Neurostimulation Perception Obeys Strength-Duration Curves and is Primarily Driven by Pulse Amplitude

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***Abstract*—Stimulation of peripheral nerves can elicit sensations that are felt on distal or amputated portions of the limb, and thus is a promising technique to provide sensory feedback for prosthetic limbs. Sensory feedback provided in this way can confer a sense of proportionality by modulating the frequency, amplitude, and duration of stimulation pulses, however the relationship between stimulation amplitude and pulse duration has not been characterized. In this study, we demonstrate that neurostimulation perception closely follows strength-duration curve models and are generally constant over the course of up to 24 months, with a median rheobasic current of 113 µA and chronaxie of 193 µs. Monotonicity and concavity of data are also demonstrated to significantly predict the confidence interval size for rheobase and chronaxie estimates. Goodness of fit for the strength-duration curve model was high for data which showed significant monotonicity. Furthermore, modeling the psychometric response of stimulation amplitude and duration modulation revealed that amplitude modulation has just-noticeable difference of 7.7%, less than half that of duration modulation at 18.3%. The results taken together suggest that the strength-duration curve framework describes both nerve excitation and perception threshold relationships, and that neurostimulation pulse amplitude primarily drives discrimination for modulating sensory feedback.**

Keywords*—*neurostimulation, sensory feedback, prosthetics, rheobase, chronaxie, pulse amplitude, pulse width

I. INTRODUCTION

Direct electrical stimulation of the nerves is an increasingly prevalent method of providing sensory feedback for prosthetic arms [1]. Such neurostimulation can elicit sensations that are perceived on the missing limb, which can confer significant benefits to user satisfaction and function in home environments [2]–[5]. Stimulation techniques can vary between applications, although most researchers have agreed upon using charge-balanced, rectangular, cathode-first stimulation with currents up to 250 µA and durations up to 400 µs [6], [7]; even so, stimulation can be varied via several parameters, and the interaction between these stimulation parameters and elicited sensations very much remains a field of active research.

Prior work has determined a just-noticeable difference (JND) for stimulation frequency between at up to 25% [8] and demonstrated that relative pulse duration discriminability is less constant when stimulating at higher frequencies [9]. However, while studies have investigated the relationship between stimulation pulse duration and frequency for both electrocutaneous [10], [11] and direct neurostimulation [12], and the relationship between stimulation current and frequency for direct neurostimulation [13], the relationship between stimulation current and pulse duration has only been investigated for electrocutaneous neurostimulation [14], [15].

The purpose of this study is to evaluate the relationship between the minimum required neurostimulation pulse amplitude and duration at perception thresholds using a strength-duration curve framework for three individuals receiving nerve cuff stimulation with an implanted neuromusculoskeletal prosthesis system [16], [17]. We evaluate goodness of fit for this model and demonstrate the stability of model estimates for up to 24 months. We furthermore investigate the ability to discriminate between stimuli with different pulse amplitudes and durations. We quantify the underlying uncertainty in estimates of intensity as they pertain to these two variables, and demonstrate that intensity perception is more strongly linked to pulse amplitude than to the overall stimulation charge.

II. METHODS

A. Subjects and Ethical Approval

Three individuals (all male) with transhumeral amputations and implanted with a neuromusculoskeletal prosthesis interface [17] participated in this study. The neuromusculoskeletal interface comprises humeral osseointegration, epimysial electrodes for EMG acquisition, and extraneural spiral cuff electrodes for direct nerve stimulation (Integrum AB, Gothenburg, Sweden).

From the onset of the study, time since amputation was 14, 6, and 20 years, and time since neuromusculoskeletal interface implantation was 51, 0, and 0 months, respectively.

The study was approved by the Swedish regional ethical committee in Gothenburg (Dnr: 769-12). All participants provided written informed consent prior to participation in the study.

B. Hardware

Electrical stimulation via extraneural electrodes was delivered by the embedded microcontroller which interfaces with the neuromusculoskeletal prosthesis [18]. Neurostimulation waveforms were generated by an on-board RHS2116 digital electrophysiology stimulator chip (Intan Technologies, USA); stimulation pulses were charge-balanced, rectangular, asymmetric, cathode-first, and current-driven, with a 50µs inter-pulse delay between cathodic and anodic currents [6], [19].

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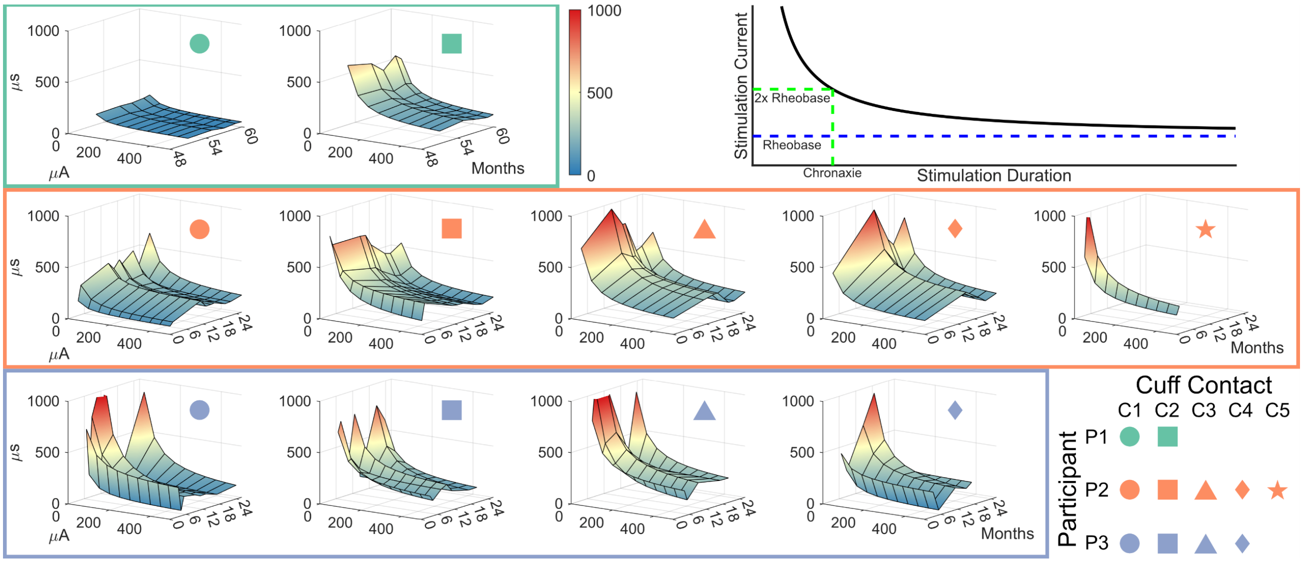

Fig. 1. Strength-Duration curves were fit to data collected during psychophysical detection threshold evaluations for three individuals implanted with spiral nerve cuff electrodes. Strength-duration curves depict the relationship between the stimulation current and stimulation duration required to elicit a perceivable sensation. Inset diagram on the top-right depicts the definitions of the rheobase and chronaxie. Each row of surface plots represents data from one participant, and each column represents a nerve cuff contact which was characterized, as shown in the key on the bottom-right.

Participant 1 (P1) had one extraneural spiral cuff electrode placed around the ulnar nerve (Contact 1 (C1) – Contact 2 (C2)). Participant 2 (P2) had two extraneural spiral cuff electrodes – one placed around the ulnar nerve (C1 – C3) and one placed around the median nerve (C4 – C5). Participant 3 (P3) had two extraneural spiral cuff electrodes – one placed around the median nerve (C1 – C3) and one placed around the ulnar nerve (C4) [17].

C. *Experimental Protocol*

Over the course of up to 24 months, participants completed laboratory assessments related to characterizing neurostimulation perception. Participants sat comfortably with the embedded microcontroller connected to the implanted sensors. An experimenter enabled communication between the microcontroller and a custom MATLAB interface via Bluetooth connection.

Two experimental protocols were conducted, as described in the following sections. During assessments, the experimenter would deliver either one stimulation pulse (*Detection Threshold* protocol) or two short trains of stimulation pulses (*Discrimination Threshold* protocol) via the neuromusculoskeletal prosthesis system before asking the participant about any elicited sensations.

1) Detection Threshold

A 2-up 1-down staircase procedure was used to identify single-pulse neurostimulation detection thresholds, varying pulse amplitude for defined pulse widths and vice versa. Defined pulse amplitudes were 100 µA, 150 µA, 200 µA, 250 µA, and 300 µA; defined pulse widths were 100 µs, 150 µs, 200 µs, 250 µs, and 300 µs. The staircase procedure was conducted until sensations were alternately below and above the detection threshold. Pulse amplitudes were capped at 500 µA, and pulse widths were capped at 500 µs; if no sensation was felt at the maximum intensity, this was noted and the data were omitted from subsequent analysis.

During study visits, participants completed this procedure once for each cuff electrode contact. These datasets form a curve illustrating the relationship between stimulation amplitude and duration at the sensation threshold. This relationship is analogous to strength-duration curves in nerve excitability studies, modeled by Lapicque's equation [20], [21]:

$$I(d) = I_b(1 + \tfrac{c}{d}) \tag{1}$$

I_b is the rheobasic current (the minimum stimulation intensity with long duration to reach excitability threshold) and c is the chronaxie (the characteristic duration for a current of double the rheobase to reach excitability) (**Fig. 1**). Lapicque's equation describes the minimum current $I(d)$ required to reach the excitability threshold for a stimulus duration d.

By describing the strength-duration relationship in (1) in terms of minimum charge $Q(d)$ instead of minimum current $I(d)$, Weiss's equation is derived [22]:

$$Q(d) = I(d)d = I_b(d + c) \tag{2}$$

The linearized form of Weiss's equation is useful for fitting data acquired with rectangular stimulation waveforms, and has been demonstrated to fit models to experimental data more accurately than Lapicque's equation [15].

For each study visit and cuff electrode contact, rheobase and chronaxie were estimated by fitting data to Weiss's equation [23] (**Fig. 1**); datasets with fewer than 4 points were excluded from analysis. Additionally, the monotonicity and concavity of each dataset was characterized using Spearman's ρ to ensure that collected data (monotonicity) and their derivative (concavity) follow the expected trend – higher stimulation amplitude should require shorter stimulation duration to elicit sensation, and vice versa. Pearson's ρ was used to evaluate the strength of correlations between monotonicity or concavity, and rheobase or chronaxie confidence intervals. Datasets which were not significantly monotonic ($p > 0.05$) were also excluded from analysis, as described in Section III (A). Finally, the coefficient of determination (r^2) for each model was saved as a measure of goodness of fit.

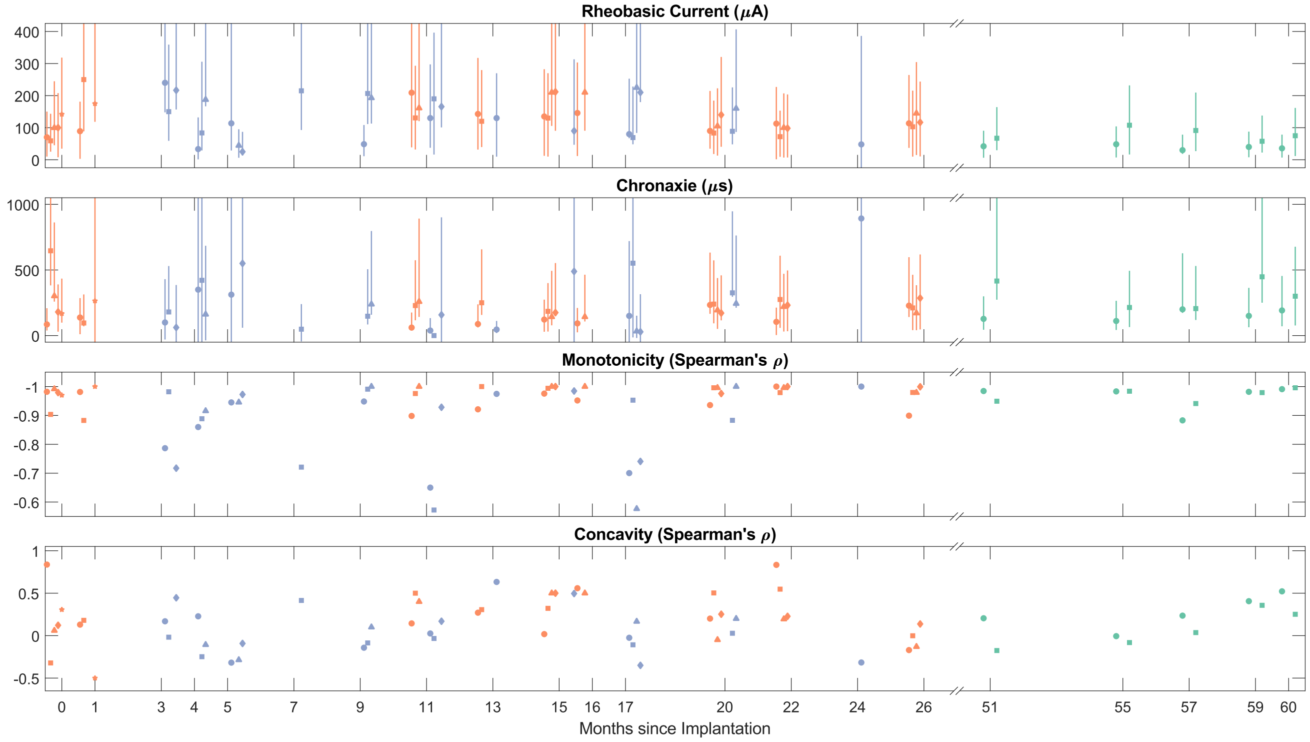

Fig. 2. Estimates for rheobasic current and chronaxie derived from modeled strength-duration curves remain generally consistent over time. Marker colors and symbols represent participants and contact numbers, respectively, as described in **Fig. 1**. 95% confidence intervals for rheobasic current are typically smaller than those for chronaxie. Monotonicity and concavity, as calculated by Spearman's ρ, were found to be a possible indicators of confidence interval spread, though these do not always indicate strong goodness of fit (r^2) of the strength-duration curve.

2) Discrimination Threshold

A 2-alternative forced-choice paradigm was used evaluate the bivariate psychometric function for stimulation amplitude and duration. The paradigm is typically used to characterize JND for perceived intensity, or the minimum required change in stimulus intensity for the perception to feel noticeably different. We were interested in determining if neurostimulation amplitude and duration had the same relative JND, or Weber constant.

A moderate intensity, reliably-perceivable stimulation amplitude and duration were identified based on subject feedback, ensuring equal-magnitude pulse amplitude (µA) and duration (µs) and that parameters 20% below baseline were at least 20% the perception threshold. Once a pair of baseline stimulation parameters was found, new pairs were created with all combinations of modifying stimulation amplitude and duration by -10%, +0%, and +10%. This yielded a total of nine pairs of stimulation parameters.

During the experiment, subjects were given two stimulation trains (at 20 Hz or 30 Hz, depending on subject and contact) for 500 ms each, with an inter-stimulation interval of 1s between pulse trains. One stimulation train used the baseline stimulation parameters, and one used one of the nine possible stimulation pairs; the order in which trains were presented was randomized. After feeling both stimulation trains, subjects were asked to identify which train they perceived as more intense, even if they felt indistinguishable. This was repeated a total of 20 times per stimulation pair.

Participant 1 repeated the entire protocol three times with Contact 1 (ulnar), Participant 2 repeated the protocol two times with Contact 1 (ulnar) and three times with Contact 4 (median), and Participant 3 repeated the protocol two times with Contact 2 (median).

Results from all participants and contacts were pooled and used to fit a two-parameter logistic regression:

$$p(\Delta_I, \Delta_d) = \frac{1}{1+e^{-(\beta_0+\beta_I\Delta_I+\beta_d\Delta_d)}} \tag{3}$$

where $p(\Delta_I, \Delta_d)$ is the probability of identifying a stimulus with a normalized change in stimulation amplitude Δ_I and duration Δ_d as more intense than the baseline stimulus.

From the modeled bivariate psychometric function, the underlying uncertainty of stimulation amplitude and duration perception can also be estimated via the 84% JND [24], [25]:

$$\sigma = \frac{JND_{84\%}}{\sqrt{2}} \tag{4}$$

3) Data Availability

Formatted data and MATLAB 2021b files related to this study are available at the Open Science Framework [26].

III. RESULTS

A. Rheobase and Chronaxie

When considering all data, monotonicity was a strong predictor for confidence interval size for rheobasic current (Pearson's ρ = 0.516, $p < 0.001$) and weakly predicted chronaxie confidence intervals (ρ = 0.200, p = 0.076). Approximately 30% of datasets were rejected on the grounds of insignificant monotonicity ($p > 0.05$) and excluded from further analyses. For remaining datasets, concavity was a strong predictor of both rheobase confidence intervals (ρ = -0.381, p = 0.002) and chronaxie confidence intervals (ρ = -0.313, p = 0.013).

Model estimates for rheobasic current and chronaxie for remaining data are shown in **Fig. 2**. Median and quartiles for rheobase were 113 µA [75 µA, 161 µA], and for chronaxie were 193 µs [127 µs, 275 µs]. Remaining datasets tended to have very high monotonicity (Spearman's ρ, median [quartiles]: -0.978 [-0.916, -0.994]), however notable exceptions were several datasets from P3, where monotonicity reached as low as -0.45. Goodness of fit for included models were generally high (r^2 = 0.887 [0.749 0.974]).

B. Psychometric Response

The bivariate psychometric function relating neurostimulation pulse amplitude and duration to subjective intensity, at a reference stimulation amplitude of 270 µA [150 µA, 300 µA] duration of 270 µs [150 µs, 300 µs], is shown in **Fig. 3**. While stronger sensations were felt by changing either pulse amplitude ($\beta_I = 0.178$, $p < 0.001$) or pulse duration (β_d = 0.075, $p = 0.028$), modulation of pulse amplitude elicited a greater change in perceived intensity than did modulation of pulse duration. This can also be seen in the calculated JND: from baseline, pulse amplitude had a JND of 7.7% and an underlying uncertainty σ_I of 5.5%, while pulse duration had a JND of 18.3% and an underlying uncertainty σ_d of 12.9%. There was no significant interaction between pulse amplitude and duration ($p = 0.717$).

IV. DISCUSSION

This study evaluated the relationship between the minimum neurostimulation pulse amplitude and duration required to elicit sensations at the threshold of perception. Our results are in agreement with prior non-invasive electrocutaneous stimulation studies which suggest that the strength-duration curve framework applies for nerve excitation as well as perception [14], [15]. As might be expected, variability in subjective responses appears to lead to higher variability in rheobase and chronaxie estimates than by using more objective measurements such as action potentials. Of particular note are the data from P3; low monotonicity is suggestive of inconsistent responses for similar conditions, which may be due in part to a high participant lapse rate.

Even for nerve excitation studies, chronaxie estimates are known to have high variability [27]. One possible explanation which becomes more relevant for the higher levels of stimulation used in sensory feedback applications is tissue inhomogeneity; differences in capacitive characteristics in different biological tissues could affect the rate and likelihood at which individual nerve fibers exceed membrane potential and elicit action potentials. In terms of model fitting, variability could also arise due to a parameterized definition of a value which has no direct physiological basis, especially compared to rheobase which can be determined analytically quite easily.

Our investigation on discrimination ability between stimulation pulse amplitude and duration revealed that the perception of intensity is more strongly driven by changes in pulse amplitude than changes in pulse duration. This suggests that discrimination is not drive by delivered charge, but instead is primarily driven by stimulation current. This is in line with prior studies which found that non-rectangular waveforms, with higher peak currents per given charge, had a higher rheobase than rectangular waveforms [14], [23].

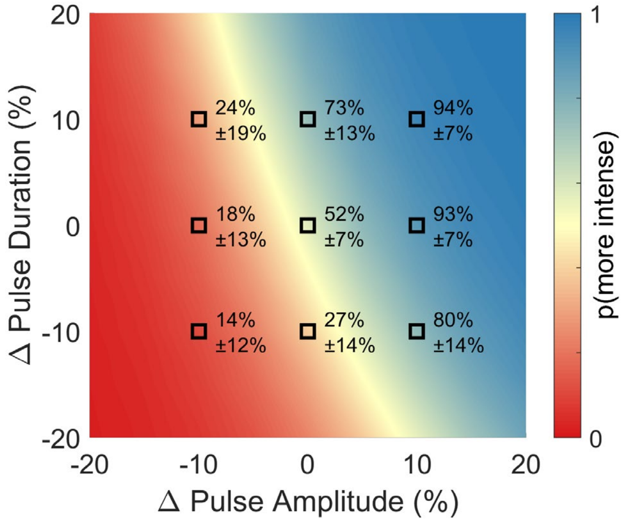

Fig. 3. An increase in neurostimulation amplitude results in a higher probability of identifying a more intense sensation than an increase in stimulation duration of the same relative magnitude. Mean ± standard deviation at the marked points describe the proportion of stimuli (from experimental data) participants judged as more intense than the reference stimulus, for each pair of stimulation parameters. The underlying color plot shows the modeled relationship between changes in stimulation pulse amplitude, pulse duration, and perceived sensation intensity, as described by a two-parameter logistic binomial regression.

The present study estimates that the uncertainty associated with pulse amplitude modulation is less than half of that associated with pulse width modulation. The reference stimulation parameters for these estimates are within typical operational ranges for neurostimulation [6], [7]. Further investigation with other reference stimulation parameters may reveal a different relationship between stimulation pulse amplitude and duration; however, our results should be generally applicable for everyday use and recommend the modulation of neurostimulation pulse amplitude (or the combination of pulse amplitude and pulse width) for the highest degree of discriminability when providing proportional sensory feedback for prosthetic limbs.

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