Electrical impedance myography: a critical review and outlook

Benjamin Sanchez, PhD[1], Orjan G. Martinsen, PhD[2,3], Todd J. Freeborn, PhD[4], and Cynthia M. Furse, PhD[1]

[1]Department of Electrical and Computer Engineering, University of Utah, Salt Lake City, Utah 84112, USA.

[2]Department of Physics, University of Oslo, 0371 Oslo, Norway.

[3]Department of Clinical and Biomedical Engineering, Oslo University Hospital, Oslo 0372, Norway.

[4]Department of Electrical and Computer Engineering, The University of Alabama, Tuscaloosa, Alabama 35487, USA.

ABSTRACT

Electrical impedance myography (EIM) technology is finding application in neuromuscular disease research as a tool to assess muscle health. Correlations between EIM outcomes, functional, imaging and histological data have been established in a variety of neuromuscular disorders; however, an analytical discussion of EIM is lacking. This review presents an explanation for clinicians and others who are applying EIM and interpreting impedance outcomes. The background of EIM is presented, including the relation between EIM, volume conduction properties, tissue structure, electrode configuration and conductor volume. Also discussed are technical considerations to guide the reader to critically evaluate EIM and understand its limitations and strengths.

Address correspondence to: Dr. Benjamin Sanchez, Sorenson Molecular Biotechnology Building, Office 3721, 36 South Wasatch Drive, University of Utah, Salt Lake City, UT 84112, USA, phone: (801) 585-9535, email: benjamin.sanchez@utah.edu.

Keywords: electrical impedance myography, volume conduction properties, near- and far-field potentials, muscle.

Highlights:

- Electrical impedance myography (EIM) measures the volume conduction properties (VCPs) of the bulk of the muscle.
- Here we introduce surface and needle EIM approaches and discuss their limitations and strengths.
- The VCPs can serve as standardized, quantitative and objective electrophysiological biomarker of muscle.

What is electrical impedance myography?

Electrical impedance myography (EIM) is a specific bioimpedance application based on recording the voltage resulting from the application of a weak, high-frequency electrical current across a region of muscle without inducing myofiber or neuronal action potentials (Grimnes and Martinsen, 2014). The relationship between current and voltage signals reflects the exogenous electrical conduction property of the bulk of the muscle (Sanchez and Rutkove, 2017a,b). These volume conduction properties (VCPs) measure how strongly muscle resists or conducts alternating electric current and how capable is muscle to store electric charge within itself. They are determined by two physical quantities: the conductivity and the relative permittivity (Duck, 1990). Alterations in the internal composition and structure of diseased muscle including denervation, atrophy, and reinnervation in amyotrophic lateral sclerosis (ALS) for example will result in an imbalance of the ionic content and membrane stability, which will affect the conductivity and the relative permittivity of muscle. The hypothesis supporting EIM is that alterations affecting the VCPs of diseased muscle can be interrogated *indirectly* by measuring electrical impedance data (i.e., resistance and reactance).

Despite 3 decades after the first use of EIM methods for neuromuscular evaluation in Duchenne dystrophy (Noshiro et al., 1993), remarkably, VCPs of diseased human muscle have not been reported in the literature yet. As we will discuss below, there is a good explanation for this seeming oversight. But first, as the reader may not be familiar with the relationship between an EIM test and the actual VCPs of muscle, we draw an analogy with the nerve conduction velocity test. In the nerve conduction velocity test, the time it takes for impulses to propagate down a neural pathway is regulated by the ability of the nerve to conduct electricity as well as the distance between stimulating and recording electrodes. As shown in Figure 1 A, to calculate the nerve conduction velocity, the distance between electrodes is divided by the impulse latency.

In this analogy (Figure 1 B), the resistance and the reactance data measured with an EIM test are equivalent to the latency; the EIM electrodes' total length has the same role; and the VCPs of muscle (i.e., the physiological factor normal or altered by disease or injury) represent conduction velocity. In a nerve conduction velocity test, latency in itself has no value since it depends on the distance between electrodes. Likewise, resistance and reactance data obtained in an EIM test have also limited value since they change with the distance between electrodes (Sanchez et al., 2016) and thus cannot be universally standardized, for example, to serve as a biomarker of disease progression and therapy effect as in (Rutkove et al., 2017a). Conversely, the VCPs of muscle are true physical properties of muscle that provide quantifiable and objective data on a standardized and universal scale and, just like the conduction velocity, they are not impacted by methodological effects such as the electrode spacing.

Hence, we face a fundamental question: *If resistance and reactance values directly measured with an EIM test are not true muscle properties, why have not the VCPs from the bulk of the human muscle been reported instead?* Having done the latter, it would had shed light upon the actual hypothesis that supports the use of EIM methods for neuromuscular evaluation, namely, if impedance changes in myopathic and neurogenic conditions reported in the literature were indeed caused by changes in VCPs of muscle and not because of other confounding factors affecting the measurement. Further, if the measurement principles of an EIM test are analogous to a nerve conduction velocity test, then *why the electrodes' separation are not divided by the impedance recorded in EIM in order to calculate the VCPs?* As explained below, measuring impedance data is a much simpler task compared to the process of calculating the true physical VCPs of the muscle that produced such impedance data.

What does electrical impedance myography measure?

The causal factor that EIM aims to measure are the constituent VCPs of diseased muscle, their alteration with disease progression and their change with therapy. The conductivity (n.b., not the resistance) is the physical property that measures the ease with which electric charge is transported through the muscle. The relative permittivity (n.b., not the reactance) is the physical property that measures the ability of muscle to store and release electromagnetic energy (Rutkove, 2020). The conductivity and the relative permittivity span across the entire frequency spectrum and they change in three major steps, each step related to specific relaxation mechanisms associated to anomalous electrical and physical behavior of molecules in diseased muscle (Supplementary Figure 1) (Schwan, 1984).

Resistance and reactance data directly measured with an EIM test arise from a complex interaction of the conductivity and the relative permittivity properties as well as their directional and frequency dependence. As an example, fatty infiltration in Duchenne dystrophy would expect to produce a net decrease of the extracellular conductivity and increase the relative permittivity of muscle. A contrary example is with increased muscle conductivity would originate due to the accumulation of fluid with high ionic strength such as interstitial edema after traumatic muscle injury. Predicting changes in resistance and reactance data in these simplified states is not straightforward since these depend on both conductivity and relative permittivity properties at the same time in a non-trivial way. To be able to separate changes in the VCPs from impedance data and remove methodological effects, it is required to have a physical model describing the propagation through the muscle of the electrical current applied during the EIM test. Once this relationship is established through a biophysical model, it may be possible to invert the resistance and reactance data –a mathematical concept broader than a simple division as in the calculation of the nerve conduction velocity–, and calculate the VCPs of muscle.

In science, the process of calculating the causes from the observations is known as solving an *inverse problem* (Figure 1). Taking a page out of mathematician Carl Jacobi's maxim "*Invert, always invert*" and Sherlock Holmes " ... *There are few people, who, if you told them a result, would be able to evolve from their own inner consciousness what the steps were which led up to that result. This power is what I mean when I talk of reasoning backward, or analytically*" (Conan Doyle, 1887), to calculate the conductivity and the relative permittivity properties (i.e., the causal factors) requires a model to "*invert*" or "*reason backward*" the measured resistance and reactance (i.e., the observation recorded). Note the calculation of the conduction velocity is an example of a simple inverse problem in which the model is the equation of linear motion (i.e., velocity equals space over time).

If inverting the impedance proves too difficult or if the model adopted fails to capture the main anatomical and experimental features, then impedance measured with an EIM test may be worthless in terms of measuring the conductivity and the relative permittivity properties of muscle and associated pathological effects.

How is electrical impedance myography performed?

Next, we discuss three EIM approaches. Typically, alternating current varying between 10 to 1,000 kHz is applied using a dedicated pair of current electrodes. Special care must be taken above this upper frequency since the combination of inductive and parasitic effects affecting the cables connecting the electrodes can lead to significant impedance artifacts. The voltage generated is then recorded by a different pair of sensing electrodes. This 4-electrode configuration is the most common measurement approach, although it is possible to increase the number of electrodes to permit more focused interrogation of

muscle itself.

Sections below show how an EIM test can provide the VCPs of muscle or can lead to significant errors when the assumptions on which these approaches are based are not experimentally met. To help the reader apply the concepts presented, the conductivity and the relative permittivity calculations including their directional dependence –a concept known as electrical anisotropy–(Gielen et al., 1984; Epstein and Foster, 1983; Gielen et al., 1986; Roth et al., 1988; Hart et al., 1999) for ex vivo and in vivo needle EIM approaches have been implemented in an Excel file made available in the supplementary material.

Electrical impedance myography on excised muscle

This is the standard EIM approach to calculate ex vivo muscle VCPs from muscle resistance and reactance data. It requires measuring an excised muscle slab using a dielectric cell (Figure 2). This method provides a highly controlled setup thus making possible to have precise tissue geometry and dimensions necessary for simplifying the calculation of the VCPs of the sample (Sanchez et al., 2014). The first compendium of ex vivo VCPs data made available online from murine models confirmed these properties change in a unique way with disease progression (Nagy et al., 2019). However, due to the invasiveness, the technique has limited clinical use. Another important limitation of measuring muscle VCPs on excised muscle is the inability to follow the natural progression of diseased muscle VCPs because of inherent sampling limitations.

Surface electrical impedance myography

A surface EIM test employs surface electrodes in contact with the skin placed above the muscle of interest. In the first clinical studies, gel-adhesive silver/silver chloride were placed on the dorsum of hands and feet to apply current and then measure the voltages of upper and lower muscles (Rutkove et al., 2005). Later, this measurement configuration changed to reduce data artifacts due to simple postural and anatomical variations between subjects. More recent studies have employed dry metal-plate electrodes embedded in a hand-held device for practical convenience and also to mitigate skin-stretch motion artifacts and misalignment artifacts when positioning wet electrodes. Metal electrodes have shown to be valuable in (pre-)clinical studies because they can be easily machined in a small form factor necessary for measuring relatively small muscles (Li et al., 2012). However, a major limitation of this approach includes a poor electrical interface between the outer layer of the skin and the metal electrodes, which might introduce noise and contact artifacts rendering multi-frequency impedance values useless (Grimnes and Martinsen, 2007).

Surface EIM test is undoubtedly attractive for its non-invasiveness and convenience; however, similarly to surface electromyography (EMG), surface impedance recordings are able to provide only a limited assessment of muscle condition. Limitations of resistance and reactance data recorded with a surface EIM test include lack of: (1) location specificity to narrow down the region/depth being measured, (2) tissue specificity (i.e., skin and subcutaneous fat tissues affect the readings), and (3) sensitivity to detect muscle changes (Rutkove et al., 2017b). While useful in certain contexts, these fundamental limitations prevent today surface EIM approaches of addressing basic electrophysiological and pathological related questions at the level of individual myofibers or motor units.

To date, most efforts have focused on correlating surface impedance data with functional, electrophysiological, imaging and histological outcomes, to compare this attribute against other measurement considered directly clinically relevant (Rutkove et al., 2014; Hamel et al., 2019). A surface EIM test thus can produce data that fulfill a clinical purpose (e.g., change over time in a progressive disease and have measurement qualities that compare to such clinically relevant endpoints to a test that is

part of the patient's standard care) (Rutkove et al., 2007). Although clinically valuable, statistical models not supported by physical principles do not provide a sounding physiological explanation for interpreting the source originating those changes and understand their relation to the VCPs of muscle and underlying pathology (Kapur et al., 2018a,b). In addition, impedance data sets used for training and testing statistical models are often not publicly available, which makes obtaining reproducible model results by other researchers a difficult task.

Here, we discuss the simplest physical model for interpreting surface resistance and reactance data (Rutkove et al., 2017b). The model neglects skin tissue and considers that the surface electrodes are in direct contact with the subcutaneous fat tissue with constant thickness. Further, the anisotropy of subcutaneous fat and muscle tissues are neglected by considering that the current for EIM measurement flows in the same way in any recording site within the tissue (Kwon et al., 2019b).

As basic as this theoretical abstraction is of an actual surface EIM test, it is already impossible to invert the measured impedance and derive an analytical expression to calculate the VCPs of the muscle. And if it was possible, it would be necessary to actually know the thickness of the subcutaneous fat tissue and its VCPs, two additional unknown parameters in the model. Considering a more realistic scenario including additional anatomical features such as the skin or the anisotropy of the muscle would only make the process of calculating the VCPs even more difficult by adding more unknown parameters to the model. Because of the mathematical difficulty, there is a lack of knowledge on how to formally calculate the VCPs of muscle and their anisotropy after a surface EIM test (Kwon et al., 2019c). Subsequently, previous surface EIM studies including (Garmirian et al., 2009; Li and Rutkove, 2012; Schwartz et al., 2015; Rutkove et al., 2016, 2017a) that attempted to remove artifacts introduced by subcutaneous fat tissue or to calculate the electrical anisotropy of muscle generated empirical results that cannot be verified or disproved by physical laws.

Further, depending on the size of the muscle studied compared to the surface electrodes' array, the electrical current applied will flow through other tissues in addition to skin and subcutaneous fat and will be affected by the finite-shape and changes of the muscle conductor volume, ultimately impacting surface impedance values in unpredictable ways. Although a repeatable surface EIM test affected by skin, subcutaneous fat and/or the finite-shape of the limb or muscle could provide self-consistent and reproducible impedance data, data would no longer be specific to the muscle of interest and the data itself may have little or no value in relation to the actual VCPs of the muscle under investigation and underlying pathology (Supplementary Figure 2). Note, the scientific premise supporting EIM would not be fulfilled in this case.

Needle electrical impedance myography

When EIM was coined to refer to the assessment of neuromuscular disorders, no terminology distinction was made to the use of this technology (Rutkove, 2009). However, in the same way that there exist two EMG modalities, there are two *in vivo* EIM approaches available: surface and needle. Similarly to standard needle EMG, an EIM needle that is inserted through the patient's skin into the muscle can provide a much richer electrical dataset than its surface non-invasive counterpart (Kalvøy et al., 2009, 2010). The needle EIM approach discussed here assumes four monopolar EMG needles inserted into the muscle. Unlike surface-based approaches, the VCPs can be calculated from measuring the impedance of muscle with the EIM needle array in the longitudinal and transverse configurations. We have recently developed a more advanced needle which integrates all four electrodes required for EIM measurement along the barrel near the tip of the needle (Figure 3), which effectively reduces the number of needle insertions (Kwon et al., 2017, 2018, 2019a). However, due to the mathematical complexity, the inversion

algorithms require multiple steps and are beyond the discussion of this review.

The spatial resolution of a needle EIM test enables simultaneous VCP data co-localization with EMG at the same recording site, a variant termed as needle impedance-EMG or iEMG (Kwon et al., 2018). Another advantage of having the needle shaft insulated throughout its entire length for EIM application is that the electrical interference and thicknesses of intermediate skin and subcutaneous fat tissues then do not contaminate resistance and reactance data when measuring either shallow or deep muscles. Unlike a surface EIM test, a needle EIM test is also robust against artifacts due to the finite-shape and volumetric alterations of the conductor volume, for example, caused by simple postural changes or changes in muscle size unrelated to disease or drug effect. Also, the contribution of muscle VCPs in needle impedance data is >97% (Kwon et al., 2017, 2018), whereas in a surface EIM test is <30% (Rutkove et al., 2017b).

Once inserted into the muscle, the needle is passed through different regions of the tissue to obtain muscle information at rest of myofibers and their microenvironment. Needle EIM during contraction can also provide information on the contractile apparatus of the muscle including abnormalities in excitation-contraction coupling. Adding more electrodes into the shaft of the needle has the potential to image the inside of the muscle and visualize the presence of interspersed extracellular inhomogeneities, a different modality termed as needle electrical impedance imaging (Rutkove et al., 2018). Needle EIM poses little risk to patients of serious adverse events and in the future it could be tolerated like needle EMG (Preston and Shapiro, 2002); however, it has limitations in that it does require inserting a needle into the muscle. Also, bleeding near the electrodes can interfere with the propagation of electric current for intramuscular impedance measurement.

What is electrical impedance myography good for?

The clinical value of the VCPs of muscle determined from EIM test for neuromuscular assessment can serve two purposes. Firstly, knowing the VCPs of muscle can expand our understanding of the electrogenesis and propagation of electrical activity through the bulk of the muscle affecting EMG and motor conduction studies. The VCPs of the bulk of the muscle are determined by the presence of capacitive cellular membranes and conductive fluids and tissues in the extracellular space. Alterations in the VCPs between the source and a distant recording electrode will exert strong frequency-dependent filtering effects on the morphology (amplitude, latency and duration) of near- and far-field potentials (Kimura et al., 1986; Dumitru and King, 1991; Stegeman et al., 1997). For example, biophysical models predict that an accumulation of electrical charge in the bulk of muscle measured by the relative permittivity property would produce a net increase of motor unit potential's amplitude and latency recorded compared to healthy muscle. An increase in the conductivity property due to the accumulation of interstitial fluid with high ionic strength would have the opposite effect and attenuate the motor unit potential's amplitude (Supplementary Figure 3). Due to the dependence of the conductivity and relative permittivity properties with frequency (Supplementary Figure 1), high frequencies content is visible only when the recording electrodes are immediately adjacent to the nerve and muscle cells (i.e., the source of electrical activity), whereas low frequency events are attenuated less by the VCPs with distance and can propagate over large distance of the extracellular media (Bédard et al., 2004). Secondly and unlike resistance and reactance values, the VCPs values of muscle are universally standard on an absolute scale. They are also quantitative and objective electrical data that can serve both as a longitudinal and as a diagnostic biomarker of muscle associated to alterations in muscle structure and composition in diseased muscle (Figure 4) (Nagy et al., 2019).

Conclusions and future directions

Lord Kelvin once said "*... when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot express it in numbers, ... you have scarcely, in your thoughts, advanced to the stage of science, whatever the matter may be*" (Thomson, 1883). Despite all the studies made over the last two decades showing impedance changes recorded with surface EIM in diverse diseases and changes with progression reviewed in (Rutkove and Sanchez, 2018), we still do not know how to "*express with numbers*" what surface EIM is supposed to measure. Subsequently, we do not know whether those changes in measured surface impedance values were uniquely caused by changes occurring in the underlying VCPs of muscle in those conditions or, if instead, they were the result of an interference from confounding sources such as changes in the conductor volume, skin or subcutaneous fat tissues underneath the electrodes. In spite the clinical progress applying surface EIM, the result today is a lack of scientific knowledge of VCPs of human muscle –i.e., the actual electrophysiological properties of muscle altered by disease or injury–, including their dependence with frequency of electrical current, sex, age, disease progression or therapy. While we have recently made the first inroads towards separating subcutaneous fat from impedance data recorded with a surface EIM test (Kwon et al., 2019c), the advent of needle EIM will allow one to measure today the VCPs of muscle in an analogous fashion to needle EMG (Kwon et al., 2017, 2018, 2019a).

New needle EIM technology has the potential to broaden our scientific understanding of alterations in the electrical conduction properties of diseased muscle. The successful adoption of needle EIM technology in the electrodiagnostic laboratory over the next years will require the use of clinically-approved systems capable to perform automated impedance and EMG data acquisition. In parallel with the development of instruments, associated algorithms, and standardization of measurement protocols, practitioners will need to get familiar with impedance, acquire new scientific knowledge and skills to perform a needle EIM test properly and minimize sources of artifact. New needle EIM technology obtained has the prospect of opening an entirely new realm of neuromuscular diagnostics beyond that possible with surface approaches and greatly enhancing already existing standard clinical neurophysiology.

Conflict of interest statement

Dr. Sanchez has equity and serves a consultant and scientific advisor to, Haystack^{Dx} Inc., Ioniq Sciences Inc., and B-Secur Ltd. Haystack^{Dx} has an option to license patented impedance technology of which Dr. Sanchez is named as an inventor. He also serves as a consultant to Myolex Inc., Impedimed Inc., Texas Instruments Inc., and Happy Health Inc., companies that develop impedance related technology for consumer, research and clinical use. This study did not employ any relevant company technology.

Acknowledgments

This work was funded by the National Institutes of Health grant R41 NS112029-01A1 (BS). The authors would like to thank Dr. Rob S. MacLeod from the Scientific Computing and Imaging Institute, Biomedical Engineering Department, Dr. Mark B. Bromberg from the Department of Neurology at University of Utah, Salt Lake City, Utah, and Dr. Seward B. Rutkove from the Department of Neurology at Beth Israel Deaconess Medical Center, Boston, Massachusetts, for their comments on an early version of this work.

References

Bédard, C., Kröger, H., and Destexhe, A. Modeling Extracellular Field Potentials and the Frequency-Filtering Properties of Extracellular Space. *Biophys. J.*, 2004, 86(3):1829–1842.

Conan Doyle, A. *A study on Scarlet*. 1887.

Duck, F. A. Electrical Properties of Tissue. In *Phys. Prop. Tissues*, pages 167–223. Elsevier, 1990. ISBN 9780122228001.

Dumitru, D. and King, J. C. Far-field potentials in muscle. *Muscle Nerve*, 1991, 14(10):981–989.

Epstein, B. R. and Foster, K. R. Anisotropy in the dielectric properties of skeletal muscle. *Med. Biol. Eng. Comput.*, 1983, 21 (1):51–55.

Garmirian, L. P., Chin, A. B., and Rutkove, S. B. Discriminating neurogenic from myopathic disease via measurement of muscle anisotropy. *Muscle Nerve*, 2009, 39(1):16–24.

Gielen, F. L. H., Wallinga-de Jonge, W., and Boon, K. L. Electrical conductivity of skeletal muscle tissue: Experimental results from different muscles in vivo. *Med. Biol. Eng. Comput.*, 1984, 22(6):569–577.

Gielen, F. L. H., Cruts, H. E. P., Albers, B. A., Boon, K. L., Wallinga-de Jonge, W., and Boom, H. B. K. Model of electrical conductivity of skeletal muscle based on tissue structure. *Med. Biol. Eng. Comput.*, 1986, 24(1):34–40.

Grimnes, S. and Martinsen, Ø. G. Sources of error in tetrapolar impedance measurements on biomaterials and other ionic conductors. *J. Phys. D. Appl. Phys.*, 2007, 40(1):9–14.

Grimnes, S. and Martinsen, O. G. *Bioimpedance and Bioelectricity Basics*. Academic Press, 3rd edition, 2014. ISBN 0123740045.

Hamel, J., Lee, P., Glenn, M. D., Burka, T., Choi, I., Friedman, S., Shaw, D., McCalley, A., Herbelin, L., Dimachkie, M. M., Lemmers, R., Maarel, S. M., Barohn, R. J., Tawil, R., and Statland, J. M. MRI Correlates with Electrical Impedance Myography in Facioscapulohumeral Muscular Dystrophy. *Muscle Nerve*, 2019, page mus.26792.

Hart, F. X., Berner, N. J., and McMillen, R. L. Modelling the anisotropic electrical properties of skeletal muscle. *Phys. Med. Biol.*, 1999, 44(2):413–421.

Kalvøy, H., Frich, L., Grimnes, S., Martinsen, Ø. G., Hol, P. K., and Stubhaug, A. Impedance-based tissue discrimination for needle guidance. *Physiol. Meas.*, 2009, 30(2):129–140.

Kalvøy, H., Tronstad, C., Nordbotten, B., Grimnes, S., and Martinsen, Ø. G. Electrical Impedance of Stainless Steel Needle Electrodes. *Ann. Biomed. Eng.*, 2010, 38(7):2371–2382.

Kapur, K., Nagy, J. A., Taylor, R. S., Sanchez, B., and Rutkove, S. B. Estimating myofiber size with electrical impedance myography: a study in amyotrophic lateral sclerosis mice. *Muscle Nerve*, 2018a, 58(5):713–717.

Kapur, K., Taylor, R. S., Qi, K., Nagy, J. A., Li, J., Sanchez, B., and Rutkove, S. B. Predicting myofiber size with electrical impedance myography: A study in immature mice. *Muscle Nerve*, 2018b, 58(1):106–113.

Kimura, J., Kimura, A., Ishida, T., Kudo, Y., Suzuki, S., Machida, M., Matsuoka, H., and Yamada, T. What determines the latency and amplitude of stationary peaks in far-field recordings? *Ann. Neurol.*, 1986, 19(5):479–486.

Kwon, H., Di Cristina, J. F., Rutkove, S. B., and Sanchez, B. Recording characteristics of electrical impedance-electromyography needle electrodes. *Physiol. Meas.*, 2018, 39(5):055005.

Kwon, H., Guasch, M., Nagy, J. A., Rutkove, S. B., and Sanchez, B. New electrical impedance methods for the in situ

measurement of the complex permittivity of anisotropic skeletal muscle using multipolar needles. *Sci. Rep.*, 2019a, 9(1): 3145.

Kwon, H., Rutkove, S. B., and Sanchez, B. Recording characteristics of electrical impedance myography needle electrodes. *Physiol. Meas.*, 2017, 38(9):1748–1765.

Kwon, H., de Morentin, M. M., Nagy, J. A., Rutkove, S. B., and Sanchez, B. Approximate complex electrical potential distribution in the monodomain model with unequal conductivity and relative permittivity anisotropy ratios. *Physiol. Meas.*, 2019b, 40(8):085008.

Kwon, H., Malik, W. Q., Rutkove, S. B., and Sanchez, B. Separation of subcutaneous fat from muscle in surface electrical impedance myography measurements using model component analysis. *IEEE Trans. Biomed. Eng.*, 2019c, 66(2):354–364.

Li, J. and Rutkove, S. B. Alteration in surface muscle electrical anisotropy in the rat SOD1 model of amyotrophic lateral sclerosis. *Clin. Neurophysiol.*, 2012, 123(1):206–210.

Li, J., Staats, W. L., Spieker, A., Sung, M., and Rutkove, S. B. A Technique for Performing Electrical Impedance Myography in the Mouse Hind Limb: Data in Normal and ALS SOD1 G93A Animals. *PLoS One*, 2012, 7(9):e45004.

Nagy, J. A., DiDonato, C. J., Rutkove, S. B., and Sanchez, B. Permittivity of ex vivo healthy and diseased murine skeletal muscle from 10 kHz to 1 MHz. *Sci. Data*, 2019, 6(1):37.

Noshiro, M., Morimoto, T., Nagao, H., and Matsuda, H. Electrical impedance in the lower limbs of patients with Duchenne muscular dystrophy: A preliminary study. *Med. Biol. Eng. Comput.*, 1993, 31(2):97–102.

Preston, D. C. and Shapiro, B. E. Needle electromyography fundamentals, normal and abnormal patterns, 2002.

Roth, B. J., Gielen, F. L., and Wikswo, J. P. Spatial and temporal frequency-dependent conductivities in volume-conduction calculations for skeletal muscle. *Math. Biosci.*, 1988, 88(2):159–189.

Rutkove, S. B., Zhang, H., Schoenfeld, D. A., Raynor, E. M., Shefner, J. M., Cudkowicz, M. E., Chin, A. B., Aaron, R., and Shiffman, C. A. Electrical impedance myography to assess outcome in amyotrophic lateral sclerosis clinical trials. *Clin. Neurophysiol.*, 2007, 118(11):2413–2418.

Rutkove, S. B. Electrical impedance myography: Background, current state, and future directions. *Muscle Nerve*, 2009, 40(6): 936–46.

Rutkove, S. B. Electrical impedance myography: MRI-like data without the need for MRI. *Muscle Nerve*, 2020, 61(5):554–556.

Rutkove, S. B. and Sanchez, B. Electrical Impedance Methods in Neuromuscular Assessment: An Overview. *Cold Spring Harb. Perspect. Med.*, 2018, page a034405.

Rutkove, S. B., Partida, R. A., Esper, G. J., Aaron, R., and Shiffman, C. A. Electrode position and size in electrical impedance myography. *Clin. Neurophysiol.*, 2005, 116(2):290–9.

Rutkove, S. B., Caress, J. B., Cartwright, M. S., Burns, T. M., Warder, J., David, W. S., Goyal, N., Maragakis, N. J., Benatar, M., Sharma, K. R., Narayanaswami, P., Raynor, E. M., Watson, M. L., and Shefner, J. M. Electrical impedance myography correlates with standard measures of ALS severity. *Muscle and Nerve*, 2014, 49(3):441–443.

Rutkove, S. B., Wu, J. S., Zaidman, C., Kapur, K., Yim, S., Pasternak, A., Madabusi, L., Szelag, H., Harrington, T., Li, J., Pacheck, A., and Darras, B. T. Loss of electrical anisotropy is an unrecognized feature of dystrophic muscle that may serve as a convenient index of disease status. *Clin. Neurophysiol.*, 2016, 127(12):3546–3551.

Rutkove, S. B., Kapur, K., Zaidman, C. M., Wu, J. S., Pasternak, A., Madabusi, L., Yim, S., Pacheck, A., Szelag, H., Harrington,

T., and Darras, B. T. Electrical impedance myography for assessment of Duchenne muscular dystrophy. *Ann. Neurol.*, 2017a, 81(5):622–632.

Rutkove, S. B., Pacheck, A., and Sanchez, B. Sensitivity distribution simulations of surface electrode configurations for electrical impedance myography. *Muscle Nerve*, 2017b, 56(5):887–895.

Rutkove, S. B., Kwon, H., Guasch, M., Wu, J. S., and Sanchez, B. Electrical impedance imaging of human muscle at the microscopic scale using a multi-electrode needle device: A simulation study. *Clin. Neurophysiol.*, 2018, 129(8):1704–1708.

Sanchez, B., Li, J., Bragos, R., and Rutkove, S. B. Differentiation of the intracellular structure of slow- versus fast-twitch muscle fibers through evaluation of the dielectric properties of tissue. *Phys. Med. Biol.*, 2014, 59(10):1–12.

Sanchez, B. and Rutkove, S. B. Electrical Impedance Myography and Its Applications in Neuromuscular Disorders. *Neurotherapeutics*, 2017a, 14(1):107–118.

Sanchez, B. and Rutkove, S. B. Present Uses, Future Applications, and Technical Underpinnings of Electrical Impedance Myography. *Curr. Neurol. Neurosci. Rep.*, 2017b, 17(11):86.

Sanchez, B., Pacheck, A., and Rutkove, S. B. Guidelines to electrode positioning for human and animal electrical impedance myography research. *Sci. Rep.*, 2016, 6(1):32615.

Schwan, H. P. Electrical and acoustic properties of biological materials and biomedical applications. *IEEE Trans. Biomed. Eng.*, 1984, 31(12):872–8.

Schwartz, S., Geisbush, T. R., Mijailovic, A., Pasternak, A., Darras, B. T., and Rutkove, S. B. Optimizing electrical impedance myography measurements by using a multifrequency ratio: A study in Duchenne muscular dystrophy. *Clin. Neurophysiol.*, 2015, 126(1):202–208.

Stegeman, D. F., Dumitru, D., King, J. C., and Roeleveld, K. Near- and Far-Fields: Source Characteristics and the Conducting Medium in Neurophysiology. *J. Clin. Neurophysiol.*, 1997, 14(5):429–442.

Thomson, W. Electrical units of measurement. In *Pop. Lect. Vol.1*, page 73. 1883.

Figure captions

Figure 1. Modeling analogy between (A) nerve conduction studies and (B) electrical impedance myography approaches. (A) Illustration representing the modeling approach used in the nerve conduction velocity test. Solving the *forward problem* consists of taking the equation of linear motion (i.e., the physical model) to predict the latency (i.e., the effect) given the conduction velocity (i.e., the causal factor) and the distance between electrodes (i.e., experimental parameter). Solving the *inverse problem* is backwards, namely to calculate the *unknown* conduction velocity given the observed latency and the distance between electrodes. (B) The same modeling principles apply to electrical impedance myography, where the causal factors altered in diseased muscle are the volume conduction properties (VCPs) of muscle –namely the conductivity and the relative permittivity including their spatial dependence–, the observed effect is the impedance (resistance and reactance) and the distance between electrodes is an experimental parameter. The VCPs are a non-measured property of muscle that might be indirectly arrived by from impedance recordings with electrodes at different points.

Figure 2. (A) Rendering of a cell for calculating *ex vivo* volume conduction properties from an excised slab of muscle. The conduction properties of muscle are calculated from impedance measurements in longitudinal and transverse directions by placing the slab with the main orientation of the myofibers (B) parallel and (C) perpendicular to the flow of electrical current, respectively.

Figure 3. Picture of a prototype 26G impedance-electromyography (iEMG) needle developed for testing of the technology in pre-clinical studies. The iEMG needle includes E1 and E2 electrodes for EMG measurement and four additional dedicated current and voltages electrodes (HCUR, LCUR, HPOT and LPOT) for EIM measurement.

Figure 4. Example of the electrical conductivity measured for various murine models of neuromuscular disorders with disease progression. Multi-frequency data from 10 kHz to 1 MHz including the relative permittivity property is freely available online (Nagy et al., 2019).

Supplementary Figure 1. Idealized drawing showing the electrical relaxations of skeletal muscle expressed in terms of the volume conduction properties (VCPs) –i.e., conductivity and relative permittivity– across the entire frequency spectrum. Muscle has also a different pair of conductivity and relative permittivity curves in the transverse direction perpendicular to the main direction of the myofibers. The α-dispersion (mHz to kHz) is determined by intracellular structures (e.g., sarcotubular system), active cell membrane effects and gated channels. The β-dispersion (Hz to 100 MHz) relates to the Maxwell-Wagner interfacial polarization effect of the myofiber cellular membrane, passive cell membrane capacitance, intracellular organelle membranes and protein molecule response. Finally, the γ-dispersion (0.1 to 100 GHz) reflects dipolar mechanisms in polar media such as

water, salts and proteins (Grimnes and Martinsen, 2014). Alterations in these structures change the VCP values in diseased muscle (Nagy et al., 2019). The conductivity increases and permittivity falls monotonically with frequency for all tissues. In electrical impedance myography, the multi-frequency resistance data does not directly measure the difficulty of passing an electrical current through a muscle. In the same way, the multi-frequency reactance does not directly measure of the charge storage within the muscle. These physical properties are uniquely and directly measured by the conductivity and the relative permittivity.

Supplementary Figure 2. Simulation example using the finite element method to illustrate the major effect of conductor volume on a surface electrical impedance myography (EIM) measurement. Two muscles are considered as ellipsoidal (left) and cylindrical (right) volume conductors. The effect of other tissues such as skin or subcutaneous fat is omitted on purpose to only evaluate the effect of the different finite-shape of the muscle conductor volumes. On both cases, the volume conduction properties (VCPs) of muscle and the position of the current (red) and voltage (blue) electrodes are exactly the same. The simulated impedance data obtained are 10% different albeit both muscles were simulated with the same exact VCP values and electrodes position. In a much simpler scenario than a real surface EIM measurement, the interaction of VCPs and conductor volume effects producing the surface EIM data is unclear and the supporting scientific premise of the surface EIM is not fulfilled –i.e., the difference between impedance data is not caused by changes in the internal composition and structure of muscle affecting its VCPs–. Note also that a repeatable surface EIM measurement affected by the finite-shape of the muscle does not guarantee that the surface impedance data is useful at measuring the VCPs of muscle. Take this simulation for example: the simulated impedance data of these two muscles are essentially different even considering a surface EIM simulation with perfect reproducibility and no experimental errors.

Supplementary Figure 3. Example of conduction effects determined by the volume conduction properties of the bulk of diseased muscle on a recorded near-field extracellular muscle potential. The muscle fiber is surrounded by extracellular inhomogeneities illustrated with pockets of fatty infiltration. In the figure, the structures forming the insterstitium produce a net decrease of the extracellular conductivity and increase the relative permittivity of muscle. Then, the primary electric field created by the propagation of a muscle unit potential (MUP) through the muscle fiber generates a spatial fluctuation of positive (in red) and negative (in blue) electrical charges which are accumulated in the structures present in the surrounding microenvironment. These “obstacles” store electrical charge themselves and create electric dipoles that, in turn, generate their own (secondary) electric field. A constructive interaction between primary and secondary electric fields will increase the MUP’s amplitude and latency recorded compared to that recorded in healthy muscle with no fatty infiltration. A contrary example is with increased muscle conductivity due to the accumulation of fluid with high ionic strength such as interstitial edema after traumatic muscle injury. Highly conductive pathways create electrical shortcuts in the medium that will attenuate the MUP’s amplitude leaving the latency unaffected.

Figure 1

Click here to access/download;Figure;Fig1.png

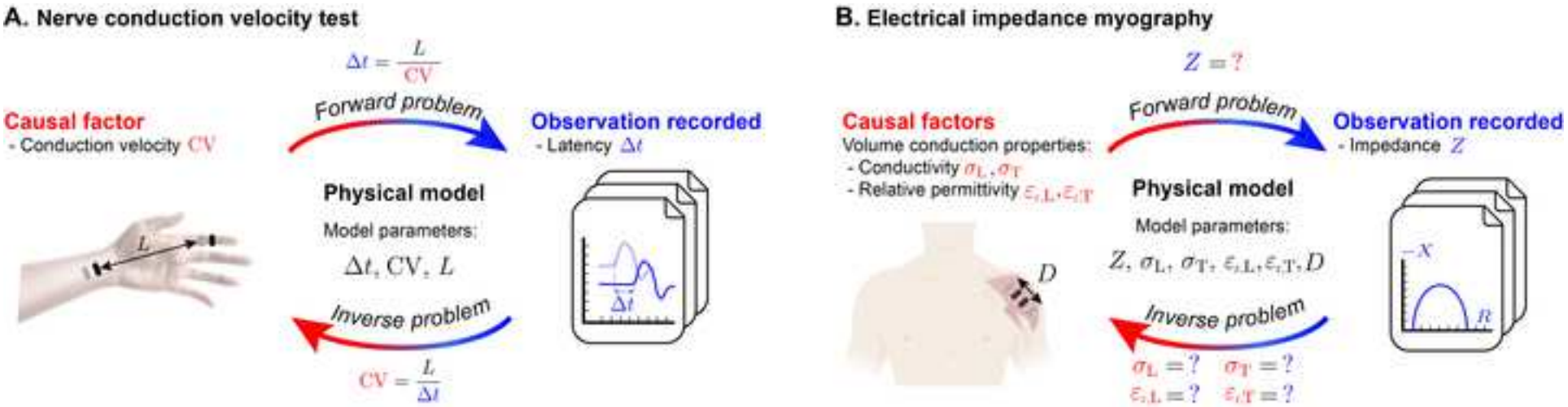


Figure 2

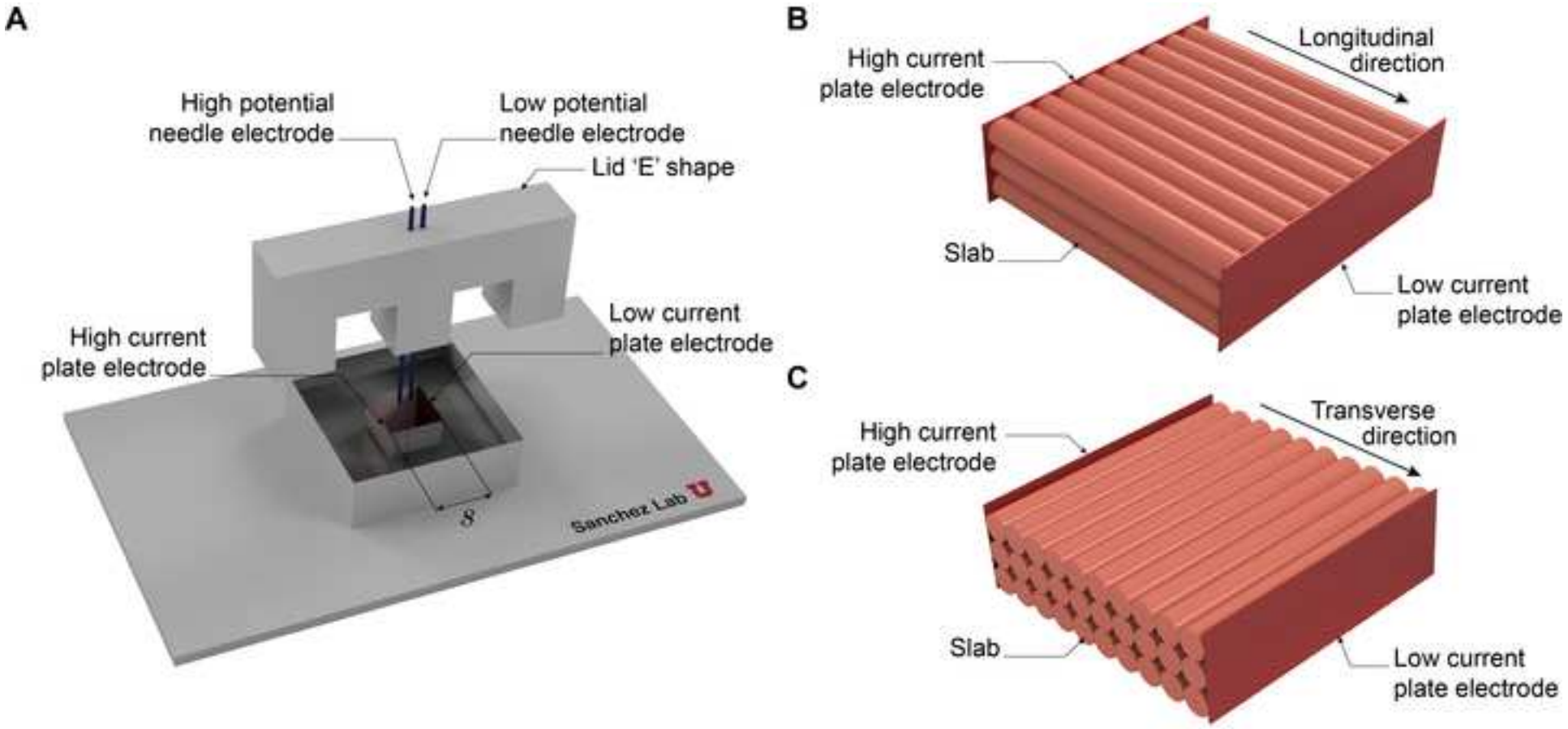


Figure 3

Click here to access/download;Figure;Fig3.png

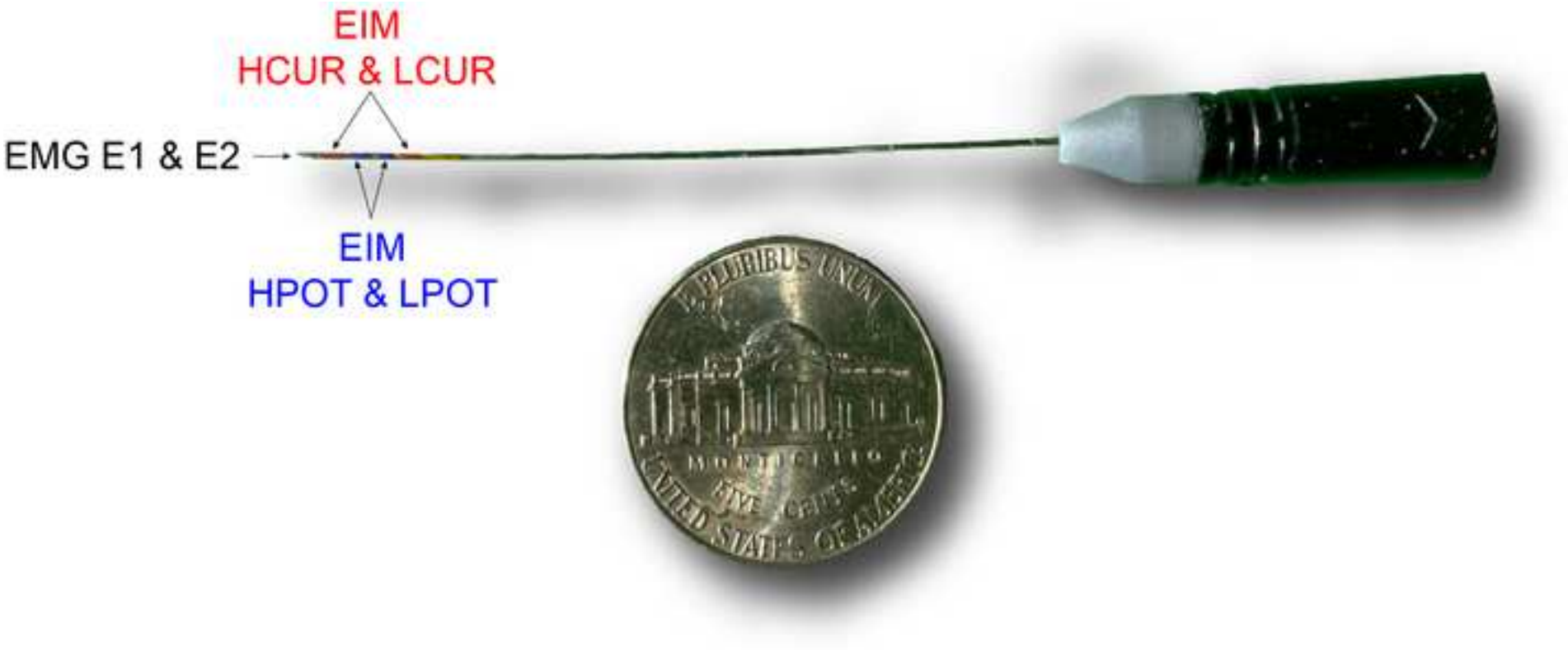
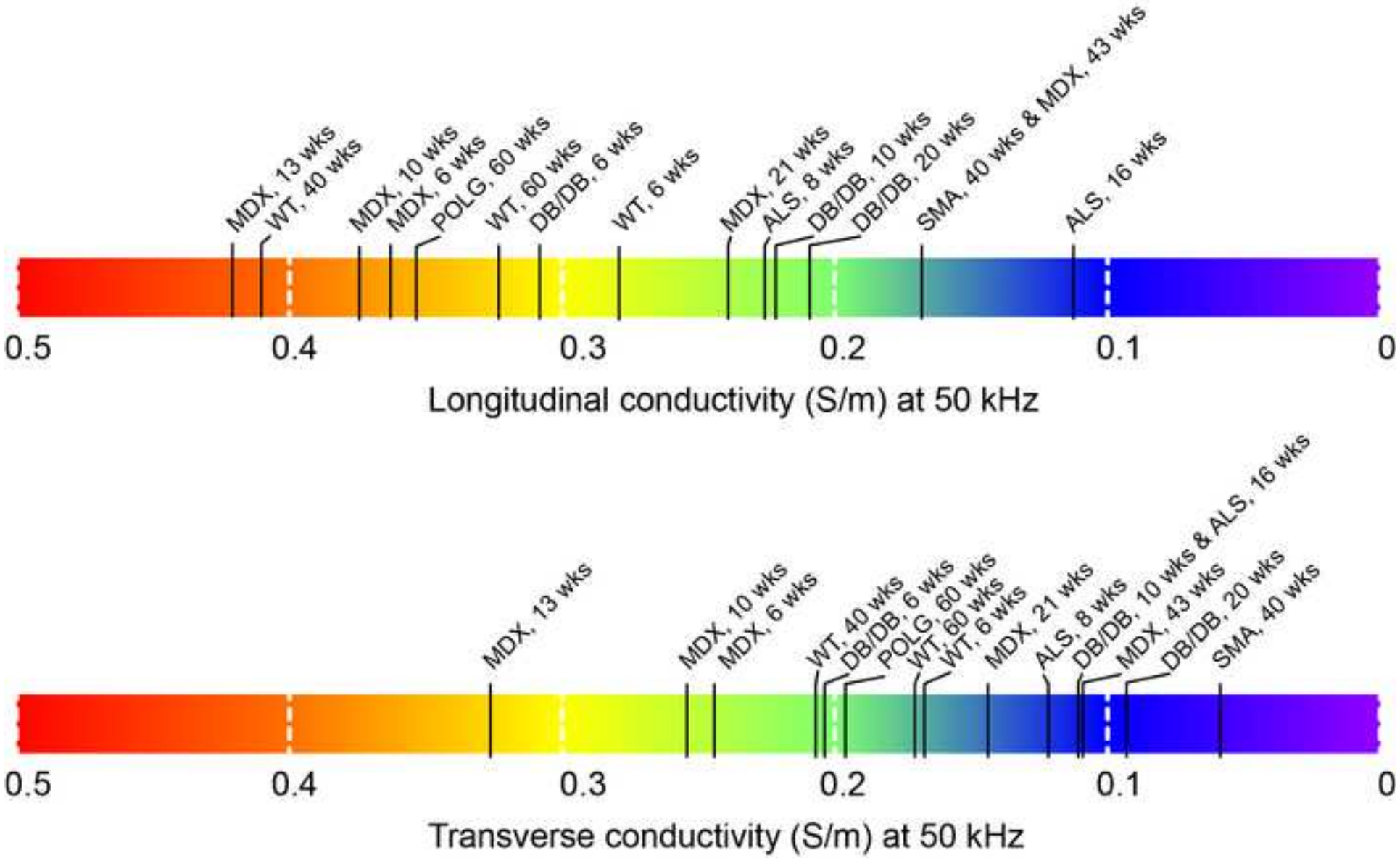
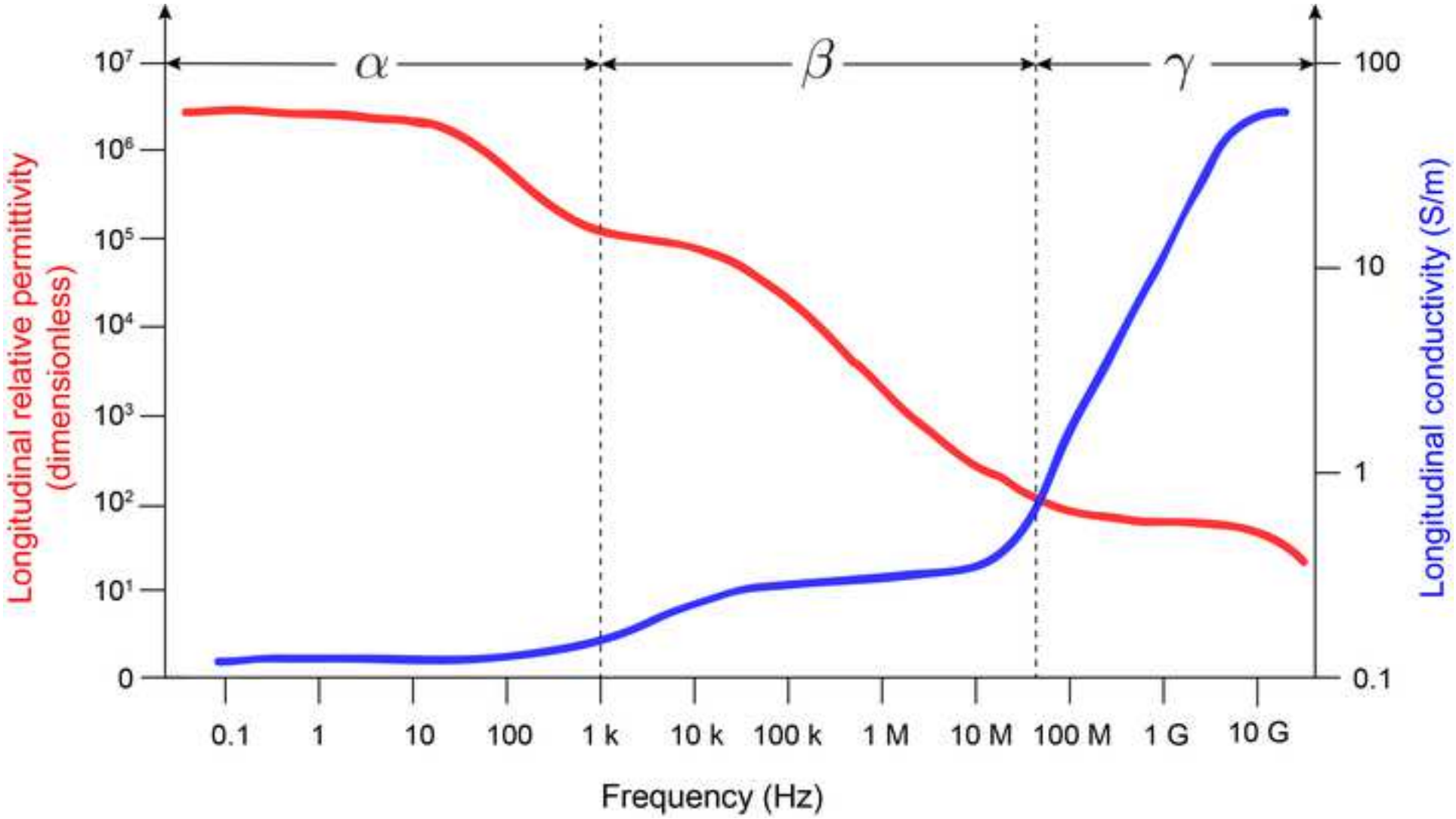


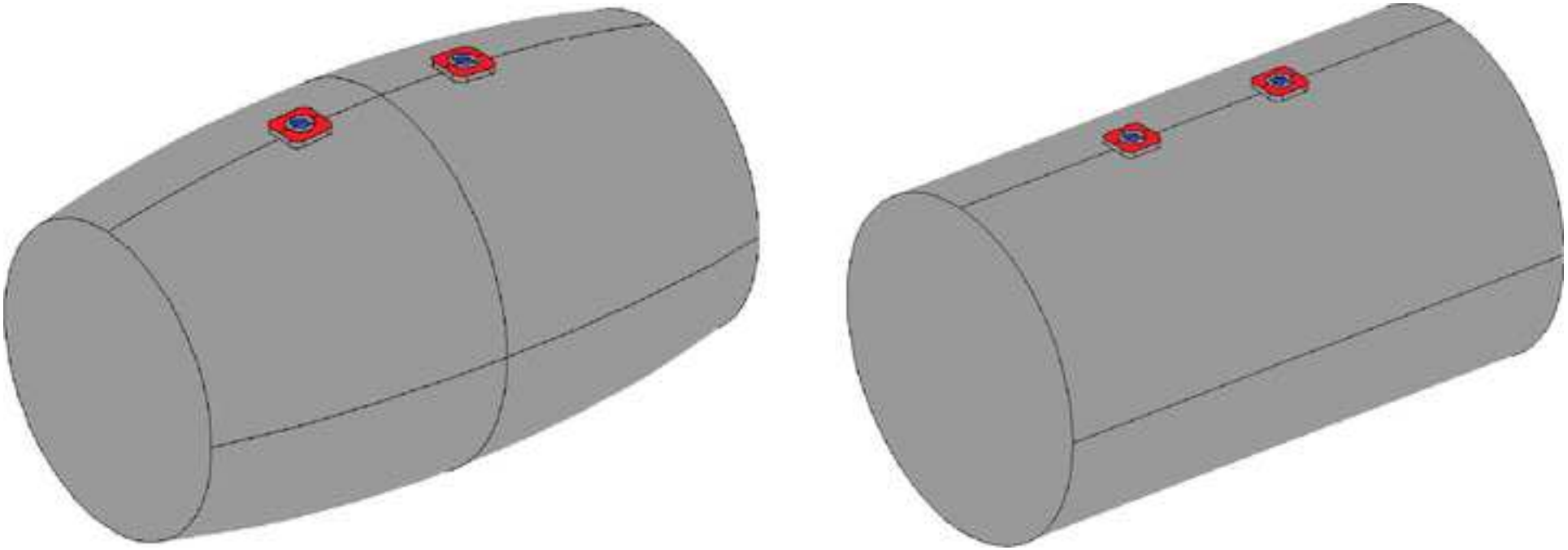
Figure 4





supp Figure 2

Click here to access/download;Figure;SuppFig2.png



supp Figure 3