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TOPICAL REVIEW

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

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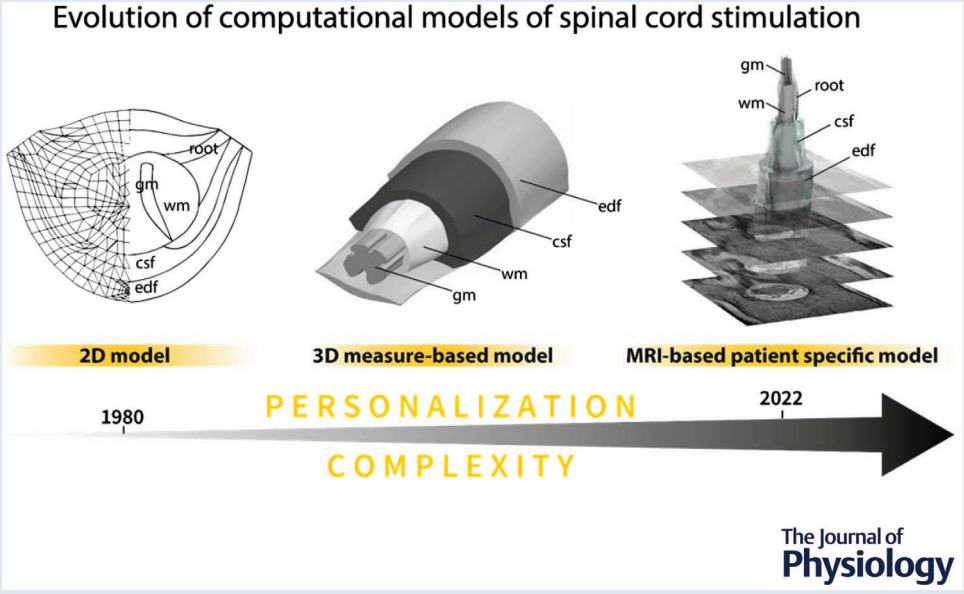

Abstract Seventy years ago, Hodgkin and Huxley published the first mathematical model to describe action potential generation, laying the foundation for modern computational neuroscience. Since then, the field has evolved enormously, with studies spanning from basic neuroscience to clinical applications for neuromodulation. Computer models of neuromodulation

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have evolved in complexity and personalization, advancing clinical practice and novel neurostimulation therapies, such as spinal cord stimulation. Spinal cord stimulation is a therapy widely used to treat chronic pain, with rapidly expanding indications, such as restoring motor function. In general, simulations contributed dramatically to improve lead designs, stimulation configurations, waveform parameters and programming procedures and provided insight into potential mechanisms of action of electrical stimulation. Although the implementation of neural models are relentlessly increasing in number and complexity, it is reasonable to ask whether this observed increase in complexity is necessary for improved accuracy and, ultimately, for clinical efficacy. With this aim, we performed a systematic literature review and a qualitative meta-synthesis of the evolution of computational models, with a focus on complexity, personalization and the use of medical imaging to capture realistic anatomy. Our review showed that increased model complexity and personalization improved both mechanistic and translational studies. More specifically, the use of medical imaging enabled the development of patient-specific models that can help to transform clinical practice in spinal cord stimulation. Finally, we combined our results to provide clear guidelines for standardization and expansion of computational models for spinal cord stimulation.

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Abstract figure legend Evolution of computational models of spinal cord stimulation. The use of computational models of spinal cord stimulation is expanding rapidly in the field of neuromodulation. Here, we evaluated the evolution of such models from the 1980s to 2022. Thanks to the advancement of medical images and computational tools, models have evolved from two-dimensional (2D) models (left) to three-dimensional (3D) models with limited realism and tissue compartments (middle), then to magnetic resonance imaging (MRI)-based patient-specific models with high realism and complex tissue compartments (right). Model figures were adapted from Capogrosso et al. (2013), Coburn (1980), and Rowald et al. (2022), with permission. Abbreviations: csf, cerebrospinal fluid; edf, epidural fat; gm, grey matter; root, roots and rootlets; wm, white matter.

Introduction

Since Hodgkin and Huxley published their numerical solutions to the set of partial differential equations describing the generation of membrane voltages in axons (Hodgkin & Huxley, 1952), computer models in neuroscience have bloomed into a myriad of applications. In addition to theoretical understanding of the neural

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code, computer models have found fertile ground in translational studies of neurostimulation (Capogrosso & Lempka, 2020). These clinically oriented applications stemmed from the need to understand the mechanisms underlying the observed experimental evidence that electrical stimulation of axons in the dorsal columns reduced chronic pain in patients with refractory pain syndrome. 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 (DBS) therapies (Capogrosso & Lempka, 2020). Here, we review the historical progression of computer models for SCS and analyse the introduction of modern imaging techniques and their impact on current and future clinical applications.

Spinal cord stimulation. Spinal cord stimulation is a US Food and Drug Administration-approved therapy for treating refractory pain, with >50,000 implants per year (Sdrulla et al., 2018). SCS for pain management dates back to 1967 (Shealy et al., 1967; Wall & Sweet, 1967). 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 fibres can interfere with nociceptive signalling through inhibitory interneurons that 'gate' pain transmission from the spinal cord to the brain. This hypothesis led to the suggestion that electrical stimulation of the dorsal columns, which carry low-threshold cutaneous afferents, would drive activity in spinal inhibitory interneurons, which would, in turn, attenuate nociceptive signalling and thereby prevent nociceptive output from the spinal cord to the brain (Lempka & Patil, 2018; Zhang et al., 2014). To this end, electrodes were placed in the dorsal epidural space to stimulate sensory afferents in the dorsal columns. Aided by the relatively low risk of the surgical procedure, SCS has since been used in investigational studies to explore a variety of clinical applications, such as improvement of motor control and autonomic functions in a variety of disorders, such as multiple sclerosis, stroke and spinal cord injury (Barola et al., 1995; Barolat-Romana et al., 1985; Cioni & Meglio, 1987; Meglio et al., 1989; Pirondini et al., 2022; Powell et al., 2022; Waltz & Andreesen, 1981).

Computational models of SCS. Computational models of neurostimulation build on the concepts developed by Hodgkin and Huxley to estimate how extracellular application of electric potentials influences the neural membrane voltage (Hodgkin & Huxley, 1952; Holsheimer, 1998). More specifically, three-dimensional (3D) volume conductor models of the spinal cord geometry, which rely on realistic anatomy that can be obtained by anatomical measures and/or medical imaging (Fig. 1*A*), are used to compute the extracellular potential. A numerical method, such as the finite element method (FEM), can then be used to calculate the potential distributions generated within these complex anatomical structures (Coburn & Sin, 1985) (Fig. 1*B*). Finally, extracellular potentials are applied to Hodgkin–Huxley neural models (Hodgkin & Huxley, 1952) to estimate the corresponding neural response (Fig. 1*C*).

Why do we need computer models of SCS? 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 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 preclinical subjects and clinical iterations of initial experimental assays.

With regard to SCS for chronic pain management, computational models have provided insights into which neural pathways primarily respond to SCS, supporting the gate-control mechanism of the therapy (Holsheimer, 2002). These computational models have 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 used in commercial clinical programming systems to determine stimulation configurations and select parameters that focus the stimulation at a desired location (selected by the user) (Veizi et al., 2017). Finally, computational network models have been used to optimize the temporal patterns of SCS waveforms (Gilbert et al., 2022). Yet, in many cases, these approaches remain to be validated clinically.

The knowledge gained from computational models of SCS for pain has permitted a rapid growth of SCS models for other applications. In experiments using SCS to improve locomotion, computational models demonstrated that myelinated afferent fibres are the primary targets of SCS, activating motoneurons and other cells via synaptic pathways (Capogrosso et al., 2013). 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 (Formento et al., 2018; Moraud et al., 2016; Sadashivaiah et al., 2018; Zhang et al., 2014). This issue was resolved by implementation of a biomimetic burst stimulation protocol spatiotemporally

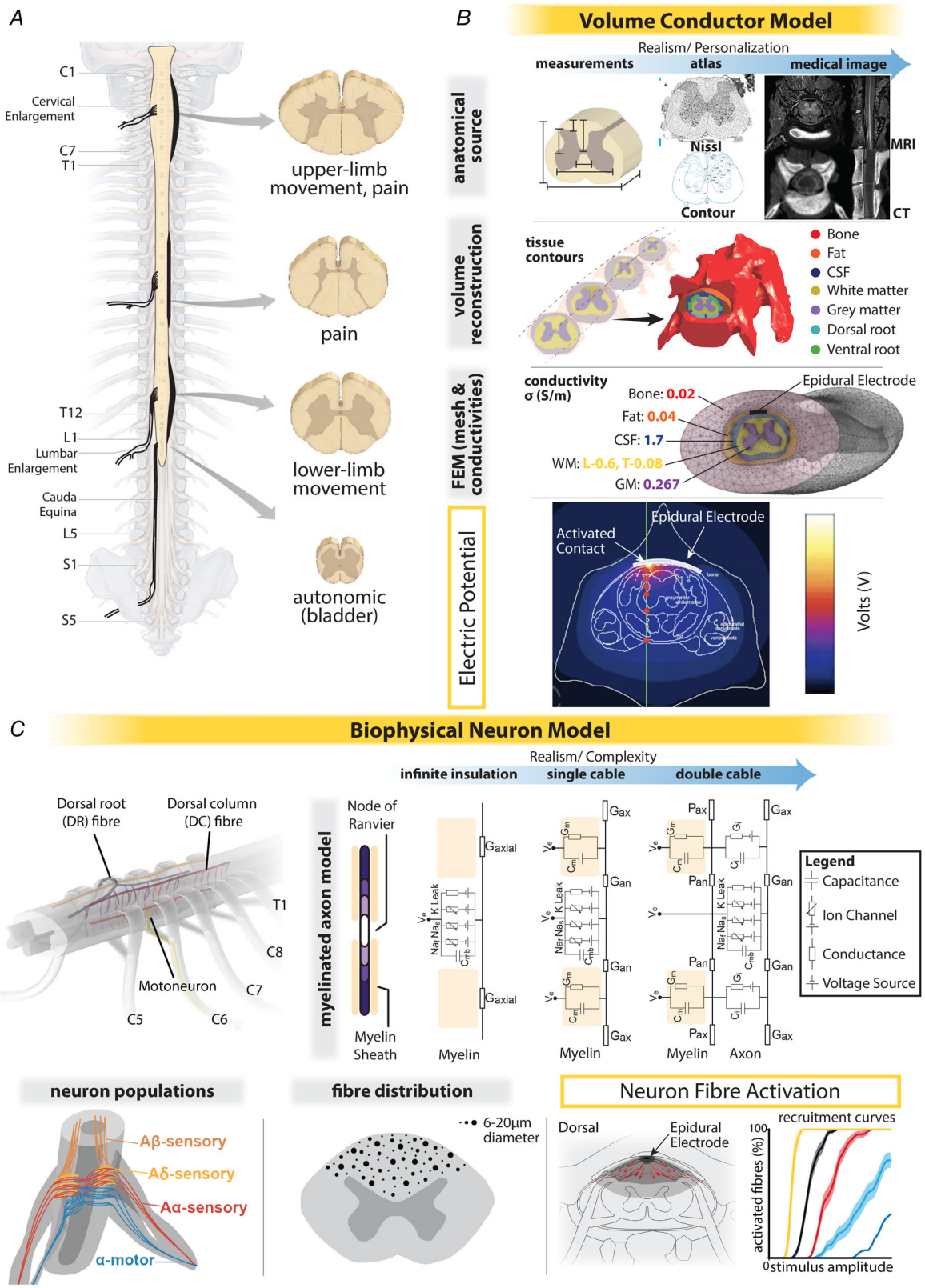

Figure 1. Spinal cord stimulation computational modelling components
A, example of the morphology of human spinal cord segments and their general applications in SCS, namely movement (movement restoration), pain (chronic pain treatment) and autonomic (autonomic

restoration/restoration of lower urinary tract function). Differences in root angle and segment shape for each spine area are highlighted with thick lines. *B*, steps for building the volume conductor model that can be used to simulate the electromagnetic fields generated by SCS: (i) tissue contours are derived from anatomical sources (i.e. measurements, atlas and/or medical images); (ii) these segmentations are then used for the three-dimensional volume reconstruction; and (iii) proper conductivity values are assigned to each tissue, and a mesh is generated to simulate electromagnetic field distributions. *C*, potential components for the biophysical neuron model. Neuron fibre activation can be simulated based on assigned fibre diameter, neuron population or neural trajectory, which, with parameter tuning based on experimental and/or clinical data, can be translated into experimental and/or clinical predictions, such as perception and discomfort thresholds, and measurements of motor restoration. Sub-panels in *C* include figures modified from Greiner et al. (2021) and de Freitas et al. (2022), with permission.

tuned to activate different spinal cord locations selectively with precise temporal resolution. This protocol was first tested through computer simulations (Formento et al., 2018; Moraud et al., 2016), followed by experiments in rats (Wenger et al., 2016) and monkeys (Capogrosso et al., 2016) and, later, in humans (Wagner et al., 2018).

Unknowns, challenges and open questions. Overall, the previous examples highlight the importance of computational simulations in the translational pathway to preclinical tests and, finally, to successful clinical implementation. 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 might be the most proper imaging techniques and protocols to capture these structures. Second, 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 have 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 were to identify overall trends, including both established and emerging indications, and to provide recommendations to standardize and expand the use of computational models to advance the field of SCS for various clinical applications.

Methods

Inclusion criteria and study search. The papers included in the present review had to comply with the following three essential criteria: (i) they had to include volume conductor models of the spinal cord; (ii) the computational model was used to simulate the field(s) generated by electrical SCS (epidural, intradural or transcutaneous); and (iii) the paper was available in English. The search for relevant papers was initially conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov/; 4 March 2022) using the keywords defined in Table 1, by means of Boolean operators, nesting and truncation.

Coding of variables. For each included paper, we extracted variables to categorize distinct aspects of the computational models. We divided these aspects into objective and derived variables. On an important note, several methods can be used to solve Maxwell's equations and calculate the applied potentials in the complex anatomical geometries. However, because the FEM is by far the most common approach, we will generally refer to these methods as FEM models.

Objective variables.

- Year of publication of the paper.
- Species on which the FEM model was based: human, monkey, dog, cat or rodent.
- SCS technique: epidural, intradural or transcutaneous.
- Spine level coverage: cervical, thoracic, lumbar/lumbosacral or whole spinal cord.
- Application for which the FEM model was used: pain, movement, autonomic function or biophysical. 'Biophysical' meant that the model was not used for a specific application, but with the goal of improving the general development of computational models (e.g. comparing the dermatomal zone selectivity of single current source and multiple current source systems within the dorsal column (Min et al., 2014)).
- The main purpose for which the model was created: to optimize stimulation parameters, optimize lead position, optimize lead design, investigate mechanism(s) of action and for modelling. 'Modelling' refers to studies that developed and released the model without a specific purpose. When there was more than one purpose in the same paper, we assigned the most relevant one.
- Anatomical sources used to create the FEM model: measure/atlas based, magnetic resonance imaging

Table 1. Keyword search table and results

Search term	Search results for PubMed (4 March 2022)	Comment
"spinal cord stimulation" AND ("finite element" OR "computation*") NOT "peripheral"	72	No filter
"spinal cord" AND "stimulat*" AND "computation*" AND model	128	No filter
"spinal cord" AND "stimulat*" AND "finite element" AND model	74	No filter
"spinal cord" AND "stimulat*" AND simulation AND model	334	No filter
Total number of publications	608	–
Total number of publications excluding duplicates	431	–

(MRI) based or MRI/measure based. 'Measure/atlas based' refers either to using basic geometric contours of shapes and sizes measured from dissections or taken from the literature or to using an atlas (i.e. by extrusion of histological cross-sectional images). 'MRI based' refers to using three-dimensional (3D) reconstructions of tissue structures through MRI segmentations. Finally, the 'MRI/measure-based' category refers to using a combination of measures and MRI-based models. It is important to note that we used the term 'MRI' to refer to medical imaging (i.e. MRI and/or computed tomography (CT)). This choice was made because only $n = 4$ articles (Greiner et al., 2021; Lempka et al., 2020; Song et al., 2015; Zareen et al., 2017) reported the use of CT as an anatomical source for specific compartments (bone and electrode). Furthermore, to date, dura mater and root/rootlet tissues have not been created in any FEM using MRI; therefore, we did not consider these structures in the classification of anatomical sources.

- Validation: no validation, qualitative validation or 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 might have been validated for other simulations in a different publication. A 'qualitative validation' corresponded to a comparison between simulated and experimental results without direct comparison of 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.

Derived variables. In addition to objective variables, we assigned different scores to the models based on two derived variables, namely personalization and complexity.

- Personalization: a variable that evaluated the extent to which the FEM model was personalized for a specific subject. We assigned a score of 0, 1 or 2. A score of '0' meant that the model was not personalized. A score of '1' meant that the model was partly personalized (e.g. variations in the dorsal cerebrospinal fluid (CSF) thickness or a modification of tissue conductivity to simulate spinal cord injury). A score of '2' meant that the model considered the realistic shapes and sizes of each anatomical compartment for a specific subject.
- Complexity: we considered two levels of model complexity: FEM model complexity and neuron model complexity.
  (a) FEM model complexity: a variable that evaluated the complexity of the tissue volumes and conductivities included in the FEM model. We calculated the complexity score for each FEM model considering the tissues that were included. Precisely, we gave one point for each tissue type that appeared in $\geq$8% of the papers (i.e. grey matter, white matter, CSF, epidural fat, bone, dura mater, vasculature, rootlets, intervertebral discs, encapsulation tissue, muscle, skin and surrounding layer/saline bath). For the other tissues (e.g. cartilage and connective tissue), which were represented in a minority of the papers, we assigned one point if at least one of these tissues was represented in the FEM model. The maximum score was 11, and we discretized the complexity score in three levels: 0 = (complexity score $\leq$ 4); 1 = (5 $\leq$ complexity score $\leq$ 7); and 2 = (complexity score $\geq$ 8).
  (b) Neuron model complexity: a variable that evaluated the complexity of the biophysical model of the neural response to SCS. We calculated this complexity by summing the complexity scores assigned for individual components of the model: axon ion channels and axon cable structure. We assigned the axonal ion channels a score of 0 (no ion channels), 1 or 2. A score of '1' meant that the ionic dynamics were derived from another species, whereas a score of '2' meant that the ionic dynamics were matched to the species for which SCS was being modelled. We assigned the axonal cable structure a score of 1, 2, 3 or 4. We applied a score of: '1' to models that did not represent the axon as

an electrical circuit, but instead used an activating function (i.e. second-order spatial derivative of the applied electric potential) to approximate neural activation (Rattay et al., 2000); '2' to models that represented axons as simple, unmyelinated cylinders and to models that represented axons as nodes of Ranvier separated by internodes with infinitely resistive myelin; '3' to models that represented axons as nodes of Ranvier connected by myelinated internodes with finite impedance; and '4' to models that used a double-cable structure to model axons with finite-impedance myelin and with a conductive pathway in the periaxonal region between the axolemma and myelin sheath. We added additional points (i.e. 1 point) if studies incorporated: (i) small-diameter collateralization of the axons; (ii) more than one fibre population; (iii) different fibre diameters; (iv) different axon locations; and/or (v) varied fibre position and/or diameter to maximize biological realism (e.g. matching fibre densities to histological data, stochastically drawing fibre diameters from an appropriately parametrized distribution). Overall, this scoring system allowed for a maximum of 11 points, and we discretized the complexity score in three levels: 0 = (complexity score $\leq$ 4); 1 = (5 $\leq$ complexity score $\leq$ 7); and 2 = (complexity score $\geq$ 8).

Data analysis. Initially, we summarized the proportional distribution of studies within each category. Next, we focused our analysis on the temporal evolution of individual variables. Finally, we analysed the relationships between the different variables. It is important to note that when analysing anatomical sources for different applications and purposes, we considered only studies published after 2010 (i.e. the year in which MRI was introduced into the construction of FEM models). Finally, we summarized key findings of human studies that used patient-specific models, which might guide future advancement of these tools.

Results

Study selection. Our search combinations resulted in a total of 431 unique papers on 4 March 2022 (Fig. 2). After an appraisal of the abstracts, 352 manuscripts were excluded owing to the absence of a volume conductor model of the spinal cord or owing to a focus on unrelated simulations, such as mechanical properties of the spinal cord. Given that computational modelling of electrical stimulation is highly interdisciplinary, for the 79 remaining papers, we examined their references to avoid oversight of relevant papers that were not in the PubMed database. As a result of this step, we added 17 papers. Of these 96 papers, nine papers were review papers,

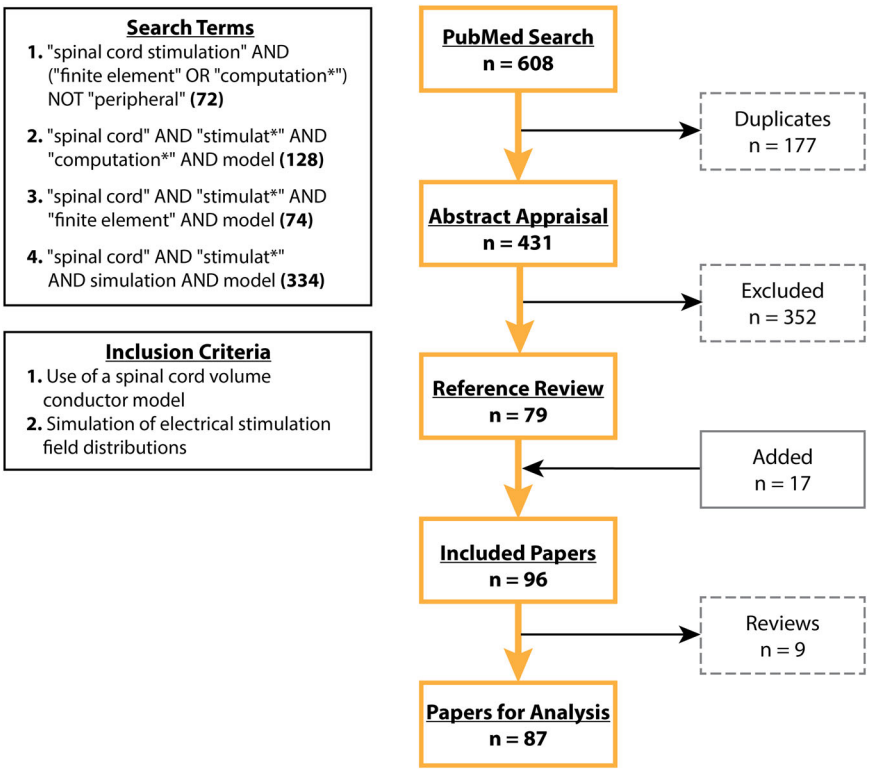

Figure 2. Flow diagram of study selection results

perspectives or book chapters and were excluded from our review. Therefore, we considered a total of 87 papers in our analyses. It should be noted that these 87 papers included only ∼41 unique spinal cord models (for details, see Tables S1–S3). Some of the models were reused in different papers with small modifications. Given that these modifications were made to simulate specific conditions or unique applications, we considered each study as a new model in our analysis.

The evolution of FEM models for SCS. Computational models of SCS were first developed in the early 1980s (Coburn, 1980; Sin & Coburn, 1983). Before approximately the year 2000, the majority of models were not developed for a specific clinical application, and studies focused mainly on understanding technical aspects of building a model and factors affecting simulation results. Thereafter, the focus evolved into more specific applications. Computer models for pain management have been and continue to be the most common application (43%; Fig. 3), and movement and autonomic function applications emerged only around the 2010s (Fig. 4*A*). Therefore, not surprisingly, most of the models (53%) focused on the thoracic spinal cord, the most common SCS target to treat lower back and leg pain. For all existing models, the most common stimulation technique was epidural stimulation (76%), and most of the computational efforts were used to model the human spinal cord (81%), where clinical interest is more abundant. A considerable portion of existing models

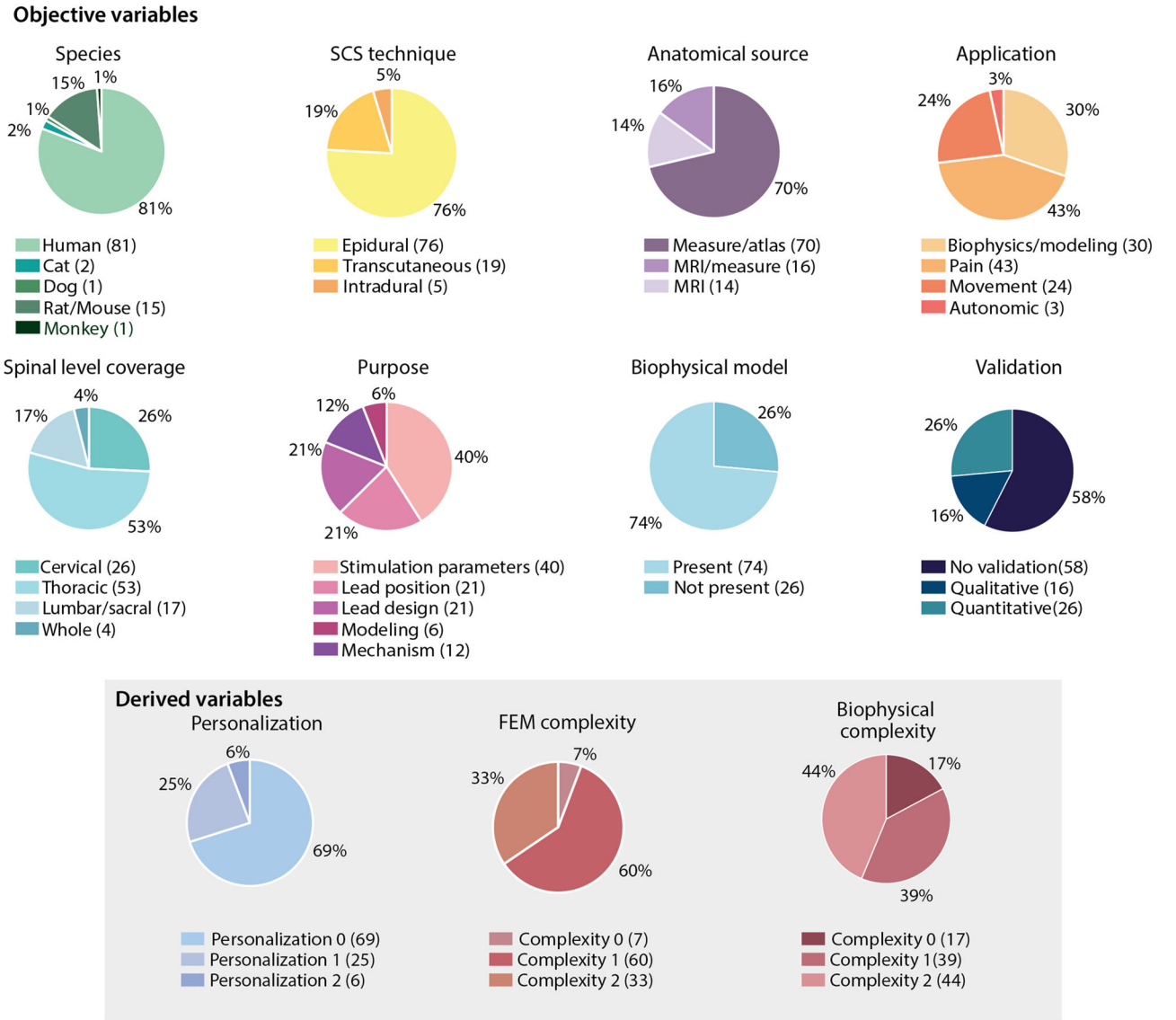

Figure 3. Pie charts of objective- and derived-variable distributions amongst the studies included in our analysis

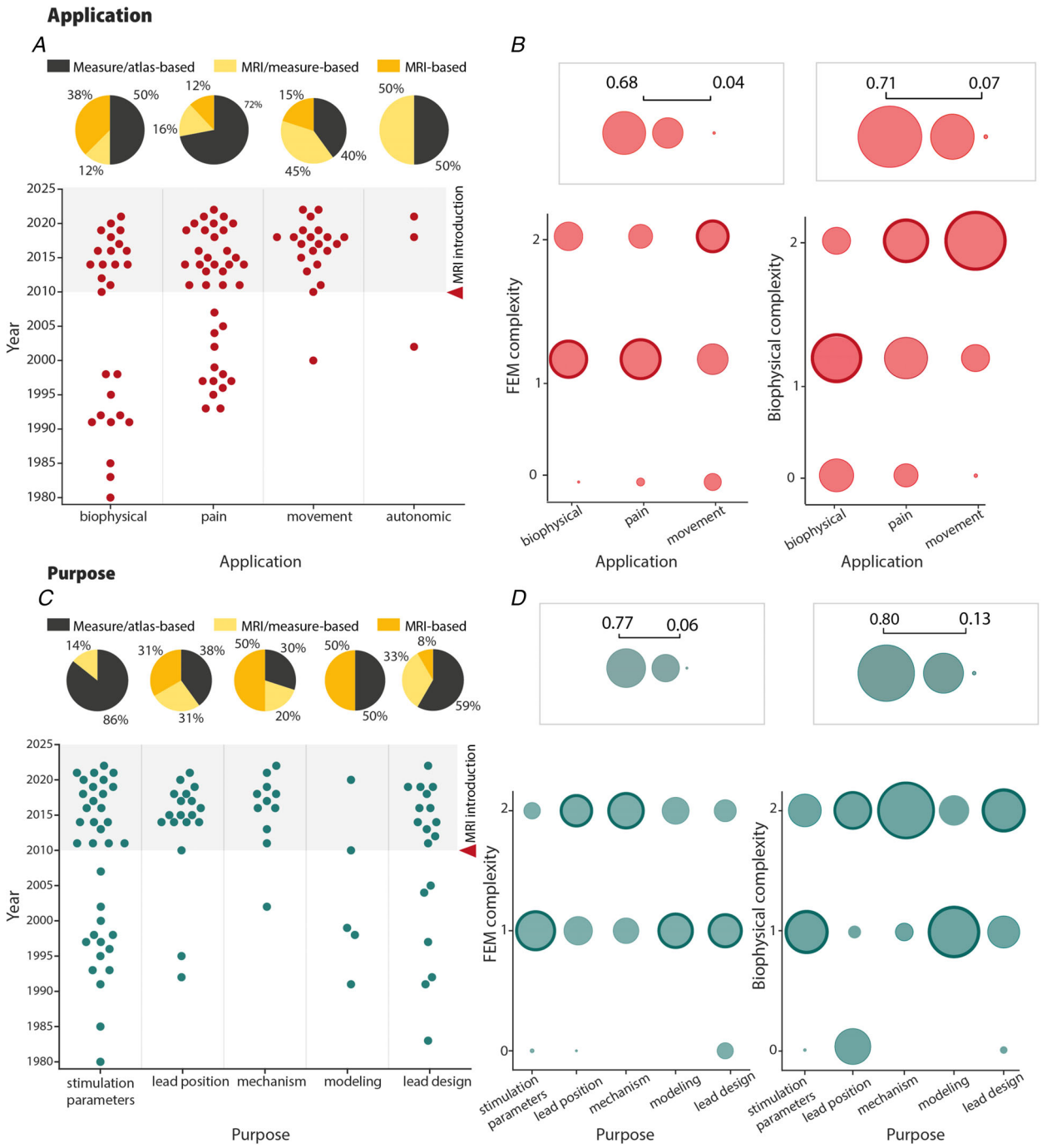

Figure 4. Spinal cord stimulation model applications and purposes
A, the plot shows the different modelling studies based on their corresponding application (abscissa) and publication year (ordinate). The pie charts show the percentages of the anatomical sources used to create models for each application. For this analysis, we considered only 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. The 'autonomic' category was not included owing to the low number of studies (n = 3). Thick outlines indicate the most frequent complexity score for each application. *C*, the plot shows the different modelling 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 considered only 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. Thick outlines indicate the most frequent complexity score for each purpose.

sought to analyse and optimize the stimulation parameters (40%). Only in the last decade (since 2010), more applied studies have been complemented with the interest in understanding the underlying mechanisms of action of SCS (Fig. 4*C*). Not surprisingly, this shift coincides strikingly well with the introduction of computational models of SCS in preclinical animal models and might be driven by the introduction of new SCS technologies, such as kilohertz-frequency (Kapural et al., 2015; Van Buyten et al., 2013) and burst SCS (Deer et al., 2018), which were proposed to improve the clinical efficacy of SCS for pain relief relative to conventional low-frequency (i.e. 40–60 Hz) stimulation. Despite the increased use of SCS models in both clinical and preclinical simulations, we found that more than half (58%) of the published simulation results were not validated experimentally, highlighting the lack of standardized guidelines for the effective use of these models.

The evolution of personalization and complexity of SCS models. Since the earliest computational models of SCS, investigators have considered the possible effects of anatomical variations (Cadotte et al., 2015; Delmotte et al., 2015; Holsheimer et al., 1991; Toossi et al., 2021) on the electric potential distributions generated during SCS and the corresponding neural activation. However, most FEM models to date incorporate no personalization (69%; Fig. 3). Only a small percentage (6%) of studies used models with a high degree of personalization (i.e. personalization score of 2), and all of these studies were published recently (2014 or later; Figs 3 and 5).

We identified an analogous pattern with regard to FEM model complexity. In the early stages, models were two-dimensional (2D) and contained limited spinal cord compartments. Probably thanks to more powerful computers, more efficient algorithms and standardized multiphysics simulation software, FEM models quickly expanded to 3D and used a medium level of complexity (i.e. complexity score of 1; 60%). However, only 33% of the models reached the highest complexity level (i.e. complexity score of 2). This increase in complexity might also be explained by the inclusion of the spinal roots and rootlet structures in 16 papers (for details, see Tables S1–S3) since 2014. Although some early modelling studies

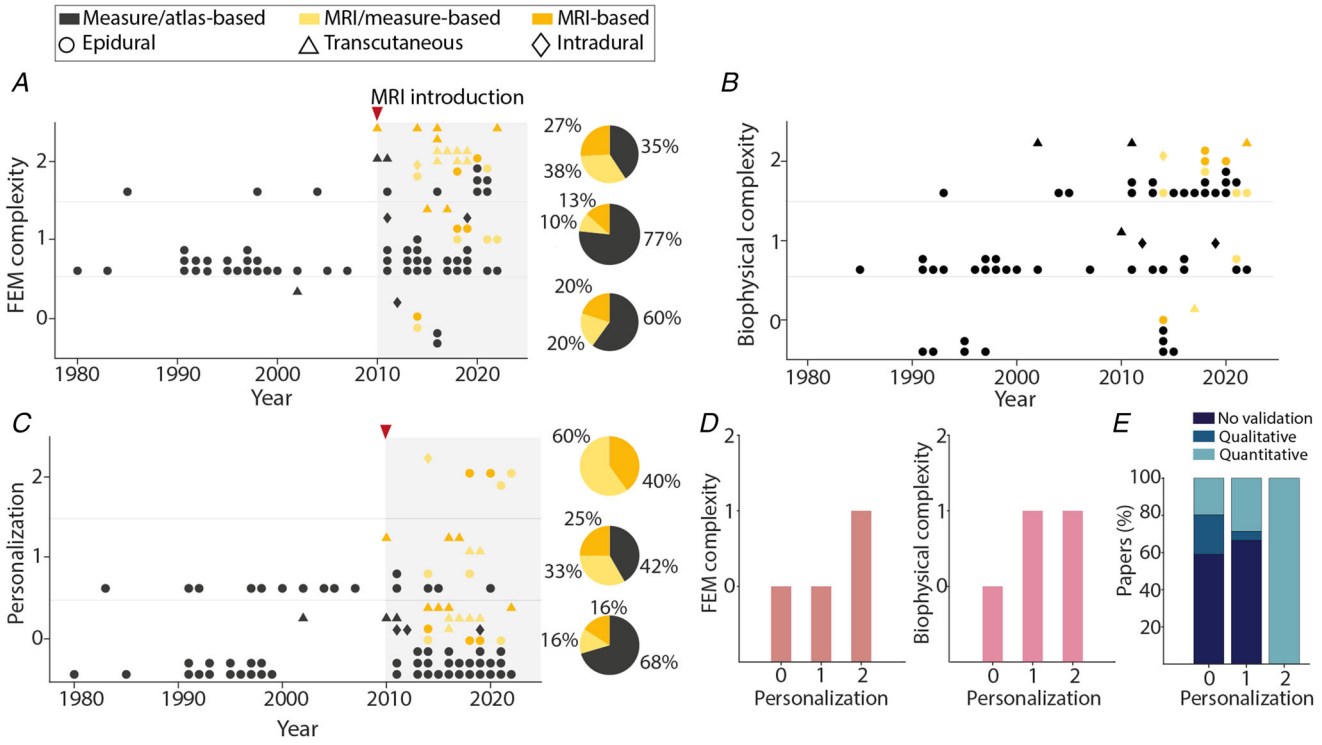

Figure 5. Spinal cord stimulation model complexity and personalization
A–C, FEM model complexity (*A*), biophysical model complexity (*B*) and personalization (*C*) scores of SCS models as a function of publication year. We have indicated the anatomical sources of the model and the corresponding SCS technique by marker colour 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 considered only 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.

of SCS for pain control included explicit representations of the spinal roots (Coburn, 1980; Coburn & Sin, 1985), recent increased attention on spinal root volume can be attributed, in part, to increased computational power that has allowed these roots to be included in complex 3D models. Multiple studies have demonstrated that dorsal root fibres are crucial stimulation targets for motor control (Capogrosso et al., 2013; Greiner et al., 2021), which highlights that the inclusion of spinal roots in the FEM model is especially important in SCS for motor control.

An equivalent analysis on the model complexity can be applied to the increase in realism over time for the biophysical neuron models. These neural components are necessary to quantify the effect of SCS-produced potential on neural behaviour directly. Coburn was the first to model the neural response to SCS directly and compared the predicted activation thresholds of dorsal column, dorsal rootlet and corticospinal tract fibres in response to epidural SCS with clinical observations (Coburn & Sin, 1985). This seminal paper applied the McNeal model of myelinated fibres, which consists of nodes of Ranvier with frog-derived ion dynamics connected by infinitely resistive myelinated internodes (Frankenhaeuser & Huxley, 1964; McNeal, 1976). After this foundational model, many studies included explicit representations of neurons (74%), with a general trend of increased biophysical complexity over time (Fig. 5*B*). Indeed, only ∼17% of biophysical models published before 2010 had high complexity, whereas 59% of those published since 2010 achieved the highest complexity score.

This increase in complexity is attributable both to an increase in the sophistication of components included in the models (e.g. fibre diameters and ion channel dynamics) and to the introduction of new levels of detail (e.g. double-cable myelin model) that provide a more complete or accurate assessment of the neural response (Richardson et al., 2000; Struijk et al., 1992; Wesselink et al., 1999). These developments have followed important findings from both studies that were specific to SCS and those for general neurostimulation purposes.

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 (Fig. 5*D*). 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 (Fig. 5*E*). Of the 23 studies with quantitative validation, 18 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 to make quantitative predictions that might inform clinical practice directly.

Increased complexity shaped the evolution of model applications and purposes. The personalization level distributions were similar across applications and purposes, whereas FEM and biophysical model complexity scores varied across different model applications (Fig. 4*B*), with movement-application models generally having a higher complexity. This higher complexity for movement-application models might be explained by their well-defined neural targets and necessary stimulation precision. Likewise, it is unsurprising that biophysical-application models, which lack a defined functional goal, have the lowest aggregate complexity scores. Moreover, this discrepancy might be explained, in part, by the fact that models were initially applied for different applications in different decades, thus reflecting the general trend for complexity to increase over time (Figs 4*A* and 5*A* and *B*).

Additionally, FEM and biophysical complexity scores also differed between study purposes (Fig. 4*D*). Interestingly, both mechanism and lead design had high complexity for both FEM and biophysical models, whereas modelling-purpose and stimulation-parameter studies had medium complexity. Interestingly, for lead position, the complexity score was higher for biophysical models (level 3) than for FEM models (level 2).

Introduction of medical imaging influenced the complexity and personalization of computer models for SCS. Until recently (2010s), the majority of the models were measure based (71%). In the early 2010s, magnetic resonance images obtained with different sequences and microCT scans were introduced, revolutionizing the way that SCS FEM models were created (Figs 3 and 4). For humans, the most common sequences have been SPACE fast turbo spin echo 3D (Christ et al., 2010) and T2 SPACE with ZOOMit (Rowald et al., 2022), whereas in animals, the most common have been TurboRARE T2 weighted pulse sequence (Zareen et al., 2017).

Despite the limited use of this technology, MRI-based models shaped applications and purposes and allowed the use of more complex and personalized models. Indeed, all models with the highest personalization level used MRI-based identification of the anatomical structures, and those with medium personalization used medical imaging in the majority of the cases (58%). The FEM complexity showed a similar trend, with 65% of the models with high complexity deploying MRI information.

Interestingly, we found that MRI-based models are used more commonly in the movement application (60% for movement *vs*. 28% for pain) and have recently expanded to the biophysical application (Fig. 4*A*). This trend suggests that, despite being the first and one of the main fields of application, the pain community is not taking full advantage of the innovations introduced by the use of MRI. Several reasons could justify this discrepancy. Rootlet fibres are often not represented explicitly in FEM or biophysical models of SCS for pain, because activation of the thoracic roots and rootlets is believed to be associated with discomfort, and the axons within the dorsal columns are the main therapeutic target. Furthermore, the most common implantation levels for SCS for pain are the lower thoracic spine levels. At these levels, it is not possible to visualize these rootlet structures. Furthermore, the anatomy of the thoracic spinal cord is also less variable across segments in comparison to the cervical and lumbosacral cord (Frostell et al., 2016; Ko et al., 2004) (Fig. 1*A*). Therefore, precise cord and rootlet shapes and dimensions are less likely to affect simulation results in the thoracic cord.

Purposes and MRI-based models had a similar evolution. Indeed, we found that from the outset (around early 2010s), mechanisms of SCS were studied mostly using MRI-based models, showing that more recent fields took full advantage of this new technology (Fig. 4*C*). Also, for lead position and design, the usage of MRI has been increasing over the years. Stimulation-parameter studies, instead, are still based mostly on measure-based models (Fig. 4*C*).

Finally, it appears that transcutaneous SCS models were mostly MRI based (Fig. 4*A*). This could be because of the necessity of capturing anatomical structure outside the bone, but also by the usage of the virtual family model (Christ et al., 2010), which is MRI based and is often reused across studies. There is, instead, nothing similar for epidural and subdural SCS.

Discussion

The rapidity at which neuroengineering and neuroscience are expanding results in a continuous demand for new tools capable of optimizing and refining the interactions with the nervous system, although the role of many structures (e.g. interneurons and fibres) is still unknown and therefore not described by computer models. This lack of knowledge about target systems represents a crucial obstacle for the development of more effective SCS therapies. In parallel, commercial systems continue to become more sophisticated, allowing an increased variety of waveform parameters, higher electrode counts and non-standardized configurations that represent an increasing variety of possibilities to interact with the system. These technical improvements exponentially increase the space of therapeutic parameters, generating a crucial need to find optimal parameter subspaces that can be tackled by accurate, realistic and highly personalized computational models. These virtual frameworks would successfully meet the need to explore these large parameter spaces efficiently and effectively, which would be infeasible experimentally. Finally, the increase of model personalization would improve the search for optimal stimulation parameters, lead configurations and lead position in patient-specific scenarios, hence overcoming current standardized practices that might select suboptimal therapy parameters. This approach could revolutionize clinical care and patient programming in SCS-based therapies.

In the present study, we classified manuscripts describing computer models of SCS to reveal trends in the evolution of applications for SCS models, realism in model components, complexity, personalization and the technological advances and clinical needs that drove these evolutions. In this section, we discuss our main findings, with additional recommendations to standardize computational models of SCS, and we provide suggestions to improve the quality of these computational approaches.

The importance of increased complexity. As stated earlier, 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 the variety of factors that can affect neural activation (e.g. branch points and 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, 2015; Khadka et al., 2019) and might serve as a useful and efficient heuristic for predicting which gross anatomical regions are likely to be affected more strongly 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 new electrode configurations or the effects of anatomical electrical properties on current flow. In contrast, 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 modelling might be unnecessary, and instead, multiphysics simulations might be more appropriate. For instance, modelling studies have

investigated the combined effects of joule heating (owing to applied electric currents) and bioheat transfer as a potential therapeutic mechanism for kilohertz-frequency SCS (Zannou et al., 2019, 2021).

Despite the quasi-uniform assumption, there is a clear trend of increasing complexity over time in both the FEM and biophysical models (Fig. 5*A* and *B*). However, a more complex model does not necessarily imply a better model, and questions naturally arise regarding the level of complexity that is necessary and/or sufficient to develop a useful model. Regarding the FEM model, the increase in complexity was possible, in part, 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 by Capogrosso and Lempka (2020), inclusion of root volumes can significantly shift fibre activation distribution and threshold, and thus affect the direct clinical applicability of simulated results. However, only three studies considered realistic representations of roots and rootlets that followed trajectories derived from anatomical measurements (Greiner et al., 2021; Khadka et al., 2020; 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 including several relevant neuronal populations (e.g. both dorsal column and dorsal rootlet fibres to compare on/off-target effects) and varying the axonal diameter and position clearly help to 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, because all models require simplifications and abstractions. However, we feel that it is good practice to consider each of these variables thoughtfully, in order 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.

In contrast, the necessary (and sufficient) complexity to model the axon geometry, and specifically the internode, is more controversial and depends largely on the study. Compelling evidence demonstrates the role of submyelin conductance in axonal behaviour and the value of representing this current pathway to improve model predictions of axonal behaviour relative to single-cable models (Cohen et al., 2020; Richardson et al., 2000). In a direct comparison between models with infinite-impedance myelin, finite-impedance myelin and a double-layer myelinated axon, Richardson et al. (2000) demonstrated that all three models could produce reasonable results in line with experimental data and that all models were sensitive to parameter choices. However, they found that only the double-cable axon representation could respond faithfully to pulse trains at frequencies of $\geq$25 Hz, as is typical in SCS. 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 can 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 can 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 McIntyre, Richardson and Grill (MRG) 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 behaviours that better match recordings from human sensory nerve fibres that are highly relevant when modelling the dorsal spinal cord for SCS applications (Gaines et al., 2018). Future work advancing these ideas, in addition to 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.

The importance of patient-specific models to improve, standardize and expand SCS. Although canonical models are still invaluable to understand the science of SCS and to improve the technical design of SCS systems, patient-specific models are essential to describe the axonal response to SCS quantitatively and to program effective stimulation parameters for each patient. Despite the small number of studies using patient-specific models of SCS (i.e. only five papers), their results parallel those of other neurostimulation applications where personalization is more established, namely DBS. Indeed, Frankemolle et al. (2010) showed that computational models of DBS provide an exemplary tool in support of clinical decisions. In their study, patient-specific computational models helped to determine stimulation parameters that provided superior clinical efficacy relative to the parameters selected through standard programming methods. In

order to obtain similar results for SCS, research groups performed in-depth studies focusing on FEM-model variations of two main structures, CSF and bone, and the corresponding changes in model predictions between highly personalized models and generalized models. Specifically, CSF thickness, which varies as a function of spinal level and body position, and across patients (He et al., 1994; Holsheimer et al., 1995), was shown to have a large effect on current penetration within the spinal cord during SCS. Specifically, an increment of the current density of 54.6% was observed when halving the CSF thickness (Sin & Coburn, 1983). The dorsal CSF thickness was demonstrated to be positively correlated with the activation threshold of dorsal column fibres (Solanes et al., 2021) and perception threshold (which increased by 50.8 and 26.6%, respectively, in the dorsal columns and the dorsal root entry zone after an increase of the dorsal CSF thickness of 1 mm) and negatively correlated with paraesthesia coverage (He et al., 1994; Holsheimer & Struijk, 1991; Holsheimer et al., 1995; Lempka et al., 2015). The transverse size of the dural sac, instead, was negatively correlated with the activation of afferent fibres (Solanes et al., 2021). Likewise, the shape of the spinal canal (Fernandes et al., 2021), size of the spine structures (Fiocchi et al., 2016) and relative position of the stimulating electrodes to the spine (Zander et al., 2020) have strong effects on the electric field and corresponding activation thresholds. Interestingly, after spinal cord injury, orthopaedic interventions (Greenberg & Arredondo, 2001) can change the spine structure and scarring can change tissues conductivities, both of which can affect the simulated electric field amplitude (Hernández-Labrado et al., 2011) and therefore need to be considered in computer simulations. In summary, these studies provide evidence of the great variability in outcome measures deriving from anatomical alterations, suggesting that increased personalization could increase model accuracy by accounting for multiple sources of inter-patient variability. Additionally, these studies suggest that CSF thickness, bone and thecal sac sizes are essential structures for accurate volume conductor models.

In this direction, Lempka et al. (2020) reported that simulated sensory thresholds obtained with patient-specific models were significantly more similar to those measured clinically than those simulated with canonical models, which underestimate the dorsal column fibre 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 models, respectively; Howell et al., 2014; Solanes et al., 2021). Likewise, 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 EMG recordings while delivering SCS. The predictions of the patient-specific model corresponded to the optimal electrode placement. Indeed, they reported 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 et al. (2022) demonstrated rapid restoration of trunk and leg motor functions in patients with complete paralysis. Finally, Veizi et al. (2017) used a canonical model with patient-specific electrode locations and implemented a patient-specific algorithm to select active electrode combinations and current amplitudes at each electrode. The personalized group demonstrated a $\sim$1.5 times higher responder rate (i.e. patients receiving $\geq$50% reduction in pain) relative to a cohort in whom stimulation parameters were selected through standard clinical methods.

Despite these extremely encouraging results, additional work using patient-specific models is now necessary to demonstrate the potential of these models to improve clinical implementation of SCS. We believe that the collection of papers reported here (see Tables S1, S2 and S3) represents a valuable summary to guide the choice of the best model designs in future work 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 note 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. Instead, spinal lead implantations are currently performed with limited image guidance and lower constraint on positioning, far from the millimetre precision required to target deep brain structures (Lempka & Patil, 2018). In this context, it is important to note that complex personalized computer models of SCS are now suggesting that new neurosurgical approaches to SCS must be developed to improve the accuracy and stability of implantation procedures to be able to target specific microstructures, such as the dorsal rootlets (Rowald et al., 2022). This provides a powerful example of how neural simulations can be ahead of clinical practice and influence the standard of care.

Medical imaging propelled personalization and complexity. Importantly, all the studies ($n = 5$) with patient-specific models deployed medical imaging for the segmentation and the quantification of the anatomical structures, suggesting that MRI is necessary to increase the accuracy and the predictive power of these models. Nevertheless, models can reach high complexity with both measure-based and MRI-based models. However, since MRI was introduced, the majority of the complex models were also MRI based. This trend was particularly true for the application of movement restoration. Although this could be explained by a tendency of newer fields to propel the use of newly available technologies, such as MRI, this could also be attributable to the difficulty in capturing structures at the thoracic level (i.e. the most common implantation level of SCS to treat pain). New advances in the field of MRI for lower cervical segments (Cohen-Adad et al., 2021) could improve these images and soon change this trend.

However, medical imaging has still not been exploited maximally for development of computational models of SCS. For instance, manuscripts often lack details describing the specific acquisition sequences, thus limiting the adaptability of these approaches. Additionally, even the models with the most complex representations of the spinal cord roots and rootlets did not model these structures directly from medical images, but instead combined anatomical measurements and mathematical algorithms to calculate assumed non-overlapping trajectories. Yet it is now well known that dorsal root diameter, fibre angles and curvature when entering the spinal cord can cause substantial differences in fibre activation threshold (Coburn & Sin, 1985; Struijk et al., 1993). Therefore, accurate images of these structures are pivotal to increase the accuracy of current models. In this direction, advanced acquisition sequences, such as diffusion-weighted MRI (Vargas et al., 2010), provide a means to capture high-resolution fibre trajectories and could be used to characterize root and rootlet shapes accurately.

Future of SCS models. Artificial intelligence-based algorithms are another important breakthrough that could be extremely advantageous for the development of personalized *in silico* models of SCS. These approaches have the potential to achieve automation of processes that are currently performed manually. Specifically, the exploitation of artificial intelligence in the automated tissue segmentation from medical images would drastically reduce the time and effort required for the creation of a patient-specific model, thus paving the way to personalized precision medicine (Capogrosso & Lempka, 2020; Gaweł et al., 2018; Perone et al., 2018).

Additionally, computational modelling of the neural network effects of SCS is another area with significant potential for development. In the related field of DBS, many researchers have developed network-based models incorporating the various basal ganglia populations to investigate the stimulation-generated effects on neural circuit behaviour (McIntyre & Hahn, 2010). These models provide a more complete picture of the neural response by incorporating interactions between relevant neural populations. A similar approach has recently begun to be adopted for SCS purposes, although the technique remains immature. For pain applications, Zhang et al. (2014) produced an SCS-based network model that included primary afferent fibres and both excitatory and inhibitory interneurons (allowing for subpopulations with different firing characteristics) and measured the output response of spinal neural networks for multiple SCS stimulation frequencies. In a contrasting approach, Arle et al. (2014) produced a comprehensive model, with hundreds of thousands of neurons and millions of synaptic connections, to examine how SCS can treat neuropathic and nociceptive pain. Although such models are impressive in scale, they highlight the difficulties, in addition to the importance of proper model parameterization and constraining models based upon high-quality experimental data. Impressive advancements continue to be made in delineating the neurochemical and electrophysiological subpopulations of the dorsal horn and their connections (e.g. Medlock et al., 2022), and integration of these data with best-practice biophysical modelling provides a promising path for understanding how SCS affects the behaviour of spinal circuits.

Lastly, although 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 fibre 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 fibre activation threshold with measured perception and discomfort thresholds (Arle et al., 2014; Holsheimer et al., 1995; Howell et al., 2014; Lempka et al., 2018, 2020; Rattay et al., 2000; Solanes et al., 2021; Struijk et al., 1998). 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 artificial intelligence, developing new 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 with standardized model validation and clinical outcome metrics, we can bridge the gap between simulations and patient care.

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Additional information

Competing interests

M.C. is an inventor on several patent applications related to concepts presented in this work. S.F.L. is an inventor on multiple patents related to concepts presented in this work, receives research support from Abbott Neuromodulation, Medtronic, plc and Presidio Medical, Inc., is a shareholder in CereGate, Hologram Consultants, LLC and Presidio Medical, Inc. and is a member of the scientific advisory boards for Abbott Neuromodulation, CereGate and Presidio Medical, Inc.

Author contributions

S.F.L. and E.P. conceived the study. L.E.F., R.A.G., M.C., S.F.L. and E.P. secured funding. L.L., A.D., M.D.B., E.R.R., S.F.L. and E.P. designed the literature research. L.L., A.D., M.D.B. and E.R.R. performed the analysis and interpretation of the data. L.L., A.D., M.D.B. and E.R.R. created the figures. L.L., A.D., M.D.B., E.R.R., S.F.L. and E.P. wrote the paper, and all authors contributed to its editing. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Keywords

chronic pain, computational models, computer simulation, electrical stimulation, medical imaging, movement restoration, personalization, spinal cord stimulation

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History
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Table S2
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