Perception Threshold Changes in Phosphenes Generated by Direct Stimulation of a Human Optic Nerve

J. Delbeke, S. Parrini, G. Michaux, A. Vanlierde, C. Veraart
Neural Rehabilitation Engineering Laboratory, 54.46, University of Louvain,
Avenue Hippocrate, 54, B-1200 Brussels, Belgium
Email: delbeke@gren.ucl.ac.be

Abstract

This study takes part in the analysis of phosphene perception thresholds as obtained by electrical stimulation through a spiral cuff electrode previously implanted around the right optic nerve of a blind retinitis pigmentosa patient.

The enhanced efficiency of higher frequency or multiple pulse stimulation trains indicate temporal integration. Similarly, spatial summation takes place with increasing intensity. Considering a uniform population of typical axons, a rough model of phosphene perception thresholds can be constructed. Therefore, the strength-duration equation is combined with an S shaped axon recruitment curve. A simplified EPSP integrating synaptic mechanism takes temporal and spatial summation into account.

Despite the crude approximations, a stable and well fitting model is identified, providing expected values against which all experimental values can be compared, showing obvious fluctuations. The observed changes demonstrate a rather negligible long term drop in the average threshold. The implanted cuff electrode thus appears stable in this human application.

Keywords: Optic nerve stimulation, implanted electrode stability, visual prosthesis, perception, recruitment.

1. Introduction

Perception threshold currents for various stimulation parameters have been obtained in the frame of the 'Microsystems based Visual Prosthesis', or 'MiViP' project. The results thus apply to the phosphenes generated by electrical stimulation of the optic nerve in a blind human volunteer [13].

Threshold monitoring allows to keep track of possible changes in the electrode characteristics [12]. However, stimulation patterns used in the context of the implanted cuff electrode are characterised by at least five dimensions (contact selected, current intensity, pulse duration, number of pulses/train and pulse frequency).

In order to be able to summarize experimental data while taking into account all the parameters above, a model was developed on the basis of simple physiologic considerations. It will be presented here along with preliminary results about short and long term threshold changes expressed here as relative differences to the model value.

2. Material and Method

2.1 Data acquisition

This project fully complies with the Declaration of Helsinki, and was approved by the Ethics committee of the School of medicine and University Hospital of the University of Louvain

A blind volunteer with retinitis pigmentosa, has been intracranially implanted with a four contact self-sizing spiral cuff electrode around her right optic nerve. The leads connected to the four contacts leave the skin below the right clavicle.

Stimuli consist in biphasic pulses with a charge recovery duration five times longer than the initial pulse. The two staircase method was used to determine the threshold current. This value is thus defined as the average of the current yielding a first perception in ascending stimulation strength, with the first missing perception in the down going test phase. Stimulation increment sizes were 30%. More than 250 phosphene perception thresholds values have been obtained spread over more than 600 days. For each contact e, the variables considered are the pulse duration (D = [25..400 µs]), the number of pulses per train (N = [1..33]), the pulse frequency (F = [40..1000 Hz]). The threshold current (I = [20..2850]) is the dependant variable.

2.2. The model

As expected from the classical strength-duration relationship, thresholds clearly did follow the predictions of Hill's equation [7]: $Ia = Ir / (1-e^{-D*\ln(2)/C})$. The corresponding characteristic parameters are the rheobase (Ir) and the chronaxy (C). Note that we are dealing here with individual fibre activation thresholds (Ia) while hereafter we shall consider the perception threshold (Ip) which is larger than Ia for most activated axons and equal to Ia for just recruited axon only.

With repeated pulse stimulations, increasing the number of pulses per train or of the pulse frequency obviously yielded lower thresholds. Such a behaviour is clearly reminiscent of the synaptic integration of

EPSP's [3]. Such a behaviour can roughly be mimicked by a simple summation of equal sized decreasing exponential curves representing the EPSP's generated by each axonal discharge (see figure 1). The characteristic values for this behaviour are the time constant (τ) of the exponentials and the perception threshold (P). This last parameter is expressed in terms of the proportion of axons that must be activated simultaneously in order for a single pulse to generate a phosphene. By approximation, it is supposed that each axon discharge results in an equivalent EPSP with fixed delay and independent of the stimulation conditions (I, D, N, F) that have led to the activation.

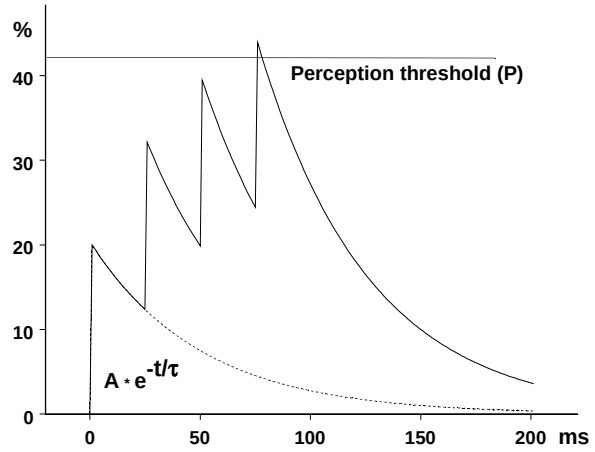

Figure 1

How the frequency and number of EPSP's (represented as simple exponentials) sum up to a fixed perception threshold level.

Another observation on which the model is established is the fact that increasing the stimulation strength can lead to perception presumably trough spatial recruitment [1]. Axons can only provide all or nothing responses to each pulse. When a phosphene is obtained with a high frequency train, reducing the frequency and/or the number of pulses increases the threshold so that all perception disappears while the remaining pulses have not changed and should thus still activate the same axons. If at that point, intensity is increased again, the phosphenes show up again, suggesting that the activity in more fibres compensates for the lower frequency and shorter pulse trains. In order to represent this spatial recruitment, as suggested by the results of modelling studies [11], an arbitrary S shaped recruitment function has been included. This function represents the proportion (R) of fibres of the nerve that are recruited at a given current intensity. This function R takes on a value zero below the rheobase g of the most sensitive axon of the nerve. A second parameter h describes the curve steepness. It is defined as the current required for half the fibre population to be activated by a very long (rheobase) duration pulse. Then,

$$R = (Ir-g) / (h+Ir-2g)$$

Because of the arbitrary character of this function, higher order forms have been put on trial but resulted in poorer fitting to the data than the expression above.

Because only a limited number of measurements results are available, the number of parameters that can be identified is limited as well. Therefore, all the parameters above have been considered equal for each of the four contacts. The differences in the individual contact thresholds is taken into account by a normalized constant Ke.

Combining the above finally yields the full model:

$$Ip = K_e \cdot \frac{g + \frac{P}{\sum_{i=1}^{N} e^{\frac{i-N}{\tau \cdot F}}} \cdot (h - 2 \cdot g)}{(1 - e^{\frac{-D \cdot Ln(2)}{C}}) \cdot (1 - \frac{P}{\sum_{i=1}^{N} e^{\frac{i-N}{\tau \cdot F}}})}$$

3. Results

Minimizing the sum of squares of the relative errors yields a stable and good fit (r^2=0.87) to the experimental data converging to the following parameters values:

Parameter	Value
C	115 µs
τ	39 ms
P	47 %
g	8.6 µA
h	318 µA

Table I

With Ke= 0.636, 0.812, 1.178 and 1.374
for e = 0°, 90°, 180° and 270° respectively.

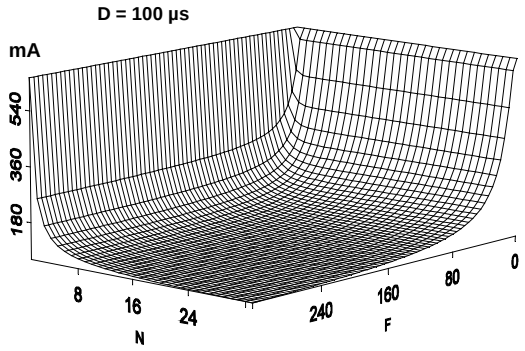

Figure 2

A plot of the model prediction for perception threshold currents. This simulation with 100 µs duration pulses sweeps from single shocks up to 32 pulse trains at frequencies up to 320 Hz.

Figure 2 represents a three dimensional slice for 100 µs pulses in the four dimensional domain considered. This figure clearly summarizes the main threshold findings in this study.

A more informative result however is obtained by comparing on a time abscissa the perception threshold values observed with the model predictions. Figure 3 indeed shows the difference between experimental results and model predictions divided by the model prediction. A regression line has been calculated excluding all values larger than 1 which are considered as outliers. The regression line displays a time dependency of –0.0006/day, which turns out to be significant (F test) at a p level less than 0.001

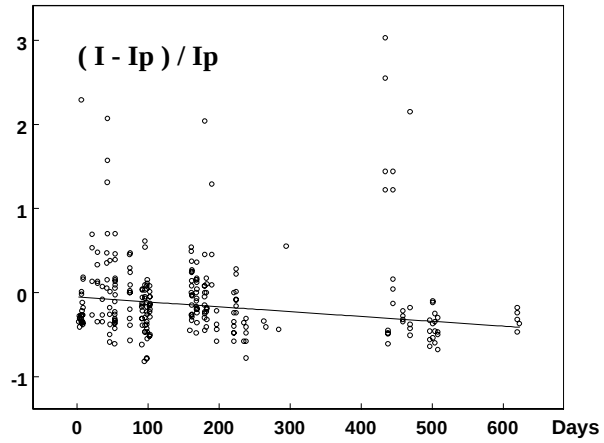

Figure 3

Relative difference between the experimental perception threshold (I) and the corresponding expected value (Ip). The regression line has been drawn after dropping all relative values above 1.

Reviewing the laboratory records did not allow us to find any clear explanation for the few obvious outliers in the perception thresholds above. Their seemingly grouped pattern could be due to the fact that threshold measurements have not been performed at a regular rate in time. A limited number of trials designed to obtain phosphenes at different times of the cardiac cycle did not show any obvious link.

4. Discussion

This discussion should first concentrate on the important assumptions made to obtain this relatively simple model. Only an average single population of typical axons has been considered to be involved in the phosphene perception. This is very rough indeed considering the broad dispersion of axon diameters found in the optic nerve [9].

All optic nerve encoding schemes have been neglected. Inhibitory synapses were ignored altogether. The well known centre to surround on/off contrasts as well as likely selective synaptic weighting and the importance of central arrival times [10] have not been considered.

The temporal recruitment is a common finding in the central nervous system but the important spatial recruitment is a more difficult problem. It cannot be explained by repetitive firing in response to stronger pulses because the longest pulses used (400 µs) would require unrealistic repetitive firing rates of 5kHz or more. The lateral geniculate [4] does not seem to provide an anatomical structure to subtend broad convergence. A cortical explanation should perhaps be considered. On the other hand, the whole complexity of the central nervous system intervening between the optic nerve and perception has been reduced to a single synapse layer.

This study has been carried out in a disease condition which we know is responsible for a significant reduction in the number of axons [8]. If these losses are distributed unevenly they could explain some differences in threshold among contacts. On the other hand, the loss of some specific axons could lead to the selective survival of a more uniform excitable population so that the good fit to the model found here might not apply very well to a healthy nerve.

Finally, no account is given here of the phosphene characteristics neither of their position within the visual field. These matters will be further explored using neuronal networks. The results obtained should thus be considered as very crude and interpreted cautiously. Introducing more complexity in the model however would have resulted in unstable identification because not enough data are available to extract more information.

Despite all the limitations above, this model turns out to work well as a useful instrument to set up stimulation patterns. It also allows to summarize all data obtained in the control of the short and long term stability of the implanted electrode notwithstanding the broad spectrum of stimulus parameters explored. A slow trend towards lower thresholds has been found thus proving very good electrode long term tolerance. The same result is obtained when only a single stimulus setting [12] is considered so that values can be compared directly with each other. In this case however, the statistical significance level reached is of course much less because of the small number of data available. The model also improves insight in the stimulation mechanisms, indicating for example that high frequency trains are required if the fibre activation has to be limited to a small portion of the nerve because a single pulse would have to activate 47% of the fibres in order to reach perception.

We have not been able demonstrate the nature of the source of variation for the perception thresholds. Psychological factors cannot be ruled out but have not been identified. Mechanical factors seem unlikely at the implantation site chosen. Blood flow is the only source of stress present but seems to have at most a limited

influence demonstrable only with a large number of trials. The discrete nature of the stimulus increment do add some variability but this can be shown to be limited to 10 % [2]. Other sources to consider are the possible interference between stimulus generated nerve activity and spontaneous subthreshold ongoing activity. That such unperceived activity is possible can be deduced from the necessary summation shown above. No attention has been paid here to the possible effects of prior activity[5]. Finally, it should be remembered that membrane and synaptic noise are well known phenomena observed directly at several levels of the nervous system [14]. Processing in the central nervous system is of a stochastic nature [6] and therefore, noise must be expected.

5. Conclusion

Phosphene perception thresholds to optic nerve stimulation can be described in terms of a few simple physiological considerations. The resulting model fits fairly well and provides expected values against which experimental results can be compared. After more than two years post implantation, the cuff electrode around the optic nerve of a blind human volunteer has proven to remain stable and even shows a slight improvement in it's efficiency with time.

Support: CEU 'Esprit' grant # 22 527 and FMSR grant # 3.4584.98.

References

[1] Delbeke J, Parrini S, Glineur O, Vanlierde A, Veraart C. (1999) Phosphene perception thresholds to direct stimulation of a human optic nerve shows spatial and temporal summation. *Soc. Neurosci. Abstr*. 25[part 1]: 1043.

[2] Delbeke J, Pins D, Parrini S, Michaux G, Wanet-Defalque M-C, Veraart C. Assessing anterior visual pathways excitability by eyelid surface electrical stimulation. (*in preparation*).

[3] Eccles JC. (1964) *The physiology of synapses*. Springer Verlag, Berlin; Göttingen; Heidelberg.

[4] Freund H-J. (1973) Neuronal mechanisms of the lateral geniculate body. In *Visual centers in the brain* (Jung R., ed), pp. 178-246. Springer-Verlag, Berlin, Heidelberg, New York.

[5] George SA, Mastronarde DN, Dubin MW. (1984) Prior activity influences the velocity of impulses in frog and cat optic nerve fibers. *Brain Res.* 304[1]: 121-126.

[6] Gray CM, McCormick DA. (1996) Chattering cells: superficial pyramidal neurons contributing to the generation of synchronous oscillations in the visual cortex. *Science* 274[5284]: 109-113.

[7] Hill AV. (1936) The strength-duration relation for electric excitation of medullated nerve. *Proceedings of the Royal Society of London, Series B* 119[815]: 440-453.

[8] Humayun MS, Prince M, de Juan E, Barron Y, Moskowitz M, Klock IB, Milam AH. (1999) Morphometric analysis of the extramacular retina from postmortem eyes with retinitis pigmentosa. *Investigative Ophthalmology and Vision Science* 40[1]: 143-148.

[9] Jonas JB, Muller-Bergh JA, Schlotzer S, Naumann GO. Histomorphometry of the human optic nerve. (1990) *Investigative Ophthalmology and Vision Science* 31[4]: 736-744.

[10] Meister M. (1996) Multineuronal codes in retinal signalling. *Proc.Natl.Acad.Sci.U.S.A.*, 93[2]: 609-614.

[11] Parrini S, Delbeke J, Romero E, Legat V, Veraart C. (1999) A hybrid finite elements–spectral method for computation of the electric potential generated by a nerve cuff electrode. *Medical & Biological Engineering & Computing* 37: 733-736.

[12] Veraart C, Delbeke J, Wanet-Defalque M-C, Vanlierde A, Michaux G, Proc IV Intern IFESS Conf, Sendai, Japan, August 1999Trullemans C, Mortimer JT. (1999) Selective stimulation of the human optic nerve, In Proc IV Intern IFESS Conf, Sendai, Japan, August 1999, pp 57-59.

[13] Veraart C, Raftopoulos C, Mortimer JT, Delbeke J, Pins D, Michaux G, Vanlierde A, Parrini S, Wanet-Defalque M-C. (1998) Visual sensations produced by optic nerve stimulation using an implanted self-sizing spiral cuff electrode. *Brain Res.*, 813[1]: 181-186.

[14] White JA, Rubinstein JT, Kay AR. (2000) Channel noise in neurons. *Trends in Neuroscience*, 23[3]: 131-137.