# modeling methodology forum

# Dynamics of pure parasystole

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GLASS, LEON, ARY L. GOLDBERGER, AND JACQUES BÉLAIR. Dynamics of pure parasystole. Am. J. Physiol. 251 (Heart Circ. Physiol. 20): H841-H847, 1986.-A mathematical model is proposed for ventricular parasystole. In this model, there are two separate rhythms, a sinus rhythm and a ventricular ectopic rhythm. An ectopic beat will occur if the ectopic depolarization falls during a time interval when the ventricles are not refractory. Following an ectopic beat there is a compensatory pause. Analysis of this model, utilizing numerical simulation and techniques in number theory, demonstrates several new rules for parasystole. Specifically, for any set of fixed values for the sinus and ectopic frequencies and the ventricular refractory time, there are at most three different values for the number of sinus beats between ectopic beats. One and only one of these values is odd, and the sum of the two smaller values is one less than the larger value. The variation in the allowed values of the number of sinus beats between ectopic beats, as a function of the parameters of the model, is classified. Clinical cases found in the literature display certain aspects of the predictions of the theoretical model. Theoretical analysis of this kind provides new approaches to assessing the mechanism of complex ventricular arrhythmias.

ventricular cardiac arrhythmia; number theory; cardiac oscillator

VENTRICULAR ARRHYTHMIAS are of major clinical importance because of their role in the pathogenesis of the sudden cardiac death syndrome. Ventricular ectopic beats may be due to at least one of the two following major mechanisms (4): abnormalities in cardiac conduction (e.g., reentry) and abnormalities in impulse formation (e.g., enhanced automaticity). Perhaps the best characterized example of abnormal automaticity is ventricular parasystole.

Ventricular parasystole is a cardiac arrhythmia characterized by three distinctive features on the electrocardiogram (19, 22) 1) variable coupling intervals between the sinus and the ventricular ectopic rhythm; 2) interectopic intervals that are multiples of a common divisor; and 3) the presence of fusion beats. The postulated mechanism for ventricular parasystole is the presence of an autonomous ectopic focus generating beats at a fixed rate. Because of entrance block, this automatic focus is not affected by the normal sinus rhythm. The ectopic focus generates a propagated action potential if the ectopic depolarization falls outside of the normal refractory period of the myocardium.

The concept of ventricular parasystole was formulated over 70 yr ago (5, 13). Subsequent research has shown that there can be complex interactions between the parasystolic focus and the sinus rhythm. For example, Levy et al. (17) demonstrated in experiments in dogs that ectopic beats lead to alterations in blood pressure which in turn affect the sinus rhythm via baroreceptor and other reflexes. More recently, Jalife, Moe, and co-workers (9-11, 20) have argued that a parasystolic focus might be influenced by the underlying normal sinus rhythm via electrotonic coupling. The sinus rhythm impulse would lead to a phase-resetting of the ectopic rhythm. The resulting rhythm, termed "modulated" parasystole would show deviation from the dynamics expected in "pure" parasystole. A number of previously reported clinical studies were shown to be consistent with modulated parasystole (9). Recent studies have shown that phase resetting curves can be derived from electrocardiogram (ECG) records in favorable situations (3, 9, 21). Furthermore, arrhythmias usually ascribed to reentry (such as ventricular bigeminy or trigeminy with fixed coupling between sinus and ectopic beats) may also result from a modulated parasystolic mechanism (9, 10).

Although several theoretical analyses of the dynamics of modulated parasystole have appeared (8, 20, 26), a careful theoretical analysis of pure parasystole has not yet been made. At first inspection, pure parasystole appears to present a straightforward situation devoid of dynamical subtleties. Detailed analysis, however, reveals that pure parasystole generates a surprising richness of dynamical behavior, including striking regularities and structure that have not been previously described. In the main body of this paper, directed toward physiologists and cardiologists, we present the model for ventricular parasystole, describe the dynamics of this model, and discuss the results in the context of clinical cardiology. In the APPENDIX, we give derivations of many of the theoretical results. This work shows how techniques in number theory (25) can be used in the analysis of cardiac arrhythmias.

## Theoretical Model of Pure Parasystole

We assume the mechanism for pure parasystole proposed by Fleming (5) and Kaufman and Rothberger (13), illustrated in Fig. 1. Assume that there is a normal sinus rhythm of period  $t_{\rm S}$  and an ectopic rhythm with period  $t_{\rm E}$  with  $t_{\rm E} \ge t_{\rm S}$ . After each sinus beat there is a refractory period,  $\theta$ . If the ectopic rhythm generates an impulse during the refractory period, then it is blocked. If the ectopic rhythm generates an impulse outside of the refractory period it leads to an ectopic beat. After each ectopic beat, the next sinus beat is assumed to be blocked, resulting in a "compensatory pause".

To simulate this on a digital computer it is essential to choose  $t_{\rm S}$ ,  $t_{\rm E}$ ,  $\theta$ , and the initial phase of the ectopic beat in the sinus cycle. For each different set of four parameters, a time sequence giving the number of sinus beats between ectopic beats is generated. Analysis of the dynamics as a function of the four parameters is obviously unwieldy. However, consideration of the mathematical structure of the model for parasystole leads to a simplification that eliminates two parameters. The following considerations simplify the numerical simulations: 1) Independent variation of both  $t_{\rm S}$  and  $t_{\rm E}$  is not needed, since we can use  $t_{\rm S}$  to set the scale of time and measure  $t_{\rm E}$  relative to  $t_{\rm S}$ . This reduces the number of parameters by 1. 2) Two numbers,  $x_1$  and  $x_2$ , are said to be rationally related if it is possible to find two integers, p and q, such that  $px_1$  equals  $qx_2$ . In this case, the ratio,  $x_1/x_2$  equals q/p, which is a rational number. In the situation that  $t_s$  and  $t_E$  are rationally related, the dynamics may be sensitive to the initial condition. This is illustrated in Fig. 2, in which we show the dynamics for two initial conditions with  $t_{\rm E}/t_{\rm S} = 1.5$  and  $\theta/t_{\rm S} = 0.4$ . In one case there is a periodic pattern in which there are two sinus beats between each ectopic beat (Fig. 2A), and in the second case there is a periodic pattern in which there are alternately no sinus beats and one sinus beat between ectopic beats (Fig. 2B). For the situation in which  $t_{\rm S}$  and  $t_{\rm E}$  are not rationally related (i.e.,  $t_{\rm E}/t_{\rm S}$  is irrational), the asymptotic properties of the dynamics are insensitive to the initial condition. In practice, it is impossible either to represent the ratio  $t_{\rm E}/t_{\rm S}$  by an irrational number, in numerical simulation, or to perform a finitely precise measurement of  $t_{\rm E}/t_{\rm S}$  that would give an irrational result. However, in the simulations, we increment the ratio  $t_{\rm E}/t_{\rm S}$  by  $0.01 \times \pi$  where  $\pi$  equals 3.141592 and iterate for 1,000 sinus cycles. By choosing ratios for which  $pt_{\rm E}$  equals  $qt_{\rm S}$  only for large values of p and q, we minimize the effects of the initial condition, and consequently simulations are carried out only from one initial condition. It would also be possible to choose values of  $t_{\rm E}$  and  $t_{\rm S}$  so that  $pt_{\rm E}$  equals  $qt_{\rm S}$  for small values for p and q, but doing so would require averaging the results over several initial conditions. The rules given in the next section are also valid for  $t_{\rm E}/t_{\rm S}$  rational (see APPENDIX).

In summary, in the mathematical model we systematically vary the refractory period and the ratio  $t_{\rm E}/t_{\rm S}$  and determine the resulting dynamics.

# **Dynamics**

One way to characterize cardiac rhythms such as parasystole in which there are frequent extrasystoles is to count the number of normal sinus beats intervening between ectopic beats. Studies have shown that occasionally the number of normal beats between ectopic beats follows some simple arithmetic laws as in the situations in which all intervals are composed of odd numbers ("concealed bigeminy"), or all intervals assume a value (3N-1) ("concealed trigeminy"; 22–24). Variants of these rhythms have also been described (16). Although the sequences giving the number of sinus beats between ectopic events and histograms of these values can be readily determined from ECG data, and readily computed in mathematical models, a systematic analysis of such distributions has not yet appeared.

We computed the histograms showing the number of sinus beats between ectopic events over a range of ratios of  $t_{\rm S}$  and  $t_{\rm E}$  and for several values of  $\theta$ . The results of the simulations can be presented graphically. Let p(a), p(b), p(c) be the probability that there are a, b, or c, respectively, sinus beats between two given ectopic events. Note that p(a) + p(b) + p(c) equals 1. We now plot p(a), p(b), p(b), p(c) = p(a) + p(c)and p(c) as a function of  $t_{\rm E}/t_{\rm S}$  for  $\theta/t_{\rm S}$  equals 0.4 in Fig. 3A, and for  $\theta/t_s = 0.6$  in Fig. 3B. The values of a, b, and c are given on the curves. It is also possible to show the allowed values of a, b, and c in the  $(\theta/t_{\rm S}, t_{\rm E}/t_{\rm S})$  plane. This is done in Fig. 4, which is based on numerical calculations and a theoretical construction described in the APPENDIX. The labeled regions show the values for the number of sinus beats between ectopic events. In the unlabeled regions, it is also possible to determine the number of sinus beats between ectopic events using the construction in the APPENDIX, but the zones become so small they are not easily presented on the scale of the figure. The following rules summarize the calculations.



FIG. 1. Schematic of the model for parasystole. Sinus rhythm (S) and ectopic rhythm (E) are shown. Refractory time is represented as a shaded region. Any ectopic beat that falls outside refractory time is conducted (filled arrows) and leads to a blocking of the subsequent sinus beat (dashed lines). Ectopic beats falling during refractory time are blocked (open arrows). In the illustration  $\theta/t_s = 0.4$ ,  $t_E/t_s = 1.65$  and there are either 1, 2, or 4 sinus beats between ectopic events.



FIG. 3. Histograms showing relative numbers of sinus beats between ectopic events as a function of  $t_{\rm E}/t_{\rm S}$ . A:  $\theta/t_{\rm S} = 0.4$ ; B:  $\theta/t_{\rm S} = 0.6$ . In the neighborhood of the integers in A and B and the half-integers in B there is an infinite cascade of peaks that is too fine to be clearly represented by this graph. We give *dotted lines* to indicate this.

Rule 1. For any ratio of  $t_{\rm E}/t_{\rm S}$  there are at most three different values for the number of sinus beats between ectopic events.

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

Rule 3. For any value of  $t_{\rm E}/t_{\rm S}$  at which there are three different values for the number of sinus beats between ectopic events, the sum of the two smaller values is one less than the larger value.

The sequences of the number of sinus beats between ectopic events also show regularities, which at the moment are not yet completely understood. However, some simple properties of the sequences can be readily determined. The following simple and useful result can be easily derived (see APPENDIX).

Rule 4. Consider the sequence giving the number of sinus beats between ectopic events in which there are

FIG. 2. Illustration showing dependence of parasystolic rhythm on initial condition when  $\theta/t_{\rm S} = 0.4$ ,  $t_{\rm E}/t_{\rm S} = 1.5$ . See Fig. 1 for explanation of symbols.

three different values for the intervals. One and only one of these values can succeed itself.

### DISCUSSION

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The proposed mechanism for parasystole can be traced at least back to 1912, when Fleming (5) described two cases in which he hypothesized "the ventricles are following a rhythm set by two pacemakers, one at the sinoauricular node, producing physiological beats, and another at an irritable focus in the ventricle, which is rhythmically discharging stimuli at the customary rate of ventricular stimulus production, thus giving rise to extrasystoles." Despite this early recognition of a plausible mechanism for parasystole and reconsideration of the rhythm innumerable times by many investigators in intervening years, a detailed study of the dynamics of parasystole has apparently not previously appeared.

Examination of the literature reveals clinical studies of parasystole displaying some of the features displayed in Fig. 3. For example, Kinoshita (14) (case 7, Fig. 5, strips 2–4) describes a case in which  $t_{\rm E} \simeq 1.65$  s,  $t_{\rm s} \simeq 1.00$ s,  $\theta \simeq 0.4$  s,  $\theta/t_{\rm S} \simeq 0.4$ ,  $t_{\rm E}/t_{\rm S} \simeq 1.65$ . Examination of the histograms shows that  $p(1) \simeq 0.43$ ,  $p(2) \simeq 0.47$ ,  $p(4) \simeq$ 0.10. In the tracing presented by Kinoshita the sequence for the number of sinus beats intervening between ectopic beats is 1, 4, 2, 2, 4, 4, 2, 1, 4. Although the only intervals which are observed are 1, 2, and 4, as predicted, the relative ratios of these intervals are not as theoretically predicted. Furthermore, the values 2 and 4 both appear as doublets, and thus rule 4 above is not obeyed. A similar case is in Schamroth (22) (case 79) in which  $t_{\rm E}$  $\simeq 1.5$  s,  $t_{\rm S} \simeq 0.92$  s,  $\theta \simeq 0.55$  s,  $\theta/t_{\rm S} \simeq 0.6$ ,  $t_{\rm E}/t_{\rm S} \simeq 1.65$ . For this case we theoretically predict  $p(1) \simeq 0.14$ ,  $p(2) \simeq$  $0.20, p(4) \simeq 0.66$ . Here, the sequence giving the number of sinus beats between ectopic beats is 1, 2, 2, 2, 2, 2, 1, 1, 4, 2, 2, 2, 2. Once again the intervals but not their relative ratios are as predicted, and *rule 4* is not satisfied.

The two above cases are of interest when considered in light of a description of a variant of concealed bigeminy (16). In this variant the number of sinus beats between ectopic events is restricted such that there is only one sinus beat or else there is an even number of sinus beats between ectopic events. Examination of the  $(\theta/t_s, t_E/t_s)$  plane of Fig. 4 shows that all points in the triangular region in which vertices are at (0, 1), (0, 3), and (1, 2) would be classified as belonging to such a variant. However, in the two cases reported in (16), the interectopic intervals are not all multiples of a common divisor, thus excluding a pure parasystolic mechanism. We propose that even with modulation of the ectopic rhythm by the sinus rhythm, large regions of parameter space will display the variant described above. We have



FIG. 4. Allowed values for number of sinus beats between ectopic events in the  $(\theta/t_s, t_E/t_s)$  plane. Allowed values in unlabeled regions can be determined using the construction in the APPENDIX. In the triangular region with vertices at (0, 1), (0, 3), (1, 2) there is either only 1 or an even number of sinus beats between ectopic events.

found this variant in unpublished numerical studies of modulated parasystole. Thus, even in cases in which there is modulated parasystole, some of the features of pure parasystole will still be present (at least in some regions of parameter space).

As a final example, a fascinating case was reported by Lightfoot (18). A careful reanalysis of the data reported by Lightfoot shows that the record displays modulation, albeit of a comparatively weak nature (9). The case reported by Lightfoot is consistent with the variant described above at one time ( $t_{\rm E} \simeq 2.0$  s,  $t_{\rm S} \simeq 0.94$  s,  $\theta = 0.36$  s,  $t_{\rm E}/t_{\rm S} \simeq 2.1$ ,  $\theta/t_{\rm S} \simeq 0.38$ ). Two hours later the parameters had changed ( $t_{\rm E} \simeq 2.39$  s,  $t_{\rm S} \simeq 0.92$  s,  $\theta \simeq 0.38$  s,  $t_{\rm E}/t_{\rm S} \simeq 2.60$ ,  $\theta/t_{\rm S} \simeq 0.41$ ). At this later time only 2, 4, or 7 sinus beats were present between ectopic events. Examination of Fig. 4 offers a clear interpretation of this puzzling finding, since there is a shift from the region consistent with the variant described above to the 2, 4, 7 region over the 2-h period.

Although detailed analysis of longer consecutive records is needed, these reported examples show that some aspects of the dynamics of parasystole observed clinically can be explained by the simple model considered here. However, the mathematical model does not account for the detailed sequence of sinus beats observed in those examples or for the relative ratios of the number of intervening sinus beats. Although at the moment, the source of these discrepancies is not understood, there are several factors that this model does not incorporate which may account for its limitations.

1) The sinus and ectopic rhythms are assumed to be constant with a fixed ratio between them. More realistically, fluctuations in sinus rhythm (for example, by respiratory sinus arrhythmia) and ectopic rhythm may occur.

2) The sinus rhythm may act to modulate the parasystolic focus (3, 9-11, 20, 21).

3) Ectopic beats may lead to fluctuations in the blood pressure, which, in turn, lead to variation in the sinus rate (17).

4) There may be variations in the refractory time. For example, such fluctuations are normally expected as a

consequence of variation of the sinus rate (12).

A consideration of the above points shows that it is unrealistic to consider parameters to be constant, as we have done, but rather parameters should be allowed to fluctuate and vary as determined by the physiological situation. We expect that one of the effects of parameter fluctuation will be to "blend together" the results from several zones which span the range of parameter fluctuation. Thus, as  $t_{\rm E}/t_{\rm S}$  normally fluctuates over a range of values (both rational and irrational), and the refractory time varies, the values for the number of sinus beats observed between ectopic beats may span several of the zones observed in Fig. 4. Further, the sequences for the number of sinus beats observed between ectopic beats will deviate from those observed with constant parameters. However, novel values (i.e., values that are not expected in that region of parameter space) for the number of sinus beats between ectopic beats may also occur, and this will confuse the interpretation and make identification of a parasystolic mechanism more difficult. Analyzing the effects of parameter fluctuation is a challenging theoretical problem requiring closer analysis.

Although we have only considered ventricular parasystole resulting from sinus and ventricular ectopic rhythms, it is important to recognize that interactions of other autonomous pacemakers can lead to other types of parasystolic rhythm. For example, atrial parasystole results from interaction of sinus and atrial ectopic pacemakers (19). Parasystolic rhythms can also be set up between junctional escape rhythms and a ventricular ectopic focus (15). Interpretation of these rhythms is often complicated by the modulation of the basic rhythm, set by the sinus or junctional pacemakers, by the ectopic pacemaker (15, 19).

From a clinical viewpoint, the results of the present investigation may be of future relevance. Lengthy records of cardiac rhythms are routinely obtained in evaluating patients with frequent ectopic beats. Conventional analysis of such records has focused primarily on the frequency of the ectopic beats and the coupling intervals between the sinus and ectopic beats. The present study suggests that such analysis is incomplete and must be extended to include the distribution of the number of sinus beats between ectopic beats and the sequence in which the number of sinus beats between ectopic beats occur. Efforts should be directed to determine histograms of the number of sinus beats between ectopic events as a function of sinus rate. On the basis of the analysis here (Fig. 4) we expect that such data will show regularities if the rhythm is generated by a parasystolic mechanism. However, further investigation is needed to determine if such measures will be useful in concrete situations.

In summary, we have shown that an analysis of the properties of a simple model of pure parasystole reveals richer dynamics than has been recognized. Extension of the present results may be useful in developing more realistic models of parasystole, including the effects of fluctuations in parameters and pacemaker interaction.

#### APPENDIX

To theoretically analyze the mathematical model for pure parasystole described in the text it is convenient to make several modifications. Specifically we shall take the unit of time to be the sinus period. In the renormalized time frame the refractory time,  $\alpha$ , =  $\theta/t_s$  and the interectopic period,  $T_{\rm e} = t_{\rm E}/t_{\rm S}$ . Also, we shall assume that the beat following an ectopic event is not suppressed. Finally we take 0 < T < 1 and extend the result outside this range subsequently. Starting at some initial time,  $t_0$ ,  $0 < t_0 < 1$  generate the sequence  $\{t_j\}$ , where  $t_j = t_0 + jT$ . Alternately, we can consider the dynamics modulo 1 and take  $\phi_i = t_i$ (mod 1) representing the dynamics as points on the circumference of a circle. The model thus corresponds to a rigid rotation,  $\phi \rightarrow \phi + T$ , on the unit circle,  $S^1$ , where a continuous portion of the circle is distinguished from the remainder of the circle. This problem has been considered previously in the context of symbolic dynamics (7). In addition, in the final stages of preparation of this manuscript, we learned that several of our main results had been previously derived by number theorists (25) who used somewhat different methods.

One basic problem is to start with an initial value,  $\phi_{0\epsilon} [\alpha, 1]$ , and to determine the smallest integer, j, such that  $\phi + jT \pmod{1} \epsilon [\alpha, 1)$ . We can be sure that if  $\phi_{0\epsilon}[\alpha, 1)$  there will be a subsequent iterate such that  $\phi + jT\epsilon[\alpha, 1)$ . Assuming T to be irrational (this will occur with probability one if T is chosen randomly in a finite interval), successive iterates  $\phi_0, \phi_1, \ldots$  where  $\phi_j = \phi_0 + jT \pmod{1}$  will be dense in  $S^1$  and will come arbitrarily close to any predetermined point of the circle. In particular, some iterate will be in  $[\alpha, 1)$ . Furthermore this shows that the precise choice of the initial condition  $\phi_0$  is not fundamental in the following sense: given  $\delta > 0$  and  $\phi \neq \psi \epsilon S^1$ , there is an iterate  $\psi + jT$  that is closer than  $\delta$  to  $\phi$ . It is important to recognize that choosing T to be rational will still give the rules derived here, but somewhat different arguments must be employed (25).

We adopt the following notation

$$t_i = F^j(t_0) = t_0 + jT (1a)$$

$$\phi_i = t_i \pmod{1} = f^j(\phi_0) = \phi_0 + jT \pmod{1} \tag{1b}$$

Starting with initial values  $\alpha$  (or 1) we wish to find the smallest integers, m (or n), such that  $f^m(\alpha)$  [or  $f^n(1)$ ]  $\epsilon(\alpha, 1)$ . Alternately, we seek the smallest values of m and n that satisfy the inequalities.

$$A_m + \alpha \le F^m(\alpha) < A_m + 1 \tag{2a}$$

$$A_n + \alpha \le F^n(1) < A_n + 1 \tag{2b}$$

where  $A_m$  and  $A_n$  are integers. Applying (Eq. 1) we derive

$$\frac{A_m}{m} \le T < \frac{A_m + 1 - \alpha}{m} \tag{3a}$$

$$\frac{A_n - 1 + \alpha}{n} \le T < \frac{A_n}{n} \tag{3b}$$

The basic picture showing the mapping of the interval  $[\alpha, 1]$  on the unit circle to itself is shown in Fig. 5 where  $r = f^{-m}(1)$  and  $s = f^{-n}(\alpha)$ . Since the map is length preserving,  $r - \alpha = 1 - f^m(\alpha)$ ,  $s - r = f^m(\alpha) - f^m(\alpha)$ .



FIG. 5. Diagram showing the mapping of the  $[\alpha, 1)$  interval into itself (see text for details).

 $f^{n}(1)$ , and  $1 - s = f^{n}(1) - \alpha$ . Let u be any point  $\epsilon(r, s)$  and let p be the smallest integer such that  $f^{p}(u)\epsilon[\alpha, 1)$ . From Fig. 5 it is clear that

$$\alpha = f^{n}(s), \qquad (4)$$
$$f^{m}(\alpha) = f^{p}(s),$$

from which we find (since T is irrational)

$$p = m + n. \tag{5}$$

Applying Eq. 2 we have

$$F^{m}(r) = 1 + A_{m},$$

$$F^{n}(s) = \alpha + A_{n}$$
(6)

However from Fig. 5 we also have

$$F^p(s) = \alpha + 1 - r + A_p \tag{7}$$

where  $A_p$  is an integer. Applying Eq. 1a and combining Eqs. 5–7 we obtain

$$A_p = A_m + A_n \tag{8}$$

It is also possible to give a complete description of the dependence of the ratios  $A_m/m$ ,  $A_n/n$  (and hence also  $A_p/p$ ) on the two parameters  $\alpha$  and T. To the best of our knowledge, this analysis has not been previously presented. To proceed it is useful to first briefly point out the properties of the Farey series (6). The Farey series of order N,  $\mathcal{F}_N$ is the ascending sequence of fractions between 0 and 1 in which the denominator does not exceed N. The following two properties of the Farey series are well known (6): 1) If P/Q and P'/Q' are successive terms in  $\mathcal{F}_N$ , then P'Q - Q'P = 1 and Q + Q' > N. 2) If P/Q, P'/Q', P''/Q'' are three successive terms in  $\mathcal{F}_N$  and P'/Q' is not in  $\mathcal{F}_{N-1}$ , then P' = P + P'', and Q' = Q + Q''; P'/Q' is called the mediant of P/Qand P''/Q'', and the latter are called its generators. In addition, the following property can be derived using a simple induction argument: 3) If P/Q and P'/Q' are successive terms in  $\mathcal{F}_N$ , then either P or P'(or both) must be odd. Likewise, either Q or Q' (or both) must be odd.

To give the dependence of  $A_m/m$  and  $A_n/n$  on  $\alpha$  and T, we use a constructive method originally employed by Allen (1) and Bélair (2) in a somewhat different context. The basic idea is to determine values of  $A_m/m$  and  $A_n/n$  that satisfy Eqs. 3a and 3b as a function of  $\alpha$  and T. First consider Eq. 3a. Since  $\alpha$  and T are between 0 and 1, we only need consider  $m > A_m \ge 0$ . For m = 1, only  $A_m = 0$  need be looked at, and the corresponding values of  $\alpha$  and  $t_{\rm E}$  satisfy  $0 \leq T < 1 - \alpha$ : this is the triangular region illustrated in Fig. 6A, with vertices in the  $(\alpha, T)$  plane at (0, 0), (0, 1), and (1, 0). For m = 2,  $A_m = 0$  or 1 and we have two sets of values satisfying Eq. 3a, namely  $0 \le T < (1 - \alpha)/2$  and  $\frac{1}{2} \le T < (2 - \alpha)/2$  $\alpha$ )/2. For the first equation, it is clear that such values of  $\alpha$  and T already satisfy  $0 \le T \le 1 - \alpha$ ; for the second one, we have values in another triangular region, with vertices at  $(\frac{1}{2}, \frac{1}{2})$ ,  $(1, \frac{1}{2})$ , and (0, 1). For m = 3, only the values  $A_m = 1$  and 2 will lead to new sets of values of  $\alpha$  and T satisfying Eq. 3a; the regions will be based at the point (1,  $\frac{1}{3}$  and  $(1, \frac{2}{3})$ , respectively, and are illustrated in Fig. 6A. The only new zones are the ones associated with irreducible fractions  $A_m/m$ , that is, fractions with the numerator and the denominator relatively prime. The boundaries of the regions are also determined by the need for the successive fractions to be generated in increasing order of the denominators. It is in this context that the Farey series naturally occurs. The results of the construction showing all ratios up to the 4th-order Farey series are shown in Fig. 6A. The same procedure can also be applied with  $\phi = 1$ , using Eq. 3b and building the Farey series of  $A_n/n$ . This leads to Fig. 6B.



FIG. 6. Permitted values of the ratios  $A_m/m$  (panel A) and  $A_n/n$  (panel B) in the  $(\alpha, T)$  plane. Shows the construction described in the text up to order 4. Values for ratios in regions that are not labeled can be determined by extending the construction in the text to higher orders.



FIG. 7. Combined values for  $A_m/m$  and  $A_n/n$  in the  $(\alpha, T)$  plane. Shows the construction up to order 3.



FIG. 8. Diagram showing the mapping of the  $[\alpha, 1)$  interval into itself, showing the two different subcases.  $A'_m$  and  $A'_n$  represent number of sinus beats between ectopic events.

The most important things to notice from these figures are the following: 1) For a set of fixed, irrational values of both  $\alpha$  and T, there are unique fractions  $A_m/m$  and  $A_n/n$ , such that inequalities (Eqs. 3a and 3b) are satisfied, the inequalities being strict in both cases. 2) For the fractions  $A_m/m$  and  $A_n/n$  satisfying inequalities (Eqs. 3a and 3b), one is a mediant of the other and some other fraction in a Farey series: for example, if n < m, then  $A_m/m$  is a mediant of  $A_n/n$  and some other fraction. It follows from this property, that n and m are denominators of consecutive elements in a Farey series, that at least one of them (maybe both) must be odd. Likewise, either  $A_m$  or  $A_n$  (or both) must be odd.

Combining the zones associated with both  $\alpha$  and 1 in the  $(\alpha, T)$  plane, we obtain the regions shown in Fig. 7. Illustrated up to the Farey series of order 3 are the values of  $\alpha$  and T satisfying the inequalities (3). Inside each of the zones, the label indicates the values of  $A_m/m$  and  $A_n/n$ , respectively, obtained from the construction just described. Unlabeled zones correspond to ratios with higher denominators, and

could, in principle, be resolved to arbitrary precision.

The symmetries in the zones can now be explicitly stated.

1. Assume the point  $(\alpha, T)$  with 0 < T < 1 is associated with ratios  $A_n/n, A_m/m, A_p/p$ . Then for T' = 1 - T, the point  $(\alpha, T')$  is associated with ratios  $(n - A_n)/n, (m - A_m)/m$  and  $(p - A_p)/p$ , respectively. 2. Assume the point  $(\alpha, T)$  with 0 < T < 1 is associated with ratios

2. Assume the point  $(\alpha, T)$  with 0 < T < 1 is associated with ratios  $A_n/n, A_m/m, A_p/p$ . Then for T' = T + J and with J, an integer, the point  $(\alpha, T')$  is associated with ratios  $(A_n + nJ)/n, (A_m + mJ)/m, (A_p + pJ)/p$ .

The final step is to come back and make the connection with the model for parasystole. In the model we assumed  $t_E > t_s$  corresponding to T > 1. The numerators of the ratios for every value of T correspond to one more than the number of sinus beats between ectopic events (since we assume compensatory pauses). Thus there are at most three values for the number of sinus beats between ectopic events (*rule 1*). Calling  $A'_m = A_m - 1$ ,  $A'_n = A_n - 1$ , and  $A'_p = A_p - 1$  we derive *rule 3* from Eq. 8 to obtain

$$A'_{p} = A'_{m} + A'_{n} + 1 \tag{9}$$

Furthermore, since at least one of the values of  $A_m$  or  $A_n$  is odd, exactly one of the values of  $A'_m$ ,  $A'_n$ , and  $A'_p$  will be odd (*rule 2*). Finally, there are two basically different geometrical arrangements for Fig. 5, which are shown in Fig. 8. In Fig. 8A, the doublets  $A'_m A'_n$ ,  $A'_p A'_n$ ,  $A'_n A'_m$ ,  $A'_n A'_p$ ,  $A'_n A'_n$  can occur. In Fig. 8B, the doublets  $A'_m A'_p$ ,  $A'_m A'_n$ ,  $A'_p A'_p$ ,  $A'_n A'_n$  can occur. This is consistent with and extends *rule 4*.

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