

# Quantifying the Complexity of Cardiac System Simulation by analyzing APD sequence

Xiaodong (Will) AN

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- Introduction
- Method (Literature Review)
- Current Result and Future Work
- Conclusion



# Introduction

- This research tries to do these things:
- 1. Quantify the complexity of cardiac system simulations with parameter changing
- 2. Quantify simulations with meandering cases.
- 3. Quantify experimental results that have noise.
- With determination of the chaotic and non-chaotic regions for different parameters, it can guide the cardiac medication to avoid deadly chaos and help us understand the cardiac model more.







## Introduction – Chaos Quantification



#### They have different complexities, but how do we quantify them?

# Introduction – Chaos Quantification

- There are **several approaches** for chaos quantification, including leading Lyapunov exponent (Characteristic exponent), Correlation dimension, and return map.
- Lyapunov exponent: Quantification of the exponential growth rate in phase space.
- Correlation dimension: The dimension of the strange attractors in phase space.
- Return map: Visualization of complexity.

## Introduction – Lyapunov Exponent (LE)

#### 2.4 Lyapunov Exponent

Lyapunov exponent is a quantitative measure of the divergence rate for nearby trajectories, implying the stability of a nonlinear system, spatially or temporally. Typically, following that basic definition, in a 1D system, the Lyapunov exponent can be naively calculated as [7]:

$$\lambda(x(0)) = \lim_{t \to \infty} \lim_{\delta x(0) \to 0} \frac{1}{t} \ln \frac{\delta x(t)}{\delta x(0)}.$$
(9)

where  $\delta x(0)$  is the initial separation of two trajectories. Now, heading to the higher dimensional system, it becomes [13]:

$$\lambda \left( \boldsymbol{X}(0) \right) = \lim_{t \to \infty} \frac{1}{t} \ln \frac{\|J^t \left( \boldsymbol{X}(0) \right) \delta \boldsymbol{X}(0)\|}{\|\delta \boldsymbol{X}(0)\|} = \lim_{t \to \infty} \frac{1}{2t} \ln \left( \hat{n}^\top J^{t\top} J^t \hat{n} \right).$$

where:

- $\hat{n} = \frac{\delta X(0)}{\|\delta X(0)\|}$  is the direction vector.
- $J^t(\mathbf{X}(0)) = \prod_{t'=1}^{t'=t} J^{t'}(\mathbf{X}(0))$  is the Jacobian matrix.
- $J_{ij}^t(\mathbf{X}(0)) = \frac{\partial \mathbf{X}_i(t)}{\partial \mathbf{X}_i(0)}$  is the element of the Jacobian matrix.

However, in actual calculation, we cannot have infinite time series, so the only one we can get is finite-time Lyapunov exponent, and it is defined as [13]:





# Introduction

#### **Simulation: 3V SIM Model**

Guide us to avoid deadly chaos and understand the cardiac model more.

**Complexity** (LE)



# Method

- 3V SIM Model
- Lyapunov Exponent:
  - Phase Space Reconstruction
  - Wolf's Algorithm
  - Spatial-Temporal Algorithm
  - Noise and Chaos Distinguishment

# Method – 3V SIM Model

- 3V SIM model or Fenton-Karma Model was developed in 1990s and it quantitatively reproduced APD vs DI curve (restitution curve) which determines the APD and relevant propagation velocity after repolarization.
- Three variables: u,v,w
- Three currents: I\_fi (Na+), I\_si (Ca2+), I\_so (K+)



Figure 1: Membrane potential by 3V SIM Model

### Method – 3V SIM Model

Finally, the equations are defined as below [6]:

$$\partial_t u(\boldsymbol{x}, t) = D\nabla^2 u - (I_{\rm fi}(u, v) + I_{\rm so}(u) + I_{\rm si}(V, w))/C_m$$
  

$$\partial_t v(\boldsymbol{x}, t) = (1 - p)(1 - v)/\tau_v^-(u) - pv/\tau_v^+(u)$$
  

$$\partial_t w(\boldsymbol{x}, t) = (1 - p)(1 - w)/\tau_w^-(u) - pw/\tau_w^+(u)$$
  

$$I_{\rm fi}(u, v) = -vp(u - u_c)(1 - u)/\tau_d$$
  

$$I_{\rm so}(u) = u(1 - p)/\tau_0 + p/\tau_r$$
  

$$I_{\rm si}(u, w) = -w(1 + tanh(k(u - u_c^{\rm si})))/(2\tau_{\rm si})$$





$$q = \mathcal{H}(u - u_v)$$

and  $\mathcal{H}()$  is Heaviside step function

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



Figure 1: Membrane potential by 3V SIM Model

(8)

10

# Method – 3V SIM Model

• Qualitatively, I (Na+) = v / tau\_d.

 $I_{\rm fi}(u,v) = -vp(u-u_c)(1-u)/\tau_d$ (4)

- So, we can regard tau\_d as the resistance of the sodium current
- In later section, I discussed the different complexity by changing tau\_d



# Method – LE (full phase space)

• We can input the full phase space (all variables) into Algo, and get LE.



# Method – LE (APD)

- We can also input the APD into Algo, and get LE.
- With less data needed, but nonlinear property retained.



**Complexity** (LE)

### Method – Taken's Theorem

• Limited observations of state variables can retain the Lyapunov exponent by proper lag-embedding.

Given a time series  $\gamma$ :

$$\gamma = \{x_i\}, i = 1, \dots, N,$$
(12)

we could recontruct the phase space  $\Gamma$  as :

$$\boldsymbol{\Gamma}^{m,\tau} = \left\{ \boldsymbol{X}_{i}^{m,\tau} = \left( x_{i}(\boldsymbol{k}), x_{i+\tau}(\boldsymbol{k}), \dots, x_{i+(m-1)\tau}, (\boldsymbol{k}) \right) \right\}, i = 1, \dots, N - m\tau + \tau.$$
(13)

where

- *i* is the time step.
- *m* is the embedded dimension of the time series.
- *τ* is the lagging of the time series.
- N is the total time steps of the time series.

### Method – Taken's Theorem



https://www.youtube.com/watch?v=6i57udsPKms&t=40s Sugihara, George, et al. "Detecting causality in complex ecosystems." *science* 338.6106 (2012): 496-500.

# **Method** – Taken's Theorem (lagging $\tau$ )

- To get the proper embedding, we decide lagging τ first and then dimension m.
- Embeddings with the same m but different  $\tau$  are equivalent in the mathematical sense for noise-free data [15]. Therefore, for the purposes of this research, where simulations are conducted without the influence of noise, a simple choice of  $\tau = 1$  is sufficient.

• For embedded dimension m, there are methods including False Nearest Neighbor (FNN) method [21].

X(n+1)





FIG. 1. The  $R^1$  and  $R^2$  embeddings of the x coordinate of the Hénon map of the plane. It is known that for this map  $d_E = 2$ . The points **A** and **B** are false neighbors while the points **A** and **C** are true neighbors.

Kennel, Matthew B., Reggie Brown, and Henry DI Abarbanel. "Determining embedding dimension for phase-space reconstruction using a geometrical construction." *Physical review A* 45.61(1992): 3403.

The optimal dimension is found when percentage of FNN is dropped to a very low value

Unwanted "crossing" in 2d projection, or a pair of false neighbors





Kennel, Matthew B., Reggie Brown, and Henry DI Abarbanel. "Determining embedding dimension for phase-space reconstruction using a geometrical construction." *Physical review A* 45.6 (1992): 3403

Method – FNN





#### Uniqueness except for this

Finally, the equations are defined as below [6]:

$$\partial_t u(\boldsymbol{x}, t) = D\nabla^2 u - (I_{\rm fi}(u, v) + I_{\rm so}(u) + I_{\rm si}(V, w))/C_m \tag{1}$$

$$\partial_t v(\boldsymbol{x}, t) = (1 - p)(1 - v)/\tau_v^-(u) - pv/\tau_v^+(u)$$
(2)

$$\partial_t w(\boldsymbol{x}, t) = (1 - p)(1 - w)/\tau_w^-(\boldsymbol{x}) - pw/\tau_w^+(\boldsymbol{x})$$
(3)

$$I_{\rm fi}(u,v) = -vp(u-u_c)(1-u)/\tau_d$$
(4)

$$I_{\rm so}(u) = u(1-p)/\tau_0 + p/\tau_r \tag{5}$$

$$I_{\rm si}(u,w) = -w(1 + tanh(k(u - u_c^{\rm si})))/(2\tau_{\rm si})$$
(6)

where:

$$p = \mathcal{H}(u - u_c) \tag{7}$$

$$q = \mathcal{H}(u - u_v) \tag{8}$$

and  $\mathcal{H}()$  is Heaviside step function

$$\tau_{v}^{-}(u) = \Theta(u - u_{v})\tau_{v1}^{-} + \Theta(u_{v} - u)\tau_{v2}^{-}.$$
<sup>20</sup>

Even with the Laplacian term, there is only 0.01% crossing in true phase space. So, FNN can work for 3V SIM Model with error of O(1e-4)

```
data length = 10000
   crossing_happen_times = 0
 3 for i in range(data_length):
        for j in range(i+1, data_length):
 4
 5
             dis = 0
 6
             dis += (V[0][0][i] - V[0][0][j]) **2
 7
             dis += (V[1][0][i] - V[1][0][i]) **2
 8
             dis += (V[2][0][i] - V[2][0][i]) **2
9
10
             if dis 〈 1e-10:
11
                 \operatorname{dis\_plus\_1} = (\forall [0] [0] [i+1] - \forall [0] [0] [j+1]) **2 + (\forall [1] [0] [i+1] - \forall [1] [0] [j+1]) **2 + (\forall [2] [0] [i+1] - \forall [2] [0] [j+1]) **2
12
                 if dis_plus_1 > 1e-10:
                      print(dis, dis_plus_1, i, j)
13
                      crossing_happen_times += 1
14
15
    print('data length is: ', data_length)
16
    print ('crossing happen times: ', crossing_happen_times)
17
```

```
9.169554004984093e-11 5.823367832391568e-06 1596 7434
data length is: 10000
crossing happen times: 1
```

### Method – Wolf's Algo



end of data set

 $\sum_{n}^{x(t_n)}$ 

Step 1: data prepare (original phase space or phase space reconstruction)

#### STEP 2: Identify Nearby Trajectories

For a point in the phase space, find a nearby point (a neighbor) that lies on a different trajectory. This neighbor should be close in space (both their magnitude and direction) but not necessarily in time to avoid correlations between temporally adjacent trajectories.

Specifically, a point  $X_i$  where  $i \approx \frac{N}{2}$  in first iteration and i = i' otherwise, is chosen, then by iterating through  $\Gamma$ , we find its nearest neighbor  $X_j$  by calculating the Euclidean distance:

$$j = \arg\min_{j} \|\boldsymbol{X}_{i}^{m,\tau} - \boldsymbol{X}_{j}^{m,\tau}\| = \arg\min_{j} L_{i} < \epsilon,$$
(15)

where

- $j \in [1, N m\tau + \tau].$ •  $j \neq i.$ •  $\frac{X_i^{m,\tau}X_j^{m,\tau}}{|X_i^{m,\tau}||X_j^{m,\tau}|} < \theta.$ •  $\theta = \frac{\pi}{|x_i^{m,\tau}||X_j^{m,\tau}|}$
- $\theta = \frac{\pi}{9}$  is the maximum initial angular distance.
- *ϵ* is the maximum initial separation.

If the algorithm cannot find a close enough pair whose Euclidean distance is smaller than  $\epsilon$ , it should report to the user and change the  $\epsilon$  accordingly. 22

### Method – Wolf's Algo



 $\begin{array}{c} x(t_n) \\ end of \\ data set \end{array}$ 

#### STEP 3: Evolve and Measure Divergence

Once we obtain a pair of neighbors, following Eq. 10, the finite-time Lyapunov exponent is then computed by monitoring the exponential divergence of the trajectory difference over a certain time interval, indicating a chaotic behavior.

Evolve  $L_i$  by one time step each until:

$$\|X_{i'}^{m,\tau} - X_{j'}^{m,\tau}\| = L_{i'} > \epsilon,$$
 (16)

or

$$i' = N - m\tau + \tau \text{ or } j' = N - m\tau + \tau,$$
 (17)

where  $\epsilon$  should be chosen sufficiently large to ensure the two neighbors exhibit chaotic behavior. If the evolved distance exceeds  $\epsilon$ , repeat **STEP 2 & 3**. If not, break the loop and continue to **STEP 4**.

#### STEP 4: Measure the Lyapunov Exponent [14]

Having obtained multiple finite-time Lyapunov exponents throughout the iterations, the next step is to compute an averaged value, yielding a more robust estimate of the system's Lyapunov exponent.

During the loop, record all the  $\frac{L_{i'}}{L_i}$ , the *i* in first loop as  $i_0$  and the *i'* in last loop as  $i_f$ . Finally, the Lyapunov exponent is:

$$\lambda = \frac{1}{i_f - i_0} \sum_{\text{All Loops}} \log_2 \frac{L_{i'}}{L_i}.$$
(18)

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or

x(t)end of

data set

Method – Wolf's Algo

Ľ,

average

 $z_{2}(t_{2})$ 

 $L'_{1}$ 

 $x(t_0)$ 

 $x(t_1)$ 

 $z_{1}(t_{1})$ 

https://home.cs.colorado.edu/~lizb/chaos/wolf-notes.pdf

$$i' = N - m\tau + \tau \text{ or } j' = N - m\tau + \tau, \tag{17}$$

where  $\epsilon$  should be chosen sufficiently large to ensure the two neighbors exhibit chaotic behavior. If the evolved distance exceeds  $\epsilon$ , repeat **STEP 2 & 3**. If not, break the loop and continue to **STEP 4**.

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 (18)

## Method – Spatial Temporal LE (SLE)



Step 1: data prepare (original phase space or phase space reconstruction)

#### STEP 2: Identify Nearby Trajectories

For each vector  $X_i^{m,\tau}(\mathbf{k}) \in \Gamma^{m,\tau}(\mathbf{k}), \forall \mathbf{k} \in \Lambda^2$ , we search its neighbor  $\mathbf{h} \in \Lambda^2, \mathbf{h} \neq \mathbf{k}$  such that the following condition holds:

$$\|\boldsymbol{X}_{i}^{m,\tau}(\boldsymbol{k}) - \boldsymbol{X}_{i}^{m,\tau}(\boldsymbol{h})\| = \sqrt{\sum_{i'=i}^{i+m\tau-\tau} \left(\boldsymbol{X}_{i'}^{m,\tau}(\boldsymbol{k}) - \boldsymbol{X}_{i'}^{m,\tau}(\boldsymbol{h})\right)^{2}} < \epsilon,$$
(23)

where  $\epsilon$  is the maximum initial separation.

# Method – Spatial Temporal LE (SLE)





(24)

At time step i, we name the certain neighboring pair by  $\langle k, h \rangle$ . Then we evolve the pair to one more step further, which is to calculate

After duration 1  $\rightarrow \rightarrow \rightarrow \rightarrow$ 

$$m{X}_{i+1}^{m, au}(m{k}) - m{X}_{i+1}^{m, au}(m{h}) \|.$$

### Method – Spatial Temporal LE (SLE)



STEP 4: Measure the Lyapunov Exponent Finally, SLE is defined as:



 $\rightarrow \rightarrow \rightarrow \rightarrow$ 



(25)

### Method – Noise Chaos distinguishment

#### • Simplex Projection



Step 1: data prepare (original phase space or phase space reconstruction)

#### STEP 2: Identify Nearby Trajectories

Then we find 3 nearest neighbors with index  $\{j, k, l\}$  to embedded data at step *i*:

$$j = \underset{j \neq i}{\arg\min} \| \mathbf{X}_{i-m\tau}^{m,\tau} - \mathbf{X}_{j-m\tau}^{m,\tau} \|, j \in [1 + m\tau, N - s],$$
  

$$k = \underset{k \neq i,j}{\arg\min} \| \mathbf{X}_{i-m\tau}^{m,\tau} - \mathbf{X}_{k-m\tau}^{m,\tau} \|, k \in [1 + m\tau, N - s],$$
  

$$l = \underset{l \neq i,j,k}{\arg\min} \| \mathbf{X}_{i-m\tau}^{m,\tau} - \mathbf{X}_{l-m\tau}^{m,\tau} \|, l \in [1 + m\tau, N - s].$$

### Method – Noise Chaos distinguishment

#### • Simplex Projection



Time

# Method – Noise Chaos distinguishment

- Unautocorrelated noise would not be predicted by similar patterns since its next data point is not correlated with current pattern.
- We can expect the chaos has decreasing prediction score with increasing prediction steps. But noise just keep a flat line.



Figure 5: Forcast Plot.  $\rho(s)$  is the correlation coefficient (prediction score) and s is the prediction step. More details can be seen in Eq. 35.

# Method - Simulation

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

Parameter	Symbol	Value
Simulation Time Step	$d\tau$	0.1 ms
Measurement Time Step	dt	4 ms
Space Step	dx, dy	$\frac{18}{512}$ cm
Texture Size	Ι Ι	512 * 512 pixels
Measurement Pixels	$\{k\}$	25 * 25 pixels
Transient Time	$T_t$	20000
Measurement Time	$\Delta T$	[20000, 70000], [20000, 340000]
# of Voltage per Pixel	$\{u(\mathbf{k})\}$	12500, 1250000
# of APD per Pixel	$\{APD(k)\}$	$\sim 200, \sim 20000$



Table 1: Information of the input data. The red color is the input data for Spatial-Temporal Algo, and the blue color is for Wolf's Algo

# **Current Result and Future Work** – FNN

• Now, by plotting the FNN percentage with respect to m, we get optimal m when it no longer decreases



Figure 3: The percentage of false nearest neighbours with input data  $x \equiv APD$ , with lag  $\tau = 1$ .<sup>32</sup>

# **Current Result and Future Work**

• For tau\_d, which is the resistance of Na+, I quantified the chaos, which qualitatively match with the simulation map.





https://chaos.gatech.edu/eaav6019/files/2D-3V-Model/index.html

Figure 7: Top: Lyapunov Exponent (scaled) for  $\tau_d$  where A, B, C represents different  $tau_d$  state. Bottom: Actual simulations of different  $\tau_d$  states. The white line represents the tip trajectory of the spiral wave. B<sub>1</sub> and B<sub>2</sub> represent two possibilities that the B state could become. State A stays chaotic, state B stays either less chaotic or quasiperiodic, and state C stays only periodic.

B<sub>2</sub>

B<sub>1</sub>

A

С

# **Current Result and Future Work**

- Quantification of more complex models/patterns
- For example, here is the LE for different tip meandering cases.
- Notice here "temporal" used TISEAN (Nonlinear Time Series Analysis)



Figure 9: (a) to (e): Different meander cases in 3V SIM Model. [(a):  $\tau_d = 0.41$ ; (b):  $\tau_d = 0.392$ ; (c):  $\tau_d = 0.381$ ; (d):  $\tau_d = 0.36$ ; (e):  $\tau_d = 0.25$ ; (f): parameter set 2<sup>1</sup>].

# **Current Result and Future Work**

- Quantification of experimental results.
- For example, here is the LE for pig hearts.





Chaotic, endocardium









Less chaotic

# Conclusion

- The 3V SIM Model is a simplified cardiac model, retaining essential activation and inactivation characteristics while having fewer variables.
- I showed that APD data could be alternative choice for determining the Lyapunov exponent.
- What's more, integrating spatial information with the Spatial-Temporal Algorithm could significantly reduce the amount of APD data needed, enabling quicker and even real-time determination of the Lyapunov exponent.
- It can help drug development by showing which particular region of parameters are sensitive and likely to induce chaotic behavior.

# Thanks to CHAOS Lab!

- Current Members:
  - Casey
  - Evan
  - Henry
  - Jimena
  - Lynn
  - Mikael
  - Mikhail
  - Will
  - Flavio (Adviser)



#### **Any Question?**