A pairwise maximum entropy model describes energy landscape for spiral wave dynamics of cardiac fibrillation

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Abstract

Heart is an electrically-connected network. Spiral wave dynamics of cardiac fibrillation shows chaotic and disintegrated patterns while sinus rhythm shows synchronized excitation patterns. To determine functional interactions between cardiomyocytes during complex fibrillation states, we applied a pairwise maximum entropy model (MEM) to the sequential electrical activity maps acquired from the 2D computational simulation of human atrial fibrillation. Then, we constructed energy landscape and estimated hierarchical structure among the different local minima (attractors) to explain the dynamic properties of cardiac fibrillation. Four types of the wave dynamics were considered: sinus rhythm; single stable rotor; single rotor with wavebreak; and multiple wavelet. The MEM could describe all types of wave dynamics (both accuracy and reliability>0.9) except the multiple random wavelet. Both of the sinus rhythm and the single stable rotor showed relatively high pairwise interaction coefficients among the cardiomyocytes. Also, the local energy minima had relatively large basins and high energy barrier, showing stable attractor properties. However, in the single rotor with wavebreak, there were relatively low pairwise interaction coefficients and a similar number of the local minima separated by a relatively low energy barrier compared with the single stable rotor case. The energy landscape of the multiple wavelet consisted of a large number of the local minima separated by a relatively low energy barrier, showing unstable dynamics. These results indicate that the MEM provides information about local and global coherence among the cardiomyocytes beyond the simple structural connectivity. Energy landscape analysis can explain stability and transitional properties of complex dynamics of cardiac fibrillation, which might be determined by the presence of ‘driver’ such as sinus node or rotor.

Keywords: Cardiac fibrillation, Spiral wave, Maximum entropy model, Energy landscape

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Introduction

Heart consists of billions of cardiomyocytes, electrically connected by cell-to-cell gap junction. Abnormal propagation of electrical wave causes harmful or life-threatening cardiac arrhythmias such as atrial fibrillation or ventricular fibrillation. Mechanism of cardiac fibrillation is still not clear because of its complex chaotic excitation pattern; however, spiral wave reentry and multiple wavelet have been known to be major mechanisms of cardiac fibrillation. Identifying stability of fibrillation states and transitional properties from disordered fibrillation states to ordered states enables therapeutic strategies to reduce mortality and morbidity.

Several recent studies tried to elucidate complex electrical communication between cardiomyocytes perturbed during arrhythmias through the information/network theoretical approaches. Similar approaches have been well established in neuroscience area to study dynamical organization and disorganization of brain activity on a large electrically-connected neural network. Under the conceptual framework of an epigenetic landscape proposed by Waddington, energy landscape analysis could be utilized to explain complex brain dynamics. One feasible method to calculate energy landscape of brain dynamics is estimating hidden functional interactions by fitting a pairwise maximum entropy model (MEM) to brain activity data.

Since heart is an electrically-connected network like brain, we estimate the energy landscape of cardiac fibrillation dynamics by applying the pairwise MEM to the sequential electrical activity maps. We simulate 2D computational model of human atrial fibrillation and generate four different types of wave dynamics: sinus rhythm; single stable rotor; single rotor with wavebreak; and multiple wavelet. Then, we estimate local minima (attractors), basin sizes, and energy barriers to describe the dynamics of cardiac fibrillation.

Methods

Simulation of cardiac fibrillation

We numerically simulated two-dimensional isotropic cardiac tissue (512×512, Δx=0.025 cm) by reaction-diffusion equation:

\[ \frac{\partial V}{\partial t} = - \frac{I_{\text{ion}} + I_{\text{stim}}}{C_m} + D \nabla^2 V \]

where \( V \) is the transmembrane potential, \( I_{\text{ion}} \) is the total ionic currents, \( I_{\text{stim}} \) is the stimulus current, \( D=0.001 \text{ cm}^2/\text{ms} \) is the diffusion coefficient, and \( C_m=100 \text{ pF} \) is the membrane capacitance. We implemented mathematical model of human atrial myocyte developed by Courtemanche et al., incorporating 12 transmembrane currents and intracellular calcium handling with a two-compartment sarcoplasmic reticulum. Four types of the electrical wave dynamics were considered: 1) sinus rhythm (no electrical remodeling, pacing cycle length=500 ms); 2) single stable rotor (\( I_{\text{CaL}} \times 0.3 \)); 3) single rotor with wavebreak (\( I_{\text{Na}} \times 0.9, I_{\text{Ko}} \times 0.3, I_{\text{CaL}} \times 0.5, I_{\text{K1}} \times 2, I_{\text{Kur}} \times 0.5, I_{\text{NCX}} \times 1.4, I_{\text{leak}} \times 0.8 \)); and 4) multiple wavelet.
(I_{\text{cal}} \times 0.5). We applied the standard S1S2 cross-field protocol to initiate a spiral wave.

**Pairwise maximum entropy model**

We fit the pairwise MEM to the electrical wave dynamics data as described in previous studies\(^{14-18}\) (see Fig. 1). The wave dynamics at time \(t\) \((0 \leq t \leq 10\) sec\) is represented as vector \(V(t) = [\sigma_1, \sigma_2, ..., \sigma_N]\) where \(N=9\) is the number of the action potential data, and \(\sigma_i\) is the binarized action potential signal. We calculated the empirical activation rate \(\langle \sigma_i \rangle = \frac{1}{T} \sum_{t=1}^{T} \sigma_i^t\) and the empirical pairwise joint activation rate \(\langle \sigma_i \sigma_j \rangle = \frac{1}{T} \sum_{t=1}^{T} \sigma_i^t \sigma_j^t\). Under the constraints preserving \(\langle \sigma_i \rangle\) and \(\langle \sigma_i \sigma_j \rangle\), the pairwise MEM maximizes the entropy \(S = -\sum_k p(V_k) \ln p(V_k)\), deriving the probability of state \(V_k\) as \(p(V_k) \propto e^{-E(V_k)}\) where \(E(V_k)\) represents the energy of state \(V_k\) as the Ising model:\(^{24}\)

\[
E = -\sum_i h_i \sigma_i - \frac{1}{2} \sum_{i \neq j} J_{ij} \sigma_i \sigma_j
\]

\(h_i\) represents the tendency of activation at region \(i\) (baseline activity) and \(J_{ij}\) represents functional interaction between region \(i\) and \(j\) (pairwise interaction). We calculated the expected activation rate \(\langle \sigma_i \rangle_m = \sum_{k=1}^{2^N} \sigma_i(V_k) P(V_k)\) and the expected pairwise joint activation rate \(\langle \sigma_i \sigma_j \rangle_m = \sum_{k=1}^{2^N} \sigma_i(V_k) \sigma_j(V_k) P(V_k)\). We used a gradient ascent algorithm to iteratively estimate parameters \(h_i\) and \(J_{ij}\) by \(h_i^{\text{new}} = h_i^{\text{old}} + \alpha \log(\langle \sigma_i \rangle / \langle \sigma_i \rangle_m)\) and \(J_{ij}^{\text{new}} = J_{ij}^{\text{old}} + \alpha \log(\langle \sigma_i \sigma_j \rangle / \langle \sigma_i \sigma_j \rangle_m)\) where \(\alpha=0.1\) is the learning rate. The accuracy of fit was calculated by \(r_D = \frac{(D_1-D_2)}{D_1}\) where \(D_k\) is the Kullback-Leibler divergence between the probability distribution of state in \(k\)th order model (\(P_k\)) and the empirical distribution of state (\(P_N\)). The reliability was calculated by \(\frac{(S_1-S_2) / (S_1-S_N)}{r_D}\) where \(S_k\) is the entropy of the distribution of state in \(k\)th order model.

**Energy landscape analysis**

We calculated the energy landscape and evaluated the local minima, basin sizes, and energy barriers as described in previous studies.\(^{16-18}\) We first searched the local minima (attractors) which have lower energy than \(N\) adjacent states. All states were classified into the basin of the local minimum by continuously moving the node to the neighbor node with the smallest energy value until reached to the attractor. The basin size was defined by the fraction of states that belonged to the basin of the attractor. We then performed the disconnectivity graph analysis.\(^{25}\) The energy barrier between two local minima \(i\) and \(j\) was defined as the \(\min\{E^b(V_i, V_j) - V_i, E^b(V_i, V_j) - V_j\}\) where \(E^b(V_i, V_j)\) is the threshold energy level calculated by the highest energy on the shortest path connecting the two local minima. We wrote the C++/MATLAB codes for the simulation, analysis, and visualization.
**Statistical analysis**

All continuous variables including \( h_i \), \( |J_{ij}| \), basin sizes, and mean energy barriers were compared using Student’s t-test. A p-value<0.05 was considered to be statistically significant.

![Diagram](image)

**Figure 1.** Schema of energy landscape analysis using pairwise maximum entropy model.

**Results**

We performed energy landscape analysis using the pairwise MEM (see Fig. 2). For all types of wave dynamics except the multiple random wavelet, the pairwise MEMs were fitted to the empirical simulation data with high accuracy(>0.90) and high reliability(>0.99); however, the multiple wavelet shows low accuracy(=0.5082) and high reliability(>0.99). Both of the sinus rhythm and the single stable rotor showed relatively high pairwise interaction coefficients among the cardiomyocytes. Also, the local energy minima had relatively large basins and high energy barrier, showing stable attractor properties. This result implies the ‘driving’ role of sinus node and rotor in cardiac electrical wave dynamics. However, in the single rotor with wavebreak, there were relatively low pairwise interaction coefficients and a similar number of the local minima separated by a relatively low energy barrier compared with the single stable rotor case. The energy landscape of the multiple wavelet consisted of a large number of the local minima separated by a relatively low energy barrier, showing unstable dynamics. Overall results show the presence of ‘driver’ such as sinus node or rotor is important to determine the dynamical stability.
Figure 2. Results of energy landscape analysis during sinus rhythm and cardiac fibrillation.

Conclusion

The maximum entropy model might uncover local/global coherence among the cardiomyocytes beyond the simple anatomical connectivity. Energy landscape analysis could explain stability and transitional properties of complex chaotic dynamics of cardiac fibrillation, which might be determined by the presence of ‘driver’ such as sinus node or rotor.
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