Hypothesis for the mechanism of action of ECAP-controlled closed-loop systems for spinal cord stimulation

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Advances in technology and improvement of efficacy for many neuromodulation applications have been achieved without understanding the relationship between the stimulation parameters and the neural activity which is generated in the nervous system. It is the neural activity that ultimately drives the therapeutic benefit and the advent of evoked compound action potential recording allows this activity to be directly measured and quantified. Closed-loop control adjusts the stimulation parameters to maintain a predetermined level of neural recruitment and has been shown to provide improved pain relief in individuals with spinal cord stimulators. However, no mechanism that relates more consistent neural recruitment to patient outcomes has been proposed. The authors propose a hypothesis that may explain the difference in efficacy between open- and closed-loop operational modes by considering the relationship between measured neural recruitment with hypothetical dose and side effect response curves. This provides a rational basis for directing clinical research and improving therapeutic systems.

1. Introduction: Spinal cord stimulation (SCS) is an effective and safe treatment for neuropathic pain. The therapy was established 50 years ago shortly after the gate theory of pain was proposed [1]. SCS devices consist of an electrode array that is implanted in the epidural space and an implantable pulse generator which generates stimulation pulses directed at the dorsal column (DC). The mechanism of SCS is not completely understood. Recruitment of large diameter DC fibres drives inhibition of dorsal horn pain processing neurons. There is a considerable amount of evidence that the inhibition is mediated by the release of inhibitory neurotransmitters including gamma-aminobutyric acid (GABA) in the dorsal horn [2]. Correlation between DC activity and neurotransmitter release has been established in animal models [3]. Titration of DC recruitment against the level of pain relief for humans has not occurred because of the lack of tools to quantify the DC stimulation response. Furthermore, patient movement changes the distance between the DC and the electrodes, changing electric field strength in the DC and thus the stimulation dose. This occurs regardless of the mechanism of action (MOA). The electrically evoked compound action potential (ECAP) is a measure of the response of DC fibres to electrical stimulation and this provides the requisite measure of activity [4]. Moreover, the DC activity can be controlled in real-time with closed-loop control, which has a profound impact on the outcomes for SCS [5, 6] making closed-loop stimulation the preferable therapy. Histograms of ECAP amplitude recorded in ambulatory patients combined with knowledge of the neuroanatomy and physiology of SCS suggests mechanisms whereby closed-loop control may improve patient outcomes, a result demonstrated in recent clinical trials. However, the reasons closed-loop stimulation provides benefits are not understood; if they were, then they could direct clinical research, allowing further improvements in clinical practice and system design.

2. Neuropathic pain and SCS: Damage to all or any sensory peripheral fibre types (Aβ, Aδ, and C) alters transduction and transmission due to altered ion channel function [7, 8]. Increased expression of Na channels leads to an increase in excitability and neurotransmitter release [9]. Loss of potassium channels is also evident in injured nerves which become hyper excitable. The remnants of intact fibres produce ectopic discharge which is experienced by the individual as pain and more insidiously leads to neuro-plastic changes in the dorsal horn referred to as central sensitisation. Tactile allodynia following peripheral nerve injury can be attributed to impulses carried centrally via Aβ fibres and can be induced without C fibre activation [10]. The repetitive firing of A fibres produces the same changes in spinal excitability as C fibres [11]. Aβ fibres have also been implicated in sending pain signals for conditions such as tactile allodynia via a normally silent pain circuit between low threshold primary efferent and nociceptive specific neurons [12].

In the rat, the primary afferents entering the spinal cord into the DC are located at the dorsolateral surface but exist more deeply and ventromedially at more rostral spinal segments [13]. The DCs also contains a major sensory pathway of myelinated, second-order neurons that propagate action potentials into the dorsal horn. This action is believed to drive segmental dorsal horn inhibition through activation of inhibitory interneurons that suppress the transmission of nociceptive information from wide-dynamic range (WDR) spinal projection neurons to the brain, effectively countering nociception [14].

For much of the history of SCS, there has been little improvement in outcomes despite attempts to change the stimulation dosage or improve targeting. Thankfully this has changed in recent times and clear differences between different stimulation algorithms and responses from populations of pain patients have been reported in recent clinical trials [5, 6, 15]. The mechanistic reasons for this are the subject of research and debate, complicated by a general lack of usage and dosage data. A confounding factor is the number of possible stimulation parameters that can be adjusted which makes an exhaustive search of the parameter space impractical. There have been suggestions that there is a relationship between the duty cycle (i.e. within a pulse train, how long the stimulation is on versus off) and clinical response, and further that the rate of charge delivery is analogous to the dosage of medication [16].

A very wide range of stimulation parameters has been tested and made clinically available. An even wider range of parameters have been explored with animal models [17] but no method has been established to select the stimulation parameters or waveform which is ideal for a patient. A rather prescient statement appears in the conclusions in ‘the concept of a SCS target pain neuron

that needs to be stimulated in an optimal way may call for the approach of 'listening' more to the nervous system instead of offering 'noise' to it to find out physiological parameters'. Feedback SCS systems 'listen' to the response of nerves to electrical stimulation and attempt to counteract the 'noise' generated by changes in patient posture and physiological changes.

3. Dose–response relationship in SCS: The relationship between stimulation parameters and therapy outcome is currently unknown and manufacturers and clinicians are forced into trial and error discovery for both individuals, for populations of pain sufferers and system designs. Inability to control the dose at the DC impedes the establishment of this relationship; however, once dose–response relationships for therapy and side-effect are established they are likely to have the characteristics of the typical dose–response curves illustrated in Fig. 1.

Studies in rats have shown that there is a relationship between the extent of neural recruitment and the effectiveness of SCS in providing pain relief. Yang *et al*. [3] in a rat model correlated the level of Aβ/α recruitment during SCS in the spinal cord to the level of neuropathic pain. These authors used the ECAP recorded on the sciatic nerve in the leg of the animal to determine the level of DC activation. They determined the electrophysiological threshold for the anti-dromic spinal cord activation, the plateau amplitude of Aβ/α response and the motor thresholds for responders and non-responders. The Aδ fibre activation was also characterised by measurement of the conduction velocity and latency of the anti-dromic responses. Yang *et al*. showed that there was no difference between electrophysiological threshold and Aβ/α plateau between the responder and non-responder groups but did show a difference in the stimulus-response curves between the two groups. The integral of the Aβ/α amplitude growth with stimulation intensity showed significant differences between responders and non-responders, providing evidence of a therapeutic dose–response curve.

A relationship between response rate and extent of DC activation as determined by compound action potential recording has been established. The activity evoked in the Aβ fibres produces a sustained depression of synaptic response to C fibre inputs to the substantia gelatinosa [18]. This depression occurs after a brief application of stimulation, persists for 20 min and inhibits monosynaptic and polysynaptic forms of C fibres. The extent of depression was frequency-dependent with 50 Hz more effective than 4 Hz or 1 kHz. Paired pulse experiments (PPR) suggest that 50 Hz Aβ electrical stimulation in naïve animals produced inhibition via a presynaptic site of action but in nerve-injured animals the PPR did not increase further suggesting that the nerve injury has resulted in a substantial neuroanatomical change in the spinal sensory circuitry.

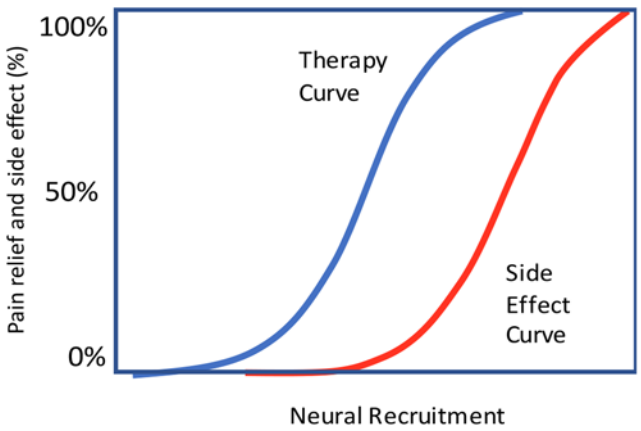

Fig. 1 *Theorised dose–response curve for SCS*

Simulation of a biophysically based network model of the dorsal horn neurons showed suppression of WDR neurons was stimulation frequency-dependent [19]. The model was sensitive to the properties of the local and surrounding dorsal horn inhibition in a manner that mimics the progression of neuropathic pain. It appears that WDR sensitisation (windup) can occur to such an extent that inhibition afforded by SCS is no longer effective. This provides physiological evidence of the existence of the side-effect curve illustrated in Fig. 1, and also that the side effect increases with the frequency of occurrence.

The observation that reducing the aberrant input and sensitisation via gabapentin or augmenting the level of inhibitory neurotransmitter with sub-therapeutic doses of baclofen can restore the efficacy of SCS suggests that a common mechanism is involved [20, 21]. Spinal cord sensitisation and windup can exceed the capabilities of traditional SCS to provide relief via the SCS GABA-mediated inhibition. The windup is driven by neuronal input to the horn and there may be mechanisms by which SCS, which aims to inhibit WDR neurons that may actually drive the windup process and exacerbate the neuropathic pain state.

Electrophysiological changes occur in the spinal cord neurons in response to neuropathic pain; there are changes in ion channel expression and concentration. The loss of function of KCC2 Cl-transporter which accompanies the generation and maintenance of neuropathic pain [22, 23] results in alteration of the anionic reversal potential and shift in membrane potential to a more excitable state. The extent of KCC2 loss correlated with the loss of WDR inhibition via GABAegric/glycernergic mechanisms.

The involvement of microglia in the modulation and maintenance of neural pathways is the subject of extensive research. Brain-derived neurotrophic factor (BDNF) produced by microglia is the signalling molecule which results in the collapse of the anion gradient and production of hyperexcitability [23, 24]. BDNF plays a central role in plasticity and formation and maintenance of synapses and is produced in an activity-dependent manner by electrical stimulation.

Electrical stimulation promotes BDNF expression in the spinal cord [25] and there is evidence to suggest that the response is a dose-independent, all-or-none process [26]. This presents a plausible mechanism where stimulation itself can result in inhibition of WDR and exacerbation of neuropathic pain but the stimulation parameter windows over which this occurs are unknown.

It is also observed clinically that the recruitment of the dorsal roots (DRs) from thoracic placed leads results in the contraction of a band of muscles around the thorax. This is unpleasant for awake patients and suggests it is likely there is more than one side-effect mechanism during SCS.

The most insidious side effects are related to long-term loss of efficacy of SCS. In a review of SCS explants, loss of efficacy occurred in 43.9% of patients (152/346), with a mean time to explant of 13 months [27] and perhaps this may occur directly from stimulation via BDNF-mediated increases in hyperexcitability. Finally, stimulation at sufficiently high levels can activate nociceptive fibres, some of which conduct in the same velocity range as the Aβ fibres [28].

There are thus multiple mechanisms by which side effects occur during SCS. These side effects could potentially lead a patient to increase the stimulation amplitude in an attempt to maintain the benefit (tolerance) or to decrease it as stimulation that was once tolerable has become intolerable (intolerance). The clinical outcome of both tolerance and intolerance is the same, the patient gradually loses efficacy from the SCS device. Technically the device is working, i.e. delivering the intended stimuli. For devices that produce it, the paraesthesia can be located in the correct place. However, the patient no longer receives pain relief. A thorough understanding of these side effects is required before they can be eliminated from the SCS population or strategies for dealing with patients with failing therapy can be derived.

The fact that there exists a relationship between the dose of electrical energy delivered to the DC and the patient's derived benefit is also evident from normal clinical device usage. Patients receive no pain relief when the device is switched off and not delivering any therapy and, through adjustment find stimulating settings they find to be optimum and which provide relief. Excessively high stimulation amplitude is unpleasant to patients and causes them to reduce it.

There is insufficient evidence to establish specific values to associate with the threshold and saturation of the therapy and side effect dose–response relationships. It is likely the therapeutic threshold is the DC Aβ fibre threshold. The threshold of the saturation of the therapeutic benefit is unknown but may be the Aδ threshold as noted previously. The side effect threshold might be the threshold of DR activation or it might be the maximum comfort level derived clinically. It is unlikely that there is any saturation of side effects, but rather new side effects accumulate as stimulus amplitude is increased.

4. Characteristics of measured evoked responses: ECAP measurement, provided by the Evoke system, affords a direct measure of the DC recruitment and its variation over time. The amplitude of the ECAP response is between 10 μV and 1.5 mV. It can be used to understand the relationship between the stimulation which is being delivered and the recruitment of the Aβ fibres of the spinal cord. There are many factors that influence this relationship including the stimulation frequency, amplitude, and pulse-width, the presence of pharmacological agents, and the proximity of the electrode to the cord. Posture, heartbeat, breathing, and coughing change the cord to electrode distance. Patients adjust stimulation amplitude. ECAP amplitude varies continuously.

The extent of posture-dependent variation can be measured by asking the patient to adopt different postures and measuring the relationship between the stimulating current and the amplitude with feedback disabled. Fig. 2 shows the amplitude of the ECAP versus current for a single patient in three postures. This plot is called an 'activation plot'.

The vertical lines in Fig. 2 denote the threshold in each posture. It is illustrative to note the currents where even the presence of an ECAP is posture dependent.

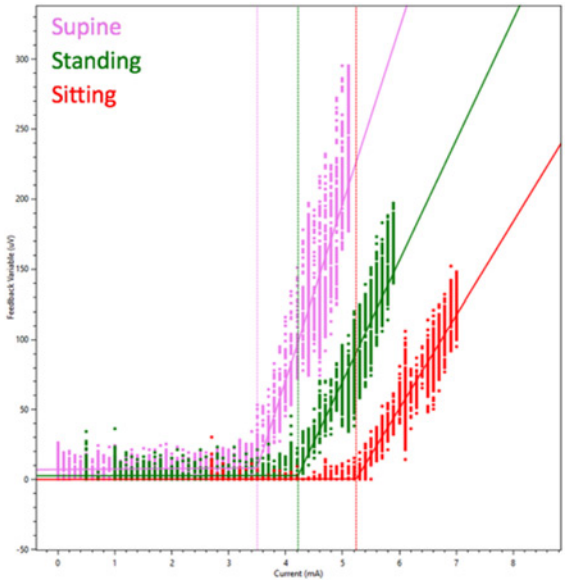

Fig. 2 *Activation plots for one patient in different postures collected with the evoke SCS system in open loop. For this patient, sitting is the least sensitive posture and supine is the most sensitive posture*

Using the Evoke system it is possible to measure the ECAP amplitude for each stimulus and collect and store these over time so they can then be plotted as a histogram. These can be obtained in both open-loop and closed-loop modes.

Fig. 3 shows the ECAP amplitude histograms for two individuals during seven days in the open- and closed-loop arms of the Saluda Evoke trial. These patients were selected to highlight what appears to be a common difference in the histograms in the two arms of the trial.

During the fitting of an SCS patient, clinicians routinely record the ECAP amplitude at which the patient feels stimulation (threshold), at the amplitude at which they feel comfortable, and at the maximum they can tolerate for one minute. Histogram data allows measurement of the percentage of stimuli below the patient's threshold and above their maximum comfort level, i.e. within their therapeutic window. Such data is shown in Table 1 which also shows that feedback is effective in keeping the ECAP amplitude within the therapeutic window.

5. Hypothesis for the MOA of closed-loop SCS efficacy: The Evoke trial demonstrated that closed-loop stimulation provides superior outcomes to open-loop [6]. Since the patient groups were carefully matched, and fitting procedures were identical for the two arms, the only difference between the two groups was the statistics of the stimulation. A possible explanation of the reason the results of the two groups differed lies in the information of Fig. 3 and Table 1.

The summary of the science of SCS is presented in Sections 3 and 4, and the observed behaviour of the Evoke system in open- and closed-loop modes presented in Sections 2–4 leads to the following hypotheses that together may explain why the closed-loop patients' performance was superior to that of the open-loop:

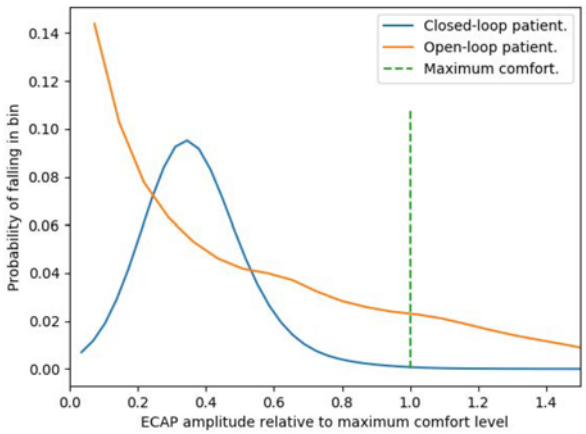

Fig. 3 *Histograms from an open-loop and a closed-loop patient from the 3-month visit from the evoke trial. These are normalised to the patient maximum comfort level. These histograms show that the open-loop patient experienced a significantly greater percentage of stimuli above the maximum comfort level indicated by the dashed green bar*

Table 1 Stimuli and therapeutic window for 1 week at 3 month visit for an open-loop and a closed-loop patient

Parameter	Open loop, %	Closed loop, %
stimuli above maximum	11.8	0.3
stimuli below minimum	26.8	2.1
stimuli in therapeutic window	61.4	97.6

(i) SCS therapy and side effects are the results of the activation of Aβ fibres.
(ii) Stimuli below the ECAP activation threshold provide no therapy.
(iii) Stimuli above the ECAP activation threshold provide therapy which increases with the degree to which they exceed the threshold and with the frequency of occurrence.
(iv) Stimuli above the ECAP maximum comfort threshold provide side effects that increase with the degree to which they exceed the side effect threshold and frequency of occurrence.
(v) The net effect is the sum of the net therapy and the net side effect.
(vi) At high ECAP amplitudes, the net side effect exceeds the net benefit, and this may lead to intolerance.

6. Interaction of dose–response relationships and feedback: A Python programme was written to illustrate the hypotheses described in this section and the interaction of closed-loop ECAP histograms and dose–response relationships. Fig. 4 shows an example. The values on these scales are hypothetical to evaluate the plausibility and consistency of the proposed mechanisms.

These calculations assume that the mechanisms of the hypotheses outlined can be combined in a simple linear way, with each stimulus being treated as an independent event. Using this approach, the probability density function for the activation can be multiplied by the dose–response relationships and summed to produce histograms of therapy and side effects. The area under these curves then provides a single number representing the net benefit or detriment. This is the simplest method of combining the effects and generates predictions and will be subject to future experiments and analyses.

Patients adjust the stimulation amplitude such that it is most comfortable, on average. In doing so they are balancing beneficial and detrimental effects. By setting the amplitude too high, the situation of Fig. 5 results. In this case, the dose–response relationships are unchanged, and the ECAP amplitude histogram has shifted to the right. The stimuli generate both therapy and side effects, and in this case, the side effect magnitude exceeds the therapy (point 6 of the hypotheses), the detriment exceeds the benefit and the patient may turn the stimulation down.

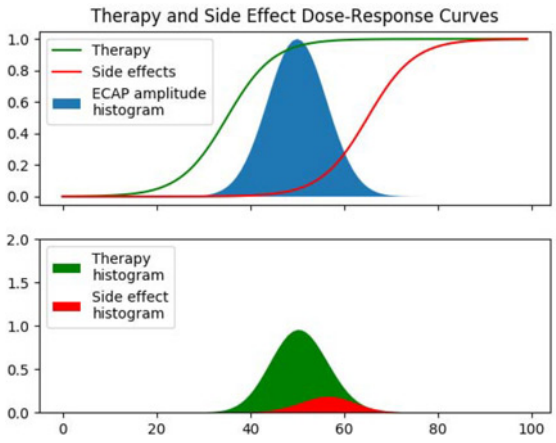

Fig. 4 *Top panel shows the hypothetical dose–response relationships for therapy and side effect introduced in Fig. 1. This also shows a closed-loop ECAP amplitude histogram similar to that of Fig. 3. The lower panel shows the ECAP histogram weighted multiplicatively by the dose–response curves (points 3, 4, 5 of the hypothesis). In this case, the stimulation histogram is between the peak of the therapy curve and the onset of the side effects. The benefit is proposed to be the difference in between the green and red areas. Since the green histogram has greater area than the red, the benefit of therapy exceeds the side effects*

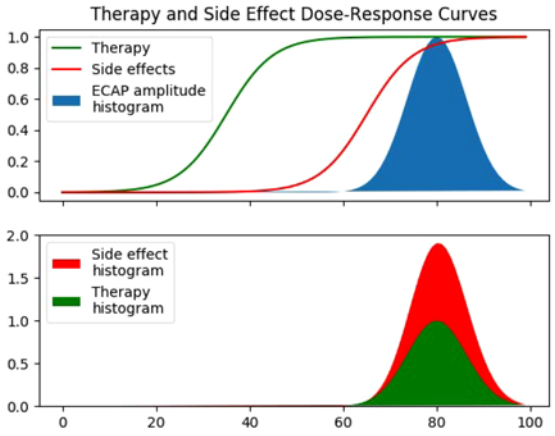

Fig. 5 *Usage of device with a high preferred ECAP amplitude level (overlaid on top of therapy and side effect dose–response curves) results in net detrimental effect. This may lead to the patient turning the stimulation down*

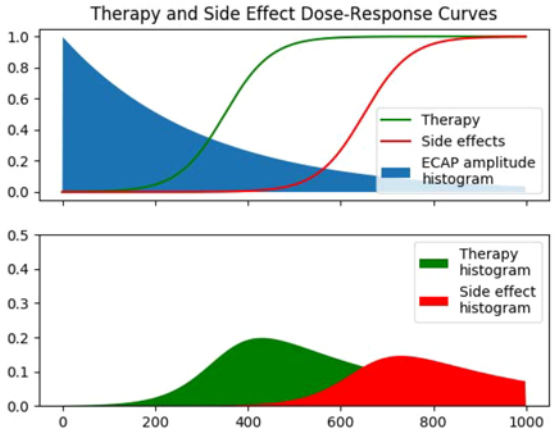

Fig. 6 *When open-loop patients turn their preferred level of stimulation down, they are essentially trying to adjust the therapy within their therapy and side-effect dose–response curves such that they get a net therapeutic benefit. However, this results in a lot of stimulation that is not therapeutic and also side-effects that exceed those of a closed-loop patient*

Table 1 shows there is a tolerable overstimulation rate for individuals and it is likely that users adjust the stimulation amplitude to reach that level. Figs. 4 and 5 show for a closed-loop patient how overstimulation varies with stimulation amplitude.

7. Comparison of open and closed-loop systems: The model allows a comparison with open-loop systems. Fig. 6 shows the effects with an open-loop histogram modelled as a falling exponential function, which is comparable with the measured histogram of Fig. 3.

Note the change in scale of the therapy and side effect histograms between Figs. 5 and 6 that were performed to make the histograms more visible. Owing to the nature of the open-loop system, fewer stimuli fall between the threshold of the therapy and side effects, and a greater number fall above the side effect threshold. This may explain the difference between open- and closed-loop performance demonstrated in the Evoke trial.

8. Conclusion: By combining an understanding of the physiological effects of SCS with measured ECAP amplitude histograms a model emerges that may explain the differences in performance between the open- and closed-loop arms of the Evoke trial and suggest further avenues for device improvement and research.

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10 References

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