Iterative Restitution Effects from Heart Rate Variability

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Abstract

Action potential duration (APD) in the heart depends on the timing of the stimuli from SA node and the preceding diastolic interval (DI), the time it rested since the previous excitation. Such effects can be described by a random iterative map involving a heart rate dependent restitution function [1]. In a steady state the stimuli form a stationary random process and iterative maps converge to stationary stochastic APD and DI sequences. We derive analytical expressions for major stochastic characteristics of such sequences (mean value, variance, etc). The results reveal a remarkable role of the slope of the restitution curve for the properties of the stationary output sequences. Our tentative computer simulations of the process corroborate our analytical results for relatively small heart rate variability.

1. Introduction

The heart rhythm originates from an anatomically separate part of the heart, Sino Atrial (SA) node, which generates a sequence of electrical stimuli that can trigger excitation/contraction waves propagating through the heart. These excitation or Action Potential (AP) waves in turn generate electric potentials on the body surface that can be recorded as a local electrocardiogram (ECG). The success or failure of the wave propagation through the cardiac conduction system and/or the ventricles determine the cardiac rhythm observed as the body surface potential records. Thus, the cardiac conduction system and the (massive) ventricles constitute "the prism" or "the transformer" that transforms the original SA node rhythm into the rhythm registered on the body surface by ECG.

The shape of each AP wave in cardiac tissue, characterised primarily by the Action Potential Duration (or APD, denoted by T_{AP}), depends on the time the tissue has rested since the end of previous excitation (Diastolic Interval, or DI, denoted by T_{DI}). The dependence $T_{AP}=r(T_{DI})$ is usually referred to as a restitution function or curve [1]. In reality, we always deal with sequences of stimuli, APDs, and DIs, so one must write $T_{AP}^{n+1} = r(T_{DI}^{n})$, where the superscript marks the cardiac cycle's number. Within one, say nth, cardiac cycle APD and DI are related by the relation $T_n = T_{AP}^{n} + T_{DI}^{n}$, where T_n is the nth cardiac cycle length (CCL). The above two relations can be combined in a single relation equivalently expressed either in terms of APD as $T_{AP}^{n+1} = r(T_n - T_{AP}^{n})$, or, in terms of DI as $T_{DI}^{n+1} = T_{n+1} - r(T_{DI}^{n})$. For certainty, we shall deal only with the latter form of the recurrent relation. In the simple case when the stimuli are strictly periodic, with the period T (a fixed rate pacemaker, $T_k=T$, k=1,2,...), the recurrent relation turns into an iterative map of the form: $T_{DI}^{n+1} = T - r(T_{DI}^{n})$. The behaviour of such non-linear iterative maps has been extensively studied in general [2] and in the context of restitution effects on the development of cardiac rhythm [3]. One can readily see that if the steady (periodic) state is reached the T_{DI} values must satisfy the equation $T_{DI} = T - r(T_{DI})$. The condition that the iterative map sequence converge to the steady state is $|r'(T_{DI})|<1$ [2,3]. When this condition is not met some interesting rhythm patterns have been shown to evolve [3,4].

In reality, due to heart rate variability a SA node generates a stimulus sequence, which is not strictly periodic, so the above mentioned considerations are not strictly applicable. The input stimulus sequence can be viewed as a signal from a "noisy metronome" with a random spacing T_n between the nth and (n-1)th stimuli. In the corresponding iterative map, $T_{DI}^{n+1} = T_{n+1} - r(T_{DI}^{n})$, the first term in the right hand side represents a random component of the map, while the second, a deterministic component. Behaviour of such nonlinear iterative maps with random elements constitutes a broad area of study. Below we shall tentatively present the necessary corrections to the case with "no heart rate variability". Assuming the timing of each stimulus from SA node to be statistically independent from the timings of all the

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previous stimuli and given statistical characteristics of such an input sequence (the moments) we analytically find major statistical characteristics (moments, auto-correlation and cross-correlation coefficients) of the output APD and DI sequences. The resulting formulas reveal a remarkable, physiologically relevant fact that all heart rate variability corrections involve a common factor that "blows up" at the heart rate corresponding to the marginal stability boundary for purely periodic iterations. We also discuss the prolongation effects of heart rate fluctuations on the average DI, which is also of physiological interest. We shall also present some illustrative computer simulations to illustrate our findings.

2. The formulation of the problem

In order to simplify the notation we shall denote by x_k, y_k, and z_k the k [th] DI, APD and CCL, respectively. The input sequence, $\{z_k\}$, representing the "ticking of an idealized SA node is assumed to be a strictly stationary stochastic process, for which all time averages, such as $\overline{z}, \overline{z^2}, \ldots$, are given time independent constants, which coincide with the corresponding ensemble averages, $\langle z \rangle$, $\langle z^2 \rangle$, ... A restitution function relating y_k and x_{k-1} is known [1] to depend also on the frequency of the conditioning stimuli. In our case, this translates into a dependence of the k[th] APD on the mean CCL, $\overline{z}$ in addition to the dependence on preceding DI, x_{k-1}. Elharrar and Surawicz [1] found that the account of the frequency dependence reduces to a simple rescaling so that the restitution curve can be presented in the form

$$(1) \qquad T_{AP} = \frac{s(\overline{T})}{\rho(\overline{T} - s(\overline{T}))}\rho(T_{DI}) \equiv r(\overline{T}, T_{DI}).$$

Here $\overline{T} = \overline{z}$ is the conditioning CCL and

$$(2) \qquad s(\overline{z}) \equiv \frac{\overline{z}}{a\overline{z} + b}, \quad \rho(x) = 1 - Ae^{-\alpha x} - Be^{-\beta x},$$

where and a,b,A,B and α,β are constants [1]. The function $s(\overline{z})$ yields the steady (periodic) state APD value, $\overline{T}_{AP}$, so that $\overline{T} - s(\overline{T}) = \overline{T}_{DI}$ is the steady (periodic) state DI. It is worth mentioning that Elharrar and Surawicz were unable to present their result in an explicit form, similar to expression (1), because of their use of acronyms instead of regular algebraic notation. We shall use a general restitution function $r(\overline{z}, x)$ for analytic analysis and the one defined by Eq-s (1) and (2) for our computer simulations.

The random map can thus be written in the form

$$(3) \qquad x_k = z_k - r(\overline{z}, x_{k-1}).$$

The map is iterative since it uses a previous x-value as an input it is also random because of the term z_k. Stochastic properties of iterations can be studied in terms of fluctuations, which are defined as follows

$$\delta x_k = x_k - \overline{x},\ \delta y_k = y_k - \overline{y},\ \delta z_k = z_k - \overline{z}, \qquad (4)$$

where the mean values are marked by the bar. According to Eq. (4) all fluctuations, have zero mean values, *i.e.*

$$\overline{\delta x_k} = 0,\ \overline{\delta y_k} = 0,\ \overline{\delta z_k} = 0. \qquad (5)$$

Averaging the relation $z_k = x_k + y_k$ and using Eq-s (4) and (5) we obtain

$$\overline{z} = \overline{x} + \overline{y},\ \ \delta z_k = \delta x_k + y_k. \qquad (6)$$

Our analytical task is to find the first corrections to the stationary case with nonrandom $z = const$ and express the stationary mean values, $\overline{x}, \overline{y}$, the variances $\sigma_x^2 = \overline{(\delta x)^2}$, $\sigma_y^2 = \overline{(\delta y)^2}$, and other statistical characteristics of the output processes (*e.g.* auto-correlation coefficients $k_x(m) = \overline{\delta x_k \delta x_{k-m}} / \sigma_x^2$) through statistical characteristics of the input stimuli sequence, $\{z_k\}$. Note that auto-correlation coefficients of the input sequence are given by

$$k_z(m) \equiv \overline{\delta z_k \delta z_{k-m}} / \sigma_z^2 = \delta_{0m} \equiv \begin{cases} 1, \text{ if } m = 0, \\ 0, \text{ if } m \neq 0. \end{cases} \qquad (7)$$

3. Analytical results

Let us write our random map (3) in terms of fluctuations (4) in the form

$$\overline{x} + \delta x_k = \overline{z} + \delta z_k - r(\overline{z}, \overline{x} + \delta x_{k-1}). \qquad (8)$$

Averaging both sides of this equation and using (4) yields

$$\overline{x} = \overline{z} - \overline{r(\overline{z}, \overline{x} + \delta x_{k-1})} \qquad (9)$$

Expanding function r in this expression into Taylor's series up to the second order and using Eq. (5) we obtain

$$\overline{x} = \overline{z} - r(\overline{x}) - (1/2)r''(\overline{z}, \overline{x})\sigma_x^2, \qquad (10)$$

where primes hereafter denote derivatives with respect to the second argument and σ_x is yet to be found. Eq. (8) within the first order yields

$$\delta x_k = \delta z_k - r'(\overline{z}, \overline{x})\delta x_{k-1} \qquad (11)$$

Squaring both sides and averaging we have

$$\overline{\delta x_k^2} = \overline{\delta z_k^2} - 2r'(\overline{z}, \overline{x})\overline{\delta z_k \delta x_{k-1}} + \left[r'(\overline{z}, \overline{x})\right]^2 \overline{\delta x_{k-1}^2} \qquad (12)$$

The cross-correlation term vanishes due to the assumed statistical independence of z_k of the timing of preceding stimuli. Thus, we obtain an interesting relationship

$$\sigma_x^2 = \frac{\sigma_z^2}{1 - \left[r'(\overline{z}, \overline{x})\right]^2}, \qquad (13)$$

which indicates that the standard deviation of DI has a singularity when $r'=1$, *i.e.* at the value of DI at which the causal iterative map loses stability. Substituting σ_x from Eq. (13) into (10) we finally find

$$\overline{x} = \overline{z} - r(\overline{z}, \overline{x}) - \frac{1}{2}\frac{r''(\overline{z}, \overline{x})\sigma_z^2}{1 - \left[r'(\overline{z}, \overline{x})\right]^2}, \qquad (14)$$

which with the account of Eq. (6) can also be written as

(15) $$\overline{y} = r(\overline{z},\overline{x}) + \frac{1}{2}\frac{r''(\overline{z},\overline{x})\sigma_z^2}{1-[r'(\overline{z},\overline{x})]^2}.$$

Relation (14) is a transcendental equation, which must be solved for $\overline{x}$ at a given value of $\overline{z}$. Equation (14) or (15) expresses the first non-vanishing order correction to the average APD for the presence of fluctuations. When the CCL fluctuations, characterized by the value of σ_z, are small, the last term is negligible and the stationary APD is approximately given by the regular restitution function. The last term represents the fluctuation correction to the mean stationary value of APD.

One can make an interesting conclusion from Eq. (15). The restitution function described by Eq-s (1) and (2) is a concave function of $\overline{x}$, which appears to be quite a general property of restitution. Therefore, $r''(\overline{z},\overline{x}) < 0$ and Eq-s (14) and (15) indicate that the fluctuation corrections to DI and APD are respectively positive and negative. Thus, the apparent effect of fluctuations is that they effectively prolong diastolic interval providing cardiac muscle with more time to recover (at a given heart rate). A metronome-like heart would have on the average less recovery time during each cardiac cycle as compared with the heart with nonzero heart rate variability.

Let us now determine how far back the DI value, x_k, still feels the effect of an earlier DI fluctuation, $x_{k\text{-}m}$. Such an effect is given by the auto-correlation coefficient

(16) $$k_x(m) = \frac{\overline{\delta x_k \delta x_{k-m}}}{\sigma_x^2}.$$

In order to find $k_x(m)$ we notice that the factor δx_{k-1} in Eq. (11) can expressed via a similar relation, $\delta x_{k-1} = \delta z_k - r'(\overline{z},\overline{x})\delta x_{k-2}$ and this process can be repeated m times to eventually yield in the first order

$$\delta x_k = \delta z_k - \sum_{j=1}^{m-1}[r'(\overline{z},\overline{x})]^j \delta z_{k-j} + [-r'(\overline{z},\overline{x})]^m \delta x_{k-m}.$$

Multiplying this relation by δx_{k-m}, and averaging we have

$$\overline{\delta x_k \delta x_{k-m}} = \overline{\delta z_k \delta x_{k-m}} - \sum_{j=1}^{m-1}[r'(\overline{z},\overline{x})]^j \overline{\delta z_{k-j}\delta x_{k-m}} + [-r'(\overline{z},\overline{x})]^m \overline{(\delta x_{k-m})^2}.$$

Due to statistical independence of the timing of the stimuli, all averages in the right hand side, except the last one, vanish and in accordance with (16) we obtain

(17) $$k_x(m) = [-r'(\overline{z},\overline{x})]^m.$$

Quite similarly, one can find the cross-correlation

(18) $$\overline{\delta x_k \delta z_{k-m}} = \overline{\delta x_k \delta y_{k-m}} = [-r'(\overline{z},\overline{x})]^m \sigma_z^2.$$

According to Eq-s (17) and (18) the "memory" of the iterative process is again fully determined by the factor $r'(\overline{z},\overline{x})$. When $r'(\overline{z},\overline{x}) = 1$ the correlation between the current value of DI and all preceding values of DI, and/or CCL and/or APD does not change with the increase of time spacing, m. This is quite a peculiar behavior. Under the same condition, $r'(\overline{z},\overline{x}) = 1$, the right hand sides of Eq-s (13)–(15) turn into infinity. Such a singular behavior is a manifestation of some new qualitative effects beyond the scope of the above expansion method. Studying such effects theoretically would require a higher level theory not limited by the expansion convergence conditions.

3. Computer simulations

The behavior of a random iterative map at high stimulation rate, in the vicinity of the point where $r'(\overline{z},\overline{x}) = 1$, can be explored numerically. Another category of effects for computer simulations is the cardiac rhythm disturbances and formation of complex rhythms arising from the stimuli that arrive during refractory period [3,4] and thus generate no AP. In our notation this corresponds to $z_k > y_{k-1}$.

We report below some tentative computer simulation results obtained using a MATLAB6 program developed for this purpose. At the first step the program generates a randomized input stimuli sequence corresponding to approximately one hour long stationary cardiac record. At the second step, this input sequence is iterated in accordance with Eq.(3) using the restitution function given by Eq-s (1) and (2). At the next step statistical characteristics of the output sequence are evaluated. The final step consists in displaying the results.

The input sequence was obtained from a Gaussian distribution with the mean value μ_0 and STD σ_0 by cutting off the portion of distribution below z=0.2 s. The original Gaussian segment consisted of 4096 cardiac cycles while the length of the cut off sequence varied depending on the values of μ and σ. It always exceeded 2500 in our simulations, which ensured sufficiently good statistics of the output. The mean value μ_1 and STD σ_1 for the cut off stimuli sequence have been evaluated in a regular manner.

Then we picked three initial DI values x_0 equal to $0.9\overline{x}, \overline{x}$, or $1.1\overline{x}$, where $\overline{x}$ is the stationary value of DI corresponding to the case with no HR variability (σ_0=σ_1=0). An initial value x_0 was used to compute x_1 in accordance with Eq. (3) using z_1 from the cutoff input z-sequence. Then the process is iterated with the new value of x for every element in the cutoff input z-sequence. Three initial values were used to ensure that the iterative process reaches a stationary state and the results are independent of the initial conditions, which was checked at the end of computations. The results were additionally averaged over the initial conditions. In contrast to Eq. (3) our simulations also reproduced the situations when a stimulus arrives before the end of the refractory period. In this case no action potential is generated, the current iteration is skipped and the next iteration is performed with the cardiac cycle length z_{n+1} in Eq. (3) prolonged by

the skipped value of CCL, z_n. Due to such skipping the output z-sequence becomes different from the input stimulus sequence. (The former can be identified with the observed RR-interval sequence.) The output sequences $\{z_k\}$, $\{x_k\}$, and $\{y_k\}$ were then processed to estimate their mean value, variance, auto-correlation and cross-correlation coefficients. The results using the three different initial conditions were graphically indiscernible. and are illustrated in Figures 1 and 2.

Figure 1 presents the mean (stationary) APD value versus $\bar{z}$ obtained at a fixed value of the initial STD, σ_{z0}, which was a STD of the initial normal distribution, before the cutoff (at z=0.2s) and other modifications of the pacing sequence. Each empty circle represents a mean value of $\{y_k\}$ ($y_k=z_k-x_k$) for a full run (approximately 3000) iterations in accordance with Eq. (3). Each run produced a mean value of the input sequence $\bar{z}$, and a value of STD, σ_z which were then substituted into Eq. (14). This turned Eq. (14) into a transcendental equation for $\bar{x}$ to be solved numerically. (See Eq-s(1) and (2).) Results of such computations are presented by a solid line in Figure 1.

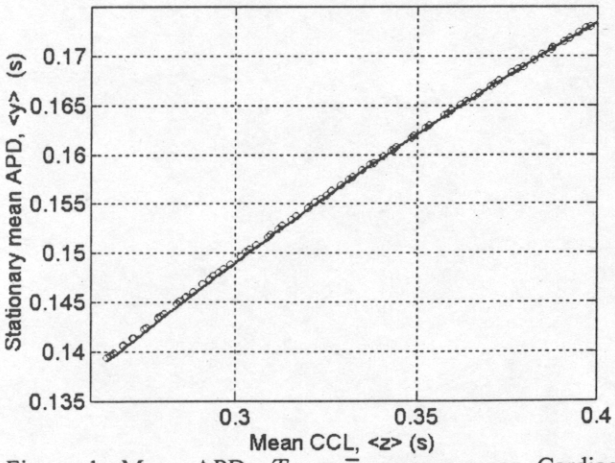

Figure 1. Mean APD, $T_{AP} \equiv \bar{y}$, versus mean Cardiac Cycle Length (CCL), $\bar{z}$ at fixed σ_{z0}=0.05. Empty circles are simulation results, solid line computed using Eq. (14).

Figure 2 presents similar results versus actual σ_z for three fixed values of the initial (uncut) mean value, $\bar{z}_0$, corresponding to the original pacing sequence before the cutoff and the z-sequence modifications arising from stimuli occurring during refractory periods (*i.e.* when x_k<0 in Eq. (3)). Note that such events were relatively rare at small values of σ_{z0}, less than 1% when σ_{z0}=0.1. Therefore, the main difference between $\bar{z}$ and $\bar{z}_0$ was due to the cutting off all CCLs shorter than 0.2s. Theoretical curves are obtained by solving transcendental equation (14) with the parameter values of $\bar{z}$, and σ_z from the actual simulations.

The apparent growth of APD with the increase of σ_z stems from strong dependence of APD on the pacing rate.

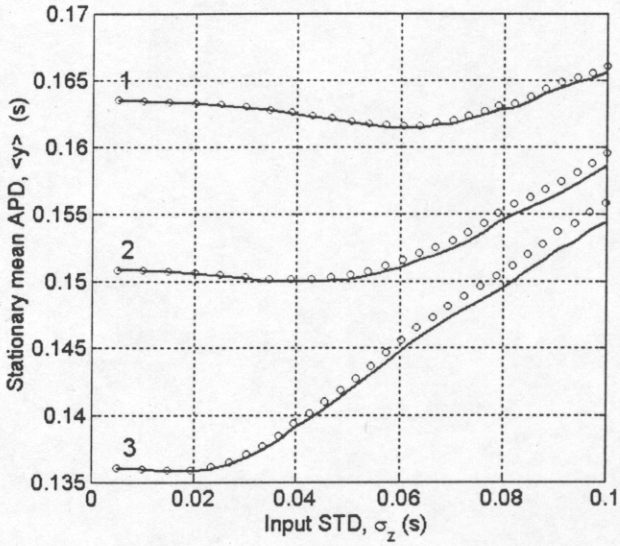

Figure 2. Mean APD, $T_{AP} \equiv \bar{y}$, versus actual STD, σ_z, at a fixed initial mean value, $\bar{z}_0$. Curves 1, 2 and 3 were computed at $\bar{z}_0 = 0.35$, 0.3 and 0.25 sec, respectively.

With the increase of the initial STD, σ_{z0} more and more short CCLs are cut off so that the actual mean value, $\bar{z}$, grows along the curves from left to right. For curve 1, $\bar{z}$ grows from 0.2501s to 0.338s, for curve 2, from 0.3001 s to 0.36 s, and for curve 3, from 0.35s to 0.3935s.

Thus, our simulations indicate that the analytical results presented above hold very well, at least for small fluctuations of the pacing rate.

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