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Sensitivity analysis of neurodynamic and electromagnetic simulation parameters for robust prediction of peripheral nerve stimulation

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Abstract

Peripheral nerve stimulation (PNS) has become an important limitation for fast MR imaging using the latest gradient hardware. We have recently developed a simulation framework to predict PNS thresholds and stimulation locations in the body for arbitrary coil geometries to inform the gradient coil optimization process. Our approach couples electromagnetic field simulations in realistic body models to a neurodynamic model of peripheral nerve fibers. In this work, we systematically analyze the impact of key parameters on the predicted PNS thresholds to assess the robustness of the simulation results. We analyze the sensitivity of the simulated thresholds to variations of the most important simulation parameters, including parameters of the electromagnetic field simulations (dielectric tissue properties, body model size, position, spatial resolution, and coil model discretization) and parameters of the neurodynamic simulation (length of the simulated nerves, position of the nerve model relative to the extracellular potential, temporal resolution of the nerve membrane dynamics). We found that for the investigated setup, the subject-dependent parameters (e.g. tissue properties or body size) can affect PNS prediction by up to ~26% when varied in a natural range. This is in accordance with the standard deviation of ~30% reported in human subject studies. Parameters related to numerical aspects can cause significant simulation errors (>30%), if not chosen cautiously. However, these perturbations can be controlled to yield errors below 5% for all investigated parameters without an excessive increase in computation time. Our sensitivity analysis shows that patient-specific parameter fluctuations yield PNS threshold variations similar to the variations observed in experimental PNS studies. This may become useful to estimate population-average PNS thresholds and understand their standard deviation. Our analysis indicates that the simulated PNS thresholds are numerically robust, which

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is important for ranking different MRI gradient coil designs or assessing different PNS mitigation strategies.

Keywords

peripheral nerve stimulation; magnetostimulation thresholds; sensitivity analysis; electromagnetic field simulation; neurodynamic model; EM exposure safety; MRI gradient coil switching

Introduction

In magnetic resonance imaging (MRI), the gradient coils apply time-varying magnetic fields (in the 100 Hz–5000 Hz range) to rapidly encode the image (Ham *et al* 1997, Okanovic *et al* 2018) as well as for signal preparation such as diffusion and velocity encoding.

Unfortunately, the time-varying magnetic fields create electric fields (E-fields) in the patient's body with frequencies and strengths such that they can induce peripheral nerve stimulation (PNS). Near the threshold of PNS, the patient typically experiences only a mild tingling sensation. However, if not properly constrained, more intense fields can cause serious discomfort or even pain (Schaefer *et al* 2000). With ever improving gradient coils and power amplifier designs, the achievable slew rate and strength of the fields has been steadily increasing to the point where PNS is becoming a principal limiting factor for imaging speed. Despite the increasing relevance of PNS as a limitation, PNS thresholds are not currently directly incorporated into the design of gradient coils. Instead, coils are designed to achieve engineering targets for maximum gradient strength ($G_{\max}$), maximum slew rate ($S_{\max}$), heat generation and removal, etc. PNS thresholds are only checked after prototype construction using experiments on healthy subjects.

Adding PNS as a target metric in the gradient coil design process has been achieved using surrogate markers of PNS performance such as linearity volume (Zhang *et al* 2003), but direct incorporation has historically been difficult because of the absence of a robust PNS simulation tool. Recently, we have developed a simulation framework for whole-body PNS prediction (Davids *et al* 2017, 2018). Our approach couples electromagnetic (EM) field simulations in realistic body models to neurodynamic simulations of the peripheral nerve response to the induced E-fields. The model reproduces experimental MRI-and magnetic particle imaging (MPI)-induced PNS in the human body within ~10% for a large variety of coils including solenoid coils as well as head and body MRI gradient coils. It correctly replicates the relative PNS performance of different gradient waveforms (sinusoidal and trapezoidal), as well as modes of coil operation (such as single axis ' X ' and combined axes ' $X+Y+Z$ ' modes) (Davids *et al* 2017, 2018). The model also accurately predicts the first site of stimulation (shoulder, nose, etc), although the experimental data to validate this is scarcer.

Although able to replicate experimental data, the widespread use of any biological simulation framework requires an understanding of the relative impact of the many model parameters used. The PNS simulation framework contains an abundance of parameters, some physiological (e.g. the body model specifications or the nerve locations and diameters, etc) and some computational (e.g. the spatial-temporal resolution of the time-varying E-

fields in the body). Most of the physiological parameters are set to the population averages. While reasonable, this does not reflect the variability of these parameters between different subjects and thus does not inform the range of thresholds that might be encountered in a population. The computational parameters, on the other hand, need to be set so as to achieve both high model accuracy and reasonable computation time. For a computational parameter, typically ‘good enough’ is identified when further refinement of the parameter does not alter the result.

So *et al* found that the size, shape, and spatial resolution of the body model have a major impact on the internal E-fields generated (So *et al* 2004), as does the position of the coil relative to the body model (Pisa *et al* 2014, So *et al* 2004). Neufeld *et al* showed that other simulation aspects such as the relative orientation of the nerve segments and the E-field or the neurodynamic model chosen to describe the nerve membrane dynamics can also have a significant impact on PNS predictions (Neufeld *et al* 2016). Given the recent successes in using EM field calculation in realistic body models together with neurodynamic simulations and the known dependency of the simulation outcome on important determinants within the simulation (Laakso *et al* 2014, Neufeld *et al* 2016, Davids *et al* 2017, 2018, Mourdoukoutas *et al* 2018), a systematic analysis of the impact of all key parameters on the predicted PNS thresholds is needed to understand the validity and robustness of the simulation results.

In this work, we systematically study the impact of nine important PNS simulation parameters on the accuracy and robustness of the predicted PNS thresholds (sensitivity analysis). We study the modeled PNS threshold sensitivity with respect to parameters of the EM field simulations (such as dielectric tissue properties, body model size and position in the coil, and body model and coil discretization resolution) as well as to parameters of the neurodynamic simulation (such as length of the simulated nerve segments, relative position of the nerve model with respect to the extracellular potential, and temporal resolution of the nerve membrane dynamics).

Methods

PNS simulation framework

The peripheral nerve stimulation (PNS) simulation framework has previously been described in detail (Davids *et al* 2017). The basic steps are outlined in figure 1. In short, the framework consists of a surface-based body model containing the major nerves of the peripheral nervous system (Step 1). Then EM field simulation determines the induced E-field distribution in the body model (Step 2). We use the low-frequency finite element method (FEM) solver of Sim4Life (Zurich MedTech AG, Switzerland) for the E-field simulation. We simulate the EM fields at a single frequency (1 kHz in this work) and then determine the field at other frequencies by simply scaling the E-field amplitude based on a linear scaling model. This allows us to quickly assess PNS in the relevant frequency range (0.46 kHz to 10.3 kHz). This simplification does not significantly affect the PNS thresholds (<3% effect). In Step 3, we project the E-field onto the nerve fibers and integrate, yielding the electric potential changes along the nerves. Finally, the response of the nerves to the coil’s E-field is computed using a model of mammalian nerve fibers, the McIntyre-Richardson-Grill (MRG) model (McIntyre *et al* 2002), in Step 4. In this neurodynamic model, the stimulus is the

electric potential modulated by the coil waveform, e.g. a trapezoidal or sinusoidal function. PNS threshold curves are computed using the so-called ‘titration process’: The coil waveform amplitude (for a given frequency) is increased until an action potential (AP) is produced somewhere in the body model. We define the PNS onset as the creation of the first AP. As a surrogate for PNS stimulation, we also compute the neural activation function along each nerve. This activation function is the 2nd spatial derivative of the electric potential along the nerve and has been shown to be a useful scalar representation of a given diameter nerve’s threshold for AP generation (Rattay 1986).

PNS threshold sensitivity with respect to EM simulation parameters

As detailed in Davids *et al* (2017), we modified the Zygote adult male and female anatomical models (American Fork, UT, USA) in order to make them suitable for PNS simulations. We used a re-meshing strategy that ensures that the surface mesh description of the organs is topologically correct, i.e. two-manifold, watertight and without intersections. The resulting models contain hundreds of surfaces classified in 21 tissue types as well as a detailed atlas of the largest nerves in the body (~1900 nerve tracks) geometrically registered within the tissues. We classified each nerve segment by the type of innervation (motor or sensory), based on information given in the literature. We then assigned the largest common axon diameters to each nerve type (20.0 μm for motor nerves, and 12.0 μm for sensory nerves). These fiber diameters have e.g. been measured in nerve conduction velocity studies (Daube and Rubin 2012). Assigning the largest axon diameters allows us to get a conservative estimate of the PNS threshold, which is lowest for large nerve fibers. We currently do not explicitly include the small autonomous nerves in our simulations due to their low PNS susceptibility.

Impact of the material database—We used two material databases for the assignment of the tissue conductivity and permittivity: The IT’IS (Zurich, Switzerland) low-frequency (LF) database (Hasgall *et al* 2015) and the Gabriel database (Gabriel 1996). The IT’IS LF database lists conductivity values based on a combination of the Gabriel dispersion relations (Gabriel *et al* 1996b, 1996c) and experimental data measured at frequencies below 1 MHz (Hasgall *et al* 2015) (the permittivity values are the same as in the Gabriel database). The Gabriel database, on the other hand, calculates conductivity and permittivity values as described in Gabriel (1996). As the IT’IS LF database is partly based on the Gabriel database, the two databases are not completely independent.

In addition to systematic variations in an organ’s population-average EM properties (as captured by the IT’IS LF and the Gabriel databases), it is known that there is biological variability between subjects for a given tissue (Gabriel *et al* 1996a, 1996c). We assessed the effect of these variations on PNS thresholds by altering the conductivity of each tissue class in the leg body model separately by $\pm 50\%$ while keeping the conductivity of all other tissue classes constant. In comparison, the IT’IS LF database reports standard deviations of the electric conductivity values for muscle, fat, nerve, and skin tissue as 56% for muscle, 85% for fat, 145% for nerve, and 66% for skin. We did not study the effect of permittivity variations since the LF solver used in this work neglects displacement currents, thus the computed E-fields are expected to be completely independent from permittivity. This

approximation was previously shown to be accurate at low frequencies (Bowtell and Bowley 2000, Bossetti *et al* 2008).

Impact of modeling of the nerve tissue—We also used two strategies to assess the importance of including the nerve fiber itself in the EM body model: We modeled the peripheral nerves considered in this work with and without the surrounding nerve tissue. For this analysis, we assigned the eight voxels surrounding each point of the nerve tracks with either the EM properties of myelinated nerve tissue or with those of the tissue classes adjacent to the nerve track and compared PNS thresholds associated with this model difference on the computed E-fields.

Impact of body size and position—The patient's size and body position in the gradient coil are also known to impact the PNS thresholds (Chronik and Rutt 2001, Saritas *et al* 2013). In particular, it is known that PNS thresholds vary inversely with the size of the body, i.e. bigger subjects have more severe stimulation (lower PNS threshold) (Irnich and Schmitt 1995, Saritas *et al* 2013). We simulated scaled versions of the female body model ($\pm 10\%$ isotropic, yielding body heights of 146 cm to 179 cm and weights of 47.3 kg to 57.9 kg) to test whether our simulations reproduce this well-established phenomenon. Resulting BMIs of the scaled body models were 22.2 and 18.1. We also simulated the original leg model translated by ± 40 mm in the axial and transverse directions with respect to the coil isocenter in order to assess the dependence of PNS thresholds on body position.

Impact of the body model resolution—The E-field distribution in the body is strongly affected by the local geometry of conductive tissues. For example, small anatomical features such as thin insulating fatty layers separating conductive muscle fiber bundles may lead to a local E-field hotspot. Therefore, it is desirable to model the body at a high resolution. Although increasing the body model resolution beyond the segmentation accuracy of the underlying anatomical model does not add any additional anatomical details, the EM field solver accuracy may still benefit from smaller hexahedral mesh cells up to a point. However, high spatial resolution increases computation complexity, memory requirements and simulation times. A tradeoff between accuracy and computational complexity is unavoidable, but ideally the PNS thresholds should converge as the spatial resolution of the model is progressively increased and an acceptable tradeoff determined. We simulated the leg model at resolutions ranging from 0.5 mm to 5.0 mm (isotropic) to assess this. In this context, 'resolution of the body model' denotes the resolution of the voxel discretization step of the original Zygote model performed before generation of EM-ready surfaces. The resolution of the FEM solver was always matched to this 'base body resolution' in order to avoid resolution mismatch artifacts, which may otherwise affect the results.

Impact of the coil discretization resolution—Most EM field simulation tools approximate curved wires as piecewise linear. Increasing the length of the linear wire segments can significantly reduce computation time, however at the cost of reduced accuracy of the winding representation and potentially the field. In order to assess the importance of this phenomenon, we simulated the solenoid coil using straight wire segments with lengths ranging from 0.6 cm to 7.6 cm (yielding between 100 and 8 straight wire

segments per turn). For each of the simplified coil models, we ensured that the average distance between the wire segments and the coil axis matches the target radius of 9.5 cm (i.e. coil models with longer straight wire segments need to be scaled up), and calculated the PNS threshold. An alternative approach would be to simply assess the magnetic field generated by the coil (being the driving function of the E-field). In other words, refining the coil windings up to the point where the B-field does not vary anymore ensures that this approximation will be sufficient for PNS modeling.

PNS threshold sensitivity with respect to neurodynamic simulation parameters

Impact of a truncated nerve model—The MRG model is an electrical circuit representation of myelinated nerve fibers (McIntyre *et al* 2002). Mathematically, the model is characterized by a set of coupled differential equations describing the ion channel dynamics. The computational complexity of the MRG model increases with the length of the modeled nerve (i.e. with the number of nodes of Ranvier included). For the leg of the female body model, a total of ~79 600 electrical compartments need to be analyzed. Processing the entire nerve tree at once would be computationally infeasible: For example, for stimuli consisting of 16 sinusoidal periods, the calculation of PNS threshold curves for the entire nerve tree would require roughly one week of computation time (no parallelization used). Therefore, instead of ‘solving’ the entire nerve atlas at once we divide it into separate ‘nerve segments’ and simulate the membrane dynamics of each nerve segment individually. Doing so is equivalent to decoupling the differential equations describing the nerve dynamics in different parts of the nerve atlas. Although necessary from a computational standpoint, this may lead to numerical inaccuracies, instabilities and unwanted artifacts, such as artificial stimulation at the boundaries of truncated nerve segments if the nerve is divided in a region of substantial transmembrane current flow. In order to minimize this phenomenon, we use the so-called activation function to separate the nerve atlas into sections which can be safely functionally decoupled, as described in Davids *et al* (2017). We investigated the impact of the nerve segment length on the PNS thresholds by calculating stimulation thresholds for four different nerves located in the leg and altering the lengths of these nerves from 3 to 45 nodes of Ranvier to assess edge effects in the neurodynamic simulations. We simulated these four nerves with a fiber diameter of 12.0 μm , which corresponds to an internodal distance of 1.3 mm (McIntyre *et al* 2002).

Impact of the node of Ranvier position—The myelin sheath is an insulator that increases the propagation velocity of APs along the nerves. Sheath segments are separated by the nodes of Ranvier. In the MRG nerve fiber model, the equivalent electrical circuits of the myelin and the nodes of Ranvier are connected in parallel to the extracellular electric potential (McIntyre *et al* 2002) (see figure 1, Step 4). The location of the nodes of Ranvier with respect to the extracellular field has an impact on the excitability of the nerve, since these are the locations where the axon is most susceptible to stimulation by electric field gradients. Since we do not know the precise location of the nodes, there is a free ‘shift’ parameter that is not specified in the nerve atlas. We quantified the shift parameter in percent of the inter-Ranvier distance relative to a reference position. We chose the peak of the activation function along the nerve track as this reference position. We computed PNS

thresholds at 1 kHz for two nerves located in the leg, assessing Ranvier shifts varying from −50% to +50%.

Impact of the nerve model solve time step—We solve the differential equations of the MRG model numerically using the backward-Euler numerical integration technique with a small time step as implemented in the NEURON simulation package (Hines and Carnevale 1997). High temporal resolution (small time steps) provides accurate modeling of the nerve dynamics albeit at the cost of long computation time. It is therefore desirable to use the coarsest temporal resolution that maintains accurate PNS threshold prediction. This optimal time step must allow accurate representation of both the nerve membrane dynamics and the coil's driving waveform. We characterized the time step's effect on PNS thresholds for both bipolar sinusoidal and trapezoidal excitations at frequencies ranging from 500 Hz to 50 kHz. We assessed 30 choices for the time steps ranging from 10 to 2000 steps per pulse duration.

Results

Figure 2 compares PNS thresholds computed using two different material databases for the assignment of dielectric properties to the body model's tissues: The IT'IS low-frequency (LF) database (Hasgall *et al* 2015) and the Gabriel database interpolated at 1 kHz (Gabriel 1996). As shown in figure 2(b), the main differences between the IT'IS LF and the Gabriel database are the electric conductivity ascribed to the nerve and skin tissues: The conductivities in the Gabriel database at 1 kHz are smaller than those in the IT'IS LF database by −10% for muscle, −27% for fat, −89% for nerve, and almost −100% for skin. Figure 2(b) shows that the E-fields are strongly shaped by the local conductivity distribution: For example, hotspots are visible in areas where the local induced current is forced into small volumes such as the shinbone-muscle connection (arrow A) and within small fatty layers (arrow B). Figure 2(c) shows that the IT'IS LF database is more accurate at predicting PNS thresholds (Gabriel database-based estimation of the PNS thresholds leads to a 21%–43% error in the 0.46 kHz to 10.3 kHz frequency range, whereas the error for the IT'IS LF database is 1%–22%).

Figure 3 shows the effect of perturbing the electric conductivity of tissues in the IT'IS LF database by $\pm 50\%$ to mimic the normal biological variability of *in vivo* EM properties at low frequencies (Gabriel *et al* 2009). The tissue conductivity with the greatest impact on the PNS threshold is muscle (11%–26% effect at 1 kHz), likely reflecting its role as the largest volume tissue class in the leg. It is interesting to note that increases/decreases of the conductivity value have opposite effects for muscle compared to the 'fatty' tissues (fat and nerve). Additionally, the impact of fat and nerve conductivity variations on the PNS threshold is $<10\%$, and the impact of skin conductivity variations is even smaller ($\sim 2\%$).

Figure 4 shows the effect of embedding the nerve tracks in nerve tissue with an electric conductivity of 265 mS m^{-1} (equivalent to white matter (Hasgall *et al* 2015)). The enlarged details show the E-field around the location of nerve stimulation. When the nerve tissue properties are included in the EM simulation step, the E-field magnitude is reduced around the nerve track, resulting in smaller amplitude activation function values and higher stimulation thresholds. Modeling the nerve tissue increases the PNS threshold by +32% at 1

kHz compared to when the nerve tissue is not explicitly modeled and, for the simulations conducted in this work, yields better agreement with the experimental data.

We found that uniform scaling of the body model size by +10% in the X , Y and Z directions leads to a decrease of the PNS threshold by -9% at 1 kHz for the female leg body model. Conversely, modeling a -10% smaller body model (by uniform scaling) increases the PNS threshold by +9%. Thus, the simulations reproduce the expected inverse correlation between stimulation threshold and body size. Translation of the leg model by ± 40 mm in the transverse directions (X and Y) leads to PNS threshold variations of up to 8% at 1 kHz, while translation of the leg model of ± 40 mm in the axial direction (Z) leads to threshold variations of up to 15%.

Figure 5 shows that insufficient body model resolution can have a negative impact on PNS prediction, but the thresholds seem to converge for model resolutions of 1.5 mm or less. This likely arises from the need to accurately represent E-field hotspots associated with 'kissing' layers of tissues where the electrical current density tends to concentrate (arrows A and B). Coarse spatial resolutions > 2 mm do not permit to accurately represent this phenomenon, which leads to errors in the estimation of PNS thresholds. For this body model, we found that using a 1 mm discretization voxel yields PNS threshold errors smaller than $\pm 5\%$ compared to the highest resolution modeled (0.5 mm isotropic).

Figure 6 shows the impact of coarsening the coil winding linear segment approximation on PNS thresholds and computation time for the solenoid coil. We found that using linear segments with a length of 7.6 cm instead of 0.6 cm decreases the simulation time by 87% at the cost of a negligible PNS threshold error of less than 0.5%.

Figure 7 illustrates the effect of the length of nerve segments (in units of number of nodes of Ranvier) used in the neurodynamic simulations on the predicted stimulation thresholds. Modeling nerve tracks consisting of less than seven nodes of Ranvier with the MRG model yields significant overestimation ($> 30\%$) of the PNS threshold. However, using nerve tracks longer than 15–20 nodes does not significantly improve the accuracy of the PNS threshold prediction.

As illustrated in figure 8, our neurodynamic simulation does not specify the locations of the nodes. Figure 9 shows that shifting the nodes along the nerve track has a moderate impact on the PNS thresholds in regions of the body model where the activation function has a single sharp peak (maximum effect of 4%). For fibers having activation functions with several peaks, the effect of this node of Ranvier shift is negligible.

Figure 10 shows PNS thresholds for the female leg model as a function of the number of time steps per E-field pulse in the MRG model solve. The PNS thresholds are normalized by their values evaluated at the finest temporal resolution (2000 time steps per pulse duration). For both sinusoidal and trapezoidal waveforms, reducing the number of time steps (i.e. using longer time steps) in the neurodynamic solver leads to an overestimation of the stimulation thresholds. The trapezoidal and sinusoidal error graphs are similar and indicate that, in both cases, 100 or more time steps per pulse duration should be used for accurate PNS prediction,

resulting in a PNS estimation error smaller than 2% while computation time is decreased by a factor of 18 compared to using 2000 time steps.

Discussion

In this work we systematically studied the effect of the simulation parameters of our newly introduced peripheral nerve stimulation (PNS) simulation framework (Davids *et al* 2017, 2018) on the predicted PNS thresholds (sensitivity study). We characterized the sensitivity of the simulation approach with respect to both EM field simulation parameters as well as parameters of the neurodynamic simulation. The parameters studied in this work can be classified as patient-specific physiological parameters (such as the dielectric tissue properties, body size and position in the coil) or as numerical simulation parameters (such as the discretization resolution of the body and coil model, the length of the modeled nerve segments, the position of the nerve model compartments relative to the extracellular electric potential, and the time step used for integration of the neurodynamic differential equations).

A prerequisite for the successful simulation of PNS is the accurate simulation of the E-fields induced in the body by the external coil. This clearly requires a body model with an adequate number of tissue classes, accurate organ/tissue geometric specification and realistic EM property assignment to the different tissues. We found that explicit modeling of the nerve tissue in the EM simulations had a large impact on the PNS thresholds. The alternative approach, omitting the EM properties of the nerve during the E-field calculation, effectively embeds the nerve tracks in the adjacent tissue class, which is most often muscle. The inclusion of the fatty nerve tissue voxels in the EM simulation appears to smooth out sharp spatial variations of the extracellular potential. This in turn decreases the value of the activation function and increases the PNS threshold providing a better agreement with the experimental leg stimulation data. Strictly speaking, the discretization resolution of our body model (1 mm) does not allow modeling the thin myelin sheath around single nerve fibers—doing so would require a spatial resolution on the order of 1 μm , which is computationally intractable. However, peripheral nerves are grouped in bundles which are up to 20 mm in diameter (Heinemeyer and Reimers 1999). Our 8-voxel modeling of nerve tissue potentially over-represents the nerve tissue in some cases, but is a computationally tractable way to account for the low conductivity environment around axons. More importantly, the modeled nerve tissue creates a homogeneous environment around the nerve fibers, partly shielding them from dielectric discontinuities at the surrounding tissue interfaces. In this work, we have not examined the anisotropic nature of the electric conductivity of nerve bundles (Gabriel *et al* 2009). Modeling this phenomenon requires describing the local nerve tissue conductivity as a tensor instead of a single scalar number, which is not supported by the EM solver used in this work.

The electric conductivity assigned to the individual tissue classes, especially muscle, was found to have a large impact on PNS thresholds. Perturbations of $\pm 50\%$ of the muscle conductivity led to a $-11\%/+26\%$ variation in PNS thresholds. This shows the importance of using an appropriate database for the assignment of tissue properties that faithfully represents population-average values at the relevant PNS frequencies (kHz). We found that the IT'IS LF database of the software Sim4Life led to the best agreement with the

experimental data. This database combines the Gabriel dispersion relations at low frequencies (Gabriel *et al* 1996b, 1996c) with a review of various experimental studies to provide average body tissue conductivity values valid for frequencies below 1 MHz (Hasgall *et al* 2015). The simulated PNS threshold curve shows some deviation from the experimental PNS data in the low-frequency range (see figure 2) At these frequencies, the experimental data exhibits an increased standard deviation (up to 30%), implying a large subject-dependence. There are a number of other factors that may affect the simulations in this frequency range (such as the response of the neurodynamic model), and we are not yet sure what causes the observed deviation. We will investigate this issue further in our future work.

Perturbations of the conductivity of fatty tissues changed the PNS thresholds in the opposite sense to the muscle conductivity perturbations: Increasing the conductivity of fatty tissue and nerve led to higher thresholds. The reason for this may be that, with muscle occupying the largest volume in the leg, its ability to conduct currents (i.e. its electric conductivity) directly affects the overall magnitude of the induced E-field, with higher E-field magnitudes leading to lower stimulation thresholds. This effect is reversed for fat/nerve tissue: For these tissues, an increase in conductivity led to an increase in PNS thresholds (i.e. the nerves become less excitable). We hypothesize that this is due to the fact that thin layers of a low-conducting tissue (e.g. fat) enclosed by a highly conducting tissue (e.g. muscle) can lead to the formation of an E-field hotspot, a situation that we have observed in our simulations and in our previous work on the simulation of the specific absorption rate (SAR) caused by MRI RF coils (Guérin *et al* 2014, 2015). A nerve running through one of these hotspots would be more likely to experience stimulation than if the fat was not present. Moreover, this effect would become less prominent as the conductivity of the insulating tissue layer (fat) approaches that of the higher conductivity tissue (muscle). An alternative explanation for the observed behavior could be a change in the dielectric contrast between muscle and fat. An increased dielectric contrast between neighboring tissues leads to a stronger E-field in the low-conductivity tissue (and therefore to a lower stimulation threshold of a nerve passing through that hotspot). This phenomenon may lead to the different relationship between conductivity and PNS threshold for muscle and fat. In this work, we investigated the impact of conductivity variations and different tissue property databases on tissues present in the leg. This sensitivity study needs to be expanded to other tissue classes and body parts, especially the thorax and the abdominal region, which are relevant for whole-body PNS simulations of MRI gradient coils. Another limitation of our study arises from the fact that we varied the conductivity of the individual tissue classes one at a time. On the one hand, this allowed us to investigate the impact of dielectric contrast variations of neighboring tissues, which may affect the PNS threshold if a nerve is running through the affected tissues. On the other hand, it may well be that some combined variation of the properties of several tissues (e.g. decreasing the conductivity of fat and nerve at once) has an even higher impact on the PNS threshold given the location of a nerve at a tissue boundary. However, exploring the effect of multiple combinations of conductivity changes opens up a large parameter space, which is beyond the scope of this study.

Variations of the body model size of $\pm 10\%$ affected the thresholds by $\pm 9\%$, while changes of the body model position in the coil of ± 40 mm had effects of up to 15%. We combined the impact of all body model parameters (i.e. size, position within the coil, and EM tissue

properties) by calculating the square root of the summed PNS threshold variances. This provides an estimate of the normal inter-subject variability of PNS thresholds in the range of 15%–35%. This approach assumes the independence of the individual physiological sources of PNS variability. Our simulation-based estimation of the inter-subject variation of PNS is comparable to the rather large experimental standard deviation of measured PNS thresholds, which is typically around or greater than 30% (Bourland *et al* 1999, Chronik and Rutt 2001, Saritas *et al* 2013). Future work will require full characterization of inter-subject variability by accurately modeling different body models with varying shapes, sizes and tissue properties. For example, we approximated different subject sizes by scaling the body model isotropically. This is a significant simplification which does not accurately represent anatomical variability. Applying morphing operations (Murbach *et al* 2017) to the same body model is an improvement over this, but does not sufficiently explore anatomical variability, as it does not introduce new tissue features or changes in the relationship between neighboring tissues. Realistic anatomical variations can likely only be modeled by using additional different body models that have been generated independently based on different underlying anatomical data.

Our results show that a high-resolution body model is essential to accurately estimate E-field hotspots near nerve locations, and thus the PNS thresholds. As can be seen in figure 2, nerves often run at the interface between different tissues, most often muscle, fat and/or bone. At these locations, the induced current density is forced into small bottleneck/hourglass geometrical shapes, which in turn creates hotspots in the E-field map. In order to accurately model this, we found that a spatial resolution of ~1.0 mm is required (to yield PNS threshold errors <5%). Using a finer FEM grid does not yield significantly different PNS predictions, but considerably increases computation time. Our use of the MRG nerve model in conjunction with the EM simulation also imposes a relatively fine spatial resolution as the electric potential needs to be sampled at least at every node of Ranvier. The myelin sheath isolates the nerve from the extracellular space between these nodes, thus the node spacing sets the effective discretization needed for spatial sampling of the potential. For large nerve fibers (diameters >10 μm), which are the most easily excitable nerves in the body, the inter-Ranvier distance is greater than 1.2 mm (McIntyre *et al* 2002), thus a spatial resolution of 1 mm is reasonable. Modeling nerves with smaller fiber diameters or without myelination, however, may require an even higher spatial resolution of the E-field. We would like to point out that hexahedral FEM simulations can suffer from so-called staircasing artifacts, which are always present when using voxelized human body models. Finite difference time domain (FDTD) methods are perhaps even more prone to staircasing. These artifacts depend on both the voxel size and the conductivity contrast of neighboring tissues and may influence PNS prediction, depending on whether they occur along a nerve path. We have analyzed the impact of staircasing on PNS only indirectly in our study of varying body model resolutions and varying tissue conductivities. A more direct analysis of the influence of staircasing could be achieved by e.g. using the smoothing technique proposed by Laakso and Hirata (2012).

The E-field map and hence the predicted thresholds are also influenced by the discretization length of the coil winding; however we found that this has a low impact compared to the spatial resolution of the body model, at least for the simple solenoid coil studied here.

Indeed, increasing the discretization of the solenoid coil winding from 0.6 cm to 7.6 cm in our simulations led to a change in PNS threshold estimates smaller than 0.5% while reducing the simulation time from 80 min to 10 min. Of course, the coil discretization should not be so coarse as to create wire intersections that are not present in reality. While the coil segment resolution does not have a large impact on the simple solenoid coil investigated here, it may be more important for more complex geometries such as MRI gradient windings. It is likely that smaller wire segments are needed to accurately predict the EM fields of these coils.

As explained in the Methods section, the exact locations of the nerve nodes are unknown. The nerve model can be shifted arbitrarily along the nerve path relative to the extracellular potential. This translation or shift value (expressed in mm or in percent of the inter-Ranvier distance) is therefore a free parameter of the simulation. We found that some nerves are mildly sensitive to this nerve model shift (up to 4% threshold variation) and others are completely insensitive to this parameter. The nerves whose excitability is affected most by shifts of the nerve model are often those having a single sharp peak in the activation function. For those nerves, increased excitability (lower threshold) occurs when the peak of the activation function coincides exactly with the location of a node of Ranvier (figure 9(c)). This suggests that for those nerves, a ‘worst case’ shift value (yielding the lowest, or most conservative, PNS threshold) could be obtained by choosing the peak in the activation function as the node location. In reality, nerve fibers are grouped in bundles containing thousands of similar size nerves. It is therefore reasonable to assume that at least one of those nerves occupies this ‘worst-case’ location. However, many of the nerve paths do not have a single sharp peak in the activation function, and for these nerves it is generally not straightforward to predict the ‘worst case’ shift value based only on the activation function. Therefore, for these nerve segments we evaluate the stimulation thresholds at ten translations of the MRG model along the nerve, ranging from 0% to 100% of the inter-Ranvier distance for that nerve. Out of these ten values, we suggest picking the shift parameter yielding the most conservative threshold estimate.

Mathematically, the nerves’ ion channel dynamics are described by a set of coupled time-domain differential equations. We found that the MRG differential equations need to be solved using 100 or more time steps per pulse duration. Fewer led to a systematic overestimation of the thresholds. This error/overestimation was worst for low frequencies and depended only slightly on the specific shape of the driving waveform (for reference, the error is ~15% at 1 kHz when using ten time steps both for sinusoidal and triangular waveforms). The ion channel dynamics impose an additional criterion for minimum time step. Approximately 10 μ s is the coarsest temporal resolution required for an accurate solve of the ion channel dynamics since the membrane time constants of peripheral nerves range between ~29 μ s and 800 μ s (Reilly 1992).

Aside from the physiological and numerical parameters investigated in this work, there are a number of other factors and missing elements in the model that can potentially affect the simulation outcome. For example, the simulation relies on the accuracy of the MRG model itself. The MRG model, in turn, relies on a large number of spatial and electrical parameters, such as the nodal conductance and capacitance (McIntyre *et al* 2002). Typical use of the

MRG model assumes constant values for an ‘average’ subject, even though these parameters could be subject to inter-and intra-subject variations. There are also limitations in our knowledge of these parameters. Additionally, the limited detail in the simulated body model is a simplification of the real human anatomy. For example, the employed nerve atlas only includes the largest peripheral nerves (approximately 1900 nerves per body model). Fortunately, most practitioners are only interested in the nerve with the lowest threshold in the exposed body part, which is likely one of the larger nerves. Only direct comparison to measured PNS thresholds can guarantee that we do not miss a small nerve passing through a high E-field region. Other simplifications include the limited number of tissue classes (we incorporate 21 in the whole body model), sharp transitions between the individual tissues, and the lack of the perineurium (the protective sheath enclosing individual nerve bundles) in the body model.

Conclusion

The quantitative results found in this work are specific to the investigated simulation setup, i.e. a leg in a solenoid coil. For example, modeling an MR gradient coil (rather than a solenoid) may require a finer discretization to accurately predict the EM fields. For other parameters, such as the body model’s spatial resolution, variations of the dielectric tissue properties, and the neurodynamic model parameters, we tested the PNS simulation for a specific geometry and body model. The results inform the range of errors possible in this specific case, and provide a general guidance to the expected errors in this sort of simulation, but caution is needed in extrapolating to other body or coil models.

We differentiate between two sources of uncertainty in our PNS prediction framework: patient-specific threshold variations (arising from varying dielectric tissue properties, size and position of the body within the coil) and numerical threshold errors (caused e.g. by the spatial resolution used for the EM field simulations or the time steps used to evaluate the MRG nerve model). For the physiological parameters we found relatively large PNS threshold variations (up to 26% for tissue conductivities varying in a natural range). This is in accordance with experimental PNS studies that report a rather large variance of the measured thresholds ($SD > 30\%$ (Bourland *et al* 1999, Chronik and Rutt 2001, Saritas *et al* 2013)). For the numerical uncertainties, we were able to reduce the associated PNS errors below 5% for all investigated parameters (see figure 11), while keeping the computational cost of the simulations at a reasonable level. Thus, we feel confident that the main error contribution in the PNS prediction can be made to arise from patient-specific variations. Eventually, PNS simulations may become useful to estimate both population-average PNS thresholds and the population standard deviation. Such an estimation will, however, certainly require a larger number of body models.

We conclude that the tested PNS prediction framework is reasonably robust against variations of key simulation parameters. Pairing these findings with an extensive evaluation of our framework using commercial MRI gradient coils (Davids *et al* 2018), this suggests that the predicted thresholds are sufficiently accurate and stable to investigate PNS mitigation approaches in the future, eventually allowing for an iterative optimization of MRI gradient coils and sequences based on PNS-critical features leading to improved designs.

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Figure 1.

PNS prediction workflow. Step 1: Preparation of the body model and nerve atlas. Step 2: Simulation of the electromagnetic (EM) fields in the body model. Step 3: Projection of the electric field (E-field) onto the nerve fibers and calculation of the electric potential changes. Step 4: The electric potential is modulated in time by the coil's driving waveform and fed into a nerve model (MRG model (McIntyre *et al* 2002)) to simulate the nerve response, including possible action potentials.

Figure 2.

Impact of tissue conductivity on PNS thresholds: use of the IT'IS low-frequency (LF) (Hasgall *et al* 2015) versus the Gabriel database (Gabriel 1996). (a) Female body model leg simulation setup showing the solenoid coil, skeleton and nerve fibers. The coil modeled here is the solenoid used in leg MPI experiments by Saritas *et al* (54 turns in a single layer, 24 cm length, 19 cm diameter, Saritas *et al* (2013)). (b) Conductivity maps for a transverse slice and associated electric fields. (c) PNS thresholds as a function of modulation frequency. The simulation results (IT'IS LF and Gabriel databases) are superimposed to the measured PNS data (Saritas *et al* 2013).

Figure 3.

Sensitivity of PNS thresholds to electric conductivity variations. All simulations were performed at a frequency of 1 kHz using the IT'IS low-frequency material database as the baseline (Hasgall *et al* 2015). The bars indicate the relative PNS threshold changes when increasing and decreasing individual tissue conductivity values by +50% and -50%.

Figure 4.

Impact of embedding the nerve tracks in the body model in nerve tissue. Top row: electric fields (E-fields) for body models with and without nerve tissue. The enlarged details show the E-field distribution around the location of nerve stimulation. Bottom row: activation functions along the most sensitive nerve for body models with nerve tissue (solid black line) and without nerve tissue (dashed red line). Modeling the nerve tissue yielded a decreased peak activation function magnitude and a PNS threshold increase of 32% at a frequency of 1 kHz.

Figure 5.

Impact of the body model's spatial resolution on PNS thresholds (all simulations were performed at 1 kHz). Top row: Body models and corresponding electric fields (E-fields) at spatial resolutions ranging from 0.5 mm to 5.0 mm isotropic. Bottom row: Relative PNS thresholds for four nerves located in the leg (nerve locations are indicated by the arrows #1–#4) as a function of the spatial resolution.

Figure 6.

Impact of simplifying the coil model by straight wire segments on the PNS thresholds (all simulations were performed at 1 kHz). Top row: Wire patterns of three solenoid coil models. The length of the straight wire segments varies between 0.6 cm, 2.4 cm and 7.6 cm, corresponding to 100, 25 and 8 wire segments per loop. Bottom row: Relative PNS threshold of the female leg body model (solid black line) and EM field simulation runtime (dashed blue line) as a function of the wire segment length.

Figure 7.

Sensitivity of PNS thresholds with respect to the length of the nerve segments. All simulations were performed at 1 kHz. Because of computational limitations, the entire nerve atlas cannot be modeled as a single system. Instead, it is divided into independent nerve tracks which can be simulated in parallel. The length of the independent nerve tracks is measured in units of numbers of nodes of Ranvier. Long tracks are more accurate but are more computationally demanding. (a) Activation function (this is the 2nd spatial derivative of the electric potential V along a nerve track) for nerve #1. The nerve track is truncated at different lengths to assess the impact of truncation on PNS estimation accuracy. (b) Relative PNS thresholds for four typical nerves.

Figure 8.

Illustration of the ‘nerve model shift’ parameter. The spacing between the nodes of Ranvier is a physiological parameter that cannot be varied. However, the absolute position of the nodes of Ranvier with respect to fixed body landmarks is not known and is therefore a free parameter of the model. Since the electric fields are ‘sampled’ by the nerve tracks at the Ranvier locations, shifting the nerve model with respect to the extracellular electric potential affects PNS thresholds.

Figure 9.

Impact of the 'nerve model shift' parameter on PNS thresholds for two different nerves. The nerve on the left has an activation function with a single sharp peak (a) whereas the nerve on the right is characterized by an activation function with several small peaks (b). On panels (a) and (b), the solid dots indicate the location of the nodes of Ranvier for shift = 0. Panels (c) and (d) show the relative PNS threshold change when adjusting the shift parameter from -50% to +50% for those two nerves.

Figure 10.

Impact of the MRG nerve model solve time step on PNS thresholds. A single nerve is modeled, with excitation modulations ranging from 500 Hz to 50 kHz. In order to show the impact of the time step duration for these different frequencies on the same graph, we plot the number of time steps per pulse duration (which is defined as the half-period of the periodic driving waveform) instead of the absolute time step value in ms.

Figure 11.

Convergence plots showing the magnitude of the PNS threshold variation for varying values of simulation parameters related to numerical aspects of the PNS simulation in the leg model. A PNS threshold of 1.0 corresponds to the threshold calculated with the set of parameter values expected to yield the most accurate simulation result. The dashed blue lines indicate the values we suggest for each parameter to keep the PNS threshold error to a minimum (<5%) in this model while achieving reasonable simulation times.