Time series analysis, data assimilation, and machine learning in network physiology

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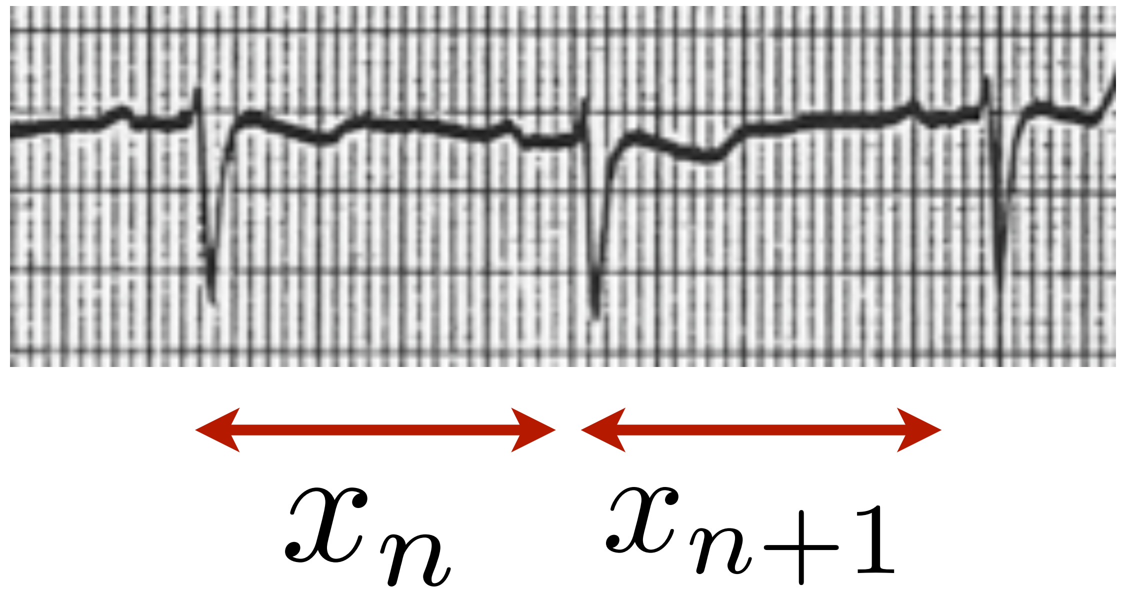
Outline

- quantifying complexity in cardiac arrhythmias using ordinal pattern and permutation entropy
- predicting complex spatio-temporal dynamics using convolutional neural networks

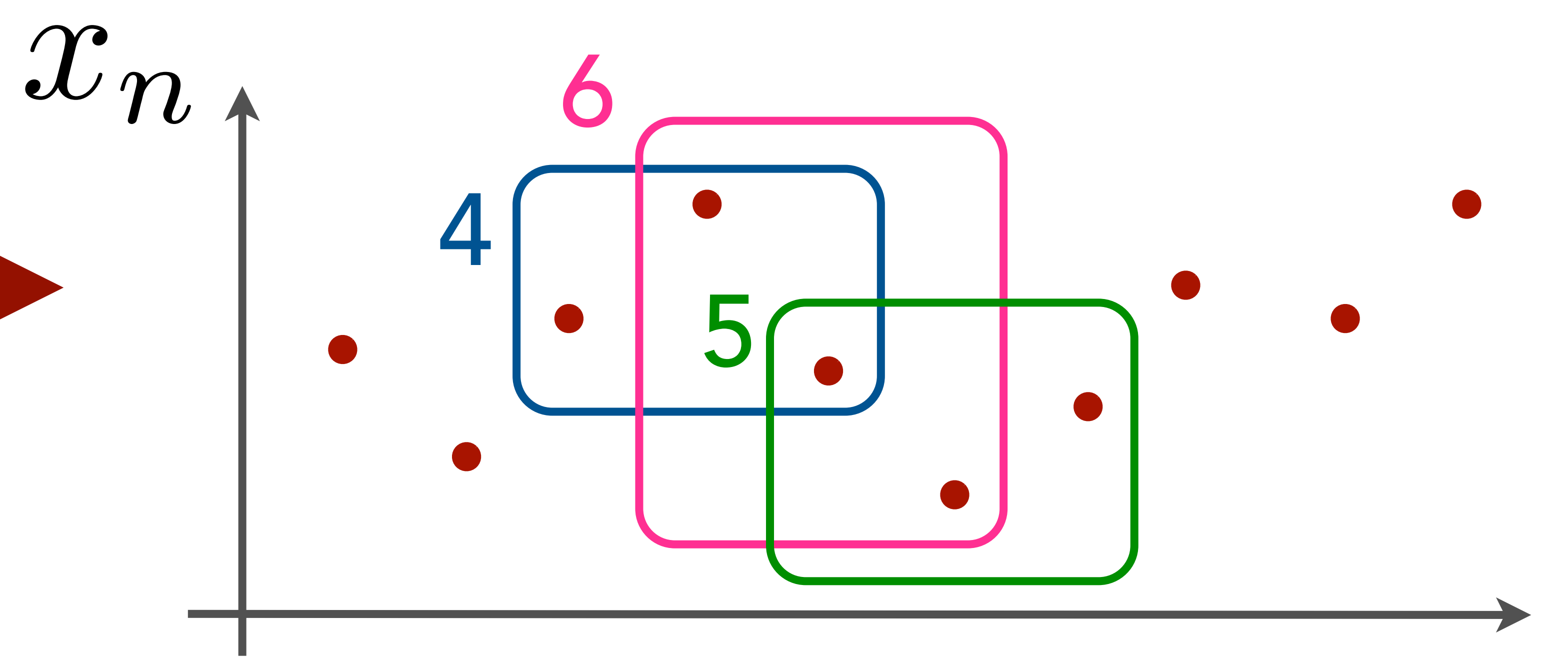
Classifying Electrocardiograms Using Ordinal Patterns

normal rhythm



beat-to-beat intervals (RR intervals)

beat-to-beat time series

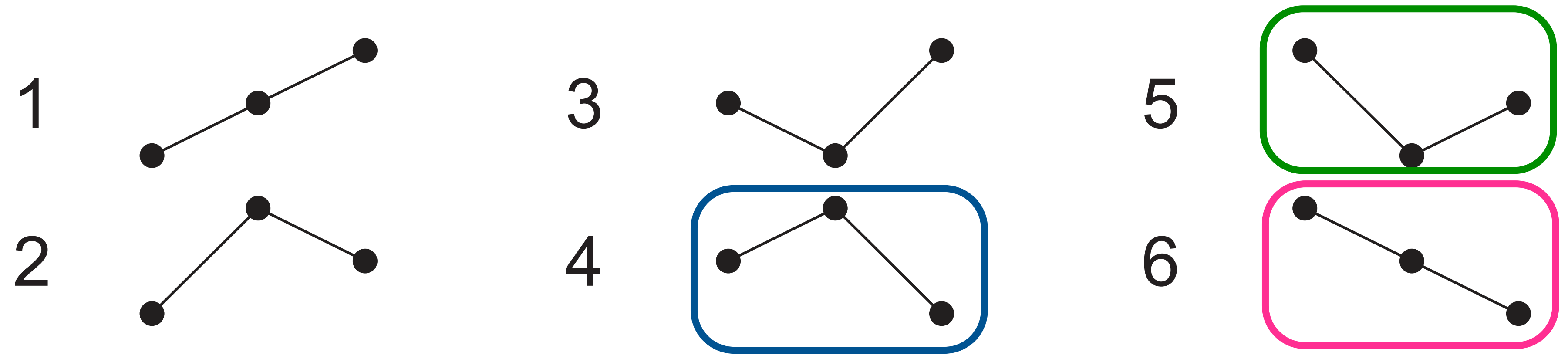


time (beat no.) n

symbolic time series

$4, 6, 5, \ldots$

Characterization of RRI-time series using ordinal patterns describing amplitude relations within segments of time series.



all ordinal patterns of length $W = 3$

p_i = probability of occurrence of pattern i

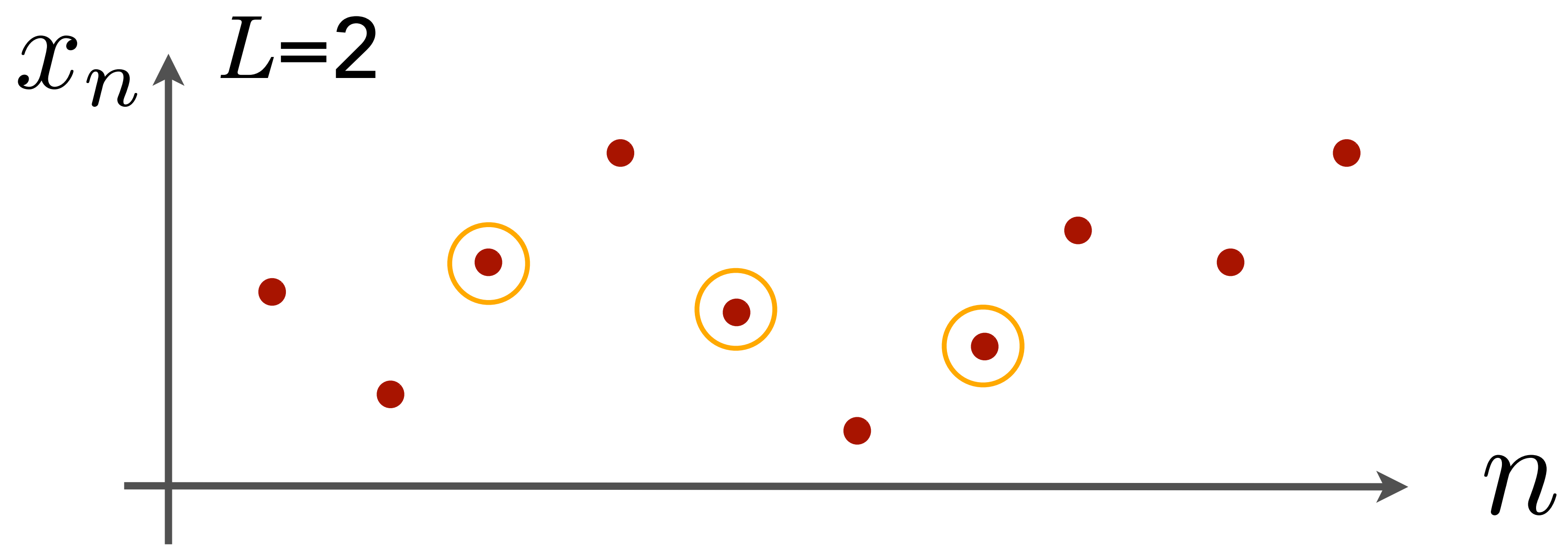
Permutation Entropy

$$PE = -\sum_{i=1}^{W!} p_i \log(p_i)$$

C. Bandt und B. Pompe, Phys. Rev. Lett.99, 174102 (2002)

Ordinal Pattern Distributions Characterizing Heart Rate Variability

Consider subsequences of beat-to-beat intervals sampled with lag L:



$$x_n,\ x_{n+L},\ x_{n+2L},\ \ldots,\ x_{n+(W-1)L}$$

Features (Heart Rate Variabilty parameters, biomarkers) based on ordinal pattern statistics:

perm(L, W, I) = probability of occurrence of patterns with permutation index I for a given lag L and length W

perm entropy(L, W) = Permutation Entropy based on all probabilities for a given lag L and a given word length W

are compared with other heart rate variability parameters

U. Parlitz et al., Computers in Biology and Medicine 42, 319-327 (2012)

Evaluation of Classification Performance

Two data sets (24h beat-to-beat intervals, @256hz):

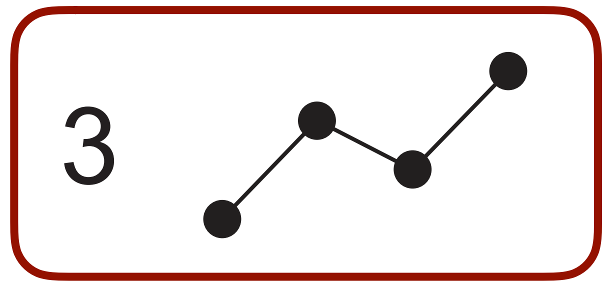
- 15 patients (11 male, 4 female, ages 56 ± 11 yr) suffering from **congestive heart failure (CHF)** (from physionet)
- 15 **healthy** subjects (11 male, 4 female, ages 56 ± 5 yr)

Task: Distinguish and classify both groups using probabilities of ordinal patterns (ordinal pattern distributions) as features.

U. Parlitz et al., Computers in Biology and Medicine 42, 319-327 (2012)

Bivariate classification using pairs of (successful) features

Distribution of CHF cases (red crosses) and healthy subjects (blue filled circles) in two-dimensional feature space. The separating (solid) lines are computed using a linear support vector machine maximizing the margins (indicated by dashed lines).

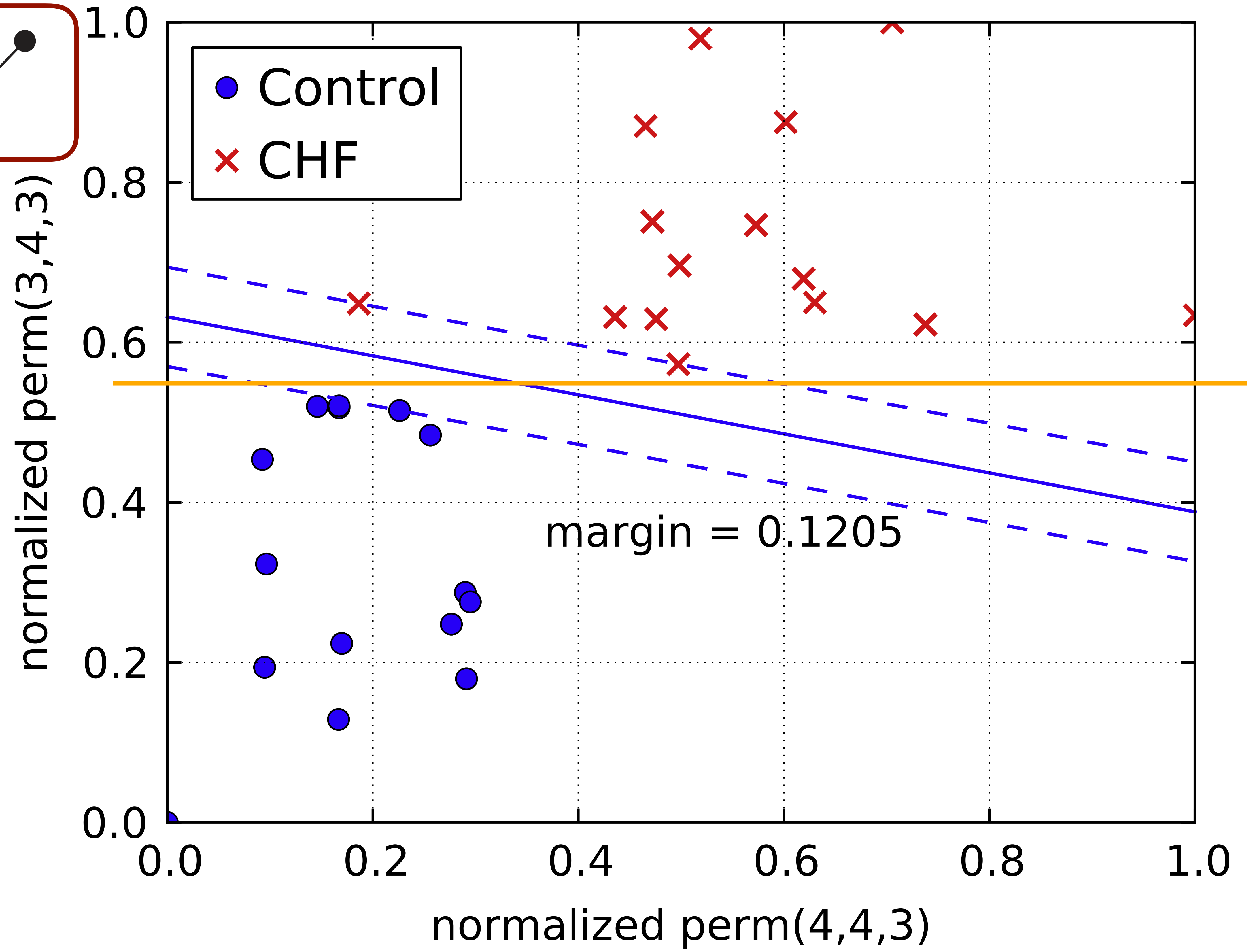


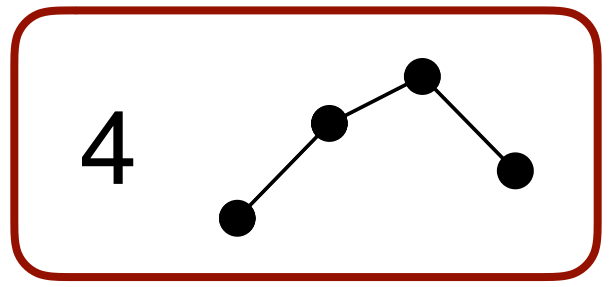
perm(L,W,I)

lag $L = 3$

word length $W = 4$

pattern no. $I = 3$





Ordinal Pattern

These features were compared with **conventional heart rate variability parameters**, like:

- meanNN = mean RRI (inversely related to mean heart rate)
- sdNN = standard deviation of RRI values
- (V)LF = (very) low frequency band (0.0033–0.04 Hz) 0.04-0.15 Hz
- HF = high frequency band 0.15–0.4 Hz
- LFn = normalized low frequency band (LF/(LF-HF))
- shannon = Shannon entropy (using amplitude binning)
- etc.

Leave-one-out cross validation for a simple classification scheme minimizing the number of misclassifications on the training set.

Ordinal Pattern

Results

Feature	p-value	% of correct class. Both	Con.	CHF
sdNN	$3.5 \cdot 10^{-6}$	90	93	87
VLF	$2.7 \cdot 10^{-5}$	80	80	80
LF	$1.6 \cdot 10^{-5}$	70	73	67
HF	$4.3 \cdot 10^{-3}$	73	80	67
perm(3,4,3)	$1.3 \cdot 10^{-8}$	100	100	100
perm(4,4,3)	$3.9 \cdot 10^{-7}$	97	100	93
perm(3,4,5)	$1.3 \cdot 10^{-6}$	87	93	80
perm(4,4,18)	$1.8 \cdot 10^{-6}$	93	100	87
perm(4,5,109)	$9.0 \cdot 10^{-8}$	97	100	93

with pre-filtering

Feature	p-value	% of correct class. Both	Con.	CHF
sdNN	$2.7 \cdot 10^{-1}$	67	87	47
VLF	$2.9 \cdot 10^{-2}$	67	80	53
LF	$2.2 \cdot 10^{-1}$	60	73	47
HF	$2.7 \cdot 10^{-1}$	70	100	40
perm(3,4,3)	$1.3 \cdot 10^{-8}$	100	100	100
perm(4,4,3)	$5.8 \cdot 10^{-7}$	97	100	93
perm(3,4,5)	$3.9 \cdot 10^{-7}$	90	93	87
perm(4,4,18)	$2.5 \cdot 10^{-6}$	97	100	93
perm(4,5,109)	$9.0 \cdot 10^{-8}$	97	100	93

without pre-filtering

artifacts: 6.8% of CHF / 3.3% of control

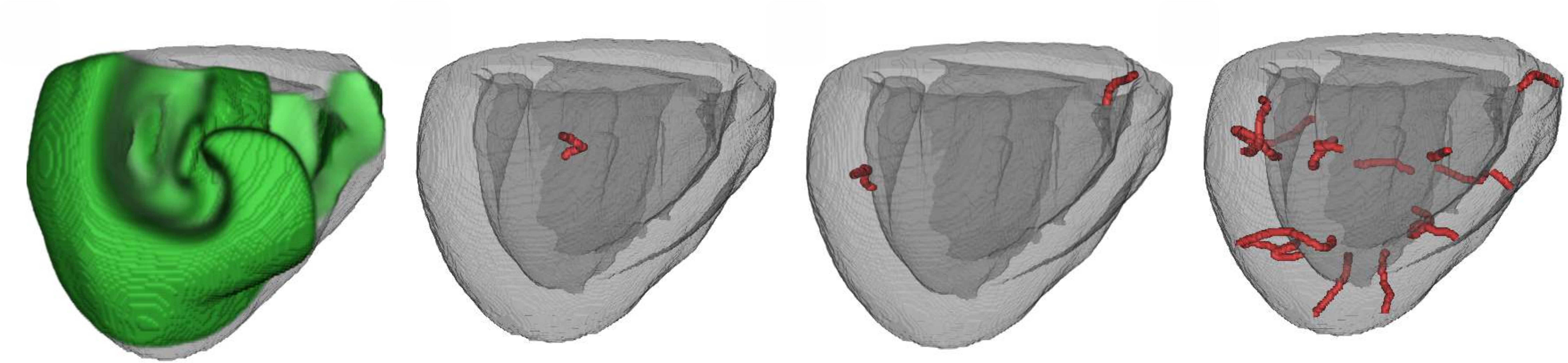
Features based on ordinal pattern are not sensitive to noise.

Complexity Fluctuations in Cardiac Dynamics

A. Schlemmer et al., *Physiol. Meas.* 38, 1561 (2017)

Complexity Fluctuations

Intermittent scroll wave dynamics in a numerical simulation



Number of scroll wave filaments NFIL fluctuates.

Fluctuations of complexity of wave dynamics → laminar phases

(How) Can we observe these complexity fluctuations in ECG data?

Complexity Fluctuations during Ventricular Fibrillation in a Rabbit Heart

ECG time series

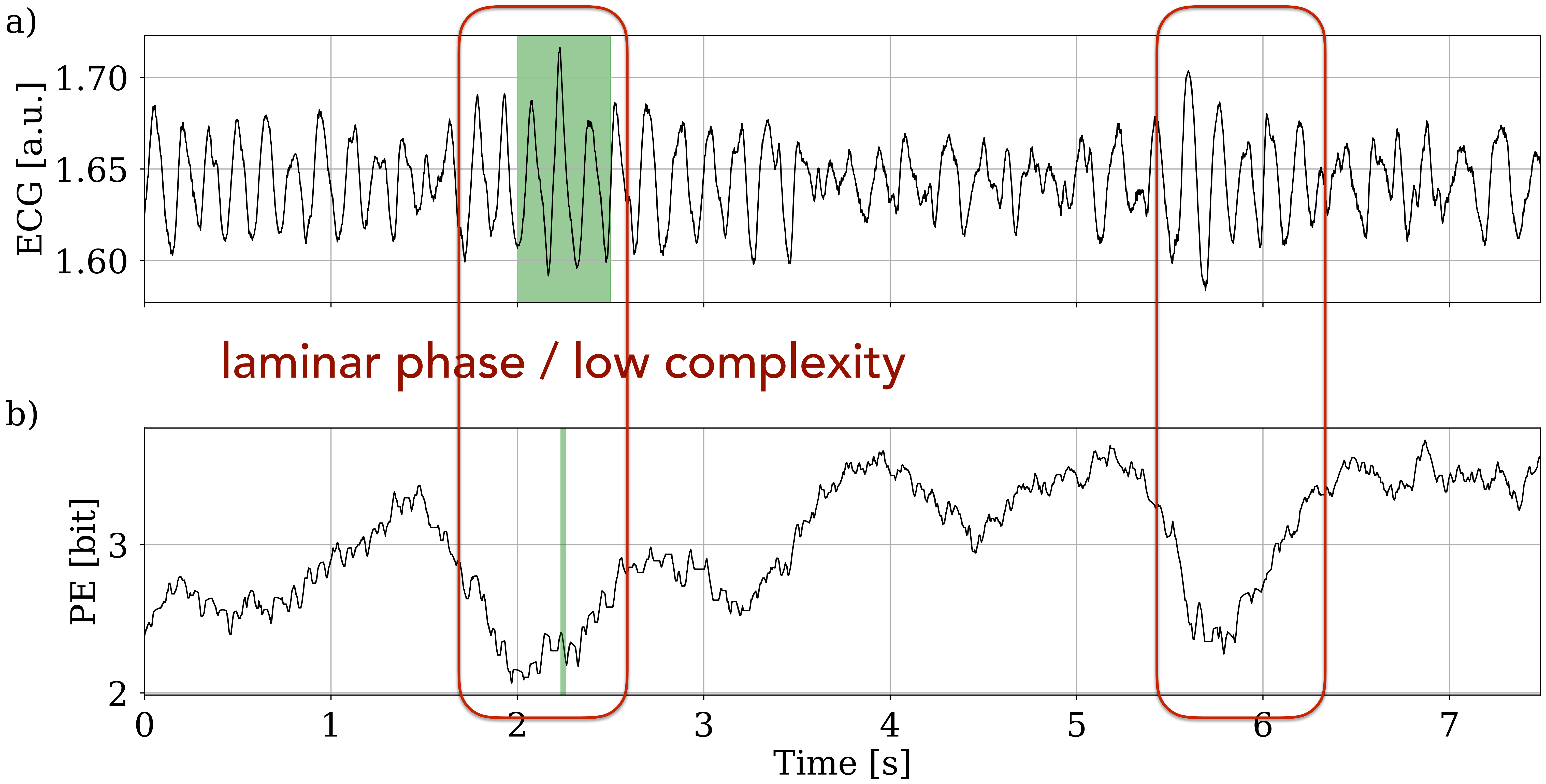
The **shaded rectangle** indicates the **0.5 s time window** from which the **corresponding Permutation Entropy** is calculated.

Permutation Entropy (PE)

$$H = -\sum_{j=0}^{n!-1} p_j \cdot \log_2 p_j$$

p_j = probability of order pattern j

ex-vivo



PE of continuous ECG signal, NOT from beat-to-beat time series!

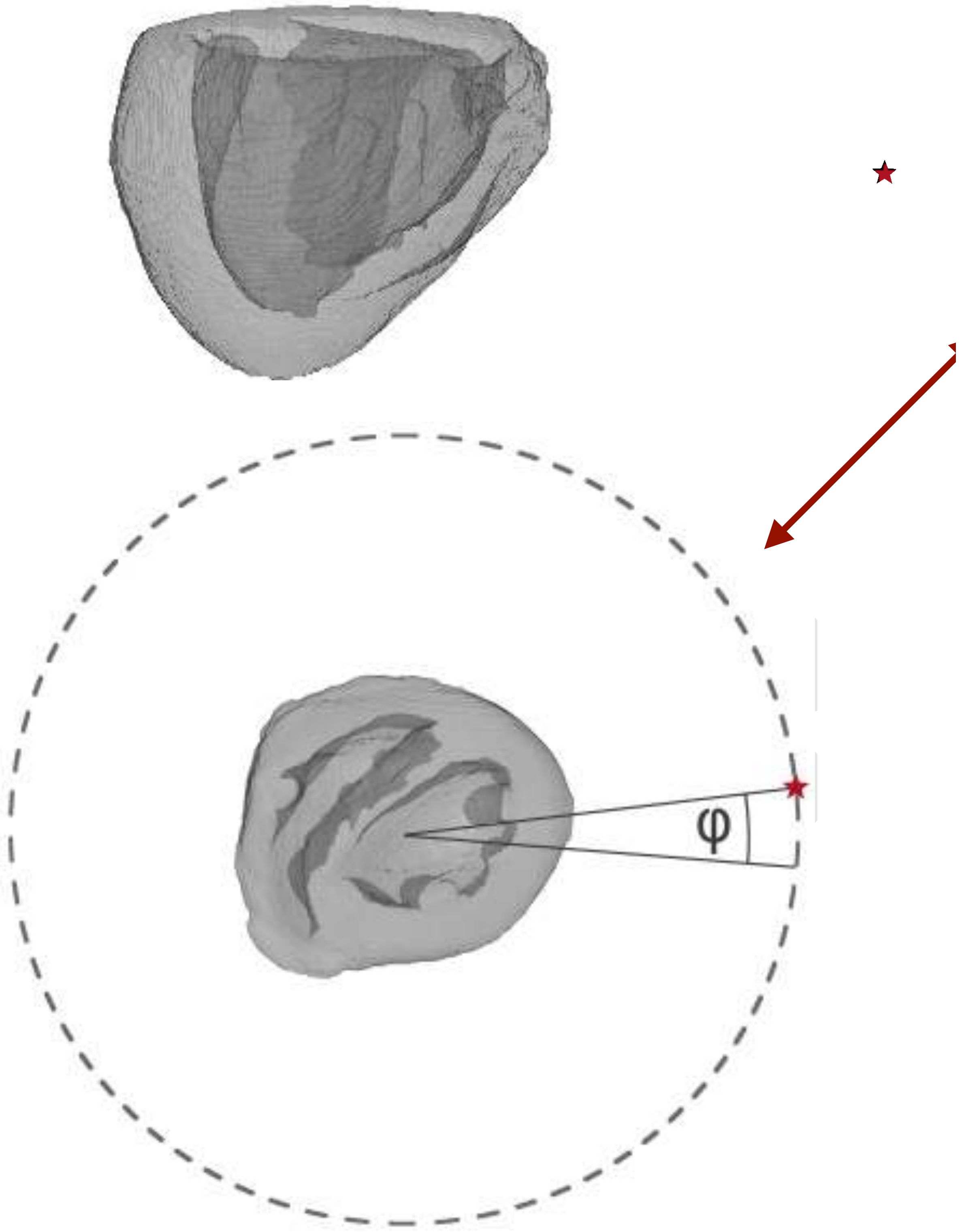
A. Schlemmer et al., *Physiol. Meas.* 38, 1561 (2017)

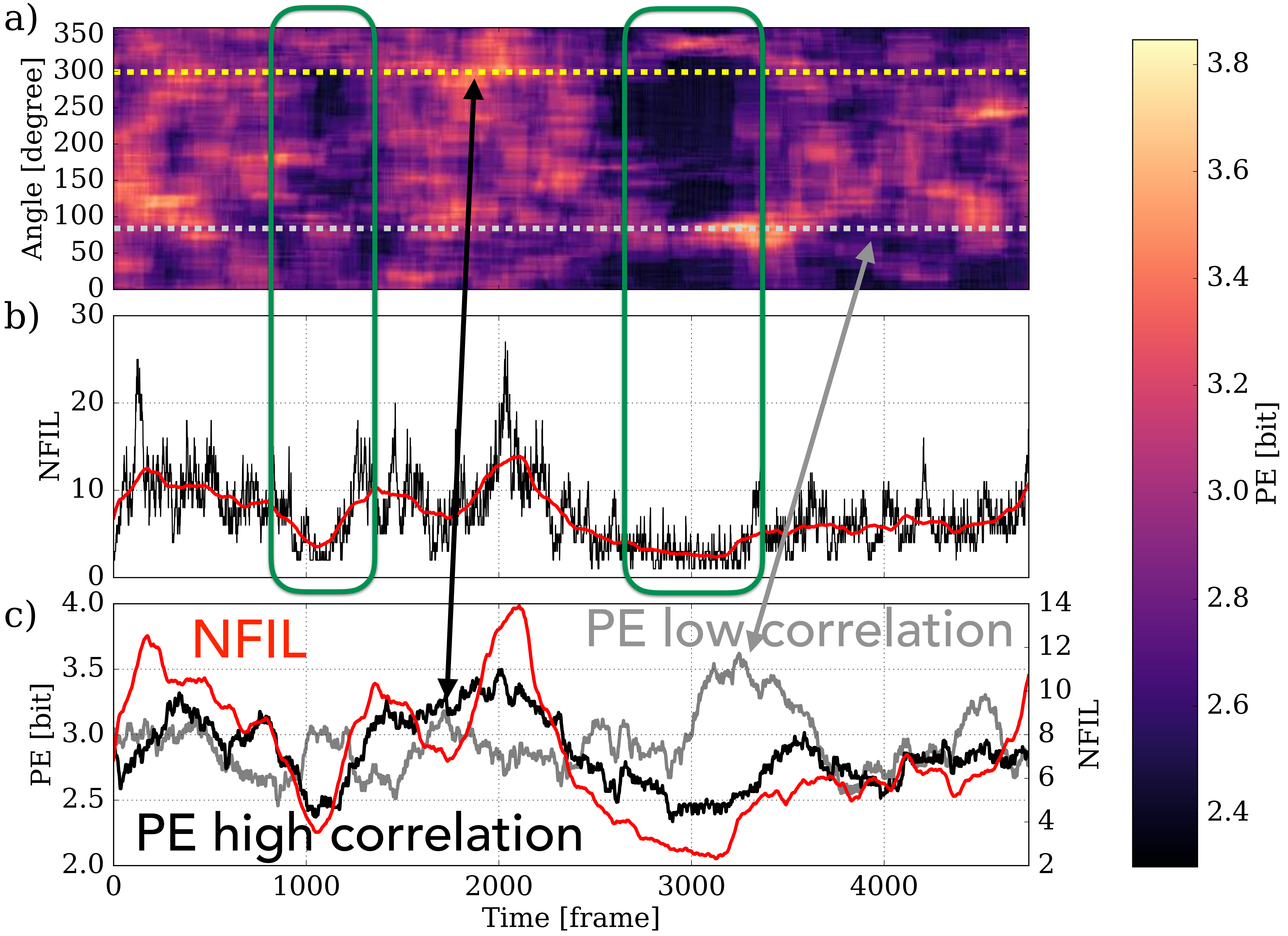
Complexity fluctuations in multi-channel ECG from simulations

permutation entropies of 360 ECG time series

simulations Fenton-Karma model

positions of ECG electrodes on a ring



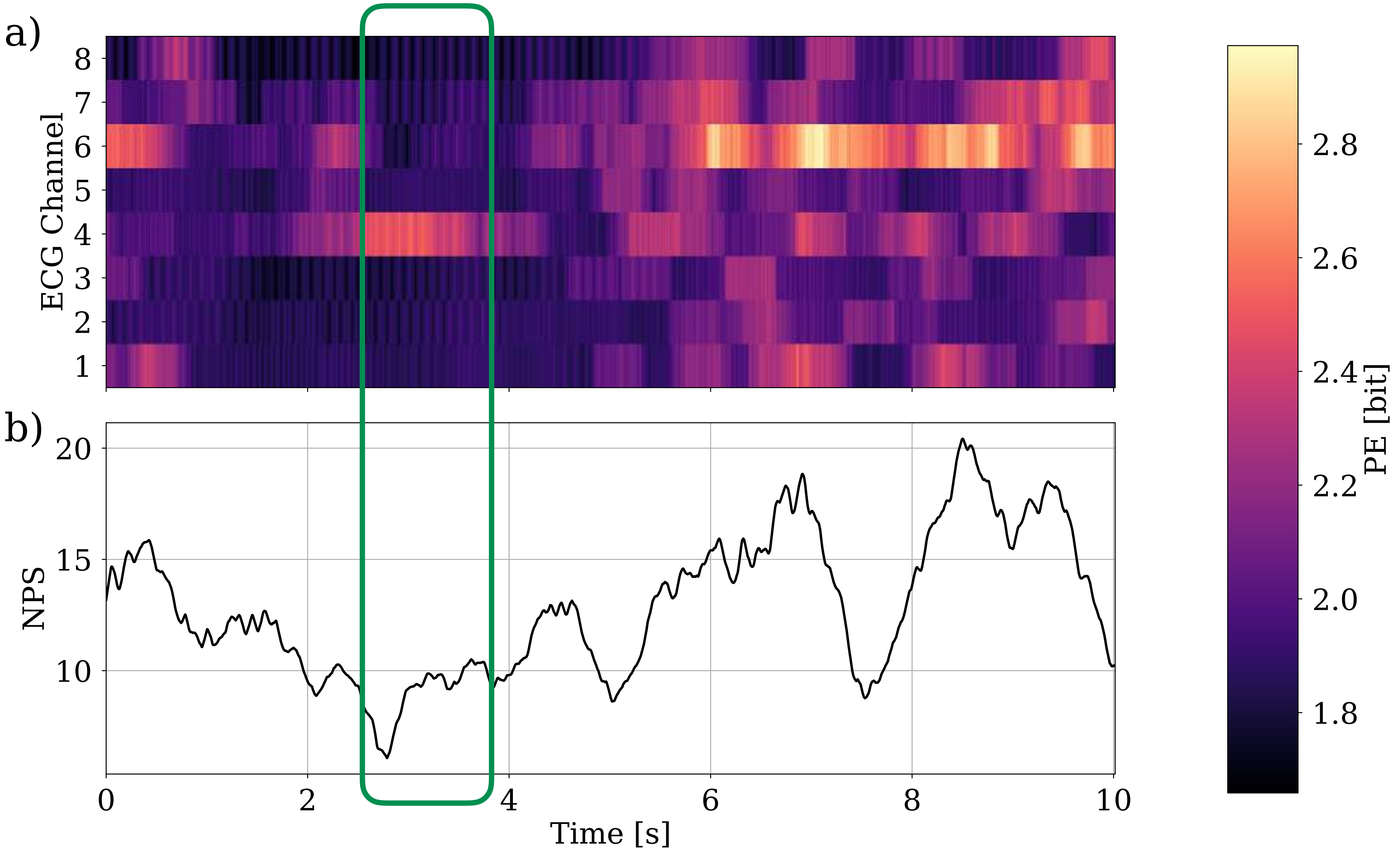


Low permutation entropy PE corresponds to low number of scroll wave filaments NFIL

Complexity fluctuations during Ventricular Fibrillation in a Langendorff-perfused rabbit heart

Permutation entropies of a network of 8 ECG electrodes on a ring around the heart

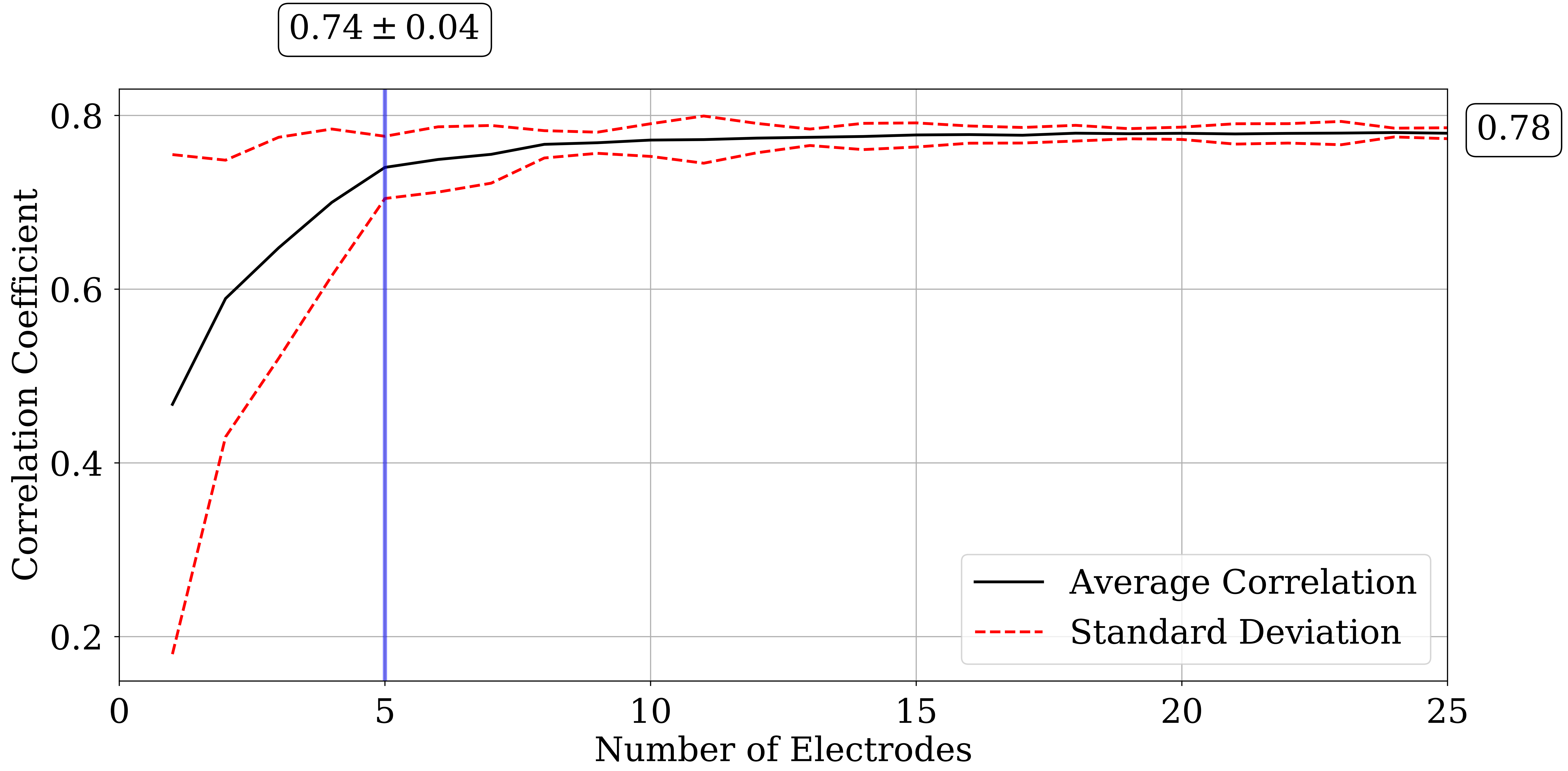
Number of phase singularities on the surface of heart (optical mapping)



laminar phase: - low no. of phase singularities / spiral waves on the surface of the heart
- still one channel / electrode with high permutation entropy

Complexity Fluctuations

Correlation between the number of filaments NFIL and the mean Permutation Entropy for different numbers of equally spaced electrodes



A single ECG electrode is not enough to evaluate the spatio-temporal state of the system.

Synchronization measure based on ordinal patterns

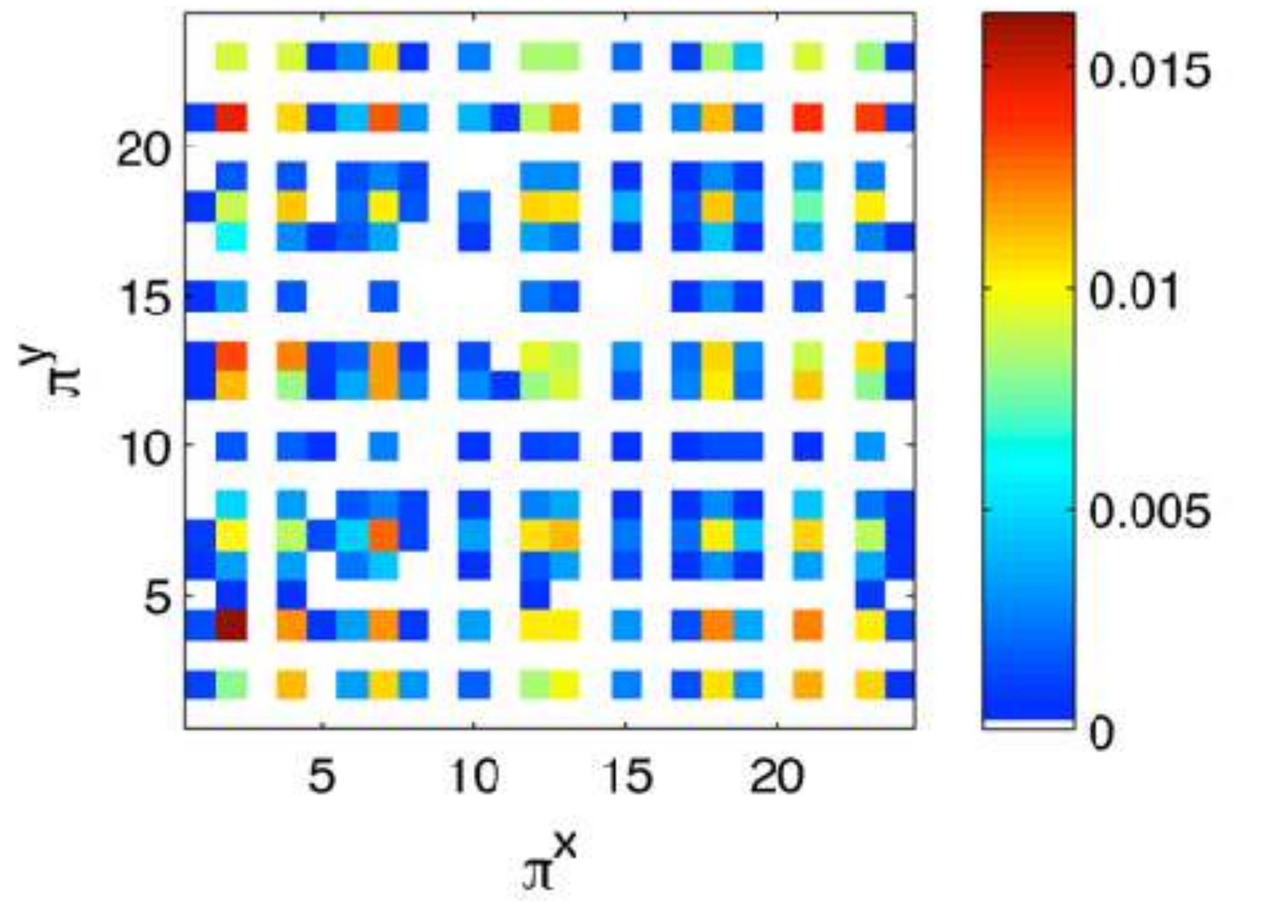
here: synchrony = simultaneous occurrence of ordinal patterns generated by two coupled systems

compute probabilities p_{ij} of joint occurrences (2D histogram)

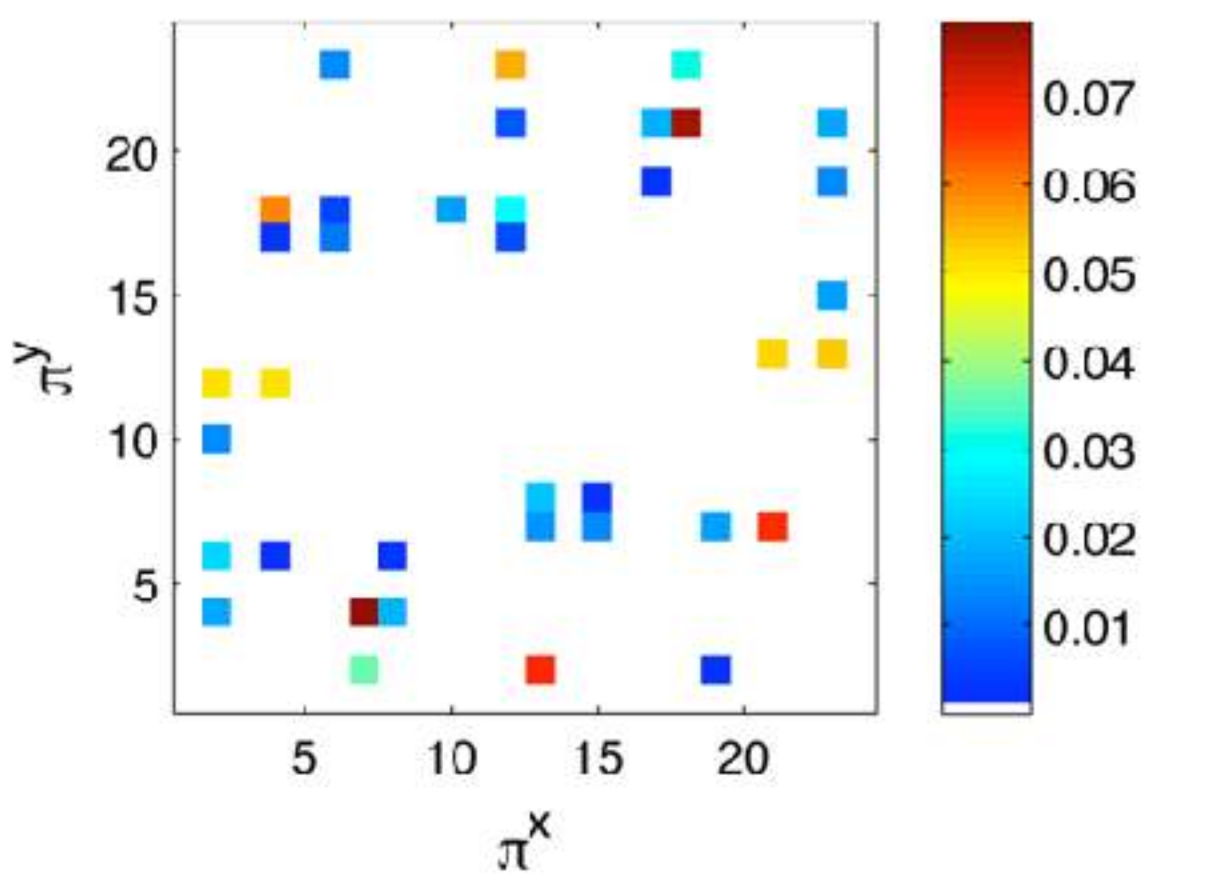
$$H_{xy} = -\sum_{i=1}^{W!}\sum_{j=1}^{W!} p_{ij}\log(p_{ij})$$ joint entropy

example: coupled Rössler sytems

no coupling



synchronisation



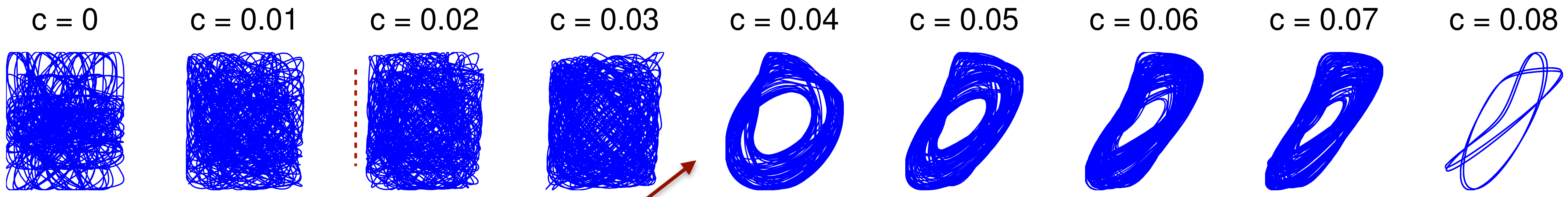
$$MI = \sum_{i=1}^{W!}\sum_{j=1}^{W!} p_{ij}\log\left(\frac{p_{ij}}{p_i p_j}\right)$$ mutual information

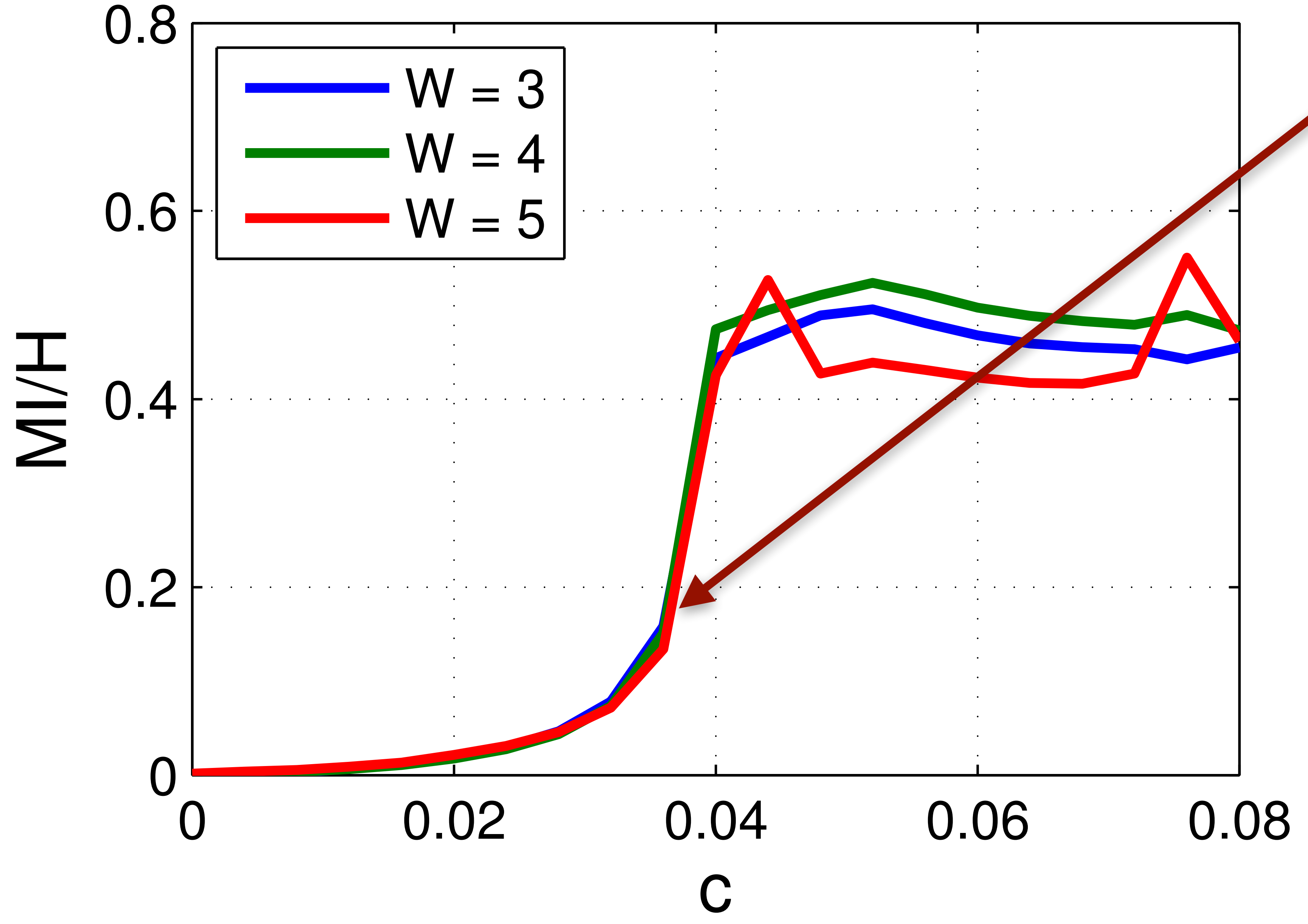
no sync $$\boxed{0 \leq S = \frac{MI}{H_{xy}} \leq 1}$$ identical sync

Detecting Interrelations

Example: (bidirectionally) coupled Rössler systems

$y_1(t)$ vs. $\mathrm{x}_1(\mathrm{t})$ for increasing coupling constant c ➞ onset of phase synchronization





A. Groth, Phys. Rev. E 72, 046220 (2005)
synchronization = high probability of identical ordinal patterns

S. Schinkel et al., Front. Comp. Neurosci. 6 (2012)
order pattern networks

M. Staniek and K. Lehnertz, Phys. Rev. Lett. 100, 158101 (2008)
generalization for detecting directionality of information flow and coupling ➞ symbolic transfer entropy

Spatio-Temporal Permutation Entropy as a Measure for Complexity of Cardiac Arrhythmia

A. Schlemmer et al., *Frontiers Physics* 6, 39 (2018)

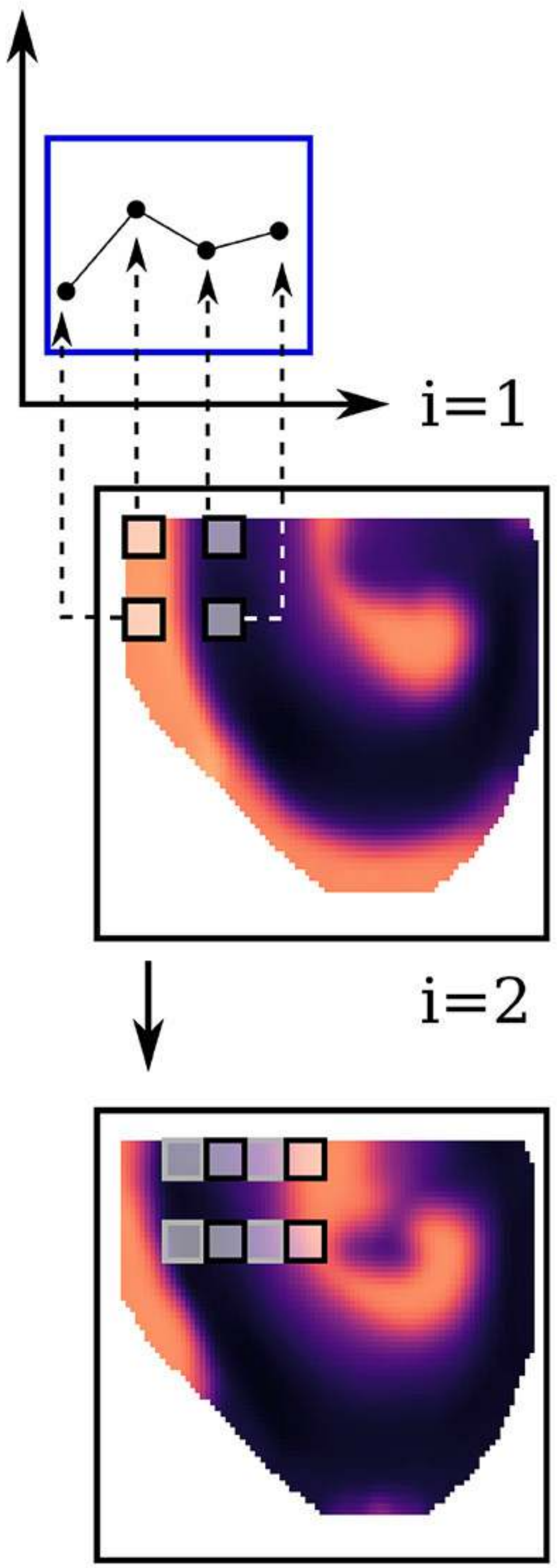
Spatial Permutation Entropy (SPE)

two-dimensional extension of PE

sampling words of size $D{\times}D$ from two dimensional data with spatial separation L_x

D = 2

$(D^2)!$ = 24 words



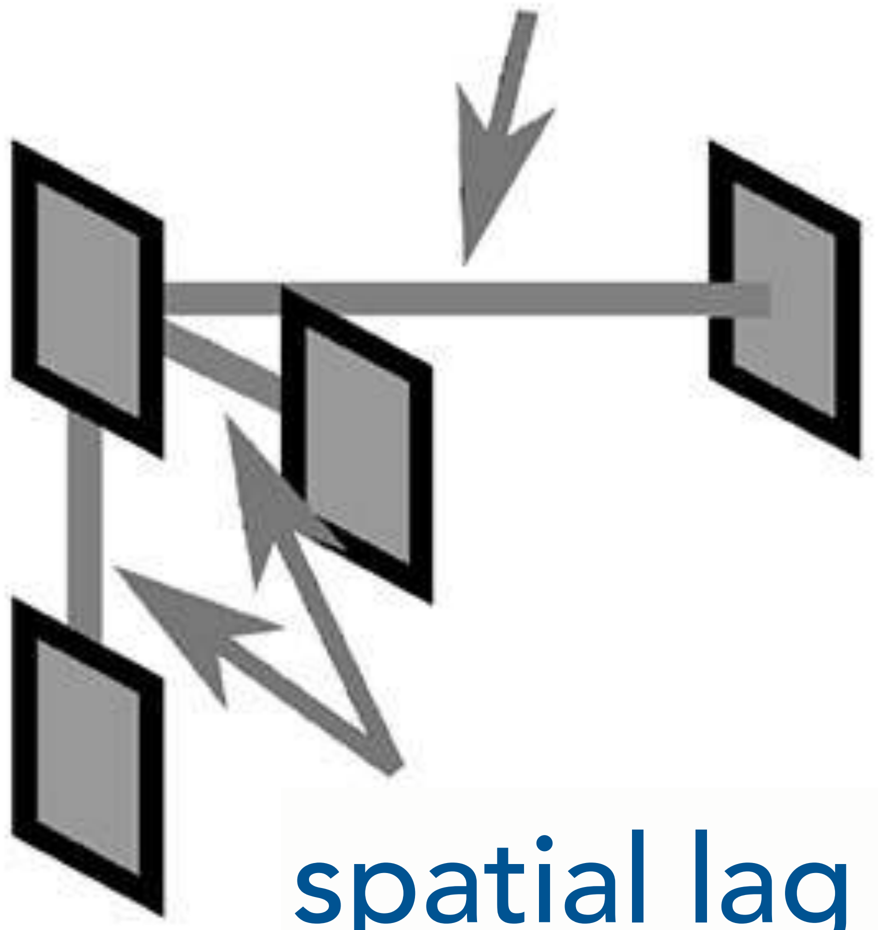
A grid is moved over all possible positions within the image leading to a probability distribution $\{p_j\}$ of symbols that are used to compute the Spatial Permutation Entropy.

H.V. Ribeiro et al., *PLoS ONE 7, e40689* (2012)

A. Schlemmer et al., In: *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC).* Milan (2015). p. 4049–4052

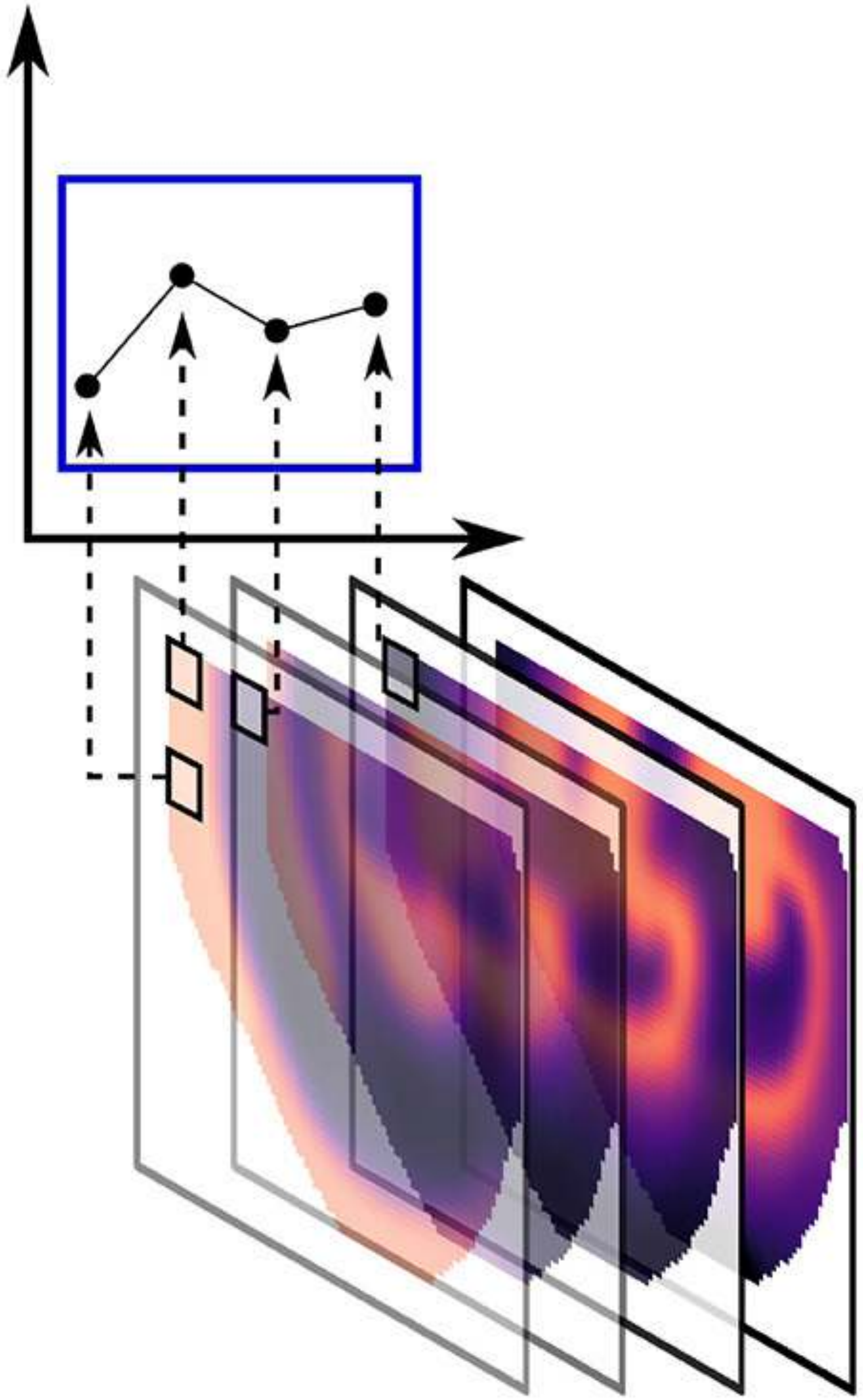
Spatio-Temporal Permutation Entropy (STPE)

sampling words from volumes using a "sampling tripod"



p_k probability of pattern k

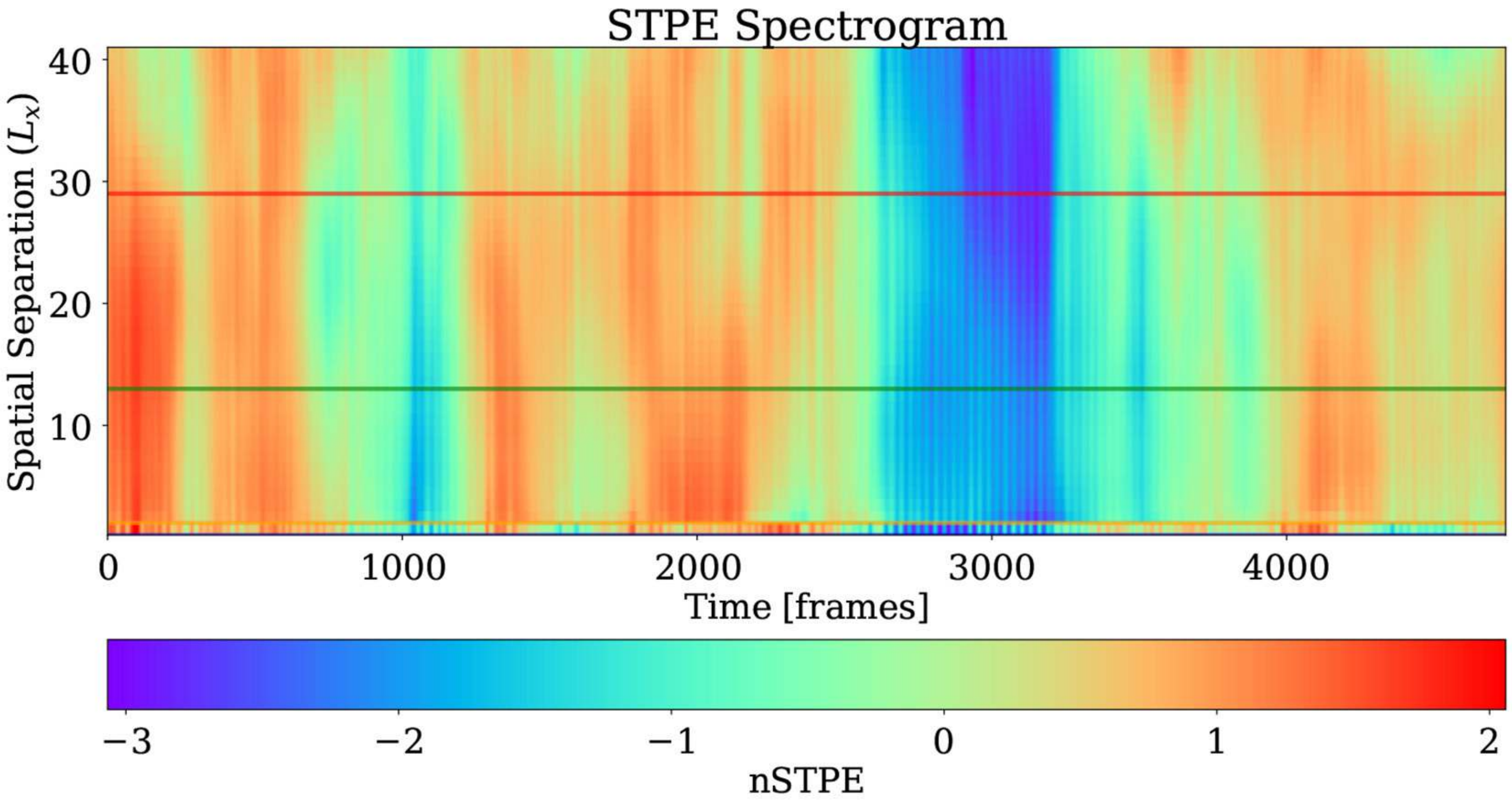
$$STPE = -\sum_k p_k \log(p_k)$$



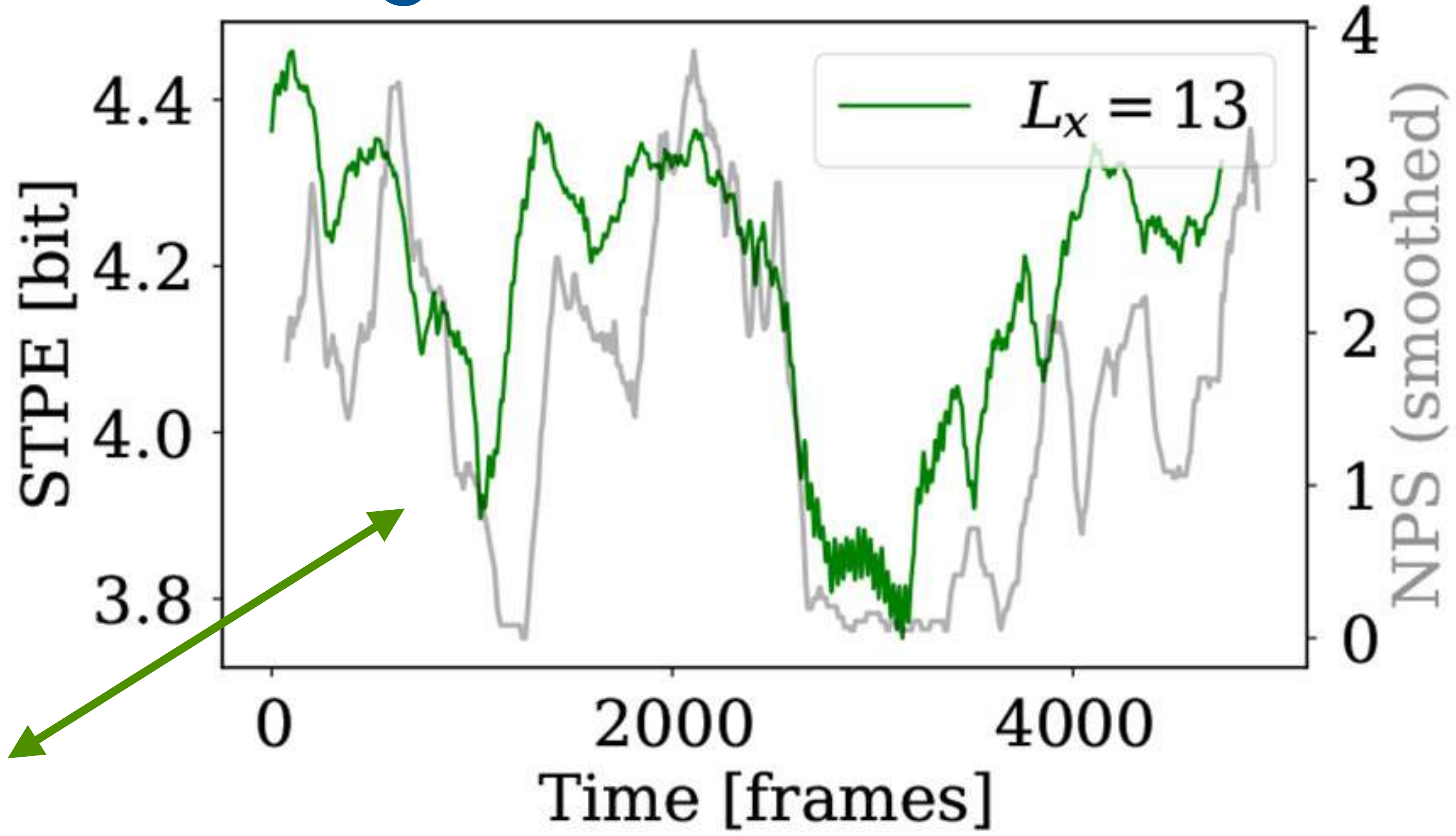
The order in which the points are sampled from images or volumes does not change SPE and STPE.

Spatio-Temporal Permutation Entropy

The impact of different values for the spatial separation L_x



STPE and no. of phase singularities NPS vs. time



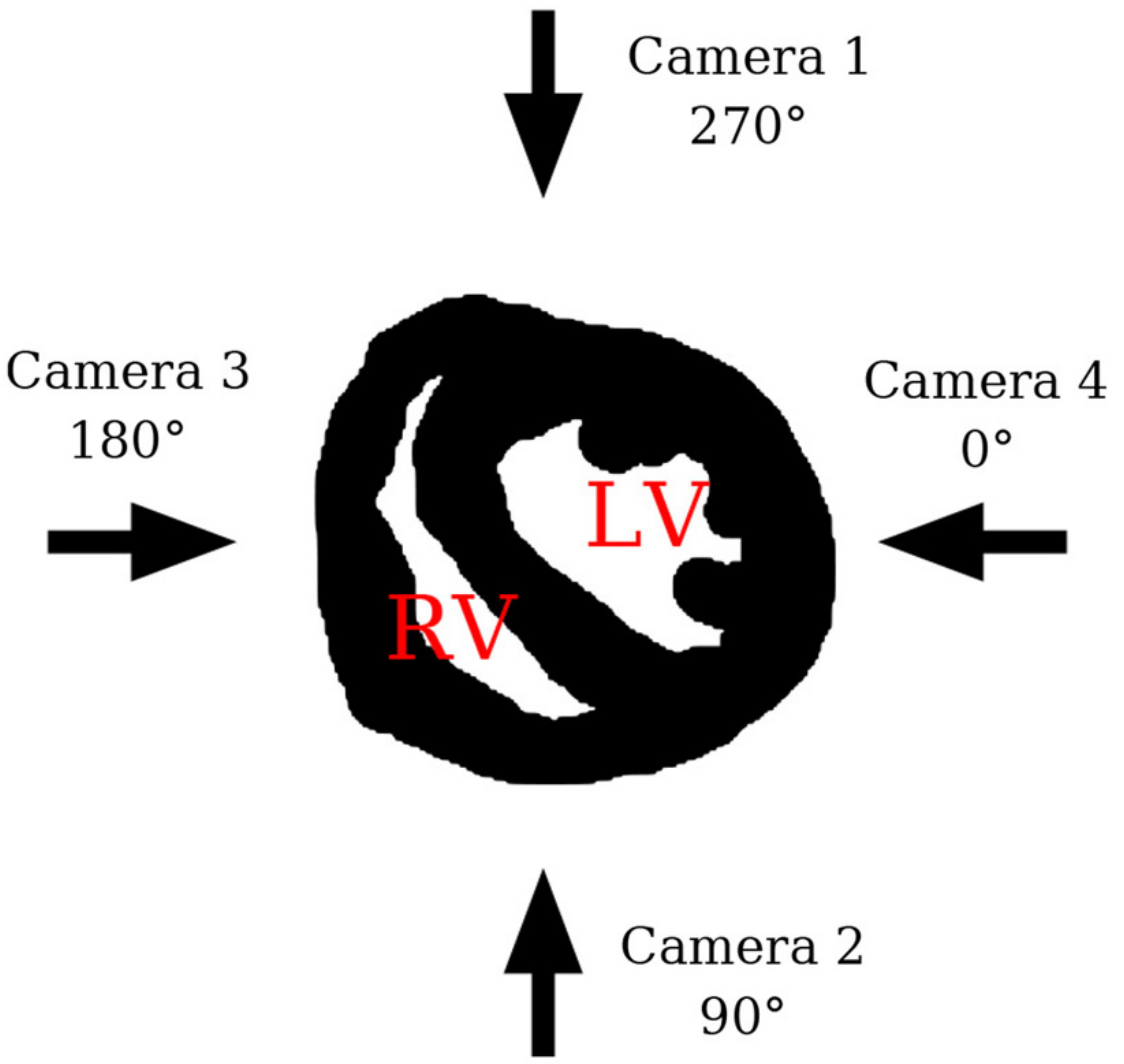
normalized spatio-temporal permutation entropy

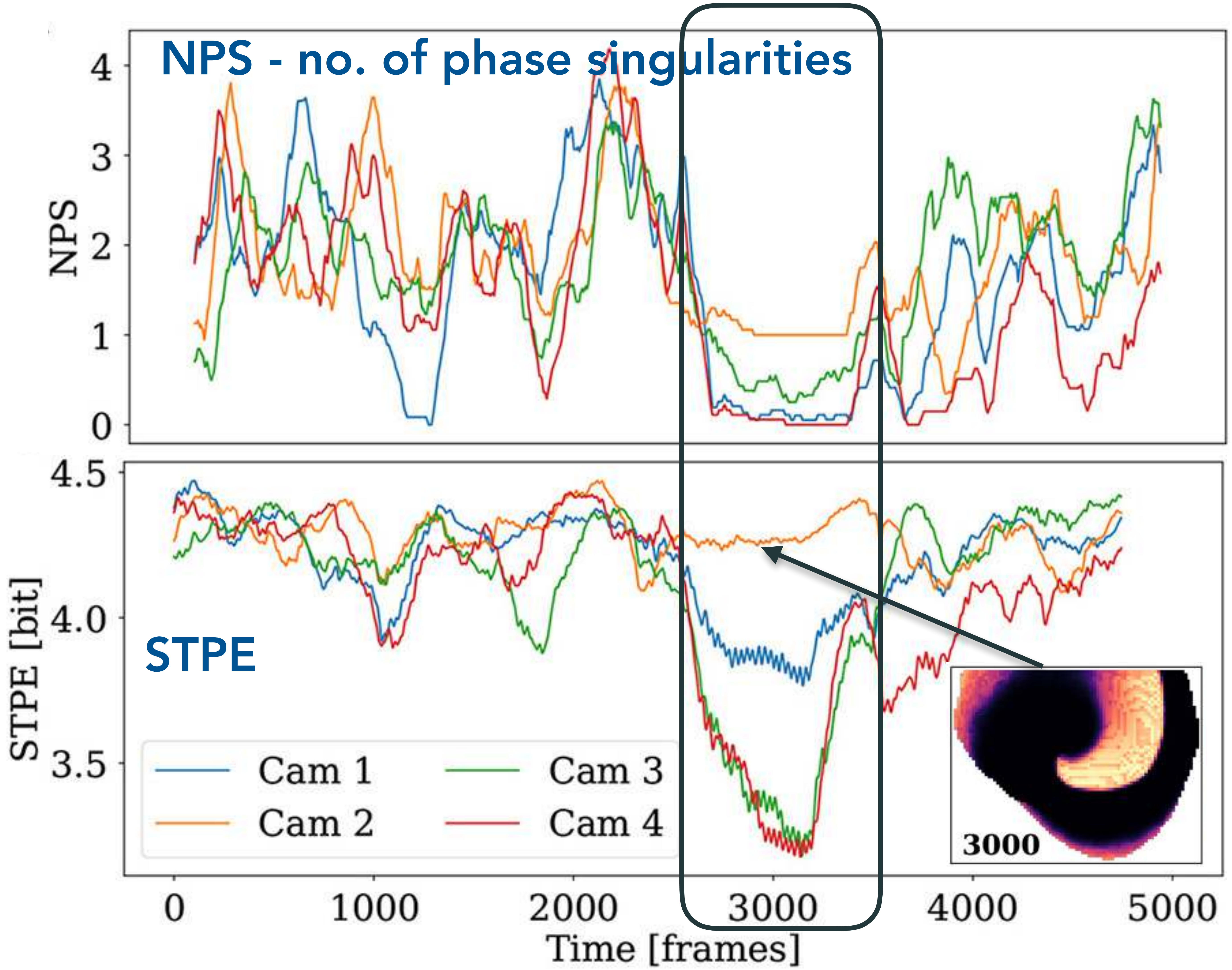
$$\mathrm{nSTPE} = \frac{\mathrm{STPE} - \mathrm{MEAN(STPE)}}{\mathrm{STD(STPE)}}$$

correlates with no. of phase singularities NPS

Spatio-Temporal Permutation Entropy

3D simulation - NPS and STPE from four different cameras perspectives



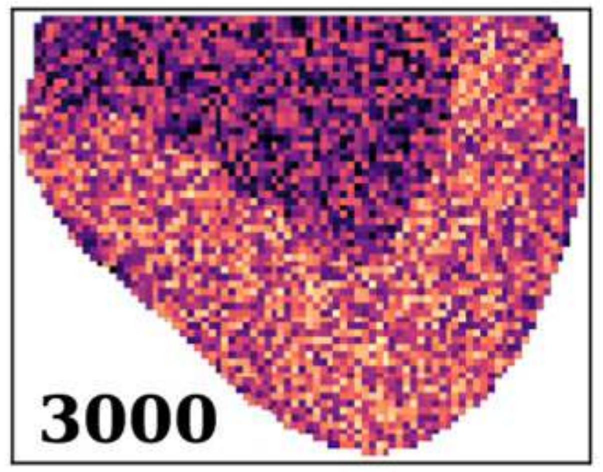


STPE shows a very pronounced drop in complexity for camera 3 and camera 4.

Spatio-Temporal Permutation Entropy

Robustness Against Noise

No Noise
Noise Level 1
Noise Level 2



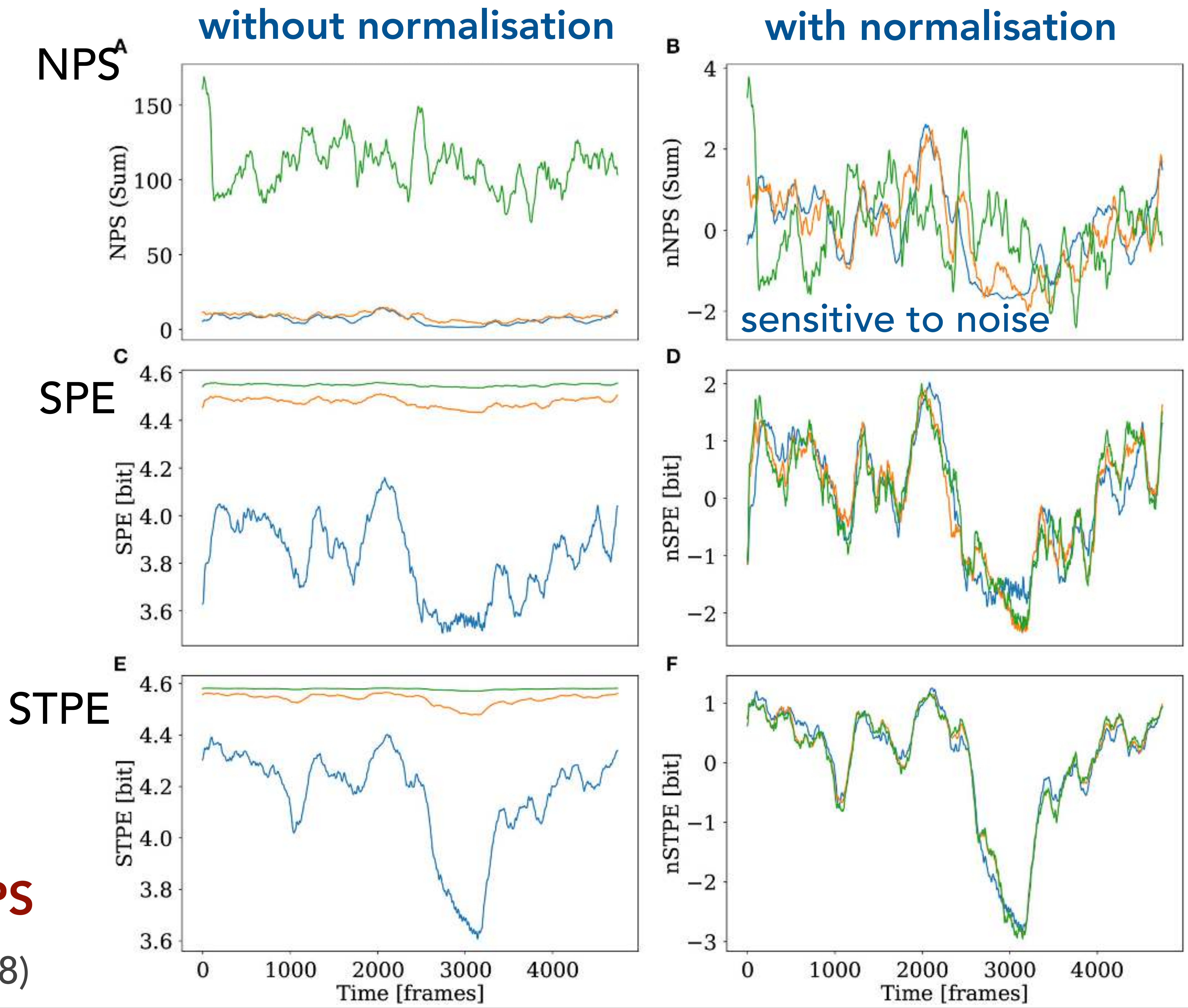
Sum of NPS over all cameras and the mean of the permutation entropy quantities are shown

normalisation:

$$\mathrm{nNPS} = \frac{\mathrm{NPS} - \mathrm{MEAN(NPS)}}{\mathrm{STD(NPS)}}$$

$$\mathrm{nSPE} = \frac{\mathrm{SPE} - \mathrm{MEAN(SPE)}}{\mathrm{STD(SPE)}}$$

$$\mathrm{nSTPE} = \frac{\mathrm{STPE} - \mathrm{MEAN(STPE)}}{\mathrm{STD(STPE)}}$$



SPE and STPE are more robust than NPS

A. Schlemmer et al., Frontiers Physics 6, 39 (2018)

Cross-estimation and forecasting of spatio-temporal chaos (in cardiac dynamics and beyond)

Data Driven Modeling of Spatio-Temporal Systems

Tasks:

- **prediction**: (iterative) forecasting of future evolution
- **cross estimation**: estimate a quantity that is difficult to observe using another variable that is more ``easy” to measure, e.g., estimate Calcium concentration from cell membrane voltage

Methods:

- nearest neighbours prediction using reconstructed local states
  J. Isensee et al., arXiv:1904.06089 (2019)
- echo state networks (reservoir computing)
  R.S. Zimmermann and U. Parlitz, Chaos 28, 043118 (2018)
- **convolutional neural networks**
  S. Herzog et al., *Front. in Appl. Math. and Stat.* 4, 60 (2018)

Modeling Cardiac Dynamics

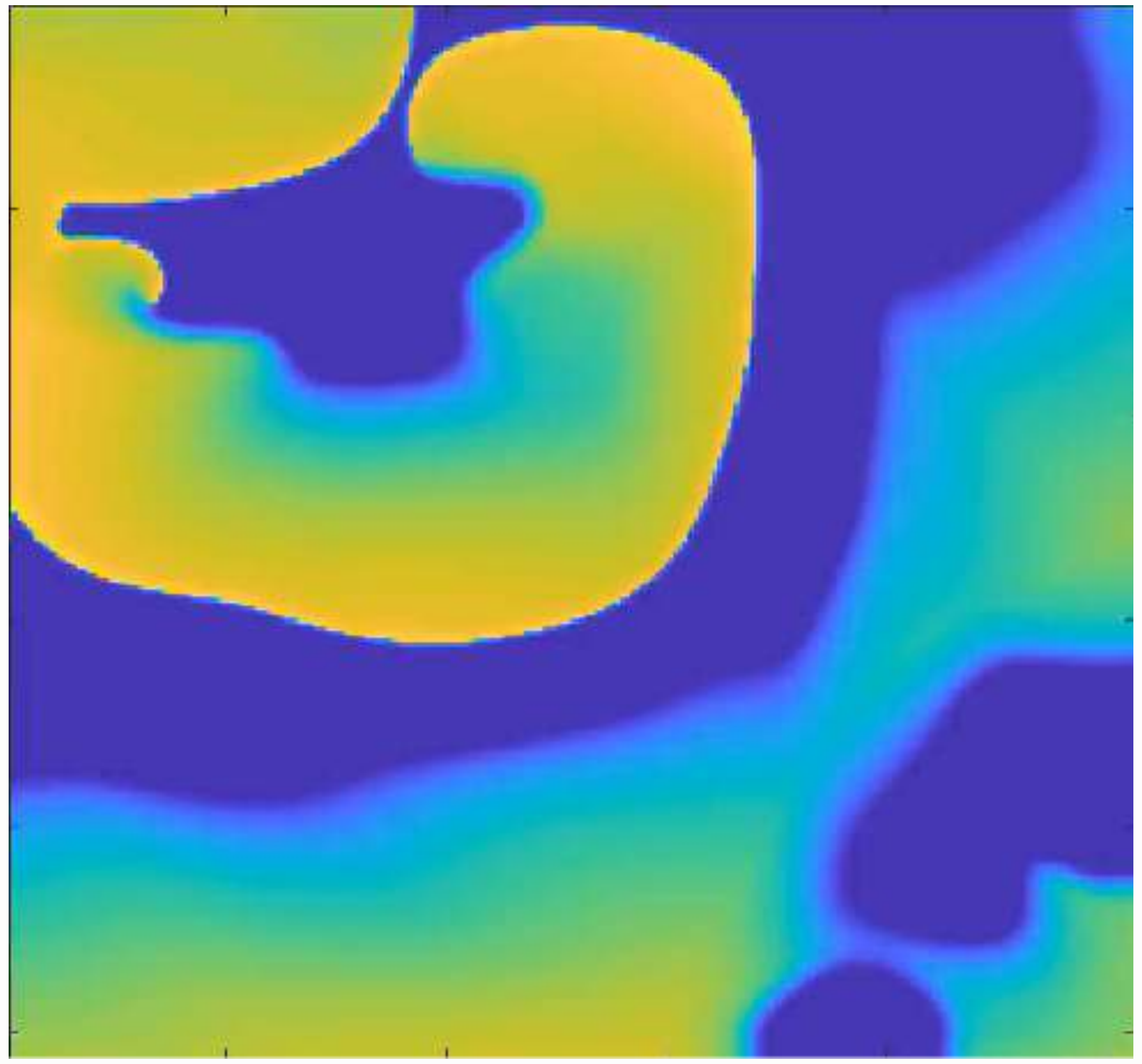
Example: The Bueno-Orovio-Cherry-Fenton model

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

PDE describing electrical excitation waves in cardiac tissue

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

***u* membrane potential**



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

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

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

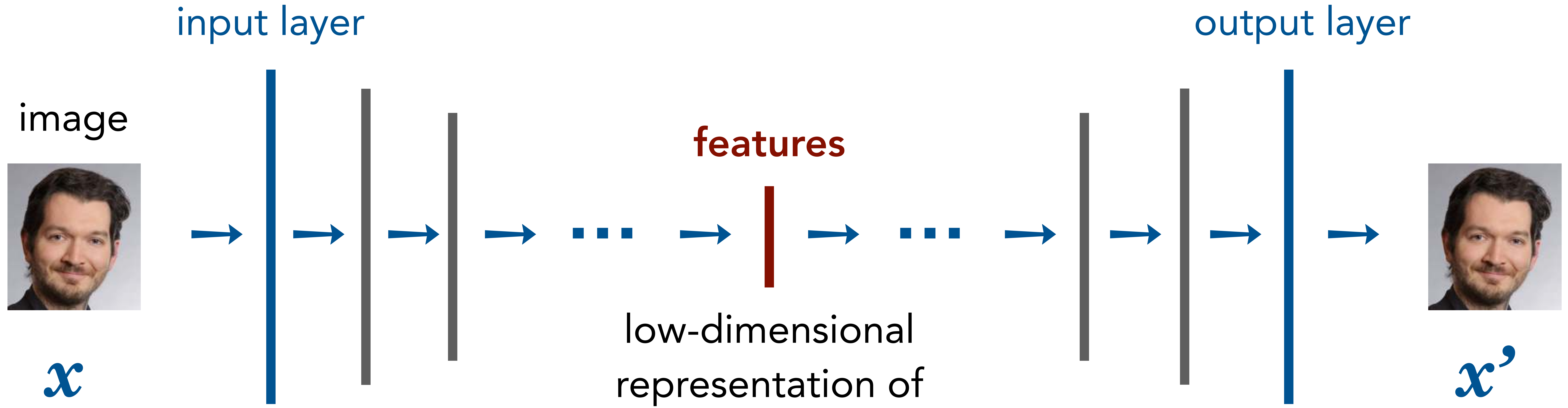
with ionic currents:

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

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

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

Convolutional Autoencoder



low-dimensional representation of input data

$$y = F(x)$$

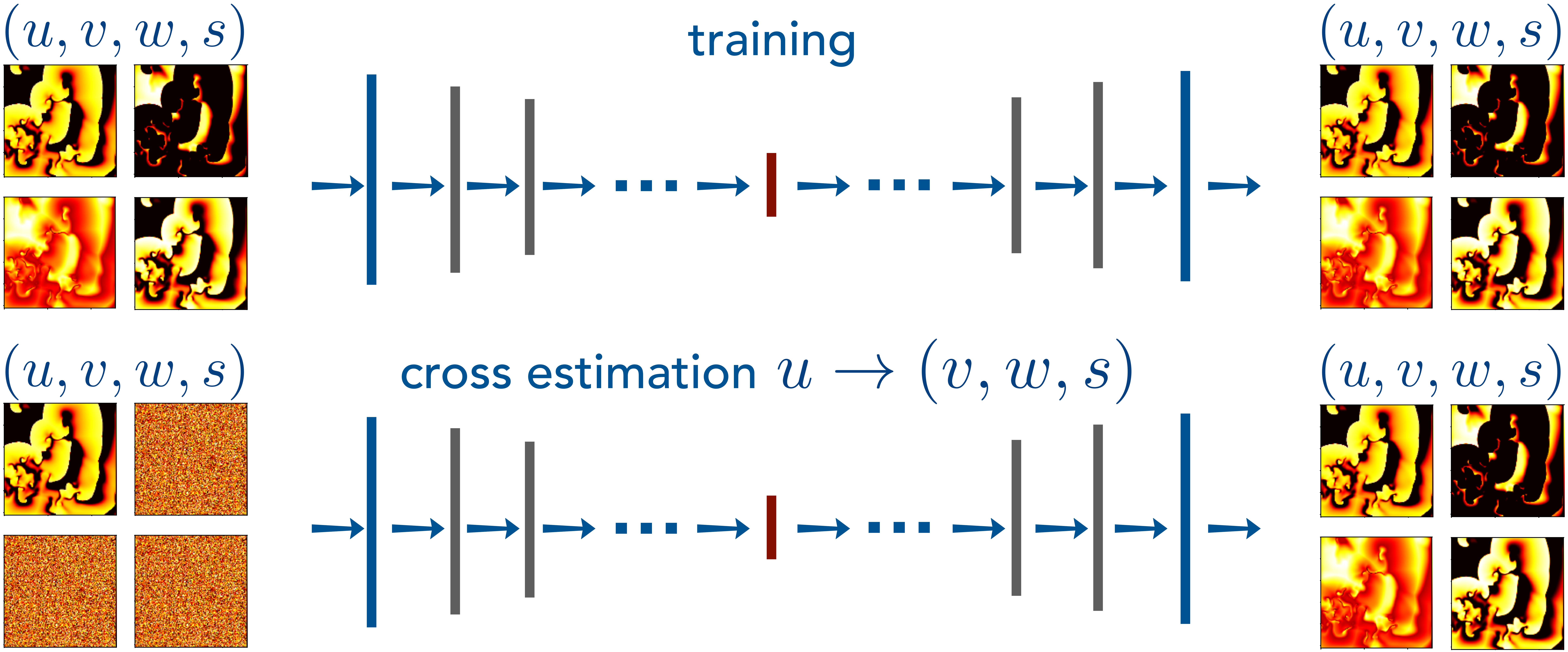
- convolutions
- pooling
- e.g., $f(z) = \max(0,z)$

- deconvolutions
- unspooling
- …

S. Herzog et al., Frontiers in Applied Mathematics and Statistics 4, 60 (2018)

Convolutional Neural Networks

Cross Estimation



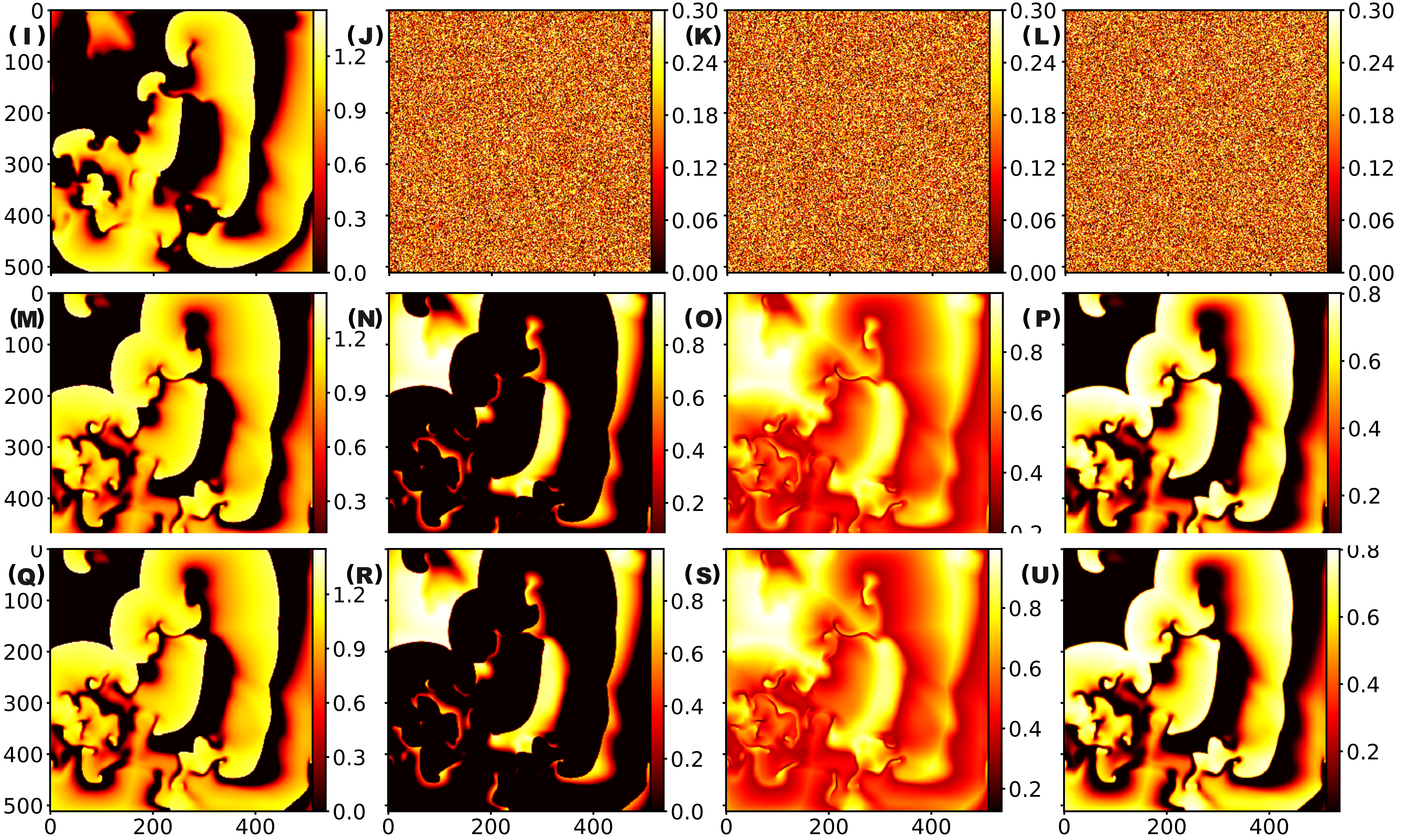
Cross Estimation

$u \to (v, w, s)$

input

estimation

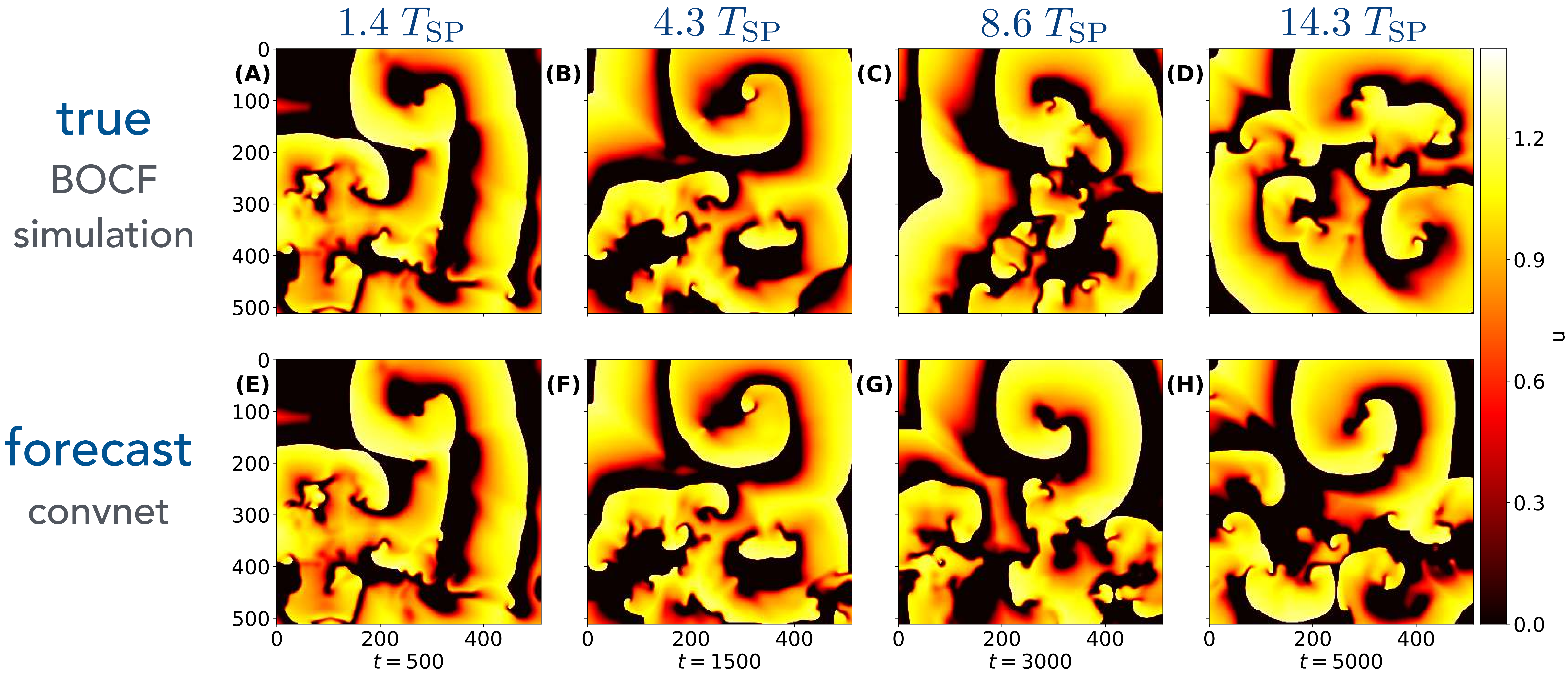
true fields



Similar results with reservoir computing: R.S. Zimmermann and U.P., Chaos 28, 043118 (2018)

Convolutional Neural Networks

Iterated Forecasting of $u(t)$



Good results for 5 spiral rotations

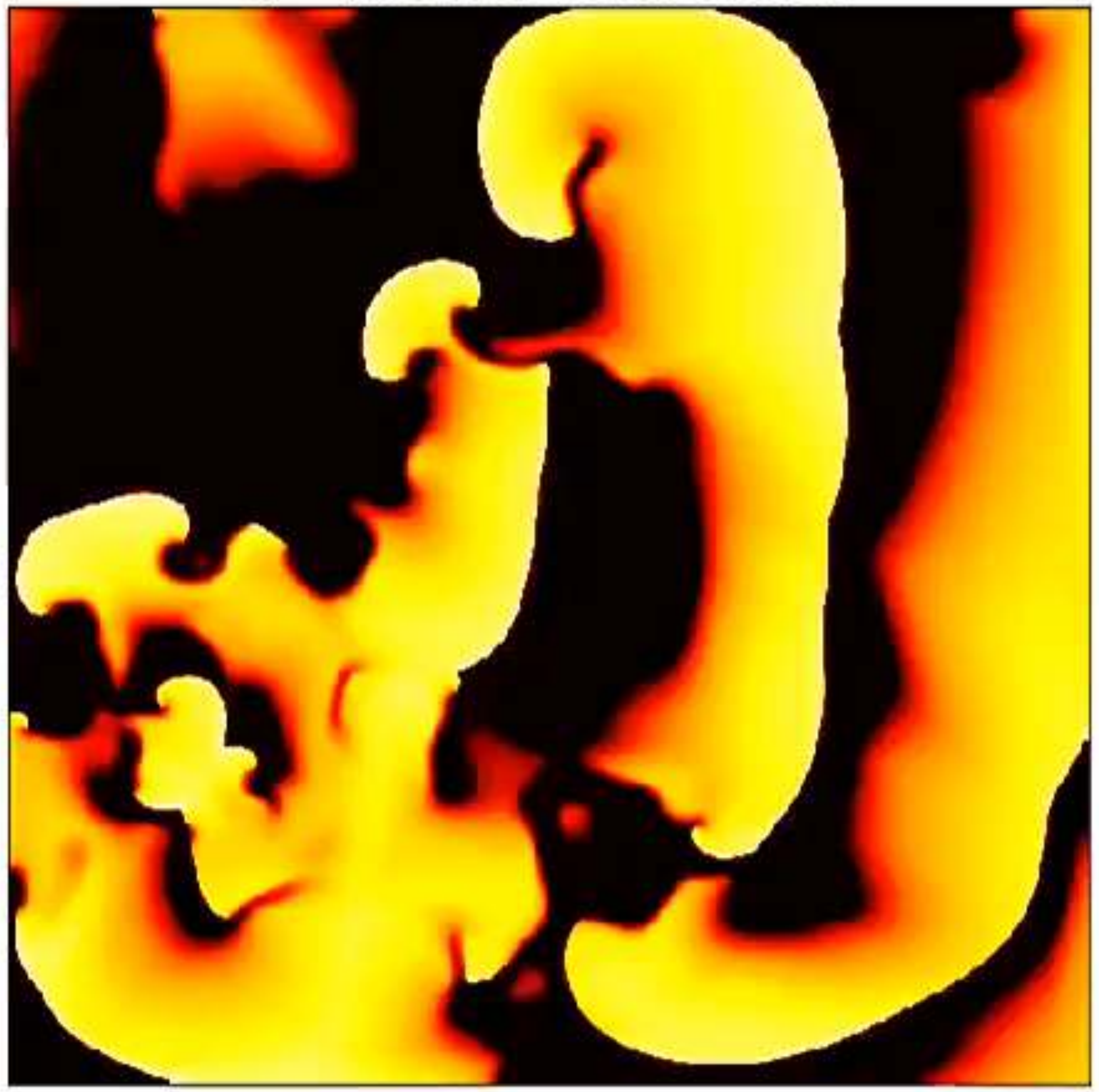
Iterated Forecasting of $u(t)$

true

u - BOCF simulation

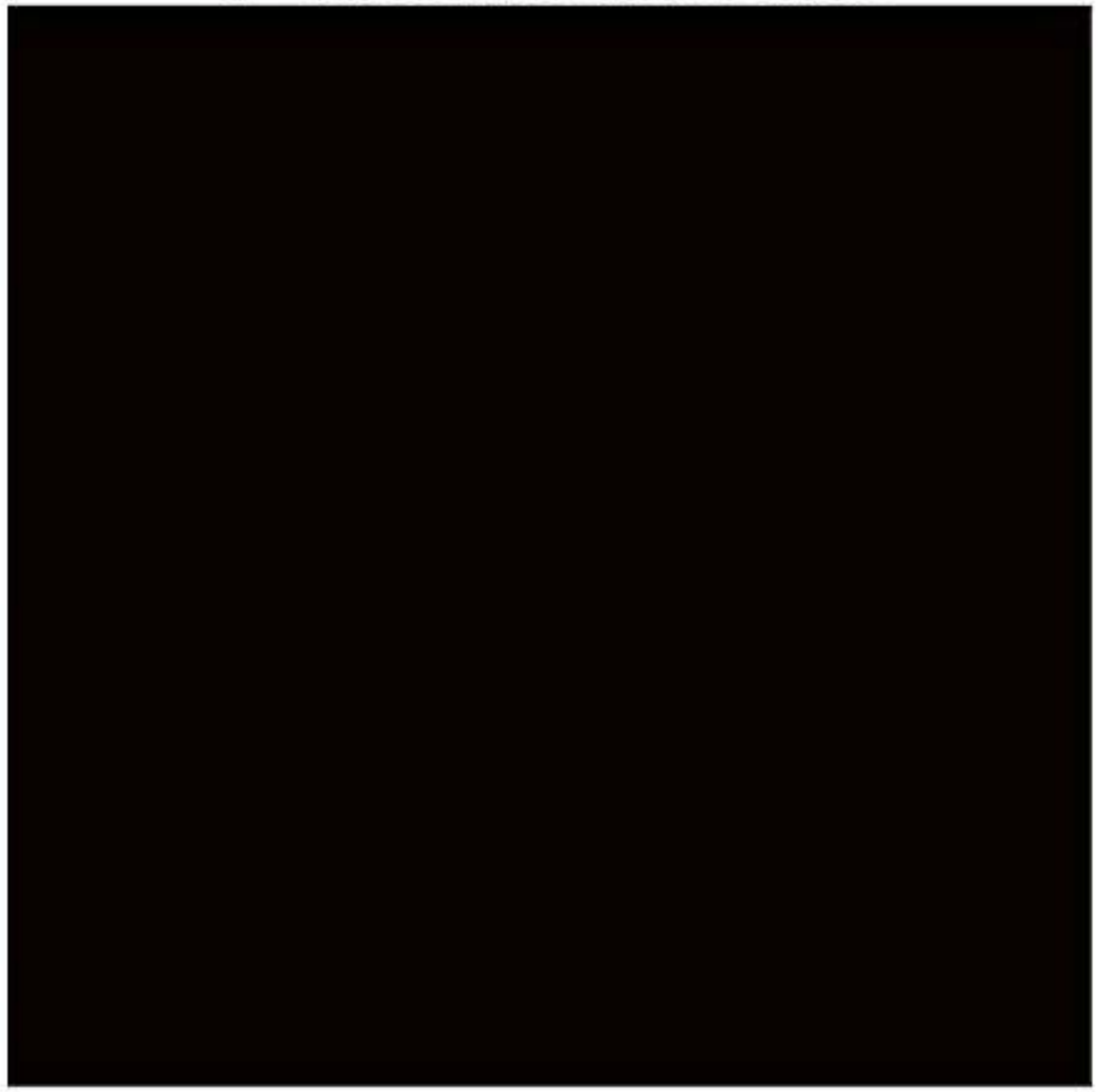
forecast

u - network forecast



difference

u - absolute difference



S. Herzog et al., Frontiers in Applied Mathematics and Statistics 4, 60 (2018)

Summary

Ordinal Pattern and Permutation Entropy

- are useful concepts for characterizing beat-to-beat time series and complexity fluctuations in cardiac arrhythmias
- are computationally efficient and very robust with respect to noise
- can also be defined for spatially extended systems
- correlate very well with the number phase singularities (spiral waves)

Complex dynamics in excitable media can be learned and predicted using convolutional neural networks (and other machine learning methods)

Acknowledgement

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Thank you!

European Commission

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