33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Predicting Phosphene Elicitation in Patients with Retinal Implants: A Mathematical Study

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Abstract— **Single pulse waveforms were considered in a recent model for phosphene elicitation in patients with a retinal prosthesis. Waveforms are constrained to charge-balanced stimuli consisting of a single cathodic and anodic pulse pair. Mathematical models of such stimuli have been constructed and presented based upon patient testimonials. In this work, we derive analytic expressions that may be employed to determine equibrightness levels for different waveforms. We provide an example calculation to show quantitative improvements in stimulation efficiency that are consistent with qualitative findings on waveform effects.**

I. INTRODUCTION

To combat retinal degeneration, there has been interest in the development of a retinal implant [1], [2], [3]. Such an implant may be analogous to the cochlear implant, restoring a degree of sight rather than hearing to patients. An important question is how to elicit visual perception from electrical stimulation of the retina, resulting in points of light called "phosphenes". Phosphenes have been described as circular or elliptical patches of light or darkness. An overview of phosphenes and potential visual representations is given in [4].

The effect of stimulation waveform has been considered for cochlear implants [5]. They investigated a variety of waveforms: mono-, bi- and tri-phasic waveforms, the effect of pulse width, chopped pulses, and asymmetric pulses. They show, among other things, that:

1) Cathodic-first stimulation results in lower thresholds than anodic-first for monophasic pulses.
2) Thresholds decrease with increasing pulse width, though efficiency in terms of total charge delivered decreases.
3) Larger interphase gaps result in lower thresholds, up to approximately $80\mu s$. Beyond that point, there is little observed difference.
4) Chopped pulses result in higher thresholds than equivalent, constant counterparts. That is, a single $60\mu s$ pulse followed by its opposite is more efficacious than appropriately charge balanced $2 \times 30\mu$s, $3 \times 20\mu$s, or $6 \times 10\mu$s pulse pairs.
5) Tri-phasic pulses had higher thresholds than bi-phasic equivalents.
6) A longer anodic charge-balancing pulse for a cathodic-first stimulation resulted in a lower threshold than a symmetric pulse.

Although their data is for the auditory nerve, it considers a wide range of stimulation parameters that should be considered for retinal stimulation.

An overview of retinal stimulation techniques has been presented in [6]. They present many concerns of stimulation waveform design, including considerations of tissue safety, material limitations, and efficacious stimulation. They present qualitative results comparing a number of waveforms, including monophasic stimulation, symmetric charge-balanced waveforms, and others.

Recently, a mathematical model for relating the electrical stimulation pattern to the appearance and/or apparent brightness of phosphenes has been formulated [7]. Our aim is to employ the results of [7] to quantify the qualitative results as presented in other studies [5], [6]. Based upon the results of [5], we wish to consider the impact of pulse width, asymmetric charge balance, and interpulse delay for rectangular biphasic pulses. We present a means to evaluate proposed waveform parameters to provide theoretically equivalent perception to the patient. In particular, by modifying interphase delay and recharge rate, the model predicts substantial savings in total charge delivery. This result is consistent with the qualitative results in [5], [6], and with results presented in [8], which showed that including an interphase delay produces stimulation thresholds similar to those of monophasic pulses.

The remainder of the paper is organized as follows. An overview of the model proposed in [7] is given in Section II. This discussion expands on the methods of [7] in an analytic manner. Next, our particular waveform parameterization is discussed in Section III where we parameterize a general charge-balanced waveform. We provide analytic calculations, as well as a numerical example, of waveform comparison in Section IV. Finally, we address some concerns from the model and suggest potential future work in Section V.

II. MODEL

A summary of the model proposed in [7] is given for completeness.

Let $f(t)$ be the stimulation current as a function of time. A diagram showing an example waveform is given in Figure 1. In [7], as well as this study, $f(t)$ is constrained to be

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rectangular, charge-balanced pulse pairs. The model from [7] may be computed as a five step process:

1) **Low-pass filter**: The stimulation is low pass filtered with time constant τ_1,

$$r_1(t) = \int_{-\infty}^{\infty} f(u) \frac{e^{-(t-u)/\tau_1}}{\tau_1} du. \quad (1)$$

2) **Sensitivity adjustment**: The accumulated charge is low pass filtered with time constant τ_2, multiplied by ϵ, and subtracted from the previous step in order to model refractory effects in the retina. Thus,

$$r_2(t) = r_1(t) - \epsilon \left(\int_{-\infty}^{\infty} c(u) \frac{e^{-(t-u)/\tau_2}}{\tau_2} du \right), \quad (2)$$

where $c(t)$ is given by

$$c(t) = \int_0^t f(x) dx \quad (3)$$

and represents the accumulated charge.

3) **Nonlinearity**: The magnitude of the result is raised to the power of a parameter, β. Analytically, this increases complexity, as the function

$$r_3 = |r_2|^\beta \quad (4)$$

would need to be expanded in a binomial series into a number of terms dependent upon β. Although one could express this as a summation of a variable number of terms, we make the simplifying assumption that $\beta = 1$, thereby neglecting this nonlinearity. It is noted that values of β were observed to be closer to unity for suprathreshold experiments than those of threshold determination, so this simplifying assumption is better for equibrightness evaluation than threshold determination. For our single pulse waveforms, with the parameter values from [7], the function $r_2(t)$ is uniformly positive or negative, depending on the sign of a. Hence, within the context of this paper, this step consists solely of taking the absolute value.
If the nonlinearity were included, the procedure could be carried out numerically.

4) **Low-pass filter**: The result is low-pass filtered again, using a different filter function. This is the final calculation in the process, and results in a function given by

$$r(t) = \int_{-\infty}^{\infty} r_2(u) \frac{e^{-(t-u)/\tau_3}}{4\tau_3} \left(\frac{u}{\tau_3} \right)^2 du. \quad (5)$$

5) **Threshold**: The maximum is taken over the time of stimulation, $\theta = \max_t r(t)$, and compared to a threshold, θ^*. If $\theta = \theta^*$, a phosphene is predicted to be perceived by the patient 50% of the time. If a phosphene is perceived by the patient, higher values of θ correspond to brighter phosphenes in a monotonic (though not necessarily linear) manner. The work of [7] indicates that waveforms with the same value of θ would result in phosphenes of the same apparent brightness, based upon patient testimony.

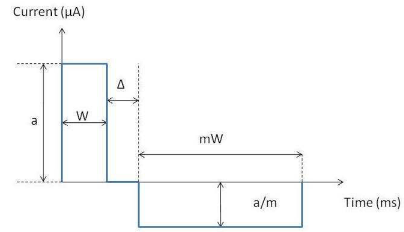

Fig. 1. Example charge balanced waveform, depicting parameters in our formulation.

This model was employed in [7] for charge balanced, biphasic pulses and corresponding pulse trains to predict current thresholds for perception. We employ the model to include additional waveform parameters, including an interphase delay (or a "dead time"), and to account for asymmetric charge balance, in which the inverse pulse has a smaller magnitude over a longer time, resulting in overall charge balance.

III. WAVEFORM

We consider a generalized, single-pulse model of a charge balanced stimulus. The waveform is a combination of types considered in [5], [6], restricted to rectangular pulses that maintain charge balance for safety concerns. We restrict our consideration to biphasic pulses with the possibility of an interphase delay and a slow recharge. We model our stimulation current waveform

$$f(t) = \begin{cases} a, & 0 \le t \le W \\ -a/m, & W + \Delta \le t \le T \\ 0 & \text{otherwise} \end{cases}, \quad (6)$$

where a is the stimulation amplitude, W is the stimulation leading pulse width, Δ is an interphase delay between the stimulation phases, m governs charge balance asymmetry, and $T = (m+1)W + \Delta$ represents the end of stimulation. Cathodic-first stimulation may be simulated by using $a < 0$. The case of a biphasic, symmetric, charge-balanced waveform may be modeled by utilizing $m = 1$ and $\Delta = 0$. Longer reversals are modeled by larger values of m; in the case of $m < 1$, a smaller pulse width is employed at a larger current level than the initial stimulus.

The accumulated charge density, $c(t)$, as given in (3), is then given by

$$c(t) = \begin{cases} at, & t \in [0, W] \\ aW, & t \in (W, W + \Delta] \\ aW - \frac{a}{m}(t - [W + \Delta]), & t \in (W + \Delta, T] \\ 0, & \text{otherwise} \end{cases} \quad (7)$$

which is a trapezoid. Charge balance is achieved in that $c(t) = 0$ for values $t \ge T$.

A. First filter

Following (1), with the stimulation waveform, $f(t)$, as parameterized in (6), the function $r_1(t)$ may be analytically integrated as

$$r_1(t) = ae^{-t/\tau_1} g(\tau_1), \tag{8}$$

where

$$g(\tau) = \left[\frac{m(1 - e^{W/\tau}) - e^{(W+\Delta)/\tau}(1 - e^{mW/\tau})}{m} \right].$$

The function $g(\tau)$ will recur throughout our analysis, and is dependent upon W, Δ, and m, but not a.

B. Second filter

The next stage, sensitivity adjustment, per (2), may again be integrated analytically. Thus,

$$r_2(t) = r_1(t) - \epsilon \left(a\tau_2 e^{-t/\tau_2} g(\tau_2) \right). \tag{9}$$

From the experimental data of [7], the time scales of the two effects of the stimulation, τ_1 and τ_2, are greatly different, as τ_2 is about two orders of magnitude greater than τ_1 for all models investigated (see [7], Supplementary Data 4).

C. Final filter

The resulting function after application of these filters, even excluding the nonlinearity of β, results in a lengthy expression. The integral in (5) may be expressed as

$$\begin{aligned} r(t) \quad = \quad & a \Big[e^{-t/\tau_3} \left\{ [\eta_{t^2,1} g(\tau_1) + \eta_{t^2,2} g(\tau_2)] t^2 \right. \\ & + [\eta_{t,1} g(\tau_1) + \eta_{t,2} g(\tau_2)] t \\ & \left. + [\eta_{3,1} g(\tau_1) + \eta_{3,2} g(\tau_2)] \right\} \\ & + e^{-t/\tau_1} \eta_1 g(\tau_1) + e^{-t/\tau_2} \eta_2 g(\tau_2) \Big], \end{aligned} \tag{10}$$

where the coefficients, η, are independent of t, but depend on other model parameters. In particular, the constants τ_1, τ_2, τ_3 relate to time scales and are taken as constant across stimulation strengths and patient; ϵ varies according to the level of stimulation relative to threshold; and W, m, Δ are chosen based upon desired stimulation waveform. Values of the constants, η, are given in the Appendix.

D. Threshold

For threshold comparison, the value of $r(t)$ depends linearly on the stimulation amplitude, a, neglecting the nonlinear effect. Due to this factoring, including nonlinear effects would depend on a^β if they were included in the model, but the remaining factors would become more complex. Analytic maximization of (10) with respect to t is not practical, as taking the time derivative results in a combination of exponential and polynomial terms. Hence, in Section IV-A, we outline the procedure of finding the maximal value.

IV. RESULTS

From the full model in (10), we outline a procedure to construct stimulation strategies resulting in apparent equibrightness to a patient. To begin, consider a "reference waveform" defined by parameters $a_{\text{ref}}, W_{\text{ref}}, \Delta_{\text{ref}}, m_{\text{ref}}$. From (10), note that a is a constant, and may thereby be factored out of the maximization. Denote the "waveform factor" as $r(t)/a = \xi(t)$, so that $\theta = a \max_t \xi(t)$ (i.e., the waveform factor, $\xi(t)$, is the term in brackets in (10)). For the parameters of our base waveform, plot $\xi_{\text{ref}}(t)$, and denote the maximum value to be Ξ_{ref}. Then, $\theta_{\text{ref}} = a\Xi_{\text{ref}}$. To generate a stimulation that would result in equibrightness, such that $\theta_{\text{ref}} = \theta_{\text{test}}$, select parameters $W_{\text{test}}, m_{\text{test}}, \Delta_{\text{test}}$. Using these new parameters, plot $\xi_{\text{test}}(t)$, and again find the maximum, Ξ_{test}. The required current would then be such that $a_{\text{test}}\Xi_{\text{test}} = a_{\text{ref}}\Xi_{\text{ref}}$. That is,

$$a_{\text{test}} = a_{\text{ref}} \times \left(\frac{\Xi_{\text{ref}}}{\Xi_{\text{test}}} \right). \tag{11}$$

A. Example calculation: interphase delay with slow recharge

Consider a reference waveform with $a_{\text{ref}} = 100\mu\text{A}$, $W_{\text{ref}} = 0.5\text{ms}$, $\Delta_{\text{ref}} = 0$, and $m_{\text{ref}} = 1$. This is a basic charge balanced waveform, with no interphase delay. For numerical values of empirical constants, we averaged the single pulse numbers as presented by [7] for their models which neglected nonlinearity (see Supplementary Data 4, Table 8 from [7]). We used $\tau_1 = 0.425\text{ms}, \tau_2 = 74.8\text{ms}, \tau_3 = 0.37\text{ms}, \epsilon = 79.6$. We construct $\xi_{\text{ref}}(t)$, and consider its graph, shown in Figure 2 (solid line). The maximum value is found to be $\Xi_{\text{ref}} = 85$.

Assume we wish to construct a more complex pulse, one parameterized by $W_{\text{test}} = 0.5\text{ms}$, $\Delta_{\text{test}} = 0.05\text{ms}$, and $m_{\text{test}} = 2$. This is the same length pulse, but includes a dead time and a slow recharge. With these parameters, we plot $\xi_{\text{test}}(t)$, and find the maximum, again in Figure 2 (dotted line). The maximum value is found to be $\Xi_{\text{test}} = 225$. Thus, we compute the current to provide equibrightness to be

$$a_{\text{test}} = 100\mu\text{A} \times \left(\frac{85}{225} \right) \approx 37.8\mu\text{A}, \tag{12}$$

which is approximately one third the current in the reference waveform. Hence, by employing an interphase delay and a slow recharge, we are able to realize $\sim 62\%$ savings in applied current with no theoretical difference in patient perception.

V. DISCUSSION

We have presented a model predicting the perceived brightness of a phosphene elicited from a stimulation consisting of a single pulse. The model predicts an increase in brightness by extending the interphase delay between stimulation and charge reversal (Δ), longer pulse width (W), and slower charge recovery (m) in a nonlinear fashion. The model does not account for some practical constraints, such

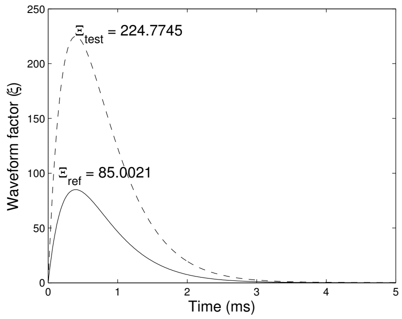

Fig. 2. Graphs of $\xi(t)$ for two sets of stimulation parameters. In each case, the maximal value is shown.

as safety assurance, aside from preserving charge balance. In contrast to observed stimulations, the model predicts no difference between anodic-first and cathodic-first stimulations.

To develop the model further and apply appropriate safety constraints, electrophysiological studies could be performed to determine ranges of model parameters that ensure stimulation is within the safe stimulation regime. As an example, the model predicts an increase in brightness with an increase in interphase delay, but the limit of $\Delta \to \infty$ results in a monophasic pulse, which is not safe. The studies surveyed in [6] also note that a faster reversal is better for safety considerations than slow reversals. This would imply that smaller recharge times are better, but the results presented are not quantitative in nature. A study showing different recharge times would be useful for determination of the time scale over which charge balance should be achieved for safe chronic stimulation.

The linearity of the model considered herein lends itself to consideration of the piecewise constant current waveforms of [9] for approximating a constant *voltage* driven waveform, as opposed to constant *current* driven waveforms.

Finally, as mentioned in [7], the patient population upon which this model has been derived is small (a total of two patients were considered). More clinical tests would be required to validate the model, either in the linear form as presented in this paper or including the nonlinearity in the full model.

VI. ACKNOWLEDGMENTS

This research was supported by the Australian Research Council (ARC) through its Special Research Initiative (SRI) in Bionic Vision Science and Technology grant to Bionic Vision Australia (BVA). The Bionic Ear Institute acknowledges the support it receives from the Victorian Government through its Operational Infrastructure Support Program. The authors would like to thank Dr. Bahman Tahayori for useful discussions.

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APPENDIX

For the model of perceived brightness (10), the coefficients, η, are given by

$$\begin{aligned}
\eta_{t^2,1} &= \frac{\tau_1}{\tau_3(\tau_1-\tau_3)}, \\
\eta_{t^2,2} &= \frac{\epsilon\tau_2^2}{\tau_3(\tau_2-\tau_3)}, \\
\eta_{t,1} &= \frac{2\tau_1^2}{(\tau_1-\tau_3)^2}, \\
\eta_{t,2} &= \frac{2\epsilon\tau_2^3}{(\tau_2-\tau_3)^2}, \\
\eta_{3,1} &= \frac{2\tau_1^3\tau_3}{(\tau_1-\tau_3)^3}, \\
\eta_{3,2} &= \frac{2\epsilon\tau_2^4\tau_3}{(\tau_2-\tau_3)^3}, \\
\eta_1 &= -\eta_{3,1} \\
\eta_2 &= -\eta_{3,2}
\end{aligned}$$

These are only valid for the special case of [7] without nonlinear effects (i.e., $\beta = 1$). Note that all values of η depend on *model* parameters, not *waveform* parameters.