Investigating Phase Transitions in a Cardiac System through Informational Properties of Renewal Process Models

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(Dated: 1 December 2018)

Development of ventricular tachycardia and degeneration of it into ventricular fibrillation can be considered a phase transition in cardiac dynamics. Characterization of the underlying physical mechanisms may lead to better prediction of the onset of this phase transition and enable efficient treatment of patients at risk. Aiming to contribute to this characterization we study time series of activity in simulated heart tissue. We use Bayesian structural inference to find the best fit models in a set of hidden Markov models representing renewal processes. We compute the entropy rate and statistical complexity of these models and compare between results for healthy heart activity, heart activity at the onset of the phase transition and heart activity after the phase transition. We discuss the advantages and shortcomings of this approach, as well as alternative improvements.

I. INTRODUCTION

Sudden cardiac death (SCD) accounts for 50% of all cardiovascular deaths, resulting in more than 300,000 deaths annually in the United States.[1] The majority of SCD results from ventricular arrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF).[2] Implantable cardioverter-defibrillators (ICDs) are the standard of care for primary prevention of SCD in high-risk patients who are yet to experience fatal events.[3] However, only a minority of ICD recipients, based on the current criteria for primary prevention, experience appropriate firings. In addition, cost, risk of complications[4], and inappropriate firings[5] do not warrant indiscriminate implantation of ICDs. Development of VT and degeneration of VT to VF can be considered as a phase transition in cardiac dynamics.[6] There is limited investigation in methods that can be used to predict the onset of phase transition.

The behavior of the cardiac transmambrane voltage time series is characterized by periods of activity, in which the voltage is measured higher than a threshold value typically defined to be 0.9 of the maximum measured voltage, followed by periods of inactivity, in which the value of the voltage remains lower then the threshold value. Given that characteristic behavior, under assumptions that will be futher discussed in the Methods section, we will model the time series of voltage activity as a renewal process represented by a hidden Markov model (HMM) and study its statistical complexity[7] and entropy rate[8] as in Marzen 2015[9].

In this work we will examine the advantages and disadvantages of using the structural and informational properties of renewal process models to describe and differentiate the dynamics underlying phase transition from normal rhythm to fibrillation. The analysis will be performed on data from simulations of cardiac transmembrane voltage of a 2 dimensional lattice in different dynamical regimes. By applying this particular methodology to simulated data we will asses the potential validity of applying it to real data.

II. CENTRAL HYPOTHESIS

The temporal dynamics of a cardiac system can be regarded as a renewal process. Inferring the causal-state minimal sufficient statistic[7] will allow computation of measures of structure (the statistical complexity) and randomness (the entropy rate) of the underlying process. This measures capture dynamical features associated with critical phase transitions.

a. Specific aim 1: to develop the methodology that will enable us to model temporal cardiac dynamics as a renewal process.

b. Specific aim 2: to compute from the models measurements such as entropy rate and statistical complexity and determine if they can contribute to detect signatures associated with the phase transition.

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III. METHODS

A. 2 Dimensional Simulations of a Cardiac System

a. Fenton-Karma ionic model. We used the monodomain formulation of the phenomenological ionic model of the cardiac action potential described by Fenton and Karma.[10] The Fenton-Karma model accurately reproduces the critical properties of the cardiac action potential to test our hypothesis, such as action potential duration restitution, development of action potential duration alternans, conduction block, spiral wave initiation and wavefront break. The model consists of three variables: the transmembrane potential v , a fast ionic gate u, and a slow ionic gate w that evolve following the equations:

$$\partial_t u = \nabla(D\nabla v) - \frac{I_{fi} + I_{si} + I_{so} + I_{ex}}{C_m} \tag{1}$$

$$\partial_t u = \frac{\Theta(v_c - v)(1-u)}{\tau_u^-} - \frac{\Theta(v - v_c)}{\tau_u^+} \tag{2}$$

$$\partial_t w = \frac{\Theta(v_c - v)(1-w)}{\tau_w^-} - \frac{\Theta(v - v_c)}{\tau_w^+)} \tag{3}$$

Here C_m is the membrane capacitance (set to 1 mF/cm^2), D is the diffusion tensor, which is a diagonal matrix whose diagonal and off-diagonal elements are 0.001 cm^2/msec and 0 cm^2/msec, respectively, to represent a 2-D isotropic lattice, and Θ is the Heavyside step function.

The fast inward current I_{fi} depolarizes the membrane when an excitation above threshold is induced (similar to sodium currents). The slow outward current I_{so} repolarizes the membrane back to the resting potential (similar to potassium currents) . The slow inward current I_{si} balances I_{so} and produce the plateau in the action potential (similar to L-type calcium currents). I_{ex} is the external current. The three currents are given by the equations:

$$I_{fi} = \frac{up}{\tau_d}(v - v_c)(1 - v) \tag{4}$$

$$I_{so} = \frac{V}{\tau_0}(1 - p) + \frac{p}{\tau_r} \tag{5}$$

$$Isi = -\frac{w}{2\tau_{si}}(1 + tanh(k(v - v_c^{si}))) \tag{6}$$

For the purposes of our analysis, we set the model parameters as described in reference[11].

b. Two dimensional simulations. We stimulated the top left component of a 2-D lattice of 25 cm x 25 cm and acquired the time series of 60 beats in each element of the lattice at three different cycle lengths (270 msec, 220 msec and 214 msec). We performed temporal integration of the model equations with the explicit Euler method (temporal discretization $\Delta t = 0.1$ msec) and spatial integration over the 2-D domain with the finite difference method (spatial discretization $\Delta x = 0.025$ cm) assuming Neumann boundary conditions. This set of parameters satisfies von Neumann stability requirement. The time series were downsampled to achieve a final sampling frequency of 1 kHz that clinically relevant measurements. Stimulation at 270 msec results in concentric 1:1 wave propagation. Stimulation at 220 msec results in action potential duration alternans and stimulation at 214 msec results in wavebreak and multiple wavelet activity.

B. Time series manipulation

With the specified parameters, the simulations output a time series of voltage for a 2-D lattice of 250×250 sites. Each of the voltage values is translated into a binary value of 0 or 1, corresponding to *inactivity* or *activity* respectively. Furthermore, we assume as in spike-train analysis, that the specific form of the activity period can be considered a single activity point, so consecutive values of 1 are turned into a single one. As a first approach to the problem this assumption allows for less computationally intensive inference of the models in the next steps of the analysis. None the less, turning activity periods into *spikes* does get rid of temporal information that can be important, we will discuss in the final section ways to avoid this assumption in the future. As an example Figure 1 shows what the resulting behaviors look like.

In the next steps we do a statistical analysis of the data that assumes little knowledge of the underlying mechanisms that generate it. This, in order to assess whether the type of analysis we propose will be useful in studying data taken directly from a patient's heart.

C. Inference of HMM

The manipulation of the time series yields a point process. Further, we make the assumption that the duration of the inactivity periods are drawn from a probability distribution that is not dependent on the duration of previous inactivity periods. This assumption is reasonable as long as the dynamic is under a specific regime (wave propagation, alternans or wavebreak regime), since the physical parameters that govern the dynamic are nearly constant relative to the inter-event timing. Under this assumption the time series represents a *renewal process.*

To study the properties of the time series, we seek to infer a HMM that accurately predicts the data with minimal memory requirement. For this we will use the

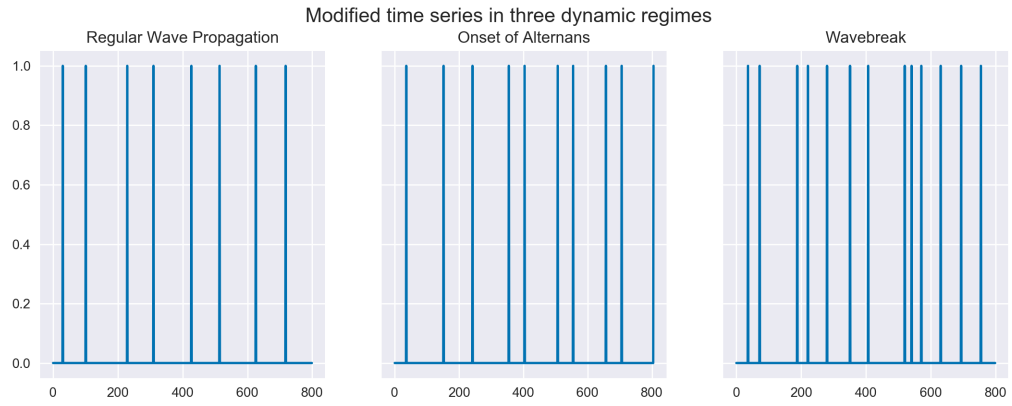

FIG. 1. An example of an 800 time steps window of the modified time series to be analyzed for one of the sites in the three dynamical regimes.

Bayesian Structural Inference (BSI) algorithm[12]. This requires the input of HMM topologies. The algorithm takes the HMM candidates and the data and calculates a posterior which defines the most likely models and model parameters and assigns them weights given the data. As described in[12], this is computationally intensive and a carefully choosing the model topologies to be considered relieves that burden.

In our case, the prior is built by considering the causal topology of renewal processes[9]. Models with 5 to 20 states are input into the algorithm along with the time series for which the models are to be inferred.

D. Calculation of expectation values of entropy rate and statistical complexity

Given the candidate HMMs from the Bayesian estimation, the estimated values and confidence intervals of the entropy rate and statistical complexity are computed.

The entropy rate[8] is a measure of the intrinsic randomness of a stochastic process. For a stochastic process X, with X_t representing the random variable at time t and $X_{t:t+l}$ the sequence of random variables from time t up to $t+l-1$, the entropy rate h_μ is defined as:

$$h_\mu = -\lim_{l\to\infty} \frac{H[X_{0:l}]}{l} \tag{7}$$

Where $H[\cdot]$ is the Shannon entropy function. From equation 7 the entropy rate is defined as the asymptotic value of the average entropy per measured symbol, that is, the rate of growth of entropy of a process. Shannon[8] showed this to be equivalent to:

$$h_\mu = -\lim_{l\to\infty} H[X_l|X_{0:l}] \tag{8}$$

Which can be interpreted as the amount of uncertainty per symbol, once all of the structure of the process has been captured. Unifilar HMMs are those in which, given a state, there is at most one outgoing edge for each symbol. The HMMs in the model class considered are all unifilar, this allows use of equation 8 to compute the entropy rate[7].

The statistical complexity C_μ is a measure of structural complexity of a stochastic process. Given the minimal HMM that accurately represents the model, the statistical complexity can be computed as:

$$C_\mu = H[\pi] \tag{9}$$

Where π is the asymptotic probability distribution over the internal states of the HMM. This can be interpreted as the minimal memory required to accurately predict the stochastic process. It can be considered a measure of structure or complexity of the process.

The expectation values of both of this quantities are computed from the candidate machines in the posterior distribution of the BSI algorithm.

IV. PRELIMINARY RESULTS

The time series of five sites in the 2-D lattice were analyzed in the three distinct dynamic regimes. The sites were chosen to be representative of qualitatively different locations with respect to the boundaries of the simulation.

In each case, the methods described above were applied. The prior model class of HMMs consisted of renewal process machines from 5 to 20 states. After running the BSI algorithm, all of the higher probability models were 5 state models. This suggests a problem with the chosen topologies and thus with the implicit assumptions which will be addressed in the discussion. An example of the HMMs with higher probability in the posterior is shown in Figure 2.

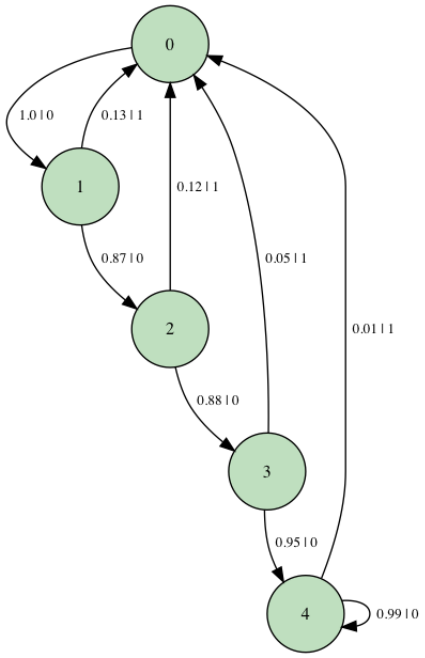

FIG. 2. Sample HMM drawn from the posterior model class inferred for the time series of a site in the lower diagonal of the 2-D lattice in the onset of alternans regime.

Subsequently, following the methodology, the estimated entropy rate and statistical complexity were computed from the posterior. The obtained values are shown in Figure 3 in an Entropy-Complexity plane. Each point describes the values obtained for the time series in a particular site, color-coded by the dynamical regime. The values of the confidence intervals are omitted because they are highly overlapping. The difference in values shown in Figure 3 should not be considered statistically significant.

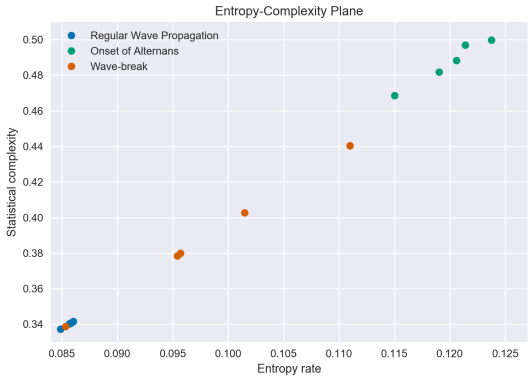

FIG. 3. Points in the plot represent estimated values of entropy rate and statistical complexity for each of the sites in the three different regimes.

The values shown in Figure 3 hint at a distinction between dynamical regimes by measures of complexity and randomness whose meaning and validity will be explored in the following section.

V. DISCUSSION

The amount of data analyzed is very limited and cannot be used to make strong claims. Taking this into account, even under the strong assumptions made above, the preliminary results shown in Figure 3 indicate that the estimated entropy rate and statistical complexity values localize dynamical phases in different regions of the entropy-complexity plane. As expected, the behavior of wave propagation simulating a healthy heart is more regular and therefore has a smaller complexity and smaller intrinsic randomness in general. The behavior of the system near the phase transition, at the onset of alternans, has the highest complexity and randomness associated to it. After that, behavior of the system after the wave break and chaotic wavelet behavior appears to have slightly more regularity than the system at the phase transition but is still more complex and random than the regular wave behavior. One of the sites has entropy rate and statistical complexity values located in closer to the values observed for healthy heart behavior. We propose that this is an artifact of the time series manipulation: the periods of activity for this particular site were long enough that considering them as spikes dropped a significant portion of the information and compromised the model inference.

As mentioned in the results, the confidence intervals are not plotted with the estimated values because there is too much overlap. This can be caused by problems with the methodology such as having small data-sets, which hinder the performance of the inference. Other shortcomings of this particular analysis can be due to the assumption of periods of activity as spikes, out-of-class modeling if the assumptions of independence of inactivity interval lengths, and more fundamentally, working with simulated data as a discrete time series instead of a continuous-time process. All of the above implies that stronger evidence is required to back the claims suggested by the preliminary results.

This work is valuable in that it indicates a possibility of using informational and structural properties of transmembrane voltage behavior to distinguish dynamic regimes. Some steps that can be taken in order to make this a more concrete possibility are:

1. In the first approximation methodology designed in this work, characterize the entire matrix as opposed to only a handful of points. This is computationally demanding but would strengthen the evidence the measures proposed do distinguish between dynamic regimes.

2. Current methodology may be improved by use of longer data-sets and consideration of the full-length

of the activity periods. Aside from this, the discretization of the time series should be chosen by a thorough analysis and not necessarily to be the same as the simulation time-discretization (even if it imposes constraints).

3. Use continuous-time Markovian processes[13] to model the time series and compute the statistical measurements.

We hope the preliminary analysis presented here will inspire further investigation into the possibility of using informational and structural properties of voltage time series to improve our understanding of cardiac dynamics.

ACKNOWLEDGMENTS

Konstantinos N Aronis is supported by the NIH grant 5T32HL007227-4. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We wish to acknowledge the support of the Santa Fe Institute and summer school faculty for their guidance and support as well as our home institutions for offering us the opportunity to participate in CSSS.

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