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RESEARCH ARTICLE

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Action potential threshold variability for different electrostimulation models and its potential impact on occupational exposure limit values

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Abstract

Occupational exposure limit values (ELVs) for body internal electric fields can be derived from thresholds for action potential generation. These thresholds can be calculated with electrostimulation models. The spatially extended nonlinear node model (SENN) is often used to determine such thresholds. Important parameters of these models are the membrane channel dynamics describing the ionic transmembrane currents as well as the temperature at which the models operate. This work compares action potential thresholds for five different membrane channel dynamics used with the SENN model. Furthermore, two more detailed double-cable models by Gaines et al. (MRG-Sensory and MRG-Motor) are also considered in this work. Thresholds calculated with the SENN model and the MRG models are compared for frequencies between 1 Hz and 100 kHz and temperatures at 22°C and 37°C. Results show that MRG thresholds are lower than SENN thresholds. Deriving alternative ELVs from these thresholds shows that the alternative ELVs can change significantly with different ion channel dynamics (up to a factor of 22). Using the double cable model could lead to approximately ten times lower alternative exposure limit values. On the contrary, using the SENN model with different membrane channel dynamics could also lead to higher alternative exposure limit values. Therefore, future exposure guidelines should take the influence of different electrostimulation models into account when deriving ELVs.

KEYWORDS

axon modeling, electromagnetic exposure, intermediate frequencies, membrane channel dynamics, safety guidelines and standards

1 | INTRODUCTION

Low-frequency magnetic fields can induce electric fields in human bodies. In turn, these electric fields can lead to the generation of action potentials in the nervous system. This type of electrostimulation is intended in some medical applications like transcranial magnetic stimulation (TMS). Besides that, however, it is considered an adverse health effect. Limit values have been introduced to restrict exposure of the

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general public and workers accordingly. Limit values exist for the body-internal electric field strengths as well as for the magnetic flux densities originating from body-external sources.

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) is the main institution providing guidelines for limit values in Europe. They named the limits for body-internal electric field strengths "basic restrictions" and magnetic flux densities originating from body external sources "reference levels." Note that limits for body external electric field strengths exist as well, but these are not considered in this work. Nomenclature differs between standards. The Institute of Electrical and Electronics Engineers (IEEE) provides similar limits and named them "dosimetric reference limits" for the body-internal electric field strengths and "exposure reference levels" for the magnetic flux densities. The IEEE standard C95.1-2019 (IEEE, 2019) is mainly used in America and Asia. Since the author's institutions are based in Europe and partially deal with occupational exposure, this work will focus on the limits and the nomenclature given in the EU directive 2013/35/EU (EU, 2013). However, similar reasoning applies for the limit values given by ICNIRP and IEEE for both the general public and occupational exposure.

The EU directive 2013/35/EU specifies occupational exposure limit values (ELVs) for adverse health effects for body-internal electric fields. These ELVs are based on recommendations given by ICNIRP for occupational exposure (ICNIRP, 2010). ICNIRP states that their recommended basic restrictions are based on electrostimulation thresholds obtained experimentally and on theoretical calculations using an axon model. Furthermore, they apply a safety factor (also called reduction factor) to account for scientific uncertainty of the available threshold data. The spatially extended nonlinear node (SENN) axon model (Reilly et al., 1985) has been used by Reilly and Diamant (2011) to derive exposure guidelines which are partially comparable to the ICNIRP guidelines and are being adopted by the IEEE standard C95.1-2019. Therefore, SENN model action potential thresholds play an important role in deriving the present ELVs for adverse health effects. Note that the EU directive 2013/35/EU also specifies ELVs for sensory effects. These are based on experimentally determined thresholds for phosphene perception and not on electrostimulation modelling results. Therefore, the present work focuses on ELVs for adverse health effects.

Both ICNIRP and IEEE mention that more research is needed to improve the modelling accuracy (ICNIRP, 2020; Reilly & Hirata, 2016). Certain assumptions about SENN model parameters must be made to derive worst-case results which in turn guarantee a high level of safety for the occupational setting. Deriving such assumptions is challenging and potential problems with the currently used parameters have been identified previously (Neufeld et al., 2016). An important choice in the SENN model is the type of membrane channel dynamics (MCDs) that is being used. All the cited work so far is based on "Frankenhaeuser-Huxley" (FH) dynamics to model ionic membrane channel currents. Tarnaud et al. (2018) presented SENN model results for four additional types of MCDs (Table 1). They showed that action potential thresholds for pulsed waveforms can significantly differ between MCDs. Here, it is shown how alternative ELVs based on different MCDs than the FH dynamics could vary compared to the current ELVs. To this end, first, it is shown how the current ELVs can be derived from SENN model results using the FH dynamics and then, second, how applying the same methodology would lead to alternative ELVs based on different MCDs. Note that this approach always applies the same safety reduction factor in the derivation of the alternative ELVs independent of the MCD being used. One could argue that this reduction factor could change depending on the MCD being used.

Another, potentially more realistic electrostimulation model than the SENN model was introduced by McIntyre et al. (2002) and is called the MRG model. The MRG model differs from the original SENN model by including

Highlights

- Different membrane channel dynamics change derived alternative exposure limit values by more than one order of magnitude.
- Double-cable models result in a reduction of derived alternative exposure limit values by one order of magnitude.
- Lower temperatures reduce the action potential thresholds at frequencies below 300 Hz.

TABLE 1 The five models for membrane channel dynamics as described in Tarnaud et al. (2018).

Model	Abbreviation	Experiments
Frankenhaeuser-Huxley	FH	Frog node
Hodgkin-Huxley	HH	Squid axon
Chiu-Ritchie-Rogart-Stagg-Sweeney	CRRSS	Rabbit node
Schwarz-Eikhof	SE	Rat node
Schwarz-Reid-Bostock	SRB	Human nerve

Note: The FH model has traditionally been used for SENN calculations in the context of exposure guidelines. Data for the models were derived from different organisms.

paranodal sections, a double-cable structure, and altered membrane channel dynamics. For example, the MRG model was successfully used to describe experimentally determined perceptual thresholds for human arms and legs exposed to magnetic fields (Davids et al., 2017). The MRG model was further refined by Gaines et al. (2018) resulting in two models: "MRG-Sensory" and "MRG-Motor" which are more specific to the type of peripheral nerve under investigation.

These two models and the SENN model with FH dynamics are implemented in the Sim4Life[1] simulation environment and were used to determine action potential thresholds for this study. Furthermore, the freely available SENN model implementation by Reilly and Diamant (2011) and another freely available SENN model implementation (called EONS[2]) by Tarnaud et al. (2022) were used. Therefore, there were five simulation setups in total: (i) SENN by Reilly & Diamant, (ii) SENN in EONS, (iii) SENN in Sim4Life, and (iv) MRG–Sensory and (v) MRG–Motor in Sim4Life as well.

The goal and novelty of this study was to compare action potential thresholds and the alternative ELVs resulting from these thresholds for different electrostimulation models. Furthermore, the influence of temperature on action potential thresholds was investigated.

The methods section starts with verification of our SENN model implementation (EONS) for the FH dynamics by comparing action potential thresholds to the values originally found by Reilly & Diamant. Furthermore, it is shown how the current ELVs for adverse health effects given in the EU directive 2013/35/EU can be derived from action potential thresholds. The same methodology will be used throughout this work to derive alternative ELVs from action potential thresholds. Next, the models and their setup are described. The results section is divided into two parts. First, alternative ELVs derived for five different MCDs are presented. Second, differences between SENN and MRG model results are shown for action potential thresholds and alternative ELVs, as well as the temperature dependency of the two models. Subsequently, the discussion compares the results of this study to previous work and highlights the potential impact of the findings on future safety guidelines.

Note, that this article is based on two previous extended abstracts presented at BioEM conferences (Soyka et al., 2022, 2023).

2 | METHODS

To investigate the different MCDs, the SENN model implementation in MATLAB (EONS) from Tarnaud et al. (2018) was used. The model parameters were adjusted to match the original parameters used for deriving exposure guidelines by Reilly & Diamant, while also including finite myelin impedance (number of myelin layers, conductance and capacitance per layer are adopted from (Gomez-Tames et al., 2019). Note that in this case, both models use the FH MCDs. Figure 1 shows that apart from small discrepancies for low frequencies the model results match very well. These small discrepancies can be attributed to differences in implementation (e.g., used discretization scheme and tolerances) and the explicit presence of internodes with finite myelin impedance in EONS. Therefore, the EONS model provides comparable results and can be used for further calculations.

For a spatially uniform time-varying electric field parallel to a straight finite myelinated axon with sealed terminals, the SENN model was used to calculate the minimum electric field amplitude at which an action potential is elicited. Figure 1 shows the excitation thresholds for sinusoidal fields of different frequencies. Alternative ELVs can be derived from action potential thresholds by placing an envelope around the thresholds and applying a safety factor. The envelope consists of two line segments. The first segment has a constant value E_0 in V/m which is defined by the lowest threshold. The second segment is proportional to the frequency (i.e., slope equal to unity in the logarithmic plot or 20 dB/decade, in agreement with the international guidelines/standards (EU, 2013; ICNIRP, 2010; IEEE, 2019), and with the strength-frequency curve of the SENN-model (Reilly, 1998). The second segment is starting from the corner frequency f_C which is chosen such that all thresholds are just enclosed by the envelope.

The ratio between the current ELVs from the EU directive 2013/35/EU and the SENN threshold envelope is 6.15 V/m/1.1 V/m ≈ 5.6. This value is used as a safety factor for deriving alternative ELVs from action potential threshold envelopes. Note that the current ELVs are defined up to a frequency of 10 MHz, but that the current study investigates thresholds only up to 100 kHz.

The presented methodology for deriving alternative ELVs from action potential thresholds could vary depending on the circumstances. One could use more than two line segments or use a different safety factor. Note that the derivation of a safety factor is a complex process, and it is not part of this work. For example, the ICNIRP guidelines from 2010 state that "defining reduction factors is to a large extent a matter of expert judgment" and they use a factor of 5 with a value of E_0 equal to 5.66 V/m (which is equivalent to 4 V/m RMS). These numbers result in basic restrictions of 1.1 V/m between 1 Hz and 3 kHz, which are the same ELVs as in the EU directive. For the sake of simplicity and comparability, the current work uses the described methodology with two line segments together with a safety

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[1] Sim4Life V7.0, ZMT, https://zmt.swiss/sim4life/

[2] https://github.com/Florian-Soyka/EONS

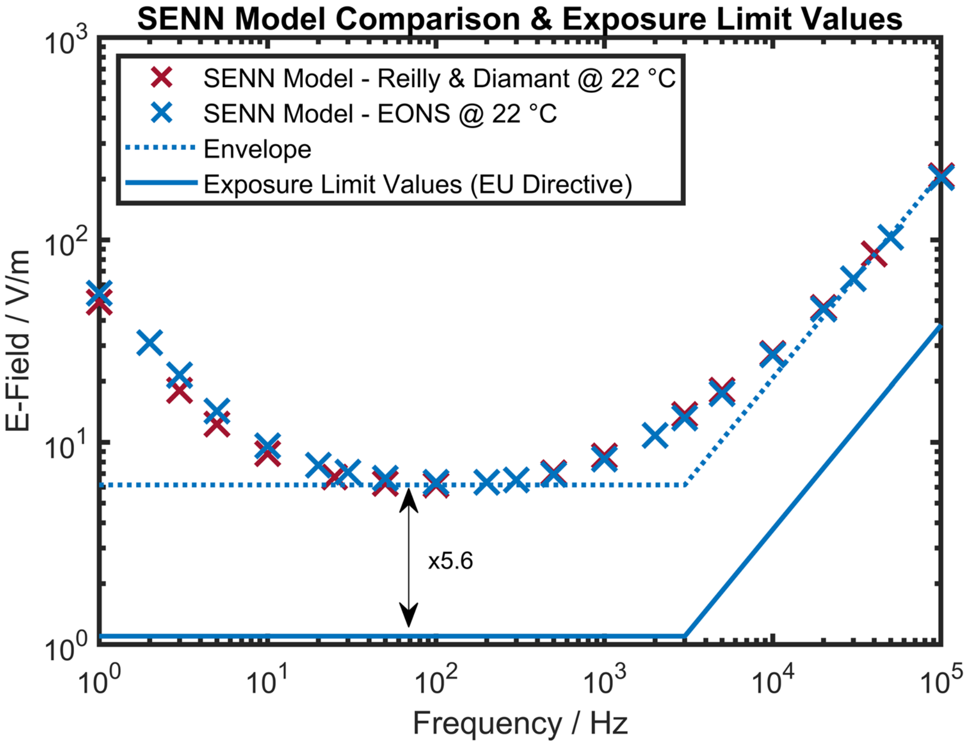

FIGURE 1 Spatially extended nonlinear node (SENN) model thresholds for action potential generation (red & blue) are given for sinusoidal waveforms as a function of frequency for two different SENN model implementations (Reilly & Diamant and the EONS model by Tarnaud et al.). The results are in good agreement. An envelope (dotted line) can be found from which exposure limit values (solid line) can be derived by applying a safety factor of 5.6. The temperature was 22°C.

factor of 5.6 for deriving all alternative ELVs. The derived action potential threshold envelopes are provided as well and allow for a comparison of values before the safety factor is applied.

Using the EONS SENN model with the original parameters used for deriving exposure guidelines by Reilly & Diamant, action potential thresholds were calculated for 5 MCDs (Chiu et al., 1979; Frankenhaeuser & Huxley, 1964; Hodgkin & Huxley, 1952; Schwarz & Eikhof, 1987; Schwarz et al., 1995; Sweeney et al., 1987). The model labels and abbreviations are given in Table 1 and further information about them can be found in Tarnaud et al. (2018).

The SENN model implementation by Reilly & Diamant represents the standard to which the other models can be compared, because its results form the basis for the current ELVs. Reilly & Diamant chose a temperature of 22°C for their studies. This temperature cannot be adjusted in their software, without modifying and recompiling the FORTRAN source code which we did not do in this study. In the Sim4Life and EONS simulation tools temperature settings can easily be adjusted. The body core temperature of 37°C was chosen as a comparison value to investigate the influence of temperature on the thresholds. The Sim4Life simulation environment allows calculating thresholds for the SENN FH and the two MRG models for both temperatures. However, in some cases, no valid thresholds could be obtained with the Sim4Life models for very low or very high frequencies. Therefore, the EONS SENN FH model implementation was used in addition which allowed the calculation of SENN model thresholds for both temperatures across the full frequency range. Furthermore, having three different simulation tools allows for a cross-comparison between the tools for the SENN model at 22°C.

All simulations used the same setup (matching the original setup by Reilly and Diamant): an axon (20 μm diameter) within and parallel to a homogenous electric field with a sinusoidally varying amplitude (a sine with frequencies from 1 Hz to 100 kHz). The simulation tools adjust the amplitudes via a titration procedure until the smallest amplitude (the threshold) is found for which an action potential (at least 80 mV depolarization of three consecutive nodes) is elicited (Reilly & Diamant, 2011). After calculating all five simulation setups at 22°C, all but Reilly & Diamant's SENN model implementation were additionally run at 37°C. Next, the methodology described above for deriving alternative ELVs from action potential thresholds was applied. The resulting alternative ELVs are compared to the current ELVs for adverse health effects from the EU directive 2013/35/EU.

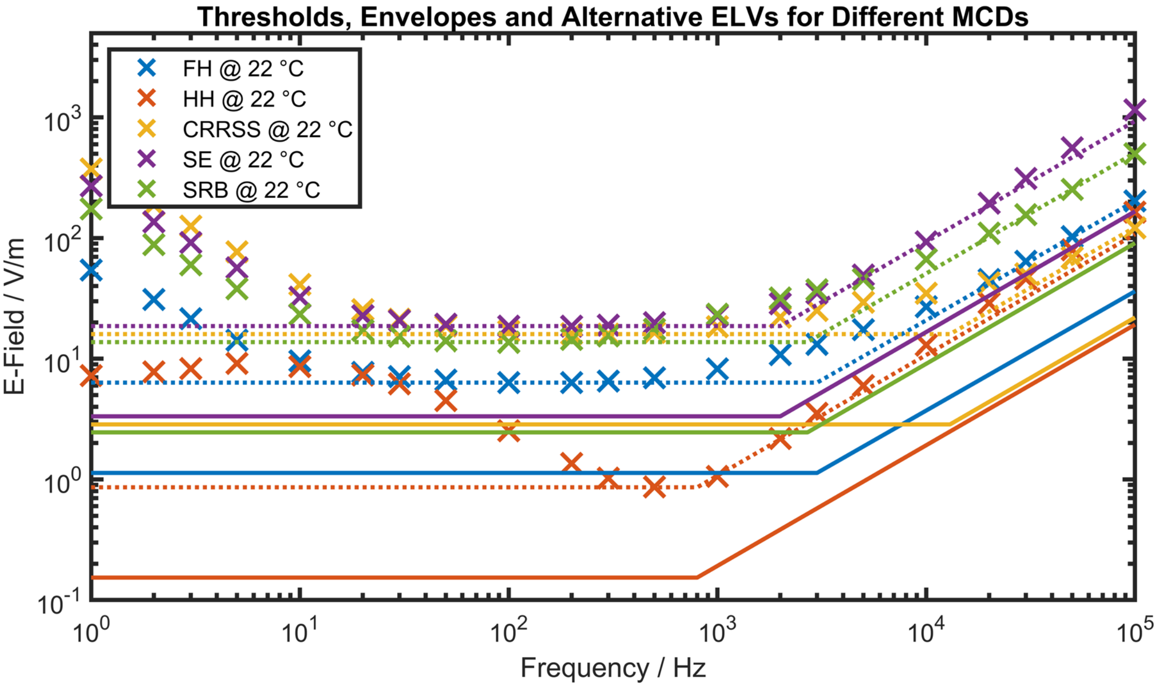

FIGURE 2 Spatially extended nonlinear node (SENN) model thresholds for five membrane channel dynamics (MCDs) calculated with EONS (see Table 1 for abbreviations). Envelopes (dotted lines) were derived for all dynamics and the resulting parameters can be found in Table 2. Alternative exposure limit values (solid lines) can differ up to a factor of 22 for the different underlying MCDs. The results for the FH dynamics are equal to the results presented in Figure 1. The temperature was 22°C.

TABLE 2 Parameters for the five envelopes which were derived from the SENN model thresholds for the different MCDs at 22°C.

MCD Model	E_0/V/m	Corner Frequency f_C/kHz
HH	0.86	0.8
FH	6.34	3.0
CRRSS	16.0	13.0
SE	18.66	2.0
SRB	13.74	2.7

3 | RESULTS

3.1 | Alternative exposure limit values derived for different membrane channel dynamics with the senn model

Figure 2 shows calculations of SENN model thresholds for five MCDs. The results for the FH dynamics are the same as in Figure 1 and can be used to derive the current ELVs given in the EU directive (EU, 2013).

Envelopes for the remaining four MCDs were derived according to the methodology described in the Methods section as well. Table 2 lists the respective parameters E_0 and the corner frequencies f_C. Alternative exposure limit values can further be derived from these envelopes by applying a safety factor of 5.6.

3.2 | Comparison between SENN and MRG model results and impact of temperature

Figure 3 shows the thresholds for the SENN (FH MCDs), MRG–Motor and MRG–Sensory simulation setups at 22°C and 37°C. The SENN thresholds (FH MCDs) at 22°C are very similar for all simulation tools (see also Figure 1 for Reilly & Diamant's model) and only show negligible differences in the low-frequency range. The Sim4Life simulation environment had difficulties finding the thresholds for some frequencies and therefore these values were excluded (missing yellow markers). The thresholds at 37°C are significantly increased below 300 Hz for all models (largest increase with a factor of 7.3 for EONS SENN), while for frequencies above 300 Hz the impact of temperature is smaller (<30%).

Figure 4 shows the thresholds for the EONS SENN model (FH MCDs) and the MRG—Sensory model at 22°C, together with the corresponding envelopes and the resulting (alternative) ELVs. The MRG—Sensory model was chosen because it has the lowest thresholds and can be seen as a worst-case scenario from an occupational safety perspective. For the same reason the thresholds at 22°C were chosen because they are lower than the thresholds at 37°C. The EONS SENN model is comparable to Reilly & Diamant's original model (Figure 1) and additionally allows

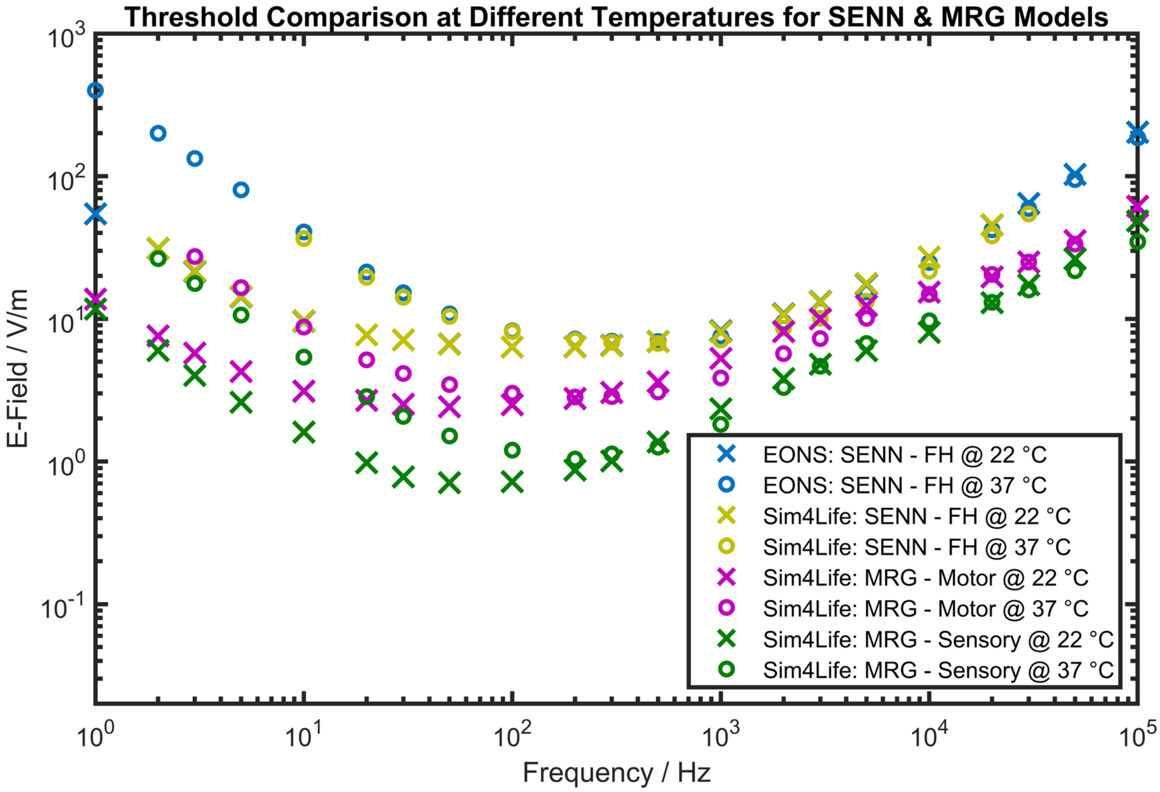

FIGURE 3 Thresholds are shown for 22°C (cross markers) and 37°C (circular markers). The EONS and the Sim4Life simulation tools give very similar results for the spatially extended nonlinear node model (FH MCDs). For frequencies below 300 Hz temperature has a significant influence, resulting in higher thresholds for higher temperatures. The MRG–Sensory model produces the lowest thresholds.

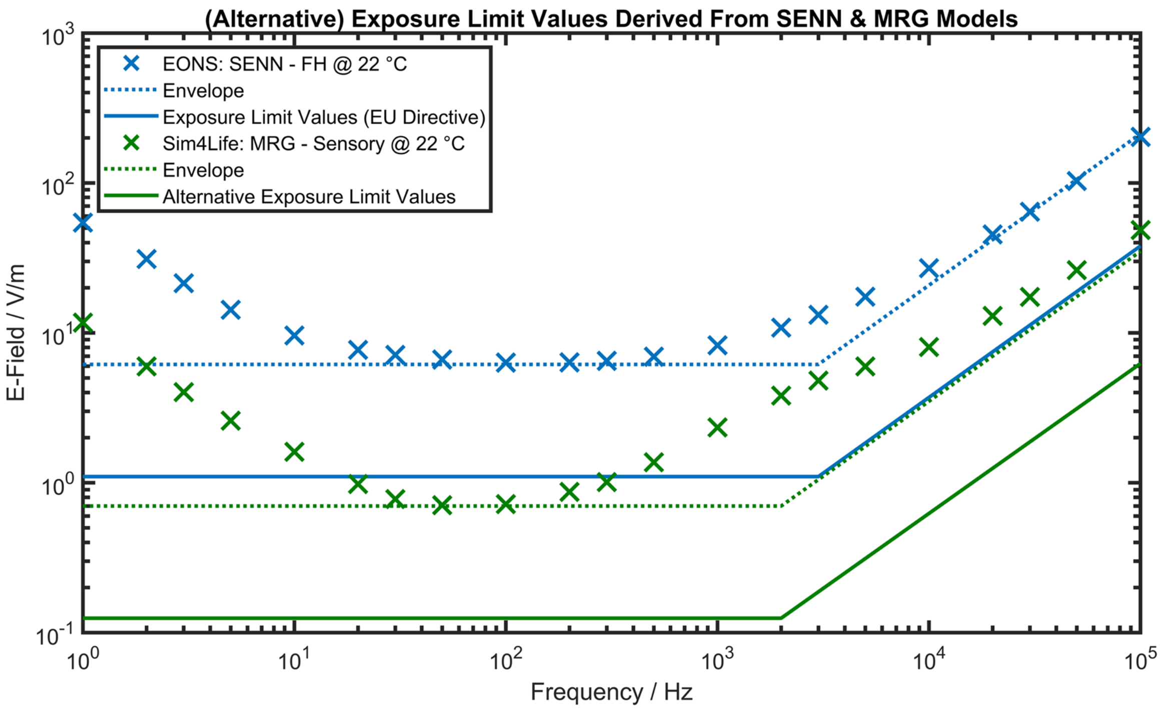

FIGURE 4 Action potential thresholds for the SENN (FH MCDs) and the MRG—Sensory models at 22°C (blue and green cross markers). The corresponding envelopes (dotted lines) are used to derive the (alternative) ELVs (solid lines) which include an additional safety factor of 5.6. The alternative ELVs based on the MRG model would be up to 10 times lower than the ELVs given in the current EU directive.

investigating the influence of temperature on thresholds. Its thresholds at 22°C represent the basis for the currently implemented ELVs in the EU directive 2013/35/EU.

The envelope for the EONS SENN model has the following parameters: lowest threshold $E_0 = 6.3$ V/m and corner frequency $f_C = 3$ kHz. And the envelope for the MRG—Sensory model has the following parameters: lowest threshold $E_0 = 0.7$ V/m and corner frequency $f_C = 2$ kHz.

4 | DISCUSSION

Figure 2 shows that alternative ELVs can differ significantly depending on the MCDs being used. The most pronounced difference can be found between the HH and the SE dynamics and corresponds to a factor of 22. Note that the differences are smaller at high frequencies because the HH dynamics have a lower corner frequency. Since the current ELVs in the EU directive are based on the FH MCDs they are rather conservative. They are smaller than the SE and SRB values, as well as the low-frequency CRRSS values. Due to the safety factor of 5.6 the FH-based ELVs are lower than the high-frequency thresholds for the HH and CRRSS dynamics (Figure 2). However below 3 kHz the HH thresholds are lower than the FH-based ELVs. In summary, the current (FH-based) ELVs might be overly conservative or not conservative enough, depending on which MCDs are used to derive them. This raises the question which MCDs are most realistic given experimental data (Reilly & Hirata, 2016; Soldati et al., 2018; Suzuki et al., 2022).

The five MCDs used in this study are the first published Hodgkin-Huxley type ion channel models, derived from voltage-clamp measurements (see Table 1). Consequently, these classical MCD models have been used in numerous neurostimulation models. For example, for the application of cochlear nerve modeling, the first four membrane models (HH, FH, CRRSS, and SE) are compared in Cartee (2000), Cartee et al. (2000) and O'Brien and Rubinstein (2016). These are all valid models and since the human nervous system includes many different types of neurons, a large variability of channel dynamics is present in humans as well. Experimental data for thresholds in humans is sparse and therefore a direct comparison is difficult. Our research is in line with a survey comparing ten numerical electrostimulation models (Reilly, 2016), which found significant differences between thresholds depending on the model. More research is needed, especially in the direction of experimental validation of the models. The current work showed that the choice of MCDs plays an important role for the derivation of the alternative ELVs.

Looking at the behavior of thresholds as a function of frequency (Figure 2) some differences can be seen between the MCDs. For example, the HH thresholds are stable for low frequencies whereas the thresholds for all other MCDs decrease. Future research should also investigate the effect of non-sinusoidal waveforms on thresholds for different MCDs since the action potential generation can be significantly different. To facilitate the analysis of different MCDs and the effects of nonsinusoidal waveforms, we propose the EONS (Evaluation of Non-Sinusoidal Magnetic Fields) software in Tarnaud et al. (2022).

Comparing the SENN model thresholds at 22°C (Figures 1 and3) shows that all three simulation tools give very similar results. The same holds true at 37°C for the Sim4Life and the EONS simulations (Figure 3). This cross-check between simulation tools provides a good indicator for the validity of the simulations. One of the goals of this study was to investigate the influence of temperature on the action potential thresholds. Figure 3 shows that for frequencies above approximately 300 Hz the thresholds for 22°C and 37°C are rather similar. Below 300 Hz the thresholds for 37°C are significantly higher than those for 22°C (e.g., 7.3 times higher for EONS-SENN at 1 Hz). An increase of the thresholds with temperature is expected at low frequencies because the ion channels' time constants become smaller at higher temperatures. At low frequencies, the effect of fast sodium activation can be neglected, compared to the relatively slow inactivation and activation of sodium and potassium currents, respectively. As a result, sodium current inactivation and potassium current activation will increasingly counteract neuronal excitation at higher temperatures, eventually resulting in heat block (Mou et al., 2012; Rattay & Aberham, 1993). In contrast, at high frequencies the sensitivity of the threshold to the temperature is small (<30% discrepancy between the 22°C and 37°C thresholds above 300 Hz), because all the gate parameters will need several periods to reach their steady-state values. As thresholds at 22°C are lower than at 37°C, they provide a conservative estimate for potentially adverse health effects. Note that current ELVs are based on SENN thresholds at 22°C (Figure 4). For future guidelines, it might be helpful to consider the temperature differences between body parts, for example, the limbs in comparison to the chest or the brain.

In general, it was found that the MRG models give up to ten times lower thresholds and alternative ELVs than the SENN model calculations with FH dynamics, in agreement with other computational exposure studies (Neufeld et al., 2016; Reilly, 2016). This is of course very important from a safety point of view since it raises the question if the current ELVs do sufficiently protect against nerve stimulation. For example, Figure 4 shows that the MRG–Sensory thresholds around 50 Hz are below the current ELVs. The thresholds for the MRG models have inflection points around 3 kHz which are not present for the SENN model thresholds. Therefore, an envelope rising linearly with increasing frequency might not be the best option for deriving alternative ELVs from these thresholds. Since both MRG models show these inflection points for both temperatures, it seems likely that this is a real effect and not some kind of artifact. Indeed, the sensory and motor MRG models include active membrane dynamics in the paranodal and internodal sections. Inflection points are expected when different frequencies result in initiation of action potentials at different locations along the axon, similar to observed deviations from classical strength-duration curves (Rattay et al., 2012).

It is very important to get good experimental data to be able to verify and choose between different models. Davids et al. describe a good fit for perceptual thresholds in arms and legs for magnetic field stimulation between approximately 0.5 and 10 kHz with the original MRG model (Davids et al., 2017). Fresnel et al. are planning on running similar studies at 50 and 60 Hz for magnetic field stimulation of the leg (Fresnel et al., 2022). Future work could pool such data and try to differentiate between different models. However, such an approach needs to model the induction of the electric field in the body as well. Properly calculating the induced electric field is important because the electrostimulation depends on the orientation of the nerve fiber with respect to the field.

5 | CONCLUSION

This work showed how the current ELVs given in the EU directive can be directly derived from SENN model action potential threshold calculations. Changing the membrane channel dynamics used in the SENN model leads to significantly different threshold values. Applying the same methodology for deriving the current ELVs to these thresholds leads to alternative ELVs which can vary up to a factor of 22. Depending on which MCDs are being used the current ELVs can be seen as either too conservative or as not conservative enough. Deriving alternative exposure limit values from MRG model thresholds in the same way as they were derived from SENN thresholds, results in approximately 10 times smaller values than those currently given in the EU directive for occupational exposure. Calculating thresholds for temperature settings of either 22°C or 37°C only made a difference for frequencies smaller than 300 Hz. Thresholds for 22°C were smaller than for 37°C and were therefore used as a basis to derive alternative ELVs.

Future work will consist of gathering experimental data, which is needed to understand which model is better suited to derive exposure guidelines. Current ELVs should only be adjusted after more experimental data points towards higher or lower thresholds. This work showed that the variation in modelling results could account for both directions. ICNIRP is currently updating their low frequency guidelines and this work could aid this process. Future guidelines should take the effect of different MCDs in the SENN model as well as the MRG model results into account.

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CONFLICT OF INTEREST STATEMENT

Florian Soyka and Carsten Alteköster are working at the German Social Accident Insurance. Their job is to protect workers from potentially adverse health effects caused by electromagnetic fields.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The EONS simulation tool is freely available on GitHub: https://github.com/Florian-Soyka/EONS.

ETHICS STATEMENT

This research did not involve animal or human experimentation.

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