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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
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Cardiac arrhythmias and circle maps—A classical problem

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(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 Kal' mozov 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 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.

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. 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. Although I have never examined the 1959 dissertation, I assume that the 1989 article summarizes the main earlier findings.

In the following I 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.

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 \( t_p, t_1, t_2, \ldots \) Each of these firing times can be associated with a phase of the forcing oscillator by \( \phi_1 = t_p (\bmod T) \). 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., \( \phi_1 = f(\phi_{n-1}) \), 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 \( \phi \) 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, \( \phi_1, \phi_2, \phi_3, \ldots \). 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 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
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1.0 r.-;--;-----.
(a)
0
1.0
(b)
0
1.0
(c)
0
1.0
(d)
0
1.0
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 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 \( \gamma_1 \) 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

\[
f_1(t) = \gamma_1(t - t_0), \quad t_0 \leq t < t',
\]

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

\[
f_2(t) = -\gamma_2(t - t_1), \quad t' < t < t_1.
\]

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. 3. Diagram of the integrate and fire model. An activity rises to an oscillatory threshold with slope \( \gamma_1 \) 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.](image)
are shown in Fig. 5. The map is invertible in the region where \( \gamma_1 \) is large, as studied carefully by Arnold and sometimes called the "sine circle map." The dynamics in the \((\tau, b)\) 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 "stochastic" dynamics in this map was made by Zaslavsky in 1978, but the first results on the detailed bifurcations in the noninvertible region came later.  

Under continuous changes of \( \gamma_1 \) and \( \gamma_2 \), Eq. (7) transforms into Fig. 5, but it is not yet clear how this comes about. Belair and I examined an intermediate case for which \( \gamma_1 = \gamma_2 \).

Other functions in addition to the sinusoidal function have been considered for the threshold in Fig. 3. Arnold reports results for periodic functions consisting of delta function spikes, rectangular pulses, and triangular pulses, partially anticipating subsequent studies. Arnold 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 atioventricular (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. Such maps can be experimentally measured and can be used to make predictions concerning complex rhythms observed in humans.

\begin{align*}
\phi_{t+1} &= \phi_t + \frac{1}{\gamma_2} + \frac{1}{\gamma_2} t' + k(\frac{1}{\gamma_1} + \frac{1}{\gamma_2}) \sin 2\pi t', \\
&= \phi_t + \frac{1}{\gamma_2} + \frac{1}{\gamma_2} t' + k(\frac{1}{\gamma_1} + \frac{1}{\gamma_2}) \sin 2\pi t', \\
\end{align*}

\begin{align*}
t' &= (\gamma_1 t_0 + \gamma_2 t_0)/(\gamma_1 + \gamma_2). \\
\end{align*}
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.\(^8\)\(^9\) 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.\(^8\)\(^9\) The periodic stimulation consists of delta function stimuli delivered with a period \(\tau\). 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 \(\phi_i\) the phase of the Poincaré oscillator just before the \(i\)th stimulus. Then

\[
\phi_{i+1} = f(\phi_i) = g(\phi_i A) + \tau \pmod{1},
\]

where \(g(\phi)\) is readily calculated\(^8\)\(^9\)\(^{30-32}\) and is given by

\[
\cos[2\pi g(\phi_i A)] = \frac{A + \cos 2\pi \phi}{1 + 2A \cos 2\pi \phi + A^2}\]

and \(\tau\) 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 (\(A < 1\)) 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-
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 predic­
tions 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 evaluat­
ing circumstances in which the simple approximations con­
sidered above are no longer applicable. 46–47 These approx­
imations break down because the periodic forcing changes
the intrinsic properties of the oscillator. To develop a the­
eoretical understanding of the resulting rhythms, it is nec­
essary 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 param­
ters 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 pa­
rameter space where the axes usually correspond to the
amplitude and relative frequency of the periodic forcing of
an intrinsic cardiac rhythm. At low stimulation ampli­
tudes, all the models share a similar topology correspond­
ing 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. 8. Electrocardiographic trace and
schematic picture of the model for para­
systole. Sinus beats are labeled S and ec­
topic beats are labeled E. Simultaneous
 timing of the sinus and ectopic beats
leads to a fusion beat of different mor­
phology 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 ts and
tE, respectively. Adapted from Ref. 44.

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 experi­
mental 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 mathema­
tics 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 in­
directly) Smale in his subsequent analysis of horseshoe
maps.50 Studies of wave propagation in excitable media by
Wiener and Rosenbluth51 have had a deep impact on cur­
current theoretical and experimental work on life-threatening
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 prob­
lems to study.

ACKNOWLEDGMENTS

The results from our group represent collaborative ef­
forts 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 Bélaire. David Campbell made helpful
suggestions concerning the presentation in Sec. II. Thanks
to the Québec Heart and Stroke Foundation and the Nat­
ural Sciences Engineering and Research Council of Canada
for financial support.

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CHAOS, Vol. 1, No. 1, 1991
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