



Inferring synaptic excitation/inhibition balance from field potentials



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ABSTRACT

Neural circuits sit in a dynamic balance between excitation (E) and inhibition (I). Fluctuations in E:I balance have been shown to influence neural computation, working memory, and information flow, while more drastic shifts and aberrant E:I patterns are implicated in numerous neurological and psychiatric disorders. Current methods for measuring E:I dynamics require invasive procedures that are difficult to perform in behaving animals, and nearly impossible in humans. This has limited the ability to examine the full impact that E:I shifts have in cognition and disease. In this study, we develop a computational model to show that E:I changes can be estimated from the power law exponent (slope) of the electrophysiological power spectrum. Predictions from the model are validated in published data from two species (rats and macaques). We find that reducing E:I ratio via the administration of general anesthetic in macaques results in steeper power spectra, tracking conscious state over time. This causal result is supported by inference from known anatomical E:I changes across the depth of rat hippocampus, as well as oscillatory theta-modulated dynamic shifts in E:I. Our results provide evidence that E:I ratio may be inferred from electrophysiological recordings at many spatial scales, ranging from the local field potential to surface electrocorticography. This simple method for estimating E:I ratio—one that can be applied retrospectively to existing data—removes a major hurdle in understanding a currently difficult to measure, yet fundamental, aspect of neural computation.

1. Introduction

Neurons are constantly bombarded with spontaneous synaptic inputs. This state of fluctuating activity is referred to as the high-conductance state (Destexhe et al., 2003), and gives rise to the asynchronous, irregular (Poisson-like) firing observed *in vivo* (Destexhe et al., 2001). In this state, neural circuits sit in a balance between synaptic excitation (E) and inhibition (I), typically consisting of fast glutamate and slower GABA inputs, respectively, where inhibition is two to six times the strength of excitation (Alvarez and Destexhe, 2004; Xue et al., 2014). Physiologically, the balance of E:I interaction is essential for neuronal homeostasis (Turrigiano and Nelson, 2004) and the formation of neural oscillations (Atallah and Scanziani, 2009). Computationally, E:I balance allows for efficient information transmission and gating (Salinas and Sejnowski, 2001; Vogels and Abbott, 2009), network computation (Mariño et al., 2005), and working memory maintenance (Lim and Goldman, 2013). Conversely, an imbalance between excitation and inhibition, during key developmental periods or tonically thereafter, is implicated in

neurological and psychiatric disorders such as epilepsy (González-Ramírez et al., 2015; Symonds, 1959), schizophrenia (Uhlhaas and Singer, 2010), and autism (Dani et al., 2005; Mariani et al., 2015; Rubenstein and Merzenich, 2003), as well as impairments in information processing and social exploration (Yizhar et al., 2011).

Given such a state of intricate balance and its profound consequences when disturbed, quantifying the E:I ratio could aid in better characterizing the functional state of the brain. Existing methods for estimating E:I ratio focus predominantly on interrogation of precisely selected cells, either through identification of excitatory and inhibitory neurons based on extracellular action potential waveforms (Peyrache et al., 2012), or by intracellular voltage-clamp recordings to measure synaptic currents (Monier et al., 2008), often combined with pharmacological or optogenetic manipulations (Reinhold et al., 2015; Xue et al., 2014). These methods are invasive and are restricted to small populations of cells, making them difficult to apply clinically and to *in vivo* population-level analyses critical for understanding neural network functioning. Other methods, such as magnetic resonance spectroscopy (Henry et al., 2011)

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and dynamic causal modeling (Legon et al., 2015), are able to provide greater spatial coverage, enabling the sampling of E:I ratio across the brain. However, this gain comes at a cost of temporal resolution – requiring several minutes of data for a single snapshot – and are based on restrictive connectivity assumptions.

Here, we aim to address this important gap in methodology to measure E:I ratio with broad population coverage and fine temporal resolution. Two recent lines of modeling work motivate our starting hypothesis. First, it has been shown that synaptic input fluctuations during the high conductance state can be accurately modeled by a summation of two stationary stochastic processes representing excitatory and inhibitory inputs (Alvarez and Destexhe, 2004). These inputs have different rates of decay, corresponding to a faster AMPA current and a slower GABA_A current, which can be readily differentiated in the frequency domain and computationally inferred from single membrane voltage traces (Pospisil et al., 2009, Fig. 1B). Second, population-level neural field recordings, such as the local field potential (LFP) and electrocorticography (ECoG), have been shown to be primarily dominated by postsynaptic currents (PSC) across large populations (Buzsáki et al., 2012; Mazzoni et al., 2015; Miller et al., 2009). Additionally, recent work by (Haider et al., 2016) observed tight coupling between the LFP and synaptic inputs in the time domain. Thus, we combine these two findings and reason that changes in the relative contribution between excitatory and inhibitory synaptic currents must also be reflected in the field potential, and in particular, in the frequency domain representation (power spectral density, or PSD) of LFP and ECoG recordings. In this work, we derive a straightforward metric that closely tracks E:I ratio via computational

modeling, and demonstrate its empirical validity by reanalyzing publicly available databases from two different mammalian species. Specifically, we test the hypotheses that anatomical and theta oscillation-modulated changes in excitation and inhibition in the rat hippocampus can be inferred from CA1 local field potentials, and that anesthesia-induced global inhibition is reflected in macaque cortical electrocorticography.

2. Materials & methods

2.1. LFP simulation

We simulate local field potentials under the high conductance state (Alvarez and Destexhe, 2004), with the assumption that the LFP is a linear summation of total excitatory and inhibitory currents (Mazzoni et al., 2015). Poisson spike trains from one excitatory and one inhibitory population are generated by integrating interspike intervals (ISI) drawn from independent exponential distributions, with specified mean rate parameter (Fig. 1A). Each spike train is convolved with their respective conductance profiles, which are modeled as a difference-of-exponentials defined by the rise and decay time constants of AMPA and GABA_A receptors (Eq. (1), Fig. 1B). Aggregate values for synaptic constants are taken from CNRGLab @ UWaterloo (see *Neurotransmitter Time Constants* in Ref; Table 1). The two resulting time series represent total excitatory (g_E) and inhibitory (g_I) conductances, respectively (Fig. 1C). E:I ratio is defined as the ratio of mean excitatory conductance to mean inhibitory conductance over the simulation time, and specific E:I ratios are achieved

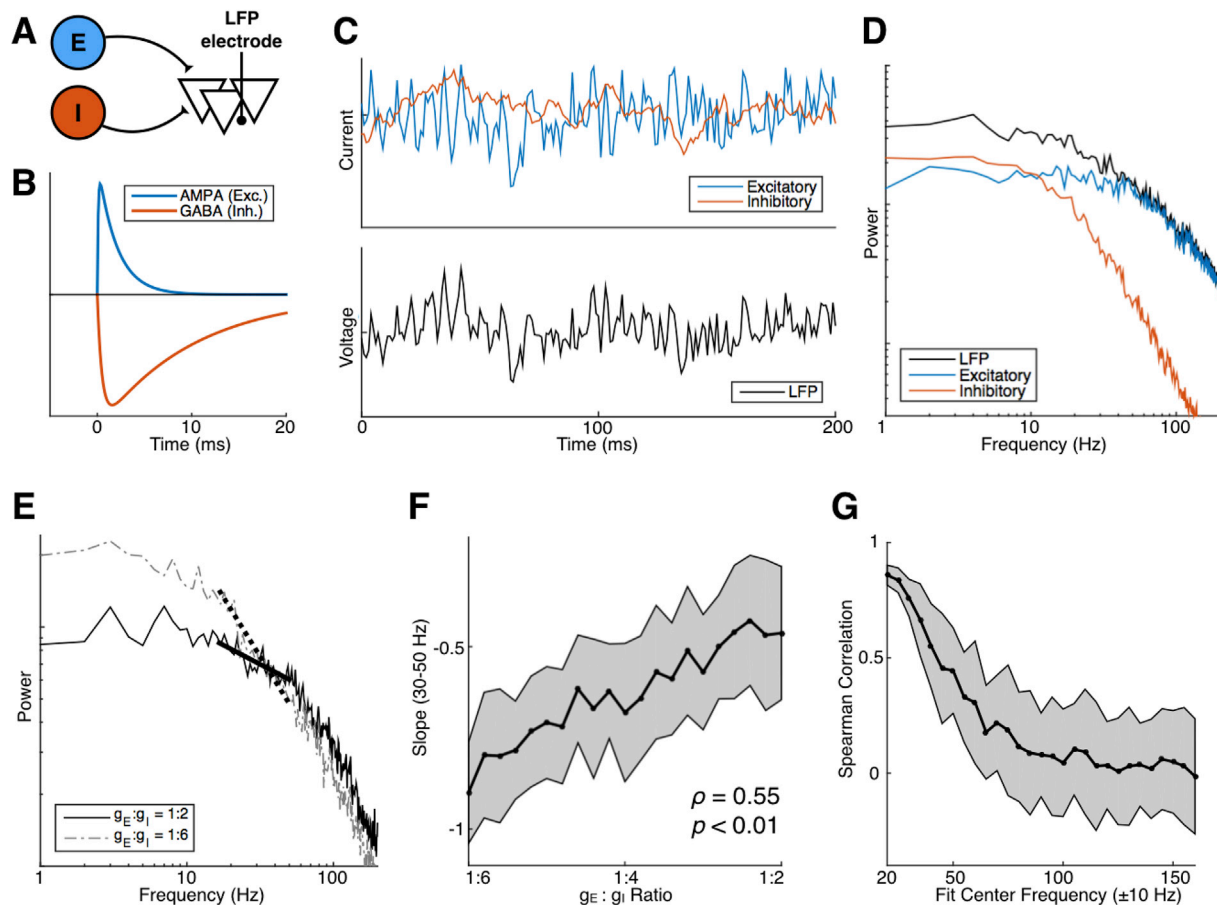


Fig. 1. E:I ratio correlates with PSD slope in simulation. (A) Model schematic: an “LFP population” receives input from two Poisson populations, one excitatory and one inhibitory. (B) AMPA and GABA_A conductance profiles follow a difference-of-exponentials with different rise and decay time constants. (C) Example time trace of simulated total synaptic currents (top) and LFP (bottom). (D) PSDs of simulated signals in (C). Note power law decays in current-PSDs that begin at different frequencies. (E) Increasing E:I ratio from 1:6 to 1:2 causes a rotation, producing a flatter PSD. (F) E:I ratio is positively correlated with PSD slope between 30 and 50 Hz. (G) Positive rank correlations between E:I ratio and PSD slope diminish with increasing frequency of fitting window, up to 100 Hz.

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