Unitary Sources Say: It Is Inhibition!

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Local field potentials (LFPs) are extracellular electric potentials that reflect transmembrane currents from nearby cells. Locally, a net-positive transmembrane current results in the formation of a *source*, and a *sink* reflects a net-negative transmembrane current. The mechanisms underlying the emergence of LFPs are complex (involving currents through receptors and ion channels, accounting for temporal structure in, spatial distribution of, and intra-/inter-cellular spatiotemporal interactions among external/local synaptic inputs) and vary across different brain regions depending on cellular morphologies and topographical arrangements (Buzsaki *et al.*, 2012; Einevoll *et al.*, 2013). In the face of such complexity, theoretical and computational modeling tools have proven to be invaluable for gaining mechanistic insights into the biophysical origin of LFPs, for explaining new findings, and in delineating the relative contributions of different circuit components to LFP (Einevoll *et al.*, 2013). A good example for this appears in the current issue of *The Journal of Physiology*, where (Telenczuk *et al.*, 2020) study the emergence of unitary LFP (uLFP) in the hippocampus.

The uLFP is generated by action potential firing in a *single* neuron (hence the term *unitary*), effectuated through local synapses formed by the axon collaterals of the neuron. Electrophysiological experiments have shown that consistently detectable *monosynaptic* uLFPs could be elicited through activation of a single inhibitory, but not excitatory, neuron in the hippocampus (Glickfeld *et al.*, 2009; Bazelot *et al.*, 2010). To explain this phenomenon, Telenczuk et al. quantitatively assess uLFPs generated by activating single *presynaptic* excitatory and inhibitory neurons using an anatomically-constrained virtual slice comprising morphologically-realistic *postsynaptic* CA3 pyramidal neurons.

In building the model, Telenczuk et al. included detailed synapse placement based on axonal arborization of a basket cell or two different pyramidal cells. Three examples involving critical attention-to-details incorporated into the model by Telenczuk et al. are (i) trimming of axonal arborization of presynaptic neurons to the realistic size of a hippocampal slice, to precisely replicate morphological characteristics of brain slices containing cut axons; (ii) matching the experimentally-determined predominant distributions of dendritic excitatory and perisomatic inhibitory synapses on postsynaptic neurons; and (iii) matching the differential local synaptic connectivity through the number of connections onto each postsynaptic neuron from the presynaptic basket cell (~6 connections) *vs.* the two presynaptic pyramidal cells (~2 connections each).

Employing carefully performed simulations with this model, Telenczuk et al. confirm electrophysiological observations (Bazelot *et al.*, 2010) that hippocampal inhibitory neurons produce larger monosynaptic uLFPs (~40 μV) compared to monosynaptic excitatory uLFPs (~10 μV). In assessing electrophysiological observations that excitatory neurons initiated disynaptic inhibitory field potentials (Bazelot *et al.*, 2010), Telenczuk et al. superimposed excitatory and inhibitory uLFPs with a synaptic delay and show that the larger inhibitory uLFPs mask their excitatory counterparts. These results quantitatively explain why excitatory and inhibitory uLFPs have the same polarity under different recording configurations, and why it can be difficult to separate excitatory and inhibitory uLFPs in interconnected circuits. Furthermore, simulations involving different presynaptic neurons with disparate axonal arborization emphasize the critical importance of axonal morphology and electrode location on uLFPs.

Importantly, based on their simulations and these quantitative outcomes, Telenczuk et al. elegantly delineate the biophysical mechanisms underlying electrophysiological observations. They argue that the high density of inhibitory receptors converging on perisomatic regions of the postsynaptic neurons allow for summation of dipole-like structures formed by synapses impinging on different neurons. In comparison, the lower density of local pyramidal-to-pyramidal excitatory synapses contributes to smaller uLFPs. An important insight about the role of synaptic localization profiles relates to *cancellation* of dipoles formed by synaptic inputs impinging on apical and basal dendrites. As dipoles produced by synaptic inputs on apical *vs*. basal dendrites are of opposite polarity, temporally-aligned inputs (in the case of uLFPs, arriving from the same presynaptic neuron) onto these postsynaptic structures would partially cancel each other, thereby resulting in small uLFPs. Together, Telenczuk et al. conclude that the high-density perisomatic nature of inhibitory inputs contributes to large monosynaptic uLFPs, whereas the low-density spatially dispersed nature of excitatory inputs results in relatively smaller monosynaptic uLFPs.

Although Telenczuk et al. focus on *unitary* LFPs, they propose extensions to their work towards reducing the tremendous computational cost involved in modeling field potentials. They suggest that spiking activity of individual point neurons arranged in space can be convolved with their uLFPs and the linear summation of these uLFPs could be used to provide faster, albeit imprecise, estimations of LFPs from an interconnected network of point neurons. While this is an enticing proposal to reduce computational cost, future studies exploring this possibility should device computational strategies to account for various non-linear mechanisms governing neuronal and glial physiology. These computational tools should recognize that field potentials in *in vivo* networks also reflect transmembrane currents triggered by *external excitatory* inputs and their *nonlinear intracellular* interactions with other (external and local) synaptic inputs. Specifically, such analyses should explicitly account for the spatiotemporal structure of the external and local inputs, the specific synaptic locations that they impinge on cellular structures, the location-dependent nonlinear sub-threshold mechanisms that are involved in somato-dendritic spatiotemporal summation, axo-somatic and dendritic spike generation, and the return currents driven by cell-type-specific non-homogeneous distributions of different ion channel conductances responding to converging inputs.

From a broader perspective, Telenczuk et al. elegantly demonstrate how detailed computational models can yield mechanistic insights about complex biological phenomena, and provide clear avenues for further exploration towards understanding field potentials, which have been demonstrably useful in assessing brain physiology and pathology (Buzsaki *et al.*, 2012).

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