Electrically evoked compound action potential recording in peripheral nerves

John L Parker^{*,1,2}, Nastaran H Shariati¹ & Dean M Karantonis¹

¹Saluda Medical Pty Ltd, Artarmon, New South Wales, Australia

²Graduate School of Biomedical Engineering, University of New South Wales, Kensington, New South Wales, Australia

* Author for correspondence: john.parker@saludamedical.com

Applications for bioelectric medicine can be found in all parts of the nervous system. The CNS – brain and spinal cord – contain targets for commercial neuromodulation therapies. Peripheral nerves are also modulated with commercially available systems during treatment for chronic pain and epilepsy, and developments are in progress for treating many other diseases. The electrically evoked compound action potential is a measure of the electrical response from the tissue to stimulation. It provides a direct insight into the electrophysiology of the stimulation, and despite its incorporation into cochlear implants it is a technology that is yet to find its way into commercial peripheral nerve stimulation applications. This review outlines the status of evoked compound action potential measurements on peripheral nerves and highlights the challenges which need to be overcome.

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Recording of the neural activity generated by electrical stimulation forms the basis of a number of diagnostic procedures. It is often performed in an acute setting and the technology has found its way into several active implantable devices. The techniques rely on a stimulus applied to the nerve or tissue to evoke a compound action potential. The stimulus simultaneously and synchronously recruits many fibers and hence the response is referred to as a compound action potential because it is the sum of the many potentials recruited. Summation and synchronous generation increase the amplitude of the response and thus makes detection feasible. Recording the electrical activity of peripheral nerve neurons is common place in a number of diagnostic procedures [1]. Nerve conduction studies are performed to assess the integrity of the nerve and form part of a diagnosis of a range of conditions including Guillain Barre, carpal tunnel syndrome [2], herniated discs, chronic inflammatory polyneuropathies and other nerve disorders including peripheral nerve injury. The direct response from the nerve or the response from a muscle that the nerve innervates is recorded (EMG) in these studies. The nerve conduction velocity is a measure of nerve health – velocities between 50 and 60 ms⁻¹ are considered in the normal range and velocities outside this range could be an indicator of disease. Neural monitoring, measurement of peripherally evoked potentials from the somatosensory cortex, is used to ensure safety during spine surgery [3]. Compound action potential measurement capabilities are built into cochlear implants and are used as objective measures during device setup and programming [4]. Peripheral nerve recordings form the basis of numerous scientific investigations and are used to assess the impact of drugs or to provide baseline calibration of neural activities as part of deeper investigations.

Recordings from the nervous system inform clinicians about the health of nerves or their safety during procedures. They inform researchers about mechanisms of action and provide fundamental data for mechanism-based research. Their scope and use is broad but here we will focus on the electrically evoked compound action potential recorded from peripheral nerves.

Here we shall briefly discuss peripheral nerve types and classifications, and then explore the technical requirements and difficulties encountered when attempting to record their electrically evoked compound action potential. Recordings from the tibial, sciatic and vagal nerves are then used to illustrate the utility of the technique and what can be learned about the electrophysiology and neuroanatomy from this data.

Figure 1. Schematic illustration of the electrically evoked compound action potential measured from a peripheral nerve and the measurement setup.

The stimulating electrodes (panel A) generate a current, which is passed to a second electrode. In this case the return electrode is also sited above the nerve to make a bipolar pair but other stimulating electrode configurations are possible including a monopole (return electrode sited some distance from nerve). The stimulus generates an action potential, which is detected on recording electrodes separated from the stimulating electrode by distance d representing the length of the nerve through which the action potential propagates. The time from the stimulus for the action potential to reach the nerve is determined by the conduction velocity of the fiber. The largest diameter fibers can propagate at 100 ms^{-1} and the smallest at 1 ms^{-1} and so the scale to capture this range of conduction velocities (for $d = 10 \text{ cm}$) requires measurement over 100 ms. The largest diameter fibers have the lowest threshold for stimulation and so their responses appear first as the current is increased. Increasing the stimulation current recruits successively smaller fiber diameters. The various peaks allow the classification of the fiber types ($A\alpha$ primary receptors of muscle spindle and Golgi tendon organ, $A\beta$ secondary receptors of the muscle spindle and low threshold mechanoreceptors and B preganglionic fibers).

Peripheral nerve fibers

The shape and form of the compound action potential for a peripheral nerve was determined by Gasser and Erlanger from oscilloscope recordings from isolated nerves in 1924 [5]. They showed a change in shape of the responses with increasing levels of stimulation current (schematically depicted in Figure 1). They surmised that this was due to different populations of fibers responding at different current levels, and this observation led to the original classification of neuron fiber types. The conduction velocity of an axon is dependent on the diameter of the fiber which produces the response [6], as is the stimulation threshold (the minimum stimulation current required to elicit an action potential), with large diameter fibers having a lower threshold than small diameter fibers. The evoked compound action potential (ECAP) is the sum of the contributions from all the fibers that respond and so as the stimulation current is increased, more fibers respond, the amplitude grows and (as illustrated in Figure 1) additional peaks appear which are responses from smaller diameter fibers. Erlanger and Gasser derived the classification of fiber types from the appearance of these peaks as the stimulation current was increased and responses from the fiber groups with distinctly different velocity ranges appeared. Subthreshold stimulus currents evoke no response but when the current is increased to threshold of the largest diameter fibers $A\alpha\beta$ (such as the motor efferent fiber- $A\alpha$; diameter $12\text{--}22 \text{ }\mu\text{m}$) are recruited. Increasing the stimulus current further recruits the next most sensitive fibers, the touch–pressure sensation afferent fiber- $A\beta$. As the current is increased still further the $A\delta$ wave (such as the pain–warm sensation afferent fiber; diameter $1\text{--}5 \text{ }\mu\text{m}$), followed by the C wave (such as postganglionic sympathetic fiber; diameter $0.1\text{--}1.3 \text{ }\mu\text{m}$) responses become visible.

This classification has led to the ‘textbook’ description that fiber function is related to the diameter of the fiber and the neat classification in Table 1 results. Recent studies revealed an overlap between function and fiber diameter across the range of fiber diameters. For instance, nociceptor fibers exist which conduct at the same velocities as $A\beta$ mechanosensory [7]. There are also unmyelinated touch sensitive fibers, which conduct at velocities within the same range as the C fibers [8]. These fibers were first found in hairy skin but now evidence is mounting that they are present in glabrous skin [9]. $A\delta$ fibers are commonly thought to be all nociceptors but in fact $A\delta$ low threshold mechanoreceptors exist in substantial proportions in different species [10].

Table 1. Conventional classification of fiber types in mixed fiber bundles.

Type of fiber	Diameter (micrometers)	Conduction velocity (m/sec)	General function
A- α	13–22	70–120	α -motoneurons, muscle spindle primary endings, Golgi tendon organs, touch
A- β	8–13	40–70	Touch, kinesthesia, muscle spindle secondary endings
A- γ	4–8	15–40	Touch, pressure, γ -motoneurons
A- δ	1–4	5–15	Pain, crude touch, pressure, temperature
B	1–3	3–14	Preganglionic autonomic
C	0.1–1	0.2–2	Pain, touch, pressure, temperature, postganglionic autonomic

Recording peripheral nerve electrically evoked compound action potentials

There are a number of prerequisites to successfully record peripheral nerve ECAPs. Here we will restrict our discussion to measurement of near-field action potentials and ignore electro microneurography [11] and measurements conducted with electrodes on the surface of the skin [12]. The size, shape and configuration of the electrodes used for recording can have a profound influence on the shape and nature of the measured compound action potential. Despite this there are few systematic studies of the influence of electrode geometry. Several approaches have been employed to interface electrodes to peripheral nerves, which are primarily designed for stimulation and recording attempted as an afterthought. Approaches to placing electrodes adjacent to the nerve, around the nerve in the form of cuffs [13–15], within the nerve (intrafascicular) [16,17] and where the nerve is pressed against a flat surface [18] have all been explored. The goals of stimulation and recording can be quite different and as most of the development is directed at deriving therapeutic benefit from stimulation it is not surprising that little work has been done on optimization of electrode design for recording. Studies have explored the effect of electrode configuration, interelectrode distance and electrode orientation on the shape, amplitude and latency of nerve action potentials measured with surface electrodes [19]. The effect of electrode spacing on the ECAP measured from the medial nerve has been studied in the rat [19] but a full characterization of the impact of recording electrode geometry on the quality of recordings has yet been done.

Peripheral nerves can be identified and divided from tissue, which allow cuff electrodes to be placed around the outside of the nerve bundle. Cuff electrodes which are designed to exert little or no pressure but fit around the nerve, have the advantage that they maintain a stable and close proximal relationship to the nerve for long periods. These advantages make them suitable for long-term implantation in the body and commercial application such as vagal nerve stimulation for the treatment of epilepsy and neurostimulation for phantom limb pain [20]. The electrode contacts are arranged radially around the nerve and in some applications where only part of the nerve trunk is targeted or can form a single band to stimulate a whole nerve. In contrast to standard epineural cuffs, which are designed to limit pressure on the nerve, flat electrodes seek to increase the specificity of stimulation by pressing the electrode against a contact surface with the goal of spreading out the fascicles within the nerve and hence achieve subfascicular specificity for stimulations [18].

Success in recording peripheral nerve compound action potentials requires careful consideration of the design of the recording electronics and the position and geometry of the electrode array. The amplitude of the recorded potential drops with the separation of the electrode from the surface of the fiber with an approximately inverse square relationship (Figure 2) and this along with nerve anatomy poses a challenge to recording. The compound action potential is the sum of the single-fiber action potentials from all the fibers that contribute to the signal. Action potential propagation generates current flow at the nodes of Ranvier for myelinated axons and it is the potential from this current flow that is recorded on an extracellular electrode some distance from the fiber. The simplest model of this is to assume that the material between the axon and the electrode is homogeneous so its characteristics can be described with a simple volume resistivity ρ . With the added simplification that the recording electrode is a single point (P) in space than at any instance the ECAP is the sum of the potential induced by all nodes which is in turn a function of the current (I_m) at the node and the resistance between the node and electrode (Figure 2).

Electrodes implanted in tissue are not ideal mathematical points, nor is the medium between the axon and electrode homogeneous. Nonetheless the amplitude of the ECAP changes with separation between the fiber and the recording electrode with the consequence that at large separations there may be insufficient signal to noise ratio to reliably record a response at all. The stimulation voltage required to deliver sufficient charge to depolarize a

Figure 2. A schematic diagram of a single fiber is shown with an idealized point measurement electrode above and the amplitude of a single fiber response as a function of fiber diameter and separation below. The measured potential is the sum of the potentials induced by the current flowing from the node of Ranvier (I_m) from the node of Ranvier (x_n) and measured as a voltage at the electrode. The electrode P is separated from the axon by h and the resistance is simply a function of the path length and ρ is the conductivity of the medium. The voltage measured at the electrode depends on the separation and the fiber diameter, and is shown below for a single fiber with an electrode fiber spacings, h , of 0.1, 1 and 10 mm.

neuron is often tens of volts. The potential produced by an axon is of the order of fractions of a microvolt, which means the difference between these potentials is more than six orders of magnitude. The consequence of this is that the volume of neural tissue which contributes to the ECAP can be significantly smaller than the volume of tissue which activated by the stimulus.

The ECAP may contain contributions from large numbers of fibers (from 100s to 1000s) and all the fibers in the bundle have slightly different properties. Comprising the ECAP are responses from neurons with a range of fiber diameters and as a result there are contributions from fast propagating and slowly propagating fibers. The dispersion of the signal changes with propagation distance simply because of the variation in the time taken for the fibers of different conduction velocities to propagate over the distance. Hence the amplitude of the ECAP drops and it 'smears out' as the propagation distance increases.

The amplitude and shape of the ECAP are both influenced by the vertical separation between the electrode and the fiber, and the propagation distance from the stimulus location. The response that is measured is also influenced by the stimulus artifact and this can be the most significant barrier to effective measurement of ECAP. The stimulus artifact is an exponentially decaying voltage, which appears on nearby electrodes as a result of the stimulus itself. The artifact behavior is complex and depends on stimulus parameters and electrode location. Recent models of the tissue are in reasonable agreement with measurements [21] and provide a means to estimate the charge delivery and size of the artifact.

It is desirable to quantify the ECAP uncontaminated by artifact and so a large number of techniques have been developed to achieve this. These techniques follow a couple of strategies: prior estimation of artifact with a model, or combining two recordings in order to remove the artifact. There are two strategies for combining recordings: one exploits the refractory period and the other the fact that the artifact changes sign with polarity. In the first method, a second measurement is made while the fibers are in their refractory period from the first stimulus. This produces a result which has artifact with no neural response and subtraction of this measurement from the first yields the

neural response alone. This method fails if the second stimulus is not completely within the refractory period for the fibers and as different fibers have different absolute refractory periods this is difficult to guarantee. Making the timing very short between the pulses to overcome this difficulty leads to a complication which arises from the integration of the two stimuli. The second method relies on the fact that the artifact changes sign depending on if its genesis is from anodic stimuli or a cathodic stimuli. This scheme is implemented with biphasic stimuli where every second stimuli in the order of the phases is changed, that is, anode first/cathode second, to cathode first/anode second, and so on [22]. Simply adding the responses from the two stimuli will result in a response which is roughly two-times the neural response without the artifact. Again this method is not perfect largely because the response, which is measured (including artifact) is changed depending on if the anode is presented first or second.

Another strategy is to ensure that the measurement is conducted only after the artifact has had sufficient time to decay to a level which does not influence the measurement. This requires a separation between stimulating and recording electrodes sufficiently large such that the time taken for the action potential volley to reach the recording electrode is passed the point where the artifact influences the response. This strategy, however, can result in low amplitude and dispersed signals due to the change in response with propagation distance. The reduction in amplitude may occur to such an extent that the response falls below the signal to noise ratio for the amplifier rendering ECAP recording impossible. There are significant advances which are still required both in the understanding and elimination of stimulus artifact and in ECAP measurement techniques.

Sensory systems convert environmental stimuli into the propagating electrochemical signals which form the action potential. The same type of electrochemical signal may be converted to environmental responses, the most obvious being movement, which can be reflexive withdrawal from a painful stimulus or a planned movement. We think about movement and sympathetic response as the primary responses to nervous system control but recently it has emerged that this control extends to metabolic regulation as well. The peripheral nerve evoked compound action potential and its characteristics form a measure of the capacity of the nerve to conduct information from the periphery, centrally for processing and for the relay of centrally generated commands to the periphery. The neural traffic which ascends centrally along peripheral nerves consists of sensory and proprioceptive information. Stimuli which are sensed, for example, light and odor, are transduced by a single mechanism except for nociception, the nervous system's response to painful or harmful stimuli. Pain is detected at the periphery by a wide range of transduction mechanisms including chemical, physical, heat and pressure. Nociceptors can change their responses and are easily modulated. Some changes can be pathological and when this occurs it can be disastrous for the afflicted. Peripheral input can wind up dorsal horn wide dynamic range neurons which leads to chronic pain [23]. It is for this reason that peripheral nervous system inputs to the spinal cord have been studied with evoked compound action potential measurements.

Studies of the electrically evoked compound action potential have been used to provide mechanistic evidence for the effect of a wide range of perturbations, which can occur to peripheral nerves. Perturbations can have a desired result, for example, application of drugs for anesthesia where others can be deleterious, for example, an injury which stretches a fiber. The sciatic nerve ECAP has been used to study the effect of high-frequency stimulation blockade [4] and the role of adjuvant drugs on prolongation of anesthetic effects [5]. The impact of stretch has been studied with ECAPs on spinal [8] and perineal nerves [14]. The influence of endogenous compounds, for example, metabolite concentration glycogen produced by Schwann cells [3] on the compound action potential of the sciatic nerve has been studied. Evidence for conduction block by applied capsaicin has also been derived from compound action potential measurements. Compound action potential measurements have been used to assess the progress and impact of disease on peripheral nerves in conditions such as diabetic neuropathy [9] and for the assessment of peripheral nerve repair techniques [24].

The fact that the ECAP is a direct measure of the capacity of the nerve to traffic its information allows it to be used to trace the flow and determine the underlying neuroanatomy. Spinal nerve compound action potentials have been used to map the connections of the radial nerve [7]. In our laboratory we measured the ECAP response to tibial nerve stimulation on the sciatic nerve, L3 spinal nerve and the dorsal column of the sheep. The tibial nerve is a mixed nerve consisting of both sensory and motor fibers, and the electrical response to the stimulation at the dorsal column consists of both stationary and propagating components. This can be easily assessed by measurement of the response on at least two different electrodes, which are displaced by some distance but parallel to the fibers where the response is measured. When there is a difference in the timing of the peaks, the signal is propagating in the direction of the axis of the electrode. Data from such an experiment are shown in Figure 3 where responses from two electrodes displaced from each by 14 mm are shown. The responses overlap each other until $t = 6$ ms

Figure 3. Measurement of the response to stimulation of the tibial nerve from the epidural space above the spinal cord in the sheep.

Responses were measured on electrodes which were placed rostral from the L3 root. The tibial nerve was stimulated with monopolar biphasic stimulation ($200\ \mu\text{s}$, $38\ \text{mA}$ with an interphase gap of $50\ \mu\text{s}$) from a hook electrode placed directly on the nerve and a large subcutaneous plate electrode as return. The response was recorded from two electrodes which were spaced ($14\ \text{mm}$ apart) and results from both are displayed. The displacement between the two responses (labeled A) is $0.4\ \text{ms}^{-1}$ and this with the distance between the electrodes allows an estimate of the conduction velocity of the fiber ($35\ \text{ms}^{-1}$). Recordings and data were collected with a multi-channel system (MCS mk II) device from Saluda Medical (Sydney, NSW, Australia), details of the measurement system and set can be found in [25].

where they separate from each other by $0.4\ \text{ms}$. The separation between the electrodes and the time difference between the peaks allow a conduction velocity of approximately $35\ \text{ms}^{-1}$ to be measured. The two responses are very similar in shape and amplitude but simply displaced in time from each other. The origin of the oscillatory signal which occurs between 1 and 6 ms cannot be identified from this data alone but the potentials are not due to neural response on the dorsal column and could be myographic response from activation of muscles innervated by motor fibers in the tibial nerve.

Propagation of the signal along the direction of measurement indicates the potential is of neural origin. The conduction velocity of the responses measured on the dorsal column indicates that it is the larger diameter A β afferent fibers that are stimulated in the tibial nerve bundle. The tibial nerve is a branch of the sciatic nerve which is derived from spinal nerves from L4 to S3. For the afferent fibers the ascending information travels along the same path and is distributed across the spinal nerves. Figure 4 illustrates that the complex response is the sum of triphasic ECAP potentials which have a $0.3\ \text{ms}$ delay between them. Each triphasic response has different amplitude and the amplitude indicates the number of fibers from each spinal root which is contributing to the response. The $0.3\ \text{ms}$ delay is a result of the difference in propagation distance for fibers which enter the dorsal column at one vertebral level versus the adjacent level. The difference in propagation distance is approximately $3\ \text{cm}$ based on a conduction velocity of $100\ \text{ms}^{-1}$, which is pleasingly close to the width of a vertebra in the sheep model. From this we can conclude that the large diameter fibers of the tibial nerve ascend and join the spinal cord through at least four vertebral segments.

The sciatic nerve, which includes the tibial nerve, has many more branches as it enters the spinal cord and the response which is measured is more complex (Figure 5). A similar pattern of repeating ECAPS with varying amplitudes occurs for the sciatic nerve but spread over a wide range of latencies (from 4.5 to $14.5\ \text{ms}$). The response measured on the sciatic nerve to stimulation of the tibial nerve is shown in Figure 5B. The multiple components to the ECAP are due to the recruitment of all the different fiber types within the nerve bundle. These include muscle efferent fibers which are not present on the surface of the dorsal column when responses are recorded from this position. The measurement of ECAPs from peripheral nerve stimulation at central locations can yield useful

Figure 4. Measurement of the compound action potential generated by stimulation of the sheep tibial nerve from epidural-placed electrodes rostral to the L3 vertebra from a single recording electrode.

The stimulus, biphasic (parameters as shown in figure n) terminates at $t = 1$ ms on the plot. A schematic diagram of the spinal cord is shown and the peaks on the response are identified and assigned to spinal nerve roots. The difference in the latencies of the peaks corresponds to conduction over a distance of approximately 3 cm, which approximates the width of vertebrae. The response recorded from a single spinal nerve root (L3) is shown for comparison.

Figure 5. Response from stimulation of the sciatic nerve measured on the spinal cord on the same two electrodes used to measure the tibial nerve responses shown in Figure 3 and the response measured on sciatic nerve to stimulation of the tibial nerve.

information about the anatomy of the nerve and its passage to the cord. This may prove to be particularly important in choosing stimulation locations for neuromodulation.

Vagal nerve compound action potential recording

The vagal nerve is responsible for carrying information to and from the brain to all the major organs. The heart, gut, sweat glands and some mouth movements are controlled and monitored by the vagal nerve. A portion of the ear canal is innervated by its afferent fibers (auricular branch of the vagal nerve). Vagal nerve stimulation has been used to control seizures in epilepsy since 1997. A meta-analysis of the clinical studies (3321 patients across 74 studies) concluded that seizures were reduced by 50% or more in approximately 50% of the patients [26].

The spread of function of the vagal nerve is matched by the breadth of applications seeking to modulate it for various disorders including Tinnitus [27], weight loss [28,29] and immune system response [30,31]. Early animal studies demonstrated that vagal nerve stimulation can prevent ventricular fibrillation [32] and improves survivability after heart failure [33] and promotes left ventricular remodeling [34]. These encouraging results in animals lead to the conduct of a clinical study [35] of 32 chronic heart failure patients, which showed an increase in left ventricular ejection fraction after 12 months.

Even though vagal nerve stimulation is a potential therapeutic goldmine, there are only limited reports of attempts to measure the compound action potential resulting from its stimulation. Acute intraoperative measurements in humans demonstrated the activation of three distinct fiber groups: A β , A δ and in some subjects C fibers [36] and suggested that efficacy of vagal nerve stimulation may not necessarily involve C fiber recruitment. This is in contrast to the early animal work which suggested that maximal activation of unmyelinated C fibers is required for therapeutic benefit and supported by the observation that C fiber destruction [37] does not alter vagus nerve stimulation seizure suppression. Later work [38] identified an indirect component in the compound action potential from measurements. Peaks were found in the evoked response measured from the pig vagal nerve which had a latency of 8.13 ± 1.12 ms but velocity along the nerve was estimated at 69 ± 17 ms⁻¹. This conduction velocity is consistent with responses evoked from A β fibers. The latency of the response measured from A β fibers evoked by the stimulus and traveling along the vagal nerve between the stimulating and recording electrode was just over 1 ms. The long latency and high conduction velocity indicate that the response, although evoked by the stimulus, is indirect and the authors thought it was likely due to efferent cardiac fibers. Figure 6 displays results obtained in our own laboratory for measurements of the ECAP's from the vagal nerve of the sheep. The left vagal nerve of a sheep was exposed and two vagal nerve leads (Cyberonics Model 302) were placed around the vagal nerve. A hook electrode on the nerve was used as the ground electrode and a needle electrode was inserted into the tissue around vagal nerve and used as a reference (REF) electrode. A multichannel recording system (MSC, Saluda Medical) was used to generate the stimulus and record the response. The current source was configured to produce biphasic, bipolar stimulation at a pulse width of 40 μ s and a frequency of 15 Hz. ECAP signals were averaged (100 samples) and the stimulation current increased. The recordings are similar to the recordings made in the pig [38]. As the current is increased and surpasses the thresholds for the various fiber types new peaks appear in the ECAP responses (Figure 6A). The amplitudes measured at a single stimulation current (3.9 mA) but at two recording locations are shown in (Figure 6B). The peak at 8.5 ms shows no shift in latency in the signal between the two sites indicating that its origin may indeed be the result of the indirect pathway. More recent high resolution measurements of vagal nerve compound action potentials in dogs demonstrated that long latency responses (10–15 ms) were a result of EMG [39]. This is generated from the larynx and is a result of directly activating the A α fibers leading to the superior and recurrent laryngeal branches. The peaks present in (Figure 6B) with 10 ms or longer latency are the result of EMG which was confirmed in additional experiments by performing a vagotomy. ECAP measurement of the vagal nerve can provide a direct indication of the fiber types recruited at therapeutic settings and even provides insight into the neural circuitry.

The realization of technology, both hardware and software, into a fully implantable device that can measure ECAPs along the vagal nerve is underway. A real-time responsive vagus nerve stimulation system has been demonstrated in rats [40]. In this system, the stimulus delivery is controlled on the basis of real-time feedback control from the measured compound action potentials. The system rapidly learns how to most efficiently activate any desired proportion of A β or C fibers over time. The stimulus artifact in this system is managed by the alternate polarity subtraction method, and better signal to noise ratio is achieved by averaging the signal over 1 s.

Modeling compound action potentials

Despite the complexity of the ECAP response and the number of parameters which influence its shape and amplitude measurement, modeling the ECAP could provide a rich source of information about the nerves which are being stimulated [41–43]. Despite the fact that the ECAP represents the responses from a large number of fibers there is sufficient information in the recorded responses and, in particular, how they change with propagation distance, to analyze them with the aim of extracting the single fiber potential and population distributions of fibers within the nerve. The distribution of conduction velocities is proportional to the distribution of fiber diameters and varies from individual to individual. A change in distribution may indicate a change in disease state or could be used to detect conduction block due to nerve compression. The largest diameter fibers exhibit conduction block due to compression before the smaller diameter fibers [44] and this may prove useful for monitoring the long-term safety of implanted cuff electrodes.

The single fiber potential, if measured or estimated, could be compared with computational models of axons and from this provide some information about ion channel conductance in the membranes of the responding axons. The study of peripheral nerve compound muscle action potentials and sensory nerve action potentials has lead the development of the concept of Node-opathys [45], which could be directly assessed with fitting of detailed models to ECAP recordings. The various attempts to model the peripheral nerve ECAP from a peripheral nerve

Figure 6. Recordings of the electrically evoked compound action potential from the left vagal nerve of the sheep. Two vagal nerve cuff electrodes (Cyberonics Model 302) were placed around the vagal nerve. A hook electrode on the vagal nerve was used as the ground (GND) and a needle electrode was inserted into muscle in the neck and used as a reference (REF) electrode.

rely on different simplifying assumptions, for instance that the form of the single fiber potential is consistent across the entire population or that the biological tissue can be considered a homogeneous conductor. The conduction velocity distributions of the sural nerve of the human have been estimated from ECAPs [46] and modeling.

Conclusion & future perspective

Compound action potential measurement of the auditory nerve in the cochlear has been conducted for more than two decades. It began as a research tool aimed at exploring the fundamentals of hearing and is today embedded in every commercially available cochlear implant. ECAPs are regarded as an essential clinical tool for cochlear implantation [47]. It is used for:

- Objective verification of auditory nerve function in response to electrical stimulation;
- Objective verification of device function;
- Assistance in programming the speech processor for individuals who cannot provide reliable behavioral responses;
- Verification or confirmation of the accuracy of questionable behavioral responses.

Neurostimulation offers the potential to control or modulate almost any organ or tissue in the body. In practice, establishing control is difficult because of the variability between patients and the variability in neural recruitment which occurs with fixed stimulation parameters. The variability is the result of constant change of the separation between electrode contact and target neurons and changes in electrophysiological response of the nerve. The response is unpredictable and so the relationship between a given dose of stimulus, neural recruitment and ultimately therapeutic effect is difficult to establish. This may be central to the very wide range of stimulation parameters which are employed [48]. There are changes which occur over time and this further complicates the relationship. Significant impedance changes occur postoperatively for implanted electrodes [49] and this has motivated the development of steroid-eluting leads to prevent this [50].

A biomarker for therapy within the ECAP response has been defined for deep brain stimulation for Parkinson's disease [51,52], but similar biomarkers remain to be discovered for the many conditions which are treated with neurostimulation. The degree of nerve activation as measured by ECAPs can be beneficially exploited to improve bioelectronics therapies [53].

Our own work has centered on the use of compound action potentials during spinal cord stimulation for pain relief, and we have developed techniques for closed-loop control of stimulation based on the compound action potential. For spinal cord stimulation (SCS), the clinical efficacy of ECAP-based feedback in small-scale clinical studies has been remarkable [54]. These early promising results compel the exploration of ECAP measurements in peripheral nerve stimulation applications. The ECAP provides a direct measure of the properties of the fibers which are being recruited and enables selection and control of stimulation parameters. ECAP measurement technology is ubiquitous in cochlear implants and will become so in bioelectric medicine applications in peripheral nerves and more broadly.

A multichannel recording system was used to stimulate and record. The current source was configured to produce biphasic, bipolar stimulation at a pulse width of 40 μ s and a frequency of 15 Hz. The upper surface plot displays the evolution of the orthodromic response measured 2.5 cm from the stimulating electrode with increasing current stimulus current. No artifact subtraction technique has been employed. The surface plot is color coded (blue-positive and red-negative voltages) and the fibers are classified according from their latency. The current threshold at which each peak occurs is clearly visible. The data from the same recording electrode presented at single stimulus amplitude are shown in panel B measured from two cuff electrodes which are positioned 5 mm from each other.

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