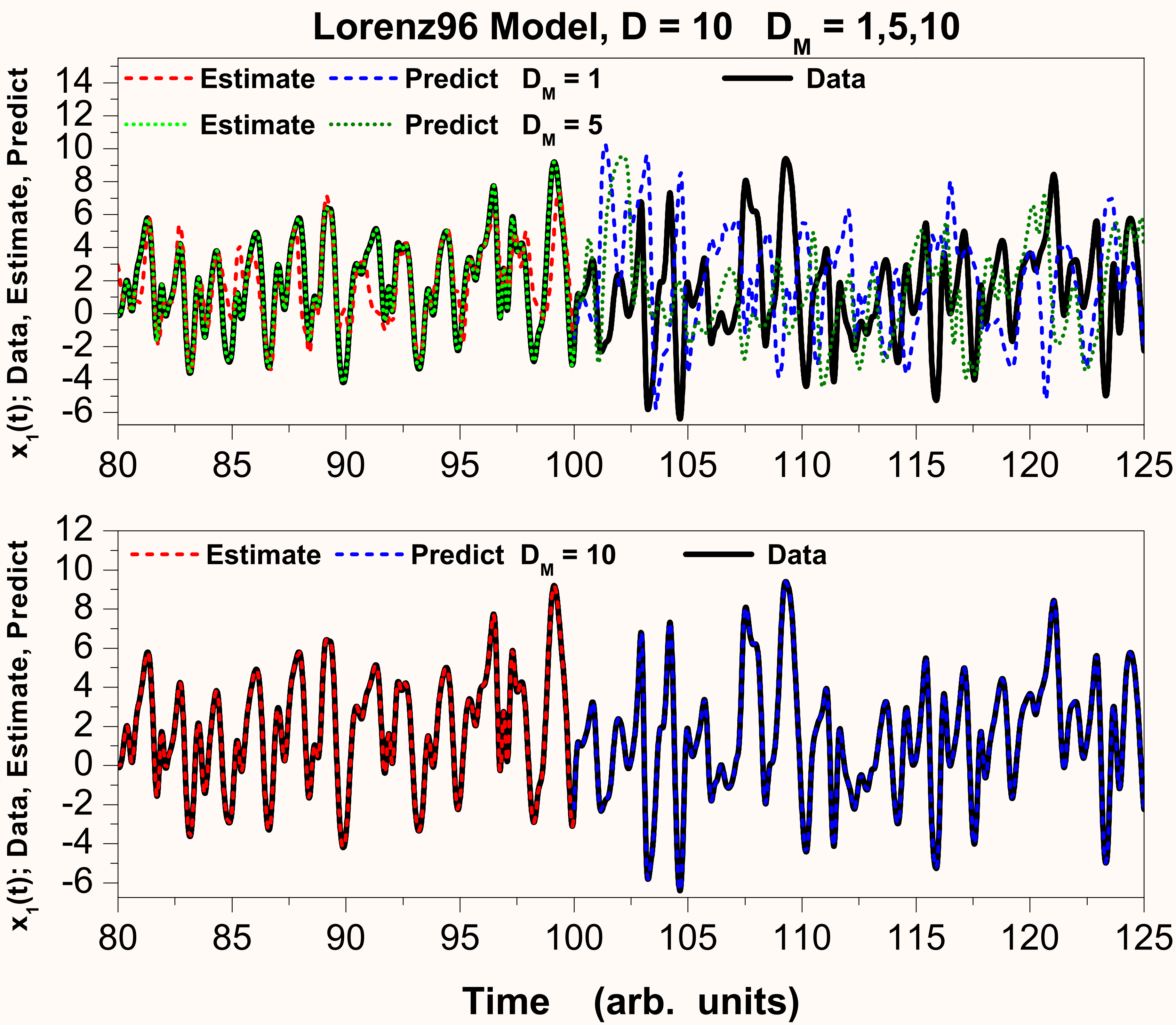
10 - dimensional Lorenz-96 model with different forcing parameters f

successful for

$$D_M > 5$$



Exploiting delay coordinates for synchronization



Optimization based state and parameter estimation

Minimize cost function taking into account (weighted) deviations from the observations and the model equations.

K. Judd, Physica D 237, 216 (2008)
H. D. I. Abarbanel et al., SIAM J. Appl. Dyn. Syst. 8, 1341 (2009)
J. Bröcker, Q. J. R. Meteorol. Soc. 136: 1906 (2010)

unconstrained 4D-Var

Optimization based state and parameter estimation

Given:

d-dimensional dynamical system $$\frac{\mathrm{d}\boldsymbol{y}(t)}{\mathrm{d}t} = \boldsymbol{F}(\boldsymbol{y}(t), \boldsymbol{p}, t)$$

with U unknown parameters $$\boldsymbol{p} = (p_1, \ldots, p_U)^{\mathrm{T}}$$

observed (given) time series $$\{\boldsymbol{\eta}(t_n)\}$$

a measurement function $$\boldsymbol{z}(t) = \boldsymbol{h}(\boldsymbol{y}(t), \boldsymbol{q}, t)$$

with V unknown parameters $$\boldsymbol{q} = (q_1, \ldots, q_V)^{\mathrm{T}}$$

Task:

Determine a (unknown) trajectory $$\{\boldsymbol{y}(t_n)\}_{n=0,\ldots,N}$$

reproducing the observed time series $$\boldsymbol{\eta}(t_n) \stackrel{!}{=} \boldsymbol{z}(t_n) = \boldsymbol{h}(\boldsymbol{y}(t_n), \boldsymbol{q}, t)$$

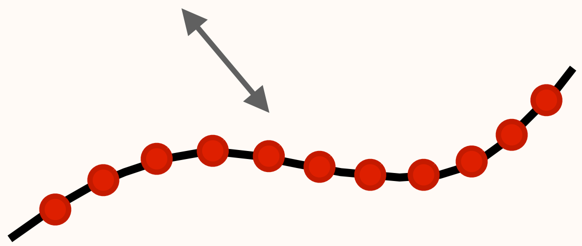
Optimization based state and parameter estimation

Let $\boldsymbol{w} = (\mathcal{Y}(0,N), \boldsymbol{p}, \boldsymbol{q})$ be the vector of all unknown quantities

states along the trajectory: $\mathcal{Y}(0,N) = \{\boldsymbol{y}(t_n) \mid n = 0, 1, \ldots, N\}$

parameters of the model: $\boldsymbol{p}$

parameters of the measurement function: $\boldsymbol{q}$



- solve optimization problem to estimate the unknown variables w
- by minimizing a cost function $C(w)$ taking into account (weighted) deviations from the observations and the model equations
- high dimensional optimization problem
- efficient optimization exploiting sparse Jacobian (sparseLM)

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

J. Schumann-Bischoff et al., Comm. in Nonl. Sci. and Num. Simul. 18, 2733 (2013)

Example: Hindmarsh-Rose neuron model

$$\frac{\mathrm{d}x_1(t)}{\mathrm{d}t} = -x_1(t)^3 + p_1 \cdot x_1(t)^2 + x_2(t) - x_3(t)$$
$$\frac{\mathrm{d}x_2(t)}{\mathrm{d}t} = 1 - p_2 \cdot x_1(t)^2 - x_2(t)$$
$$\frac{\mathrm{d}x_3(t)}{\mathrm{d}t} = p_3 \cdot (x_1(t) + p_4 \cdot (p_5 - x_3(t)))$$

noise

data: $\eta(t_n) = x_1(t_n) + 1.8 + \mathcal{N}_n(0, 0.13)$

estimated:

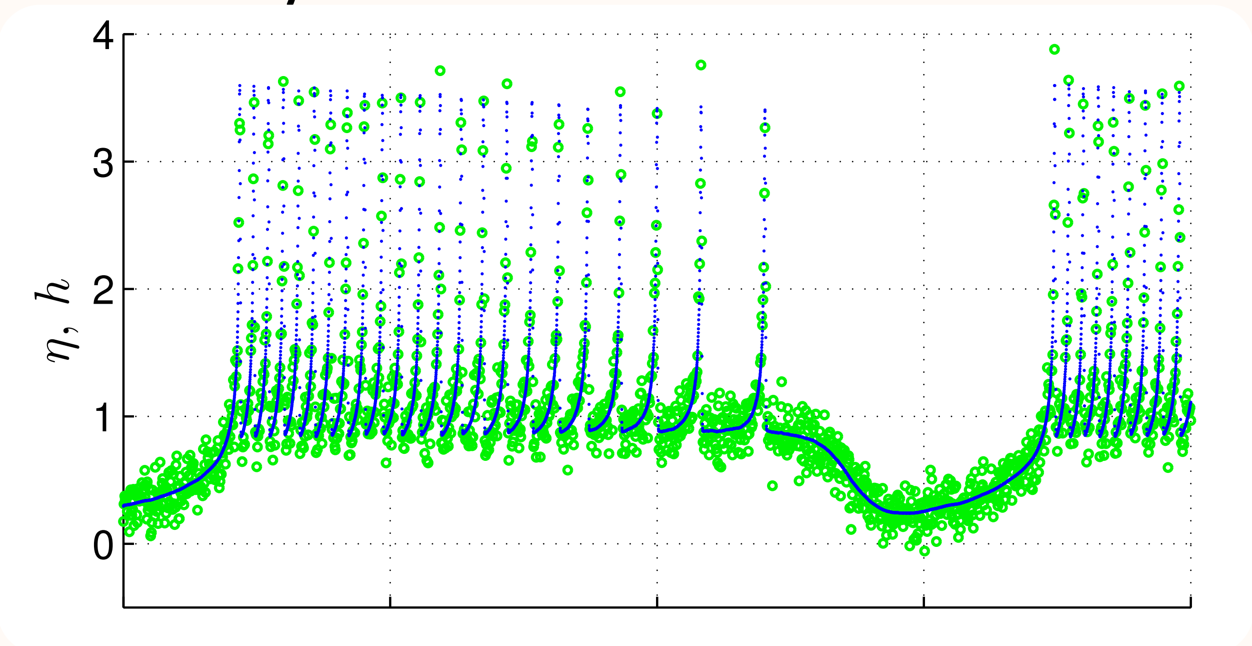
$p_1 = 3$ $\quad p_2 = 5$

$p_3 = 0.004$ $\quad p_4 = 3.19$

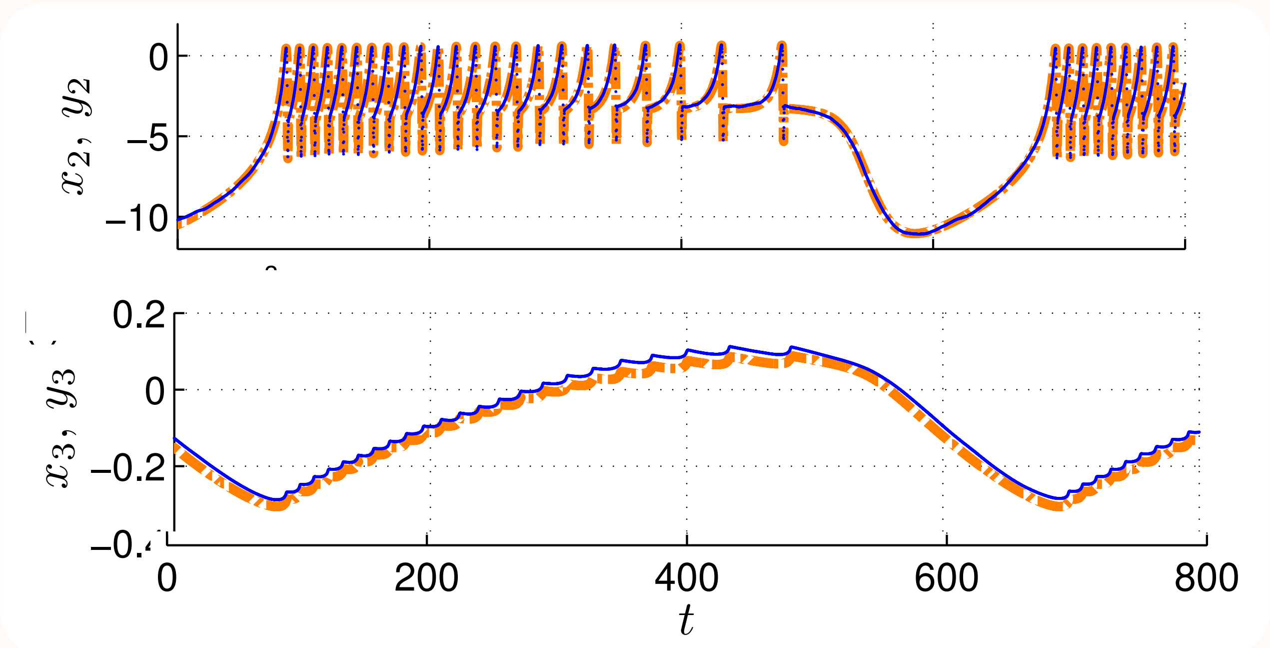
not estimated:

$p_5 = 0.25$

noisy time series and fit



estimated variables



estimated: p = (2.99, 4.98, 0.00397, 3.19) q = 1.791

true: (3, 5, 0.004, 3.19) 1.8

Observability of state variables and parameters of continuous systems

Example: Hindmarsh-Rose neuron model

$$\frac{\mathrm{d}x_1(t)}{\mathrm{d}t} = -x_1(t)^3 + p_1 \cdot x_1(t)^2 + x_2(t) - x_3(t)$$
$$\frac{\mathrm{d}x_2(t)}{\mathrm{d}t} = 1 - p_2 \cdot x_1(t)^2 - x_2(t)$$
$$\frac{\mathrm{d}x_3(t)}{\mathrm{d}t} = p_3 \cdot (x_1(t) + \underline{p_4} \cdot (\underline{p_5} - x_3(t)))$$

data: $\eta(t_n) = x_1(t_n) + 1.8 + \mathcal{N}_n(0, 0.13)$

estimation results: (x_1, x_2, x_3) and

(p_1, p_2) works

(p_4, p_5) fails

Success in parameter and state estimation depends on

- observable and the
- particular variable (parameter) to be estimated

Which variables and parameters can be estimated using a given time series (observable) ?

→ Observability

U. Parlitz, J. Schumann-Bischoff, and S. Luther,
Quantifying uncertainty in state and parameter estimation
Phys. Rev. E 89, 050902(R) (2014)

U. Parlitz, J. Schumann-Bischoff, and S. Luther,
Local observability of state variables and parameters in nonlinear modeling quantified by delay reconstruction
Chaos 24, 024411 (2014)

Summary

- cardiac tissue is an excitable medium
  - spiral waves → tachycardia
  - spatio-temporal chaos → fibrillation
- fluorescent dyes enable visualization of electrical activity
- state and parameter estimation
  - synchronization (observer)
  - optimization