CHAPTER 24

On the Non-linear Equilibrium of the Heart: Locking Behavior and Chaos in Purkinje Fibers*

D. R. Chialvo and J. Jalife

Irregularities of heart rate and rhythm have long been of interest to clinicians and basic scientists. When attempting to understand such irregularities, they all have the same goal in mind; namely, to find a rule or set of rules that would allow the accurate prediction, description, and prevention of arrhythmic cardiac activity. The emerging science of non-linear dynamics, if used appropriately, may provide tools and insight into the laws that govern cardiac rhythm disturbances. This chapter describes our efforts at applying these mathematical tools to the analysis of complex excitation patterns in isolated cardiac tissues.

The strategy used in our investigation derives from the theory of dynamical systems (Glass and Mackey, 1988; Thompson and Stewart, 1986; Moon, 1987). Such a strategy consists of concentrating the analysis on the beat to beat changes of those few action potential parameters that are known to have a non-linear relationship to time. In general, in excitable tissues, the prototypical functions with non-linear time courses of recovery with respect to a previous response are action potential duration (APD), activation threshold, and stimulus to response latency or, in the case of activation of large numbers of cells in a tissue, conduction velocity. During repetitive electrical stimulation, such non-lineairities confer these tissues with certain properties that allow them to behave either periodically (i.e., stable Mobitz I or II type of block) or chaotically, depending upon the stimulus magnitude and cycle length. When attempting to understand these behaviors, a very important task is to identify which relevant function (e.g., APD, latency, and so on) is responsible for the non-linearities. In the presence of a given rate-dependent activation pattern, microelectrode recordings can show wide variations in both APD and delay to activation. However, these data are usually not sufficient to allow a detailed mechanistic explanation of the phenomenon in question. Consequently, the lack of a general theoretical framework for all these rate-dependent processes has led to speculation in terms of “multilevel block” or “concealed conduction” (Langendorf, 1956) as the mechanism of production of cardiac rate-dependent block processes.

This chapter has two major objectives: (1) to discuss recent evidence suggesting that the great majority of rate-dependent block processes occurring in cardiac non- pacemaker tissues is explained merely on the basis of intrinsic electrophysiological non-linearities (even without any spatial considerations) and (2) to identify and characterize in isolated cardiac Purkinje fibers the relevant non-linear function or functions responsible for the dynamics that allow block processes to undergo transitions from regular and periodic to irregular and chaotic. At this point, an apparent link between supernormal recovery of excitability and development of chaotic rhythms is analyzed. Finally, a simple model for excitable non-pacemaker tissues emphasizing the role of non-linearities is postulated for the establishment of rate-dependent block.

PURKINJE FIBERS AS A NON-LINEAR DYNAMICAL SYSTEM

The appearance of rate-dependent block processes in non-pacemaker cardiac tissues resembles the establishment of “phase-lock or mode-lock,” a well-known time-dependent phenomenon in many non-linear dynamical systems (Berge et al., 1984; Moon, 1987). By “dynamical system” we mean any system, whatever its nature (physical, chemical, electromechanical, biological, economic, and so on) in which there is a temporal dependence on the relevant variables (Moon, 1987; Thompson and Stewart, 1986). Phase- or mode-locking in these systems is defined as a characteristic parameter to response pattern that may be maintained (i.e., “locked”) for a given range of parameter values and suddenly replaced by a different pattern as a result of a parameter change.

Rate-dependent block in cardiac tissues follows a phase- locking behavior. As in other non-linear dynamical systems, the mechanism of such behavior could be linked to the presence of a non-linear recovery of its relevant parameters. Indeed, it is well known that excitability in these tissues has a slow, non-

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linear recovery after each action potential (Rosenblueth, 1958). Slow recovery of excitability means that when the beat to beat activation patterns are analyzed during periodic stimulation at increasing frequency, a stepwise decrease in the activation ratio (AR, defined as m:n ratio, where m = number of action potentials or responses and n = number of stimuli) should be observed. Several non-linear dynamical systems with finite "recovery time" behave in much the same way (Bak, 1986). Provided that the relevant parameters recover monotonically, the sequence of m:n patterns (hereafter referred to as stimulus to response locking, or locked patterns) that occurs as the stimulation frequency is systematically altered can be predicted theoretically by the so-called Farey tree (Fig. 24-1; Guevara et al., 1988).

On the basis of previously described data (Landahl and Griffeth, 1971), Sato (1972) and later Keener (1981) formulated theories describing these dynamics. Both authors used simplified models of excitable tissue activation in which APD was constant, and the only relevant parameter was a monotonic recovery of excitability. The results of both investigators showed that under these particular circumstances, the response of excitable tissues to periodic stimulation at increasing rates is completely predicted by the Farey tree.

However, excitability in cardiac tissues need not recover monotonically after an action potential. In fact, Purkinje fibers may show a relatively supernormal phase of excitability (Spear and Moore, 1974) at early diastolic intervals. In addition, APD changes significantly as a function of activation rate. Together, these factors may result in more complex types of phase-locking behavior in these tissues. Indeed, several unexpected n:m patterns have been observed in both experimental (Chialvo and Jalife, 1987) and clinical (Halpem et al., 1983) studies, including 4:2 and 5:2 block patterns, both of which are easily explained on the basis of supernormal excitability. In fact, even more complex and extremely irregular (i.e., chaotic) activation patterns were found in our experiments (Chialvo and Jalife, 1987), in which a supernormal phase was demonstrable for excitation and action potential propagation.

The universal behaviors described by the Farey tree, as well as for more complex phenomena (e.g., period-doubling bifurcation and chaos), have been extensively described in a number of oscillatory systems that include aggregates of embryonic heart cells undergoing self-sustaining pacemaker activity (Guevara et al., 1981). Conversely, until recently the mechanisms responsible for the regular and chaotic regimes in non-pacemaking cardiac tissues, and the potential pathophysiological implications of deterministic chaos in cardiac excitation and conduction had not been previously investigated. Recently (Chialvo and Jalife, 1987), a first experimental attempt was made to show that these universal dynamics are not restricted to oscillators, suggesting that recovery of excitability itself, rather than pacemaker activity, might be the relevant dynamical property inducing those behaviors.

## DYNAMICAL DESCRIPTION OF RATE-DEPENDENT BLOCK PROCESSES

### Periodic Rhythms

In our initial experiments, the objective was to determine accurately the behavior of non-pacemaking Purkinje fibers in response to repetitive electrical stimulation. We analyzed which kinds of steady state dynamics would be obtained for any particular combination of stimulus parameters used to drive the preparation. In those experiments (Chialvo and Jalife, 1987), we studied quantitatively the overall hierarchical structure and the scaling properties (i.e., the relative proportions of locking patterns) of the behavior of our preparations in the space of parameters for the application of depolarizing pulses.

Thin, externally unbranched sheep Purkinje fibers were
driven with depolarizing current pulses applied through a suction pipette. Steady state strength-duration curves were determined at various basic cycle lengths (BCLs). For each duration at a constant BCL, current strength was decreased in steps of 1 to 2 μA, beginning at levels of 1:1. For each curve (Fig. 24-24), each data point represents the minimal current needed to sustain a given stable locking. Figure 24-24 was obtained at a BCL of 700 msec; points falling on or above the 1:1 curve (line connecting open squares) correspond to 1:1 patterns. Triangles connecting the lowest curve indicate the boundary of 1:0 locking. Below this line, all stimuli are subthreshold. Other types of BCL-dependent locking are represented at values between these 1:1 and 1:0 boundaries.

A more complete picture of the dependence of the activation patterns on the stimulation parameters is shown in Figure 24-2B, plotted from the same experiment as in Figure 24-2A. A pulse duration of 15 msec was selected, and the steady state limits of several locking patterns were determined at various BCLs. The lines are the limits of the most important isoperiodic areas (1:1, 2:1, 3:1, and 1:0) found in this representative preparation. The largest area between 1:1 and 1:0 was 2:1; between 1:0 and 2:1, it was 3:1; between 3:1 and 1:0, it was 4:1, and so on. Curiously, Wenckebach-like patterns were manifested in an area (arrow in Fig. 24-2B) that was proportionately narrower than that between 1:0 and 2:1. Yet, the overall hierarchy followed Farey's series. Hence, for a given range of BCL, the largest area between n:m and N:M was always n + N:m + M; where, again, n and N are the number of pulses and m and M the number of action potentials. Hence, our data demonstrate that the Farey tree structure (see Fig. 24-1) is not restricted to self-sustained oscillators. In fact, we (Chialvo and Jalife, 1987) and others (Schrier et al., 1987) have proposed that this simple rule can be very useful when attempting to predict the development of different rate-dependent block processes in cardiac non-pacemaking tissues when a given stimulation parameter is changed.

The applicability of a complementary dynamical law was demonstrated also by our initial experiments (Chialvo and Jalife, 1987). If we define activation as 1 and failure as 0, any given pattern can be represented as a particular binary sequence. For example 1:1 will be described by an uninterrupted repetition of 1s (i.e., 1, 1, 1, 1, ... ) and 1:0 by a succession of 0s, and so on. Interestingly, the order of action potentials and dropped beats in any periodic pattern is accurately predicted by the concatenation of neighboring sequences. For instance, in the binary system the pattern 5:3, which is predicted by the Farey tree to be found for values of parameters between those of 2:1 and 3:2 (Fig. 24-3), is defined exclusively by the sequence 0,1,1,0,1. In fact, the binary structure constructed using such a rule (Fig. 24-4) predicts all the possible theoretical combinations of dropped and successful beats. Moreover, any apparently random sequences detected experimentally in cardiac tissues can be tested for consistency using this simple rule.

Non-periodic Rhythms

The regular patterns discussed are characterized by the periodic repetition of particular sequences of action potentials and dropped beats. In contrast, for certain values of stimulation

![FIGURE 24-3. Periodic patterns obtained when the current strength was decreased gradually from 39 μA (1:1 locking, uppermost trace) through 25 μA (1:0 locking; bottom trace). Numbers at left indicate current strength in microamperes, numbers at right denote stimulus to response ratios, Pulse duration, 5 msec; BCL, 300 msec. Calibrations: vertical 60 mV; horizontal 600 msec for all, except bottom trace (1500 msec). (Reproduced from Chialvo DR, Jalife J: Nature 330:749-752, 1987, by permission.)](image)

![FIGURE 24-4. Binary tree for the first five hierarchical levels showing the structure of any given periodic pattern predicted in the Farey tree (see text for further explanation).](image)
parameters, more complex irregular phenomena may also appear. Figure 24–28 shows that the hierarchical structure described is lost at values of BCL and strength such as those within the stippled area of the figure. In this region we found irregular dynamics, with patterns not predicted by the Farey tree, as well as coexistence (multistability) of several forms of complex activity that were highly dependent on the initial conditions (see further on). Because of the complexity of these patterns, specific experiments were designed to unravel their mechanism or mechanisms and the precise circumstances in which they may appear.

# MECHANISMS OF REGULAR AND IRREGULAR RHYTHMS

Our experiments described previously (Chialvo and Jalife, 1987) already suggested that rate-dependent activation of isolated cardiac Purkinje fibers can be linked with non-linear time-dependent changes in excitability and APD. To further investigate these links, a second group of experiments (Chialvo et al., in press) was designed to analyze which parameters are relevant to this behavior and to use these parameters as variables for the formulation of a simplified analytical model. In turn, the model was used to predict a wide spectrum of behavioral responses under our specific experimental conditions.

A full description of the methods can be found in Chialvo and coworkers (in press). Briefly, 2- to 5-mm-long isolated sheep cardiac Purkinje fibers were superfused with a modified (2 to 8 mM KCl) Tyrode solution. Preparations were driven near one end with rectangular constant depolarizing current pulses (duration, 10 to 20 msec) applied through a suction pipette (outer diameter, 0.3 mm). Current strength was measured as the voltage drop across a 1-kΩ resistor in series with the suction pipette. Transmembrane potentials were recorded with a glass microelectrode placed at a distance of 1 to 2 mm from the stimulation electrode. Strength-interval curves were determined using single test pulses (S0) delivered after every tenth basic pulse (S1) at a BCL of 3 seconds. The S1-S2 interval was decreased progressively from the BCL value to the refractory period, while measuring the threshold current at each step. After the excitability curves were obtained, the response of the preparation to periodic stimulation at several cycle lengths was determined under similar experimental conditions, using values of current strength close to the measured threshold curve. The test was always initiated after at least 10 seconds of quiescence, and the resultant pattern was evaluated after a steady state was reached (whenever possible). Similar measurements were repeated at low and high KCl concentrations (usually 2 and 8 or 4 and 7 mM). Restitution of APD and latency to activation curves were measured in both conditions. All data were collected from preparations in which there was no spontaneous activity.

# DIFFERENT TIME COURSES OF RECOVERY OF EXCITABILITY YIELD DIFFERENT BEHAVIORS

The time course of excitability recovery can be easily modified in cardiac Purkinje fibers (Spear and Moore, 1974) by changing the KCl concentration in the superfusing Tyrode solution. In our experiments, changing the KCl concentration led to two major types of behavior in response to repetitive stimulation, depending upon the time course of recovery of excitability. As shown in the example of Figure 24–5, when the KCl concentration of the Tyrode solution was decreased from 7 mM (Fig. 24–5A) to 4 mM (Fig. 24–5B), the excitability recovery function consistently changed from monophasic (“normal”) to triphasic (“supernormal”).

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**FIGURE 24–5.** Strength-interval curves (A1, B1) and action potential duration (APD) restitution curves (A2, B2) obtained from a sheep Purkinje fiber preparation at a basic cycle length (S0-S1) of 3000 msec. In both (A1 and B1), an action potential is presented (lower left) to indicate the phase of membrane potential at which the test stimulus was applied. Calibration bars in A1 and B1 are for the action potentials and represent 30 mV. KCl concentration was 7 mM for A1 and 4 mM for B1. Although no supernormality is present at the higher concentration (A1), it becomes evident at the lower concentration (B1). Arrows indicate the stimulus amplitude used during the repetitive stimulation shown in Figures 24–6 and 24–7. (From Chialvo DR, Jalife J: Circ Res. In press.)
followed by 0.50 (2:1 locking). Additional abbreviations of the stimulus BCL yielded smaller ARs, including 0.4 (5:2) between 320 and 310 msec and 0.3 (3:1 locking) for BCLs between 310 and 240 msec. With still further decreases in the BCL, AR continued to diminish until a 7:1 pattern (AR = 0.14) was recorded at a BCL of 150 msec. Clearly, in this representative example, there was a monotonic relationship between the AR and the stimulus cycle length.

In all experiments in which the recovery of excitability was monotonic, the AR versus BCL plot showed the characteristic staircase exemplified in Figure 24–6B. An important theoretical feature of this type of staircase (already mentioned in relation to the Farey tree; see Fig. 24–1) is that if one explores carefully between any two adjacent steps of n:m and N:M patterns (using very small BCL changes), it should be possible to find additional smaller steps whose AR is equivalent to n + N:m + M. For example, between 2:1 and 3:1 one should detect 5:2 (i.e., 2 + 3:1 + 1) and between 5:2 and 2:1 one would expect to find 7:3 (i.e., 2 + 5:1 + 2). Obviously, an infinite construction could be made by adding smaller and smaller adjacent steps. Yet, experimentally this would be impossible because the presence of noise would impede the observation of the predicted patterns.

When similar measurements were repeated during exposure to 4 mM KCl, a completely different picture emerged (Fig. 24–7A) with many complex cycle length–dependent changes in the AR. Indeed, under these conditions (pulse amplitude, 27 μA; duration, 20 msec; see arrow in Fig. 24–5B), the pattern changed directly from 1:1 locking to 2:1 when the BCL was abbreviated to 1500 msec. In addition, as shown in Figure 24–7B, further abbreviation did not change the AR until a 3:1 phase-locking pattern was established, at just less than 1000 msec. Additional BCL decreases led to discontinuities in the curve, in which the AR increased and decreased several times over a given BCL range. For example, at BCLs between 450 and 400 msec, the 3:1 pattern was replaced by a 4:2 locking, and that was followed by 5:2. The 4:2 pattern consisted of two successive action potentials followed by two failures (Fig. 24–7A, left column), whereas 5:2 was characterized by two successive action potentials followed by three dropped beats (not shown). Finally, as shown by the AR versus BCL plot (Fig. 24–7B), and also by the analog recordings of Figure 24–7A (right column), at the very brief BCL of 200 msec, unstable sequences of 7:2 → 10:3 (not shown) and 9:3 → 5:2 appeared, which eventually stabilized in 2:1 pattern.

Clearly, under these conditions there is a complex relationship between the stimulation cycle length and the changes in AR. In fact, unlike the monotonic case, the presence of supernormality at 4 mM KCl induces the recurrence of some of the ARs at various cycle length ranges. For instance, the AR of 0.5 was obtained at three different BCL ranges; 0.33 as well as 0.4 was detected twice (Fig. 24–7B). Interestingly, in the presence of relative supernormality, the shape of the AR-BCL staircase and the presence or lack of pattern recurrences were strongly dependent upon the strength of the current pulse.

### DIFFERENT BEHAVIORS DEPEND ON THE STIMULUS STRENGTH (RELATIVE TO THE STRENGTH-INTERVAL CURVE)

In the presence of supernormality, the dynamical behavior of the Purkinje fibers in response to repetitive stimulation depended on the strength and position of the current pulse in relation to the strength-interval curve. Figure 24–8 shows a schematic representation of a strength-interval curve, which has been divided into three different ranges of current intensity.
Diastolic interval

FIGURE 24-8. Schematic representation of a non-monotonic strength-interval curve with relative supernormality. Labels indicate those ranges (Range I, Range II, Range III) of stimulus intensity in which different behaviors were observed experimentally during repetitive stimulation. (From Chialvo DR, Jalife J: Circ Res. In press.)

3:1, 4:1... N:1, and finally 1:0 at very brief BCLs. However, unlike the monotonic case (see Fig. 24-6B), no intermediate locking patterns were observed under the condition of supernormality (i.e., low KCl superfusion) when the current pulse strength was within either the I or III range.

In contrast, stimulus strengths within the critical range (range II in Fig. 24-8) brought about a rich variety of regular and irregular BCL-dependent activation patterns, including those already presented in Figure 24-7. In addition, within this range of current amplitude, and for some BCL values, we commonly observed at least three forms of irregular (aperiodic) dynamics. One type, which we have termed multirhythmicity, consisted of apparently random pattern fluctuations occurring at fixed stimulus magnitude and BCL. An example of multirhythmicity obtained from a Purkinje fiber superfused with 4 mM KCl Tyrode solution is presented in Figure 24-9. In all panels, the top trace is the transmembrane potential and the bottom trace is the current monitor. At constant pulse amplitude (64 μA), duration (20 msec), and BCL (190 msec), the responses fluctuated back and forth between three different stimulus to response patterns. An apparently stable 2:1 pattern (Fig. 24-9A) suddenly changed to a 6:3 (Fig. 24-9B), which eventually gave way to 16:8. Clearly, in this case the presence of supernormal excitability led this Purkinje fiber to random transitions between multiple patterns whose common AR was 0.5.

Another type of irregular activity occurring at range II in the supernormal strength-interval curve (Fig. 24-8) was characterized by "recurrent fluctuations" between regular and irregular activation patterns. In the example presented in Figure 24-10, the preparation was superfused with 4 mM KCl; the stimulus parameters were the same (BCL, 370 msec; pulse amplitude, 54.5 μA; duration 20 msec) for all three panels. Under these conditions the tissue underwent a behavior that began with a transition from an unstable 5:3 pattern (Fig. 24-10A) to 7:5 (Fig. 24-10B) and eventually settled into an irregular periodicity (Fig. 24-10C, I.D.). The latter was characterized by a single 2:1 pattern interrupting an apparently stable 1:1 locking at intervals that were completely aperiodic. In Figure 24-10C, a sequence of 12 consecutive successful activations was suddenly interrupted by a failure leading to a single 2:1 event that was followed by four successive 1:1 responses. In a long run of hundreds of action potentials, the number of intervening 1:1 responses (e.g., 12 and 4 in Fig. 24-10C) never repeated. Finally, although not very apparent in Figure 24-10, during 1:1

Range I corresponds to stimulus amplitudes that are less than the minimum current requirement at the relatively supernormal phase; range III corresponds to stimulus amplitudes higher than the peak threshold current at intermediate intervals near the supernormal phase; and range II, also termed the critical range, lies within the boundaries between I and III. When the stimulation strength was selected to be within the range of either I or III, increases in stimulation rate led to monotonically decreases in the AR. In fact, the usual patterns observed were those of "period-adding" sequences (N:1 for N = 1 to ∞), which began at the 1:1 level at long BCLs and changed to 2:1,
activation in any sequence of random fluctuation, there were small alternations in APD, which decreased progressively and were eventually interrupted by the dropped beat. The significance of these phenomena in the mechanisms of irregular activity at the critical range of current magnitude will become apparent further on.

A third type of irregular behavior (termed chaotic activity) observed within the critical range was characterized by highly aperiodic activity, with APD alternans. As shown by the recordings in Figure 24–11, the most important feature of this chaotic activity is that during the successful 1:1 runs, the magnitude of APD alternation increases in a beat to beat manner and eventually leads to a failure. In this case also, the number of 1:1 responses within a given run never repeated, even when the recording periods encompassed 100 stimuli or more.

### ANALYTICAL SOLUTION OF EXPERIMENTAL OBSERVATIONS

#### The Difference-Differential Model

The working hypothesis in our approach is that complex dynamics could arise as a direct consequence of the peculiar mode of restitution of three parameters: excitability, latency, and APD, modulated by an additional slow ("memory") process.

Figure 24–12 shows the action potential parameters used in the model formulation. As is generally accepted for experiments using the "S-S protocol" (Spear and Moore, 1974), the threshold (Th), APD, and latency (L) are determined by the diastolic interval (DI) after the tenth beat of a train elicited at...
constant BCL. DI can be calculated as the coupling interval minus the last apd minus / (latency of the tenth beat). Threshold (Th) also can be described as a function of the diastolic interval. These functions can be written as

\[
\begin{align*}
\text{DI} &= (S_i - S_j) - \text{apd} - \text{I} \\
L &= F(\text{DI}) \\
\text{APD} &= R(\text{DI}) \\
\text{Th} &= Z(\text{DI}) \\
&\quad \text{For } St > \text{Th}
\end{align*}
\]

The L value is a function of both the degree of recovery of excitability (2) and the particular stimulus strength (St). Function R is the APD restitution curve, which is also known as the Purkinje fiber (Elharrar and Surawicz, 1983); it decreases monotonically as DI decreases. The Z function (threshold) is the strength-interval curve obtained experimentally.

Figure 24–12B illustrates the condition during periodic stimulation. Here S1 represents the first stimulus following a sudden change in frequency (i.e., equivalent to an S2 in Fig. 24–12A), after which constant BCL (i.e., equivalent to the S1–S2 interval in Fig. 24–12A) is maintained. Using the same formulation as before, we can rewrite [Eq 1] as

\[
\begin{align*}
\text{DL} &= \text{BCL} - \text{APD}_n - L_n \\
L_{n+1} &= F(\text{DL}) \\
\text{APD}_{n+1} &= R(\text{DL}) \\
\text{Th}_{n+1} &= Z(\text{DL})
\end{align*}
\]

Then, during repetitive stimulation, the recovery of the membrane during the n-th cycle (i.e., at the S, S+1, interval) will determine the value of APD, Th, and L in the next cycle, and so on.

Basically [Eq 2] is an algebraic representation of the conceptual steps usually followed in the literature for the analysis of rate-dependent block processes. However, the characteristics of the function governing APD under these circumstances are known only for two very particular cases: (1) during the steady state (i.e., after several beats at the same BCL), described as a hyperbolic process, and (2) during the stimulation described by the restitution curve, which is responsible for the short-term APD adjustment as a function of the previous diastolic interval (Elharrar and Surawicz, 1983; Elharrar et al., 1984; Boyett and Fedida, 1984). The latter is well fitted by two exponentials and is described by the following equation

\[
\begin{align*}
\text{APD} &= \text{APD}_{\text{max}} \times [1 - (A_1 \times e^{-(\text{DI}/T_1)}) \\
&\quad - (A_2 \times e^{-(\text{DI}/T_2)})]
\end{align*}
\]

where DI is the diastolic interval. APDmax is the maximum APD, and A and T are the amplitude and time constant of the fast (A1, T1) and slow (A2, T2) exponential components of the curve.

To provide for a continuous estimation of APD not only as a function of the last diastolic interval (i.e., using [Eq 3]) but also as affected by several previous beats. We propose here that R in [Eq 2] is shifted at each beat gradually from one case (restoration) to the other (steady state) by the memory dissipation (M). Based on previously reported models (Guljarani, 1987), we considered M as growing exponentially toward 1 during each action potential and decreasing in reverse fashion toward 0 during the diastolic interval. M is thus described by the following equation

\[
M = \partial \text{APD} - M / dt
\]

where \( \Delta \) is the memory time constant and \( \partial \text{APD} = 1 \) during the action potential and 0 otherwise; then during the action potential, memory grows from the previous value \( \text{M}_{\text{ini}} \) as described by

\[
\text{M}_{\text{ini}} = 1 + [(\text{M}_{\text{ini}} - 1) \times e^{-(t/\Delta)}]
\]

where \( t = \text{APD} \). From \( \text{M}_{\text{ini}} \) during the diastolic interval memory decays following the equation

\[
\text{M}_{\text{i}} = \text{M}_{\text{ini}} \times e^{-(t/\Delta)}
\]

where \( x = \text{DI} \).

By using [Eq 4], it becomes possible to rewrite [Eq 2] to incorporate the memory effect. Thus

\[
\begin{align*}
\text{DL} &= \text{BCL} - \text{APD}_n - L_n \\
L_{n+1} &= F(\text{DL}) \\
\text{APD}_{n+1} &= R(\text{DL}) \times (1 - M) \\
\text{Th}_{n+1} &= Z(\text{DL})
\end{align*}
\]

The iterative procedure used to solve [Eq 5] is as follows: first, assuming that the initial conditions are such that \( \text{APD}_n = 0 \) and \( L_n = 0 \) (i.e., there was no previous beat), for a given BCL calculate the recovery (DL), which will determine (b) the next latency \( L_{n+1} \), and (c) \( \text{APD}_{n+1} \) as well as (d) \( \text{Th}_{n+1} \). Furthermore, since each beat modifies the value of M, the next APD is affected (solving [Eq 4]) proportionally. The values
obtained are now used to establish the next recovery time (DL).

The condition of suprathreshold stimulus (St > Th) is also
tested for each beat. If that comparison results in St < Th, DLn-1
is calculated as BCL + DL. The overall procedure is repeated
iteratively until a steady state response is achieved. We used an
iterative program, which was written in BASIC and run on a
personal computer.

The parameter values incorporated in the model are rep-
resentative of our experimental data and are consistent with
previously reported measurements (Eiharrar and Surawicz,
1983). The APD restitution curve parameters were as follows:
A1 = 0.4; T1 = 150 msec; A2 = 0.13; T2 = 1400 msec. Mem-
ory was calculated solving [Eq 4] in each iteration for dAP =
0 during a time equal to the previous diastolic interval; and for
dAP = 1 for an interval equal to the APD, using the solutions
in [Eq 4b] and [Eq 4c], respectively. Memory time constant (Δ)
as was assumed to be 100 seconds (Vick, 1971). To mimic the
strength-interval curve, a three- or four-step linear piecewise
approximation was used. Threshold current in this curve was
normalized, in arbitrary units (AU), taking the late diastolic
threshold as the minimum (e.g., 2.5 AU in Fig. 24-17 A,B) and
the threshold corresponding to the absolute refractory period as
10 AU. It has been shown (Spear and Moore, 1974) that the
totality to activation for a given stimulation amplitude is
directly related to the threshold function. Thus, for the sake of
simplicity, L was considered to be proportional to the calcu-
lated threshold (e.g., Th = 2 AU → L = 2 msec).

PERIODIC AND NON-PERIODIC
RHYTHMS CAN BE EXPLAINED
BY THE NON-LINEARITIES

Example

By using the analytical model, it becomes possible to pre-
dict both graphically and numerically how rate-dependent ac-
tivation patterns are established and which are the most critical
parameters in the establishment of these behaviors. To intro-
duce these results, let us consider the dynamics associated with
a sudden BCL change in a purely hypothetical example of a
Purkinje fiber being driven by repetitive current pulses. For
simplicity’s sake, we will describe first the dynamical analysis
of a situation in which latency to activation is neglected. Thus,
the overall behavior in this case is determined solely by the
diastolic interval dependence of APD (i.e., the restitution curve).
We will assume also that the APD in a given beat (APDn) during a
repetitive stimulation is determined exclusively by the preceding
diastolic interval (DL). This assumption requires that we ignore for
the moment the contribution of memory (M) in determining beat to beat APD changes. The set of equations in [Eq 5] can then be simplified to

\[ DL_n = BCL - APD_n \]  
\[ APD_{n+1} = R(DL) \]

In this example, the stimulus amplitude is selected to be
suprathreshold at any diastolic interval greater than zero. If the
function R is known, [Eq 6] can then be solved either numerically
or graphically. In Figure 24--13, the restitution curve (R) was
approximated in a piecewise manner (three pieces), as repre-
sented by the thick solid line. For DI values higher than 600
msec, APD is constant at 370 msec. For DI values lower than
600 msec, APD decreases linearly with two different slopes, one
from 600 msec to 200 msec, and the other from 200 msec to
zero DI. Note that Figure 24--13 represents expression (b) of
[Eq 6], in which the abscissa is DI in the nd beat and the ordi-
nate is the predicted APD in the nd + 1 beat. The diagonals
(labeled BCL lines) represent the graphic calculation of BCL -
APDn (step a of [Eq 6]) at the indicated BCLs.

The evolution of this system for an initial condition of
BCL = 700 msec and APD = 365 msec, and a sudden change
to BCL = 400 msec is presented in Figure 24--13. The
sequence of calculations used to obtain the beat to beat APD
values after a change in BCL are shown by the inset. Given the
initial conditions of BCL = 700 msec and APD = 365 msec,
the solution was carried out as follows: (1) calculate DL after
the last action potential before the BCL change: that is, BCL -
APD = 400 - 365 = 35 msec. (2) Find on the R function
the first APD value (APD1) that corresponds to DL = 35 msec
after the BCL change. In this case, APD1 = 270 msec. (3)
Repeat step 1 using APD1 to find DI1 (130 msec). (4) Repeat
step 2 for APD1 using DI1, (5) Use APD2 (320 msec) to find DI2,
and so on. These iterations are continued in search of a steady
state value of APD.

The graphical solution of [Eq 6] is also straightforward, as
indicated by the sequence of arrows in Figure 24--13. Each time
BCL - APD is calculated, the resultant DI value falls on the
straight line with slope = -1, whose origin on the abscissa cor-

![Figure 24--13. Graphic prediction, in a hypothetical case, of the dynamics induced by a sudden basic cycle length change from 700 msec (BCL1) to 400 msec (BCL2). Parameters used for the graphic solution are defined in the panel to the right. Numbered trajectories indicate the following steps of the solution: From 1 to 2, BCL - APD = DL0, 2 to 3, APD1 = f(DL0); 3 to 4, BCL - APD = DI1; 4 to 5, APD2 = f(DI1). Successive steps (from point 5 on) follow the same rules. Dotted vertical lines indicate the predicted diastolic intervals (DI). Horizontal dotted lines indicate predicted action potential durations (APD). (From Chialvo DR, Jalife J: Circ Res. In press.)](image-url)
responds to the BCL. Hence, to solve [Eq 6] for APD at any given BCL, the following steps are traced: (1) from the starting point on the R function before the BCL change (i.e., at APD, = 365 msec), a horizontal arrow of magnitude BCL - APD, will hit the BCL line exactly at the DI, value of 35 msec (dotted vertical line in figure); (2) from DI, one must now draw a vertical toward the R function to find APD; and (3) then move again horizontally toward the BCL line to find DI, and so on. Eventually, this iteration of R will encounter the steady state value of APD. In this particular case, such a value falls at the intersection of the R function with the BCL line. This simple procedure allows one to investigate the asymptotic behavior of any given function relating APD to the previous diastolic interval.

In the example of Figure 24-13, a change of BCL from 700 to 400 msec leads to a series of APD alternations of decreasing amplitude, but the system eventually settles into a steady state APD and maintains a stable 1:1 pattern. Intuitively, it is obvious that changing the slope of the R function at the intersection with the BCL line, or increasing the rate, will change the magnitude of the APD alternation, as well as the number of iterations needed to reach the steady state. In fact, at certain critical slope values, a steady state with constant APD may never be reached. Indeed, when the slope is 1, the conditions for non-damped APD alternans hold, giving rise to a 2:2 pattern. However, because the BCL range in which the slope value of 1 exists is very narrow, a small perturbation can induce a transition from 2:2 to 1:1 locking. In conclusion, when APD changes are the exclusive determinants of the behavior, an increase in stimulus rate eventually leads from 1:1 to 2:1 after undergoing a brief unstable transition in which a 3:2 pattern is recorded. Following the same line of thought, a direct transition from 2:1 to 3:1 should be expected as the BCL is further abbreviated. The point is that if [Eq 6] is solved graphically or numerically (Fig. 24-13) for a wide range of BCLs, the predicted locking patterns will be generally stable and will follow the so-called period-adding sequence, defined as N:1 with N growing from 1 to ∞ (see Fig. 24-1).

POSTPolarization
REFRactoryness and the FAREY TREE

The effects of latency on the behavior can be neglected when the absolute value of latency is small in relation to the APD changes. However, when substantial activation delays occur, for example, in the presence of postpolarization refractoriness (Rosenblueth, 1958), the latency function becomes the relevant variable, particularly if it is prolonged at relatively late diastolic intervals: that is, at intervals at which APD remains unchanged. In this case, the DI of any beat is determined by the contribution of both APD and latency. Therefore, the set of equations describing this situation is

\[ \text{DI}_n = \text{BCL} - \text{APD}_n - L_n \quad (a) \]

\[ \text{APD}_{n+1} = R(\text{DI}_n) \quad (b) \]

\[ L_{n+1} = F(\text{DI}_n) \quad (c) \]

In Figure 24-14, idealized F and R functions are plotted in the manner described previously (see Fig. 24-13). In this case, however, a new function (dotted line in figure) results from the addition of F and R. This new function, together with the diagonals (BCL line), is used to solve graphically step (a) in [Eq 7]. The asymptotic behavior for any BCL can now be investigated using a similar iterative procedure as that described for APD in Figure 24-13. However, because the relevant function here has a positive slope, it is predicted that a new kind of activation pattern should emerge as the rate is increased. The typical conditions for 1:1 locking are represented in Figure 24-14, whereas the conditions for the occurrence of a 4:3 Wenckebach pattern and 2:1 block during systematic BCL shortening are presented in Fig. 24-14B and C, respectively. The overall results indicate that when latency becomes the relevant parameter, predictable phase-locking patterns of the n + N:m + M type should be recorded at wide ranges of BCL. In fact, according to the model, the conditions used to obtain the data in Figure 24-14 predict the construction of a complete Farey tree when an appropriate range of BCL is carefully explored.

SUPERNORMALITY INDUCES DISCONTINUITIES IN THE RELEVANT FUNCTION

As can be concluded from the previous two sections, depending upon the experimental conditions, the dynamics of two different types of rate-dependent block processes can be explained by the dependence of DI on the previous latency or APD value. In either case (Figs. 24-13 and 24-14), the relevant function (APD restitution or latency curves) used to predict the dynamics is continuous over a range of diastolic intervals limited by the refractory period. In both cases, the recovery of
excitability was considered to be monotonic and, consequently, in both cases, activation failure would occur only when a given stimulus falls at the earliest diastolic intervals (i.e., during the refractory period). However, the presence of supernormality in the recovery of excitability can create discontinuous functions, in which case the definition of refractory period becomes ambiguous. Discontinuity itself induces new kinds of rate-dependent block processes that are not predicted by the Farey tree and that may be demonstrated to correspond to deterministic chaos.

Figure 24-15 illustrates the conditions in which such a discontinuity is created when an appropriate stimulus strength is selected in a tissue showing supernormality and which nevertheless can give rise to regular rhythms at wide ranges of BCL. The three graphs shown in each panel correspond to the R function (top), the strength-interval curve (middle), and the predicted beat to beat APD changes (bottom) for the particular BCL. The R function was reconstructed using experimental data values (APD and diastolic interval, dots in top graph) obtained from the patterns (1:1; 2:1; 3:1, and 4:2) illustrated in Figure 24-7. In the strength-interval curve (already presented in Fig. 24-5B.), the shaded region indicates the stimulation current strength (27 μA). Since strength is constant, it is subthreshold for an intermediate range of diastolic intervals and

**FIGURE 24-15.** Graphic solutions for different periodic dynamics (A, 1:1; B, 2:1; C, 3:1; D, 4:2) associated with supernormality using the reconstructed function from the experimental traces presented in Figure 24-4A (BCLs of 2000, 1000, 500, and 400 msec for A to D, respectively). In each panel, top graphs are recovery (i.e., "G-function") maps, middle graphs are excitability curves, and bottom graphs show predicted beat to beat APD changes. Solid diagonal lines indicate BCL, or in case of failure, multiples of BCL (2*BCL, 3*BCL). In each panel, dotted vertical lines mark the boundaries in the discontinuity in the G-function resulting from the relatively low current pulse strength (shaded region). (From Chialvo DR, Jalife J: Circ Res. In press.)
yields a discontinuity in the R function (dotted vertical lines in figure), which means that those intermediate APD values could not be observed at this stimulus amplitude. The diagonals in each top graph represent the BCL (as in Fig. 24-13) or, after a dropped beat, a multiple integer of BCL (i.e., 2*BCL or 3*BCL). Figure 24-15A through D shows the dynamics predicted for various cycle lengths. As in the case of Figure 24-13, the graphics iteration begins by drawing a horizontal arrow from the asymptotic value of APD at the starting cycle length to the new BCL line. In Fig. 24-15A (BCL = 2000 msec), the system rapidly settles into a steady state 1:1 pattern with constant APD (424 msec, point 1). In Fig. 24-15B, the second iteration occurs within the discontinuity in the R function and failure occurs (point 2). The diastolic interval in the next beat is equal to DI + BCL. Graphically, this operation can be solved using a second diagonal (indicated as 2*BCL), whose intersection with the R function predicts the next APD value (point 1). In this condition, a stable 2:1 pattern is established in which the APD alternates between 0 and 428 msec, and recovery time changes between 575 msec and 1575 msec. A 3:1 pattern is predicted in Fig. 24-15C when the BCL is shortened to 500 msec. In this case, one action potential (APD = 420 msec, DI = 1090 msec, point 1) is followed by two consecutive failures at diastolic intervals of 90 (point 2) and 590 msec (point 3). Finally, the development of a 4:2 pattern is predicted by the solution presented in Fig. 24-15D when the BCL is shortened to 400 msec. In this case, the second iteration (point 2) occurs at the supernormal phase (DI = 10 msec), predicting a relatively short action potential (APD = 265 msec). Two successive dropped beats occur at 400, 400, and 400 msec (points 3 and 4, respectively) before the iteration returns to the allowed portion of the R function (point 1: APD = 410 msec, DI = 935 msec).

When a careful analysis at cycle lengths intermediate to those illustrated in Figure 24-15 is carried out, the model predicts that the unique sequence at this particular stimulation amplitude is 1:1 -> 2:1 -> 3:1 -> 4:2, which agrees with the experimental results shown in Figure 24-7. A second type of 2:1 response at an even longer BCL is also observable in the graphical solution (not illustrated). In this case, the BCL line intersects the R function on the left side of the discontinuity.

Moreover, our analysis indicates that this 2:1 pattern is preceded by unstable patterns like those illustrated in Figure 24-7. Hence, the model results, together with the experimental finding, suggest that in the presence of supernormality in the recovery of excitability, the same pattern can reappear at two widely different BCLs (e.g., 2:1 at BCLs 1200 msec and 200 msec in Fig. 24-7), which would be incompatible with the monotonic case.

In summary, from the analysis of Figure 24-15, it is clear that the different behaviors observed experimentally in the three ranges of stimulus intensity (see Fig. 24-9) can be related to the presence or lack of discontinuity in the R function. In range I, this function is continuous and non-linear. Consequently, the expected behavior for any stimulation intensity within this range is a period-adding sequence (1:1, 2:1, 3:1, and so on). Upon increasing the stimulus strength to range II, the function becomes discontinuous (see Fig. 24-15) and divides into a linear portion at short diastolic intervals and a non-linear portion at short diastolic intervals. This results in much more complex excitation patterns, such as those illustrated in Figure 24-15.

Finally, in range III, the R function is again continuous and non-linear as in the hypothetical example of Figure 24-13 (see previous text).

CHAOTIC RHYTHMS AND SUPERNORMALITY

One of the most interesting dynamical consequences of the presence of supernormality is the generation of discontinuities, which explains the appearance of complex sequences of stable locking patterns as the BCL is shortened. Moreover, when the R function is both discontinuous and non-linear, chaotic dynamics can be demonstrated. The conditions necessary to produce such very irregular activity are illustrated in Figure 24-16. For this example, experimental APD-DI data pairs from Figure 24-9 were used to reconstruct the R function. Similar results can be obtained from the data presented in Figure 24-11. The most relevant feature in this case is that the slope of the R function is slightly greater than 1. Points 1 through 6 show the predicted graphical solution in complete agreement with the evolution of the experimental data presented in Figure 24-9. Application of a very simple stability analysis highlights the essential property determining chaotic dynamics under this condition. When an initial condition (asterisk) different from point 1 (APD 5 msec and DI 100 msec longer) is chosen, it is possible to determine the way in which any initial "error" is handled by the system and consequently to know whether or not a stable steady state will be achieved. When the same procedure is applied to the previous examples of regular rhythms (Figs. 24-13 through 24-15), any difference in initial conditions is dampened in a few beats. Therefore, in such cases the asymptotic behavior is labeled as stable.

However, under the conditions of deterministic chaos, the system will never reach a unique steady pattern, which is one reason why deterministic chaos is also known as the most complex form of steady state (Moon, 1987). For illustration purposes, dark shaded areas in Figure 24-16 can be regarded as the predicted trajectories for the range of initial conditions between point 1 and the asterisk. From points 1 to 4, the initial 5-msec difference in APD is amplified up to 30 msec, and the predicted trajectories are split into two groups: one group (stippled region) predicts two successive action potentials (close to points 3 and 4), whereas the other group (grid region) leads to two dropped beats (close to points 5 and 6) before reaching the vicinity of point 1 with a difference smaller than the initial one. In successive iterations, this remaining error increases and decreases but never dissipates. This results in an extremely aperiodic activity in which the main characteristic is a cycle of a variable number of action potentials with increasing alternans.
(i.e. amplification) followed by one or two dropped beats that "reset" the system, although not completely. In any non-linear chaotic system, this property of "amplification and reset" (which has also been termed stretching and folding [Moon, 1987]) is essential for demonstrating deterministic chaotic motion. Thus, we have concluded that as in other non-linear systems, multirhythmality is an expression of deterministic chaos in our preparations.

In these tissues, the "amplification" or "stretching" is provided by a critical value (higher than 1) of the slope of the R function at very early diastolic intervals, whereas the presence of supernormality at these same intervals induces a discontinuity in the restitution function, leading to "reset" or "folding." Together these features produce this characteristic sensitivity to initial conditions, which distinguishes deterministic chaotic activity from any other irregular phenomenon resulting from the influence of external random noise.

■ MEMORY VERSUS CHAOS

The analysis of the experimental results predicts the demonstration of sensitivity to initial conditions and chaotic dynamics of excitation when there is supernormal excitability, as well as a critical slope in the APD restitution function. Conversely, our results (Chialvo et al., in press) and those of others (Elharrar et al. 1983) indicate that a "memory" process during repetitive stimulation leads to a gradual decrease in the steepness of the APD versus DI function by modifying the original restitution curve. Thus, it would be expected that the possibility of demonstrating chaotic dynamics should decrease as the memory process gradually develops. Indeed, results from numerical simulation (Chialvo et al., in press) have shown that the additional of memory should suppress the chaotic dynamics. However, in these simulations the establishment of regular periodicity required more than 200 consecutive events. From a rigorous mathematical point of view, this behavior can be regarded as transient chaos (Moon, 1987). Yet, for practical purposes, and because of its potential electrophysiological implications, such a transient event is long enough to be considered more than a mathematical curiosity.

■ SUMMARY OF PREDICTED BEHAVIORS

Several simulations have been carried out by numerical solution of our difference-equation model for monotonic as well as non-monotonic forms of recovery of excitability. In each case, wide ranges of BCLs (1-msec steps) and current strengths (0.1μA-steps) were explored in an effort to search for the presence or lack of responses characterized by constant n:m ratios. Also in each case, at any selected combination of BCL and strengths, the activation n:m ratio was calculated (after transients) for every single iteration, until a constant pattern, or lack thereof, was detected.

The results of these simulations are presented in the form of parameter planes. In Figure 24–17A, data were obtained for the case of monotonic recovery, Figure 24–17B shows the results gathered in the presence of supernormal excitability. The lines are the boundaries between the most important ARs. When supernormality (Fig. 24–17A) is lacking, gradual changes in BCL, or strength yield gradual and predictable changes in the AR. In Figure 24–17B, it is clear that a horizontal section through this plane at any level of strength greater than the "0" boundary results in a staircase plot similar to that found experimentally during high KCl superfusion (see Fig. 24–5). In contrast, when the supernormal recovery of excitability is incorporated into the model equation, the structure of the parameter plane (Fig. 24–17B) was similar to that inferred from the experimental results during low KCl superfusion (see Fig. 24–6). In Figure 24–17B, the parameter plane has been divided into three major regions, depending on the patterns recorded. Within region I, the organization of the various stimulus to response sequences is similar to that described for the entire parameter plane of Figure 24–17A; any change in BCL or strength led to a predictable change in conduction ratio. The same holds true for region III above the upper boundary of the parameter plane. However, between two boundaries there lies a "critical zone" (region II), in which parameter changes may lead to complex ARs (dashed regions) and to apparently unpredictable transitions.

■ CONCLUSIONS AND FUTURE DIRECTIONS

Whether or not chaos theory is relevant to cardiac electrophysiology, and whether or not the dynamic approach used in our investigation can improve our present understanding of the electrophysiological basis of cardiac rhythm disturbances, may depend on finding answers to the following questions:

1. Is the chaotic activation originated in a main Purkinje branch transported downstream to the ventricular muscle with which it connects?

![Figure 24-17](image-url)
2. Are there any other cardiac tissues or perhaps mechanisms through which non-linearities induce chaotic dynamics?
3. Is chaotic cardiac activity a mathematical curiosity that is demonstrable only under artificial conditions or does it actually occur in vivo? If it does, what are the relationships among chaotic activity, vulnerability, and fibrillation?
4. Is there a cause and effect relationship between chaotic activation and dispersion of refractoriness?
5. Should the whole concept of vulnerability to arrhythmia be redefined using these concepts?
6. Do antiarrhythmic agents decrease the non-linearities of the relevant functions in Purkinje or ventricular muscle, or both?
7. Would a new view of anti- or proarrhythmic effects, which takes into consideration only the degree of non-linearity in the system, be consistent with the postulated mechanism of ventricular arrhythmias?

We have already suggested that deterministic chaos may be relevant to the study of irregular cardiac rhythms, particularly in relation to potential manipulation of non-linear parameters. By focusing on the role of non-linear electrical properties of cardiac tissues and their modification by various manipulations, further studies using a dynamical systems approach might help to answer many of these questions and determine whether antiarrhythmic and proarrhythmic effects could be predicted. In this regard, recent results (Varro et al., 1985, 1987) in dog Purkinje fibers and ventricular muscle have shown that some of the class I antiarrhythmic drugs, (i.e., quinidine, lidocaine, mexiletine, and flecaïnine) decrease the average slope of the restitution curve at premature coupling intervals. Depending on the drug used, such effects could be related to a slowing of Na-current kinetics, a shift in the restitution curve, or a prolongation of the effective refractory period. Whatever the mechanism, it might be possible that in all cases the net effect might have been a reduction in the non-linearities of the fibers' electrical properties. In other words, the dynamical effect of class I antiarrhythmic agents may be similar to that of memory, which would tend to suppress the chaotic behavior. Conversely, the proarrhythmic (prochaotic?) effects of some of these agents (e.g., quinidine) might be explained on the basis of an increase in the slope of the APD restitution at very short coupling intervals.

REFERENCES