# Research Proposal

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Investigating the effect of impermeant anions and electrodiffusion on the computational properties of neurons

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**Plagiarism Declaration**

I know that plagiarism is wrong. Plagiarism is to use another’s work and pretend that it is one’s own. I have used the American Medical Association (AMA) convention for citation and referencing. Each contribution to, and quotation in, this research proposal from the work(s) of other people has been attributed and has been cited and referenced.

This research proposal is my own work.

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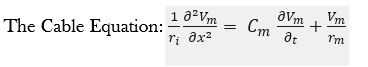
# Background

Computational models describing the dynamic biophysical properties of neurons have significantly aided modern understanding of how the brain processes information. Most detailed computational models focus on how dendrites modulate synaptic inputs and convey their electrical signals towards the soma1. Two of the most popular models, the Equivalent Circuit Model and Cable Theory, fail to couple the simultaneous electrical and osmotic changes which drive ionic currents. An Electrodiffusion based model been proposed to overcome the limitations of previous models but requires each variable in the model to be calculated for every time step. Due to the computational complexity this entails, electrodiffusion based models have been out of favour, however with the speed of modern electronic systems this challenge can be overcome.

Recent work by our group using a multicompartment model incorporating electrodiffusion found that impermeant anions may play a role in neural function. Few studies have looked at the role impermeant anions and even fewer have examined the role spatial inhomogeneities of these impermeant anions may have on the electrical and computational properties of dendrites. Herein we propose to probe the implications and possible functions spatial inhomogeneity of impermeant anions may play by using an electrodiffusion based multi-compartment neuronal model.

**Most popular models:**

Neurons are traditionally modelled using the cable theory or equivalent circuits. In such models the equilibrium potential of each ion is represented by a battery whose driving force (EMF) is given by the Nernst Potential. Changes in the membrane permeability are modelled by changes to conductances. Such changes to conductances do not change the equilibrium potentials of the neuron.



**Limitations of current models:**

Cable theory is useful in modelling many neuronal processes, however there are limitations to its applicability. In areas of small intracellular volume (e.g. dendritic spines), the ionic concentrations can change rapidly (e.g. calcium transients). Such concentration changes are not accounted for in cable theory as ionic reversal potentials are fixed and not dependant on concentration changes with time. Thus an additional term is needed to account for this, and the equation needs to be computed for each ion in time.

**Electrodiffusion model:**

Electrodiffusion based models incorporate the electrical driving forces (drift) of ions, as well as the movement of ions along their concentration gradients (diffusion). Albert Hodgkin, one of the pioneers in the field of neuronal modelling, makes the following analogy: “*diffusion is like a hopping flea… electrodiffusion is like a flea that is hopping in a breeze”*  2*.* To make this analogy more complete we need to consider different fleas moving at different speeds with different breezes. Moreover, each flea is impact the other as a function of time.

Clearly modelling this highly dynamic and complex process requires significant computational power. This factor has dissuaded computational biologists from pursuing such models, however with the computational resources publicly available in the year 2020/2021, such computations can be performed in a few hours as opposed to days or weeks.

**Our electrodiffusion model:**

**The biophysical effects of impermeant anions**

Dusterwald et. al3 showed that the addition of impermeant anions in a multicompartmental model effects the electrical and osmotic functions of dendrites.

In a single compartmental model, Dr. Dusterwald showed that altering the concentrations of impermeant anions intracellularly or extracellularly does not change the steady state concentrations of the major ionic species due to balanced osmotic changes. However, when the average charge of impermeant anions changes there are significant changes to reversal potentials of various ions, as well as changes to the membrane potential. Due to the relatively constant ratio of these changes the driving force (Vm – Reversal potential) of the various ions do not significantly change.

Similar effects were demonstrated in a multicompartmental model, however the changes to the driving force were even less due to the impact electrodiffusion had on the sodium ion concentrations thus impacting the Na\_K\_APTase.

In both the single and multicompartment simulations, impermeant anion concentrations were key determinants of cell/compartment volumes. Similarly changing the average charge of impermeant anions had a persistent impact on cell volume.

As impermeant anions had significant effect on cell volumes it was postulated that adding impermeant anions in the apical portions of the dendrites may mimic the increases in cell size of a growth cone. This too was shown via simulations thus illustrating the potential ability of impermeant anions to grow neuronal processes, and it may be possible that neurons could use the transport and tethering of impermeant anions to grow or modify the volume of neuronal compartments

Don’t know what the effect of varied Vm on these properties will be

Recent work by our group has manipulated the properties of impermeant anions in both single and multicompartmental models. It has been shown that changing the intracellular, or extracellular concentrations of impermeant anions has no effect on the steady state membrane potential or reversal potentials of sodium, chloride and potassium. Dynamically increasing the amount of impermeant anion inside the cell does however lead to a transient hyperpolarization of the membrane while the dynamic addition is take place, but similarly returning to steady state once the addition of impermeant stops.

Although there were very minimal effects on the electrical properties of the neuron there were significant changes in the volume of the cell. There appears to be a linear relationship between the initial intracellular concentrations of impermeant anions and the final volume of the neuron.

Changing the average charge of impermeant anions did change the absolute values of the various ionic reversal potentials and the membrane potential, but in such a ratio to keep the changes to the ionic driving forces negligible.

**Dendritic computation**

**Role in disease:**

Impermeant anions such as intracellular proteins play an important role in several disease processes. The more salient of these are the Tauopathies which hallmark neurodegenerative disorders. In Alzheimer’s Disease the Tau protein builds up intracellularly and starts off as a soluble protein but as it becomes phosphorylated and bundled together with microtubules these proteins become insoluble and thus are trapped within the intracellular compartment. The progression of Alzheimer’s Disease is described by Braak’s staging which is based on the spread of Tau inclusions from the entorhinal cortex (Braak stage I and II), to the hippocampus (stage III), then to the neocortex (stage IV and V). The spread of intracellular Tau proteins also reflects the symptom progression in Alzheimer’s Disease from asymptomatic to deficits in memory and ultimately higher cortical functioning.4

What is the average intracellular charge of Tau proteins?

Several other neurodegenerative disorders are also characterised by subcellular protein build up. In Parkinson’s Disease intracellular alpha-synuclein deposition and is also correlated to disease progression and symptomatology. Similarly, in Pick’s Disease, Pick bodies can be found inside neurons. Interestingly, Tau proteins can also accumulate in glial cells and play a role in Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD). Increased Tau proteins in astrocytes have also been linked to aging.

Extracellular protein deposition also occurs in Huntington’s disease, Multiple Sclerosis, Spinocerebellar Ataxia and Transmissible Spongiform Encephalopathy (the most common being Jakob-Creutzfeldt disease)5

A common theme throughout the disease spectrum is neurodegenerative change associated with subcellular build up of protein. Perhaps such intracellular protein deposition plays a role in the electrical and computational properties of dendrites and thus may contribute disease processes.

Prion disease

Huntington’s disease

These models make use of the Cable Theory by Rall which assumes that the ionic reversal potentials remain constant along the length of the cable6. Recent work by our group has suggested that variable activity of chloride channels along dendrites may result in local changes to chloride reversal potentials resulting in non-isopotential dendritic compartments– thus violating a core assumption in Cable Theory. Investigating what the implications of this violation are on the electrical and information processing properties of the neuron may shed further light on how the brain is able to function and may better depict how neurons behave in certain disease states.

Status quo did not include impermeant anions and electrodiffusion.

Why haven’t they been done before

Computational expensive – but now feasible?

Don’t go into the mathsy part of it

**Model**

The Cable Theory of Rall was devised to model the attenuation of electrical signal across a dendrite. The full derivation of the Cable equation and its steady state solution are made in Appendix A and B respectively.

The Cable Equation:

With this equation we can integrate and solve for Vm. The steady-state solution to the cable equation is:where,

According to this solution the membrane voltage is dependent on the initial voltage multiplied by an exponential function reflecting the decay of the signal based on the distance along the cable and inherent cable properties7.

In this equation there is no consideration for the dynamic effects of the reversal potential based on rapid changes in ions. Moreover, as the reversal potentials of the ions are considered constant, the equation fails to consider the fact that impermeant anions may be distributed in a spatially heterogenous manner.

**Spatial aspects of synaptic integration**

* In pyramidal cells, distal inputs are amplified via dendritic spikes or plateau potential supporting local coincidence detection and gain modulation
* Dendritic inward currents play a major role in control of spiking or response to synchronous inputs (plasticity)
* Dendritic branching structures and axonal geometries

**Disease**

* Detailed spatial representations help predict the effects of extracellular electrical stimulation. This is essential for deep brain stimulation used in the treatment of Parkinsons Disease.
* CCCs in disease (Kalia paper)

One of the fundamental assumptions of the cable theory is that the voltage across the dendritic compartment is uniform. This assumption is critical as it provides the basis for the cable equation which calculates the voltage across the dendrite at any point in time.

# Aims and objectives

The overall aim of my thesis is to use a biophysical computational neuronal model to investigate the implications of non-isopotential dendrites on the electrical and information processing properties of neurons.

The objectives are as follows:

1. Develop a computational tool to dynamically model ion homeostasis, volume regulation, and electrical changes that occur within a neuron.
   1. Create a single compartment model.
   2. Create a multicompartment model incorporating the properties of electrical drift and diffusion.
   3. Create a tool to visualize the changes to the ionic concentrations, electrical properties and cell volume within each compartment as these properties vary with time.
2. Investigate the effects of adding excitatory or inhibitory synaptic input to the non-isopotential dendrite on each of the dendritic compartments as well as at the soma.
3. Investigate the effect non-isopotential neurons have on information processing and dendritic computation
4. Explore how any observed effects may be relevant to disease processes.
   1. How do impermeant anion concentrations change in diseases. Can this be modelled.

* 1) To develop a ^^\*\*computational biophysical model\*\*^^ of a neuron
  + 1.1 - Develope a single compartment neuronal model similar to Dr. Dusterwald and Dr. Currin in the python programming language
  + 1.2 - Ensure that the model is bio realistic by comparing to laboratory data
  + 1.3 - Develope a multicompartmental model similar to Dr. Dusterwald and Dr. Chris Currin
  + 1.4 - Create a tool to visualize what is occuring in each compartment
    - Visualize the voltage, ion concentration, and volume of each compartment
* 2) To explore the^^ \*\*feasibility of non-isopotential dendrites and spatial inhomogeneities in dendritic voltages\*\*^^
  + 2.1 - Are there fundamental assumptions that are being broken when we making the neurons non-isopotential
  + 2.2- Why does NEURON assume that dendrites are isopotential
* 3) To explore how impermeant anions and non-isopotential dendrites affect ^^\*\*inhibitory and excitatory processing\*\*^^
  + 3.1 - Add excitatory stimulation to the neuron and identify the changes that occur in the various compartments
  + 3.2 - Same as the above but with inhibitory stimuli
* 4) Determining the^^ \*\*information processing \*\*^^effect at neural outputs and local dendritic processing
  + 4.1 - Summarize the work on [[dendritic processing]] by Dayan and Abbot
  + 4.2 - Think about how non-isopotential neurons may affect dendritic processing
* 5) Exploring the relevance to^^ \*\*disease processes\*\*^^
  + 5.1 - Do a mini-literature review on how various diseases may change the impermeant intracellular anions
  + 5.2 - Incorporate these findings into the model and identify how the system then functions

# Research plan

# References

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# Appendix A – derivation of the cable equation

# Appendix b – steady state solution to the cable equation