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Mammalian Circadian Rhythms: A Neural Network Model

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ABSTRACT. A neural network model provides behavioral, physiological, and anatomical predictions of how circadian rhythms are generated by the suprachiasmatic nuclei (SCN) of the mammalian hypothalamus. The 4-dimensional basic gated pacemaker model is defined in terms of on-cell/off-cell populations whose positive feedback signals are gated by slowly accumulating transmitter substances. The slow accumulation rate determines the approximate (circadian) period of the pacemaker. The relative insensitivity of period to other parameters demonstrates the clocklike nature of the model. 'Chaotic" solutions, period-doubling, and slow modulation of the envelope of solutions can occur in some parameter ranges. The model consists of two symmetric pairs of fast-slow equations with inhibitory cross-coupling. In the uncoupled or weakly coupled state, no oscillations occur. Augmented versions of the model include "fatigue", a negative feed-

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back signal which decays on an ultradian time scale; and a very slow gain control process, which buffers the pacemaker on a time scale of months.

Phenomena explained or predicted by the model include the complementary reactions to light of diurnal and nocturnal mammals, as well as their similar phase response curves (PRC's); the "dead zone" of the nocturnal PRC; the suppression of rhythmicity by high light intensities; the effects of partial SCN ablations; the role of eye closure during sleep; the nature of parametric (constant light) vs. non-parametric (alternating light-dark) effects; split rhythms; long-term after-effects; the consistent adherence to Aschoff's rule (the effect of constant light level on period) of nocturnal mammals, in contrast to the inconsistent responses of diurnal mammals; the consistent adherence to the circadian rule (the effect of constant light level on activity level) of both nocturnal and diurnal mammals; the tendency of nocturnal mammals to lose circadian rhythmicity at lower light levels than do diurnal mammals; and the stability of circadian period.

1. INTRODUCTION: A NEURAL NETWORK MODEL OF THE CIRCADIAN SYSTEM IN THE MAMMALIAN SUPRACHIASMATIC NUCLEI

For many years, exact identification of the brain loci which generate mammalian circadian rhythms eluded investigators, although lesion experiments provided a wealth of related information (Richter, 1965). In 1972, it was discovered that light signals project directly from the retina to the suprachiasmatic nuclei (SCN) of the hypothalamus along the retinohypothalamic tract (RHT) (Moore and Eichler, 1972; Stephan

and Zucker, 1972). This discovery led to the recognition that the SCN play a crucial role in the pacemaker system generating the wake-sleep and activity-rest rhythms of mammals.

This article presents a neural network model of the mammalian SCN system, along with a variety of parametric data which the model helps to explain (Carpenter and Grossberg, 1982, 1983a, 1983b, 1984, 1985a). The model, called the gated pacemaker, was constructed from neural components that have also been used to model motivated behaviors, such as eating and drinking, that are controlled by other hypothalamic circuits (Grossberg, 1972a, 1972b, 1975, 1982a, 1982b, 1984a; Olds, 1977). Thus our SCN model forms part of a larger theory of how hypothalamic circuits are specialized to control different types of motivated behaviors. Models described in several other articles in this volume focus primarily on circadian rhythms in humans (Beersma, Daan, and Dijk; Kronauer; Strogatz, this volume). The present article focuses on parametric data about the wake-sleep, activity-rest cycles of non-human mammals. Physiological and anatomical studies are consistent with a microscopic interpretation of gated pacemaker components. The model thus suggests a neural microstructure for a single pacemaker embedded in a system which may have other pacemakers as well. In fact, our analysis complements model analyses which postulate coupled temperature and sleep-wake oscillators, but which do not specify a physiological structure underlying either pacemaker system (Carpenter, 1985).

2. THE GATED PACEMAKER MODEL

Mathematical and numerical analysis of the the gated pacemaker model has led to quantitative simulations of a large body of circadian data. These data include Aschoff's rule in nocturnal and diurnal mammals (Aschoff, 1960) and exceptions to Aschoff's rule in diurnal mammals (Aschoff, 1979); the circadian rule in nocturnal and diurnal mammals (Aschoff, 1960); the tendency of nocturnal mammals to lose circadian rhythmicity in bright light (Aschoff, 1979; Enright, 1980); the increase of circadian period during a self-selected light-dark cycle in diurnal and nocturnal mammals (Aschoff, 1979; Wever, 1979); and the phase response curves to pulses of light in diurnal and nocturnal mammals, including the "dead zone" of phase resetting insensitivity during the subjective day of a nocturnal mammal (Daan and Pittendrigh, 1976; DeCoursey, 1960; Kramm, 1971; Pohl, 1982). The model also simulates several types of long-term after-effects (Aschoff, 1979; Pittendrigh, 1960, 1974; Pittendrigh and Daan, 1976a), split rhythms (Earnest and Turek, 1982; Hoffmann, 1971; Pittendrigh, 1960; Pittendrigh and Daan, 1976b), and SCN ablation studies (Pickard and Turek, 1982).

Due to the fact that every process in the gated pacemaker model has a physical interpretation, it suggests a number of anatomical, physiological, and pharmacological tests. Notable among these are predictions about how slowly varying transmitter gating actions form part of the SCN pacemaker. A functional similarity exists between the gated pacemaker model and a model of the transduction of light by vertebrate photoreceptors (Carpenter and Grossberg, 1981). This relationship suggests how photoreceptor machanisms may be modified to form retinal circadian pacemakers, as in the isolated eye of *Aplysia* (Jacklet, 1969) and the frog *Xenopus laevis* (Iuvone, Besharse, and Dunis, 1983). The models of vertebrate photoreceptor, SCN circadian pacemaker, and hypothalamic motivational circuits are all variations of a neural network design called a *gated dipole* (Grossberg, 1972b, 1975). Gated dipoles model opponent processes wherein slowly accumulating chemical transmitters are depleted, or habituated, by gating signals which are energized by tonic arousal and phasic inputs. A gated dipole anatomy which supports sustained oscillations constitutes the basic pacemaker of the model.

Three types of phasic inputs modulate the basic pacemaker dynamics. Two are "internal zeitgebers" and the other is the external zeitgeber light. Both of the internal zeitgebers have homologs in the model eating circuit. One is a negative feedback signal to the pacemaker that serves as an index of "fatigue." This zeitgeber, which is suggested to reach the pacemaker via the bloodstream, has the same formal properties as the sleep-dependent Process S that was discovered

by Borbély (1982) using EEG methods. (See Beersma, Daan, and Dijk, this volume.) The EEG techniques of Borbély provide an independent experimental procedure for testing properties of the fatigue signal. In the model eating circuit, the feedback signal, homologous to the fatigue signal, is a satiety signal that acts through the bloodstream (Grossberg, 1982b, 1984a).

The second type of internal zeitgeber is a slowly varying gain control process that buffers the model's reaction to adventitious lighting changes, such as cloudy weather, but alters the model's properties in response to statistically reliable lighting changes, such as seasonal fluctuations. The gain control signal is physically interpreted in terms of the production and release of a chemical transmitter substance. In the model eating circuit, homologous gain control signals control the conditioned reinforcing properties of food-related sensory cues.

In summary, components of the gated pacemaker function on four distinct time scales, each mediated by its own chemical process. The basic pacemaker is an oscillating circuit with a slowly accumulating transmitter that gates, or multiplies, internal feedback signals. The time scale on which this transmitter is produced determines the circadian (~24-hour) time scale of the circuit. Many copies of each basic pacemaker circuit are assumed to exist in each SCN. This "perfect clock" basic pacemaker is subject to ecological influences acting on

fast or slow time scales. Light, acting on a time scale of seconds, is registered immediately. A key element of our model analysis is the role played by the attenuation of light input to the pacemaker during sleep. The second ecological influence, fatigue, acting on an ultradian (~4-hour) time scale, curbs excessive activity and stabilizes the circadian period. Finally, the gain control process provides a seasonal buffer acting on a time scale of months.

3. THE GATED PACEMAKER MODEL EQUATIONS

The gated pacemaker model describes the dynamics of on-cell/off-cell pairs, in which the on-cells and the off-cells mutually inhibit one another. The following processes define the gated pacemaker dynamics (Figure 1).

1. Slowly accumulating transmitter substances are depleted, or habituated, by gating the release of feedback signals.

2. The feedback signals are organized as an on-center off-surround, or competitive, anatomy.

3. Both on-cells and off-cells are tonically aroused.

4. Light excites the on-cells of a diurnal model and the off-cells of a nocturnal model.

5. The on-cells drive observable activity, such as wheel-turning, in both the diurnal and the nocturnal model.

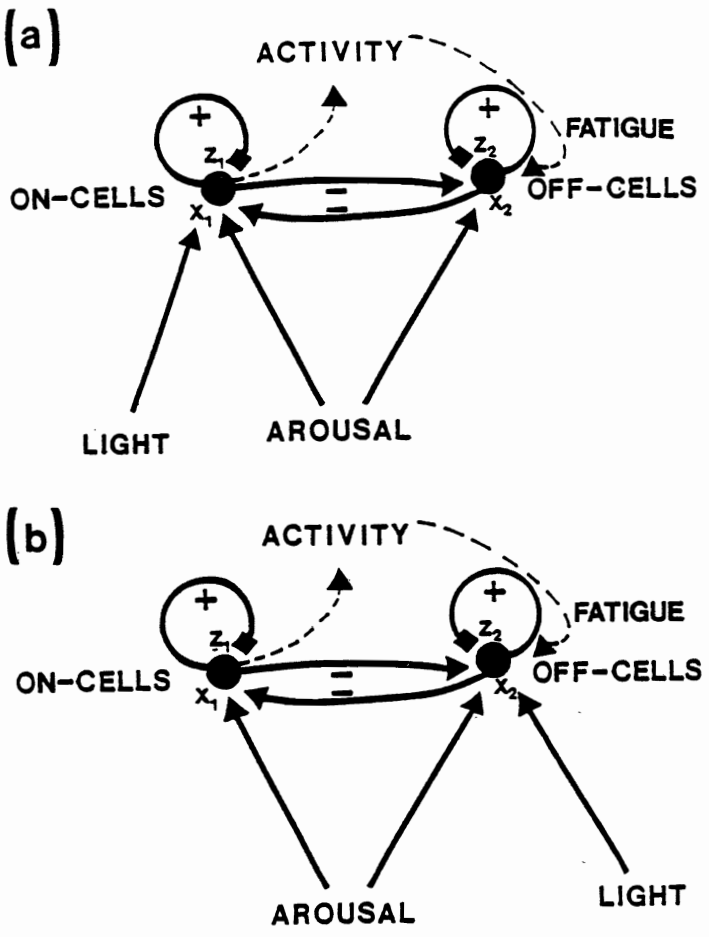

Figure 1. Anatomy and physiology of the diurnal (a) and nocturnal (b) gated pacemaker circuits. The potential x_1 of an on-cell (population) and the potential x_2 of an off-cell (population) obey membrane equations (1) and (2), respectively. Transmitter substance z_1 gates the positive feedback signal $f(x_1)$ from the on-cell (population) to itself, and transmitter substance z_2 gates the positive feedback signal $f(x_2)$ from the off-cell (population) to itself. Term I is the nonspecific arousal level, which excites the on-cells and off-cells equally.

6. On-cell activity gives rise to a fatigue signal that excites the off-cells in both the diurnal model and the nocturnal model. The fatigue signal is a time-average of the on-cell output signal on an ultradian time scale.

7. A slowly varying gain control signal excites the on-cells in both the diurnal model and the nocturnal model. The gain control signal is a time-average of the output signal on a time scale of months.

The general model equations for a nocturnal gated pacemaker are defined as follows.

Figure 1 (continued) Term F is the fatigue feedback signal, which excites the off-cells. The light input $J(t)$ excites the on-cells of the diurnal model (a) and the off-cells of the nocturnal model (b). Transmitter z_1 in (3) accumulates via term $D(E - z_1)$ and is released at rate $-Hf(x_1)z_1$. A similar law governs z_2 in (4). The fatigue signal F in (5) builds up during the wakeful state via term $h(x_1)$ and decays at a constant rate via term $-KF$. The conditionable slow gain control process y activates on-cells in both diurnal and nocturnal circuits. Many copies of each circuit are assumed to be distributed throughout each SCN.

NOCTURNAL MODEL EQUATIONS

On-Potential

$$(1n)\quad \frac{dx_1}{dt} = -Ax_1+(B-x_1)[I+f(x_1)z_1+Sy]-(x_1+C)g(x_2),$$

Off-Potential

$$(2n)\quad \frac{dx_2}{dt} = -Ax_2 + (B-x_2)[I + f(x_2)z_2 + F + J(t)] - (x_2 + C)g(x_1),$$

On-Gate

$$(3)\quad \frac{dz_1}{dt} = D(E - z_1) - Hf(x_1)z_1,$$

Off-Gate

$$(4)\quad \frac{dz_2}{dt} = D(E - z_2) - Hf(x_2)z_2,$$

Fatigue

$$(5)\quad \frac{dF}{dt} = -KF + h(x_1),$$

Gain Control

$$(6)\quad \frac{dy}{dt} = -Uy + Vf(x_1).$$

Variable x_1 in equation (1n) is the potential of an on-cell (population) v_1. Variable x_2 in equation (2n) is the potential

of an off-cell (population) v_2. Both x_1 and x_2 obey classical membrane equations. In (1n) and (2n) the parameter $-A$ in the terms $-Ax_1$ and $-Ax_2$ determines the fast decay rate of the potentials x_1 and x_2. Also in (1n) and (2n), term I represents the constant arousal level that equally excites v_1 and v_2. In (1n), the transmitter substance z_1 gates the nonegative feedback signal $f(x_1)$ from v_1 to itself. Term $f(x_1)z_1$ is proportional to the rate at which transmitter is released from the feedback pathway from v_1 to itself, thereby re-exciting x_1. Term Sy describes the effect of the gain control process y on v_1 (Figure 2). Term S is a signal that is gated by y, thereby generating a net excitatory input Sy at the on-cells v_1. The off-cells v_2 inhibit the on-cells v_1 via the nonnegative signal $g(x_2)$ in term $-(x_1 + C)g(x_2)$. Equation (2n) is the same as equation (1n), except that the indices 1 and 2 are interchanged; both the light input $J(t)$ and the fatigue signal F excite v_2 but not v_1; and the slow gain control process excites v_1 but not v_2.

Equations (3) and (4) define the transmitter processes z_1 and z_2. In (3), the transmitter z_1 accumulates to its maximal level E at a slow constant rate D via the term $D(E-z_1)$. This slow accumulation process is balanced by the release of z_1 at rate $Hf(x_1)z_1$, leading to the excitation of x_1 in equation (1n). A similar combination of slow accumulation and gated release defines the dynamics of transmitter z_2 in (4).

The endogenous interactions between potentials x_1 and x_2

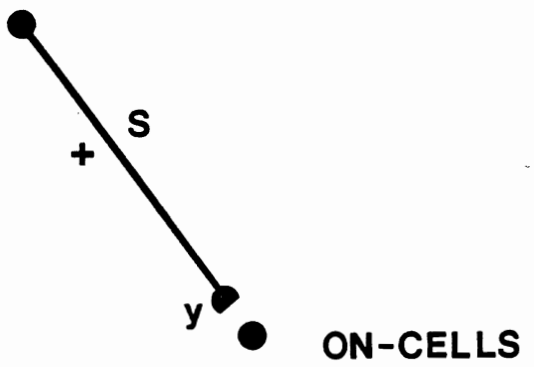

Figure 2. The slow gain control process y gates the performance signal S. The gated signal Sy activates the on-cell potential x_1.

and transmitters z_1 and z_2 define a clock-like pacemaker (Carpenter and Grossberg, 1983b). This pacemaker has a stable period in the dark that varies inversely with the transmitter accumulation rate. Any genetic or prenatal factor capable of fixing this accumulation parameter could thus specify the approximate period of the clock in the dark. The remaining processes F and y modulate the behavioral patterns that are generated by the pacemaker, as during split rhythms and long-term after-effects, but are not the source of the pacemaker's clock-like properties. Both F and y are homeostatic, average indices of pacemaker activity. They do not represent independent oscillators.

The fatigue signal F in (5) is a time-average of $h(x_1)$,

which increases with on-cell activity x_1. Speaking intuitively, an increase in x_1 and a decrease in x_2 arouse neural circuits that support the awake state. Fatigue builds up as a function of increased metabolic activity during the awake state. Fatigue, in this sense, can thus build up in an alert but physically restrained animal as well as during overt activity. Since F excites the off-cells v_2 in (2n), it indirectly inhibits the arousal generated by the pacemaker. The decay rate K of the fatigue signal F is assumed to be ultradian. In particular, $A > K > D$, so that the potentials x_1 and x_2 react faster than the fatigue signal F, which in turn reacts faster than the pacemaker gates z_1 and z_2.

The slow gain control process y in (6) is also a time-average, but on a time scale that is much slower than the circadian time scale. Process y averages term $Vf(x_1)$ at an averaging rate U. Then Sy in (1n) acts as an excitatory input to the on-cells v_1. Term Sy in equation (1n) and equation (6) formally define a long-term memory trace y. In all the simulations, terms S, U, and V are chosen to be constant, or to vary as a function of light or on-cell activity. A single choice of these terms is used in all the long-term after-effect simulations. Within the context of the gated pacemaker model, parametric properties of after-effect data lead to choices of U and V whose properties may be experimentally tested (Carpenter and Grossberg, 1985a).

The diurnal model differs from the nocturnal only in the

equations (1d) and (2d) that define its on-cell and off-cell potentials. In particular, light input $J(t)$ excites the on-cells but not the off-cells of the diurnal model. However, the fatigue input F excites off-cells in both the diurnal and the nocturnal models, and the slow gain input y excites on-cells in both diurnal and nocturnal models. The diurnal model equations are listed below.

DIURNAL MODEL EQUATIONS

On-Potential

$$(1d) \qquad \frac{dx_1}{dt} = -Ax_1 + (B - x_1)[I + f(x_1)z_1 + J(t) + Sy] - (x_1 + C)g(x_2),$$

Off-Potential

$$(2d) \qquad \frac{dx_2}{dt} = -Ax_2 + (B - x_2)[I + f(x_2)z_2 + F] - (x_2 + C)g(x_1),$$

On-Gate

$$(3) \qquad \frac{dz_1}{dt} = D(E - z_1) - Hf(x_1)z_1,$$

Off-Gate

$$(4) \qquad \frac{dz_2}{dt} = D(E - z_2) - Hf(x_2)z_2,$$

Fatigue

$$(5) \qquad \frac{dF}{dt} = -KF + h(x_1),$$

Gain Control

$$(6) \qquad \frac{dy}{dt} = -Uy + Vf(x_1).$$

4. SIGNAL FUNCTIONS, ACTIVITY THRESHOLDS, AND ATTENUATION OF LIGHT INPUT DURING SLEEP

The models in equations (1)–(6) are completely defined by a choice of the signal functions f, g, and h; the light input $J(t)$; the signals S, U, and V; and the parameters. In all the simulations, the output signal functions $f(w)$ and $g(w)$ in (1)–(6) are chosen to be threshold-linear functions of activity w, such as $[w]^+ \equiv \max(w, 0)$, or S-shaped functions of activity, such as

$$(7) \qquad \frac{([w]^+)^2}{W^2 + ([w]^+)^2}.$$

The signal function $h(w)$ in (5) is defined by

$$(8) \qquad h(w) = M \max[f(w) - N, 0].$$

The definition of $h(w)$ can be interpreted as follows. We assume that $f(x_1(t))$ is the output signal of the pacemaker.

Behavioral activity is supported when $f(x_1(t))$ exceeds a positive threshold, N. The function $h(x_1(t))$ defined by (8) can then be interpreted as an index of behavioral activity. If $f(w) = w$ when $w \geq 0$, we can simplify the definition of $h(w)$ in (8) to

$$h(w) = M \max(w - N, 0). \tag{9}$$

Equation (5) says that under normal circumstances the fatigue signal F builds up at a rate proportional to behavioral activity $h(x_1(t))$. Activity ceases when $x_1(t) \leq N$. Then fatigue decays at the ultradian rate K. Defining fatigue in this way enables us to provide a relatively simple description of the model. In more complex versions of the model, the pacemaker output modulates the arousal level of motivational circuits. This arousal level helps to determine the sensitivity of these circuits to external and internal cues which trigger incentive motivational signals that energize observable behaviors. The resultant behaviors have metabolic consequences that contribute to the fatigue signal. However, metabolic sources other than overt activity may also contribute significantly to the fatigue signal. Thus an alert but physically restrained animal or a human subject confined to bed may still generate fatigue feedback to the pacemaker.

In the circadian literature (Aschoff, 1960), the total period (τ) is broken up into the time (α) during which the animal engages in overt activity and the remaining rest time (ρ). When equation (9) describes pacemaker support of activity, the time α corresponds to the time during which

$$x_1(t) > N, \tag{10}$$

since (10) holds when $h(x_1(t)) > 0$. In our analysis, we subdivide ρ into the *sleep* time and a transitional time of *wakeful rest* before, after, and possibly within the overt activity or sleep cycle. To distinguish mathematically these two states, we assume that a sleep threshold P exists such that when

$$P < x_1(t) \leq N, \tag{11}$$

the model is in a state of wakeful rest. When

$$x_1(t) \leq P, \tag{12}$$

the model is in a state of sleep.

We operationally define sleep in terms of its effects on the pacemaker. The main effect of sleep in the model is the attenuation of the light input to the pacemaker. This attenuation

could be due, for example, to eye closure, retreat to a dark nest, or a self-selected light-dark cycle, or to circadian variations in light registration at the retina itself (Terman and Terman, 1983). Letting $L(t)$ be the light input that reaches the pacemaker during wakefulness the net light input in equations $(1d)$ and $(2n)$ is defined to be

$$J(t) = \begin{cases} L(t) & \text{if } x_1(t) > P \\ \theta L(t) & \text{if } x_1(t) \leq P \end{cases}. \tag{13}$$

Parameter θ is a light attenuation factor during sleep. When $\theta = 1$ no light attenuation occurs during sleep. When $\theta = 0$ complete light attenuation occurs during sleep. If light pulses are able to to phase shift a mammal's circadian rhythm while the mammal is asleep, then θ must be greater than 0. In our analysis of Aschoff's rule, light attenuation during sleep contributes to violations of the rule by diurnal mammals but not by nocturnal mammals (Carpenter and Grossberg, 1984, 1985b).

The model definitions of wakeful rest and sleep are chosen for simplicity. In species for which a separate temperature pacemaker helps to control sleep onset, a more complex definition is needed to discuss situations wherein the SCN and temperature pacemakers become desynchronized (Beersma, Daan, and Dijk, this volume; Czeisler, Weitzman, Moore-Ede, Zimmerman, and Kronauer, 1980; Kronauer, this volume; Strogatz, this volume; Wever, 1979). Also, our definition of the fatigue feedback signal assumes that no fatigue accumulates during wakeful rest. The simulations thus make the approximations that the fatigue signal builds up much faster during overt activity than during wakeful rest, and that all the oscillators controlling sleep onset are approximately synchronized.

The remainder of the article presents some of the data simulations generated by the model. Theoretical and mathematical analyses of these simulations are found in previous articles.

5. OSCILLATIONS OF THE BASIC PACEMAKER

This section describes the oscillations that are generated by the basic pacemaker, equations (1)-(4), when fatigue (F), gain control (y), and light inputs (J) are switched off. The basic pacemaker model consists of the pair of equations (1) and (3) for the variables x_1 and z_1 and a symmetric pair of equations (2) and (4) for x_2 and z_2. The pairs (x_1, z_1) and (x_2, z_2) become uncoupled if the function $g(x_i) \equiv 0$. In this case, all variables approach stable limits. All model oscillations require significant inhibitory coupling between the pairs (x_1, z_1) and (x_2, z_2), which constitute a single oscillator. In order to help visualize the dynamics of this 4-dimensional system, solutions are plotted in three different ways. In Figure 3a, each of the variables x_1 and z_1 is plotted as a function of

time. In Figure 3b, both pairs (x_1, z_1) and (x_2, z_2) are plotted in the (x, z) coordinate plane through time. In Figure 3c, each of the variables x_1 and x_2 is plotted as a function of time.

Figure 3a illustrates how transmitter concentration z_1 accumulates when x_1 is small and is depleted when x_1 is large. This overshoot in the graph of x_1 is due to the multiplicative form of the feedback signal $f(x_1)z_1$ (Carpenter and Grossberg, 1981; Grossberg, 1968, 1981, 1984a). Term $f(x_1)z_1$ reaches its maximum value when x_1 and z_1 are large. Then z_1 starts to deplete so the product $f(x_1)z_1$ also decreases. As a result, x_1 decreases to a plateau value until the balance of terms causes a rapid switch in the relative sizes of x_1 and x_2.

Figure 3b shows that the two pairs (x_1, z_1) and (x_2, z_2) approach the same limit cycle from their distinct initial values in (x, z) space. Figure 3c shows that the x_1 and x_2 potentials are out-of-phase with each other near the limit cycle. In particular, the rapid decay of x_1 occurs during the rapid rise of x_2, and conversely.

Figure 4 illustrates the oscillator's clock-like property. Figure 4a shows that the period of the basic pacemaker, in the dark is, inversely proportional to the transmitter accumulation rate. Figure 4b illustrates the fact that the period is relatively insensitive to other parameter choices within the clock's range of oscillation. Thus if the *single* parameter, transmitter accumulation rate, is specified by a genetic or

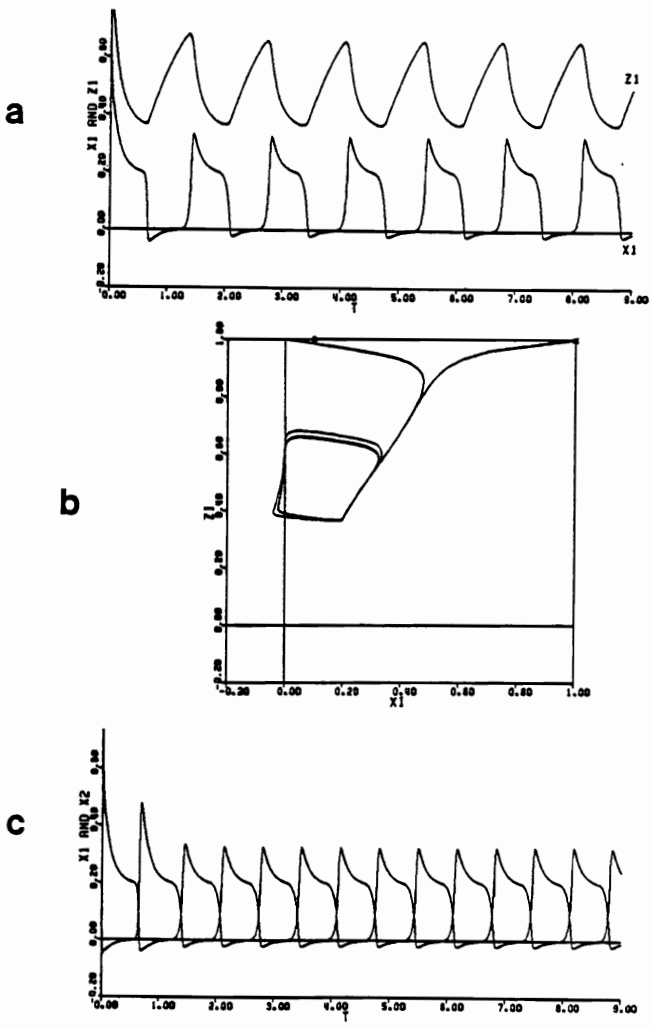

Figure 3. Three ways to plot gated pacemaker trajectories. (a) Functions $x_1(t)$ and $z_1(t)$ are plotted through time. (b) The phase portraits of $(x_1(t), z_1(t))$ and $(x_2(t), z_2(t))$ are plotted through time in (x, z) coordinates. (c) Functions $x_1(t)$ and $x_2(t)$ are plotted through time.

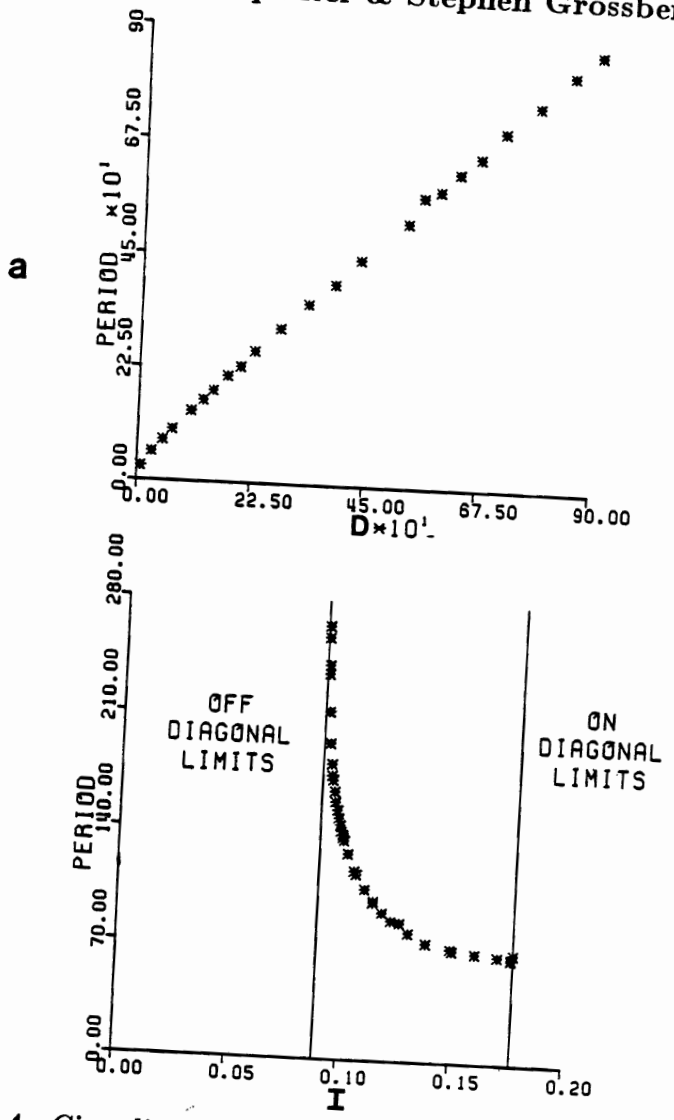

Figure 4. Circadian period (threshold-linear case). (a) For small values of the transmitter accumulation rate D, the period varies linearly with D^{-1}. When D is sufficiently large, the system goes to diagonal limits. (b) The period is relatively insensitive to the arousal level I except near its extreme values where oscillations break down.

prenatal signal, then the period of the basic pacemaker in the dark is essentially fixed. The period will remain stable despite wide variations in other factors such as arousal.

The basic pacemaker, even without external forcing by the light input function, is capable of generating a remarkable series of bifurcations as its parameters are varied near the range where oscillations cease. Figure 5 describes a series of bifurcations that occur when the threshold W of the signal function in (7) is increased. Note the period doubling in Figure 5e, the slowly modulated waves in Figure 5f, the repeated sequences of complex oscillation clusters in Figure 5g, and the triplets in Figure 5h.

6. PHASE RESPONSE CURVES IN DIURNAL AND NOCTURNAL GATED PACEMAKERS

In the gated pacemaker model, the assumption that light inputs excite the on-cells of diurnal animals and the off-cells of nocturnal animals is compatible with the familiar day activity of diurnal animals and night activity of nocturnal animals. Although these hypotheses generate complementary activity cycles in response to a daily cycle of light-dark episodes, they also imply that isolated light pulses delivered to an animal living in the dark reset the phases of both diurnal and nocturnal models in a similar way, as the data demand (DeCoursey, 1960; Pittendrigh, 1960; Kramn, 1971; Daan and Pittendrigh, 1976; Pohl, 1982). This property of gated pace-

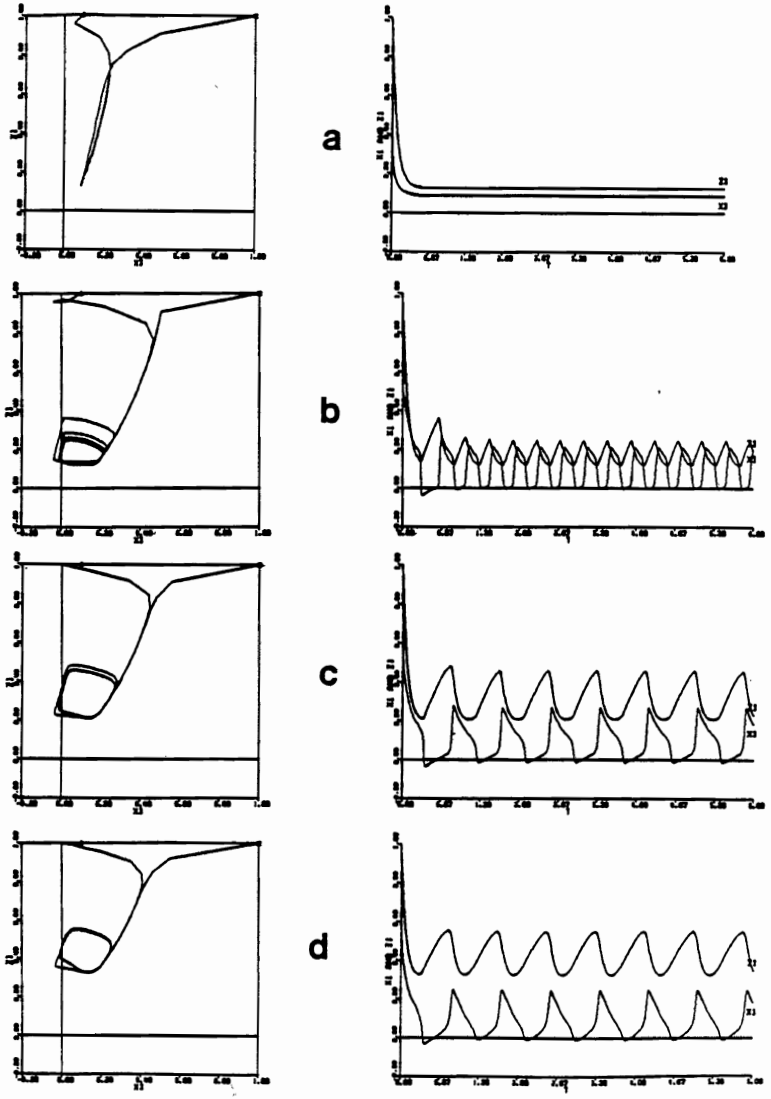

Figure 5. Oscillation sequence in response to an increase in the half-maximum argument $w = W$ of the sigmoid signal $f(w)$ in equation (7). (a) Diagonal limit ($W = .0577$). (b) Fast large amplitude oscillation ($W = .0578$). In this case, the

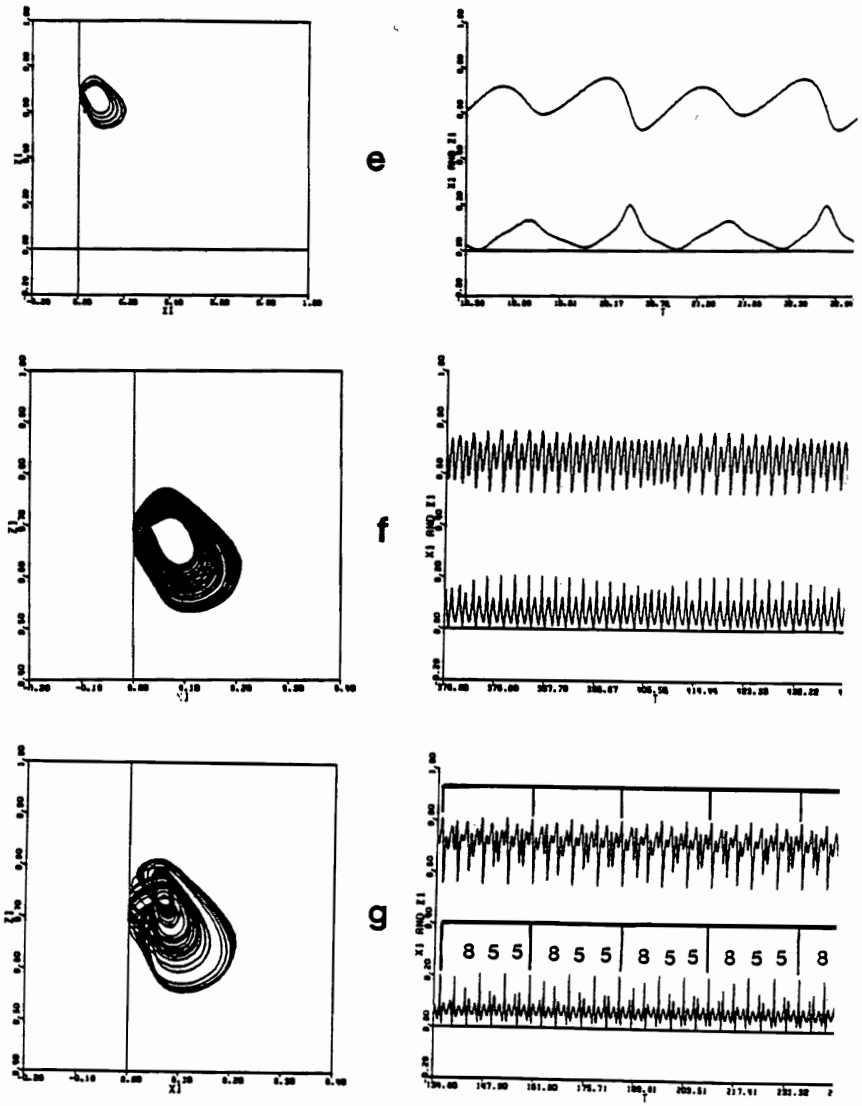

Figure 5 (continued) values of z_1 are so small that the graphs of $x_1(t)$ and $z_1(t)$ intersect. (c) Longer period and larger amplitude oscillation ($W = .17$). (d) Smaller amplitude oscillation and same period as in (c) ($W = .25$). (e) Mittens ($W = .348$). (f) Oyster shells ($W = .35$). (g) $(8, 5, 5)$ sequence cluster ($W = .36$).

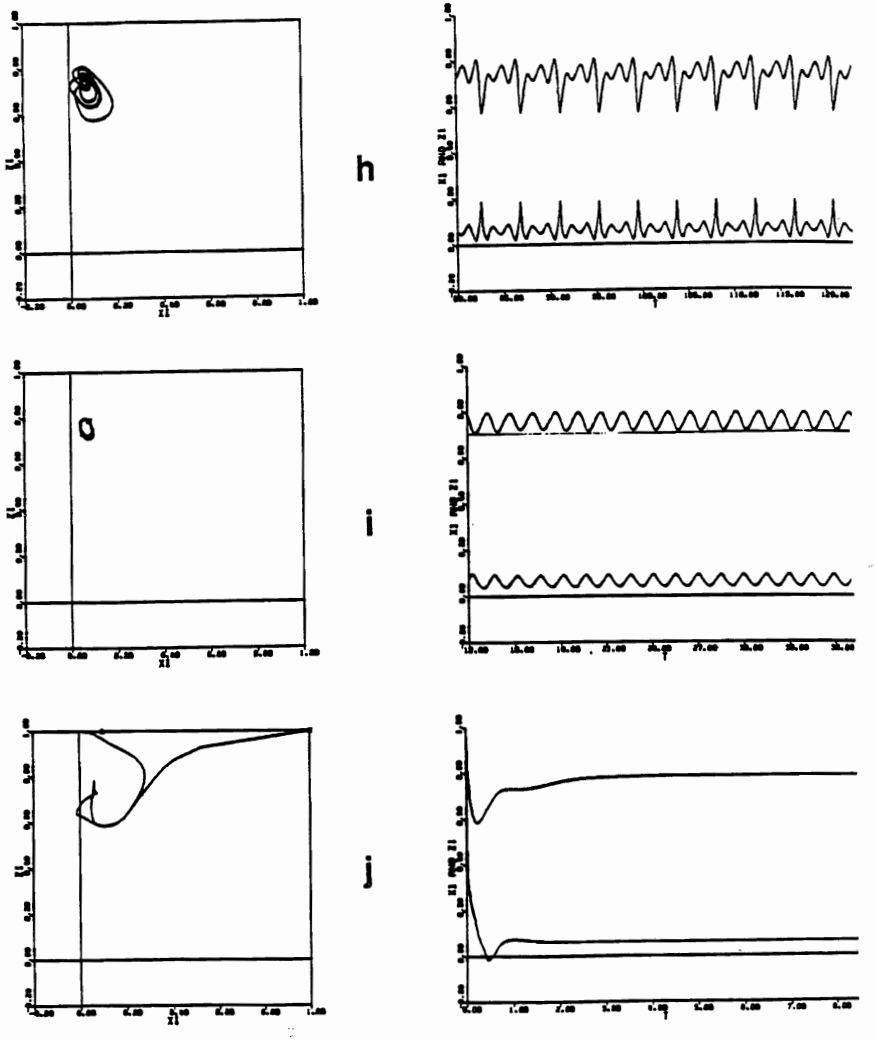

Figure 5 (continued) (h) Triplets ($W = .363$). (i) Unstable small amplitude oyster shells become regular periodic ($W = .368$). (j) Diagonal limit ($W = .375$). The phase portraits have been enlarged in (f) and (g).

makers contrasts with the explanation of phase resetting that is suggested when van der Pol oscillators are used to model the pacemaker. The latter approach suggests that complementary reactions to light of diurnal and nocturnal animals are controlled by interactions that occur beyond the SCN pacemaker stage. As Moore-Ede, Sulzman, and Fuller note:

> "The circadian systems of diurnal and nocturnal species must be organized differently to account for the dramatic differences in the phase relationships of their rhythms to the light-dark cycle [i.e., day-active vs. night-active]. It is possible that the differences lie in the coupling between zeitgeber and pacemaker. However ... the similarities between nocturnal and diurnal species in the way that light resets circadian pacemakers [i.e., the phase response curves] makes it more likely that the differences in the coupling mechanisms between the circadian pacemaker and the rhythms it drives" (Moore-Ede, Sulzman, and Fuller, 1982, pp.81-82).

Figure 6 depicts the phase response curves of diurnal and nocturnal basic pacemakers in response to light pulses for the case when the light input is unattenuated during sleep. In this case, $\theta = 1$ in equation (13), so the nocturnal model (equations (1n), (2n), (3) and (4)) and the diurnal model (equations (1d), (2d), (3), and (4)) are symmetric. Therefore the two PRC's in Figure 6 are identical.

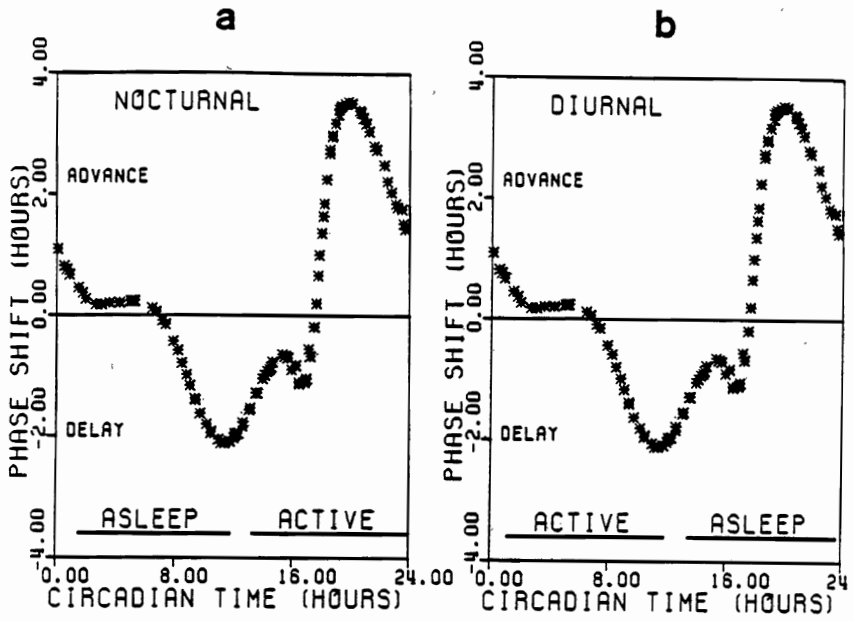

Figure 6. Phase response curves of nocturnal and diurnal gated pacemakers with no light attenuation during sleep. (a) A typical phase response curve for a nocturnal pacemaker. Simulated light pulses were flashed for 30 minutes. (b) A typical phase response curve for a diurnal pacemaker. Parameters are chosen as in (a), and $\theta = 1$.

Figure 6 shows how complementary light-dark cycles and similar phase response curves can coexist at the SCN level if these structures are built up from gated pacemaker opponent processes. However, PRC's of nocturnal mammals typically differ in some ways from PRC's of diurnal mammals. In particular, nocturnal mammals show a "dead zone" of unresponsiveness to light during their sleep phase (subjective day). In contrast, diurnal mammals are comparatively sensitive to light during their sleep phase (subjective night) (Kramm, 1971; Pohl, 1982). In the basic gated pacemaker, the symmetry between the nocturnal and diurnal models is broken if the light attenuation factor θ is less than 1. Equation (13) implies that if $0 \leq \theta < 1$, the PRC curves of Figure 6 are compressed toward the axis of 0-phase resetting during

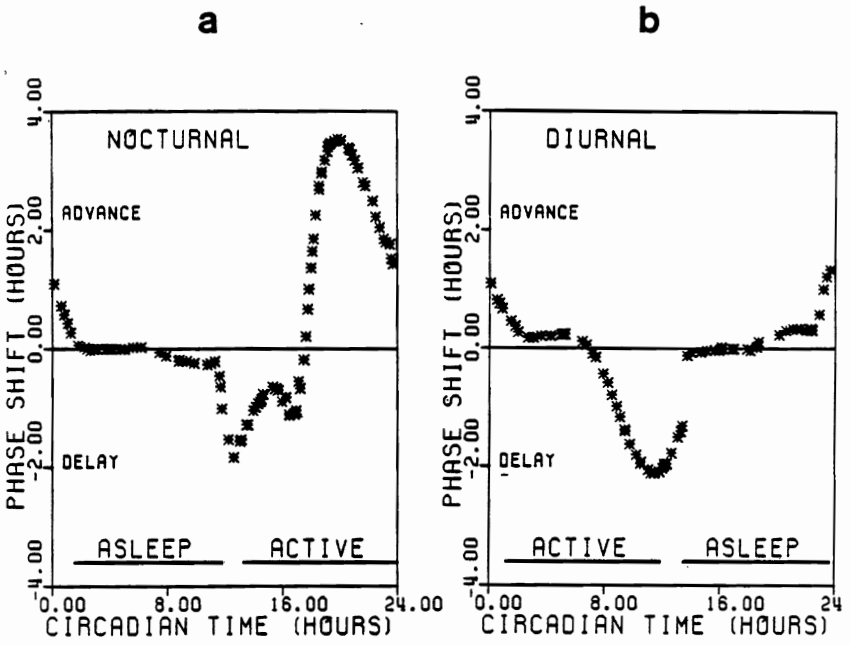

Figure 7. Phase response curves of nocturnal and diurnal gated pacemakers with light attenuation during sleep. (a) A typical phase response curve for a nocturnal pacemaker with $\theta = .1$. All other parameters are chosen as in Figure 6. (b) A typical phase response curve for a diurnal pacemaker with all parameters chosen as in (a).

the sleep phase of either the diurnal or the nocturnal mammal. This compression leads to the nocturnal "dead zone" in Figure 7, where $\theta = .1$.

7. ASCHOFF'S RULE, THE CIRCADIAN RULE, AND EXCEPTIONS

In 1960, Aschoff reviewed the experimental literature on free-running animals exposed to constant light. By examining the differential effects of parametric increases in light intensity, he formulated general rules to summarize the trends he observed (Aschoff, 1960). Enright describes these generalizations, which have come to be known as Aschoff's rule and the circadian rule, as follows:

> "1. 'Aschoff's rule': For diurnal animals, the free-running period of a circadian activity rhythm usually decreases with increasing light intensity; the brighter the constant light, the faster the animal's 'clock' runs. For nocturnal animals, the converse is usually observed: the free-running period of the rhythm increases with increasing light intensity.
>
> 2. The 'circadian rule': For diurnal animals, brighter constant light prolongs daily wakefulness under free-running conditions, and also increases the level of arousal, as indicated by the intensity of locomotor activity. For nocturnal animals, the converse is true: brighter light usually shortens the duration of wakefulness and decreases the intensity of activity" (Enright, 1980, p.21).

The circadian rule, which says that light stimulates activity in diurnal animals and inhibits activity in nocturnal animals, is intuitively plausible. It is, in fact, close to the very

definition of nocturnal and diurnal. In contrast, Aschoff's rule would be more difficult to predict *a priori*. For a nocturnal animal, Aschoff's rule says that as light intensity increases, the duration of rest time (ρ) increases *more* than the decrease in activity time (α) predicted by the circadian rule, so that the total circadian period ($\tau \equiv \alpha + \rho$) increases. For a diurnal animal, Aschoff's rule says that as light intensity increases, the duration of rest time (ρ) decreases *more* than the increase in activity time (α) predicted by the circadian rule, so that the total circadian period decreases.

In fact, Aschoff's rule fails to hold consistently for diurnal mammals. Aschoff's original formulations were based upon a relatively small number of experiments on a wide variety of species (Aschoff, 1960). When Aschoff again analyzed published data many years later, the number of experiments was so much larger that he was able to separate diurnal and nocturnal animals into smaller categories, such as birds and mammals (Aschoff, 1979). Aschoff discovered that the original "Aschoff's rule" still held for some of these categories but not for others:

> "For night-active species of mammals ... there is again an unambiguous picture: With the exception of the fruit bat, *Rousettus aegyptiacus*, all species lengthen τ [period] as I_{LL} [light intensity] increases ... [but] ... a bimodal [decreasing-then-increasing] dependence of τ on I_{LL} could be characteristic for at least some species of night-active mammals. Other than the quite uniform τ-characteristics obtained from night-active mammals and day-active birds, the daytime species of mam-

> mals ... show large differences in the dependence of τ on I_{LL}. A lengthening of τ with increasing I_{LL} prevails, but four species shorten τ, at least within certain ranges of intensities ..." (Aschoff, 1979, p.235).

Thus diurnal and nocturnal mammals are asymmetric with respect to how consistently they obey Aschoff's rule. Nocturnal mammals obey the rule more consistently than diurnal mammals. Where nocturnal mammals do not obey Aschoff's rule, a shortening of period usually occurs at low light levels but then lengthens at high light levels. Remarkably, a similar shortening followed by a lengthening of period occurs in many diurnal mammals that do not obey Aschoff's rule (Aschoff, 1979), thereby sharpening the sense in which diurnal and nocturnal animals asymmetrically follow the original rule.

8. THE ASYMMETRY OF FATIGUE AND LIGHT IN DIURNAL AND NOCTURNAL MODELS

Both Aschoff's rule and its exceptions can be understood by analysing the interactions between steady light inputs, light attenuation during sleep, the fatigue signal, and the basic pacemaker. In particular, the different ways in which diurnal and nocturnal activity durations and periods react to different levels of steady light are traced to asymmetries in the action of light input and fatigue signal on the diurnal and nocturnal model pacemakers. Both light and fatigue tend to inhibit activity-generating output of a nocturnal pacemaker; in

contrast, light excites and fatigue inhibits activity-generating output of a diurnal pacemaker. The more regular adherence of nocturnal mammals than of diurnal mammals to Aschoff's rule is traced to this asymmetry.

The circadian rule is robustly obeyed by the model except in situations where long-term after-effects predominate. The action of light input on both diurnal and nocturnal models generally implies the circadian rule, even in parameter ranges where the F signal plays a role in causing exceptions to Aschoff's rule.

9. ASCHOFF'S RULE AND ITS EXCEPTIONS: NUMERICAL STUDIES

Parametric numerical studies indicate the dynamical factors subserving Aschoff's rule and its exceptions in the gated pacemaker model. Aschoff's rule and the circadian rule are mathematically analysed in Carpenter and Grossberg (1984). The analysis of the effects of light attenuation leads to the prediction that a diurnal mammal should obey Aschoff's rule less consistently during a self-selected light-dark cycle than in constant bright light.

The numerical studies consider eight cases that arise from combining the following three alternatives in all possible ways:

1. nocturnal vs. diurnal;
2. no fatigue signal vs. large fatigue signal; and

3. no light attenuation during sleep ($\theta = 1$) vs. maximal light attenuation during sleep ($\theta = 0$).

The main mechanistic conclusion about Aschoff's rule is that fatigue feedback is necessary for the rule to hold. The asymmetric frequency with which the rule holds in diurnal vs. nocturnal mammals is traced to the asymmetric way in which light perturbs diurnal and nocturnal models with respect to the site of action of fatigue (Figure 1).

Figure 8 summarizes how the circadian period τ varies with increasing steady light levels in the eight cases. In parts a-d, all model parameters are held constant, other than the parameters controlling light attenuation (θ) and the amount of fatigue (M in equation (8)). The parameters θ and M were chosen in the simulations to maximize the differences between small and large light attenuation and fatigue effects. In particular, the case $\theta = 0$ (Figures 8b and 8d) illustrates maximal light attenuation during sleep. The case $\theta = 1$ (Figures 8a and 8c) illustrates no light attenuation during sleep. Figures 8c and 8d, with $M = F(0) = 0$, illustrate the model without any fatigue feedback. In Figures 8a and 8b, M was chosen to maximize the effects of fatigue. Very large values of M cause such a large fatigue signal that behavioral activity is suppressed almost as soon as it begins. A comparison of Figures 8a and 8c, and of Figures 8b and 8d, shows that the choice $M = .1$ causes a significant effect due to the fatigue signal without preventing sustained bouts of behavioral

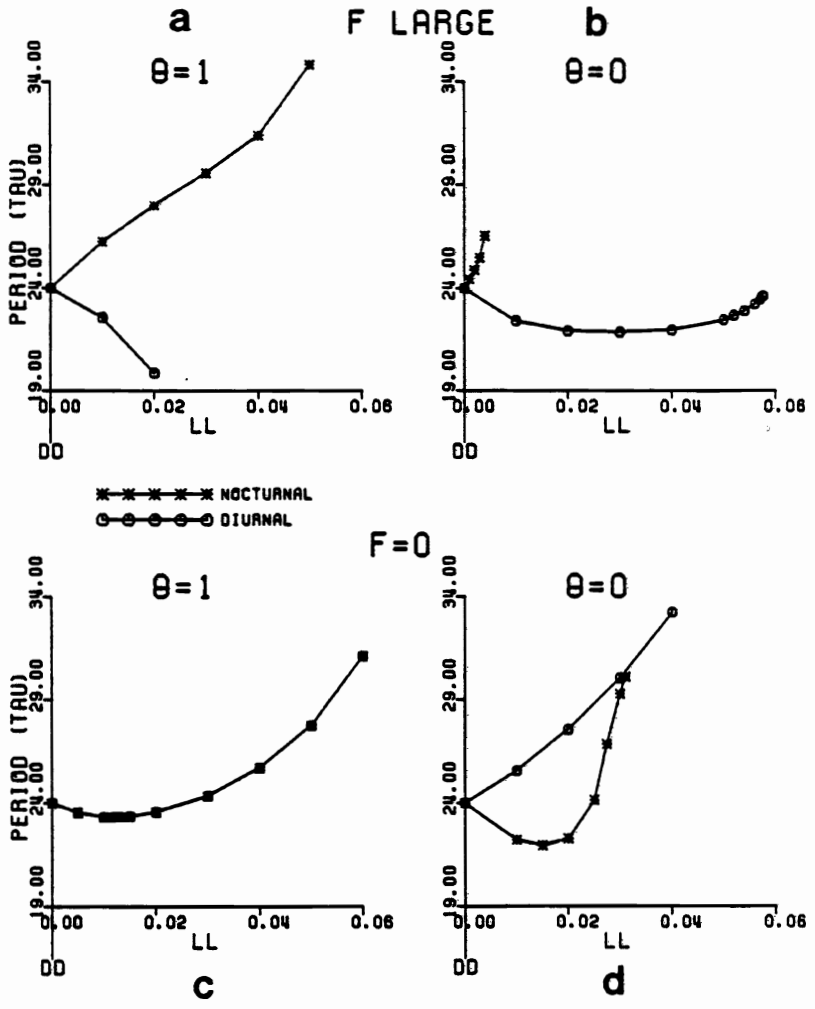

Figure 8. Period τ as a function of light intensity LL. The eight curves correspond to the eight combinations of nocturnal vs. diurnal, $\theta = 1$ vs. $\theta = 0$, and F large vs. $F \equiv 0$. The variable LL is a linear function of the logarithm of ambient light intensity. This logarithmic transformation is assumed to occur between retinal receptors and the SCN.

activity.

Each graph in Figure 8 depicts the period of the nocturnal model and the diurnal model as a function of parametric increases in steady light level (LL). Figure 8c describes the case of no light attenuation ($\theta = 1$) and no fatigue ($F \equiv 0$). Since both the nocturnal model and the diurnal model then have the same period at each light level, only one curve appears. As a function of increasing LL, this curve decreases before it increases. Thus the curve does not obey Aschoff's rule for either nocturnal or diurnal mammals. On the other hand, there do exist both nocturnal and diurnal mammals whose period changes in the manner of Figure 8c as a function of LL.

In Figure 8a, there is no light attenuation during sleep ($\theta = 1$), but there is a significant fatigue signal. The fatigue signal causes distinct τ values to occur in the nocturnal and diurnal models at each steady light level. Moreover, each of the graphs of τ vs. LL exhibits Aschoff's rule. The comparison between Figures 8a and 8c, and between Figures 8b and 8d, is the basis for our thinking that fatigue, or negative feedback to the pacemaker, is a primary factor in generating Aschoff's rule. This comparison leads to the prediction that a nocturnal mammal which obeys Aschoff's rule will either be arhythmic or will violate Aschoff's rule if the fatigue signal is blocked before it can feed back to modulate the SCN pacemaker. To a first approximation, the combined action of

light and fatigue can be seen to generate Aschoff's rule (when $\theta = 1$) as follows. For the diurnal model, increasing the constant light input first (approximately) shifts the graph of the output, $x_1(t)$, upward by a constant. Such a shift increases α and decreases ρ, but leaves τ constant. However, during the active phase, negative feedback (F) pulls α back toward the value it had in the dark. Fatigue has little effect on the pacemaker during rest. Thus the net effect of increased constant light on the diurnal model is to increase α somewhat (the circadian rule), decrease ρ by a greater amount, and decrease the total $\tau \equiv \alpha + \rho$. Hence Aschoff's original rule holds for the diurnal model when $\theta = 1$. A similar argument implies Aschoff's rule for the nocturnal model.

Deviations from Aschoff's rule are explained by the joint action of fatigue and light attenuation during sleep. A comparison between Figures 8a and 8b illustrates one of these deviations. In the two figures, fatigue feedback is equally effective. The figures differ only in how much light attenuation occurs during sleep. In Figure 8b, the nocturnal model continues to obey Aschoff's rule, whereas the diurnal model does not. This fact is a basis for our explanation of the greater tendency of nocturnal mammals than of diurnal mammals to obey Aschoff's rule. The differential reactions of nocturnal and diurnal models to the interacton between light attenuation and fatigue reflects the asymmetric sites of action of these factors in the nocturnal and diurnal pacemakers.

The rate-limiting role of fatigue in generating Aschoff's rule is again shown by comparing Figures 8b and 8d. In both figures, light is significantly attenuated during sleep. In Figure 8d, however, no fatigue is registered at either pacemaker. At low light levels, the slope of each curve is opposite that predicted by Aschoff's rule. However, the period τ of the nocturnal model in Figure 8d does increase with LL at large values of LL. Thus in all cases, the nocturnal model obeys Aschoff's rule more consistently than the diurnal model.

10. LONG-TERM AFTER-EFFECTS DUE TO PARAMETRIC AND NON-PARAMETRIC LIGHT REGIMES

Concerning long-term after-effects, Pittendrigh has written:

> "They are more widespread than the current literature suggests; they are not accounted for by any of the several mathematical models so far published; and they must be reckoned with in the mechanisms of entrainment" (Pittendrigh, 1974, p.441).

Again in 1976, Pittendrigh and Daan wrote:

> "The literature has paid little attention to after-effects in the 15 years since they were first reported" (Pittendrigh and Daan, 1976a, p.234).

Long-term after-effects are changes in activity and/or period that persist in the dark after their inducing light regimes are terminated (Pittendrigh, 1960). These changes can remain in effect for months. Long-term after-effects with ostensibly contradictory properties are caused by parametric and non-parametric light regimes. A parametric light regime is one in which a steady light is maintained for a number of days before the animal free-runs in the dark. A non-parametric light regime is one in which light and dark intervals alternate for a number of days before the animal free-runs in the dark.

Table 1

(Pittendrigh and Daan, 1976a)

Light Regime	After-Effect
LD 1:23	larger τ_{DD}
LD 18:6	smaller τ_{DD}
LD 12:12	smaller τ_{DD}
LL	larger τ_{DD}

The main paradox that is raised by parametric and non-parametric light regimes is summarized in Table 1. After stating the paradox, we will describe related data and simulations.

The notation LD M:N means that a nocturnal mammal is placed in M hours of light followed by N hours of darkness for a number of days before being allowed to free-run in the dark (DD). The notation LL means that the animal is placed in steady light for a number of days before being allowed to free-run in the dark. The notation τ_{DD} stands for the steady

circadian period during free-run in the dark following a given light regime.

A comparison between the two non-parametric cases LD 1:23 and LD 18:6 shows that τ_{DD} is smaller following a light regime with 1 hour of light per day than it is following a light regime with 18 hours of light per day: here, more light implies a *smaller* τ_{DD} after-effect. In contrast, however, a comparison between the non-parametric case LD 12:12 and the parametric case LL shows that τ_{DD} is larger following a light regime with 24 hours of light per day than it is following a light regime with 12 hours of light per day: here, more light per day implies a *larger* τ_{DD} after-effect. Why does the total amount of light have opposite effects on τ_{DD} after parametric vs. non-parametric light regimes?

One explanation for the paradoxical after-effect data of Table 1 is that constant light (LL) acts by altering a pacemaker parameter, whereas a non-parametric (LD) light regime acts by differentially phase resetting constituent pacemaker oscillators (Pittendrigh, 1974; Pittendrigh and Daan, 1976a; Daan and Berde, 1978). However, this explanation relies on the hypotheses that external light onset and/or offset during an LD regime has a unique effect not shared by the many other onsets and offsets of light input to the pacemaker, due, for example, to eye closure, during a typical LD regime or LL regime; and that the parametric shift effected by LL is somehow blocked during an LD regime with as much as 18

hours of light per day.

Our analysis of after-effects makes no assumptions about differential parametric vs. non-parametric actions of pacemaker light input. But then how can the differences between *LD* and *LL* light regimes on subsequent τ_{DD} be explained? A key observation is that during an LD 18:6 regime a nocturnal animal is forced to be active in the dark, whereas during an LL regime the nocturnal animal is forced to be active in the light.

Figure 9 describes a simulation showing long-term after-effects of photoperiod in the nocturnal model. Just as individual animals exhibit distinct activity cycles, different parameter choices exhibit individual differences in circadian period and the patterning of activity (dark lines) while sharing the qualitative properties described in Table 1. The model simulation in Figure 9 illustrates the non-parametric after-effect experiments that Pittendrigh (1974, p.438) and Pittendrigh and Daan (1976a, pp.240-243) carried out using the white-footed deermouse *(Peromyscus leucopus)*. In Figure 9, 1 hour of light alternated with 23 hours of darkness (LD 1:23) for 60 days. The bracketed white regions define the time intervals during which light was on. A free-run in the dark (DD) for 30 days followed. Then 18 hours of light alternated with 6 hours of darkness (LD 18:6) for 60 days, followed by a 30-day free-run in the dark.

In the simulation, the free-running period in the dark

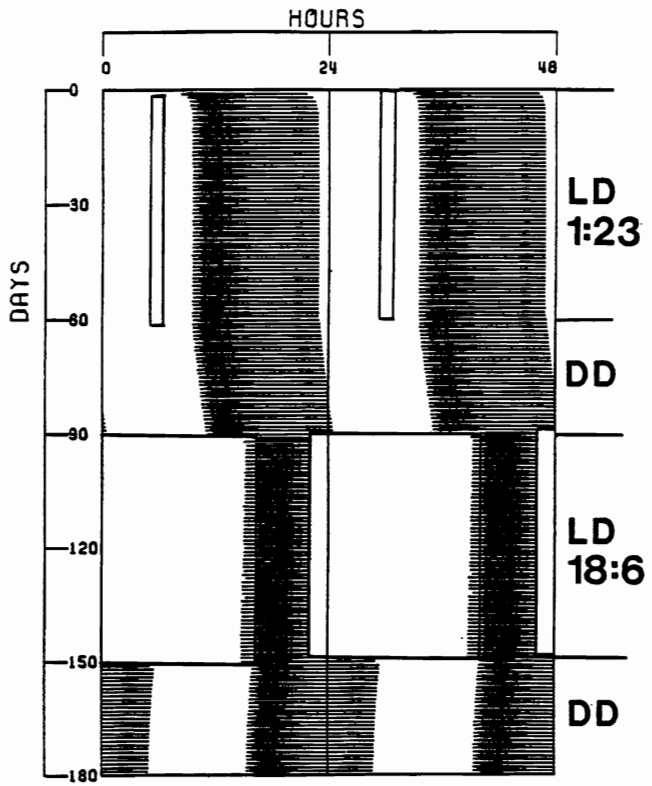

Figure 9. Simulation of photoperiod after-effects: The model is exposed to an LD 1:23 lighting regime (1 hour of light every 24 hours) before free-runing in the dark. Then the model experiences an LD 18:6 lighting regime before free-runing in the dark. The free-running activity levels and periods depend upon the prior lighting regimes and persist throughout the 30-day free-run intervals. The figure is a double-plot. Two successive days are plotted in each row and each successive day is plotted in the left-hand column. Thus the day plotted in the right-hand column of row i is also plotted in the left-hand column of row $(i + 1)$.

(τ_{DD}) is shorter after LD 18:6 than after LD 1:23. In Figure 9, the two periods are 24.04 hours (days 60-90) and 23.96 hours (days 150-180).

Figure 10 shows a simulated after-effect of constant light (LL). In this parametric setting, steady light significantly increases the period both in the light and, subsequently, in the dark (Pittendrigh and Daan, 1976a, p.239). In both the deer-mouse and the model, the after-effect due to an LD 12:12 non-parametric light regime was compared with the after-effect due to an LL parametric light regime. In both the experiments and the simulations, the free-running period following LL exceeds the free-running period following LD 12:12.

Thus, although an increase in light duration (as in LD 1:23 vs. LD 18:6) decreases circadian period in a non-parametric paradigm, an increase in light duration (as in LD 12:12 vs. LL) increases circadian period in a parametric paradigm. The simulations in Figures 9 and 10 hereby reproduce the main data features described in Table 1. In Figures 9 and 10, the identical model and light intensity are used to simulate the non-parametric and parametric after-effects.

The simulated properties of Figures 9 and 10 depend upon the action of the slow gain control process $y(t)$. The process $y(t)$ slowly averages pacemaker activity through time (equation (6)). Then $y(t)$ modulates the activity of the pacemaker by acting as a gain control signal (equation (1)). Thus process $y(t)$ is part of a feedback loop whereby past levels of pace-

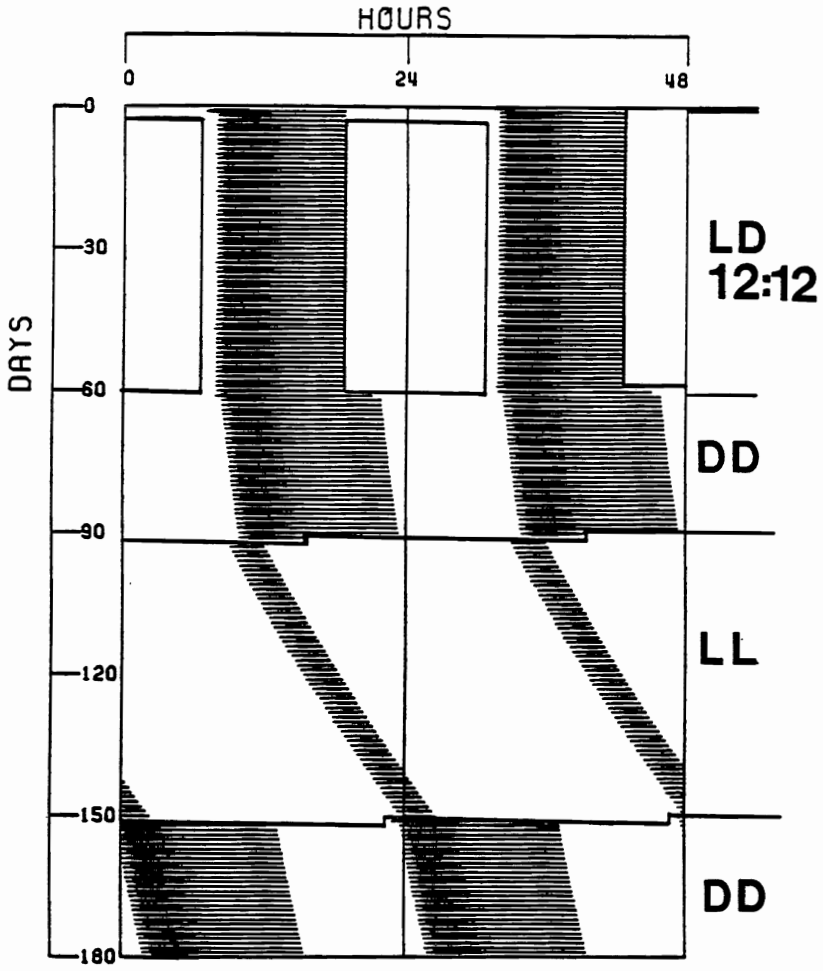

Figure 10. Simulation of an after-effect of constant light: An LD 12:12 lighting regime followed by a free-run in the dark (DD) establishes a baseline free-run circadian period τ_{DD}. Then the model experiences constant light (LL) before again free-running in the dark. After the transition from DD to LL, the circadian period increases, as expected by Aschoff's rule for nocturnal mammals (Aschoff, 1960, 1979; Carpenter and Grossberg, 1984). The free-running period after LL is greater than after LD 12:12. Model parameters and light intensities are the same as in Figure 9.

maker activity modulate future levels of pacemaker activity.

The gated pacemaker model simulates after-effects by causing different lighting regimes to generate different patterns of pacemaker activity which, in turn, have differential effects on the slow gain control process. For example, the model is much more active during the 6 hours of darkness in LD 18:6 than it is in the light in LL, or even during the 23 hours of darkness in LD 1:23. Such differences also occurs in the data (Pittendrigh and Daan, 1976a). The differences between activity patterns induce different values of the gain control variable, which lead to the different long-term after-effects.

Finally, another aspect of LD 12:12 vs. LL experiments is also explained by our model. Pittendrigh and Daan write:

> "What these records show convincingly is that the bimodal pattern of activity in LD 12:12 is indeed produced by the same two components diverging during the DD-interval from their prior compressed state in LL" (Pittendrigh and Daan, 1976b, p.341).

Figure 10, shows the bimodal nature of the simulated activity pattern during LD 12:12 and DD as well as its unimodal form during LL.

11. SPLIT RHYTHMS: INFLUENCES OF LIGHT, HORMONES, AND SCN ABLATION

Pittendrigh (1960) first noted and recognized the importance of the phenomenon of split rhythms. Split rhythm experiments have shown that about half of all golden hamsters

with a single daily activity cycle in the dark (DD) generate an activity cycle which splits into two components in constant light (LL). The split does not usually occur until about two months after the hamster begins to free-run in constant light (Pittendrigh, 1974). Several other examples of split rhythms have also been discovered. Hoffmann (1971) described a diurnal mammal *(Tupaia belangeri)* whose rhythm splits when the level of illumination is reduced. Gwinner (1974) noted that the hormone testoserone induces split rhythms in starlings. Aschoff, Pittendrigh, and others have also noted that many animals have bimodal activity patterns even when the activity pattern does not split.

We suggest that certain split rhythms and ultradian rhythms are caused by the negative feedback signal due to fatigue, and that a slow onset of split rhythms can be traced to the slow time scale of the gain control process y in equation (6). Our model thus claims that certain split rhythms may be due to the joint action of two biologically useful processes acting on different time scales.

Figure 11 depicts a model simulation of a split rhythm and SCN ablation experiment on golden hamsters (Pickard and Turek, 1982). The dark bars indicate the times at which the model animal is active. In Figure 11, the nocturnal model is kept in the dark (DD) for 20 days and then is placed in constant light (LL). Initially, the free-running period (τ) increases, as predicted by Aschoff's rule (Aschoff, 1960, 1979).

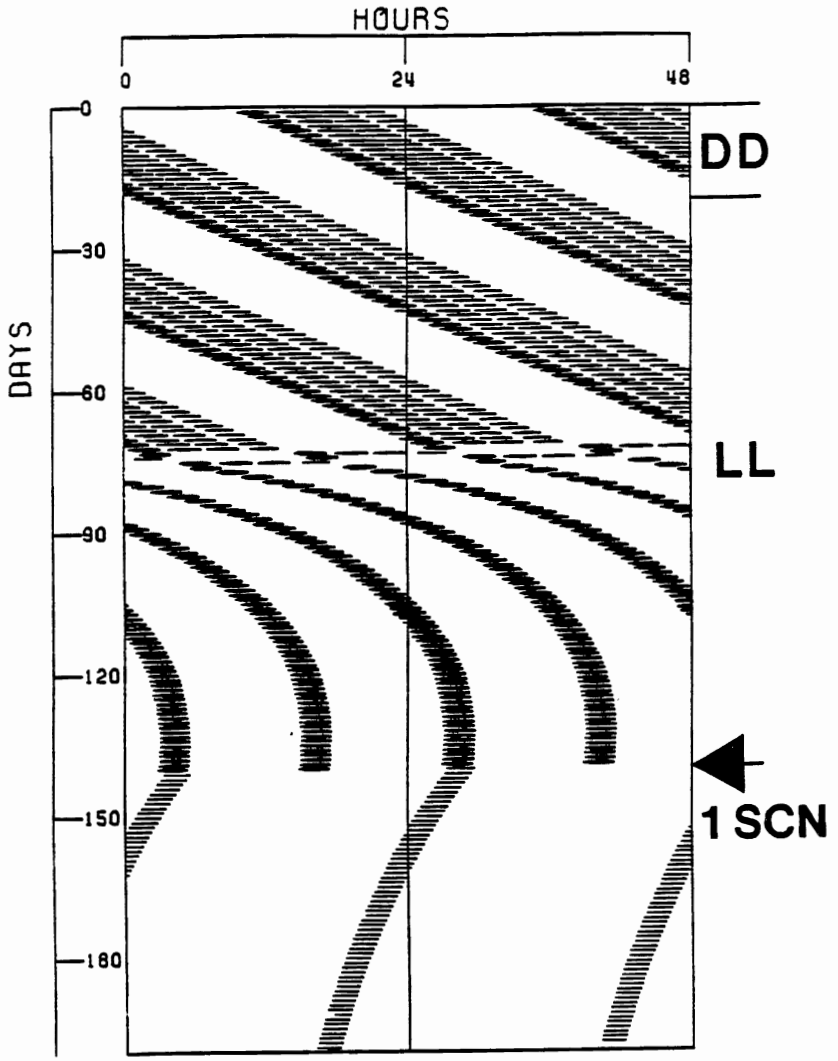

Figure 11. A split rhythm and SCN ablation simulation: The text describes how the activity rhythm starts to split 52 days after being placed in steady light (LL) and how the split rhythm is abolished by ablation of one model SCN.

On day 72, the rhythm starts to split. The split rhythm stablizes after 5 days of transitional activity. The split period is shorter than the period prior to the split, as in the data. One model SCN is ablated on day 140, after which the split rhythm is abolished. The subsequent τ is shorter than any previous τ, as in the data. In the model analysis, fatigue feedback induces both split rhythms and bimodal or multimodal activity patterns. When one model SCN is ablated, the resulting decrease in net pacemaker output leads to a rapid decrease in F, which abolishes the split and at the same time instates a unimodal activity pattern.

In summary, the underlying period of the pacemaker in the dark is controlled by the accumulation rate of the transmitter gates within the basic pacemaker's positive feedback loops (Figure 1). A fatigue signal exercises a homeostatic role that prevents the pacemaker from generating excessive bouts of activity. A slow gain control process enables the pacemaker to adapt its activity cycles to long-term trends in the light-dark cycle. For example, the slow gain control process can enable a nocturnal model animal to become very active during the short nights of summer, while the fatigue feedback process prevents this heightened activity level from exhausting the model animal. Our theory thus indicates how biologically useful modulatory mechanisms can generate quantitative simulations of difficult data which, on the surface, appear to be paradoxical.

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