Post-inhibitory rebound interacts with preventing or deleting mechanisms to generate thetaspiking resonance in hippocampal CA1 pyramidal cells

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A crucial issue in the understanding of neuronal oscillations is to elucidate the microcircuits that are the substrate to these rhythms in the different brain areas. The question arises whether rhythmic activity results solely from the network properties (e.g., excitation and inhibition, topology) or it involves the interplay of the latter with the intrinsic properties of the participating neurons (e.g., ionic currents). We address this issue theoretically in the context of the hippocampal area CA1 microcircuits, which include excitatory (PYR) and inhibitory (INT) cells. It has been observed in in vitro experiments that PYR exhibit a preferred subthreshold frequency response to oscillatory inputs (subthreshold or membrane potential resonance) at theta (4 - 10 Hz) frequencies (Hu *et al.*, 2002, 2009; Zemankovics et al, 2010). Previous in vivo work (Stark *et al.*, 2013) has shown that, contrary to expectation, these cells do not exhibit spiking resonance in response to direct oscillatory optogenetic activation, but, surprisingly, spiking resonance in PYR occurs when INT are activated in this way. We explain the underlying mechanisms by combining biophysical modeling, numerical simulations and dynamical systems analysis. The PYR subthreshold resonance fails to be communicated to the spiking regime by direct PYR activation because of the relatively strong effect of the oscillatory input amplitude that causes the spiking activity to spread over a broad range of input frequencies (for which the voltage response is above threshold) as shown theoretically (Rotstein 2017). PYR theta-band resonance through direct INT activation results instead from a combination of (i) rebound spiking, and (ii) a timing mechanism. Rebound spiking is responsible for the "spiking low-pass filter" (generation of spikes for input frequencies that are low enough for the voltage responses of both PYR and INT to be above threshold), but it is not enough to generate spiking resonance since spikes are generated for arbitrary low input frequencies. The timing mechanisms are responsible for either 'erasing" the spikes generated by input frequencies lower than theta (deleting mechanisms) or failing to produce spikes for these input frequencies (preventing mechanisms). We identified three such mechanisms: (i) network-mediated inhibition from OLM cells, (ii) synaptic depression of INT synapses, and (iii) subthreshold gamma resonance in INT, which has been shown to be present *in vitro* (Pike et al 2000). Overall, these results provide a mechanistic understanding of network resonance at theta frequencies and make several predictions. The principles identified in this study are applicable not only to CA1 networks, but also to other systems that exhibit theta resonance such as neocortical networks (Stark *et al.*, 2013). Finally, the results and ideas that emerge from our study are seminal for the construction of a theoretical framework

for the investigation of the preferred frequency responses of neuronal networks to oscillatory inputs at a variety of biophysically realistic frequency bands.

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