Understanding Electric Brain Stimulation Through the Reciprocity Theorem

Torbjørn V. Ness[a,*], Christof Koch[b] & Gaute T. Einevoll[a,c]
[a] Department of Physics, Norwegian University of Life Sciences, Ås, Norway
[b] Allen Institute, Seattle, WA, USA
[c] Department of Physics, University of Oslo, Oslo, Norway
* Corresponding author: torbjorn.ness@nmbu.no

Abstract
Lee et al. recently reported robust, frequency-independent subthreshold membrane coupling to extracellular current stimulation across cell classes and brain regions, in both human and mice cortical slices. Specifically, small extracellular sinusoidal electrical stimulations (ES) at frequencies between 1-140 Hz induced a local oscillation in the extracellular potential, leading to sub-threshold (< 0.5 mV) sinusoidal potentials across the cell membrane of nearby cell bodies. Surprisingly, these induced changes in Vm did not decrease with frequency. This seems to imply that ES is a fundamentally different stimulus than equivalent intracellular stimulation that results in strong membrane filtering, caused by the frequency-dependent membrane capacitance. Here we would like to draw attention to the reciprocity theorem as a powerful and (to the best of our knowledge) as-of-yet-unused tool for understanding the effects of ES on neural dynamics, and this counterintuitive result in particular.

It is quite common that studies of ES give counter-intuitive results; consider our lack of truly understanding ES-based therapies – such as *Deep Brain Stimulation*[3] or *Temporal Interference Stimulation*[4]. As the underlying biophysics of ES is fairly well understood,[5] this lack of insight arises from the large number of factors involved in determining how cells and networks are affected by ES.

This is exemplified by the results of Lee et al.[1], where even the single-cell subthreshold case is hard to understand, despite the involved dynamics presumably being approximately passive and linear. To make full use of ES-based therapies in the future we must eventually understand how ES affects neural activity, and this understanding must entail active conductances and spiking. However, one must learn how to walk before one can learn how to run, and to understand non-linear effects, one must first understand linear ones[2].

The reciprocity theorem of classical electromagnetism, first applied to biophysics in the 1850s by Helmholtz, states that for any electrical network that consists entirely of ideal capacitances, inductances, and resistances, the current at one point in the circuit due to a voltage at a second point is the same as the current at the second point due to the same voltage at the first. That is, switching the location of a current source and a measurement electrode will not affect the measured potential. In the context of ES (see Supplementary Information for additional details), this means that for all passive cell models the somatic

membrane potential response $V_m(r_{soma})$ from an extracellular current injection I_{stim} at location r_{EC}, will be identical to the extracellular potential $V_e(r_{EC})$ from a somatic current injection I_{stim},

$$V_{\mathrm{m}}(r_{\mathrm{soma}}) = \mathrm{F}(I_{\mathrm{stim}}(r_{\mathrm{EC}})) \Leftrightarrow V_{\mathrm{e}}(r_{\mathrm{EC}}) = \mathrm{F}(I_{\mathrm{stim}}(r_{\mathrm{soma}})), \quad (1)$$

where F is a function linking the stimulus current to the potential response.
This is convenient because we have a good understanding of how neurons generate extracellular potentials[5].

Lee et al. injected current at different frequencies extracellularly while measuring the resulting membrane potential response across the membrane of nearby somas (~50 µm away from the injected current). According to the reciprocity theorem, the measured membrane potential response is equivalent to the extracellular potential ~50 µm away from the soma, resulting from somatic intracellular current injection.

Close to the soma, biophysics tells us that the extracellular potential will be dominated by the membrane current of the soma compartment alone[6],

$$V_{\mathrm{e}}(r) \approx \frac{I_{\mathrm{m}}^{\mathrm{s}}}{4\pi\sigma r}, \quad (2)$$

where σ is the extracellular conductivity and r is the distance from the soma. According to theory, this approximation will be accurate as long as the distance from the soma is substantially smaller than the frequency-dependent length constant of the cell[5], or alternatively, within the region where the extracellular potential is better described by the single somatic current source than as a dipole. Further, the somatic membrane current itself will be dominated by the injected current. Under these conditions, the amplitude of the extracellular potential will be frequency-independent, since the amplitude of the injected current is frequency-independent. Through the reciprocity theorem, this implies that the membrane potential response to ES will be frequency-independent, consistent with Lee et al.'s measurements.

To illustrate, consider a 100 pA somatic current injected into a cortical layer V pyramidal cell (Fig. S1A, C) and a GABAergic cell (Fig. S1B, D) with active Hodgkin & Huxley-like voltage-dependent membrane conductances. Given that the induced changes in $V_m(r_{soma})$ are subthreshold (4 mV and 8 mV at 1 Hz for the pyramidal cell and the interneuron respectively), the cells behave approximately linearly, and the reciprocity theorem holds (Fig. S1A, B). As previously demonstrated[7] the resulting extracellular potential has a dipole-like shape, and the spatial extent of the dipole is in general influenced by the frequency of the injected current (Fig. S1C, D, F). Note, however, that close to the soma (< ~50 µm), the amplitude is close to frequency-independent (Fig. S1E, F). According to the reciprocity theorem, this implies that neurons generally respond more strongly to low-frequency ES, except when the injected current is very close to where the membrane potential is measured, as was the case in Lee et al.'s experiments.

The reciprocity theorem also teaches us a few more general insights. Close to a soma receiving a current input, $V_e(r)$ is dominated by the somatic membrane current (eq. 2), decaying with the distance proportionally to $1/r$ ("monopole"-like)[6]. Far away from a somatic current input, $V_e(r)$ will instead decay with distance as $1/r^2$ ("dipole"-like)[6] (Fig. S1E). These rules of thumb will also apply to the membrane potential response from ES.

In response to somatic current input, extracellular potentials tend to take on the shape of a dipole, implying that the same extracellular current can have opposite effects on the somatic membrane potential, depending on the exact location. This translates into the general feature of ES that an extracellular current stimulation will always depolarize one part of a cell and hyperpolarize another part, depending on the exact geometry[8].

For somatic current into the pyramidal neuron, the resulting dipole is aligned with the pia-to-layer-6 direction (Fig. S1C). For the interneuron, the extracellular potential is more like a tilted dipole (Fig. S1D). As interneurons lack the consistent asymmetry introduced by the apical dendrite, their dipoles are not expected to be aligned.[7] Interestingly, in analogy to how pyramidal neurons dominate LFP/EEG/MEG signals because they are geometrically aligned,[5] this geometrical alignment also predicts that pyramidal cells with the same orientation relative to an extracellular current source will be affected similarly. We can therefore expect distant current sources to have a synchronizing effect on similarly oriented populations of pyramidal neurons, while the response of interneurons will be more erratic.

Lee et al.'s observations of a frequency-independent subthreshold membrane coupling to extracellular current stimulation are easy to understand in light of the reciprocity theorem. Furthermore, it predicts that the observed frequency-independence will only occur for current injections close to the measured membrane potential. Far away, the membrane response will be frequency-dependent.

Declaration of interests

The author declares no competing interests.

References

1. Lee, S. Y. *et al.* Cell class-specific electric field entrainment of neural activity. *Neuron*.
2. Koch, C. *Biophysics of Computation*. (Oxford Univ Press, Oxford, 1999).
3. Ashkan, K., Rogers, P., Bergman, H. & Ughratdar, I. Insights into the mechanisms of deep brain stimulation. *Nat. Rev. Neurol.* **13**, 548–554 (2017).
4. Mirzakhalili, E., Barra, B., Capogrosso, M. & Lempka, S. F. Biophysics of Temporal Interference Stimulation. *Cell Syst.* **11**, 557-572.e5 (2020).
5. Halnes, G. *et al. Electric Brain Signals: Foundations and Applications of Biophysical Modeling*. (Cambridge University Press, Cambridge, 2024).
6. Pettersen, K. H. & Einevoll, G. T. Amplitude variability and extracellular low-pass filtering of neuronal spikes. *Biophys. J.* **94**, 784–802 (2008).
7. Lindén, H., Pettersen, K. H. & Einevoll, G. T. Intrinsic dendritic filtering gives low-pass power spectra of local field potentials. *J. Comput. Neurosci.* **29**, 423–44 (2010).
8. Basser, P. J. & Roth, B. J. New Currents in Electrical Stimulation of Excitable Tissues.

Annu. Rev. Biomed. Eng. **2**, 377–397 (2000).

Supplemental information

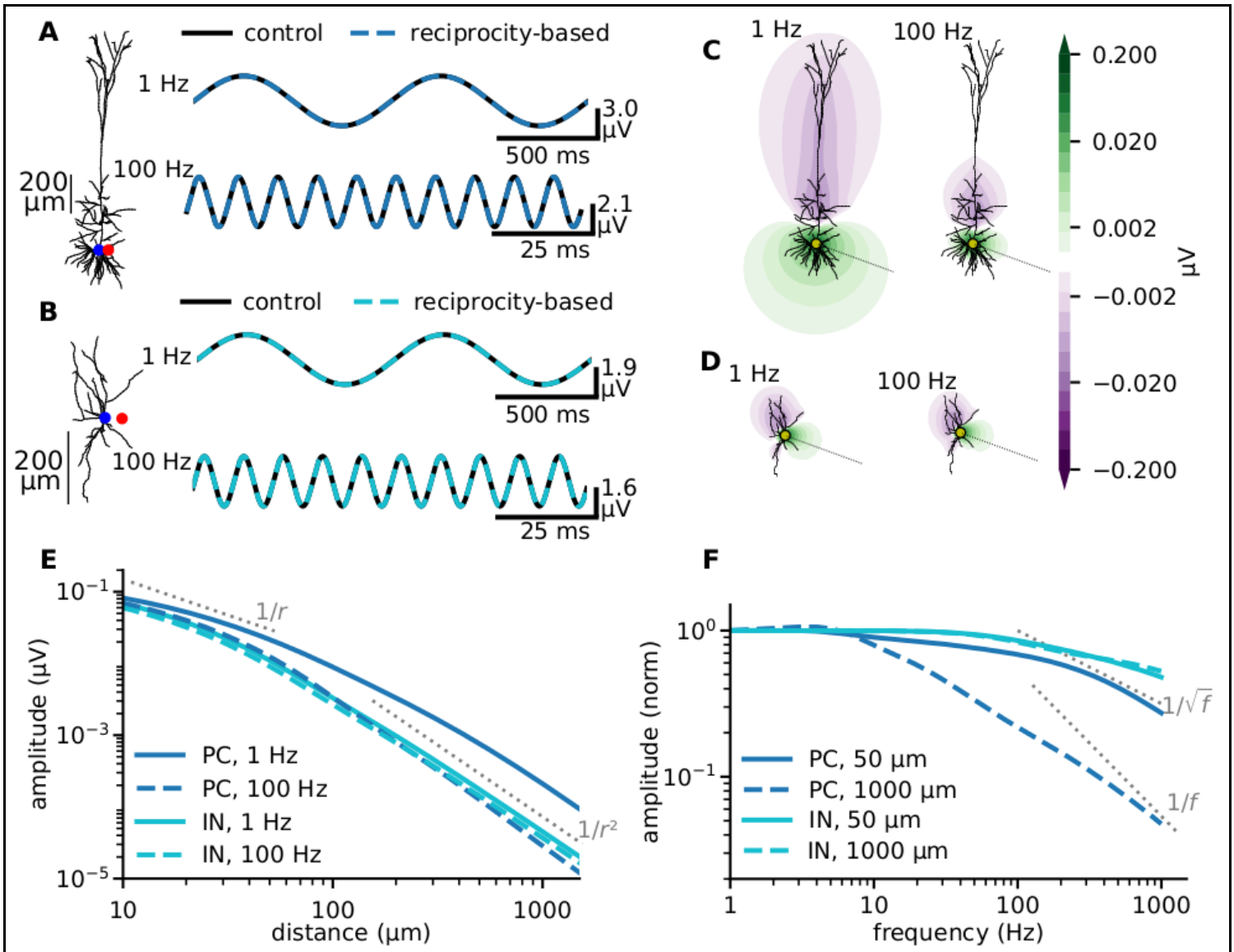

Figure S1: **A:** A demonstration of the validity of the reciprocity theorem. An extracellular current source (location marked by the red dot) with an amplitude of 100 pA stimulates a pyramidal cell model at 1 Hz (top) or 100 Hz (bottom). The resulting membrane potential response ('control'; black lines) is measured in the soma (location marked by the blue dot). As predicted by the reciprocity theorem, this is observed to give indistinguishable results when the same current is instead injected in the soma, and the extracellular potential calculated at the location of the red dot ('reciprocity-based'; dark blue lines). **B:** Same as panel A, but for a GABAergic mouse cell model. **C:** A snapshot of the extracellular potential at the time of the maximum somatic membrane current is plotted on a dense grid around the pyramidal cell from panel A. The amplitude of the sinusoidal current input was 100 pA. **D:** Same as in panel C, but for the interneuron model in panel B. **E:** Amplitude of the extracellular potential as a function of distance from the input site, calculated along the dotted lines in panels C-D, that is, -20 degrees relative to the horizontal direction. Different colors correspond to different cell models, full lines correspond to 1 Hz input, and dashed lines correspond to 100 Hz input. **F:** Amplitude of the extracellular

potential as a function of frequency for white-noise current input, calculated at two different distances along the dotted lines in panels C-D, that is, -20 degrees relative to the horizontal direction. Different colors correspond to different cell models, full lines correspond to a distance of 50 µm, and dashed lines correspond to a distance of 1000 µm. All amplitudes are normalized to the value at 1 Hz.

Methods

The pyramidal cell model used here was the rat cortical layer 5 cell model presented by Hay et al. (2011), where the somatic input resistance was 42 MOhm and the neuronal time constant was 10 ms (measured as the time it took to reach a fraction (1-1/e) of the steady-state potential following subthreshold current stimulation). The interneuron model was a perisomatic layer 5 aspiny cell from the mouse primary visual area from the Allen Brain Atlas (celltypes.brain-map.org/; electrophysiology ID: 490387590; model ID: 491623973). The somatic input resistance was 79 MOhm and the neuronal time constant was 1.7 ms.

All neural simulations and calculations of extracellular potentials were done through LFPy 2.3 (Hagen et al. 2018) running on NEURON 8.1 (Carnevale & Hines 2006). For simulating extracellular stimulation, we used the 'insert_v_ext' function in LFPy, centered around the 'extracellular' mechanism in NEURON, where the extracellular potential outside each neural compartment was calculated from treating the extracellular current injection as a point current source. The intracellular current injections were modeled as controllable synaptic currents ('POINT_PROCESS' in NEURON). The injected current was either a sinusoidal with a given frequency (Fig. S1A-E), or a white noise-current input (Fig. S1F), that is, the sum over all frequency component in the considered frequency range, where each frequency component had the same amplitude and a random phase (Halnes et al. 2024). The resulting white-noise current input was scaled to ensure that the cell models were in the subthreshold regime with somatic membrane potential fluctuations in the range of 0.1 - 0.3 mV.

The reciprocity theorem is valid for any electrical network that consists entirely of ideal capacitances, inductances, and resistances, that is, passive electrical networks. The resting membrane potential is introduced into equivalent electrical circuits by adding additional voltage sources (batteries) across the membrane. The superposition theorem states that in a passive electrical network, the effect of each current- or voltage source can be treated independently. For simplicity, one can therefore start by analyzing the electrical network in the absence of the resting membrane potential, because the principle of superposition ensures that the resting membrane potential can be added afterward as additional voltage sources in the equivalent circuit. Because of sign conventions regarding the direction of membrane currents in NEURON, a sign change is needed for the intracellular current injection in the application of the reciprocity theorem.

Supplemental References

Hay, E., Hill, S., Schürmann, F., Markram, H. & Segev, I. (2011), 'Models of neocortical layer 5b pyramidal cells capturing a wide range of dendritic and perisomatic active properties', PLoS Computational Biology 7, 1–18.

Hagen, E., Næss, S., Ness, T. V. & Einevoll, G. T. (2018), 'Multimodal Modeling of Neural Network Activity: Computing LFP, ECoG, EEG, and MEG Signals with LFPy 2.0', Frontiers in Neuroinformatics 12(92).

Carnevale, N. T. & Hines, M. L. (2006), ‘The NEURON Book’, Cambridge University Press, Cambridge.

Halnes, G. et al. (2024) ‘Electric Brain Signals: Foundations and Applications of Biophysical Modeling’, Cambridge University Press, Cambridge.