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Switching mechanisms and bout times in a pair of reciprocally inhibitory neurons

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Abstract Within the appropriate parameter regime, a deterministic model of a pair of mutually inhibitory neurons receiving excitatory driving currents exhibits bistability—each of the two stable states corresponds to one neuron being active and the other being quiescent. The presence of noise in the driving currents results in a system that randomly switches back and forth between these two states, causing alternating bouts of spiking activity. In this work, we examine the random bout durations of the two neurons and dependence on system parameters. We find that bout durations of each neuron are exponentially distributed, with changes in system parameters altering only the mean of the distribution. Synaptic inhibition independently controls the bout durations of the two neurons—the mean bout time of a neuron is a function of efferent (or outgoing) inhibition, and is independent of afferent (or incoming) inhibition. Furthermore, we find that the mean bout time of a neuron exhibits a critical dependence on the time course (rather than amplitude) of efferent inhibition—mean bout time of a neuron grows exponentially with the time course of efferent inhibition, and the growth rate of this exponential function depends only on the excitatory driving current to that neuron (and not on any other system parameters). We discuss the relevance of our results to the regulation of sleep-wake cycling by medullary and pontine structures within the brain.

Keywords Reciprocal inhibition · Mutual inhibition · Bout durations · Sleep-wake · Stochastic switching · Noise in bistable systems · Neuron network motif

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1 Introduction

Adult mammals cycle between the behavioral states of sleep and wakefulness, spending a random amount of time within each state (even in diurnal mammals such as humans, long stretches of nightly sleep tend to be punctuated by periods of wakefulness). The duration of each sleep bout is an exponentially distributed random variable, while the duration of a wake bout follows a heavy-tailed distribution (which resembles a power-law), with both sleep and wake bouts exhibiting no bout-to-bout memory; in other words, the duration of the current bout is statistically independent of the duration of prior bouts (Halász et al. 2004; Lo et al. 2002, 2004). Sleep-wake cycling within infant mammals, however, is not only much more rapid, but also displays qualitatively different dynamics. Recent investigations indicate that in infant mammals *both* sleep and wake bouts have an exponential distribution, with a heavy-tailed wake bout distribution appearing only later in life (Blumberg et al. 2005; Gall et al. 2009; Karlsson et al. 2004, 2005; Kleitman and Engelmann 1953).

Behavioral sleep and wake states are each correlated with the activity of 'sleep-active' (e.g., nucleus pontis oralis cells) and 'wake-active' (e.g., dorsolateral pontine tegmentum cells) populations within the brain that may reciprocally inhibit each other. During a sleep bout, 'sleep-active' neurons fire and 'wake-active' neurons are quiet, while during

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a wake bout, 'wake-active' neurons fire and 'sleep-active' neurons are silent (Blumberg et al. 2005; Karlsson et al. 2005). 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 the two stable states given by spiking of one population and quiescence of the other. Without noise, the system will permanently settle into one state or the other, but in the presence of noise the system will flip back and forth between the two states.

In order to study stochastic switching in a system with reciprocal inhibition, we employ a simple and intuitively tractable model consisting of a pair of integrate-and-fire neurons, each of which receives an independent noisy excitatory current and synaptically inhibits the other neuron (Fig. 1). We find that within the appropriate parameter regime, the two neurons exhibit alternating bouts of spiking activity with exponentially distributed bout durations. We show that mean bout times can be independently controlled by inhibition—varying the inhibition delivered by neuron j (efferent inhibition of neuron j) changes the mean bout time of neuron j alone, and leaves the mean bout time of the other neuron untouched. On the other hand, varying the excitatory driving current to one neuron changes the mean bout time of *both* neurons (i.e., no independent control). Furthermore, we find that the mean bout time of neuron j is an exponential function of the time course of efferent inhibition, and we find that the growth rate of this exponential function depends only on the excitatory driving current to neuron j. Finally, we discuss the insights that our results can provide into some of the basic principles governing sleep-wake cycling in infant rats.

2 Model

The model consists of two integrate-and-fire neurons, each of which receives a noisy excitatory driving current and provides synaptic inhibition to the other neuron (Fig. 1).

2.1 Membrane potential

Each of the two cells within our system is modeled as an integrate-and-fire neuron. The (nondimensionalized) membrane potential $V^{(j)}(t)$ of each neuron $j \in \{1, 2\}$ is governed by an equation of the following form:

$$\frac{dV^{(j)}}{dt} = -g_L\left(V^{(j)} - E_0\right) - g_{inh}^{(j)}(t)\left(V^{(j)} - E_{inh}\right) + i^{(j)}(t) \tag{1}$$

$$V^{(j)}(t) = E_0 \text{ for } t \in (s, s + r), \text{ if } V^{(j)}(s) = E_{th}. \tag{2}$$

$V^{(j)}(t)$ is the membrane potential of neuron j, $g_L = 0.05$ ms^{-1} is the leak conductance, $E_0 = 0$ is the resting potential, and $E_{inh} = -0.67$ is the reversal potential for synaptic inhibition. The model has nondimensional membrane potential, time in units of ms, while conductance g_L and $g_{inh}^{(j)}(t)$ and the current $i^{(j)}(t)$ are in units of ms^{-1}. A spike is recorded when $V(t)$ reaches a threshold value $E_{th} = 1$, with $V(t)$ being instantaneously reset to rest $V_{reset} = E_0 = 0$ following a spike. An absolute refractory period of $r = 2$ ms is imposed by holding the membrane potential at rest for 2 ms following a spike. Details of the reduced dimensional model are given in Tao et al. (2004).

2.2 Excitatory drive

Each neuron j receives an independent noisy excitatory current (referred to as the excitatory drive to neuron j) described by the $i^{(j)}(t)$ term:

$$i^{(j)}(t) = \sum_{n=1}^{\infty} a_j e^{-b_j\left(t - \tau_{k-1}^{(j)}\right)} \mathbb{1}_{\left\{\tau_{k-1}^{(j)} \le t\right\}} \tag{3}$$

The excitatory drive $i^{(j)}(t)$ jumps by a constant value a_j at a Poisson rate of λ_j (this models excitatory spikes from outside the two-cell system), and decays at a constant rate of $b_j = 1/3$ ms^{-1}. The time of the i-th spike in the excitatory drive to neuron j is denoted by $\tau_i^{(j)}$. Standard

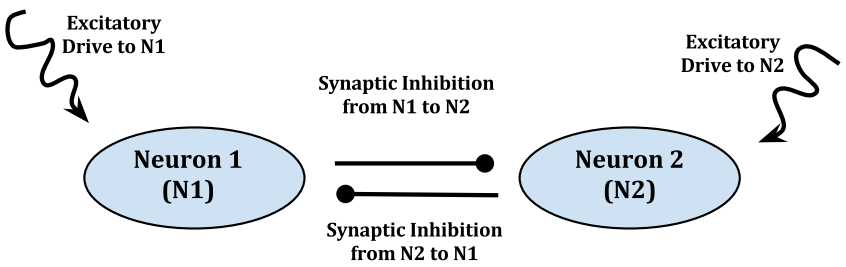

Fig. 1 A pair of mutually inhibitory neurons, each of which receives an excitatory driving current. In our model, the neurons are integrate-and-fire neurons with noisy excitatory drive

values of the rate and amplitude parameters are given by $\lambda_j^* = 1$ ms^{-1} and $a_j^* = 0.075$ ms^{-1}. All nonstandard excitatory drives are described in terms of these reference values.

We refer to $M_j = a_j\lambda_j$ as the *strength of the excitatory drive to neuron* j and we refer to $N_j = \frac{a_j}{\lambda_j}$ as the *noisiness of the excitatory drive to neuron* j. To change the strength of the excitatory drive to neuron j by a factor c (without varying the noisiness), we set the rate parameter to $\lambda_j = \sqrt{c}\lambda^*$ and we set the amplitude parameter to $a_j = \sqrt{c}a^*$. To vary the noisiness of the excitatory drive to neuron j by a factor d (without changing the strength), we set the rate parameter to $\lambda_j = \frac{\lambda^*}{\sqrt{d}}$ and we set the amplitude parameter to $a_j = \sqrt{d}a^*$. We denote the strength and noisiness of the standard excitatory drive by $M^* = \lambda^* a^*$ and $N^* = \frac{a^*}{\lambda^*}$. Figure 2 depicts the effects of varying M and N on the excitatory drive.

$$\frac{dV^{(j)}}{dt} = -g_L\left(V^{(j)} - E_0\right) - \beta_k R_h^{(j)}(t)\left(V^{(j)} - E_{inh}\right) + \sum_{n=1}^{\infty} a_j e^{-b_j\left(t-\tau_{k-1}^{(j)}\right)}\mathbb{1}_{\left\{\tau_{k-1}^{(j)} \le t\right\}}$$

$$V^{(j)}(t) = E_0 \text{ for } t \in (s^+, r), \text{ if } V^{(j)}(s) = E_{th}$$

Parameter	Notation	Value(s)
Leak conductance	g_L	0.05 ms^{-1}
Resting potential	E_0	0
Inhibitory reversal potential	E_{inh}	-0.67
Spiking threshold	E_{th}	1
Refractory period	r	2 ms
Resting potential	E_0	0
Decay rate of excitatory current	b	0.33 ms^{-1}
Poisson rate of jumps in excitatory current	λ	Variable, standard value 1 ms^{-1}
Amplitude of jump in excitatory drive	a	Variable, standard value 0.075 ms^{-1}
Amplitude of jump in inhibitory conductance	β	Variable, standard value 0.35 ms^{-1}
On-time of inhibitory conductance	h	Variable, standard value 6 ms^{-1}

2.3 Synaptic inhibition

Synaptic inhibition is conductance-based and modeled through the $g_{inh}(t)$ term. Let $R^{(j)}(t)$ denote the number of spikes of neuron j before time t. Let $R_h^{(j)}(t) := R^{(j)}(t) - R^{(j)}(t-h)$ be the number of spikes of neuron j during the interval $(t-h, t]$ for $h \ge 0$. For $k \ne j \in \{1, 2\}$,

$$g_{inh}^{(k)}(t) = \beta_j R_h^{(j)}(t) \tag{4}$$

Thus, if neuron 1 spikes at time s, then $g_{inh}^{(2)}(t)$ is incremented by an amount β_1 at time s and decremented by β_1 at time $s + h_1$. Likewise, if neuron 2 spikes at time s, then $g_{inh}^{(1)}(t)$ is incremented by an amount β_2 at time s and decremented by β_2 at time $s + h_2$. We refer to β_j and h_j as the *amplitude of inhibition of neuron* j and the *time course of inhibition of neuron* j, respectively. Standard values for the amplitude and time course of inhibition are given by $\beta = 0.35$ ms^{-1} and $h = 6$ ms, though $\beta_1, \beta_2, h_1, h_2$ are varied in some simulations. We note that β inherits units from g_{inh}. Both β and g_{inh} have the nonstandard units of ms^{-1} as a consequence of the reduced dimensional nature of the integrate-and-fire model that we employ.

2.4 Bouts

A bout of neuron j is defined as beginning at the first spike of neuron j (following either a spike of the other neuron or the beginning of a trial), and ending as soon as the other neuron fires a single spike. The duration of a bout is a random variable.

Trials were simulated in blocks of 1500 s (a time interval chosen to be sufficiently greater than the longest bouts of a few hundred seconds in our simulations). A minimum of 500 bouts were gathered to compute a mean bout time; the final bout in each trial was discarded (since the final bout was curtailed by the end of the trial). Simulations were carried out using the explicit Euler method with a time step of 0.01 ms.

3 Results

Our system consists of a pair of mutually inhibitory integrate-and-fire neurons, each of which receives a noisy excitatory driving current (Fig. 1). Inhibitory synapses are modeled as conductance-based, and a spike of neuron j produces a transient positive inhibitory conductance in the other neuron modeled as a square pulse; we refer to the height of this square pulse (β_j) as the amplitude of inhibition from neuron j to the other neuron, while we refer to the temporal length of this square pulse (h_j) as the time course of inhibition from neuron j to the other neuron. The time course and amplitude of inhibition from one neuron to the other, as well as the strength and noisiness of the excitatory drive to each neuron (M_1,N_1,M_2,N_2), are parameters that we varied during the course of our investigation (see Section 2).

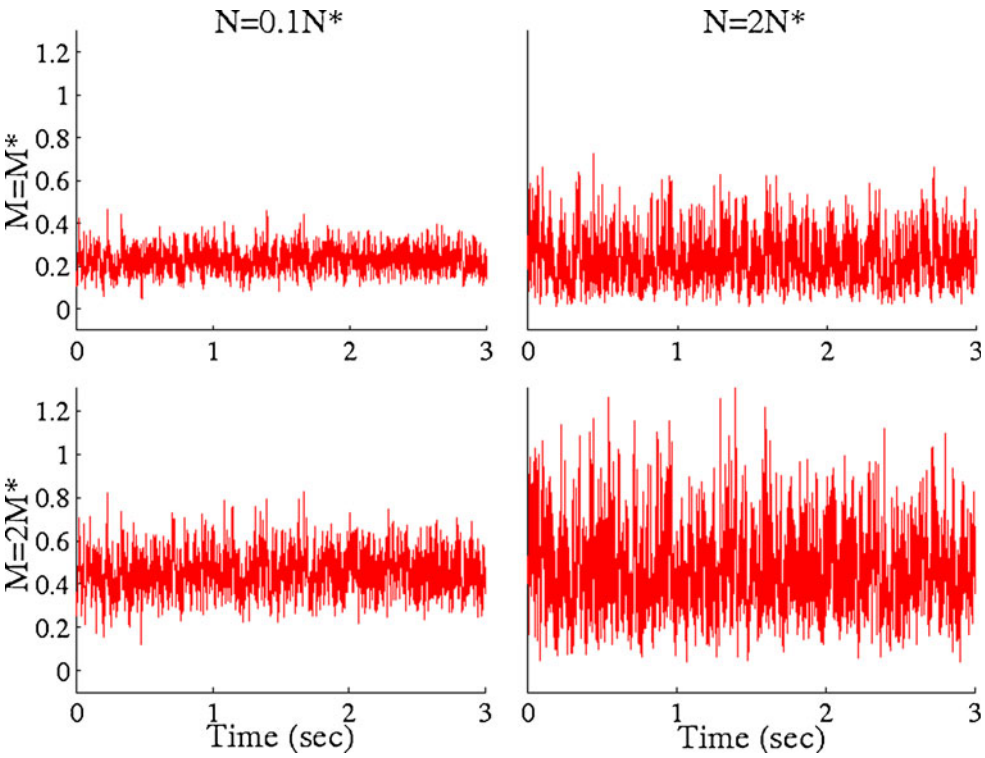

Fig. 2 Effect of varying the strength (M) versus the noisiness (N) of the excitatory drive. One realization of the excitatory drive $i^{(j)}(t)$ is shown for different combinations of strength (*rows*) and noisiness (*columns*)

3.1 Bistability and stochastic switching

We begin by considering the case where both neurons receive the same constant excitatory drive and inhibit each other with a fixed time course. In this deterministic system, reciprocal inhibition with a weak amplitude of inhibition results in a monostable system, while strong mutual inhibition yields bistability. Weak inhibition results in oscillatory spiking—both neurons fire at the same frequency but with a fixed phase difference (Fig. 3, left). A large body of prior

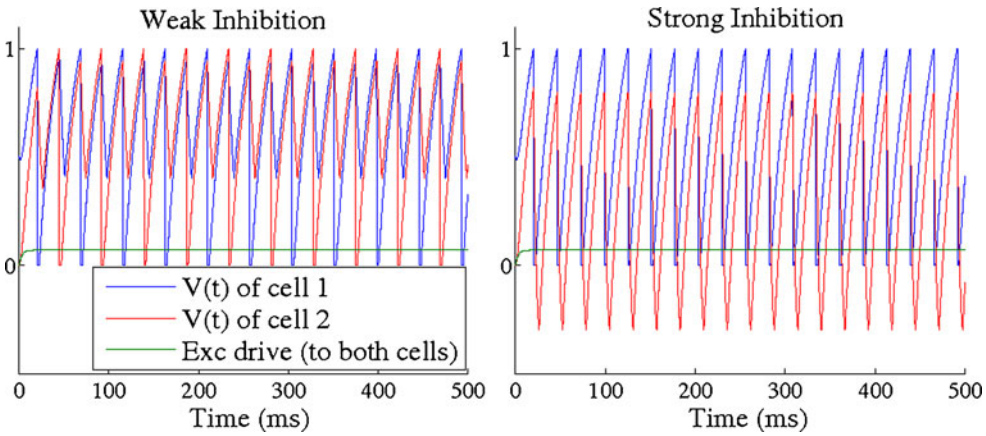

Fig. 3 Dynamical behavior of a pair of symmetrically coupled integrate-and-fire neurons. Each neuron receives a constant excitatory drive as well as synaptic inhibition from the other neuron. *Left:* In the case of weak inhibitory coupling (inhibitory amplitude: $\beta_1 = \beta_2 = 0.1$ ms^{-1}), the system is monostable. The two neurons oscillate and alternate spikes, with mutual inhibition causing the spikes of the two neurons to lock into a precise phase relationship. Nearly all initial conditions converge to this attractor. (However, if the two neurons have precisely identical initial conditions, then they will fire in perfect synchrony, implying that perfect synchrony represents unstable steady-state behavior of the system). *Right:* In the case of strong inhibitory coupling (inhibitory amplitude: $\beta_1 = \beta_2 = 0.35$ ms^{-1}), the system is bistable. The right panel shows neuron 1 firing at a constant frequency with neuron 2 quiescent due to inhibition, corresponding to one stable state of the system. Since all parameters are symmetric, a reversal of the two neurons' initial conditions would result in neuron 2 firing at a constant frequency with neuron 1 silent, corresponding to a second stable state of the system. Depending on the initial conditions, the system converges to either one stable state or the other. The time course of inhibition is fixed at $h_1 = h_2 = 6$ ms for these simulations

work has explored the effects of weak inhibitory coupling on the dynamics of reciprocally connected neurons (e.g., see Elson et al. 2001; Jalil et al. 2010; Rowat and Selverston 1997; Van Vreeswijk et al. 1994), or has explored strong inhibitory coupling, but only in the deterministic setting (Skinner et al. 1994; Terman et al. 1998; Wang and Rinzel 1992); we do not consider the weak coupling regime any further in this paper.

Strong inhibition, however, causes one neuron to spike at a fixed frequency while the other displays subthreshold oscillations for all time. Since the system is symmetric, the identities of the active and suppressed neurons are determined by the initial conditions, indicating the existence of two stable states within the system (Fig. 3, right). We note that the parameters need not be symmetric—the system can remain in the bistable regime even with asymmetry in the parameters governing inhibition or the excitatory drive, though the attraction domains of each stable state may be altered. We find that the amplitude of synaptic inhibition is one of the major factors that determines whether the system is monostable or bistable (data not shown). Unless otherwise specified, we will choose synaptic inhibition to be strong enough to place the system in the bistable regime. For the special case where the system parameters are symmetric along with the dynamical equations, the dynamics are studied in more detail, and formulated as a Markov chain, in Kirillov et al. (1993).

In the deterministically bistable regime, the presence of noisy excitatory drives can cause the system to stochastically switch back and forth between the two stable states (i.e., to randomly transition from neuron 1 firing with neuron 2 silent to neuron 2 spiking with neuron 1 quiescent, and vice versa). The system therefore alternates between bouts of spiking activity of neuron 1 and neuron 2, and we can measure the durations of these bouts to assess the behavior of the system (Fig. 4; see Section 2.4 for definition of a bout). The primary quantity of interest is the sequence of random bout durations

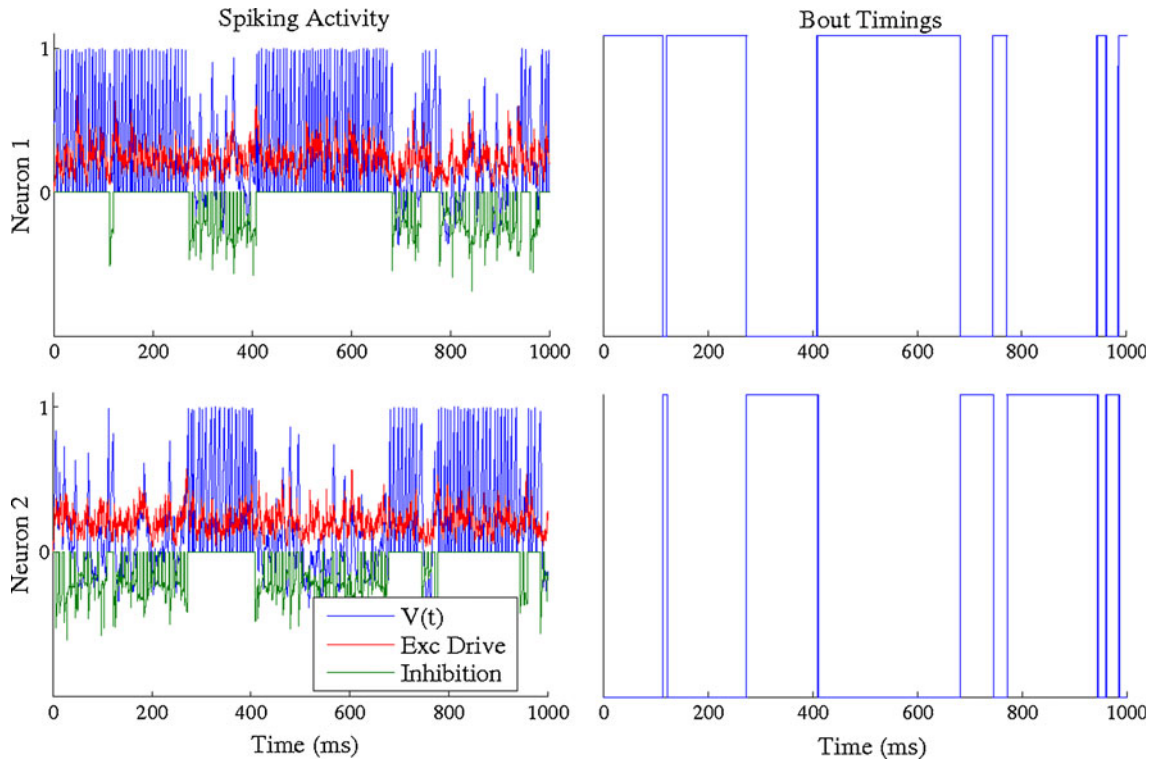

Fig. 4 Dynamical behavior of a pair of symmetrically coupled integrate-and-fire neurons in the presence of noise. Each neuron receives independent realizations of a noisy excitatory drive with fixed statistical structure as well as synaptic inhibition from the other neuron. The corresponding deterministic system is bistable, and hence the noise added to the excitatory drive causes stochastic switching between the two stable states. *Left:* Membrane potential, excitatory drive, and synaptic inhibitory current for neurons 1 and 2. One neuron spikes for a random amount of time, inhibiting the other neuron while it is spiking. At some point, due to noise within the system, the other neuron is able begin spiking, inhibiting the first neuron, and a bout switch ensues. In this manner, the two neurons alternate bouts of spiking activity, with each bout lasting for a random length of time. *Right:* Bouts of spiking activity of neurons 1 and 2 (see Section 2 for the definition of a bout). For these simulations, the synaptic inhibition has an amplitude of $\beta_1 = \beta_2 = 0.35$ ms^{-1} and a time course of $h_1 = h_2 = 6$ ms. The strength and noisiness of the excitatory drives to the two neurons are given by the standard reference values: $M_1 = M_2 = M^*$ and $N_1 = N_2 = N^*$ (see Section 2 for details)

$\left(T_1^{(1)}, T_1^{(2)}, T_2^{(1)}, T_2^{(2)}, T_3^{(1)}, T_3^{(2)}, \ldots\right)$, where $T_n^{(j)}$ is the duration of the nth bout of neuron j.

3.2 Exponential distribution of bout length

We find that the bout durations $T_n^{(j)}$ are independent of each other for all j and n, and that the bout durations $T_1^{(j)}, T_2^{(j)}, T_3^{(j)}, \ldots$ are identically distributed for fixed j. In other words, each bout duration is independent of previous bout durations (either past bouts of the same neuron or past bouts of the other neuron), and all bout durations of a particular neuron have the same distribution.

Since all bout durations of a particular neuron are independent and identically distributed, we can pool bouts of neuron j in order to empirically compute the distribution of neuron j's bout durations. We find that the empirical complementary cumulative distribution of bout durations of each neuron j has an exponential form: $\mathbf{P}(T^{(j)} > s) = e^{-s/m_j}$, and that modifying parameter values alters only the mean m_j of the distribution, not its exponential nature. Figure 5 shows the exponential distribution of bout lengths of one of the two neurons for two different parameter values. Since an exponential distribution is completely determined by its mean, it is sufficient to identify the mean bout length m_j.

A fundamental property of the exponential distribution is memorylessness; moreover, this property characterizes the distribution (i.e., a random variable is exponentially distributed if and only if its distribution is memoryless). The property of memorylessness, within the current context, can be described as follows: whilst in the midst of a spiking bout, the subsequent amount of time that spiking will continue is independent of the time elapsed since the beginning of the bout. In other words, neuron j has no memory of how long it has been spiking; if the neuron is s ms into a spiking bout, the future duration of the bout has no dependence on s. When an exponential distribution arises in nature, we can therefore ascertain why the distribution arises by understanding why there is a lack of memory within the system.

Why is there a lack of memory within a spiking bout? Within the confines of our system, there are only two vehicles for the creation of memory: the noisy excitatory drive or the synaptic inhibition. The mean of the excitatory drive to either neuron is constant through time (and fluctuations occur over time scales that are fast relative to bout times), implying that the system cannot keep track of how long a neuron has been spiking through the excitatory drive. When neuron j is spiking, the other neuron is inhibited, and as the bout continues the inhibitory current to the suppressed neuron approaches a steady-state mean value. Even though the inhibitory current is noisy, once the mean has approached a steady-state the inhibition provides no information about the prior duration of the ongoing bout. However, depending on the time course of synaptic inhibition, there is a time scale at the beginning of a bout over which the inhibition rises to reach its steady-state mean value. For longer inhibitory time courses, a bout switch is more likely to occur

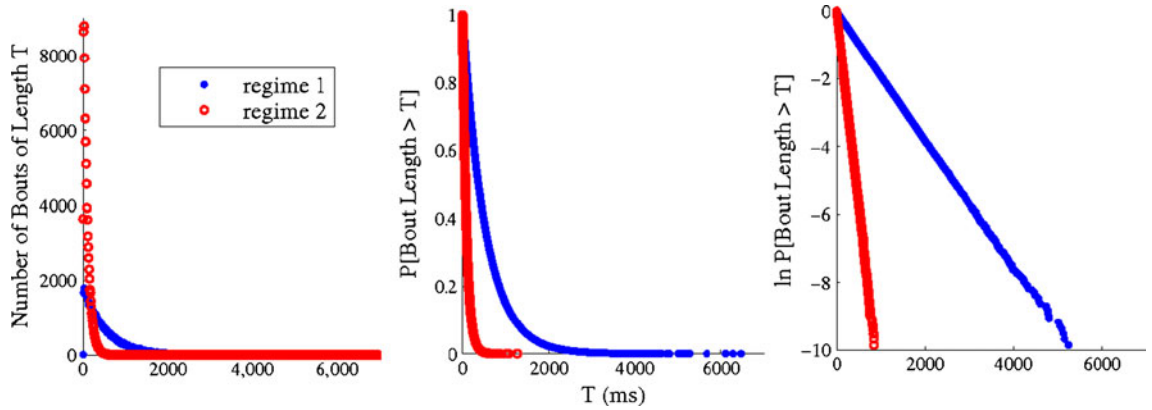

Fig. 5 For a pair of mutually inhibitory neurons receiving noisy excitatory drives, bout length for a particular neuron is always an exponentially distributed random variable, regardless of system parameters. Changes in system parameters alter only the mean of the distribution, but not its exponential nature. Bout lengths of neuron 1 are shown in two sample network regimes; in regime 1, the inhibitory time course is set at $h_1 = h_2 = 9$ ms, while in regime 2 the inhibitory time course is set to $h_1 = h_2 = 6$ ms. Parameter values are symmetric for the two neurons. In each regime, approximately 100,000 bout lengths were computed. *Left:* Number of bouts of length T versus T, with data pooled in 10 ms bins. *Middle:* Empirical complementary cumulative distribution function, $\mathbf{P}(\text{Boutlength} > T) =$ Fraction of Bouts of Length $> T$ versus T. *Right:* Semilog version of the middle panel. The linear relationships are characteristic of exponentially distributed random variables. Mean bout length in regime 1 is $m_1 = m_2 = 533$ ms, while mean bout length in regime 2 is $m_1 = m_2 = 96$ ms. For these simulations, the inhibitory amplitude is set at $\beta_1 = \beta_2 = 0.35$ ms^{-1}, and the strength and noisiness of the excitatory drives to the two neurons are given by the standard reference values: $M_1 = M_2 = M^*$ and $N_1 = N_2 = N^*$

at the beginning of a bout, while the inhibitory current is making its approach to steady-state behavior, which may create memory within the system and break the exponential distribution. This does not occur because we find that mean bout length increases exponentially as a function of inhibitory time course (Fig. 8, left), so that the time scale over which the inhibitory current approaches steady-state is always negligibly small compared to the time scale of bout lengths.

3.3 Escape vs. release

Two mechanisms may contribute to a bout switch: 1) *escape via excitation*, or 2) *release from inhibition*; more generally—a combination of the two mechanisms may be needed for a bout switch. A large, positive fluctuation in the excitatory drive to the suppressed neuron may allow its membrane potential to surmount the incoming inhibition and climb to threshold, with a bout switch ensuing (*escape*). Alternatively, a gap in incoming inhibition may allow the silent cell's membrane potential to respond to the excitatory current and meander to threshold, resulting in a bout switch (*release*).

The convolved mechanisms of release and escape can be teased apart by modulating the noisiness of the excitatory drive to one of the neurons. Consider the extreme case where the excitatory drive to one neuron (denoted as neuron $n \in \{1, 2\}$) has positive noisiness, while the other neuron (neuron $f(\neq n) \in \{1, 2\}$) receives a flat excitatory drive of the same strength ($N_n > 0$, $N_f = 0$, $M_n = M_f = M$). In this scenario, bouts of neuron n end purely as a consequence of release: if neuron n is in the middle of a bout, then neuron n is spiking and neuron f is silent, and since the excitatory drive to neuron f is constant, a gap in the inhibitory current delivered by neuron n is the only way neuron f can reach threshold to cause a bout switch. Bouts of neuron f, on the other hand, end purely as a consequence of escape: if neuron f is in the middle of a bout, then neuron f is spiking and neuron n is silent; since the excitatory drive to neuron f is flat, neuron f spikes and delivers inhibition regularly, so that neuron n can cross threshold and cause a bout switch only via a positive fluctuation in its own excitatory drive.

In order to quantify the contribution of the release mechanism to bout switches, we define the *release ratio* ρ of the two-neuron system (for fixed $\beta = \beta_1 = \beta_2$ and $h = h_1 = h_2$) by

$$\rho_{\beta,h}(M, N_n) := \frac{m_f}{m_n + m_f}, \tag{5}$$

where m_j denotes the mean bout duration of neuron j. We will fix β and h at their standard values (0.35 ms^{-1} and 6 ms, respectively); henceforth, we will drop the subscript and refer to the release ratio as $\rho(M, N_n)$.

When neuron f is in a bout, neuron n must escape to cause a bout switch, while when neuron n is in a bout, neuron f must be released for a bout switch to ensue. Thus, if release is the primary mechanism by which bout switches occur (and escape is rare), then bouts of neuron f will be substantially longer than bouts of neuron n ($m_f >> m_n$), and ρ will be close to 1. However, if escape is the dominant mechanism by which bout switches occur (and release is rare), then bouts of neuron n will be considerably longer than bouts of neuron f ($m_n >> m_f$), and ρ will be near 0. The value of ρ therefore tells us about the relative contributions of the escape and release mechanisms to bout switches in the original system (the system with $M_1 = M_2 = M$, $N_1 = N_2 = N_n$). ρ close to 1 implies that (in the original system) release is the primary mechanism of bout switches (and the role of escape is negligible), while ρ close to 0 implies that (in the original system) escape is the chief trigger for bout switches (and the role of release is negligible). More generally, $0 \leq \rho < 1/2$ if escape dominates release and $1/2 < \rho \leq 1$ if release dominates escape.

Since in our original system the excitatory drives have standard noisiness ($N_1 = N_2 = N^*$), we will consider the case where $N_n = N^*$. In Fig. 6a (top), we fix $N_n = N^*$ and plot $\rho(M, N_n)$ as a function of $M (= M_n = M_f)$. For low values of M, we find that $\rho > 1/2$, while for high values of M we find that $\rho < 1/2$. Thus, we conclude that for low values of M (values near $M = 1$) release from inhibition is the primary mechanism by which bout switches occur in the original system, while for higher values of M (values near $M = 2$) escape via excitation is the chief bout switching mechanism in the original system. Moreover, since ρ decreases monotonically from $\sim 1 \rightarrow \sim 0$ as M is increased from $1 \rightarrow 2$, we conclude that as the strength of the excitatory drives is increased from $M = 1$ to $M = 2$, the escape mechanism contributes more while the release mechanism contributes less to initiating bout switches in the original system (for M near 1.5, $\rho \sim 1/2$, implying that in this case escape and release play comparable roles in eliciting bout switches in the original system).

Figure 6a (top) also shows that for very low values of M (i.e., for $M \leq 1$), ρ is an increasing function of M. This occurs because for very low values of M, the time-averaged mean value of the excitatory drive to the two cells is insufficient (even without inhibition) to push the membrane potential of either cell to threshold. Thus, below $M = 1$, (in the original system) a cell can spike only if a positive fluctuation in its excitatory drive occurs, and hence the escape mechanism must contribute to bout switches. As M assumes smaller values below $M = 1$, the size of the positive fluctuation in a cell's excitatory drive required to

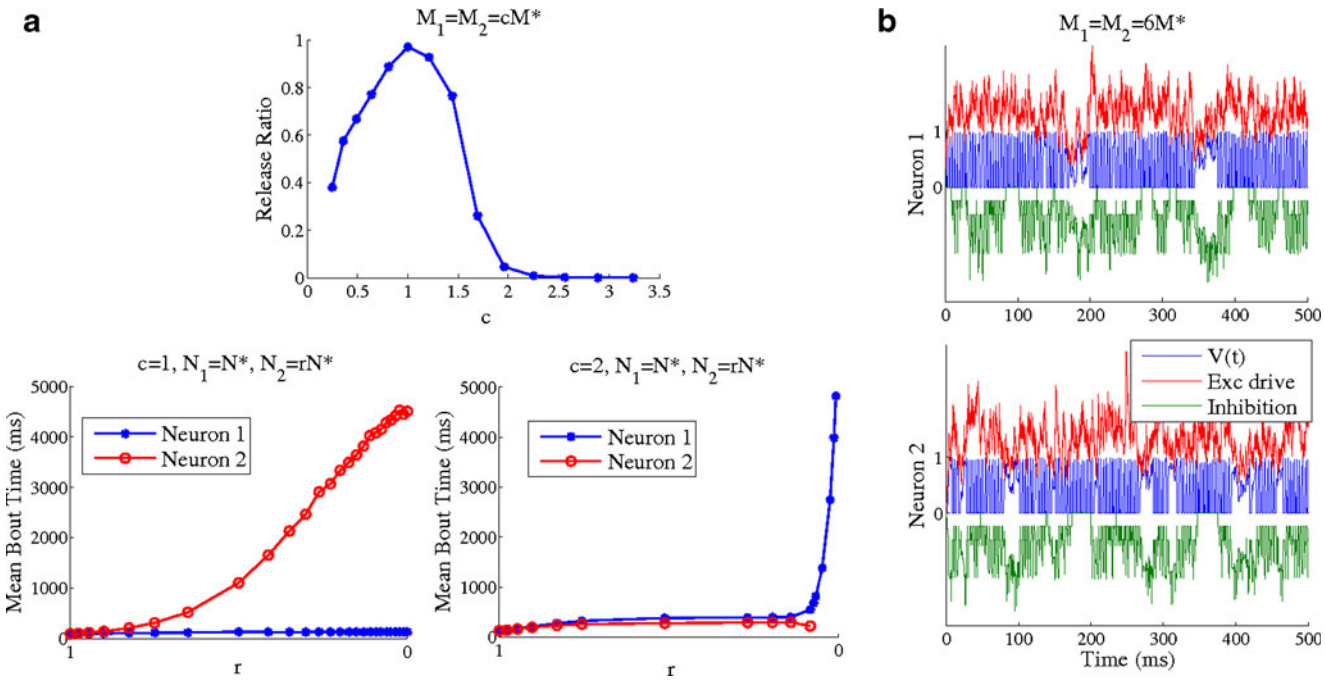

Fig. 6 A pair of mutually inhibitory neurons receiving noisy excitatory drives. For parameter regimes in which alternating activity bouts occur, a switch from a spiking bout of one neuron to a spiking bout of the other neuron can occur via two mechanisms: 1) a gap in the incoming inhibition to the suppressed neuron can allow it to begin spiking (release), or 2) a positive fluctuation in the excitatory drive to the silent neuron can allow it to overcome inhibition and reach spiking threshold (escape). **a** In the top panel, the release ratio of the two neuron system $\rho(cM^*, N^*)$ (see text) is plotted for c ranging from 0.25 to 3.25 (to maintain computationally tractable bout times, N_f, rather than being set to $N_f = 0$, is set to $N_f = \epsilon N^*, \epsilon = 10^{-4}$). In the bottom panels, we fix the strength of the excitatory drive to both neurons at either a value where the primary bout switching mechanism is release ($M_1 = M_2 = M^*$) or at a value where the primary bout switching mechanism is escape ($M_1 = M_2 = 2M^*$); we plot the mean bout time of the two neurons as the noisiness of the excitatory drive to neuron 2 is varied from noisy ($N_2 = N^*$) to nearly flat ($N_2 = \epsilon N^*$, $\epsilon = 10^{-4}$) and the noisiness of the excitatory drive to neuron 1 is fixed at $N_1 = N^*$. The x-axis is on a log scale for visualization. *B)* Once the strength of the excitatory drive is very large, alternating bouts of spiking activity no longer occur. Plots show the spiking activity of neurons 1 and 2, with the strength of the excitatory drive to the two neurons set at $M_1 = M_2 = 6M^*$. The noisiness of the excitatory drive to the two neurons is fixed at the standard value ($N_1 = N_2 = N^*$). For all simulations, the inhibitory time course is fixed at $h_1 = h_2 = 6$ ms and the inhibitory amplitude is fixed at $\beta_1 = \beta_2 = 0.35$ ms^{-1}

induce it to spike becomes larger, and the escape mechanism contributes correspondingly more to bout switches.

Why is it the case that (in the original system) release is dominant for low M while escape prevails for higher M? When the strength of the excitatory drive to the two neurons is low (relative to synaptic inhibition), inhibition eclipses excitation within the system. Within this *inhibition-dominated bout regime*, inhibition will keep the membrane potential of the suppressed neuron far below threshold, and hence a positive fluctuation in the silent neuron's excitatory drive sufficiently large to allow its membrane potential to overcome inhibition and reach threshold will be a highly unlikely event. Since the strength of the excitatory drive to the active neuron is relatively low, a large interspike interval in the firing of the active neuron (causing a gap in the inhibitory current to the suppressed neuron) is a far more likely event, and release will be the primary bout switching mechanism.

The opposite occurs when the strength of the excitatory drive to the two neurons is high (relative to synaptic inhibition). In this case, the system is within an *excitation-dominated bout regime*—the large excitatory drive to the suppressed neuron implies that the inhibitory current from the active neuron keeps the silent cell's membrane potential only slightly below threshold. Thus, in order for the suppressed cell to reach threshold, either a small positive fluctuation in the excitatory drive to the suppressed cell is required (a likely event) or a gap in the inhibitory current to the silent neuron is needed (an unlikely event, since the relatively high excitatory drive to the active neuron causes it to spike frequently). In the excitation dominated regime, escape will therefore be the principal mechanism by which bout switches occur.

If the strength of the excitatory drive is fixed at a very large value (relative to synaptic inhibition), excitation becomes overwhelmingly powerful, with inhibition having little impact on the system—alternating bouts of activity no longer occur, and both neurons spike continuously and nearly independent of each other. Figure 6b shows the independent, continuous spiking activity of the two neurons

within our system when the strength of the excitatory drives is set at a very high value ($M_1 = M_2 = 6M$; other system parameters assume their standard values). A detailed analysis of the transition of the system from 'having bouts' to 'not having bouts', as well as of the escape and release mechanism, will be presented elsewhere.

3.4 Control of mean bout time

The bout durations of the two neurons are a function of system parameters, including those that govern synaptic inhibition and those responsible for the excitatory drive. In this section, we determine the effects of varying the excitatory drive parameters versus those of varying the synaptic inhibition parameters on mean bout times. In Fig. 7 (left), we fix the strength of the excitatory drive to neuron 1 at $M_1 = M^*$ and vary the strength of the excitatory drive to neuron 2 (M_2). The graph shows that as M_2 is increased, the mean bout time of neuron 1 (m_1) decreases while the mean bout time of neuron 2 (m_2) increases. In order to explain the origin of this behavior, we consider the case where $M_2 > M_1 = M^*$. $M_2 > M_1 = M^*$ implies that when neuron 2 is active, neuron 2 spikes more frequently than in the case $M_2 = M^*$ and sends high time-averaged inhibition to neuron 1, resulting in a longer mean bout time for neuron 2 (than in the case $M_2 = M^*$). When neuron 1 is active, neuron 1 spikes at the standard rate corresponding to excitatory drive $M_1 = M^*$, sending the standard value of time-averaged inhibition to neuron 2; however, the high excitatory drive to neuron 2 ($M_2 > M_1 = M^*$) implies that a bout switch can be initiated more easily than in the case $M_2 = M^*$, yielding a shorter mean bout time for neuron 1 (than in the case $M_2 = M^*$). An analogous argument explains why in the case $M_2 < M_1 = M^*$, m_2 decreases and m_1 increases. Thus, these results imply that varying the excitatory drive to *one* neuron modulates the mean bout time of *both* neurons.

Inhibition, on the other hand, exerts *independent control* over the mean bout time of the two neurons, in the sense that inhibition from neuron i to neuron j only affects m_i (with no effect on m_j). In other words, *the mean bout time of a neuron is a function of it's efferent inhibition but is independent of it's afferent inhibition*. Figure 7 plots m_1 and m_2 as the amplitude β_2 (middle panel) or time course h_2 (right panel) of inhibition from neuron 2 to neuron 1 is varied (with the amplitude β_1 and time course h_1 of inhibition from neuron 1 to neuron 2 held fixed). The two plots show that as either β_2 or h_2 is increased, m_2 rises while m_1 remains fixed. These results imply that (for $i \neq j$), m_i is independent of β_j and h_j. The intuition behind this independent control is the following: when neuron i is in the midst of a bout, the other neuron does not fire, and hence inhibition from the other neuron can have no impact on the duration of neuron i's bout.

Furthermore, Fig. 7 (middle) shows that the amplitude of inhibition exerts little influence over bout length—once inhibitory magnitude is sufficiently large, mean bout time appears to saturate. On the other hand, Fig. 7 (right) shows mean bout time seems to show no saturation and grows rapidly with the inhibitory time course. In order to examine the dependence of m_i on h_i, we plot mean bout time versus inhibitory time course with a log scale on the y-axis in Fig. 8 (left); the striking linear relationship on a log scale indicates an exponential dependence of mean bout time on the time course of synaptic inhibition (i.e., there exists a number σ_i such that $m_i \propto e^{\sigma_i h_i}$ over at least five orders of

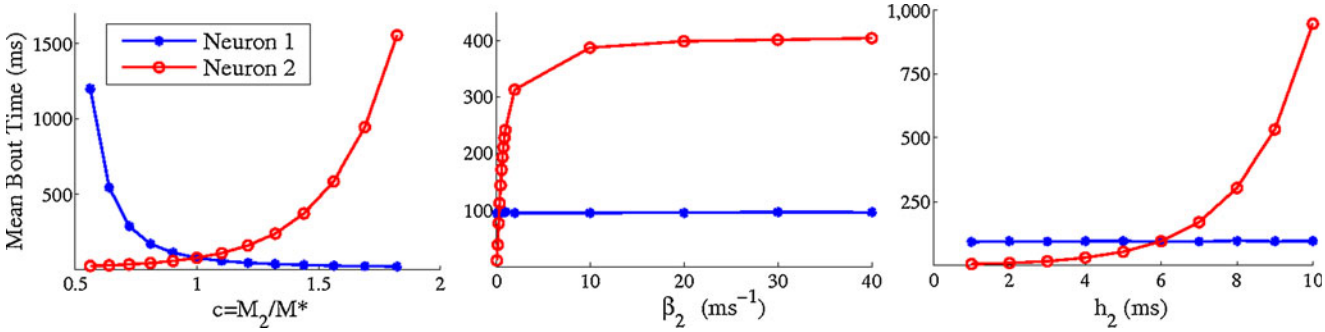

Fig. 7 Synaptic inhibition exerts independent control over the mean bout time of each of the two neurons, while excitatory drive does not. *Left:* The excitatory drive to neuron 1 has fixed strength $M_1 = M^*$, while the strength of the excitatory drive to neuron 2 is given by $M_2 = cM^*$, where c ranges from 0.5 to 2. The noisiness of the excitatory drive to both neurons is fixed at $N_1 = N_2 = N^*$. For both neurons, the time course and amplitude of inhibition are fixed at $h_1 = h_2 = 6$ ms and $\beta_1 = \beta_2 = 0.35$ ms^{-1}, respectively. *Middle:* The amplitude of inhibition from neuron 1 to neuron 2 is fixed at $\beta_1 = 0.35$ ms^{-1}, while the amplitude of inhibition from neuron 2 to neuron 1 is varied from $\beta_2 = 0.1$ to $\beta_2 = 40$ ms^{-1}. The inhibitory time course for both neurons is set to $h_1 = h_2 = 6$ ms, and the strength and noisiness of the excitatory drive to both neurons are set at the standard values: $M_1 = M_2 = M^*$ and $N_1 = N_2 = N^*$. *Right:* The time course of inhibition from neuron 1 to neuron 2 is fixed at $h_1 = 6$ ms, while the time course of inhibition from neuron 2 to neuron 1 is varied from $h_2 = 1$ ms to $h_2 = 10$ ms. The amplitude of inhibition for both neurons is $\beta_1 = \beta_2 = 0.35$ ms^{-1}, and the strength and noisiness of the excitatory drive to both neurons are set at the standard values: $M_1 = M_2 = M^*$ and $N_1 = N_2 = N^*$

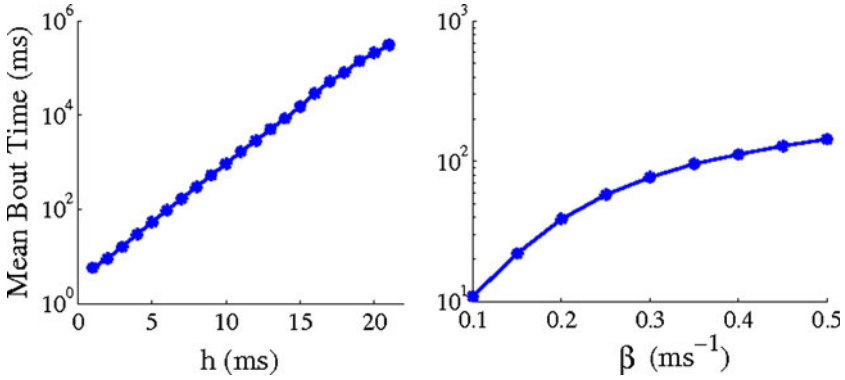

Fig. 8 Dependence of mean bout time on inhibition for a pair of reciprocally coupled inhibitory neurons. *Left:* Semilog plot of the mean bout time of neuron 1 (m_1) as a function of the time course of inhibition from neuron 1 to neuron 2 (h_1). There is a nearly perfect exponential relationship given by $m_1(h_1) = \tau_1 e^{\sigma_1 h_1}$, where $\sigma_1 = 0.56$ ms and $\tau_1 = 3.1$ ms^{-1}. Amplitude of inhibition is fixed at $\beta_1 = \beta_2 = 0.35$ ms^{-1}. *Right:* Semilog plot of the mean bout time of neuron 1 (m_1) as a function of the amplitude of inhibition from neuron 1 to neuron 2 (β_1). Time course of inhibition is fixed at $h_1 = h_2 = 6$ ms. For all simulations, the strength and noisiness of the excitatory drive to both neurons are fixed at the standard values: $M_1 = M_2 = M^*$ and $N_1 = N_2 = N^*$. The relationships seen in both panels are qualitatively similar for all parameter regimes in which bouts are observed

magnitude). A slight deviation from linearity can be seen for the longest h_i, but this is an implementation issue—we ran trials in 1500 s blocks, so for very long mean bout times we miss some of the longest bouts, leading to means that are slightly reduced from their true values. Since mean bout duration is modulated primarily by the time course, rather than the amplitude, of inhibition (compare the left and right panels of Fig. 8), we focus on the dependence of mean bout time on the time course of synaptic inhibition.

Lengthening the time course of inhibition can yield arbitrarily large bout durations; as shown in Fig. 8 (left), varying the inhibitory time course from 1 ms to 25 ms causes mean bout time to change through several orders of magnitude (from $\sim$ 50 ms to $\sim$ 500 s). Moreover, the left panel shows that mean bout time is well-described as an exponential function of inhibitory time course. For the parameter regime employed in Fig. 8, we find that this relationship is given by $m_1(h_1) = \tau_1 e^{\sigma_1 h_1}$, where h_1 is the time course of inhibition from neuron 1 to neuron 2, $\tau_1 = 3.1$ ms, and $\sigma_1 = 0.56$ ms^{-1}. τ_1 represents the y-intercept of the exponential (the mean bout time when the time course of inhibition is 0 ms), while σ_1 describes the growth rate of the exponential (i.e., the sensitivity of mean bout time to changes in the time course of inhibition).

3.5 Inhibitory sensitivity

In terms of synaptic inhibition, time course is therefore the chief determinant of mean bout time, with an exponential relationship given by $m_j(h_j) = \tau_j e^{\sigma_j h_j}$. The growth rate of this exponential, σ_j, describes the sensitivity of bout durations to inhibitory time course, and hence is indicative of robustness to small changes in the time scale of inhibition. Large values of σ_j signify exquisite sensitivity of mean bout length to tiny variations in inhibitory time course, while more diminutive values of σ_j imply robustness of mean bout time to small fluctuations in the time course of inhibition. Due to the importance of this growth rate, we define

$$\sigma_j = \text{inhibitory sensitivity of neuron } j, \text{ with } m_j(h_j) = \tau_j e^{\sigma_j h_j},$$

where m_j is the mean bout length of neuron j, h_j is the time course of synaptic inhibition from neuron j to the other neuron, τ_j is the y-intercept of the exponential function $m_j(h_j)$, and σ_j is the growth rate of the exponential function $m_j(h_j)$.

We can then inquire as to the dependence of the inhibitory sensitivity on various system parameters. Figure 9 shows that changing the amplitude of inhibition from neuron 1 to neuron 2 has no impact on σ_1, and hence affects m_1 only by varying the y-intercept τ_1 (i.e., through vertical translations of the exponential function $m_1(h_1)$). Variations in the excitatory drive, however, do modulate the inhibitory sensitivity. As the strength of the excitatory drive to neuron 2 (M_2) is increased (with M_1,N_1,N_2 fixed), σ_2 rises and σ_1 remains fixed (Fig. 9a, left), while τ_1 shrinks and τ_2 remains approximately constant (Fig. 10a, right). As the noisiness of the excitatory drive to neuron 2 (N_2) is increased (with (N_1,M_1,M_2 fixed), σ_2 decays and σ_1 remains fixed (Fig. 9b, left), while τ_1 remains constant and τ_2 grows (Fig. 9b, right). Thus, even though the excitatory drive does not exhibit independent control of mean bout time (i.e., varying the excitation to *either* neuron changes the mean bout durations of *both* neurons; Fig. 7, left), the excitatory drive *does* exert independent control over inhibitory sensitivity (i.e., σ_j depends on the excitatory drive to neuron j, but is independent of the excitatory drive to the other neuron). The

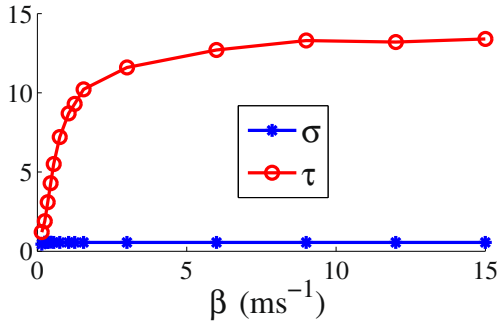

Fig. 9 With other parameters fixed, the mean bout time of neuron 1 (m_1) is an exponential function of the time course of inhibition from neuron 1 to neuron 2 (h_1), with $m_1(h_1) = \tau_1 e^{\sigma_1 h_1}$ (see text). The inhibitory sensitivity (σ_1) as well as τ_1 are plotted as a function of the amplitude of inhibition from neuron 1 to neuron 2 (β_1). Amplitude of inhibition has no effect on σ_1 ($\sigma_1 = 0.56$ for all amplitude values). Both neurons receive excitatory drives with standard strength and noisiness ($M_1 = M_2 = M^*$, $N_1 = N_2 = N^*$)

excitation to neuron j affects bout lengths of the other neuron (neuron i) only through the y-intercept τ_i of the exponential function $m_i(h_i)$.

The inhibitory sensitivity σ_j is therefore dependent only on the strength and noisiness of the excitatory drive to neuron j, and is impervious to all other system parameters (an analysis of this phenomenon is presented in the next section). Large values of the inhibitory sensitivity yield delicate sensitivity to inhibitory time course, while a small inhibitory sensitivity results in bout lengths that are more robust to tiny variations in the time course of inhibition. Within the context of sleep-wake cells within the brain, robustness is likely a crucial quality—it would be detrimental to sleep-wake cycling if tiny fluctuations in the inhibitory time course resulted in radical shifts in bout durations. Independent control of inhibitory sensitivity by the excitatory drive provides a mechanism for creating the desired robustness; if the excitatory drives to the two neurons (independently) have low strength and high noisiness, the inhibitory sensitivities σ_1 and σ_2 can be kept small, yielding robust mean bout times within the system (Fig. 11).

4 Mathematical insights

While a detailed analysis of the system of stochastic differential equations governing the switch arising from mutual inhibition is beyond the scope of this exploratory study, we may gain some insight into both the exponential nature of bout time distributions and the exponential growth of mean bout time as a function of the inhibitory time course by examining simpler toy models. As observed earlier, bout changes in the full system involve a combination of release and escape. We will isolate the two mechanisms of release and escape by constructing separate toy models for the pure release and pure escape scenarios. Though highly simplified, our release and escape toy models capture the essential features of bout switches caused by either the release or escape mechanisms in the full system.

4.1 Pure release case

We start first with the mechanism of release. In the *inhibition-dominated bout regime*, release is dominant and a bout switch ensues when there is a sufficient reduction in the inhibition delivered by the active neuron. For the purposes of our release toy model, we will neglect the temporal dynamics of the inhibitory current delivered by the active neuron; hence, we will assume that each time the active neuron spikes, the inhibitory current to the passive neuron instantaneously jumps up by a value β and instantaneously jumps down by β after h ms. This assumption is reasonable because (in the full model) the temporal dynamics of the inhibitory current occur over time scales that are fast relative to h. Furthermore, we will neglect the amplitude of inhibition β and regard the inhibitory current to the passive neuron as either being 'on' or 'off'; this assumption is reasonable because in the full model, for sufficiently large β, the mean bout duration exhibits only slight dependence on β (note in Fig. 8 that $\frac{\partial(\ln m)}{\partial \beta}$ approaches 0 for large β; in comparison, $\frac{\partial(\ln m)}{\partial h}$ is much greater than zero for all h). Finally, we invoke the *pure release assumption*: we will assume that a bout switch occurs when the inhibitory current to the passive neuron is 'off' for h_0 ms (since we are assuming that bout switches occur due to inhibitory release, we neglect fluctuations in the excitatory drive to the suppressed neuron, implying that once the inhibitory current turns 'off', the silent neuron will climb to threshold if the inhibitory current remains 'off' for a fixed length of time). This assumption is consistent with our earlier discussion of the release ratio (in which neuron f receives a flat excitatory drive, and hence when neuron n, which receives a noisy excitatory drive, is in a bout, release is the only way neuron f can cause a bout switch). Under these assumptions, it is clear that a bout switch will occur in our toy model if and only if an interspike interval (ISI) of length $h' = h + h_0$ ms (or greater) occurs in the ongoing spiking activity of the active neuron.

We will argue that the waiting time for an ISI of size greater than a threshold h' is exponentially distributed. Since the membrane potential of a neuron is reset to 0 following a spike, and since the statistics of the excitatory drive exhibit no temporal dependence, the membrane potential of the active neuron is a renewal process, and the ISIs $\tau_1, \tau_2, \ldots$ are independent and identically distributed random variables. Thus, in the release toy model, the probability that a bout change will occur between spikes k and

$k+1$ is independent of k. In other words, the number of spikes during a bout is a geometrically distributed random variable, which we denote by K. It follows that a bout duration is given by the random sum $T = \sum_{i=1}^{K} \tau_i$. Since the probability of a bout switch between spikes is small, K is large with high probability. For large K and independent and identically distributed $\{\tau_i\}$, a law of large numbers argument indicates that $T \approx K\mathbf{E}(\tau)$, where $\mathbf{E}(\tau)$ represents the mean of an ISI. Since we consider bouts that are several orders of magnitudes larger than $\mathbf{E}(\tau)$, (*i.e.* in the case where $K >> 20$), the geometric distribution of K implies that T is closely approximated by an exponential.

We will now argue that in the release toy model, not only are bouts exponentially distributed, but mean bout time is an exponentially growing function of the time course of efferent inhibition h. Let $T_n = \tau_1 + \tau_2 + \ldots + \tau_n$ and $J = \min\{j : \tau_j > h'\}$. In order to characterize the exponential bout time distribution $T_{J-1} + h'$, it suffices to calculate the expectation $\mathbf{E}(T_{J-1} + h')$:

$$\mathbf{E}(T_{J-1}) = \mathbf{E}(J-1)\mathbf{E}\left(\tau | \tau < h'\right) \tag{6}$$

where J is a geometric random variable with success probability given by $p = \mathbf{P}\left(\tau > h'\right)$. So $\mathbf{E}(J) = 1/p$ and $\mathbf{E}(J-1) = \frac{\mathbf{P}(\tau<h')}{\mathbf{P}(\tau>h')}$. This implies that

$$\begin{aligned}\mathbf{E}\left(T_{J-1} + h'\right) &= h' + \frac{\mathbf{E}\left(\tau; \tau < h'\right)}{\mathbf{P}(\tau > h')} \\ &= h' + \frac{\mathbf{E}(\tau) - \mathbf{E}\left(\tau; \tau > h'\right)}{\mathbf{P}(\tau > h')}\end{aligned} \tag{7}$$

We will additionally assume that τ has an exponential tail with parameter λ (see Ostojic 2011 for evidence that ISIs of a neuron being driven by a noisy current have an exponential tail). In other words, there is an $\bar{h}$ such that for all $h' > \bar{h}$,

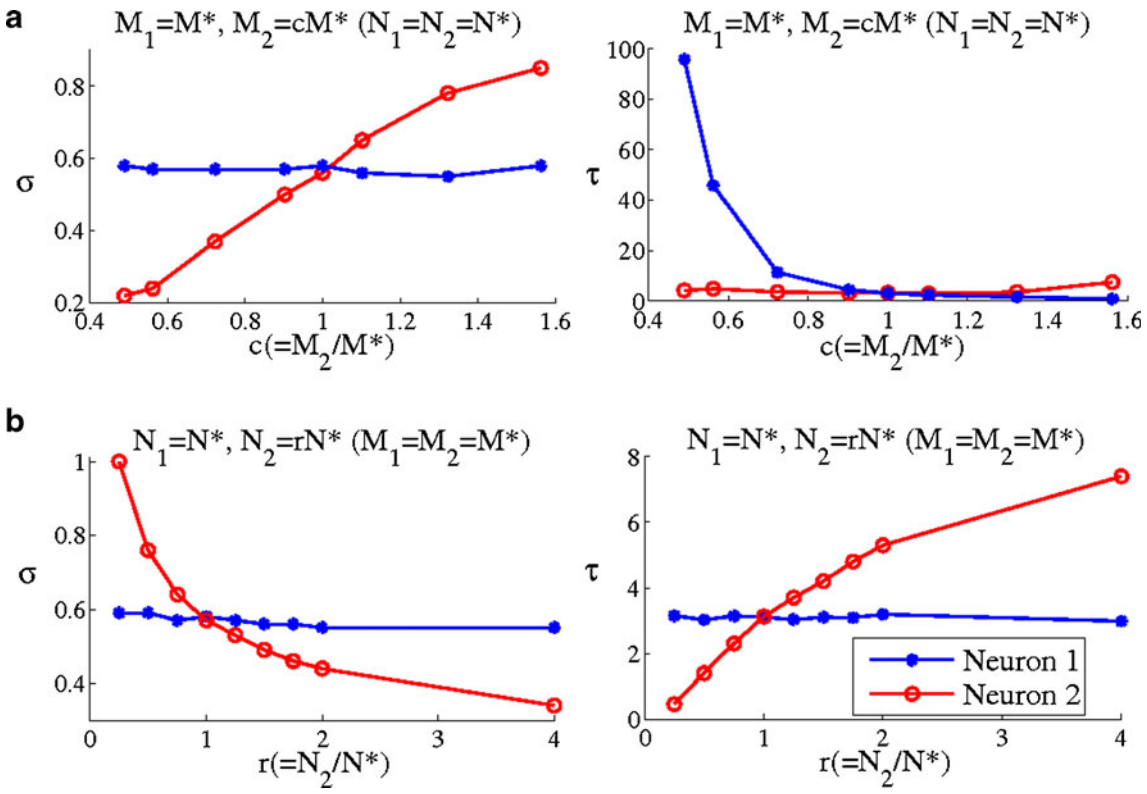

Fig. 10 With other parameters fixed, the mean bout time of neuron j (m_j) is an exponential function of the time course of inhibition from neuron j to the other neuron (h_j), with $m_j(h_j) = \tau_j e^{\sigma_j h_j}$ (see text). **a** σ_1, σ_2 and τ_1, τ_2 are plotted as the strength of the excitatory drive to neuron 2 is varied (from $M_2 = 0.25M^*$ to $M_2 = 1.75M^*$) while the strength of the excitatory drive to neuron 1 is fixed at $M_1 = M^*$. The noisiness of the excitatory drive to both neurons is fixed at the standard value ($N_1 = N_2 = N^*$). **b** σ_1, σ_2 and τ_1, τ_2 are plotted as the noisiness of the excitatory drive to neuron 2 is varied (from $N_2 = 0.25N^*$ to $N_2 = 4N^*$) while the noisiness of the excitatory drive to neuron 1 is fixed at $N_1 = N^*$. The strength of the excitatory drive to both neurons is fixed at the standard value ($M_1 = M_2 = M^*$). The excitatory drive to neuron j independently controls the inhibitory sensitivity of neuron j. For all simulations, the amplitude of inhibition is fixed at $\beta_1 = \beta_2 = 0.35\ \text{ms}^{-1}$

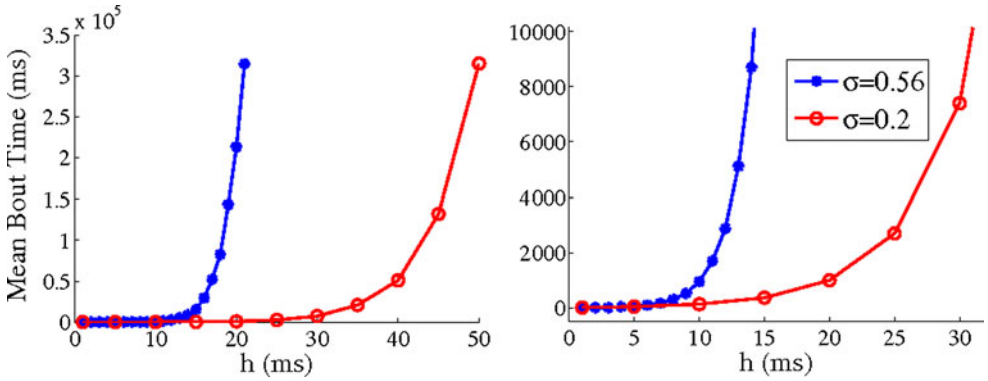

Fig. 11 Mean bout time is plotted as a function of the time course of inhibition for two different excitatory drives. The first excitatory drive has standard strength and noisiness: $M_1 = M_2 = M^*$ and $N_1 = N_2 = N^*$ (inhibitory sensitivity given by $\sigma_1 = \sigma_2 = 0.56$). The second excitatory drive has a lower strength and a higher noisiness: $M_1 = M_2 = 0.6M^*$ and $N_1 = N_2 = 3N^*$ (inhibitory sensitivity given by $\sigma_1 = \sigma_2 = 0.2$). Data shown are for neuron 1, but since all parameters are symmetric mean bout times for neuron 2 are the same. The right panel is a zoom-in of the left panel. Amplitude of inhibition is fixed at $\beta_1 = \beta_2 = 0.35\ \text{ms}^{-1}$

$\mathbf{P}(\tau > h') \approx e^{-\lambda h'}$ and $\mathbf{E}(\tau; \tau > h') \approx \left(h' + \frac{1}{\lambda}\right) e^{-\lambda h'}$. Substituting these in Eq. (7), we find that

$$\mathbf{E}\left(T_{J-1} + h'\right) \approx \mathbf{E}(\tau) e^{\lambda h'} - \frac{1}{\lambda} \tag{8}$$

which shows the exponential growth of mean bout time with h.

4.2 Pure escape case

We now turn to the mechanism of escape. In the *excitation-dominated bout regime*, escape is dominant and a bout switch is initiated by a sufficiently large positive fluctuation in the excitatory drive to the suppressed neuron. To construct our escape toy model, we invoke the *pure escape assumption*: we will neglect the stochastic dynamics of the inhibitory current to the silent cell (i.e, we will assume that the active neuron spikes regularly with a fixed ISI and delivers a periodic inhibitory current). This assumption is consistent with our earlier discussion of the release ratio (in which neuron f receives a flat excitatory drive and hence spikes regularly when in a bout, delivering periodic inhibition to neuron n and forcing neuron n to escape to elicit a bout switch).

Thus, within our escape toy model, the passive neuron receives a periodically fluctuating inhibitory current, and (since the excitatory drive to the active neuron is high within an excitation-dominated bout regime, causing the active neuron to fire at a high rate) the period of the inhibitory current is on a time scale of a few milliseconds. Additionally, the silent cell receives a noisy excitatory drive whose time-averaged mean value is constant (with fluctuations occurring on a time scale of a few milliseconds). It follows that the only time dependence in the hazard rate (the instantaneous rate at which a bout switch can occur) is on a time scale of a few milliseconds. The system therefore "remembers" a history of at most a few milliseconds, and on the time scale of bouts, the hazard rate is effectively constant. An effectively constant hazard rate implies that bouts appear exponentially distributed.

5 Discussion

In this work, we examined the distribution of bout durations in a system consisting of two mutually inhibitory neurons driven by noisy excitatory currents. We showed that strong synaptic inhibition results in a bistable system, with noise causing stochastic switching between stable states (i.e., alternating bouts of activity). We found that (in the parameter space where alternating activity bouts are observed), an *inhibition-dominated bout regime* results in bout swithes that are primarily a consequence of release from inhibition, while within an *excitation-dominated bout regime* escape via excitation is the dominant bout switching mechanism. We also showed that bout length is always exponentially distributed, and that inhibition exerts independent control of bout duration (i.e., inhibition delivered by neuron j affects the mean bout time of neuron j alone) while the excitatory drive does not exhibit independent control of bout length (i.e., changing the excitatory drive to neuron j alters the mean bout time of both neurons).

Additionally, we found that while inhibitory amplitude has little impact on bout duration, mean bout time is well-described as an exponential function of the time course of synaptic inhibition. We defined the growth rate of this exponential for neuron j (σ_j) as the inhibitory sensitivity of neuron j, with a small inhibitory sensitivity indicating a mean bout time that is robust to small changes in inhibitory time course, and a large inhibitory sensitivity signifying

delicate sensitivity of mean bout time to small fluctuations in the time course of inhibition. We showed that the excitatory drive is the sole determinant of inhibitory sensitivity, and furthermore that the excitatory drive exerts *independent control* over inhibitory sensitivity (i.e., the excitation to neuron j modulates σ_j alone).

5.1 Sleep-wake cycling

The inspiration for this investigation arose from experimental studies of sleep-wake cycling in young mammals: at the neuronal level, bouts of sleep and wakefulness are correlated with the activity of populations of 'sleep-active' and 'wake-active' brainstem neurons that may reciprocally inhibit each other (Karlsson et al. 2005). In infant mammals, bouts of sleep and wakefulness are exponentially distributed, with the mean duration of sleep and wake bouts increasing as the infant ages. Furthermore, sleep and wake bouts are thought to be separately regulated—the mean duration of sleep bouts is controlled independently from the mean duration of wake bouts (Blumberg et al. 2005).

Our simple two-neuron system can provide qualitative insights into some of the physiological mechanisms that may underlie these experimental observations. The exponential distribution of bout times arises naturally within our system (as a consequence of the fact that the time course of inhibition is always negligibly small compared to mean bout time). Hence, we claim that to create memory within the system and break the exponential distribution of bout length multiple time scales of activity must exist—a single time scale (e.g., a single time course of inhibition) is insufficient. Inhibition also provides a mechanism for independent regulation of sleep and wake bouts—by unidirectional modification of the time course of inhibition, the mean duration of sleep and wake bouts can be controlled separately. Moreover, independent control of inhibitory sensitivity by the excitatory drive implies that as long as the strength of excitation within the system is low but the noisiness is high, sleep and wake bout durations can be independently controlled by inhibition in a highly *robust* manner.

Of course, while the results obtained in this paper can provide qualitative insights into basic principles that may govern sleep-wake switching, a pair of mutually inhibitory neurons is not a biologically realistic model of the sleep-wake system. The brainstem sleep-wake system likely consists of two mutually inhibitory *populations* of neurons, and hence a realistic model would need to take into account intra-population connectivity, inter-population connectivity, and population sizes (though, unfortunately, experimental data to guide such investigations is currently scarce). A more realistic model of two mutually inhibitory populations can then be used to provide quantitative (rather than just qualitative) explanations of the sleep-wake data. In preliminary investigations, we find that the general principles obtained in our two-neuron system are equally applicable to the case of two mutually inhibitory neuronal populations.

In older mammals, however, experimental evidence suggests that the duration of wake bouts develops a heavy-tailed distribution (which resembles a power-law, though controversy exists over whether the distribution is a true power law), while the length of sleep bouts remains exponentially distributed (Blumberg et al. 2005; Chu-Shore et al. 2010). This qualitative transformation of the wake bout distribution is thought to be due to the elaboration of sleep-wake structures within the brain through development, a likely candidate proposed by Gall et al. (2009) being the locus coeruleus. Regardless of the exact neuronal populations involved in the transformation, the results from our two-neuron system suggest that these neuronal populations must introduce additional time scales into wake bout dynamics in order to modify the exponential distribution of wake bout duration.

Many existing models of sleep-wake cycling focus on transitions between the sleep and wake states (or between REM sleep and non-REM sleep) in adult mammals, where the time scale of bouts is on the order of several hours. These mathematical models range from utilizing statistical approaches to employing constructions involving deterministic differential equations (Borbély et al. 1989; Lu et al. 2006; Phillips et al. 2010; Rempe et al. 2010; Robinson et al. 2011). However, the rapid cycling between sleep and wake states seen in infant mammals and the associated exponentially distributed bout durations cannot arise in these deterministic models—random switching between states requires a source of noise. Stochastic models which have produced switching between sleep and wake states, and for which the statistical distribution of bouts within the model have been analyzed, can be found in Behn and Booth (2011), Behn et al. (2008). Another approach that is capable of capturing stochastic switching is to model the spiking activity of each of two interacting neuronal populations as a doubly stochastic Poisson process, an approach that is adopted by Joshi (2009). In the current paper, we address the question of whether the random switching behavior suggested by infant sleep-wake cycling can be generated within a biophysical model; we show that, even though action potentials occur on the time scale of $\sim$2 ms, our simple two-neuron system is able to capture bout durations on time scales of seconds to hundreds of seconds.

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Conflict of interest The authors declare that they have no conflicts of interest.

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