Recruitment and Comfort of BION Implanted Electrical Stimulation: Implications for FES Applications

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***Abstract*—Restoration of motor function to paralyzed limbs by functional electrical stimulation (FES) has been hampered by the lack of precise and gradual control over muscle recruitment. A suitable interface should provide selective stimulation of individual muscles with graded recruitment of force. The BION was developed to enable neuromuscular stimulation through a miniature, self-contained implant designed to be injected in or near muscles and peripheral nerves. In this study, recruitment properties and comfort of the BION implanted electrical stimulation were systematically evaluated in subjects who participated in a clinical trial. Recruitment properties were qualitatively similar to other methods of implanted neuromuscular stimulation: thresholds and steepness of recruitment were negatively correlated and depended on stimulus charge (product of pulse current and duration). Perceived comfort was not affected by the choice of stimulus parameters, thus their choice can be based purely on technical considerations such as efficiency or resolution of recruitment.**

***Index Terms*—BION, comfort, electrical stimulation, functional electrical stimulation (FES), muscle.**

I. Introduction

THE goal of functional electrical stimulation (FES) is to restore movement in paralyzed limbs by replacing voluntary activation of muscles with electrical stimulation of their motor axons. Achieving precise control of muscle recruitment is a requirement that has been difficult to meet. In theory, intramuscular electrodes should offer advantages over transcutaneous stimulation, but actual performance depends on factors specific to the design, placement and mechanical stability of those electrodes.

The BION is one technology that enables neuromuscular stimulation through a miniature, self-contained implant designed to be injected in or near muscles and peripheral nerves. Each BION receives power and commands from a telemetry link and delivers current pulses of the requested duration and amplitude via electrodes that are mechanically fixed on either end of its elongated capsule (2 mm diameter × 16 mm long) [1]. Patients who have experienced stroke or who have arthritis and are waiting for a total knee replacement have been implanted with BIONs in several research centers with the intent of strengthening muscles, improving functionality of the joints and reducing pain [2], [3].

The percentage of muscle recruitment can be estimated from the amplitude or area-under-the-curve of the *M*-wave, the myoelectric signature generated by the combined action currents of all activated muscle fibers following each stimulus pulse. Typically, one stimulus parameter, either pulse duration or current is fixed while the other is increased from threshold for the smallest detectable *M*-wave to saturation when no additional recruitment is possible. For intermediate values of both parameters, recruitment tends to be linearly related to stimulus charge, the product of current times duration. The actual relationship depends on several factors.

1) *Effect of the stimulus pulse duration*: For the case of current pulses, the charge at threshold is a monotonically rising function of the pulse duration [4]; therefore, more charge needs to be delivered for the same amount of activation as the pulse duration increases.
2) *Different stimulation threshold for different motor axons*: larger axons that innervate larger numbers of mostly fast fatigable muscle fibers have a lower threshold than smaller axons innervating smaller numbers of fatigue resistant muscle fibers. Because the amplitude of the *M*-wave is related to the number of activated muscle fibers, stimulation of only a single or a few large motor axons may give rise to an *M*-wave of substantial amplitude. Thus, if all other factors are the same, the growth of the *M*-wave should be steeper at the beginning than the end of the curve. This should be particularly expected when the BION is implanted very close to a main nerve trunk, where all of the motor axons are at a similar distance from the stimulating electrode.
3) *Distance of the motor axons from the current source*: When motor nerves enter a muscle, they split into successively finer nerve branches that innervate different compartments of the muscle. The motor endplate region (MER) of a muscle, which is typically a target location for BION implants, covers an extensive area, and the spatial distribution of the nerve branches in the MER is quite complex [5]. The precision with which the BION implants can be placed at a desired location is limited by the current

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implantation technique [1], so the BION implanted in the MER will likely lie close to some of these branches and be further from others. Because tissue acts as a volume conductor, the electrical field strength of a current applied by an electrode decreases rapidly as it spreads throughout the muscle. Thus, small axons lying close to the BION are likely to be recruited at lower stimulus strength than larger axons that course at a greater distance; this will depend on the specific distances between the BION and the axons and on the axon diameters. This is believed to underlie the shallow, often step-wise recruitment pattern seen with intramuscular stimulation [6], [7].

4) *Branching patterns of axons*: The MER is not the only possible location of the BION implant. At other intramuscular sites the fine, distal branches of the motor axons would tend to be recruited first [1], [2]. As the axons start to divide upon entering a muscle, their diameter progressively decreases. Because the large axons innervate more muscle fibers, they need to divide more often, which means that the diameters of the branches of large motor axons become similar in size to those of smaller motor axons as they approach their target muscle fibers. Therefore, for BIONs implanted intramuscularly stimulation in the vicinity of the terminal axonal branches might recruit equally the small, fatigue resistant motor units and the large, fatigable motor units [8]. This means that the recruitment pattern will be closer to linear in this case. How much of the muscle could be activated in this way depends on how many of the muscle units have at least one axonal branch within range of the stimulating electrode.

Another issue that has an important implication for FES applications is comfort of stimulation. With surface electrical stimulation, many cutaneous sensory nerve fibers are unavoidably activated along with the targeted motor fibers, which typically lie deeper in the body. Therefore, superficial electrical stimulation is almost always accompanied with various cutaneous sensations, whose quality and intensity depend on the choice of stimulus parameters, and may range from slight tingling to annoying discomfort and even pain. Stimulus parameters deemed most comfortable have been evaluated through a variety of means and guidelines have been provided to optimize comfort for surface neuromuscular stimulation protocols [9], [10]. The parameter of greatest importance appeared to be pulse duration: at the levels of contraction commonly used in clinical practice (20%–30% of maximal contraction strength or 3+/5 manual muscle grade), the midrange of pulse durations, between 200 and 400 ms was found to be most comfortable [9]. Because the BION microstimulator is typically implanted in the vicinity of the motor entry point of a muscle, the cutaneous sensory fibers are circumvented and only the sensory fibers within the nerve innervating the muscle might be activated by the stimulation along with the motor fibers. However, muscle nerves contain a wide variety of sensory fibers, including large diameter, myelinated proprioceptors such as spindle and Golgi tendon organ afferents and smaller diameter myelinated and unmyelinated axons serving transducers for vibration, temperature, pain, pH, and oxygen saturation [11]–[13]. The threshold for excitation of these fibers via intramuscular stimulation depends on their proximity to the stimulation electrodes, their axon diameter, and myelination, and the duration and waveform of the stimulus pulse [14]. It is unclear which of these afferents might activated by intramuscular stimulation and what sensation they would evoke. The picture is additionally complicated by the fact that many of the patients who might benefit from FES will have some degree of somatosensory loss.

The objectives of the present study were as follows.

1) To study systematically the relationship between the percentage of a muscle recruited by electrical stimulation and the full range of pulse parameters.
2) To determine preferred stimulus parameters that allow for graded muscle activation while keeping the design and the control of the stimulator as simple as possible.
3) To determine whether stimulus pulses with widely different durations that produce equivalent muscle recruitment result in different subjective sensations.

II. Methods

A. Subjects

Eight poststroke subjects who had been implanted with BIONs as a part of other studies [2] participated in this study. Six subjects had implants in the forearm (to stimulate wrist and finger extensor muscles to treat flexor contractures), located near the posterior interosseus membrane (PI) or radial nerve near the elbow (RN). One of these subjects had two forearm implants: one at the posterior interosseus membrane and another at the radial nerve. Two subjects had implants in their middle deltoid (MD) muscle to treat shoulder subluxation. Due to the limitations of the implantation technique that has been used so far (the details of which are described in [2]), the position of the BION in relation to the MER or the target nerve trunks can only be estimated based on the stimulus strength that elicits a minimal contraction, as presented in Section III. The patients were 3–10 years poststroke and had been using their implanted BIONs for at least one year of regular, scheduled stimulation. Information about the subjects, their test sites and clinical status is provided in Table I.

Sensory perception of the subjects was assessed through the two-point discrimination and joint angle perception test. Both tests belong to the standard neurological armamentarium: the first assesses the perception from the superficial touch receptors in the skin whereas the second is used to test the deep proprioception [15]. Sense of joint perception was tested in shoulder, elbow and wrist, regardless of implant site. Three subjects had normal results on both tests, three had preserved proprioception but lacked cutaneous sensation, whereas two showed loss of both proprioception and superficial sensory perception. Therefore, the subjects were divided into two groups: Group 1-6 patients (seven BIONs) with at least preserved proprioception, and Group 2-2 patients with complete sensory loss.

B. Implants

Two of the subjects had BION1-2 implants, while the remaining five (one of them having two implants) had BION1 implants. They differ in the resolution of the pulse parameters that can be produced, as shown in Table II.

TABLE I
SUBJECTS WHO PARTICIPATED IN THE STUDY

Subject number	Age (years)	Sex	Implantation site tested	Time after stroke (years)	Time since implant (months)	Sensory status
3009	66	F	shoulder (MD)	8	23	intact
4001	38	M	forearm (PI and RN)	4.5	26	intact
4012	44	F	forearm (PI)	5.5	24	intact
3006	57	M	shoulder (MD)	4.5	20	joint position sense
4003	61	M	forearm (PI)	4.5	25	joint position sense
4009	74	M	forearm (PI)	3.5	13.5	joint position sense
4002	60	F	forearm (PI)	10.5	28	complete loss
4007	51	M	forearm (PI)	3	18	complete loss

TABLE II
DIFFERENCES BETWEEN THE TWO GENERATIONS OF THE BION

Stimulator type	Pulse duration	Current amplitude
BION 1	2 – 512us in steps of 2us	0-30mA in two ranges: 0 - 3mA in steps of 0.2mA, 4 – 30mA in steps of 2mA
BION 1-2	8-512us in steps of 8us	0-31.5mA, in steps of 0.5mA

We did not expect these differences to interfere with the aims of our study because the somewhat coarser pulse duration of the BION1-2 as compared to the BION1 can be compensated by a finer current amplitude resolution of the former. Therefore, wide enough ranges of both stimulus current and pulse duration can be chosen for both implant types to characterize completely the recruitment for various stimulus strengths. In the second experiment, where we tested the differences in the perceived comfort for predetermined pulse durations, values of 48, 104, 304, and 504 μs were used for BION1-2 implants as the closest available match to the values of 50, 100, 300, and 500 μs but all results are reported as 50, 100, 300, and 500 μs without stressing whether they come from a BION1 or 1-2.

C. EMG Recording

EMG was recorded with surface electrodes in a bipolar configuration with a built-in preamplifier stage (B&L Engineering A3729). The electrodes were 1 cm in diameter, 2 cm apart from each other, positioned in parallel with the presumed muscle fiber orientation. The gain of the preamplifier stage was 330, with bandwidth 12–3000 Hz, followed by custom-made amplifier circuitry with a gain of 5 and bandwidth of 12–3000 Hz, so that the overall gain was approximately 1650. The processed EMG signal was digitized at 6000 samples/s. Following the digitization, EMG was filtered with a fourth-order Butterworth low-pass filter with cutoff frequency of 1000 Hz, and with a sharp notch at 60 Hz. The low-pass filtering was required to completely remove pickup from the 480-kHz telemetry coil used to power and control the BION implants.

The electrodes were placed over the belly of the target muscle: extensor carpi radialis for the forearm implants, or the middle deltoid for the shoulder implants, using standard skin preparation (cleaning the skin with ethanol, followed by mild abrasion with sandpaper to reduce the electrode-skin impedance). Data acquisition was triggered every time a stimulation pulse was delivered, and 30 ms of EMG following the stimulation pulse was recorded. Area under the elicited *M*-waves was calculated to quantify the recruitment for various stimulus parameters. The beginning and the end of *M*-waves were determined at the beginning of the experiment visually by a certified electromyographer, and the time window for *M*-wave area calculation was then fixed for the rest of the experiment on that subject. In order to compensate for the fact that the various BIONs had widely different thresholds and maximal recruitment values for stimulus strength, muscle recruitment (R) for each of the subjects was expressed as a ratio (percentage) of the maximal recruitment in each patient, according to the following formula:

$$R(i) = \frac{A(i) - N}{A_{\max} - N} \tag{1}$$

where i indexes the parameter varied (pulse duration or current), $A(i)$ is an absolute value of the area under the *M*-wave, $A_{\max}$—absolute value of the area for the maximal recruitment (the value at which EMG response plateaus), and N is an average value of areas calculated in the same window for recordings containing no *M*-waves (subthreshold stimuli), therefore reflecting the average amount of noise in the recordings.

D. Study Protocol

The study included two experiments that were conducted on subjects during the same visit. There was a break of about 10

min between the experiments to minimize muscle fatigue but the electrodes were not repositioned. If a subject had more than one BION tested, the implants were tested on separate visits.

Experiment 1. Mapping the EMG Responses for a Wide Range of Stimulus Currents and Pulse Durations: The subject was comfortably seated in an armchair with their impaired arm lying freely on a supportive horizontal surface. The angle between the upper and lower arm was approximately 135°. The arm was not fixed, and the contractions were not isometric; the experiment was designed to replicate the configuration these subjects used at home for their rehabilitative treatment. The stimulation coil was positioned over the implant, and the communication between the coil and the implant was confirmed by delivering a few pulses at 1 pps, with stimulus parameters similar to those used in therapy. Recruitment curves at six different pulse durations (50, 100, 200, 300, 400, and 500 μs) were recorded to establish the range of pulse parameters from threshold to saturation to be studied in detail. Frequency of stimulation was 1 pps, while current swept through the whole available range for a given BION type. A computer algorithm then generated a set of pairs of stimulus parameters (current amplitude and pulse duration) so that the stimulus strength lay between 0.8 times charge at threshold and 1.3 times charge at the point of saturation. The number of generated pairs depended on the values for charge at threshold and saturation, and varied from one subject to another, but was limited to a maximum of 1200 stimulus pulses to minimize fatigue. The computer then delivered the generated sequence in a random order at the frequency of 2 pps, and the *M*-waves elicited by the stimulation were acquired and quantified as described above. Total duration of this part of the experiment was about 20 min (not more than 10 min for the recruitment curves, and exactly 10 min for the stimulation with the computer-generated sequence).

Area under the *M*-waves elicited by the stimuli of various pulse duration and amplitude were calculated and used to construct 3-D surface and contour plots of muscle recruitment (expressed as percentage of the maximal recruitment) versus pulse duration and amplitude. From these data, strength-duration curves were constructed by plotting a current at the threshold for stimulation for each pulse duration. The strength-duration curves were used for sanity check, as we wanted to see how the chronaxies determined by our methodology compare with the values established in the literature. Chronaxies were determined from these curves in the following way (Fig. 1): the threshold current for the longest pulse duration where the curve flattens would be considered a rheobase current, and the pulse duration at which the threshold current was twice the rheobase was a chronaxie. In case there were several pulse durations with the same threshold current (which was due to dealing with discrete values of both parameters), the shortest duration was considered the chronaxie. The limitations of the output of the BION stimulator in terms of both the range and resolution of either the pulse duration or pulse current decrease the accuracy of our estimates of the rheobase and chronaxie, allowing only for qualitative comparisons. The average value for chronaxie was 117.6 μs (SD $= 3.28$ μs, $N = 8$), which is consistent with the time constant of myelinated motor axons reported in the literature [16].

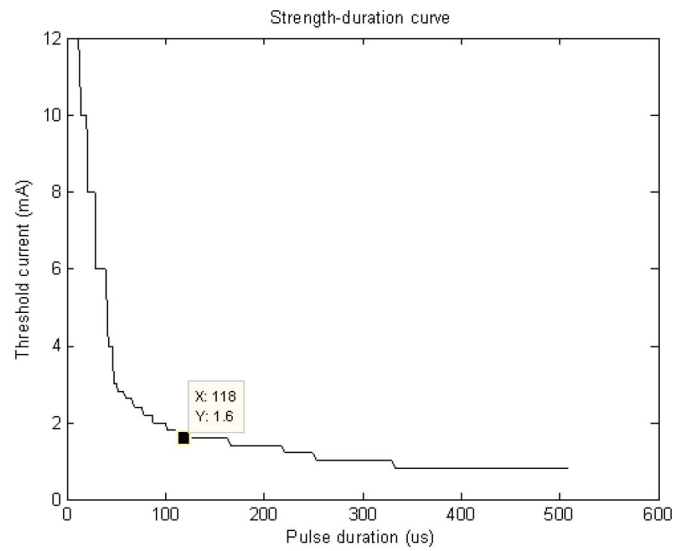

Fig. 1. Strength-duration curve for one of the subjects. *X* value in the box is a chronaxie (in microseconds), while the rheobase current can be arrived at by dividing *Y* value by two.

Recruitment curves were extracted from these data for a variety of pulse durations or amplitudes, by fixing either pulse duration, or pulse amplitude and plotting the percentage of recruitment against the other parameter. In order to compensate for the fact that different steps for pulse duration and amplitude had been used in different subjects, the empirical curves were fit to a sigmoid function using the modified equation from [17]

$$y = \frac{1}{1 + \exp\left(\frac{-(x - x_0)}{b}\right)} \tag{2}$$

where y goes from 0 to 1 (0–100% of recruitment), b defines a steepness of the curve, and the current or pulse duration required to reach 50% of recruitment is given by x_0. In order to compare different ways of modulating stimulus parameters, the width of the recruitment curves W (as a measure of steepness), and the linearity ratio were calculated from these fits as in [17] and [18]. W was the difference in logarithms of one of the stimulus parameters (while the other was fixed) between points with 10% and 90% of maximum recruitment, calculated as

$$W = \log_{10} P_{90} - \log_{10} P_{10} \tag{3}$$

where P_{10} and P_{90} stand for the values of the parameter varied that correspond to 10 and 90% of recruitment respectively. The linearity ratio was defined as

$$LR = \frac{\Delta R_{\min}}{\Delta R_{\max}} \tag{4}$$

where $\Delta R_{\max/\min}$ correspond to the minimum/maximum change in the recruitment per step of a parameter (either pulse duration or pulse amplitude) for the part of the slope between 10% and 90% of recruitment. Therefore, $LR = 1$ means a straight line, while $LR < 1$ for any changes in the slope that might occur. The step for pulse duration was set to 8 μs,

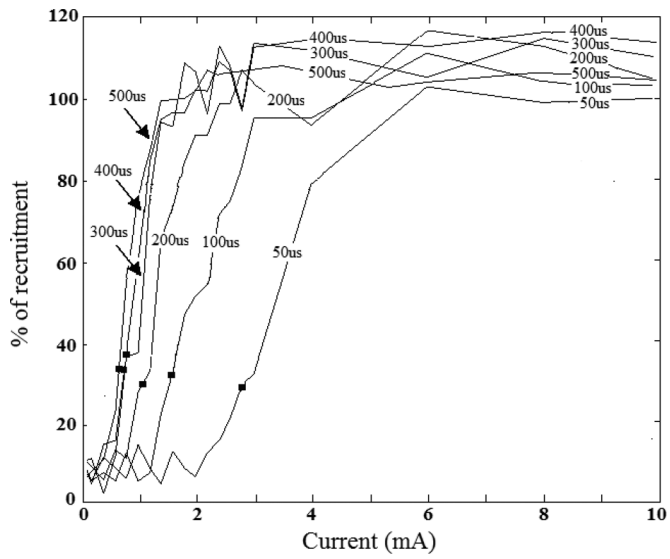

Fig. 2. Recruitment curves for one of the subjects. Squares mark the parameters chosen for Experiment 2.

and for pulse amplitude to 0.5 mA in these calculations, as implemented in the BION1-2.

Experiment 2. Comfort of Stimulation at Different Pulse Durations: Following a 10 min break after the first experiment, the recruitment curves registered in Experiment 1 were used to determine the stimuli that elicited *M*-waves between 25% and 35% of the maximal activation—one for each of the pulse durations (Fig. 2). This level of muscle activation is typically used in therapy regimens for strengthening and reeducating muscles after stroke, spinal cord injury and traumas or operative procedures on joints and ligaments [18]. The computer generated a sequence containing 10 of each of the chosen stimuli for durations 100, 200, 300, and 400 μs, and 15 of the stimuli chosen at 50 and 500 μs; the sequence would therefore contain 70 stimuli. There were intentionally more stimuli at the shortest and longest pulse durations because subjects in surface stimulation experiments were able to distinguish between very short and very long pulses, but not between pulses in the range 200–400 μs [9]. The order of the stimuli in the sequence was randomized by the computer so that the subjects were not aware of which pulse duration they were receiving.

The subjects were presented with 6 s trains of stimulation for each of the 70 stimuli in the sequence, with 20 s pause between trains. Frequency of stimulation was 25 pps. The parameters were chosen that mimic those used in therapeutic applications of the BION [2], [3]. EMG was recorded to control for the consistency of muscle electrical activation during the stimulation. In order to avoid rapidly fatiguing the target muscle, after every 10 trains a break of 3 min was given to the subjects. The overall duration of the whole session was approximately 45 min, with the total time of stimulation being 30 min, about the same as their therapeutic sessions.

After each stimulus train, the subject was asked to mark the level of comfort associated with that train on a visual-analog scale (VAS), which was presented to the subject on a portable computer with a touch-screen. The scale was made a continuous horizontal line of length of 10 cm (defined as 100%), and the

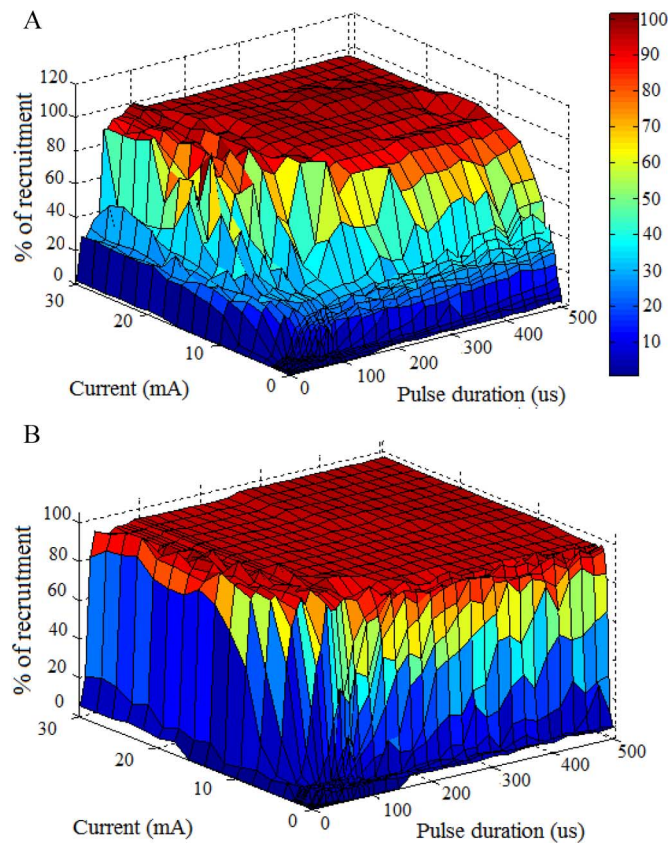

Fig. 3. Surface plots of EMG recruitment of two representative subjects. A: In this subject, the recruitment is much more gradual (albeit not very linear) except for the extreme values of either stimulus current or pulse duration. B: Slope of the recruitment surface of the other subject is very steep.

computer would measure a distance from the left end to where the subject would touch the scale. There were three anchors: the ends were defined as "very uncomfortable" (left) and "very comfortable" (right), while the midpoint was explained to the subjects as "neither good, nor bad." The choice of anchors is crucial for preventing biases when comparing scores between individuals, but neither anchors nor other measurement biases associated with VAS are considered important when making intrapersonal comparisons [20].

Areas under the *M*-waves elicited during the second part of the experiment were analyzed to verify the consistency of activation. If the level of activation varied by more than $+/-5\%$ that train was discarded. In total, 26.6% of all trains needed to be discarded (ranging from 8/70 to 27/70 in various subjects). Within-subject ANOVA was performed on the VAS scores for the accepted trains for all subjects in Group 1, with pulse duration as the independent factor. The level of significance was taken as $p = 0.05$. Subjects with complete sensory loss were not included in the analysis.

III. Results

Experiment 1: Three-dimensional surface plots for two typical subjects are shown on Fig. 3. Four subjects showed a gradual pattern of EMG recruitment at most stimulus strengths excluding those with very high currents, and at very long pulse durations. Recruitment surfaces for the other four subjects

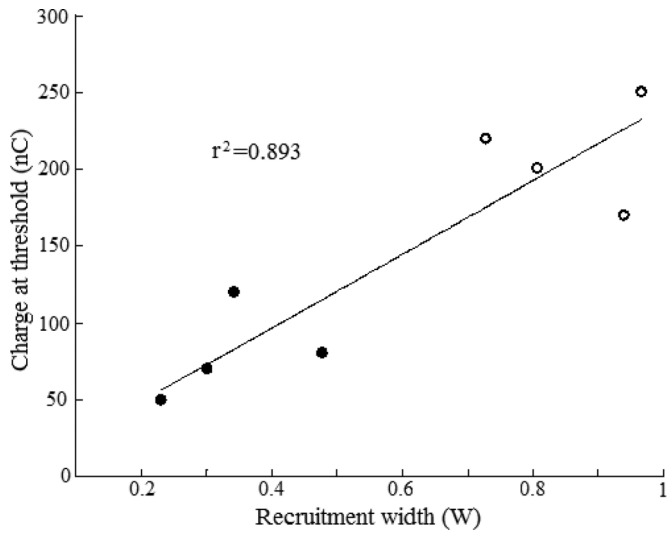

Fig. 4. Scatter plot of charge at threshold versus recruitment width. Plot suggests there are two subgroups of subjects: one with steep recruitment and low thresholds (filled circles) and another with wide shallow recruitment and larger thresholds (empty circles).

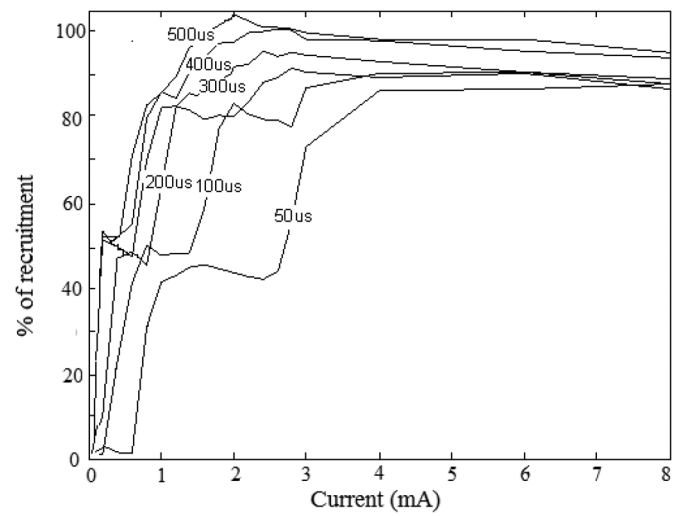

Fig. 5. Recruitment curves of one subject (forearm implant, posterior interosseus nerve) showing steep initial rise, intermediate leveling off and then another steep rise up to the level where the response saturates. This suggests that at least two nerve branches were being stimulated.

(five BIONs) had a very steep transition between the minimal (threshold) and maximal activation in all regions of the pulse duration—pulse amplitude plane.

A plot of the charge at threshold against the recruitment width (Fig. 4) confirmed that the subjects could be divided into two subgroups based on the recruitment pattern. The recruitment width was correlated with the stimulus charge at threshold ($r^2 = 0.893$, see Fig. 4). The stimulation threshold was significantly different between the groups upon t-test ($t = 2.981$, $\mathrm{df} = 6$, $p = 0.0246$): an average charge at threshold was 210 nC ($\mathrm{SD} = 33.6$) in the group with gradual recruitment, while only 100 nC ($\mathrm{SD} = 47.8$) for the subjects with steep recruitment surfaces. The range of stimulus strength also differed between the two recruitment patterns: while the EMG response saturated at the strength that equals approximately 8–10 times threshold (average 9.2) in the group with the gradual recruitment, the saturation was reached at twice the threshold strength for most subjects showing the steep pattern. The subjects with different implant types and locations were almost equally split between the two recruitment patterns, so neither the BION type nor anatomical location seems to be predictive of the recruitment pattern.

Analysis of the recruitment curves also showed that only one subject exhibited a step-wise recruitment with a steep initial rise, an intermediate leveling off and then another steep rise up to the level at which the EMG response saturated (Fig. 5).

Systematic analysis of how the recruitment properties change with either the pulse duration or pulse amplitude was done separately for the two subgroups. Recruitment width decreases as the pulse duration and pulse amplitude increase, this effect being more pronounced for pulse amplitude (Fig. 6). This finding suggested that it might be more beneficial to modulate the pulse amplitude in logarithmic rather than linear steps, exploiting thereby more the lower range of currents, where the recruitment width is favorable. Indeed, the linearity ratio increased when logarithmic steps were used for pulse amplitude instead of linear steps (Fig. 7), albeit moderately. The same effect can be visually assessed in Fig. 8, where the recruitment surfaces of the same subject were replotted with pulse duration plotted on linear, and pulse amplitude on either the linear or the log axis. It can be observed that the S-shaped steep transition region from the left figure transformed into a visually more linear plot after the current was plotted on the log axis.

Experiment 2: The results for subjects whose examination did not reveal complete sensory loss are shown in Fig. 9. In only one subject there was an obvious preference to longer pulse durations ($F = 2.7138$, $p = 0.0293$, $n1 = 5$, $n2 = 54$). The remaining subjects that were intact upon neurological testing showed a similar trend, but it did not prove to be significant statistically. Among the subjects with preserved proprioception only, one showed a weak negative trend, i.e., he seems to have preferred shorter pulses, while the other two perceived no difference. Overall, ANOVA did not show a significant effect of pulse duration ($F = 0.0562$, $p = 0.997$, $n1 = 5$, $n2 = 35$). Both subjects with complete sensory loss did not perceive any significant difference in comfort during the stimulation either. They both graded the stimulation as comfortable (VAS scores 80–90).

IV. Discussion

The goal of FES is to stimulate the paralyzed muscles in as natural a manner as possible. This requires that muscles be activated selectively, and produce graded forces reproducibly and without objectionable sensations. Thus, it would be desirable to obtain shallow, smooth and consistent recruitment curves over a wide range of pulse durations and pulse currents. However, many poorly controllable factors related to neuromuscular anatomy and electrode placement can make these goals difficult to achieve.

The recruitment data shown in Figs. 1 and 2 were qualitatively similar to published data from previous studies on direct nerve stimulation with cuff electrodes [18], [21], intramuscular needle electrodes [8], or epimysial stimulation [22]. It is

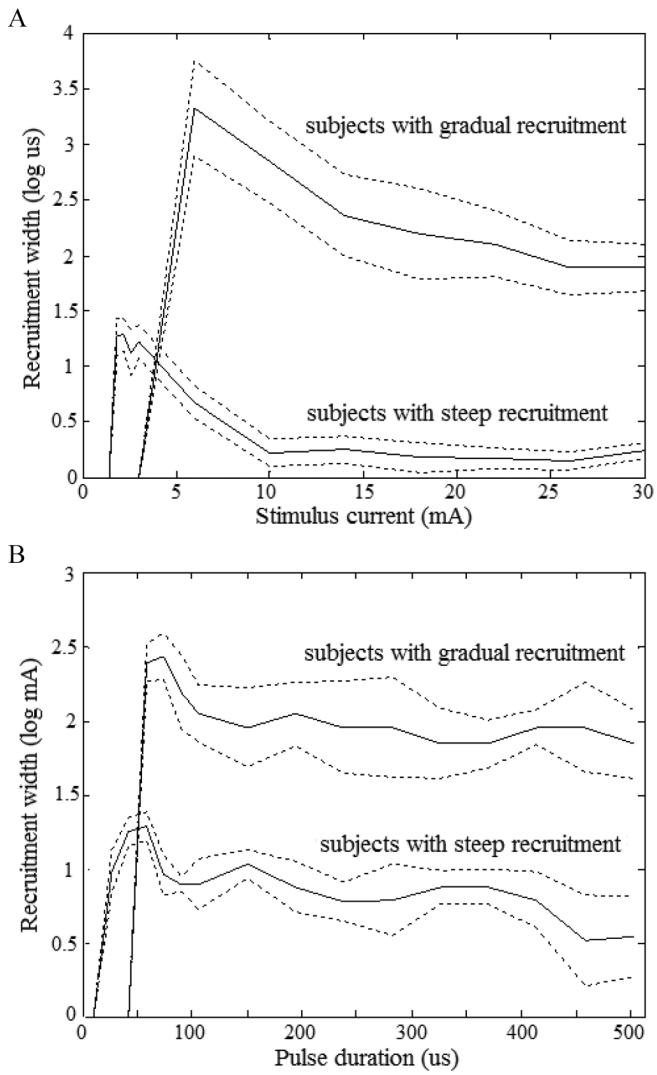

Fig. 6. A: Recruitment width as a function of pulse amplitude. B: Recruitment width as a function of pulse duration. Dotted lines present $+/-1$ SD. Only those values for which 90% of recruitment had been reached were plotted on the horizontal axes; therefore, the curves do not start from zero.

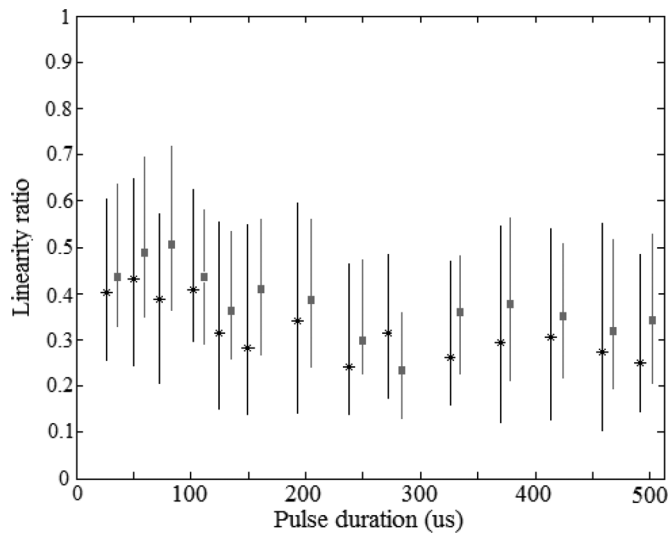

Fig. 7. Linearity ratio (means and ranges) at different pulse duration for linear (black, asterixes) and logarithmic (gray, squares) current steps. For the logarithmic steps current was doubled in each step, starting from 0.5 mA.

well known that the localization of implants bears the most important impact on the selectivity, steepness and linearity of recruitment [8], [14]. In our case, intramuscular implants to the middle deltoid and to the posterior interosseus nerve were expected to benefit from lying closer to some of the intramuscular nerve branches and further from the others; this would result in less steep recruitment, with potentially step-wise appearance of the recruitment curves, having one or more intermediate plateaus before the saturation plateau is reached. On the other hand, the radial nerve implant that lies next to the large nerve containing fibers that innervate eight different muscles in the posterior forearm was expected to show a relatively steep initial recruitment of large motor units, followed by a shallower portion as the smaller motor units were recruited last. Also, the selectivity of activation in this case is likely to be low, and the detected electromyographic response could be expected to have different morphology at different stimulus strengths. Implants tended to divide into two groups with different recruitment widths, and different average charges at threshold. Low thresholds for stimulation and steep recruitment suggest that the implants were sitting close to the target nerve, while higher thresholds together with shallower recruitment seem likely to correspond to BIONs lying further apart from the nerve and perhaps closer to the point where the target nerve branches. However, the recruitment curve in only one case suggested that at least two branches lying at different distances from the BION were stimulated (Fig. 5).

The *M*-wave provides a reasonable estimate of the percentage of muscle fibers that have been activated, but this is only the first step in using neuromuscular electrical stimulation to achieve useful clinical effects. Excitation itself and concomitant calcium fluxes may be the driving factor for therapeutic effects on disuse atrophy [23]. In order to achieve functional reanimation of the limb, many other factors must be considered, including the frequency and history of stimulation and the length and velocity of the muscle fibers. All of these have complex interactions that affect the force produced by individual muscles [24]–[27]. In general, net torque achieved at a specific joint depends, in turn, on the forces contributed by many muscles, active and passive, as well as the moment arms of those muscles at each joint they cross, which may themselves be dependent on posture [28]. Resultant motion of the limb depends further on the mechanical properties and interaction of multiple limb segments plus any externally applied forces and gravity.

Regarding the comfort of stimulation, in all but one subject no differences in the perceived comfort were found when stimulating at similar recruitment levels but widely different pulse durations. For some of our subjects this might follow from the sensory impairment caused by the stroke; one also needs to be cautious when making conclusions on a small set of subjects, some of them having large standard deviations of the VAS scores at many or all pulse durations. It might be useful to repeat the study on subjects without sensory impairments who have been implanted with BIONs, such as knee arthritis patients [3]. However, we believe that the fact that all but one of them did not notice any significant difference in comfort most likely means

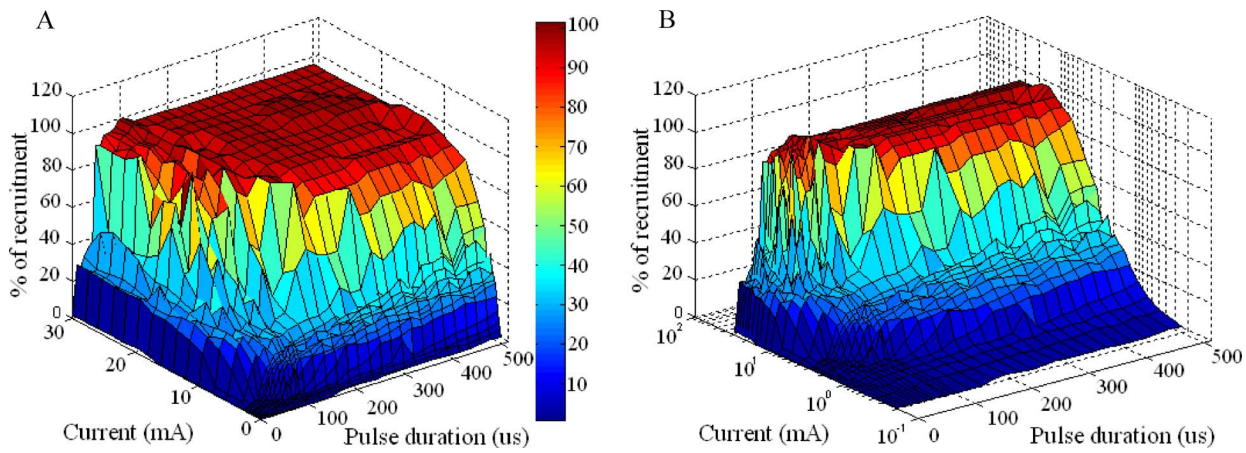

Fig. 8. A: Recruitment surface of one subject, with stimulus current plotted on linear axis. B: Recruitment surface of the same subject on logarithmic axis. Slope of the recruitment looks more linear when the current changes in logarithmic steps.

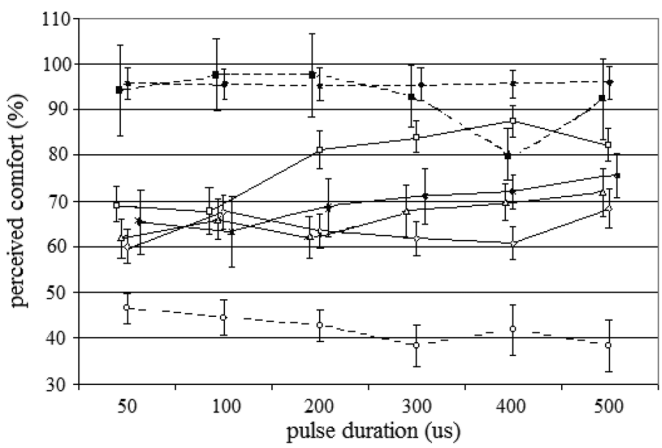

Fig. 9. Perceived comfort at different pulse durations (bars indicate +/- one standard deviation) for subjects who had at least preserved proprioception. Average VAS scores of different subjects for the same pulse duration have been slightly shifted off left or right from each other, in order to avoid overlapping which would make the graph unclear. Full lines indicate subjects (one of them having two BIONs) that had satisfactory cutaneous perception, dashed lines subjects with only proprioception preserved.

that intramuscular stimulation at these levels does not activate a substantial amount of sensory fibers, at least not in pathways involved in pain and/or discomfort perception. Therefore, stimulus parameters can be selected based on technical considerations (e.g., efficiency, resolution) without worrying about perceptual effects.

An important question in design of implantable intramuscular stimulators has been whether it is preferable to modulate pulse amplitude while the pulse duration is fixed [pulse amplitude modulation (PAM)], or to fix the pulse amplitude and modulate the duration [pulse duration modulation (PDM)]. Our results show that for PAM there is only a slight difference between the recruitment widths at different pulse durations in all subjects. In case of PDM the difference in the recruitment width between the low and high currents is more prominent, and moderate current levels (1–10 mA) and pulse durations between 50 and 250 μs should be used. Pulse duration resolution should be as fine as possible (steps of 2 μs, as used in the BION 1 would be recommended), while the current can be changed in coarser steps, preferably logarithmic, in order to improve the linearity of the recruitment. Precise control of pulse duration is also desirable from an electronic perspective because it can be clocked by a digital counter whereas pulse current must be set by analog circuitry. Pulse durations above 300 μs should be avoided, because the efficacy of stimulation drops significantly, and the power consumption would increase without a benefit in recruitment width. This is similar to what McNeal *et al.* found for the nerve cuff electrode [19], albeit the values for stimulus currents were much lower for the nerve cuff electrodes. Theoretically it should be possible to combine pulses from two or more BIONs in order to make the recruitment more gradual and biomimetic by interleaving responses from different subpopulations of motor units. The feasibility of this will depend on the compartmentalization of the neuromuscular architecture [31]. Such a requirement has not been encountered yet in practice because the clinical applications of the BION have concentrated on simple exercise of paretic muscles, where the steepness of recruitment is not of great importance.

Another parameter that can be modulated in clinical application of FES is frequency of stimulation, which also has a significant effect on the strength and smoothness of muscle contractions [25], [26]. Frequency modulation has been used to minimize fatigue while maximizing force [29]. The effects of frequency are more pronounced in fast twitch motor units, which are likely to be first recruited when the electrodes are close to the muscle nerve. In a study with nerve cuff electrodes McNeal *et al.* compared the recruitment curves for single twitches and tetanic contractions, and found that they differed mostly at relatively low stimulus intensities, where the tetanic curves were shifted to the left [19]. Stimulation frequency may well have different effects on the quality of sensation [30]. We did not address this question in our study because we had put it in the context of the current clinical application of the BION technology, in which patients are stimulated with a fixed frequency while the pulse duration or pulse amplitude are modulated in order to achieve the desired level of muscle activation [2], [3].

About one quarter of all collected data were disarded because of significant intrasubject variability of the elicited levels of muscle activation. Most of the variability could be attributed

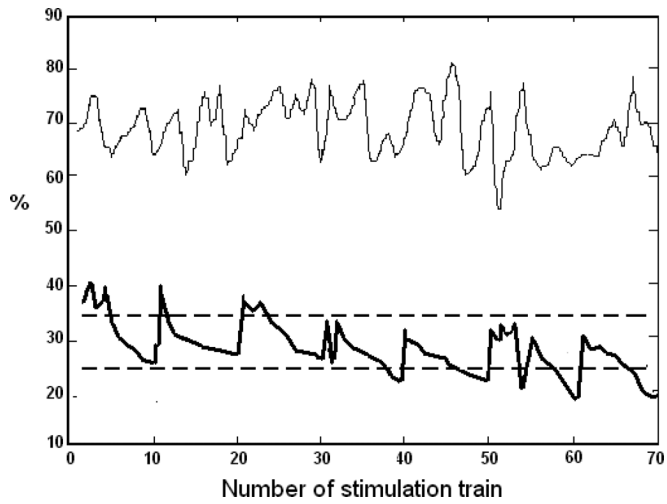

Fig. 10. Muscle activation level (thick curve) and perceived comfort of stimulation (thin curve) of a typical subject as a function of time (expressed here as the chronological number of the stimulation train). Activation level decreased gradually with time as the fatigue developed but increased after every 3 min break (given after every 10 trains). Dashed lines mark 25% and 35% percent of maximum recruitment, and the trains out of this range were not used in the data analysis. Variability of the perceived comfort appeared to be unrelated to the fatigue.

to muscle fatigue that developed to a various extent in all our subjects in spite of our attempts to minimize it by giving frequent breaks during the stimulation. This resulted in a gradual decrease of the *M*-waves as the stimulation progressed, followed by an incomplete recovery after each break (Fig. 10). This pattern is consistent with findings of Singh *et al.* [8], who reported a gradual decrease in muscle force during intramuscular stimulation of the cat medial gastrocnemius, which would stabilize after approximately 5 min. The fact that the fatigue in our subjects seems to have developed somewhat faster than in the cited study could be explained by the differences in fiber compositions of feline hindlimb and human shoulder and forearm muscles, and by the well-known fact that affected muscles in stroke survivors undergo disuse atrophy and become more prone to fatigue.

One limitation of our study is that the position of the joints during the stimulation was not being controlled. We did so intentionally because our goal was to replicate the existing clinical applications of the BION, particularly when BION implants are used to activate finger extensors in order to prevent contractures from developing. However, as we observed, the stimulation of forearm muscles resulted in wrist movements only at the beginning of each train of stimuli, the posture then being stable until the stimulation ceased. In case of the shoulder stimulation the posture changed minimally, if at all, even at the beginning of the stimulation. In FES applications that intentionally produce large limb movements, it will be important to measure the stability of recruitment as a function of joint and limb posture.

FES applications such as grasping or walking are also likely to require higher levels of activation than those studied here, at least for brief intervals. Anecdotally, patients implanted with BIONs have not reported discomfort during a wide range of stimulus intensities and frequencies explored during the setting of their exercise parameters, but systematic studies under other conditions may eventually be warranted.

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