Do neurons generate monopolar current sources?

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According to the "standard model," electric potentials such as the local field potential (LFP) or the electroencephalogram (EEG) are generated by current dipoles made by cerebral cortex neurons arranged in parallel. In this issue of *Journal of Neurophysiology*, Riera et al. (2012) present experimental evidence that this standard model may be insufficient to account for LFP and EEG signals in the rat brain. The authors have designed a set of technically impressive experiments that question the validity of the dipole model. We briefly summarize these findings and then speculate on possible physical mechanisms to explain these surprising results.

According to the standard model, a given current source (for example due to the opening of a postsynaptic conductance as in Fig. 1*A*) will be instantaneously balanced by an extracellular current and a "return current", which will enter the neuron at another location (for example the soma; see Fig. 1*B*). This configuration implies that a dipole will instantaneously appear in the neuron, as illustrated in Fig. 1. In these conditions, the system is described by Kirchhoff's laws, similar to an electronic circuit (see Fig. 1, *bottom*, for an example of equivalent circuit).[1]

According to this model, the instantaneous dipole that appears in asymmetric neurons (such as pyramidal cells) will be responsible for the production of an electric field outside of the neurons. If these cellular dipoles are oriented in parallel, a situation which is called "open field" configuration (Lorente de No 1947; such as typically in cerebral cortex), the field generated by the different dipoles will summate and create a signal strong enough to be recorded with extracellular microelectrodes, the LFP, or even give rise to potentials recordable at the surface of the scalp, such as the EEG. Motivated by this standard model, a number of methods have appeared to estimate the dipolar sources from LFP or EEG recordings (Jones et al. 2007; Pascual-Marqui et al. 1994; Ramirez 2008). These methods are quite popular in the EEG literature, and there exists several commercial or open-source programs to perform this estimate of underlying dipolar sources from the EEG (Pascual-Marqui et al. 2002; http://www.uzh.ch/keyinst/loreta.htm) and/or from magnetoencephalographic (MEG) recordings. These estimates are of course entirely dependent on the standard dipole model.

In their study, Riera et al. (2012), investigated the validity of this model in several ways. They first recorded local neuronal activity in three dimensions, using a set of multicontact electrodes inserted in the rat barrel cortex (spanning several barrels). The system records both units and LFPs at all locations,
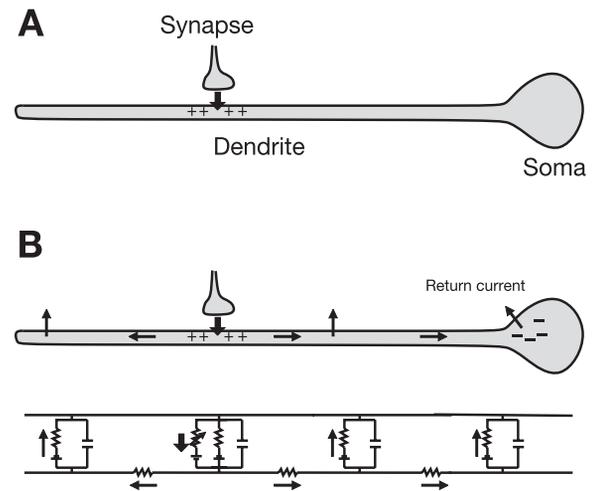

Fig. 1. Illustration of the flow of ions following the activation of a synaptic conductance. *A*: activation of a synaptic conductance at a given position in the dendrite of a neuron The conductance is assumed in this example to be associated to a net entry of positive ions. *B*: according to the "standard model," the synaptic current (downward arrow) is instantaneously balanced by a return current in another region of the neuron, resulting in a dipole. The equivalent electrical circuit corresponding to this situation is shown at bottom.

thereby providing a dense three-dimensional coverage of this area of cerebral cortex. By applying variants of the current-source density (CSD) analysis (Nicholson and Freeman 1975), which estimates current sources (without making dipole assumptions), they demonstrate that, following whisker activation, there appears current sources and sinks, which are not necessarily balanced. Most interestingly, they designed a procedure to estimate the different multipolar components of the current profiles and quantified their respective importance.[2] Surprisingly, while there were significant dipolar and multipolar components as expected, they also found an unexpected strong monopolar component. This component was necessary to explain the data.

In a second series of experiments, Riera et al. (2012) directly tested the dipolar assumption in the rat brain. They conceived a high-resolution EEG cap for the rat brain, specifically designed for this purpose (a quite impressive achievement in itself), and used standard dipolar source estimation techniques to estimate the underlying dipoles in cerebral cortex. This estimate was aided by a three-dimensional reconstruction of the rat cerebral cortex and electrode position using magnetic resonance imaging (MRI). The MRI images were used to constrain the location of the dipoles in cerebral cortex, as is routinely done in human EEG (Dehghani et al. 2010b). In addition, the laminar LFPs were simultaneously recorded using microelectrodes. By using an approach that takes into account

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[1] According to Kirchhoff's current law, the sum of the currents at any node of a circuit is zero, which implies that there cannot be any charge accumulation at any node of the circuit.

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[2] Note that this estimate of the different multipolar contributions is made based on a very simplified model of the LFP, and this estimate could be different with a more realistic model.

different multipolar configurations, the same result as above was obtained, namely that dipolar and higher order multipolar components were observed, but there was also a strong monopolar component in the data, thus confirming the estimates using microelectrodes.

Thus, using these two independent methods, which are both technically impressive, the authors succeeded in bringing decisive data that put into question the standard dipolar model of the EEG. More importantly, they inferred that the estimation of sources, if uniquely based on dipoles, can be flawed because the monopolar components are erroneously "absorbed" in the dipoles. If confirmed, this finding has potentially devastating consequences for the estimates of dipolar sources from the EEG or MEG. Indeed, there is evidence that the dipolar model cannot predict simultaneously recorded EEG and MEG signals, either during interictal activity (Huiskamp et al. 2004; Fernandes et al. 2005) or during normal rhythms such as sleep spindle oscillations (Dehghani et al. 2010 a,b).

Where to go from there? It is of course imperative to seek for confirmation of these results. An important property is that monopolar sources have a very different distance dependence than dipolar sources, fields generated by electric monopoles decay with the inverse of distance ($1/r$), while dipolar fields vary as the inverse of the squared distance ($1/r^2$) and thus attenuate much more steeply. As a consequence, estimates at different distances from the sources should reveal differences. Indeed, recent measurements seem to confirm that in some cases the distance decay of LFP amplitude unexpectedly follows $1/r$ profiles (Hunt et al. 2011), consistent with electric monopoles. This is important because if a given method to estimate neuronal activity from LFP and EEG assumes the wrong distance dependence, then this method will evidently provide wrong estimates.

Another way to test the presence of monopolar sources would be to use coregistered surface EEG and electrocorticogram to determine whether a unique set of dipolar sources can account for both signals, or if monopolar contributions should be assumed. It is also possible to estimate monopolar contributions from CSD profiles, as proposed recently (Bédard and Destexhe 2011).

Even more critical is how to explain the genesis of electric monopoles. If the neuron strictly obeys Kirchhoff's laws, then monopoles are impossible, because as soon as there is a current source, a dipole instantaneously appears (Fig. 1). Since in theory they are impossible but seem to be observed, what plausible physical explanations can be given?

A first possible cause of monopolar contribution is that neurons may not strictly obey Kirchhoff's laws.[3] According to the standard model, the charges are assumed to move instantaneously (infinitely fast), which gives rise to the fact that the return current appears immediately. However, in reality, there is an inertia time to charge movement, because the mobility of ions in a homogeneous electrolyte is finite and is considerably slower compared to electrons in a metal. For example, the mobility of Na^+ in sea water is of 5.19×10^{-8} $m^2 = sV$ (Hille 2001) and is of the same order for other ions such as K^+, Ca^{2+}, and Cl^- (Hille 2001). In contrast, the mobility of electrons in

copper is of 4.45×10^{-3} $m^2 = sV$ for a temperature of $298.15°K$ (Philip and Bolton 2002), which is $\sim$105 times larger than ion mobilities.

As a consequence, when ionic channels open (such as the postsynaptic currents indicated in Fig. 1), the setting of extracellular current and return current will not be instantaneous, and there will be a transient time during which charges will accumulate in the postsynaptic region. During this transient time, Kirchhoff's current rule does not apply (the local charge accumulation is contrary to Kirchhoff's current law), and the postsynaptic region may act as a monopole. After this transient time, the charge movement settles into a stationary regime, in which the currents are balanced, there is no charge accumulation, and the system obeys Kirchoff's laws. Thus, the dipole model would only apply to this stationary regime.[4]

Another possible contribution to monopolar effects is the resistance to the lateral movement of charges in the membrane. While this movement is also considered as instantaneous (charges are usually assumed to instantaneously reequilibrate), there is evidence that in fact, charges do not move instantaneously but take some time due to residual friction tangential to the membrane (Bédard and Destexhe 2008). This effect will also cause an inertia of charge movement, as above, and will contribute to the transient regime in which the currents are not balanced. Moreover, the complex morphology of neurons (dendrites, spines, and axons) will further reduce ionic mobility. Consequently, if a membrane current suddenly appears in a given region of cerebral cortex, it is not instantaneously equilibrated by an opposite current. There is a transient time in which the system is outside of equilibrium and during which Kirchoff's rules do not apply. During this transient time, it is possible that the extracellular electric field is dominated by monopolar components.

Further work is obviously necessary to first confirm the experimental observation of a strong monopolar component in neurons. Second, work is needed to develop in detail the theory to account for the genesis of monopolar current sources by neurons. One may need to profoundly revise the current theories, both at the level of single neuron cable theory, which entirely depends on Kirchhoff's laws, and at the level of population activity. If confirmed, the presence of monopolar sources in neurons will require to reevaluate electric field interactions between neurons (which may be stronger than expected), as well as methods to estimate neuronal sources from EEG or LFP data.

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[3] More generally, that for a given region of the neuron, the current entering is not equal to the current exiting that region, therefore causing accumulation of charges (positive or negative) in that region.

[4] The duration of this transient time depends on the diffusion time of charges in the dendrite. For a 1-nA current in a dendrite of 5-μm diameter, the mean drift velocity is $\sim$1 mm/s, so this transient time may indeed be significant.

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