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DISCUSSION OF DIFFERENCE EQUATION MODEL OF VENTRICULAR PARASYSTOLE AS AN INTERACTION BETWEEN CARDIAC PACEMAKERS BASED ON THE PHASE RESPONSE CURVE

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Abstract

A ventricular parasystole is a cardiac rhythm resulting from an irregular discharge of an ectopic pacemaker to the sinoatrial node (sinus pacemaker). The intrinsic cycle length of the ectopic pacemaker is influenced by the impulses of the sinus pacemaker. This influence is described by a phase response curve (PRC). The stimulus phase of a ventricular parasystole is modeled by a discontinuous difference equation developed from the PRC by Ikeda *et al.* This study analyzes the periodic solutions of Ikeda *et al.* (1983) difference equation with different phase response curves.

1 INTRODUCTION

The purpose of our project is to revisit and extend via numerical simulations the results obtained by Ikeda *et al.* (1983). Ikeda and collaboration used a phase response curve (PRC), which is a function that describes the dynamics of the phase shift provoked by the sinoatrial (S-A) node on the ectopic pacemaker, and a difference equation model to describe the interaction of the S-A node and the ectopic node, which has formed in the ventricle. We

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will introduce a new PRC functional form and incorporate this function into the difference equation model proposed by Ikeda *et al.* and look at its effect on coupled pacemaker dynamics.

The heart is divided into four cavities and has an electrical and a mechanical system. Its role is to deliver the oxygen-rich blood to every cell in the body. This process is accomplished via the circulatory system, which is a continuous circuit of arteries and veins. The arteries are the passageways through which the blood is delivered. The largest artery is the aorta, which branches off the heart and then divides into many smaller arteries. The veins carry the deoxygenated blood back to the lungs to pick up more oxygen, before returning to the heart.

In the heart, the sinus node normally generates the electrical impulses that drive the heart. These impulses are carried by the muscle in the atria (upper chambers) to the atrioventricular (A-V) node, which connects the atria and the lower chambers of the heart (the ventricles). Impulses are carried to the His-Purkinje system through the A-V node, which carries them to the ventricles (Figure 1). The atria and the ventricles, which are normally separated by electrical insulation, contract in response to the stimulus, thus generating the blood flow in the body. Pacemaker activity can be defined as the ability to initiate a propagated action potential. The dominant, fastest pacemaker (S-A node) is normally in control of the heart because its rate of rhythmic discharge is greater than that of any other part of the heart. Therefore, the S-A node is called the normal pacemaker of the heart. Nevertheless, other parts of the heart (specifically, the A-V node and the His-Purkinje system) are also capable of generating impulses.

Almost all heart tissue is capable of starting a heartbeat. In other words, another part of the heart can become the pacemaker. When this happens, it causes an arrhythmia, which is an abnormal rhythm of the heart. An arrhythmia occurs when the heart's natural pacemaker develops an abnormal rate or rhythm, the normal conduction pathway is interrupted; or when another part of the heart takes over as pacemaker. When a different part of the heart takes over as pacemaker it occurs because the impulses of the S-A node cannot penetrate into the ectopic pacemaking focus, which as a result is able to discharge at its own, inherent, and usually slower rate.

This protective mechanism is probably a diminution in the Phase 4 "resting" potential of the parasystolic pacemaking cell, which is the case of a ventricular parasystole. Therefore, a ventricular parasystole could be defined as a dual rhythm wherein two pacemakers concurrently and independently contribute to the rhythm of the heart. Additionally, the ectopic pacemaker

is protected from the impulses of the other pacemaker; such protection being situated within, or in the immediate vicinity of the ectopic center.

An electrocardiogram (ECG) is the recording of the electrical potentials generated by the heart; it is composed of a P wave, a QRS complex, and a T wave. The P wave is caused by electrical currents generated at the atria prior to contraction, and the QRS complex is caused by currents generated when the ventricles are prior to contraction, that is, as the depolarization wave spreads through the ventricles. The T wave is caused by currents generated as the ventricles recover form depolarization. A ventricular ectopic beat can produce a pause when the sinus P wave fires on time, but, in this case, it does it while the ventricular ectopic beat is spreading across the ventricles. As a result, the P wave is "buried" in the QRS and is not visible. Further, when the atrial impulse reaches the A-V node, it encounters tissues that have already been discharged by the ventricular ectopic beat and cannot conduct the S-A impulse. There is a pause until the next sinus impulses crosses the atria and is conducted through the A-V node to the ventricles. This mechanism is called a Compensatory Pause.

Arrhythmias are characterized by definite syndromes with typical clinical pictures as well as established prognosis and therapeutic procedures. In numerous cardiac patients an important part of management is the treatment of specific arrhythmias. Arrhythmias can alter clinical aspects of underlying diseases when viewed in physiological terms. In a given heart disorder, as far as prognosis and management is concerned, the condition of the patient, may vary depending on whether or not an arrhythmia accompanies the disease as well as upon the type. Failure to recognize the importance of certain type of arrhythmia may lead to a physician-induced disease.

In this paper, we will discuss the derivation of Ikeda's model (Ikeda *et al.*, 1983) in Section 2. Moreover, we will further classify the impulses known as ectopic impulses. We will present the periodic solutions to the difference equation model of Ikeda while varying specific parameters (Section 3). The analysis and the biological meaning of specific periodic solutions as well as of bifurcation diagrams is the focus of Section 4. Finally, we will introduce a different PRC and compare and contrast the results we obtained for each PRC (Section 5) to those obtained by Ikeda and collaboration.

2 ANALYSIS OF THE MODEL PROPOSED BY IKEDA *et al.*

Various mathematical approaches can be used when studying the dynamics of arrhythmias. The model that we implement identifies qualitative aspects of certain arrhythmias through the analysis of its periodic solutions. To describe the interaction between the S-A node (S) and the ectopic pacemaker(E), we assume the following:

1. S sends an impulse (stimulus) at a constant intrinsic cycle length T_S. Similarly, E sends an impulse at an intrinsic cycle length of T_E.

2. T_E is influenced by the impulse sent by S.

3. $T_E > T_S$

4. The impulse of S immediately imposes a delay on T_E. The delay is the interval between the reset impulse of E and its preceding impulse.

(Ikeda *et al.*, 1983)

We define the delay as $\Delta_n = T_E f(t_{n/T_E})$, where f is the PRC describing the effect that the S has on E. A linear approximation to the PRC is given by the function:

$$f(x) = \begin{cases} ax & x < w \quad (1a) \\ bx - b & x \geq w \quad (1b) \end{cases}$$

where $0 < a < 1$, $0 < b < 1$, $0 < w < 1$

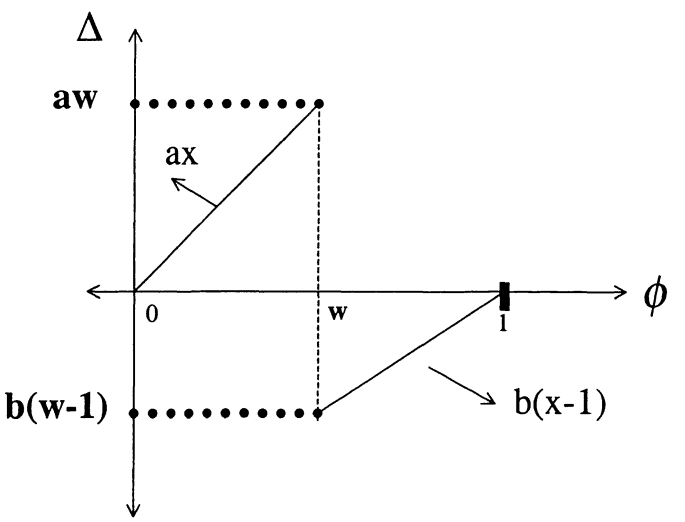

Figure 2. This is a graph of the PCR, which plots the stimulus phase, ϕ, versus the delay, Δ.

Equation (1a) describes the case in which a stimulus sent by S produces a positive delay for the following impulse of E. Whereas, equation (1b) describes a negative delay for the following impulse of E.

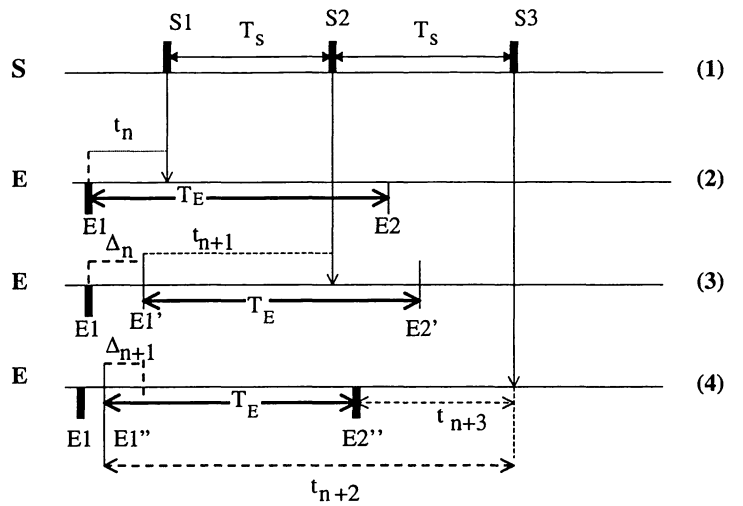

Figure 3. Illustration of the interaction between S and E (Ikeda *te al.*, 1981).

The following four parts are a description of Figure 3.:

(1) This is a representation of T_S, which is assumed to be constant.

(2) The stimulus phase t_n represents the time interval between E and the following impulse of S. If T_E is not influenced by S, then the next stimulus sent by E will be denoted by$E2$.

(3) The stimulus sent by S causes a delay Δ_n on T_E, where Δ_n could be positive or negative. A new reference point is defined by $E1' = E1 + \Delta_n$, and t_{n+1} is defined as the time interval between $E1'$ and the next stimulus sent by S, $S2$. If $t_{n+1} < T_E$, S sends a stimulus and this causes another delay on E. The new reference point is redefined as $E1"= E1'+\Delta_{n+1}$ and t_{n+2} is given by the time interval between $E1''$ and the following stimulus sent by S, $S3$.

(4) If $t_{n+2} < T_E$, the process is repeated as in **(3)**. If $t_{n+2} > T_E$, then E sends a stimulus (E2") before S3.

(N. Ikeda *et al.*, 1981)

The relation described above can be expressed by the following difference equation.

$$t_{n+1} = \begin{cases} t_n + T_s - \Delta n & t_n < T_E \quad (2a) \\ t_n - T_E & t_n \geq T_E \quad (2b) \end{cases}$$

Equation (2a) describes the period where stimuli are sent by S, and Equation (2b) represents the region where stimuli are sent by E. Substituting $t_n = T_E * x_n$, $T_S = T_E * N$, and $\Delta_n = T_E f(t_{n/T_E})$ and dividing by T_E, Equation (2) becomes:

$$x_{n+1} = \begin{cases} (1-a)x_n + N & 0 \leq x_n < w \quad (3a) \\ (1-b)x_n + N + b & w \leq x_n < 1 \quad (3b) \\ x_n - 1 & 1 \leq x_n < 1 + N \quad (3c) \end{cases}$$

To further analyze the interaction between the S and E pacemakers, we need to consider the conditions that arise when a stimulus sent by S is suppressed following a E stimulus. These conditions are due to the ventricular refractory period of E, which is given by δ. The refractory period takes place when excited myocardial cells can not respond to stimulus. We will refer to γ as the refractory period due to an impulse sent by S. The small duration of time during which each of the impulses reach the ventricle will be denoted by ϵ.

We need to closely analyze the proposed difference equation for the periods on which the ectopic pacemaker sends its stimulus because of the role of the refractory period. That is, we must incorporate the following phases: Fusion (F), Compensatory Pause (C), Interpolation (I), and Silent beat (q). During Fusion, both S and E excite the ventricle even though their impulses are sent at different times. A Compensatory Pause takes place when a stimulus sent by S offsets the cycle of the next stimulus sent by E. This causes a premature heart beat, resulting in an arrhythmia. Interpolation takes place when a stimulus sent by S does not affect the subsequent stimulus sent by E. During the silent beat, a stimulus is sent by S but fails to terminate its cycle, therefore having no effect on E. The function x_{n+1} incorporates the various phases that originate when a stimulus sent by the S-A node affects the next impulse of E.

$$x_{n+1} = \begin{cases} (1-a)x_n + N & 0 \leq x_n < w \\ (1-b)x_n + N + b & w \leq x_n < 1 \\ x_n - 1 & 1 \leq x_n < 1 + \epsilon N \\ x_n + N - 1 & 1 + \epsilon N \leq x_n < 1 + \delta N \\ x_n - 1 & 1 + \delta N \leq x_n < 1 + (1-\gamma)N \\ x_n - 1 & 1 + (1-\gamma)N \leq x_n < 1 + N \end{cases} \quad (4)$$

.

The interval $0 \leq x_n < 1$ represents impulses of S. The remaining regions illustrate impulses of E.

To simplify notation, we will use the following symbolic representation of Equation 4

$$u_{n+1} = \begin{cases} a & 0 \leq u_n < \omega \\ b & \omega \leq u_n < 1 \\ F & 1 \leq u_n < 1 + \epsilon N \\ C & 1 + \epsilon N \leq u_n < 1 + \delta \mathrm{N} \\ I & 1 + \delta \mathrm{N} \leq u_n < 1 + (1 - \gamma)\mathrm{N} \\ q & 1 + (1 - \gamma) \leq u_n < 1 + \mathrm{N} \end{cases} \quad (5)$$

3 PERIODIC SOLUTIONS

The Compensatory Pause (C) and the Interpolated Beat (I) have an effect on the natural rhythm of the heart and these arrhythmic patterns will be studied in more detail. Table 1 presents the six parameter values a, b, ω, ϵ, δ, and γ in combinations according to the intensity of the PRC and the refractory conditions. If the interaction level between S and E is high, then the intensity of the PRC measured by a and b will be high. Whereas, if the interaction level between S and E is low, then the intensity of the PRC will be low. This intensity level is denoted by the numbers 1, 2, 3, and 4, where 1 represents the lowest intensity and 4 represents the highest intensity of the PRC (Moe *et al.*, 1977). Additionally, the parameters ϵ, δ, and γ denote the refractory conditions of the sinus and ectopic pacemakers.

Model	a	b	ω	γ	δ	ϵ	Intensity Levels
C1	0.100	0.200	0.600	0.375	0.625	0.025	Compensatory Pause, very weak PRC
C2	0.250	0.375	0.600	0.375	0.625	0.025	Compensatory Pause, weak PRC
C3	0.364	0.444	0.550	0.375	0.625	0.025	Compensatory Pause, medium PRC
C4	0.500	0.500	0.500	0.375	0.625	0.025	Compensatory Pause, strong PRC
I2	0.250	0.375	0.600	0.375	0.375	0.025	Interpolated Beat, weak PRC

Table 1. Models (N. Ikeda *et al.*, 1983)

By investigating the nature of the periodic solutions to the models in Table 1, one can determine the arrhythmic patterns for specific parameter

values. The ratio R introduced by Ikeda et al. (1983) is the key bifurcation parameter. Using several values for the ratio R, where R=1/N=T_E/T_S, we can study the dynamics of the interaction between the pacemakers.

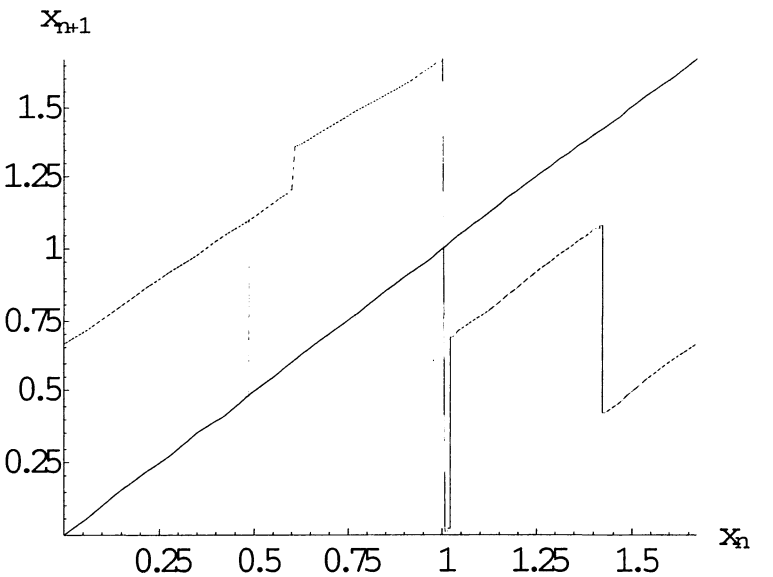

Figure 4. This graph of x_{n+1} has a cobweb depiction of model C1, where R=1.5, to show the periodic points graphically. Through graphical analysis, the period-4 cycle can easily be found.

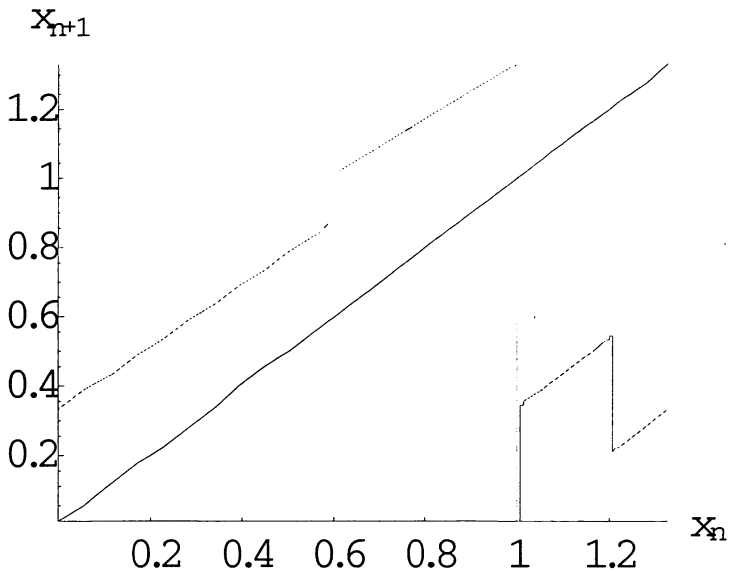

Figure 5. This is a graph of the model C1 when R=3.

When R=1.5, model C1 has the period-4 orbit 1.47619, 0.476191, 1.09524, 0.761905 (Figure 4), which can also be denoted by the symbolic notation C, b, q, a. Another example of a periodic solution to model C1 is illustrated in Figure 5. We found that it has the period-3 solution 0.761905, 1.14286, 0.47619, which may be written as b, C, a. When R=2.3, we obtained the period-10 cycle of Figure 6. Table 2 exemplifies the variety of periodic solutions that may be obtained by varying the parameter R for model C1.

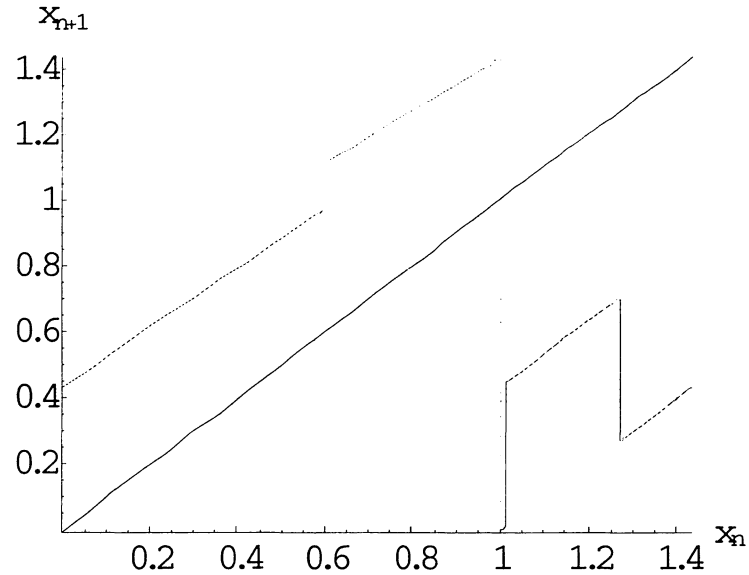

Figure 6. This is the cobweb of Model C1 where R=2.3.

R value	Periodic Orbit	Periodic Solutions
1.50	period-4	a, C, b, q
1.82	period-14	a, b, q, a, b, q, a, C, a, C, b, C, b, q
2.30	period-10	b, C, a, b, q, a, b,C, b ,C
2.45	period-26	q, a, b, C, b, C, a, b, q, a, b, C, a, b, q, a, b, C, a, b, q, a, b,C, a, b
2.60	period-5	C, b, C, a, b
2.71	period-9	a, b, q, a, b, C, a, b, C
2.94	period-3	C, a, b
3.23	period-17	C, a, b,C, a, b,C, a, b,C, a, b, b, q, a, a, b

Table 2. These are the periodic solutions to Model C1 varying the parameter R. This table classifies complex rhythms of the heart, with an ectopic pacemaker, for various R values. In the arrhythmic patterns of the firing of the ectopic pacemaker, there is a compensatory pause and a silent beat.

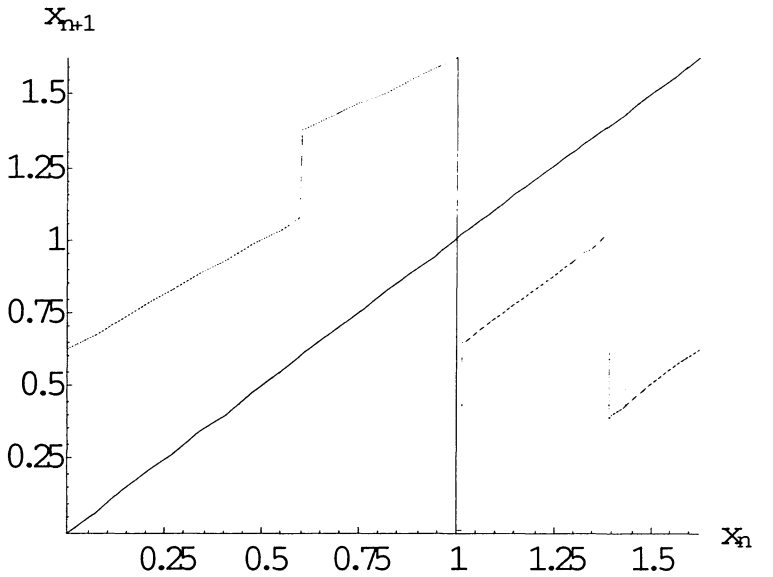

Figure 7. The cobweb of the Model C2 where R=1.6

In Figure 7 we have the period-7 solution a, C, b, q, a, b, q for model C2. Table 3 depicts the periodic solutions of the model C2 for distinct R values. Through analyzing the periodic orbits of the various models, one can determine the arrhythmic patterns of the heart such as bigeminy, trigeminy, and quadrageminy. [1]

R Value	Periodic Orbit	Periodic Solutions
1.60	period-7	{a, C, b, q, a, b, q}
1.80	period-3	{a, b, q}
2.16	period-5	{C, b, q, a, b}
2.25	period-2	{C, b}
2.40	period-8	{a, b, C, b, C, a, b, q}
2.46	period-6	{a, b, C, a, b, q}
3.38	period-7	{a, a, b, C, a, b, C}

Table 3. The periodic solutions of the model C2 for various R values.

[1] See Appendix

4 GLOBAL ANALYSIS and BIFURCATION DIAGRAMS

Before starting the global analysis of x_{n+1}, we need some definitions. A periodic point x of a function F is *attracting* if it has a neighborhood where all points in this neighborhood approach x under further iteration. Whereas, a periodic point x of F is repelling if every neighborhood has at least one point that moves away from x under iteration. A Bifurcation is a change in the dynamics of a family of functions, such as a change in the number of fixed or periodic points and their attracting or repelling nature, as a key parameter(s) is (are) varied. The bifurcation diagrams plot the attracting periodic orbits of a system as the parameter(s) is (are) varied.

Figures 8, 9 and 10 plots the bifurcation diagrams of models C1, C2, and I2, respectively. Figure 8 shows a bifurcation diagram for the model C2 as R varies from 1 to 18. For $R > 16.2$, the solution has an attracting fixed point. Although Figure 8, 9, and 10 have different periodic orbits for many values of R, their basic qualitative structures appear to be the same. Moreover, in certain intervals of the parameter R, Figure 8, 9, and 10 have the same periodic orbit. For instance, when $1.8 < R < 2.1$, all models have period-3 solutions.

Figure 8. The Bifurcation Diagram of the Model C1 plots the parameter r=R along the x-axis and the stable periodic points $x_n$along the y-axis.

Figure 9. The Bifurcation Diagram of the model C2 plots the parameter r=R against the attracting periodic points x_n.

Figure 10. The bifurcation diagram of the model I2, plotted against the parameter r=R.

The bifurcation diagrams are sectioned into regions according to the intervals defined in Equation (5). For instance, periodic solutions in the region $1+\epsilon N \leq x_n < 1+\delta N$ imply that there is a compensatory pause. However, for various values of R in that region, there is no compensatory

pause. An example of this situation is shown in Figure 8, where 1.9 < R < 2.2. Note that in model C2 there is no compensatory pause when 1.8 < R < 2. Moreover, in Figure 10, there is no interpolated beat when 1 < R < 1.6 and no compensatory pause when 1 < R < 2.7 .

The bifurcation diagrams help find the intervals of R where there is no compensatory pause, interpolated beat, silent impulses, or fusion beats. The bifurcation diagram seems to possess a fractal structure, that is, in some small regions of R, the structure is similar to the general Bifurcation Diagram.

5 NEW PHASE RESPONSE CURVES

Recall that the PRC function given was found by fitting data to a line. In order to determine the sensitivity of this fitted PRC, we introduce a different nonlinear discontinuous PRC function given by

$$g(x) = \begin{cases} \frac{a}{\omega}x^2 & x < \omega \quad \text{(6a)} \\ \frac{b}{\omega - 1}(x-1)^2 & x \geq \omega \quad \text{(6b)} \end{cases}$$

where 0<a< 1, 0<b< 1, and 0< ω < 1

Once g(x) is substituted into Equation (4), we obtain the new equation,

$$v_{n+1} = \begin{cases} -\frac{a}{\omega}\mathrm{v}_n^2 + \mathrm{v}_n + N & 0 \leq \mathrm{v}_n < w \\ \frac{-b}{w-1}(\mathrm{v}_n - 1)^2 + \mathrm{v}_n + N & w \leq \mathrm{v}_n < 1 \\ \mathrm{v}_n - 1 & 1 \leq \mathrm{v}_n < 1 + \epsilon N \\ \mathrm{v}_n + N - 1 & 1 + \epsilon N \leq \mathrm{v}_n < 1 + \delta N \\ \mathrm{v}_n - 1 & 1 + \delta N \leq \mathrm{v}_n < 1 + (1-\gamma)N \\ \mathrm{v}_n - 1 & 1 + (1-\gamma)N \leq \mathrm{v}_n < 1 + N \end{cases} \quad (7)$$

In Figure 11, we have the cobweb of v_{n+1}, which shows the same periodic orbit as x_{n+1} at R=1.5 for Model C1. Although the periodic solutions are slightly different, the symbolic representation of the periodic cycles are the same.

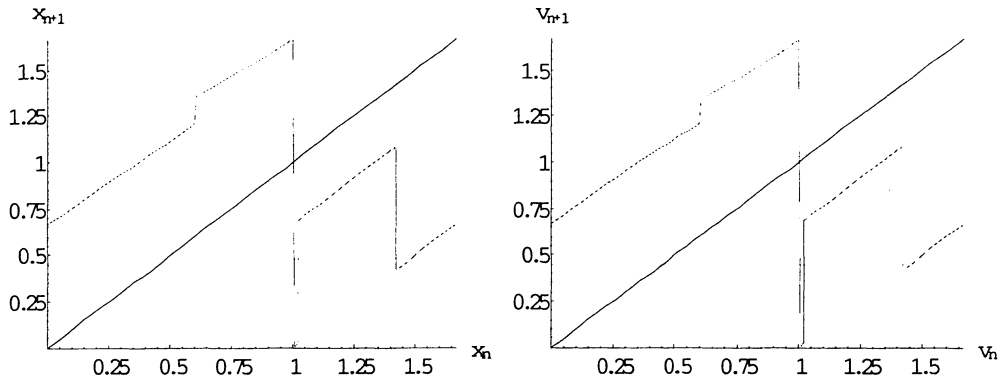

Figure 11. This is the cobweb of new function $v_{n+1}$and x_{n+1}, respectively, with the Model C1 at R=1.5. Through graphical analysis, we found that there is period-4 cycle for v_{n+1}. Although the two functions have the same parameter values with slightly different PRCs, the periodic solutions are distinct.

The periodic solutions of C1 with R=1.5 v_{n+1} are 1.07732, 0.743988,1.44343, 0.443426, which may also be represented as a, C, b, q. Although v_{n+1} and x_{n+1} both have period-4 solutions, the numerical values are different numerical periodic solutions. Figure 12 describes the model C1 for R = 3.

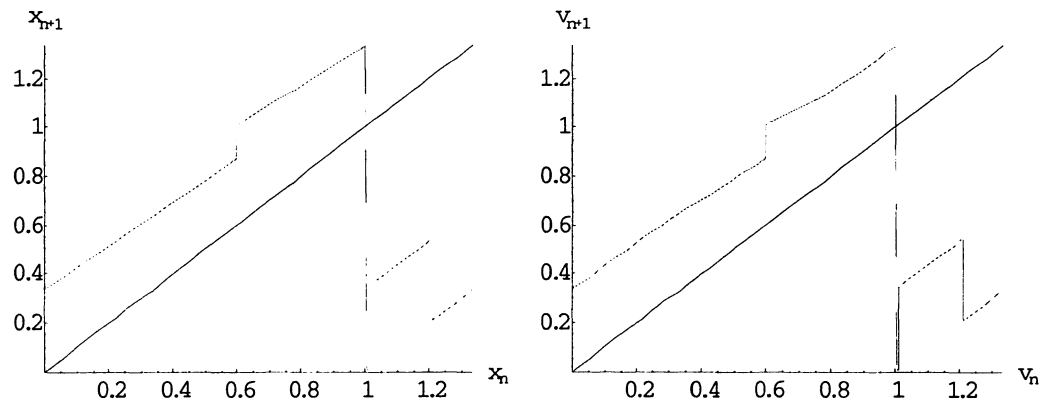

Figure 12. This is a cobweb of the Model C1 of the functions x_{n+1} and v_{n+1} at R=3. The function v_{n+1} has a period-3 orbit, which is the same as the periodic orbit of x_{n+1}.

For R = 3, the periodic solution for model C1 is 1.11009, 0.443426,

0.743988. A further example of the periodic solutions v_{n+1} is of model C1 with R = 2.3.

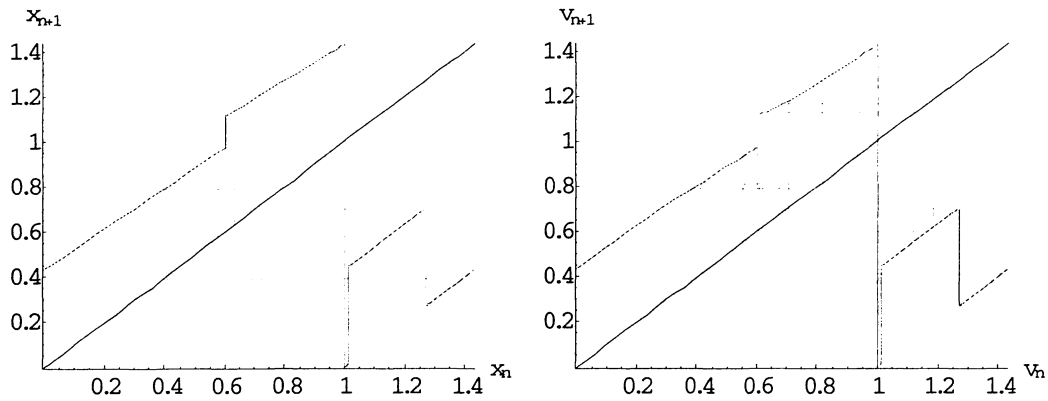

Figure 13. This cobweb of the Model C1 of v_{n+1} at R=2.3 has a periodic orbit of period-28, which is the same as the periodic cycle of x_{n+1}.

The periodic solution of v_{n+1} at R=2.3 is {0.601515, 1.11569, 0.550476, 0.934754, 1.37167, 0.371665, 0.783426, 1.24166, 0.676443, 1.16357, 0.598353, 0.973464, 1.4086, 0.408599, 0.815556, 1.26735, 0.702131, 1.18128, 0.616059, 1.12455, 0.55933, 0.941971, 1.37844, 0.378437, 0.789351, 1.24632, 0.681102, 1.16673} which is symbolized by {b, q, a, b,C, b, C, b, C, a, b, q, a, b, C, b, C, a}.

The various periodic solutions of model C1 are presented in the following table:

R Values	Periodic Orbit	Symbolic Periodic Solutions
1.50	period-4	a, C, b, q
1.82	period-14	b,C, b, q, a, b, q, a, b, q, a, C, a, C
2.3	period-28	b, C, b, C, a, b, q, a, b, C, b, C, b, C, a, b, q, a, b, C, b, C, a, b, q, a, b, C
2.45	period-6	q, a, b, C, a, b
2.6	period-14	a, b, C, b,C, a, b, C, a, b, q, a, b, C
2.71	period-13	b, C, a, b, C, a, b, q, a, a, b, q, a
2.94	period-3	C, a, b
3.23	period-21	a, a, b, C, a, b, C, a, b, C, a, b, C, a, b, b, q, a, b, b, q

Table 4. This table presents the periodic solutions of the Model C1 for v_{n+1}. Although many of the periodic solutions are similar to the Model C1

for x_{n+1}, there are some differences in periodic orbit for the same R values. For example, at R=2.3 for x_{n+1} and v_{n+1} have period-10 and period-28 respectively.

When Table 4 is compared with Table 2, there are many similarities in the periodic orbits. For example, when R=1.50, 1.82, and 2.94 both exhibit the same periodic cycles. However, for other values of R, the periodic cycles are distinct. To illustrate other similarities and differences between x_{n+1} and v_{n+1}, we constructed the cobweb of Figure 13, which has a large periodic orbit. Therefore, it is difficult to determine the periodic orbit through graphical analysis. The bifurcation diagrams are important to determine the pattern of the periodic orbit as the parameter R is varied.

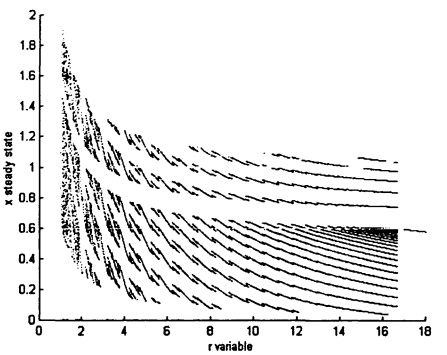

Figure 14. The bifurcation diagrams of the Model C1 of x_{n+1} and v_{n+1}, respectively, plots the parameter r=R along the x-axis and the stable periodic points of x_n and v_n along the y-axis.

R Values	Periodic Orbit	Periodic Solutions
1.60	period-7	C, b, q, a, b, q, a
1.80	period-3	a, b, q
2.16	period-2	b, C
2.25	period-2	b, C
2.40	period-8	a, b, q, a, b, C, b, C
2.46	period-6	a, b, C, a, b, q

Table 5. Model C2 of v_{n+1} varying the parameter R

The periodic solutions of model C2 in Table 3 are different from those in Table 5. Hence the PRC does influence the periodic solutions for specific R values. Thus, given a set of parameter values, we may have different qualitative behavior. However, the bifurcation diagrams presented in Figure 6 and Figure 12 are similar. Hence, qualitatively both PRCs seem to give the same global dynamics even if for specific R values they may in fact generate distinct oscillatory patterns.

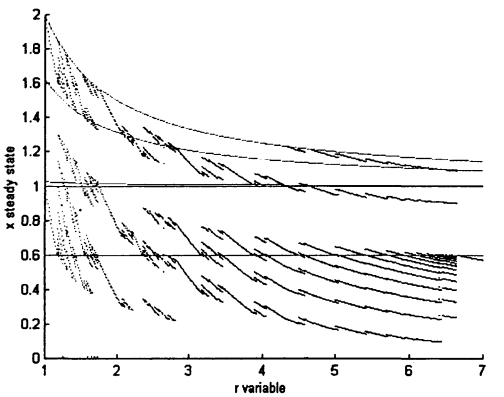

Figure 15. This is a bifurcation diagram of the Model C2 of x_{n+1}.

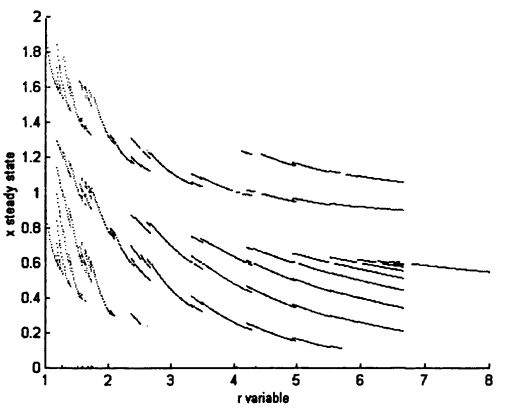

Figure 16. This is a bifurcation diagram of the model C2 of v_{n+1}, where the parameter r=R is varied.

DISCUSSION

Ikeda *et al.* (1983) analyzed a model, which describes ventricular parasystole using a piecewise continuous linear PRC. In this paper, we expanded on the results obtained by Ikeda *et al.*, while introducing a new PRC, to check the sensitivity of the model to slight changes to the structure of the PRC. With this new phase response curve, we noticed that the bifurcation diagrams of the models are similar in structure. The periodic orbits for some values of R appear to be the same, while for others we obtained different results. Recall that the periodic points represent arrhythmic patterns of the heart induced by ectopic impulses.

Cardiac disorders are mainly due to two principal electrophysiological mechanisms: 1) re-entry or circus movement and 2) automaticity or repetitive firing of an ectopic focus. Both mechanisms can be demonstrated experimentally (Ikeda, et al., 1983). The rational use of pharmacologic agents or electrical devices in terminating or preventing cardiac arrhythmias depends on which mechanism is responsible for the disorder. It is important to link specific pharmacologic agents to particular rhythm disorders. This can only be accomplished with a complete understanding of the electrophysiological events that occur during the cardiac cycle.

The effectiveness of an antiarrhythmic drug treatment depends upon its ability to reduce spontaneous diastolic depolarization, depress the rapid upstroke of phase 0 (initial fast inward movement of sodium), prolong the refractory period of cardiac cell, and affect the slow calcium current in the A-V node. Antiarrhythmic drugs were first classified depending on their major effects on the heart by Vaugham Williams in 1970. (APPENDIX-Table 1, Table 2). We have seen that different PRC curves may give different periodic solutions. However, not all heart arrhythmias are life-threatening. Thus it is important to know, given a set of parameter values, exactly which type of periodic solution we have. Although the bifurcation diagrams using the two proposed PRC functions exhibit the same qualitative global behavior, we have noticed that the same set of parameter values give different periodic solutions. Hence, a successful drug treatment must take into account the type of arrhythmia that is occurring for each individual and not just its "R" value.

Although the overall behavior of the model does not change when the PRC is modified, we may have drastic changes in the nature of periodic solutions for specific when varying certain parameter values. Hence, the dynamics of the model depends on the PRC to some extent. Since these

periodic solutions determine the type of cardiac arrhythmia one has, it is important that the model is accurate even with minor changes in the structure of the PRC. However, it remains open to research the possibility of finding other PRC functions fitted to experimental data.

As a final test of the sensitivity of our results to the PRC, we selected to approximate it using a Fourier Series approximations. Although we have never really measured how closed the PRCs resemble each other (using some statistical approach) and have not fitted them to data (a real possibility), our analysis suggest that Fourier approximations may indeed have a drastic impact on the global dynamics (bifurcation diagram) or can be seen from Figure 17 were we observe qualitatively different dynamics for values of R.

Our analysis suggest that although models do provide a qualitative picture of coupled pacemaker dynamics, it is also clear that treatment protocols must be tailored to each particular patient as it may not be unlikely to find a world of where everybody has a unique bifurcation diagram. In other words, when it comes to the heart the answer may still be inside an individual (C. Castillo, 1998).

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GLOSSARY

Bigeminy: an abnormal but usually harmless rhythm characterized by occurrence of one ventricular premature complex after every normal QRS complexes. This rhythm usually does not progress to dangerous forms of fast ventricular rhythms. In this rhythm, two ventricular premature complexes never occur one right after the other.

Trigeminy: an abnormal but usually harmless rhythm characterized by occurrence of one ventricular premature complex after every two normal QRS complexes.

Quadrigeminy: an abnormal but usually harmless rhythm characterized by occurrence of one ventricular premature complex after every three normal QRS complexes.

Bifurcation: change in the dynamics in a family of functions, such as a change in the number of fixed or periodic points and their attracting or repelling nature, as the parameter(s) is varied.

Phase Response Curve (PRC): is a function which describes the dynamics of the phase shift that the S-A node provokes on the ectopic pacemaker.

Fusion: when two different activating waves fuse to form a single QRS complex. For a fusion to occur a ventricular ectopic fucus must be discharging, producing characteristic ventricular ectopic beats.

Compensatory Pause: the P wave is "buried" in the QRS and is not visible. Further, when the atrial impulse reaches the A-V node, it encounters tissues that have already been discharged by the ventricular ectopic beat and cannot conduct the S-A impulse. There is therefore a pause until the next sinus beat crosses the atria and is conducted through the A-V node to the ventricles.

Interpolation: when the first premature systole, which produces the second QRS complex, does not interfere with either the initiation or conduction of the following sinus beat.

Silent Beat: when the discharge of an ectopic impulse is sufficiently low that it does not cause a premature beat.