Third Quarterly Progress Report
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The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation

J.T. Rubinstein, C.A. Miller, H. Mino, P.J. Abbas

Department of Otolaryngology - Head and Neck Surgery
Department of Speech Pathology and Audiology
Department of Biomedical Engineering
University of Iowa
Iowa City, IA 52242

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1 Introduction

The purpose of this contract is to explore issues involving the transfer of information from implantable auditory prostheses to the central nervous system. Our investigation is being pursued along multiple tracks and include the use of animal experiments and computer model simulations to:

1. Characterize the fundamental spatial and temporal properties of intracochlear stimulation of the auditory nerve.
2. Evaluate the use of novel stimuli and electrode arrays.
3. Evaluate proposed enhancements in animal models of partial degeneration of the auditory nerve.

In this third quarterly progress report (QPR), we focus on a quantitative analysis of electrophysiologic data recently submitted as a manuscript to Hearing Research. In it, comparisons between monophasic, pseudomonophasic and biphasic stimuli are made. Systematic differences in threshold and latency were obtained and a simple linear analysis explains much of what was found experimentally. In addition, the use of the computational model permits comparison of our experimental results with those of others using different stimulus parameters. The result is a cohesive quantitative explanation of the differences between the response patterns to monophasic, pseudomonophasic and biphasic stimuli. Given the clinical importance of charge balance, the potential for improved spatial selectivity with pseudomonophasic stimuli, and the basic biophysical importance of the monophasic stimulus, these relationships are of some significance.

2 Summary of activities in this quarter

In our third quarter (1 April - 30 June, 2000), the following activities related to this contract were completed:

1. We have worked with the University of Michigan Center for Neural Communication Technology in developing a new electrode probe design to be used with experiments proposed for this contract. The new design features electrode shank geometries and electrode site spacings appropriate for insertion into the feline auditory nerve for the purpose of multi-site recording of evoked potentials. The new design will be

completed and fabricated in the next few months. We have also acquired an existing electrode design from the U of M CNCT that will expedite more accurate measurement of auditory nerve conduction velocities. We have also completed design of an integrated series of headstage unity-gain amplifiers, gain-stage amplifiers, and programmable low-pass filters to be used in conjuction with these new electrodes.

2. Considerable progress has been made in developing new data collection software for our physiological animal experiments. The software, based upon Labview code, features integrated stimulus control and data acquisition (our current software system distributes these two tasks across two computers and limits the speed and flexibility of our data collection). Test versions of the new code successfully generate and control stimuli, acquire evoked potentials, perform signal averaging, and perform basic analysis of the acquired waveforms. The new code also allows the option of off-line data analysis. We now are addressing the simultaneous collection of multiple channels of data so that the new system can be used with the multiple-channel electrode designs described above.

3. We have submitted a manuscript for peer review and publication that details the neurophysiological responses to monophasic, biphasic, and pseudomonophasic stimuli.

4. We have collected considerable data from feline subjects describing single-fiber responses under conditions of relative refractoriness. We presently have data sets from over 25 fibers detailing how threshold, latency, jitter, and relative spread vary as a function of masker-probe interval (MPI). Effects that have been noted include prolonged response latency during relative refractoriness and responses at MPI values as short as 750 microseconds. Additional analyses will be conducted and the data presented in a later QPR.

5. We have completed installation of "Appleseed", a four processor Macintosh G4 supercomputer running the Message Passing Interface. This has freed us from dependence on resources provided by outside supercomputer centers. The system is highly scalable with the addition of further Macintosh systems and runs supercomputer code developed for Crays and IBM SPs with minimal changes. It is currently linked

via 100 Mbit ethernet but Gigabit connections are planned in the near future.

3 Erratum

An error appears in the previous (2nd) QPR of this contract, which compared the electrically evoked compound action potential produced by monophasic and biphasic current pulses in experimental animals. In one comparison, we compared the slope of amplitude-level functions for these two stimuli using a normalized measure of amplitude-level slope. The data plotted in Figure 3-D are incorrect due to a miscalculation of the normalized slopes. In actuality, data are scattered randomly around the diagonal line such that the normalized slopes do not demonstrate any systematic bias toward either biphasic or monophasic stimuli. Thus, our data show similar rates of gross-potential amplitude growth with biphasic and monophasic stimuli.

4 Monophasic and biphasic thresholds and latencies

In 27 units of 4 cats, monophasic and biphasic thresholds were obtained using cathodal and cathodal first pulses respectively. Pulse duration was 40μs/phase. Figure 1 demonstrates a histogram of the monophasic biphasic threshold ratio. It is clear that there are three outliers where biphasic is less than monophasic threshold. As descussed in detail in Miller et al (submitted) these units have a number of anomalous properties suggesting that with cathodal-first biphasic stimulation, the "anodic site" is being excited. The remainder of these units are likely being activated at the "cathodal site" by these stimuli and we will restrict further analysis to these more typical units.

Figure 2 illustrates the statistically significant relationship ($p = .027, r = .45$) between the monophasic/biphasic threshold ratio and the monophasic-biphasic latency difference. It is apparent then that when the "cathodal site" is being activated, biphasic thresholds are uniformly greater than monophasic thresholds and biphasic latency is typically less than monophasic latency. In addition, the threshold ratio is predictive of the latency difference. A computational simulation of monophasic and biphasic threshold activation is illustrated in Figure 3 and suggests that current integration may be entirely responsible for this phenomenon. The phase reversal of the biphasic

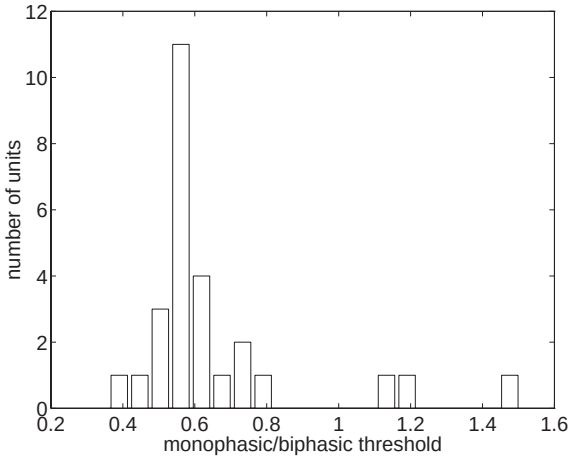

Figure 1: Histogram of monophasic/biphasic threshold ratios. For most units, this ratio is less than one.

pulse prevents what would be a threshold monophasic stimulus from activating the voltage-sensitive sodium channel. For a biphasic pulse to reach threshold, threshold must be reached some time in advance of the phase reversal, t_{act}. This results in higher thresholds and shorter latencies.

4.1 Linear Analysis

Using the definitions from Figure 3 and assuming a linear "integrate to threshold" model:

$$V_m = I_m R(1 - e^{-t/\tau}) \tag{1}$$

and

$$V_b = I_b R(1 - e^{-t/\tau}) \tag{2}$$

and

$$V_m = I_b R(1 - e^{-(t-t_{act})/\tau}) \tag{3}$$

where V_m is the potential reached at the end of a monophasic, threshold stimulus, V_b is the potential reached at the end of the first phase of a cathodal-first biphasic, threshold stimulus τ is the membrane time constant, R is the membrane resistance, t is the pulse width per phase.

Equations 1 and 3 together yield

$$I_m/I_b = \frac{1 - e^{-(t-t_{act})/\tau}}{1 - e^{-t/\tau}} \tag{4}$$

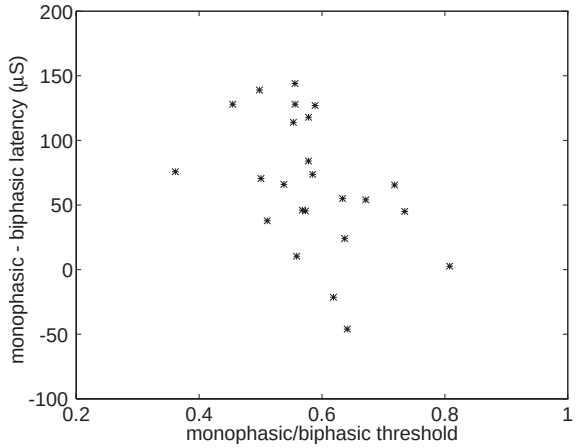

Figure 2: There is a statistically significant relationship ($p = .027, r = .45$) between the monophasic/biphasic threshold ratio and the monophasic-biphasic latency difference.

where equation 4 relates pulse width to the monophasic/biphasic threshold ratio. The nonlinear properties of threshold are collapsed into a single variable t_{act} which might be expected to vary across fibers as would the threshold ratio I_m/I_b.

A parametric analysis of equation 4 is illustrated in Figure 4 which demonstrates that equation 4 is relatively insensitive to the membrane time constant τ for the physiologically reasonable range of $\tau = 150 - 400\mu s$ as long as the pulse width is less than τ. Due to this insensitivity, it is reasonable to assign a membrane time constant and not vary it further. A value of $\tau = 235\mu s$ is chosen for the remainder of the analysis as it provides a best fit to the experimental data.

4.2 Results

Equation 4 allows calculation of the threshold ratio I_m/I_b from t_{act} and stimulus duration t, or t_{act} from the threshold ratio and t. Using the stochastic axonal computational model with $t = 40\mu s$, the threshold ratio is calculated and using Equation 4, determined to correspond to $t_{act} = 8.7\mu s$. From the single-unit data of Miller et al. (submitted) in Figure 1 of this QPR, this value for t_{act} is reasonable as the experimental data spans a range of $7.5\mu s < t_{act} < 25\mu s$. In Figure 5 equation 4 is plotted as a smooth function of t using $t_{act} = 8.7$. Individual data points represent results obtained by

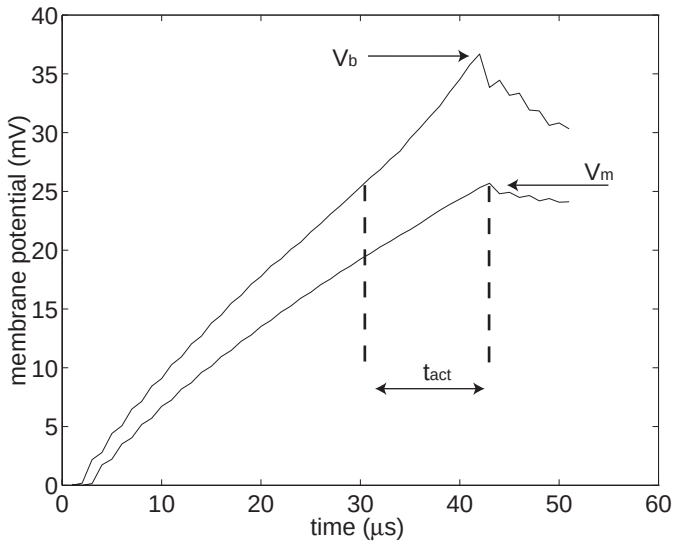

Figure 3: Threshold responses of a computational model to monophasic and biphasic stimuli. The monophasic pulse is cathodal and 40μs in duration. The biphasic pulse is cathodal-first and 40μs/phase. Some symbol definitions are also illustrated. V_m is the maximum potential achieved by the monophasic stimulus during the pulse. V_b is the maximum potential achieved by the biphasic stimulus during the cathodal phase. t_{act} is the "activation time", the time required by the membrane to achieve an irreversible action potential trajectory prior to the phase reversal of the biphasic pulse.

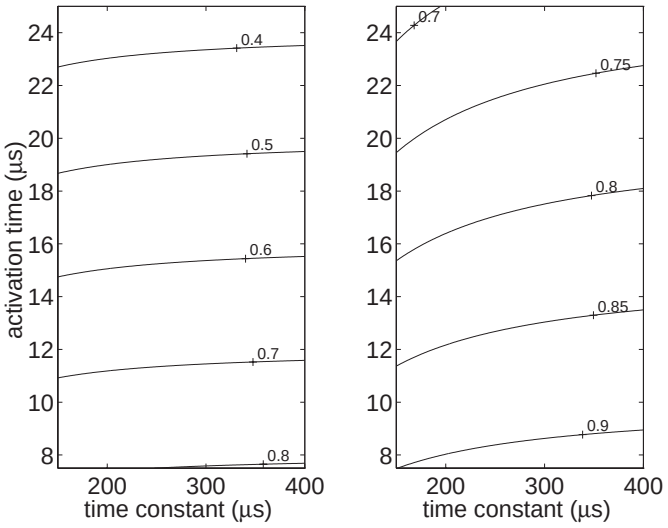

Figure 4: Contour plots of the threshold ratio I_m/I_b as calculated from equation 4. The left plot is for pulse width $t = 40\mu s$ and the right is for $t = 100\mu s$. The contours are labeled with the threshold ratio.

the computational model. It is clear that equation 4 captures the fundamental non-linear relationship between phase duration and the threshold ratio I_m/I_b despite its linearity. It does this by compacting the membrane's non-linear behavior into the parameter t_{act}. The dependence of t_{act} on membrane parameters is a complex subject that will be addressed in a future QPR.

In contrast to the value obtained with our model, the mean experimental threshold ratio from the units of Miller et al (submitted) obtained from Figure 1 corresponds to $t_{act} = 16\mu s$ (range 7.5—$25\mu s$). Figure 6 plots the threshold ratio I_m/I_b from equation 4 as a function of phase duration t using $t_{act} = 16\mu s$. This curve allows extrapolating the data of Miller et al (submitted), obtained at a phase duration of 40 μs, to longer phase durations. From this Figure, the predicted threshold ratio at $t = 100\mu s$ is -1.2 dB. This is precisely the threshold ratio obtained by Shepherd and Javel (1999) at a phase duration of $100\mu s$ and demonstrates the validity of the t_{act} parameter.

The previous calculations suggest that the threshold ratio I_m/I_b is largely determined by a fiber parameter, t_{act} and a stimulus parameter, the phase duration t. Given the relationship between the threshold ratio and the latency difference seen in Figure 2, it is likely that the latency difference

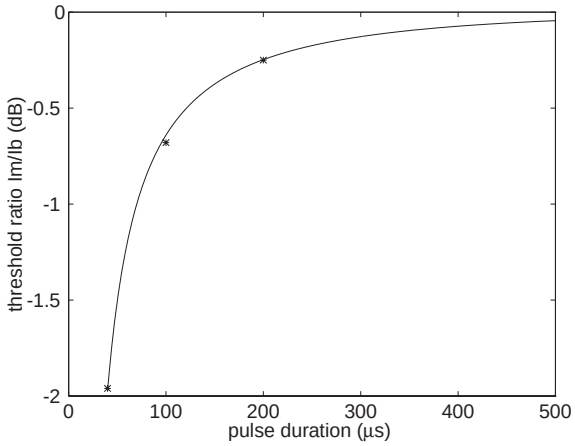

Figure 5: Monophasic/biphasic threshold ratio I_m/I_b plotted from equation 4 as a function of stimulus phase duration t. t_{act} set at $8.7\mu s$, a value obtained from the computational model at $t = 40\mu s$. Individual data points are the threshold ratio determined empirically from the computational model at $t = 100\mu s$ and $t = 200\mu s$.

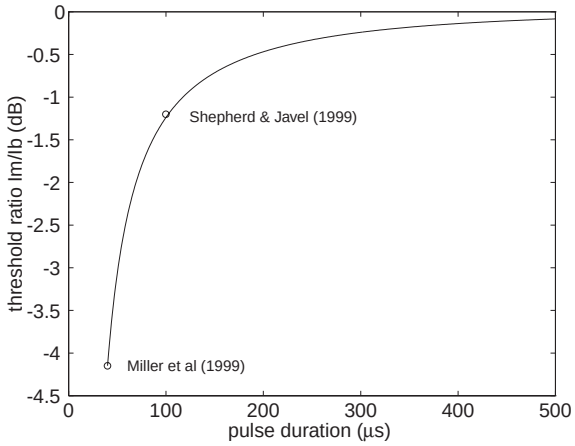

Figure 6: Monophasic/biphasic threshold ratio I_m/I_b plotted from equation 4 as a function of stimulus phase duration t. t_{act} set at $16\mu s$, the mean value obtained experimentally by Miller et al (submitted) at $t = 40\mu s$. At $t = 100\mu s$, the curve predicts the threshold ratio to be -1.2 dB, a value identical to that obtained experimentally by Shepherd and Javel (1999).

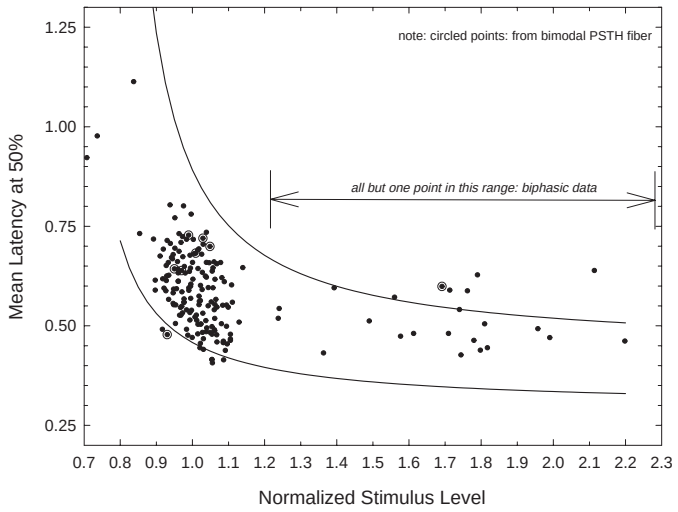

Figure 7: Latency-intensity data for both monophasic and biphasic stimuli for the units in Figures 1 and 2. Data obtained with biphasic stimuli are restricted to the region of stimulus levels greater than 1.2. All data points at stimulus levels below 1.2 represent monophasic stimuli. The two smooth curves indicate minimum and maximum limits for a population of fibers stimulated with monophasic pulses as described in Miller et al (1999).

between cathodal monophasic and cathodal-first biphasic stimulation is also determined by t and t_{act}. In other words, the shorter biphasic latency should be due to the higher membrane potential, V_b achieved for a threshold stimulus I_b; this activates the fiber at an intensity higher on its latency-intensity curve. For the computational model, this was demonstrated to be true. The latency for biphasic stimulation was found to be identical to the monophasic latency achieved at the biphasic threshold current. For the single-units described in this QPR, we do not have monophasic latencies at such high presentation levels. Figure 7 plots all of the monophasic latencies obtained, as well as the biphasic latencies for the same units. Also plotted are the minimum and maximum limits for the latency-intensity functions published in Miller et al (1999). It can be seen that most of the biphasic latencies are consistent with the hypothesis that they arise from the monophasic latency-intensity function at the higher, biphasic threshold current.

The above analysis of latency and threshold effects of monophasic and biphasic stimuli suggests that equation 4 and the parameter t_{act} unifies experimental data performed under these different conditions and with differ-

ent pulse durations. Given the clinical importance of biphasic stimuli for neural prostheses, and the fundamental importance of monophasic stimulation, such a unifying theory should prove useful.

5 Plans for the next quarter

In the fourth quarter, we plan to do the following:

- Continue optimization of our code for the Altivec vector processor on the Macintosh G4.
- Detailed exploration of the model biophysical parameters that correspond with the phenomenological parameter t_{act}. Also more detailed explorations of which parameter variations might fit the computational model better to our experimental data.
- Exploration of further alternative algorithms for stochastic simulations of neurons.
- Two presentations at the World Congress of Biomedical Engineering and one at the Collegium ORL.

6 Appendix: Presentations and publications

The following presentations were made:

- Abbas, PJ, Miller, CA, Brown, CJ, Rubinstein, JT & Hughes, M (2000). Electrophysiological measures with cochlear implants: basic response properties, "Otolaryngology - Head and Neck Surgery for the next Century", University of Iowa, April, 2000.
- Abbas, PJ,, Brown, CJ, Hughes, ML, Wahl, B, & Gehringer, A (2000). Measurements of electrically evoked responses to pulse trains using neural response telemetry. 5th European Symposium on Paediatric Cochlear Implantation, Antwerp, June 2000.
- Rubinstein, J.T, R.S. Tyler, K. Gfeller, A. Wolaver, M. Lowder, M. Mehr, C.J. Brown. High-rate conditioning pulses: Effects on speech, music & tinnitus perception. 5th European Symposium on Paediatric Cochlear Implantation, Antwerp, June 2000.

The following manuscript has been submitted for publication in Hearing Research:

- Miller CA, Robinson BK, Rubinstein JT, Abbas PJ, Samuelson CR. Auditory nerve response to monophasic and biphasic electric stimuli.

References

[1] Miller CA, Abbas PJ, Robinson BK, Rubinstein JT, Matsuoka AJ. Electrically evoked single-fiber action potentials from cat: responses to monopolar, monophasic stimulation. Hearing Research, 130(1-2), 197–218, 1999.

[2] Miller CA, Robinson BK, Rubinstein JT, Abbas PJ, Samuelson CR. Auditory nerve response to monophasic and biphasic electric stimuli. (submitted to Hearing Research)

[3] Shepherd RK and Javel E. Electrical stimulation of the auditory nerve: II. Effect of stimulus waveshape on single fibre response properties. Hearing Research 130, 171-188, 1999.