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# A Simplified model of mutually inhibitory sleep-active and wake-active neuronal populations employing a noise-based switching mechanism



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## HIGHLIGHTS

- Switching between 2 populations occurs with strong mutual inhibition and noise.
- Noise-based switching leads to random, exponential bout durations.
- Interpopulation inhibition and intrapopulation excitation allow independent regulation of bouts.
- Noise-based switching naturally explains sleep-wake switching in rats during early infancy.

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## ABSTRACT

Infant rats switch randomly between the sleeping and waking states; during early infancy (up to postnatal day 8), sleep and wake bouts are random, brief (with means on the order of several seconds) and exponentially distributed, with the length of a particular bout independent of the length of prior bouts. As the rat ages during this early period, mean sleep and wake bout lengths gradually increase, though sleep and wake bouts remain exponentially distributed. Additionally, sleep and wake bouts are regulated independently of each other – alterations in the development of sleep (wake) bouts has no impact on the regulation wake (sleep) bouts. Sleep and wake bout behavior is associated with the activity of mutually inhibitory sleep-active and wake-active brainstem populations. In this work, I employ a simplified biophysical model of two mutually inhibitory populations consisting of ten integrate-and-fire neurons each and a noise-based switching mechanism. I show that such a noise-based switching mechanism naturally accounts for the experimentally observed features of sleep-wake switching during early infancy – random alternating activity bouts occur as a consequence of noise (provided inhibition is strong relative to excitation), bout durations are exponential (due to a lack of memory within the system), and cross-population inhibition or intrapopulation excitatory coupling provide mechanisms for changing and independently regulated sleep and wake bout means.

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## 1. Introduction

Infant mammals randomly cycle between the behavioral states of sleep and wakefulness, with the length of a particular sleep or wake bout independent of the length of prior bouts (i.e., random bout durations with no bout-to-bout memory) (Lo et al., 2004; Blumberg et al., 2005). Furthermore, in infants sleep and wake bout durations are exponentially distributed; successive sleep bout lengths are exponential i.i.d. (independent and identically distributed) random variables with mean  $\mu_s$ , while successive wake bout lengths are exponential i.i.d. random variables with mean  $\mu_w$  (Karlsson et al., 2004). Through early infancy in rats, from

birth to about postnatal day 8 (P2–P8), the sleep and wake bout means  $\mu_s$  and  $\mu_w$  increase ( $\mu_s$  increases from  $\sim 10$  s to  $\sim 35$  s,  $\mu_w$  increases from  $\sim 5$  s to  $\sim 10$  s), but the two are regulated independently of each other and the exponential distribution of bout lengths persists (Blumberg et al., 2005; Karlsson et al., 2004).

Behavioral sleep and wake bouts are correlated with the activity of ‘sleep-active’ and ‘wake-active’ populations within the brain that are likely to reciprocally inhibit each other. During a sleep bout, ‘sleep-active’ neurons fire and ‘wake-active’ neurons are quiet, while during a wake bout, ‘wake-active’ neurons fire and ‘sleep-active’ neurons are silent (Karlsson et al., 2005; Saper et al., 2001). Numerous ‘sleep-active’ and ‘wake-active’ populations have been found. Examples of sleep-active populations include the ventrolateral preoptic area (VLPO), medullary inhibitory area (MIA), nucleus pontis oralis (PO), and subcoeruleus (subLC). Wake-active populations are

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divided into two branches: (1) the thalamic branch (e.g., laterodorsal tegmentum or LDT, pedunculopontine tegmentum or PPT); and (2) the hypothalamic branch (e.g., dorsal raphe nuclei or DR, tuberomammillary nucleus or TMN) (Schwartz and Roth, 2008).

This picture is reminiscent of stochastic switching within a bistable system; from a dynamical systems perspective, sleep and wakefulness represent two deterministically stable states of the system, with one stable state given by high activity of ‘wake-active’ neurons and quiescence of ‘sleep-active’ neurons, while the other stable state is given by spiking of sleep-active neurons and silencing of wake-active neurons. Without noise, the system will permanently settle into one state or the other, but in the presence of noise the system will randomly alternate between the two stable states (Gardiner, 2009; van Kampen, 2007). Thus, in early infancy, it is possible that sleep–wake switching is primarily noise driven – strong reciprocal inhibition between sleep-active and wake-active populations creates the two distinct states of sleep and wakefulness (i.e., the inability of sleep-active and wake-active cells to be simultaneously active precludes the existence of intermediate states), and switching between states may be driven by noise.

In an extension of previous work on a pair of mutually inhibitory neurons (Patel and Joshi, 2014), in this work I examine the basic properties of stochastic switching and alternating activity bouts in a computational model of two reciprocally inhibitory populations of neurons. Since detailed data on the physiology of sleep-active and wake-active populations is lacking, I do not attempt to construct a biologically realistic model of these populations. Rather, the goal of this work is to uncover the fundamental principles governing alternating activity bouts in a simplified biophysical model of mutually inhibitory populations, and to examine whether stochastic switching between two mutually inhibitory populations driven by external noise can qualitatively account for experimentally observed features of infant sleep–wake cycling during the P2–P8 period.

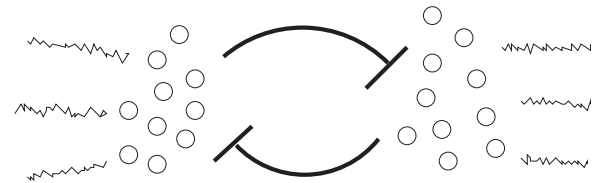
The simplified biophysical model in this work consists of two populations of ten integrate-and-fire neurons each; synaptic inhibitory coupling between populations is all-to-all, and all neurons are driven by a Poisson process of excitatory spikes arriving from outside the two population system. I examine both the case where there is no intrapopulation coupling and the case where excitatory coupling within a population is permitted. A model schematic is shown in Fig. 1. I show that clear-cut alternating activity bouts occur when inhibition is strong relative to excitation, and that exponential bout distributions arise naturally within the system. Furthermore, I examine the conditions under which the phenomenon of independent control – the ability to independently regulate the bout times of the two populations – emerges in the model, as well as the ability of interpopulation synaptic inhibition and intrapopulation excitatory coupling to provide putative mechanisms for achieving independent control.

## 2. Results

The model consists of two mutually inhibitory populations of 10 integrate-and-fire neurons each; synaptic inhibitory coupling between populations is all-to-all, with no intrapopulation coupling, and each neuron receives an independent noisy excitatory driving current constructed as a Poisson process of spikes (with constant rate) arriving from outside the two population system (Fig. 1). Standard parameters are symmetric for the two populations and details are given in the Methods.

### 2.1. Bout occurrence and exponential distribution of bouts

For sufficiently strong inhibition, clear-cut alternating bouts of random duration are seen to occur (Fig. 2(A) and (B)) with bout



**Fig. 1.** The model consists of two populations of ten neurons each, with all-to-all inhibitory coupling between populations and no intrapopulation coupling. Each neuron receives an independent excitatory drive constructed as a Poisson process of incoming spikes.

durations for each population displaying an exponential distribution (Fig. 2(C)). The exponential nature of bout durations arises as a consequence of a lack of memory within the system. Suppose population 1 is in the midst of a bout (i.e., population 1 is active while population 2 is suppressed). Only two vehicles exist that may enable the system to keep track of how long population 1 has been in the midst of a bout – the excitatory driving current supplied to neurons within the system and synaptic inhibition. The excitatory driving current is delivered at a constant Poisson rate; the mean level of excitation received by each neuron is constant, while fluctuations occur over time scales that are much shorter than the time scale of bout lengths, and hence the excitatory driving current provides no information about the current duration of population 1's bout (as is apparent from the plot of the excitatory driving current in Fig. 1(A)). A similar argument applies to synaptic inhibition – once population 1 begins firing at the start of a bout, the firing rate of population 1 quickly approaches a steady-state mean value (since the mean excitation received by population 1 is constant), and the inhibition delivered by population 1 to population 2 likewise rapidly approaches a steady-state mean value, and therefore is unable to provide information on the current duration of population 1's bout (see the plot of synaptic inhibition in Fig. 1(A)). Thus, the system has no means to keep track of the duration of population 1's bout, and the lack of memory within the system implies that population 1's bouts will appear exponentially distributed (the same argument applies to population 2).

As long as the system is in a regime in which alternating activity bouts occur, bout lengths are exponentially distributed, due to the reasons explained above. Under what conditions do crisp alternating activity bouts occur? As shown in Fig. 3, alternating activity bouts occur when cross-population synaptic inhibition is strong relative to excitation. Fig. 3(A) shows that as the amplitude of synaptic inhibition is decreased, alternations in activity become less distinct and ultimately vanish, while Fig. 3(B) shows that once excitation is strengthened sufficiently, bout behavior disappears. In order for bout behavior to occur, excitation must be strong enough to ensure that (without inhibition) the mean level of excitation is sufficient to keep neurons in a continuously spiking state, while inhibition must be sufficiently potent to allow the active population to suppress the quiescent population (that is being driven by the excitatory Poisson current) below spike threshold. It is therefore the *ratio* of inhibition to excitation that determines whether the system is in a bout regime – excitation must be strong enough to allow the active population to remain in a continuously spiking state, but weak in comparison to synaptic inhibition in order to enable the active population to keep the quiet population (on average) below spike threshold. Under these conditions, a bout switch then ensues when either a random positive fluctuation in the net excitation to the quiet population allows it to surmount the incoming inhibition and emit a burst of spikes or a random negative fluctuation in the net excitation to the active population reduces its firing rate and causes inhibition to the quiet population to temporarily relent (or a combination of the two mechanisms). The potency of synaptic inhibition (relative to excitation) precludes a state in which both populations are simultaneously active.

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