AIP | Chaos
An Interdisciplinary Journal of Nonlinear Science
25TH ANNIVERSARY

Cardiac arrhythmias and circle maps−A classical problem

Leon Glass

Citation: Chaos **1**, 13 (1991); doi: 10.1063/1.165810
View online: http://dx.doi.org/10.1063/1.165810
View Table of Contents: http://scitation.aip.org/content/aip/journal/chaos/1/1?ver=pdfcov
Published by the AIP Publishing

Cardiac arrhythmias and circle maps—A classical problem

Leon Glass
Department of Physiology, McGill University, 3655 Drummond Street, Montréal, Québec H3G 1Y6, Canada

(Received 8 January 1991; accepted for publication 12 April 1991)

The periodic forcing of nonlinear oscillations can often be cast as a problem involving self-maps of the circle. Consideration of the effects of changes in the frequency and amplitude of the periodic forcing leads to a problem involving the bifurcations of circle maps in a two-dimensional parameter space. The global bifurcations in this two-dimensional parameter space is described for periodic forcing of several simple theoretical models of nonlinear oscillations. As was originally recognized by Arnold, one motivation for the formulation of these models is their connection with theoretical models of cardiac arrhythmias originating from the competition and interaction between two pacemakers for the control of the heart.

Q: What was Kolmogorov like as a supervisor?
A: ...He stood out from other professors I met by his complete respect for the personality of the student. I remember only one case when he interfered with my work: in 1959, he asked me to omit from the paper on self-maps of the circle the section on applications to heartbeats, adding: "That is not one of the classical problems one ought to work on." The application to the theory of heartbeats was published by L. Glass 25 years later, while I had to concentrate my efforts on the celestial-mechanical applications of the same theory.[1]

I was taken aback when I read this comment that appeared in a 1987 interview with V. I. Arnold. I had no idea that Arnold had considered applications of circle maps to the study of hearts. And it seemed possible that much of the work done by our group at McGill over the preceding decade may have been carried out much earlier by Arnold, but not published.

In the Spring of 1990, Arnold sent me a short article of his that appeared in the collected papers of I. M. Gel'fand published in 1989.[2] This article, which is the preceding article in this issue, contained excerpts from Arnold's 1959 diploma dissertation that were omitted in the published version of this work.[3] Although I have never examined the 1959 dissertation, I assume that the 1989 article summarizes the main earlier findings.

In the following I first present several mathematical concepts useful to discuss circle maps and then provide a brief overview of the various theoretical models involving circle maps that have been applied to the theory of cardiac arrhythmias. There is now a good deal of experimental support for some of these theoretical formulations, and we are beginning to understand where they break down.

I. MATHEMATICAL BACKGROUND

A circle map f is a function that maps the circumference of a circle onto itself. Circle maps arise naturally in the periodic forcing of oscillators, and in the discussion that follows, I assume that this is their origin. Some cardiac arrhythmias are due to competition and interaction between two spontaneous cardiac pacemakers; thus circle maps may be an appropriate mathematical model. This section gives an informal introduction to the mathematics of circle maps. More detailed discussions can be found in standard texts.[4,5]

Let us assume that the periodic forcing function has a period T and that the forced oscillator has some easily identifiable marker event, which we call the "firing." Say that the forced oscillator fires at the sequence of times $t_0,t_1,t_2,\ldots$. Each of these firing times can be associated with a phase of the forcing oscillator by $\phi_i = t_i(\text{mod } T)$. Here, phase is normalized to lie between 0 and 1. If the time of one firing is a function only of the time of the immediately preceding firing, i.e., $\phi_i=f(\phi_{i-1})$, then f is a circle map. In general $f(0)=f(1)$.

A circle map f can either be continuous or discontinuous. In the event that f is continuous, it can be classified by its topological degree. This gives the number of times f winds around the circle, as ϕ winds around the circle once. Thus $f(\phi)=0.5$ has degree 0, $f(\phi)=0.5+\phi$ (mod 1) has degree 1, and $f(\phi)=0.5+2\phi$ (mod 1) has degree 2. Circle maps of degree 1 are either 1:1 invertible, or noninvertible. Several different types of circle map are schematically depicted in Fig. 1.

Iteration of the circle map f leads to a sequence of phases, $\phi_1,\phi_1,\phi_2,\ldots$. If this sequence is periodic, then there is phase locking between the two rhythms. This means that the frequencies of the two oscillators are rationally related with periodic phases of firing. Aperiodic sequences of phases can also occur under iteration of circle maps. This can occur in two different ways. If starting from two initial phases near each other, subsequent iterates remain near to each other, then the dynamics are called quasiperiodic. If on the other hand two initial phases near each other diverge under subsequent iterations, there is sensitivity to initial conditions and the dynamics are chaotic. Quasiperiodicity is only found in degree 1 invertible maps, and chaos is only found in noninvertible circle maps. For noninvertible maps, two different initial conditions can sometimes lead to different asymptotic behaviors in time, i.e., there is

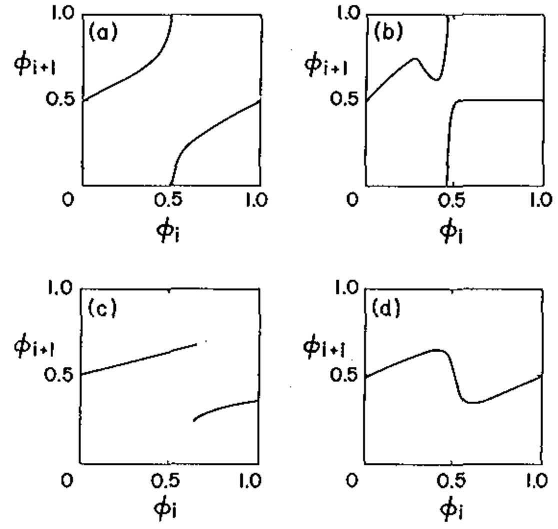

FIG. 1. Different types of circle maps (a) 1:1 invertible, degree 1; (b) noninvertible, degree 1; (c) discontinuous, piecewise increasing; (d) degree 0.

bistability. For example, in a single map there can asymptotically be both periodic dynamics and chaotic dynamics depending on the initial condition.

An additional mathematical concept needed to discuss circle maps is the rotation number. Loosely, this corresponds to the average number of firings of the forced oscillator for each cycle of the forcing cycle. Thus for 2:1 (stimulus frequency: driven oscillator frequency) phase locking, the rotation number is 1/2. Phase locked rhythms always have a rational rotation number, and quasiperiodic rhythms always have an irrational rotation number. Chaotic dynamics can either have a rational or irrational rotation number.

These concepts are all needed to consider the problem of the global organization of the different zones of dynamic behavior as a function of the frequency and amplitude of periodic stimulation of a nonlinear oscillator. Arnold showed that for periodic forcing described by 1:1 invertible circle maps, the phase locking zones have the structure

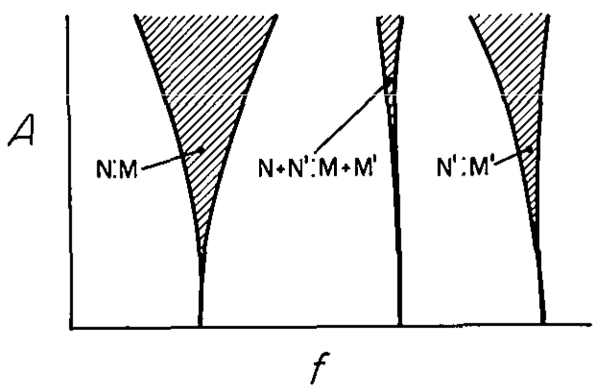

FIG. 2. The classic Arnold tongue structure for phase locking zones of periodically forced nonlinear oscillators in two-dimensional parameter space. The amplitude of the forcing is A and the frequency is f.

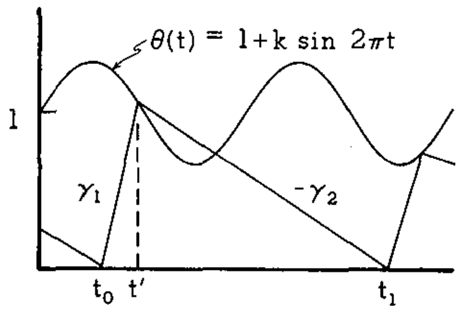

FIG. 3. Diagram of the integrate and fire model. An activity rises to an oscillatory threshold with slope γ_1 and descends toward 0 with slope $-\gamma_2$, generating a sequence of times $t_0, t_1, t_2, \ldots$, when the activity equals 0. Adapted from Ref. 9.

schematically shown in Fig. 2.[3] In any given shaded region, now called an Arnold tongue, all initial conditions lead to the same phase locked rhythm, say $N{:}M$ (stimulus frequency: driven oscillator frequency), where N and M have no common divisors. Between any two Arnold tongues corresponding to $N{:}M$ and $N'{:}M'$ phase locking, there is another Arnold tongue corresponding to $(N+N'){:}(M+M')$ phase locking. As the frequency of the stimulation changes, the rotation number is a continuous function that is piecewise constant inside the Arnold tongues. The organization in Fig. 2, which I call the classic Arnold tongue picture, is the usual behavior for low amplitudes of stimulation in the simple theoretical models I consider here. However, as the amplitude of the periodic forcing increases, this structure breaks down in a number of different ways.

II. THE INTEGRATE AND FIRE MODEL

A useful idealization of some periodically forced oscillators is the Gel'fand and Tsetlin model,[6] also called the integrate and fire model.[7–10] As shown in Fig. 3, a quantity that we call the "activity" rises linearly with slope γ_1 to an oscillating threshold given by $\theta(t) = 1 + k\sin(2\pi t)$ until it reaches the threshold, at time t'. Then the activity falls linearly with slope $-\gamma_2$ to the baseline. This "sawtooth motion" of the activity defines one time-dependent motion; the periodic oscillation of the threshold defines another. The problem is to describe the resulting dynamics as a function of the parameters of the model.

From Fig. 3 we see that the linear portion rise of the activity from t_0 to t' is given by

$$f_1(t) = \gamma_1(t - t_0), \quad t_0 \leqslant t \leqslant t', \tag{1}$$

whereas the linear fall from t' to t_1 is given by

$$f_2(t) = -\gamma_2(t - t_1), \quad t' \leqslant t \leqslant t_1. \tag{2}$$

It follows directly from Fig. 3, that at $t = t'$,

$$\theta(t') = 1 + k\sin(2\pi t') = \gamma_1(t' - t_0) = \gamma_2(t_1 - t'). \tag{3}$$

From (3) it follows that

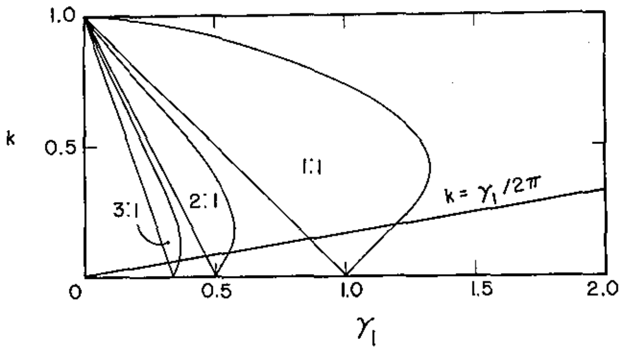

FIG. 4. The parameter plane showing dynamics when $\gamma_2=\infty$ in Fig. 3. Below the solid line the map for the dynamics is invertible. The labels give the ratio between the number of cycles of the sine wave:number of cycles of the sawtooth in each repeating sequence. The region below the solid line corresponds to the classic Arnold tongue structure. All Arnold tongues continue smoothly above the solid line. Independent presentation of these results are found in Refs. 2, 7, and 12. Adapted from Ref. 9, based on computations in Ref. 7.

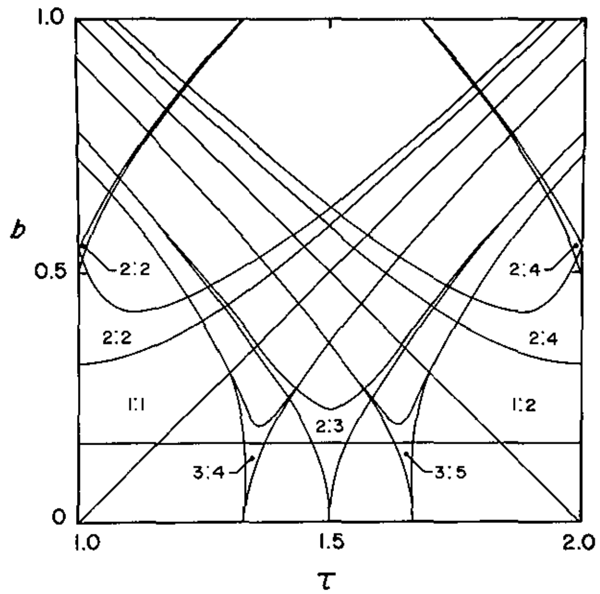

FIG. 5. The parameter plane showing the dynamics in Eq. (7). This can be derived from the integrate and fire model when $\gamma_1=\infty$ (see text and Ref. 14). The labels give the ratio between the number of cycles of the sawtooth:number of cycles of the sine wave in each repeating sequence. The region below the solid line corresponds to the classic Arnold tongue structure, Refs. 2–4. Above the line there are complex bifurcations and chaotic dynamics first described in Refs. 14 and 15. Adapted from Ref. 14.

$$t_1=t_0+\frac{1}{\gamma_1}+\frac{1}{\gamma_2}+k\left(\frac{1}{\gamma_1}+\frac{1}{\gamma_2}\right)\sin 2\pi t', \tag{4}$$

where

$$t'=(\gamma_1 t_0+\gamma_2 t_1)/(\gamma_1+\gamma_2). \tag{5}$$

Equations (4) and (5) therefore provide an implicit equation relating t_1 and t_0. Consequently, given any t_0, the subsequent iterates $t_1, t_2,...$ can be determined. From the discussion in Sec. I, we take $\phi_i=t_i$ (mod 1), and thus the process defines a circle map.

It is useful to study various limits of the integrate and fire model. In Fig. 4 we show the phase locking regions in the limiting case $\gamma_2\to\infty$. Equations (4) and (5) can be written

$$\phi_{i+1}=\phi_i+1/\gamma_1+(k/\gamma_1)\sin(2\pi\phi_{i+1}) \quad (\mathrm{mod}\ 1). \tag{6}$$

Below the dotted line given by $k=\gamma_1/2\pi$ the maps are invertible and the classic Arnold tongue picture is found. Above the dotted lines the maps are discontinuous, similar to that shown in Fig. 1(c), and the bifurcations in this case have been described by Keener.[11] The Arnold tongues continue, without being destroyed, and without further complex bifurcations. However, the irrational rotation numbers occur on a set of measure 0, whereas they occur on a set of positive measure for the 1:1 invertible maps. It is curious that the results in Fig. 4 have apparently been discovered independently at least three times: by Builder and Roberts in 1939,[12] by Arnold in 1959,[2] and by Mackey and myself in 1979.[7]

The situation is different in the limit $\gamma_1\to\infty$. In this case, the integrate and fire model can be given as

$$\phi_{i+1}=t_i+\tau+b\sin 2\pi\phi_i \quad (\mathrm{mod}\ 1), \tag{7}$$

where $\tau=1/\gamma_2$ and $b=k/\gamma_2$. This situation was considered carefully by Arnold[3] and is sometimes called the "sine circle map." The dynamics in the (τ,b) parameter plane are shown in Fig. 5. The map is invertible in the region below the solid line and we once again observe the classic Arnold tongue picture. For parameter values above this line, there are two critical points in the right-hand side of Eq. (7), and complex bifurcations and chaos. The observation of "stochastical" dynamics in this map was made by Zaslavsky in 1978,[13] but the first results on the detailed bifurcations in the noninvertible region came later.[14,15] The dynamics in Eq. (7) continue to be the subject of intensive study.[16–21].

Under continuous changes of γ_1 and γ_2, Fig. 4 transforms into Fig. 5, but it is not yet clear how this comes about. Bélair and I examined an intermediate case for which $\gamma_1=\gamma_2$.[9]

Other functions in addition to the sinusoidal function have been considered for the threshold in Fig. 3. Arnold[2] reports results for periodic functions consisting of delta function spikes, rectangular pulses, and triangular pulses, partially anticipating subsequent studies.[22,23]

Arnold[2] discusses briefly the application of the maps obtained from these models to study Wenckebach cardiac arrhythmias in which some impulses are blocked in their passage through the atrioventricular (AV) node, leading to rhythms in which the atria and ventricles set up complex rhythms, e.g., 4:3 AV block. Subsequent workers have established that piecewise monotonic, discontinuous maps similar to those found in this model, Fig. 1(c), arise in theoretical models of the coupling between the atria and ventricles in AV block.[24,25] Such maps can be experimentally measured and can be used to make predictions concerning complex rhythms observed in humans.[26]

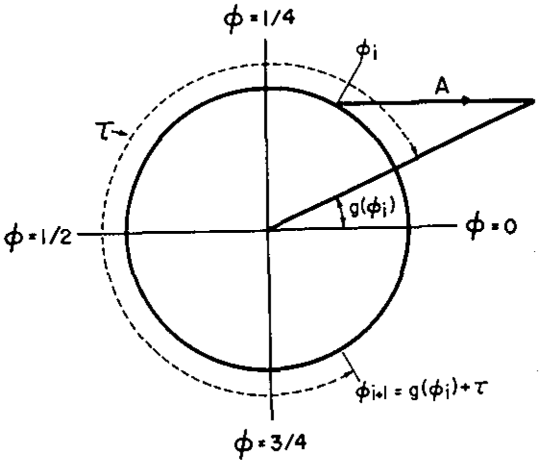

FIG. 6. Diagram showing the perturbation of the Poincaré oscillator with a periodic delta function stimulus delivered with a period τ. Each stimulus induces a horizontal translation A. The dynamics are given by Eqs. (8) and (9). Adapted from Ref. 36.

III. PERIODIC FORCING OF LIMIT CYCLE OSCILLATIONS

Cardiac electrophysiologists usually assume that nonlinear ordinary differential equations containing stable limit cycle oscillations represent an appropriate model for the generation of periodic activity in the heart.[27–30] I now consider the effects of delta function stimuli on a limit cycle oscillation. The simplest such model, which I call the Poincaré oscillator, is illustrated in Fig. 6. There is a stable limit cycle attractor that is a circular trajectory.[10,13,30] The periodic stimulation consists of delta function stimuli delivered with a period τ. Each stimulus leads to a horizontal shift of magnitude A followed by an immediate relaxation to the limit cycle along a radius of the circle. The net result is a phase resetting of the oscillation. Call ϕ_i the phase of the Poincaré oscillator just before the ith stimulus. Then

$$\phi_{i+1}=f(\phi_i)=g(\phi_i,A)+\tau \pmod 1, \tag{8}$$

where $g(\phi)$ is readily calculated[30–32] and is given by

$$\cos[2\pi g(\phi,A)]=\frac{A+\cos 2\pi\phi}{(1+2A\cos 2\pi\phi+A^2)^{1/2}} \tag{9}$$

and τ represents the time between the stimuli relative to the intrinsic cycle length of the oscillation.

This theoretical model for periodically stimulated limit cycles has also been proposed independently by several investigators,[13,31–35] but as far as I can tell, not by Arnold. For low-amplitude stimuli ($A \leqslant 1$) the topology of the entrainment zones is as before, the classic Arnold tongue structure. However, for higher amplitude stimuli ($A > 1$) the dynamics are described by a circle map of topological degree 0, and the continuation of the Arnold tongues is complex, Fig. 7. Except for the 1:N tongues, the tongues bend over and are annihilated at the $A=1$ boundary. Moreover, there are complex bifurcations that lead to period doubling and chaos.

This model, although differing from accurate electrophysiological models, reproduces surprisingly well many of the features observed in experimental studies of periodically stimulated aggregates of chick heart cells.[36,37] For example, we observed period doubling bifurcations and chaotic dynamics for stimulation of heart cell aggregates at frequencies slightly slower than the intrinsic frequency at a moderate stimulus amplitude, and this behavior is also observed in the Poincaré oscillator.[31–34]

The periodic forcing of limit cycles has a direct application to the study of an arrhythmia found in humans, called ventricular parasystole. An abnormal (ectopic) pacemaker located in the ventricles can beat spontaneously and compete with the normal (sinus) rhythm. The sinus rhythm can phase reset the ectopic rhythm.[38,39] If the ectopic beat falls outside of the refractory period of the ventricles, the ectopic beat is observed, and the next sinus beat is blocked, Fig. 8. This model can be used to make predic-

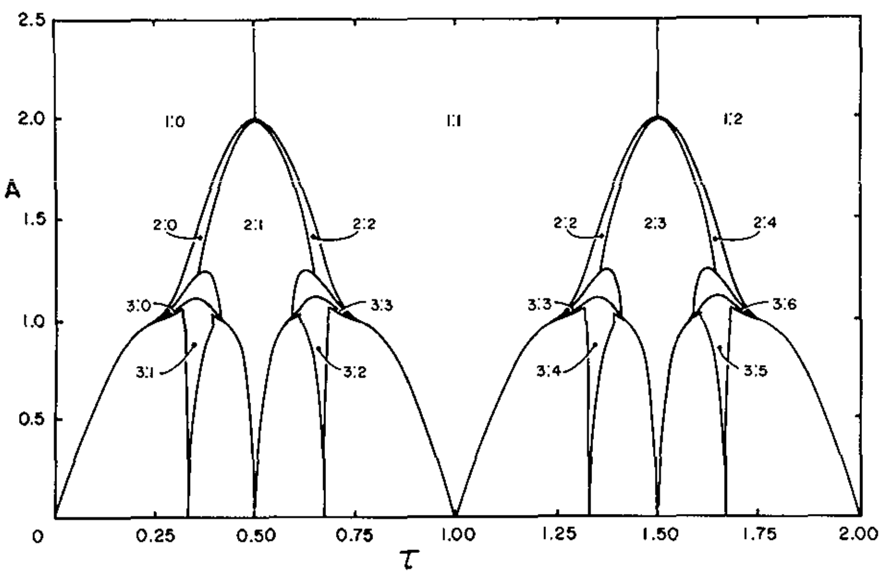

FIG. 7. The parameter plane showing the dynamics in the periodically stimulated Poincaré oscillator. Below $A = 1$ the dynamics are described by an invertible circle map and the topology of the phase locking zones corresponds to the classic Arnold tongue structure. Above $A = 1$, there are complex bifurcations and chaotic dynamics over a medium range of values of A. Adapted from Ref. 36, based on computations in Refs. 31 and 33.

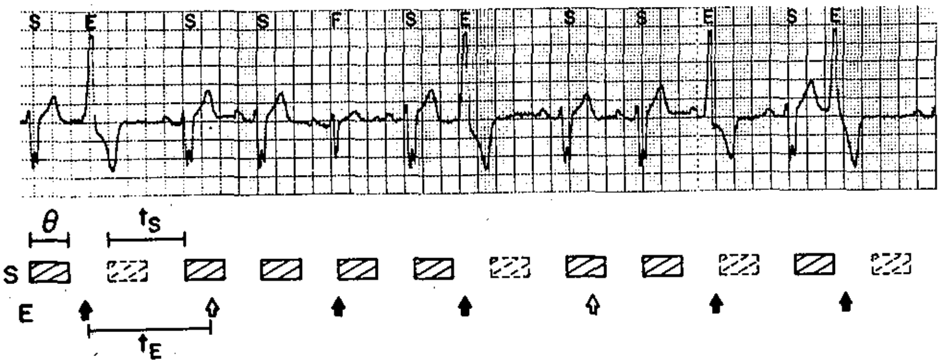

FIG. 8. Electrocardiographic trace and schematic picture of the model for parasystole. Sinus beats are labeled S and ectopic beats are labeled E. Simultaneous timing of the sinus and ectopic beats leads to a fusion beat of different morphology labeled F. Ectopic beats that fall during the refractory period of the sinus beat θ are not observed. Ectopic beats that fall outside this period are observed, but the following sinus beat is blocked. The sinus and ectopic periods are t_S and t_E, respectively. Adapted from Ref. 44.

tions concerning the sequences of sinus and ectopic beats in patients with ventricular parasystole.[38-44]

In the limit of very weak phase resetting, these predictions have a curious number theoretic flavor.[41-44] Consider the sequence of integers representing the number of sinus beats between ectopic beats. In this sequence there are at most three numbers, one and only one is odd, and the sum of the two smallest is one less than the largest. Analytical computation of the various triplets of allowed values is possible in the limit of no phase resetting of the ectopic pacemaker by the sinus rhythm,[41] Fig. 9. Remarkably, Figs. 7 and 8 from Arnold[2] play a role in the derivation of the boundaries of the zones, even though the model is superficially different from that considered by Arnold. An interesting sidelight is that the mathematical theory of parasystole is tied to a classical problem in number theory called the "gap" problem.[45]

IV. BREAKDOWN OF THE CIRCLE MAP APPROXIMATION

In recent experimental studies, we have been evaluating circumstances in which the simple approximations considered above are no longer applicable.[46,47] These approximations break down because the periodic forcing changes the intrinsic properties of the oscillator. To develop a theoretical understanding of the resulting rhythms, it is necessary to study in some detail the kinetics of changes in the parameters describing the models. The basic theoretical notion is that as a result of stimulation there can be slow progressive but transient changes in some of the parameters of the model. For example, it is well known that rapid stimulation of cardiac oscillators may lead to a progressive slowing of the intrinsic frequency—a phenomenon called overdrive suppression.[48] Consequently, when computing the phase of a given stimulus it is necessary to take into account the current value of the intrinsic cycle length. The simplest sorts of approximations of these processes lead to two-dimensional annulus maps. Although simulations show correspondence between theory and experiment, a detailed study of the bifurcations in these systems has not yet been attempted.

V. CONCLUSIONS

Bifurcations in mathematical models of the activity of the heart have been considered in a two-dimensional parameter space where the axes usually correspond to the amplitude and relative frequency of the periodic forcing of an intrinsic cardiac rhythm. At low stimulation amplitudes, all the models share a similar topology corresponding to the classic Arnold tongue structure. At higher amplitudes, this structure breaks down in many different ways. *Thus there is not a universal global organization of the phase locking zones in the different models.* Further study is needed to classify the various topologies that can arise

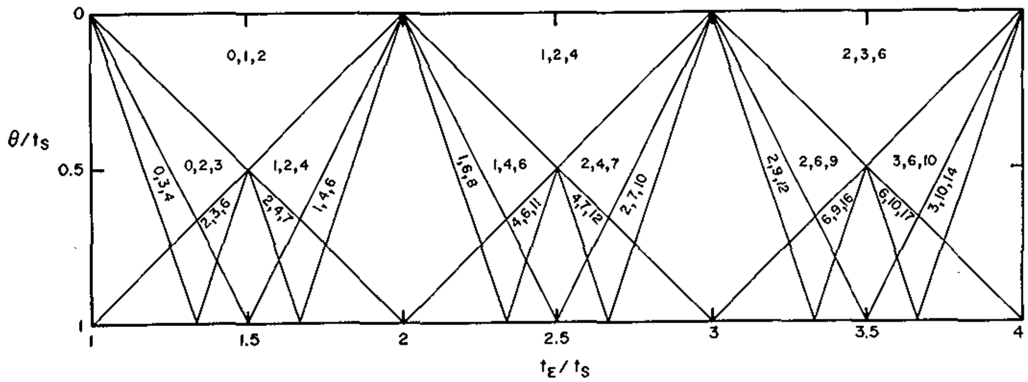

FIG. 9. Parameter plane showing the numbers of sinus beats between ectopic beats during pure parasystole when there is no resetting of the ectopic pacemaker by the sinus rhythm. Adapted from Ref. 41.

from periodic stimulation of nonlinear oscillators. Many of the complex phenomena observed in the simple theoretical models are also observed in experimental systems, and even in the intact human heart. However, recent experimental studies show the necessity of extending the circle map approximation to account for time-dependent changes in parameters during stimulation.

The study of circle map models pioneered by Arnold is but one of the important connections between mathematics and cardiac arrhythmias that have been exploited in this century. In 1928, Van der Pol and Van der Mark studied the periodic forcing of limit cycles as a model for the heart.[49] This work helped motivate the formulation of the integrate and fire models and also influenced (at least indirectly) Smale in his subsequent analysis of horseshoe maps.[50] Studies of wave propagation in excitable media by Wiener and Rosenblueth[51] have had a deep impact on current theoretical and experimental work on life-threatening cardiac arrhythmias.[52–54]

It is now more than 30 years since Arnold was asked to omit his work on heartbeats from his diploma dissertation. This is enough time so that we can now redefine the study of circle maps and cardiac arrhythmias as a "classical" problem. These problems have relevance to human health, and there remain a number of intriguing and difficult problems to study.

ACKNOWLEDGMENTS

The results from our group represent collaborative efforts between many individuals. Contributions to the work reported here have been made by Michael C. Mackey, Michael R. Guevara, Alvin Shrier, Rafael Perez, James P. Keener, and Jacques Bélair. David Campbell made helpful suggestions concerning the presentation in Sec. II. Thanks to the Québec Heart and Stroke Foundation and the Natural Sciences Engineering and Research Council of Canada for financial support.

[1] S. Zdravkovska, "Conversation with Vladimir Igorevich Arnol'd," Math. Intell. **9** (4), 28–32 (1987).

[2] V. I. Arnold, "Cardiac arrhythmias and circle mappings," in *Izrail M. Gelfand: Collected Papers*, edited by S. G. Gindikin, V. W. Guillemin, A. A. Kirilov, B. Kostant, and S. Sternberg (Springer-Verlag, Berlin, 1989), Vol. III. Reprinted in Chaos **1**, 20–24 (1991).

[3] V. I. Arnold, "Small denominators. I. Mappings of the circumference onto itself," Am. Math. Soc. Transl. Ser. 2 **46**, 213–284 (1965).

[4] V. I. Arnold, *Geometrical Methods in the Theory of Ordinary Differential Equations* (Springer-Verlag, New York, 1983).

[5] J. Guckenheimer and P. Holmes, *Nonlinear Oscillations, Dynamical Systems and Bifurcations of Vector Fields* (Springer-Verlag, New York, 1983).

[6] I. M. Gel'fand and M. L. Tsetlin, I have been unable to locate the original article as it is not directly cited in Ref. 2: *Models of the Structural-Functional Organization of Certain Biological Systems*, edited by I. M. Gel'fand, V. S. Gurfinkel, S. V. Fomin, and M. L. Tsetlin (MIT, Cambridge, 1971) (translated from Russian) contains an article by M. B. Berkinblit that refers (p. 161) to a model by Gel'fand and Tsetlin (1958) that seems to be the same as Arnold describes without giving a definite citation.

[7] L. Glass and M. C. Mackey, "A simple model for phase locking of biological oscillations," J. Math. Biol. **6**, 207–223 (1979).

[8] J. P. Keener, F. C. Hoppensteadt, and J. Rinzel, "Integrate and fire models of nerve membranes response to oscillatory inputs," SIAM J. Appl. Math. **41**, 503–517 (1981).

[9] L. Glass and J. Bélair, Continuation of Arnold tongues in mathematical models of periodically forced biological oscillations," in *Nonlinear Oscillations in Biology and Chemistry,* Lecture Notes in Biomathematics, Vol. 66, edited by H. G. Othmer (Springer-Verlag, Berlin, 1986), pp. 232–243.

[10] L. Glass and M. C. Mackey, *From Clocks to Chaos: The Rhythms of Life* (Princeton U.P., Princeton, NJ, 1988). This is being translated into Russian and will be published by MIR.

[11] J. P. Keener, "Chaotic behavior in piecewise continuous difference equations," Trans. Am. Math. Soc. **261**, 589–604 (1980).

[12] G. Builder and N. F. Roberts, "The synchronisation of a simple relaxation oscillation," Australas. Wireless Assoc. Tech. Rev. **4**, 165–180 (1939). This paper was pointed out to me by Tracy T. Allen, subsequent to the publication of Ref. 7.

[13] G. M. Zaslavsky, "The simplest case of a strange attractor," Phys. Lett. A **69**, 145–147 (1978).

[14] R. Perez and L. Glass, "Bistability, period doubling bifurcations and chaos in a periodically forced oscillator," Phys. Lett. A **90**, 441–443 (1982).

[15] L. Glass and R. Perez, "The fine structure of phase locking," Phys. Rev. Lett. **48**, 1772–1775 (1982).

[16] M. J. Feigenbaum, L. P. Kadanoff, and S. Shenker, "Quasiperiodicity in dissipative systems: A renormalization group analysis," Physica D **5**, 370–386 (1982).

[17] S. Ostlund, D. Rand, J. Sethna, and E. Siggia, "Universal properties of the transition from quasi-periodicity to chaos in dissipative systems," Physica D **8**, 303–342 (1983).

[18] M. Schell, S. Fraser, and R. Kapral, "Subharmonic bifurcation in the sine map: An infinite hierarchy of cusp bistabilities," Phys. Rev. A **28**, 373–378 (1983).

[19] J. Bélair and L. Glass, Universality and self-similarity in the bifurcations of circle maps," Physica D **16**, 143–154 (1985).

[20] R. Mackay and C. Tresser, "Transition to topological chaos for circle maps," Physica D **19**, 206–237 (1986).

[21] W.-Z. Zeng and L. Glass, "Symbolic dynamics and skeletons of circle maps," Physica D **40**, 218–234 (1989).

[22] T. T. Allen, "On the arithmetic of phase locking: Coupled oscillators as a lattice on R^2," Physica D **6**, 305–321 (1983).

[23] J. Bélair, "Periodic pulsatile stimulation of a nonlinear oscillator," J. Math. Biol. **24**, 217–232 (1986).

[24] J. P. Keener, "On cardiac arrhythmias: AV conduction block," J. Math. Biol. **12**, 215–225 (1981).

[25] L. Glass, M. R. Guevara, and A. Shrier, "Universal bifurcations and the classification of cardiac arrhythmias," Ann. (NY) Acad. Sci. **504**, 168–178 (1987).

[26] A. Shrier, H. Dubarsky, M. Rosengarten, M. R. Guevara, S. Nattel, and L. Glass, "Prediction of atrioventricular conduction rhythms in humans using the atrioventricular nodal recovery curve," Circulation **76**, 1196–1205 (1987).

[27] R. E. McAllister, D. Noble, and R. W. Tsien, "Reconstruction of the electrical activity of cardiac Purkinje fibers," J. Physiol. (Lond.) **251**, 1–59 (1975).

[28] D. DiFrancesco and D. Noble, "A model of cardiac electrical activity incorporating ionic pumps and concentration changes," Philos. Trans. R. Soc. London Ser. B **307**, 353–398 (1985).

[29] A. Shrier and J. R. Clay, "Repolarization currents in embryonic chick atrial heart cell aggregates," Biophys. J. **50**, 861–874 (1986).

[30] A. T. Winfree, *The Geometry of Biological Time* (Springer-Verlag, New York, 1980).

[31] M. R. Guevara and L. Glass, "Phase locking, period doubling bifurcations, and chaos in a mathematical model of a periodically driven oscillator: A theory for the entrainment of biological oscillators and the generation of cardiac dysrhythmias," J. Math. Biol. **14**, 1–23 (1982).

[32] F. C. Hoppensteadt and J. Keener, "Phase locking of biological clocks," J. Math. Biol. **15**, 339–349 (1982).

[33] J. Keener and L. Glass, "Global bifurcations of a periodically forced oscillator," J. Math. Biol. **21**, 175–190 (1984).

[34] E. J. Ding,"Analytic treatment of a driven oscillator with a limit cycle," Phys. Rev. A **35**, 2669–2683 (1987).

[35] L. Schamroth, D. H. Martin, and M. Pachter, "The extrasystolic mechanism as the entrainment of an oscillator," Am. Heart J. **104**, 1363–1368 (1988).

[36] M. R. Guevara, A. Shrier, and L. Glass, "Chaotic and complex cardiac rhythms," in *Cardiac Electrophysiology: From Cell to Bedside*, edited by

D. P. Zipes and J. Jalife (Saunders, Philadelphia, 1990), pp. 192–201.
[37] M. R. Guevara, L. Glass, and A. Shrier, "Phase-locking, period-doubling bifurcations and irregular dynamics in periodically stimulated cardiac cells," Science **214**, 1350–1353 (1981).
[38] G. K. Moe, J. Jalife, W. J. Mueller, and B. Moe, "A mathematical model of parasystole and its application to clinical arrhythmias," Circulation **56**, 968–979 (1977).
[39] J. Jalife, C. Antzelevitch, and G. K. Moe, "The case for modulated parasystole," Pace **5**, 911–926 (1982).
[40] N. Ikeda, S. Yoshizawa, and T. Sato, "Difference equation model of ventricular parasystole as an interaction of pacemakers based on the phase response curve," J. Theor. Biol. **103**, 439–465 (1983).
[41] L. Glass, A. L. Goldberger, and J. Bélair, "Dynamics of pure parasystole," Am. J. Physiol. **251**, H841–H847 (1986).
[42] L. Glass, A. L. Goldberger, M. Courtemanche, and A. Shrier, "Nonlinear dynamics, chaos, and complex cardiac arrhythmias," Proc. R. Soc. London Ser. A **413**, 9–16 (1987).
[43] M. Courtemanche, L. Glass, M. D. Rosengarten, and A. L. Goldberger, "Beyond pure parasystole: Promises and problems in modelling complex cardiac arrhythmias," Am. J. Physiol. **257**, H693–H706 (1989).
[44] M. Courtemanche, L. Glass, J. Bélair, D. Scagliotti, and D. Gordon, "A circle map in a human heart," Physica D **40**, 299–310 (1989).
[45] N. B. Slater, "Gaps and steps for the sequence $n\theta$ mod 1," Proc. Cambridge Philos. Soc. **63**, 1115–1123 (1967).
[46] M. Talajic, D. Papadatos, C. Villemaire, L. Glass, and S. Nattel, "A unified model of AV node conduction predicts dynamic changes in Wenckebach periodicity," Circ. Res. (in press).
[47] W.-Z. Zeng, J. Morissette, R. Brochu, L. Glass, and A. Shrier, "Complex rhythms resulting from overdrive suppression in electrically stimulated heart cell aggregates," PACE **13**, 1678–1695 (1990).
[48] A. Pelleg, S. Vogel, L. Belardinelli, and N. Sperelakis, "Overdrive suppression of automaticity in cultured chick myocardial cells," Am. J. Physiol. **238**, H24–H30 (1980).
[49] B. Van der Pol and J. Van der Mark, "The heartbeat considered as a relaxation oscillation and an electrical model of the heart," Philos. Mag. **6**, 763–775 (1928).
[50] S. Smale, "Differentiable dynamical systems," Bull. Am. Math. Soc. **73**, 748–817 (1967).
[51] N. Wiener and A. Rosenblueth, "The mathematical formulation of the problem of conduction of impulses in a network of connected excitable elements, specifically in cardiac muscle," Arch. Inst. Cardiol. Mex. **16**, 205–265 (1946).
[52] V. I. Krinskii, "Fibrillation in excitable media," Systems Theory Res. (Prob. Kyb.) **20**, 46–65 (1968).
[53] A. T. Winfree, *When Time Breaks Down: The Three-Dimensional Dynamics of Electrochemical Waves and Cardiac Arrhythmias* (Princeton U.P., Princeton, NJ, 1987).
[54] V. S. Zykov, *Simulation of Wave Processes in Excitable Media* (Manchester U.P., Manchester, England, 1987).