Measures of Dosage for Spinal-Cord Electrical Stimulation: Review and Proposal

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***Abstract*— This manuscript proposes an electrical definition of therapeutic dose for spinal-cord systems used for the treatment of chronic pain, analogous to the pharmacological definition. Dose-response relationships are fundamental to pharmacology, radio-therapy, and other treatments, but have never been properly established for neuromodulation. This manuscript offers a robust measure of dose, pre-requisite to establishing a reliable and repeatable dose-response relationship. The new definition, enabled by the system transresistance obtained from measurement of evoked action potentials, recognizes the mechanism of action of spinal cord stimulation (SCS), and should improve acceptance of the therapy as compared to pharmacological treatments which are currently used more frequently for the treatment of chronic pain. The new definition suggests methods for personalization and standardization of the dose in SCS, and is potentially generalizable to all neuromodulation therapies in which nervous tissue is excited including sacral nerve stimulation (SNS), vagal nerve stimulation (VNS) and deep-brain stimulation (DBS). Formulas are provided, and applied using patient data. Powerful conclusions are drawn from application of the new measure.**

***Index Terms*— Neuromodulation, spinal cord stimulation, dose response relationship, chronic pain, evoked action potential, evoked compound action potential.**

I. Introduction

SPINAL cord stimulation (SCS) has recently been described as "the precise, targeted delivery of electrical energy to the spinal cord for drug-free chronic pain control". [1] Those authors continue "a given set of stimulation parameters may be sub-perception for one posture but not another". In this context perception describes a patient's subjective experience of SCS-induced sensation. The contradiction between these statements may be attributed to the therapy delivery mechanism of SCS: stimulation may be delivered precisely by electrodes, but therapy happens in the spinal cord which is in constant motion relative to the stimulating electrode. This signals a dosage problem.

In order for precise therapy to be provided to the spinal cord, the correct dose at the intended location is required. In pharmaceutical research an equivalent understanding is ascertained through pharmacodynamic studies that assess the concentration of compound in target tissues. Existing measures of neuromodulation dosage refer to measurements, such as current, at the electrode not *at the spinal cord* itself.

There are multiple theories as to the mechanism of action (MOA) of SCS for the treatment of chronic pain. These are proposed to differ for different stimulation paradigms. [2], [3], [4] However, a central assumption underlying all the proposed MOAs is that spinal cord stimulation activates (or modulates) the activity of cellular elements in the spinal cord close to the stimulating contacts. As such, understanding the strength of the generated electric field at the spinal cord is important for all SCS parameters. This manuscript will focus on stimulation paradigms that activate dorsal column (DC) axons, evidenced either by a stimulation induced percept or by recording Evoked Compound Action Potentials (ECAPs) with conduction velocities indicative of DC activation.

With such DC stimulation the putative therapeutic mechanism of action is that the activation of DC fibres triggers action potentials (ECAPs) to travel in both an orthodromic and antidromic direction. [5] Antidromic signals are thought to activate inhibitory interneurons, particularly GABAergic neurons to release GABA extracellularly which reduces the volley of nociceptive signals from the spinal dorsal horn (SDH) [6], [7]. Orthodromic signals are believed to engage a supraspinal network that triggers descending inhibition via serotonergic neurons that also activate inhibitory interneurons in the SDH. [8]

The therapeutic range, or therapeutic window, of dorsal-column SCS (DC-SCS) is bounded below by the threshold of efficacy, and above by the patient reported maximum comfort level and stimulation side-effects e.g. the onset of cramping [9] accompanied by an electro-myogram (EMG) [5]. A review of historical definitions of dose combined with more recent measurements and simulations suggests a scale that interpolates between these points and can be derived from electrode measurements during therapy. This manuscript will propose this as a definition of "dose" for DC-SCS. This definition can easily be extrapolated for paradigms that do not aim to elicit stimulation-induced sensations.

II. Definitions of Dose in Pharmacology and SCS

For pharmacology, the National Cancer Institute defines "dose" as "the amount of medicine taken, or radiation given, at one time," "concentration" as "the amount of a substance, such as a salt, that is in a certain amount of tissue or liquid, such as blood" and "efficacy" as "the ability of an intervention

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(for example, a drug or surgery) to produce the desired beneficial effect". [10]

For SCS, "dose" refers to the amount of therapy delivered *by the electrodes*. The "field" refers to the driver of currents at the spinal cord and is analogous to concentration. The term "activation" is a measure of the excitation of the spinal cord axons, and "efficacy" is the ability of the stimulation to produce the desired beneficial effect.

Prior to the advent of ECAP measurement, the effects of the field and the concomitant activation could be observed only subjectively. ECAP measurements now allow deeper understanding of historical experiences and point to future possibilities. The SCS dose measure need no longer be limited to what is delivered by the electrodes, but what impact that therapy has.

The reader may wonder why it is sufficient in the case of pharmacology to use the "the amount of medicine taken" as the definition of dose, yet the equivalent might be unsatisfactory in the world of neuromodulation. The resolution of this paradox lies in the relative variability of the strength of connection between what is administered and the therapy delivered. A drug has known, repeatable rates of absorption and removal [11], so that a given regime, for example 2 tablets taken three times a day, leads to a safe and effective concentration in the location of interest in a patient of known mass. As will be evident from following sections, the connection between stimulus delivered in neuromodulation and the therapy achieved is much less reliable. Pharmacologists have definitions of dose that are repeatable, reliable, and transferable, but as yet this has not been achieved for spinal-cord neuromodulation.

III. The History of Dose in SCS

The first attempts to characterize the dose required for neural activation were made decades ago by Weiss and Lapicque [12] who mapped the pulse-width vs current relationship of single axons. They found a relationship, characterized by the chronaxie and rheobase, that provides constant activation. At short pulse-widths, the activation function is controlled by the total charge, but for long pulse-widths the activation is controlled by amplitude alone. This is so well understood that throughout the SCS industry the term "current" denotes "current for a given pulse width" without any clarification being necessary.

Washburn specified dose in terms of voltage and current. [13] However, given the patient anatomy and postural variation in the field in the spinal cord noted by Holsheimer [9] and others, these measures are subject to postural variation. This will be discussed in section V.

Holsheimer improved the understanding of stimulation by conducting numerical modelling of the three-dimensional structure in the DC allowing characterization of activation. He mapped the variation in activation with nerve fiber diameter and cerebrospinal fluid (CSF) thickness. He observed the need to take account of the therapeutic range (TR) for SCS, defining this as the ratio of discomfort threshold (DT) to perception threshold (PT). He also noted, following [14] that the "ratio of DT to PT is obviously more important than their difference". Holsheimer defined a therapeutic ratio for current

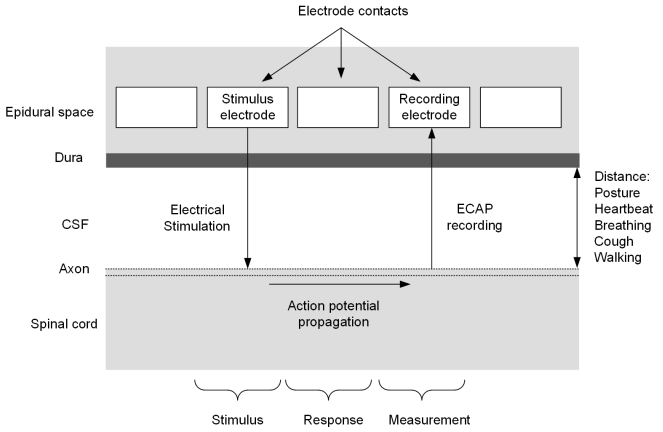

Fig. 1. Geometric layout of an implanted SCS lead. Current from stimulating electrodes crosses the dura and CSF to stimulate the spinal cord. This generates an action potential which travels along the spinal cord and can be recorded by other electrodes in the electrode array.

controlled stimulation, with V_T being the applied voltage at the perception threshold and V_D being the applied voltage at the discomfort threshold:

$$\mathrm{TR} = \frac{V_D}{V_T} - 1 \tag{1}$$

Holsheimer's work related objective measurements of currents with subjective measurements of threshold and comfort, and so related the definition of dose to activation. He noted therapeutic range (TR) typically takes on a value of 0.4 (stimulation at 1.4 times threshold), with a value of 0.2 (stimulation at 1.2 times threshold) as often being efficacious. More recent work has slightly refined these values. [15] This could be considered to be the first transferrable definition or measure of dose in the field of SCS. However, he also observed posture affected the voltage-to-activation relationship.

Miller et al. [16] considered charge per second (average current) as a definition of dose for 10 kHz, burst and tonic stimulation. This is an excellent measure for comparing total power requirements and partially accounts for the change of threshold with frequency as described by Gmel [17]; however it is possible to construct an example that demonstrates shortcomings of this method for stimulation frequencies below 100 Hz. If we consult Table 3 from Abejón and colleagues [18], we can see that at 40 Hz and 300 µs pulse duration, the therapy threshold is 8.17 mA and thus the charge per second under those conditions is $40 \times 300e^{-6} \times 0.00817 = 98\,\mu\mathrm{A}$. If the frequency was increased from 40 Hz to 80 Hz, the charge per second doubles to 196 µA. We could also double the 'dose' expressed as charge per second, from 98 µA to 196 µA in our example, by doubling the stimulation intensity from 8.17 mA to 16.34 mA. Under these circumstances, by Miller's definition the dose is unchanged, yet 16.34 mA would be above the discomfort threshold of 8.58 mA. This value is almost twice the current at which discomfort was experienced by their study population (9.2 mA). Miller et al.'s [16] definition (charge per second) is not transferable and so is not a suitable dose measure.

Parker et al., demonstrated that the voltages generated by stimulation, the evoked compound action potentials (ECAPs), could be measured by means of unused contacts of an SCS electrode array as shown in Figure 1. [5] This voltage,

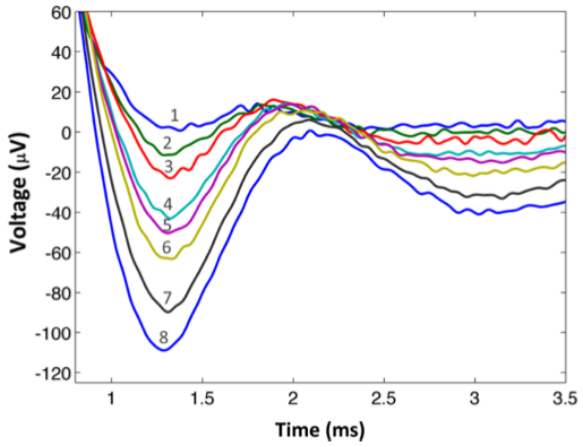

Fig. 2. Early recordings of ECAPs in sheep dorsal column revealing amplitude increasing monotonically for stimulus current up to 2.5mA. From [5] with permission.

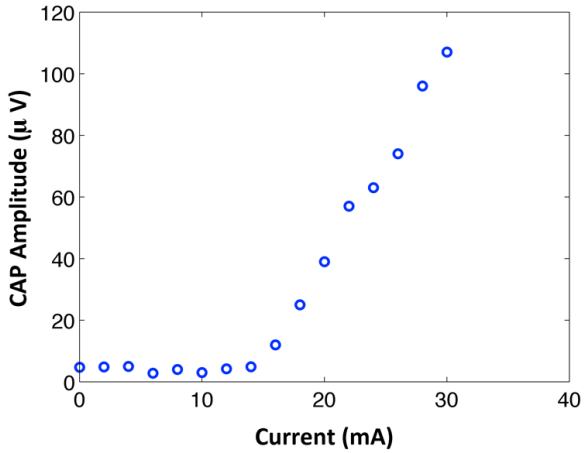

Fig. 3. Plot showing that ECAP amplitude increases linearly with current. Reproduced from [5] with permission.

measured as the N1-P2 height from response waveforms as shown in Figure 2, increases approximately linearly above a threshold, refer to Figure 3. The plot appearing in Figure 3 is referred to as an "activation plot". At a sufficiently high current muscles are activated, as evidenced by an electromyogram (EMG), exemplified in Figure 4. This behaviour is analogous to the effect of many drugs, and thus Parker et al. suggested that SCS should exhibit a dose-response relationship similar to that used in pharmacology and shown in Figure 5. However, to characterize such a relationship meaningful measurements must be assigned to the axes.

In using a fixed ECAP amplitude target as the set-point for a feedback loop, Parker implicitly used ECAP amplitude as the definition of dose. [21]

There is some evidence that ECAP amplitude could be used as a definition of dose: Figure 6 using data from [22] represents statistics from a broad population pool. Patient perceived intensity monotonically increases with ECAP amplitude. This study showed that higher ECAPs were associated with better outcomes. It has also been shown that for a given stimulus the ECAP amplitude and its signal-to-artefact ratio vary with the specific recording electrode selected. [23], [24] Figure 7 shows an amplitude difference of 3.5:1 between different recording electrodes. These observations suggest that ECAP amplitude

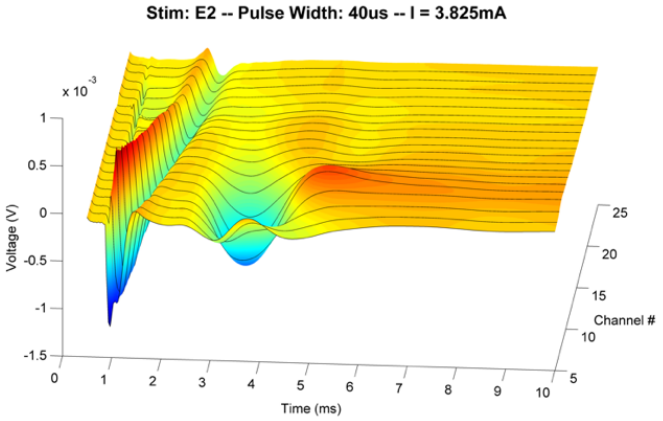

Fig. 4. Recordings from multiple electrodes in a sheep DC showing both the ECAP at 1-2ms and an EMG at 3-4ms. From [19] with permission.

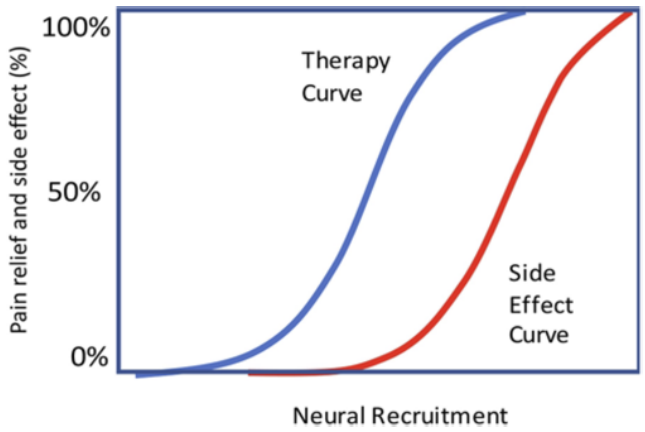

Fig. 5. Format of a dose/response relationship analogous to that in pharmacology, as SCS might follow. The therapy might be pain relief, the side effect discomfort or muscle activation. Reproduced from [20].

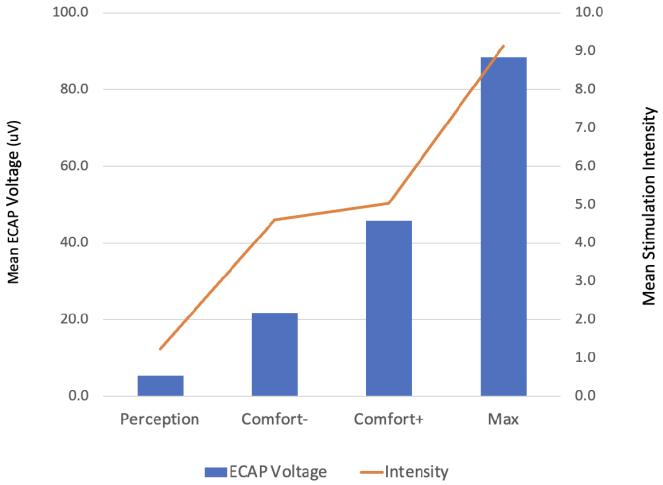

Fig. 6. Stimulation intensity (mA) and measured ECAP (μV) for a population of patients in various therapy regimes by perception. Observe that ECAP amplitude increases in line with patient perceived intensity of therapy. Sample sizes were N=55 for investigational arm and N=49 for control arm. Data was taken at 12 months. [22].

is a relevant measure of dose for epidemiological studies but specific values relevant to one patient may not be appropriate for another, or even for another electrode within the same patient. [17] As a definition of dose, ECAP is not reliably transferable.

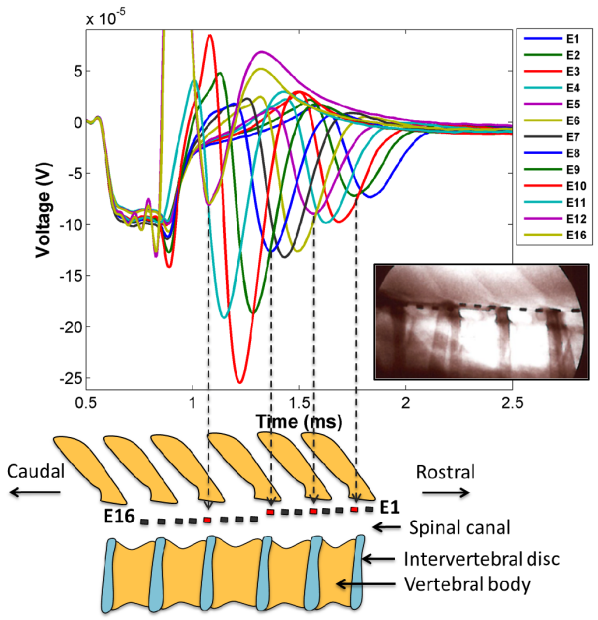

Fig. 7. ECAP amplitude varies with recording electrode distance from the stimulation site and location of inter-vertebral segments. From [23] with permission.

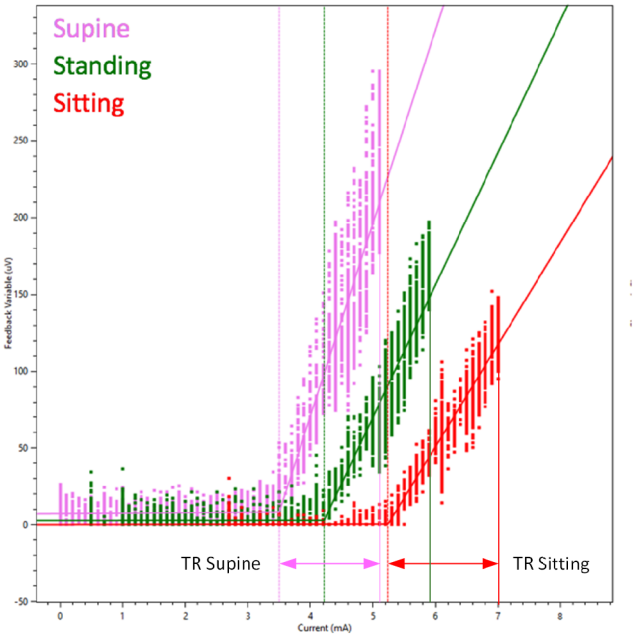

Fig. 8. Activation plot from one patient in three postures reproduced from Parker et al [20]. Stimulation is interrupted when the patient reaches their maximum comfort level. Lines of best fit showing variation of ECAP amplitude with posture are calculated to obtain sensitivity for each posture (refer to Table I).

Parker et al. [20] also showed that activation plots are affected by posture as shown in Figure 8. Referring to this plot, both threshold where ECAP first appears, and the "sensitivity" or the slope of the amplitude vs current line, change with posture. These values will be used in this manuscript to derive an improved definition of dose. The ratio of the stimulation current and the ECAP threshold current provides an objective dose measure analogous to that used by Holsheimer. This will be developed in section IV.

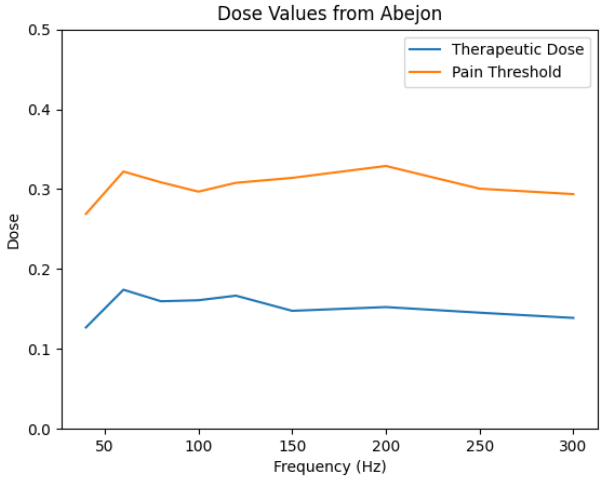

Fig. 9. Clinical data extracted from [18] shows the ratio of current to current at threshold for the therapeutic and maximum dose is stable over a wide range of stimulation frequencies.

It is important to note that for the typical activation plot shown in Figure 8, the therapeutic ranges in the supine and sitting postures *do not overlap*. Therefore there exists no single stimulus current value that can be therapeutic in both postures. Stimulation above the maximum value is unpleasant for the patient; stimulation below will consume battery energy without benefit.

Abejon et al., measured the variation of the threshold and comfort currents with frequency. Figure 9, based on Table 3 from [18], shows TR from (1) is independent of frequency. This shows that a given TR value can be used at different stimulation frequencies, representing another example of transferability.

None of the previous definitions of dose are entirely sound. The use of various definitions for the term "dose" can give rise to considerable confusion. In this manuscript we will refer to the measure developed in the next section as the "proposed measure", "proposed definition" of dose, or simply "proposed dose".

IV. Activation as Dose Measure

In this section we propose a new definition of dose, A. Returning to equation (1), note that tissue voltage is proportional to current, so (1) can be equivalently expressed as

$$\mathrm{TR} = \frac{I_D}{I_T} - 1 \tag{2}$$

where I_T is the current at threshold and I_D is the current at discomfort. ECAPs facilitate objective measure of the lower bound of threshold and thus I_T. [1] The maximum tolerable stimulus value, I_D, can be measured either subjectively or from the objective onset of involuntary reaction via an EMG. [5] Values within the therapeutic range define an activation A for any $I > I_T$ of

$$A = \frac{I}{I_T} - 1 \tag{3}$$

and within the bounds,

$$0 \leq A \leq \mathrm{TR}. \tag{4}$$

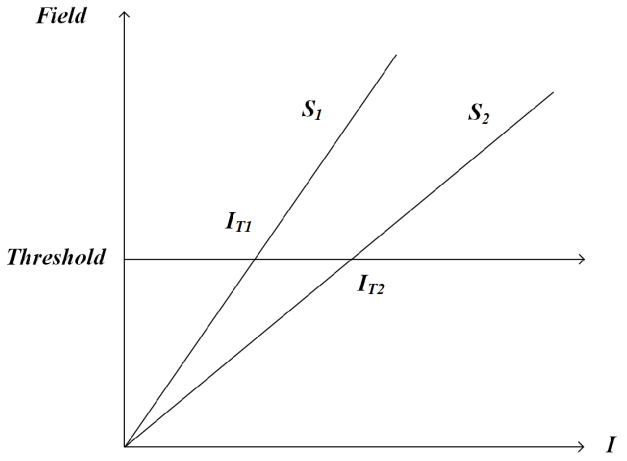

Fig. 10. The electrical field strength at the dorsal column as a function of stimulus current in two postures.

With the data available from ECAP recordings, the ECAP voltage from Figure 2 can be linearly approximated by:

$$V = \begin{cases} S(I - I_T), & \text{if } I > I_T \\ 0, & \text{otherwise} \end{cases} \tag{5}$$

where S, the "sensitivity", is the change of ECAP amplitude with current and curiously has units of Ohms; I is the stimulation current, and as usual I_T is the threshold current. Dividing both sides of (5) by SI_T gives

$$\frac{V}{SI_T} = \frac{I}{I_T} - 1 \tag{6}$$

and combining this with (3) gives the proposed measure and definition of dose:

$$A = \frac{V}{SI_T}. \tag{7}$$

I.e. for any posture where the sensitivity S, the threshold I_T, and an ECAP voltage measurement are known, the activation A can be calculated. A is readily measurable, and is our proposed definition of dose. An ECAP feedback target for providing a specific A can be found by inverting (7) to produce:

$$V = ASI_T \tag{8}$$

Figure 10 gives insight into this measure. A neuron is induced to fire by the electrical field strength, in volts per meter (V/m), and its variation, across the cell membrane. Finding that field strength for any given stimulus is a numerically complex problem involving Maxwell's equations and, to determine the impact, the Hodgkin-Huxley model [25]. This is well understood with it being accepted that activation is caused by the second-order spatial derivative of the applied potential field. [26], [27] Nevertheless, the mechanism is linear, and obeys such properties as decreasing intensity with increasing distance, so that we may refer to field strength without specifying exact numbers without loss of generality. This figure shows the electrical field strength at the spinal cord without numbers for two distances between the stimulating electrodes and the cord. From [1] the electric field must exceed a threshold before neurons are activated. If the number of activated fibers increases linearly with the field above this value and the ECAP is proportional to the number of activated fibers, then the ECAP will be proportional to the degree by which the field exceeds the threshold. This gives rise to the ideal traces in the figure. The reader is invited to compare the upper half of Figure 10 with Figure 8.

Laird-Wah [22] performed detailed field modelling of the spinal column, finding that the number of activated fibres N can be represented by the equation

$$N \propto Ix^{-n} - T_0 \tag{9}$$

where I is the stimulating current as usual, x is the distance (spacing) from electrode to cord, n is a constant over the range of x relevant to SCS, and T_0 is some threshold value. Dividing by x^{-n} and including a constant of proportionality, k, leads to

$$N = kx^{-n}(I - x^n T_0), \tag{10}$$

i.e. the number of activated fibres N increases linearly with current. If the measured ECAP is proportional to N, then this would produce an activation plot of the form of Figure 8.

Since both (7) and (10) have a threshold followed by a linear increase with current, and (10) models a linear increase in number of activated fibres, they support the hypothesis that the activation of SC fibres contribute to the mechanism of action (MOA) of SCS. The term in x^{-n} models the observed increase in threshold with distance. Laird-Wah also modelled the recorded voltage as

$$V \propto Nx^{-m} \tag{11}$$

where x is still the electrode-to-cord distance, and m is another exponent independent of the electrode-to-cord distance over the range relevant to SCS. The terms n and m may take on different values owing to the use of electrodes in different positions and owing to the dispersion of ECAPs with distance along the spinal cord. These equations might permit the calculation of ECAP at the spinal cord. This is an appealing promise. ECAP at the spinal cord might represent an ideal measure/definition of dose. Unfortunately, to the authors' best knowledge, this possibility has not yet been realized owing to the difficulties of calibration to find m and n in a patient. In contrast, all the information required to evaluate the proposed measure A from (7) can be collected objectively, and thus automatically (refer to section IV-A). As will be demonstrated in section V, activation A is a practical, if ultimately imperfect, definition of dose.

Laird-Wah calculated that approximately 5000 activated fibres are required to reach ECAP voltages similar to those of Figure 8. However, since the distance between the electrodes and the SC is not known for this patient, it is not possible to use these measurements to confirm his calculations.

It is worth noting that relationships such as (5), exemplified in Figure 8 and Figure 5 of [28], expose the risk that response of the spinal cord to fixed-current stimulation at typical settings could be very sensitive to posture and current. In particular, it may be difficult to maintain accurate activation in systems that attempt to operate very close to threshold, such as those in [3] and [29]. This can be visualized graphically or exemplified numerically. Referring to Figure 8, a stimulus

current of 4.5 mA in the standing case would deliver no useful therapy sitting, but several times the activation when supine. Numerically, if the activation is set to 0.2, a typical value, then from (3):

$$\frac{I}{I_T} - 1 = 0.2 \tag{12}$$

and

$$\frac{I}{I_T} = 1.2 \tag{13}$$

so a reduction of threshold current I_T by 10% (e.g. due to a change in posture) will increase the activation to 0.33, an increase of 66%. This amplification (i.e. the large change in activation with small change in threshold or current) increases as the target activation becomes smaller.

If the definition of (7) is accepted, (9) predicts that the voltage recorded by the electrodes will vary with distance. A feedback loop that maintains even a perfectly precise ECAP at the recording electrodes will exhibit *some* fluctuation of A with posture. The methods developed in this analysis allow calculation of that fluctuation.

A. Measurement of Activation

We asserted that activation, A, can be objectively and automatically measured. In (7), the sensitivity, S, is the change of ECAP amplitude with stimulus current and I_T is the threshold current. These are the slope and x-axis intercept of the line of best fit to measurements of ECAP, V, as a function of stimulus current, as shown in Figure 8. Thus a small perturbation of stimulus current in the theraputic region yields these values through straight-line fitting. Such a fitting is easily carried out automatically provided the ECAP signal is visible. This fit process can be carried out as a function of posture (or any other stable cause of variation).[1]

The process is objective, since it does not rely upon any perception or patient report. Once an ECAP signal is detected, an implant can make this measurement in response to a request from the clinician. There is not even a requirement that the patient experience any theraputic effect, although that would normally be the case.

Traditonally, patient fitting is performed by adjusting stimulation amplitude to determine a comfortable current. Patients are provided with a remote control to further adjust this.

The proposed definition from (7) provides an alternative method: With a patient in a convenient posture, a clinician could measure the ECAP threshold. A value for the proposed dose could then be chosen based on experience, or hopefully and at a future time, on an established dose/response relationship. Using this ratio, the current is set to an appropriate value and the corresponding ECAP amplitude is recorded. This is set as the feedback loop target. If standards were established, this could be performed automatically and in the operating theatre. At the same time, the system could confirm that the therapeutic level is well below the onset of the EMG to ensure the stimulation is not unpleasant. If the EMG is present at the prescribed dose, the stimulating leads could be repositioned. This, combined with feedback, would eliminate stimulation at uncomfortable levels at any point in the fitting procedure or during therapy. [30]

[1]Both breathing and heartbeat (blood pressure) are known to modulate stimulation to the extent that patients can perceive their impact. It would be interesting to fit activation with breath held for example, to quantify the phenomenon and objectively verify patient reports of reduced variation in the presence of feedback.

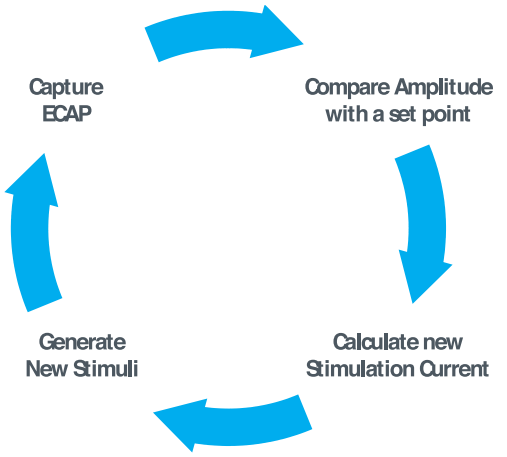

Fig. 11. Feedback controlled SCS updates the current after every stimulus pulse based on the ECAP amplitude from the previous cycle.

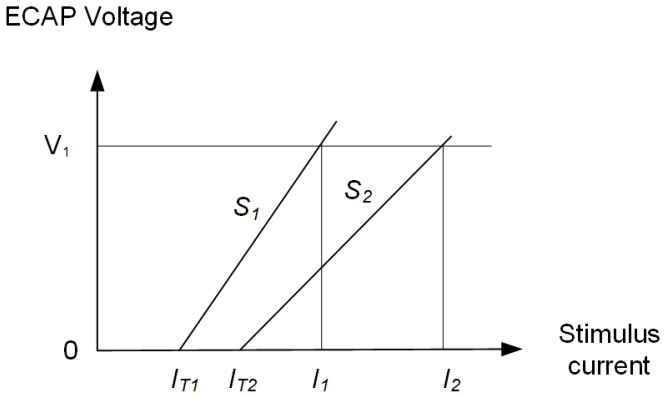

Fig. 12. An ideal activation plot with two postures.

V. Example Application of Proposed Dose Measure

With a view to reducing variation in activation during posture change and changes in the electrode-to-cord distance (CSF thickness) during the respiratory cycles, Parker et al. first proposed the use of a feedback loop to automatically adjust stimulation current to maintain a constant measured evoked response. Figure 11 illustrates the algorithm used by this device. By maintaining a constant ECAP voltage this therapy represents a departure from open-loop stimulators that typically hold a constant current. Parker et al. implicitly defined ECAP amplitude as a measure of dose; the loop kept it perfectly constant. The proposed measure A allows comparison of constant-current and constant-ECAP therapies.

Consider the ideal activation plot in Figure 12. This shows ECAP amplitudes from two postures having thresholds I_{T1} and I_{T2} and having sensitivities S_1 and S_2. Suppose the stimulus current is set to I_1. The variation in activation as the patient moves between these postures (Activation 2 divided by

TABLE I
VALUES EXTRACTED FROM THE ACTIVATION PLOTS IN FIGURE 8 AND COMPARISON OF ACTIVATION IN OPEN AND CLOSED-LOOP

Posture	Supine	Standing	Sitting
I_T (mA)	3.5	4.2	5.2
I_D (mA)	5.1	5.9	7.0
S (μV/mA)	138	86.3	65.7
A_O	0.78	0.48	0.2
Δ_O(%)	391	240	100
A_C	0.14	0.19	0.2
Δ_C(%)	71	94	100

Activation 1), based on (3) is:

$$\Delta_O = \frac{A_{2O}}{A_{1O}} = \left(\frac{I_1}{I_{T1}} - 1\right) / \left(\frac{I_1}{I_{T2}} - 1\right) \tag{14}$$

where the O subscript is for Open loop. A similar value would be obtained if a stimulation voltage dose was specified.

To facilitate comparison, data is read from Figure 8 and values are tabulated in Table I. The first three rows of Table I present parameters extracted from Figure 8, essentially indicating the x-axis intercept and slope of the straight-line approximations, and the upper limit of current for comfort. The fourth and sixth rows give the activation in the case of open- and closed-loop systems in each posture, given a nominal value of $A = 0.2$ in the sitting posture for each system, as calculated below. The fifth and seventh rows show the variation from the nominal value in the sitting posture in percent (hence the value is exactly 100% in the sitting-posture column). It will become clear that numbers in the seventh row are independent of the choice of A.

Taking the values from the upper lines of the table, and assuming a target activation of $A = 0.2$ with an initial current of $1.2 \times 5.2 = 6.4$mA, the variation in activation is:

$$\Delta_O = \left(\frac{6.24}{3.5} - 1\right) / \left(\frac{6.24}{5.2} - 1\right) = 3.91 \tag{15}$$

or an increase of 3.91 times above the initial setting

This current of 6.24mA exceeds the maximum comfort level when supine. This can be avoided by reducing the current. Suppose the maximum current is set to 4.8mA, the maximum comfort level while supine. This would lead to a lack of therapy when sitting. In this case the activation range calculation would have a zero in the denominator and variation would be infinite. The lack of a single therapeutic current in all postures is a consequence of the gap between the non-overlapping regions in the activation plot of Figure 8.

Consider now the closed-loop case. The variation in activation between these postures based on (7) becomes:

$$\Delta_C = \frac{A_{2C}}{A_{1C}} = \left(\frac{V}{S_{T2} I_{T2}}\right) / \left(\frac{V}{S_{T1} I_{T1}}\right) = \frac{I_{T1} S_1}{I_{T2} S_2} \tag{16}$$

where the C is the subscript for closed-loop.

$$\Delta_C = \frac{65.7 \times 5.2}{138 \times 3.5} = 0.71 \tag{17}$$

or a drop of 29% below the initial setting. This drop is very likely due to the reduction in distance between recording electrode and the spinal cord increasing the recording sensitivity.

Note that the target voltage term, V, cancels in equation (16). Hence the *variation in activation is constant with respect to set point* in the constant-ECAP case. Any ECAP target less than 110 µV is comfortable in all postures. This is in contrast with the open-loop case epitomized by (14), where the variation depends on the current value set point and no single therapeutic current is comfortable in all postures.

Based on Holsheimer's definition of activation, these calculations show that for dose specified as a fixed current, the change in activation with posture for this patient almost quadruples, but with dose specified as a constant ECAP, the activation falls by 29%. Observe that in the case of feedback, the proposed definition of dose returns values that are relatively constant, as well as independent of set point.

VI. CONCLUSION

The history of electrical stimulation for the relief of pain is long and venerable. [31] This manuscript adds an objective measure of activation to the canon, derived from transresistance relationships obtained through measured ECAPs. It further proposes an advance in the form of a practically-measurable and transferable definition of dose applicable to spinal-cord stimulation. The method offers the prospect of obtaining all required parameters from automated electrical measurements. The proposed measure is consistent with the work of Holsheimer, Parker, and Laird-Wah, and the established gate theory of pain. The approach is equally applicable to any neuromodulation therapy where evoked neural responses are measured. No practical, reliable, transferable measure was previously available.

We have used the proposed measure of dose to give an insightful comparison of activation in open- and closed-loop situations. The example comparison shows the variation of activation with posture is reduced by more than a factor of 10 using a closed-loop compared to an open-loop algorithm and provides stimulation that is comfortable in all postures. Having obtained an objective definition dose that can be calculated from available measurements, there is the possibility of algorithms that control for this value. We have also shown that, in a fixed-current therapy, the variation in activation with distance increases as the current set-point decreases, but for a fixed-ECAP therapy the variation from set-point remains constant.

An old adage states that "you cannot control what you cannot measure". The need to measure dose is particularly important in the case of SCS. For many patients there exists no fixed level of stimulation that falls in the theraputic range for all postures and circumstances, as typified by Figure 8. Continuous, effective therapy requires control of a relevant measure of dosage. Whether provided by feedback, or some other means, measurement of that dosage will be required. The methods provided in this manuscript enable that measurement with sufficient relevance for the first time.

The data presented in Figure 8 was selected from measurements made on a number of patients. The authors infer that there must be many patients who have non-overlapping theraputic ranges for different postures in their activation plots. Conventional open-loop therapy delivers a constant stimulus

current. This means that manual adjustment to allow for posture changes is vital to maintain effective therapy for such patients. The authors further speculate that loss of efficacy and subsequent explantation of stimulators may be associated with patient inability to handle this requirement. Support for this speculation is evident in the 24-month data from a feedback-controlled stimulator. [32]

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