**EXPLORING SOURCES OF VARIABILITY IN ELECTROPHYSIOLOGY DATA OF MAMMALIAN NEURONS**

by

Dmitry Tebaykin

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# Abstract

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The abstract is a concise and accurate summary of the research contained in the thesis. It states the problem, the methods of investigation, and the general conclusions, and should not contain tables, graphs or illustrations. It **must not** exceed 350 words, and should contain relevant keywords that will make your thesis more likely to be found in an electronic search. **Do not** put a separate list of keywords. There must be a single abstract for the entire thesis.

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# Acknowledgements

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The following are usually mentioned in the Acknowledgements:

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* Grant support
* Helpful fellow students, lab mates, etc.
* Family support

Acknowledgements may extend for more than one page, but should be no longer than two pages.

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I offer my enduring gratitude to the faculty, staff and my fellow students at UBC, who have inspired me to continue my work in this field. I owe particular thanks to Dr. J. M. Schneider, whose penetrating questions taught me to question more deeply.

I thank Dr. O. Meyer for enlarging my vision of science and providing coherent answers to my endless questions.

Special thanks are owed to my parents, whose have supported me throughout my years of education, both morally and financially.

# Dedication

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## Introduction

Electrophysiological (ephys) recordings are widely used for characterizing neuron function. The field of electrophysiology focuses on studying electrical properties of neurons, their action potential and synaptic activity. Many different cell types in the brain possess different intrinsic electrophysiological properties that enable them to perform crucial and highly specific functions.

Electrophysiology as a field is moving towards larger kinds of data analyses trying to not only understand one neuron type in isolation, but to study many kinds of neurons simultaneously. For example, the first goal of the US NIH BRAIN project is to generate a “census of cell types”, involving neuron comparison using genetic, morphological and electrophysiological characteristics. However, the common practice among neurophysiologists is to only analyze data that they have collected themselves. This is largely because it is colloquially accepted that subtle variation in experimental conditions introduces certain variation into the corresponding measurements. However, this approach imposes sample size restrictions, since a single scientist or lab can only collect and analyze a limited amount of data on their own. The goal of my project is to enable the comparison and aggregation of electrophysiological data across different experiments.

To provide some context for the methodology used in intracellular electrophysiology, a typical experiment involves: extracting the brain of an anesthetized animal and cutting thin slices from the brain; letting the slices recover in a bath of a carefully designed solution; transferring a designated slice to a recording chamber, where the ephys measurements are taken. In the recording chamber a brain slice is continuously perfused with the recording (external, extracellular) solution at a constant temperature. Finally, a recording electrode is inserted inside the neuron, allowing for injection of electrical current and the quantification of electrophysiological parameters. The electrode also contains the internal solution (intracellular, pipette), which in the case of patch-clamp electrodes completely dialyzes the cell and replaces its intracellular milieu.

Combining and comparing electrophysiology data across labs directly and on a large scale is, perhaps, questionable because such data is often collected under different experimental conditions. In the past, ephys data has been shown to be sensitive to experimental conditions. For example, differences in animal ages, especially during development (Suter et al. 2013); or varying extracellular Ca2+ concentrations (Aivar et al. 2014) result in changes in electrophysiological properties of neurons. Therefore, comparing data across differently designed experiments without accounting for variability introduced by experimental conditions could lead to incorrect or inconsistent results.

A series of five landmark papers published in 1952 by Hodgkin and Huxley unveiled many of the basic mechanisms that govern neuron electrophysiology, providing neurophysiologists with the initial sodium-potassium mechanism of neuron action potentials. At rest, a typical neuron maintains a high concentration of potassium and a low concentration of sodium ions inside relative to the outside. This causes sodium (ENa) / potassium (EK) reversal potentials, calculated using the Nernst equation (Schmidt-Nielsen, pp. 478-480), to be respectively very high / similar, relative to the resting membrane potential. Additionally, ionic driving forces across the neuron membrane are calculated as a difference between their reversal potentials and the membrane potential. During the neuron action potential (AP), sodium ion permeability (GNa) across the cell membrane increases dramatically, allowing Na+ ions to flood inside the neuron due to the driving force of sodium. As the AP approaches its peak, both sodium driving force and permeability decrease, but potassium permeability (GK) and driving force rise, causing it to flood outside of the neuron, eventually restoring membrane potential to its resting state. Thus, neuron electrophysiological properties depend heavily on the precise ion concentrations inside and outside of the cell.

Many neurophysiologists address the task of exploring the effects of experimental conditions on neuron ephys properties using experimental electrophysiology techniques (Kim et al. 2012, Armentia et al. 2004, Lee et al. 2004). However, this experimental approach is limited to varying a single condition and studying one or several neuron types at a time. Therefore, it is unclear how well the discovered relationships between electrophysiology properties and experimental conditions would generalize to other neuron types, animal species, ages and other confounding factors that typically remained fixed throughout each experiment.

Previously, my colleague, Shreejoy Tripathy designed and created NeuroElectro, an online database that contains text-mined and curated population mean electrophysiological measurements, neuron type and experimental setup information from normal control samples of published neuroscientific studies. Using a large-scale meta-analysis method, he showed that animal age, recording temperature, electrode type choices significantly correlate with the study-to-study variance in reported ephys values (Tripathy et al. 2015)

Since a typical electrophysiological experiment uses carefully designed solutions inside and outside the measured neurons, I hypothesized that study-to-study ephys variability could be partially explained by the experimental setup (metadata) differences, focusing on the recording and pipette solution compositions. To test my hypothesis, I employed a combination of text-mining and curation approaches to extract experimental solutions used in published neurophysiological articles. Then, I integrated my solution extraction algorithms into the NeuroElectro database. Once the data was collected, I applied univariate linear models to uncover the effects of solutions on the measured ephys values. These initial models proved ineffective, which prompted me to use a non-linear multivariate approach. Additionally, I explored the external and internal solution recipes commonly used by electrophysiologists.

I found the effect of solution compositions on the variance in electrophysiological properties to be relatively small, likely because different labs use similar solutions, thus their explanatory power is limited. Additionally, using experimental conditions (neuron type, recording temperature, animal age, species, solution compositions, etc.) I created custom models for ephys properties commonly reported by neurophysiologists. My models can be used to remove a portion of the ephys variance when comparing results from different experiments, making such comparisons more reliable. Further applications of the models include normalization of ephys values and adjusting them from one set of experimental conditions to another. To validate and showcase the last scenario, I adjusted a portion of NeuroElectro data to experimental conditions used by Allen Institute for Brain Science and compared the respective ephys properties before and after the adjustment.

### Section

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### Section

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The account of the research should be presented in a manner suitable for the field and include the following:

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* A brief synopsis at the beginning of each research chapter
* A description of methods used, in sufficient detail to enable a reader to understand how the data were gathered and to apply similar methods in another study
* A complete account of the research presented in a systematic manner typical of the field of study

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* Conclusions regarding goals or hypotheses of the thesis that were presented in the Introduction, and the overall significance and contribution of the thesis research
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* Discussion of any potential applications of the research findings
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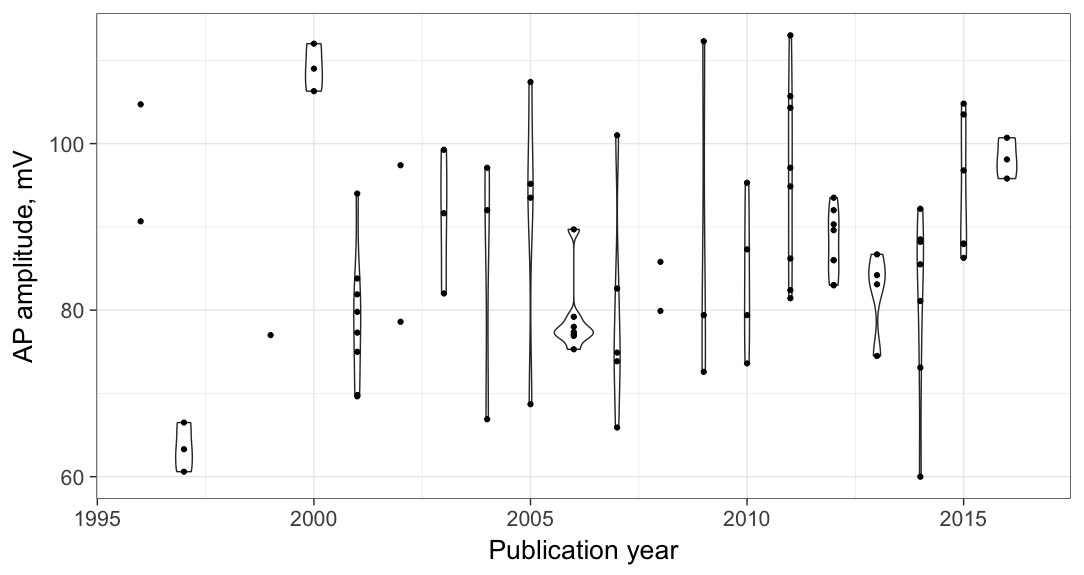


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### Section

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1. Additional details of methodology and/or data
2. Diagrams of specialized equipment developed
3. Copies of questionnaires or surveys used in the research. Please ensure that personal information (e.g., names or contact information of subjects and/or researchers) is removed and/or blacked out from your questionnaire/survey copies.

Sub-Appendix

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Sub-Appendix

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This is Appendix B.

Sub-Appendix

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