Spinal Cord Neural Modeling for Clinical Applications

Senior Thesis

Presented to
The Faculty of the School of Arts and Sciences
Brandeis University
Undergraduate Program in Neuroscience
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In partial fulfillment of the requirements for the degree of Bachelor of Science

by
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May 2013

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Acknowledgments & Caveat

The text of this thesis and the accompanying table and figure captions, citations, and bibliography were written solely by the author Nicolae Adrian Iftimia; however, the information presented herein describes not only the work of the author but the collective efforts of the research team Arle et al. The members of this group and the specific role of each in this research are indicated below.

**Jeffrey Arle, M.D., Ph.D.** (Board-certified, fellowship-trained neurosurgeon and Associate Chief of Neurosurgery at Beth Israel Deaconess Medical Center) was responsible for initiating, leading, and supervising this research. He conceived and wrote the original version of the neural simulation software, UNCuS, described in this paper. As part of this ongoing research project he is performing clinical studies on patients that he has implanted with thoracic Spinal Cord Stimulators.

**Jay Shils, Ph.D.** (neurophysiologist, biomedical and electrical engineer, and Director of Intraoperative Monitoring at Lahey Hospital & Medical Center) also helped to lead and supervise this research. In addition, he obtained electrophysiological (e.g., EMG) recordings from patients in the clinic, which were used for calibration and validation purposes.

The author would like to acknowledge that, were it not for Dr. Arle and Dr. Shils as well as his Brandeis faculty sponsor Dr. Miller, this research and the resulting thesis would not have been possible. The author is tremendously grateful for their invaluable feedback, guidance, and support.

**Kris Carlson** (computer scientist at Beth Israel Deaconess Medical Center) refined and added functionality to UNCuS, including a novel datasheet interface permitting larger models, and modeled the electrodes and three-dimensional geometry of the thoracic spinal cord and surrounding tissues. He calculated the number of afferent fibers of different types and diameters within the dorsal columns of the spinal cord. He also calculated axonal delays for afferent and efferent fibers, and set appropriate axonal delays for the (contralateral, inter-laminar, and intra-laminar) connections within the gray matter as well. Carlson ran the majority of the UNCuS simulations and presented the team with simulation results. He performed the H-reflex calibration, and tested and improved the model’s stability and robustness.

**Longzhi Mei** (programmer at Beth Israel Deaconess Medical Center) rewrote and refined parts of the UNCuS program in collaboration with Carlson, and likewise ran some of the UNCuS simulations.

**Nicolae Adrian Iftimia** (undergraduate student at Brandeis University and the author of this thesis paper) was personally responsible for: finding and conducting an extensive review of the relevant medical and scientific literature; compiling and critically assessing all cellular, topographic, and connectivity (including synaptic location and density) data extracted in this process, while managing, formatting, and citing the appropriate references; obtaining and then processing (using ImageJ software) transverse section images in order to ascertain percentages of gray matter and percentages of each lamina; rendering the three-dimensional geometry of the entire spinal cord based on segmental measurements in the literature; developing and documenting a methodology for calculating numbers of neurons, and subsequently (once Dr. Arle had approved the logic of this methodology) performing these calculations; and ultimately assembling a model of currently known spinal cord circuitry. He manually entered all information into an Excel spreadsheet (in an UNCuS-compatible format specified by Carlson), which Carlson then imported into UNCuS to auto-generate the circuitry encoded in this spreadsheet. Iftimia also visually represented the global circuitry as well as particular subcircuits of interest by drawing these in PowerPoint, and was able to trace standard motor reflex arcs which he then highlighted on these slides. He derived several sets of hypotheses regarding pain transmission and inhibition from the connectivity, and illustrated these in PowerPoint as well. After familiarizing himself with the UNCuS graphical user interface, he provided instructions and guidance to Carlson and Mei for running simulated experiments (i.e., what to stimulate and in which manner, which cells to monitor at which time, etc.), and interpreted simulation results. In parallel with Carlson, he too developed a method for calculating numbers of dorsal column fibers, and independently obtained similar values. Thanks to the generosity of Dr. Arle and Dr. Shils, he also observed Spinal Cord Stimulation procedures and electrophysiological recordings in the clinic, and incorporated these observations into his research.
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I. Abstract

Spinal Cord Stimulation (SCS) is a procedure used extensively in neurosurgery. It has demonstrable therapeutic benefits for an assortment of sensorimotor disorders, notably intractable neuropathic pain of the limbs and lower back. Although SCS is known to stimulate the A-β afferent fibers of the dorsal columns (DCs), it remains unclear precisely how this leads to the appropriate neuromodulation resulting in analgesia. Attaining a greater understanding of this process is imperative, as it would allow for more rational design, placement, and programming of the stimulating electrodes, thereby informing SCS and potentially enhancing its efficacy in pain management. Yet the absence of a comprehensive model of the underlying neural circuitry and dynamics poses a significant challenge. An additional obstacle is the dearth of detailed information on the interaction of this circuitry with applied electric fields. We created a biologically-constrained computational model of the circuitry present in the L1 segment of the adult human spinal cord. The model is scaled such that the number of neurons forms a ratio of 1:50 to the developmentally average adult. Replication of standard motor reflexes (e.g., monosynaptic H-reflex) served as an initial validation and calibration. When we generated a virtual “pain” signal, C afferents excited a set of wide dynamic range (WDR) neurons to fire. We subsequently activated SCS electrodes, which stimulated certain DC A-β afferents. This resulted in WDR inhibition, blocking pain transmission to the brain. Pain relief hypotheses were developed and tested using this model, and clinical predictions were made based on the results.

II. Introduction

Spinal Cord Stimulation (SCS) is a common, well-established, and relatively cost-effective neurosurgical technique that is currently used in the treatment of various chronic pain conditions, including neuropathic and ischemic pain (Compton et al., 2012; Epstein et al., 2012; Falowski et al., 2008; Jeon et al., 2009; Jeon, 2012; Kumar et al., 2002; Kumar et al., 2008; Mailis-Gagnon et al., 2004; Simpson et al., 2009; Taylor et al., 2004), when other, more conservative treatment modalities have failed. Its success rate is typically in the range of 50-70%, and has been improving (Henderson et al., 2006; Smits et al., 2013; Stojanovic et al., 2002). SCS has also proven to be of therapeutic value in certain motor disorders, such as spasticity (Barolat et al., 1995; DiMarco et al., 2009a; DiMarco et al., 2009b; Dimitrijevic et al., 1986a; Dimitrijevic et al., 1986b; Tator et al., 2012; Waltz et al., 1981; Waltz et al., 1987), which may themselves contribute to chronic pain (Robaina et al., 1989). Notably, to some extent SCS can restore impaired movement such as locomotion, as well as the ability to stand, in patients who are paralyzed (Carhart et al., 2004; Harkema et al., 2011; Herman et al., 2002; Huang et al., 2006; Iwahara et al., 1991; Iwahara et al., 1992; Tator et al., 2012). Collectively, these sensory and motor dysfunctions are typical of spinal cord injury or trauma (Adams et al., 2005; Rogano et al., 2003), degenerative and demyelinating diseases of the central nervous system such as multiple sclerosis (Burkey et al., 2010; Illis et al., 1980; Read et al., 1980), or non-progressive diseases such as cerebral palsy (Hugenholtz et al., 1988). Spinal cord injury alone affects over a million patients in the United States (Fehlings et al., 2011) and costs billions of dollars annually (DeVivo, 1997).

Although SCS works directly at the level of the spinal cord, through neuromodulation, it is not necessarily limited to alleviating illnesses that originate in the cord. For instance, it is beneficial in the case of cerebral palsy (Hugenholtz et al., 1988), which originates in the brain. As
a further example, more recently SCS has succeeded in controlling Parkinsonian symptoms (Agari et al., 2012; Fénelon et al., 2012; Fuentes et al., 2009; Fuentes et al., 2010). Previously, the only neuromodulatory techniques that could achieve this were those that targeted the brain, such as the essentially analogous but more invasive therapy known as Deep Brain Stimulation (DBS) (Fuentes et al., 2009; Fuentes et al., 2010; Limousin et al., 2008). Likewise, the analgesic effects of SCS are not restricted to back pain. SCS has been used to ameliorate post-stroke pain (Aly et al., 2010), pain associated with cancer even in remote parts of the body (Nouri et al., 2011; Yakovlev et al., 2008; Yakovlev et al., 2010), and to a limited degree the “phantom limb” pain that emerges subsequent to amputation (McAuley et al., 2012; Viswanathan et al., 2010). It is not surprising that SCS can have such widespread effects, as spinal nerves innervate almost every structure of the body; in addition, the spinal cord is connected to the brain through numerous ascending and descending pathways.

In its most common form SCS entails surgical placement of a paddle-type stimulator lead adjacent to the dorsal (the most accessible) side of the spinal cord, near the midline, within the epidural space (Fig. 1) (Fukazawa et al., 2009; Rainov et al., 2007). The array of stimulating electrodes is connected via a subcutaneous extension wire (Fig. 2) to a small (wirelessly rechargeable) battery-powered pulse generator usually implanted in the gluteal, lower back, or lower abdominal area (Compton et al., 2012; Falowski et al., 2008). For back pain, the electrodes are typically inserted into the thoracic region, at spinal levels T7-T11 (Buvanendran et al., 2008; Duyvendak 2007; Feirabend et al., 2002). Stimulator designs initially consisted of a single lead with two electrode contacts (bipolar). Modern stimulators can employ multiple leads, each with four contacts (quadripolar) or more arranged in various configurations (Costantini, 2005; Oakley et al., 2006; Rigoard et al., 2012; Waltz et al., 1981). Electrode geometry and placement (two-dimensionally within the transverse plane) are key factors in establishing the pattern, polarity, and depth of the applied electric field (Holsheimer, 2002. Even minor variations in these parameters could lead to drastically different effects on the patient. Furthermore, depending on the exact level that is stimulated (electrode position along the rostrocaudal axis or third dimension), different dermatomes of the body will be recruited (Waltz et al., 1987). The settings with which the electrodes are programmed are likewise crucial; these parameters include pulse width, amplitude, and frequency of stimulation (Abejón et al., 2010). The exact mechanisms of action of SCS have not been entirely elucidated (Hegarty, 2012; Mailis-Gagnon et al., 2004), so finding the optimum parameters is still largely a process of trial-and-error.

SCS is known to induce activation of the dorsal columns (DCs), a set of white matter tracts located in the dorsal portion of the spinal cord (Fig. 1) (Shealy et al., 1967; Smits et al., 2012; Stojanovic et al., 2002); this is not surprising, as the DCs are the structures in closest proximity to the electrodes. The DCs consist predominantly of afferent fibers, which originate from the two symmetrical dorsal roots that are found at each spinal cord segment (Fig. 1) (Carpenter, 1991; Davidoff, 1984). Afferent axons form monosynaptic contacts on many of the neurons within the gray matter of the spinal cord, bringing in sensory information from the body for processing. The subset of afferents that pass through the DCs usually ascend ipsilaterally for a significant distance, and many project on the brainstem, which relays the signals to various thalamic nuclei (Carpenter, 1991; Davidoff, 1984); there are known descending inhibitory (e.g., GABAergic) pathways from the brainstem and thalamus to neurons in the dorsal horn (Fig. 3) that are involved in nociception (Ab Aziz et al., 2006; Besson et al., 1975; Gjerstad et al., 1999; Hall et al., 1982; Todd, 2010). Some DC afferents do not reach as far as supraspinal centers but instead branch and terminate in the gray matter (typically at a different segment than the dorsal roots from which they originated), and do so primarily on the neurons of the dorsal horn, where most spinal
sensory processing including nociceptive processing occurs (Davidoff 1984; Willis et al., 2004). At standard SCS levels, the first and most likely the only DC fibers to be activated are the cutaneous A-β afferents, and this activation is restricted to those larger than a certain diameter (≥9.4 μm; see Table 1) and located most superficially (up to a maximum depth of 0.25 mm) (Feirabend et al., 2002; Holsheimer, 2002). A-β fibers are relatively large-diameter fibers (~5-12 μm) (Cousins et al., 1998) that only transmit innocuous/non-noxious sensory stimuli (Table 1). Large-diameter fibers in the DCs tend to be found most dorsally, whereas smaller-diameter fibers lie closer to the gray matter (Willis et al., 2004). It is to be expected then, that large-diameters fibers such as the A-β would be the first and most strongly activated. There is evidence suggesting that perhaps even activation of a single A-β fiber is sufficient to produce analgesia (Holsheimer, 2002), but this is still under debate. Taking all of this into consideration, A-β fibers are the most probable candidate for mediating SCS-induced pain relief.

Thus, electrical stimulation of the DCs could indirectly modulate neural activity in the spinal cord via two pathways: (1) by exciting long A-β fibers that synapse in the brain, thereby activating descending inhibitory influences on spinal circuits; (2) through retrograde activation of A-β fibers that branch and synapse on the spinal circuitry at lower segmental levels (De Andres et al., 2013; Long, 1978; Smits et al., 2013). These pathways are not mutually exclusive; indeed, it may be the case that both are involved in the artificial inhibition of nociception during SCS. The classic “gate control theory” of pain developed by Melzack and Wall (Melzack et al., 1965) proposed a mechanism by which large-diameter non-nociceptive afferents such as the A-β could close an alleged neural “gate” within the spinal cord that controls pain transmission to the brain. According to the theory, the gate is normally open, allowing pain signals carried by the small-diameter nociceptive afferents such as C fibers (Table 1) to pass through; closing the gate blocks the noxious information from reaching the brain and being consciously perceived. However, this theory is only loosely based on the known spinal circuitry; some of the neurons and connections that might permit such a mechanism have yet to be fully identified, if they exist at all. Although the macroscopic anatomy and function of the spinal cord have long been definitively established, our knowledge at the circuit level is not as concrete, nor as complete.

A better understanding of the mechanisms by which SCS evokes analgesia would allow for a more rational design and programming of the stimulating electrodes, and would help to logically guide their placement. Such a theory-driven approach could potentially amplify the existing therapeutic effects of SCS and lead to superior results at least in a subset of the patients undergoing this procedure for pain relief. The development of a detailed, comprehensive model of the known spinal circuitry and its electrophysiology would be useful in addressing this research problem, as in principle such a model would allow us to precisely determine the full effects of any given electric field configuration upon spinal information processing. We have constructed such a model (Arle et al., 2013; Iftimia, 2009; Iftimia, 2011; Iftimia, 2013), which to our knowledge is the first of its kind. Although conceptual models of simple spinal subcircuits have existed for some time, there have not been prior attempts to incorporate all documented cell types and connections into one consistent and unified framework. Studying only isolated areas or pathways in this massively interconnected circuit cannot reveal higher-level “emergent” interactions, nor the full ramifications that applying an electric field can have on distant or what may (in the context of pain processing) initially be considered irrelevant parts of the circuit.

To this end, we have chosen to employ a computational approach, which facilitates rigorous study of systems of this scale and complexity within a practical timeframe. Such an approach has been successfully applied before in SCS research and clinically validated (Smits et al., 2013). Certainly no computational model is a perfect reproduction of reality, but it does not
have to be. Such models are still useful, helping to integrate and streamline our understanding and to explain observations and lead to new insights. Virtual testing is no substitute for traditional “wetware” experiments, but it can complement them and augment our existing knowledge base. In silico experiments are advantageous in cases in which the analogous in vivo experiments would be impractical or impossible (e.g., recording from all individual neurons simultaneously, “rewinding” the system to its initial conditions, performing experiments under exactly identical conditions while only one parameter of interest is varied), or would be deemed unethical. Our model aims to illuminate certain aspects of the fine-scale mechanisms by which SCS achieves its analgesic effects, and to allow us to derive predictions regarding optimal electrode parameters (e.g. placement) for producing pain relief. Those predictions are then to be tested in clinical trials; if successful, they would help to validate the model. Eventually, if they meet standards, they could lead to novel surgical guidelines and stimulation paradigms that increase the success rate of SCS. In the reverse direction, feedback obtained from the operating room and data from the laboratory drive the perpetual refinement of the model, and lead to new questions that can initially be investigated by running simulations.

It should be noted that epidural SCS is generally safe (Barolat et al., 1995; Cameron, 2004; DiMarco et al., 2009b), reversible (De Andres et al., 2013; Hegarty, 2012; Tronnier et al., 2012), and not as invasive as other spinal procedures used in the treatment of refractory pain, such as intraspinal drug administration (Burchiel, 2002; Hegarty, 2012; Rainov et al., 2007; Stojanovic et al., 2002; Tanei et al., 2012). However, there is of course an omnipresent risk inherent in any surgical operation. Complications, though rare (Hegarty, 2012), can occur especially in the case of electrode migration or improper electrode placement. These include inflammation, nerve injury, hematomas, incision scarring and fibrosis, infection, cerebrospinal fluid leak, and adverse sensorimotor effects (Barolat, 2000; Compton et al., 2012; Falowski et al., 2008). By informing the placement of electrodes, computational modeling in the future may also help to reduce the risk and gravity of some of these complications.

III. Materials & Methods

Using our own neural simulation software, Universal Neural Circuitry Simulator (UNCuS) (Arle, 1992), we built a dynamic computational model of the known circuitry in the first lumbar segment (L1) of the adult human spinal cord. This circuitry is essentially repeated at every segment, with only minor variations (most notably in the number of neurons). In a typical SCS procedure, the electrodes are implanted in the lower thoracic region (Buvanendran et al., 2008; Duyvendak 2007; Feirabend et al., 2002), so retrograde activation of the DCs will affect the neural circuitry in the region beneath, which is the lumbar enlargement (De Andres et al., 2013). Consequently, we chose to model around this level. UNCuS is written in C++, but new functionality has also been added with Mathematica. In addition, Java is used in the program’s interface. The GUI (Fig. 4) is such that neurons are organized into labeled groups, which are sectors of larger neuron populations represented as labeled pie charts. Connections (excitatory or inhibitory) can exist between groups of the same or different populations. Neuron populations and connections can be drawn directly in UNCuS; however, for large circuits this becomes impractical, so instead these are programmed into an Excel spreadsheet which is then fed into UNCuS, auto-generating the circuit. UNCuS was designed to provide a reasonable compromise between biological realism and computational efficiency for the purpose of clinical applications. Using this
UNCuS also provides the capacity to simulate the interaction of electrodes (Figs. 4, 5) with the neural circuitry. The user sets the cell, connection, electrode, and simulation parameters. UNCuS has been used previously to model the circuitry of the cochlear nucleus (Arle et al., 1991; Arle, 1992) and the basal ganglia in Parkinson’s patients undergoing DBS treatment (Arle et al., 2008a; Arle et al., 2008b).

In UNCuS, neurons are based on a modified MacGregor spiking neuron model (MacGregor, 1987; MacGregor, 1993), which itself is a simplification of the classic Hodgkin-Huxley model. The MacGregor model is a member of the integrate-and-fire category of neuron models but also resembles the ion channel model. However, rather than simulating every channel type separately, it treats the inhibitory and excitatory synaptic conductance changes holistically by performing a weighted summation of all contributions of the IPSPs and EPSPs, respectively. Synaptic alpha functions are used to mimic the excitation and inhibition dynamics, with different time constants for IPSPs versus EPSPs. Only the potassium (K⁺) channel behavior is individually and very carefully modeled. It is described by the state equation for refractory properties:

\[
\frac{dG_K}{dt} = \frac{-G_K + B \cdot S}{\tau_{GK}}.
\]

In this differential equation, \( t \) is time, \( G_K \) is the transmembrane potassium conductance (the ratio of the potassium resting conductance \( g_K \) to the membrane resting conductance \( G \)), \( B \) is the channel’s conductance strength (which establishes the postfiring \( K^+ \) increment), \( S \) is the spiking variable, and \( \tau_{GK} \) is the time constant of \( G_K \) decay. The subthreshold membrane potential is also carefully modeled. Yet an additional simplification is employed: the generation of the output spike is modeled as a “digital” process, as shown in the following piecewise state equation:

\[
S = \begin{cases} 
1 & \text{if } V \geq Th \\
0 & \text{if } V < Th.
\end{cases}
\]

Here, \( S \) again is the spiking variable, \( V \) is the transmembrane potential, and \( Th \) is the voltage-dependent time-varying threshold. The neuron fires when \( S = 1 \) (the transmembrane potential has reached or crossed the threshold). This simplification permits a larger time-step, reducing the computational load of integration. MacGregor spiking neurons are capable of adapting to stimuli.

UNCuS modifies the MacGregor model by incorporating a second, “lumped” conductance term (Fig. 6) that collectively accounts for any additional conductances which may contribute to a cell’s current-voltage curve (Fig. 7). Through accurate simulation of this \( I-V \) relationship, the model captures the essential characteristics and input-output transfer function of any individual neuron. Cell voltage \( V \) is repeatedly computed over time \( t \), at each discrete time-step \( dt \), using the ordinary differential equation:

\[
\frac{dV(t)}{dt} = -V(t) + \frac{G_K(t)}{G} [V_K - V(t)] + \frac{G_B(t)}{G} [V_B - V(t)] + \frac{I_{soma}(t)}{G},
\]

where \( G_K(t) \) is the time-varying component of the delayed rectifier potassium conductance (which is still modeled as in Eq. 1), \( G_B(t) \) is the time-varying component of the lumped conductance (all other conductances), \( G \) is the total membrane resting conductance (the sum of the potassium resting conductance, \( g_K \), and the resting component of the lumped conductance, \( g_B \)), \( V_K \) is the transmembrane potassium potential (the difference between \( E_K \), which is the potassium resting potential or the reversal potential of the “K branch” (Fig. 6), and the membrane resting potential
\( E_r \), \( V_B \) is the transmembrane lumped potential (the difference between \( E_B \), which is the lumped resting potential or the reversal potential of the “B branch” (Fig. 6), and the membrane resting potential \( E_r \)). \( I_{\text{som}}(t) \) is the current (either synaptic or step) at the soma, and \( \tau_n \) is the time constant of the resting cell membrane (Arle, 1992; Arle et al., 2008a). The lumped time-varying conductance \( G_B \) is modeled using an exponential function:

\[
G_B(t) = g_B(e^{V(t)/V_{nl}} - 1),
\]

where \( g_B \) again represents the lumped resting conductance, and \( V_{nl} \) is a non-linear voltage constant (Arle, 1992). UNCuS includes several pre-built standard cell models (e.g., stellate, bushy, fusiform) (Fig. 7) that are all varieties of this same modified MacGregor model, differing only in the values assigned to some of the parameters in these equations. The user also has the option of implementing new, customized varieties as well by selecting other values. In this manner, neurons exhibiting highly nonlinear behavior can be simulated if properly defined. In the spinal cord model, all neurons are currently set as ordinary stellate cells (linear current-voltage relationship). The values of key parameters that define the stellate model are presented in Table 2. For this particular cell model, a \( dt = 0.25 \) msec time-step is used.

Dendritic processing of synapses is accomplished by assigning each synapse in one of ten “dendritic compartments” representing different electrotonic distances (up to 1 lambda away) from the cell body on a logarithmic scale. This method is based on Rall’s cable theory of dendrites (Rall, 1962). The 0\(^{th}\) compartment is reserved for direct connections onto the soma (e.g., axosomatic synapses). Dendritic compartment connectivity partly determines the “connection strength,” which is also influenced by axonal branching patterns (Connection Range and Selection Range parameters). Total current at the axon hillock, where action potentials arise, is calculated by summing the contributions of all synaptic inputs as well as any intrinsic current due to step-current inputs or induced by electrodes that may be in proximity. Results are numerically approximated using an improved Euler method applied iteratively until the desired level of precision is achieved. There are 23 different pseudorandom number generators in UNCuS, which increase realism. Gaussian noise is added to the general background input current into each cell, as well as to stimuli. Each of the neuron parameters also includes a Gaussian noise term. Altogether, this ensures that every cell is inherently unique and will produce a slightly different response to the same given input. The noise factors can be removed if desired, in which case two simulations with the same starting conditions will yield identical results.

In our previously published UNCuS model of Parkinsonian circuitry, the potential field distributions of DBS electrodes were solved using a closed-form mathematical function (Arle et al., 2008a). Our spinal cord plus stimulator model is orders of magnitude more complex; in this case we settled on a finite element analysis (FEA) method to simulate electrodes. In SolidWorks/COMSOL software, three-dimensional FEA was used to model standard epidural SCS electrodes (Medtronic, Inc. paddle stimulator lead); the geometry and electrical properties of the thoracic-level spinal cord and surrounding layers were also modeled. Electrode geometry was partitioned into triangular mesh elements, and the potential at any point in space (e.g., location of a neuron or nerve fiber) in proximity to the electrode was found by numerically integrating across the potential contributions from all of its elements (as well as from additional neighboring electrodes if present). A finer mesh typically results in a more accurate solution but in exchange is also more computationally intensive. Of the resulting potential distribution, a portion penetrates into the white matter (the DCs). The interaction was computed by solving the Laplace equation:

\[
\nabla^2 V_e \cdot \sigma = \Delta V_e \cdot \sigma = 0,
\]

(Eq. 5)
where $\sigma$ is the conductivity of the tissue and $V_e$ is the extracellular potential in the vicinity; the $\sigma$ parameter has a substantial effect on the local potential distribution (Struijk et al., 1991). For the DCs, $\sigma \approx 0.0826$ S/m in the transverse direction and 0.472 to 0.725 S/m in the longitudinal direction, as calculated from resistivity ($\rho = 1/\sigma$) values (Ranck et al., 1965). Subsequently, the activating field for the DC axons was imported into UNCuS, where it was used to calculate the electrophysiological responses of these axons and ultimately the response of the lumbar circuitry that they connect with. The gray matter of the spinal cord is classically divided into ten cytoarchitectural zones known as the Rexed laminae (Fig. 3); we retained this topographic division in our model by dividing the same given cell type into multiple groups, one for each lamina wherein those cells are found. This allows us to distinguish between the responses of different laminae to (afferent and/or electrode) stimulation, and permits much more precise comparisons to behaviors reported in the literature, as well as more precise predictions. Finer topographic specifications (i.e., the exact location or distribution of a cell type within a lamina) are rare in the literature and we have disregarded them. We also divided each lamina into its left and right sides, which doubled the number of groups; this allows us to distinguish between ipsilateral and contralateral circuitry. In the current model, we have chosen to exclude all ascending and descending connections with the brain, in order to test whether retrograde stimulation alone is sufficient to produce analgesia.

We now describe the methodology that we used to devise the spinal cord neural network model. First, we conducted an extensive review of the relevant medical/scientific literature (e.g.: Brown, 1981; Carpenter, 1991; Davidoff, 1984; Willis et al., 2004) in order to amass data on all documented cell types and topological connectivity within the spinal cord, including intra-laminar, inter-laminar, contralateral, afferent, and efferent connectivity. As anticipated, some details were highly substantiated while others were not as well-supported or were more speculative in nature. Each detail was individually assessed on the basis of accuracy and verifiability, and was included or excluded accordingly. Preference was given to information corroborated by later research and more modern experimental techniques. In some cases human studies were lacking, so we looked at animal studies instead and invariably selected the nearest available phylogenetic relative (e.g., rhesus monkeys instead of rats). However, if that species was still too evolutionarily distant from Homo sapiens then the information was omitted. It should also be noted that only information pertaining to the adult stage of development was included. For instance, earlier in development there are A-$\beta$ afferents that terminate on lamina I cells, but these axons later withdraw (Beggs et al., 2002; Fitzgerald et al., 1994) as synaptic pruning occurs; thus, we have not included such a connection in our model. A guiding principle throughout our research was to limit bias by assembling the model bottom-up from known data, making no assumptions regarding the higher-order behavior implied by the circuitry. Function “emerges” of its own accord when the model is run dynamically. Beyond experimentally established circuitry the model is inherently agnostic with respect to any proposed pain theory, including the gate theory (Melzack et al., 1965). In addition, no assumptions were made about the intrinsic features of any cell type (e.g., “endogenous bursters” in the motor network) unless that cell had been studied in complete isolation, so the default model for all cells is stellate. In a few cases the literature provided qualitative information regarding the density and locations – proximal, distal, or both (in relation to the soma) – of synaptic connections on the dendrite, or specified that a synapse occurred on the soma. We incorporated such biological constraints into the model by assigning synapses into the appropriate dendritic compartments. Axonal delays to/from the body were calculated for each fiber type (Table 1) based on conduction velocity data and approximate length to their sensory receptors or effectors; the fibers in the model were programmed accordingly. Likewise,
connections within the gray matter were programmed to have a slight (on the order of a few msec) axonal delay, with contralateral connections having a longer delay than inter-laminar connections, which in turn have a longer delay than intra-laminar connections. Estimates of the number of neurons of each type within every lamina of all 31 segments are not available in the literature, but we were able to derive them. All cellular and connectivity data was manually defined in an Excel spreadsheet, which was then imported into UNCuS to generate the circuitry.

A brief description of the logic underlying our neuron and DC fiber calculations follows (Arle et al., 2013). It is known that in total there are on the order of 100 million neurons intrinsic to the human spinal cord (in the developmentally average adult) (Longstaff, 2005). This is 0.1% (Burish et al., 2010) of the ≈100 billion neurons that constitute the central nervous system (Leyssen et al., 2007), and is approximately the same as the number in the enteric nervous system (Kandel, 2000). Based on measurements of spinal cord segments taken from adult human cadavers (Ko et al., 2004), we calculated the volumes of all 31 segments (by modeling them as truncated cones, which is more accurate than modeling them as perfect cylinders). Using estimates of percent gray matter (as computed with ImageJ software) obtained from transverse section images (Carpenter, 1991; Netter et al., 2003), we subsequently determined the gray matter volume in every segment and hence were able to find the proportional neuron count, assuming relatively constant density along the length of the cord. We then estimated the unique laminar distribution of neurons in each individual segment. The percent area of each lamina (also computed in ImageJ) was derived from transverse section images (Greenstein et al., 1999; Noback et al., 1971), and interpolated for segments where no such imagery was available. A weighting factor based on certain parameters characteristic to each lamina (mean neuron size, mean neuron density) was applied in order to account for the substantial cytoarchitectural variations existing among the laminae (Brown, 1981; Nögrádi et al., 2000). Finally, the resulting values were scaled down by a factor of 50 for the UNCuS model. Specific neuron groups and subgroups within each lamina were assigned equal proportions of the total number of laminar neurons unless evidence allowed for more refined estimates. In addition, based on the transverse area of the DCs at various spinal levels (Carpenter, 1991; Ko et al., 2004; Netter et al., 2003) and reported DC fiber densities and cross-sectional dimensions of these fibers (Feirabend et al., 2002), we were able to estimate the total number of DC fibers in a lower thoracic segment as 225,000; we also determined how this number is distributed among the different fiber types/diameters that are present in the DCs. Our calculations took into consideration the degree of branching of axon collaterals (Struijk et al., 1992). Having calculated these values, we tested which and how many fibers are recruited in SCS.

An initial calibration of the model’s overall parameter space (i.e., connection strengths) was performed by reproducing standard motor reflexes (e.g., the monosynaptic stretch or H-reflex) reported in the clinical and experimental literature, since these are the best-known behaviors in the spinal cord in terms of their input-output correlations (Braddom et al., 1974; Pierrot-Deseilligny et al., 2000). Successfully accounting for such reflexes (after a reasonable adjustment of the appropriate parameters) was also a method for validating the model, in certain respects. Additionally, we compared the simulation results with electromyographic (EMG) recordings obtained from patients in our own clinic as a means of further validation. Afterwards, we derived hypotheses from the connectivity regarding the neural pathways by which SCS interferes with pain processing. These hypotheses were evaluated in simulations; if they were corroborated by simulation results, further in silico testing was performed and clinical predictions were thereby developed regarding optimal electrode placement and electrode settings for effecting analgesia. Those predictions are currently undergoing testing in patients that are being trialed for thoracic-
level epidural SCS in our clinic. This clinical research is still ongoing, as is our refinement and improvement of the model.

IV. Results

Prior to generating the model in UNCuS, we assembled detailed schematics of the neural circuitry, such as the one in Fig. 8 which depicts the full circuit in a stereotypic segment of the cord. The entire L1 neural network as seen in the UNCuS GUI is presented in Fig. 9. Our renderings of the three-dimensional geometry of the spinal cord are shown in Fig. 10. In the UNCuS format, the model currently consists of 12 neuron populations comprising around 500 neuron groups total; there are more than 11,000 connections among these neuron groups. However, each defined connection is such that it actually accounts for the computation of multiple synapses. Thus, when the model is run it results in dendritic processing of over 60 million synapses. In total, the model contains approximately 360,000 unique and individually rendered neurons (Arle et al., 2013). The model as a whole is relatively stable and robust as a pain stimulus and the electrode interference signal are varied over a broad range of intensities. Likewise, varying all the connection strength parameters (degree of axonal branching, synaptic density and location) in the model and/or varying the resting membrane potential of cells had little effect overall on the model’s stability. Furthermore, none of these variations had a significant impact on the results described herein. Yet it should be noted that this is a highly interconnected and recurrent neural network with predominantly excitatory connections, so occasionally it reveals local instabilities and hyperactivity; this is compounded by the fact that we have chosen to exclude the descending connections from the brain, which are a powerful source of inhibition, in this initial study. In our first experiment with this model, we found that under typical conditions the paddle stimulator lead resulted in activation of ≈500 large-diameter A-β afferents in the DCs. All simulations described in this section were performed with the full model running; the signal-to-noise ratio was exploited to make a behavior of interest stand out.

We have succeeded in mapping several well-established motor reflexes onto our circuit model, including the monosynaptic H-reflex and its associated gamma loop (Fig. 11), the disynaptic reflex, the inverse myotatic reflex, and the flexor crossed extensor reflex. After slightly tuning certain connection strength parameters, we were able to replicate the standard H-reflex arc including its characteristic refractory time (Fig. 12), as described in the literature (Braddom et al., 1974; Pierrot-Deseilligny et al., 2000), and the H-reflex EMG results we obtained from patients in our clinic. Providing the appropriate input (stimulation of a somatotopic region of the Ia subcategory of somatic A-α afferents, as if a certain muscle were stretching) to the circuit was found to activate the excitatory monosynaptic pathway to the alpha motor neurons, which subsequently exhibited increased firing when monitored. These neurons then caused contraction of the same virtual muscle (via A-α efferent fibers), which is the expected output. Virtual EMG results demonstrated that the H-reflex activity was typical.

Based on the known circuitry, we formulated and virtually tested several sets of hypotheses regarding the transmission and inhibition of pain; we present here our foremost set of hypotheses. However, some background knowledge must be presented first. We will focus on laminae II and V, but will also refer to laminae I and IV. We have created a Neuron Key that lists every cell type in the spinal cord, its basic behavior (excitatory versus inhibitory), and its “cell label” or abbreviation that we have employed in the model. Our classification scheme consistently
unifies multiple taxonomies of spinal cord neurons that have been developed. The portion of the Neuron Key that is relevant here is shown in Table 3, and is largely based on the nomenclature of Perl et al. (Perl et al., 2002; Todd, 2010). Most important are the class 1/pyramidal cells, the class 2/wide dynamic range (WDR) cells, and the class 3/nociceptive-specific (NS) cells; these are all projection neurons in the dorsal horn with long axons connecting directly to the brain. In our model we have labeled them C1-PYR, C2-WDR, and C3-NS, respectively. Lamina I is known to contain all three (Davidoff, 1984; Hughes, 2008; Ma et al., 1996; Todd, 2010), as is lamina V (Davidoff, 1984; Holden et al., 1984; Hughes, 2008). Lamina IV is known to contain C1-PYR and C2-WDR (Davidoff, 1984; Hughes, 2008; Ma et al., 1996). These projecting neurons are not typically found in Lamina II; rather, the most prominent cells in that lamina are short-axoned local interneurons (Davidoff, 1984).

If the appropriate afferent fibers are available in a given lamina, C1-PYR cells will be stimulated exclusively by innocuous input (A-α, A-β afferents), whereas C3-NS will only respond to noxious input (A-δ, C afferents); C2-WDR cells receive connections from both non-nociceptive (A-α, A-β) and nociceptive (A-δ, C) fibers, and process both types of signals (Table 4) (Cervero et al., 1976; Cervero et al., 1977). Thus, of these cell types WDR and NS are the two that transmit pain information to the brain; WDR cells also transmit innocuous information, as do pyramidal cells. Let us mention the afferent connectivity to each lamina of interest here: lamina I receives predominantly A-δ afferents but also C afferents; lamina II receives mostly C afferents but also A-δ afferents as well as some A-α and/or A-β; lamina IV has powerful A-β and also A-α afferent input and in addition probably receives a few A-δ and C fibers; lamina V not only has strong afferent input from A-β fibers but receives some A-δ fibers as well and at least a few C fibers (Ammons et al., 1985; Cousins et al., 1998; Phillips et al., 2004; Price et al., 1978; Strominger et al., 2012; Todd, 2010; Yang, 2010). All three classes of projection cells are excitatory on their targets in the brain (Todd, 2009). The primary target of these cells is the thalamus, with their axons forming the spinothalamic tract (Davidoff, 1984). Wide dynamic range cells are so-named because they signal non-nociceptive information at low frequencies (e.g. 5-25 Hz), but if the elicited output lies in a higher frequency range then the brain will interpret it as noxious (Davidoff, 1984). It has long been thought that the firing of WDR projection cells, the most common dorsal horn neurons (Raj, 2000), is sufficient and perhaps even necessary for the perception of pain (Coghill et al., 1993; Davidoff, 1984; Donkelaar, 2011; Mayer et al., 1975; Price et al., 1975). Although WDR cells in laminae I, IV, and V can all contribute to pain signaling, those in lamina V in particular are thought to be both necessary and sufficient to evoke pain (Price et al., 1975; Price et al., 1978; Willis et al., 1997) – but this has not been without dispute (Craig et al., 2004).

Our main hypothesis for pain relief centers on a unique group of cells in lamina II that correspond to the alleged “inverse” cells of Cervero et al. (Cervero et al., 1979). Although all afferent fibers are excitatory in their direct monosynaptic effects on target cells within the dorsal horn (Broman et al., 1993; Cervero et al., 1979; Todd et al., 2003; Todd et al., 2009; Todd, 2010), electrophysiological studies undertaken by Yezierski et al. and capsaicin injections performed by Dougherty et al. have demonstrated that, more generally, some class 1, 2, and 3 cell types can have inhibitory receptive fields (typically surrounding their standard excitatory fields), allowing for complex responses depending on the nature and location of the input (Dougherty et al., 1999; Yezierski et al., 1986; Yezierski et al., 1987); this could be explained by an inhibitory interneuron (Cousins et al., 1998). Cervero et al. discovered three novel classes of cells, denoted 1, 2, and 3; these cells demonstrably exhibit “inverse” electrophysiological responses to afferent signals relative to the standard class 1, 2, and 3 cells, respectively – i.e., class 1 cells are excited by noxious input and inhibited by innocuous input, class 2 cells are inhibited by both (and excited by
neither), and class $\tilde{3}$ cells are excited by innocuous stimuli but inhibited by noxious (Table 4) (Brown, 1981; Cervero et al., 1979). These cells’ inhibitory responses to afferent input, which are most probably mediated by yet-unidentified interneurons that may also lie in lamina II (Cervero et al., 1979), are very conspicuous (Cervero et al., 1979). As background activity, all reported inverse cells had discharge rates falling in the range of 1–40 Hz, with a mode of 5-10 Hz; this intense background activity appeared to be most strongly influenced by the afferent input to these cells (Cervero et al., 1979).

Besides inverted responses, there are two additional noteworthy distinctions (Cervero et al., 1979; Lima et al., 1991): (1) inverse cells, unlike the non-inverse class 1-3 cells, do not seem to project directly to the brain, but rather appear to act as local short-axon interneurons; (2) unlike their larger excitatory counterparts, inverse cells are inhibitory. In our model, we have created three groups of interneurons – INT_1, INT_2, and INT_3 – in lamina II that correspond to class $\tilde{1}$, $\tilde{2}$, and $\tilde{3}$ inverse cells, respectively, and have the appropriate afferent connectivity (Fig. 13). We have set the behavior of the INT cells as inhibitory. Of the total inverse cell population studied, almost a tenth were reported as class $\tilde{1}$ cells, over half were class $\tilde{2}$ cells, and approximately a third were class $\tilde{3}$ cells (Brown, 1981; Cervero et al., 1979). In our model, we used these proportions to obtain a rough estimate for the absolute number of cells we should assign in each INT group, based on the neuron count values that we had calculated for lamina II. For the inhibitory interneurons that mediate the disynaptic inhibitory effects of certain afferents on the inverse cells, we have labeled them inh-AFF in our model (Fig. 13).

Based on their experimental results, Cervero et al. proposed that inverse cells connect directly to the various projection cells of laminae I, IV, and V, exerting tonic inhibition on these neurons (Cervero et al., 1979; Lima et al., 1991). This direct inhibition of projection cells by inverse cells could allow for a “gating mechanism” possibly in accord with the classic gate theory. However, it must be emphasized that we did not intentionally program the salient features of the gate theory into our model, only the known circuitry. Lamina V is known to contain certain neurons including projection cells such as WDR with dendrites that extend dorsally (Davidoff, 1984) as far as lamina II (Wei et al., 1997) or III (Raj, 2000), where the dendrites receive direct contacts from the axon terminals of lamina II interneurons (Braz et al., 2005; Raj, 2000); at least some of the contacts occur on GABAergic terminals (Wei et al., 1997), indicative of inhibition. This further supports the existence of a monosynaptic connection from certain inhibitory interneurons located in lamina II to the projection cells of the deeper dorsal horn. Some of these GABAergic inhibitory interneurons are excited by large-diameter/low-threshold afferents to inhibit the nociceptive (WDR, NS) spinothalamic tract projection cells in laminae I and V (Benarroch, 2006). This is consistent with the afferent connectivity of the class $\tilde{3}$ inverse cells. In our model, we have drawn monosynaptic connections from the INT cells to the appropriate projection neurons (Fig. 13). We have made no assumptions as to which INT class connects to which projection cell class.

In the classic gate theory, unidentified inhibitory interneurons in the substantia gelatinosa or lamina II tonically inhibit pain projection cells (originally referred to as transmission or T cells by Melzack and Wall) located somewhere in the dorsal horn. Large-diameter (A-$\alpha$, A-$\beta$) afferents provide excitatory innocuous input to the pain projection cells and inhibitory interneurons. The small-diameter (C, A-$\delta$) afferents excite the pain projection cells but inhibit the inhibitory interneurons. If a noxious enterics enters the circuit, via the small-diameter afferents, it prevents the interneurons from inhibiting the pain projection cells, which allows the pain signal to pass through and ultimately reach the brain. The pain “gate” is open in this scenario. However, if sufficiently strong innocuous (e.g., mechanical) stimulation is concurrently applied, then the inhibitory
interneurons are excited to inhibit the projection neurons, closing the gate and thereby blocking pain signals from reaching the brain (Melzack et al., 1965) (Fig. 14). This would explain why some animals have evolved to instinctively rub a sore or painful spot, for instance.

Let us now see how our pain circuit model (Fig. 13) could allow for a gating mechanism used in endogenous and SCS-induced pain relief. The class 3 inverse cells appear under experimental conditions to be directly (monosynaptically) excited, without delay, by cutaneous mechanical stimulation (Brown, 1981; Cervero et al., 1979); such afferent signals are only carried by A-α and A-β fibers. SCS is known to overstimulate A-β fibers, so hypothetically analgesia could be produced because the A-β fibers are monosynaptically exciting the class 3 inverse cells (Cervero et al., 1978) to monosynaptically inhibit the WDR (as well as NS) projection cells (Fig. 15H,I). Mechanical stimulation (e.g., vigorous rubbing) of a painful area increases the firing of non-nociceptive afferents such as A-β fibers, so the same proposed mechanism could underlie the endogenous suppression of pain. Yet SCS has a more pronounced effect on the A-β fibers and thus greater analgesic potential.) In other words, SCS could work simply by amplifying activity in the standard neural pathways that the body uses to attenuate pain, without needing to recruit a different, typically dormant pathway. If we accept that class 3 inverse cells are excited by innocuous stimuli but inhibited by noxious, while themselves inhibiting WDR projection cells, this positions them in the exact role of the unidentified inhibitory interneurons that Melzack and Wall proposed were a crucial component of the gate. In other words, although we did not start out with the assumption that the gate theory is correct, it appears to map relatively well onto the known circuitry. One notable difference is that Melzack and Wall originally represented the inhibitory interneurons as presynaptically inhibiting the projection neurons through axoaxonic connections with the afferents that contact these cells (Melzack et al., 1965); we have not found evidence of this (compare Fig. 13 to Fig. 14).

In order to test the aforementioned hypothesis, we performed several trials of the following simulated experiment (Fig. 16), which all gave similar results. The entire circuit was turned on for the duration of the simulation (340 msec), including the lamina II INT_3 cells, which tonically inhibited WDR projection cells in laminae I, IV, and V. The first phase of the simulation served as the control, in which no pain or SCS activity was present. By activating a somatotopic area of somatic C afferents, we generated a “pain” signal at 40 msec (by which point any transient effects of the INT_3 cells had already reached a steady state). We chose C fibers because they mediate persistent or long-duration pain, as opposed to the A-δ fibers which carry “fast” pain (Bender, 2000); our aim, after all, was to study the effects of SCS on chronic pain. This signal was sufficiently strong to deactivate the INT_3 cells (disynaptically) and overcome their inhibitory effect, thereby activating an analogous somatotopic set of WDR projection cells. Subsequently, cutaneous A-β afferents were activated by SCS from 140-200 msec. When we monitored the INT_3 cells, we found that they were excited approximately during this time range. Also roughly over this period (after a slight axonal delay) many laminae I, IV, and V WDR projection cells were inhibited from firing, thus significantly diminishing nociception. Hence, simulation results supported our hypothesis. It was found that the effects of SCS did not persist after its application, but ended when the electrodes were turned off. The SCS electrodes were calibrated at four clinically standard stimulus strengths; simulation results showed that analgesia was enhanced as this setting increased. However, above the standard range SCS eventually began to have adverse repercussions, due to fan-out: it started to interfere with the normal function of other pathways connected to the pain circuit or receiving A-β afferents. Below the standard range, the reduction in pain was not as statistically significant. Varying electrode strength and placement within the epidural space allowed us to determine the optimal theoretical values of these parameters for
inverse cell-mediated pain relief. Preliminary paired pulse results from clinical trials using these optimized parameters are encouraging.

It should be noted that besides the INT_3 cells in our model, the INT_1 and INT_2 groups also have important functional implications, which we have likewise verified by running simulations. Circuits involving INT_1 cells are particularly interesting. For instance, circuits in which INT_1 cells connect to WDR or NS projection cells (Fig. 15B,C) exhibit negative feedback, in which noxious stimuli elicit disynaptic inhibition of these projection cells. This prevents them to some extent from transmitting the noxious information; thus, pain signals self-regulate or limit themselves from becoming too strong. This could be a long-term mechanism for pain habituation or for preventing excessive pain, keeping it to a manageable level such that it still informs the organism but the organism does not overreact. This could also be a mechanism for hyperstimulation analgesia, in which one form of pain (moderate and temporary) alleviates another (chronic and extreme), as has been purportedly experienced (to a greater degree than can be attributed exclusively to placebo) by patients undergoing intramuscular stimulation via needle, heat, electrical, ultrasound, or laser “acupuncture” under controlled laboratory conditions (Melzack, 1973; Melzack, 1981). Noxious negative feedback loops have been reported involving supraspinal structures as well (Bouhassira et al., 1995). In the case of an INT_1 cell connected to a pyramidal or WDR projection cell (Fig. 15A,B), noxious stimulation will elicit disynaptic inhibition of the projection cell, blocking transmission of innocuous sensory information; here we see a mechanism for pain “overriding” or dominating over non-painful stimuli. Common experience supports the existence of such an override process (e.g., losing fine sensation of texture when touching a painfully hot stove). This is the mirror image of what occurs in pain relief, when non-painful stimuli override pain. It is perhaps a useful protective adaptation for animals in threatening environments requiring urgent action.

Circuits in which INT_1 or INT_2 cells connect to WDR or NS projection cells (Fig. 15B,C,E,F) could provide a mechanism for allodynia and hyperalgesia. Allodynia occurs when normally nonpainful stimuli are interpreted as painful; hyperalgesia is increased sensitivity to pain. These abnormal pain states are typically caused by nerve injury or tissue inflammation. Innocuous stimulation would inhibit INT_1 and INT_2 cells from inhibiting the projection neurons. These disinhibited projection neurons would exhibit an increased firing rate relative to the baseline rate, when the stimulation is absent and the INT cells are therefore inhibiting them. Although the original signal is innocuous, it will be miscoded: the firing of the NS cells will be interpreted as pain, as will that of the WDRs if it crosses the threshold. The increased firing rate also means that less noxious afferent input is now necessary to achieve a given intensity of perceived pain, so sensitivity to pain has increased. Consistent with these proposed mechanisms, blocking or reducing interneuron-mediated GABAergic and/or glycinegenic inhibitory transmission within the spinal cord has been found in some cases to lead to allodynia and hyperalgesia (Sandkuhler, 2009; Sivilotti et al., 1994; Todd, 2010; Yaksh, 1989). Furthermore, experiments have revealed increased sprouting of A-β fibers and facilitated A-β transmission into lamina II following nerve injury and tissue inflammation (Baba et al., 1999; Okamoto et al., 2001; Woolf et al., 1992). This should provide INT_1 and INT_2 cells, which are located in lamina II, with ample opportunity to receive increased innocuous input, potentially activating the aforementioned mechanisms. It appears that by disrupting or altering primary afferent signaling, nerve injury and tissue inflammation can recruit neural pathways typically reserved for noxious transmission, even when no such noxious stimulus is actually present (Schoffnegger et al., 2008). Thus, our circuit model can potentially explain several pain conditions and unique characteristics of pain, in addition to SCS-induced as well as endogenous pain relief.
V. Discussion

Although computational models of SCS have been developed before (Lee et al., 2011; Lee et al., 2012; Manola et al., 2007; Struijk et al., 1991; Struijk et al., 1992; Struijk et al., 1996), these were limited to the electrodes and the nerve fibers of the DCs. They did not include the gray matter circuitry which is coupled to the DC fibers. At the other end of the spectrum are non-SCS models of the spinal gray matter circuitry (Bashor, 1998; Borisyuk et al., 2011; McCrea et al., 2007; Rybak et al., 2006). In relation to all of these, our model is innovative in that it combines the circuitry with the DC fibers and electrodes. The aforementioned circuitry models focus on motor processing (reflexes, central pattern generators, etc.); although models of sensory and specifically pain transmission exist (Farajidavar et al., 2006), these are just models of the afferent fibers, not the actual circuitry. Our model seamlessly bridges the sensory and motor aspects of the spinal cord, provides relatively wide explanatory power for sensorimotor functions (e.g., various pain states, reflexes), and allows us to test potential mechanisms for pain transmission and inhibition within the circuit. Furthermore, our model is not just a simple connectome (Borisyuk et al., 2011), but a highly complex and dynamic representation of the human spinal cord. It is perhaps the most detailed and comprehensive spinal cord model to date. The model has significant implications in clinical practice as it permits a more informed, theory-driven approach to SCS, potentially increasing the efficacy of this procedure in pain treatment and beyond. It is also significant in the theoretical realm as it integrates much of what is currently known about neural information processing in the spinal cord, and opens opportunities for new insights.

We are continually refining and improving the model, and critically evaluating the results. Further clinical testing is needed to assess the validity of our simulation results regarding the optimal electrode parameters for pain relief. In our simulations we found that ≈500 DC afferent fibers are recruited during SCS; this is similar to the values (≈380-460) determined by Lee et al. (Lee et al., 2012). Our simulation results for the H-reflex matched well with the literature and our own clinical findings, including the refractory time. When the virtual SCS electrodes were calibrated using standard clinical settings, they had the expected effects on pain transmission: producing analgesia in correlation with stimulus strength. However, in our simulations the analgesic effect ended abruptly upon termination of the initial applied electric field. In real patients, analgesia can persist for a significant time after the stimulation has ended, especially after repeated or long-term use (Cogiamanian et al., 2008). This discrepancy warrants additional investigation. We have yet to test the effects of prolonged or frequent SCS on the circuitry, but intend to do so in the future. One particularly significant result of our simulations is that retrograde stimulation alone appears to be sufficient for effecting analgesia, even without activation of the DC ascending pathways to the brain (since these were excluded from our model).

The model has several notable limitations, and there are multiple potential sources of error that may have affected our results. In certain cases no experimental data could be found on humans or even primate species in general. In these cases, we cautiously selected the phylogenetically closest model organism available, bearing in mind that some of the circuitry may be vestigial, non-existent, or drastically different in humans, which could lead to significantly different results. Another shortcoming is the ambiguity and incompleteness of information in the literature pertaining to biological constraints (neuron counts, membrane properties, axonal delays, and especially connection strengths). For instance, there was no quantitative data on synaptic density and location, only qualitative – and even that was rare. (In addition, the lack of transverse section imagery for certain segments meant that some data had to be interpolated for the neuron
calculations.) If more such information were available, it would have helped to further constrain the model biologically and produce more rigorous results. A third caveat is that the model does not presently include the brain or any ascending and descending connections, which have a significant effect on spinal cord neural activity (being vital to non-reflexive, voluntary movement and cognitive modulation of the spinal processing of sensory information including pain) and hence would affect simulation results. However, as previously noted, this allowed us to isolate the actions of retrograde DC stimulation and assess its sufficiency for pain relief. As it currently stands, the model only represents one of the 31 spinal cord segments. All neurons are modeled as stellate, with a simple linear current-voltage relationship. The model does not elucidate any of the underlying biochemical pathways, nor does it account for all the complex spatiotemporal characteristics and perceptual dimensions of pain or explain the full gamut of clinical pain conditions and disorders.

This is an ongoing research project. In the future, we can anticipate that the addition of the largely inhibitory descending connections from the brain will help to further stabilize the model, especially in light of experiments with decerebrated animals which have demonstrated a role for these connections in controlling spasticity and rigidity by diminishing excess excitatory activity in the cord (Burke et al., 1972). Incorporating supraspinal structures into our model would also allow us to test some of the indirect pain pathways as well. An eventual goal is to model the electrophysiological profiles of relevant neurotransmitters and other neuromodulatory molecules in UNCuS, allowing us to test pharmacological blockade of pain as an alternative to or in conjunction with SCS (Kunnumpurath et al., 2009). The flexor crossed extensor reflex, which we have already mapped onto our model, provides another potential avenue for studying the pain response in UNCuS, via the indirect effect of pain on the virtual muscles. The pathways of this reflex connect the dorsal and ventral horns. When a noxious stimulus is applied on one side of the body, to a limb for instance, C afferents are activated that contact interneurons; through polysynaptic pathways, different alpha motor neurons are excited and inhibited so as to cause the flexors to contract and extensors to relax in the ipsilateral limb while causing the opposite reaction on the contralateral side. Thus, the affected limb withdraws from the noxious source, as an evolved protective response, while the opposite limb extends for postural support (Valero-Cabré et al., 2002). Demonstrating reasonable reproduction of this reflex in silico by administration of a pain signal would provide additional support for our unified sensorimotor model of the spinal cord, and is thus part of our aims as we continue to refine the model and bring it closer to clinical application. Although we use typical dimensions for the spinal cord, our translational “bench to bedside” approach entails a growing emphasis on the patient as an individual. To that end, we are using parameter sweeps to explore how wide variations in certain parameters affect the model’s performance. We intend to provide workers in the field with a background knowledge repertoire of the effects of these variations (e.g., width of the CSF layer, which is known to affect electric field geometry in SCS (Struijk et al., 1991) and can be visualized by MRI) on the outcome of SCS, so that this procedure may be better personalized and its therapeutic potential may be further increased. We are also modeling the presence of scar tissue, which is electrically resistive or low in conductivity, on the surface of the dura mater beneath the electrode (Fig. 1). Using MRI plus contrast agent, we can visualize variations in scar tissue formation between patients, and virtually test how a particular scar geometry interferes with SCS. This would allow us to more effectively reprogram the SCS electrodes to maximize analgesia. Ultimately, we aim to extend our model to cover the full lumbo-thoracic region or even the entire spinal cord.
Bibliography


Appendix

Part 1 – Tables

**Fiber Types and Characteristics**

<table>
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<tr>
<th>Fiber Type</th>
<th>Diameter (μm)</th>
<th>Conduction velocity (m/sec)</th>
<th>Myelination</th>
<th>Information transferred</th>
<th>Calculated axonal delay (msec)</th>
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<td>31.178</td>
</tr>
<tr>
<td>A-δ</td>
<td>1-4</td>
<td>12-30</td>
<td>moderate</td>
<td>noxious afferent</td>
<td>40.086</td>
</tr>
<tr>
<td>B</td>
<td>1-3</td>
<td>14.8</td>
<td>light</td>
<td>efferent</td>
<td>77.944</td>
</tr>
<tr>
<td>C</td>
<td>0.5-1</td>
<td>1.2</td>
<td>none</td>
<td>efferent; noxious afferent</td>
<td>501.071</td>
</tr>
</tbody>
</table>

**Table 1.** The characteristics of each type of fiber (Cousins et al., 1998; Raj, 2000) are summarized. Small-diameter afferents (A-δ, C) are nociceptive whereas large-diameter afferents (A-α, A-β) are non-nociceptive. Based on the conduction velocity data shown here and the estimated length to the effector or sensory receptor, axonal delays were calculated for each fiber type; example values are presented in this table based on the length to the tibialis anterior muscle (≈702 mm).

**Stellate Model Properties**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{st}$ (mV)</td>
<td>0.0</td>
</tr>
<tr>
<td>$E_K$ (mV)</td>
<td>-65.0</td>
</tr>
<tr>
<td>$E_B$ (mV)</td>
<td>-65.0</td>
</tr>
<tr>
<td>$g_k$ (nS)</td>
<td>10.0</td>
</tr>
<tr>
<td>$g_B$ (nS)</td>
<td>10.0</td>
</tr>
<tr>
<td>$\tau_{GK}$ (msec)</td>
<td>2.0</td>
</tr>
<tr>
<td>$\tau_m$ (msec)</td>
<td>5.0</td>
</tr>
<tr>
<td>$B$ (nS)</td>
<td>500.0</td>
</tr>
<tr>
<td>$Th_0$ (mV)</td>
<td>12.0</td>
</tr>
<tr>
<td>$dt$ (msec)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**Table 2.** Some of the parameters that describe the standard stellate model (Arle, 1992) are listed; each parameter here is defined in the text. $Th_0$ specifically represents the cell’s resting threshold. Note that the time-step is $dt=0.25$ msec.
Neuron Key

<table>
<thead>
<tr>
<th>Cell Label</th>
<th>Name/Description</th>
<th>Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-PYR</td>
<td>class 1 or pyramidal projection neurons</td>
<td>excitatory</td>
</tr>
<tr>
<td>C2-WDR</td>
<td>class 2 or wide dynamic range projection neurons</td>
<td>excitatory</td>
</tr>
<tr>
<td>C3-NS</td>
<td>class 3 or nociceptive-specific projection neurons</td>
<td>excitatory</td>
</tr>
<tr>
<td>I-LTM</td>
<td>low-threshold mechanoreceptive islet cells</td>
<td>inhibitory</td>
</tr>
<tr>
<td>I-WDR</td>
<td>wide dynamic range islet cells</td>
<td>inhibitory</td>
</tr>
<tr>
<td>I-NS</td>
<td>nociceptive-specific islet cells</td>
<td>inhibitory</td>
</tr>
<tr>
<td>C-sI[exc]</td>
<td>central or small islet cells</td>
<td>excitatory</td>
</tr>
<tr>
<td>C-sI[inh]</td>
<td>central or small islet cells</td>
<td>inhibitory</td>
</tr>
<tr>
<td>V-SL-WDR[exc]</td>
<td>wide dynamic range stalked/limiting cells, a subset of vertical cells</td>
<td>excitatory</td>
</tr>
<tr>
<td>V-SL-NS[exc]</td>
<td>nociceptive-specific stalked/limiting cells, a subset of vertical cells</td>
<td>excitatory</td>
</tr>
<tr>
<td>V-SL-WDR[inh]</td>
<td>wide dynamic range stalked/limiting cells, a subset of vertical cells</td>
<td>inhibitory</td>
</tr>
<tr>
<td>V-SL-NS[inh]</td>
<td>nociceptive-specific stalked/limiting cells, a subset of vertical cells</td>
<td>inhibitory</td>
</tr>
<tr>
<td>V-ANT[exc]</td>
<td>antennae cells, a non-stalked/limiting subset of vertical cells</td>
<td>excitatory</td>
</tr>
<tr>
<td>V-ANT[inh]</td>
<td>antennae cells, a non-stalked/limiting subset of vertical cells</td>
<td>inhibitory</td>
</tr>
<tr>
<td>V-ARB</td>
<td>arboral cells, a non-stalked/limiting subset of vertical cells</td>
<td>inhibitory</td>
</tr>
<tr>
<td>V-BORD</td>
<td>II-III border cells, a non-stalked/limiting subset of vertical cells</td>
<td>inhibitory</td>
</tr>
<tr>
<td>RAD-ST</td>
<td>radial or stellate cells</td>
<td>excitatory</td>
</tr>
<tr>
<td>INT</td>
<td>interneurons in lamina II corresponding to the “inverse cells” of Cervero et al.</td>
<td>inhibitory</td>
</tr>
<tr>
<td>inh-AFF</td>
<td>interneurons mediating inhibition of other dorsal horn neurons when stimulated by afferent input</td>
<td>inhibitory</td>
</tr>
</tbody>
</table>

Table 3. A sample portion of our Neuron Key is presented (Arle et al., 2013).

This table is the author’s own work, but also appears in Arle et al., 2013.

Response Properties of Key Cell Types to Afferent Input

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Excited by</th>
<th>Inhibited by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1 inverse cells</td>
<td>noxious</td>
<td>innocuous</td>
</tr>
<tr>
<td>Class 2 inverse cells</td>
<td>N/A</td>
<td>innocuous, noxious</td>
</tr>
<tr>
<td>Class 3 inverse cells</td>
<td>innocuous</td>
<td>noxious</td>
</tr>
<tr>
<td>Class 1 (pyramidal) projection cells</td>
<td>innocuous</td>
<td></td>
</tr>
<tr>
<td>Class 2 (WDR) projection cells</td>
<td>innocuous, noxious</td>
<td></td>
</tr>
<tr>
<td>Class 3 (NS) projection cells</td>
<td>noxious</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. The response to afferent input for each of the three classes of projection cells and their inverse counterparts is summarized (Arle et al., 2013). Compare to Fig. 15.

This table is the author’s own work, but also appears in Arle et al., 2013.
Part 2 – Figures

**Figure 1.** Shown is a schematic of a typical transverse cross-section of the spinal cord and surrounding region. The cord is roughly cylindrical in shape; in this slice, the circular white matter (myelinated axons) can be seen enclosing the butterfly-shaped gray matter (cell bodies and associated neuropil, predominantly unmyelinated axons). On both the left and right, incoming dorsal roots (*red*) bring sensory/afferent information into the spinal cord for processing, while outgoing ventral roots (*green*) send motor/efferent commands to the body, as indicated by arrows. Together, the dorsal and ventral spinal roots on each side form a spinal nerve. The meninges (dura, arachnoid, and pia mater) and their cavities, as well as the bone of the vertebra, are shown here on the dorsal side; in reality, however, they encircle the entire spinal cord. During SCS, electric fields emanating from electrodes placed in the epidural space (typically near the midline) induce activation of certain large-diameter afferents of the dorsal columns (*blue*) in the white matter, thereby indirectly modulating neural activity within the gray matter.

Image source: [http://commons.wikimedia.org/wiki/File:Medulla_spinalis_-_tracts_-_English.svg](http://commons.wikimedia.org/wiki/File:Medulla_spinalis_-_tracts_-_English.svg). Licensed under Creative Commons to copy, distribute, and adapt. The image has been modified here to include the bone, electrode, meninges, and spinal roots, and to emphasize the dorsal columns, midline, and anatomical directions. Appropriate labels have been added. All other white matter tracts and labels have been omitted.
Figure 2. X-ray radiograph of the vertebral column in a patient with an implanted Spinal Cord Stimulator. A lead with multiple electrode contacts stimulates the spinal cord as it receives signals from a pulse generator (not shown), mediated by a conducting extension wire.

Image source: [http://en.wikipedia.org/wiki/File:Anterior_thoracic_SCS.jpg](http://en.wikipedia.org/wiki/File:Anterior_thoracic_SCS.jpg). Licensed under Creative Commons to copy, distribute, and adapt. The image has been modified by adding appropriate labels for the different components of the SCS device.

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Figure 3. Shown is a diagram of a typical transverse cross-section of the spinal cord gray matter, with the ten Rexed laminae denoted. Laminae I-VI form the dorsal or posterior horn, which contains most of the circuitry for sensory including nociceptive processing; lamina VII is the intermediate zone; laminae VIII-IX form the ventral or anterior horn; lamina X is the central zone surrounding the central canal. Motor circuitry is distributed in laminae VII-X. Compare to Fig. 1.

Image source: [http://en.wikipedia.org/wiki/File:Medulla_spinalis_-_Substantia_grisea_-_English.svg](http://en.wikipedia.org/wiki/File:Medulla_spinalis_-_Substantia_grisea_-_English.svg). Licensed under Creative Commons to copy, distribute, and adapt. The image has been modified to omit the gray matter nuclei and to emphasize anatomical directions.
Figure 4. Screenshots of the UNCuS graphical user interface (Arle et al., 2013). This figure is the author’s own work, but also appears in Arle et al., 2013.

Figure 5. Three-dimensional potential fields for various standard electrode configurations (monopolar as well as multipolar) in UNCuS. Each green or yellow shell represents an equipotential surface (i.e., all points on this surface are at the same voltage), with outer shells being at a lower voltage than inner shells due to increased distance from the surface of the electrode. Blue electrode contacts are negative in polarity; red contacts are positive (Arle et al., 2008a; used with permission).
**Figure 6.** Recreated here is the equivalent circuit for any generic neuron as modeled in UNCuS. It is similar to the classic Hodgkin-Huxley circuit, but in addition to the potassium or “K” branch it includes a “B” branch representing lumped conductance; $g_B$ and $G_B(t)$ are its resting and time-varying components, respectively (based on Arle *et al.*, 2008a; used with permission).
Figure 7. Linear (stellate) and nonlinear (bushy, fusiform) current-voltage relationships for pre-built cell models in UNCuS (Arle et al., 2008a; used with permission). In the spinal cord model, all neurons are currently set as ordinary stellate cells.
Figure 8. Shown is our initial schematic or wiring diagram of the entire neural circuit within a typical spinal cord segment, presented as an isomorphic map of its biological analogue. Labeled in Roman numerals are the ten cytoarchitectural divisions of the gray matter, the Rexed laminae. Both intra- and inter-laminar connections between neuron groups are included; in addition to these intra-segmental connections, incoming and outgoing inter-segmental connections can be seen (light blue), at the top of the diagram. Sensory information enters via the primary afferent fibers found in the dorsal roots (black), visible here to the left of the circuit. In parallel, motor commands are relayed through the efferent fibers of the ventral roots (black), shown on the right. Finer axons of these afferent and efferent fibers can be differentiated (orange) as they synapse with the circuit. Ascending axons to various brain regions (dark blue) and descending connections from the brain (turquoise), which course through the white matter, are represented at the bottom. However, these are currently omitted from the computational model; they will probably be incorporated in the near future. This basic circuitry is iterated throughout the spinal cord, with minor variations in connectivity but more significant variations in neuron count (Arle et al., 2013).

This figure is the author's own work, but also appears in Arle et al., 2013.
Figure 9. An auto-generated isomorphic representation of the spinal cord model (as shown in Fig. 8) is displayed in the UNCuS GUI. Blue: excitatory connections; green: inhibitory connections (Arle et al., 2013; used with permission).
Figure 10. Our renderings of the three-dimensional structure of the spinal cord, not showing its curvature: A) Whole view. B) Regional view. C) Segmental view. D) Various transverse views of the geometry and electrical properties of the spinal cord at the thoracic level, also showing the influence of SCS electrodes.

Parts A-C of this figure are the author’s own work. Part D was created by Carlson (member of Arle et al.) and is used here with his permission. This figure does not appear elsewhere.
Figure 11. Close-up view of the motor division of the main circuit presented in Fig. 8, on one (either) side of the cord. Excitatory and inhibitory connections are denoted; contralateral and inter-segmental connections are omitted. This network spans the ventral horn and intermediate and central zones; laminae VII-X are “collapsed” here into one system. A) Sensory input enters via multiple types of primary afferent fibers originating from the agonist (left) and antagonist (right) muscles, while motor output is transmitted to the muscles by the efferent axons of the alpha, beta, and gamma motor neurons (bottom). Renshaw cells and Ia and Ib inhibitory interneurons are included. B) The monosynaptic pathway of the H-reflex is highlighted (yellow) for the agonist, along with the coactivated gamma loop (light blue). The pathway for the antagonist H-reflex is symmetrical on this diagram. We have also mapped other key reflexes onto our model (not shown), including the disynaptic, inverse myotatic, and flexor crossed extensor (Arle et al., 2013).

This figure is the author’s own work, but also appears in Arle et al., 2013.
Figure 12. Simulation results for the monosynaptic stretch or H-reflex. A) Post-synaptic potentials were generated at three different time points (12 msec, 47 msec, and 82 msec) within a somatotopic region of dorsal root ganglion (see Fig. 1) cells that give rise to the Ia afferents from a muscle of interest. Each sample graph displays the behavior of one individual cell. Variations are due to random noise. B) A typical alpha motor neuron located in lamina IX responded by firing at 12 msec (arrow on the left) and at 82 msec (arrow on the right), but did not fire at 47 msec (arrow in the center). This shows refraction after the 12 msec potential from the Ia fiber. The hyperpolarization of the neuron subsequent to each of these three times also demonstrates refraction. The other alpha motor neurons displayed similar behavior. Ultimately, the excitation of the alpha motor neurons by the Ia afferents led to contraction of the virtual muscle via A-α efferents (the axons of the alpha motor neurons). These results are consistent with clinical and experimental data (Arle et al., 2013; used with permission).
Figure 13. Shown here is circuitry relevant to our pain transmission and inhibition hypotheses. Compare to Figs. 14 & 15. Highlighted (orange) are the pathways activated by SCS interference leading to pain relief. Dashed/dotted lines represent connections with brain structures: Th = thalamus, LRt = lateral reticular nucleus. Afferent fibers are color-coded, with arrow thickness intended as a qualitative indicator of connection strength. A) Collapsed view, showing the basic circuit. B) Expanded view, showing the laminar distribution of the circuit. Afferent input is indicated locally for each cell group. Connections do not necessarily represent the physical extent of the axon – e.g., INT axons may terminate in lamina II or III, where they contact the long dendrites of laminae IV-V projection neurons (Arle et al., 2013).

This figure is the author’s own work, but also appears in Arle et al., 2013.
Figure 14. Schematic of the classic Melzack and Wall gate control theory (Melzack et al., 1965) described in the text. SG refers to inhibitory interneurons in the substantia gelatinosa, lamina II; T refers to the “transmission cells,” now known as WDR projection cells, in the dorsal horn. Signals reach the action system of the brain, which perceives and responds to pain. Descending connections can modulate the gate mechanism, and these can be influenced by the dorsal columns (Arle et al., 2013). Compare to Fig. 13.

This figure is the author’s own work, but also appears in Arle et al., 2013. It is inspired by the original figure in Melzack et al., 1965.
Figure 15. Enumerated in this matrix are the various possible circuit combinations involving INT cells and projection neurons. The unique functionality of certain combinations is described in the text (Arle et al., 2013). Compare to Fig. 13.

This figure is the author’s own work, but also appears in Arle et al., 2013.
Figure 16. Simulation results for SCS-induced inhibition of pain when the inverse cell hypothesis was tested. Each sample graph displays the behavior of one individual cell. Variations are due to random noise. A) A topographically isolated region of dorsal root ganglion (see Fig. 1) cells that give rise to somatic C afferents was activated in order to send a “pain” signal into the circuitry at 40 msec, and this was continued for the duration of the experiment. B) From 140-200 msec, cutaneous A-β afferents were stimulated by SCS electrodes. C) All INT_3 cells in lamina II were turned on for the entire duration of the experiment, as was the rest of the circuit. As expected, these cells were inhibited (after a slight delay, due to the disynaptic connectivity) when the C afferents fired, except for a block from ≈140-200 msec; this block was concurrent with SCS-induced activation of A-β afferents, which (monosynaptically) excite INT_3 cells. D) WDR projection cells in laminae I, IV, and V tended to start firing at ≈40 msec, when the pain signal came on, but were inhibited from ≈140-200 msec, concurrent with the firing of the INT_3 cells that (monosynaptically) connect to them. E) A close-up view of the behavior of a representative WDR projection cell in lamina V. F) Simulation parameters are summarized in the table (Arle et al., 2013; used with permission).