Investigating the effect of E-I imbalance, and its effects

Part I: Case for support

Neuroscience background

Computational neuroscience is a branch of neuroscience which studies information processing in the brain using mathematical models. These models are usually too complex to be studied analytically so must be solved numerically using a computer. Research institutes such as the Allen Institute for Brain Science have conducted morphology and electropyhsiology experiments on both human and mouse neurons. Their data is made freely available and can be used to fit parameters for biologically accurate mathematical models of neurons. These models can then be used to directly test hypotheses about the biological systems that they represent.

The mammalian brain is made up of several billion neurons. Neurons consist of a cell body (soma), many dendrites and a singular axon. Incoming signals arrive at the dendrites, if there is enough stimulation an action potential is created that propagates down the neuron to the axon terminals. The space between the axon terminals and the dendrites of the next neuron is called a synapse. At a synapse the electrical signal from an action potential is converted into a chemical signal in the form of different types of neurotransmitter. This neurotransmitter travels across the synaptic cleft to the post-synaptic neuron's dendrite where it binds to a receptor.

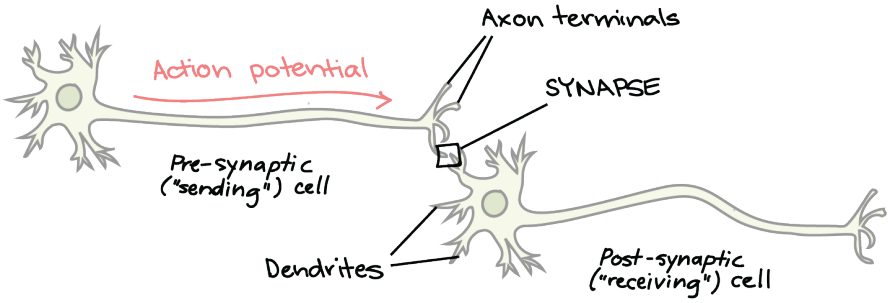


Figure 1: *Two neurons connected by a synapse. Image taken from Khan Academy, CC BY-NC-SA 4.0*

In some cases this neurotransmitter will cause the post synaptic neuron to depolarise and therefore more likely to create an action potential, this is called an excitatory post synaptic potential. Otherwise the neurotransmitter will cause the membrane potential to decrease and the neuron will be less likely to create an action potential, this is called an inhibitory post synaptic potential.

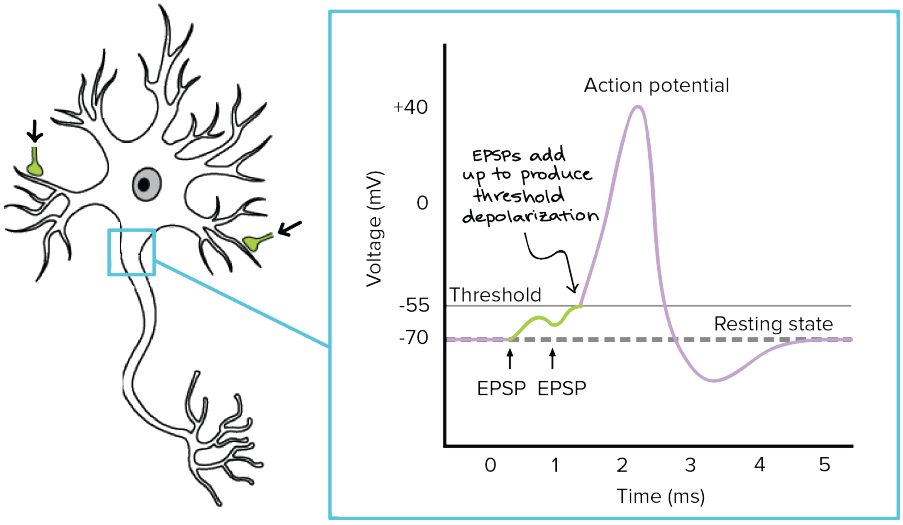


Figure 2: *A typical action potential produced from several excitatory post synaptic potentials. Image taken from Khan Academy, CC BY-NC-SA 4.0*

Autism spectrum disorders

Autism spectrum disorders are a group of lifelong neurodevelopmental disorders. Autistic individuals often have problems with social interactions and communication, restricted interests and repetitive behaviours. The most recent prevalence studies show that 1.1% of the UK population may be on the autism spectrum[1]. This is about 700,000 people and including affected families, autism spectrum disorders affect about 2.8 million people. The prevalence of autism spectrum disorders also has a marked influence on the UK economy. An individual with ASD and an intellectual disability is estimated to cost $£1.5m$ over the course of their lifetime[2]. These costs are mostly due to the provision of special education, lost employment (from the individual and the parents of the individual), and specialised residential care.

Care must be taken in steering away from the idea that autism can be cured, some see it as a normal variation in the human genome and a cure would be taking away from what makes an individual who they are. However, it cannot be ignored that ASD has a huge impact on the individuals diagnosed with the disorder, their families and society as a whole. Therefore, with more research, treatments can be developed that reduces these impacts whilst retaining the essence of the individual.

Currently only behavioural and pharmacological treatments are available that help with the symptoms of ASD (such as anxiety and ADHD), and these are only effective for a fraction of patients. There is no known medication that can alleviate the central symptoms of autism, that is the social and communication deficits[3].

E-I imbalance

Despite recent research linking several genes to autism, the underlying neurological causes are still a mystery. However, the leading theory for the aetiology of autism spectrum disorders is that there is some imbalance in the ratio of excitation to inhibition in the brain. Excitatory signals cause target neurons to fire whilst inhibitory signals suppress target neurons. The ratio of these two signals is called E-I balance. E-I balance is vital in maintaining normal brain function as it regulates the transfer of information throughout the brain. Too much excitation and neurons will constantly spike whereas if there is too much inhibition the neurons will not spike at all. In either of these states no information can be transferred (this is a similar concept to how in binary a series of just 1s or just 0s transfers no information, it is the combination of both in certain patterns that encodes data).

An early study by Rubenstein and Merzenich[4] linked some forms of autism with high levels of excitation or low levels of inhibition in brain areas associated with sensory, mnemonic, social and emotional systems. They also postulated that E-I imbalance was caused by both genetic and environmental variables affecting a given neural system. Since then there has been plenty of research into the subject and any links to autism spectrum disorders[5–7].

Excitation-inhibition imbalance has been clearly observed in mouse models of autism spectrum disorders. Pharmacological or cell type-specific gene rescue carried out on these models rescues any autistic like symptoms. These studies into animal models have shown that there is a clear link between E-I imbalance and ASD, however, they are all using invasive techniques such as optogenetics or using genetically modified mice. Obviously these techniques cannot be used in humans, and therefore, we do not know if the mechanisms studied in mice bare any relevance to ASDs in humans. Quantifying the relationship between mouse and human neurons under the influence of different E-I conditions will be the basis of this project.

Integrate and fire models

The simplest model of a neuron is the leaky integrate and fire neuron. This was proposed in 1907 by Louis Lapicque who modelled a neuron as a resistor and capacitor in series.

Project Objectives

The overarching aim of the research will be to investigate the links between E-I imbalance and autism spectrum disorders, and whether there is any substantial difference between the effects of E-I imbalance

in human and animal models. This will be done through the use of computational models of neurons which have inputs from both excitatory and inhibitory synapses. Both mouse and human neurons will be simulated with varying inputs. The results from the models will then be compared to see if there is any difference in how sensitive the neurons are to changes in excitatory and inhibitory inputs.

Work package 1:
To accomplish this a generalised leaky integrate and fire simulator will be written in Python based on the equations proposed in the Allen Institute's GLIF technical paper[8]. The simulator will allow for inputs from both excitatory and inhibitory synapses and output a voltage trace and mean firing rate. The synapses will be simulated using Poisson spike trains with refractory periods. Creating the functions for this simulator will make up work package 1.

Work package 2:
Once the simulator is completed several experiments will be conducted using it. The first experiment will examine the effect of changes in synaptic weight on the output of a neuron. A metric will be created for each neuron that shows how sensitive it is to changes

The second experiment will involve varying the firing rates of the excitatory and inhibitory synapses and observing the outputs. Again

Using doubly stochastic spike trains to correlate

All the experiments will be run on the 1218 neurons with GLIF models available from the Allen institute. Each experiment will be run several times and results averaged as they will be slightly different given the random nature of the Poisson inputs. Several runs of each simulation combined with the number of neurons means this will be a very compute-intensive project.

Work package 3:
The third work package will contain similar experiments to work package 2. However, instead of running experiments on a single neuron, a network of neurons will be created. This requires many of the individual neuron simulators from work package 1 to be hooked up together. The network will be tested with varying excitatory and inhibitory synaptic weight and output analysed. It will then be tested with varying firing rate for the first layer of neurons. As there are many neurons in the network computation time multiplies, and so, there may not be enough time to simulate all of the neurons available. However, simulating the network with a reasonable subset of the neurons available should still provide some meaningful results that can be analysed.

Work package 4:
All of the simulators created will be wrapped up in a GUI driven software package that will be distributed open source to the neuroscience community. This will allow experimental neuroscientists, who may not be familiar with programming, to input their neuronal data and conduct similar experiments to those that were done in work package 2 & 3 without the need to code their own simulations.

Work package 5:
Work package 5 will mainly consist of publicising the findings,
2 parallel projects one on single neurons one with bigger networks contingencies

Part II: Budget

- computer
- phd student or two
- brain simulation software. maybe
- cost of publishing a paper

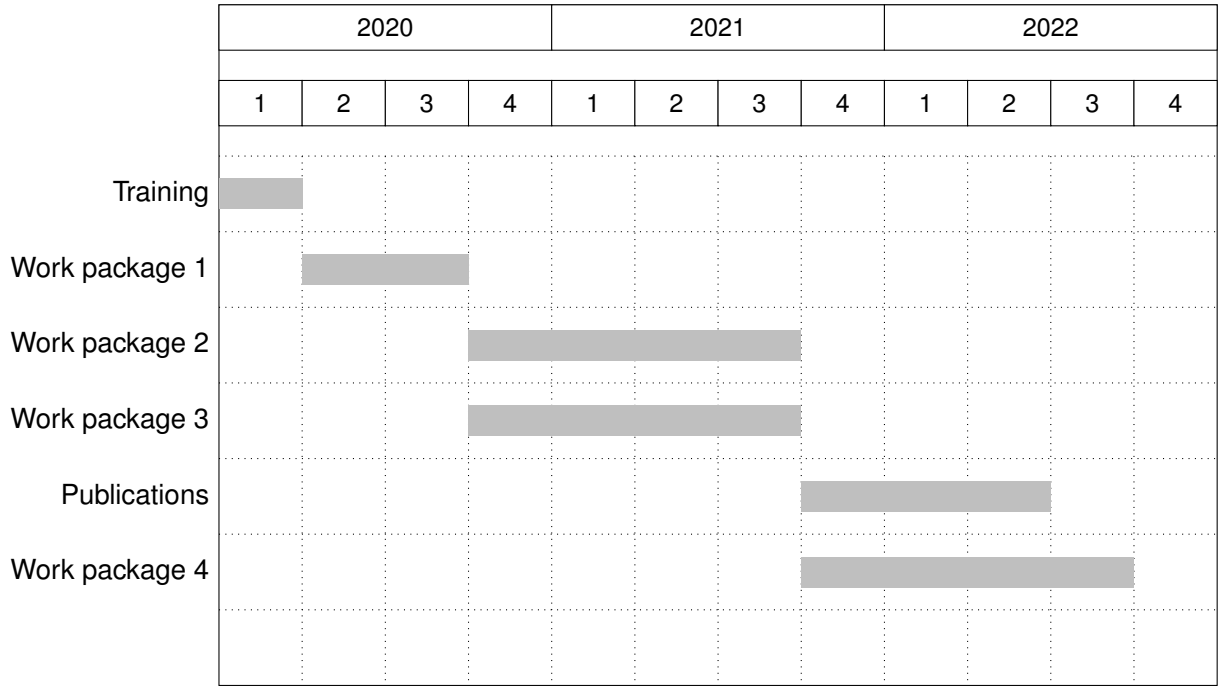
Description	Purpose	Cost
PhD Student	To do some research	$£100,000$
PhD Student	To do some research	$£100,000$
Conferences	4 Researchers and myself to go to one conference each year for the three years of the project. Including travel expenses, accommodation, food and conference fees.	$£100,000$
Technician	To help with creating the software package. Most likely a graduate with programming experience	$£30,000$
Publishing costs	Cost of publishing a paper to	$£100$
Salary	I will devote 20% of my time to overseeing the project	$£20,000$
		$£100,000$

Part III: Justification for resources

Part IV: Impact plan

distributed to therapeutics companies? Myself and the PhD students and Post Docs will attend the Bernstein computational neuroscience conference each year of the project. In the final third year of the project we will present our findings and software to paper published? engage with public. parents of autistic children usually interested in work

Part V: Work plan



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