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Contribution of dielectric dispersions to voltage waveforms arising from electrical stimulation

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***Abstract*—This study presents an analysis of the effect of incorporating a subset of the complete set of dielectric dispersions in electric field models of implanted electrical stimulation. An analytic volume conductor model was used to determine the voltage waveform at a distance of 5 mm from a point current stimulus for 17 different biological tissues. The RMS error of the voltage waveform resulting from the incorporation of a subset of all poles with respect to the voltage waveform resulting from the incorporation of the complete set of dispersive poles was calculated. The stimulus amplitude necessary to elicit action potential propagation in a myelinated mammalian nerve fibre in each of the dispersive models was also determined using a multicompartment cable axon model. It was found that, for all tissues, removal of dispersions with pole frequencies greater than 1 MHz had a negligible effect on the threshold stimulation amplitude, suggesting that they may be neglected when constructing volume conductor models of electrical stimulation. However, removal of low-frequency dispersions below 1 MHz resulted in greater reductions in the threshold stimulus amplitudes necessary for activation of axons, with errors of up to 86 % observed.**

I. Introduction

A large proportion of models of electrical stimulation assume that the quasi-static approximation is valid [1]. Under this approximation, capacitive, inductive and propagation effects may be assumed to be negligible [2]. Neglect of capacitive effects is generally considered to be the weakest of these assumptions, however inductive and propagation effects have been comfirmed to be negligible for frequencies and volume conductor dimensions of interest [1]. In the case of implanted electrical stimulation, specifically deep brain stimulation, it has been shown that incorporation of tissue capacitance into models of the electric field reduced the simulated volume of neural tissue activated by the stimulus [3].

The dielectric properties of many biological tissues are known to be frequency dependent, or dielectrically dispersive [4], [5], [6], [7], [8]. Recent computational studies have shown that the effect of incorporating dispersion depends on whether a controlled voltage or current is used for stimulation [9], [10]. It has also been suggested that dispersion may be approximated by resistive [1] and capacitive [10] models in certain circumstances by estimating material properties at an appropriate frequency.

Dielectric tissue models typically express dispersions in the form of multiple Debye, Lorenz or Cole-Cole poles, which individually correspond to different physical processes [6], [7], [8]. Dispersions in the GHz region are reported to be due to the polarisation of water molecules [6]. Those in the MHz region correspond to polarisation of cellular membranes, while low frequency dispersions are attributed to ionic diffusion processes across the cell membrane [6]. To date, studies incorporating dispersive electric field models have included all of the dispersive poles for a given tissue type [1], [10]. It is not therefore known which physical processes and their corresponding dispersions have a functional influence on the efficacy of a given stimulus in activating neural tissue, and which dispersions may be neglected.

Models incorporating capacitance, including those incorporating dispersion, have most frequently used a frequency-domain solution [3], [1], [10]. Approaches have been suggested towards reducing the computational burden associated with frequency-domain models [11]. While each additional dispersion contributes minimal additional memory storage requirements for frequency-domain solutions, time-domain solutions, which can have computational advantages over frequency-domain solutions, increase linearly in complexity as additional dispersive poles are added [12]. Therefore, the ability to appropriately simplify dielectric models by removing poles that do not functionally affect the predicted outcome of stimulation may be advantageous.

The aim of this study was to quantify the effect of using a subset of dispersions instead of all dispersions on the output waveform in the vicinity of the stimulating electrode and on the threshold for activation of a generalised myelinated mammalian axon.

II. Methods

The voltage waveforms and threshold stimulus amplitudes for neural activation were determined for 17 tissues as described in [6], and compared for cases where subsets of the complete set of dispersive poles were incorporated.

A. Stimulation

The trigonometric fourier coefficients were determined for a generic cathodic rectangular waveform, with pulse frequency, f_p, of 100 Hz and pulse duration, τ_p, of 400 µs. Stimulus pulses were then synthesised in the time-domain using 2000 terms of the trigonometric fourier series, with the lanczos sigma approximation applied to reduce the Gibb's phenomenon. The sampling frequency of the waveform, f_s, was well above twice the maximum frequency component of 200 kHz.

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B. Volume conductor model

An homogeneous volume conductor of infinite extent was considered. The complex permittivity, $\hat{\epsilon}$, as a function of the angular frequency, ω, is given by the Cole-Cole equation.

$$\hat{\epsilon}(\omega) = \epsilon_\infty + \sum_n \frac{\Delta\epsilon_n}{1 + (\frac{j\omega}{f_n})^{(1-\alpha_n)}} + \frac{\sigma_i}{j\omega\epsilon_0} \tag{1}$$

For a given material, the permittivity at infinity ϵ_∞ and the intrinsic conductivity σ_i govern its behaviour at excitation frequencies of infinity and zero. Each dispersion, n, contributes an increment in complex relative permittivity, $\Delta\epsilon_n$, at the pole frequency, f_n, with the Cole-Cole spreading parameter, α_n.

For a given point current source, with injected current I_S, the transfer function, H, which relates the voltage at a distance r from a unit input current as a function of frequency was given by

$$H(r, \omega) = \frac{1}{4\pi\sigma(\omega)r} \tag{2}$$

Using the Fourier transform, $\mathcal{F}$, the periodic voltage waveform, y, in the tissue at a point at a distance r from the stimulating point current source was given by

$$y(r, t) = \mathcal{F}^{-1}\left[H(r, \omega) \cdot \mathcal{F}\left(x(t)\right)\right] \tag{3}$$

Simulation of the voltage waveform resulting from stimulation was implemented in Python using the SciPy FFT library [13].

C. RMS error of voltage waveform

For each material, dispersions were successively removed in order of descending frequency. As n dispersions were removed, the voltage waveform, $y_n(t)$, at a given distance from the point of stimulation was simulated and the RMS error, E_n, with respect to the voltage waveform, $y_a(t)$, with all dispersions incorporated was calculated over the pulse duration from the rising edge of the pulse at t_0 to the falling edge of the pulse at $t_0 + \tau_p$ as follows

$$E_n = \sqrt{\int_{t=t_0}^{t=t_0+\tau_p} \left(\frac{y_n(t) - y_a(t)}{y_a(t)}\right)^2 \mathrm{d}t} \tag{4}$$

D. Axon model

The mammalian myelinated axon model developed by McIntyre *et al.* [14] was applied to quantify the effect of removing individual poles dispersive poles on the required stimulation amplitudes necessary to elicit action potential propagation. Axons included of 21 nodes of ranvier, with internodal spacing of 500 µm. The fibre diameter was set to 5.7 µm, with all dependent parameter values set equal to those given in [14].

The axon model was implemented using NEURON 7.1 in conjunction with the Python interpreter [15]. The voltage at each of the 21 nodes was calculated and applied as an extracellular potential to each node. The time step was set to 1.0 µs, which was equal to that used in the volume conductor model.

Determination of the minimum stimulus amplitude necessary to elicit action potential propagation, to a tolerence of 1 µA, was performed using the Brent method, as implemented in the SciPy optimisation library for an axon located 5 mm from the stimulation point [13].

III. Results

The voltage waveform in the tissue in response to a 1 A stimulus current is presented for grey matter in Figure 1 and for muscle tissue in Figure 2.

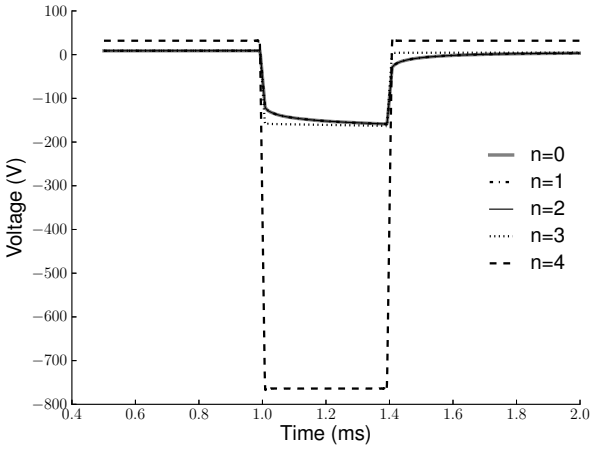

Fig. 1. Voltage waveform 5 mm from the stimulating point current source in grey matter. n denotes the number of dispersions removed, in order of descending pole frequency.

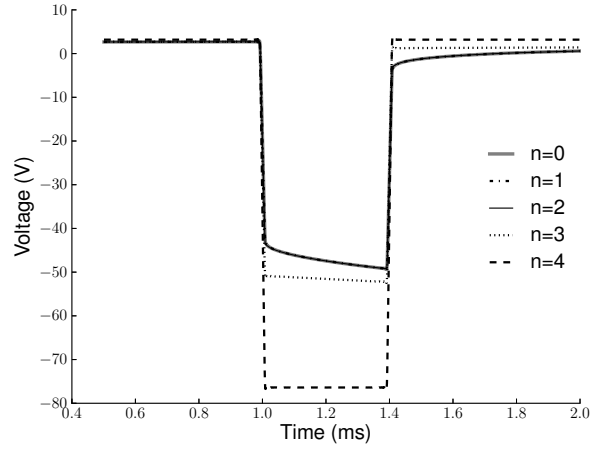

Fig. 2. Voltage waveform 5 mm from the stimulating point current source in muscle. n denotes the number of dispersions removed, in order of descending pole frequency.

For each of the 17 tissues described in [6], the RMS error of the voltage waveform at a distance of 5 mm following the

TABLE I

RMS ERROR, E_n, OF THE VOLTAGE WAVEFORM AT A DISTANCE OF 5 mm FOLLOWING THE REMOVAL OF POLES 1 TO n IN ORDER OF DESCENDING POLE FREQUENCY WITH RESPECT TO THE VOLTAGE WAVEFORM SIMULATED WHERE ALL POLES WERE INCORPORATED. THE POLE FREQUENCY OF THE n^{th} DISPERSION IS DENOTED BY f_n. BLOOD AND DRY SKIN HAVE TWO DISPERSIONS, ALL OTHER TISSUES HAVE FOUR.

Tissue	**Pole 1 removed**		**Poles 1-2 removed**		**Poles 1-3 removed**		**Poles 1-4 removed**	
	f_1 (GHz)	E_1	f_2 (MHz)	E_2	f_3 (kHz)	E_3	f_4 (Hz)	E_4
Blood	119.33	0.00	7.54	0.01				
Bone (cancellous)	75.41	0.00	12.57	0.01	6.28	0.09	62.83	0.20
Bone (cortical)	75.41	0.04	12.57	0.75	6.28	3.39	62.83	3.40
Brain (grey matter)	125.63	0.00	62.81	0.01	9.43	6.06	188.50	44.31
Brain (white matter)	125.63	0.00	125.63	0.00	18.85	3.16	125.66	11.84
Fat (infiltrated)	125.63	0.00	62.81	0.00	6.28	8.72	62.83	11.82
Fat (non infiltrated)	125.63	0.00	62.81	0.00	6.28	8.10	125.66	24.93
Heart	125.63	0.00	6.28	0.09	13.82	34.54	0.22	34.57
Kidney	125.63	0.00	5.03	0.05	12.57	6.72	219.93	20.45
Lens cortex	125.63	0.00	12.57	0.01	6.28	0.23	62.83	0.27
Liver	113.12	0.00	1.88	0.20	43.98	2.71	62.83	15.25
Lung (inflated)	125.63	0.00	15.71	0.01	6.28	9.26	125.66	27.90
Muscle	138.31	0.00	2.83	0.47	3.14	261.80	439.75	621.79
Skin (dry)	138.31	0.29	30.79	3.33				
Skin (wet)	125.63	0.05	12.57	0.39	628.93	38.78	628.14	66.23
Spleen	125.63	0.00	15.71	0.04	3.77	7.85	157.08	35.48
Tendon	81.70	0.00	156.99	0.00	3.14	0.67	754.15	7.03

successive removal of dispersions in order of descending pole frequency with respect to the voltage waveform simulated where all poles were incorporated is given in Table I.

Removal of dispersions in the GHz frequency range had a negligible effect on the voltage waveform in all tissues with errors of less than 5 % except for dry skin in which an RMS error of 0.29 was observed. Similarly, removal of dispersion in the MHz range had a small effect on the voltage waveform in most tissues. RMS errors of over 10 % were observed in the case of cortical bone, liver, muscle and skin. Removal of dispersions in the kHz region introduced RMS errors of up to 10 in most tissues, although errors of 34.54, 261.8 and 38.78 were observed for heart, muscle and wet skin, respectively. Errors in excess of 100 % were also observed for all tissues except cancellous bone and lens cortex following removal of low-frequency dispersions.

The minimum amplitude of the stimulus pulse required to elicit action potential propagation in an axon at a distance of 5 mm from the cathodic point current source stimulus, is presented in Table II. The effect of removing dispersions in both the GHz and MHz frequency ranges on threshold amplitudes for stimulation was negligible. Reductions in threshold stimulus amplitudes were observed for all tissues when dispersions in the kHz region were removed, and to a greater extent where low-frequency dispersions less than 1 kHz were removed.

IV. DISCUSSION

This study presents an analysis of the errors introduced by utilising a subset of the four primary dispersions when estimating the electric field due to stimulation in 17 different materials.

It was found that dispersions in the MHz and GHz frequency ranges had negligible effect on the voltage waveform due to stimulation in most tissues. In addition, it was found that these dispersions had a negligible effect on the threshold stimulus amplitude required to activate an axon at a distance of 5 mm from the stimulating electrode. These results suggest that polarisation of water molecules does not affect the functional behaviour of electrical stimulation, and that the high-frequency dispersions in the MHz and GHz frequency ranges may be neglected when constructing volume conductor models for analysing the effect of electrical stimulation under commonly used stimulation parameters.

However, removal of dispersions below 1 MHz resulted in large RMS errors in the voltage waveform and corresponding changes in the threshold stimulation amplitude. In particular, removal of dispersions below 1 kHz reduced the threshold stimulation amplitude by over 50 % in many cases. These results suggest that ionic diffusion processes at the cell membrane and polarisation of the cell membrane contribute to the functional electrodynamical effects of the tissue and should be included when constructing volume conductor models for analysing the effect of electrical stimulation under commonly used stimulation parameters.

Application of the results will depend on the question of interest. Axonal fibres are not found in many of the tissues simulated in this study. However, the electrodynamical behaviour of these tissues is relevant to volume conduction studies incorporating material homogeneities [10], [16], since their electrodynamical behaviour may alter the temporal voltage waveform observed at neural structures of interest.

The results of this study have the potential to reduce the computational burden of simulation, depending on the method used to solve for the spatio-temporal electric field. Using the frequency-domain method as employed in this study, reductions in memory usage or computation time would be negligible. However, in the time-domain, where

TABLE II

STIMULATION CURRENT AMPLITUDE, a_n, REQUIRED TO ELICIT AXONAL ACTIVATION AT A DISTANCE OF 5 mm FROM THE STIMULUS POINT CURRENT SOURCE FOR AN AXON LOCATED IN A HOMOGENEOUS ISOTROPIC MEDIUM WITH THE PROPERTIES OF EACH TISSUE. n IS THE NUMBER OF POLES REMOVED, IN ORDER OF DESCENDING FREQUENCY. THE POLE FREQUENCIES ARE THE SAME AS THOSE IN TABLE I.

Tissue	**All poles included** a_0 (µA)	**Pole 1 removed** a_1 (µA)	**Poles 1-2 removed** a_2 (µA)	**Poles 1-3 removed** a_3 (µA)	**Poles 1-4 removed** a_4 (µA)
Blood	5019	5019	5019		
Bone (cancellous)	584	584	584	581	502
Bone (cortical)	145	145	145	145	142
Brain (grey matter)	722	722	722	682	142
Brain (white matter)	429	429	429	423	142
Fat (infiltrated)	301	301	301	291	252
Fat (non infiltrated)	160	160	160	154	72
Heart	453	453	453	359	359
Kidney	829	829	829	777	359
Lens cortex	2351	2351	2351	2312	2150
Liver	304	304	304	294	142
Lung (inflated)	581	581	581	536	215
Muscle	2303	2303	2303	2126	1433
Skin (dry)	2	2	2		
Skin (wet)	14	14	14	5	2
Spleen	743	743	743	713	215
Tendon	2730	2730	2730	2721	1793

memory storage requirements are linearly related to the number of dispersions [12], exclusion of the higher-frequency poles may reduce the computation burden. The results of this study suggest that a 50 % reduction in memory usage may be achievable for many tissues.

This study contained a number of limitations. To ensure uniformity of method, this study incorporates the 17 tissue types described in [6] only. However, other dispersive tissue models including those published for brain tissue [8] and muscle [7] may be analysed using the same methods. Tissues were assumed to be homogeneous and isotropic. Furthermore, the analytical volume conductor neglected other dynamical components that may be present, such as the frequency-dependent electrode-tissue interface.

V. CONCLUSION

For the all biological tissues examined, except dry skin, errors in the voltage waveform were small when dispersions with pole frequencies greater than 1 MHz were removed. The results of this study suggests that dispersions with pole frequencies greater than 1 MHz may be neglected in most tissues by volume conductor models that analyse the effect of electrical stimulation on neural activation under commonly used stimulation parameters. However, large RMS errors in the voltage waveform and in the threshold stimulus amplitude necessary to elicit axonal activation were observed when dispersions with pole frequencies below 1 MHz were removed.

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