RESEARCH ARTICLE

Circadian Synchrony in Networks of Protein Rhythm Driven Neurons

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The interaction between gene activation and cellular activity has recently emerged as a critical aspect of brain behavior, but the dynamics of networks incorporating these interactions are poorly understood. An interesting phenomena arises when the genetic activation oscillates endogenously and a network of such cells synchronize to a coherent rhythm, such as is the case with the suprachiasmatic nucleus. To explain this synchronization, we propose a model in which a mRNA/protein expression cycle drives neurons electrical activity, and synaptic activation shifts the phase of the protein rhythm. Using lattice networks, we demonstrate that these interactions are sufficient to generate coherent oscillation. © 2006 Wiley Periodicals, Inc. *Complexity 12: 67–72, 2006*

Key Words: synchronicity; suprachiasmatic nucleus; protein expression; circadian rhythms

INTRODUCTION

Syncronicity has been examined in many natural systems. Pendulums placed on the same wall synchronize their swing. The rhythmic firing of groups of fireflies creates a visually spectacular form of synchrony. Most fireflies light under their own sense of timing, creating a seemingly random array of lights. But certain species of fireflies synchronize their rhythm based on the flashes of other nearby fireflies, until the whole group fires as one mass [1].

Synchronicity of oscillators is crucial in the human body. Plasma insulin oscillates with frequency of 5–10 min. Similarly the secretion from individual beta cells in the pancreas are also synchronized. The beta cells are organized into islets and synchronize both within and between islets [2]. Perhaps most important, the healthy human heart beats at regular intervals of about 60 to 100 times per minute at rest. This is initiated at the sinoatrial node (SAN) of the right atrium, which is considered the heart's pacemaker [3]. Our main focus in this article is on cells that control many

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circadian rhythms, such as the sleep–wake cycle and rhythms of hormone release.

The suprachiasmatic nucleus (SCN), located within the hypothalamus of the mammalian brain, is the master circadian pacemaker. As such, it is responsible for coordinating peripheral oscillators such as the liver and lungs [4], as well as daily activity rhythms. The 15,000–20,000 neurons comprising the SCN coordinate their circadian rhythms (~24 h) in both protein expression and firing rates. However, these neurons show a wide range of free running periods when dissociated from the SCN [5–8]. Understanding how individual SCN cells communicate in vivo to maintain synchrony is essential to advancing knowledge about the circadian system and its resynchronization after disruption of circadian timing, such as during jet lag and shift work [9,10].

We address the general question of interactions between protein expression and neural activity by modeling these processes as they are here hypothesized to occur in the SCN. The neurons of the SCN are ideal units for modeling these interactions because of their stable firing rate and because their protein expression rhythm has been researched experimentally. As with all modeling research, we cannot prove that the biology chooses the exact method synchronization we propose, but we hope that it will spark future biological experiments. In addition, because of the ubiquity of synchronizing systems, our fundamental work may be applicable to many biological systems as well as to the construction of oscillator networks in the field of biotechnology.

Increasing evidence implies that SCN cells may synchronize via firing rates [11,12]. Most recently it was shown that after a week of treatment with tetrodotoxin, an action potential inhibitor, protein rhythms of individual cells maintain a circadian oscillation, but are no longer synchronized [13]. In order for neural activity to effectively communicate circadian phase between SCN cells, two mechanisms must exist. First, a neuron's firing rate must be driven by the state of the molecular clock. It has been shown that light-induced changes in the level of core clock protein per1 within an SCN cell can regulate K^+ channels and thus modify the firing rate of the cell hours after light exposure [14]. Further support comes from the fact that many dissociated SCN neurons continue to show a circadian firing rate rhythm when dissociated from other neurons, suggesting that the molecular clock is likely driving this rhythm [6,15]. Second, input from other neurons must be able to phase-shift the molecular clock. It has been shown that in the hippocampus, synaptic activation of neurons can effect mRNA transcription through a second-messenger system [16,17]. It has also been shown that the rate of mRNA transcription of per1 increases in response to light, which is thought to cause photic phase shifts [14]. We hypothesize that this mechanism of changing mRNA transcription rates to phase shift SCN cells may not solely be used to entrain to photoperiods, but also for synchronization.

Extensive modeling has been done on the molecular circadian clock of a single cell; however, only a few recent studies have focused on the circadian system at a communication-network level. Kunz and Achermann [18] demonstrated that some circadian properties can be simulated using a network of simple oscillators that communicate phase angle directly. Zariffa et al. [19] discussed more biologically plausible connections, but did not show that their model can be extended beyond two oscillators. More recently, Gonze et al. [20] showed that synchrony can be achieved through a phase-dependent neurotransmitter release in a population of oscillators that are globally coupled. Our focus is on communication via interactions between molecular clocks and membrane potentials driving neural firing rates in the SCN. We will show that synchrony can be achieved with a local coupling only.

MODEL

At the heart of our theory is a model neuron whose firing rate is driven by the state of a circadian molecular clock. The molecular clock is independent of the activity of the neuron it is within; however, when two or more neurons are synaptically connected the molecular clock of the postsynaptic neuron is affected by the firing rate of the presynaptic neurons. We call these genetically regulated oscillatory spiking (GROS) neurons (Figure 1).

The molecular clock of the GROS neuron is a limit cycle oscillator, and following Scheper et al. [21] is modeled by two fundamental state variables: the level of mRNA, M, and the level of protein P. These peak out of phase with one another but with the same period. Although the protein is not specified, the equations describe realistic dynamics of the entrainment and phase response curves (PRCs). This clock model does not depend on a large number of biological rate constants that are presently not fully known and thus is general enough to be applied to many genetic oscillatory systems, whose core clocks vary in their constituent proteins and interactions.

The coupled dynamics of the molecular clock is described by the following:

$$\frac{dM}{dt} = \frac{r_M}{1 + P^h} - q_M M \tag{1}$$

$$\frac{dP}{dt} = r_P M^\delta(t - \Delta) - q_P P \tag{2}$$

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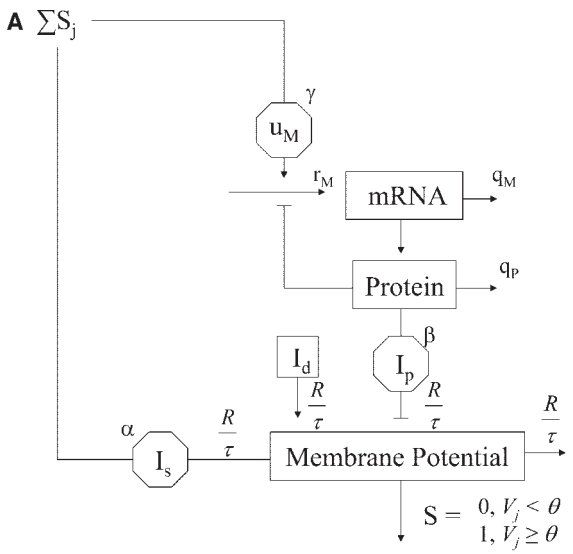
FIGURE 1



B

Parameters and Variables

Parameters	*Value*
R, resistance	1
I_D, internal drive	200
μM, endogenous rate of mRNA production	1 hr^{-1}
r_P, rate of protein production	1 hr^{-1}
q_M, rate of mRNA degeneration	0.21 hr^{-1}
q_P, rate of protein degradation	0.21 hr^{-1}
h, Hill coefficient	2.0
δ, nonlinearity in synthesis cascade	2.5-3.5
γ, scaling constant	0.000005
Δ, duration of synthesis cascade	4 hr
α, scaling constant	10
β, scaling constant	10
τ, membrane time constant	200

Variables
r_M, rate of mRNA production
M, mRNA level
V, membrane potential
P, protein level
S, synaptic input
I_S, synapse dependent current
I_P, protein dependent current

GROS neuron. (A) Circuit diagram of the GROS neuron. Input from presynaptic neurons arrives at ΣS_j, and ouput to postsynaptic neurons is through S. (B) Parameters and variables of the GROS neuron.

where r_P is the rate of protein production, q_M is the rate of mRNA degradation, q_P is the rate of protein degradation, δ is the nonlinearity of the protein cascade, Δ is the duration of the protein synthesis cascade, and h is a Hill coefficient. The Hill coefficient defines the form in which the protein inhibits mRNA production.

In the GROS neuron the production rate, r_M, is affected by both the endogenous mRNA production rate, μ_M, and the spiking rate of presynaptic neurons, S_j. Here we describe the effect on a neuron i from all neurons j, where the set K_i consists of all neurons presynaptic to the neuron i:

$$r_{Mi} = \mu_M + \sum_{j \in K_i} \gamma S_j \tag{3}$$

where γ is a constant that converts the sum of oscillating neurons synaptic inputs to mRNA production.

A GROS neuron is based on the leaky integrate and fire neuron model [22]. However, the internal steady current, I_D, that drives the membrane potential V is now inhibited by current from both the synaptic inputs, I_S, and from the protein level, I_P, of the molecular clock. The development of the neurons membrane potential is described by the following equation:

$$\tau \frac{dV_i}{dt} = -R \sum_{j \in K_i} I_{S_j} + R(I_{D_i} - I_{P_i}) - V_i \tag{4}$$

where $I_{S_j} = \alpha S_j$, $S_j = 0$ for $V_j < 0$ and $S_j = 1$ for $V_j \geq 0$. $I_{P_i} = \beta P_i$, whereas P_i is the amount of clock protein. R is the resistance potential of the neuron, τ is the membrane time constant, and α and β are scaling constants that convert the inputs of active synapses and the molecular clock protein, respectively, to values and units of currents that affect the membrane potential. The set K_i again consists of all neurons presynaptic to the neuron i. Action potentials occur in the cell when V reaches the threshold voltage θ. An action potential that occurs in cell j activates the synapses, S_j, of all its postsynaptic cells.

SIMULATION RESULTS

In the computer implementation, the above differential equations are time-discretized. Equations (1) and (2) are discretized to 6-min time steps. Synaptic inputs to the clock, as in Eq. (3), are summed over the preceding 6-min time step, Eq. (4) is discretized to 10^{-2} s.

We next consider a network of coupled GROS neurons. For biological plausibility, the nonlinearity in the protein cascade parameter, δ, is set randomly within the range of 2.5–3.5, resulting in oscillatory periods in the range of ~23–25 h. The clocks are initialized to random phases within a 24-h window. Parameter values for I_D and β are set to provide a biologically plausible firing rate of ~10 Hz during subjective day, and 0 Hz during subjective night. The firing rate oscillates roughly anti-phase to the level of protein.

We demonstrate here that a network of GROS neurons is able to synchronize to a coherent rhythm through communication that occurs at the speed of neural firing (Figure 2), rather than by directly shifting the phase of the

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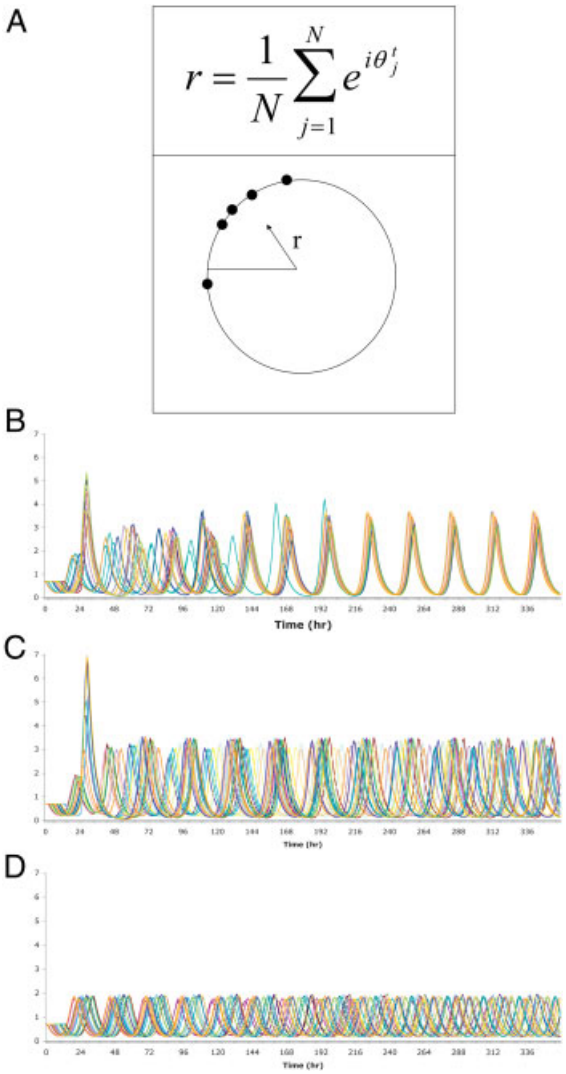
FIGURE 2



Synchrony simulations. (A) The degree to which the population is synchronized, r, is measured using the Kuramoto order parameter that averages over the angles of the oscillators, $\theta(t)_j$, at time t. (B) Fully connected Network of 20 neurons with a γ value of 0.00005. With normal GROS neurons and all connections intact, synchrony arises ($r = 0.97$). (C) To verify the necessity of the effect of the molecular clock on the membrane potential, we set parameter β to 0, and the correlation value reaches 0.26, indicating the lack of synchronization. (D) To verify the necessity of the effect of presynaptic neurons to the postsynaptic molecular clock, we set parameter γ to 0, and the correlation value reaches 0.22, indicating no synchronization.

clocks—as had previously been assumed (e.g., [18,23]). Population synchrony, r, is measured by the Kuramoto order parameter [Figure 2(A)] [24]. The value of r approaches 0 when the population of oscillators' peaks are uncoordinated, and approaches 1 when the population peaks together. After 20 simulated days, using a network of fully connected GROS neurons, the correlation value reaches 0.97, indicating a high level of synchrony. To validate that synchrony arose out of interactions between the molecular clock and the electrical firing components of the GROS neuron, two options are tested: with no effect from the molecular clock to the membrane potential [Figure 2(C)], and with no effect from the presynaptic neurons to the postsynaptic molecular clock [Figure 2(D)]. Both result in an r value of less than 0.26 after 20 days of simulation, indicating a lack of synchrony. We thus conclude that synchronization of GROS-like neurons requires both of these effects.

To test the GROS neurons sensitivity to network topology, a lattice network is compared to a small world network. The small world network architecture, a combination of stochastic connectivity and the bias of having more neighboring nodes connected than distant ones [25,26], was found previously to improve global synchrony of Kuramoto oscillators [27]. The same architecture was found to reduce synchrony of integrate and fire oscillators [28]. Here we investigate how a small world topology changes in the flow of activity in networks of GROS neurons.

To determine the consequence a small world topology has on network dynamics we recorded starting at a desynchronized initial state and advancing toward the steady state. In simulations with locally connected networks, a number of distinct clusters of neurons are formed, but these clusters never synchronize into a unified population rhythm [Figure 3(A)]. Applying a small world network architecture to these neurons creates links between separate clusters, resulting in neurons synchronizing into a coherent rhythm [Figure 3(B)]. Interestingly, recent biological studies of core clock gene mper1 activation in mice shows a wave that travels from one side of the SCN to the other over the course of the day [14]. Similar waves of activity occurred in our observed simulations, as demonstrated in Figure 3(C).

DISCUSSION

The interaction between firing rates and protein expression is modeled for the circadian rhythm, by introducing a new kind of neuron that combines spiking with protein oscillations. We believe that this as of yet poorly understood interaction could be crucial to understanding much of human body and behavior.

Antle et al. [23] have shown that a population of limit cycle oscillators can be synchronized by nonoscillating cells. They propose that these nonoscillating cells act as a threshold function, sending a synchronizing signal based on the global output of the oscillators. The model is based on studies showing that lesioning a subsection of the SCN that contains these nonoscillating cells marked an expression of protein calbindin-D (CalB), disrupts all circadian rhythms in the animal [29]. It has also been

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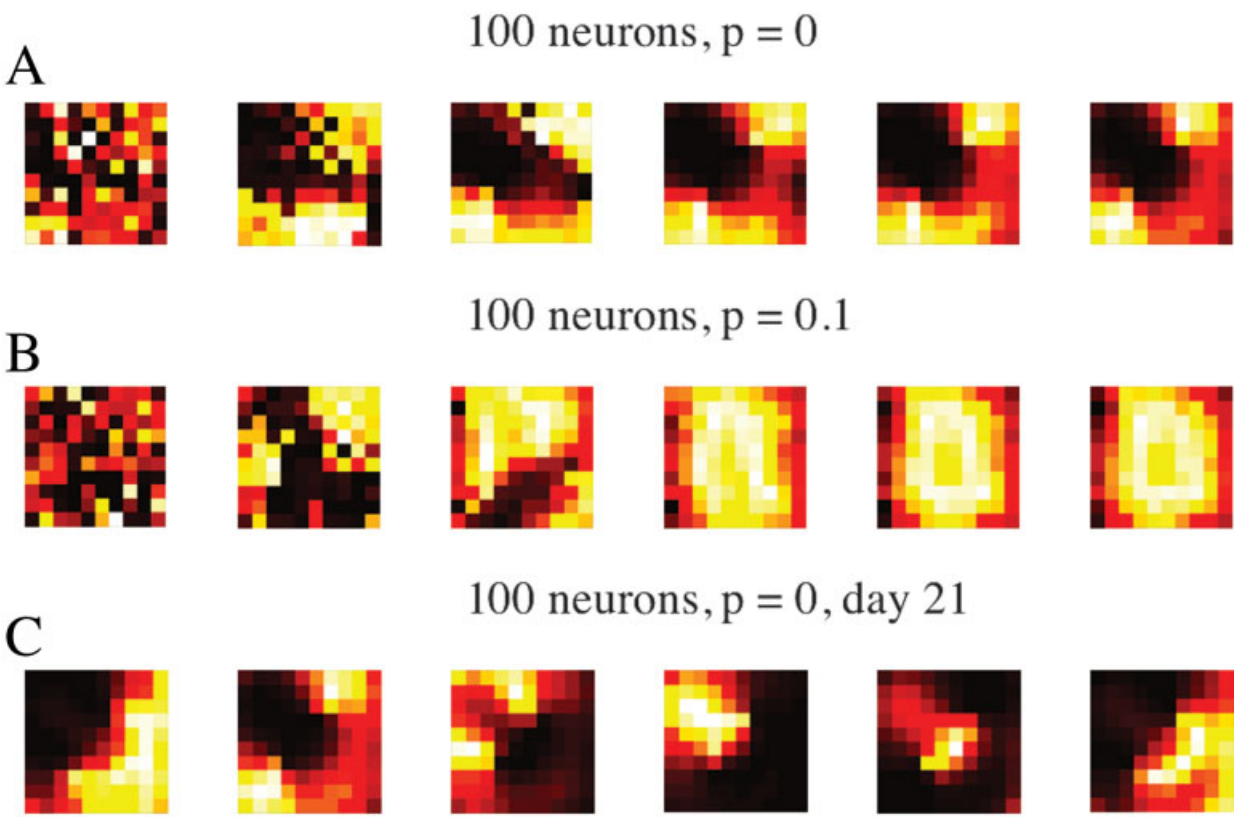
FIGURE 3



Frames from 100 neuron simulations. The color of each square represents the level of mRNA of the neuron at that location: brighter squares represent higher mRNA levels, and darker squares represent lower mRNA levels. The first frame is from day 2 (on day 1 not all of the molecular clocks have become active). (A) $p = 0.0$; there is no rewiring: distinct clusters form. (B) $p = 0.1$; approximately 1 of every 10 connections is rewired: a more robust global rhythm. (C) The progression of the network shown in (A) over 25 h. These frames are taken from day 21 and demonstrate the flow of mRNA peaking through the network. Movies are available for download at http://binds.es.umass.edu/download/.

found that if the dorsal one-third of the SCN is separated from the ventrolateral section, neurons in the dorsal section will continue to oscillate but will lose coherency in their oscillations [13]. Both of these studies rely on lesioning or slicing experiments, in which it is difficult to know exactly what important aspects of the network might be disrupted by the procedure. In both cases the lack of synchrony that resulted could be the result of removing CalB cells from the oscillating neurons, or they could be the result of removing critical connections between oscillating cells in different sections of the SCN. Although not proving via biological experiments, we do show that synchrony may occur already through the interaction between just the oscillating cells of the SCN.

Work remains to be done modeling the mammalian circadian system, both with more detailed models and with models at a higher level of abstraction. In the current work, the choice of a molecular clock using only one protein allowed investigation of network level interactions among oscillators. Models at a finer level of detail could incorporate known interactions between clock proteins and ionic conductance [16,17], but these would be less suitable for larger network simulations. At a higher level of abstraction, the SCN consists of heterogeneous populations of neurons that respond differently to light, not all of which cycle and some of which have specific projections to other SCN regions [30–33]. For these, networks of GROS neurons can be connected into larger networks, enabling models that capture heterogeneous tissues within the mammalian SCN, connections with peripheral oscillators, and entrainment of complex networks. Such networks of networks can be used to address questions about the interactions and dynamics that control phase angles between peripheral oscillators, explore the splitting phenomena and also lead to techniques that mitigate the disruption of the circadian system caused by shift work and jet lag.

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