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Nonlinear dynamics, chaos and complex cardiac arrhythmias

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Periodic stimulation of a nonlinear cardiac oscillator *in vitro* gives rise to complex dynamics that is well described by one-dimensional finite difference equations. As stimulation parameters are varied, a large number of different phase locked and chaotic rhythms is observed. Similar rhythms can be observed in the intact human heart when there is interaction between two pacemaker sites. Simplified models are analysed, which show some correspondence to clinical observations.

1. INTRODUCTION

The normal adult human heart at rest usually beats at a rate of between 50 and 100 times per minute. In many circumstances, some of which are life-threatening, but most of which are not, the normal rhythmicity is altered, resulting in abnormal rhythms called cardiac arrhythmias. The point of this paper is to show that a branch of mathematics called nonlinear dynamics may be useful in the analysis of physiological processes believed to underlie normal heart rate regulation and some cardiac arrhythmias.

The idea that mathematical analysis can play a role in understanding cardiac arrhythmias is not novel. Indeed, in the 1920s it was demonstrated that as parameters in mathematical models for the heart were varied, several different rhythms that resembled clinically observed arrhythmias could be generated (Mobitz 1924; van de Pol & van der Mark 1928). In nonlinear mathematics, these changes in the qualitative features of the rhythms that are observed as parameters vary are called bifurcations. Thus the problem of understanding cardiac arrhythmias in the human heart is identified with understanding the bifurcations and complex dynamics in mathematical models of the human heart.

One type of dynamic behaviour that is the object of intensive analysis in mathematics is chaos. Loosely, chaos is defined as aperiodic dynamics in deterministic systems in which there is sensitive dependence to the initial conditions. This means that although in principle one could determine precisely the future evolution of the system starting from some initial condition, for chaotic dynamics any difference in the initial condition, no matter how small, will eventually lead to marked differences in the future evolution of the system. Although the existence of chaos was known to Poincaré and others since the end of the last century, in the

past decade there has been a recognition of the potential significance of chaos in understanding the genesis of aperiodic dynamics experimentally observed in the natural sciences (Cvitanovic 1984). Unfortunately, there is in our view not yet an adequate operational definition for chaos in experimental or naturally occurring systems, but see Mayer-Kress (1986) for recent advances. The concept of chaos excludes non-deterministic stochastic processes, such as the Poisson process or random walk. It is not yet known how to measure the relative contribution of chaos as opposed to non-deterministic stochastic processes in experimental data.

Normal individuals show marked fluctuations in heart rate (Kitney & Rompelman 1980; Kobayashi & Musha 1982; Pomeranz *et al.* 1985; De Boer *et al.* 1985). In addition, cardiac arrhythmias are often extremely irregular and unstable (Pick & Langendorf 1979; Schamroth 1980). The adjective 'chaotic' is sometimes used to characterize cardiac arrhythmias that are believed to arise when there are several pacemaker sites competing for control of the myocardium (Katz 1946; Phillips *et al.* 1969; Chung 1977). It has been proposed that chaotic dynamics, in the mathematical sense, may underlie normal heart-rate variability (Goldberger *et al.* 1984; Goldberger & West 1987) as well as certain cardiac arrhythmias in humans (Guevara & Glass 1982; Smith & Cohen 1984; Glass *et al.* 1986*b*). The absence of a clear definition for chaos in experimental data has led to controversy. For example,ventricular fibrillation, an arrhythmia that leads to rapid death, is frequently called chaotic by clinicians, and it has been proposed that it may be associated with chaos in deterministic systems (Smith & Cohen 1984). However, there are marked periodicities during ventricular fibrillation, and the presence of deterministic chaos in this arrhythmia has been questioned (Goldberger *et al.* 1985, 1986).

In humans it is frequently difficult to analyse the mechanism underlying an arrhythmia, and systematic experimental studies are usually not feasible. One means of analysis is from the electrocardiogram (ECG), a record of electrical potential differences on the surface of the body that reflects the electrical activity associated with the heartbeat. Because the ECG can be obtained with lightweight monitors, it can be readily recorded over long time intervals. The ambulatory (Holter) ECG is an important means for evaluating patients. Holter recordings for as long as 24 h can be readily obtained, but conventional analysis of such records is limited. The great wealth of data about the dynamics of the heart that is contained in such records is generally distilled to characterize the mean heart rate and range. The presence and frequency of abnormal electrocardiographic complexes, which reflect abnormalities in cardiac impulse formation and propagation, are also determined. However, the analysis of long-term fluctuations in the Holter ECG is largely ignored.

One class of arrhythmias that has recently been the subject of much attention results from the presence of two pacemakers: the normal (sinus) pacemaker and a pacemaker at an ectopic (non-sinus) location. Such rhythms, whose existence has been recognized since the start of this century (Fleming 1912; Kaufmann & Rothberger 1917) are now called parasystolic rhythms. The possibility for interactions between the sinus rhythm and the ectopic rhythm often complicates

interpretation of such rhythms. However, recent workers have made great progress in developing both experimental (Jalife & Moe 1976; Jalife & Michaels 1985) and theoretical (Moe *et al.* 1977; Swenne *et al.* 1981; Ikeda *et al.* 1983) models for parasystole. Interpretation of ECG records has led to the recognition of the importance of parasystolic mechanisms (Jalife *et al.* 1982; Nau *et al.* 1982; Castellanos *et al.* 1984).

Here we consider the interaction between a fixed periodic stimulus and a cardiac oscillator. Such a problem is of interest because it is amenable to experimental and theoretical analysis and because of its relevance to the interpretation of parasystolic rhythms. In §2 we consider the effects of periodic stimulation of spontaneously beating aggregates of cells from embryonic chick heart (Guevara *et al.* 1981; Glass *et al.* 1983, 1984, 1986*b*). Theoretical analysis of this system shows that periodic dynamics are expected at some stimulation frequencies and amplitudes, whereas chaotic dynamics are expected for other stimulation parameters. Experiments are in close agreement with the theory. In §3 we develop a theoretical model for parasystole. The model extends previous theoretical models of parasystole (Moe *et al.* 1977; Swenne *et al.* 1981; Ikeda *et al.* 1983; Glass *et al.* 1986*a*). We describe the bifurcations in the theoretical model and show that chaotic dynamics is expected over some regions of parameter space. In §4 we discuss Holter ECG records from ambulatory patients who display frequent ectopic beats. These records may show extremely irregular dynamics which we discuss in the context of chaotic dynamics and modulated parasystole. Finally, the significance of this approach to the analysis of cardiac dynamics is discussed.

2. Periodic stimulation of a cardiac oscillator

In this section we describe the effects of single and periodic stimulation of an aggregate of spontaneously beating cells from embryonic chick heart. As this work has been described in several recent publications, we briefly summarize the main results and refer the reader elsewhere for more details (Guevara *et al.* 1981; Glass *et al.* 1983; Glass *et al.* 1984; Glass *et al.* 1986*b*; Guevara *et al.* 1986).

Spontaneously beating aggregates of ventricular heart cells are formed by dissociating the ventricles of seven-day embryonic chicks and allowing the cells to reaggregate in tissue culture medium. The resulting aggregates are approximately 100–200 μm in diameter and each beats with its own intrinsic frequency, which lies in a range of about 60–120 times per minute (DeHaan & Fozzard 1975). A glass microelectrode is inserted intracellularly and can be used to inject single and periodic current pulses into the aggregate. In the present context, the electrical stimulator is analogous to the sinus rhythm, and the aggregate is analogous to an ectopic focus. Clearly, this represents a gross oversimplification of the anatomically complex heart, as it in no sense takes into account the spatial heterogeneity of cardiac tissue nor the various feedback mechanisms that act to modulate cardiac activity *in vivo*. Nevertheless, as stimulation parameters are varied, this model system generates a great variety of rhythms that resemble clinically observed arrhythmias. Some of these rhythms are periodic with N cycles of the periodic stimulation for each M cycles of the cardiac oscillation (N:M phase locking).

Other rhythms are aperiodic (figure 1). The dynamics of this system can only be understood by using techniques in nonlinear dynamics. Thus, this model system is useful to fix ideas and to form a foundation for the analysis of more complex situations.

In response to a single pulse of electrical current, the phase of the oscillation is usually reset. The magnitude of the resetting is proportional to the amplitude and the phase of the current pulse. Generally within a few cycles, the rhythm is re-established at the same frequency as before but with a permanent shift of phase. The re-establishment of the same amplitude and frequency of the oscillation following a perturbation, indicates that from a mathematical point of view it should be useful to think of the cardiac oscillation as a stable limit cycle oscillation. A stable limit cycle oscillation represents a periodic solution of a differential equation that is attracting in the limit $t \rightarrow \infty$, for points in the neighbourhood of the cycle.

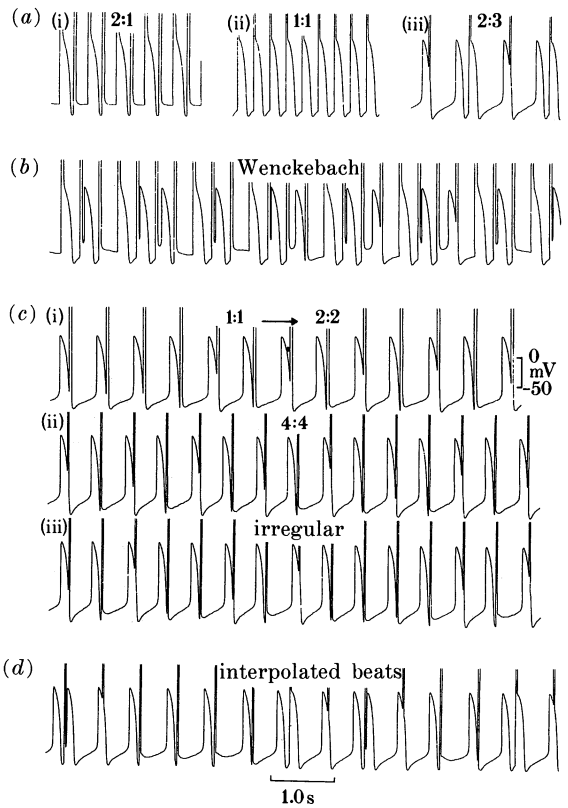

FIGURE 1. Representative transmembrane recordings showing the effects of intracellular periodic stimulation *in vitro* of spontaneously beating embryonic heart cells from chick. The stimulus artifact is observed as a narrow upward deflection. The broader complex is the action potential which corresponds to the contraction of the aggregate. (*a*) Stable phase-locked rhythms; (*b*) rhythms in which the time from the stimulus artifact to the action potential progressively increases until a beat is dropped; this is analogous to the Wenckebach phenomenon in electrocardiology (Pick & Langendorf 1979); (*c*) period-doubling bifurcations and irregular chaotic dynamics; (*d*) irregular rhythm in which there are more action potentials than stimuli. From Guevara *et al.* (1981).

Theoretical analysis of this system is possible by assuming that following a stimulus, the return to the cycle is extremely rapid (figure 2). Thus, if a periodic train of stimuli is delivered to the system with a time interval of T between the stimuli, then the effects of periodic stimulation can be computed from the finite difference equation

$$\phi_{i+1} = g(\phi_i) + \tau \,(\mathrm{mod}\ 1), \tag{1}$$

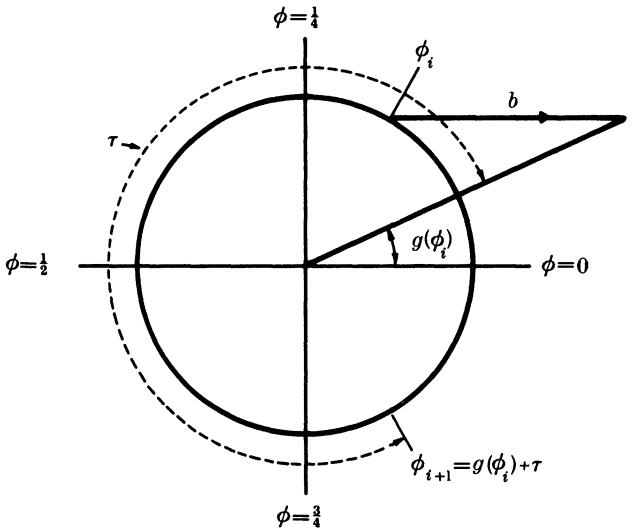

FIGURE 2. A schematic model for the perturbation of a limit cycle oscillation by a periodic stimulus. Provided that the relaxation to the limit cycle following a stimulus is rapid, (1) can be derived.

where ϕ_i is the phase of the ith stimulus and $\tau = T/T_0$, where T_0 is the control cycle length of the aggregate. The function g, called the phase transition curve, depends on the strength of the electrical current and can be measured from the phase resetting resulting from a single stimulus (Perkel *et al.* 1964; Pavlidis 1973; Guevara *et al.* 1981; Glass *et al.* 1983, 1984).

Equation (1) is a finite difference equation and the analysis of bifurcations of such equations is a topic of much current interest. In the present case, the finite difference equation takes a point on the circumference of a circle, ϕ_i, and generates a new point also on the circumference of a circle, ϕ_{i+1} (it is called a circle map). The analysis of circle maps was initiated by Poincaré and major advances in analysing the bifurcations of circle maps were made by Arnol'd (1965) for the case of invertible (for each ϕ_i there is a unique ϕ_{i+1} and vice versa) circle maps. In the practical situations that arise in the experimental system the circle maps are not always invertible and an extension of the theory of invertible circle maps was carried out (Guevara & Glass 1982; Glass *et al.* 1983, 1984; Keener & Glass 1984; Belair & Glass 1985). The analysis of bifurcations of noninvertible circle maps provides a fertile field for mathematical research (for a recent study and references to other work see MacKay & Tresser 1986).

From (1) it is possible to compute the effects of periodic stimulation at any

frequency once g, which is measured experimentally, is determined (figure 3). The following are the main conclusions derived from the experimental and theoretical studies. (i) There is a well-defined ordering of phase-locked rhythms corresponding to theoretical predictions based on the analysis of circle maps; (ii) for some stimulation parameters for which one theoretically computes that there should be

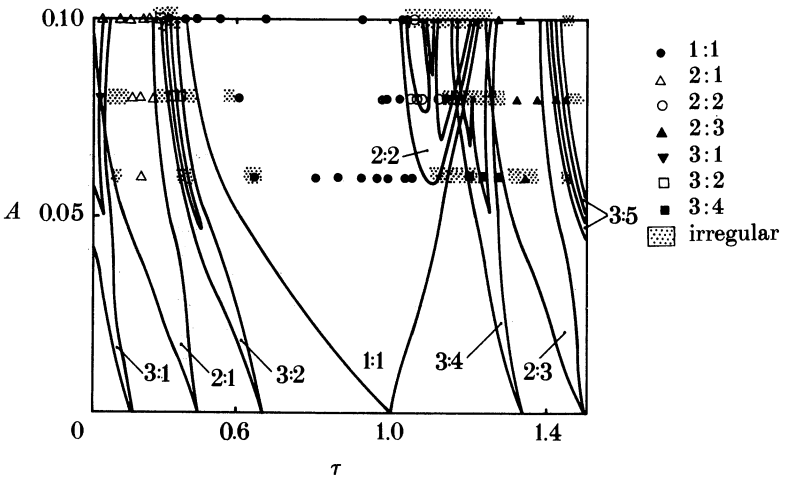

FIGURE 3. Experimentally observed dynamics for periodically stimulated aggregates of chick heart cells superimposed on theoretically computed phase locking zones. The computations use (1) and experimentally measured phase transition curves as described in Glass *et al.* (1984). τ represents the period of the stimuli divided by the period of the oscillations in the aggregates. A is the amplitude of the stimulus in arbitrary units. The circle map in (1) is invertible for $0 < A < 0.039$ and the Arnol'd tongue structure is observed. From Glass *et al.* (1984).

chaotic dynamics, aperiodic dynamics are experimentally observed; (iii) for situations in which the dynamics are believed to be chaotic, if ϕ_{i+1} is plotted as a function of ϕ_i from experimental data then the results are in good agreement with maps calculated based on single pulse phase resetting studies. Thus, our ability to compute theoretically the bifurcations for this system, and the strong agreement between theory and experiment, gives us confidence that the aperiodic dynamics in some regions of parameter space would still be present even if it were possible to eliminate all environmental noise (i.e. the dynamics is chaotic for some parameter values).

3. THEORETICAL MODELS FOR PARASYSTOLE

In parasystole there is competition between the normal sinus pacemaker and a pacemaker which is present at some ectopic (i.e. non-sinus) focus. Although the ectopic focus can be present in either the atria or ventricles, for the current discussion we assume that the ectopic focus is present in the ventricles. The recognition of the possibility of ventricular parasystole dates back at least as far as Fleming (1912) who based his work on the analysis of pulse pressure data. In

the ideal situation the two rhythms have their own set frequencies and there is no phase resetting of the ectopic focus by the sinus rhythm. This 'pure' parasystole has recently been analysed (Glass *et al.* 1986*a*) and we follow the treatment there. It is also possible that the sinus rhythm can act to modulate the ectopic rhythm (Jalife & Moe 1976; Moe *et al.* 1977; Swenne *et al.* 1981; Ikeda *et al.* 1983). For this case of 'modulated' parasystole we follow the basic ideas sketched out in these earlier papers, but try to place the analysis in the context of current studies in nonlinear dynamics and give some new computations. The above formulations assume that parameters remain constant. In realistic situations, the parameters may in fact fluctuate. Accordingly, we consider some effects of parameter fluctuation in the above models.

(*a*) *Pure parasystole*

We assume the mechanism for parasystole considered by Fleming (1912) and Kaufman & Rothberger (1917); figure 4. There is a normal sinus rhythm with period t_s and an ectopic rhythm with a period t_e, where $t_e > t_s$. After each sinus beat there is a refractory period θ. If the ectopic focus generates an impulse during the refractory period it is blocked, but otherwise it will lead to an ectopic beat which can be recognized on the electrocardiogram because of its abnormal morphology. After each ectopic beat, the next sinus beat is assumed to be blocked, resulting in a 'compensatory pause'.

FIGURE 4. Schematic model for pure parasystole. Sinus rhythm (s) and ectopic rhythm (e) are shown. Refractory time is represented as a shaded region. Any ectopic beat that falls outside the refractory time is conducted (filled arrows) and leads to a blocking of the subsequent sinus beat (dashed lines). Ectopic beats falling during the refractory time are blocked (open arrows). In the illustration $\theta/t_s = 0.4$, $t_e/t_s = 1.65$, and there are either 1, 2 or 4 sinus beats between ectopic beats. From Glass *et al.* (1986*a*).

Remarkably, the hypothesized mechanism for pure parasystole is equivalent to a well-studied problem in number theory (Slater 1967) and a very detailed analysis of the dynamics for fixed t_e, t_s and θ can be given (Glass *et al.* 1986*a*). In particular, we have found the following rules for parasystole.

Rule 1. For any ratio of t_e/t_s there are at most three different values for the number of sinus beats between ectopic beats.

Rule 2. One and only one of these values is odd.

Rule 3. For any value of t_e/t_s at which there are three different values for the number of sinus beats between ectopic beats, the sum of the two smaller values is one less than the larger value.

Rule 4. Consider the sequence giving the number of sinus beats between ectopic beats. One and only one of these values can succeed itself.

To illustrate these rules we have numerically computed the sequences giving the number of sinus beats between ectopic beats for fixed parameter values. For any fixed set of parameters call $p(a)$, $p(b)$ and $p(c)$ the probability that there are a, b

or c sinus beats between ectopic beats, where $p(a)+p(b)+p(c) = 1$. In figure 5 we display these probabilities as a function of t_e/t_s for $\theta/t_s = 0.4$. In figure 6 we show the number of sinus beats between ectopic events in the $(t_e/t_s, \theta/t_s)$ plane. The regions that are not labelled contain smaller zones which can be readily determined by using the procedures in Glass *et al.* (1986*a*). Some of the features theoretically

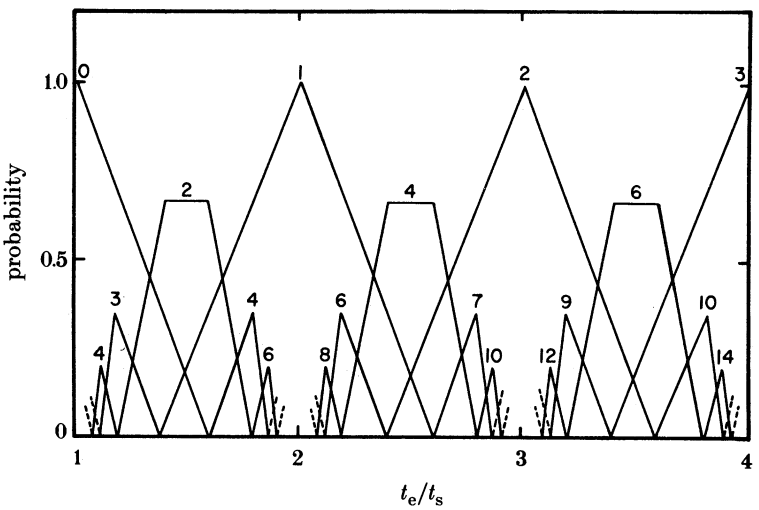

FIGURE 5. Histograms showing relative numbers of sinus beats between ectopic beats for pure parasystole for $\theta/t_s = 0.4$. From Glass *et al.* (1986*a*).

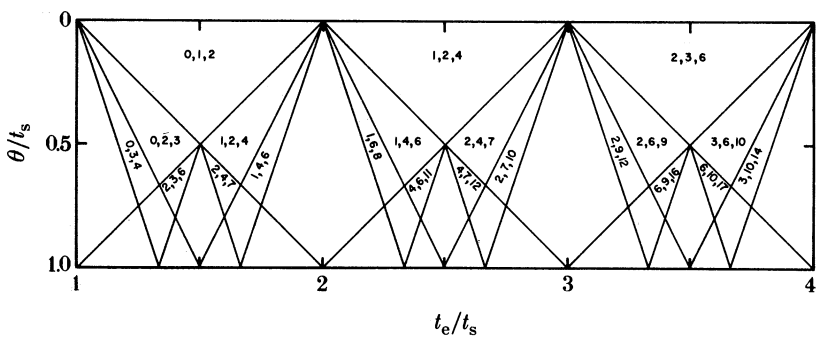

FIGURE 6. Allowed values for the number of sinus beats between ectopic beats for pure parasystole. Allowed values in the unlabelled regions can be determined from the construction described in Glass *et al.* (1986*a*). From Glass *et al.* (1986*a*).

predicted can be found in published reports of parasystolic rhythms. For example Kinoshita (1978, case 7) and Schamroth (1980, case 79) report patients who display either 1, 2 or 4 sinus beats between ectopic beats for parameters that fall in the 1, 2, 4 zones in figure 6 and Lightfoot (1978) describes transitions that arise as the sinus frequency varies that are also consistent with this figure. However, these reports as well as others in the literature, are not consistent with all the four rules above. Deviations from the rules of pure parasystole would be expected if there

was modulation of the ectopic rhythm by the sinus beat, and also if there were fluctuations in the sinus or ectopic rhythms. We now consider the effects of these modifications.

(*b*) *Modulated parasystole*

The theoretical model for modulation of an ectopic ventricular pacemaker by the sinus rhythm developed by Moe *et al.* (1977) is quite close to the theoretical model for the periodically stimulated heart-cell aggregates outlined in §2. The normal sinus pacemaker is analogous to the microelectrode, and the ectopic focus is analogous to the spontaneously beating aggregate of heart cells. However, sinus beats which fall after an ectopic beat are blocked and consequently the sinus beat following an ectopic beat does not act to phase reset the ectopic rhythm. In addition, ectopic beats which fall during the refractory time of the ventricles are not observed (they are concealed).

We assume that the sinus rhythm acts to reset the ectopic focus, and call ϕ_i the phase of the ith sinus beat in the ectopic cycle. Assume that the ith sinus beat acts to phase reset the ectopic cycle. Then we expect that the phase of the next sinus beat will be at the phase $g(\phi_i)+\tau$ where $\tau = t_s/t_e$. However, if $g(\phi_i)+\tau > 1$ and if also $1-g(\phi_i) > \theta/t_e$ then there will be an ectopic beat before the next sinus beat and the next sinus beat will not lead to a phase resetting. From the above, it can be shown that the only sinus beats that do not lead to phase resetting occur in the interval $0 < \phi < \tau-\theta/t_e$. Thus, the finite difference equation for modulated parasystole can be written

$$\left.\begin{aligned} \phi_{i+1} &= \phi_i+\tau, \quad 0 < \phi_i \leqslant \tau-\theta/t_e, \\ \phi_{i+1} &= g(\phi_i)+\tau \,(\mathrm{mod}\ 1), \quad \tau-\theta/t_e < \phi_i \leqslant 1. \end{aligned}\right\} \tag{2}$$

This is equivalent to the formulation by Ikeda *et al.* (1983). For the special situation in which there is no phase resetting of the ectopic cycle $g(\phi) = \phi$, and the model is identical to the model for pure parasystole. If each sinus beat were effective in phase resetting the ectopic rhythm, the model would be identical to the model for periodically stimulated heart cells, except not every action potential of the heart cells would be observed.

It is straightforward to iterate (2) to determine the expected dynamics for a given function g. Such computations have been carried out with a number of different functional forms for g. Because of the compensatory pause, the sinus beat following an ectopic beat does not lead to a phase resetting of the ectopic rhythm and consequently the finite-difference equations for modulated parasystole can display discontinuities (see fig. 3 of Ikeda *et al.* 1983). Further the observation or non-observation of ectopic beats depends sensitively on the refractory time. As a consequence of these technicalities, the mathematical analysis of modulated parasystole presents greater difficulties than the analysis of entrainment of the chick heart cell aggregates or pure parasystole. Despite the difficulties of a general theory some observations can be made. For phase resetting curves measured experimentally, the effects of a stimulus in the immediate aftermath of an action potential are negligible. This is so, for example, for the phase resetting for the chick heart cell aggregates. For such circumstances, there is

expected to be close correspondence between the entrainment zones using either (1) or (2) because $g(\phi) = \phi$, for small values of ϕ. Thus in such circumstances there will be zones of entrainment of the ectopic oscillator similar to the zones of the Arnol'd tongues observed in figure 3 (see fig. 5 of Moe *et al.* 1977). However, whether or not an ectopic beat will be observed is parameter-sensitive. Thus in the 2:1 zone it is possible to observe no ectopic beats, or alternations of sinus and ectopic beats (bigeminy). Similarly, in the 3:1 zone, one can observe either no ectopic beats, or periodic sequences in which two sinus beats are followed by an ectopic beat (trigeminy). Furthermore, because of non-monotonicity of g at some stimulation strengths, the mathematical model for modulated parasystole is also capable of displaying chaos (see also Ikeda *et al.* 1983).

In view of the above considerations, it is not practical to give a complete analysis of the dynamics of modulated parasystole. However, to illustrate some of the properties of modulated parasystole we show results from a simulation using a phase resetting curve obtained from the chick heart cell experiments. The use of such a curve for modelling purposes is justified in view of the similarities between phase resetting behaviour in the chick heart cell aggregates and in clinical data (Jalife *et al.* 1982; Nau *et al.* 1982; Castellanos *et al.* 1984). Such a curve may be more appropriate than the piecewise linear functions used by other workers (Moe *et al.* 1977; Swenne *et al.* 1981; Ikeda *et al.* 1983). The results of the calculations are shown in figure 7. We show the allowed values for the number of sinus beats between ectopic beats. For some parameter values, the allowed values for the

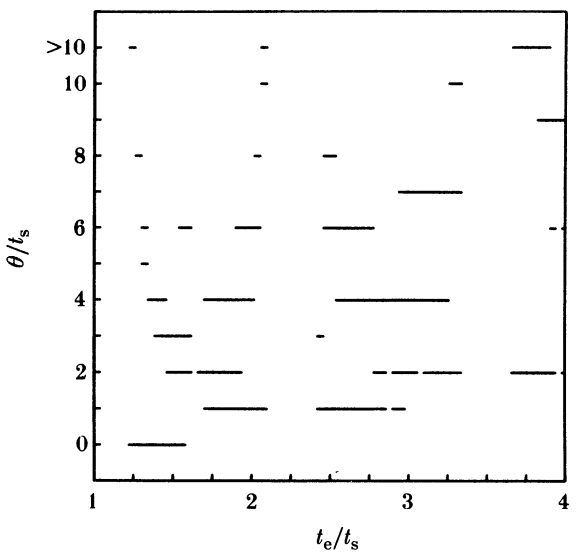

FIGURE 7. Allowed values for the number of sinus beats between ectopic beats for modulated parasystole from (2). Horizontal bars show the range of values of t_e/t_s for which a given value for the number of intervening sinus beats can be found. The narrow gaps in the horizontal bars correspond to stable phase locking zones in which a particular value for the number of intervening sinus beats is not found. A histogram in the same format as figure 5 is not possible because the curves are jagged, where the degree of jaggedness depends on the fineness of the step size of the abscissa. The simulation used the same function as the phase resetting of chick heart cells with $A = 0.02$ and $\theta/t_s = 0.4$.

number of sinus beats between ectopic beats still obey the rules for 'pure' parasystole. However, there are also regions in which there are no ectopic beats observed. This is due to the phase locking of the ectopic oscillator to the sinus oscillator in such a fashion that all the ectopic beats fall in the refractory time following a sinus beat. Curves that give the probabilities for expected numbers of sinus beats between ectopic beats (as in figure 5) are extremely jagged for the parameter values in figure 7. This jaggedness depends on the fineness of the iteration.

The above analysis shows that the theoretical model for modulated parasystole, which has been developed by cardiologists and basic scientists with physiological and clinical data, can be cast as a problem about the bifurcations of circle maps. Because these maps are not necessarily invertible, and can be discontinuous, a challenging set of problems for mathematicians arises.

(*c*) *Variation of parameters*

Until now, we have only considered a few different ways that parameters can vary. The particular sorts of fluctuations that have been considered are motivated by the clinical records that will be discussed in §4, and also by known physiological mechanisms.

Although the sinus rhythm is frequently considered to be regular, all quantitative studies of the sinus rhythm have shown a surprising richness of behaviour with striking variability (Kitney & Rompelman 1980; Kobayashi & Musha 1982; Pomeranz *et al.* 1985; de Boer *et al.* 1985). There is a normal modulation of the sinus frequency with respiration, the so-called respiratory sinus arrhythmia. As well, some studies show fluctuations at a frequency of about 0.1 Hz which are

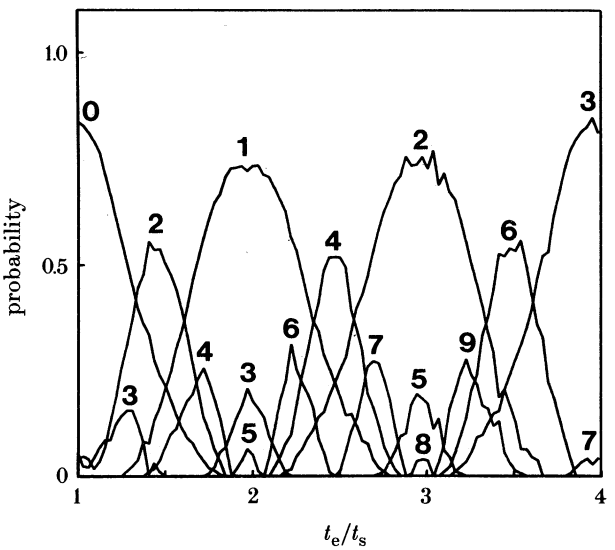

FIGURE 8. Histograms showing the relative number of intervening sinus beats between ectopic beats for pure parasystole with sinusoidal modulation of the sinus frequency. The modulation has a period of 5 t_s and an amplitude of 0.15 t_s with $\theta/t_s = 0.4$.

attributed to instabilities in the baroreceptor reflex (Kitney & Rompelman 1980). To assess the effects of sinus rate modulation we assume a sinusoidal modulation of the sinus rhythm.

We first consider the effects of sinusoidal modulation of the sinus rhythm during pure parasystole. Figure 8 shows the histograms showing the relative number of sinus beats between ectopic events as a function of t_e/t_s. In the region of the ratio, $t_e/t_s = 2$ and $t_e/t_s = 3$ new values not present for pure parasystole are found. In fact, the values for the number of sinus beats between ectopic events falls in the series $2n-1$ in the neighbourhood of the value $t_e/t_s = 2$ (i.e. the values are odd), and in the series $3n-1$ the neighbourhood of $t_e/t_s = 3$, where n is an integer. These rhythms are called concealed bigeminy and trigeminy respectively (Schamroth & Marriott 1963; Schamroth 1985).

Now consider the effects of sinusoidal modulation of the sinus rhythm during modulated parasystole in which the ectopic pacemaker is being reset. We consider an example in which the sinus rate modulation occurs in the 3:1 zone in which there is trigeminy (i.e. 2 sinus beats followed by an ectopic beat repeating periodically). Associated with the modulated sinus rate are shifts in the intervals from the sinus to the ectopic beats (R–X intervals) and the ectopic to the sinus beats (X–R intervals) which parallel the intervals between consecutive sinus beats (R–R intervals), figure 9. The shifts that are found parallel shifts observed in a clinical case of parasystole (see §4).

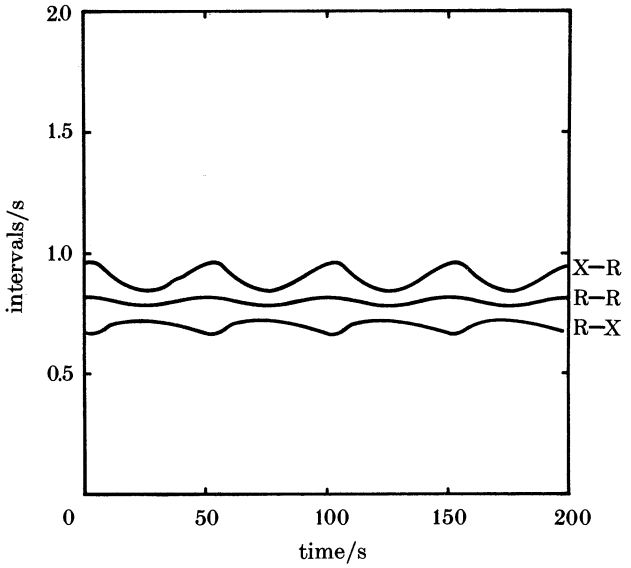

FIGURE 9. Time series showing the effects of sinusoidal modulation of the sinus rhythm in a mathematical model of modulated parasystole, equation (2), during trigeminy in which there are two sinus beats followed by an ectopic beat. The variations of the intervals between sinus beats (R–R), the interval from the sinus beat to the ectopic beat (R–X) and from the ectopic beat to the sinus beat (X–R) are shown. The modulation was assumed to have a period of 50 s and an amplitude of 0.16 s. The same phase resetting curve used for the chick heart cell simulations in figure 3 were used with $A = 0.046$. Other parameters are $t_s = 0.8$ s, $t_s/t_e = 0.265$, $\theta/t_s = 0.4$.

4. Analysis of Holter records

Previous studies of ECG records provide convincing demonstration that the mechanism of modulated parasystole is applicable in at least some circumstances (Jalife *et al.* 1982; Nau *et al.* 1982; Castellanos *et al.* 1984). However, arrhythmias in which there are frequent ventricular ectopic beats are extremely common in clinical practice and it is currently not clear the extent to which modulated parasystole will successfully account for the observed arrhythmias. Furthermore, detailed analysis of arrhythmias over extended periods of time is not generally attempted. We briefly discuss Holter recordings from two patients who display frequent ectopy.

First consider the ECG of an elderly patient who displayed long periods of intermittent ventricular trigeminy (figure 10*a*). This patient also had Cheyne–Stokes ventilation characterized by a regular waxing and waning of ventilation with a period of about 50 s. Holter records from this patient were obtained and digitized, and interbeat time intervals were measured. The time series reveals oscillations of all three component heart rate intervals (R–R, R–X, X–R) at the same frequency as the Cheyne–Stokes cycle (figure 10*b*). These shifts display the same phase relation as the theoretical model of modulated parasystole with slowly oscillating sinus frequency (figure 9). Periodic relations between heart rate,

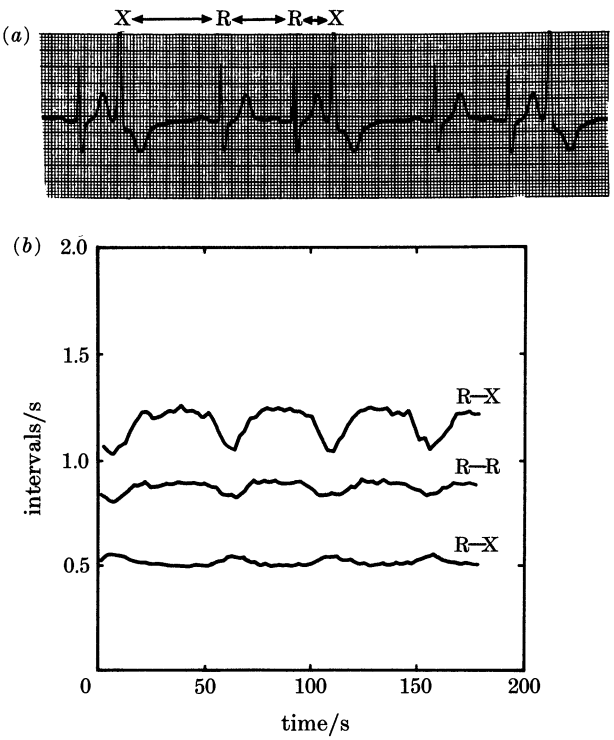

FIGURE 10. (*a*) Ambulatory ECG record of an elderly man with Cheyne–Stokes breathing showing episodes of ventricular trigeminy. (*b*) Time series showing the variation of the R–R, R–X and X–R intervals.

breathing and ventricular ectopy have been previously reported (Findley *et al.* 1984).

A second example is a middle aged patient with frequent ventricular ectopic beats (figure 11*a*). A 30 min record was printed on standard ECG paper at 25 cm s^{-1} and the intervals between the R-waves of sinus beats and ectopic beats were digitized. The number of consecutive sinus beats between ectopic beats fell in the

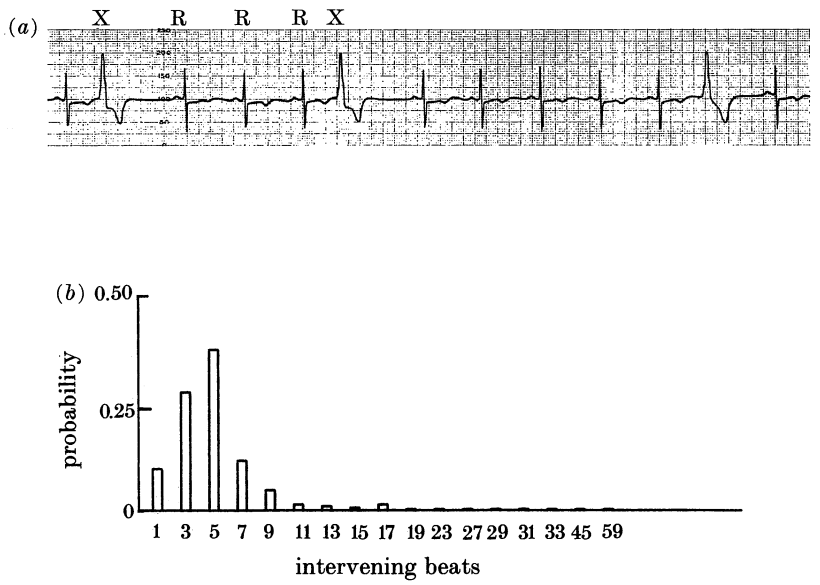

FIGURE 11. (*a*) Ambulatory ECG record of a middle-aged man with frequent ventricular ectopic beats. The number of sinus beats between ectopic beats over a 30 min period was always an odd number. This phenomenon is referred to as concealed bigeminy (Schamroth & Marriott 1963). (*b*) A histogram showing the relative numbers of intervening sinus beats between ectopic beats over a 30 min period.

range between 1 and 59. During this period the patient only displayed an odd number of sinus beats between ectopic events, i.e. there was concealed bigeminy (figure 11*b*). Figure 12 shows the consecutive values for the number of sinus beats between ectopic beats and also the sinus rate over a 30 min period.

A possible mechanism for this record is that there is a broad range of 2:1 entrainment between the sinus rhythm and the ectopic focus, but that some ectopic beats are blocked because of random fluctuation of the refractory time. If there are random fluctuations of the refractory time, then the probability for n sinus beats between ectopic beats decreases geometrically and is given by $p(1-p)^{\frac{1}{2}(n-1)}$, where n is an odd positive integer. However, an interesting feature of this record is that the histogram giving the number of sinus beats between ectopic beats is peaked around the value 5 (figure 11*b*), and this excludes a simple random flucturation of the refractory time.

An alternate hypothesis can be developed based on experimental studies in dogs. An electrical stimulus was delivered to the ventricles following every second

(*a*)

7 , 7 , 7 , 7 , 59 , 7 , 3 , 1 , 27 , 3 , 11 , 7 , 15 , 23 , 5 , 7 , 5 , 33 ,
3 , 7 , 5 , 17 , 7 , 5 , 9 , 5 , 3 , 5 , 3 , 5 , 3 , 3 , 3 , 5 , 5 , 5 ,
5 , 5 , 7 , 3 , 7 , 3 , 1 , 5 , 3 , 3 , 3 , 3 , 5 , 9 , 7 , 5 , 7 , 3 ,
5 , 13 , 7 , 7 , 3 , 9 , 3 , 5 , 1 , 31 , 7 , 1 , 7 , 7 , 45 , 5 , 5 , 5 ,
9 , 5 , 5 , 5 , 7 , 5 , 5 , 3 , 5 , 5 , 1 , 5 , 3 , 5 , 3 , 1 , 7 , 9 ,
5 , 3 , 9 , 3 , 5 , 3 , 5 , 5 , 5 , 3 , 9 , 5 , 3 , 7 , 3 , 9 , 1 , 5 ,
3 , 1 , 5 , 5 , 5 , 1 , 5 , 13 , 5 , 5 , 5 , 5 , 5 , 5 , 3 , 5 , 3 , 1 ,
1 , 7 , 3 , 11 , 5 , 5 , 5 , 3 , 3 , 5 , 3 , 5 , 1 , 5 , 3 , 5 , 1 , 5 ,
1 , 1 , 1 , 1 , 5 , 29 , 5 , 5 , 3 , 3 , 3 , 9 , 9 , 3 , 7 , 7 , 5 , 5 ,
1 , 3 , 7 , 3 , 5 , 11 , 5 , 17 , 7 , 1 , 3 , 3 , 3 , 15 , 1 , 5 , 3 , 5 ,
5 , 5 , 3 , 5 , 3 , 5 , 5 , 3 , 5 , 5 , 3 , 3 , 5 , 1 , 5 , 3 , 3 , 5 ,
5 , 3 , 3 , 3 , 3 , 5 , 5 , 3 , 7 , 3 , 7 , 19 , 9 , 5 , 3 , 11 , 3 , 3 ,
3 , 5 , 3 , 5 , 5 , 5 , 5 , 5 , 5 , 13 , 5 , 5 , 7 , 3 , 3 , 5 , 3 , 9 ,
17 , 3 , 1 , 7 , 9 , 1 , 17 , 5 , 3 , 5 , 3 , 5 , 5 , 3 , 5 , 3 , 1 , 5 ,
1 , 5 , 3 , 5 , 3 , 7 , 3 , 5 , 5 , 1 , 5

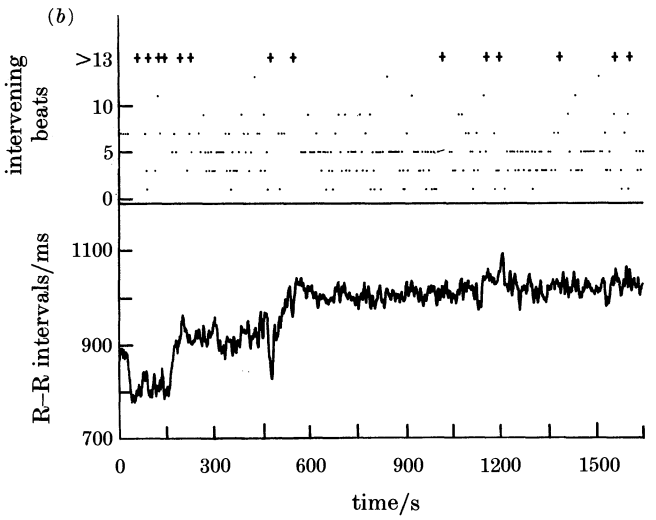

FIGURE 12. (*a*) Sequence of intervening sinus beats between ectopic beats for the patient in figure 11 over a 30 minute period. (*b*) The number of intervening sinus beats (upper) and the average R–R interval (lower) as a function of time. The R–R values represent a five-beat moving average.

sinus beat (Lee *et al.* 1974). It was found that even though the electrical stimulus was delivered at the same phase of the cycle (i.e. at a fixed delay) the effects were not the same; some stimuli were blocked whereas others were not. The interpretation of this finding was that the conduction of one ventricular stimulus increased temporarily the refractory time to subsequent stimuli. Simulations were carried out assuming the mechanism of modulated parasystole with a refractory period of the ventricles which is geometrically decreasing following an ectopic beat. With these assumptions it is possible to approximately reproduce the statistical features of the observed histograms if additional stochastic noise is

added to the refractory time and a conduction delay is assumed. The simulations also showed that at faster sinus rates, an even number for the number of sinus beats between ectopic beats should be observed. In fact, in other portions of the record in which the R–R intervals were 700–800 ms, an even number of sinus beats between ectopic beats were occasionally observed. We hope to present a more complete analysis of this case in a subsequent publication.

From the above discussion it should be clear that a detailed analysis of dynamic data can be used to exclude plausible hypotheses about the underlying physiological mechanisms of these arrhythmias. However, it is extremely difficult to establish unambiguously the mechanism for the arrhythmias. Alternative hypotheses for these rhythms may also be consistent with the observed dynamics.

5. Discussion

Simple biological and mathematical models of the intact heart display some features that can be found in clinically observed cardiac arrhythmias. This observation has implications both for basic science as well as clinical cardiology.

The simple model systems considered here are extreme caricatures of the anatomically and electrophysiologically complex human heart. A more complete mathematical model of the human heart must necessarily be formulated as nonlinear partial differential equations. We expect that the bifurcations and dynamics in these more realistic models should bear striking similarities to the bifurcations observed here.

Although we expect that the parasystolic mechanisms considered here are important in the generation of ventricular ectopy, other mechanisms such as reentry (Lee *et al.* 1974; Pick & Langendorf 1979) and delayed after depolarizations (Ferrier 1977; Wit *et al.* 1980) are also believed to be important. Consequently, it is likely that ventricular ectopic beats in any given individual may be due to one (or more) of several different mechanisms. Differential diagnosis of plausible mechanisms is difficult. Conventional analyses of ECGs that are now done, do not take into account the long-term fluctuations such as those presented in figure 12. An intriguing possibility is that nonlinear dynamics may eventually be useful in helping in diagnosing the mechanism and guiding the therapy of complex arrhythmias.

The human heartbeat shows striking fluctuations in rate during normal sinus rhythm and also during various arrhythmias. Although in some instances the fluctuations may be easy to characterize, more typically the dynamics are rich and highly complex. As an example, the sequences of the numbers of sinus beats between ectopic beats at first sight appear 'random' but contain regularities that reflect the underlying physiological mechanisms. The relative roles of 'stochastic noise' and 'deterministic chaos' in generating normal rhythms and arrhythmias are not clear. A full understanding will only be achieved from the integration of nonlinear mathematics with experimental physiology and clinical cardiology.

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