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Commentary

Dangerous Phase

Steven J. Schiff

Krasnow Institute, George Mason University, Fairfax, VA, USA. E-mail: sschiff@gmu.edu

"Use a quiet reference." How many times have we heard this mantra during training or practice, interpreting electroencephalogram (EEG) tracings, or implanting intracranial electrodes? How many of us have used common reference EEG for synchrony studies in recent years? Far too many.

Perhaps one source of this problem is the number 104. This is the relatively small number of citations to the reference Fein et al. (1988), which should have put to rest any further use of referential EEG for coherence measurements. And in retrospect, a more careful reading by us of Nunez's (1981) text would have instructed us not to do this. How such warnings have managed to escape integration into common knowledge and practice is troublesome.

Electrical potentials are all measured with respect to other potentials. Technically, a potential difference is calculated by integrating the electrical field over a given path from one place to another—in EEG terms, we measure a potential with respect to another potential, measured at one or more electrodes. All EEG potential measurements reflect the paths used to measure those potentials, and do not directly reflect localized regions of the brain beneath one electrode. Worse, in scalp EEG, the layers of cerebrospinal fluid, dura, skull, and scalp serve to smooth, filter, spread out, and redirect currents generated within the brain so that the measured scalp potentials bear a rather tenuous relationship to the underlying (presumably dipole) current sources.

In calculating coherence, it is easy to show that if the potential differences are all made with respect to a common reference, then the amplitude of the reference can dominate the coherence estimate (Fein et al., 1988). In recent years, phase synchronization has been increasingly applied to analyze the dynamics of nonlinear systems (Pikovsky et al., 2000). In Guevara et al. (in this issue), we see the extension of Fein's results for phase coherency. The geometry of Fig. 1 in Guevara et al. should be imprinted on all of us—the amplitude of a common reference can dominate the calculated phase synchronization. There is far too much literature within the past decade that calculated phase synchronization from common referenced EEG.

The good news is that the fix to remove common reference artifacts is simple. The bad news is that the interpretation of reference-free synchronization results from brain signals requires considerable caution.

First, although one might be able to salvage useful data by examining the common reference EEG with care (Zaveri et al., 2000), one should probably never use the common referential EEG without reformatting. Subtracting the potentials from two nearby electrodes, each referenced to a common reference, will remove the common reference. This “biopolar” montage is reference-free, but one must bear in mind what such signals represent. Helmholtz understood this in his 1853 reciprocity theorem (clearly discussed by Nunez, 1981), which guides us to understand how a pair of electrodes will pick up dipole sources within a conductor. Such electrode pairs are sensitive to dipole location and orientation within the conductor. Hence, a given bipolar montage will completely miss dipoles with certain locations and orientations. Reformatting the EEG to give multiple different bipolar orientations such as transverse vs anterior–posterior (“double banana”) will help.

Average common referential EEG is another option, but as Guevara et al. (in this issue) note there are complications here. Physically, the surface integral of potentials over the outside of a conductor will be zero if all the dipoles and the current sources are contained within the conductor (an extension of Gauss’s law, Jackson, 1975; *see* EEG interpretations in Bertrand et al., 1985, Nunez and Srinivasan, 2005). If little current from the brain leaves the head, and if we were to place electrodes very close to one another and cover the entire head (including the base of the skull), the average common reference is adequate. In practice, however, this means that unless extensive head coverage is provided with high density EEG (>128 electrodes), the common average reference will likely be inadequate. The use of the standard 10-20 scalp EEG montage is not going to work here. Even with suitable electrode coverage, one should anticipate spuriously large coherencies from superficial dipoles at large interelectrode distances with the average common reference (Nunez et al., 1997). Calculating a common average reference from a selection of implanted grids, strips, and depth electrodes is not well supported geometrically. In a recent work, dynamically selecting the electrodes to average is potentially of value in dealing with artifacts (Orekhova et al., 2002), but one cannot hope to escape the underlying physics with any means short of better geometrical sampling.

Finally, one can use one of the forms of Laplacian derivations. A second spatial derivative, this montage strategy can be used to estimate divergence of current (current source) within the scalp, or reflected onto the dura or the image of the brain. Such calculations are reference-free, but again, must be interpreted with care. Laplacians calculated with nearest neighbor electrodes spatially filter EEG significantly, so that long-range (small wave number) characteristics are eliminated and coherencies at long-range are underestimated. Nevertheless, when properly performed, Laplacians give the best intermediate spatial range estimates of coherence.

So it is true. Acquiring the most advanced EEG equipment in the world and applying the most advanced signal processing techniques on the referential signals obtained will give junk measures of synchronization. With the above information, one can get around this problem, but only by using a combination of reference-free montages (bipolar, common average, and Laplacian), and interpreting the results with an understanding of the limitations of each approach.

Will supplanting EEG by MEG solve the issue? No—EEG and MEG signals measure different sources. Will using a more distant reference such as a toe, or the laboratory sink, be adequate? No, for all the reasons discussed by Nunez (1981). Will, as I have tried, the use of cerebellar midline screw reference electrodes in animal experiments or inverted (outward facing) strip electrodes in a subgaleal-location as a reference for human intracranial EEG be advantageous? Now I have considerable doubts.

Finally, one must remember that the calculation of correlation or coherency measures are also influenced by the frequency content of each signal when the data length sampled is relatively short. Although we have powerful methods to estimate the spurious coherence or correlation for uncoupled systems of a given finite data length (reviewed in Netoff and Schiff, 2002), we rarely apply such confidence limits to EEG correlations. An alternative approach is to bootstrap such confidence limits from a model of uncorrelated sources within the head (Nunez et al., 1997, 1999). The point is that the inference of synchrony through measures of correlation or coherence, whether phase or amplitude, requires that the numbers obtained are compared with reasonable null hypotheses that the signals might have come from an uncoupled system.

Perhaps the mantra should now be: "Use contrasting reference-free EEG montages, suitable statistical null hypotheses, and be prepared to deal with the complexity of interpreting the result."

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