CHAOS Lab

Complex Heart Arrhythmias and other Oscillating Systems

Characterizing the Complexity of Fibrillation from Models and Experiments with Lyapunov Exponents

Will AN

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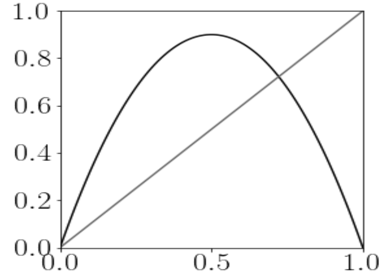
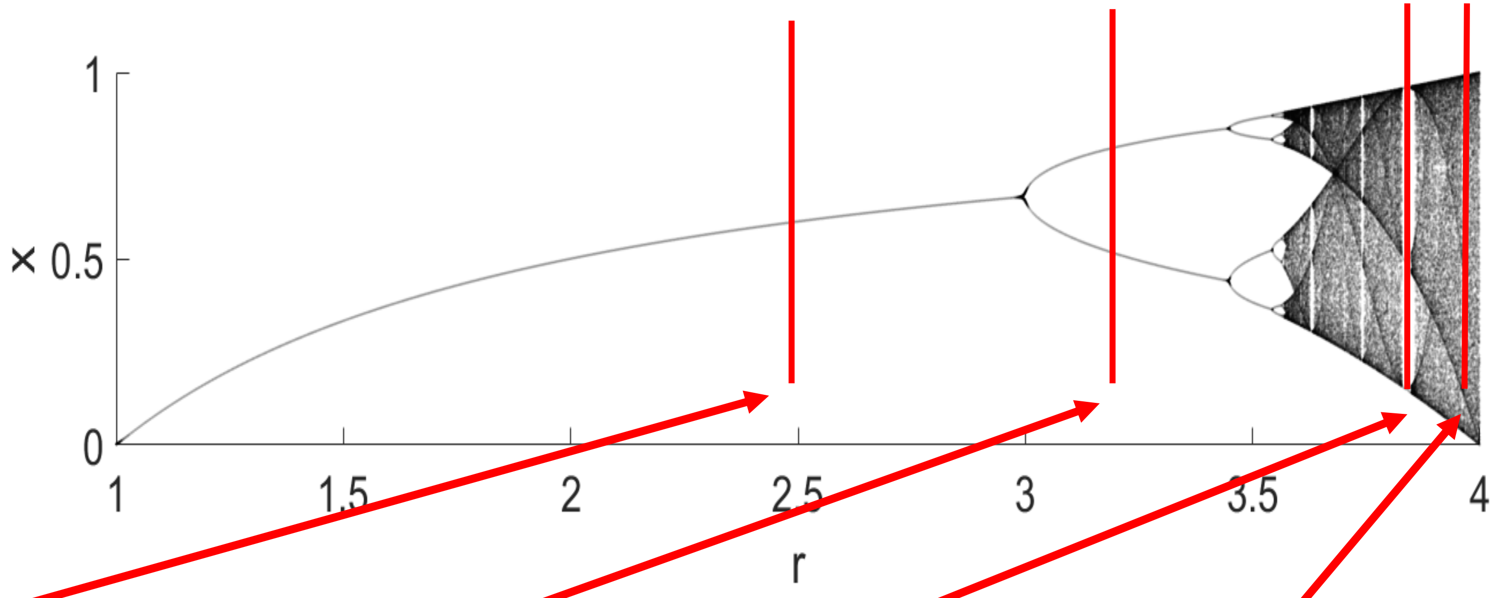
Some brief introduction to Chaos

Chaos in 1-D Logistic Map

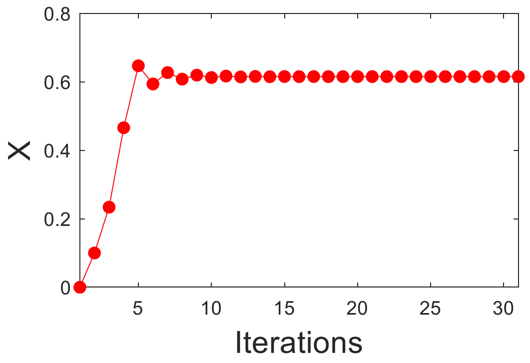
$$x_{n+1} = r\, x_n(1 - x_n)$$

r: rate of population growth
x: population fraction

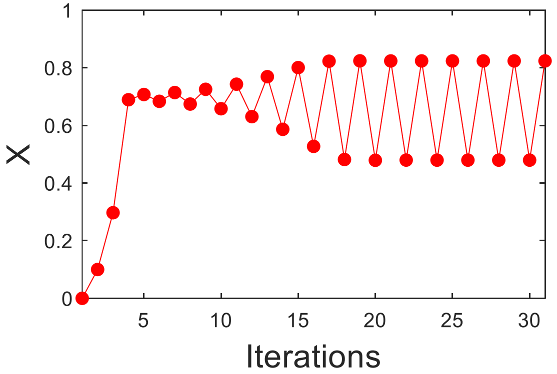




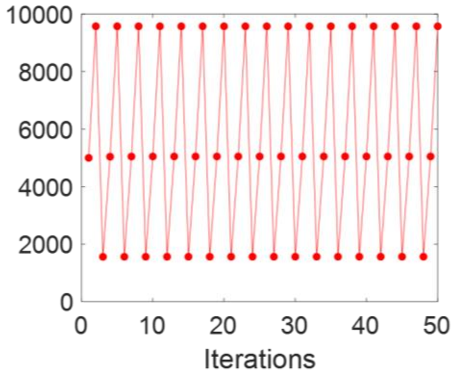
r=2.6



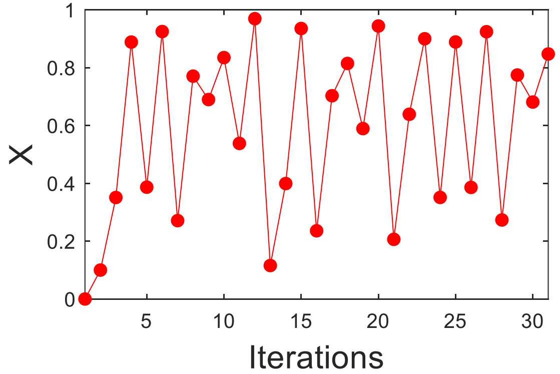
r=3.3



Period 3 Implies Chaos



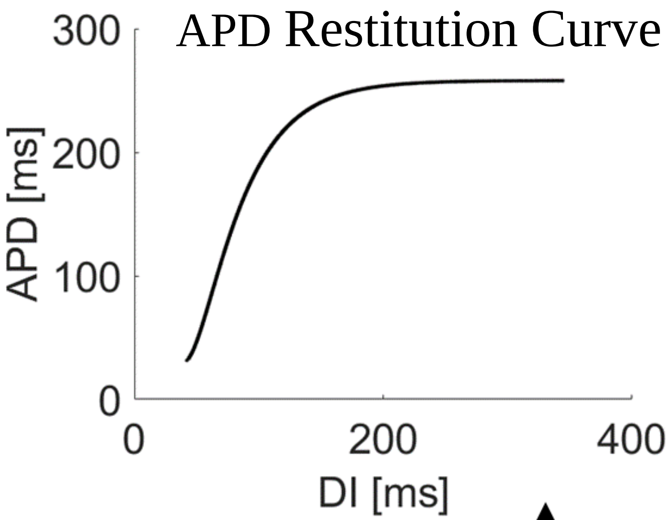
r=3.9

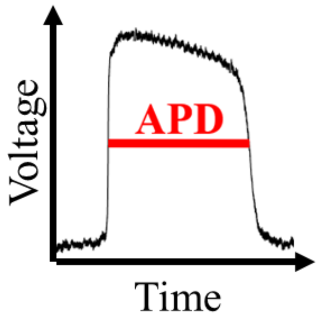


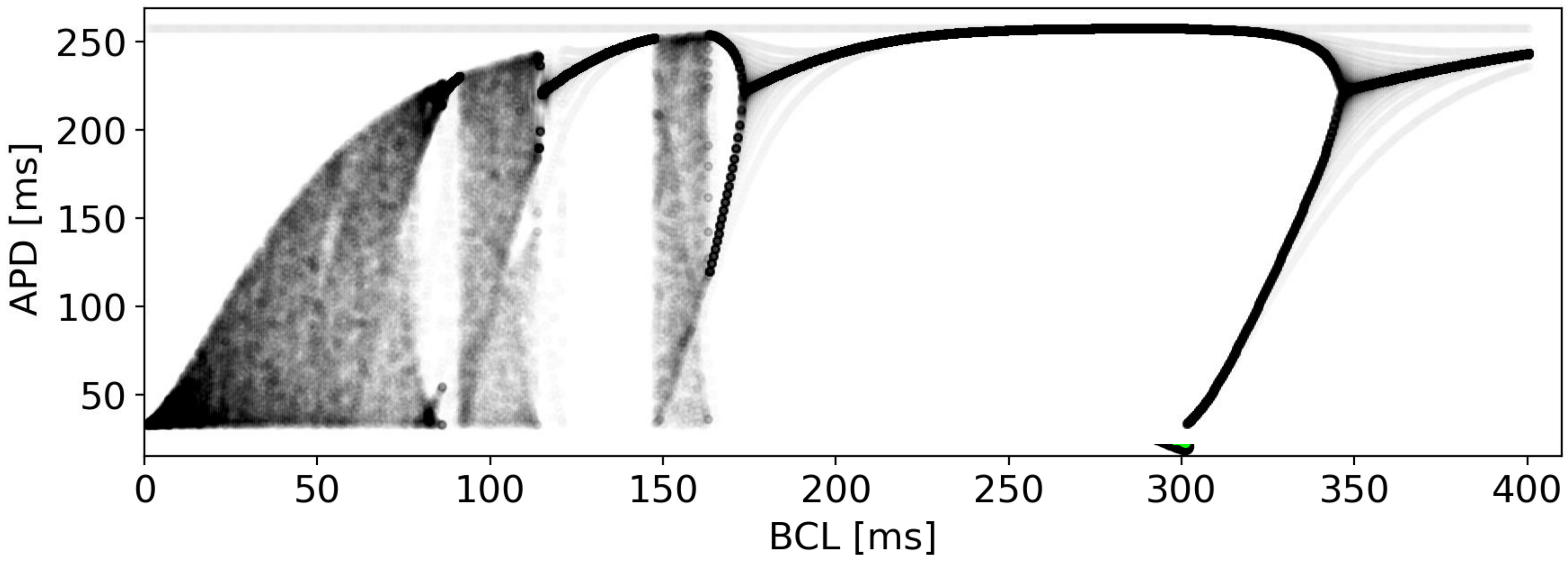
Showing chaos in cardiac map model

Beeler-Reuter cardiac model

Restitution map: $APD_{n+1} = 258 + 125e^{(-0.068*(BCL-APD_n-43.54))} - 350e^{(-0.028*(BCL-APD_n-43.54))}$



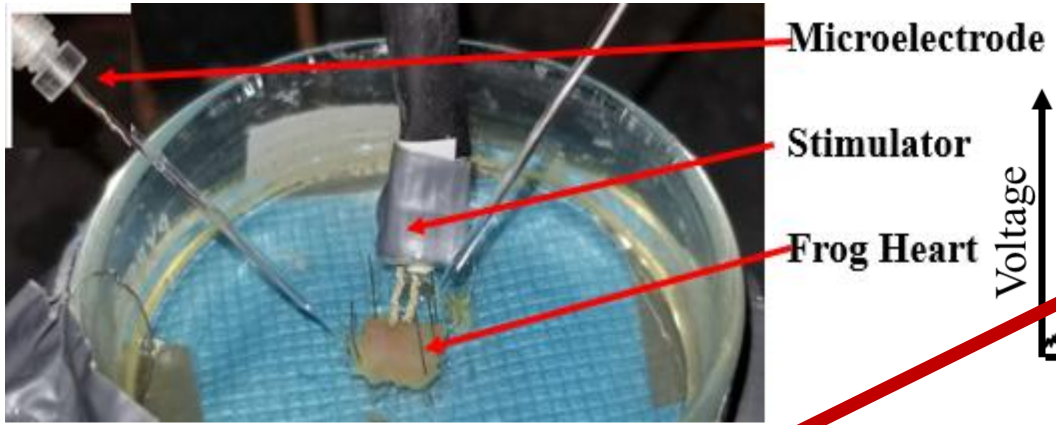


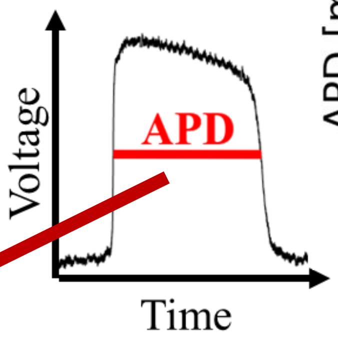


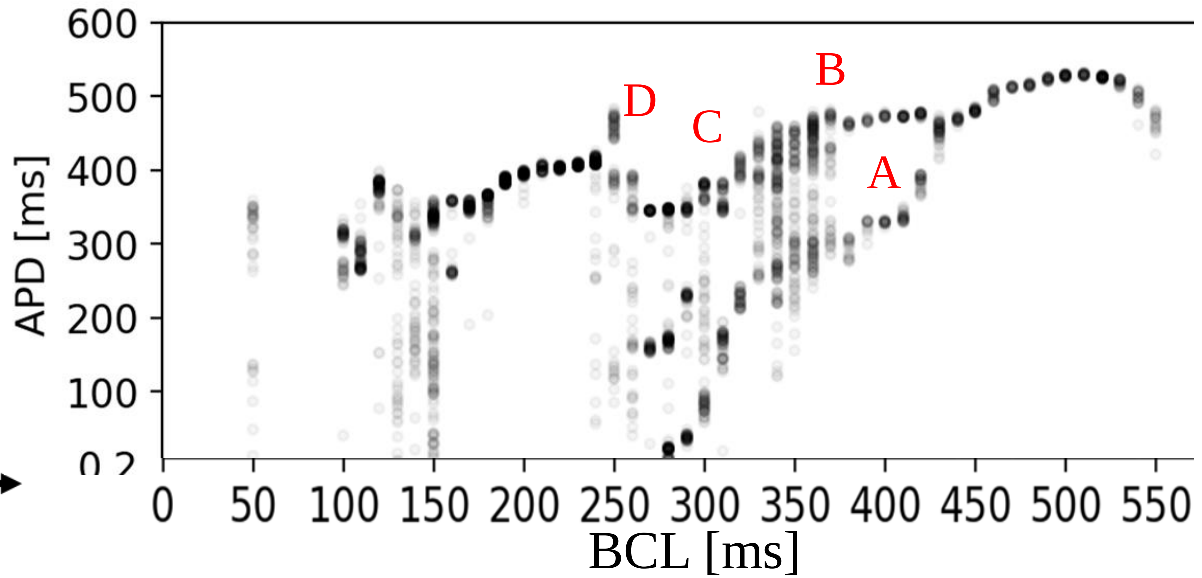
(Basic Cycle Length / Pacing Period)

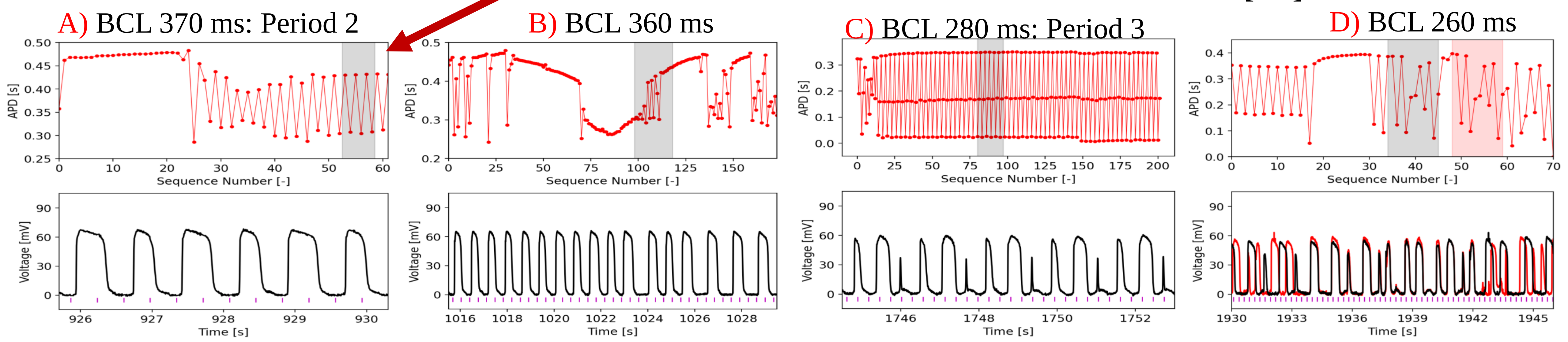
Showing chaos in experimental data

Frog heart experiment









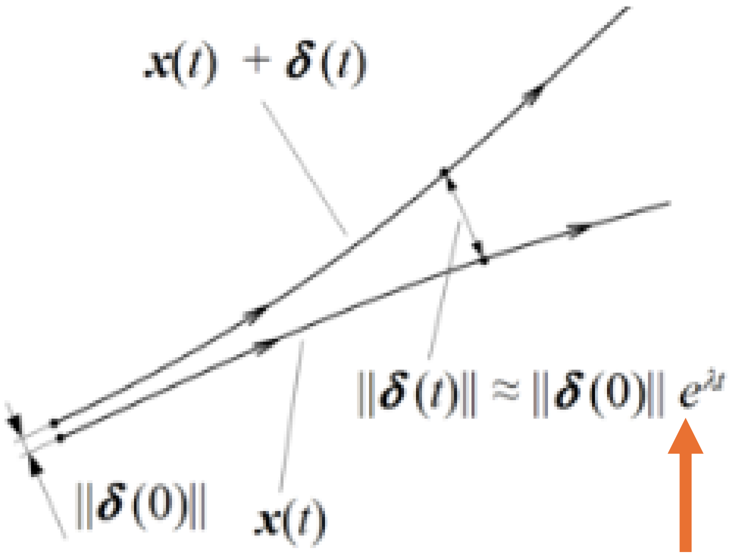
Just like in the logistic map, it is possible to obtain a bifurcation diagram from fast pacing in cardiac tissue

How can we characterize the amount of complexity “chaos” from temporal and spatiotemporal data obtained in numerical models and in experimental data?

Quantify fibrillation in the heart: Lyapunov exponent

- Lyapunov exponent of a dynamical system is to characterizes the rate of separation of infinitesimally close trajectories.
- Formula for LE

$$\lambda = \lim_{t\to\infty} \lim_{|\delta_0|\to 0} \frac{1}{t} \log \frac{\delta_t}{\delta_0}$$



This means chaos

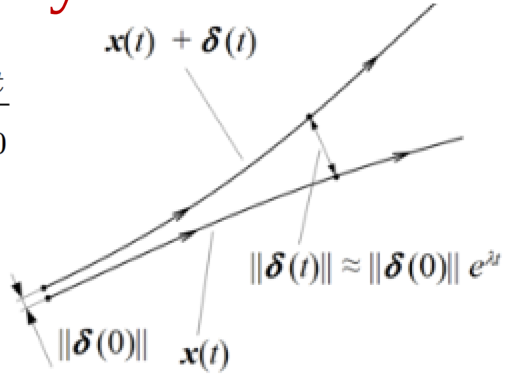
- λ > 0: chaotic system
  - δ(t)>>δ(0) (difference has exp growth)
- λ = 0: periodic
  - δ(t)=δ(0) (difference has no growth)
- λ < 0: stable (convergence)

- Usually, we use the maximal Lyapunov exponent (MLE)
- Which is the maximum possible LE you could get during iterations.

Quantify fibrillation in the heart: Lyapunov exponent

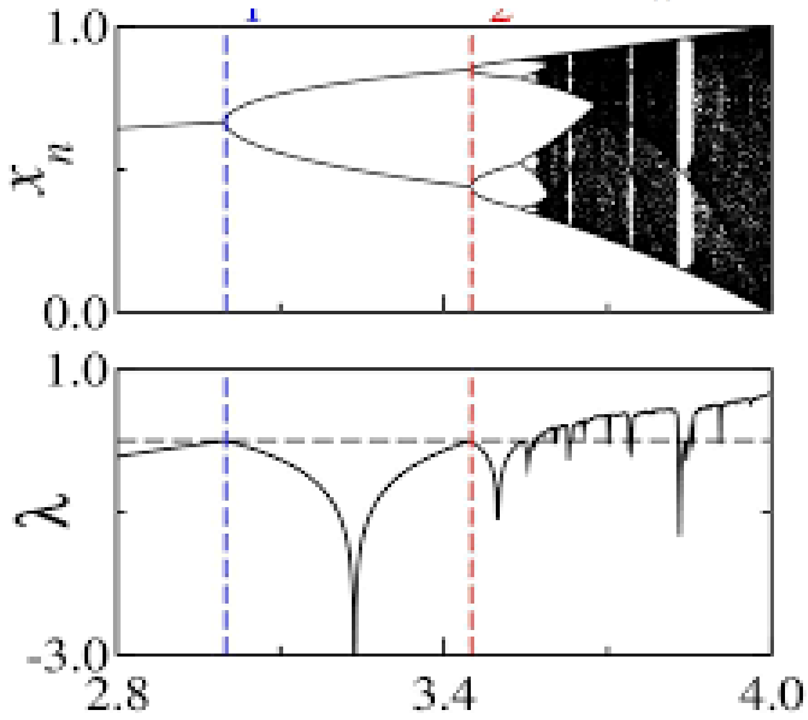
It is relatively easy to calculate the Lyapunov exponent from mathematical equations

$$\lambda = \lim_{t\to\infty} \lim_{|\delta_0|\to 0} \frac{1}{t} \log \frac{\delta_t}{\delta_0}$$

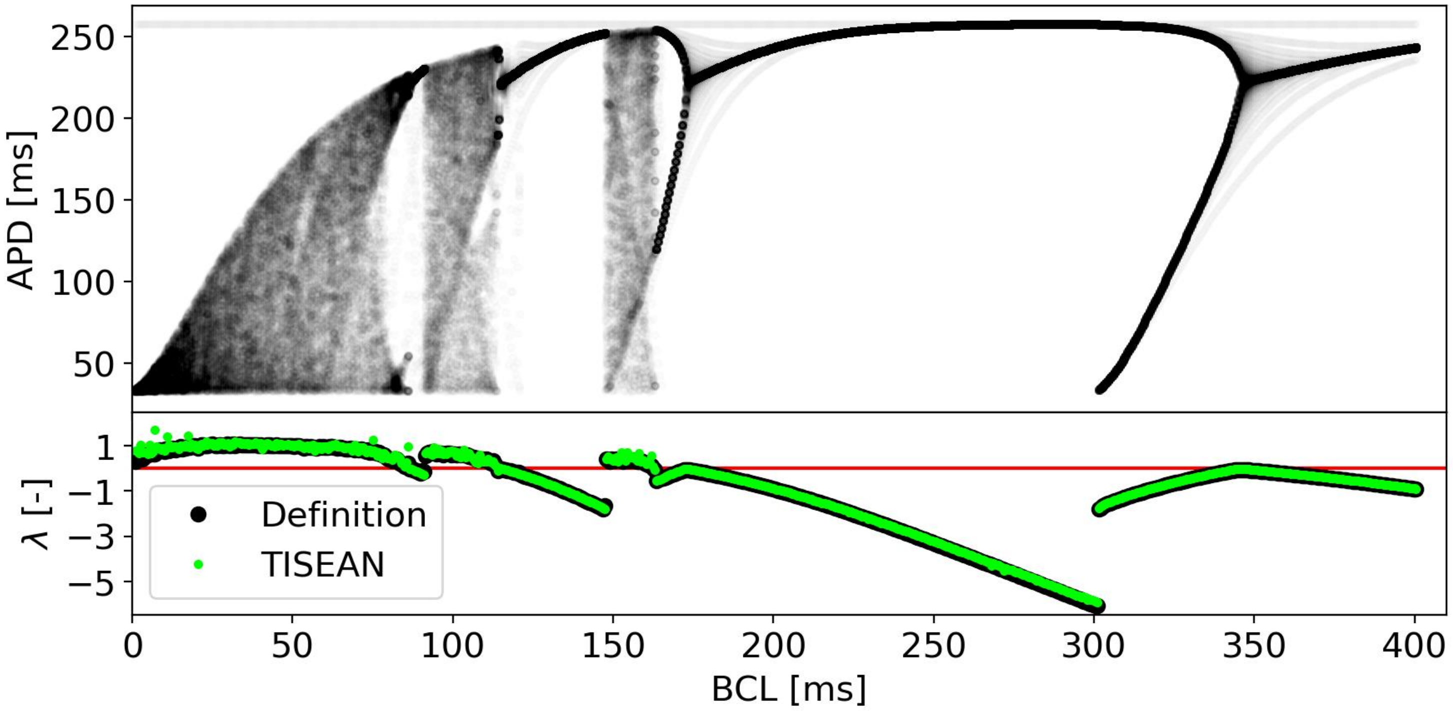


But not from time series (simulations or experimental)
for this we will use TISEAN software

Logistic map



Beeler-Reuter cardiac map

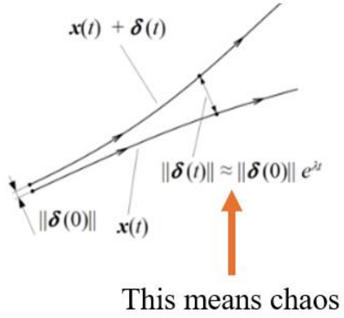


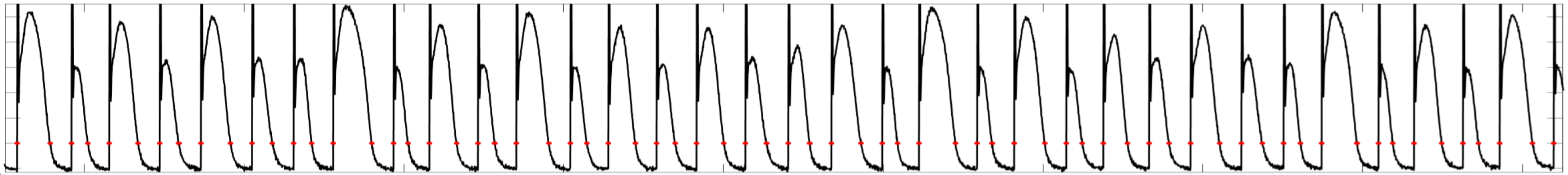
Temporal Method

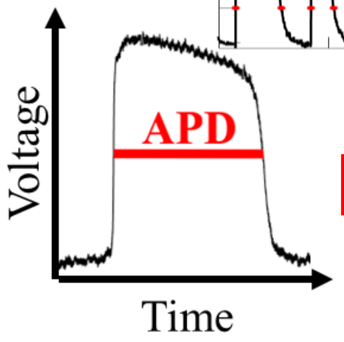
: Nonlinear Time Series Analysis (TISEAN).

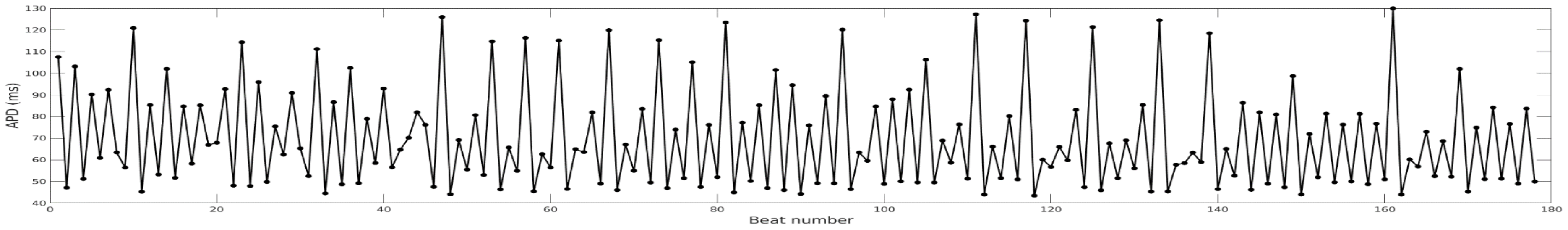
$$S(\Delta n) = \frac{1}{N}\sum_{n_0=1}^{N} \ln\left(\frac{1}{|\mathcal{U}(\mathbf{s}_{n_0})|}\sum_{\mathbf{s}_n \in \mathcal{U}(\mathbf{s}_{n_0})} |s_{n_0+\Delta n} - s_{n+\Delta n}|\right).$$

- Basically, TISEAN will do self correlation analysis inside the temporal data series by picking similar data points and see how they diverge from each other.
- For example, the two data points in circle are similar, and TISEAN will calculate their evolution after some beat numbers.
- Then according to the definition, if any exponential growth, we can find the Lyapunov exponent.
- The slope of the robust linear region during evolution will be considered as Lyapunov Exponent.









Hegger, R., Kantz, H., & Schreiber, T. (1999). Practical implementation of nonlinear time series methods: The TISEAN package. Chaos (Woodbury, N.Y.), 9(2), 413–435. https://doi.org/10.1063/1.166424

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m = 4, τ = 1, ε = 70

$$\mathbf{s}_n = (s_{n-(m-1)\tau}, s_{n-(m-2)\tau}, \ldots, s_{n-\tau}, s_n).$$

- Basically, TISEAN will do self correlation analysis inside the temporal data series by picking similar data points and see how they diverge from each other.
- For example, the two data points in circle are similar (euclidian distance < ε), and TISEAN will calculate their evolution after some beat numbers.
- Then according to the definition, if any exponential growth, we can find the Lyapunov exponent.
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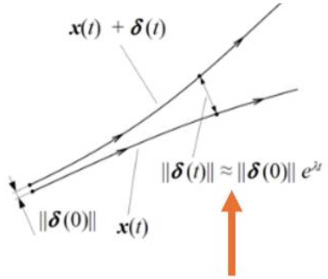
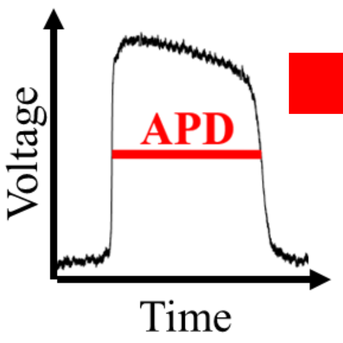
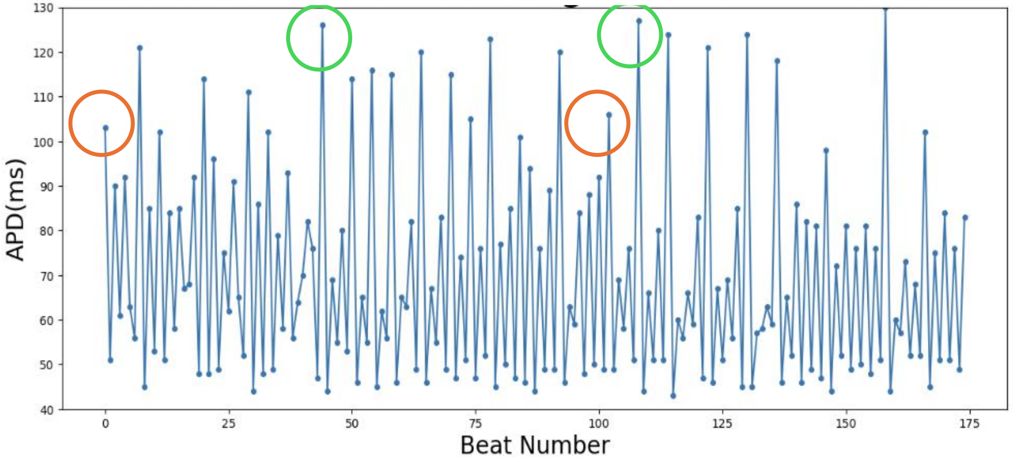
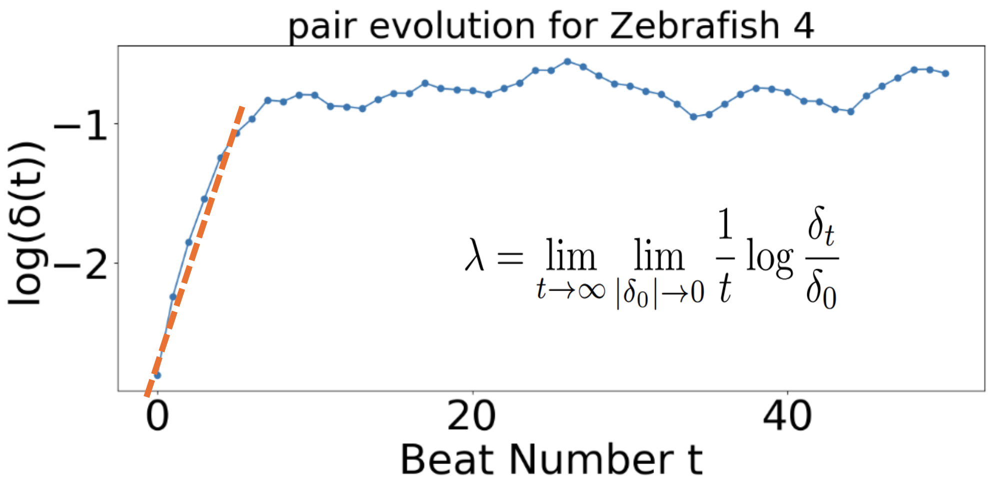


This means chaos

APD signals from zebra fish heart experiment







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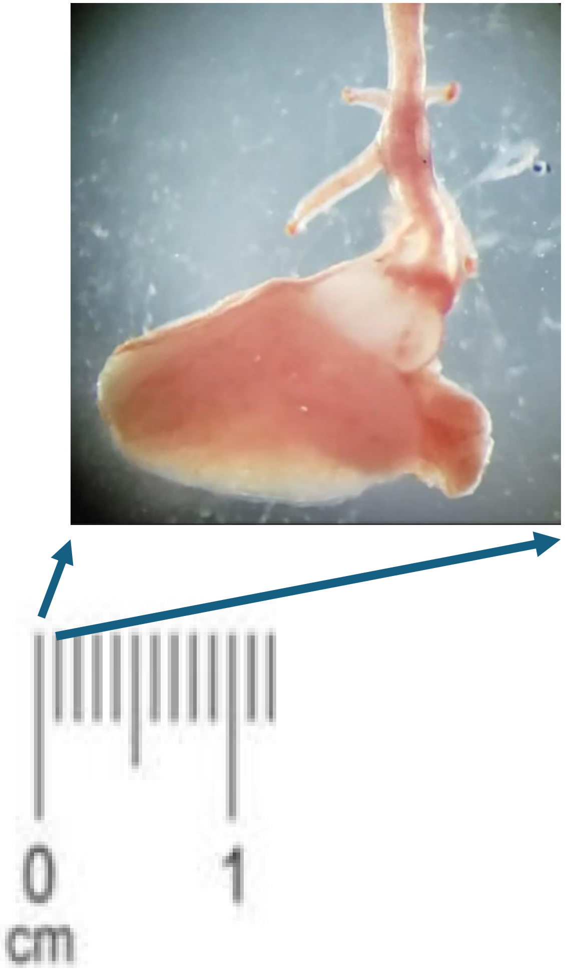
Quantify fibrillation in the heart: Lyapunov exponent

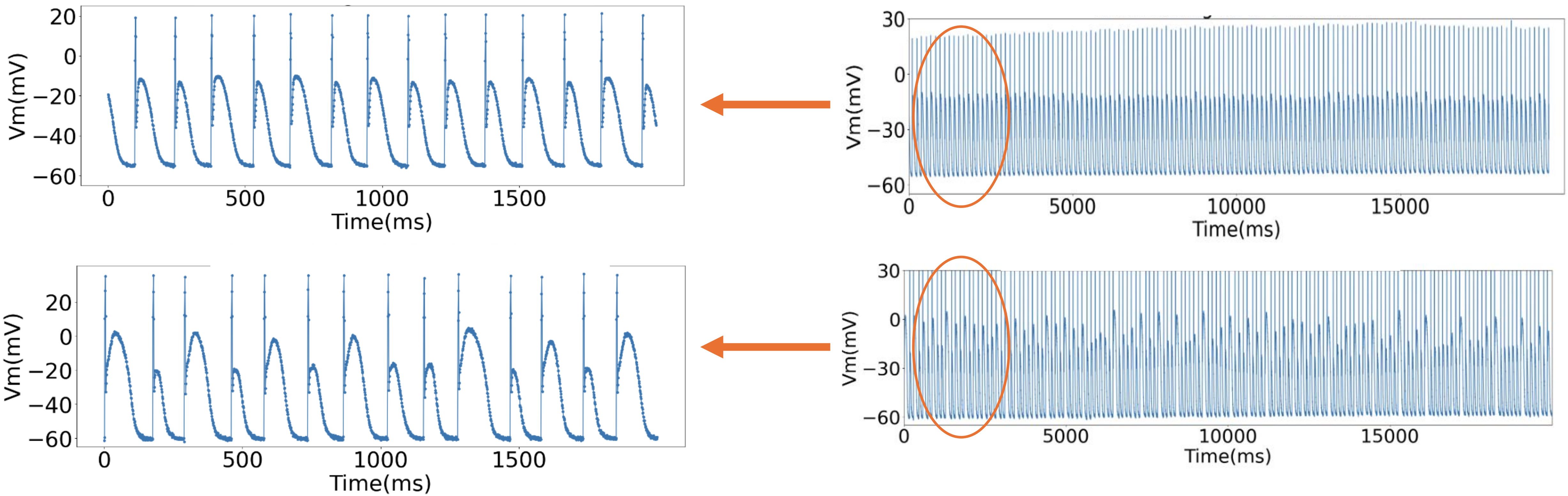
Example: *Zebra fish heart experiment*



Quantify fibrillation in the heart: Lyapunov exponent

Example: *Zebra fish heart experiment*

Two experimental examples, one more irregular than the other

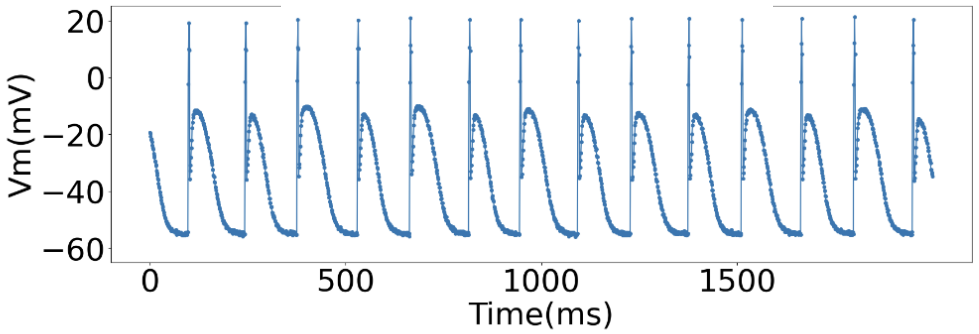


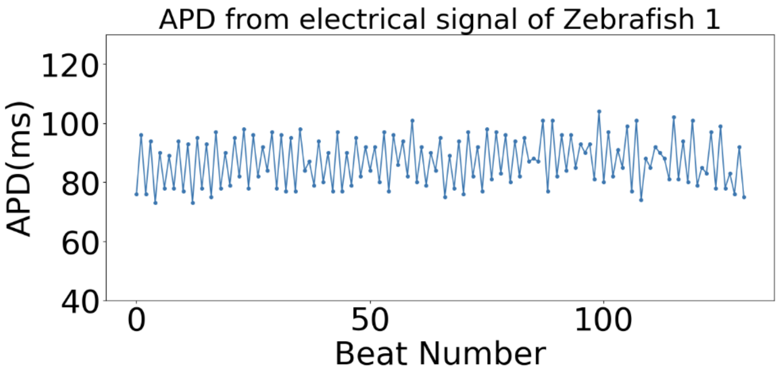
Quantify fibrillation: Temporal Method

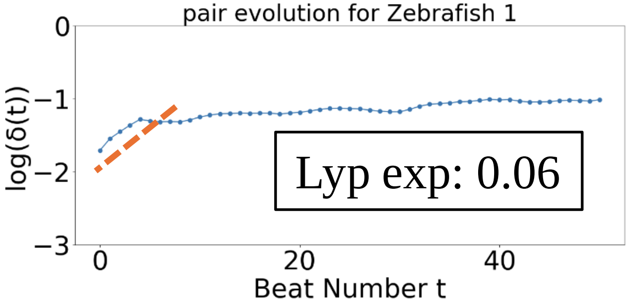
Now, let's see what we get for Zebrafish heart experiments (m = 4, ε = 70):

Experiments 1 and 2

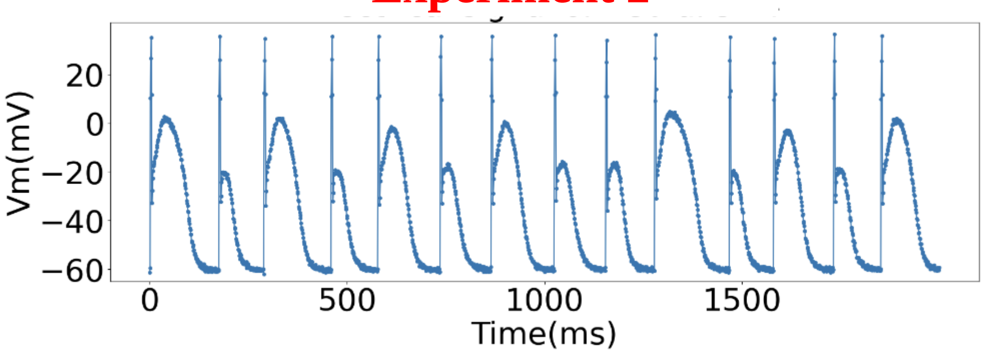
Experiment 1

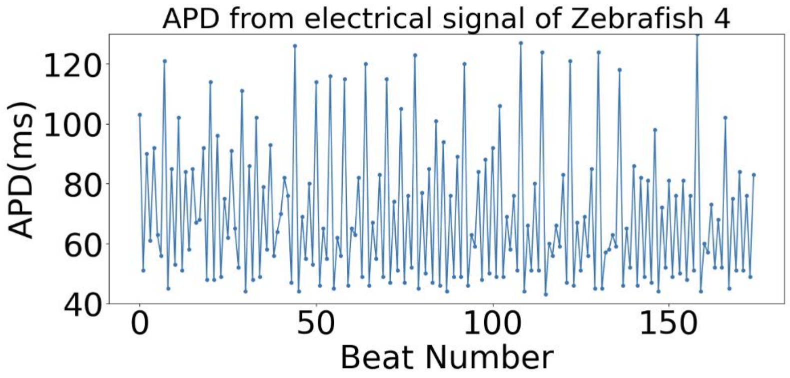


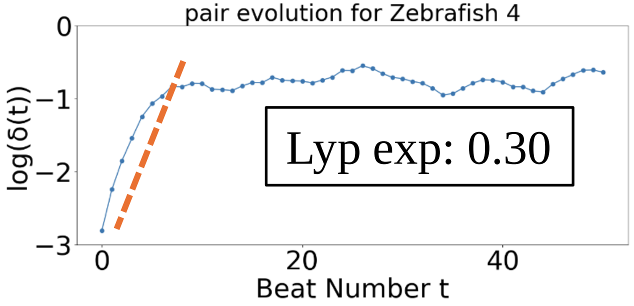




Experiment 2





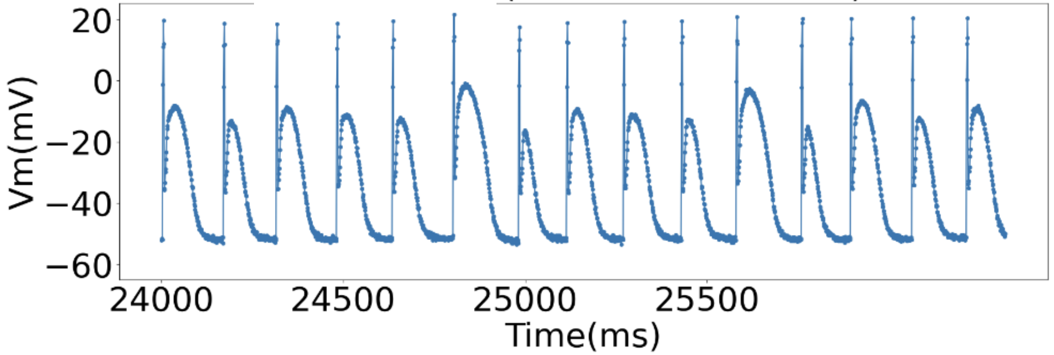


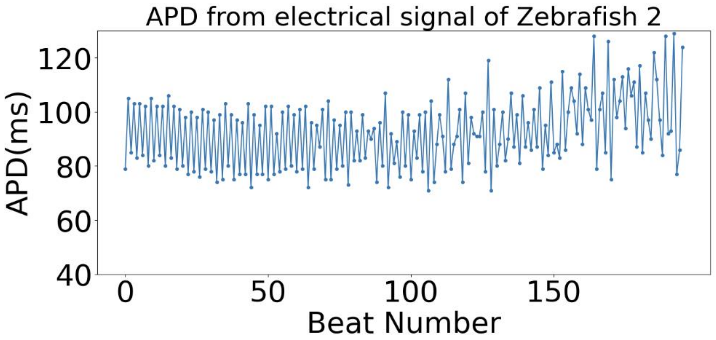
Quantify fibrillation: Temporal Method

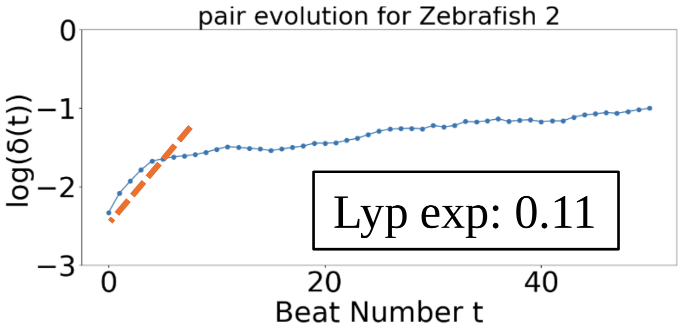
Now, let's see what we get for Zebrafish heart experiments:

Experiments 3 and 4

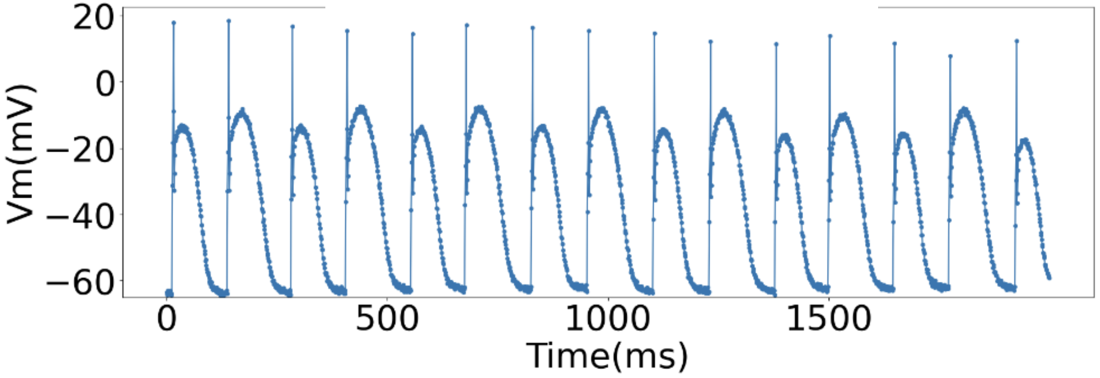
Experiment 3 (Beat 160 - Beat 175)

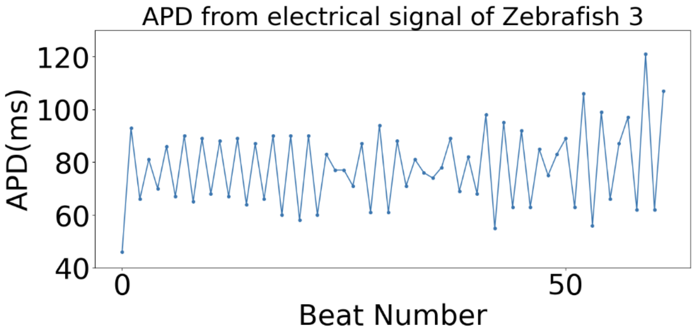


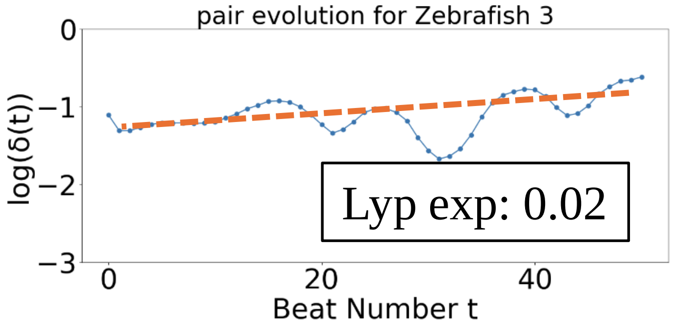




Experiment 4



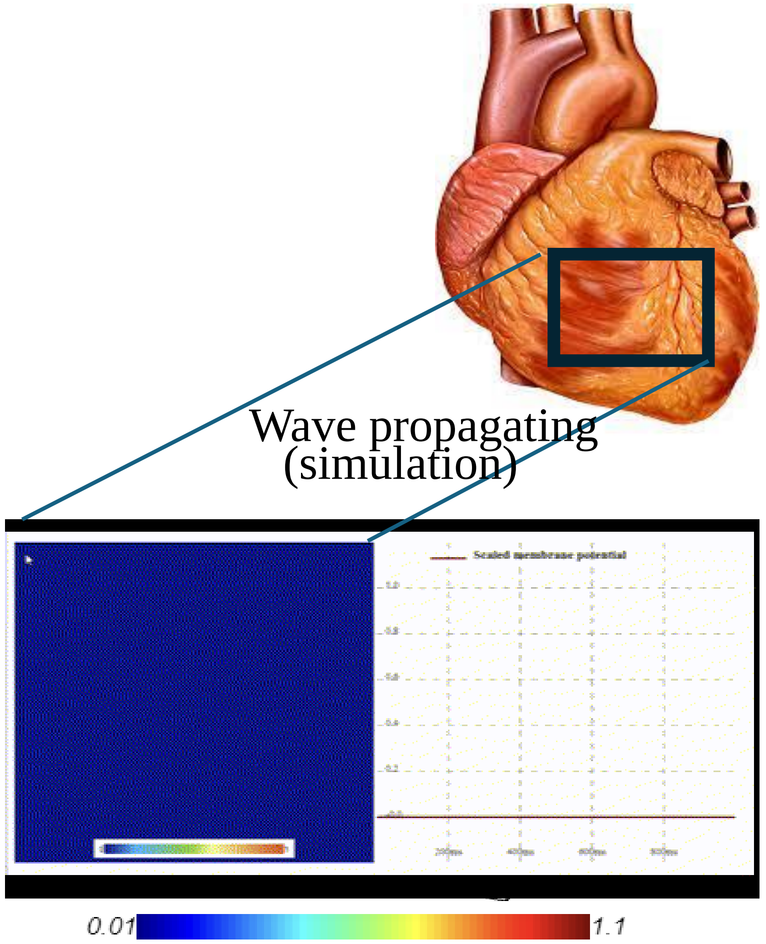




Spatiotemporal Temporal Method for Lyapunov Exponent:

We can calculate temporal and spatiotemporal Lyapunov Exponents from simulations and experiments in tissue.

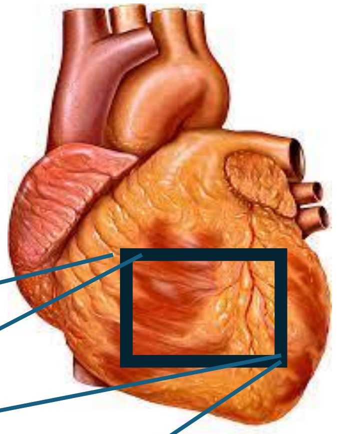
- We take advantage of fast GPU simulations using webGL.
- https://abubujs.org/ (Dr. Abouzar Kaboudian)
- It can run real-time simulation on PC, tablet and even cell phone.

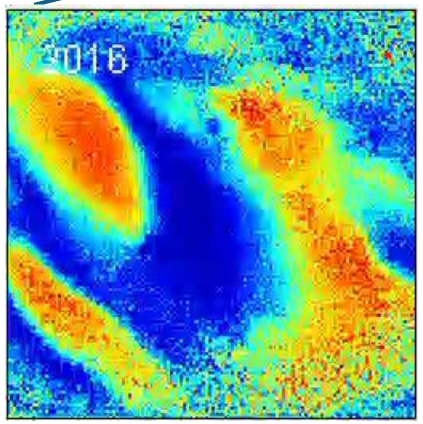


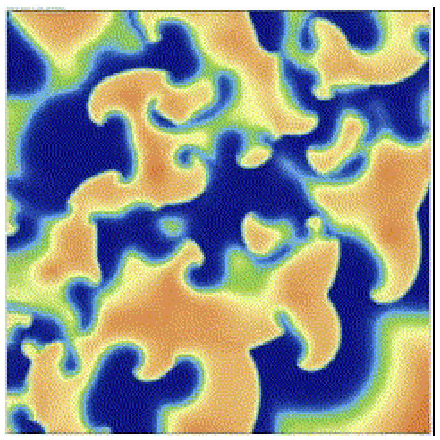
Spatiotemporal Temporal Method for Lyapunov Exponent:

We can calculate temporal and spatiotemporal Lyapunov Exponents from simulations and experiments in tissue.

- We use a 3V-SIM ionic model for simulations.
- Optical mapping experiments from rabbit and pig hearts.







Spatiotemporal Temporal Method for Lyapunov Exponent:

- A spatiotemporal LE is defined:

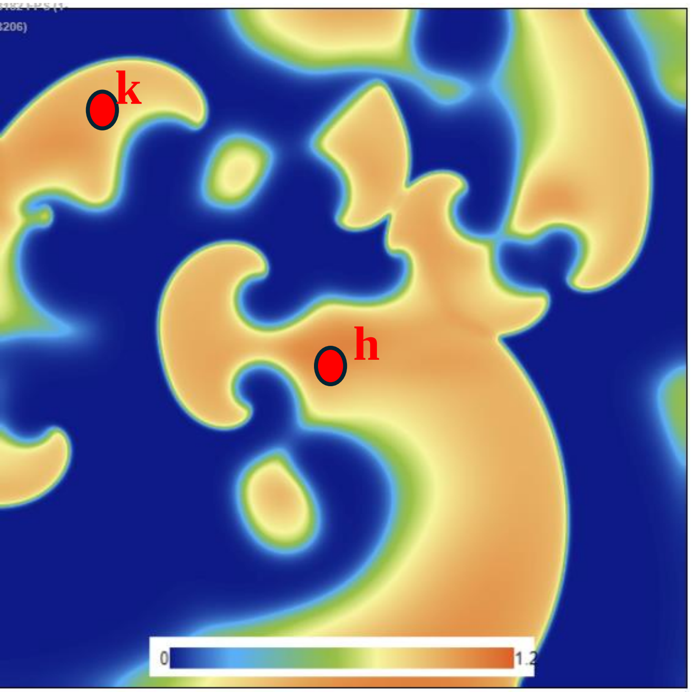
$$\lambda_s(d)=\frac{1}{N_p}\sum_{i=1}^{m-d}\sum_{\langle \mathbf{k},\mathbf{h}\rangle} Ln\left[\frac{\|\mathbf{X}_{i+1}^{j}(\mathbf{k})-\mathbf{X}_{i+1}^{j}(\mathbf{h})\|}{\|\mathbf{X}_{i}^{j}(\mathbf{k})-\mathbf{X}_{i}^{j}(\mathbf{h})\|}\right]. \qquad \|\mathbf{X}_{i}^{j}(\mathbf{k})-\mathbf{X}_{i}^{j}(\mathbf{h})\|=\left[\sum_{u=i}^{i+d-1}(x_u^j(\mathbf{k})-x_u^j(\mathbf{h}))^2\right]^{1/2}<\epsilon$$

  - s means spatial
  - k = every point of 2D map from t_i to t_(i+d)
  - h = neighboring points of k from t_i to t_(i+d) (neighbor distance < a small value)
  - d = embedded dimension
  - N_p = number of <k, h> pairs (take average)
  - j = type of X variable
  - i = time step

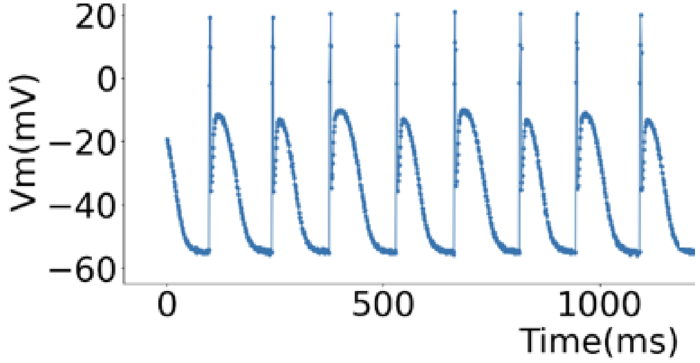
Solé, R. V., & Bascompte, J. (1995). Measuring chaos from spatial information. *Journal of Theoretical Biology*, *175*(2), 139–147. https://doi.org/10.1006/jtbi.1995.0126

Spatiotemporal Temporal Method for Lyapunov Exponent:

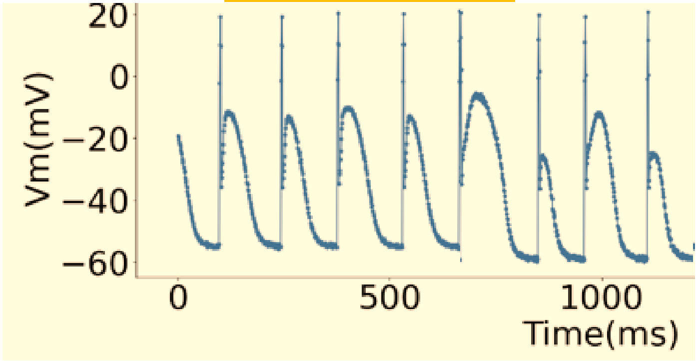
- We first calculate APD sequence for n points (depending on how many we want)
- Then we find any points that have similar APD at same Beat Number.



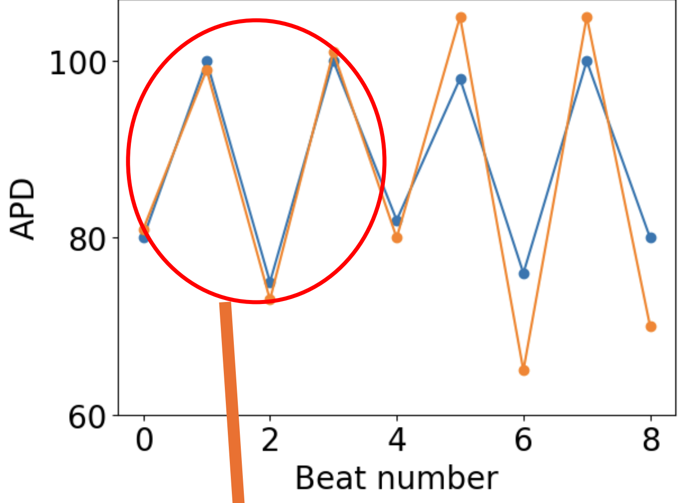
Voltage for k



Voltage for h



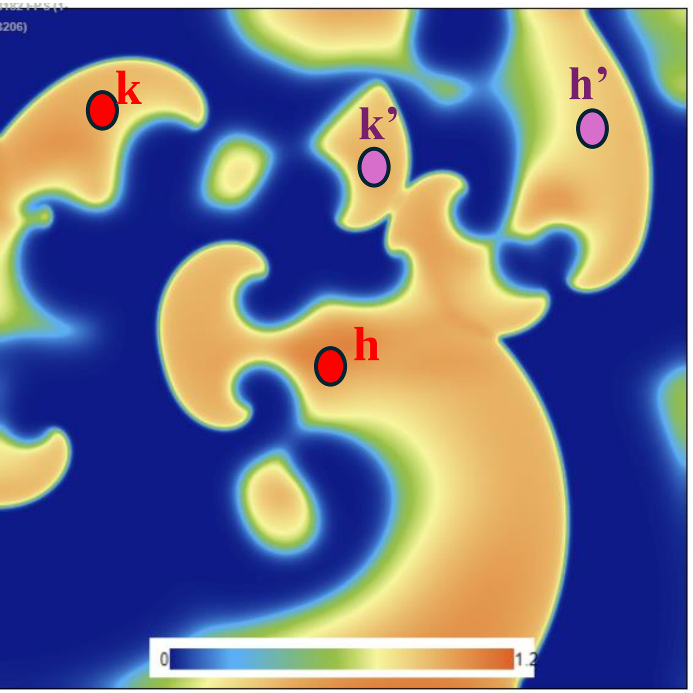
APD compare (k vs h)



$$\|\mathbf{X}_i^j(\mathbf{k})-\mathbf{X}_i^j(\mathbf{h})\| = \left[\sum_{u=i}^{i+d-1}\left(x_u^j(\mathbf{k})-x_u^j(\mathbf{h})\right)^2\right]^{1/2} < \epsilon$$

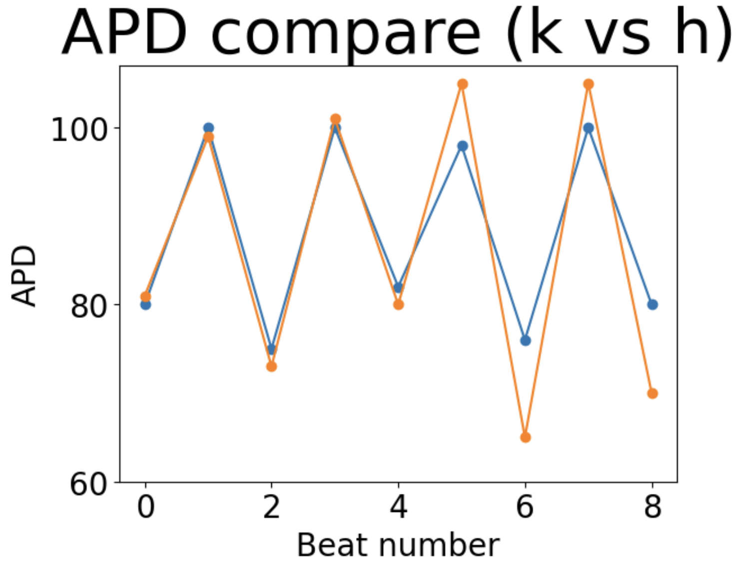
Spatiotemporal Temporal Method for Lyapunov Exponent:

- Then it iterates through all possible spatial pairs in map.
- And evolve all the pairs, to see how they diverge.
- Finally, after spatially and temporally averaged, we get spatial Lyapunov exponent



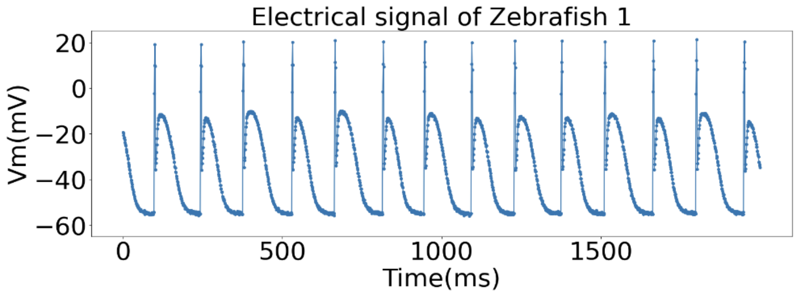
$$\| \mathbf{X}_i^j(\mathbf{k}) - \mathbf{X}_i^j(\mathbf{h}) \| = \left[\sum_{u=i}^{i+d-1} (x_u^j(\mathbf{k}) - x_u^j(\mathbf{h}))^2 \right]^{1/2} < \epsilon$$

$$\lambda_s(d) = \frac{1}{N_p} \sum_{i=1}^{m-d} \sum_{\langle \mathbf{k},\mathbf{h} \rangle} Ln \left[\frac{\| \mathbf{X}_{i+1}^j(\mathbf{k}) - \mathbf{X}_{i+1}^j(\mathbf{h}) \|}{\| \mathbf{X}_i^j(\mathbf{k}) - \mathbf{X}_i^j(\mathbf{h}) \|} \right].$$



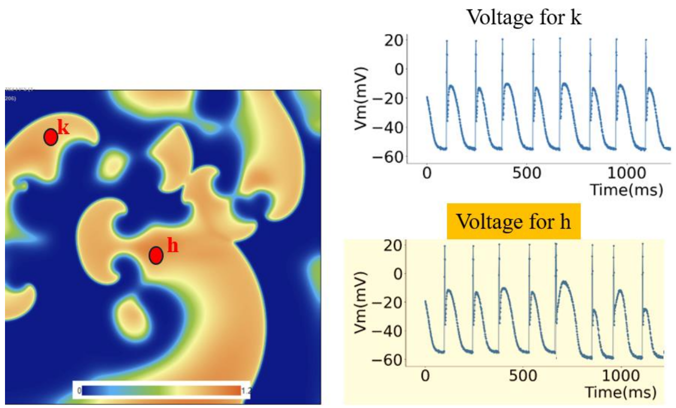
Method – Temporal and Spatial

- Both temporal and spatial methods can be used to calculate LE
  - We can use temporal method when we have temporal information



  - We can use spatial method when we have both spatial and temporal information.

  - Let’s see how they work in simulation and experiment.
    - Simulation: Temporal and Spatial
    - Experiment 1: Temporal
    - Experiment 2: Spatial



Simulation – 3V SIM model

- 3V: three variables (u: membrane voltage, v: fast ionic gate and w: slow ionic gate)
- It is a model that retains the minimal ionic complexity

$$\partial_t u = \nabla \cdot (\widetilde{D} \nabla u) - J_{\mathrm{fi}}(u;v) - J_{\mathrm{so}}(u) - J_{\mathrm{si}}(u;w),$$

$$\partial_t v = \Theta(u_c - u)(1-v)/\tau_v^-(u) - \Theta(u-u_c)v/\tau_v^+,$$

$$\partial_t w = \Theta(u_c - u)(1-w)/\tau_w^- - \Theta(u-u_c)w/\tau_w^+,$$

$$\tau_v^-(u) = \Theta(u-u_v)\tau_{v1}^- + \Theta(u_v - u)\tau_{v2}^-.$$

$$J_{\mathrm{fi}}(u;v) = -\frac{v}{\tau_d}\Theta(u-u_c)(1-u)(u-u_c),$$

$$J_{\mathrm{so}}(u) = \frac{u}{\tau_o}\Theta(u_c - u) + \frac{1}{\tau_r}\Theta(u-u_c),$$

$$J_{\mathrm{si}}(u;w) = -\frac{w}{2\tau_{\mathrm{si}}}(1+\tanh[k(u-u_c^{\mathrm{si}})]).$$

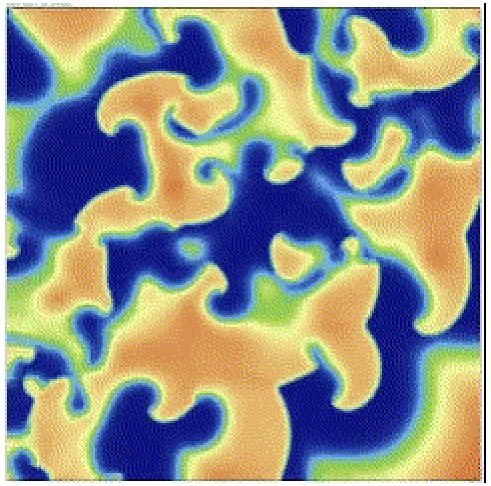
Ifi , Isi and Iso correspond to the fast and slow inward, and slow outward (or to be simplified, Na, Ca, and K) currents

Simulation – 3V SIM model

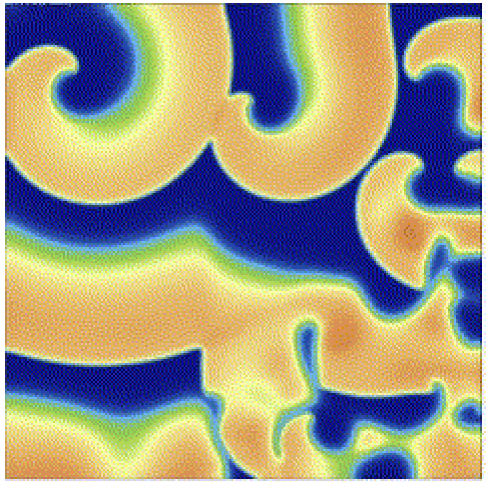
$$J_{fi}(u;v) = -\frac{v}{\tau_d}\,\Theta(u-u_c)(1-u)(u-u_c),$$

- By proper modification of parameters, we have three simulation with different chaotic degree.

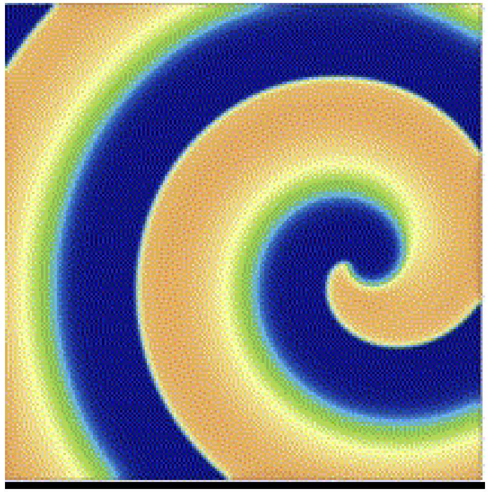
Tau_d = 0.4

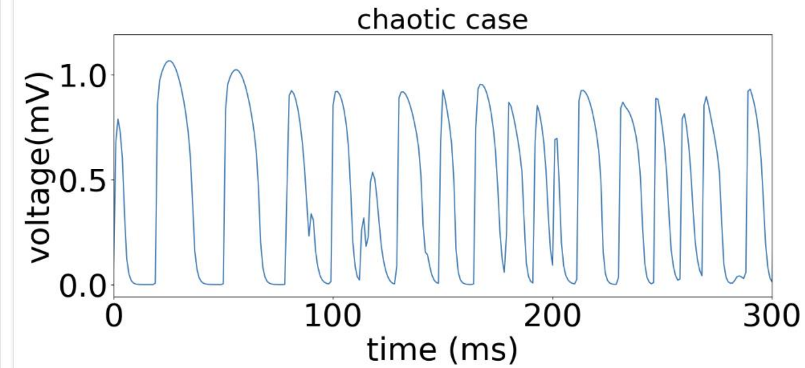


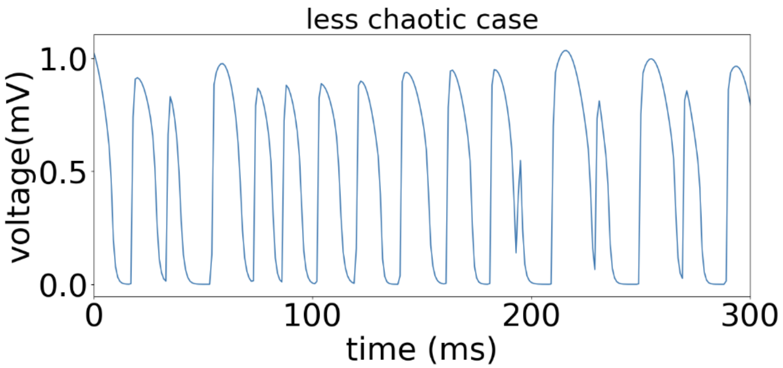
Tau_d = 0.41

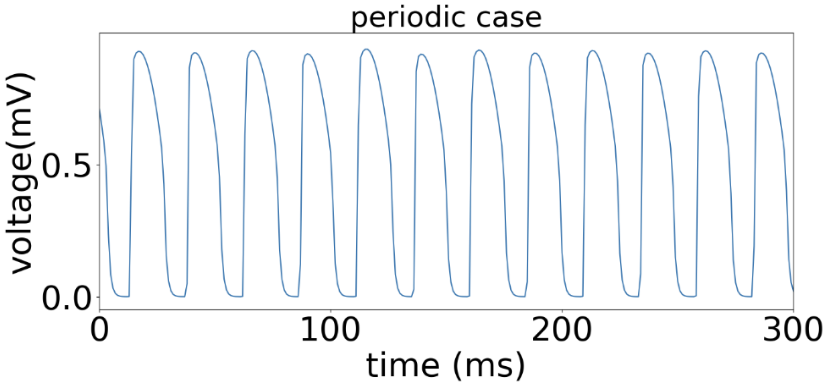


Tau_d = 0.42

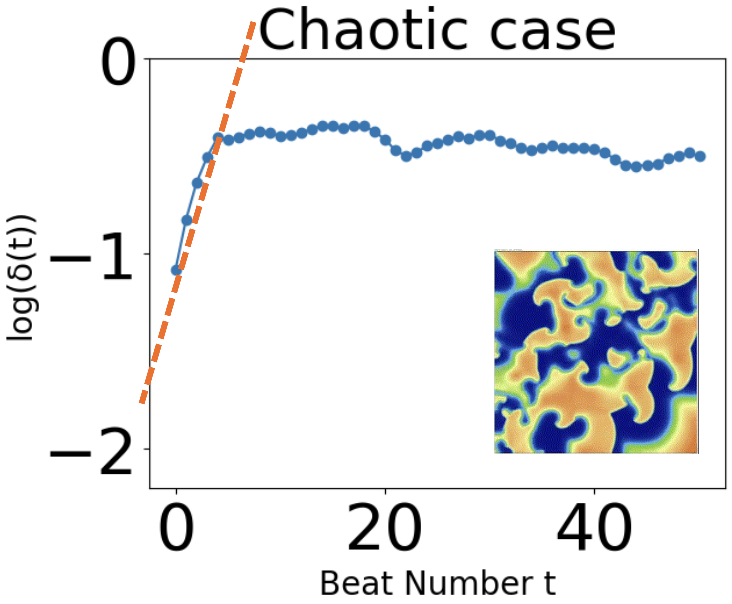


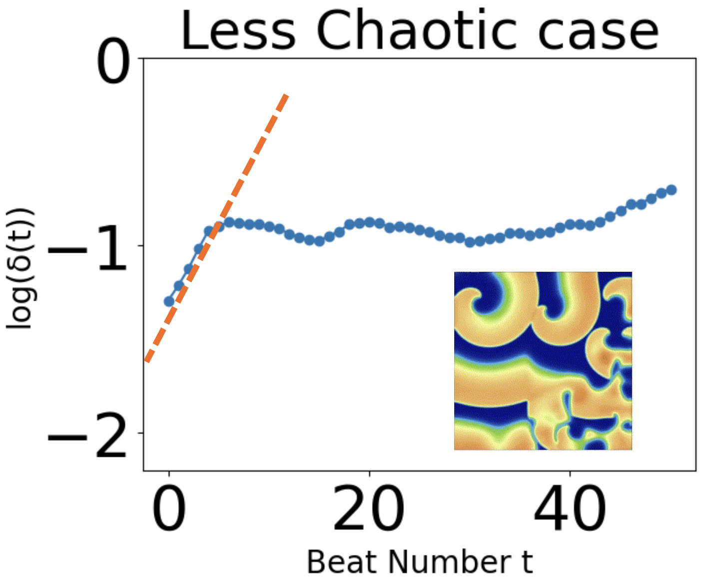


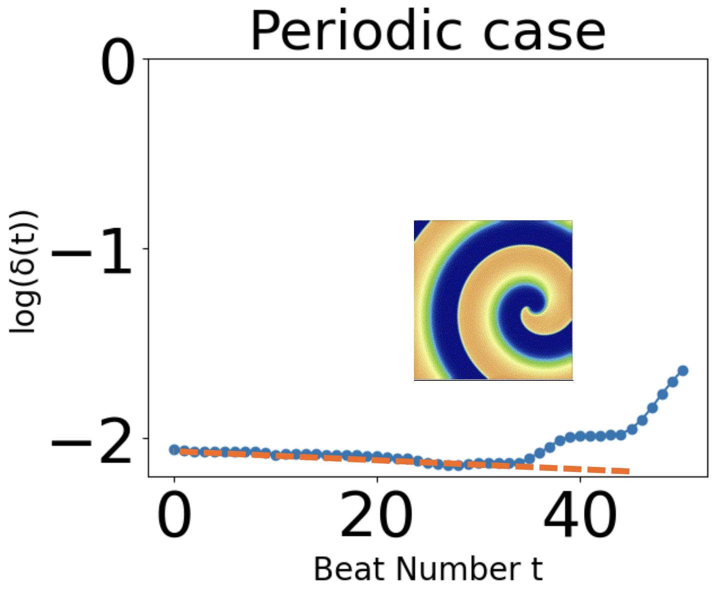




Simulation – 3V SIM model







Temporal LE ~ 0.14
Spatial LE ~ 0.63

Temporal LE ~ 0.11
Spatial LE ~ 0.4

Temporal LE ~ -0.02
Spatial LE ~ -0.01

- Then according to the definition, if any exponential growth, we can find the Lyapunov exponent.
- The slope of the robust linear region during evolution will be considered as Lyapunov Exponent.

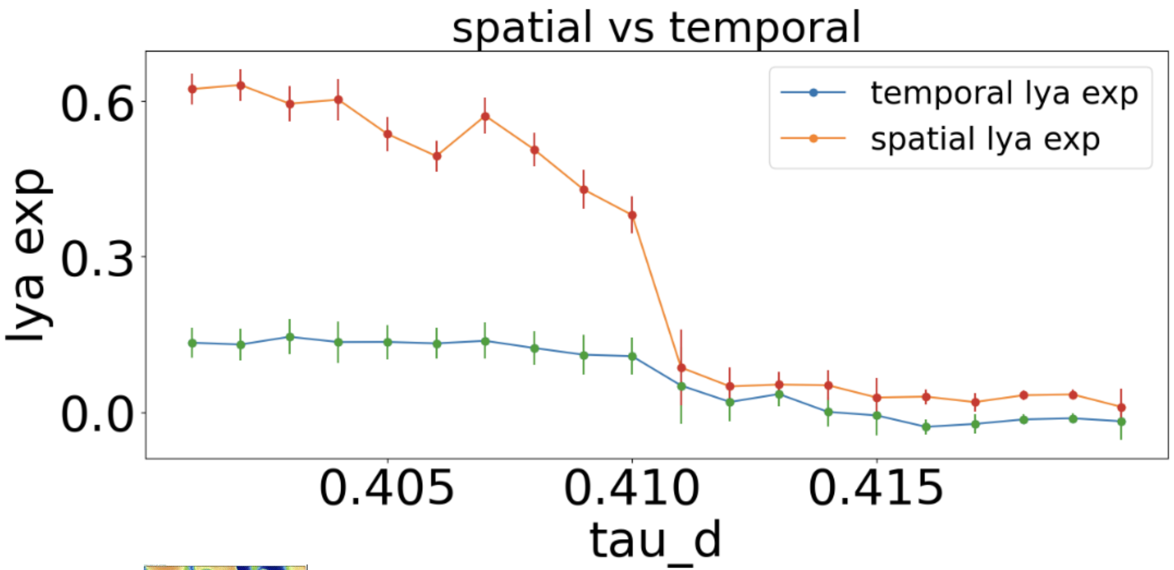
- Formula for LE

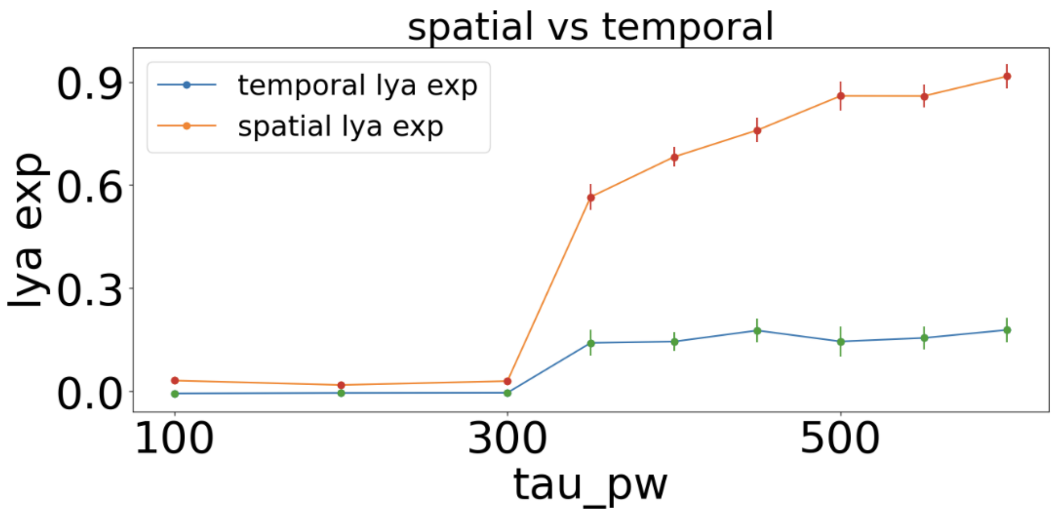
$$\lambda = \lim_{t\to\infty} \lim_{|\delta_0|\to 0} \frac{1}{t} \log \frac{\delta_t}{\delta_0}$$

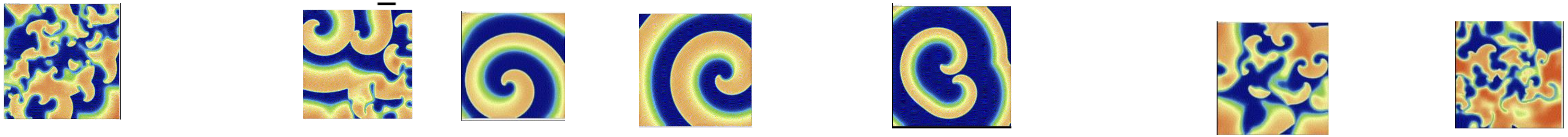
- $\lambda > 0$: chaotic system
  - δ(t)>>δ(0) (difference has exp growth)
- $\lambda = 0$: periodic
  - δ(t)=δ(0) (difference has no growth)
- $\lambda < 0$: stable (convergent to fix point)

Simulation

- Real-time simulation demonstration

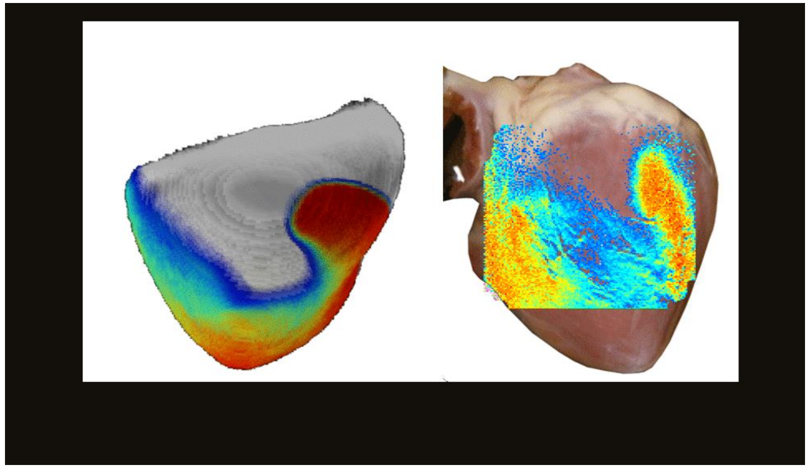


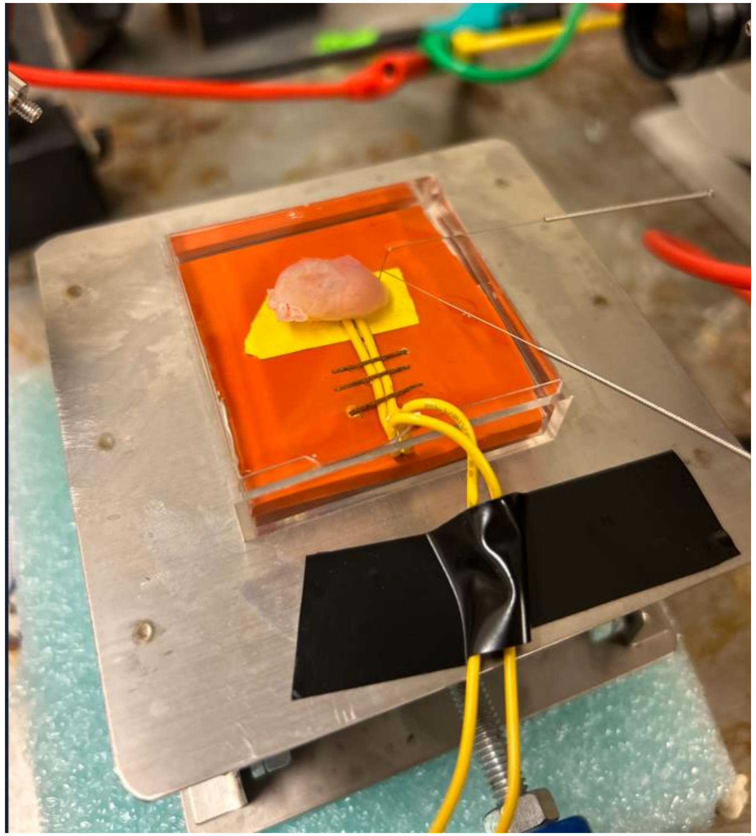




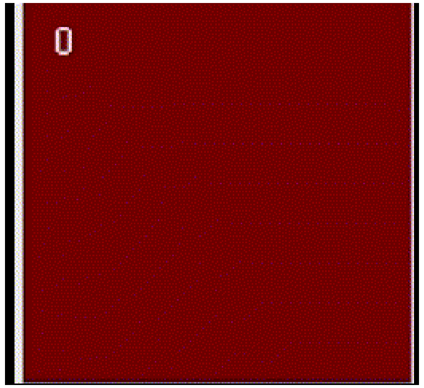
Quantify fibrillation of heart – Experiment 2

- Optical Mapping setup

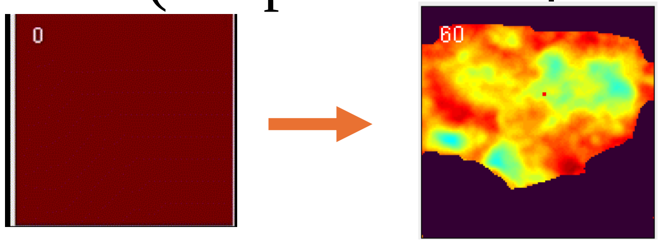


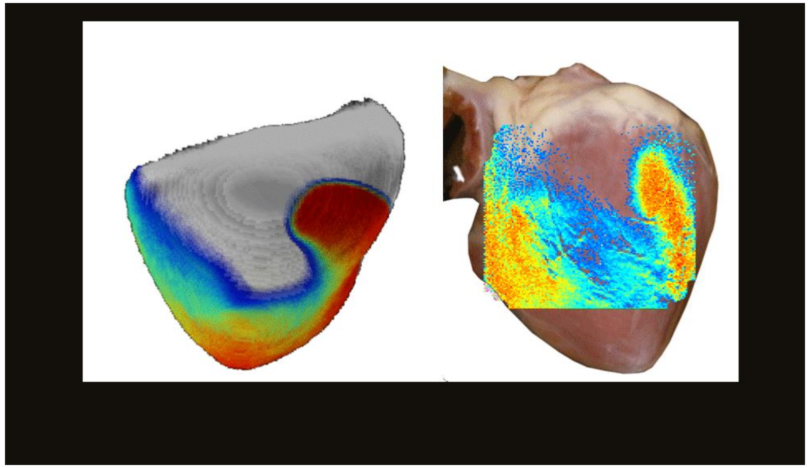


Quantify fibrillation of heart – Spatial Method (Result)

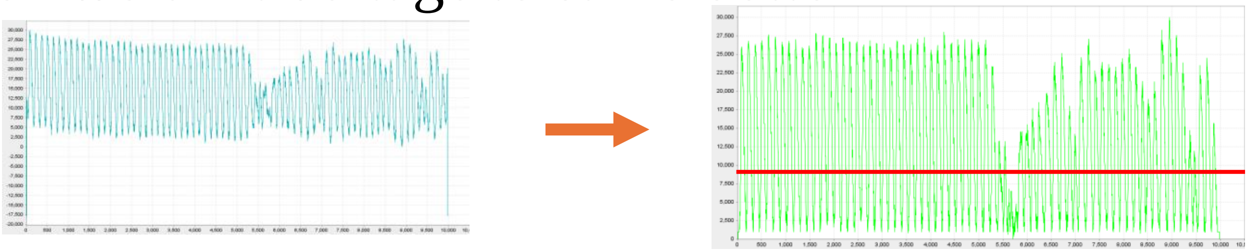


- How we handle the data.
  - We first do noise elimination (temporal and spatial)
  - Then mask out noise





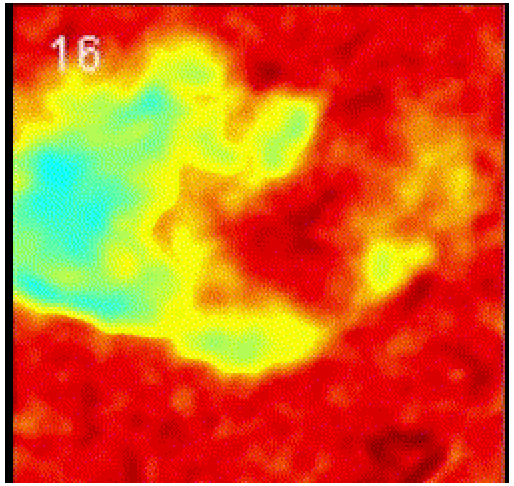
  - Then we drift voltage to same bottom



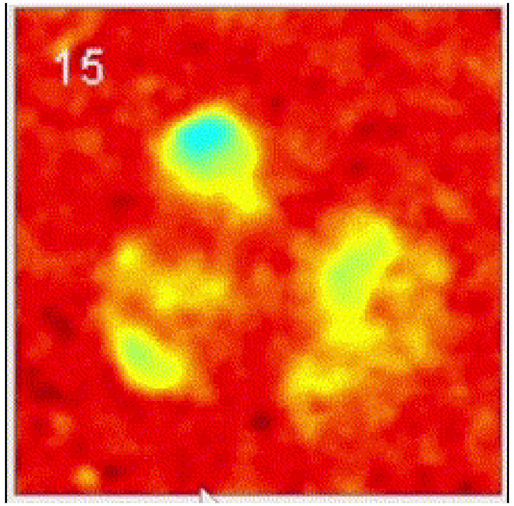
  - We plot the bottom line as the APD threshold (red line) and obtain APD based on that

Quantify fibrillation of heart – Spatial Method (Result)

Chaotic fibrillation in pig heart captured by two cameras

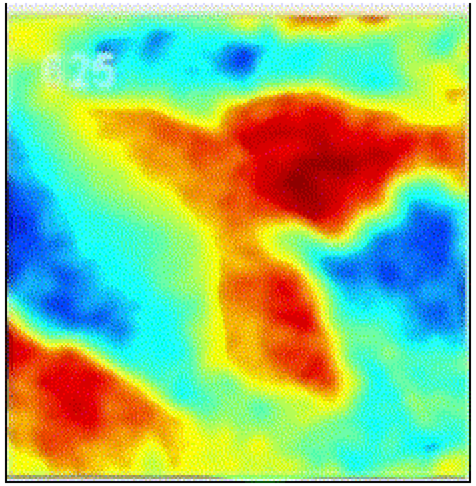


endocardium

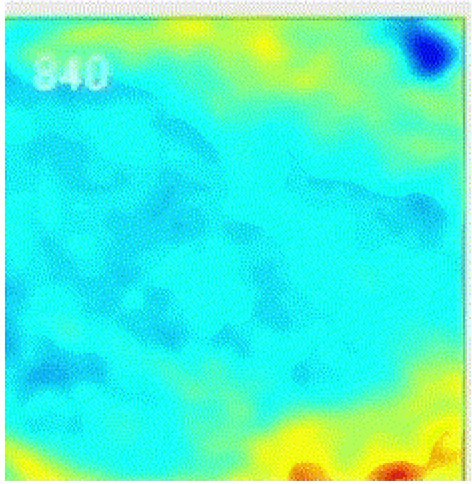


epicardium

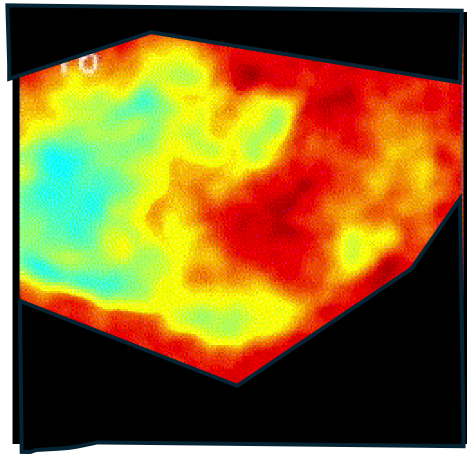
Less chaotic fibrillation



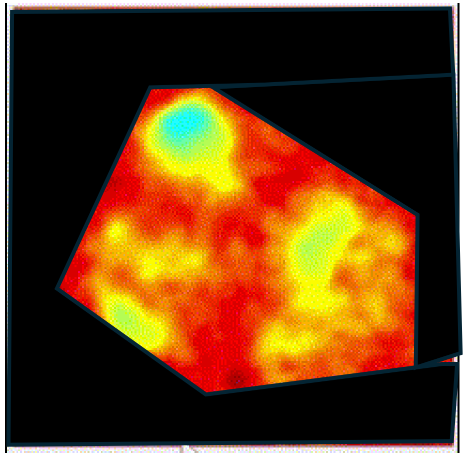
Healthy heart (Periodic)



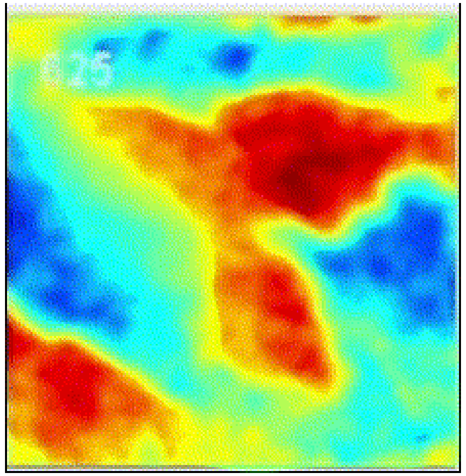
More result from optical mapping (cam 1)



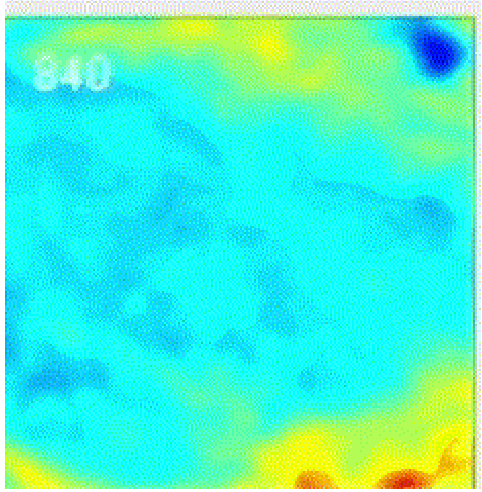
Chaotic, endocardium



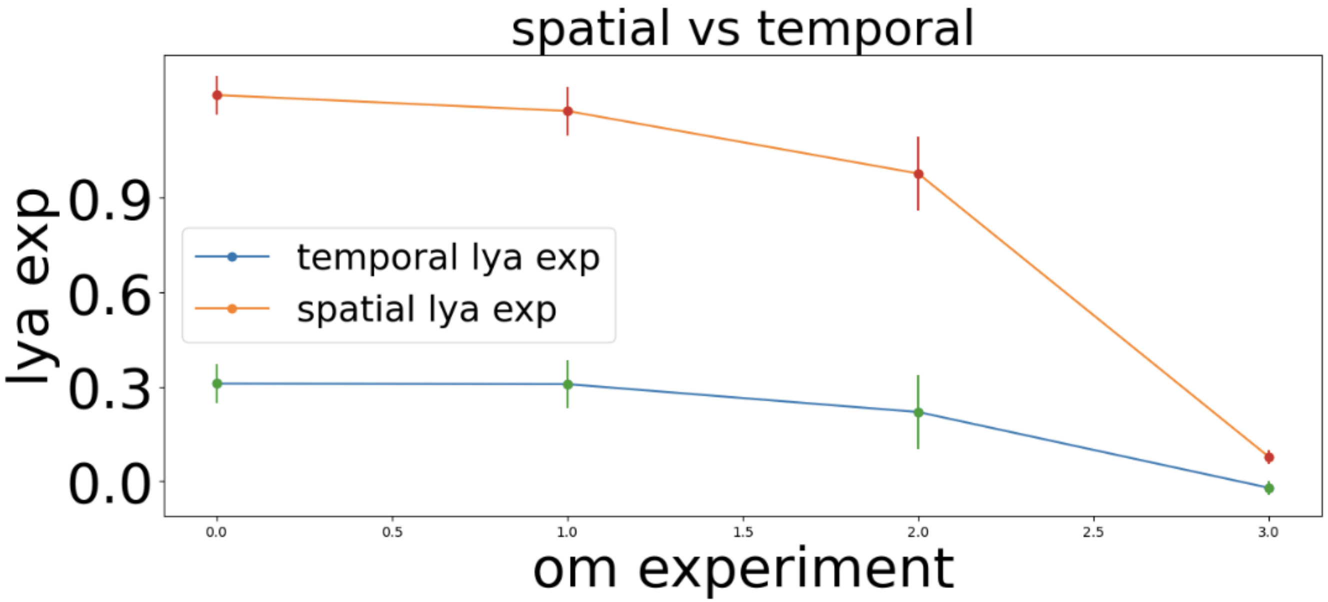
Chaotic, epicardium



Less chaotic



Periodic



Conclusions

- We have shown that it is possible to quantify the fibrillation of heart by calculating Lyapunov exponent of APD with spatial and temporal methods.
- Since the WebGL makes simulation computationally cheap, we could do fibrillation analysis quantitatively on different parameter sets and related studies on drug effect with even more complicated model.
- Besides simulation, the methods mentioned here works well in experiment to distinguish chaotic and non-chaotic patterns.
- Future studies on hyperparameters (embedded dimension, neighboring distance) in those methods with their effect on Lyapunov exponent calculation in cardiac system could be done.

- We have also shown that different camera in optical mapping experiment won’t change the spatial or temporal Lyapunov exponent of system dramatically.