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Editorial

Informing dose design by modeling transcutaneous spinal direct current stimulation

See Article, pages 2260–2270

Computational modeling of neuromodulation by electrical stimulation is necessary to inform clinical trial design and to describe the underlying mechanism of action (Ahmed, 2011, 2014; Bikson and Datta, 2012; Rahman et al., 2013). These models characterize the relationship between stimulation dose (the parameters controlled by the operator; Peterchev et al., 2012) and the resulting current flow and neuromodulation in order to advise electrotherapy design (Sunderam et al., 2010; Bikson et al., 2012). In this issue of Clinical Neurophysiology, Parazzini et al. (2014) report the first model predicting current density (J) generated by transcutaneous spinal direct current stimulation (tsDCS) in humans.

We review important tsDCS model features employed by Parazzini et al. and suggest others that may influence selection of dose. Incorporating additional model features may enhance precision but at the cost of technical complexity and computational resources. It is therefore useful to evaluate the utility of the model features by considering their final effect, if any, on dose design. Ongoing data from human trials (Cogiamanian et al., 2008, 2011; Kitano and Koceja, 2009; Winkler et al., 2010; Lim and Shin, 2011) can serve for model validation.

Parazzini et al. adapted three realistic human models from the "Virtual Population" (Christ et al., 2010) that were based on high-resolution MRIs of healthy volunteers and developed with computer-aided design representation of organ surfaces. Parazzini et al. modeled three different electrode montages, each with the anode over the spinal process of the tenth thoracic vertebra. The three cathode locations were: above the right arm, over the umbilicus and over Cz. The injected current was held constant across all montages at 3 mA. Electrodes were modeled as rectangular pads of dimensions $5 \times 7.5\ cm^2$ or $5 \times 9.5\ cm^2$ within rectangular sponges of dimensions $7 \times 8\ cm^2$ or $7 \times 10\ cm^2$, for active and reference electrodes, respectively.

The models developed by Parazzini et al. highlight important features for subsequent modeling work in tsDCS. To represent the spinal anatomy, it was necessary to precisely segment the bone, soft, and nervous tissues around the spinal cord, and thus include a wide range of tissues with varevaluate the utility of the model features by considering their final ied conductivity. This detail is then multiplied by the inter-individual differences, the impact of which was considered by modeling three subjects.

Models may be used to optimize dose for maximum intensity and/or preferred focality at a given target (Dmochowski et al., 2011). For tsDCS applications such as rehabilitation, these considerations may naturally focus on relative neuromodulation of spinal cord segments across the cervical, thoracic, lumbar and sacral/coccygeal levels while taking into consideration the function of the associated downstream peripheral nerves (Ahmed, 2011, 2014; Aguilar et al., 2011). The use of percentile-based metrics, coefficient of variation and other measures of dispersion and numerical noise reduction across the different levels of the vertebral column may facilitate dose design in this regard.

The intensity and focality the of current density, or more directly electric field (E-Field), provides a basic estimate of neuromodulation (Bikson et al., 2013) but as with other nervous system structures (Chan and Nicholson, 1986; Rahman et al., 2013, 2014; Salomons, 1992) the orientation of the E-field with respect to cell morphology is also critical to describe cellular polarization and the associated functional effects (Kabakov et al., 2012; Rahman et al., 2013; Ranck, 1975). In the spinal cord, the white matter afferent/efferent tracks are, to first order, orthogonal to the spinal nerves. For tsDCS, representation of E-Field magnitude in the longitudinal and transversal components (relative to the spinal cord) may provide a basic approximation of influence on these cellular targets. These may then be aggregated at the different levels of the vertebral column (e.g., Parazzini et al. used the ratio of longitudinal and transversal components as a proxy).

In addition to the features of the computational model used by Parazzini et al., other features possibly affecting stimulation dose design may be considered in tsDCS modeling. Peripheral and cranial nerve stimulation may substantially influence the physiological outcome of transcranial direct current stimulation (tDCS) but require special attention because of limited MRI resolution (typically on the order of 1 mm^3 voxel size in more recent publications).

Since myelinated white matter tracks comprise the much of the spinal cord, introducing tissue anisotropy in the spinal cord model (as has already been applied in some cranial modeling; Shahid et al., 2013, 2014; Wagner et al., 2014) may substantively change tsDCS model output. Parazzini et al. claimed, based on the models adapted from the "Virtual Population", the longitudinal component of the J generally dominates across the spinal column, a result that may be magnified by inclusion of spinal anisotropy.

Accurate description of the path of current flow is also important. The spinal cord and protruding spinal nerve fibers are surrounded by an irregular spectrum of tissue types (CSF, fat, ligament, bone, muscle, et cetera), some of which have a fiber-like

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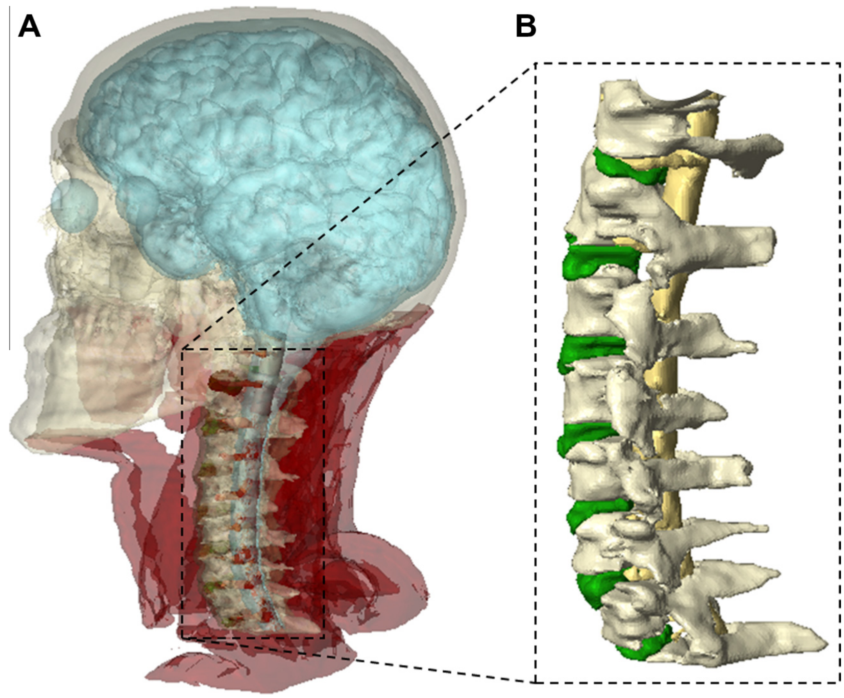

Fig. 1. 3D Rendering of cranial and cervical tissue segmentation based on 1 mm resolution MRI scan for FEM modeling of transcutaneous direct current stimulation. (A) Including transparent masks: bone, muscle, ligament, CSF, WM, GM and opaque masks: spinal cord, spinal nerves, intervertebral disks. (B) Including opaque masks: spinal cord and spinal nerves, bone, intervertebral disks. Tissue variability (intra- and inter-individual differences) and conductivity specificity present highly sensitive variables in tsDCS modeling. Structural regularity and directionality of the spinal cord suggest substantive anisotropic effects. Renderings retrieved from manuscript under development from Toshev et al.

regularity in composition that may require anisotropic model amendments themselves (Fig. 1). It will be instrumental to consider (with respect to electrode polarity) the passage of current beginning from the skin on the surface of the back through all the channels serving as points of entry to the spinal cord. This, in turn, will be useful to develop dose and montage optimization heuristics for tsDCS clinical trials (Hamid and Hayek, 2008; Nitsche et al., 2008; Brunoni et al., 2012; Datta et al., 2012; Capogrosso et al., 2013; Guleyupoglu et al., 2013).

As noted by Parazzini et al., the substructure within the spinal cord itself also presents a challenge to tsDCS modeling. The H-shaped central grey matter and the motor (ventral)/dorsal (sensory) axonal tracts appear at the limit of the resolution of current MRI-based tDCS modeling work. *A priori* information about sub-mm anatomy and cellular morphology can be used to enhance modeling precision beyond MRI scan resolution. Ultimately, finer grained segmentations of these substructures may improve the fidelity of the model output.

Finally, there has been modeling for invasive spinal stimulation using a compartment model approach where individual neurons and processes are represented (Capogrosso et al., 2013; Hernandez-Labrado et al., 2011). Such an approach depends on significant morphological and membrane biophysics data, with complexity quickly scaling with increasing network size (McIntyre et al., 2004). Further investigation will show how the simplified approaches indicated above, ranging from E-field intensity maps (under quasi-uniform assumption), to spinal segment level longitudinal/orthogonal E-Field component distributions, to approaches based on gross representation of nerve fibers with anisotropic conductivity, can provide sufficient information for the purposes of tsDCS dose selection and optimization.

The progression of tsDCS as an effective therapeutic modality in the treatment of movement disorders and neurorehabilitation depends on a series rigorous clinical trials. With a near infinite combination of dose designs and trial protocols, the evolution of this clinical work will greatly benefit from effective tsDCS models.

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