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Volume conductor model of transcutaneous electrical stimulation with kilohertz signals

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Abstract

Objective—Incorporating high-frequency components in transcutaneous electrical stimulation (TES) waveforms may make it possible to stimulate deeper nerve fibers since the impedance of tissue declines with increasing frequency. However, the mechanisms of high-frequency TES remain largely unexplored. We investigated the properties of TES with frequencies beyond those typically used in neural stimulation.

Approach—We implemented a multilayer volume conductor model including dispersion and capacitive effects, coupled to a cable model of a nerve fiber. We simulated voltage- and current-controlled transcutaneous stimulation, and quantified the effects of frequency on the distribution of potentials and fiber excitation. We also quantified the effects of a novel transdermal amplitude modulated signal (TAMS) consisting of a non-zero offset sinusoidal carrier modulated by a square-pulse train.

Main results—The model revealed that high-frequency signals generated larger potentials at depth than did low frequencies, but this did not translate into lower stimulation thresholds. Both TAMS and conventional rectangular pulses activated more superficial fibers in addition to the deeper, target fibers, and at no frequency did we observe an inversion of the strength-distance relationship. Current regulated stimulation was more strongly influenced by fiber depth, whereas voltage regulated stimulation was more strongly influenced by skin thickness. Finally, our model reproduced the threshold-frequency relationship of experimentally measured motor thresholds.

Significance—The model may be used for prediction of motor thresholds in TES, and contributes to the understanding of high-frequency TES.

Keywords

computational model; surface stimulation; high-frequency nerve stimulation; transdermal amplitude modulated signal; dispersive tissues

1. Introduction

Electrical stimulation of the peripheral nervous system relies, in many cases, on implantation of an electrode in proximity to the nerve and connected to an implanted stimulator. Transcutaneous electrical stimulation (TES) with external electrodes and stimulator is a noninvasive alternative for peripheral nerve stimulation that reduces the risks and costs associated with implanted devices. In TES, electrical currents in the form of rectangular pulses are applied to the skin. The pulse rate of stimulation can range from few to hundreds of Hz, and stimulation can be delivered in bursts or single pulses. High frequency sine waves on the order of a few kHz (*e.g.*, interferential currents, in which the paths of two kHz currents cross and generate an amplitude modulated signal) as well as other non-conventional waveforms (*e.g.*, H-wave, which is a biphasic exponentially decaying waveform) have also been explored, albeit with equivocal outcomes (Sluka *et al* 2009).

The use of high frequency waveforms for TES is suggested by the reduced impedance of the skin with increasing frequency (Rosell *et al* 1988). Thus, it may be possible to reach deeper structures by adding high frequency components to the stimulation waveform. Specifically, a transcutaneous amplitude modulated signal (TAMS), in which a high frequency (210 kHz) sinusoidal carrier is modulated by a traditional rectangular pulse, was proposed as a non-invasive neurostimulation approach that can modulate bladder activity similarly to direct pudendal nerve stimulation (Shen *et al* 2011, Tai *et al* 2012). However, the mechanisms of actions of TAMS, which may differ substantially from conventional low-frequency stimulation, remain largely unexplored.

The potentials generated in the tissue by an electrode in contact with the skin are dependent on the electrical properties of the electrode-tissue interface and tissue and the geometry of the electrode and tissue. In the frequency range commonly used for peripheral nerve stimulation, tissues are considered as purely resistive, and capacitive, inductive and propagation effects are neglected through the quasi-static assumption (Plonsey and Heppner 1967). Under certain conditions, however, these simplifications may not be appropriate (Bossetti *et al* 2008), particularly in cases where the frequency content of the signal extends to the kHz range. In this study, we present a model of TES in which we calculate the distribution of potentials without invoking the quasi-static assumption. Although in the past many studies have used volume conductor models to estimate the potentials generated during TES, only a few have considered transcutaneous stimulation in the kHz range without relying on the quasi-static assumption (Kuhn *et al* 2009, Hartinger *et al* 2010, Mesin and Merletti 2008).

We implemented a two-step model (McNeal 1976) of TES using a distributed parameter volume conductor model to quantify the spatiotemporal distribution of potentials in the tissue, and a cable model of a mammalian myelinated axon to quantify excitation of peripheral nerve fibers. Our objective was to determine whether the introduction of high frequency components, up to hundreds of kHz, made it possible to reach deeper structures, thereby facilitating nerve fiber excitation. The results contribute to understanding the mechanisms of TES with novel high frequency waveforms such as TAMS.

2. Methods

2.1 Volume conductor model

We calculated the potentials in a volume conductor consisting of three planar layers of tissue with frequency-dependent dielectric properties (figure 1). We applied voltage or current source stimulation on the most superficial layer, including a model of the electrode-skin interface impedance. The potential in the modeled tissue, Φ , is described by the inhomogeneous Helmholtz equation (for a derivation of this equation see, for example, Bossetti *et al* (2008)), which is expressed in the frequency domain as:

$$\nabla^2 \Phi - \gamma^2 \Phi = \nabla \cdot \mathbf{J} / (\sigma(\omega) + j\omega\epsilon_0\epsilon(\omega)) \quad (1)$$

where ω is the angular frequency, $\mathbf{J}$ is the current density vector, σ is the conductivity, ϵ is the relative permittivity, ϵ_0 is the permittivity of free space, and γ is the complex propagation constant. Following the approach of Mesin and Merletti (2008) and Farina and Rainoldi (1997), we found an analytical solution of (1) in a multi-layer planar geometry neglecting propagation effects, as this is an appropriate approximation for living tissues (Tracey and Williams 2011). We Fourier-transformed the x and z space variables into the spatial frequencies k_x and k_z , respectively. Thus, the problem was described by the ordinary differential equations in the depth y :

$$\partial_{yy}\varphi_{skin} - k_y^2\varphi_{skin} = 0 \quad 0 < y < h \quad \partial_{yy}\varphi_{fat} - k_y^2\varphi_{fat} = 0 \quad h < y < h+d \quad \partial_{yy}\varphi_{muscle} - k_{ya}^2\varphi_{muscle} = 0 \quad y > h+d \quad (2)$$

where φ_{tissue} is the potential in the transformed domain, h and d are the thicknesses of the skin and fat layer, respectively, $k_y^2 = k_x^2 + k_z^2$, and $k_{ya}^2 = k_x^2 + k_z^2(\sigma_L + j\omega\epsilon_L)/(\sigma_T + j\omega\epsilon_T)$, where the muscle layer was anisotropic with different conductivity and permittivity values in the transverse (T) and longitudinal (L) directions (Gabriel *et al* 1996a). The solution of (2) is written as:

$$\varphi_{tissue}(y) = A_{tissue}\exp(k_{ya}y) + B_{tissue}\exp(-k_{ya}y). \quad (3)$$

where coefficients A_{tissue} and B_{tissue} are dependent on the boundary conditions, *i.e.*, they are calculated by imposing continuity of voltage and the normal component of the current density at the boundaries between layers (see Appendix).

We incorporated the impedance of the electrode-skin interface via a thin-layer approximation (Cantrell *et al* 2008, Grant and Lowery 2010). Assuming that all current flowing through the interface is normal to the skin surface, we imposed the following boundary condition:

$$-\mathbf{J} \cdot \mathbf{n} = (V_{source} - V_0) \cdot Y_{interface}. \quad (4)$$

where V_{source} is the voltage delivered by the electrode (voltage-controlled stimulation), V_0 is the potential on the skin surface and $Y_{interface}$ is the admittance of the electrode-skin interface. For current-controlled stimulation we imposed continuity of the normal component of the current density on the surface of the skin. We used measurements of the impedance of the electrode-skin interface for carbon rubber electrodes with a dry-skin/pre-

gelled electrode condition (Kaufmann *et al* 2013), which fall within the same range (*i.e.*, tens of Ω) of that used by Kuhn *et al* (2009) for square pulses. In the simulation of the Ward and Robertson experiment (2001) (see section 2.5 Model validation), we used the “constant phase angle impedance” model of the electrode-skin interface with the parameters reported by McAdams *et al* (1994) for hydrogel-based electrodes. In this model, the interface is represented by a large resistance, R_p , in parallel with a constant phase angle impedance, Z_{CPA} , so that the admittance of the interface is expressed as:

$$Y_{interface} = \frac{1}{R_p} + \frac{1}{Z_{CPA}} = \frac{1}{R_p} + \frac{(j\omega)^\alpha}{K} \quad (5)$$

where K is a constant with units $\text{Ohm/sec}^{-\alpha}$, α is a deviation factor from the pure capacitive behavior, and ω is the angular frequency.

For a particular depth y , we inverted the 2-D Fourier transform to obtain the potential phasor (time-harmonic), $\Phi(\omega)$, in the entire volume. Additionally, to compute the time-domain solution of the potential, we inverted the 3-D Fourier transform constructed by varying the frequency over the $[0, f_s/2]$ interval, where f_s is the sampling frequency. We used a sampling frequency at least 10-times higher than the maximum frequency of the stimulation waveform to avoid aliasing. The model was implemented in MATLAB, and was 128 mm wide (x) by 128 mm long (z) with a spatial resolution of 1 mm. We used disk- and rectangular-shaped electrodes, and sine and TAMS waveforms in the 0 – 210 kHz frequency range. The MATLAB code of the volume conductor model is available at https://github.com/leonelmd/three_layers_model.

For each layer, we defined the penetration distance as the length constant of a single exponential decay model of the voltage along the y -axis just below the center of the electrode (*i.e.*, a penetration distance larger than the layer thickness means that the decay of the potential across the layer was less than 63 %). We fitted the data using non-linear least squares with a termination tolerance of 10^{-6} , and the coefficient of determination, R^2 , was larger than 0.9 in all cases.

2.2 Frequency-dependent dielectric properties

The dielectric properties of each tissue layer (figure 1b) were modeled using multiple Cole-Cole (Cole and Cole, 1941) dispersions (α , β , γ and δ) and the complex relative permittivity, ϵ_c , was estimated as (Gabriel *et al* 1996b):

$$\epsilon_c(\omega) = \epsilon - j \frac{\sigma}{\omega \epsilon_0} = \epsilon_\infty + \sum_{n=1}^4 \frac{\Delta \epsilon_n}{1 + (j\omega \tau_n)^{(1-\alpha_n)}} + \frac{\sigma_i}{j\omega \epsilon_0} \quad (6)$$

The parameters of Eq. (6) were taken from Gabriel *et al* (1996b). Note that the relative permittivity is simply the real part of ϵ_c , whereas the conductivity is determined by multiplying the imaginary part of ϵ_c by $\omega \epsilon_0$.

To quantify the filtering properties of the axonal membrane, we used purely resistive media with no dispersion. In this case, the conductivity of each layer was set to the static

conductivity of the layer (*i.e.*, frequency approaching zero), and we neglected capacitive effects.

2.3 Cable model of a myelinated nerve fiber

We quantified nerve fiber excitation via TES using the McIntyre-Richardson-Grill (MRG) cable model of a myelinated mammalian axon (McIntyre *et al* 2002). We used 5.7 to 16 μm diameter fibers with 101 nodes of Ranvier, and took all other parameters from McIntyre *et al* (2002). We adopted the modelDB version (<http://senselab.med.yale.edu/modeldb/ShowModel.asp?model=3810>) of the MRG model in NEURON (Hines and Carnevale 1997), and used the “extracellular” mechanism to implement extracellular stimulation. We used the Crank-Nicholson method for integration of the transmembrane voltage in response to extracellular stimulation with a time step given by the sampling frequency used for the volume conductor model. We positioned the model nerve fibers parallel to the skin surface at distances of 0.5 to 20 mm from the fat muscle boundary, with the central node randomly positioned with respect to the center of the surface electrode, but no further than half the internodal length. For the strength-distance relationship we also positioned fibers in the skin and the fat at depth multiples of 0.5 mm. Linear spatial interpolation of the potentials computed with the volume conductor model was used to calculate the extracellular voltage outside each axon compartment in the nerve fiber models. We used a binary search to estimate excitation thresholds to within $\pm 0.1\%$, *i.e.*, the smallest stimulation amplitude that elicited an action potential.

The coupled volume conductor/nerve fiber model of TES is illustrated in figure 1c. In this example, the stimulus generated potentials on the order of 30 V in the skin that declined to the mV range in the muscle, where the nerve fiber was positioned, and a propagating action potential was initiated in the mid-axon below the electrode. In all our simulations, we verified fiber excitation by determining whether an action potential propagated to one end of the axon.

2.4 Stimulation waveforms

We simulated voltage and current controlled stimulation using TAMS, rectangular pulses, and zero mean (*i.e.*, zero dc offset) sine waveforms. TAMS is composed of a sine carrier of 210 kHz modulated by 1 ms square pulses at a much lower pulse repetition frequency (less than 100 Hz), and with a non-zero dc component equal to half the amplitude of the sinusoid. We varied the frequency of the carrier from 100 Hz to 210 kHz, and used a sufficiently long pulse to have at least one complete sine cycle for the lowest frequency. Threshold for the TAMS waveform was defined as the dc component of the pulse, whereas for rectangular pulses and zero-offset sine waves, the threshold was the peak amplitude of the signal.

2.5 Model validation

We simulated the experimental measurements of Ward and Robertson (2001) and Slovak *et al* (2013), respectively, and compared motor thresholds to our model predictions. First, we simulated voltage-controlled stimulation using the same 40×44 mm electrode of Ward and Robertson (2001), with thicknesses of 1.5 and 2.5 mm for skin and fat, respectively, to represent the forearm (Kuhn *et al* 2009), and applied two different waveforms: a 10 ms burst

of sinusoidal stimulation and a single-cycle sine. We used the constant phase angle impedance model of the electrode-skin interface (McAdams *et al* 1994) as a representation of nonlinear processes that can occur at the interface. We used a frequency-dependent deviation factor, α , so that $\alpha=0.8$ for $f<2$ kHz and $\alpha=0.9$ otherwise, which is within the experimentally measured range (McAdams *et al* 1994). Lastly, we simulated current-controlled bipolar stimulation using 2 cm diameter disk electrodes placed 3 cm apart, and skin and fat thicknesses of 1.5 and 2.5 mm, respectively, to represent the forearm (Kuhn *et al* 2009). We compared the voltage across the electrodes and estimated thresholds from our model to those measured by Slovak *et al* (2013).

3. Results

3.1 Distribution of potentials and penetration distance

We quantified the decay of potential versus depth in the model tissues as a function of frequency for the geometry illustrated in figure 2a. When a 1 V voltage-controlled sine waveform was applied, the potential decayed across the skin-electrode interface by less than 8% for low frequencies (<1 kHz) but by up to 36% at 10 kHz. In a purely resistive medium with no dispersion, however, the potential decayed by less than 2% across the skin-electrode interface, and this voltage drop decreased monotonically with increasing frequency. For low frequencies (<1 kHz) the voltage dropped almost entirely across the skin layer, and the voltages in the muscle were on the order of a few millivolts. However, for higher frequencies (>10 kHz) the potential decayed more gradually across the tissue layers and three-fold larger potentials were present in the muscle. Figure 2b shows representative voltage waveforms at different depths for voltage and current control using TAMS.

The frequency-dependent decay of the potential in the tissues is summarized in figure 2c. While the penetration in the skin showed a very strong dependence on frequency, the penetration in muscle showed comparatively much smaller variation with frequency. As a result, and in accordance with the potential profile of figure 2a, the total penetration (dotted line in figure 2c) exhibited frequency-dependent behavior, which suggests that high-frequency components may reach deeper structures. In addition, we calculated the peak of the second spatial difference of the extracellular potentials between three consecutive nodes along the model axons, ${}^2\Phi$, which is proportional to the activating function that has been used as estimator of nerve fiber excitation (Rattay 1989, Warman *et al* 1992). The maximum ${}^2\Phi$ varied with frequency depending on the type of source. For voltage controlled TES, ${}^2\Phi$ increased by nearly one order of magnitude between low (<1 kHz) and high frequencies (>10 kHz) (figure 2d), while for current-controlled TES, ${}^2\Phi$ decayed monotonically with frequency.

3.2 Fiber excitation with TAMS and conventional pulses

The results for 7 different geometries of the volume conductor, using cathodic regulated voltage and cathodic regulated current stimulation, are summarized in figure 3. Threshold was strongly dependent on the carrier frequency for both types of stimulation, with a minimum around 200 Hz. The threshold for voltage controlled stimulation did not significantly vary with the fat thickness (grey squares versus black diamonds in figure 3a).

However, increasing the skin thickness from 1.5 to 3.5 mm increased the threshold across all carrier frequencies. Similarly, thresholds increased with nerve depth in muscle (*i.e.*, distance from fat-muscle interface to fiber), although the changes were less pronounced than when the skin thickness was increased. Conversely, for current controlled stimulation, nerve depth had a strong influence on thresholds, whereas neither skin thickness nor fat thicknesses significantly affected thresholds (figure 3b). In addition, we estimated the threshold for conventional rectangular pulse stimulation for all 7 geometries. The rectangular pulse threshold approximately equaled the dc component of the TAMS waveform with the highest carrier frequency for all geometries and for both voltage and current regulated stimulation. Additionally, as shown in figure 3c, TAMS with a low frequency carrier (*i.e.* <1 kHz) delivered less energy than rectangular pulse for all 7 model variants.

Thresholds increased rapidly with nerve depth, and fibers with smaller diameters exhibited higher stimulation thresholds (figure 4). For voltage and current regulated stimulation, the current-distance relationship obtained with TAMS was a vertically shifted version of that with rectangular pulse stimuli. These results did not indicate that TAMS is more effective than conventional stimulation since both activate deeper axons at higher thresholds than more superficial fibers, regardless of the nerve fiber diameter or the waveform characteristics.

3.3 Filtering properties of the axonal membrane

We assessed the filtering properties of the axonal membrane and the possible influence on nerve activation by quantifying the attenuation of the transmembrane potential, V_m , as a function of the sinusoidal frequency. For these simulations, we configured our volume conductor model as a purely resistive medium by neglecting capacitive effects and setting the conductivity of each layer constant and equal to its value at frequency approaching zero (*i.e.*, no dispersion). For sinusoidal stimulation, the excursion of V_m strongly depended on frequency (figure 5a), and the 200 kHz signal was almost entirely attenuated. If a dc component was added, then the 200 kHz carrier was again filtered out, and V_m resembled that generated by the rectangular pulse (figure 5a). The ratio of the RMS of V_m to the maximum depolarization generated by a rectangular pulse was used to summarize this filtering effect (figure 5b). The ratio decayed monotonically with frequency for all fiber diameters, indicating that the membrane acts as a low pass filter, and in the hundreds of kHz range the changes in V_m are nearly completely attenuated (*i.e.*, ratio approaches zero). However, if a nonzero offset is added, as in TAMS, the dc component contributes to fiber activation and the threshold rises more gradually with frequency than for stimulation with a zero offset sine wave (figure 5c).

3.4 Prediction of experimentally measured thresholds

We determined whether the model could predict motor thresholds obtained for TES with sinusoidal regulated voltage stimuli applied to the forearm with two carbon rubber electrodes (Ward and Robertson, 2001). Initially, across the 1 – 25 kHz frequency range tested by Ward and Robertson (2001), our model showed monotonically increasing thresholds with frequency (figure 5c). However, after introducing nonlinearity into the electrode-skin interface impedance (*i.e.*, frequency-dependent deviation factor, as described

in Methods), the calculated threshold versus frequency curve showed a remarkably similar shape to that of the experimental motor thresholds (figure 6). The model reproduced both the non-monotonic relationship of threshold with frequency, including a minimum around 5 kHz for the single-cycle waves, and lower thresholds for the 10 ms burst with respect to the single-cycle waves. However, the model did not capture the rate of increases in threshold with frequency for 10 ms bursts. This deviation may be due to differences in detection of single action potential thresholds in the model axon versus thresholds for torque generation measured experimentally, where temporal summation may influence detection of the threshold response.

Finally, we modeled TES of the forearm with TAMS as in Slovak *et al* (2013). They measured sensation and motor thresholds with both current-controlled TAMS and conventional pulses for TES over the ulnar nerve. Similar to their measurements, our model showed that the voltage on the skin surface was a low-pass filtered version of the applied current and looked quite similar for TAMS and a conventional pulse (figure 7). Further, in agreement with Slovak *et al* (2013), we observed little difference in the thresholds with TAMS and rectangular pulses (Table 1).

4. Discussion

The objective of this study was to quantify the effects of frequency in a model of transcutaneous electrical stimulation (TES). We focused on frequencies higher than those typically used in neural stimulation, *i.e.*, the kilohertz range. We developed a multilayer volume conductor model that included dispersive tissues and capacitive effects, and tested whether incorporating high-frequency components into the stimulation waveform could facilitate excitation of peripheral nerve fibers. We observed larger voltages at depth (*i.e.*, greater penetration) in the kHz range, but this did not translate into lower thresholds. The possible benefits of less attenuated extracellular potentials - and the spatial derivatives of the extracellular potentials - at deeper locations in the tissue, as a result of the tissue filtering properties, were offset by the filtering properties of the membrane, where higher frequencies produced smaller changes in transmembrane voltage. Further research is needed to determine the potential contributions of ion channel dynamics to the increases in threshold with frequency.

4.1 Filtering properties of biological tissue

Our multilayer volume conductor model revealed that the frequency-dependent effects on penetration were greatest in the skin layer. The penetration in the skin increased dramatically above ~ 10 kHz, whereas in the remaining layers there was a comparatively smaller decline in penetration with frequency (figure 2). The conductivity of the skin increases by approximately three orders of magnitude from 1 to 100 kHz, while the conductivity of both fat and muscle show little variation in the same frequency range (Gabriel *et al* 1996a). On the contrary, the permittivity of both fat and muscle, but not skin, decay strongly with frequency. Therefore, the deeper total penetration observed in the high frequency range (> 10 kHz) is dependent on the dielectric properties of the skin, particularly the conductivity. This is consistent with the findings of Bossetti *et al* (2008), who showed

that the potential in a homogenous, isotropic volume conductor was more strongly dependent on the conductivity than the permittivity of the medium. Accordingly, removing the capacitive effects from our model did not substantially change the penetration profile of all three layers. Similarly, Grant and Lowery (2010) found that, under certain conditions of deep brain stimulation, neglecting dispersion could generate large errors in the calculated potentials. This further emphasizes the need to incorporate dispersion, although in our model the main contributor for the variations in voltage with frequency was dispersive conductivity.

4.2 Influence of the electrode-skin interface (ESI)

The ESI has a strong influence on the relationship between threshold and frequency. Our model of the Ward and Robertson (2001) experiment initially showed strictly increasing thresholds over the 1 – 25 kHz range that they tested. However, after introducing nonlinearity to the deviation factor, α , of the constant phase angle impedance, our model reproduced quite well the experimentally measured motor thresholds (figure 6). Even though we were not able to find experimental studies assessing a direct dependency of α on frequency, we varied it over the experimentally measured range for hydrogel skin electrodes (McAdams *et al* 1994). In estimating the parameters of the constant phase angle impedance, McAdams *et al* (1994) assumed that α was frequency-independent. Cantrell *et al* (2008) also assumed frequency-independent α , but since α shows a dependency on the electrode overpotential for large voltages, it can indirectly depend on frequency. Nonetheless, our frequency-dependent α might reflect other nonlinear processes occurring at the ESI. For example, Wei and Grill (2009) found that the impedance of deep brain stimulation electrodes could be well described by nonlinear circuit elements. Additionally, Dorgan and Reilly (1999) introduced a nonlinear model of the skin impedance under neuromuscular stimulation. Thus, in the Ward and Robertson experiment, the ESI, the skin impedance, or both, might have included nonlinearities, which our model captured in the deviation factor of the ESI.

4.3 The transdermal amplitude modulated signal (TAMS)

The TAMS waveform has been used for bladder control via transcutaneous stimulation of the pudendal nerve in cats (Shen *et al* 2011, Tai *et al* 2012). Activation of the pudendal nerve was verified by observing anal sphincter activity, and by comparing the results to similar studies employing direct stimulation of the pudendal nerve. The authors assumed that TAMS was “optimal for stimulating nerves under the skin and muscle” since the skin impedance is minimal at the frequency of the carrier (210 kHz). However, both TAMS and conventional stimuli might also activate both nerve fibers in the skin and in the underlying muscles as our analysis failed to reveal any inversion of the strength-distance curve that would allow stimulation of deep fibers at lower thresholds than more superficial fibers. It then follows that to excite a nerve located at a specific depth from the skin surface, both TAMS and conventional stimuli would activate the same population of more superficial fibers and thus would be at least equally effective. Further, we observed little difference in thresholds with TAMS and conventional pulses, in agreement with the experimental observations of Slovak *et al* (2013).

4.4 Voltage versus current stimulation

The use of either voltage- or current-controlled stimulation has a direct impact on the properties of nerve excitation since regulated current, but not regulated voltage, generates the same current flow through the tissue regardless of the impedance (Durand *et al* 2005). Thus, even though voltage-controlled stimulation is generally considered lower risk in transcutaneous electrical stimulation, it produces less predictable forces (Chen *et al* 2012). We simulated both types of stimulation and found that the filtering properties of the tissue substantially differed, as reflected in the opposite effects of frequency on $^2\Phi$, *i.e.*, high-pass and low-pass behavior for voltage- and current-controlled stimulation, respectively. For the geometries tested here, we found that fat thickness had little influence on threshold across all carrier frequencies of TAMS, regardless the type of stimulation. This can be interpreted as an effect of the great dissipation of energy in the skin and at the electrode-skin interface, which may reduce the impact of fat thickness. This latter observation is confirmed by the strong effect of skin thickness on thresholds for voltage controlled stimulation. These results support the use of one or the other type of stimulation depending on the geometry of a particular application, *i.e.*, they favor voltage stimulation for thin skin, and current stimulation for more superficial nerves.

4.5 Conduction block

Although in our study we did not directly assess conduction block, we tested frequencies that have been used for this purpose, *i.e.*, from 600 Hz to 40 kHz (for a review see Kilgore and Bhadra, 2004). Block generally employs a continuous ac signal, and it is unclear whether pulses of ac, as used in this study, can produce conduction block. The initiation of the ac block signal produces an 'onset response' (Gerges *et al* 2010), *i.e.*, the initial fiber activation transiently triggered by the kHz-frequency block signal. It is possible that in our study we observed a similar phenomenon, in which the transient phase of the stimulation waveform was responsible for axon firing. However, we only used single pulses and therefore further investigation is needed to determine the properties of nerve excitation and block with modulated ac signals. The modeling study by Rattay (1986) suggests that modulated ac can indeed produce synchronous activation under certain conditions, but it remains unclear whether similar results can be obtained with extracellular stimulation of more complex nerve fiber models. kHz-frequency continuous signals applied to the MRG model do indeed produce conduction block (Bhadra *et al* 2007, Ackermann *et al* 2011), and in accordance with our results the onset response as described above was observed for both block and non-block signals. In addition, conduction block of superficial fibers and activation of deeper fibers may occur concomitantly with kHz frequency TES leading to less discomfort.

4.6 Model limitations

One of the limitations of our approach was not accounting for the more complex geometry of the tissues. For a particular application, a more detailed description of the geometry may be necessary to predict more accurately stimulation thresholds at different tissue depths and waveform frequencies. The Fourier-based solution presented here dramatically increases in complexity as the number of boundaries increases, particularly for non-planar shapes. In

these cases, a numerical approach (*e.g.*, finite element method) is likely to be more appropriate. However, our approach was suitable to generate an understanding of the properties of high-frequency TES as a step preceding application-specific solutions. In addition, the truncation of the digitized Fourier transform can introduce artifacts in the spatiotemporal distribution of potentials. However, preliminary assessments showed variations in the potential $\sim 5\%$ when the spatial resolution was changed from 1 mm to 0.5 mm.

Another limitation may arise from the use of a nerve fiber model that has not been thoroughly validated for kHz-frequency stimulation signals. Although we replicated the results of two prior experimental studies of high frequency stimulation, not all conductances present in human peripheral myelinated nerve fibers are included in the MRG model (*e.g.*, Howells *et al* 2012). As well, Haydon *et al* (1980) found that membrane capacitance declines by a factor of two between dc and 100 kHz, and this may affect excitation thresholds in range of frequencies that we tested. Preliminary assessments showed that reducing the membrane specific capacitance from 2 to 1 $\mu\text{F}/\text{cm}^2$ caused thresholds for 100 kHz signals to vary by less than 10%. However, since stimulation waveforms may present broad frequency content, further research is required to assess the potential impact of a frequency-dependent formulation of the membrane capacitance in the nerve fiber model.

Finally, we focused on large diameter fibers within the muscle layer. In TES, comfort can be an important factor for patient acceptance, and thus modeling studies have addressed the activation of superficial nerve endings (Kuhn *et al* 2010, Morch *et al* 2011). Our model could be used to study cutaneous activation by placing unmyelinated fibers in the skin layer in different orientations, but multiple layers of cutaneous tissue, as in Hartinger *et al* (2010), may be necessary as they can have substantially different dielectric properties. Additionally, the number of action potentials generated in superficial versus deep fibers may help explain differences in comfort level with high frequency TES and conventional stimulation. In general we observed single action potentials using just above threshold stimulation, but as the stimulus strength increased, multiple action potentials were elicited with long duration stimuli.

5. Conclusion

We implemented a multilayer model of TES that accounted for dispersive tissues and capacitive effects, thereby providing a framework suitable for kHz frequency TES simulations. Our model suggests that high-frequency signals generate larger potentials at depth than low frequencies. However, incorporating kHz signals in the stimulation waveform does not necessarily facilitate fiber excitation. We quantified the effects of a novel signal, TAMS, and observed non-monotonic variation of threshold as a function of the carrier frequency. Additionally, both TAMS and conventional rectangular pulses activated more superficial fibers in addition to the deeper, target nerve fibers. Our results suggest that current regulated stimulation is more strongly influenced by fiber depth, while voltage regulated stimulation is more strongly influenced by skin thickness. Finally, our model reproduced the threshold-frequency relationship of experimentally measured motor thresholds.

Appendix

The coefficients of equation (3) were:

- Voltage-controlled stimulation

$$\begin{aligned}
 B_{skin} &= \frac{V_{source} \cdot Y_{interface} + A_{skin}(\alpha_{skin} \cdot k_y - Y_{interface})}{Y_{interface} + \alpha_{skin} \cdot k_y} \\
 A_{skin} &= \frac{V_{source} + (Y_{interface} + \alpha_{skin} \cdot k_y)(X \cosh(k_y \cdot h) - Z \sinh(k_y \cdot h)) - V_{source} \cosh(k_y \cdot h)}{2(Y_{interface} \sinh(k_y \cdot h) + \alpha_{skin} k_y \cosh(k_y \cdot h))} \\
 B_{fat} &= X - A_{fat} \\
 A_{fat} &= \frac{(\alpha_{fat} \cdot k_y - \alpha_{muscle} \cdot k_{ya}) \exp(-k_{ya}(h+d)) B_{muscle}}{2\alpha_{fat} k_y \exp(k_y(h+d))} \\
 B_{muscle} &= \frac{X \cosh(k_y(h+d)) - Z \sinh(k_y(h+d))}{\exp(-k_{ya}(h+d))} \\
 A_{muscle} &= 0
 \end{aligned}$$

where

$$\begin{aligned}
 X &= \frac{-\alpha_s \cdot Y_{interface} \cdot V_{source}}{\sinh^2(k_y h)(\alpha_{fat} Y_{interface} + \alpha_{skin}^2 k_y Z) - \cosh^2(k_y h)(\alpha_{skin} \alpha_{fat} k_y Z + \alpha_{skin} Y_{interface}) + \sinh(k_y h) \cosh(k_y h)(\alpha_{skin} \alpha_{fat} k_y + (\alpha_{fat}^2 - \alpha_{skin}^2) Z)} \\
 Z &= \frac{\alpha_{fat} k_y \tanh(k_y(h+d)) + \alpha_{muscle} k_{ya}}{\alpha_{muscle} k_{ya} \tanh(k_y(h+d)) + \alpha_{fat} k_y}
 \end{aligned}$$

$Y_{interface}$: admittance of the electrode-skin interface.

$$\alpha = \sigma + j\omega\epsilon$$

- Current-controlled stimulation

$$\begin{aligned}
 B_{skin} &= \frac{I_{source}}{\alpha_{skin} \cdot k_y + A_{skin}} \\
 A_{skin} &= \frac{I_{source}}{2(\alpha_{skin} \cdot k_y)} (\tanh(k_y h) - 1) W (1 - Z \tanh(k_y h)) \\
 B_{fat} &= W - A_{fat} \\
 A_{fat} &= \frac{(\alpha_{fat} \cdot k_y - \alpha_{muscle} \cdot k_{ya}) \exp((-k_{ya} + k_y)(h+d)) B_{muscle}}{2\alpha_{fat} k_y} \\
 B_{muscle} &= \frac{W \cosh(k_y(h+d)) - Z \sinh(k_y(h+d))}{\exp(-k_{ya}(h+d))} \\
 A_{muscle} &= 0
 \end{aligned}$$

$$\text{where } W = \frac{I_{source}}{k_y(\alpha_{fat} Z + (\alpha_{skin} - \alpha_{fat}) \sinh(2k_y h)/2 + (\alpha_{fat} - \alpha_{skin}) Z \sinh^2(k_y h))}$$

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Figure 1. Model of transcutaneous nerve stimulation

(a) A volume conductor model of three planar layers of skin, fat and muscle, a disk electrode in contact with the skin, and a distributed impedance representing the electrode-skin interface (ESI). (b) Conductivity, σ , and relative permittivity, ϵ , as a function of frequency for the three tissues included in the volume conductor (parameters from Gabriel *et al* 1996b). (c) The potentials calculated from the volume conductor model were coupled to a cable model of a mammalian nerve fiber, located 7 mm from the skin surface in this example. The membrane voltage, v_m , at 9 different nodes of Ranvier is shown on the left. Skin thickness: 1.5 mm, fat thickness: 2.5 mm. Electrode diameter: 2 cm.

Figure 2. Decay of potentials in the modeled tissue as a function of frequency

(a) Voltage as a function of frequency and depth along a line perpendicular to the electrode for the geometry illustrated to the left. Stimulation amplitude was 1 V. (b) Voltage waveform at different depths generated by a voltage source (top) and a current source (bottom) using the Transdermal Amplitude Modulated Signal (left) with two different carrier frequencies, 1 kHz and 100 kHz. Geometry as in (a). (c) Penetration distance (mean $\pm$ standard error of the length constant of a single exponential decay model of the potentials) as a function of frequency for the three layers, averaged across skin thicknesses from 1.5 to

4 and fat thicknesses from 1 to 7 mm. Dotted line: total penetration. (d) Maximum of the second spatial difference of the potential, $\text{Max}\{\nabla^2\Phi\}$, for a 14 μm fiber as a function of frequency for voltage-(solid line) and current- regulated (dotted line) sources. The lines represent the average over depths in the muscle layer from 0.5 to 10 mm and fat thicknesses from 1 to 7 mm, and the shaded area illustrate the range. Inset: Stereotypical second spatial difference of the potentials along a model axon (101 nodes).

Figure 3. Stimulation threshold as a function of carrier frequency of the Transdermal Amplitude Modulated Signal (TAMS) for 7 different geometries of the volume conductor model

(a) Voltage-controlled stimulation. (b) Current-controlled stimulation. Threshold is defined as the dc component of TAMS. (c) Same as in (a), but with threshold measured as the total energy delivered by the voltage source. Threshold for conventional rectangular pulses is shown in the shaded area and corresponds to the amplitude of the pulse in (a) and (b), and to the energy in (c). Each plot shows the thresholds for seven geometries that differed from the base condition (diamonds, solid line) in a single parameter. The base condition was: skin thickness: 2.5 mm, fat thickness: 2.5 mm, and nerve depth in muscle: 3 mm. Pulse width: 10 ms in all cases. Electrode diameter: 2 cm. Fiber diameter: 14 μ m.

Figure 4. Strength-distance relationship for the Transdermal Amplitude Modulated Signal (TAMS) and rectangular pulses

Thresholds for three fiber diameters (fiberD) as a function of distance from the skin surface to the nerve fiber when administering (a) voltage-regulated stimulation, and (b) current-regulated stimulation. Dotted vertical lines in (b) indicate the location of the interfaces between tissue layers. Skin thickness: 1.5 mm, fat thickness: 2.5 mm. Pulse width: 1 ms.

Figure 5. Transmembrane voltage response to sinusoidal stimulation

(a) Time course of the reduced transmembrane potential, $V_m - V_{rest}$, at the central node of a 14 μm fiber (bottom row) for five sub-threshold stimulation waveforms (top row) in a purely resistive medium. (b) Ratio of the root mean square (RMS) value of the reduced transmembrane potential (V_{RMS} , as depicted in (a), second panel from left) generated by sinusoidal stimulation with a fixed amplitude to the maximum depolarization generated by a sub-threshold rectangular pulse ($V_{dep\ max}$, as depicted in (a), leftmost panel). The ratio is plotted against frequency for five fiber diameters (fiberD). (c) Comparison of thresholds for zero offset sine waveforms, measured as the signal amplitude, and the Transdermal Amplitude Modulated Signal (TAMS), measured as the dc component. Electrode diameter: 2 cm. Fiber to electrode distance: 7 mm.

Figure 6.

(a) Motor thresholds reported by Ward and Robertson (2001). (b) Single action potential thresholds obtained with the model. Skin thickness: 1.5 mm. Fat thickness: 2.5 mm. Electrode: 40×44 mm.

Figure 7. Waveforms from the model of the Slovak *et al* (2013) experiment

Input current (*top*) and voltage across the electrodes (*bottom*) for the forearm model.

Waveforms are shown for the Transdermal Amplitude Modulated Signal (TAMS) (*left*) and for conventional rectangular pulse (*right*). Skin thickness: 1.5 mm. Fat thickness: 2.5 mm.

Electrode diameter: 2 cm. Inter-electrode distance (center to center): 3 cm.

Table 1

Thresholds obtained with the forearm model and motor thresholds reported by Slovak *et al* (2013).

	Rectangular pulse	TAMS
Model	3.52 mA	3.38 mA
Slovak <i>et al</i> (2013)	3.84 ± 0.68 mA	3.81 ± 0.77 mA