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Network properties of a computational model of the dorsal raphe nucleus

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ABSTRACT

Serotonin (5-HT) plays an important role in regulating mood, cognition and behaviour. The midbrain dorsal raphe nucleus (DRN) is one of the primary sources of 5-HT. Recent studies show that DRN neuronal activities can encode rewarding (e.g., appetitive) and unrewarding (e.g., aversive) behaviours. Experiments have also shown that DRN neurons can exhibit heterogeneous spiking behaviours. In this work, we build and study a basic spiking neuronal network model of the DRN constrained by neuronal properties observed in experiments. We use an efficient adaptive quadratic integrate-and-fire neuronal model to capture slow afterhyperpolarization current, occasional bursting behaviours in 5-HT neurons, and fast spiking activities in the non-5-HT inhibitory neurons. Provided that our noisy and heterogeneous spiking neuronal network model adopts a feedforward inhibitory network architecture, it is able to replicate the main features of DRN neuronal activities recorded in monkeys performing a reward-based memory-guided saccade task. The model exhibits theta band oscillation, especially among the non-5-HT inhibitory neurons during the rewarding outcome of a simulated trial, thus forming a model prediction. By varying the inhibitory synaptic strengths and the afferent inputs, we find that the network model can oscillate over a range of relatively low frequencies, allow co-existence of multiple stable frequencies, and spike synchrony can spread from within a local neural subgroup to global. Our model suggests plausible network architecture, provides interesting model predictions that can be experimentally tested, and offers a sufficiently realistic multi-scale model for 5-HT neuromodulation simulations.

1. Introduction

Serotonin (5-HT) is an important neurochemical that innervates throughout the brain, modulating neural activities, and thus regulating mood, cognition and behaviour (Giovanni, Matteo, & Esposito, 2008; Tseng & Atzori, 2007). The midbrain dorsal and median raphe nuclei are the sources of 5-HT. Within the dorsal raphe nucleus (DRN), about one- to two-thirds of the neurons contain 5-HT (Jacobs & Azmitia, 1992; Köhler & Steinbusch, 1982). Abnormal 5-HT activity levels have been implicated in devastating mental illnesses such as major depressive disorder, anxiety disorder and schizophrenia (Giovanni et al., 2008). Studies on psychotropic drugs, especially antidepressant drugs, have focused extensively on the 5-HT system, targeting its release, reuptake and various 5-HT receptors (Carr & Lucki, 2011; Cryan & Leonard, 2000; Giovanni et al., 2008). However, despite considerable research effort, an integrated understanding of how 5-HT and related drugs actually affect neuronal circuits in multifaceted ways remains unresolved (Pacher & Kecskemeti, 2004).

Various electrophysiological, pharmacological, immunohistochemical and morphological studies of the raphe nuclei neurons have been conducted (Beck, Pan, Akanwa, & Kirby, 2004; Calizo et al., 2011; Giovanni et al., 2008; Hajós, Sharp, & Newberry, 1996; Kirby, Pernar, Valentino, & Beck, 2003; Kocsis, Varga, Dahan, & Sik, 2006; Li, Li, Kaneko, & Mizuno, 2001; Marinelli et al., 2004; Vandermaelen & Aghajanian, 1983). According to the classical and convenient identification, 5-HT neurons are presumed to have relatively slow and regular firing, broad action potentials, affinity to inhibitory feedback from 5-HT_{1A} autoreceptors, or slow after-hyperpolarization (AHP) after a spike (Aghajanian & Vandermaelen, 1982; Hajós et al., 1996; Sprouse & Aghajanian, 1987; Vandermaelen & Aghajanian, 1983). However, more recent studies have shown that some of these suggested characteristics may not be highly reliable. Most electrophysiological properties are now found to be similar between 5-HT- and non-5-HT-containing neurons over various regions of the raphe nuclei (Allers & Sharp, 2003; Beck et al., 2004; Calizo et al., 2011; Kirby et al., 2003; Marinelli et al., 2004). Action potentials do not differ much between 5-HT- and non-5-HT-containing neurons, and 5-HT_{1A} autoreceptors can be found in both 5-HT- and non-5-HT-containing neurons (Calizo et al., 2011). Heterogeneity of neuronal activities in the DRN has also been observed in various experiments (Fig. 1), including behaving animals (Bromberg-Martin, Hikosaka, & Nakamura, 2010; Nakamura, Matsumoto, & Hikosaka, 2008; Ranade & Mainen,

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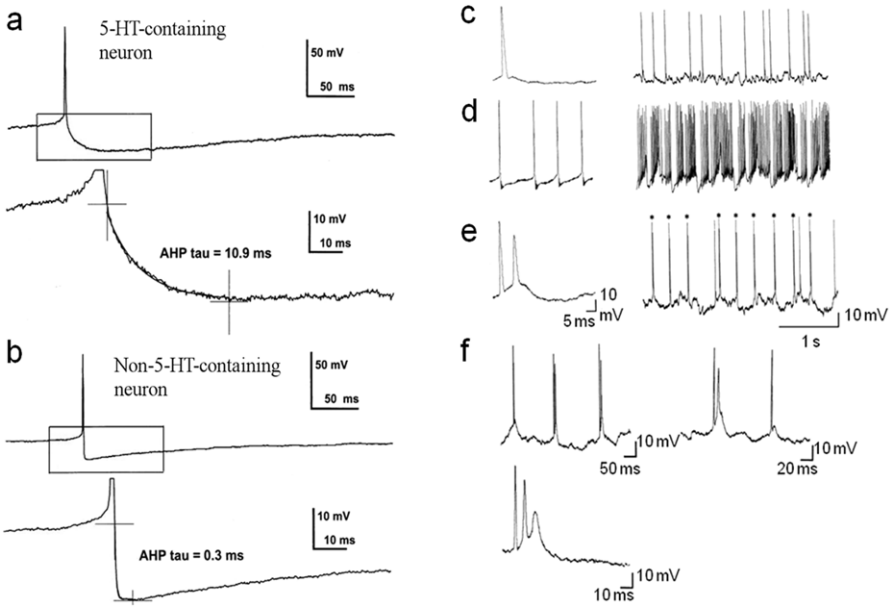

Fig. 1. Some heterogeneous neuronal properties found in experiments. (a–b) Decay time constants of afterhyperpolarization (AHP) in a 5-HT-containing (a) and a non-5-HT-containing (b) neuron in the rat DRN (an *in vitro* intracellular study. (c–f) Variety of spiking behaviours of a presumably 5-HT neuron (c), a non-5-HT neuron (d), and a burst-firing 5-HT neuron (e), in the DRN of anaesthetized rat. Right panel of (e): asterisks denote spike doublets. Left panel: magnified to show spike doublets. (f) Spike singlets, doublets and triplets can be observed in a burst-firing 5-HT neuron. Scales for time and membrane potential magnitude are shown by the horizontal and vertical bars, respectively.
Source: (a, b) adapted from Kirby et al. (2003) and (c–f) from Hajós et al. (1996).

2009). Recent advanced experimental tools have also shown that bursting DRN neurons, with similar electrophysiological properties as "classical" DRN neurons, are more reliably identified as 5-HT containing (Hajós et al., 2007, 1996; Kirby et al., 2003) (Fig. 1(e) and Fig. 1(f)). Overall, the mechanisms underlying these heterogeneous neuronal behaviours and their functions have yet to be fully understood.

Previous computational models of the 5-HT systems have been useful in illuminating insights into either "low-level" single presynaptic terminal or "high-level" behavioural levels (Best, Nijhout, & Reed, 2010, 2011; Daw, Kakade, & Dayan, 2002; Dayan & Huys, 2009; Doya, 2002; Stoltenberg & Nag, 2010). However, neither accounts for the various neuronal properties of the 5-HT neurons nor attempts to understand at the intermediate circuit level. To further understand this complex and heterogeneous 5-HT system, it is pertinent to build multi-scale computational models with sufficient biological realism to provide more quantitative, systematic, predictive and integrated accounts of various neural and cognitive/behavioural effects (e.g. Wong-Lin, Prasad, & McGinnity, 2011).

In this work, we make use of a spiking neuronal model to efficiently account for the heterogeneous DRN neuronal spiking behaviours. Then we combine the neurons to build a plausible network, comparing its activity to that recorded in animals performing a memory-guided decision task, and infer possible network architecture. Finally, we explore how the network model responds under various conditions, and discuss the implications.

2. Methods

2.1. Basic adaptive quadratic integrate-and-fire neuronal model

To model the DRN neurons, we choose the quadratic integrate-and-fire (QIF) neuronal model with a recovery variable as a compromise between computational efficiency and rich spiking dynamics properties (Izhikevich, 2003). The model, also known as the Izhikevich model, can be described by the coupled dynamical equations of the membrane potential, V, and some recovery variable, U:

$$\frac{dV}{dt} = 0.04V^2 + 5V + 140 - U + I \quad (1)$$

$$\frac{dU}{dt} = a(bV - U) \quad (2)$$

with the after-spike resetting condition: if $V \geq V_{\text{peak}}$ (in mV), then V is reset to a lower value c, and U is increased to $U + d$. Here V_{peak} is the peak of an action potential, and a, b, c and d are constants. In our simulations, we found the parameter d does not affect our results much, and we fix it at 2. We retain the same value of parameter b at 0.2 as in Izhikevich (2003). We can emulate the slow AHP current by allowing slow decay dynamics of the recovery variable. This is achieved by setting c at higher values (~ -57 mV) and $a = 0.005$ such that recovery operates in the timescale of $\sim$200 ms (Hajós et al., 1996). As shown in Izhikevich (2003) and Wong-Lin et al. (2011), higher c values can result in bursting behaviours (two or more spikes per burst within less than 10 ms). This is consistent with experiments that had shown slow regular-spiking 5-HT neurons and bursting 5-HT neurons tend to have very similar basic electrophysiological properties. Inhibitory non-5-HT neurons are modelled in a way similar to the fast-spiking GABAergic interneurons in the cortex with parameters $b = 0.28$, and $c = -65$ mV (Izhikevich, 2003).

The recovery variable U represents the activation of some inactivating currents (e.g. potassium ionic currents). For simplicity, we define I to be the afferent input current per membrane capacitance C ($\sim$39 pF for both 5-HT neurons and non-5-HT neurons in Marinelli et al., 2004); hence the unit is in A/F, which we will henceforth not explicitly mention for the sake of brevity. The neuronal spiking behaviours are to some extent, similar to that of Hodgkin–Huxley type models as discussed in (Izhikevich, 2003, 2007). The term $0.04V^2 + 5V + 140$ is chosen so that V has a resting potential between -65 mV and -75 mV as observed in experiments (e.g. Hajós et al., 1996; Kirby et al., 2003), and more importantly to allow ease of extension to model other brain regions