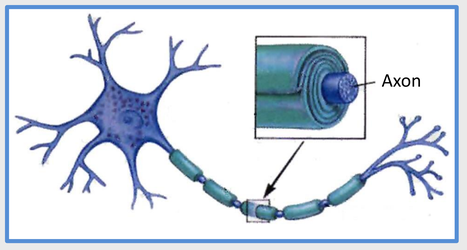
Modeling Threshold Tracking in Axons

Daniel Sigouin and Dr. Béla Joós, *Department of Physics*, University of Ottawa
Dr. Catherine E. Morris, *Ottawa Hospital Research Institute*



Introduction

What is threshold tracking?

Threshold tracking is a method which is used to determine the current needed to launch an action potential. It is used clinically in order to pre-emptively detect the presence of nerve damage which affects this threshold. These damages can be precursors originating from many sources including diabetes, multiple sclerosis, nerve trauma, etc. Once the damage is identified, the appropriate treatment is administered in order to prevent the neuropathy from developing.

Why model threshold tracking?

Little research has been done to study the effect of different damage types on axon action potential threshold. This project uses the Hodgkin-Huxley mathematical neuron model to simulate threshold tracking in both a healthy and damaged axon using a program coded in Python. The results for axons can then be extrapolated for an entire nerve. Afterwards, experimental results can be obtained and compared to the models to confirm the predicted effect on the threshold of a given nerve damage. This will allow laboratories to correlate the threshold tracking results obtained clinically to a damage model. A precise diagnostic of a patient's condition can then be made and a targeted treatment can be administered to prevent the damage from becoming a neuropathy.

Method

This project simulated the clinical approach for threshold tracking seen in the 1998 Bostock review (see Figures 1 and 2) using a Python program. In order to model threshold tracking, the simulation was first run for healthy (control) and then damaged axon models. To simulate the damage, a 1mV left-shift was applied to the kinetics of the Na^+ ion channels in the axon. Each system's respective thresholds were determined. The simulation ran for an overall duration of 110ms. The system was given 10ms to stabilize, after which, a 100ms conditioning pulse representing a fraction of the threshold was applied to the axon. Conditioning pulses of -40%, -20%, 0%, +20% and +40% of the rheobase were used. Then, a 1ms test pulse was applied to the axon. The test pulse represents the minimum remaining current required to launch an action potential in the axon in addition the conditioning pulse. Starting from 0 $\mu A/cm^2$, the test pulse was incremented until the neuron membrane's potential reached 35mV confirming that the action potential had been launched. To measure the relation of the test pulse with time, the program generated a test pulse every millisecond for the duration of the conditioning pulse. Graphs were generated of the test pulse current value in function of the delay at which it was applied.

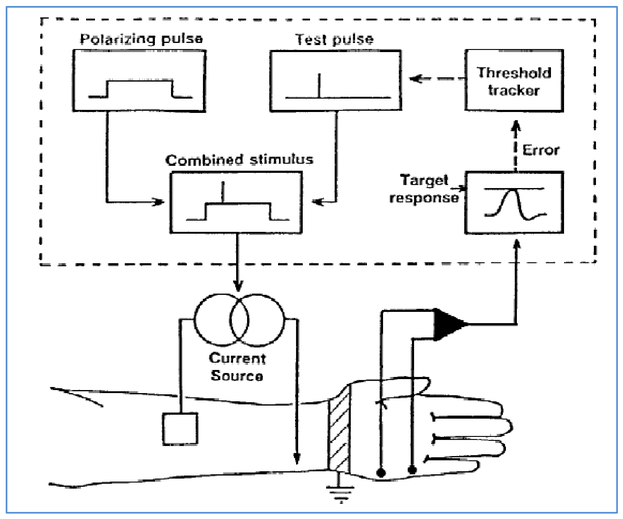


Figure 1: Clinical setup used in the 1998 Bostock review. A 1ms stimulus is applied to the ulnar nerve and the response is measured in the hypothenar muscle.

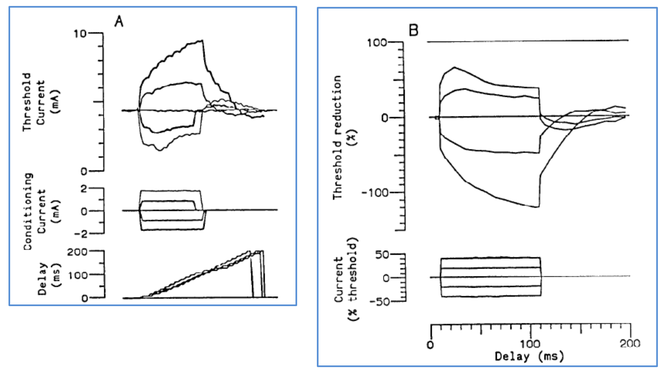


Figure 2: Threshold tracking results obtained with the Bostock method in a healthy subject. (A) Measured threshold currents for the 5 conditioning pulses, conditioning pulses for -40%, -20%, 0%, +20%, +40% (from top to bottom) (B) Threshold reduction % for the 5 conditioning pulses,+40%, +20%, 0%, -20%, -40% (from top to bottom), measured from the threshold current values in (A)

Conclusion

Threshold tracking was used to model an axon suffering from left shift damage. The data shows that, for the damaged axon model, the required test pulse currents were lower than in the healthy model. The figures generated by the simulation are similar to those from the clinical results of the 1998 Bostock review. Generating threshold tracking damage models does have a use in a clinical environment. Using the said models, the clinical results obtained from a patient's threshold tracking can be correlated to a specific damage type and severity. This allows for early detection of the cause of axon damage and the determination of the treatment can be applied before the neuropathy develops. More simulations need to be made to generate models for different damage types in the entire nerves. With these models, pre-emptive diagnostics of a variety of nerve damage will be possible.

Acknowledgements

I would like to thank Dr. Béla Joós for his guidance and advice especially during the software development phase of the project and Dr. Catherine E. Morris for her input during discussions.

Results

Figure 3: Threshold tracking data was generated to produce a model for a healthy and a damaged axon. The healthy model (A) and (B) had a 6.85 $\mu A/cm^2$ threshold. The 1mV left shift damage model (C) and (D) had a 4.69 $\mu A/cm^2$ threshold.
Graphs (A) and (C): Test pulses measured in order to launch action potential at given delay for a healthy and damaged axon respectively. Simulations were run for -40%, -20%, 0%, +20%, +40% conditioning pulse as shown in the charts.
Graphs (B) and (D): Threshold reduction% of test pulses in function of delay. The threshold reduction was measured using the threshold and test pulse values from (A) and (C).

In the data obtained from both the healthy and damaged models, when a positive conditioning pulse is applied an initial reduction in threshold current is seen. This reduction drops due to inactivation of axon membrane ion channels. The system then stabilizes at a new threshold current value. For the negative conditioning pulses, the reverse effect can be seen. The duration of the spike is longer for the positive conditioning pulses.

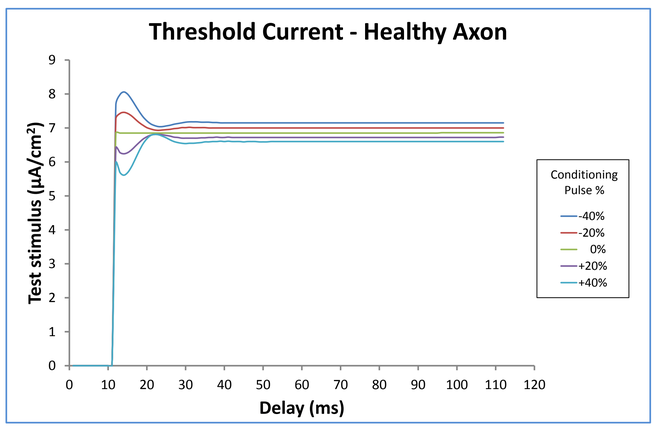


Figure 3 – (A)

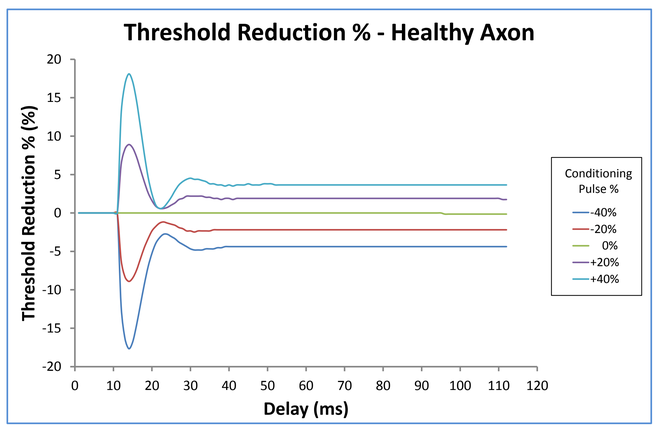


Figure 3 – (B)

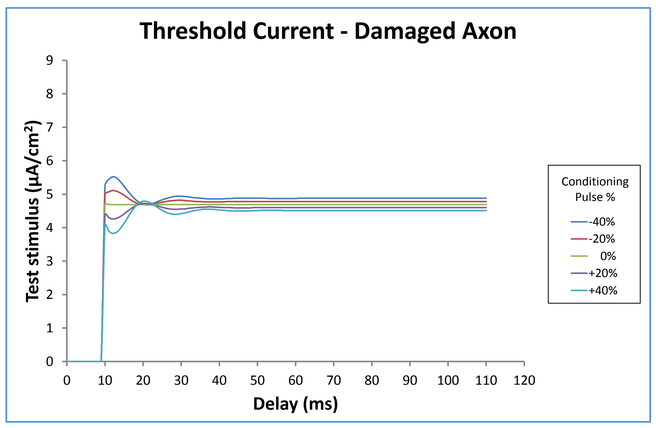


Figure 3 – (C)

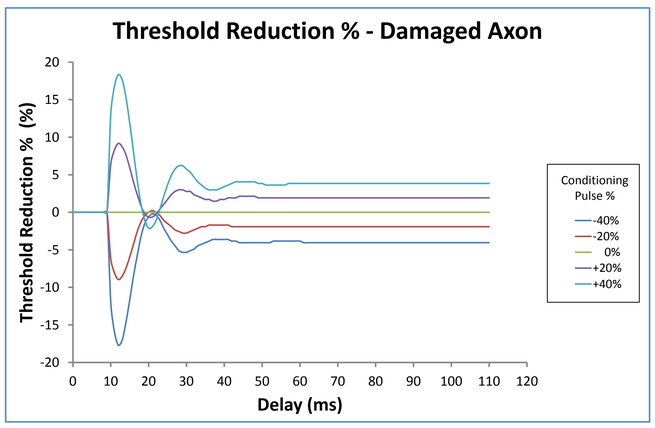


Figure 3 – (D)

References

Figures 1 and 2 taken from Hugh Bostock, Katia Cikurel, David Burke. "Threshold Tracking Techniques in the Study of Human Peripheral Nerve" *Threshold Tracking in Nerve* (1998), 137–158.

Pierre-Alexandre Boucher, Béla Joós, Catherine E. Morris. "Coupled left-shift of Nav channels: modeling the Na^+-loading and dysfunctional excitability of damaged axon" *J Comput Neurosci* (2012) 33:301–319.

S.E. Han, Robert A. Boland, Arun V. Krishnan, Steve Vucic, Cindy S.-Y. Lin, Matthew C. Kiernan. "Changes in human sensory axonal excitability induced by an ischaemic insult" *Clinical Neurophysiology* 119 (2008) 2054–2063.

ArunV. Krishnan, Cindy S.-Y. Lin, Susanna B. Park, Matthew C. Kiernan. "Assessment of nerve excitability in toxic and metabolic neuropathies" *Journal of the Peripheral Nervous System* 13:7–26 (2008).

Takehito Hayami, Keiji Iramina, Xian Chen, Kenji Sunagawa. "Simulation Study on the Effect of Fiber Loss to the Compound Action Potential of a Sural Nerve" (2007)2396–2399

David Sterrat, Bruce Graham, Andrew Gillies, David Willshaw. *Principles of Computational Modelling in Neuroscience*. Cambridge: Cambridge University Press, 2011.

Neuron picture from http://beforeitsnews.com/mediadrop/uploads/2013/38/a31669175d695ad762f2e95da10e50b3912705c2.jpg

Contact Information

Daniel Sigouin
Second Year Undergraduate Student
Honours BSc with Specialization in Physics-Mathematics
Faculty of Science
University of Ottawa
daniel.sigouin@gmail.com
613-824-7974