Published in final edited form as:
Clin Neurophysiol. 2010 December ; 121(12): 2177–2180. doi:10.1016/j.clinph.2010.04.029.

REST: A Good Idea but Not the Gold Standard

Paul L. Nunez[*]

Kayser and Tenke (2010) provide a nice history and editorial review of the critical EEG reference electrode issue and critique of REST, *the reference electrode standardization technique*, apparently first implemented by Yao (Yao, 2001; Yao et al, 2005; Qin et al, 2010). For many years, EEG scientists seemed to insist (based on both word and deed) that if only some body location could be found with no active local sources, such reference location would allow for genuine reference-free recordings. This old idea has long been discredited in many publications using both simulations and genuine data (Rush and Driscoll, 1969; Nunez, 1981; Nunez and Srinivasan, 2006, Yao et al, 2007).

I will refer here to the *reference-free potential* or *nominal potential with respect to infinity*. The label “nominal” reminds us that even if it were possible to measure scalp potentials with respect to “infinity” (or a distant wall of the laboratory), such large potentials (measured in volts) would have no physiological relevance, being dominated by power line fields and other environmental sources. The “nominal potential with respect to infinity” is defined here as the potential with respect to infinity due only to sources generated by the brain. While we have often advocated the common average reference (AVE) as the best available reference option, Nunez and Srinivasan (2006) state, “…like any other choice of reference, the average reference provides biased estimates of reference-independent potentials…when used with large numbers of electrodes…it often performs reasonably well…” Thus, if AVE has actually become somewhat of a consensus “gold standard” as Kayser and Tenke (2010) suggest, it was evidently not because our advice was followed closely.

Here I address several caveats and areas of possible minor disagreement with REST advanced by Yao and colleagues and the Kayser and Tenke editorial. I begin with the bottom line:

- REST is an interesting and potentially useful approach to the EEG reference problem.
- Neither REST nor AVE can qualify as a “gold standard;” however, both seem to be superior to all other known references.
- Because the origins of error in these two approaches are somewhat different, each can serve as a partial check on the other. In other words, any EEG clinical or research outcome showing substantial material change when AVE is replaced by REST (or vice versa) is probably suspect.

Aside from artifact, AVE errors are due to (1) limited electrode density and (2) incomplete electrode coverage (sampling only the upper part of head). If these errors were fully eliminated (only possible in detached heads), AVE would provide the desired gold standard; that is, the

---

[*]Corresponding author, Cognitive Dissonance, LLC, 162 Bertel Drive, Covington, Louisiana 70433 USA, Tel: +1-985-893-4775, pnunez@tulane.edu.

nominal reference with respect to infinity. REST errors are also due to (1) electrode density and (2) electrode coverage, but suffer additional errors due to (3) head model uncertainty. The extra error origin (3) might seem to discourage implementation of REST and is perhaps the reason no one tried it earlier. But, this superficial view is misleading because the three error sources are correlated. In particular, the coverage error (2) is expected to become smaller as the head model improves. Thus, it is possible for REST (with error sources 1, 2, and 3) to be more accurate than AVE (with only the error sources 1 and 2) if the head model is sufficiently accurate for the particular (unknown) source distribution. In fact, in idealized simulations (Marzetti et al, 2007; Qin et al, 2010) where the head model used to estimate *G* is very similar to model used to estimate errors, REST outperforms AVE. From this argument we see that the choice between AVE and REST largely boils down to questions of *genuine* head model accuracy, leading to the following semi-technical discussion. I present here a simplified interpretation of the physical basis for REST (Yao, 2001; Qin et al, 2010) to address the model accuracy issue.

Scalp potentials $V(\mathbf{r},t)$ are generated by vector "mesosources," the millimeter or macrocolumn scale dipole moments per unit volume given the vector symbol $\mathbf{P}(\mathbf{r},t)$. Note that every small mass (voxel) containing brain tissue is likely to produce some source activity, although most voxel sources may make only negligible contributions to scalp potentials. The nominal scalp potential with respect to infinity may be expressed generally by the following integral over the entire brain volume *W* (Nunez and Srinivasan, 2006):

$$V(\mathbf{s},t)=\iiint_W \mathbf{H}(\mathbf{s},\mathbf{r})\cdot\mathbf{P}(\mathbf{r},t)dW(\mathbf{r}) \tag{1}$$

Alternately, this same potential may be expressed in terms of the scalar monopole sources:

$$V(\mathbf{s},t)=\iiint_W G(\mathbf{s},\mathbf{r})S(\mathbf{r},t)dW(\mathbf{r}) \tag{2}$$

Here $S(\mathbf{r},t)$ is source current per unit volume. Current conservation in the brain requires the constraint:

$$\iiint_W S(\mathbf{r},t)dW(\mathbf{r})=0 \tag{3}$$

All the complications of the volume conductor (both geometric and conductive) are accounted for by a Green's function, either **H** or *G*, which may viewed as an "inverse electrical distance" between sources and scalp; that is, larger *G* or smaller distance tends to result in larger scalp potentials if source strengths are fixed. Whereas any head model may employ a relatively simple **H** or *G*, the genuine Green's function is certain to be quite complicated because it depends on inhomogeneous and anisotropic tissue properties that are poorly known. Contrary to the apparent opinion of some, the accuracy of volume conduction calculations seems to be limited much more by minimal knowledge of the conductivity tensor in individual subjects than by computer power or mathematical sophistication.

In the following discussion, I avoid the important issues of artifact and numerical methods and focus only on the physics of volume conduction. For the sake of simplicity, I will employ Eq (2), which depends on the scalar Green's function rather than Eq (1). By approximating the integral by a sum, Eq (2) may be approximated by the following matrix multiplication to obtain the scalp potential due to monpolar sources:

$$V_s = G_s S \tag{4}$$

The subscript s indicates scalp location where potential is recorded. S is a column matrix with number of rows N equal to the (arbitrary) number of assumed “equivalent sources.” G_s is an $N \times M$ matrix, where M is the number of electrodes, excluding reference. The best fit solution for the equivalent sources is:

$$S = [\![G_s]\!]^{-1} V_s \tag{5}$$

Here $[\![G_s]\!]^{-1}$ is essentially the pseudo (Moore-Penrose) inverse matrix constrained by current conservation Eq (3). There are about a million possible mm scale sources (brain volume in mm^3) so the equivalent sources S will typically fail to provide genuine relationships to actual sources (Nunez, 1981;Yao, 2000;2001;Yao et al, 2004). In other words, the well worn reminder that “the inverse problem is non-unique,” represents a substantial understatement (Nunez and Srinivasan, 2006). The advantage of REST, however, is that it never confuses these fictitious equivalent sources with genuine sources; rather, sources are employed only as an intermediate step to estimate “reference-free” scalp potentials. The (reference) potential difference between any two scalp locations (s, R) may be expressed in matrix form:

$$V_{sR} = V_s - V_R \tag{6}$$

From Eqs (5) and (6), we obtain an estimate of the nominal scalp potential with respect to infinity at the scalp locations s in terms of the recorded (reference) potential difference V_{sR}:

$$V_s = G_s [\![G_s - G_R]\!]^{-1} V_{sR} \tag{7}$$

Equation (7) demonstrates the essence of REST. Note that these same methods can be used to estimate the potential distribution (nominal with respect to infinity) on the dura surface V_d, that is:

$$V_d = G_d [\![G_s - G_R]\!]^{-1} V_{sR} \tag{8}$$

Such dura imaging (aka “cortical imaging” or “de-blurring”) is often applied to EEG (Nunez et al, 1997). This later operation then raises the following question: If we really trust our head model, why should we even care about scalp potentials using Eq (7)? Why not just estimate dura potential using Eq (8), thereby obtaining a much better idea of brain source characteristics? Qin et al (2010) offer two plausible answers to this question. First, our EEG culture is based on years of experience with scalp potentials, insuring that such measure will stay with us a long time; thus, we require scalp potentials for making meaningful comparisons across laboratories. Second, the dura potential (V_d) errors due to limited sampling and head model uncertainty may be much larger than the corresponding errors in scalp potential V_s. To appreciate this possibility, consider the following example. A broad distribution of many cortical sources might be reasonably represented at the scalp by only a few equivalent sources S, especially in cases with minimal electrode coverage. Such simple fits are expected because it is easy to fit a smooth potential surface to a few widely separated points. But, the predicted dura potential due to these so-called “equivalent” sources might bear little relationship to the actual dura potential generated by the real sources.

Since the accuracy of REST, dura imaging, BESA, LORETA, and several other data transformation methods depends on head model accuracy, I offer the following critique. The most popular head model consists of 3 or 4 concentric spherical shells representing, brain, CSF, skull, and scalp tissue (Rush and Driscoll, 1969; Nunez, 1981; Nunez and Srinivasan, 2006). The spherical symmetry allows for relatively simple analytic solutions to the forward problem. On the other hand, this model is based on idealized spherical geometry and isotropic tissue properties. While some have claimed more accurate finite element or boundary element models based on MRI brain images, even models with perfect geometry (brain tissue surfaces) are severely limited by resistivity uncertainty. The resistance of any current path is proportional to the product of tissue resistivity (inverse conductivity) and distance. Even if the distance is known perfectly, brain resistivity can easily be in error by factors of 2 to 5 or more, as in skull. Furthermore, both the (3 layered) skull and white matter are known to be strongly anisotropic (direction-dependent resistivity). In summary, resistivity uncertainty seems to be a much more serious problem for head models than geometric errors.

Despite these limitations, simple head models can be extremely useful, typically by proving that many EEG analysis methods proposed over the past 50 years or so will NOT work. For example, the so-called quiet reference myth is easily discredited with simple models (Rush and Driscoll, 1969; Nunez, 1981; Nunez and Westdorp, 1994; Nunez and Srinivasan, 2006). Or, distortion by reference and volume conduction is shown to produce very large errors in scalp coherence estimates (Nunez et al, 1997, 1999; Srinivasan et al, 1996, 1998; Marzetti et al, 2007). Moderate head model inaccuracy does not change the central conclusions of these studies. Simulations using simple head models then provide a critical “filter” through which mathematical methods must first pass to be considered further by serious scientists. We must be continually reminded that *fancy mathematics can never trump physical principles*. The Qin et al (2010) study has passed this important first test by showing that REST works with simple head models and certain assumed source distributions, but its accuracy with read heads and other source distributions is unknown. For this reason, I suggest that REST and AVE be adopted as reference partners, at least until better information becomes available. After all, it is a simple matter to re-reference any data set by simple computer transformation.

Another EEG option discussed in the Kayser and Tenke editorial is the (reference-free) Laplacian, which provides complementary measures of brain dynamics, allowing for more robust estimates of changes in functional coupling with brain state changes using coherence or other measures of partial phase locking (Nunez, 1995; Srinivasan et al, 1996, 1998; Nunez et al, 1997, 1999; Nunez and Srinivasan, 2006; Marzetti et al, 2007). The scalp Laplacian acts as a band pass spatial filter with peak sensitivity to 3–6 cm scale synchronous cortical source regions (the very approximate diameter), whereas potentials are most sensitive to roughly the 5–15 cm scale. Complex adaptive systems for which brains provide the pre-eminent examples, typically exhibit nested hierarchies of structure and function (Nunez, 2010). Because neocortical dynamic behavior is highly complex with fractal-like features, dynamic measures are scale-sensitive. For example, coherence at one spatial scale or frequency band need not match coherence at another scale or band (Nunez, 1995; Nunez and Srinivasan, 2006; Nunez, 2010). Thus, scalp Laplacian and potential measures are complementary rather than competing measures of the brain dynamic behavior correlated with cognitive and clinical states.

I end my letter with a technical point that may impact further developments in the REST area. Rather than express scalp potential in terms of the monopole sources $S(\mathbf{r},t)$ and the scalar Green’s function $G(\mathbf{s},\mathbf{r})$, Qin et al (2010) have appropriately used Eq (1) involving dipole sources $\mathbf{P}(\mathbf{r},t)$ and the vector Green’s function $\mathbf{H}(\mathbf{s},\mathbf{r})$. For example, one such implementation assumes that all equivalent sources are radial (Yao and He, 2003), remembering that these are only equivalent sources not real sources. I don't expect the dipole and monopole approaches to necessarily yield identical results. Equation (1) is based on local current conservation, whereas Eq (3) assumes only full brain current conservation. While the dipole approach seems to be appropriate for cortical sources, the issue is somewhat clouded by the shunting influence of the skull and CSF layers, possibly allowing for synaptic return current from distant regions, that is, from multiple monopoles. Also, action potential sources in the myelinated corticocortical axons are essentially monopoles widely distributed along the fibers; their dipole and quadrupole representations are only valid at distances much larger than distances to head surfaces (Nunez and Srinivasan, 2006). Of course, these monopole sources could produce quite different potential maps on the dura that still might not substantially alter the estimated reference-free scalp potentials. Furthermore, given that heads are not isolated from bodies, the influence of applying Eq (3) to reference-free algorithms is unknown. My guess is that much of the current passing through the neck is low frequency artifact caused by the heart and other sources. The influence of such artifact on REST or AVE is unknown; there are still many things left to study but Yao and colleagues seem to be on the right track.

References

Kayser J, Tenke CE. In search of the Rosetta Stone for scalp EEG: Converging on reference-free techniques. Clin Neurophys. 2010 This Issue.

Marzetti L, Nolte G, Perrucci MG, Romani GL, Del Gratta C. The use of standardized infinity reference in EEG coherency studies. NeuroImage 2007;36:48–63. [PubMed: 17418592]

Nunez, PL. Electric Fields of the Brain: The Neurophysics of EEG. First Edition. New York: Oxford University Press; 1981.

Nunez, PL. Neocortical Dynamics and Human EEG Rhythms. New York: Oxford University Press; 1995.

Nunez, PL. Brain, Mind, and the Structure of Reality. New York: Oxford University Press; 2010.

Nunez PL, Westdorp AF. The surface Laplacian, high resolution EEG and controversies. Brain Topogr 1994;6:221–226. [PubMed: 8204409]

Nunez, PL.; Srinivasan, R. Electric Fields of the Brain: The Neurophysics of EEG. Second Edition. New York: Oxford University Press; 2006.

Nunez PL, Srinivasan R, Westdorp AF, Wijesinghe RS, Tucker DM, Silberstein RB, Cadusch PJ. EEG coherency I: Statistics, reference electrode, volume conduction, Laplacians, cortical imaging, and interpretation at multiple scales. Electroencephalogr Clin Neurophysiol 1997;103:516–527. [PubMed: 9402882]

Nunez PL, Silberstein RB, Shi Z, Carpenter MR, Srinivasan R, Tucker DM, Doran SM, Cadusch PJ, Wijesinghe RS. EEG coherence II: Experimental measures of multiple EEG coherence measures. Clin Neurophysiol 1999;110:469–486. [PubMed: 10363771]

Qin Y, Xu P, Yao D. A comparative study of different references for EEG default mode network: the use of the infinity reference. Clin Neurophysiol. 2010 This Issue.

Rush S, Driscoll DA. EEG electrode sensitivity: an application of reciprocity. IEEE Trans Biomed Eng 1969;16:15–22. [PubMed: 5775600]

Srinivasan R, Nunez PL, Tucker DM, Silberstein RB, Cadusch PJ. Spatial sampling and filtering of EEG with spline-Laplacians to estimate cortical potentials. Brain Topogr 1996;8:355–366. [PubMed: 8813415]

Srinivasan R, Nunez PL, Silberstein RB. Spatial filtering and neocortical dynamics: estimates of EEG coherence. IEEE Trans Biomed Eng 1998;45:814–825. [PubMed: 9644890]

Yao D. High-resolution EEG mappings: a spherical harmonic spectra theory and simulation results. Clin Neurophysiol 2000;111:81–92. [PubMed: 10656514]

Yao D. A method to standardize a reference of scalp EEG recordings to a point at infinity. Physiol Meas 2001;22(4):693–711. [PubMed: 11761077]

Yao D, He B. Equivalent physical models and formulation of equivalent source layer in high-resolution EEG imaging. Phys Med Biol 2003;48:3475–3483. [PubMed: 14653557]

Yao D, Yin Z, Tang X, Arendt-Nielsen L, Chen ACN. High-resolution electroencephalogram mapping: scalp charge layer. Phys Med Biol 2004;49:5073–5086. [PubMed: 15609559]

Yao D, Wang L, Oostenveld R, Nielsen KD, Arendt-Nielsen L, Chen AC. A comparative study of different references for EEG spectral mapping: the issue of the neutral reference and the use of the infinity reference. Physiol Meas 2005;26(3):173–184. [PubMed: 15798293]

Yao D, Wang L, Arendt-Nielsen L, Chen AC. The effect of reference choices on the spatio-temporal analysis of brain evoked potentials: the use of infinite reference. Comput Biol Med 2007;37(11): 1529–1538. [PubMed: 17466967]