Statistical properties of heartbeat intervals during atrial fibrillation

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Atrial fibrillation is a common cardiac arrhythmia in which there is an irregular heartbeat. This paper develops a theoretical model for the intervals between successive heartbeats during atrial fibrillation based on the following ideas. There is an irregular pattern of activation of the upper chambers (atria) of the heart. Excitation travels from the atria through the specialized conducting tissue called the atrioventricular node to the lower chamber of the heart (ventricles). We model this situation by a stochastic map. If the map is linear, then it is possible to compute analytically the probability density for the timings between ventricular activations. Numerical simulations of nonlinear maps show correspondences with clinical data. Thus this work casts a clinical medical problem in the context of stochastic maps. [S1063-651X(96)00108-0]

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I. INTRODUCTION

In the normal human heart, the rhythm is set by an autonomously driven pacemaker, the sinus node that is located in one of the upper chambers of the heart, the right atrium. The rhythm set by the sinus node propagates through the right and left atria, and then through a specialized region of the heart called the atrioventricular node which provides an electrical pathway between the atria and the main pumping chambers of the heart (the ventricles). In the healthy heart, each impulse generated in the sinus node is conducted down to the ventricles leading to ventricular excitation and contraction (a heartbeat) [1].

This paper deals with atrial fibrillation, a common cardiac arrhythmia in which the rhythm in the atria is no longer set by the sinus node. During atrial fibrillation, irregular patterns of electrical activation are usually found in the atria. These are believed to be associated with fractionated and multiple waves, circulating and propagating through the atria [2,3]. The usual circumstance is that some of the excitations in the atria are propagated through the atrioventricular node to the ventricles while others are blocked. The combination of irregular inputs and blocked propagation results in an irregular heartbeat. The irregular heartbeat can be easily monitored—either by feeling the pulse, or by measuring the electrocardiogram, a measure of potential differences on the body surface associated with the cardiac electrical activity.

There is an extensive literature in cardiology that documents the statistical properties of the ventricular activity during atrial fibrillation, with emphasis on measurement of the histograms (probability density) [3–9] and autocorrelation functions [5–7,9,10] of interbeat intervals.

Despite the medical importance of atrial fibrillation, there have been limited attempts to develop theoretical models to analyze the probability density or autocorrelation function of interbeat intervals during this arrhythmia. An early attempt in this direction was carried out by Cohen, Berger, and Dushane who assumed that the atrioventricular node was a spontaneous oscillator subject to random small inputs [7]. However there is much debate concerning whether in usual circumstances the atrioventricular node is a spontaneous oscillator [9,11,12], and we consider a different approach that deals in a more direct fashion with measurable physiological properties of the atrioventricular node.

An alternative theoretical approach to studying the physiological properties of the atrioventricular node is to model it by a nonlinear finite difference equation. Shrier and colleagues showed how to experimentally measure the nonlinear functions underlying atrioventricular nodal activity and demonstrated that this formulation successfully describes the ventricular response during stimulation of the atria with periodic inputs [13]. A review of this approach is in [14].

During atrial fibrillation, the atrioventricular node is not subjected to periodic inputs, but rather to irregular inputs resulting from irregular activity in the atria. Therefore, a theoretical model that is appropriate for this situation is a stochastic difference equation. This class of equations has been studied extensively because of its relevance to a variety of problems in mathematics and physics [15–19].

In Sec. II we give some additional information concerning the physiology of the atrioventricular node, and statistical properties of atrial and ventricular activity during atrial fibrillation. In Sec. III, we consider special cases in which the atrioventricular node is modeled by a linear stochastic difference equation. The equation for the probability density and the autocorrelation function of the ventricular interbeat interval can be solved analytically. Section IV considers more realistic examples and treats these analytically and numerically. We discuss the limitations of our approach in Sec. V.

II. DIFFERENCE EQUATION MODELS OF THE VENTRICULAR RESPONSE DURING ATRIAL FIBRILLATION

In this paper, we analyze the ventricular response to atrial fibrillation based on the conduction properties of the atrioventricular node. The conduction time $AV$ is defined as the time interval from the start of activation of the atria to the start of activation of the ventricles. The recovery time $VA$ is defined as the time interval from the start of activation of the ventricles to the start of activation of the atria. Our starting point is to assume that $AV$ is determined by the preceding recovery time $VA$, summarized by the equation

$$AV = f(VA), \quad (2.1)$$
During atrial fibrillation there is usually irregular activation of the atria. Experimental analysis of the dynamics of atrial activation during atrial fibrillation is difficult since this requires direct measurement of atrial activity from electrodes placed on the inner or outer surfaces of the atria. Moreover, the atrial activity will vary depending on the exact placement of the electrodes. However in a variety of clinical circumstances it has been possible to measure in patients the timing of atrial activations during atrial fibrillation [3,8] as well as the timing of ventricular activations. In Fig. 2 we show representative data from Kirsh et al. [8]. The histogram of the time intervals between atrial activations from a site in the atria are approximated by a normal distribution, centered around 146 msec with a standard deviation of about 33 msec. The histogram representing the interbeat intervals from the ventricles is approximated by a normal distribution with a mean value of about 461 msec and a standard deviation of about 98 msec. The mean value of the time intervals between ventricular responses is significantly greater than the mean value of the atrial activations indicating that not all atrial activations are successfully transmitted through the atrioventricular node. Thus the larger mean value of the time intervals between ventricular responses is associated with the blocking of some of the atrial activations in the atrioventricular node.

FIG. 3. Schematic representation of the time intervals associated with conduction through the atrioventricular node when each atrial input conducts to the ventricles. The diagram represents the passage of excitation from the atria (top of the figure) to the ventricles (bottom of the figure). The atrioventricular nodal recovery time \( VA_i \), determines the conduction time \( AV_{i+1} \), the time interval between atrial activations is designated \( AA_i \), and time interval between ventricular activations is designated \( VV_i \), where the subscripts identify the beat numbers.

III. THE LINEAR STOCHASTIC DIFFERENCE EQUATION

A schematic representation of atrioventricular nodal conduction is shown in Fig. 3. Let \( AA_i \) be the time interval between the \((i-1)\)st and the \(i\)th atrial inputs and \( VV_i \) the associated ventricular interval. \( VA_i \) is the recovery time, measured from the last excitation of ventricles to the beginning of the \((i+1)\)st atrial input. \( AV_i \) represents the time interval that it takes the \(i\)th atrial input to cross the atrioventricular node.

In this section we first assume that each atrial impulse is conducted to the ventricles and that there is a linear atrioventricular nodal recovery curve. These assumptions are not realistic, but they allow us to cast the problem of ventricular response during atrial fibrillation into a familiar context of a linear stochastic map for which an analytic solution is possible [16,19]. Assume that the atrioventricular nodal recovery curve can be represented by

\[
AV_{i+1} = f(VA_i) = \alpha - \beta VA_i, \tag{3.1}
\]
where $\alpha$ and $\beta$ are positive numbers. This linear function is consistent with the observation that the atrioventricular nodal conduction is a monotonically decreasing function of the recovery time. However, the decrease is usually a nonlinear function, see Fig. 1, and the conduction is blocked if $VA_i < \theta$, where $\theta$ is the refractory period. The condition that ensures all atrial inputs are conducted to the ventricles is that for each $i$, $AA_i > AA_c$ where $AA_c = \alpha + \theta(1 - \beta)$. In the next section we consider the more general case in which some inputs are blocked.

From Eq. (3.1) and the relationship $AV_{i+1} = VV_{i+1} - VA_i$ we find

$$VA_i = \frac{VV_{i+1} - \alpha}{1 - \beta}. \tag{3.2}$$

The relationship between $AA_i$ and $VV_{i+1}$ is (Fig. 3)

$$VV_{i+1} = AA_i + AV_{i+1} - AV_i. \tag{3.3}$$

Substituting Eqs. (3.1) and (3.2) into Eq. (3.3) we obtain

$$VV_{i+1} = (1 - \beta)AA_i + \beta VV_i. \tag{3.4}$$

We rewrite Eq. (3.4) as

$$x_{i+1} = \beta x_i + (1 - \beta)\xi_{i+1}, \tag{3.5}$$

where $x_i = VV_i$, and $\xi_i = AA_i$.

We want to determine the probability density of the interventricular intervals $x_i$, given a random atrial input $\xi_i$. Equation (3.5) describes a discrete dynamical system with a random perturbation $\xi_i$. The uniqueness and asymptotical stability for the probability density of the time sequence has been considered by many investigators [15,17,18]. We follow results developed by Talkner and Hanggi [19] who calculated the probability density from the master equation.

Assume that the probability density of the intervals between atrial inputs is distributed normally

$$\rho(\xi) = \frac{1}{\sqrt{2\pi\sigma}} \exp\left(-\frac{(\xi - \mu)^2}{2\sigma^2}\right), \tag{3.6}$$

with standard deviation $\sigma$ and mean $\mu$. Let $W(x)$ be the probability density for the interventricular intervals $x$. $W(x)$ is given by the master equation

$$W(x) = \frac{1}{\sqrt{2\pi\sigma(1 - \beta)}} \int_{-\infty}^{\infty} \exp\left(-\frac{(x - \beta y - \mu)^2}{2(1 - \beta)^2\sigma^2}\right) W(y) dy \tag{3.7}$$

for $\beta < 1$. If we assume that $W(x)$ is a Gaussian distribution [16], the integral on the right can be computed by completing the squares in the exponent. After some algebra we find

$$W(x) = \frac{\gamma}{\sqrt{2\pi\sigma}} \exp\left(-\frac{\gamma^2(x - \mu)^2}{2\sigma^2}\right), \tag{3.8}$$

where $\gamma = \sqrt{1 - \beta^2}/(1 - \beta)$.

Equation (3.8) shows that the probability density of interventricular intervals is a Gaussian with the same mean as the probability density of the atrial inputs but a different standard deviation. Figure 4 illustrates the probability density of the interatrial activation times, solid line [Eq. (3.6)], and interventricular times, dashed line [Eq. (3.8)] assuming normally distributed atrial inputs with $\mu = 150$ msec, $\sigma = 30$ msec, and a linear recovery curve with $\beta = 0.4$.

The autocorrelation function can also be readily obtained for this example. The average value of $x$ is designated $\langle x_i \rangle = \mu$. The autocorrelation function for a variable $x$ is defined as

$$R_n = \frac{\langle x_n x_i \rangle - \mu^2}{\langle x_i^2 \rangle - \mu^2}. \tag{3.9}$$

It then follows from Eq. (3.9) and the lack of correlation of the random inputs that

$$R_n = \beta^n. \tag{3.10}$$

This computation shows that there is correlation between the successive ventricular intervals. Correlations between interbeat intervals are sometimes observed in clinical data [10].

Considering now the data shown in Fig. 2, we see that the probability density of the atrial inputs is centered at 146.2 msec with a standard deviation 33.6 msec. The probability density of ventricular beats is centered at 461.20 msec with a standard deviation 33.6 msec. The data suggest that there may be three atrial inputs for each ventricular output since the ventricular rate is about one third of the atrial rate. Although a consideration of this situation in detail requires iteration of the appropriate finite difference equation considering conduction block (see Sec. IV), a simple computation allows us to approximate the probability density of the ventricular interbeat intervals.

Assume that $n$ atrial impulses always combine together for each ventricular beat. Then, if the interatrial activation times are normally distributed with a standard deviation $\sigma$ and Eq. (3.1) holds, the probability density of the interventricular responses is

$$W(x) = \frac{\gamma}{\sqrt{2\pi n\sigma}} \exp\left(-\frac{\gamma^2(x - n\mu)^2}{2n\sigma^2}\right), \tag{3.11}$$
where $\sigma$ is the standard deviation of the atrial inputs.

According to this simplified theoretical approach, the standard deviation of the ventricular response is

$$\sigma \sqrt{n} / \gamma.$$

For $0 < \beta < 1$, the maximum value of the standard deviation occurs when $\beta = 0$, so that for a combination of three atrial activations, according to Eq. (3.11) the maximum value of the standard deviation of the ventricular response would be $\sqrt{3} \sigma$. For the data in Fig. 2, this would be $\approx 58$ msec. This is much smaller than the observed value of 97.9 msec.

IV. CONDUCTION BLOCK

We now assume that there is a refractory time $\theta$. If the recovery time since the passage of the last atrial input through the ventricles is less than $\theta$, conduction is blocked. Call $\tau_i$ the recovery time that determines whether the $(i+1)$st atrial input will be conducted to the ventricles. Notice that if the $i$th atrial input was conducted to the ventricles, $\tau_i = V_A \alpha_i$ as in Sec. III. If the $i$th atrial input was not conducted to the ventricles then we determine $\tau_i$ recursively by the expression

$$\tau_i = \tau_{i-1} + \Delta \alpha_i.$$

(4.1)

Given any sequence of atrial inputs, a recovery curve, and a refractory time, the conduction through the atrioventricular node can be explicitly computed

$$AV_{i+1} = f(\tau_i) \text{ for } \tau_i > \theta.$$

(4.2)

If the recovery time is less than $\theta$ the atrial input is blocked and the recovery time to the next atrial input is computed from Eq. (4.1).

A. Fixed conduction times and single blocked inputs

We first consider a special case to illustrate a way in which multimodal probability densities can arise in an analytically tractable situation. We assume that for conducted beats, $\beta = 0$ in Eq. (3.1) so that the conduction time $\alpha$ is a constant. We also assume that there can be conduction block of a single atrial input, but not of two consecutive inputs. Assume that conduction block occurs when the first atrial input arrives at the atrioventricular node during its refractory state. Assuming the linear recovery curve, we find that

$$VV_{i+1} = 2 \Delta \alpha_i + \Delta \alpha_j.$$  (4.3)

To simplify notation, call $2 \Delta \alpha_i = \xi_i$. An atrial input will be blocked if $\xi_i < AA_A$, where $AA_A = \alpha + \theta$. Assume that the probability density of the atrial inputs is normally distributed as in Eq. (3.6). The fraction of blocked impulses $c$ is

$$c = \int_0^{AA_A} \rho(\xi) d\xi.$$

(4.4)

The probability density for the interventricular intervals is given

$W(x)$.

FIG. 5. The probability density from Eq. (4.6) assuming $\mu = 150$ msec, $\sigma = 30$ msec, $AA_A = 150$ msec. We assume a linear recovery curve with $\beta = 0$. The theoretical curve is superimposed on the results from a simulation (histogram) with 8000 atrial inputs.

$W(x) = H(x - AA_A)\rho(x) + \int_0^{AA_A} \rho(x - \xi)\rho(\xi) d\xi,$

(4.5)

where the Heaviside function $H(u) = 0$ for $u < 0$, and $H(u) = 1$ for $u \geq 0$. Substituting Eq. (3.6) into Eq. (4.5) we compute

$$W(x) = \frac{H(x - AA_A)}{\sqrt{2\pi\sigma}} \exp \left( - \frac{(x - \mu)^2}{2\sigma^2} \right)$$

$$+ \frac{B(x)}{2\sqrt{\pi}\sigma} \exp \left( - \frac{(x - 2\mu)^2}{4\sigma^2} \right),$$

(4.6)

where

$$B(x) = \frac{1}{\sqrt{\pi}\sigma} \int_0^{AA_A} \exp \left( - \frac{(\xi - \frac{x}{2})^2}{\sigma^2} \right) d\xi.$$

(4.7)

Figure 5 shows the probability density from Eq. (4.6) assuming $\mu = 150$ msec, $\sigma = 30$ msec, $AA_A = 150$ msec. The theoretical curve is superimposed on the results from a simulation (histogram) with 8000 atrial inputs. The peak at about 160 msec is associated with conduction of a single atrial input. The peak at about 280 msec arises as a consequence of blocking of a single atrial input due to the refractory period of the atrioventricular node.

If $AA_A \gg \mu$, then the first atrial input will always be blocked so that $c = 1$ and we have a 2:1 conduction block $B(x) = 1$ and we obtain Eq. (3.11) for $n = 2$ and $\gamma = 1$ (recall $\beta = 0$).

B. Nonlinear recovery curve

We now consider the general situation in which the recovery curve is a nonlinear function. We demonstrate that changes in the recovery curve and the properties of the atrial inputs lead to differences in the density distribution and autocorrelation function of the interventricular intervals.

We first assume the recovery curve in Fig. 1 with normally distributed atrial inputs with $\mu = 150$ msec and
The theoretical model can also be used to compute the results using other sequences of atrial inputs. The current study represents an attempt to apply this model using random inputs. In this case, the model is a stochastic map. We have shown that in some special cases in which the recovery curve is a linear function and the probability density of the interatrial activation times is a Gaussian, it is possible to compute analytically the probability density of the interventricular activation times.

Several conclusions can be made.

(1) Techniques developed for the analysis of stochastic maps are directly applicable to study an important medical problem—the ventricular response during atrial fibrillation.

(2) With the application of a single linear recovery curve of atrioventricular node, peaks in the probability density of the ventricular response can occur at approximate multiples of the mean value of the interatrial activation times.

(3) The autocorrelation function for the random atrial input is zero. However the autocorrelation function for the ventricular output may be nonzero. Thus, this study shows how physiological properties of the atrioventricular node could lead to correlations in the timing of ventricular activations even in the absence of correlations in the atrial activity. This may partially explain correlations observed clinically during atrial fibrillation [5,10].

The further development of this area requires careful analysis of ventricular responses in circumstances in which it is possible to measure atrial activity and also to characterize the atrioventricular node. A variety of different factors can strongly influence the function of the atrioventricular node including: summation of activation of the atrioventricular node from wave fronts originating at different locations [22], drugs [23], and prior stimulation history [2,20]. Future development will be facilitated if theoretical studies are carried out in conjunction with experimental and clinical work.

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