*Note added in proof: Since this report was accepted for publication, Chu and Bloom (*20*) have reported that 9 of 30 presumed norepinephrine-containing neurons in the LC region decreased rate in transition from the synchronized to the desynchronized phase of sleep.

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Neuronal Excitability Modulation over the Sleep Cycle: A Structural and Mathematical Model

Abstract. *A model for control of the desynchronized phase of the sleep cycle postulates reciprocal interaction between cells in the pontine gigantocellular tegmental field (FTG cells) and cells in the nucleus locus coeruleus and nucleus subcoeruleus (LC cells). This physiological model leads to equations of the Lotka-Volterra type; the time course of activity predicted by the model is in good agreement with actual long-term recordings of FTG cells and single-cycle data for LC cells.*

The existence of a cell group in the region of the nucleus locus coeruleus (LC) of the cat with discharge activity curves opposite to those of cells in the gigantocellular tegmental field (FTG) has been documented by Hobson *et al.* (*1*). It was proposed that reciprocal interaction between excitatory and inhibitory neural populations may determine the alternation of sleep cycle states. We now present a simple structural and mathematical model for sleep cycle control based on the reciprocal interaction hypothesis and consider aspects of FTG and LC unit discharge activity curves in terms of the model (*2*).

The temporal organization of discharges in the FTG with respect to the sleep-waking cycle is illustrated in Fig. 1 for an FTG neuron recorded continuously for 10.5 hours. The most striking features of this discharge time course are the periodically occurring peaks of discharge activity, each of which corresponds to a desynchronized sleep episode. This regular, nonsinusoidal modulation of discharge activity was noticed in all of the six pontine reticular neurons recorded over 10 to 18 sleep-waking cycles (recording duration, 4.7 to 17.5 hours), although there was variability in the extent of modulation and cycle length. The presence of periodicity was confirmed by peaks in serial correlation coefficients and a dominant peak in the power spectral density (*3*).

For a detailed examination of the time course of discharge activity over the sleep-waking cycle, we normalized the duration of each cycle and averaged the activity over many cycles. Figure 2C presents the average activity curve for 12 cycles of FTG neuron 568, whose average cycle length was about 20 minutes. Note that the form of the activity curve is in general agreement with that in Fig. 1. What mechanism might be involved in generation of these nonsinusoidal, periodic neuronal activity curves? A detailed autocorrelation analysis of the discharge pattern of brainstem neurons gave no evidence for the regular, stereotyped discharge patterns generated by invertebrate pacemaker neurons involved in control of rhythmic activity (*4*). We were thus led to pursue the implications of the hypothesis that the time course of FTG unit activity is the result of reciprocal interaction with LC neurons.

Figure 2A shows the structural connections and the signs of influence that we have postulated. Golgi studies indicate the presence of FTG recurrent collaterals (*5*), and we have observed that the process of transition to high discharge levels in desynchronized sleep in FTG neurons is of exponential order, a finding compatible with self-excitation via such collaterals (*6*). Studies using Golgi (*7*) and Nauta (*8*) techniques have indicated the presence of a projection from FTG to LC cells which is postulated to utilize acetylcholine and to be excitatory. The available histochemical evidence points to the FTG cells as both using acetylcholine as a neurotransmitter and being influenced themselves by synaptically released acetylcholine (*9*). Connections from LC to FTG and from LC to LC cells are indicated by Golgi work (*7*) and by the presence of norepinephrine-containing varicosities in each area (*10*); these synapses are assumed to utilize norepinephrine as a neurotransmitter and to be inhibitory (*11*). Hobson *et al.* (*1*) discuss the problem of identification of the norepinephrine-containing cells with those recorded by us.

With this basic structural model, we proceeded to develop a parallel quantitative model of interaction. The mathematical form of terms describing the influence of each population on itself is suggested by evidence that the rate of change of activity levels in the FTG population is proportional to the current level of activity (*6*), and we propose that the same is true for the LC population, but with a negative sign because the recurrent feedback is inhibitory. The highly nonsinusoidal nature of FTG activity suggested that nonlinear FTG-LC interaction was to be expected. We model this effect by the simplest form of nonlinearity, the product of activities in the two populations; this is in accord with the reasonable physiological postulate that the effect of an excitatory or inhibitory input to the two populations will be proportional to the current level of discharge activity. Let $x(t)$ be the level of discharge activity in FTG cells; $y(t)$ the level of discharge activity in LC cells; and a, b, c, and d positive constants identified with

the strength of the connections outlined in Fig. 2A. These terms are related by the equations

$$dx/dt = ax - bxy$$
$$dy/dt = -cy + dxy$$

This system of equations is that of Lotka and Volterra, originally proposed as a model for prey-predator interaction. In our model, the FTG (excitatory) cells are analogous to the prey population, and the LC (inhibitory) cells are analogous to the predator population. These equations and more complicated variants have been extensively studied and the character of their solutions has been well documented (*12, 13*), although no explicit solution in terms of elementary functions is available. For the simple model and the parameters used here, there is a periodic solution with neutral stability (*12, 13*). Hobson *et al.* (*1*) have presented a qualitative account of the events leading to periodic cycles, and the time course of FTG activity over several sleep-waking cycles predicted by the model is sketched in Fig. 2B (*14*).

In Fig. 2C we compare a theoretical curve derived from the model with the actual data values for the average of 12 cycles of unit 568 (*15*). The overall match is rather good. Specifically, both curves show a nadir in the first third of the cycle, a long period of slow growth of activity, and a rapid acceleration as the time of desynchronized sleep onset is approached. The average time of desynchronized sleep onset occurs at about the same time as the theoretical curve crosses the equilibrium point, and the approach to the peak is less steep than the decline. Comparisons of similarly derived theoretical and observed data curves from other units showed about the same degree of fit (see also Fig. 2B). The model predicts that LC activity levels should decline steadily in synchronized sleep to a low point at desynchronized sleep onset, and then show a rapid rise in the last portion of desynchronized sleep (see the theoretical curve in Fig. 2C) (*16*). To determine if the LC pool shows this behavior, we averaged the activity curves of ten LC cells, drawn from the population discussed in Hobson *et al.* (*1*), during successive quartiles of desynchronized sleep and for periods of equal duration before and after desynchronized sleep. The sketch of the observed data in Fig. 2D is in reasonably good agreement with the theoretical curve in Fig. 2C. Note that the increase in discharge activity occurred before the end of the desynchronized sleep episode in the averaged data; this important feature was present in each of the ten LC cells. Point by point comparisons of LC data with the theoretical curve will be

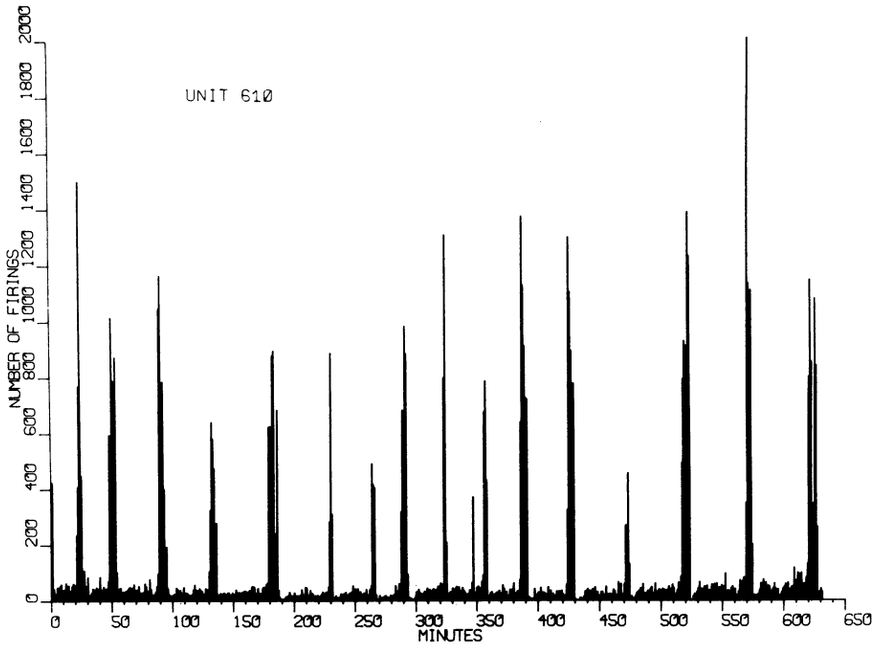

Fig. 1. Discharge activity of FTG neuron 610 recorded over multiple sleep-waking cycles. Each peak corresponds to a desynchronized sleep episode, and a regular trend of discharge activity over a cycle is observable: a peak in desynchronized sleep; a rapid decline at the end of the desynchronized sleep episode; a trough, often associated with waking; a slow rise (in synchronized sleep); and an explosive acceleration at desynchronized sleep onset. Note also the extreme modulation of activity and the periodicity.

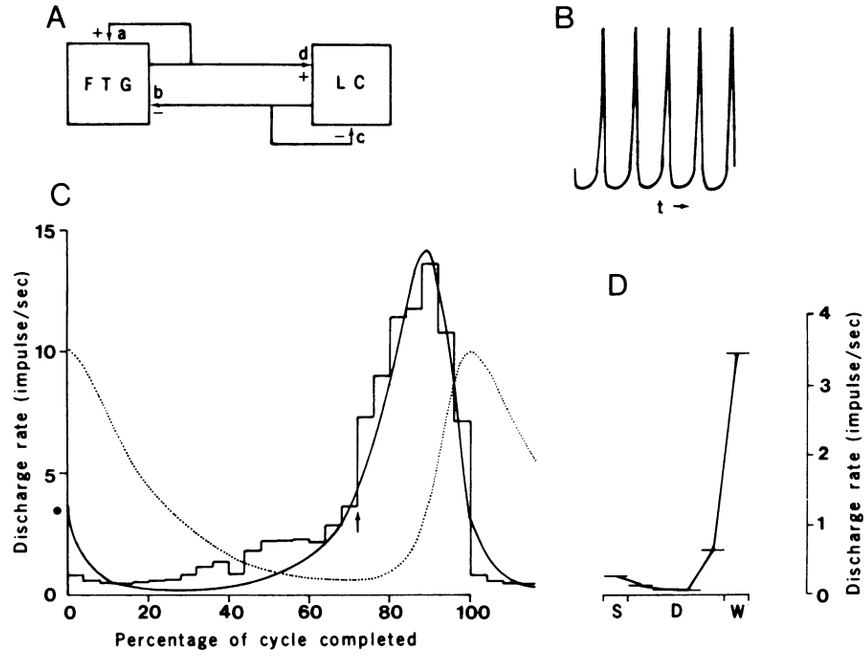

Fig. 2. (A) Structural model of interaction between FTG and LC cell populations. The plus sign implies excitatory and the minus sign inhibitory influences. The letters *a, b, c,* and *d* correspond to the constants associated with the strength of the connections and included in the text equations. (B) Theoretical curve derived from the model that best fits the FTG unit in Fig. 1. In this fit, $a = 0.3029$, $c = 0.1514$, and the initial conditions (amplitude unscaled) were $x(0) = 1$ and $y(0) = 4.5$. (C) The solid line histogram is the average discharge level of FTG unit 568 over 12 sleep-waking cycles, each normalized to constant duration. The cycle begins with the end of desynchronized sleep, and the arrow indicates the bin with the most probable time of desynchronized sleep onset. The solid curve describes the FTG fit and the dotted line the LC fit derived from the model with the values $a = 0.5490$, $c = 0.2745$, $x(0) = 1$, and $y(0) = 3.0$ (amplitude unscaled). The dot in the ordinate scale indicates the equilibrium values for the two populations. (D) Geometric mean values of the discharge activity of ten LC cells before (synchronized sleep, *S*), during (desynchronized sleep, *D*), and after (waking, *W*) a desynchronized sleep episode. Each time epoch is equal to one-quarter of a desynchronized sleep period. Note that the discharge rate increase begins in the last quarter of *D*.

possible with multiple-cycle LC cell recordings.

The reciprocal interaction model for sleep cycle control is explicit and testable. It helps to order a confusing pharmacological literature and suggests critical experiments to test its postulates. For example, the model predicts that suppression of LC activity or its postsynaptic effects will produce augmented FTG activity and hence more desynchronized sleep. Indeed, more desynchronized sleep has been found to result from administration of substances blocking alpha-adrenergic receptors (*17*) and norepinephrine synthesis (*18*). These results run counter to the theory that desynchronized sleep phenomena are actively generated by the LC, but are entirely consonant with our model. An interesting but so far untested corollary prediction about cellular events is that the LC cells normally showing a marked decrease in discharge activity with the advent of desynchronized sleep should show a less marked decline following the administration of these drugs, since the inhibitory feedback will be less potent. The model further predicts that another approach to desynchronized sleep enhancement—through direct increase of FTG activity—would be to administer compounds that simulate the effect of acetylcholine in the FTG; this prediction of the model is also confirmed by several experiments (*19*). The parallel prediction that injection of such cholinomimetic compounds into the LC should result in less FTG activity and thus less desynchronized sleep because cells inhibitory to the FTG are being stimulated has not been tested. We conclude that the model offers a good first approximation to the discharge activity curves of FTG and LC cells and is consonant with anatomical, physiological, and pharmacological data.

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14. An important temporal feature postulated by the model and present in the data is the phase lag between the FTG and LC activity peaks; this is on the order of several minutes in duration in the cat's usual cycle. The mechanisms of this phase lag are not explicitly included in the model, but the duration of the phase lag suggests the presence of transmitter effects whose duration extends into the minute range. Such long-duration effects for the transmitters postulated in our model have been reported to occur at several synap→ M. Segal and F. E. Bloom, *Brain Res.* **72**, 79 (1974); F. Weight, in *The Neurosciences, Third Study Program*, F. O. Schmitt and F. G. Worden, Eds. (MIT Press, Cambridge, 1974), p. 929.
15. Numerical integration of the second-order nonlinear differential equations derived from the text equations was done by the method of continuous analytic continuation, as outlined in (*12*). With the start of the curve set at the end of the desynchronized sleep cycle, $x(0)$ is fixed at the equilibrium value and $dy/dt = 0$ at $t = 0$. The values of $y(0)$ (or, alternatively, dx/dt at $t = 0$) and the constants a and c were set to match the observed modulation during the sleep cycle and scaled for the appropriate duration. The constants b and d scale the amplitude of the FTG and LC activity curves.
16. Note that, unlike the onset and end of desynchronized sleep periods defined by crossing of the FTG equilibrium values, the portions of the theoretical cycles to be identified with the behavioral states of waking and synchronized sleep are more fuzzy, since the model attempts only to show the control mechanisms for desynchronized sleep. On a probabilistic basis, the first fifth of the cycle is most often associated with waking, and synchronized sleep includes the rest of the cycle up to desynchronized sleep onset, although arousals may sometimes occur during this period.
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Colonial Nervous Control of Lophophore Retraction in Cheilostome Bryozoa

Abstract. *Nervous impulses causing lophophore retraction over large areas of* Membranipora membranacea *and* Electra pilosa *were recorded with external electrodes. The response propagates at about 100 centimeters per second, presumably through the colonial nerve plexus of Hiller and Lutaud. Impulses are rapid up to 200 per second. A second impulse was recorded from individual zooids, probably generated by the polypide's nervous system. The retractor muscle shortens at more than 20 times its own length per second and is apparently the most rapidly contracting muscle known.*

Various authors have investigated the control of behavior by simply organized nervous systems in colonial invertebrates [for example, see (*1, 2*)]. Except for recordings of the Hydrozoa (*2, 3*), however, no direct electrophysiological recordings of colonial nervous activity have been made. Marcus (*4*) claimed that no colonial coordination existed in the gymnolaemate Bryozoa. This view, supported by Silen (*5*) and others, has been widely accepted in the last 50 years. Hiller (*6*) and more recently Lutaud (*7*) presented histological evidence for a colonial nervous plexus in *Electra* (formerly *Membranipora*) *pilosa* (L.) to support the behavioral data of Bronstein (*8*).

Our work has shown that there is a high degree of coordination between zooids in the two species we have studied—*Membranipora membranacea* and *Electra pilosa*. Furthermore, electrophysiological recordings indicate that a highly active colonial nervous system is involved.