**A MATHEMATICAL MODEL OF THE VAGALLY DRIVEN
SA NODAL PACEMAKER**

by

E.C. Greco and J.W. Clark, Jr.

January 1975

TECHNICAL REPORT #7506

A MATHEMATICAL MODEL OF THE VAGALLY DRIVEN SA NODAL PACEMAKER*

E.C. Greco and J.W. Clark, Jr.
Bioengineering Group
Department of Electrical Engineering
Rice University
Houston, Texas

ABSTRACT

A model is developed for the vagal control of SA nodal activity in the heart and consists essentially of a modified Bonhoeffer-Van der Pol (BVP) model of the "free-running" SA node and a lumped model of the neural terminations in that region. The model is capable of mimicing both the driven transient behavior of the node in terms of pacemaker and inhibition curves, as well as steady-state entrainment phenomena. The model data also agrees very well with experimental data from dog experiments performed in our laboratory. The model is described by a set of nonlinear, third-order, ordinary differential equations and provides a relatively uncomplicated functional model of heart period changes due to vagal stimulation patterns.

*This work was supported by Grants #HE-09251 and HL-13330 from the National Heart and Lung Institute, National Institutes of Health; and Grant #GB-43619 from the National Science Foundation.

A MATHEMATICAL MODEL OF THE VAGALLY DRIVEN SA NODAL PACEMAKER

E.C. Greco and J.W. Clark, Jr.
Bioengineering Group
Department of Electrical Engineering
Rice University
Houston, Texas

1. INTRODUCTION

The concept of vagal control of heart rate has, for generations, been based on the idea that vagal nerve impulses to the SA node occur in a relatively uniform pulse train which is slowly modulated by afferent neural input to the central nervous system. Several studies [1-6] have implicitly utilized this concept in either designing experiments and/or developing mathematical models of parasympathetic heart-rate control. More recent experimental data, however, show that the response of the cardiac pacemaker to vagal activity depends on the particular phase of the cardiac cycle at which a neural impulse (or group of impulses) arrives at the SA node [7-10]. As a result of this phase-dependency, a number of phenomena may be observed in response to either repetitive, or single-burst, vagal stimulation patterns. To explain this in greater detail, consider figs. 1(a) and (b) where the temporal relationships between vagal and cardiac events for single-burst and repetitive stimulation patterns are shown. Here the initiation of vagal activity is represented, for example, by the pulse waveform $v(t)$ representing the delivery of a single or multiple suprathreshold electrical stimuli to the right cervical vagus. The pulse waveform $p(t)$ consists of a pulse train representing the occurrence of an atrial P-wave (this signal, easily obtained via an intracardiac catheter electrode system, indirectly reflects pacemaker activity).

That efferent vagal activity tends to be burst-like and clustered into certain phases of the cardiac cycle has been demonstrated in the literature [11,12]. It has also been demonstrated that a single stimulus applied to the carotid sinus nerve appears reflexly as a discrete burst of impulses in efferent cardiac vagal fibers [13,14]. This natural grouping of efferent vagal activity most probably reflects periodic stimulation of the baroreceptors by the arterial pulse wave and, as shown by Levy and Zieske [15], the discharge of the cardiac pacemaker becomes synchronized with neural activity in the baroreceptor reflex arc.

As can be surmised from Fig. 1, single-burst vagal stimulation is used to study the transient nature of the phase-dependency of the cardiac pacemaker while repetitive-burst stimulation patterns, at various repetition rates, are used to study the steady-state characteristics of the SA nodal oscillator. In transient studies, the delay φ of the onset of vagal stimulation (Fig. 1(a)) may be varied over the interval $-\rho \leq \varphi \leq P_0 - \rho$ where P_0 is the control heart period and ρ is referred to as the "no effect" period (see Fig. 2). This period is attributed to vagal transmission delay, synaptic delays occurring at the parasympathetic ganglion and neuromuscular junctions within the SA node; and, to a large extent, the electrical refractory period of SA nodal cells undergoing excitation in a synchronous fashion. The data in Fig. 2 are plotted as the point set (φ^j, P_1^j) for $j = 1, 2, \dots, n$. Here one will recall from Fig. 1 that the stimulus always lies in the region $-\rho$ to $P_0 - \rho$ where the origin is the boundary between periods P_0 and P_1 . The procedure followed in constructing a pacemaker plot is to select a trial delay φ^j for delivery of a

single burst vagal stimulation. The resulting heart period P_1^j associated with this stimulus is recorded and sufficient time is allowed for the system to return to control values prior to application of another test stimulus at a different value of φ . From Figure 2 it is clear that as stimulus latency φ^j is increased from zero the resulting heart periods (P_1^j) increase until a maximum (φ^j) is reached. Beyond this maximum delay, rapid decreases in values of P_1^j occur until at sufficiently large φ^j , $P_1^j = P_0$. The stimuli delivered in this "no effect" zone thus have no effect on the test heart period, but do, in fact, affect the following heart period P_2 . Similarly, test stimuli delivered prior to the beginning of test heart period P_1 [i.e., in the "no effect" zone ($-\rho \leq \varphi \leq 0$) of the control heart period P_0] will have an effect on P_1 , but not on P_0 .

Since a single vagal burst is capable of affecting the heart period for several successive heart periods [16,17,18], transient information regarding the phasic relationship existing between heart period and stimulus latency, for several post-stimulation heart periods, is frequently displayed in the form of an inhibition curve [16,17]. This curve represents the alignment of temporal sequences of heart period changes following single burst vagal stimulation with respect to the onset of stimulation. As one will note from Fig. 3, the ordinate of this curve is a normalized heart period (y_k) given by the equation

$$y_k = (P_k - P_0)/P_0 \quad k = 1, 2, \dots, m \quad (1)$$

where m periods following stimulation are measured. The abscissa for this curve is time from stimulus onset to the end of the k^{th} heart period and is

given as

$$t_k = \left(\sum_{i=1}^k P_i \right) - \varphi \quad k = 1, 2, \dots, m \quad (2)$$

Fig. 3 is then a continuous curve passed through the data set (t_k, P_k) .

There is understandably an interrelationship between the pacemaker curve of Fig. 2 and the inhibition curve of Fig. 3, since both are methods of presenting transient data on single-burst vagal stimulation. The inhibition curve, however, presents information on changes in heart periods other than P_1 . If only the first heart period is considered (that is $k = 1$) then from equations (1) and (2)

$$y_1 = (P_1 - P_0)/P_0 \quad (3)$$

and

$$t_1 = P_1 - \varphi \quad (4)$$

for φ values in the range $-\rho \leq \varphi \leq P_0 - \rho$. Thus for the minimum delay ($\varphi = -\rho$) $t_1 = P_1 + \rho$; for $\varphi = 0$, $t_1 = P_1$ and for the maximum delay ($\varphi = P_0 - \rho$), $t_1 = P_1 - P_0 + \rho$. For slight increases in delay beyond the maximum, the stimulus has no effect on the first heart period and $P_1 = P_0$. Therefore, for a delay $\varphi = P_0 - \rho$, $t_1 = \rho$.

In the case of repetitive asynchronous vagal stimulation as in Fig. 1(b), resulting heart period data are usually plotted vs stimulus interval T_v (see Fig. 4).^{*} Typically, a repetition interval (T_v) is chosen and sufficient time is allowed for transients to decay (~ 1 minute) prior to recording the mean heart period during a specific number of vagal stimulations. The steady-state

^{*} The range of variation for T_v is usually $1/2 P_0 \leq T_v \leq 4P_0$.

relationship between the stimulus repetition period (T_v) and heart period is decidedly different from what would be expected from a linear pacemaker oscillator responding to a periodic input. Rather, the diagram exhibits zones of entrainment wherein the frequency of the heart oscillator is equal to that of the neural stimulation frequency. Entrainment phenomena at sub- and super-harmonics are also observable in such diagrams particularly when several stimuli are delivered per burst. The purpose of the present work is the development of a mathematical model that is capable of mimicking both the transient and steady state behavior of the vagally driven SA nodal oscillator. Data from dog experiments performed in our laboratory is used to validate the model.

II. MODEL DESCRIPTION

The general aspects of the vagally driven cardiac pacemaker system are shown in Fig. 5 wherein the SA node proper is considered as a population of cells capable of firing spontaneously and rhythmically in a nearly synchronous fashion. Here $f_v(t)$ is vagal stimulation frequency, $p(t)$ represents heart period and $f_a(t)$ is an impressed driving function producing induced effects on the nodal membrane potential analogous to those effects produced by the neurotransmitter Ach. The pacemaker potential of a representative SA nodal cell in this population is given qualitatively as the solution of a set of differential equations known as the Bonhoffer-Van der Pol (BVP) equations. Fitzhugh [23] has used these equations to describe qualitatively the single nerve action potential as well as repetitive neural firing. These ordinary differential equations are modified slightly for our purposes and mimic to a considerable extent the relaxation-oscillation behavior of the driven and un-

driven SA nodal cell.

The specific equations utilized in this study are essentially those used by Fitzhugh [23] modified to include a third equation that provides negative feedback to the basic BVP model with gain K and time constant $1/\alpha$. The equations are:

$$\begin{aligned}\dot{x}_1 &= \epsilon(1 - x_1^2/3)x_1 - x_2 \\ \dot{x}_2 &= \varphi(x_1 + a - bx_2) - x_3 + w_1 f_a(t) \\ \dot{x}_3 &= Kx_1 - \alpha x_3\end{aligned}\tag{5}$$

Here ϵ , φ , a , b , K and α are constants and $x_1(t)$ is an "activation variable" analogous to the membrane potential of the SA nodal cell. The variable $x_2(t)$ is viewed as a "recovery variable" primarily responsible for repolarization of the cell. The simultaneous diminishment in the magnitude of $x_2(t)$ and increase in the feedback variable $x_3(t)$ * account for the slow potential increase during the electrical diastolic phase of $x_1(t)$ (see Fig. 7a). The feedback variable x_3 also tends to stabilize the oscillator output in the face of strong inhibitory inputs $f_a(t)$ by preventing an excessively large increase in x_2 .

The impressed driving function $f_a(t)$ is a two-component linear function and w_1 in (5) is a nonlinear gain term. The decision to use this two-component forcing function stems directly from observations of our experimental data, particularly inhibition curves. This point will be discussed later under results. The first component of $f_a(t)$ is

$$f_1(t) = K_1 t e^{-k_1 t} u(t)\tag{6}$$

* This feedback has been suggested previously by Chess and Calaresu [19]. The primary effect of the negative feedback voltage is to decrease the sensitivity of the model to the applied vagal forcing function $f_v(t)$.

where K_1 and k_1 are constants. This analytical form has been used to describe the temporal form of the end-plate potential recorded at many types of neuromuscular junctions [20,21]. The second component f_2 is delayed from the first by T seconds and is given by

$$f_2(t) = K_2 [e^{-k_2(t-T)} - e^{-k_3(t-T)}] u(t-T) \quad (7)$$

The total driving function is therefore

$$f_a(t) = f_1(t) + w_2 f_2(t) \quad (8)$$

where w_2 is a nonlinear gain term. This second component represents an indirect effect on transmembrane potential that may be due to either neurotransmitters or the intrinsic electrical behavior of the nodal cell itself as suggested by Calaresu, et al. [19,22]. The forcing function realization is given in Fig. 6 and the model response to $f_a(t)$ is given in Fig. 7b.

The model was implemented on an EAI 680 analog computer. Time scaling, with capacitors, reduced the control period of the nodal oscillator from 10 sec to 1 sec (see Fig. 7). All model parameters remained unchanged. The vagal stimulation, $f_v(t)$ (see Fig. 5), is a series of delta functions, one delta function to each burst (1,3, or 5 pulses) of vagal stimulation. Delta functions are best realized on an analog computer with a momentary initial condition setting. With a stimulus burst beginning at $t = t_0$, the initial condition for the forcing function $f_1(t)$ was set to 1 at t_0 and for $f_2(t)$ at $t_0 + T$. The magnitude of the stimulation (1,3, or 5 PPB) was determined by the multiplicative constants K_1 and K_2 .

There is, of course, a delay in output response from the input stimula-

tion in both model and experimental preparations. The delay in the experimental case is contributed by a number of factors including transmission time from the stimulating site to the neural termination (including synaptic delay at the parasympathetic ganglion) and transmitter release, diffusion, and utilization at the post-synaptic membrane. This delay is manifested in the transient response, inhibition curve, and, in the model's case, is dependent on the definition of cycle boundary (zero crossing of $x_1(t)$ with $\dot{x}_1(t) > 0$) and time constant of the forcing function, $f_1(t)$. Since the delay is simply a constant time shift in the inhibition curve, it can be incorporated into the model by simply shifting the model's inhibition curve by a constant value. This constant time shift, however, has no physical significance since it is a function of an arbitrary choice of period boundaries. In the steady-state response this time delay is, of course, unobservable.

III. EXPERIMENTAL PROCEDURES

Three mongrel dogs (~ 20 kg) were anesthetized with an intravenous injection of sodium pentobarbital (Nembutal) at 10 mg/kg and Innovar-Vet (.4 mg/cc Fentanyl and 20 mg/cc Droperidel) at .2 cc/kg. Propanalol (1 mg/kg) was also administered to block sympathetic postganglionic activity. The trachea was cannulated and both cervical vagus nerves were ligated. A tripolar stimulation electrode assembly was placed on each nerve peripheral to the site of ligation; the most peripheral pole was grounded to minimize stimulus artifact. The right external jugular vein was exposed and a bipolar catheterization electrode was inserted and positioned at the level of the right atrium. This local

right atrial bipolar ECG exhibited large P-waves for convenient determination of the P-P interval. A standard lead II ECG was also recorded as part of the physiological data.

The supramaximal vagal stimulus was provided by a Grass Stimulator (Model S-44) and associated stimulus isolation unit (Model SIU5). The stimulator was gated with a signal generator (Wavetek Model 112) to produce a burst of 1, 3 or 5 pulses of 1 msec duration, an interspike period of 11 msec, and adjustable amplitude (see Fig. 8a). In the case of synchronous stimulation, the P-wave of the atrial bipolar ECG was used to trigger an adjustable delay circuit that, in turn, triggered the gating Wavetek square-wave generator. The result was a burst of 1, 3 or 5 stimulating pulses delivered to the vagus with a predetermined latency ϕ with respect to the P-wave. A pulse associated with the atrial P-wave was used to trigger an on-line data acquisition system (Fig. 8b) that employed a Digital Equipment Corp. PDP-12 digital computer to calculate the required time events and intervals of interest (e.g., heart period P_i , delay ϕ , and P-R interval). Specifically, the analog derivatives of the atrial and lead II ECG's were taken (with suitable low-pass filtering (20 Hz cutoff) to help remove the high frequency noise associated with differentiation) and fed to the input of the clock channels of the PDP-12. The differentiated atrial ECG waveform was used to indicate the time of occurrence of the P-wave while the differentiated lead II ECG was used to indicate the occurrence of the R-wave. These signals were detected by the machine as interrupts and an appropriately triggered real-time clock was used to determine the required data time intervals. With single-burst synchronized stimulation,

eight successive cardiac periods (P_i) were recorded for each delay ϕ^j . Subsequently, the pacemaker curve (Fig. 2) could be displayed on the cathode ray tube of the PDP-12 as data was being gathered.

In the case of asynchronous stimulation, the vagus was driven in a burst format of 1, 3 or 5 impulses with an inter-stimulus period of 11 msec and a burst repetition period (T_v) chosen in the range of $P_o/2 \leq T_v \leq 4P_o$ where P_o is the control heart period. Applying this repetitive asynchronous stimulation, sufficient time (~ 1 minute) was allowed for transients to decay prior to taking data on eight successive heart periods. The data acquisition system again allowed the experimenter to observe the averaged data in the form of a normalized heart period vs stimulus period plot on the c.r.t. of the PDP-12, as data was taken.

IV. RESULTS

The experimental results from dog #3, a typical sample for this experimental protocol, are included here. Data from the single-burst synchronous stimulation protocol are presented in terms of pacemaker curves Fig. 9 and inhibition curves Figures 10 and 11. In Fig. 9 it can be clearly seen that increasing the number of pulses per burst (PPB) increases the magnitude of the pacemaker curve. As the number of pulses per burst increases, the peak of the primary wave of the inhibition curve also increases (Fig. 10); the magnitude of the negative dip and the time (τ)* at which it occurs increase as well. The magnitude of the secondary peak of this

* τ defined as t/P_o .

triphasic waveform is changed very little. A comparison of the inhibition curves obtained from right, left and combined vagal stimulation is greater than left and, furthermore, appears to dominate the temporal course of the response to combined stimulation.

In Fig. 12 the model output for 1, 3 and 5 PPB is compared with the experimental data of Fig. 10; the correspondence is quite good as one may observe. Good fits are also obtained to the pacemaker curve data of Fig. 9 as one would expect since there is a direct relationship between the initial portions of the inhibition curve and the pacemaker curve. The model parameters obtained from trial-and-error estimation of the inhibition curves (Figure 10) for 1, 3 and 5 PPB are given in Tables 1 and 2. The nonlinear gain terms, w_1 and w_2 , are both 1 for parameters listed in Table 2.

The experimental results from asynchronous stimulation are presented in the form of average heart period vs inter-burst stimulus period, for bursts containing 1, 3 and 5 stimuli (Fig. 13). For 1 PPB there is a general inverse relationship exhibited between mean heart period and stimulus repetition period. As the number of stimuli delivered per burst is increased this relationship undergoes considerable change and well-defined zones of entrainment at sub- and super-harmonics of the fundamental (1:1) of the stimulus period appear giving this steady-state input-output characteristic of the node a saw-tooth appearance. This data is in general agreement with that of Dong and Reitz [9] and Levy, et al. [7]. Note that in an entrainment zone, decreasing stimulus period brings about a decreasing mean heart period or, equivalently, an increasing heart rate with increased vagal stimulation frequency; the paradox-

ical effect of vagal nerve stimulation on heart rate described by Levy, et al. [7]. The model output for asynchronous steady-state stimulation is given in Fig. 14 and observing this figure, one will note that strong similarities exist and the model adequately predicts the entrainment phenomena at 1, 3 and 5 impulses/burst. The gain coefficients, K_1 and K_2 , obtained in the transient case provide 3 points for the nonlinear gain terms w_1 and w_2 , respectively (see Fig. 6). The nonlinear gains act as a saturation effect on the forcing function which is particularly necessary in the case of $f_2(t)$ which contains a relatively long time constant, $1/k_2$.

V. DISCUSSION

The modified Bonhoeffer-Van der Pol (BVP) model used in this study adequately predicts the SA nodal response to both transient and steady-state vagal stimulation (Figs. 12 and 14). The model is characterized by a set of third-order, non-homogeneous nonlinear differential equations that differ from those used by Fitzhugh [23] by the addition of a third state variable x_3 that has its main effect during the middle and latter portions of the diastolic phase of the pacemaker action potential (see Figs. 7a and b). In effect, the interaction of the x_1 and x_2 variables produce the spike portion of the waveform, while the interaction of the x_2 and x_3 variables influence the interspike interval.

This concept is consistent with published voltage clamp data of Connor and Stevens [24] on isolated invertebrate pacemaker motoneurons (which may be

considered somewhat analogous to pacemaker cells in the heart). Here the interaction of a sodium activation channel and a repolarizing potassium channel (g_{k_1}) produced the spike portion of the pacemaker waveform, while the interspike interval was characterized by the interaction of g_{k_1} and a second operationally distinct potassium channel (g_{k_2}) acting in the later portions of the interval. The soma of these invertebrate neurons are quite large and can be easily isolated via ligature, making an ideal preparation for voltage clamp studies on the membrane dynamics of a typical pacemaker neuron. SA nodal cells in contrast are small and are not easily isolated, rendering voltage-clamp studies unfeasible at the present time. The Hodgkin-Huxley type differential equations used by Connor and Stevens to describe their experimental results were of seventh order and required the specification of some ten nonlinear functions of membrane voltage. Experimental and theoretical results in these studies [24] compared very favorably.

When one considers the problem of modeling SA nodal activity, a question naturally arises as to modeling objectives and specifically whether, based on the question one intends to ask of the model, a "functional" model is required or a more "fundamental" model delving into basic questions regarding membrane dynamics. Properly structured, a Hodgkin-Huxley type model of SA nodal membrane activity would result in a system of equations of relatively high order compared with the simple third-order model presented in this study. The model parameters (e.g., ϵ , φ , a , b) used in this study have little or no physiological significance, yet the questions asked of the model concern simply temporal information (namely, changes

in the heart period). Changes in membrane potential waveform were of little concern in the present study and, clearly, if they were part of the modeling objective, the third-order BVP model would be considered a relatively poor model compared with the capability of a higher order Hodgkin-Huxley (H-H) type model. The data used to validate the H-H model, however, would be quite difficult to obtain (i.e., voltage-clamp studies on single SA nodal cells together with action potential data; the electrophysiological data utilized in this study consists of intra-atrial ECG data and is adequate for heart period determination only). Weaver and Dong [35] have used a modified version of Noble's* H-H model for the Purkinje fiber to characterize the electrical behavior of the SA nodal cell. The model consists of a set of fourth-order nonlinear ordinary differential equations requiring the specification of seven rather complex functions of membrane voltage, as well as other parameters. The approach is subsequently complicated in a numerical sense and, as previously stated, data does not exist to validate the model. In addition, the electrical characteristics of nodal pacemaker cells are quite different from other types of heart cells (such as atrial, Purkinje, or ventricular cells) and evidence exists† to indicate that the model used by Weaver and Dong [25] would require some degree of modification if the modeling objective were to be accurate simulation of the excitable behavior of nodal (or atrial) cells. Therefore, it is

* See [26].

† See, for example, Noble, et al. [27,28], Conner and Stevens [24], and the model of Rougier, et al. [29] for the frog atrial action potential.

our opinion that the modeling objectives of this study are "functional" in nature and do not warrant the increased complexity of a modified H-H type model.

The driving function f_a in this study (equations [6-8]) consists of two distinct components, the first acting strongly to bring about the primary negative chronotropic effect seen in the inhibition curves, while the second component acts in a delayed fashion to bring about the second peak of negative chronotropic effect. Our experimental data indicate the presence of an acceleratory peak (below the abscissa) between the two peaks and the model results predict this behavior (Fig. 12). Further, the experimental data presented in Figure 10 indicates that as the number of vagal impulses per burst is increased, the primary peak amplitude increases, but the secondary peak amplitude remains essentially constant and is delayed more and more as the number of impulses/burst increase. Due to the difference in the behavior of the two negative chronotropic peaks to increasing numbers of vagal stimuli, we were unable to use the method of Iano, Levy and Lee [8] for separating total vagal effect into negative and positive components. This technique defines the positive chronotropic effect as the amount of divergence of the actual time course of the inhibition curve from a hypothetical time course that consists of the initial negative peak of the inhibition curve data, followed by a single or double exponential decay. The method is illustrated in Fig. 4 of reference [8] and consists of replotting the exponential data on semilog paper, linearly extrapolating the secondary portion of the inhibition curve to the logarithmic peak

of the primary waveform and then subtracting points below this line to ultimately construct the positive component of vagal effect. In our studies, the secondary peak frequently did not extrapolate backwards in time to the positive peak and we therefore abandoned the method in favor of the two negative component driving function used in this study.

The negative-positive driving function concept of Iano, Levy and Lee is very attractive in terms of some of the current hypotheses attempting to explain the acceleratory phase of the inhibition, as well as other phenomena such as postvagal tachycardia. Various theories propose that these effects are produced by sympathetic postganglionic fibers in the vagus, by active parasympathetic fibers secondarily discharging sympathetic nerve terminal endings or exciting chromaffin cells in the nodal area, etc. Burke and Calaresu [22] and Chess and Calaresu [19] propose, however, that such acceleratory behavior is not mediated by sympathetic mechanisms, but is related to inherent regulatory mechanisms within the cell. Our experimental and theoretical results would tend to agree with those of Calaresu, et al. [19,22], however, further quantitative investigation must be carried out.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Stuart O. Zimmerman, Chairman, Biomathematics Department, M.D. Anderson Hospital and Tumor Institute, Houston, Texas for providing an EAI-680 analog computer used for part of these simulation studies. A special thanks to Mr. Cliff Siegel and Mr. Kim Wertheimer for their assistance in these experiments.

REFERENCES

1. Rosenblueth, A. and F.A. Simeone (1934) "Interrelations of vagal and acceleration effects on the cardiac rate," Amer. J. Physiology 110: 42-55.
2. Warner, H.R. and A. Cox (1962) "A mathematical model of heart rate control by sympathetic and vagus efferent information," J. Appl. Physiol. 17: 349-355.
3. Warner, H.R. and R.O. Russell, Jr. (1969) "Effect of combined sympathetic and vagal stimulation on heart rate in the dog," Circ. Res. 24: 567-573.
4. Katona, P.G. (1967) "Computer simulation of the blood pressure control of the heart period," in Baroreceptors and Hypertension, P. Kezdi, ed., 191-199.
5. Chess, G.F. and F.R. Calaresu (1971) "Frequency response model of the vagal control of heart rate in the cat," Amer. J. Physiol. 220: 554-557.
6. Chess, G.F. and F.R. Calaresu (1971) "Model of dynamic behavior of heart period during bilateral vagal stimulation in the cat," Amer. J. Physiol. 221: 593-596.
7. Levy, M.N., et al. (1969) "Paradoxical effect of vagus nerve stimulation on heart rate in dogs," Circ. Res. 25: 303.
8. Iano, T., et al. (1973) "An acceleratory component of the parasympathetic control of heart rate," Amer. J. Physiol. 224: 997-1005.
9. Dong, E. and B.A. Reitz (1970) "Effect of timing of vagal stimulation on heart rate in the dog," Circ. Res. 27: 635-646.
10. Glaze, H.J., Jr. (1971) "Mathematical models for heart rate responses to vagal nerve stimulation," Ph.D. Thesis, Stanford University, Stanford, California.
11. Jewett, D.L. (1964) "Activity of single efferent fibers in the cervical vagus nerve of the dog, with special reference to possible cardioinhibitory fibers," J. Physiol. 175: 321-357.
12. Katona, P.G., et al. (1970) "Cardiac vagal efferent activity and heart period in the carotid sinus reflex," Amer. J. Physiol. 218: 1030-1037.

13. Iriuchijima, J. and M. Kumada (1963) "Efferent cardiac vagal discharge of the dog in response to electrical stimulation of sensory nerves," Japanese J. Physiol. 13: 599-605.
14. Iriuchijima, J. and M. Kumada (1964) "Activity of single vagal fibers efferent to the heart," Japanese J. Physiol. 14: 479-487.
15. Levy, M.N. and H. Zieske (1972) "Synchronization of the cardiac pacemaker with repetitive stimulation of the carotid sinus nerve in the dog," Circ. Res. 30: 634-641.
16. Brown, G.L. and J.C. Eccles (1934) "The action of a single vagal valley on the rhythm of the heart beat," J. Physiol. 82: 211-240.
17. Brown, G.L. and J.C. Eccles (1934) "Further experiments on vagal inhibition of the heart beat," J. Physiol. 82: 244-257.
18. Levy, M.N., et al. (1970) "Effects of single vagal stimuli on heart rate and atrioventricular conduction," Amer. J. Physiol. 218 (suppl. 5): 1256-1262.
19. Chess, G.F. and F.R. Calaresu (1974) "A mathematical model of the vagus-heart period system in the cat," IEEE Trans. on Biomed. Engr. 21: 21-27.
20. Katz, B. and R. Miledi (1965) "Propagation of electrical activity in motor nerve terminals," Proc. Roy. Soc. B. 161: 453-482.
21. Katz, B. and R. Miledi (1967) "A study of synaptic transmission in the absence of nerve impulses," J. Physiol. 192: 407-436.
22. Burke, G.H. and F.R. Calaresu (1972) "An experimental analysis of the tachycardia that follows vagal stimulation," J. Physiol. 226: 491-510.
23. Fitzhugh, R. (1969) "Mathematical models of excitation and propagation in nerve," in Biological Engineering, H. Schwan, ed., McGraw-Hill Book Co., pp 1-85.
24. Connor, J.A. and C.F. Stevens (1971) "Prediction of repetitive firing behavior from voltage clamp data on an isolated neurone soma," J. Physiol. 213: 31-53.
25. Weaver, C.S. and E. Dong (1972) "A phase-sensitive vagal heart-rate control model," J. Theoretical Biol. 36: 291-311.
26. Noble, D. (1962) "A modification of Hodgkin-Huxley equations applicable to Purkinje fiber action and pacemaker potentials," J. Physiol. 160: 317-352.

27. Noble, D. and R.W. Tsien (1969) "Outward membrane currents activated in the plateau range of potentials in cardiac muscle fibers," J. Physiol. 200: 255-265.
28. Hauswirth, O., D. Noble and R.W. Tsien (1969) "The mechanism of oscillatory activity at low membrane potentials in cardiac Purkinje fibers," J. Physiol. 200: 205-231.
29. Rougier, O., et al. (1969) "Existence and role of a slow inward current during the frog atrial action potential," Pflüger's Arch. 308: 91-110.

TABLE 1. Oscillator Model Parameter Values

$a = .2410$	$\epsilon = 3.6580$
$b = .0597$	$\alpha = .0055$
$\varphi = .9995$	$K = .0100$

TABLE 2. Forcing Function Parameter Values*

$$k_1 = 0.35 \text{ sec}^{-1}$$

$$k_2 = 0.005 \text{ sec}^{-1}$$

$$k_3 = 0.16 \text{ sec}^{-1}$$

$$K_1 = 0.140 \text{ -- 1 PPB}$$

$$= 0.297 \text{ -- 3 PPB}$$

$$= 0.344 \text{ -- 5 PPB}$$

$$K_2 = 0.097 \text{ -- 1 PPB}$$

$$= 0.114 \text{ -- 3 PPB}$$

$$= 0.113 \text{ -- 5 PPB}$$

$$T = 1.44 \text{ sec -- 1 PPB}$$

$$= 2.78 \text{ sec -- 3 PPB}$$

$$= 3.12 \text{ sec -- 5 PPB}$$

* Weighting coefficients w_1 and w_2 from (5) and (8) are both 1.

FIGURE CAPTIONS

FIG. 1 Temporal relationship between vagal, $v(t)$, and cardiac, $p(t)$, activity for single (a) and repetitive (b) burst stimulation; three pulses occurring at a relatively high intra-burst frequency are shown. In (a), φ is the delay between the end of the control heart period P_0 and the onset of vagal stimulation. The range in which φ can vary affecting only P_1 is indicated, i.e., $-p \leq \varphi \leq P_0 - p$. The time origin for each stimulus is taken as the beginning of period P_1 . In (b), the inter-burst interval of the repetitive stimulation is T_v , while the intra-burst interval between spikes is constant at a value of h .

FIG. 2 Typical family pacemaker curves for vagally driven cardiac pacemaker where vagus is supramaximally stimulated with a single burst containing 1, 3, or 5 stimulating pulses. The single stimulation burst is delivered with a delay φ relative to the occurrence of the P-wave and the maximum delay of interest is P_0 , the control heart period. See, for example, reference [9]. Points a, b, and c are presented in the inhibition curve format in Figure 3.

FIG. 3 Typical form of the inhibition curve of Brown and Eccles [16,17]. The ordinate, y , is discrete and defined by equation (1) and the abscissa is also discrete defined by equation (2). The continuous curve shown is an approximation to all points contained in the point set defined by equations (1) and (2). Points a, b, and c are presented in the pacemaker curve format in Figure 2. The circled data points correspond to values of y for successive heart periods in response to a single stimulus at an arbitrary constant delay φ .

FIG. 4 Average heart period during a continuous sequence of repetitive vagal stimulations as a function of stimulus repetition period T_v (see [9]). The continuous curve is an approximation to the discrete set for all points within this range of T_v .

FIG. 5 General schematic of vagally driven cardiac pacemaker. The input, $f_v(t)$, is the stimulation to the vagus nerve; $f_a(t)$ represents the effect the neural transmitter, Ach, has on the nodal cells; and the output, $P(t)$, represents the occurrences of the P-wave.

FIG. 6 Realization of the forcing function, $f_a(t)$, including the saturation effects.

FIG. 7 Model state variables (x_1, x_2, x_3) as functions of time for the un-driven (a) and driven (b) case.

FIG. 8 (a) Synchronous stimulation system. The electrical activity associated with the P-wave of the EKG was discriminated and delayed to serve as a trigger signal to the signal generator (Wavetek). The Wavetek provides a gating pulse to the stimulator; stimulator frequency is set to the intra-burst frequency and the gating pulse duration determined the number of pulses per burst. Asynchronous stimulation is accomplished by driving the Wavetek with another oscillator set to the inter-burst frequency. (b) Real time data acquisition system used to obtain $P(t)$, ϕ , $v(t)$, and P to R wave intervals. Results displayed on CRT during data acquisition.

FIG. 9 Pacemaker curves from single burst right vagal stimulation. The ordinate and abscissa values are normalized to the control heart period, P_0 .

FIG. 10 Inhibition curves obtained from single burst right vagal stimulation; (a) 1 pulse/burst; (b) 3 pulses/burst; (c) 5 pulses/burst. Ordinate and abscissa values have been normalized to the control heart period, P_0 .

FIG. 11 Inhibition curves obtained from single burst vagal stimulation at 5 pulses/burst; (a) right vagal stimulation; (b) left vagal stimulation; (c) combined vagal stimulation. Ordinate and abscissa values have been normalized to the control heart period, P_0 .

FIG. 12 Experimental and theoretical inhibition curves obtained from single burst right vagal stimulation; (a) 1 pulse/burst; (b) 3 pulses/burst; (c) 5 pulses/burst. The points represent data from the dog experiments; the continuous curves represent the response of the vagally driven SA nodal model. The continuous curve is produced by linearly interpolating between discrete data points produced by the model. The ordinate and abscissa values are normalized to the control heart period, P_0 .

FIG. 13 Steady-state nodal response as a result of continuous asynchronous vagal stimulation. The ordinate is the mean heart period increase obtained over eight consecutive heart periods normalized to the control period, and the abscissa is the inter-burst stimulus period normalized to the control period. The diagonal lines shown represent the locus of points where the stimulus period is exactly proportional to mean heart period.

FIG. 14 Model stimulation of the steady-state response from continuous asynchronous vagal stimulation. Ordinate and abscissa are normalized as in Fig. 13.

003