Entrainment Versus Chaos in a Model for a Circadian Oscillator Driven by Light-Dark Cycles

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Circadian rhythms occur in nearly all living organisms with a period close to 24 h. These rhythms constitute an important class of biological oscillators which present the characteristic of being naturally subjected to forcing by light-dark (LD) cycles. In order to investigate the conditions in which such a forcing might lead to chaos, we consider a model for a circadian limit cycle oscillator and assess its dynamic behavior when a light-sensitive parameter is periodically forced by LD cycles. We determine as a function of the forcing period and of the amplitude of the light-induced changes in the light-sensitive parameter the occurrence of various modes of dynamic behavior such as quasi-periodicity, entrainment, period-doubling and chaos. The type of oscillatory behavior markedly depends on the forcing waveform; thus the domain of entrainment grows at the expense of the domain of chaos as the forcing function progressively goes from a square wave to a sine wave. Also studied is the dependence of the phase of periodic or aperiodic oscillations on the amplitude of the light-induced changes in the control parameter. The results are discussed with respect to the main physiological role of circadian rhythms which is to allow organisms to adapt to their periodically varying environment by entrainment to the natural LD cycle.

KEY WORDS: Limit cycle oscillations; chaos; periodic forcing; entrainment; model; circadian rhythms.

1. INTRODUCTION

Periodically forcing an oscillator is a common mode of generating chaos in chemical, physical and biological systems.[1–7] Rhythmic phenomena are encountered at all levels of biological organization, with periods ranging

from a fraction of a second to years.[8, 9] Circadian rhythms which occur in nearly all living organisms with a period of about 24 h play an important role in allowing them to adapt to their periodically varying environment.[10] Among biological rhythms circadian oscillations possess the unique characteristic of being continually subjected to periodic forcing. Indeed, although they can occur in constant darkness or light, circadian rhythms are naturally driven by light-dark (LD) cycles.[10]

Given that chaos can readily result from periodic forcing of an oscillator, the question arises as to whether the forcing of circadian oscillations by LD cycles can produce chaos, besides entrainment which is the response expected and generally observed in physiological conditions.[10] If the physiological role of circadian rhythms is to adapt the living organism to its environment, then chaos could indeed represent a mode of dynamic behavior less advantageous than regular oscillations entrained to the external period. To investigate the effect of LD cycles on circadian rhythms it is useful to resort to a molecular model for circadian oscillations and to determine theoretically the various modes of dynamic behavior which can arise in this model as a result of periodic forcing.

Thanks to rapid experimental advances on the biochemical mechanism of circadian clocks made in recent years, particularly in the fly *Drosophila*[11, 12] and in the fungus *Neurospora*,[13, 14] molecular models for circadian rhythms in these organisms have been proposed.[9, 15–18] In both systems the mechanism of circadian oscillations involves a negative autoregulatory feedback loop on gene expression. Thus, in *Drosophila*, the protein products PER and TIM of the genes *period* (*per*) and *timeless* (*tim*) form a complex that enters the nucleus and represses the transcription of the genes *per* and *tim*.[11, 12] In *Neurospora*, it is the protein product FRQ of the gene *frequency* (*frq*) that represses *frq* transcription.[13, 14] The effect of light, however, differs in the two organisms: in the fly light induces TIM degradation,[12] while in the fungus it triggers *frq* transcription.[14, 19] In mammals, many of the circadian clock genes are the same as in *Drosophila*, but the effect of light appears to be similar to that in *Neurospora*, i.e., light triggers gene expression rather than protein degradation.[14]

To investigate the effects of periodic forcing of circadian oscillations by LD cycles, we will consider a simple three-variable model proposed for circadian rhythms in *Neurospora*.[17, 18] We will determine the patterns of dynamic behavior of the forced system as a function of the period of forcing and of the amplitude of the light-induced changes in the maximum rate of gene transcription which represents the light-sensitive control parameter. The influence of the form of forcing will also be determined; thus the form of the periodically varying parameter will range from that of a square wave to a sine wave. The case of the square wave corresponds to LD cycles

generally realized in laboratory conditions, but the parameter changes induced by light may not follow precisely the waveform of the LD cycle, and the natural LD cycle itself clearly differs from a square wave.

In Section 2 we briefly present the molecular model used for the forcing of circadian oscillations by LD cycles. In Section 3 we determine by numerical simulations the different modes of dynamic behavior resulting from this periodic forcing. The domains of quasi-periodic oscillations, entrainment, and chaos are found as a function of the period of forcing and of the amplitude of the forced, light-sensitive parameter. We determine the phase of quasi-periodic, entrained and chaotic oscillations with respect to the phase of the LD cycle. The influence of the waveform of the light-controlled parameter is considered in Section 4. The occurrence of entrainment versus chaos is discussed in Section 5 with respect to the main putative role of circadian rhythms which is to synchronize the temporal dynamics of living organisms with their periodically varying environment.

2. MODEL FOR CIRCADIAN OSCILLATIONS

In *Neurospora* the mechanism of circadian rhythmicity relies on the negative regulation exerted by the protein FRQ on the transcription of its gene *frq* into the messenger RNA (mRNA), the translation of which leads to the synthesis of FRQ.[13, 14] A simple model for circadian oscillations of the protein FRQ and its mRNA in *Neurospora* (Fig. 1) is governed by the system of three kinetic equations (1a)–(1c):

$$\frac{\mathrm{d}M}{\mathrm{d}t} = v_{\mathrm{s}} \frac{K_{\mathrm{I}}^{n}}{K_{\mathrm{I}}^{n} + F_{\mathrm{N}}^{n}} - v_{\mathrm{m}} \frac{M}{K_{\mathrm{m}} + M} \tag{1a}$$

$$\frac{\mathrm{d}F_{\mathrm{C}}}{\mathrm{d}t} = k_{\mathrm{s}} M - v_{\mathrm{d}} \frac{F_{\mathrm{C}}}{K_{\mathrm{d}} + F_{\mathrm{C}}} - k_{1} F_{\mathrm{C}} + k_{2} F_{\mathrm{N}} \tag{1b}$$

$$\frac{\mathrm{d}F_{\mathrm{N}}}{\mathrm{d}t} = k_{1} F_{\mathrm{C}} - k_{2} F_{\mathrm{N}} \tag{1c}$$

In these equations, the three variables M, F_{C}, and F_{N} denote, respectively, the concentrations (defined with respect to the total cell volume) of the *frq* mRNA and of the cytosolic and nuclear forms of FRQ. Parameter v_{s} denotes the rate of *frq* transcription; this parameter increases in the light phase.[14, 19] The other parameters appearing in these equations are the constant K_{I} related to the threshold beyond which nuclear FRQ represses *frq* transcription, the Hill coefficient n characterizing the degree of cooperativity of the repression process, the maximum rate v_{m} of *frq* mRNA degradation and the Michaelis constant K_{m} related to the latter process,
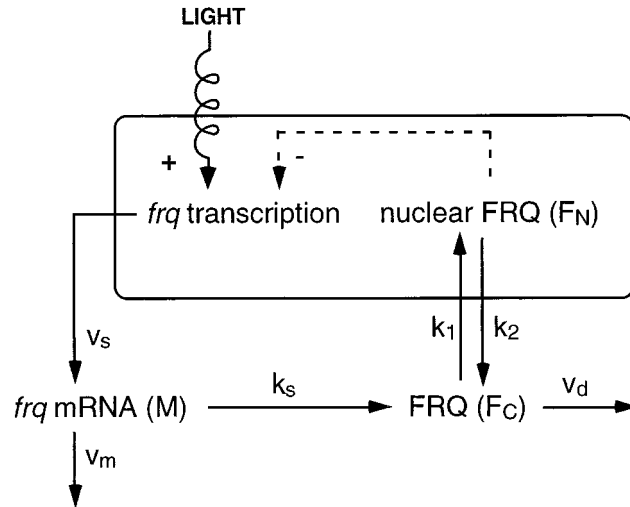
Fig. 1. Scheme of the model for circadian oscillations in *Neurospora*. The model is based on the negative regulation exerted by the FRQ protein on the expression of the *frq* gene; light controls the rhythm by enhancing the maximum rate of *frq* transcription, v_s. The model includes gene transcription in the nucleus, accumulation of the corresponding mRNA in the cytosol with the associated synthesis of protein FRQ, followed by FRQ transport into and out of the nucleus. Also indicated is the negative feedback regulation of gene expression by the nuclear form of the FRQ protein.

the apparent first-order rate constant k_s measuring the rate of FRQ synthesis which is assumed to be proportional to the amount of *frq* mRNA present in the cytosol, the maximum rate v_d of FRQ degradation and the Michaelis constant K_d related to this process, and the apparent first-order rate constants k_1 and k_2 characterizing the transport of FRQ into and out of the nucleus.

3. ENTRAINMENT AND CHAOS

Sustained oscillations of the limit cycle type occur in the model in conditions of constant darkness (Fig. 2A) with a period close to 21.5 h, as observed in the experiments.[13] When the system is driven by LD cycles, the effect of light must be incorporated into the model. As indicated above, the parameter that varies with light is the rate of *frq* transcription, v_s.[19] We shall first consider the case where the LD cycle corresponds to a square-wave variation of the light-sensitive parameter (the effect of other waveforms is considered in Section 4). Thus, in a LD cycle, parameter v_s remains at a low value (equal to that corresponding to continuous darkness
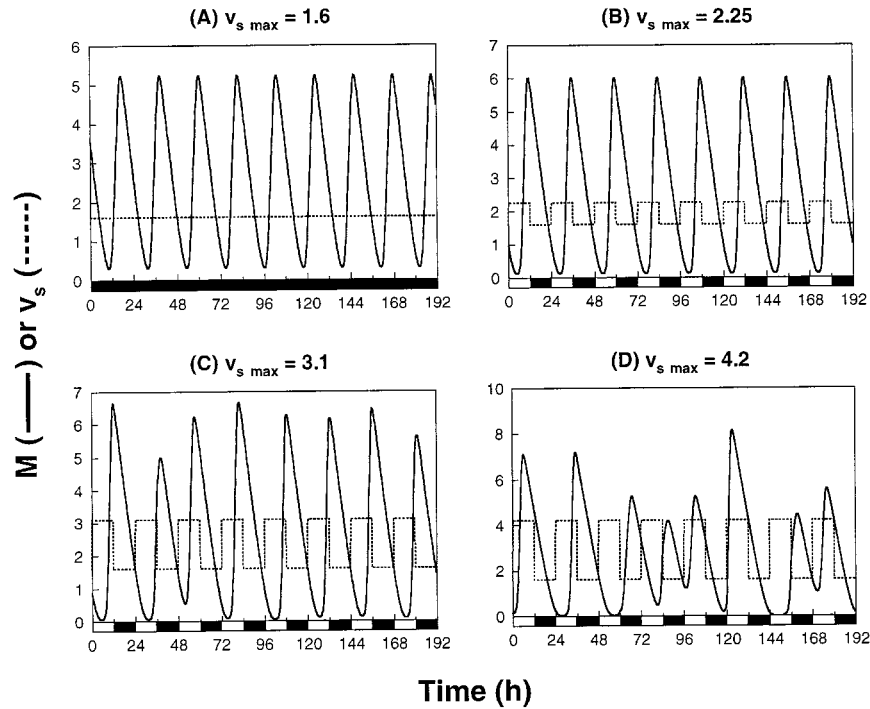
Fig. 2. Dynamics of the circadian oscillator model in continuous darkness or LD cycles. (A) Autonomous oscillations in continuous darkness. (B) Entrainment by LD cycles. (C, D) Chaotic oscillations in LD cycles. Continuous darkness is symbolized by the black bar; LD cycles are symbolized by the alternation of white and black bars. The curves have been obtained by numerical integration of Eqs. (1). Parameter values are: $n = 4$, $v_m = 0.505$ nMh^{-1}, $v_d = 1.4$ nMh^{-1}, $k_s = 0.5$ h^{-1}, $k_1 = 0.5$ h^{-1}, $k_2 = 0.6$ h^{-1}, $K_m = 0.5$ nM, $K_d = 0.13$ nM. Parameter v_s (in nMh^{-1}) remains constant and equal to 1.6 in panel A, and varies in a square wave manner with a minimum value of 1.6 (in dark phase) and maximum value of 2.25, 3.1, and 4.2 in B, C, and D respectively. The concentration scale in each graph is expressed in nM.

in Fig. 2A) during the dark phase and increases up to a higher value during the light phase. In the following, v_s will be expressed in nM h^{-1}.

Shown in panels B–D in Fig. 2 are some of the various modes of dynamic behavior observed at a given forcing period of 24 h in a LD cycle of 12 h of light, 12 h of dark when the maximum amplitude of parameter v_s (denoted $v_{s\,max}$) during the light phase increases and when the minimum value of v_s during the dark phase remains unchanged and equal to 1.6. The particular period of 24 h is selected because it corresponds to the period of natural LD cycles. When $1.6 < v_{s\,max} < 1.91$, quasi-periodic oscillations are obtained (results not shown). For $1.91 < v_{s\,max} < 2.64$, the oscillations of

21.5 h period obtained in constant darkness (Fig. 2A) are entrained to the period of the LD cycle, i.e., 24 h (Fig. 2B). For $2.64 < v_{s\,max} < 2.82$, a series of period-doubling bifurcations occurs, leading to chaos for $v_{s\,max} > 2.82$. Examples of chaotic oscillations are shown in Fig. 2C and 2D for two distinct values of $v_{s\,max}$. The variability of the amplitude of aperiodic oscillations becomes more pronounced as $v_{s\,max}$ increases.

The results of a more comprehensive study of the effect of the forcing period and of the value of $v_{s\,max}$ in the light phase are summarized in Fig. 3 where the external period varies from 20 to 30 h, and $v_{s\,max}$ increases from 1.6 to 6. As $v_{s\,max}$ rises, for periods below or above the autonomous period of 21.5 h, quasi-periodic oscillations are first observed (but not when the external period precisely matches the autonomous period); thereafter entrainment occurs, followed by a sequence of period-doubling bifurcations (only the domains of period-2 and period-4 oscillations are shown) and chaos. At large values of the driving period, around 29 h, a second domain
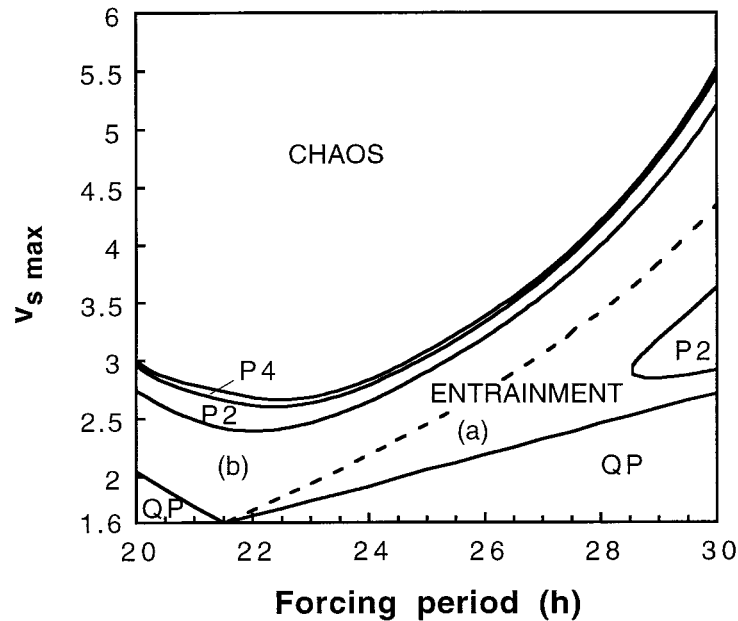

Fig. 3. Types of dynamic behavior observed as a function of the forcing period and of the maximum value $v_{s\,max}$ of the light-sensitive parameter in the light phase. QP, P-2, P-4 denote quasi-periodic oscillations, period-2 and period-4 oscillations, respectively. In the domain of entrainment, (a) and (b) correspond to two types of entrainment varying by the phase relationship with respect to the LD cycle; the phase after entrainment is either to the left or to the right of the threshold depicted in Fig. 4. Parameter values are the same as in Fig. 2.

of period-2 oscillations is obtained within the domain of entrainment. The different modes of dynamic behavior have been characterized by means of return maps (results not shown) where the maximum (minimum) of a variable is plotted as a function of the preceding maximum (minimum).

The dashed line in Fig. 3 separates two types of entrainment which differ by the phase of the oscillations with respect to the driving LD cycle. At a given forcing period, the phase of the oscillations for each of the three variables indeed varies in a sigmoidal manner as $v_{s\,max}$ increases (Fig. 4). For an external period of 24 h, the threshold of these sigmoidal variations is located in $v_{s\,max} = 2.2$. The domains of entrainment below and above the dashed line in Fig. 3 correspond to conditions of entrainment to the left and to the right of the threshold value of $v_{s\,max}$ in Fig. 4.

Shown in panels A and B of Fig. 5 are the strange attractors corresponding to the two typical cases of chaotic oscillations shown in Fig. 2C and 2D, respectively. The timing of the peak in cytosolic FRQ (variable F_c) is represented in panels C and D of Fig. 5 with respect to the phase of the external LD cycle for 1200 successive cycles on the strange attractors of Figs. 5A and B, respectively. The corresponding distribution of peak to peak intervals for F_c is shown in panels E and F. A comparison of panels A, C, E with panels B, D, F indicates that the variability of the phase and cycle length of chaotic oscillations increases when the value of $v_{s\,max}$ during the light phase of the forcing LD cycle rises.
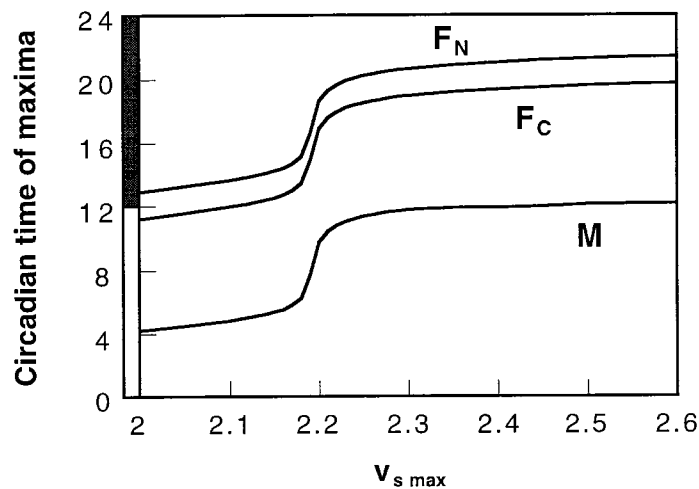

Fig. 4. Phase of the oscillations after entrainment, as a function of $v_{s\,max}$. The phase of the maximum in each of the three variables of the model is shown with respect to the phase of the LD cycle, for a forcing period fixed to 24 h. The white/black bar symbolizes one LD cycle. Parameter values are the same as in Fig. 2.
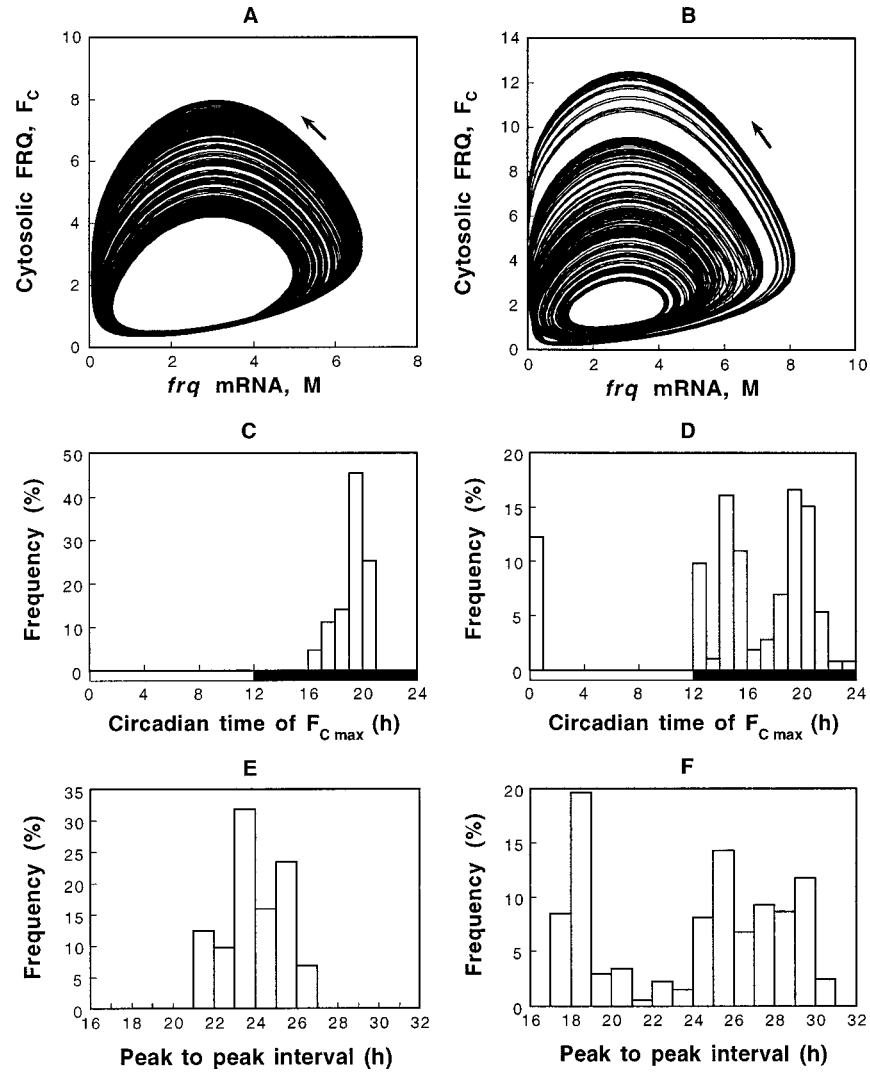
Fig. 5. Chaotic oscillations under forcing by LD cycle. (A) and (B) Strange attractors corresponding to the chaotic oscillations of panels C and D in Fig. 2, obtained for $v_{s\,max} = 3.1$ and 4.2 nMh^{-1}, respectively. (C) and (D) Distribution of the timing of the peak in cytosolic FRQ (F_c) with respect to the phase of the external LD cycle, established for 1200 successive cycles on the strange attractors of A and B, respectively. (E) and (F) Distribution of peak to peak intervals for F_c, established for the successive cycles used for plotting the phase distributions in C and D. The white/black bar symbolizes one LD cycle. Parameter values are the same as in Fig. 2.

4. INFLUENCE OF THE FORM OF PERIODIC FORCING

Although the square wave generally represents the on/off variation of light during an LD cycle in laboratory conditions, it is only an approximation of the associated variation in parameter v_s. The latter, indeed, may follow the light changes only after a lag and may saturate, i.e., reach a maximum value at intermediate light intensities. Furthermore, in natural conditions, the LD cycle does not take the form of a square wave; rather, it may take forms intermediate between square wave and sine wave.

To investigate the influence of the waveform of the periodic change in the light-sensitive parameter we have considered a piecewise variation (see Appendix) such that v_s remains at a maximum value during a time τ_1, at a minimum value during a time τ_2, and undergoes a transition from the maximum to the minimum value following a sinusoidal function over a transition time τ_{12}, while the reverse transition from minimum to maximum occurs following a sinusoidal function over a transition time τ_{21} (Fig. 6b). This particular form of periodic variation allows us to encompass all situations comprised between square wave (Fig. 6a) and sine wave (Fig. 6c). Thus, the values $\tau_{12} = \tau_{21} = 0$ with $\tau_1 = \tau_2 = 12$ h correspond to the case of the square wave of 24 h period considered in Section 3, while the values $\tau_{12} = \tau_{21} = 12$ h with $\tau_1 = \tau_2 = 0$ correspond to a sinusoidal variation of 24 h period.

We have determined by numerical simulations as a function of $v_{s\,max}$ the different modes of dynamic behavior resulting from the forcing by a variation in v_s, for a forcing period of 24 h, with transition times $\tau_{12} = \tau_{21} = 0$ (case of square wave; Fig. 6a), 1, 2, 3, 6, or 9 h (intermediate cases exemplified by Fig. 6b), or 12 h (case of sinusoidal variation; Fig. 6c). The values $\tau_{12} = \tau_{21} = 1$, 2, 3, 6 or 9 h correspond to situations in which v_s switches back and forth, more or less rapidly but in a smooth, sinusoidal manner, between its maximum and minimum values (Fig. 6b). Figure 7 indicates that the form of the periodic forcing has a marked influence on the dynamic behavior of the circadian oscillator driven by LD cycles. The most striking result is that no chaos is obtained over a wide range of $v_{s\,max}$ values extending from 1.6 to 10 when the system is forced by a sinusoidal variation in the light-sensitive parameter v_s. Only quasi-periodic oscillations and entrainment are observed in these conditions (Fig. 7, last column).

The transition from a square wave to a sine wave can be effected continuously by increasing the value of the transition times $\tau_{12} = \tau_{21}$ (see Fig. 6). The results obtained for the case of a square wave (Fig. 7, 1st column) are not significantly modified as long as the transition times remain small relative to the overall period (Fig. 7, columns 2 to 4, established for
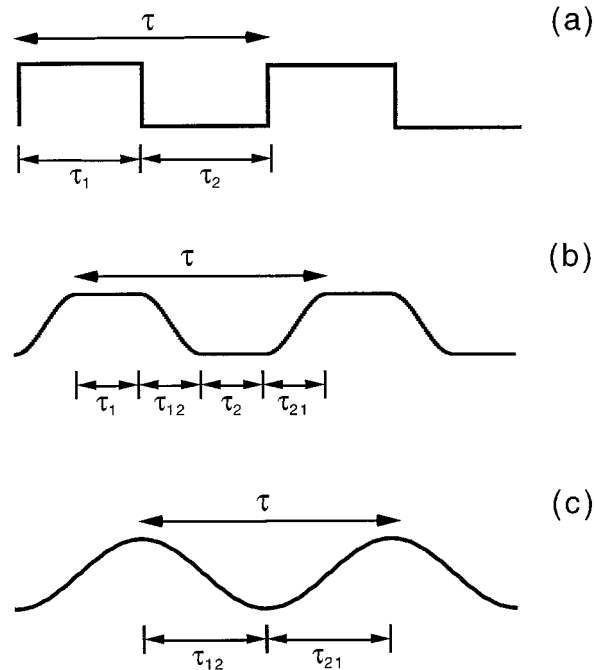
Fig. 6. Waveform considered for the forcing of the light-sensitive parameter. The waveform (see Appendix) goes from square wave (a) to sine wave (c), and passes through a series of intermediate waveforms (b). Durations τ_1, τ_2, τ_{12}, τ_{21} are defined graphically with respect to period τ. (a) $\tau_1 = \tau_2 = \tau/2$, $\tau_{12} = \tau_{21} = 0$; (b) $\tau_1 = \tau_{12} = \tau_2 = \tau_{21} = 6$ h; (c) $\tau_{12} = \tau_{21} = \tau/2$, $\tau_1 = \tau_2 = 0$.

$\tau_{12} = \tau_{21} = 1$, 2 and 3 h, respectively). As the values of $\tau_{12} = \tau_{21}$ further increase, the domains of quasi-periodicity, entrainment, period-doubling and chaos are shifted toward larger values of $v_{s\,max}$ (Fig. 7, columns 5 and 6, established for $\tau_{12} = \tau_{21} = 6$ and 9 h, respectively). This is particularly noticeable when the transition times have a value of 9 h, meaning that the parameter v_s stays only 3 h at its maximum and at its minimum, and undergoes back and forth, in 9 h, the transition from one to the other extreme value. The results of Fig. 7 thus show that chaos is favored by a square-wave variation in v_s while entrainment is favored at the expense of chaos as the waveform of the parameter approaches that of a sine wave.

5. DISCUSSION

One of the most conspicuous properties of circadian rhythms is that the natural environment in which they occur varies in a periodic manner.
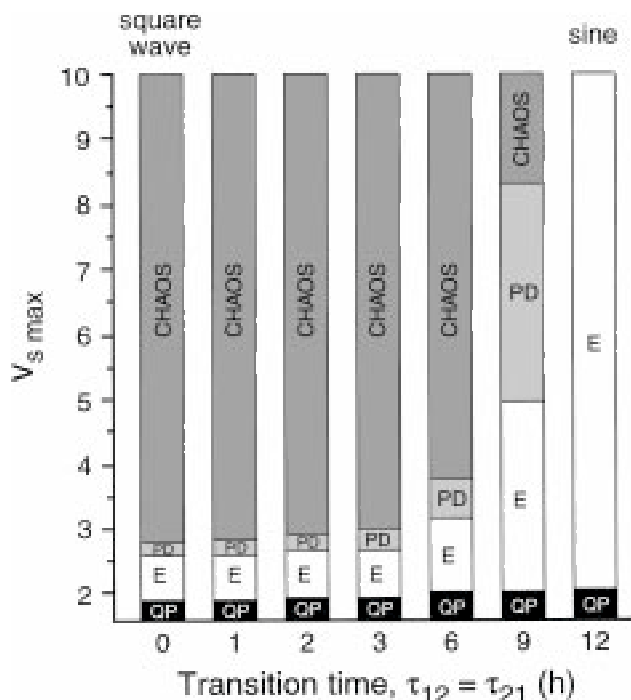
Fig. 7. Influence of the type of periodic forcing on the dynamics of the circadian oscillator model subjected to LD cycles. Shown are the ranges in which quasi-periodic oscillations (QP), entrainment to the forcing period (E), period-doubling (PD) and chaos occur as function of $v_{s\,max}$, for different waveforms (see Fig. 6) ranging from a square wave (1st column: $\tau_1 = \tau_2 = 12$ h, $\tau_{12} = \tau_{21} = 0$) to a sine (last column: $\tau_1 = \tau_2 = 0$, $\tau_{12} = \tau_{21} = 12$ h). Other columns refer to intermediate waveforms (see Appendix) going, from left to right, from square wave to sine wave (the value of transitions times $\tau_{12} = \tau_{21}$ is indicated under each column, with $\tau_1 = \tau_2 = 12 - \tau_{12}$). In each case the period of forcing is equal to 24 h. Parameter values are the same as in Fig. 2.

To adapt to the recurrent alternation of day and night, nearly all living organisms have evolved the capability of oscillating autonomously with a period close to 24 h. These oscillations are generally entrained by natural LD cycles so that most physiological functions operate with 24 h periodicity.[10] The fact that chaos can readily originate from the periodic forcing of an oscillator[1–7] raises the possibility that the forcing of circadian rhythms by LD cycles may generate chaos rather than entrainment. Such a transition to chaos might have profound consequences with respect to the physiological role of circadian rhythms.

The goal of this paper was to investigate the possibility of chaotic dynamics in a mathematical model for circadian limit cycle oscillations

driven by LD cycles. The model is based on a molecular mechanism in which a protein represses the transcription of its gene. Such a negative autoregulatory feedback loop on gene expression underlies circadian oscillations in several organisms investigated so far, including *Drosophila*, *Neurospora*, mammals, plants, and cyanobacteria.[11–14] The particular form of the model considered here was proposed for circadian rhythms of the FRQ protein in the fungus *Neuropora*,[17, 18] but it is closely related to a minimal version of the model proposed for circadian oscillations of the PER protein in *Drosophila*.[9, 15]

The effect of light in *Neurospora* is to induce the expression of the gene *frq* that codes for its the protein product FRQ.[14, 19] Thus we have represented the effect of LD cycles by a periodic variation in the rate of transcription of the *frq* gene, v_s. When the variation of this parameter takes the form of a square wave, quasi-periodic behavior, entrainment, period doubling and chaos are successively observed as the maximum value of v_s, denoted $v_{s\,max}$, progressively increases at a given value of the forcing period (Figs. 2 and 3).

Autonomous chaos has not been observed in the three-variable model governed by Eqs. (1). The latter phenomenon has been observed, however, in the absence of periodic forcing in a more extended, 10-variable model proposed for circadian oscillations of the PER and TIM proteins in *Drosophila*.[20] Chaos occurs in that model in a restricted domain of parameter values which is much smaller than the domain of periodic oscillations. In that model we have found that autonomous chaos can be suppressed by sinusoidal as well as square-wave LD cycles and that, like in the present model, LD cycles may induce the transition from limit cycle oscillations to chaos for other parameter values.

The phase of circadian oscillations is an important characteristic from a physiological point of view since it relates the timing of the peak of a given variable to the phase of the applied LD cycle. In the domain of entrainment, the simulations of the model indicate that the phase of the oscillations varies in a sigmoidal manner as a function of $v_{s\,max}$ (Fig. 4). The value of the threshold characterizing this sigmoidal curve is close to 2.2 in the conditions of Fig. 4 where the forcing period is equal to 24 h; this threshold value is precisely the one that would yield an autonomous period of 24 h if v_s were held constant at that value.

In the domain of quasi-periodic behavior, the phase corresponding to the peak of any of the three variables sweeps the whole range of the 24 h LD cycle (data not shown). In the domain of chaos, the phase of the forced oscillations also varies, though to a lesser extent: the distribution of this phase for the peak in cytosolic FRQ protein (F_c) extends over 5 h in the dark part of the LD cycle in the conditions of Fig. 5C, but the range over

which it varies is much wider at the larger value of $v_{s\,max}$ considered in Fig. 5D. In the latter case, indeed, the phase varies over the 12 h of the dark part and the first hour of the light part of the LD cycle.

If the occurrence of a fixed phase relationship with respect to the periodic environment represents a functional advantage, then we may expect that quasi-periodic behavior and chaos were selected against in the course of biological evolution, and that living organisms have evolved instead to operate in conditions where entrainment occurs with respect to the natural LD cycles. Although the present results were obtained in a particular molecular model for circadian rhythmicity, this model is representative of a class of mechanisms based on autoregulatory negative feedback loops on gene expression. The results should therefore be of general significance for the forcing of circadian rhythms by LD cycles, even though the effect of light at the molecular level may vary in different organisms (see Section 1).

When the variation of the light-controlled parameter v_s becomes periodic, entrainment occurs when the amplitude of the light-induced change in this parameter is in a range bounded by two critical values. When the amplitude of v_s is below this range, quasi-periodic oscillations occur, whereas above this range chaos is found after a cascade of period-doubling bifurcations. Thus, the circadian oscillatory system could have evolved so as to operate in a range of parameter values such that the light-induced value of the light-sensitive parameter lies in the entrainment range and not in the range producing either quasi-periodicity or chaos.

The data of Fig. 7 show that the waveform of the periodic variation in the light-controlled parameter has a marked influence on the type of dynamic behavior resulting from the forcing of the circadian oscillator by LD cycles. At a fixed value of the forcing period, as the maximum value of the light-sensitive parameter v_s increases in the light phase of the LD cycle, the domain of entrainment grows at the expense of the domain of chaos when the waveform tends to become more of a sine curve and less of a square wave. As shown in Fig. 7, when the forcing period is equal to 24 h, chaos has disappeared altogether in the range considered for v_s when the variation becomes sinusoidal. (Chaos can nevertheless be obtained with a sinusoidal variation for other forcing periods and other choices of the maximum and minimum values of v_s, e.g., for a sinusoidal variation between 0.7 and 2.5 with a period of 29 h.)

In natural conditions, light does not vary like a square wave over 24 h, even though such a square wave variation is achieved and commonly used in laboratory conditions. Even so, however, it is likely that the light-sensitive parameter does not follow a square wave and that its variation is intermediate betwen a square wave and a sine function. The present results suggest that the form of the changes induced by the LD cycle in the light-sensitive

parameter could have been selected so as to favor the occurrence of entrainment instead of quasi-periodic behavior or chaos.

Besides its relationship to the physiological significance of circadian rhythms in natural conditions, the present study suggests a procedure for studying experimentally the occurrence of entrainment or chaos in circadian oscillators forced by LD cycles of varying period and amplitude. The application of the present analysis to such experiments would require the quantitative determination of how the light-sensitive biochemical parameter controlling circadian oscillations varies as a function of light intensity.

APPENDIX: FUNCTION USED FOR PERIODIC FORCING WITH WAVEFORM GOING FROM SQUARE WAVE TO SINE WAVE

The function representing the periodic variation in the light-sensitive parameter (see scheme in Fig. 6b) is defined as follows:

— When $0 < t \pmod{\tau} \leqslant \tau_{21}$:

$$v_s = v_{s\,min} + \frac{v_{s\,max} - v_{s\,min}}{2}\left(1 + \sin\left(\frac{2\pi}{2\tau_{21}}\,t_{21}\right)\right)$$

— When $\tau_{21} < t \pmod{\tau} \leqslant (\tau_{21} + \tau_1)$: $v_s = v_{s\,max}$
— When $(\tau_{21} + \tau_1) < t \pmod{\tau} \leqslant (\tau_{21} + \tau_1 + \tau_{12})$:

$$v_s = v_{s\,min} + \frac{v_{s\,max} - v_{s\,min}}{2}\left(1 + \sin\left(\frac{2\pi}{2\tau_{12}}\,t_{12}\right)\right)$$

— When $(\tau_{21} + \tau_1 + \tau_{12}) < t \pmod{\tau} \leqslant \tau$: $v_s = v_{s\,min}$

where:

$t =$ time;

$v_{s\,min} =$ minimum value of v_s (corresponding to the D phase of the LD cycle);

$v_{s\,max} =$ maximum value of v_s (corresponding to the L phase of the LD cycle);

$\tau =$ forcing period $= \tau_{21} + \tau_1 + \tau_{12} + \tau_2$;

$\tau_1\ (\tau_2) =$ duration of the L (D) phase of the LD cycle;

$\tau_{21}\ (\tau_{12}) =$ transition time from $v_{s\,min}(v_{s\,max})$ to $v_{s\,max}(v_{s\,min})$;

$$t_{21} = t(\text{mod } \tau) - \tau_{21}/2;$$
$$t_{12} = t(\text{mod } \tau) - (\tau_{21} + \tau_1) + \tau_{12}/2.$$

When $\tau_{21} = \tau_{12} = 0$, the function becomes a square wave (Fig. 6a), while for $\tau_1 = \tau_2 = 0$ and $\tau_{21} = \tau_{12}$ it reduces to a sine wave (Fig. 6c).

ACKNOWLEDGMENTS

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