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# A systematic review of computational models for the design of spinal cord stimulation therapies: from neural circuits to patient-specific simulations

Lucy Liang, Arianna Damiani, Matteo Del Brocco, Evan R. Rogers, Maria K. Jantz, Lee E. Fisher, Robert A Gaunt, Marco Capogrosso, Scott F. Lempka, and Elvira Pirondini
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*The referees have opted to remain anonymous.*

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*Senior Editor: Katalin Toth*

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## Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. Depending on transfer agreements, referee reports obtained elsewhere may or may not be included in this compilation. Referee reports are anonymous unless the Referee chooses to sign their reports.)

Dear Dr Pirondini,

Re: JP-TR-2022-282884 "A meta-analysis on computational models for the design of spinal cord stimulation therapies: from neural circuits to patient-specific simulations" by Lucy Liang, Arianna Damiani, Matteo Del Brocco, Evan R. Rogers, Maria K. Jantz, Lee E. Fisher, Robert A Gaunt, Marco Capogrosso, Scott F. Lempka, and Elvira Pirondini

Thank you for submitting your manuscript to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 3 Referees and the reports are copied below.

I regret to say that the manuscript has not been accepted for publication.

Some positive comments were made on the manuscript. Unfortunately, they did not outweigh the more serious criticisms which led the Reviewing Editor to recommend rejection.

I am sorry to have to pass on this disappointing news, and hope it will not discourage you from making future submissions of new work to The Journal of Physiology.

However, we believe your manuscript is worthy of further consideration and suggest that you transfer your manuscript to Physiological Reports (https://physoc.onlinelibrary.wiley.com/hub/journal/2051817X/aims-and-scope/read-full-aims-and-scope), a peer-reviewed, open access, interdisciplinary journal, jointly owned by the American Physiological Society and The Physiological Society.
To transfer your manuscript to Physiological Reports, the corresponding author must send authorization within 120 days of receipt of this letter. Please use this link Transfer to Physiological Reports to send an authorization email to transfer your manuscript. If your manuscript does not require additional peer review, the editors of Physiological Reports will aim to give you an initial decision within 3 working days. In fact, >80% of transferred submissions are accepted for publication. Please note, of course, that we cannot guarantee final acceptance.

I hope you will take advantage of the opportunity to allow the editors of Physiological Reports to evaluate your manuscript.

You may be able to publish Open Access with no direct cost to yourself. You can check your eligibility here https://secure.wiley.com/openaccess?

Yours sincerely,

Katalin Toth
Senior Editor
The Journal of Physiology

EDITOR COMMENTS

Reviewing Editor:

The referees highlight the importance of this review topic; however, they raise a number of key issues. Of particular importance referee #1 highlights that supporting evidence/analysis is not provided to support key statements / conclusions - this needs to be addressed. In addition there is no 'meta-analysis' provided rather the article comprises a systematic review (please also see comments from statistics editor referee #3). A number of other points are made by both referees that require consideration.

Please note a revised version needs to

• include whether there was validation of the model calculations and (quantitative) comparison of model predictions to experimental measurements.

• analysis of whether increases in model complexity and personalization lead to more accurate match or prediction of experimental or clinical results

• synthesis to make clear what are the important unknowns, challenges, and open questions

Please note that supplementary figures and tables (and therefore table references) are not permitted

Senior Editor:

The authors indicated in their initial letter to us that the work would be a meta-analysis, and this is stated in the title as well. This would have been quite interesting given the importance and complexity of the problem. However, based on our assessment the study is not a meta-analysis but rather a systematic review.

**********

REFEREE COMMENTS

Referee #1:

This manuscript is an important and timely review, as models are proliferating and, in many instances, becoming more complicated, yet there has been inadequate assessment of the necessity (or effects) of this complexity. The strengths include the highly systematic selection of papers and analysis of model structure, as well as the high quality and very informative figures. While there is an abundance of documentation and summary, there is a paucity of analysis. Overall, the theme seems to be that increased model complexity and personalization are necessary and beneficial, but there is little evidence provided to support this point of view.

A critically important dimension that was not considered is whether there was validation of the model calculations and (quantitative) comparison of model predictions to experimental measurements. Overall, there is inadequate attention to the veracity of models - do they get the correct answers?

There is very little synthesis to make clear what are important unknowns that limit accuracy of models, e.g., we need to know more accurately the conductivity of the CSF because ..., to summarize the open questions and challenges, and to identify important directions for the future.

The statements, "new levels of detail that provide a more complete or accurate assessment of the neural response" and "MRI is necessary to increase the accuracy and the predictive power of these models", require evidence that, in fact, the accuracy of the model simulations, relative to experimental measurements, was indeed increased. Similarly, there is no analysis or support provided for the conclusion, "the increase of model personalization would improve the search for optimal stimulation parameters, lead configurations, and lead position in patient-specific scenarios.", nor any evidence to support the conclusion, "patient-specific models are essential to quantitatively describe the axonal response to SCS and to program effective stimulation parameters for each patient". While there is a brief discussion of the Lempka et al. study, the above conclusions require a broader (and quantitative) assessment of the benefits of model complexity and personalization on accuracy. For example, in the Rowald study, was there any comparison to less complex / personalized models and did this difference translate to differences in the clinical effects of stimulation. Further analysis is required to determine whether the documented increase in complexity (and personalization) is a good thing, i.e., do these models match more closely experimental data or do a better job at predicting experimental or clinical results.

It is not clear that there are data to support the assertion, "attention on spinal root volume can be attributed in part to access to increased computational power, but more importantly, to the increased use of SCS models for limb movement", as the early models by Coburn and Holsheimer and colleagues, focused on pain control, included representations of the dorsal roots and predated the cited "limb movement" models.

There is inadequate analysis and summary of the types of models used to represent dorsal column and dorsal root axones. This appears to have evolved from the McNeal model, to the more mammalian appropriate Wessalink model, and the current state of the art is the (now 20 years old) so-called MRG model, yet it is not considered whether this complexity is necessary or sufficient, or whether new neurone models are required.

This is not a "metanalysis", which is a specific statistical technique to combine data from multiple studies to assess an effect size and variance. Rather, the present manuscript is best characterized as a "systematic review".

The manuscript is in need of careful editing by the more senior authors as there are many throw away, meaningless sentences, e.g., "Basic science on the neural mechanisms of each of specific conditions is required to improve the outcomes of computer models.", and range of statements (see below) that are not correct.

The term "potential field" is used throughout, but potential is not a field variable, as it a scalar with magnitude only, not direction.

The citation, in a review, of other reviews is not helpful, as the reader should be directed to the original source material. For example, "introduction of new SCS technologies, such as kilohertz-frequency and burst SCS (Lempka & Patil, 2018; Capogrosso & Lempka, 2020)", should reference the original publications on kilohertz and bursts SCS, not reviews by the same authors as the present manuscript.

Figure 1 would benefit from scale bars to indicate the relative sizes of anatomical structures and the dorsal column axones. "Potential" is not a field variable, as it a scalar with magnitude only, not direction. Very hard to see neurone populations in panel C.

The effort by Howell and colleagues appears to make use of MRI, personalization and dorsal root models for pain study, and thus contradicts the assertions in the paragraph starting "Interestingly, we found that MRI-based models...".

Too much general background with several statements that require specific support through clear examples:

• The assertion is made that, "computer simulations of SCS have led the way to other translational applications, such as nerve and deep brain stimulation therapies", but this is not correct as the clinical applications led by many years any modeling efforts. Similarly, the statement is made that, "models provide a platform for initial testing or verification of stimulation techniques that would be difficult or impossible to achieve solely based on experimental evidence", yet I am not aware of a single instance where a model has been used to generate a change in therapy, for SCS or otherwise, that preceded the clinical application.

• Further, the statement, "computational models have also led to dramatic improvements in lead designs, stimulation configurations, waveform parameters, and programming procedures", needs to be supported by specific examples. I am aware of only one specific effort here, the development of the transverse tripole by Holsheimer and colleagues, and in this instance the clinical results - no improvement in performance - contradicted the model predictions.

• The gate theory does not hypothesize presynaptic interactions but rather interactions via an intervening interneuron.

• The interaction "interference" of SCS evoked antidromic activity and ongoing sensory activity was analyzed also by Sarma and colleagues and Zhang et al. in their modeling works and these should be included.

• Computational Models ... H&H did not consider extracellular stimulation in any of their analyses.

Avoid passive voice, e.g., simply state "investigators considered", rather than "investigators have considered", "studies utilized", not "studies have utilized", etc.

"SCS-induced potential fields" ... SCS does not operate by induction, c.f., magnetic stimulation

"with regard to", not "with regards to"

Suppl. Fig 2 requires scale bars

Page numbers (and line numbers), please, to facilitate review

Referee #2:

No surprise given who the authors are, this is a well thought our an organized document. I dont think its intended to be "innovative" but it does include novel ways to organize the literature and I think this will be a universally useful resource for modelers in the field. My only minor concerns are more derived from own pet thoughts:

I would like to authors to address the "quasi-uniform assumption" in two ways. First, implicitly this is used in EVERY paper that does not model neurons - the fact thats its unstated is now a "weakness" as long as its recognized as an assumption. Second, in may area like tES is basically the default. In other areas like DBS, it increasingly seems that all the fanciest neuron models predict regions of stimulation that just look like electric field (with some cut-off). On a principled level, if the neuronal elements are either termination (dendrite or synapse), or bends, or changes in environment, or whole neurons etc. then electric field is what governs polarization. So please expand on what this means for SCS? Do NEURON models for example make suggestions on which electrodes to use that is different then just plotting electric field? Maybe but maybe not always? And certainly maybe not in new areas like slow waveforms?? this is not just an academic question but suggest the entire NEURON model step can be ignored in some cases?

While almost no model care about heating some (basically me) do find this interesting. It matters from a methods perspective since the workflow is different. Regions of influence derive from local heat deposition.

Patient specific models: One way to know if they are good is if ONLY from the MRI one can make a prediction across individuals (threshold for undersized motor response, pain control). On some area like TMS (and maybe DBS) this "proof in the pudding" examples are hard to find, largely because we dont actually know what neuronal elements are stimulated to produce what outcomes. How does this go for SCS? The authors hint at this with Lempka work but I am not clear how good / reliable this idea is? Ready for products?

How "shocking" (lets roll with this pun) is the lack of standard use of MRI derived models in SCS, compared to other fields. Even non-invasive spinal cord stimulation seems well aligned with using MRI derived models. SCS is an anomaly?

How can MRI based papers show up after introduction of MRI (e.g. Figure 3)

Referee #3:

I have been asked for a statistical opinion on this paper, further to concerns expressed during the review process.

Reviewer 1 states: 'This is not a "metanalysis", which is a specific statistical technique to combine data from multiple studies to assess an effect size and variance. Rather, the present manuscript is best characterized as a "systematic review".' This reviewer highlights multiple instances where she/ he feels that the opinions/ conclusions are unsupported by quantitative data. I agree that this work should not be labelled as a meta-analysis - there is no quantitative synthesis of effects/ associations herein and no meta-analysis methods are described. Rather, I suggest that the work is perhaps best framed as a systematic review with a qualitative meta-synthesis - something quite different to a meta-analysis. In doing this the authors can address the reviewers' comments by reworking the whole paper. I have no statistical comments, as no analyses were

conducted.

**Authors' answers to remarks on manuscript**

Dear Dr. Katalin Toth and Reviewers,

We would like to thank you for your constructive feedback on our manuscript, and we are happy that we have been given the opportunity to submit a revised version of our manuscript. We greatly appreciate your valuable inputs and have tried our best to consider them in the revised version of the manuscript.

In this document, you can find the decision letter, in which we have separated and numbered the different remarks of the Reviewers. We have added our responses to the remarks (in blue) and, where appropriate, indications about the actions in the text (in red) directly below the corresponding remark.

We believe that the modifications have significantly improved our manuscript. We greatly appreciate you considering publication of our manuscript in *The Journal of Physiology*.

Yours sincerely,

Dr. Elvira Pirondini
Dr. Scott Lempka
*Corresponding authors*

**Reviewer #1**

This manuscript is an important and timely review, as models are proliferating and, in many instances, becoming more complicated, yet there has been inadequate assessment of the necessity (or effects) of this complexity. The strengths include the highly systematic selection of papers and analysis of model structure, as well as the high quality and very informative figures. While there is an abundance of documentation and summary, there is a paucity of analysis. Overall, the theme seems to be that increased model complexity and personalization are necessary and beneficial, but there is little evidence provided to support this point of view.

**Authors' answer:** We thank the Reviewer for highlighting the importance of our work and for the appreciation of our systematic review. We agree with the Reviewer that additional analyses would strengthen the relevance of our work. We have performed additional analyses and substantially revised the manuscript to support our point that increased personalization and complexity are necessary and beneficial. The modifications are highlighted below in the point-to-point replies to the Reviewer's comments.

**R1.1** A critically important dimension that was not considered is whether there was validation of the model calculations and (quantitative) comparison of model predictions to experimental measurements. Overall, there is inadequate attention to the veracity of models - do they get the correct answers?

**Authors' answer:** We thank the Reviewer for this comment. To address this important point, we have performed a deeper analysis of the existing literature by including an additional variable. This variable, which we termed Model Validation, indicates whether or not there was an experimental or clinical validation of the simulated results, and whether this validation was quantitative or qualitative. In this analysis, we found that the majority of the models do not provide model validation, and that quantitative validation was performed in models with higher personalization. We did not find any studies that reported significant deviation between model simulation and experimental evidence.

**Actions in the text:** This new variable is added in the *Coding of Variables* section under the *Methods* section. Categorization of this variable for each study is reported as an additional column in **Tables 2-4.**

- **Validation: no validation, qualitative validation, and quantitative validation. We assigned a study "no validation" if the main conclusions drawn from the simulations were not validated against any experiments. However, note that the model may have been validated for other simulations in a different publication. A "qualitative validation" corresponded to a comparison between simulated and experimental results without directly comparing numerical values. A "quantitative validation" involved direct comparison of values, such as compound muscle action potential amplitudes (Laakso *et al.*, 2014). For studies with both qualitative and quantitative validation, we placed them in the quantitative validation group.**

We also included the results from this new variable in the *Results* and *Discussion* sections to address the importance of validation, and the need for standardized validation metrics for clinical utility.

Results:

**"Despite the increased use of SCS models in both clinical and preclinical simulation, we found that over half (58%) of the published simulation results were not validated experimentally, highlighting the lack of standardized guidelines for the effective use of these models."**

"**When comparing model complexity and personalization, we found that,** despite the limited number of papers with high personalization (n=5), which prohibited statistical analysis, there is a clear trend showing that higher levels of personalization are paralleled by higher levels of complexity in both the FEM and biophysical models (**Figure 5D**). **Interestingly, studies using highly personalized models were more likely to perform a quantitative validation of the simulation results, with 100% of the most personalized models having a quantitative validation (Figure 5E). Out of the 23 studies with quantitative validation, 18 of these studies were published in the last decade (since 2012). These results show that researchers are placing an increased emphasis on model validation, and with enough personalization and complexity, computer models have the capability of making quantitative predictions that may directly inform clinical practice.**"

Discussion:

"**Lastly, while recent studies have increasingly included quantitative comparisons of simulations and experimental results, the validation metrics used for these comparisons have been inconsistent. Inconsistency in these validation metrics creates difficulties in comparing the predictions across multiple models and impedes the development of clinically meaningful standards for effective treatment predictions. For example, in the field of motor function, studies have compared the model-based predictions of large sensory fiber activation thresholds with experimentally observed motor thresholds** (de Freitas *et al.*, 2022) **and response latency** (Capogrosso *et al.*, 2013)**, simulated motoneuron activation with specific muscle force** (Wagner *et al.*, 2018)**, and simulated and measured compound muscle action potential amplitudes** (Laakso *et al.*, 2014)**. When using computational models to study SCS for pain, validation metrics have been applied more consistently, with most studies comparing simulated dorsal root and dorsal column fiber activation threshold with measured perception and discomfort thresholds** (Holsheimer *et al.*, 1995**;** Struijk *et al.*, 1998**;** Rattay *et al.*, 2000**;** Arle *et al.*, 2014**;** Howell *et al.*, 2014**;** Lempka *et al.*, 2018**;** Lempka *et al.*, 2020; Solanes *et al.*, 2021)**. As the use of SCS continues to increase and expand to new indications, it will be important to establish a standardized set of validation metrics to assist implementation of simulation results in a clinical setting.**

To conclude, we strongly believe that, by taking full advantage of MRI techniques and AI, developing novel circuit networks, and increasing computational power, we can develop realistic and highly accurate virtual frameworks to understand the mechanisms of SCS and develop optimal SCS therapies and surgical strategies. **With more complex and personalized models, and standardized model validation and clinical outcome metrics**, we can bridge the gap between simulations and patient care."

**R1.2** There is very little synthesis to make clear what are important unknowns that limit accuracy of models, e.g., we need to know more accurately the conductivity of the CSF because ..., to summarize the open questions and challenges, and to identify important directions for the future.

**Authors' answer:** We agree that the manuscript misses a clear synthesis of the still open questions and challenges that limit the accuracy of the computational models. Indeed, thanks to the Reviewer's comments, we have identified the following open questions:

1) Which anatomical structures are essential for accurate volume conductor models?
2) What imaging techniques can capture these anatomical structures and their morphology?
3) Do increased complexity and personalization improve model accuracy?
4) Which physical material properties (e.g., electrical conductivity values and thermal properties) should be applied to simulate electromagnetic fields?
5) Are biophysical neuron models necessary for accurate simulations? If so, which models?
6) What are the best methods to standardize model validation and clinical outcome metrics for future studies?

We have addressed the reviewer's comment by detailing these challenges in the *Introduction*, providing a clear summary of open questions and insights for future directions.

**Actions in the text:** We have enriched our manuscript in the *Introduction* section by providing an accurate description of current challenges and unmet questions.

"**Unknowns, challenges, and open questions**
Overall, these examples highlight the importance of computational simulations in the translational pathway, to pre-clinical tests, and finally to successful clinical trials. Computational models support and expedite the development, optimization, and implementation of innovative neurostimulation therapies. **Yet, there are still important questions to be addressed. First, there is no consensus on which anatomical structures are essential for accurate volume conductor models and what are the most proper imaging techniques and protocols to capture these structures. Secondly, there is still controversy on how several factors influence model accuracy, such as the presence and characteristics of a biophysical neuron model, the applied physical material properties (e.g., electrical conductivity), and the necessary levels of model complexity and personalization. Finally, the best methods to standardize model validation and clinical outcome metrics are not established, resulting in a dramatic lack of defined guidelines that consequently limits the effective use of computational models in clinical applications. To answer these questions**, we reviewed the evolution of computer models of SCS since their introduction in the early 1980s (Coburn, 1980; Sin & Coburn, 1983). The goals of this review are to identify overall trends, including both established and emerging indications, as well as provide recommendations to standardize and expand the use of computational models to advance the field of SCS for various clinical applications."

**R1.3** The statements, "new levels of detail that provide a more complete or accurate assessment of the neural response" and "MRI is necessary to increase the accuracy and the predictive power of these models", require evidence that, in fact, the accuracy of the model simulations, relative to experimental measurements, was indeed increased. Similarly, there is no analysis or support provided for the conclusion, "the increase of model personalization would improve the search for optimal stimulation parameters, lead configurations, and lead position in patient-specific scenarios.", nor any evidence to support the conclusion, "patient-specific models are essential to quantitatively describe the axonal response to SCS and to program effective stimulation parameters for each patient". While there is a brief discussion of the Lempka et al. study, the above conclusions require a broader (and quantitative) assessment of the benefits of model complexity and personalization on accuracy. For example, in the Rowald study, was there any comparison to less complex / personalized models and did this difference translate to differences in the clinical effects of stimulation. Further analysis is required to determine whether the

documented increase in complexity (and personalization) is a good thing, i.e., do these models match more closely experimental data or do a better job at predicting experimental or clinical results.

**Authors' answer:** We thank the reviewer for pointing out the lack of details to support some of our statements. Indeed, we agree that a broader and quantitative assessment of the benefits of model complexity and personalization on accuracy is required. However, because of a paucity of comparable outcome variables across studies and the presence of only a small number of studies that directly compare the predictions from models of different complexities to experimental or clinical data, a deep analysis was not possible. However, we have enriched our manuscript in the *Discussion* section with numerical examples that document that higher complexity and personalization result in simulations that more closely match experimental data and better predict clinical results.

**Actions in the text:** We have enriched our manuscript in the *Discussion* section with quantitative and detailed examples that document the importance of patient-specific models compared to generalized canonical models.

"In this direction, Lempka and colleagues (Lempka *et al.*, 2020) reported that simulated sensory thresholds obtained with patient-specific models were significantly more similar to those clinically measured than those simulated with canonical models, which underestimate the dorsal column fiber activation thresholds. **Additionally, they quantified the effect of pulse-width variation on sensory thresholds, identifying a mean absolute percentage error of 8.9% and 44.9% relative to the clinically measured value, for the patient-specific and canonical models, respectively. Two other studies** found similar results in which model predictions of perception and discomfort thresholds were more consistent with the clinical measurements using patient-specific models **(specifically, the difference with respect to clinically measured perception threshold was 6.4% and 171% for the patient-specific and canonical model, respectively)** (Solanes *et al.*, 2021; Howell *et al.*, 2014). Similarly, in the "movement" application, Rowald *et al*. 2022 developed highly personalized patient-specific models for the purpose of restoring locomotion. **The authors performed an intraoperative validation of the simulated lead position by monitoring electromyographic recordings while delivering SCS. The predictions of the patient-specific model corresponded to the optimal electrode placement; indeed, the study reports that a 2 mm displacement from the predicted location caused a drop in selectivity. Interestingly, the use of a generic (i.e., not personalized) model failed to reach the same accuracy.** Thanks to the optimized lead position, contact location, and stimulation configuration for each patient, **Rowald and colleagues demonstrated rapid** restoration of trunk and leg motor functions in these patients with complete paralysis. Finally, Veizi and colleagues **used a canonical model but with patient-specific electrode locations and implemented a patient-specific algorithm to select active electrode combinations and current amplitudes at each electrode (Veizi *et al.*, 2017). The personalized group demonstrated an approximately 1.5 times higher responder rate (i.e., patients receiving ≥50% reduction in pain) relative to a cohort in which stimulation parameters were selected through standard clinical methods**."

Additionally, we have added a new section in the *Discussion* section titled "*The importance of increased complexity*" in which we have discussed the importance of complexity both for the FEM and the biophysical models. Reviewer can refer to question R1.5 for details about the addition in the revised manuscript.

**R1.4** It is not clear that there are data to support the assertion, "attention on spinal root volume can be attributed in part to access to increased computational power, but more importantly, to the increased use of SCS models for limb movement", as the early models by Coburn and Holsheimer and colleagues, focused on pain control, included representations of the dorsal roots and predated the cited "limb movement" models.

**Authors' answer:** The reviewer raises a good point and we have modified the relevant text in the Results section accordingly.

**Actions in the text:** We have modified this concept in the paragraph, *"The evolution of personalization and complexity of SCS models,"* in the *Results* section.

**"While some early modeling studies of SCS for pain control included explicit representations of the spinal roots (Coburn, 1980; Coburn and Sin, 1985), recent increased** attention on spinal root volume can be **partly** attributed to increased computational power **that allow these roots to be included in complex 3D models.** Multiple studies have demonstrated that dorsal root fibers are critical stimulation targets for motor control, **which highlights that the inclusion of spinal roots in the FEM model is especially important in SCS for motor control.**"

**R1.5** There is inadequate analysis and summary of the types of models used to represent dorsal column and dorsal root axones. This appears to have evolved from the McNeal model, to the more mammalian appropriate Wessalink model, and the current state of the art is the (now 20 years old) so-called MRG model, yet it is not considered whether this complexity is necessary or sufficient, or whether new neurone models are required.

**Authors' answer:** We thank the Reviewer for this thoughtful comment. Therefore, in the *Discussion* section, we have summarized some of the studies highlighting the importance of biophysical model complexity and example applications in which reduced models (e.g., single-cable models) may be sufficient and other applications in which more complicated models (e.g., double-cable models) are necessary. Finally, we highlighted that future work may significantly improve the specificity and accuracy of predictions generated by biophysical models.

**Actions in the text:** We have added a new section in the *Discussion* section titled "*The importance of increased complexity*" in which we have discussed the importance of complexity both for the FEM and the biophysical models.

**As previously stated, computational models can simply include a volume conductor model to simulate the electromagnetic fields generated by SCS or can incorporate a biophysical neuron model to understand ionic current flows in individual neurons** (Chakraborty *et al.*, 2018)**. It has been proposed that, given the complex anatomical structure and variety of factors that can affect neural activation (e.g., branch points, axonal bends), the electric field will best predict neural polarization and neuromodulation, in contrast to the activation function (i.e., the second-order spatial derivative of the electric potential). This approach has been formalized as the "quasi-uniform assumption" (Bikson *et al.*, 2013; Bikson *et al.*, 2015; Khadka *et al.*, 2019) and may serve as a useful and efficient heuristic for predicting which gross anatomical regions are likely to be more strongly affected by the stimulation. Thus, this approach is well-suited for applications in which precise identification of which neurons are being activated is not the primary objective, such as studies investigating**

**novel electrode configurations or the effects of anatomical electrical properties on current flow. On the other hand, for studies investigating precise biophysical activation profiles or evaluating new temporal stimulation patterns, a biophysical model is better able to account for the subtle effects of ion channel dynamics and neural morphology on activation properties. Finally, for putative mechanisms of action other than direct electrical stimulation, biophysical neuronal modeling may be unnecessary and instead multiphysics simulations may be more appropriate. For instance, modeling studies have investigated the combined effects of joule heating (due to applied electric currents) and bioheat transfer as a potential therapeutic mechanism for kilohertz-frequency SCS (Zannou *et al.*, 2019; Zannou *et al.*, 2021).**

**Despite the quasi-uniform assumption, there is a clear trend of increasing complexity over time both in the FEM and biophysical models (Figure 5A and 5B). However, a more complex model does not necessarily imply a better model, and questions naturally arise as to what level of complexity is necessary and/or sufficient to develop a useful model. Regarding the FEM model, the increase in complexity was partially possible because of the use of MRI techniques to capture gross anatomical structures, such as the spinal roots that are the neural target in the movement field. As discussed in Capogrosso & Lempka 2020, inclusion of root volumes can significantly shift fiber activation distribution and threshold, and thus affect direct clinical applicability of simulated results. However, only three studies considered realistic representations of roots and rootlets that followed trajectories derived from anatomical measurements (Khadka *et al.*, 2020; Greiner *et al.*, 2021; Rowald *et al.*, 2022) and implemented curvilinear anisotropic conductivities (Greiner *et al.*, 2021; Rowald *et al.*, 2022)**

**Regarding the biophysical model, we considered several factors when scoring complexity. We believe that the value of including several relevant neuronal populations (e.g., both dorsal column and dorsal rootlet fibers to compare on/off target effects) as well as varying axonal diameter and position clearly helps improve the translatability of model predictions. Furthermore, studies have clearly demonstrated the importance of using species-appropriate ion channels** (Wesselink *et al.*, 1999) **and including branch points** (Struijk *et al.*, 1992) **in biophysical models of SCS. For each of these variables, maximizing their complexity is not strictly necessary to produce a useful model, as all models require simplifications and abstractions. However, we feel that it is good practice to thoughtfully consider each of these variables to provide a more complete and realistic prediction of the neural response, and accounting for these variables in the models is typically feasible without an unreasonable increase in effort or computational resources.**

**On the other hand, the necessary (and sufficient) complexity to model the axon geometry, and specifically the internode, is more controversial, and largely depends on the study. Compelling evidence demonstrates the role of submyelin conductance in axonal behavior, and the value of representing this current pathway to improve model predictions of axonal behavior relative to single-cable models (Richardson *et al.*, 2000; Cohen *et al.*, 2020). In a direct comparison between models with infinite-impedance myelin, finite-impedance myelin, and a double-layer myelinated axon, Richardson et al. demonstrated that all three models could produce reasonable results in line with experimental data, and that all**

**models were sensitive to parameter choices. However, Richardson et al. found that only the double-cable axon representation could faithfully respond to pulse trains at frequencies of at least 25 Hz, as is typical in SCS** (Richardson *et al.*, 2000)**. Thus, for studies investigating the response to sequential stimuli (rather than activation by a single pulse), a double-layer axon structure is the appropriate model. For studies considering a single stimulus pulse, using a simplified representation may be sufficient to produce a reasonably accurate prediction of the neural response, and will reduce the number of parameters and the corresponding computational complexity. Additionally, simplified approaches may prove valuable and sufficient in situations in which reduced accuracy is acceptable for the accompanying gains in efficiency. For instance, these simplified models could provide a useful heuristic in producing real-time predictions of the neural response to various stimulation configurations while programming devices in the clinic.**

**Looking forward, significant model improvements remain attainable by generating high-quality experimental data to parameterize biophysical models. The gold standard remains the MRG (McIntyre, Richardson and Grill) model (or derivatives thereof) of the spinal motor axon that was developed two decades ago** (Richardson *et al.*, 2000)**. Promising developments, such as adding additional channel conductances (e.g., active submyelin conductances), have produced model behaviors that better match recordings from human sensory nerve fibers which are highly relevant when modeling the dorsal spinal cord for SCS applications** (Gaines *et al.*, 2018)**. Future work advancing these ideas, as well as investigating the local properties in different regions of the axon (e.g., the axon terminal), will further enhance our ability to model the neural response to SCS.**

**R1.6** This is not a "meta-analysis", which is a specific statistical technique to combine data from multiple studies to assess an effect size and variance. Rather, the present manuscript is best characterized as a "systematic review".

**Authors' answer:** We thank the reviewer for this comment. As pointed out in our manuscript, the lack of standardized and homogenized outcome metrics is one of the main challenges of this field. Therefore, it was not possible to perform a quantitative meta-analysis as clarified by the Review, but only a qualitative analysis as we performed in our manuscript. We agree with the Reviewer that the present manuscript is best characterized as a "systematic review" with a qualitative meta-synthesis. We apologize for the incorrect wording choice. As also suggested by Reviewer #3, we have addressed the reviewers' comments by reworking the manuscript to clearly state that this was a systematic review with a qualitative meta-synthesis and not a meta-analysis.

**R1.7** The manuscript is in need of careful editing by the more senior authors as there are many throw away, meaningless sentences, e.g., "Basic science on the neural mechanisms of each of specific conditions is required to improve the outcomes of computer models.", and range of statements (see below) that are not correct.

**Authors' answer:** We thank the reviewer for this comment. We have substantially revised the manuscript to remove unnecessary and meaningless sentences.

**R1.8** The term "potential field" is used throughout, but potential is not a field variable, as it a scalar with magnitude only, not direction.

**Authors' answer:** We appreciate the Reviewer's comment. Yes, electric potentials are scalars that only include a magnitude and no direction. Therefore, the potential is a scalar field and not a vector field and it is accurate to use the terminology "potential field." However, to avoid potential confusion, we have updated our text by referring to it as "electric potential" or "potential distribution."

**R1.9** The citation, in a review, of other reviews is not helpful, as the reader should be directed to the original source material. For example, "introduction of new SCS technologies, such as kilohertz-frequency and burst SCS (Lempka & Patil, 2018; Capogrosso & Lempka, 2020)", should reference the original publications on kilohertz and bursts SCS, not reviews by the same authors as the present manuscript.

**Authors' answer:** We agree with the Reviewer's comment. We, therefore, introduced two additional references to help the readers that describe the results of multi-center pivotal trials using these forms of SCS.

For kilohertz-frequency SCS technology, we added the citation:

Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, Amirdelfan K, Morgan DM, Brown LL, Yearwood TL, Bundschu R, Burton AW, Yang T, Benyamin R & Burgher AH (2015). Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. *Anesthesiology* **123,** 851-860.

For burst SCS technology, we added the citation:

Deer T, Slavin KV, Amirdelfan K, North RB, Burton AW, Yearwood TL, Tavel E, Staats P, Falowski S, Pope J, Justiz R, Fabi AY, Taghva A, Paicius R, Houden T & Wilson D. Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform. *Neuromodulation* **21,** 56-66.

**R1.9** Figure 1 would benefit from scale bars to indicate the relative sizes of anatomical structures and the dorsal column axones. "Potential" is not a field variable, as it a scalar with magnitude only, not direction. Very hard to see neurone populations in panel C.

**Authors' answer:** We thank the Reviewer for pointing this out. We have modified Figure 1 accordingly, changing "potential field" to "electric potential" and highlighting each neuron population in panel C. We believe that the Reviewer is referring to the fiber distribution panel when suggesting the addition of scale bars, however, the relative size of anatomical structures to axons are different for different species. Here, our goal was to point out that the fiber sizes and distributions should be considered when constructing a computational SCS model, thus the axon fibers are not drawn to scale and it would be difficult to include a scale bar.

**R1.10** The effort by Howell and colleagues appears to make use of MRI, personalization and dorsal root models for pain study, and thus contradicts the assertions in the paragraph starting "Interestingly, we found that MRI-based models...".

**Authors' answer:** The Reviewer is correct in pointing out that Howell and colleagues used MRI to build a computational model of SCS for pain (Howell et al., 2014). Additionally, a few other works utilized MRI to build SCS for pain (Howell et al., 2014; Huang et al., 2014, Solanes et al.,

2021; Miranda et al., 2016; Lempka 2020). Yet most of the computational models for pain were built using measures extracted by atlases or from literature. The message that we wanted to convey with our statement was that even though there are computational models in the pain field built using MRI, this is not the majority (only 28%). In the field of movement, instead, a higher percentage of models are built based on MRI images (60%). We apologize for this confusion and we have clarified this message in the revised manuscript.

**Actions in the text:** We have modified the sentence in the paragraph *Introduction of medical imaging influenced the complexity and personalization of computer models for SCS* in the *Results* section.

"Interestingly, we found that MRI-based models are **used more commonly** in the movement application **(60% for movement versus 28% for pain)** and have recently expanded to the biophysical application (**Figure 4A**)."

**R1.11** Too much general background with several statements that require specific support through clear examples. The assertion is made that, "computer simulations of SCS have led the way to other translational applications, such as nerve and deep brain stimulation therapies", but this is not correct as the clinical applications led by many years any modeling efforts. Similarly, the statement is made that, "models provide a platform for initial testing or verification of stimulation techniques that would be difficult or impossible to achieve solely based on experimental evidence", yet I am not aware of a single instance where a model has been used to generate a change in therapy, for SCS or otherwise, that preceded the clinical application.

**Authors' answer:** We agree with the Reviewer's comment that examples should have been provided to support our claims. Regarding the sentence, "*Computer simulations of SCS have led the way to other translational applications, such as nerve and deep brain stimulation therapies,*" this was poor wording and we apologize. The Reviewer is correct that clinical applications/testing will probably always lead modeling efforts. What we meant to state was that computational modeling tools developed to study SCS were adapted for studying other neurostimulation technologies, such as deep brain stimulation (DBS) and peripheral nerve stimulation (PNS). So these computational tools for SCS paved the way for the use of computational tools in DBS, PNS, etc., to help investigate the mechanisms and optimize these technologies. We have now reworded the sentence to better convey our message.

Regarding the absence of an example where a model has been used to generate a change in therapy, one example could be the works of Moraud et al., 2016 and Formento et al., 2018. In these works, an animal model of SCS for locomotion revealed that antidromic action potentials elicited in primary sensory afferents by SCS interfere with natural sensory feedback, which is crucial for coordinated limb movements. Therefore, a coordinated pattern of locomotion was possible only when different locations of the spinal cord were stimulated at different points in time leading to what is nowadays called spatiotemporal SCS. Following this work, Wenger and colleagues (Wenger et al., 2016) compared spatiotemporal SCS to continuous SCS demonstrating the superiority of the former in eliciting locomotion after spinal cord injury in rats. Similar results were successively reported in monkeys (Capogrosso et al., 2016) and in humans (Wagner et al., 2018). We have modified our text to highlight this example.

**Actions in the text:** We have changed the following sentences in the *Introduction* section.

"This technology, known as spinal cord stimulation (SCS), is now the most widely adopted neurostimulation therapy, and computer simulations of SCS **have paved the way for the use of**

**computational tools in other neurostimulation technologies,** such as nerve and deep brain stimulation therapies (Capogrosso & Lempka, 2020)."

"In translational applications of SCS, *in silico* neural models **provide a platform for investigating mechanisms of neurostimulation technologies and optimizing the therapy in ways that would be difficult, time consuming, and expensive to be perform experimentally (Capogrosso & Lempka, 2020).For example, computer models can be used to restrict the parameter space to be tested experimentally. This accelerates development and mitigates safety and ethical concerns by reducing the number of pre-clinical subjects as well as clinical iterations of initial experimental assays.**"

"These models also revealed that antidromic action potentials elicited in primary sensory afferents by SCS interfere with natural sensory feedback, which is crucial for coordinated limb movements **(Zhang *et al.*, 2014; Sadashivaiah *et al.*, 2018**; Moraud *et al.*, 2016; Formento *et al.*, 2018). This issue was resolved by implementation of a biomimetic burst stimulation protocol **spatiotemporally tuned to selectively activate different spinal cord locations with precise temporal resolution. This protocol** was first tested through computer simulations **(Moraud *et al.*, 2016; Formento *et al.*, 2018) and then** followed by experiments **in rats** (Wenger *et al.*, 2016)**,** monkeys (Capogrosso *et al.*, 2016), and later in humans (Wagner *et al.*, 2018)."

**R1.12** Further, the statement, "computational models have also led to dramatic improvements in lead designs, stimulation configurations, waveform parameters, and programming procedures", needs to be supported by specific examples. I am aware of only one specific effort here, the development of the transverse tripole by Holsheimer and colleagues, and in this instance the clinical results - no improvement in performance - contradicted the model predictions.

**Authors' answer:** We agree with the Reviewer that we should have given more explicit examples. Computational models have been used to develop or validate other lead designs, such as Medtronic's Specify 5-6-5 and Abbott's Penta lead (Kent et al., 2014). Computational models are also utilized in Boston Scientific's clinical programming system to determine stimulation configurations and select stimulation parameters (primarily electrode combinations and current distributions) that focus the stimulation at a desired location (selected by the user) (Veizi et al., 2017). Finally, Gilbert et al., 2022 showed how a computational network model could be used to optimize the temporal patterns of the SCS waveform. Yet, in many cases, the clinical usability of these approaches remains to be validated.

**Actions in the text:** We have added these examples in the paragraph *Why do we need computer models of SCS?* in the *Introduction* section.

"These computational models also led to dramatic improvements in lead designs, stimulation configurations, waveform parameters, and programming procedures (Lempka & Patil, 2018). **For instance, they have been used to develop or validate new lead designs (Kent et al., 2014). Computational models are also utilized in a commercial clinical programming system to determine stimulation configurations and select parameters that focus the stimulation at a desired location (selected by the user) (Veizi et al., 2017). Finally, a computational network model has been used to optimize the temporal patterns of a SCS waveform (Gilbert et al., 2022). Yet, in many cases, these approaches remain to be clinically validated**."

**R1.13** The gate theory does not hypothesize presynaptic interactions but rather interactions via an intervening interneuron.

**Authors' answer:** To avoid confusion and incorrect terms as 'presynaptic inhibition,' we have better detailed the mechanism of the gate-control theory in the *Introduction* section.

**Actions in the text:** We have modified the description of the gate-control theory in the *Introduction* section.

"It was originally developed on the premise of the gate-control theory of pain (Melzack & Wall, 1965), in which Melzack and Wall theorized **that the activation of cutaneous fibers can interfere with nociceptive signaling through inhibitory interneurons that 'gate' pain transmission from the spinal cord to the brain.**"

**R1.14** The interaction "interference" of SCS evoked antidromic activity and ongoing sensory activity was analyzed also by Sarma and colleagues and Zhang et al. in their modeling works and these should be included.

**Authors' answer:** We thank the Reviewer for the suggestion. We have now added the two references in the revised version of the manuscript.

**Actions in the text:**
"It was also revealed that antidromic action potentials elicited in primary sensory afferents by SCS interfere with natural sensory feedback, which is crucial for coordinated limb movements **(Zhang *et al.*, 2014; Sadashivaiah *et al.*, 2018**; Moraud *et al.*, 2016; Formento *et al.*, 2018)."

**R1.15** Computational Models ... H&H did not consider extracellular stimulation in any of their analyses.

**Authors' answer:** We agree with the Reviewer that our reference to the work of Hodgkin-Huxley was not correct. We have now modified the sentence to correct for our mistake.

**Actions in the text:** We have adjusted the sentence in the *Introduction* section.

"Computational models of neurostimulation **build on** the concepts developed by Hodgkin-Huxley to estimate how **extracellularly applied** electric potentials influence the neural membrane voltage (Hodgkin & Huxley, 1952; **Holsheimer, 1998**)"

**R1.16** Avoid passive voice, e.g., simply state "investigators considered", rather than "investigators have considered", "studies utilized", not "studies have utilized", etc.

**Authors' answer:** We thank the reviewer for the comment. We have now modified the manuscript accordingly.

**R1.17** "SCS-induced potential fields" ... SCS does not operate by induction, c.f., magnetic stimulation

**Authors' answer:** We thank the reviewer for the comment. We had chosen the word in its broader sense to mean "brought about", but we recognize the confusion. We have replaced "induced" with "generated" and "produced" in the corresponding text.

**R1.18** "with regard to", not "with regards to"

**Authors' answer:** We thank the Reviewer for pointing this out. We have modified the text to accordingly.

**R1.18** Suppl. Fig 2 requires scale bars

**Authors' answer:** We thank the Reviewer for pointing this out. We have decided to not include this figure anymore because we have been asked by the Editor to remove supplementary material.

**R1.19** Page numbers (and line numbers), please, to facilitate review

**Authors' answer:** We thank the Reviewer for the suggestion. We have now included page numbers and line numbers to facilitate review.

**Reviewer #2**

No surprise given who the authors are, this is a well thought our an organized document. I dont think it's intended to be "innovative" but it does include novel ways to organize the literature and I think this will be a universally useful resource for modelers in the field. My only minor concerns are more derived from own pet thoughts.

**Authors' answer:** We thank the Reviewer for the strong appreciation of our work. In the point-to-point below we have addressed the Reviewer's thoughts and we believe that the manuscript has been further improved thanks to these suggestions.

**R2.1** I would like to authors to address the "quasi-uniform assumption" in two ways. First, implicitly this is used in EVERY paper that does not model neurons - the fact thats its unstated is now a "weakness" as long as its recognized as an assumption. Second, in may area like tES is basically the default. In other areas like DBS, it increasingly seems that all the fanciest neuron models predict regions of stimulation that just look like electric field (with some cut-off). On a principled level, if the neuronal elements are either termination (dendrite or synapse), or bends, or changes in environment, or whole neurons etc. then electric field is what governs polarization. So please expand on what this means for SCS? Do NEURON models for example make suggestions on which electrodes to use that is different then just plotting electric field? Maybe but maybe not always? And certainly maybe not in new areas like slow waveforms?? this is not just an academic question but suggest the entire NEURON model step can be ignored in some cases?

**Authors' answer:** We thank the Reviewer for the suggestion and we agree that we should have further discussed the necessity of biophysical models. Specifically, models that include biophysical representations of neural structures are directly applicable to understand how, in some cases, the electric field directly drives membrane polarization, notably at axon terminals. Specifically, models that estimate electric fields are well suited for applications in which precise identification of which neurons are being activated is not the primary objective, such as studies investigating novel electrode configurations or the effects of anatomical electrical properties on current flow. On the other hand, for studies investigating precise biophysical activation profiles or evaluating new temporal stimulation patterns, biophysical models are better able to account for the subtle effects of ion channel dynamics and neural morphology on activation properties. Finally, for putative mechanisms of action other than direct electrical stimulation, such as tissue heating,

biophysical neuronal modeling may be unnecessary and instead a multiphysics simulation may be more appropriate.

**Actions in the text:** We have added the following text to the new paragraph *"The importance of increased complexity"* in the Discussion section.

"**As previously stated, computational models can simply include a volume conductor model to simulate the electromagnetic fields generated by SCS or can incorporate a biophysical neuron model to understand ionic current flows in individual neurons** (Chakraborty *et al.*, 2018)**. It has been proposed that, given the complex anatomical structure and variety of factors that can affect neural activation (e.g., branch points, axonal bends), the electric field will best predict neural polarization and neuromodulation, in contrast to the activation function (i.e., the second-order spatial derivative of the electric potential). This approach has been formalized as the "quasi-uniform assumption" (Bikson *et al.*, 2013; Bikson *et al.*, 2015; Khadka *et al.*, 2019) and may serve as a useful and efficient heuristic for predicting which gross anatomical regions are likely to be more strongly affected by the stimulation. Thus, this approach is well-suited for applications in which precise identification of which neurons are being activated is not the primary objective, such as studies investigating novel electrode configurations or the effects of anatomical electrical properties on current flow. On the other hand, for studies investigating precise biophysical activation profiles or evaluating new temporal stimulation patterns, a biophysical model is better able to account for the subtle effects of ion channel dynamics and neural morphology on activation properties. Finally, for putative mechanisms of action other than direct electrical stimulation, biophysical neuronal modeling may be unnecessary and instead multiphysics simulations may be more appropriate. For instance, modeling studies have investigated the combined effects of joule heating (due to applied electric currents) and bioheat transfer as a potential therapeutic mechanism for kilohertz-frequency SCS (Zannou *et al.*, 2019; Zannou *et al.*, 2021).**"

**R2.2** While almost no model care about heating some (basically me) do find this interesting. It matters from a methods perspective since the workflow is different. Regions of influence derive from local heat deposition.

**Authors' answer:** The Reviewer is correct on pointing out that thermal properties are important to be considered and we have therefore referenced to previous modeling studies that investigated the combined effects of joule heating (due to applied electric currents) and bioheat transfer as a potential therapeutic mechanism for high-frequency SCS (Zannou *et al.*, 2019; Zannou *et al.*, 2021).

**Actions in the text:** We have added reference to these models in the *Introduction* section.

"**For instance, modeling studies have investigated the combined effects of joule heating (due to applied electric currents) and bioheat transfer as a potential therapeutic mechanism for kilohertz-frequency SCS (Zannou *et al.*, 2019; Zannou *et al.*, 2021).**"

**R2.3** Patient specific models: One way to know if they are good is if ONLY from the MRI one can make a prediction across individuals (threshold for undersized motor response, pain control). On

some area like TMS (and maybe DBS) this "proof in the pudding" examples are hard to find, largely because we dont actually know what neuronal elements are stimulated to produce what outcomes. How does this go for SCS? The authors hint at this with Lempka work but I am not clear how good / reliable this idea is? Ready for products?

**Authors' answer:** Currently, from MRI we can extract information regarding potential differences in gross anatomical structures that could influence SCS parameters. However, it can be difficult to use medical imaging to predict stimulation efficacy across patients purely by considering factors, such as lead position (e.g., Delmotte et al., Neurochirurgie 2015). It can be possible to use some parameters, such as the thickness of the dorsal CSF, to make some predictions regarding factors like stimulation thresholds. Indeed, we know that the CSF thickness, which varies across patients, has an impact on the electric field generated within the spinal cord during SCS (Sin & Coburn, 1983). Furthermore, the activation thresholds of dorsal column fibers, perception threshold, and paresthesia coverage are also related to the dorsal CSF thickness (Solanes et al., 2021, He et al., 1994; Holsheimer & Struijk, 1991; Holsheimer et al., 1995; Lempka et al., 2015). However, as pointed out by the Reviewer, we do not have a clear understanding of the putative neural targets in SCS, especially for emerging applications and novel waveforms. This knowledge gap makes it difficult to simply use medical imaging to make clinical predictions. Therefore, more complex and personalized models are necessary to characterize the neuronal elements activated and to determine optimal parameters of stimulation. In this regard, MRI could be used to build patient-specific models as demonstrated in a few recent examples. Indeed, Lempka et al., 2020; Solanes et al., 2021; Howell et al., 2014; Rowald et al. 2022 showed that results obtained with patient-specific models are significantly more similar to clinical measurements than predictions generated with canonical models. These works show quantitative data to assess these statements proving the validity of the models. Unfortunately, widespread clinical use of complex patient-specific models is currently not possible primarily due to the effort required to build and analyze these models. Future work will be necessary to improve the tractability of these models for clinical decision support. We have added these considerations in the Discussion section.

**Actions in the text:** In the *Discussion* section, we have enriched our manuscript by adding quantitative and detailed examples that document the importance of patient-specific models compared to generalized canonical models (see Response 1.3 for these changes).

Additionally, we have added consideration towards the need for novel and more accurate MRI protocols.

"Despite these extremely encouraging results, additional work using patient-specific models is now necessary to further demonstrate the potential of these models to improve clinical implementation of SCS. We believe that the collection of papers reported here (see **Tables 3** and **4**) represents a valuable summary to guide the choosing of the best model designs in future works and boost the use of patient-specific approaches. **However, wider adoption of SCS models impels the improvement and standardization of MRI protocols that capture relevant structures, such as CSF and spinal roots.**"

**R2.4** How "shocking" (lets roll with this pun) is the lack of standard use of MRI derived models in SCS, compared to other fields. Even non-invasive spinal cord stimulation seems well aligned with using MRI derived models. SCS is an anomaly?

**Authors' answer:** MRI-derived models in SCS are not easy to develop, since the spinal cord structure is a small complex structure that is encapsulated in the vertebrae bones that are surrounded by muscles. This tissue heterogeneity creates distortion artifacts and makes it difficult to image the spinal cord. These considerations make it difficult to enhance the contrast of some tissues, especially for rootlets and gray matter, which are pivotal structures in SCS. Furthermore, each level of the spine is structurally different that can necessitate segment-specific MRI protocols. Finally, the majority of the studies that used MRI to construct the models do not share their acquisition protocols preventing homogenization of protocols across studies. Importantly, several groups are actively working to improve MRI spinal cord acquisitions and hopefully these efforts will help increase the number of computational SCS models that use MRI.

**Actions in the text:** We have extended consideration towards the need for novel and more accurate MRI protocols in the *Discussion* section and the comparison with DBS.

"Despite these extremely encouraging results, additional work using patient-specific models is now necessary to further demonstrate the potential of these models to improve clinical implementation of SCS. We believe that the collection of papers reported here (see **Tables 3** and **4**) represents a valuable summary to guide the choosing of the best model designs in future works and boost the use of patient-specific approaches. **However, wider adoption of SCS models impels the improvement and standardization of MRI protocols that capture relevant structures, such as CSF and spinal roots.**"

Finally, it is important to notice that personalization of DBS models was driven **not only by the availability of higher-resolution brain MRI but especially** by needs for precision in neurosurgical implantation procedures."

**R2.5** How can MRI based papers show up after introduction of MRI (e.g. Figure 3)

**Authors' answer:** We are not sure to understand the question of the reviewer. MRI based models can only appear after the introduction of MRI, which occurred around 2010. For this reason, when calculating the percentages of models that used MRI-based information, we only considered works after 2010. We have now better specified this approach in the Figures caption.

**Actions in the text:** We have clarified the captions for Figures 4 and 5, which were previously Figures 3 and 4, respectively, in the original submission.

"**Figure 4.** SCS model applications and purposes. (**A**) The top plot shows the different modeling studies based on their corresponding application (abscissa) and publication year (ordinate). The pie charts show the percentages of the anatomical sources used to create models for each application. **For this analysis, we only considered models published after the introduction of MRI to SCS models in 2010.** (**B**) Bubble charts illustrating the distributions of FEM and biophysical complexity scores for different applications. Autonomic was not included due to the low number of studies (n=3). Bold outlines indicate the most frequent complexity score for each application. (**C**) The bottom plot shows the different modeling studies based on their corresponding purpose (abscissa) and publication year (ordinate). The pie charts show the percentages of the anatomical sources used to create the models for each purpose. **For this analysis, we only considered models published after the introduction of MRI to SCS models in 2010.** (**D**) Bubble charts illustrating the distributions of FEM and biophysical complexity scores for different purposes. Bold outlines indicate the most frequent complexity score for each purpose."

"**Figure 5.** FEM model complexity (**A**), biophysical model complexity (**B**) and personalization (**C**) scores of SCS models as a function of publication year. We have indicated the anatomical sources of the model and the corresponding SCS technique by marker color and shape, respectively. The pie charts in A and C indicate the corresponding percentage of anatomical sources for each complexity and personalization score: 0 (bottom), 1 (middle), and 2 (top). **For this analysis, we only considered models published after the introduction of MRI to SCS models in 2010.** (**D**) Bar plots representing the mode of complexity scores for the FEM and biophysical models for each personalization level. **(E) Bar plots representing, for each level of personalization, the percentage of papers with no validation, a quantitative validation or a qualitative validation**."

**Reviewer #3**

I have been asked for a statistical opinion on this paper, further to concerns expressed during the review process.

**R3.1** Reviewer 1 states: 'This is not a "metanalysis", which is a specific statistical technique to combine data from multiple studies to assess an effect size and variance. Rather, the present manuscript is best characterized as a "systematic review".' This reviewer highlights multiple instances where she/ he feels that the opinions/ conclusions are unsupported by quantitative data. I agree that this work should not be labelled as a meta-analysis - there is no quantitative synthesis of effects/ associations herein and no meta-analysis methods are described. Rather, I suggest that the work is perhaps best framed as a systematic review with a qualitative meta-synthesis - something quite different to a meta-analysis. In doing this the authors can address the reviewers' comments by reworking the whole paper. I have no statistical comments, as no analyses were conducted.

**Authors' answer:** We thank the Reviewer for this comment. As pointed out in our manuscript, the lack of standardized and homogenized outcome metrics is one of the main challenges of this field. Therefore, it was not possible to perform a quantitative meta-analysis as clarified by the Reviewer, but only the type of qualitative analysis that we performed in our manuscript. Indeed, we agree that the present manuscript is best characterized as a "systematic review" with a qualitative meta-synthesis. We apologize for the incorrect wording choice. We have addressed the Reviewer's comments by reworking the manuscript to clearly state that this manuscript presents a systematic review with a qualitative meta-synthesis and not a meta-analysis.

**Senior Editor**

The authors indicated in their initial letter to us that the work would be a meta-analysis, and this is stated in the title as well. This would have been quite interesting given the importance and complexity of the problem. However, based on our assessment the study is not a meta-analysis but rather a systematic review.

**Authors' answer:** We apologize to the Editor for the incorrect wording choice. As also mentioned above, because the outcome measures from the computational models used in the existing studies are not standardized and homogenized, it was not possible to perform a quantitative meta-analysis but only the type of qualitative analysis that we performed in our manuscript. We have revised the manuscript to clearly state that this manuscript presents a systematic review with a qualitative meta-synthesis and not a meta-analysis. Moreover, we have performed some

additional analysis to further support our point that increased model complexity and personalization are necessary in computational models of SCS.

**Reviewing Editor**

The referees highlight the importance of this review topic; however, they raise a number of key issues. Of particular importance referee #1 highlights that supporting evidence/analysis is not provided to support key statements / conclusions - this needs to be addressed. In addition there is no 'meta-analysis' provided rather the article comprises a systematic review (please also see comments from statistics editor referee #3). A number of other points are made by both referees that require consideration.

**Authors' answer:** We would like to thank the Reviewers and the Editors for their constructive critiques and the opportunity to submit a revised version of our manuscript. We believe that the manuscript has significantly improved thanks to these comments.

Please note a revised version needs to

• include whether there was validation of the model calculations and (quantitative) comparison of model predictions to experimental measurements.

**Authors' answer:** As also suggested by the Reviewer #1, we have performed a deeper analysis of the studies included in our review by including an additional variable in our analysis. This variable, which we called Model Validation, indicates whether or not there was an experimental validation of the model calculations, and whether such validation was quantitative or qualitative.

• analysis of whether increases in model complexity and personalization lead to more accurate match or prediction of experimental or clinical results

**Authors' answer:** We agree that our statements regarding increased model complexity (and personalization) and its benefits were too general and not supported by analysis. However, it is difficult to perform an extensive analysis because of a paucity of comparable outcome variables across studies and only a small number of studies directly compare the predictions from models of different complexities to experimental or clinical data. However, we added more quantitative details about the four papers that used highly complex and personalized models (Howell et al., PLoS One 2014; Lempka et al., Neuromodulation 2020; Solanes et al., J Neural Eng 2021; Rowald et al., Nat Med 2022). Additionally, we have also highlighted the tremendous impact that complex and personalized models have had in advancing the science and efficacy of other neurostimulation technologies, such as deep brain stimulation.

• synthesis to make clear what are the important unknowns, challenges, and open questions.

**Authors' answer:** We agree that the manuscript missed a clear synthesis of the still open questions and challenges that limit the accuracy of the computational models. Therefore, in the *Introduction* section, we have identified and highlighted the important unknowns, challenges, and open questions that can be summarized here:

1) Which anatomical structures are essential for accurate volume conductor models?
2) What imaging techniques can capture these anatomical structures and their morphology?
3) Do increased complexity and personalization improve model accuracy?

4) Which physical material properties (e.g., electrical conductivity values and thermal properties) should be applied to simulate electromagnetic field distributions?
5) Are biophysical neuron models necessary for accurate simulations? If so, which models?
6) What are the best methods to standardize model validation and clinical outcome metrics for future studies?

Please note that supplementary figures and tables (and therefore table references) are not permitted.

**Authors' answer:** We have moved supplementary figures and tables to the main text.

Dear Dr Pirondini,

Re: JP-TR-2022-282884R1-A "A systematic review of computational models for the design of spinal cord stimulation therapies: from neural circuits to patient-specific simulations" by Lucy Liang, Arianna Damiani, Matteo Del Brocco, Evan R. Rogers, Maria K. Jantz, Lee E. Fisher, Robert A Gaunt, Marco Capogrosso, Scott F. Lempka, and Elvira Pirondini

I am pleased to tell you that your Topical Review article has been accepted for publication in The Journal of Physiology, subject to any modifications to the text that may be required by the Journal Office to conform to House rules.

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Yours sincerely,

Katalin Toth
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EDITOR COMMENTS

Reviewing Editor:

Both referees are positive about the comprehensive revision of this manuscript that is now framed as a systematic review and qualitative meta-synthesis. There are no outstanding concerns.

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REFEREE COMMENTS

Referee #1:

The authors are to be commended for their clear, compelling and complete revisions of the manuscript to address the concerns of the reviewers.

Referee #2:

My concerns are addressed.

**1st Confidential Review** **14-Oct-2022**