

## Beyond a pacemaker's entrainment limit: phase walk-through

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ERMENTROUT, G. BARD, AND JOHN RINZEL. *Beyond a pacemaker's entrainment limit: phase walk-through*. Am. J. Physiol. 246 (Regulatory Integrative Comp. Physiol. 15): R102–R106, 1984.—Desynchronization occurs when a pacemaker is externally stimulated at too high a rate, beyond the entrainment limit. One may then observe phase walk-through: the pacemaker and stimulus phase difference, rather than lock to a fixed pattern, may cycle repeatedly through all values. By means of a simple but nonlinear one-variable model we describe qualitatively the properties of entrainment, loss of entrainment, and phase walk-through for rhythmically stimulated pacemakers. We obtain an expression for the cycle length (beat period) of the repetitive phase walk-through. This shows, in contrast to the simplest treatment, that in general beat frequency is not a simple linear function of the difference between the pacemaker and stimulus frequencies. Our results are illustrated in the context of a model experimental pacemaker, the rhythmically flashing firefly. We discuss how these modeling results apply in a much more general setting.

desynchronization; phase-locking; biological oscillators; beat frequency; firefly

NUMEROUS EXAMPLES (2, 5, 13, 15, 16) illustrate the ability of an external periodic stimulus to entrain a biological pacemaker. One-for-one entrainment is typically observed over a range of stimulus frequencies that includes the pacemaker's intrinsic frequency. When the stimulus frequency is tuned beyond the pacemaker's entrainment limit, desynchronization may occur. In many cases this loss of entrainment is only transient, and the pacemaker may again lock into a fixed-phase relationship with the stimulus but not in a one-for-one fashion. In other cases, e.g., for a weaker stimulus, desynchronization may persist. The pacemaker and stimulus phase difference, rather than lock to a fixed simple pattern, may cycle repeatedly through all values. This has been called phase walk-through (5). We will focus on this latter phenomenon and present a simple but nonlinear, one-variable model that qualitatively describes the properties of entrainment, loss of entrainment, and phase walk-through for rhythmically stimulated pacemakers. Moreover we obtain a quantitative expression

(Eq. 4), for the cycle length (beat period) of the repetitive phase walk-through. We illustrate these results in the context of a model experimental pacemaker, the rhythmically flashing firefly (2, 3, 5). The modeling results we present are robust. They apply in a much more general setting for the case of a weak periodic stimulus acting on a strongly attracting oscillator. Since this treatment does not include the special case of a weakly nonlinear oscillator that is weakly driven, we do not find the desynchronization phenomenon of "phase-trapping" (see 7).

### FIREFLY PACEMAKER

Certain Southeast Asian fireflies are known to flash rhythmically at intervals ranging from 400 to 5,000 ms in different species but typically at about 1-s intervals. These insects have the ability to synchronize their flashing with either an external source (zeitgeber) or with other fireflies of the same species. Current evidence suggests that the control of the rhythmic flashing is via a cellular pacemaker of unknown origin [see (2, 3, 5) for reviews]. The flashing, synchrony, and associated phenomena make the firefly a good model for other biological rhythms. Hanson (5) describes how the properties of the firefly oscillator are very similar to circadian pacemakers. Among the several known qualitatively different firefly pacemakers, we focus on *Pteroptyx malacca*, a common species from Malaysia. Certain of the data from *P. malacca* suggest that it falls into the weak forcing case.

Let  $T_0$  denote the natural period of the free-running firefly oscillator and  $T$  denote the period of the stimulus. For *P. malacca*,  $T_0 \approx 920$  ms. If  $T$  is sufficiently close to  $T_0$ , then the animal will entrain to the external forcing and flash with a period  $T$  at a distinct phase  $\phi$  of the stimulus cycle. In general,  $\phi$  will be a function of  $T$ . If  $T$  is too different from  $T_0$ , the animal cannot precisely entrain and the phenomenon of phase walk-through occurs; i.e.,  $\phi$  traverses all phases rather than remaining at a fixed phase. This phenomenon is depicted in Fig. 1. When  $T = 770$  ms the animal is able to entrain, but at the slightly higher frequency,  $T = 750$  ms, entrainment no longer occurs. Rather the animal flashes at many

different phases in the cycle, as illustrated by the lower curve. The top graph is the interval between successive flashes. During entrainment this interval is exactly  $T$ , the period of the zeitgeber. But during phase walk-through there is a long time scale, apparently periodic, modulation of the flashing interval with peak-to-peak times of the order of 10 s. Phase walk-through is a property (although not exclusively) of weakly stimulated oscillators. Additional evidence that *P. malaccæ* is experiencing a weak stimulus is its phase resetting curve [see (5), Fig. 6C], which is of *type 1* rather than *type 0*.

To reiterate, our goal is to give a simple, qualitative, mathematical description of phase walk-through, as well as to make some rigorous quantitative estimates. We show that the "beat periods," the long peak-to-peak times between maximal firing intervals during phase walk-through, are not simple linear functions of the difference between the oscillator and stimulus frequencies as suggested by Pavlidis (12). Rather they are nonlinear functions of the difference between the frequency of the zeitgeber and the limiting entrainment frequency. We find that our simple model also predicts the curvature seen in the phase plots of Fig. 1, as well as the "peakedness" of the firing interval plots. As stated previously and shown in the APPENDICES, the model is an example of a canonical description for weak forcing and phase walk-through of a much more general oscillator.

#### PHASE MODEL

Since the firefly oscillator is stable, it is not unreasonable to suppose the underlying physiological variables lie on an attracting limit cycle. Since such a cycle is equivalent to a circle, each point in the cycle can be described by a phase  $0 \leq \theta \leq 2\pi$ . That is, if a zero phase is chosen, i.e., the point at which the signal to flash is sent from the pacemaker, then all the states of the oscillator can be described by the phase, the time since the last signal was sent. The simplest model for this cycle is then

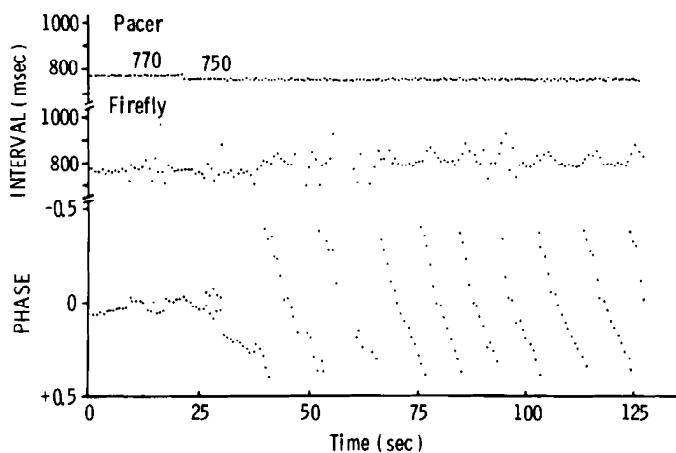


FIG. 1. Flash response of firefly *Pteroptyx malaccæ* for periodic stimulus with period near entrainment limit. Intervals of pacer (upper trace) and firefly (middle trace), and phase between them (lower trace), are plotted as functions of time. At beginning of graph, pacer period = 770 ms and mean phase =  $24 \pm 5$  (SE) ms; switching pacer period to 750 ms results in phase walk-through. [From Buck et al. (3).]

$$\frac{d\theta}{dt} = \frac{2\pi}{T_0} \quad (1)$$

Here,  $\theta$  goes from 0 to  $2\pi$  in  $T_0$  ms. The effect of the periodic stimulus must now be described. For convenience we suppose the stimulus acts continuously (non-constant) on the oscillator rather than impulsively. The external signal can lengthen or shorten the pacemaker's cycle duration by altering the rate  $d\theta/dt$  at which the oscillator pursues its trajectory. A point on the intrinsic cycle moves with an angular velocity  $\omega_0$ ,  $\omega_0 = 2\pi/T_0$ , whereas we suppose the zeitgeber travels at a velocity  $\omega$ ,  $\omega = 2\pi/T$ . The following assumptions are made: 1) if the zeitgeber is ahead of the firefly then  $d\theta/dt$  increases and thus the pacemaker fires earlier; 2) if the zeitgeber is behind the firefly then  $d\theta/dt$  decreases and the insect will fire later; and 3) the amount of increase or decrease of  $d\theta/dt$  is a function (e.g., linear) of  $\phi$  with no adjustment when  $\phi$  is a multiple of  $2\pi$ . Thus if  $0 < \phi < \pi$ , then the insect shortens the cycle (increases the flash frequency) and if  $-\pi < \phi < 0$  or  $\pi < \phi < 2\pi$ , the insect lengthens its cycle (decreases the frequency). This is illustrated in Fig. 2 for two cases, a direct linear dependence, solid, and a smoother dependence, qualitatively similar to  $\sin(\phi)$ .

With the phase difference given by  $\phi = \omega t - \theta$ , a simple model satisfying the above hypotheses is

$$\frac{d\theta}{dt} = 2\pi/T_0 + \beta \sin(\omega t - \theta) \quad (2)$$

where  $\beta$  measures the relative influence of the zeitgeber. Equation 2 shows that if  $0 < \phi < \pi$ , then the pacemaker speeds up, whereas for  $-\pi < \phi < 0$  the pacemaker slows down. This model, a particular example of a general one-variable description for a weakly forced oscillator (see APPENDIX A), can be solved exactly.

#### ENTRAINMENT AND PHASE WALK-THROUGH

First note that entrainment implies  $\phi$  remains fixed at some particular value for all times; i.e., the firefly always flashes at the same phase relative to the zeitgeber. To solve Eq. 2 we use  $d\theta/dt = \omega - (d\phi/dt)$ , so Eq. 2 becomes

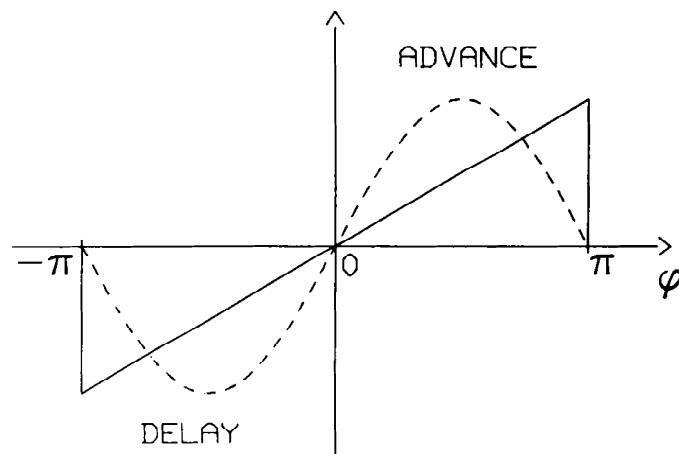


FIG. 2. Two examples of assumed dependence of phase adjustment on phase difference  $\phi$  between stimulus and pacemaker.

$$\frac{d\phi}{dt} = \frac{2\pi}{T_0 T} (T_0 - T) - \beta \sin(\phi) \quad (3)$$

In Fig. 3,  $d\phi/dt$  is illustrated for  $T_0 - T$  small and for  $T_0 - T$  large. If  $T_0 - T$  is not too large (Fig. 3A),  $\phi$  comes to rest at a fixed stable  $\phi_0$ . For  $T_0 - T$  too large (Fig. 3B)  $d\phi/dt$  is always positive and  $\phi$  never comes to rest but rather traverses the entire range of phases. Figure 4 depicts this phase walk-through behavior from the numerical solution to Eq. 2. Note the remarkable similarity to the firefly data of Fig. 1.

Figure 3B can be used to understand qualitatively and quantitatively Figs. 1 and 4. In Fig. 3B there are two distinct regions, shaded and unshaded. In the shaded region  $\phi \approx \pi/2$  and  $d\phi/dt$  is very small. Thus  $\phi$  spends most of its time nearly constant, near  $\phi \approx \pi/2$ . By substituting this into Eq. 2, one sees that  $d\theta/dt \approx \omega_0 + \beta$  for most of the time. This shows that the average frequency is much higher than that of the free-running pacemaker. The decreased average firing interval corresponds to Hanson's observation (5) that the average interval during walk-through is 814 ms, well below the free-running period 920 ms. Equation 2 and Fig. 3B also show that the minimum firing interval is approximately

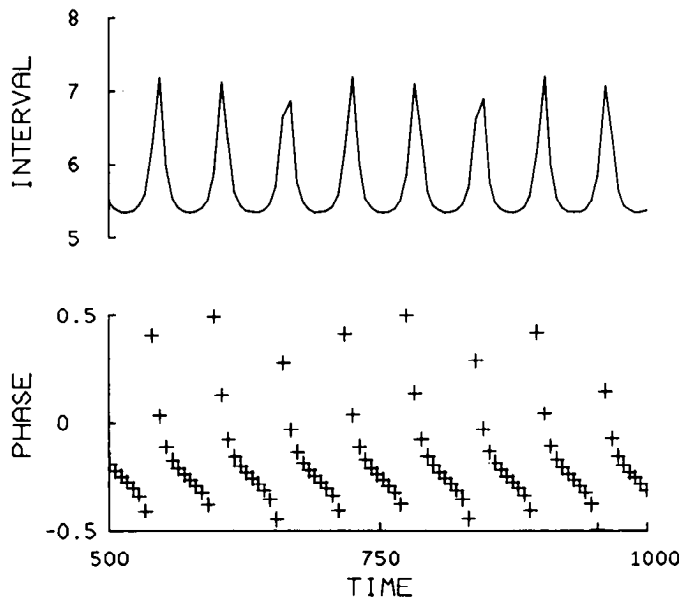


FIG. 4. Phase walk-through exhibited by numerical solution of Eq. 2 for  $T < T_c$ . Intervals between successive firings (i.e., when  $\theta = 0$  modulo  $2\pi$ ) and the phases (modulo  $T$ ) at which firing occurs are plotted vs. time: upper and lower curves, respectively. Parameter values:  $\beta = 0.17$ ,  $T = 2\pi/1.2$ ,  $T_0 = 2\pi$ .

$2\pi/(\omega_0 + \beta)$  and the peak interval is  $2\pi/(\omega_0 - \beta)$ . Hanson further comments on the curvature of the phase plots during walk-through. Although curvature is evident in Fig. 1, it is much clearer in Fig. 4, the computer solution. This curvature is again related to Fig. 3B. The portion with a gradual slope in Fig. 4 corresponds to the shaded region in Fig. 3B where  $\phi$  changes very slowly. The steeper portion of the phase plots corresponds to the unshaded region where  $\phi$  changes more rapidly.

Equation 2 allows one to make some quantitative predictions about the most evident properties of walk-through: the periodic variation (beating) of the firing intervals. In APPENDIX B the following formula is derived for calculating the beat period  $T_{\text{beat}}$  during walk-through

$$T_{\text{beat}} = \frac{C(T_c, T_0)}{\sqrt{\frac{T_c}{T} - 1}} \quad (4)$$

where  $C$  is a complicated function of  $T_c$ , the minimum period of entrainment, and  $T_0$  is the pacemaker's intrinsic period. Equation 4 may be applied to predict quantitatively the separation of firing interval peaks during walk-through once a few constants are known. In particular, if  $T_c$  can be found, then  $C$  can be computed from a single walk-through experiment. Once  $C$  and  $T_c$  are known, the dependence of  $T_{\text{beat}}$  on  $T$  is given by Eq. 4. If we take  $T_c = 770$  ms for the firefly data, then, calculating  $C$  from Eq. B5, we obtain

$$T_{\text{beat}} = 1.35/\sqrt{T_c/T - 1} \text{ (seconds)}$$

For a stimulus with period  $T = 750$  ms we get  $T_{\text{beat}} \approx 8.3$  s, which compares quite favorably with Fig. 1. We note that the simplest theory of beating between noninteracting oscillators (12) yields the estimate  $T_{\text{beat}} = (T - T_0)/T_0 T$ , which for these data equals 4.1 s. To better compare

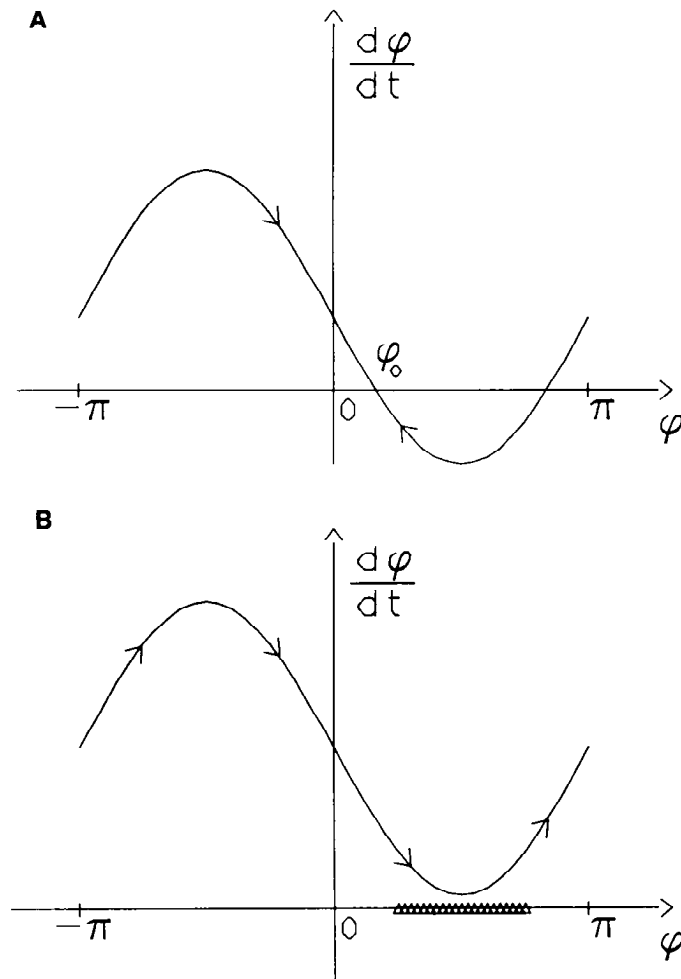


FIG. 3. Dynamics for phase difference, based on one-variable phase model. A: entrainment occurs for stimulus period  $T$  near intrinsic pacemaker period  $T_0$ ; constant stable phase difference ( $\phi_0$ ) is maintained. B: for  $T$  just beyond entrainment limit, phase walk-through occurs;  $\phi$  continually increases, although slowly for  $\phi$  in shaded interval.

our theory with experiment, the beat frequency as a function of the stimulus period should be measured. Such experiments have not yet been done.

## DISCUSSION

With a simple one-variable model we have described various properties of entrainment and loss of entrainment (desynchronization) for periodically stimulated pacemakers. The model predicts phase walk-through when the stimulus frequency is tuned just beyond the oscillator's entrainment limit (cf. Figs. 1 and 4). A formula has been obtained (Eq. 4) for the beat period of the walk-through pattern. The analysis also shows that most of the time during walk-through the instantaneous frequency exceeds the oscillator's intrinsic frequency so the firing interval plots exhibit localized peaks (cf. Figs. 1 and 4). We emphasize that a one-variable treatment and these properties (and formulas analogous to Eq. 4) characterize all stable oscillators when (weakly) driven beyond their entrainment limits (see APPENDICES). Furthermore, although the discussion and Figs. 1–4 concern phase walk-through when the stimulus frequency is too high, similar results obtain if the pacemaker is forced at low frequencies. Qualitatively the only difference will be that the firing interval curves will be flipped over (the troughs will be sharp and the peaks will be flat), and so the average firing interval will be much greater than the free-running interval. All other calculations remain approximately the same.

We have studied behavior near the entrainment limit by considering Eq. 3 for  $\phi$ . In the case of phase walk-through,  $\phi$  (modulo  $2\pi$ ), by definition, is periodic of period  $T_{\text{beat}}$ . Nevertheless this does not imply that  $\theta$  (modulo  $2\pi$ ) has period equal to  $T_{\text{beat}}$  (e.g., in Fig. 4,  $\theta$  has period  $3 T_{\text{beat}}$ ). Indeed  $\theta$  could be aperiodic. To characterize the  $\theta$ -dynamics an alternate viewpoint and analysis of Eq. 3 are useful [e.g., see (6) for references and exposition]. Let  $\theta_n$  be the pacemaker phase at the beginning of the  $n$ th stimulus cycle. The relationship  $\theta_n \rightarrow \theta_{n+1}$  is called the Poincaré map, and it defines a mapping of the circle  $(0, 2\pi)$  onto itself. A classic way to describe the behavior of such circle mappings is in terms of the rotation number  $\rho$  defined by

$$\rho = \lim_{n \rightarrow \infty} \frac{\theta_n}{2\pi n} \quad (5)$$

It equals the average number of pacemaker cycles per stimulus cycle. Note that when  $\rho$  is rational the response is periodic, but when  $\rho$  is irrational aperiodic behavior occurs. In the case  $T > T_c$  the map has a stable fixed point that corresponds to one-for-one entrainment with  $\rho = 1$ . Beyond the entrainment limit,  $T < T_c$ , we have  $\rho = 1 - T/T_{\text{beat}}$ , which takes on rational and irrational values as  $T$  is tuned. From our approximation for  $T_{\text{beat}}$  when  $T_c - T$  is small, we find  $\rho \approx 1 - \text{const} \sqrt{T_c - T}$ . Such square-root dependence near criticality is typical; another example of this is described by Hoppensteadt and Keener (6).

On closer examination of the interval plots in Fig. 1, we observe that the firing interval during phase walk-

through traverses well below the pacemaker's intrinsic period but barely exceeds this period at the peaks. This feature cannot be explained by a simple sinusoidal phase function as in Fig. 3 and Eq. 2. Rather a more general phase function is required. Let  $H(u)$  be such a function with  $H(0) = 0$  and  $H'(0) > 0$ . Let  $\bar{h} = \max H > 0$  and  $\underline{h} = \min H < 0$ ; for  $H = \sin(u)$ ,  $\bar{h} = 1$ ,  $\underline{h} = -1$ . Then it is clear that the maximum firing interval during phase walk-through is  $I_{\text{max}} = 2\pi/(\omega_0 + \beta\bar{h})$  and the minimum is  $I_{\text{min}} = 2\pi/(\omega_0 + \beta\underline{h})$ . From Hanson's observation that  $I_{\text{max}}$  approximately equals the intrinsic period, we conclude that  $\bar{h}$  must be very nearly zero. Also,  $I_{\text{min}}$  is much less than  $T_0$ , so that  $\bar{h}$  is far from zero. This result implies that the pacemaker will have much more trouble entraining to stimuli with longer periods than its intrinsic period. Thus, based on the data from the high-frequency phase walk-through, we can make predictions about the low-frequency response.

There are other oscillatory systems that occur in biology and for which walk-through is quite apparent. A well-known example occurs in free-running circadian experiments (see 15). In these protocols the activity rhythm stays with the temperature rhythm for a long time and then breaks away. A lesser-known and poorly understood example of phase walk-through occurs in models of the small intestine (see 10). Rather than one oscillator "breaking away" from another, a whole group separates, leading to the so-called frequency plateaus.

The firefly model has an advantage over these other oscillators in that the period of the oscillation is about 1 s. Thus many different experiments can be done in a short period of time. Systematic data is unavailable for the beat frequency as a function of the period of the zeitgeber in the firefly model. Other oscillators should qualitatively behave the same way after entrainment is lost, and Eq. 4 should hold for these systems also.

Phase-locking and walk-through have been considered in quite different contexts in a more mathematical setting by a number of authors. For example, Kuramoto and Yamada (8), Aizawa (1), and Fujii and Sawada (4) studied the behavior of a simple model similar to Eq. 3 in the context of chemical wave formation. Neu (11) studied the coupling of two oscillators with emphasis on phase-locking. He mentioned phase walk-through as a consequence of losing the synchronization of the two cycles. In a different context, Winfree (16, chapt. 3, sect. C) examined an equation similar to Eq. 3 and derives a formula for the "period" of the walk-through. Finally, Rand and Holmes (14) considered a similar phenomenon, but the attractivity of the oscillators was weak, so that their analysis was necessarily more complex and can also lead to phase-trapping.

## APPENDIX A

Let  $\mathbf{X}(t)$  be a vector describing the relevant physiological components of the pacemaker. We suppose  $\mathbf{X}$  satisfies the system of differential equations

$$\frac{d\mathbf{X}}{dt} = \mathbf{F}(\mathbf{X}) \quad (A1)$$

For example, the van der Pol oscillator has formed the basis of some other pacemaker models (e.g., see 4). Suppose  $\mathbf{X}_0(t)$  is a stable periodic solution to (A1) with period  $T_0$ , i.e.

$$\mathbf{X}_0(t + T_0) = \mathbf{X}_0(t)$$

$\mathbf{X}_0$  represents the intrinsic oscillation of the pacemaker with frequency  $\omega_0 = 2\pi/T_0$ . Let  $G(\mathbf{X}, \omega t)$  be a vector of periodic stimuli, possibly  $\mathbf{X}$  dependent, such that  $G(\mathbf{X}, \omega t + 2\pi) = G(\mathbf{X}, \omega t)$ . Thus the period of the stimulus is  $T = 2\pi/\omega$ . Let  $a$  be a small nonnegative number and suppose that

$$\omega - \omega_0 = 2\pi/T - 2\pi/T_0 = a\Delta \quad (A2)$$

where  $\Delta$  is order 1; i.e., the difference in the frequencies of the oscillator and the stimulus is small. Furthermore suppose the effect of the rhythmic stimulation on the pacemaker is weak [relative to the attractiveness of  $\mathbf{X}_0(t)$ ]. Then the equation for the periodically forced oscillator is

$$\frac{d\mathbf{X}}{dt} = F(\mathbf{X}) + aG[\mathbf{X}, (\omega_0 - a\Delta)t] \quad (A3)$$

In a classic paper, Levinson (9) proved that Eq. A3 is equivalent to

$$\frac{d\theta}{dt} = \omega_0 + aH[(\omega_0 - a\Delta)t - \theta] + a^2 \text{ terms} \quad (A4)$$

where  $\theta$  is the phase along the cycle and  $H(u)$  is a  $2\pi$ -period function of the phase difference ( $\phi$ ), qualitatively similar to  $\sin(u)$ . Intuitively, the theorem says, when there is no coupling, the forcing function and the oscillator cycle independently. They can be described individually by their respective phases, which lie on the circle  $(0, 2\pi)$ . The two circles form a surface, the torus, each point  $(\theta_0, \theta_1)$  of which corresponds to a state of the pair of cycles. The first part of the theorem says that because the pacemaker is stable, this surface persists when  $a$  is small and nonzero. Since the difference in frequencies between the oscillator and the forcing function is small, the second part of the theorem says that you can average over the forcing period. This reduces the system to a single equation for  $\phi$ . Now with  $\phi$  given by

$$\phi = (\omega_0 - a\Delta)t - \theta = \omega t - \theta$$

we find, from Eq. A4 that  $\phi$  satisfies

$$\frac{d\phi}{dt} = a[\Delta - H(\phi)] + a^2 \text{ terms} \quad (A5)$$

Since  $a$  is small, the  $a^2$  terms are neglected and Eq. A5 is thus a generalized version of Eq. 3. Hence the qualitative results on the phase model can be expected to hold for a much more general set of equations (e.g., Eq. A3).

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## APPENDIX B

We consider

$$\frac{d\phi}{dt} = \omega - \omega_0 - \beta \sin(\phi) \quad (B1)$$

where  $\omega_0 = 2\pi/T_0$  and  $\omega = 2\pi/T$ . Suppose  $\omega > \omega_0$ ; i.e., the driving frequency is greater than the natural frequency of the pacemaker (the opposite case is analyzed similarly). As long as

$$\omega - \omega_0 < \beta \quad (B2)$$

entrainment occurs, since there is a solution to Eq. B1 for  $d\phi/dt = 0$ ; i.e., there is a unique stable  $\phi$  between the zeitgeber and the pacemaker. The entrainment limit,  $\omega = \omega_e = 2\pi/T_e$  is obtained when Eq. B2 becomes an equality

$$\omega_e - \omega_0 = \beta$$

From this we see that experimental knowledge of  $\omega_e$  and  $\omega_0$  thus determines  $\beta$  in this model. Now suppose  $\omega$  exceeds the entrainment limit,  $\omega - \omega_0 > \beta$ . Then  $d\phi/dt$  is always positive, and we integrate Eq. B1 to obtain

$$\int_0^\phi \frac{du}{\omega - \omega_0 - \beta \sin(u)} = t \quad (B3)$$

The beat period  $T_{\text{beat}}$  is time taken by  $\phi$  to proceed from 0 to  $2\pi$  (i.e., a total walk-through of phase). Thus we have

$$T_{\text{beat}} = \int_0^{2\pi} \frac{d\phi}{\omega - \omega_0 - \beta \sin(\phi)} = \frac{2\pi}{\sqrt{(\omega - \omega_0)^2 - (\omega_e - \omega_0)^2}} \quad (B4)$$

where we have expressed  $\beta$  in terms of  $\omega_e$  and  $\omega_0$ . For  $\omega$  near  $\omega_e$ , Eq. B4 simplifies to

$$T_{\text{beat}} \approx \frac{2\pi}{\sqrt{2(\omega_e - \omega_0)}\sqrt{\omega - \omega_e}}$$

or, in terms of periods

$$\begin{aligned} T_{\text{beat}} &\approx \frac{T_e}{\sqrt{2(1 - T_e/T_0)}} \frac{1}{\sqrt{T_e/T - 1}} \\ &= C(T_0, T_e) \frac{1}{\sqrt{T_e/T - 1}} \end{aligned} \quad (B5)$$

The authors are grateful to Drs. John Buck and Frank E. Hanson for several helpful discussions.

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Received 31 May 1983; accepted in final form 19 September 1983.

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