# Anti-coincidence detection in the dendrites of human layer 2/3 neocortical neurons

MASTER THESIS

by

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*“ It has been said that the great events of the world take place in the brain.”*
*-Oscar Wilde, The picture of Dorian Grey*

# Abstract

**Abstract**

The purpose of this thesis is to implement a biophysical detailed single neuron model to investigate the active properties that underlie the dendritic computations in human layer 2 and 3 (L2/3) cortical neurons with the usage of Boolean Algebra. Due to evolutionary pressure, the human cortex over periods of years gained two major properties. First, it is extraordinary thick, especially the L2/3 supragranular layers, and, second, it has vast dendritic trees receiving numerous synaptic inputs. The experimental data to fit the model were produced by dual somato-dendritic patch clamp and two-photon imaging from Dr. Albert Gidon (Larkum Lab, Humboldt Universität, Berlin). They observed a fast dendritic calcium action potential (dCaAP), with previously unknown active properties. This dendritic action potential contributes to the repertoire of transformations from synaptic inputs to action potentials (APs) in human L2/3 neurons. The dendritic activation function, namely, the amplitude of those dCaAPs' as a function of the intensity of the current injection in the dendrite, was sharply tuned to an optimal input and progressively suppressed for stronger inputs. This indicated that dendrites of human L2/3 neurons are intrinsically capable of computing anti-coincidence functions like the XOR. To expand this computational modeling approach, it was investigated under which conditions (such as number and type of synaptic inputs) other activations functions from Boolean Algebra can be implemented. When implementing the coupled mode, meaning that dendritic response initiated somatic spikes, the latter was able to reproduce all logical operations except the negative ones. Interestingly, when implementing the uncoupled one with only the dendritic response, all logical operations including the negative ones were reproduced. These suggest that dendrites in human cortical neurons expand the computational power of neurons even to perform negative computations and provide evidence for a dendrite-centered theory of neuronal function. Thus, is important to investigate the capacity of these dendritic computations. The model also investigates what is the contribution of apical and basal dendrites of the L2/3 single neuron when only the basal sub-region is stimulated and under specific conditions of N- methyl-D-aspartate receptor (NMDA) spiking activity. Future work involves further investigation of the computation and cellular substrate, e.g. spines and morphological features of the human cortical neurons, towards a more thorough functional application of this novel dendritic activation mechanism to human cognition.

**Keywords:** human L2/3 cortical neurons, neocortex, anti-coincidence detection, Boolean algebra, logical gating, capacity of dendritic computation, apical and basal dendrites, NMDA receptor.

**AIM**: The purpose of this thesis is to give comprehensive insights into the computational power and biophysical properties of human cortical neurons.

# Preamble

**Acknowledgments**

I would like to express my gratitude to my supervisor Dr. Panayiota Poirazi for her warm welcome in her lab, and all the useful comments and remarks through the learning process of this master thesis. The door to Dr. Poirazi's office was always open whenever I ran into a trouble spot or had a question about my research or writing. Her intelligence, spark, excitement, and engagement in research will always be an exemplar on my scientific pathway. Furthermore, I would like to thank Dr. Athanasia Papoutsi for introducing me to the topic, as well as, for her kind guidance on the way. This accomplishment would not have been possible without her. In addition, I would like to thank all members of Poirazi lab, past and new, for all the fruitful discussions in the lab meetings and beyond. Also, I would like to thank all professors and tutors of the Master's program in Bioinformatics for the skills and expertise I gained these two years. Moreover, I would like to express my very profound gratitude to my parents, my siblings, my friends and to my partner for providing me with unfailing support and continuous encouragement throughout my years of study. They might be out of the scientific pathway, but they were present every time I needed them. Thank you for that. Last but not least, I would like to acknowledge the difficult time of the fire in the student housing of the University of Crete I experienced. I will never forget the day I lost everything. So, cheers to that day that made me stronger! So stronger, I am now a Marie Skłodowska-Curie PhD Fellow at the University of Cyprus and Center for Applied Neuroscience, where I am trying to correlate neurobiology with behavior for neurodegenerative disorders, having a balanced work and personal life. Sky is the limit!

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# Introduction

*“ Computational neuroscience provides us with the tools and methods for doing three different things. One is characterizing what the nervous systems does. The second is determining how it functions. And finally, the third is, understanding why it operates in particular ways.”*
*-P. Dayan and L. Abbott*

## 1.1 The neocortex of the humans

Understanding how the brain works is one of the fundamental challenges in science today, with profound implications not only for how we treat neurodegenerative diseases, but also for how we view ourselves as humans. The cerebral cortex is characterized by an extremely dense connectivity, with each pyramidal neuron receiving between 5000 and 60000 synaptic contacts. A large part of this connectivity originates from the cortex itself (Braitenberg and Schuez, 1998, DeFelipe and Farinas, 1992). The neocortex is part of the human brain that is involved in higher-order functions such as conscious thought, spatial reasoning, language abstract thought, imagination, generation of motor commands, rationalism and sensory perception. It is consisted of discrete sections – each one with different functions: the frontal lobe for executive functions, thinking, planning, organizing, problem solving, emotions, behavioral control, personality, the motor cortex for movement, the sensory cortex for sensations, the parietal lobe for perception, and making sense of the world, arithmetic, spelling, the occipital lobe for vision, and the temporal lobe for memory, understanding, and language. In comparison with other species, human neurons are particular different, having a thicker (~3mm) cortex and larger dendritic arbors (Defelipe, 2011; DeFelipe et al., 2002; Mota and Herculano-Houzel, 2015; Sun and Hevner, 2014). As a result, the supragranular layers (L2/3) have a disproportional thickening (Mohan, 2015) and numerous synaptic inputs in their vast dendritic trees (Deichter, 2017). Those evolutionary insights make their biophysical properties unique. The neocortex is made up of six layers, labeled from the outermost inwards, 1 to 6. The synaptic input in the L2/3 pyramidal neurons stems either from other L2/3 pyramidal neurons or from layer four (L4) spiny stellate neurons according to Lübke, 2003 and Binzegger, 2004.

| Layers | Components | Schematic | Afferents | | Efferents |
|---|---|---|---|---|---|
| I – Molecular | Axons and Dendrites (Cell processes) | | From other regions of Cortex and Brainstem | Epomedicine.com | To other regions of cortex (Intra-cortical Association functions) |
| II - External granular | Densely packed Stellate cells + Small pyramidal cells | | | | |
| III – External pyramidal | Loosely packed Stellate cells + Medium pyramidal cells | | | | |
| IV – Internal granular | Densely packed Stellate cells only | | | + From Thalamus | |
| V – Internal pyramidal | Large pyramidal cells only (few stellate cells) – Giant Pyramidal cells of Betz | | | + From Brain stem | To Brain stem & Spinal cord (Projection fibers) |
| VI - Multiform | Multiple sized pyramidal cells + Loosely packed stellate cells | | | | To Thalamus |

Figure 1.1: Layers of the neocortex.[1]

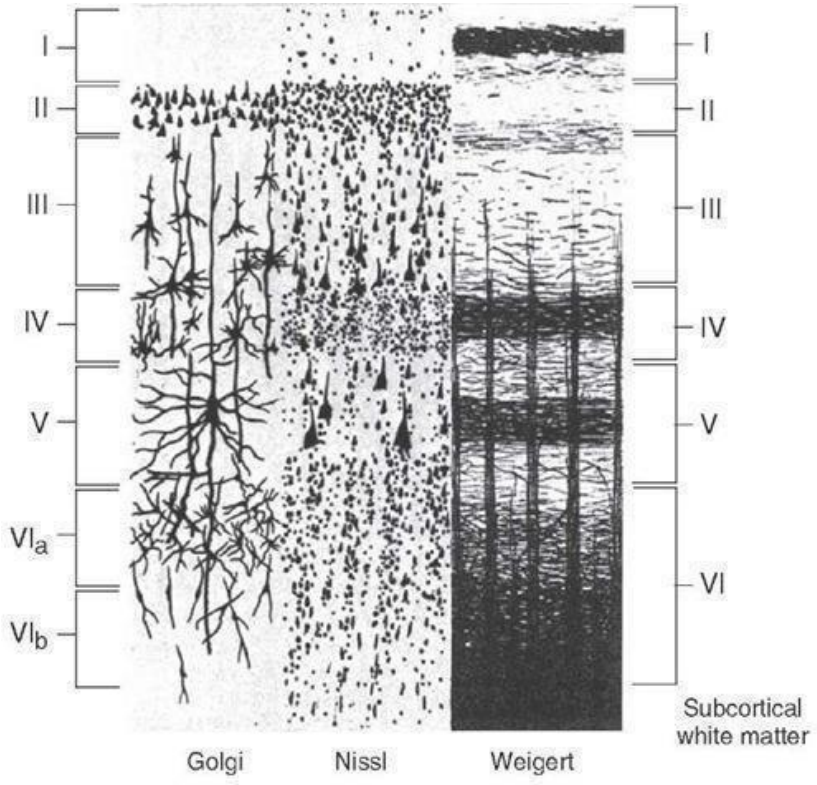


Figure 1.2: Staining across layers of the neocortex revealing the position of neuronal cell bodies and the intracortical axon tract.[2]

[1] https://epomedicine.com/medical-students/cerebral-cortex-layers-microanatomy-simplified/

[2] https://healthlifemedia.com/healthy/cortical-layers-of-the-cerebral-cortex/

In this thesis, the experimental data to fit the single neuron model were obtain from simultaneous intracellular electrical recordings from the soma and apical dendrite in human neocortex acute slices from surgically resected brain tissue of epilepsy and tumor patients from their temporal, temporomesial and frontal lobe in L2/3. All human experiments were approved by the Ethics Committee of the Charité Universitätsmedizin Berlin and performed in agreement with the Declaration of Helsinki. Dual whole-cell voltage recordings and two- photon imaging were performed from the soma and dendrites of non-pathological neocortical tissue resected from twenty-three epilepsy patients and three patients with brain tumor (Gidon et. al, under revision 2019).

## 1.2. Dendritic action potentials in rodents

In computational terms, a model can be defined by a function, estimated mathematically. What is trying to be estimated is an encoding function - one which converts a stimulus into a neurological response. At the soma, after crossing a threshold, a greater response corresponds to the generation of spikes, also known as action potentials (APs). The computational power of a neuron is constituted by the transformation from synaptic inputs to APs. A spike is defined by a threshold and a non-linear jump. Dendrites are branched extensions of a neuron and receive chemical signals emitted from projecting neurons and transfer these signals to the cell body, or soma. It is common knowledge that ion channels are membrane proteins that function as electrical signal transducers. They govern the electrical properties of all living cells. The function of ion channels is regulated by a number of signaling molecules. Their classifications include potassium, sodium, and calcium ion channels. Ion channels are divided into voltage-gated and ligand-gated channels based on the type of physiological stimulus activator. A cortical neuron receives thousands of inputs from other neurons and its dendritic tree performs nonlinear transformations to those synaptic inputs, sometimes resulting in a sublinear way (Longoro et al., 2013) or in supralinear integration of those inputs (Losonczy and Magee, 2006; Nevian et al., 2007; Branco and Häusser, 2011; Makara and Magee, 2013). Thus, cortical neurons integrate thousands of synaptic inputs in their dendrites in highly non-linear ways called dendritic non- linearities. Local non- linear summation of excitatory inputs, namely a dendritic spike refers to an AP generated in the dendrite of a neuron. The dendrites of pyramidal neurons can support sodium, calcium and N-methyl-D-aspartate (NMDA) spikes. These nonlinearities have been traditionally studied from the perspective of single-neuron computations, using a few well- controlled synaptic stimuli, revealing a remarkable repertoire of arithmetic operations that the dendrites of cortical neurons carry out (Poirazi and Mel, 2001; London and Häusser, 2005; Branco et al., 2010) including additive, multiplicative and divisive ways of combining individual synaptic inputs in the cell's response (Silver,2010).

In Figure 1.3, dendritic APs recorded from the mouse brain alongside with their duration are depicted showing the different kinetics of the different types of dendritic spikes. Back propagating APs are also considered, that are not depicted here.

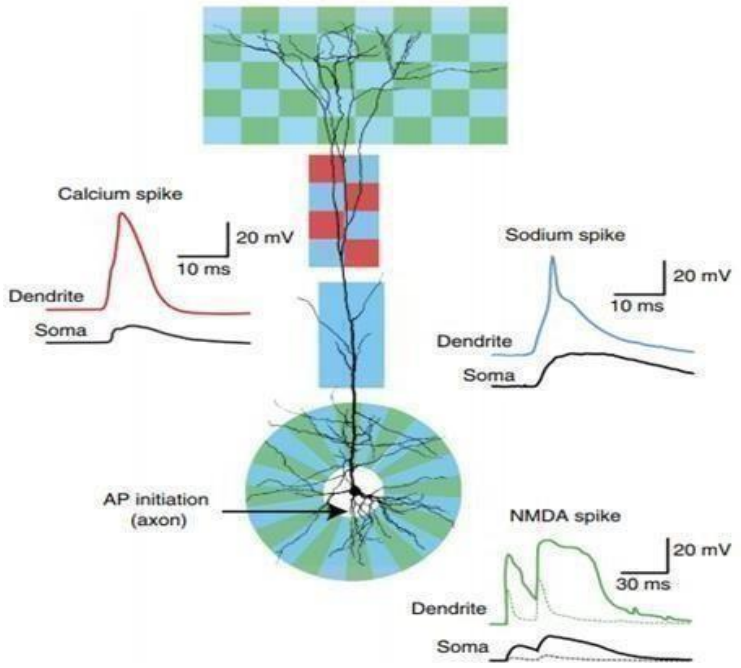


Figure 1.3: Dendritic integration: 60 years of progress.[3]

3. Stuart, G.J., Spruston, N. (2015), Nature Neuroscience, Dec;18(12):1713-21.

# 1.3 Dendritic properties of human neurons

However, the knowledge on how dendritic factors in human neurons contribute to input-to-output transformations in human cortical neurons is still an open topic. Some of their unique properties enable human neurons to perform various functions. Through the literature, there are six papers to my knowledge which deal with the human dendritic properties using either experimental or computational approaches (from non-post-mortem tissue). In general, human neurons have larger dendritic arbors, and thus improved encoding capabilities (Eyal et. al, 2014). Their large dendritic load enables high frequency modulation by axonal spikes. Their dendritic length is 3-fold larger than other model organisms like mouse or macaque with an increased branch complexity in size and shape (Mohan et. al, 2015). Moreover, they have faster action potentials than mouse AP. Interestingly, human neurons have a specific value of membrane capacitance set to 0.45 μf/cm2, which is also used in the thesis model and is unique in the literature (Eyal et. al 2016). In addition, their basal terminal is particularly elongated, enabling multiple nonlinear processing units and the distal dendrites of human neurons provide limited excitation to the soma (Deichter et. al 2017). Last but not least, there is a specific number of synapses from experimental and modeling approaches so as to generate somatic sodium spikes (Beaulieu-Laroche et. al 2018). Last but not least, Eyal et. al, 2018 predicted particularly larger AMPA- and NMDA-conductances and spiking compared to rat cortex. Overall, all these properties, make the neuron distinct in comparison to other model organisms that are evolutionary close to human. Nevertheless, human cortical neurons are not “scaled-up” versions of rodent or macaque, but have unique and functional properties which enable the human brain to perform higher cognitive functions. Deriving from those properties, Gidon et. al (under revision 2019) pinpoint a fast dendritic calcium AP. Thus, the aim of this thesis is to expand the findings from the latter work and investigate what computations human neocortical neurons of L2/3 are able to perform using this novel AP and Boolean Algebra.

# 1.4. McCulloch-Pitts neuron

But first, let's see if the scientific community over the years has been interested in a topic like this. Why and how Boolean Algebra can assist understand the functional properties of human neocortical neurons? It is very well known that the most fundamental unit of deep neural networks is called an artificial neuron. In 1943, neuroscientist Warren McCulloch and logician Walter Pits took the first step toward this artificial neuron, by mimicking the functionality of a Biological neuron. The neurons they used were simple threshold neurons, called the perceptrons. They are known as pioneers to formally define neurons as computational elements.

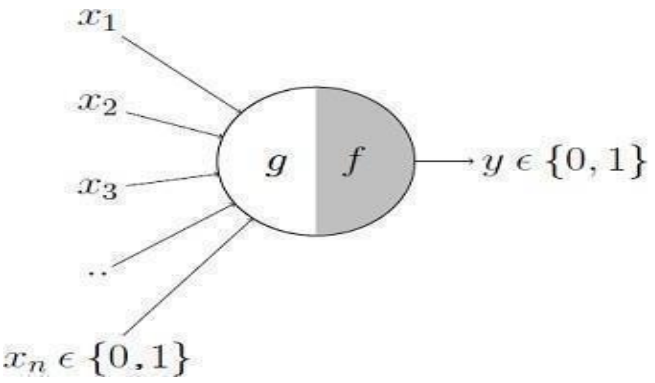


Figure 1.4: The part g takes an input, performs an aggregation and based on the aggregated value the second part f makes a decision. They first established the neural activity of an artificial perceptron using logical gating to a mathematical model of a biological neuron.

Their idea explores simplified neural models to get the essence of neural processing by ignoring irrelevant details and focusing in what is needed to do a computational task.

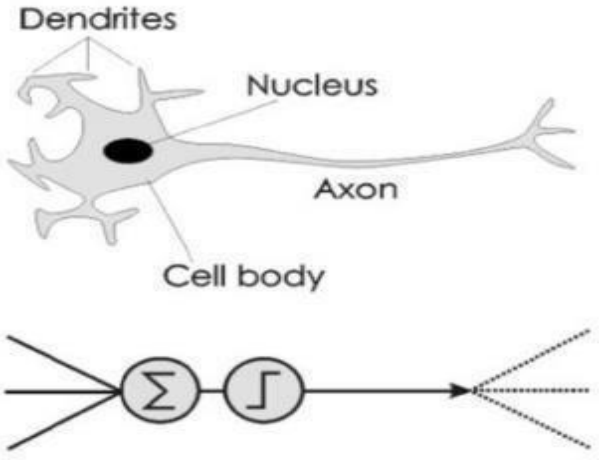


Figure 1.5: Neural processing of an artificial neuron.[4]

McCulloch and Pitts knew that spikes, or APs, somehow carry information throughout the brain.

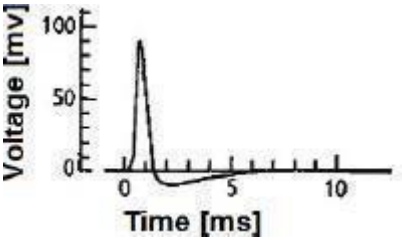


Figure 1.6: Each spike would represent a binary 1, each lack of spike would represent a binary 0.[5]

So, as a rule, McCulloch-Pitts neurons are binary. They take as input and produce as output only 0's or 1's.

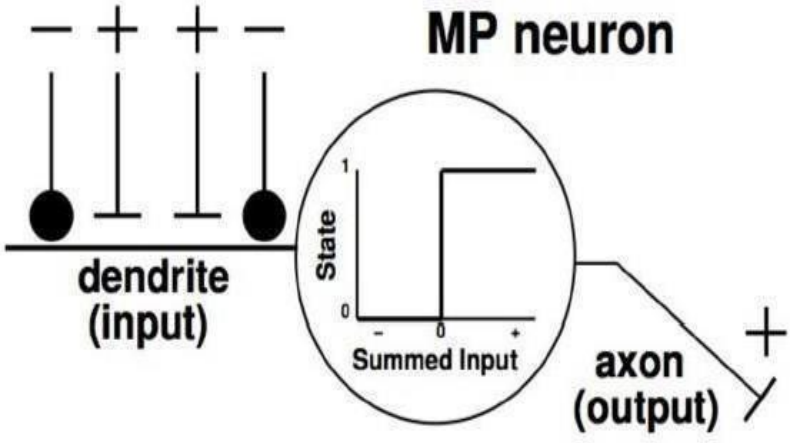


Figure 1.7: Activations from other neurons are summed at the neuron and outputs 1 if threshold is reached and 0 if not.[6]

In mathematical terms,

$$y = \varphi\left(\sum_{i=1}^{n} w_i \cdot x_i\right)$$

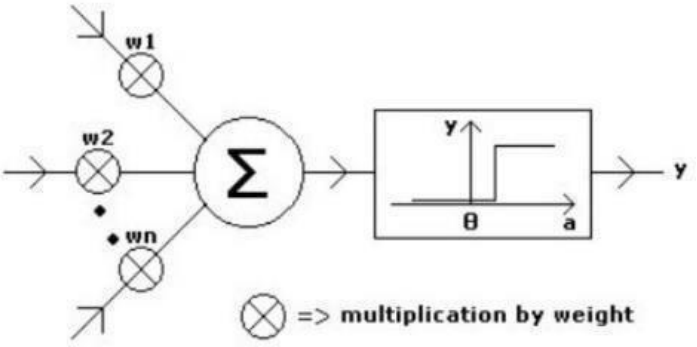


Figure 1.8: where φ represents a threshold or a sigmoid function.[7]

[4,5,6,7] Lectures in Computational Neuroscience course, M.Sc. Bioinformatics

In their paper, they showed how spikes could be combined to do logical and arithmetical operations.

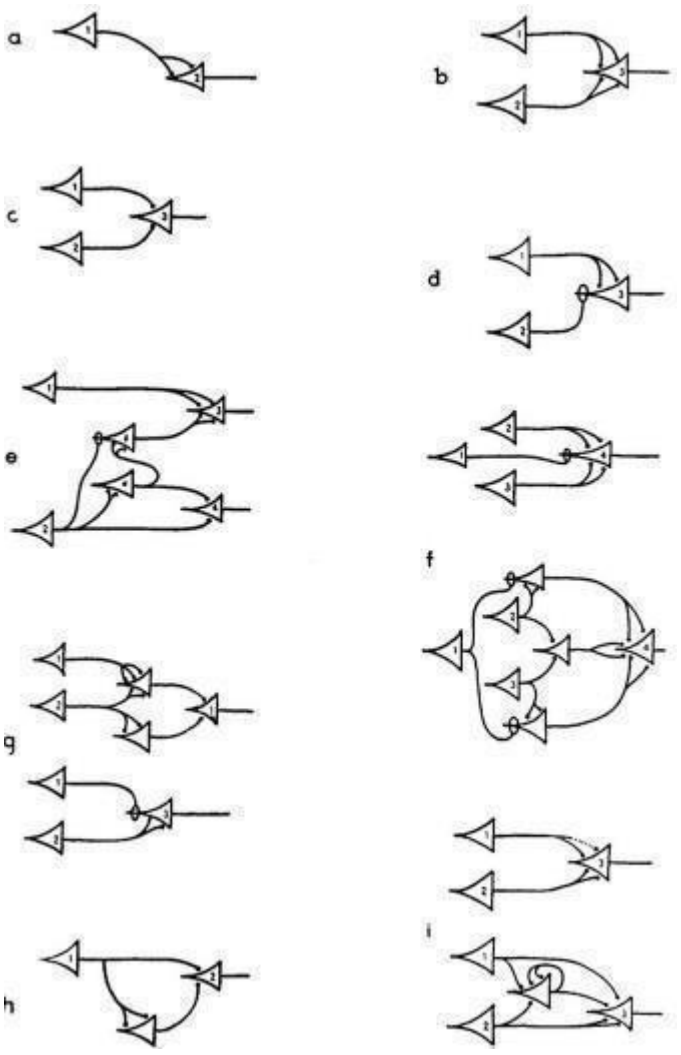


Figure 1.9: A logical calculus of ideas immanent in nervous activity. The numbers in the cell bodies are the thresholds of the respective neurons.

In 1958, Frank Rosenblatt, an American psychologist, proposed the classical perception model, the mighty artificial neuron as a linear classifier. It is a more generalized computational model than the McCulloch and Pitts neuron where weights and thresholds can be learnt over time. In their model, you need more neurons and inputs so as to potential model logical gating in the brain. This, however, exceeds the purposes of the biophysically detailed single neuron modeling which is discussed in this thesis and the first idea of McCuloch-Pitts binary threshold neurons will be in a greater favor.

## 1.5 Logical gating in neuroscience

So, how can we link logical gating and neuroscience? Can a neuron be seen as a computational binary element and perform logical gating as McCulloch and Pitts proposed? In the brain, neuronal cells function in a more complex yet similar way to logic gates in digital computers. Unlike most cells, neurons have a structure of axons and dendrites for transmitting and encoding signals. As we saw, a neuron receives a range of inputs from its dendrites, integrates them, and produces an output in the axon depending on the type and frequency of the input signal. That signal provides input to other neurons. The input to a neuron must surpass a threshold to cause it to spike. The input signal depends on whether the synapse, the collection of signals between the axon and dendrites of neurons, is strong, or weak, excitatory, or inhibitory. A neuron with two inputs can act in different modes depending on the type and strength of its inputs. The output of a neuron's axons is a series of pulses of on and off signals as seen in computers' logic gates. Albeit, neurons are much more complex and versatile than computers, since they integrate thousands of inputs from dendrites, and process them both temporally and spatially. Computers must only execute a function or program in a sequence of steps. For example, the logical function of two strong excitatory inputs of logic OR the neuron will be stimulated if either input is active. In the logic AND of two weak excitatory inputs both must be active to stimulate the neuron. In biology, the activity of a neuron depends on the activity of the stimulus. Neurons, unlike computer logic gates, are adaptable. Internal and external factors may change the neurons' functions. Neurons can memorize information for a short- term by a electrochemical process or long-term by structural means. With electrical memory, ions flow due to transmission and basic information processing lasting 1 to 100 milliseconds. Chemical change may create a second to a minute of memory as balances and secondary messengers affect receptors and ion channels in the cell membranes. Memory lasting for 1 to 24 hours occurs by molecular synthesis and gene expression leads to long- term modification. Structural changes in the cell itself last from 1 to 365 days. This alters information processing and also changes membrane extensions like synapses and dendrites connecting to other neurons and the outside. So, how could the concept of logical gating be incorporated in a biological neuron? In figure 1.10 from Häusser and London explain that in layer 5 (L5) of rat model logical operations can be implemented. This is a schematic figure highlighting four key dendritic mechanisms, mapped onto a L5 pyramidal neuron morphology, which can allow dendrites to act as computational elements. These mechanisms can coexist in the same neuron and be active in parallel or in a hierarchical manner. In the top left we can see that nonlinear interaction between excitation and shunting inhibition on small dendritic branches can implement logical operations. The branch marked by an arrow sums up the current from the two subtrees, such that its output would be a logical OR on their output. Each of the subtrees will in turn inject current if and only if the excitation AND-NOT the inhibition will be active onto a different branch (open circles) are only slightly influenced by this spike. In the top right: the L5 cortical pyramidal neurons, as depicted here, coincidence detection between the apical and basal dendritic compartments is achieved by active dendritic mechanisms. A backpropagating action potential, which coincides with a distal synaptic input, will trigger a dendritic $Ca^{2+}$ spike, which depolarizes the whole apical dendrite and drives a burst of spikes in the axon.

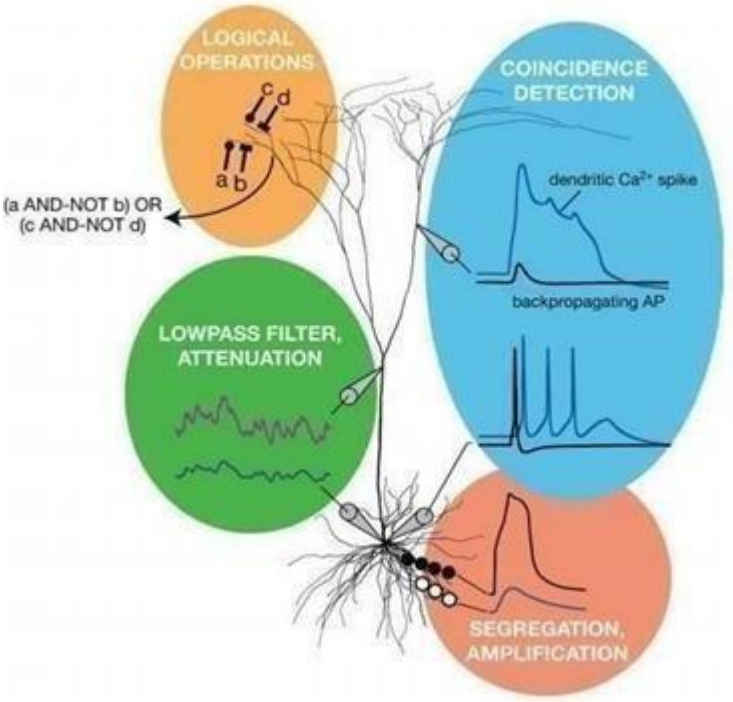


Figure 1.10: A schematic figure highlighting four key dendritic mechanisms, mapped onto a L5 pyramidal neuron morphology, which can allow dendrites to act as computational elements.

All these, are discussed because the single neuron in our model tries to mimic a threshold neuron so as to investigate if logical gates exist in cortical computation. And if all of this seems a little far removed from biology, it actually seems like the hierarchy of processing areas such as visual information travels throughout in the brain are organized in chains of AND and OR gates. First the AND neurons search for co-active patterns of activation, then the OR neurons fire to signal if a pattern has been sensed anywhere in their receptive field, according to whether any of the AND gates presynaptic to them are active. One big question that is generated is: What dendritic computations underlie the distinct somatic and dendritic spike properties that make human neurons unique? Are logical operations a plausible answer?

Following, we will focus on the XOR function (Figure 2.1). The XOR function is considered a non-linear gate, due to the fact that you cannot draw a straight line to separate the points (0,0),(1,1) from the points (0,1),(1,0). In computer science and machine learning, this is the so called XOR affair that will engage a major part of this thesis work, and it is considered to only be solved in multilayer networks.

# 2
# Materials & Methods

*" Neuroscience is by far the most exciting branch of science because the brain is the most fascinating object in the universe. Every human brain is different - the brain makes each human unique and defines who he or she is."*

*-Stanley B.Prusiner*

## 2. 1 Boolean Algebra

Let's see how many combinations two binary variables can generate to build logical operations, apart from the famous XOR function.

| X | Y | F0 | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | F15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |
| 1 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 |

Figure 2.1: Truth table listing all possible functions for two variables.

By definition, we can see that the number of logical operations derived from two binary inputs, are sixteen. Can these operations be performed by the dendrites of our model?

For visualization purposes, below are the graphical representations of the logical operations. A logical gate can be classified as linear if and only a single line can separate the activated output point from the inactivated one.

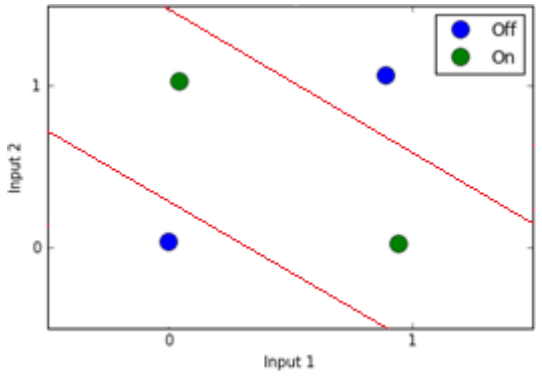


Figure 2.2: XOR gate (non-linear). Mathematical representation: F = xy +x'y'

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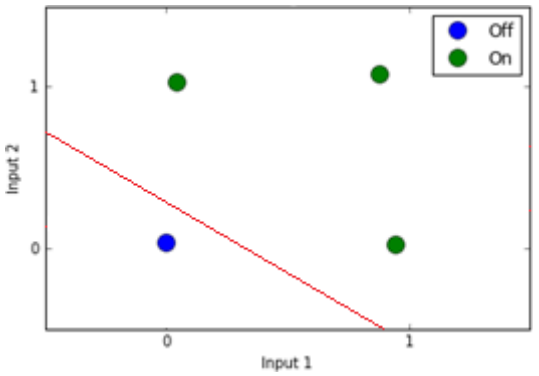


Figure 2.3: OR gate (linear). Mathematical representation: F = x + y.

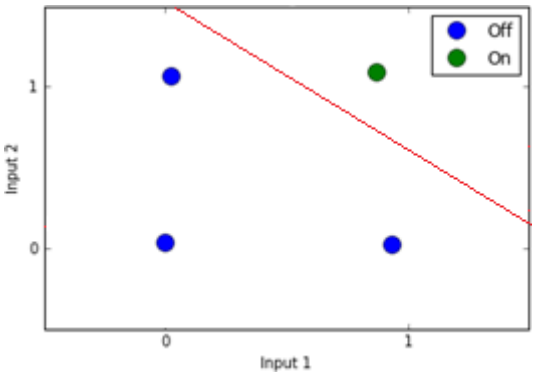


Figure 2.4: AND gate (linear). Mathematical representation: F = x*y.

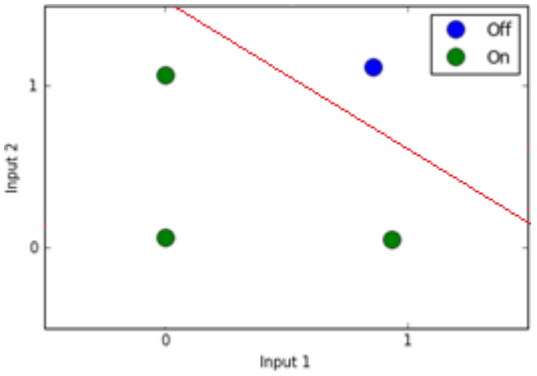


Figure 2.5: NAND gate. Mathematical representation: F = (x*y)'.

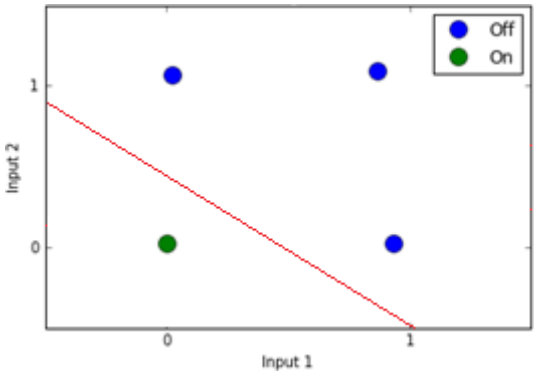


Figure 2.6: NOR (linear) gate. Mathematical representation: F=(x+y)'.

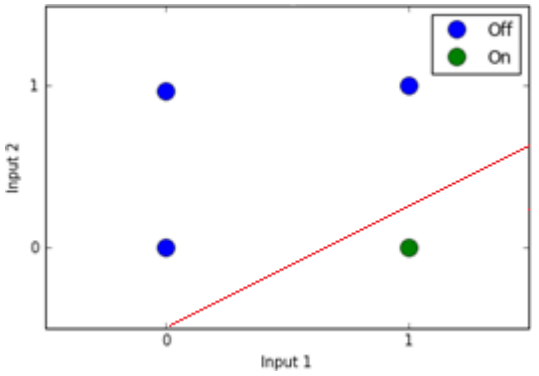


Figure 2.7: F2 (linear) gate. Mathematical representation: F = x*(y)'.

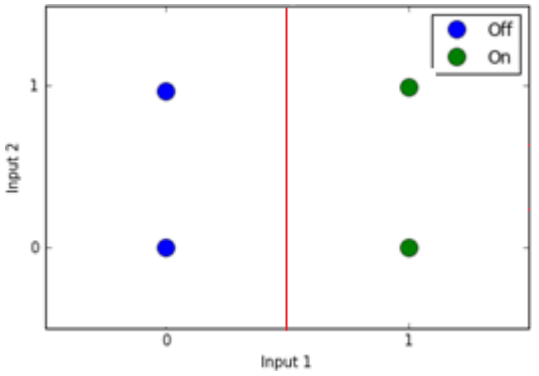


Figure 2.8: F3 (linear) gate. Mathematical representation F = x.

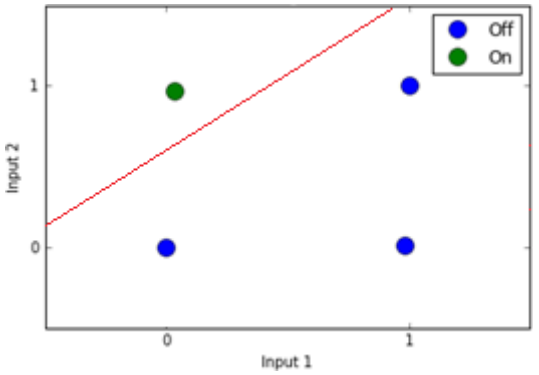


Figure 2.9: F4 (linear) gate. Mathematical representation: F = x'y.

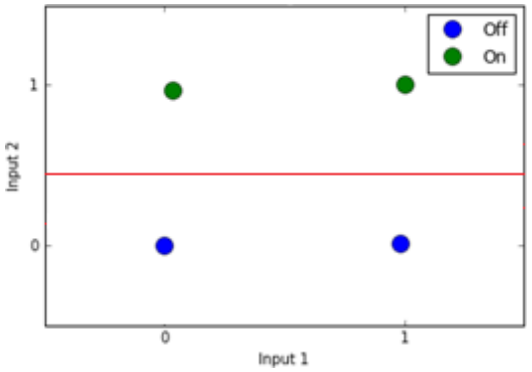


Figure 2.10: F5 (linear) gate. Mathematical representation: F = y.

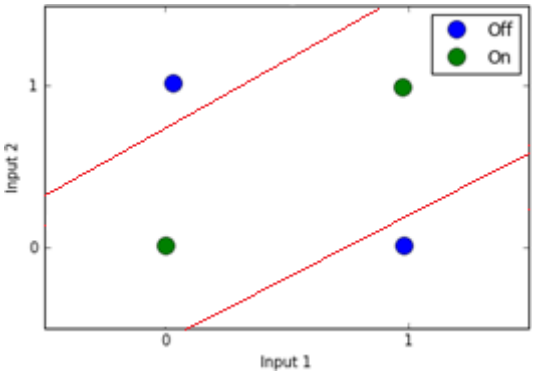


Figure 2.11: F9 (non linear) gate. Mathematical representation: F = xy + x'y'.

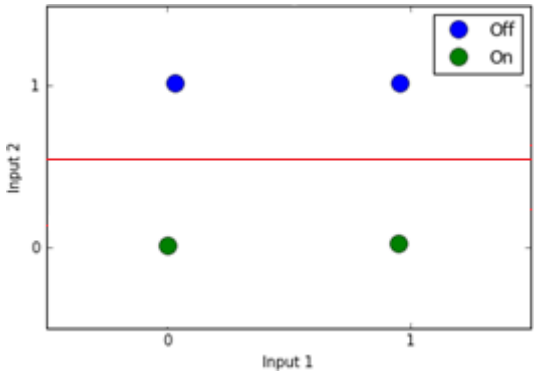


Figure 2.12: F10 (linear) gate. Mathematical representation: F=y'.

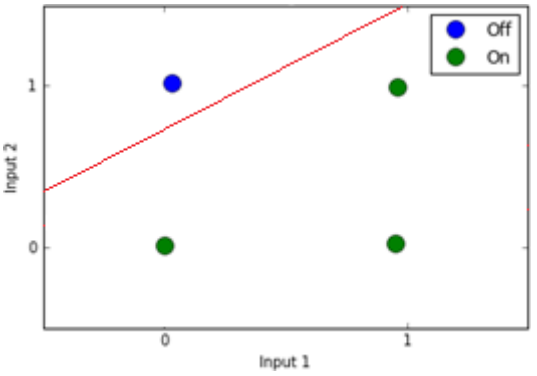


Figure 2.13: F11 (linear) gate. Mathematical representation: F=x+y'.

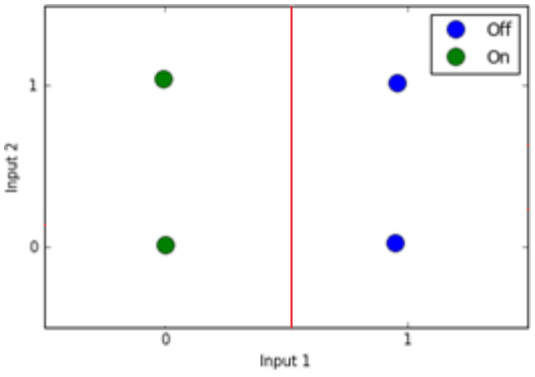


Figure 2.14: F12 (linear) gate. Mathematical representation F= x'.

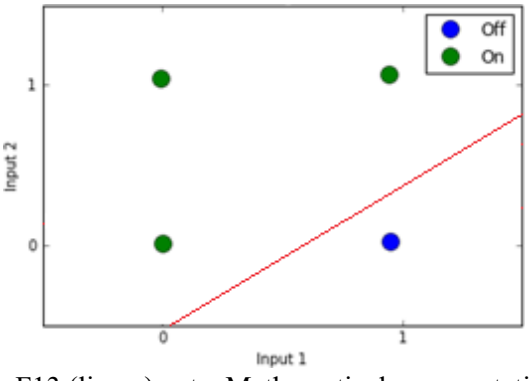


Figure 2.15: F13 (linear) gate. Mathematical representation = x' + y.

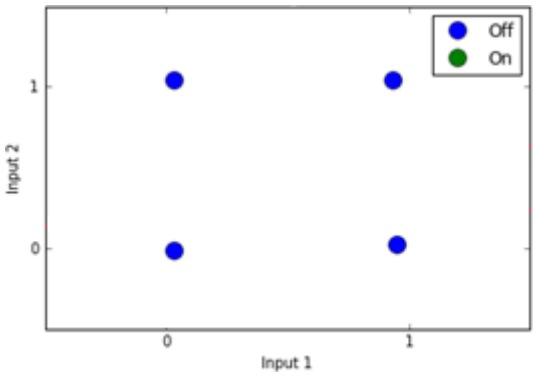


Figure 2.16: F0 null (linear) gate. Mathematical representation: F = 0.

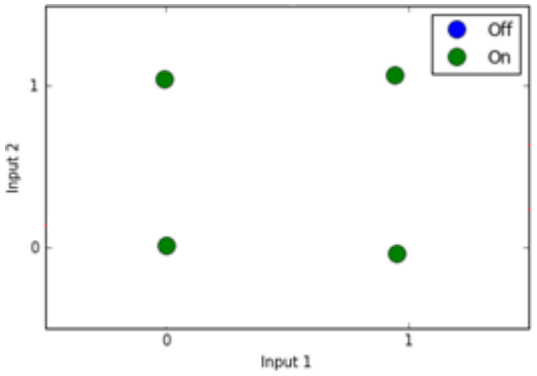


Figure 2.17: F15 identity (linear) gate. Mathematical representation: F = 1.

The following table summarizes the linear and non-linear gates.

| Linear gates | Non-linear gates |
|---|---|
| AND | XOR |
| OR | EX-NOR |
| NAND | |
| NOR | |
| F2 | |
| F3 | |
| F4 | |
| F5 | |
| F10 | |
| F11 | |
| F12 | |
| F13 | |
| F0 | |
| F15 | |

Table 2.1: Linear and non-linear gates.

## 2.2 Non-separable Boolean functions in single dendritic computation

It is a common belief that single neurons are incapable to perform linearly non-separable computations like the famous XOR. In Romain Cazé thesis (Cazé et. al 2013), it is demonstrated that all neurons possessing a single passive dendritic branch are capable of logical computations. The so-called dendritic spikes, result in independent spiking dendritic sub-units, which turn pyramidal neurons into two-layer neural networks capable of computing linearly non- separable functions, such as the XOR. This work involved determining if binary neurons can also compute linearly non-separable Boolean functions implementable by a binary neuron model with a linear sub-unit and either a single spiking or a saturating dendritic sub- unit. Specifically, they showed show that non-linear dendritic sub-units, in addition to the somatic non-linearity, are sufficient to compute linearly non-separable functions. They proved that, with a sufficient number of saturating dendritic sub-units, a neuron can compute many functions computable with purely excitatory inputs. And that these linearly non-separable functions can be implemented with at least two strategies: one where a dendritic sub-unit is sufficient to trigger a somatic spike; another where somatic spiking requires the cooperation of multiple dendritic sub-units.

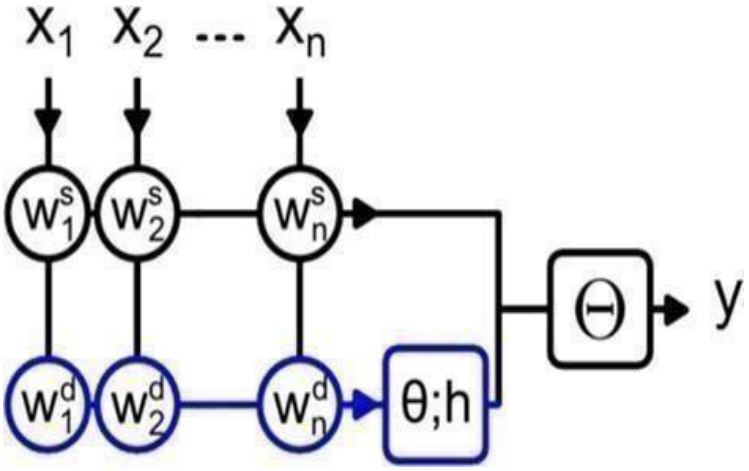


Figure 2.18: A two stage neuron model with one dendritic subunit. Structure and parameters of the neuron model: x, and y are binary variables describing pre and post-synaptic neuronal activity; in circles are two independent sets of non-negative integer-valued synaptic weights respectively for the linear (black) and the non-linear (blue) subunits; in the blue square, θ and h are the non-negative integer-valued threshold and height that parameterize the dendritic activation function D; in the black square Θ is a positive integer-valued threshold determining post-synaptic firing.

Specifically, it is shown that a two-stage neuron without inhibition can implement only and all positive Boolean functions with as many dendritic units.

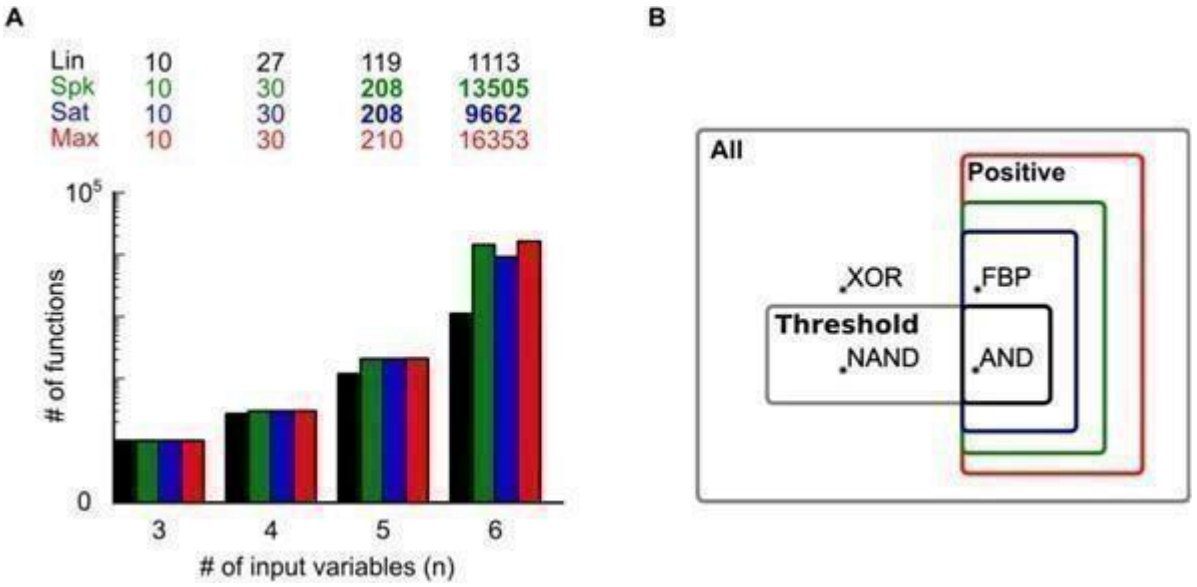


Figure 2.19: A. Number of computable representative positive Boolean functions depending on the number of input variables n and on the type of synaptic integration (black – linear, green – linear with a spiking dendritic subunit, blue – linear with saturating dendritic subunit, red – maximan number of positive representative function) B. Venn diagram for sets of Boolean function for n>=6

As a consequence, they proved that dendritic spikes, combined with somatic non-linearity, enable a neuron to compute positive linearly non-separable Boolean functions. A year after this work, using again a binary neuron model in conjuction with Boolean Algebra, they suggested that dendritic saturations as well as dendritic spikes enhance single neuron computation even if when they cannot directly make the neuron fire, they enhance a single neuron computation in the binary neuron model (Cazé et. al 2014). The implementation of these functions does not require the dendritic non-linearity to make the neuron spike. Within these models and contrary to the binary model, the dendritic and somatic non-linearity are tightly coupled. Yet, they showed that these neuron models are capable of linearly non- separable computation.

So, taking all the above about logical gating and neuroscience into consideration, and study in parallel the new work of Gidon et. al, we wanted to see how many Boolean functions could be reproduced in the latter model apart from the XOR. We took into consideration, the number and type of synaptic input for the specific pathways the model is utilizing and other logical operations from Boolean Algebra. In the next section, all these combinations of logical gating are generated according to the number of synapses for each pathway of the single neuron model, so as to give an intuition on how human cortical dendrites of L2/3 may compute.

# 2. 3 The biophysical model

First, let's validate with the assistance of a python script how many combinations we have when we have two binary inputs:

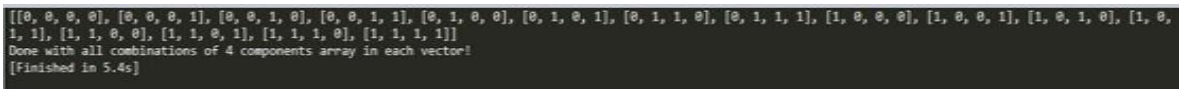


Figure 2.20: Output from python script. Generate a set of input vector with n components and containing equal/different number of ones given ex. Returns set of 0/1 vectors to be classified.

Now, let's see the model of Gidon et. al (under revision, 2019). Here, the description of the detailed biophysical model of L2/3 neuron is discussed. It consists of 101 basal and 81 apical dendrites, a somatic compartment, and an axonal cable (1000 µm length, 1 µm diameter). Compartments lengths were at most 30 µm.

| Biophysics | Active properties | Passive properties | Passive properties from soma to axon | Cell properties | Origin cell | Model cell |
|---|---|---|---|---|---|---|
| Celcius = 37 | gNabar_ traub = 0.1 | Rm = 37 | G_pas = 0 | Del = 300 | Rin = 41 | Rin = 40 |
| | gKbar_traub = 0.015*3 | G_pas = 1/Rm/1000 | gLbar_traub = 1/Rm/1000 | Dur = 1000 | Tau = 14 | Tau = 14 |
| | | E_pas = -80 | E_l = -80 | Amp = 0.4 //0.1 | Somatic resting = -75 | Somatic resting = -70 |
| | | Rheobase = -3 | E_k = -85 | Tstop = 15000 | Somatic rheobase = 0.4 | Somatic rheobase 0.05 |
| | | Cm = 0.45 | E_Na = 90 | | | |
| | | Ra = 100 | | | | |

Table 2.2: Description of the model of Gidon et. al.

Membrane capacitance ($C_m$) and axial resistance ($R_i$) were uniformly set to 0.45 μF $cm^2$ (Eyal et. al) and 100 Ω×cm, respectively, over the entire dendrite. These values resulted in somatic input resistance ($R_{in}$) and membrane time constant ($\tau_m$) of 40 MΩ and 14 ms, respectively, similar to the experimental values ($R_{in}$ = 41MΩ and $\tau_m$ = 14 ms). The single neuron model of Gidon et. al derives from morphological detailed reconstructions from acute slices of L2/3 neurons from presumably non-pathological surgically resected neocortical tissue from the anterior temporal lobe of twenty-three epilepsy patients and three patients with brain tumor using dual somato-dendritic patch clamp and two-photon imaging. Sodium (INa), and potassium delayed rectifier (IKdr) currents, with the corresponding maximal conductances, gNa = 0.1 S/$cm^2$, gK = 0.045 S/$cm^2$ and reversal potentials, EK = -85 mV, ENa = 90 mV. Rm was 37 MΩ×$cm^2$. The rate functions for the sodium and potassium channels where adapted from Traub et al. (1991), with a slight modification for the potassium channels whereby the activation time constant, $\tau_n$, was reduced by a factor of two, and all activation curves were shifted by to –35 mV. In addition, the model uses synaptic mechanisms for α- amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), NMDA, and γ-aminobutyric acid (GABA) receptors described above.

| Synaptic mechanisms | Gmax | tau_r | tau_d | Mg | Gamma | Se |
|---|---|---|---|---|---|---|
| **AMPA** | 0.1e – 3 | 0.3 | 1.8 | 0 | - | - |
| **NMDA** | 0.1e – 3 | 8 | 35 | 1 | 0.06 | - |
| **GABA** | 0.1e – 3 | 0.5 | 20 | 0 | - | -80 |

Table 2.3: Synaptic mechanisms

All those active properties of L2/3 revealed a previously unknown mechanism that included fast calcium APs in their dendrites (dCaAPs). dCaAPs were simulated at one dendritic compartment where threshold, width, and height as a function of the input strength were simulated by sum of current sources with a sigmoidal shape. Specifically, the dCaAP current,

$$I_{dCaAP} = -wK(v)(A - B)$$

was triggered when membrane potential crossed –35 mV. *w* is a parameter such that the dCaAP amplitude was about 40 mV at threshold. A and B, the rise and decay of the dCaAP current were given by sigmoid functions. The dCaAP inactivation, set as a function of the membrane potential, *K*(*v*) (where in our passive dendritic model approximate dCaAP inactivation as a function of the current *K*(*i*)), is

$$K(v) = exp[\frac{F \times (v - v_{th})}{\tau_{inac}}]$$

where v is the membrane potential at the location of the dCaAP, vth is the threshold (–36 mV) for dCaAP, F = 1/(vth – vrest), is a normalization factor. $\tau_{inac}$ was set to 0.3. We set the refractory period to 200 ms so that dCaAPs fired with 5 Hz or less. The novelty of this model, is the new dCaAPs observed which suggest that human neurons fire dendritic action potentials

with unique shape, complex temporal properties (e.g. delayed impact on the soma) and computational characteristics that herald a new approach to distributed computation in neural networks.

## 2.4 Novelty of dCaAPs

Action potential propagation links information processing in different regions of the dendritic tree. Those dendrites are not just bits of wire: they also have their own apparatus for making spikes. If enough inputs are activated in the same small bit of dendrite then the sum of those simultaneous inputs will be bigger than the sum of each input acting alone. In this picture it is shown that the dendrites of human L2/3 neurons are intrinsically capable of computing anti-coincidence functions like XOR, which is conventionally considered to be possible only in multi-layer networks. XOR gate is known as an anti-coincidence gate, meaning that this gate gives output high when inputs are opposite (anti-coincidence).

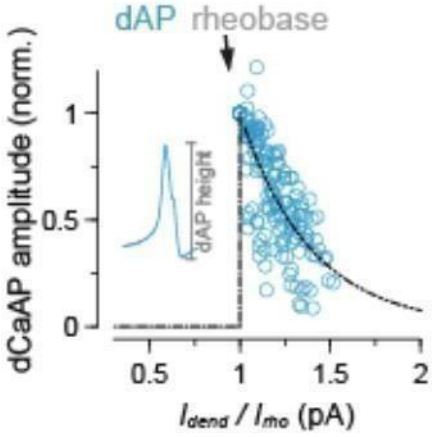


Figure 2.21: dCaAP amplitudes as a function of the input current strength ($I_{dend}$) normalized by rheobase ($I_{rhe}$) for 21 dendrites and exponential fit (dashed line).

Here it is depicted that when current is injected, a jump in amplitude is reported, the current begins to exponentially decline in a non-linear way. As a result, dCaAps in L2/3 dendrites provide a unique activation function, so as to compute the XOR operation by suppressing the amplitude of dCaAP when the input is above an optimal strength.

## 2. 5 Anti-coincidence detection in the dendrites of human L2/3 neurons

To further investigate what this unique dCaAP activation function is capable of computing, a compartmental modelling approach of Gidon et. al tried to fit and predict the experimental data. The computational model represents a L2/3 pyramidal neuron morphology, which was digitally reconstructed and modelled in the NEURON simulation environment. It is, therefore, a single neuron detailed biophysical model with a realistic input situation consisting of background synaptic excitation distributed all over the entire dendritic tree. The background synapses are

650 in number and represented by gray dots in figure 2.3 (A). To simulate two distinct classes of inputs like a binary neuron model discussed in the introduction, pathways *X* and *Y* were constructed. They are represented by green and red dots in figure 2.3 (A,B,C) and both pathways have 80 excitatory synapses. The pathways have also 20 GABAergic with yellow color. Pathways X and Y were added targeting a sub-region of the apical dendrite, as in the experimental data. With these values for number of synapses for each pathway and all the above active properties described, each of these groups of synapses, and as a consequence, each pathway, were able to trigger dCaAPs by themselves as we can observe in figure 2.3 (A). Due to the selectivity to particular input strengths of the dCaAPs, coincident activation of two synaptic input pathways diminished the dCaAP amplitude, as seen in figure 2.3 (D). Interestingly, when we have those pathways in the stimulated apical subregion and add inhibition, the dCaAPs regain their amplitude.

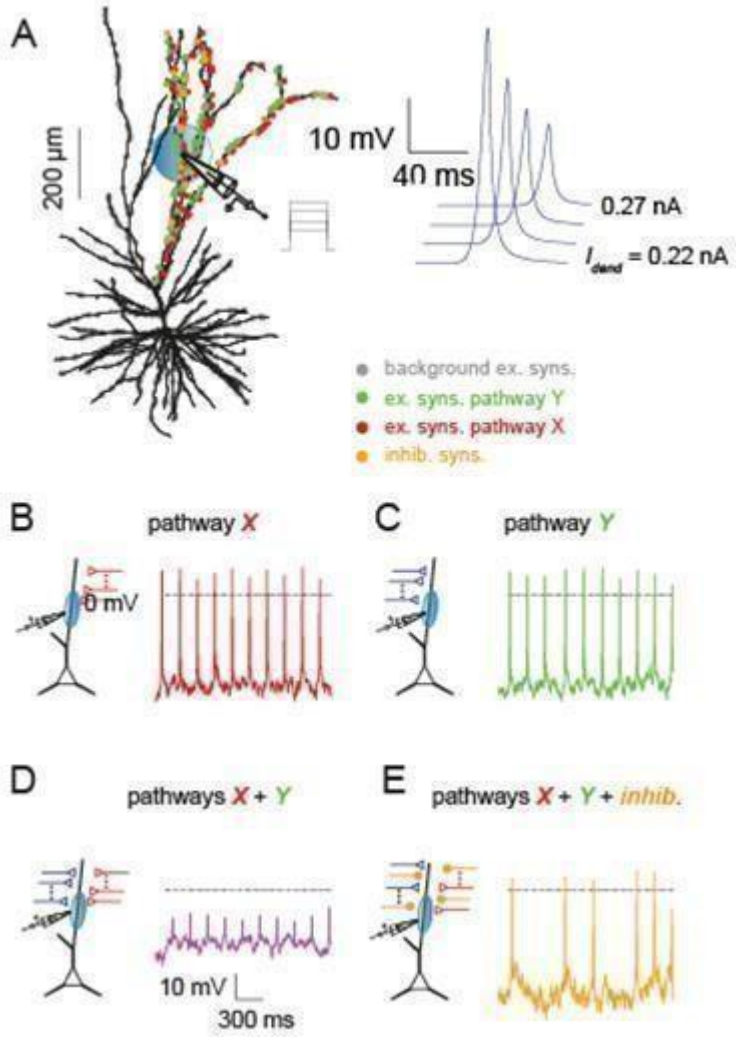


Figure 2.22: Anti-coincidence in layer 2/3 of the human cortex.

Left. A. L2/3 neuron modeled by passive membrane and dCaAPs mechanism at the apical dendrite 76 located demarcated by the blue circle. 650 background excitatory synapses marked by gray dots were randomly distributed over the entire dendritic tree. Pathway *X* and *Y* with 80 excitatory synapses each (red and green dots) targeted only a sub-region of the apical dendrite. Additionally, on the same sub-region, 20 GABAergic synapses were distributed with conductance of 0.3nS (yellow dots). All excitatory synapses consisted of NMDA and AMPA conductance, 0.3nS each. Background synapses were activated in all the simulations (B – E).

Right. The modeled dCaAP amplitude depended on the stimulation current intensity with decay constant of 0.3. dCaAP threshold was set to –36 mV with 0.2 pA current pulse. B. dCaAP recorded at the dendrite during activation of pathway *X* (red synapses). C. As in B but for pathway *Y* (green synapses). D. dCaAPs diminish when both, pathway *X* and *Y* are activated. E. An inverse impact of excitation and inhibition due to dCaAP activation curve; dCaAPs regain their amplitude when inhibitory synapses were activated.

## 2. 6 The XOR affair

The model has two major functions, the coupled and the uncoupled one. In the first one the response of the single neuron comes both from the soma and the dendrite. The isolated response of the dendrite is termed uncoupled. So, using this new dCaAP mechanism at the apical dendrite subregion, Gidon et. al provided a solution for the XOR classification problem. Specifically, as we see in figure 2.4 (up part of F & G) *X* and *Y* inputs to the apical dendrites trigger dCaAP for (*X*,*Y*) input pairs of (1,0) and (0,1) marked by black crosses, but not for (0,0) and (1,1) marked by the empty crosses. As a result, dCaAP mechanism solves the XOR affair. Interestingly, Gidon et. al provided also a solution for the AND/OR classification, now at the soma of the L2/3 neuron. As we see in figure 2.4 (bottom part of F & G), somatic AP is triggered for (*X*,*Y*) input pairs of (1,1), (0,1) and (1,0) but not for (0,0), which is a solution for OR logical operation. Thus, in this simplified model of L2/3 pyramidal neuron, in the apical dendritic compartment (blue color in figure 2.3 (G) ), dCaAPs could reproduce XOR logical operation, and in the somatic compartment and activation of AP (green color in figure 2.3 (G) ), the OR logical operation. Due to NMDA spikes (Eyal et. al 2018), the basal and tuft dendritic branches as seen in gray background in figure 2.3 (G), could reproduce AND logical operation.

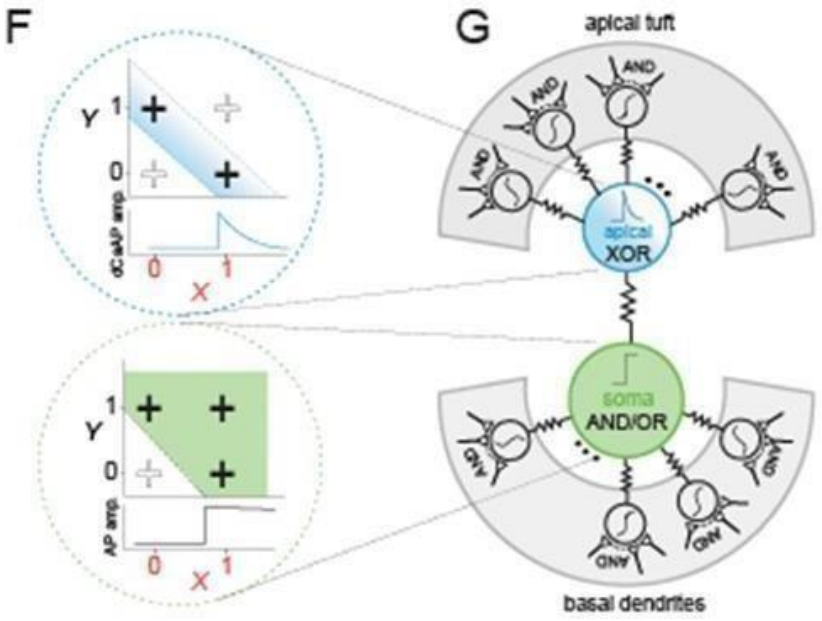


Figure 2.23: Logical operations on apical and basal dendrites

Nevertheless, AND/OR logical operations here use a classical sigmoid function for thresholding the spiking activity of the neuron, and not the new dCaAP mechanism which showed a solution for the XOR affair. So, taken all these into consideration, the major research question of this master thesis was to see if other logical operations, apart from the XOR could be reproduced in the dendrites of human L2/3 cortical neurons using the new dCaAP mechanism as their activation function. This research question thrives from the novelty of the model of Gidon et. al representing the somatic and dendritic compartments of L2/3 neuron as a network of coupled logical operators with their corresponding activation functions. To expand their approach, it is further investigated what computations - in both coupled and uncoupled modes of the model – can a two-stage neuron in human cortical neurons of L2/3 perform. The novel activation function of the dCaAP mechanism is used as the activation function along with the logical operations from Boolean Algebra, as stated in the literature before, linking logical gating and neuroscience. To reproduce these logical operations, we depend on the number and type of synaptic inputs and how away we are from the soma of the neuron, with the proximal and distal dendrites in the coupled and in the uncoupled mode respectively. To put it in other words, where the coupled function is called specific values for the number of synapses are distributed all over the apical subtree and the dCaAP mechanism is stimulated in proximal or the distal dendrites. In the uncoupled function, the dCaAp mechanism is performed on apical dendrite 60 (600 μm from the soma). The background activity is randomly distributed. For the coupled function, the dCaAP mechanism is 216 μm from the soma. Again, the background activity is randomly distributed. Then inhibition is in one branch localized. This means higher excitability of the cell, but not all over it. Interestingly, the amplitude of dendritic APs was sharply tuned to an optimal input intensity and progressively suppressed for stronger inputs and this will be addressed as a research question in the thesis work with respect to proportionally or not spiking activity of the neuron. In the next section, the results of all these approaches are discussed along with scientific questions regarding the capacity of those computations and if we observe differences in apical and basal dendrites.

In this section, only the uncoupled function is activated, meaning we only have dendritic response. This is of vital importance, because in the work of Gidon et. al it is interesting how cortical neurons have higher amplitude regardless the number of spiking activity. Specifically, in figure 3.7 (B3) the dCaAP mechanism has a greater value of max amplitude even if the spikes are less.

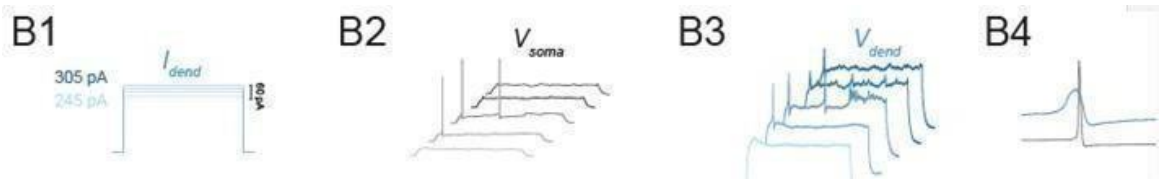


Figure 2.24: B1. Current stimulus injected into the dendrite (Idend) 417 μm from the soma (B1) and corresponding somatic (B2) and dendritic traces (B3). B2. Idend of 260 pA and 275 pA, but neither smaller nor larger current, resulted in somatic APs. B3. Idend of 260 pA and 275 pA maximized dCaAP amplitudes whereas Idend > 275 pA dampened them. B4. dCaAP (in blue) precedes the somatic AP (in gray) traces are magnified from B2 and B3. C. Isoma

# 3
# Results

*"Any man could, if he were so inclined, be the sculptor of his own brain."*
*-Santiago Ramon y Cajal, Advice for a young Investigator*

## 3. 1 Synaptic integration

Using the above dCaAP mechanism as the activation function for the simulations, we model logical operations in the subdomain of the apical tree, as in the solution for XOR classification problem we saw in both the computational modeling approach and the experiments. Specifically, to explore how dendrites contribute to the computations of human L2/3 neocortical neuron, we stimulate in the uncoupled mode the apical dendrite 76 (600μm from the soma) with the dCaAP mechanism, and in the coupled mode we stimulated the dCaAP mechanism in the apical dendrite 60 (215μm from the soma). With an ultimate goal of understanding how human cortical neurons compute and are distinct, the dendritic factors governing the input-to-output transformations are explored and the single neuron is being tested as a binary threshold neuron finding the golden section between excitation and inhibition of the cell. Both in coupled and uncoupled mode, we record the traces, both dendritic and somatic, from the background and the pathways X, Y, and XY. These four traces are seen as the desirable output of each logical gate. To generate an input to this output transformation, we investigated the number and type of synapses as stemming from the synapse doctrine for learning and memory. That is the reason why along with the novel dCaAP activation function, the number of synapses play a significant role in modelling the logical operations as input variables for the pathways X, Y, XY and the background activity. This results in a specific synaptic parameter space for both the coupled and uncoupled mode, as discussed in the table below.

In the table 3.1, the number of synapses for each pathway is being presented. This derives from trial and error simulations of the single detailed biophysical neuron using all the synaptic and active properties as in the model of Gidon et. al. The two synaptic inputs, synapses – 1 and synapses – 2, are seen as two independent pathways, pathways X and Y respectively, and when stimulated together they must give the specific binary output each gate is requesting to be modeled, namely the pathway XY. All pathways use the new dCaAP mechanism as their activation function represented by the binary pathways X and Y to generate the output combinations of the gate. The number of the background synapses mostly is 650, randomly distributed in apical subdomain. It is also set to a higher value of 850, when needed to activate the state of the background of a gate when it is an on state. Someone would argue that tuning the background activity exceeds the purposes of the neuron seen as a binary threshold neuron, with the background seen as a third variable. This is something valid to an extent. Nevertheless, neurons receive different levels of background activity depending on the state of the animal.

However, in this particular case, we are more interested to understand the dendritic computations in the single neuron level and generate the logical gates there. To do this, we must tune the background activity, because, as we will see later, some of the gates require high background activity as an input so as for their output to be in an active state. Discussing how many inputs are required to perform and generate logical operations by many dendrites of human L2/3 neuron, exceed the purposes of this thesis, moving from a detailed biophysical single neuron level to a network level.

| Gate (output) | Synapses - background | Synapses 1 | Synapses 2 | Synapses 1 & 2 |
|---|---|---|---|---|
| **XOR (0,1,1,0)** | 650 | 120 | 120 | 240 |
| **AND (0,0,0,1)** | 650 | 60 | 60 | 120 |
| **OR (0,1,1,1)** | 650 | 120 | 420 | 540 |
| **F2 (0,0,1,0)** | 650 | 100 | 150 | 250 |
| **F3 (0,0,1,1)** | 650 | 10 | 120 | 130 |
| **F4 (0,1,0,0)** | 650 | 100 | 60 | 160 |
| **F5 (0,1,0,1)** | 650 | 120 | 10 | 130 |
| **F9 (1,0,0,1)** | 850 | 120 | 200 | 320 |
| **F10 (1,0,1,0)** | 850 | 180 | 10 | 190 |
| **F11 (1,0,1,1)** | 850 | 120 | 80 | 200 |
| **F12 (1,1,0,0)** | 850 | 120 | 20 | 140 |
| **F13 (1,1,0,1)** | 850 | 100 | 80 | 180 |
| **NULL (0,0,0,0)** | 0 | 0 | 0 | 0 |
| **IDENTITY (1,1,1,1)** | 850 | 240 | 240 | 480 |
| **NAND (1,1,1,0)** | - | - | - | - |
| **NOR (1,0,0,0)** | - | - | - | - |

Table 3.1: Number of synapses for coupled function.

As depicted in the above table, using specific numbers of synaptic inputs, other gates apart from the XOR, could be reproduced. In the model of Gidon et. al the XOR solution needs 80 synapses to be generated in the apical subdomain. To specify how dendrites perform computations in L2/3 neurons, we stimulate the dCaAP mechanism to proximal apical dendrite 60. To generate again the XOR gate the apical dendrite 60 needs 120 synapses, a higher value than before. Gate AND gives an active state of an output when only the two inputs coincide.

This requires a lower value in the number of synapses than the XOR solution for example. OR gate on the other hand, has three activated outputs except the background activity. To generate a pattern like this, a greater number of synapses are needed for the second input variable. F2 gate needs a higher number for the second input variable, but a lower number of synapses in the first input variable in comparison with the XOR solution respectively input for example, for only one output to be activated. For F3 gate, we need a low synapse input for the first input variable so as to activate one pathway and still activate the pathway with a summed output. F4 resembles the F2 gate in the activating pattern and synaptic input variables. F5 gate is the exact opposite from F3 gate, with again a summed output but the other pathway activated. Moving on to gates F9 to F13, we observe a desirable output pattern in the background activity. To activate this, and still model those gates, the default background activity is tuned to a higher value. In the F9 gate, to have a summed output and a background activity, the second input variable needs to be higher than the first one, with the first input variable not surpassing the value for the XOR solution for example. F10 gate requires the background activity and one pathway activated, thus, the first input variable needs to be much greater than the other. F11 gate is activates also one pathway apart from the background and the summed output and for this purpose the second input variable is lower in value, but greater than the previous example. F12 gate does not have a summed output pattern, but only a background and an activated pathway, so the second input variable needs to be low in value. Finally, F13 gate has the background activity, the summed pattern and one pathway activated as an output, so the two input variables are similar in value to give a summed output, but not that high to generate more than one pathway. Null gate needs zero number of input variables, and identity gate requires the doubled value of input variable from XOR gate, so as all output patterns will be activated. Thus, this interplay of optimal synaptic strength for the two input variables reproduces logical operation in the apical dendrite 60 on L2/3 neocortical neuron. However, it needs to be reported here, that the inhibitory logical operation like NAND and NOR could not be reproduced in this stimulation. Due to the fact that the inhibition is localized in one tree and the excitability of the cell is high enough, but not in the soma, we thought that stimulating a dendrite with different morphological properties may assist this. Activating only the uncoupled mode of the model when only dendritic response of the cell is recorded, the dendrite is more distal, both temporally and spatially, with its morphology being thinner in diameter and therefore small cell accumulation.

Upon stimulating the dCaAP mechanism of the distal apical dendrite 76 in the uncoupled mode, a different parameter space of synaptic inputs needs then to be explored. The same question remains. If any other gates could be modeled in a dendrite that is not close to the soma of the neuron, that will expand the dendritic computation capability of the Gidon et. al model, and if negative logical operations could be performed there.

| Gate (output) | Synapses - background | Synapses 1 | Synapses 2 | Synapses 1 & 2 |
|---|---|---|---|---|
| **XOR (0,1,1,0)** | 650 | 120 | 120 | 240 |
| **AND (0,0,0,1)** | 650 | 60 | 60 | 120 |
| **OR (0,1,1,1)** | 650 | 120 | 420 | 540 |
| **F2 (0,0,1,0)** | 650 | 100 | 150 | 250 |
| **F3 (0,0,1,1)** | 650 | 10 | 120 | 130 |
| **F4 (0,1,0,0)** | 650 | 100 | 60 | 160 |
| **F5 (0,1,0,1)** | 650 | 120 | 10 | 130 |
| **F9 (1,0,0,1)** | 850 | 120 | 200 | 320 |
| **F10 (1,0,1,0)** | 850 | 180 | 10 | 190 |
| **F11 (1,0,1,1)** | 850 | 120 | 80 | 200 |
| **F12 (1,1,0,0)** | 850 | 120 | 20 | 140 |
| **F13 (1,1,0,1)** | 850 | 100 | 80 | 180 |
| **NULL (0,0,0,0)** | 0 | 0 | 0 | 0 |
| **IDENTITY (1,1,1,1)** | 850 | 240 | 240 | 480 |
| **NAND (1,1,1,0)** | - | - | - | - |
| **NOR (1,0,0,0)** | - | - | - | - |

Table 3.2: Number of synapses for uncoupled function.

The same approach for the uncoupled mode, as before in the coupled one, stands for the background synaptic input, and the pathways X and Y. Specific values of randomly distributed number of synapses are tested in simulations to try and explain with a specific thesholding in excitation and inhibition of the two pathways, so as to explore if other logical operation from Boolean algebra with different synaptic inputs could be implemented upon using the dCaAP distally. Specifically, XOR gate requires exact half of the values for the two input variables than in the coupled mode for XOR. AND gate requires an input that together will generate only the summed output. OR gate needs a higher value in the second input variable to activate the pathways except the background activity. F2 gate needs a high value of the first input variable to generate only one output pathway. F3 gate needs a low first input variable and simultaneously a higher than before second input variable to generate only one pathway and the summed output pattern. F4 gate requires a high value for the second input variable and a mediocre first input variable that will not activate the output summed pattern. F5 gate needs a low first input variable and a higher vale in the second input variable than the

threshold value in the previous gates, so as the summed output and only one pathway be generated. Again, from gates F9 to F13, the background activity is on an on state, so it is again tuned to 850 synapses than the default value of 650. F9 gate requires a similar value in the input variables for the summed output to be activated. F10 gate needs a lower value of the second input variable for only one pathway activated in the output and not their summed pattern. F11 needs a greater value in the second input variable than the previous gate, so as to activate also the summed output. F12 needs a lower first input variable than the previous gate, with a simultaneous low second input variable for only one pathway to be activated in the output. F13 gate requires a high number of the second input variable for the summed output to be activated along with one pathway and the background activity. Again, null gate requires zero value of input variables, and identity gate needs the threshold values to generate all outputs. Interestingly, in the uncoupled mode, the negative dendritic computations are performed. The NAND gate requires a higher value of first synaptic variable than before and the second input variable is half in value to generate all outputs expect the summed one. The NOR gate needs a high value of the second input variable that will balance with the background activity and not give as an output the summed pattern. As a result, in the uncoupled function of the model, all logical operations including the negative NAND and NOR could be modeled. Something like that expands the computational capacity of human neocortical neurons of the L2/3, with dendrites being more close to the soma of such an ion channeled and synaptic neuron contributing more to the dendritic computation of the human neocortex.

The following picture visualizes the grouped number of synapses in the two major functions of the model, coupled and uncoupled, which reproduce the logical Boolean operations. With blue color, the pair of logical operations in the coupled mode is being depicted; while the green color represent the number of paired synapses of the pathway X and Y that reproduce the logical operations. It is observed that in the uncoupling way, with only the dendritic response, a higher value in the number of synapses is being required to model the Boolean functions, and that would be an indicator of why even the negative logical operations were able to be reproduced.

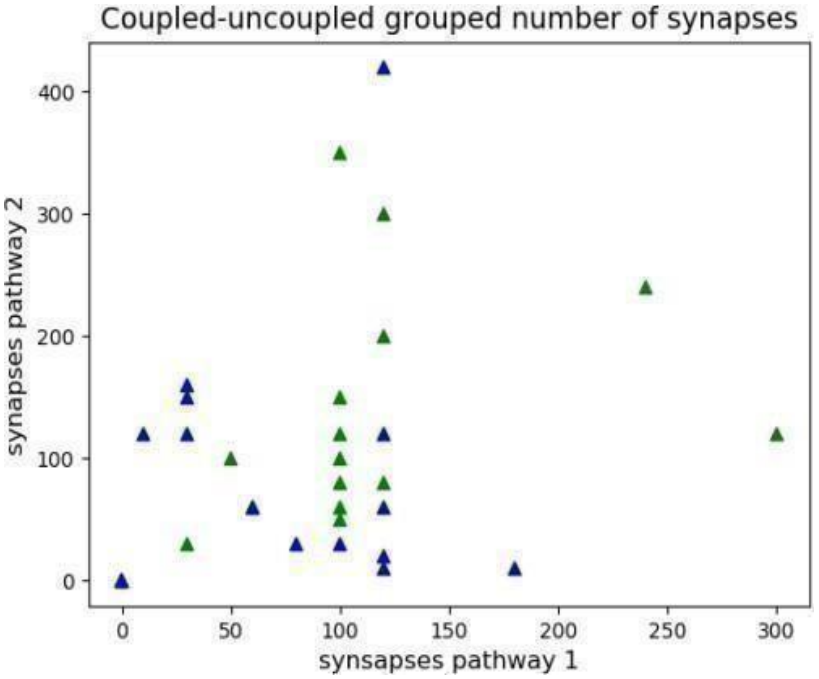


Figure 3.1: Coupling and uncoupling pathways visualizing the number the paired synapses need to construct Boolean functions.

## 3.2 Modelling the gates using the dCaAP mechanism on proximal and distal dendrite

Here, we use the above number of synapses as in table 3.1 and 3.2, and five repetitions to approach the results of the modeled logical operations for a period of time of 20.000 ms, where in each repetition, the exact location of the pathway-synapses changed, as well as the instance of the Poisson process. Again, all logical gates, except for the inhibitory ones are implemented in the coupled mode and all Boolean function in the uncoupled mode. We decided to visualize the modeled logical gates as a function of the mean firing rate for each pathway. In the next figure, we are in the coupled mode, when we have both dendritic and somatic response by stimulating the apical dendrite 60. We only depict the somatic one, due to the fact that the dendritic activity in the coupled mode was not in high value. In the x axis we have the background activity (Bg), the pathway X, the pathway Y, and the pathway XY. In the y axis, we have the mean firing frequency, which is being measured with the assistance of python script counting the number of spikes of the recorded traces. As mean firing frequency we set the number of spikes measured for each pathway and background activity divided by the time of the simulations for five runs along with their standard deviation. In the legend of each subplot the desired output of the logical gate is written for comprehensive purposes. One is represented as an activated output and zero as an inactivated one.

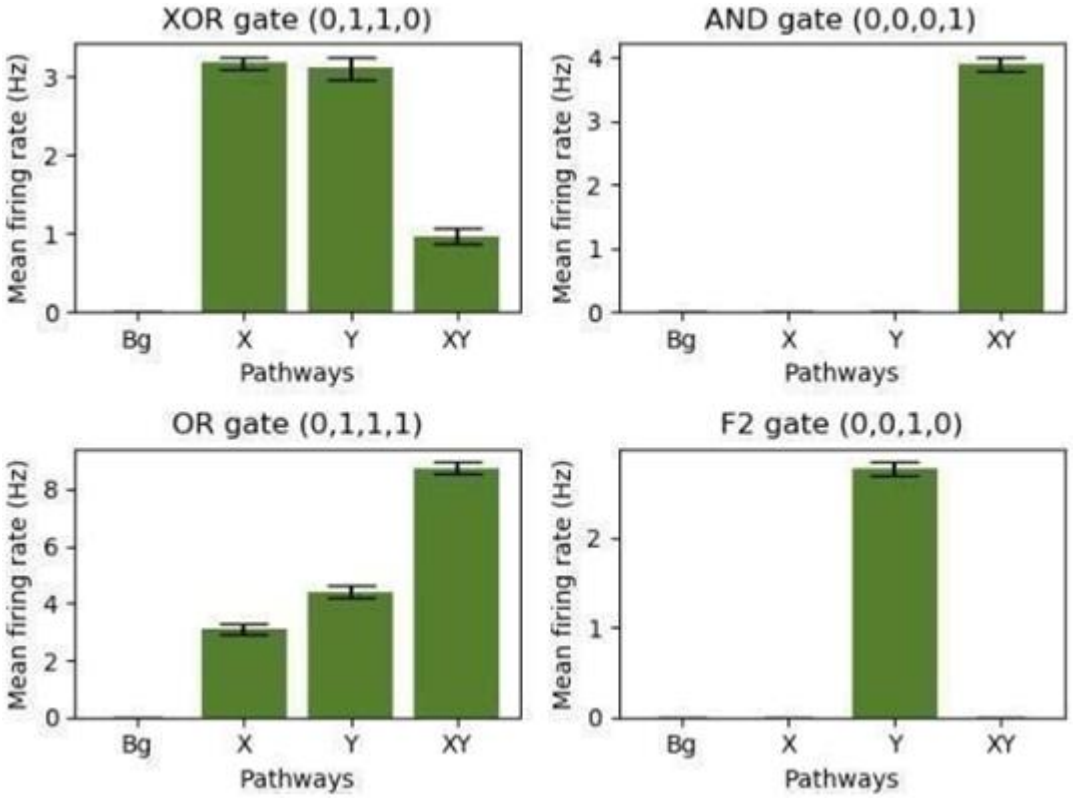


Figure 3.2: Implementation of XOR, AND, OR, F2 gates on apical dendrite 76.

Here, XOR and AND logical operations have similar values for the mean firing frequency, while OR gate has a higher mean firing frequency and F2 gate a lower one. This is explained by the number of the synaptic input and the background number of synapses being used to threshold the neuron and reproduce each gate.

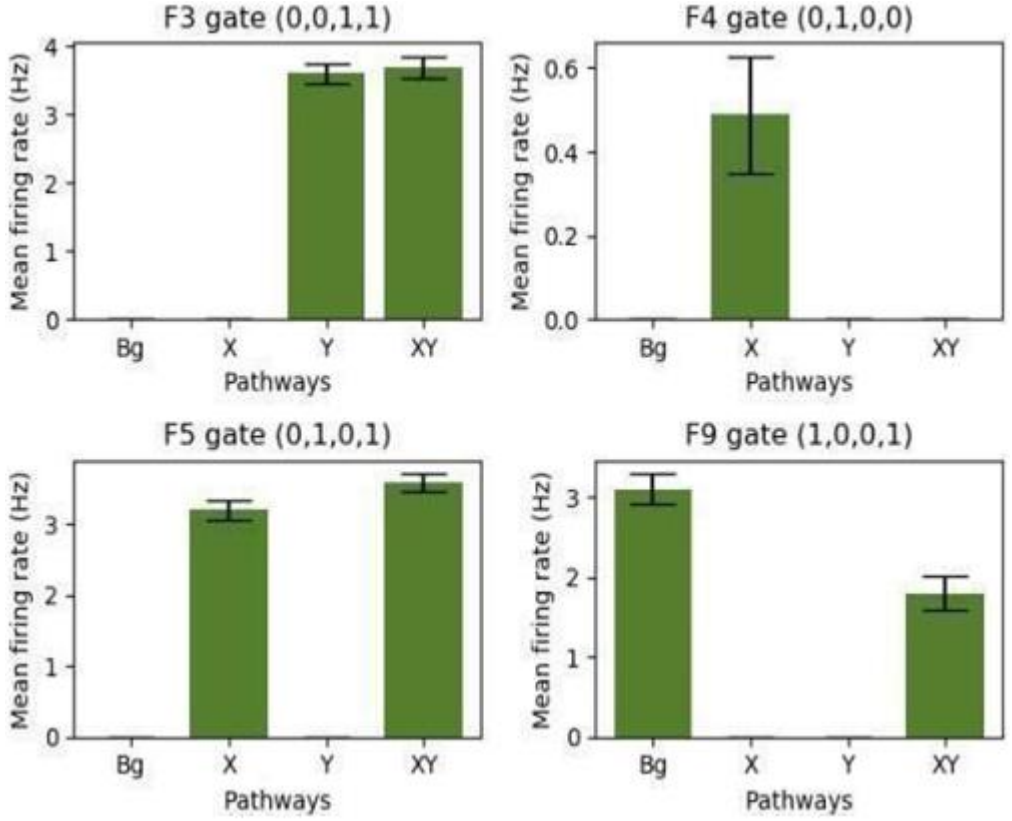


Figure 3.3: Implementation of F3, F4,F5, F9 gates on apical dendrite 76.

Here logical gates F3, F5, F9 have similar mean firing frequency as a sequence of similar values of number of synapses to model them, while F4 gate has a low value for mean firing frequency when implemented. This is because as thresholding the binary neuron only the excitation of pathway X must be kept for the latter logical operation with the other input variable being lower in synaptic input to keep the balance in the two variables.

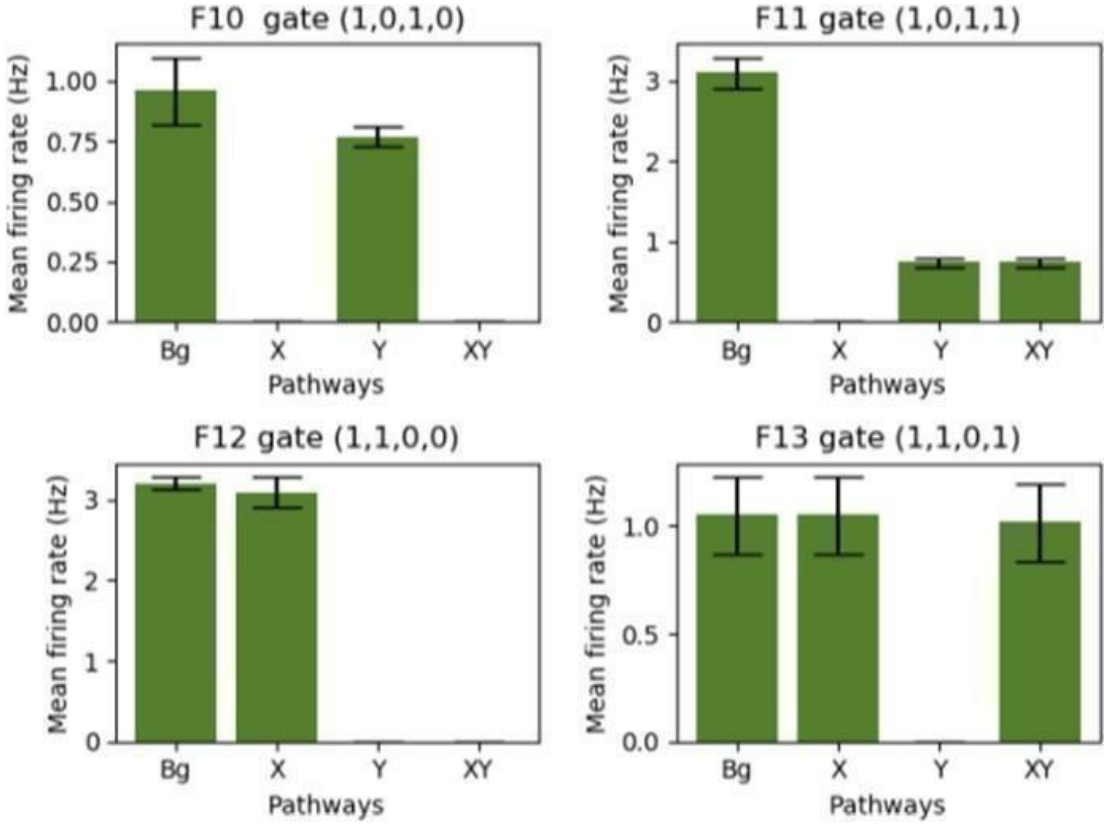


Figure 3.4: Implementation of F10, F11, F12, F13 gates on apical dendrite 76.

Here, F11 and F12 gates have similar mean firing frequency as some of the above mentioned logical operations, and Boolean functions of F10 and F13 have lower mean firing frequency due to the fact that one of their pathways should reach the threshold to surpass the other pathway for activation.

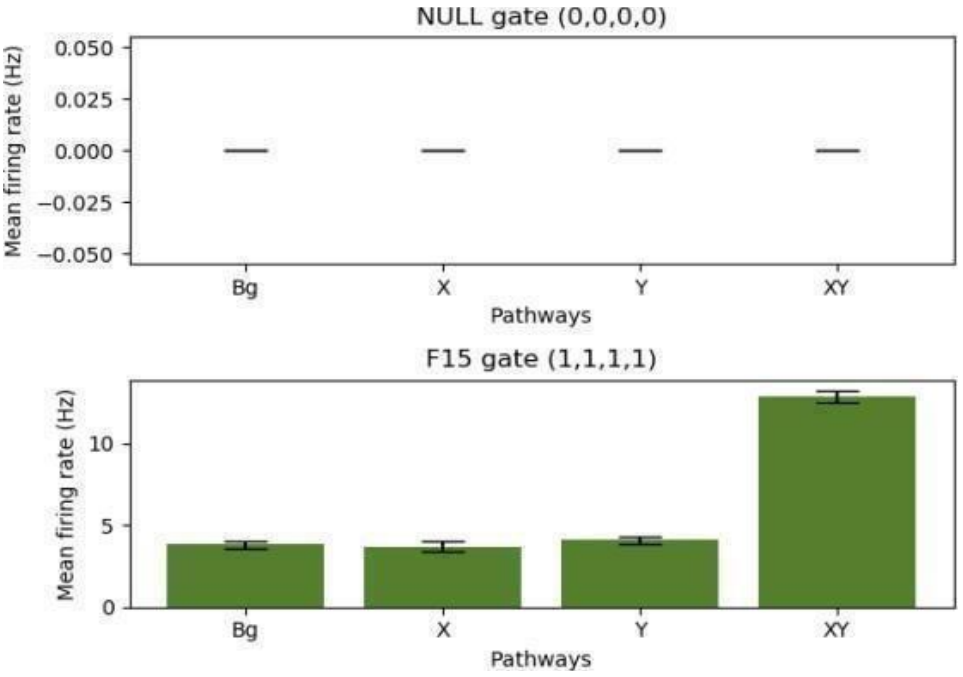


Figure 3.5: Implementation of null and identity gates on apical dendrite 76.

Here, the NULL gate gives zero value for each pathway, and the F15 gate activates all outputs with a highest detected mean firing frequency as a consequence of higher number of synapses for all the pathways.

To provide a mechanism for making quantitative decisions about the validity of constructing the logical gates, we used ANOVA Tukey's statistical test. This test compares all possible pairs of means, and is based on a studentized distribution. Tukey's test will pairwaise compare every means of the pathways and identify any difference between two means that is greater than the expected standard error. Our null hypothesis here is that the mean of a pathway should be different from the other pathway, and from the background as well.

Specifically, for XOR gate in figure 3.2, we want to observe if the XY pathway has a statistical significance on pathway X and Y. Here is the result from Python analysis on the logical gate XOR mean firing frequency for the five runs:

```
One-way ANOVA
=============
F value: 4.086102979163082
P value: 0.044316669461226046

 Multiple Comparison of Means - Tukey HSD, FWER=0.05
====================================================
group1 group2 meandiff p-adj   lower    upper  reject
----------------------------------------------------
     X     XY     -0.8    0.9 -33.9826 32.3826  False
     X      Y    -31.2 0.0661 -64.3826  1.9826  False
    XY      Y    -30.4 0.0738 -63.5826  2.7826  False
----------------------------------------------------
['X' 'XY' 'Y']
[Finished in 4.6s]
```

Figure 3.6: ANOVA Tukey's test to compare the means for each pathway of the XOR gate.

As the p-value is below the confidence interval value of 0.05, the hypothesis has statistical significance value, with the means of each pathway being statistically significant.

So, with the assistance of a python script measuring the max amplitude from the recordings of the dendritic traces again for five repetitions and for a time period of 20.000 ms, as in the coupled mode, we move closer to the soma, in the dendrite 76, to explore if again logical operations can contribute in dendritic computation of L2/3 human cortical neuron using the number of synapses stated in the table 3.2.

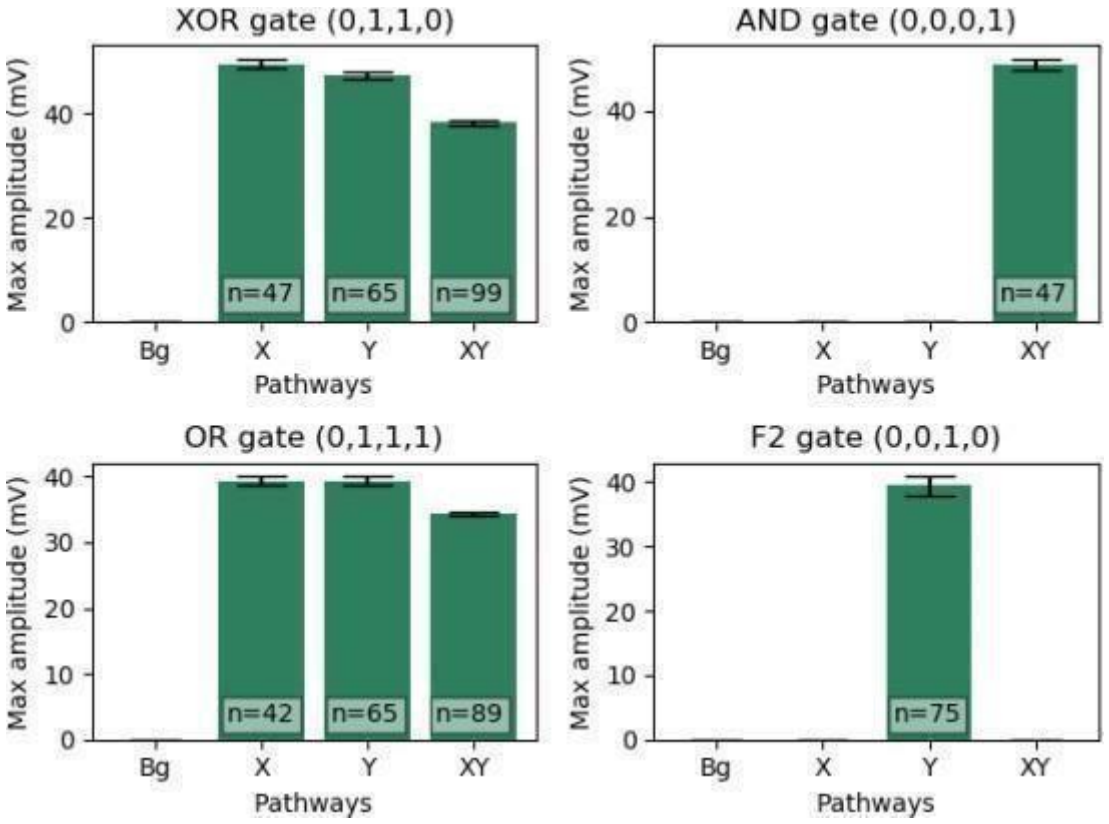


Figure 3.7: Implementation of XOR, AND, OR, F2 gate with the dendritic response measured in max amplitude on apical dendrite 60. N is the number of spikes for each bar.

As in the coupled mode, the x axis represents each pathway and the background activity. In the y axis, we measure the mean max amplitude for the five repetitions. Here we can observe that the max amplitude of gates XOR, AND, OR and F2 is close to 40 V. However, the within box on the barplots representing the measured number of spikes for each pathway is not proportional with the max amplitude. For example, in the XOR gate, the XY pathway has max amplitude of 38 V, but the number of spikes is 99 for the pathway XY. This is something that comes in line with the finding of Gidon et. al. about spiking activity and amplitude, making the dCaAP mechanism having a unique functionality when it comes to dendritic computation on closer dendrites of human neocrtical neuron in L2/3.

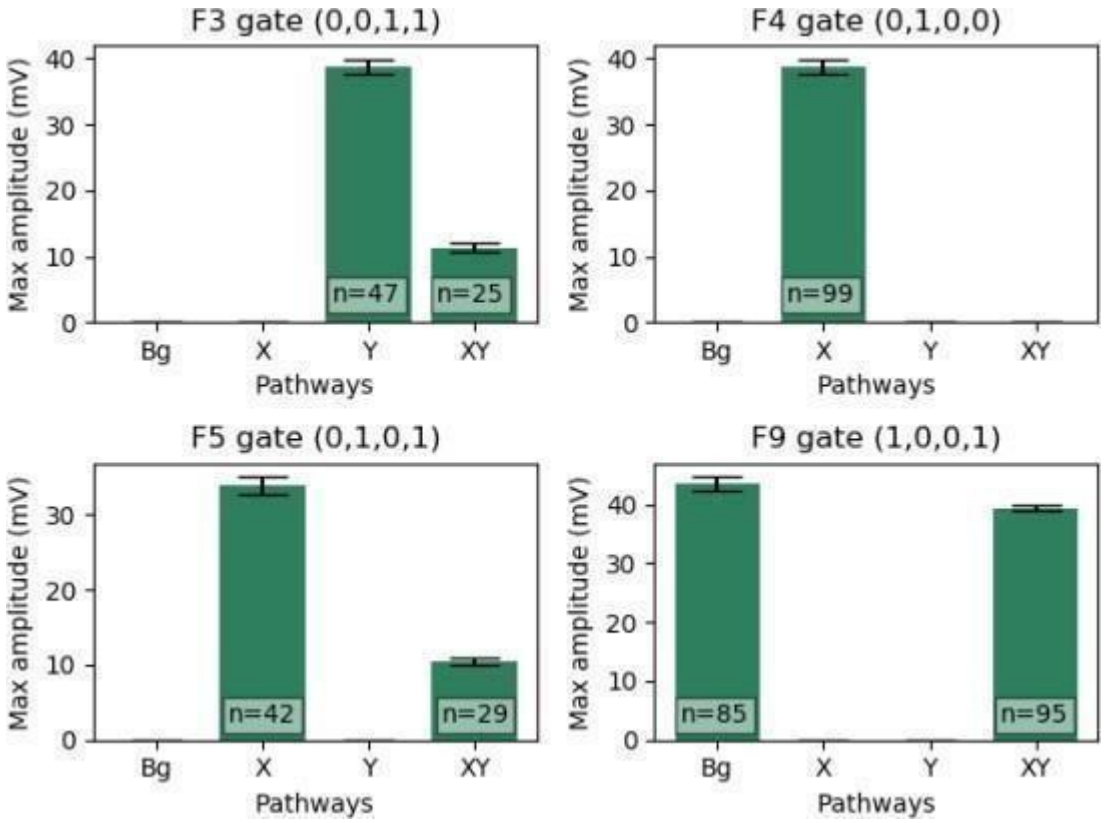


Figure 3.8: Implementation of F3, F4, F5, F9 gate with the dendritic response measured in max amplitude on apical dendrite 60. N is the number of spikes for each bar.

Here, gates F3, F4, F9 have similar max amplitude as before, but F5 gate has a lower value of max amplitude with less number of spikes for pathway X perhaps compared with the X pathway of gate F4 with a similar max amplitude, but more spikes.

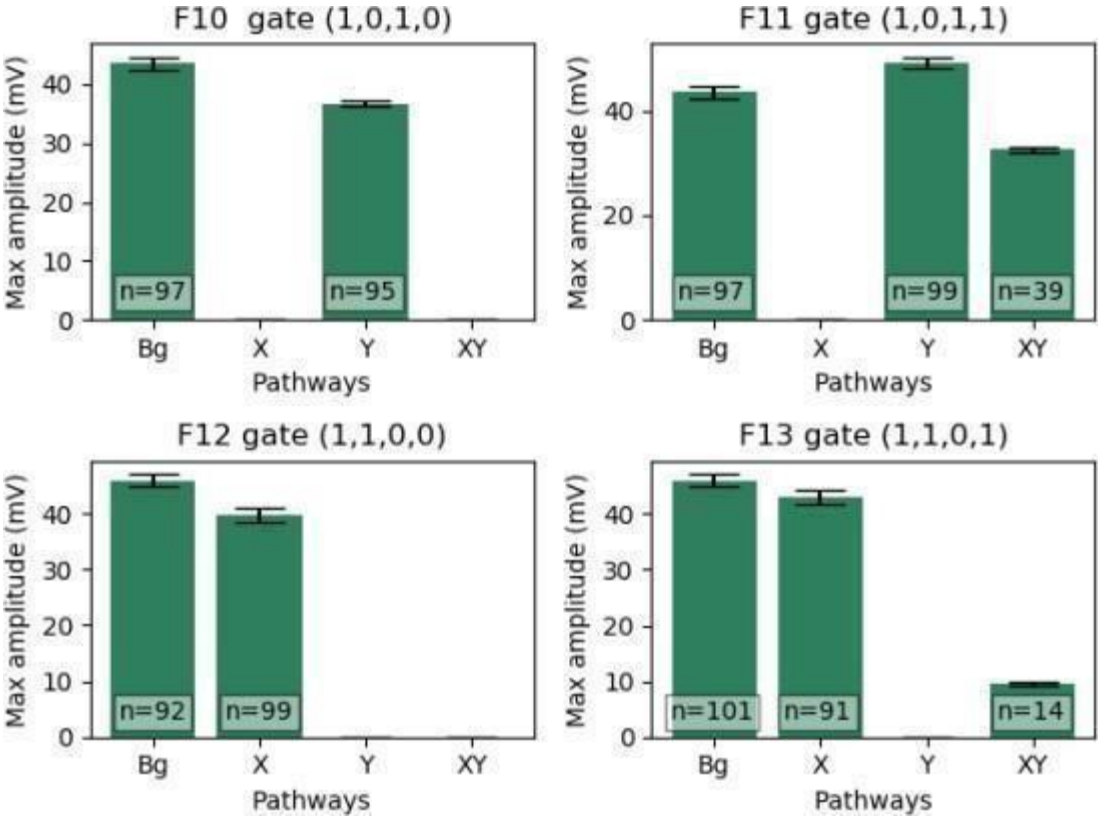


Figure 3.9: Implementation of F10, F11,F12,F13 gate with the dendritic response measured in max amplitude on apical dendrite 60. N is the number of spikes for each bar.

Here F10, F11, F12, and F13 gates have similar value of max amplitude as before, with again a spiking activity disproportional to their max amplitude.

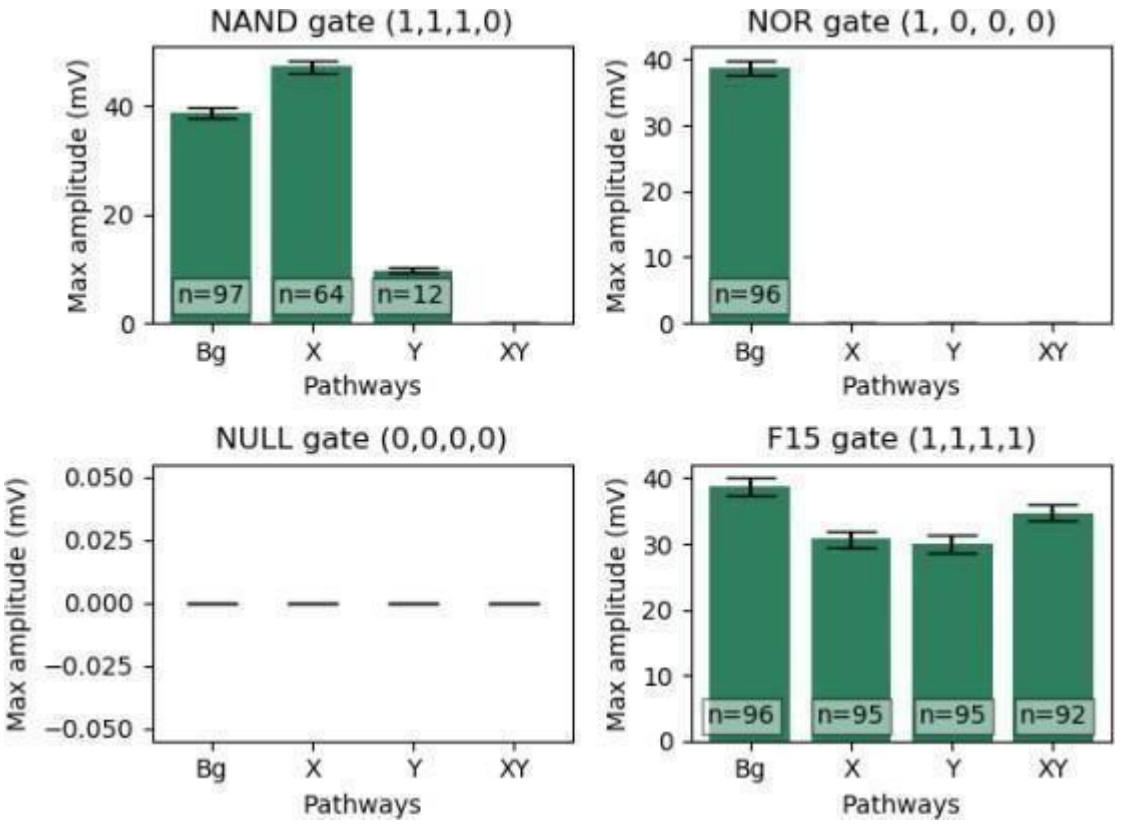


Figure 3.10: Implementation of NAND,NOR, NULL, F15 gate with the dendritic response measured in max amplitude on apical dendrite 60. N is the number of spikes for each bar.

Here, NULL gate has zero values for each pathway, and F15 gate similar value of max amplitude as before, with an increased number of spikes for each pathway. Interestingly, here the gates NAND and NOR are being reproduced with a similar max amplitude and same philosophy in the spiking activity.

Overall, from the above figures, we can observe in some of the cases, that when the max amplitude is low, the spiking activity is high validating the results of Gidon et. al. So, is this negative integration in the dendrites more close to the soma a bug or a feature? This remains an open question that needs special attention so as to understand the functionality of the new dCaAP mechanism in human neurons. These results may suggest that each dendrite is a computational element like a threshold binary neuron, when you are closer to the soma you have more dendritic operations and computations, enabling each neuron behave as a network finding dynamically logical patterns of activity as the output from Boolean functions.

Again, for the statistical significance of the means for each pathway, ANOVA Tukey's statistical test is being implemented for the XOR gate to compare the means.

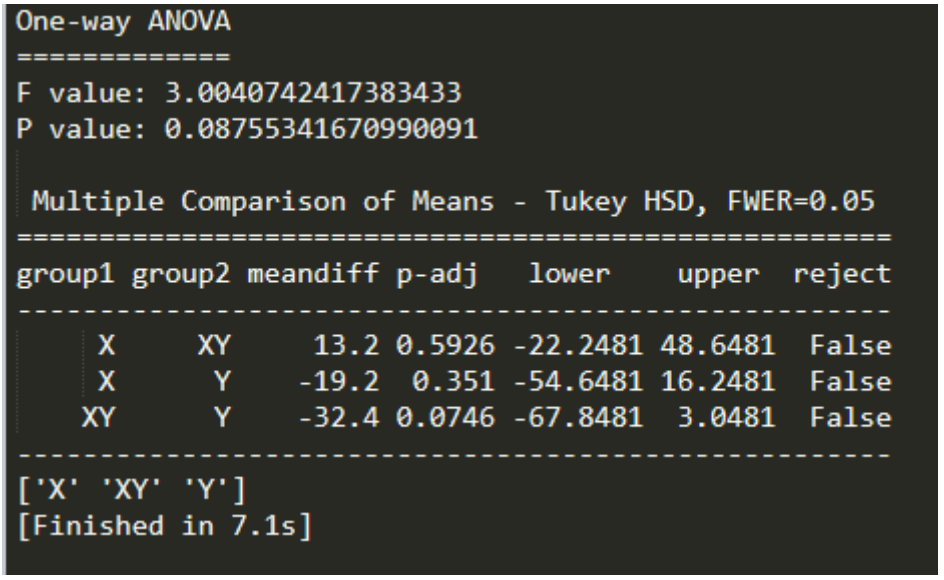


Figure 3.11: ANOVA Tukey's test to compare the means for each pathway of the XOR gate.

As the p-value is below the confidence interval value of 0.05, the hypothesis has statistical significance value, with the means of each pathway being statistically significant.

# 3. 3 Lookup tables for logical operations

Here, we generalize the results to all combinations that could possibly explain a logical operation. For all combinations in both functions the simulations runs for a duration of ts = 4s for four repetitions, and the maximum number of synapses of pathways X and Y are 360, with a step of 20 synapses. In the coupled mode, upon stimulating the dCaAP mechanism on proximal dendrite, we can explain a gate with the assistance of measuring the number of spikes, and in the uncoupled mode by measuring the maximum amplitude of the dCaAP. We present two colormaps, due to the fact that we have two modes of background activity. We saw before, that some gates require high background activity on their output, and some lower or not at all. That is the reason why, using a deductive method to explain each gate, we categorize the background activity as the first step of explain the output of a gate. The figures are arrays that replaces runtime computation of measuring the number of spikes and the max amplitude in both states of background activity with a simpler colormap array indexing each logical operation. Thus, we provide a solution space for logical operations.

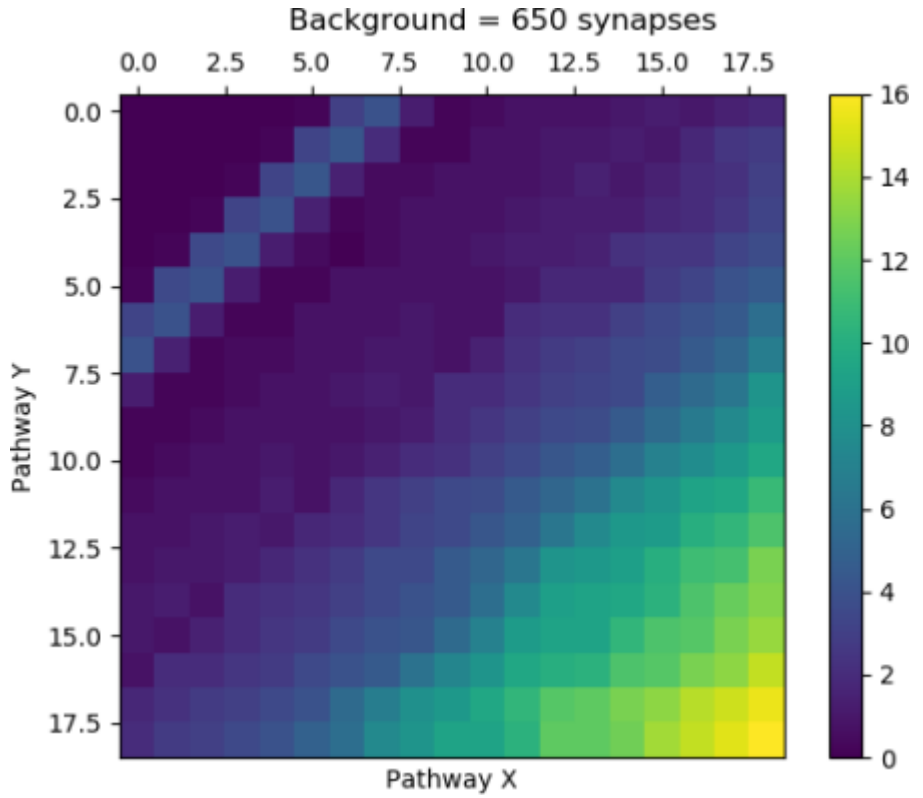


Figure 3.12: Lookup table for coupled mode (firing frequency).

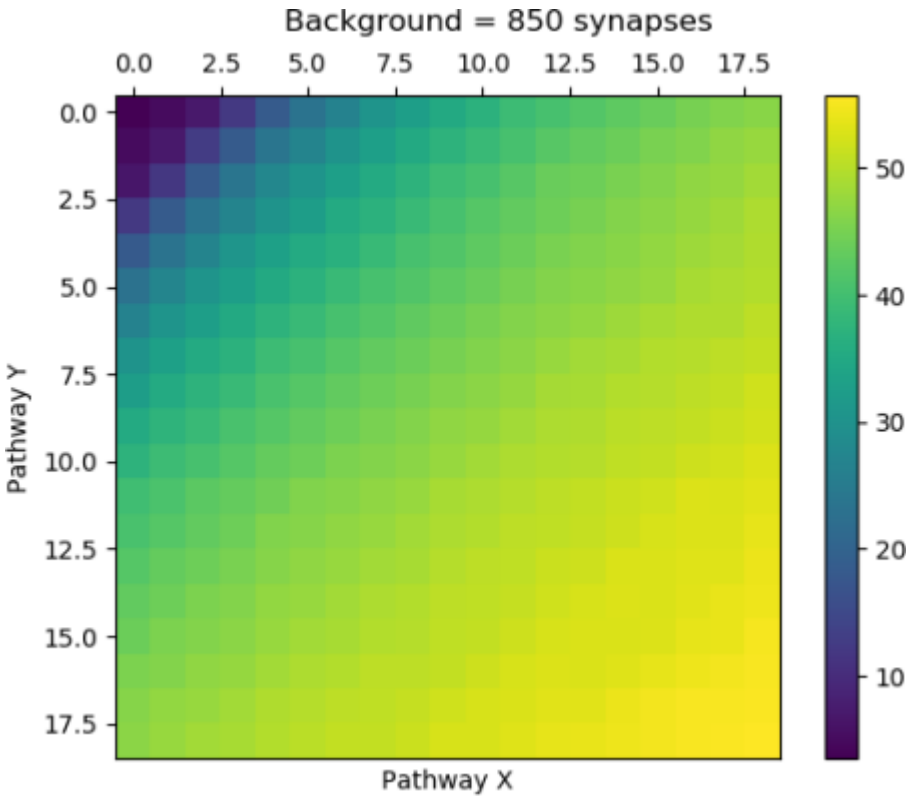


Figure 3.13: Lookup table for coupled mode (firing frequency).

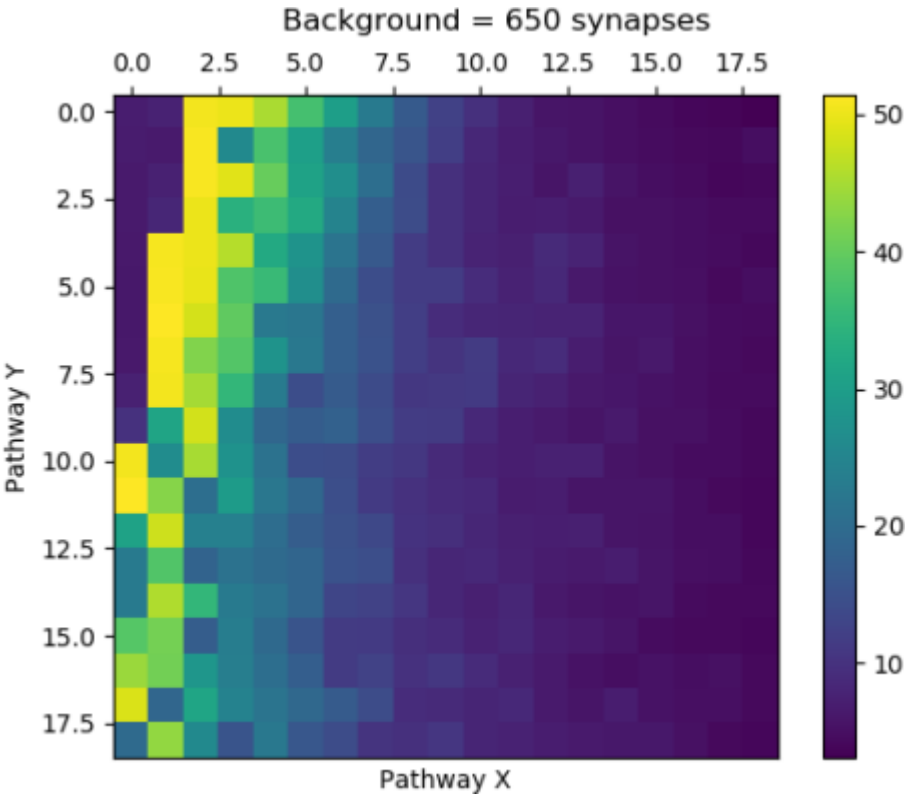


Figure 3.14: Lookup table for uncoupled mode (max amplitude).

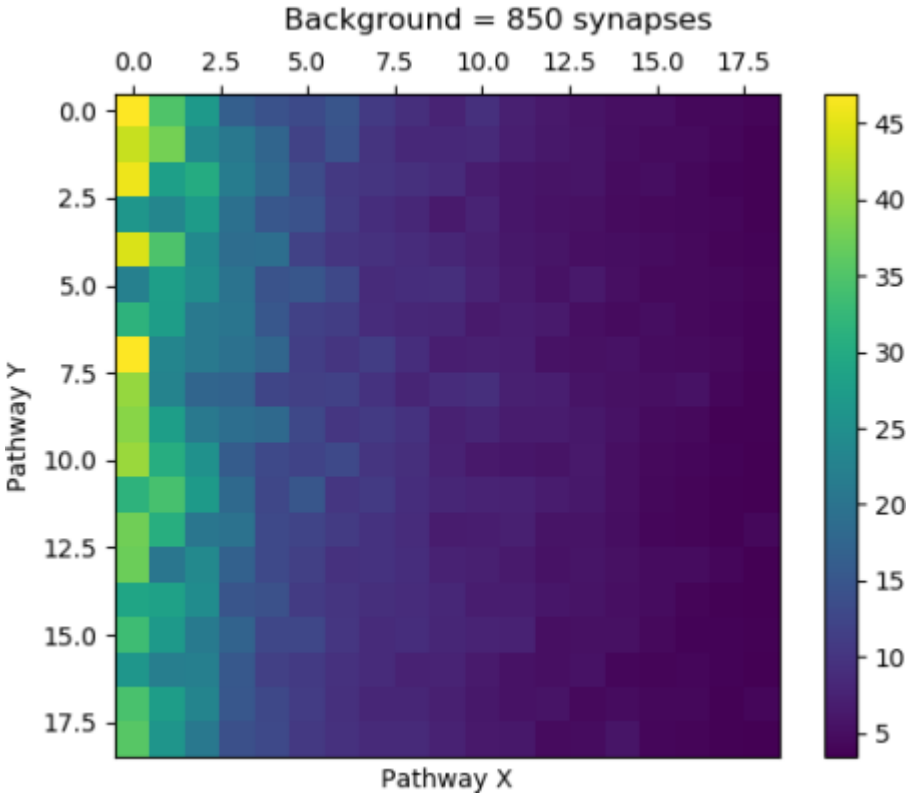


Figure 3.15: Look-up table for uncoupled mode (max amplitude).

# 3. 4 Tuning curve of dendritic computation

As it has already been understood, dendrites are active neuronal structures. They are one of the major factors in long-term potentiation. With a sigmoid function as activation function Wu et. al. 2009 showed the capacity-enhancing synaptic learning rules in a medial lobe online learning. The capacity of computation for information theory and entropy purposes on the apical subdomain here comes in line with the aforementioned paper, with the activation function being the novel dendritic mechanism and not a classic sigmoid. Neural encoding is merely a transformation from physical space. To understand the encoding of a neuron and a functionality of the new dCaAp mechanism, the concept of tuning curve is performed. Commonly, it is assumed that a neuron's role is to encode the stimulus at the tuning curve peak, because high firing rates are the neuron's most distinct responses. Tuning curves are the functions that relate the responses of sensory neurons to various values within one continuous stimulus dimension. Here, the activation function is not a sigmoid as seen before, but this new dCaAP mechanism. It depicts the neuronal integration, firing rate, and encoding of the human neocortical neuron of L2/3.

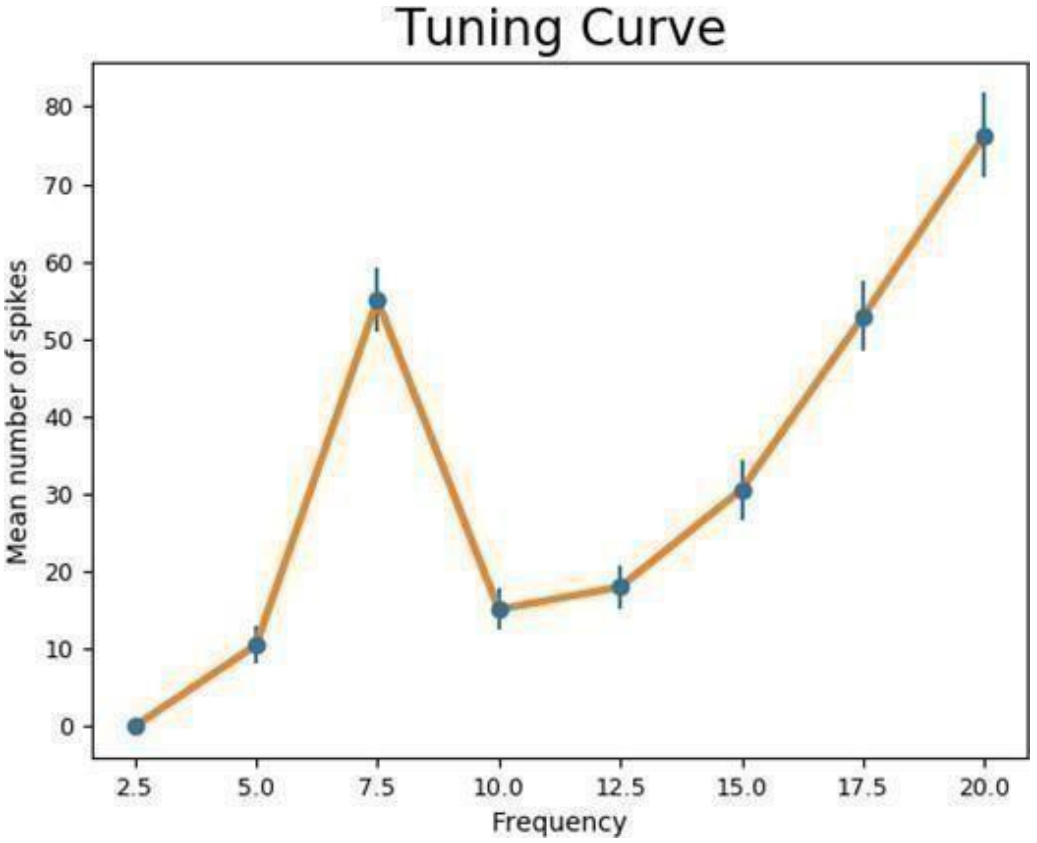


Figure Figure 3.16: Tuning curve of coupled pathway X with ts=20000 ms. In the x axis the frequency (number of synapses needed for the pathway/20 s) is shown, while in the y axis the mean number of spiking for five runs along with their standard deviation.

This tuning curve stands as a prediction of the model. First, it validates the dCaAP mechanism, by sharply increasing its activity when we have an input strength at 7.5 Hz and then declining in a non linear way as the dCaAP activation function. However, when the input becomes stronger, the spiking activity increases by making the cell more excitable providing a duality solution for the model. So, what additional computing power do human dendrites add to a neuron? Previous work using artificial neural networks has suggested that active dendrites improve the computing power of CA1 pyramidal neurons by increasing the number of possible input/output relationships (Poirazi et. al. 2001) and that we must consider the dendritic tree as a two layer neural network with excitatory connections, such as the approach of Poirazi et. al. (2003) for the CA1 pyramidal neuron. However, several key questions remain open: what characterizes these new input/output behaviors of the dCaAP mechanism in human dendrites with the excitatory and inhibitory thresholding pathways? Is there a specific dendritic morphology which maximally increases the computational power of such dendritic neuron potentially performing Boolean operations? And which physiological parameters of the neuron should change to reach this maximal computational power except the number and type of synaptic inputs?

# 3. 5 NMDA receptor

In the biophysical model, the dendritic Boolean computations were different between apical and basal dendrites (figure 2.4). So, apart from the main research question of this thesis which was if other logical operations could be reproduced, we wanted to explore what will happen if now we stimulate not an apical subdomain of the modelled cortical neuron, but a random basal one with respect to NMDA spiking activity. In other words, the apical had as activation function the new dendritic action potential, whereas the basal dendrites preferred the sigmoid function and gave NMDA spikes. Therefore, it is crucial to observe their difference with respect to dendritic and somatic response on the L2/3 neuron as well as the NMDA spiking activity. We have four groups for the basal subdomain. Given the coupling of the basal tree to the soma, NMDA spiking at the basal tree always induced somatic spiking, For coupled mode of the apical tree, with somatic spiking or not, we measure basal NMDA spiking activity in contrast to the apical 60 dendrite, whereas in the uncoupled mode in the apical tree, with somatic spiking or not, we measured basal NMDA spiking activity in contrast to the apical dendrite 76. We have only somatic response here and the duration of the simulation is set again to 20.000 ms. According to Cazé, the number of dendrites should match and not exceed the dimensionality of space spanned by the inputs. We investigated under which synaptic inputs NMDA spiking can be observed or not.

The four conditions with their synaptic inputs, are:

| | **Synapses (coupled-uncoupled)** | **Synapses (NMDA-no NMDA)** |
|---|---|---|
| **Coupled – no NMDA** | 80 | 120 |
| **Coupled – NMDA** | 80 | 220 |
| **Uncoupled – no NMDA** | 60 | 60 |
| **Uncoupled – NMDA** | 60 | 320 |

Table 3.3: NMDA conditions and number of synapses

The question addressed here is if basal and apical dendrites have different computations in the soma rather than in the dendrite. So, a 3D scatter plot may reveal shared features for apical and basal dendrites.

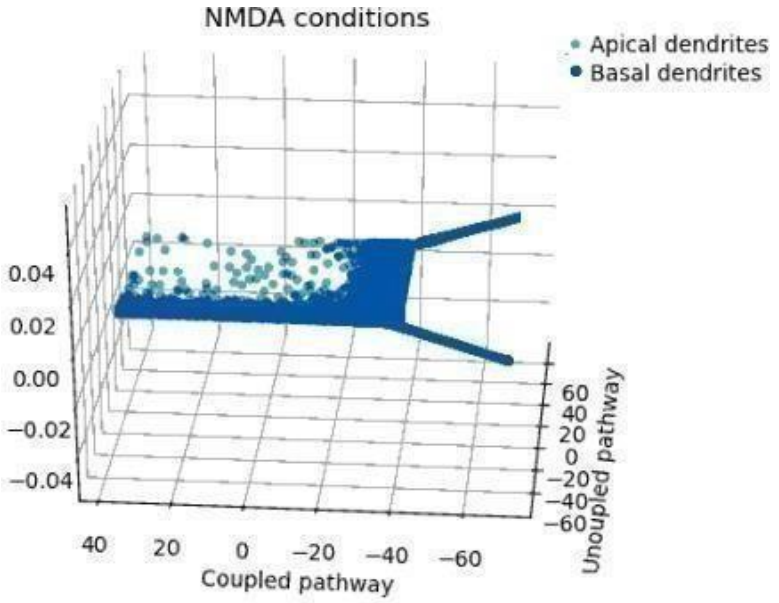


Figure 3.17: Scatter plot for NMDA conditions showing that apical dendrites have higher divergence.

Here is depicted that with respect to NMDA spiking activity, apical dendrites have greater capabilities compared to the basal dendrites, and that would be an indicator why the new dCaAP mechanism is observed when we stimulated the apical subdomain.

Overall, we have shown that the Boolean operation can be potentially implemented using both a specific parameter space and when you move to more than one simulation for all possible combinations. When the dCaAp is on a distal dendrite, intrinsically it computes rather negative integrations. In addition, the computational capacity described, explains the firing frequency of the model and predicts a duality. The apical and basal differences with respect to NMDA activity require further investigation. A limitation of this work is that the inhibition in the model is in one subtree localized and not distributed all over it. As a consequence, it was not explored as a synaptic input variable. Moreover, future work involves investigating specific features of apical and basal dendrites and the morphology of the cell in general, either again in a single neuron level or in a network level. Nevertheless, the results described in this thesis suggest a wider range of human cortical neurons as computational building block, using this new dCaAP mechanism, something that can have a major impact on artificial intelligence and if our human brain perform operations as in a computer.

# 4
# Discussion

*"Life is not easy to for any of us. But what of that? We must have perseverance and above all confidence in ourselves. We must believe that we are gifted for something and that this thing must be attained."*
*-Marie-SkłodowskaCurie*

## 4. 1 New approach to distributed dendritic computation

Several studies have demonstrated that dendritic spikes can amplify coincident dendritic inputs, e.g., in layer 5 pyramidal neurons in the rodent cortex or in CA1 neurons of the rodent hippocampus. The simulation of Gidon et. al is a simple and explicit demonstration of how the dendritic mechanism observed in human L2/3 pyramidal neurons computes the anti- coincident function for multiple input pathways, limiting the number and/or strength of inputs integrated in the dendrite. Interestingly, when we introduce inhibition to the model (20 GABAergic synapses) in addition to the two excitatory pathways, the hyperpolarization of the membrane caused by the inhibition led to recovery of the dCaAPs. In the expansion of the model, when we moved closer to the soma negative integration by the dendrites could be performed. These results suggest that the net input strength, such as the precise balance between excitation and inhibition, is necessary for firing dCaAPs and propose a counter- intuitive role of inhibition in increasing the dendritic spikes amplitude, as we observed the spiking activity and the max amplitude of closer dendrites. The transformation of input to output represents the computational function of a neuron. It has long been assumed that the summation of synaptic inputs at the dendrite and the output at the axon can only instantiate simple (i.e. linear) logical operations such as the AND and OR gates. Traditionally, more complex, non-linear operations (like the XOR affair) has been thought to require a network solution. Gidon et. al found that, dCaAPs in L2/3 dendrites have a unique activation function that allowed them to effectively compute the XOR operation in the dendrite by suppressing the amplitude of the dCaAP when the input is above an optimal strength. In the thesis work, this assumption is expanded to more logical operations. Thus, we consider a novel model based on the results in this study of Gidon et. al that portrays the somatic and dendritic compartments of L2/3 neuron as a network of coupled logical operators and corresponding activation functions. Like the XOR logical operation could be potentially be computed in the apical dendrites and the AND/OR in the basal ones, our results on more logical gates implemented by the dendrites on L2/3 human neurons could assist dynamically to this interplay. In this model, the apical dendrite performs XOR wit h dCaAP, whereas the soma and tuft/basal dendrites perform AND/OR operations with sodium and NMDA spikes respectively. That would explain a dynamic pattern of more logical operations performed by

our dendrites to perform higher level functions, like cognition, utilizing this new dCaAP mechanism. Finally, the findings that human neurons fire dendritic action potentials which have unique shape and computational characteristics like the tuning curve, and specific active properties between apical and basal dendrites herald a new approach to distributed dendritic computation in the level of single neuron and beyond with a major impact on artificial intelligence and neural networks.

# 4. 2 Does our cortex mimic a computer?

It is a common ground, that to learn and mimic how the brain processes information has been a major research challenge for decades. Despite the efforts, little is known on how we encode, maintain and retrieve information. It is good to keep in mind, though, that inputs from dendrites process the integration both temporally and spatially. The human brain is the most powerful computer the world has ever seen! The bigger question here is addressing how does the brain compute. It is certainly very tempting to conclude that generally neurons in the brain simply put just complex multi-function logic gates and that the output of a neuron's axons is a series of pulses on and off signals as seen in computers' logic gates. But of course, someone needs to extend the metaphor, as a neuron doesn't just have two inputs, it - usually - has thousands. Especially if we talk about the neocortex. And of course, it isn't just any two, so it's like a massive "AND" gate and the "AND" gate is when a certain percentage of the inputs are active, not all of them. And then you need to put in a few inputs capable of shutting down output, kind of like putting an inverter running into an AND gate, but of course it isn't a simple any gate. And then it appears that in certain neurons, areas that are close together form individual computation units, for example when you have one AND gate with e.g. 100s of inputs and a threshold and then it's output connects into a hub, with lots of others of the AND gates, and the hub is a giant OR gate. Thus, Boolean algebra computations depend on the number of input and hugely on the cell type and the biophysical mechanisms and morphology of the cell. Does our in silico cell resemble the in vivo one? According to the researchers, the neocortex contains thousands of models functioning not only in hierarchy, but also in parallel (numenta) putting aside the long-standing view that the neocortex receives input from a sensory organ and processes it in a series of hierarchical steps. Theoretical studies have proposed that dendritic compartments can perform parallel processing as well as subsequent nonlinear transformations prior to final integration at the axon ((Häusser and Mel, 2003; Jadi et al.,2014; London and Häusser, 2005; Poirazi et al., 2003; Polsky et al., 2004; Tran-Van-Minh et al., 2015). With more isolated or additional compartments capable of nonlinear transformations, the electrical structure of human dendrites could provide single neurons with a richer cortical computational repertoire. So, are human beings the ideal decoders? Are neurons in the brain simply put complex multi-function logic gates, or does their function go much deeper than that? If we think of a brain as a device that transforms inputs to outputs, then, inexorably, the computer becomes our analogy of choice. But the brain isn't a computer. Each neuron is a computer. Your cortex contains 17 billions computers! It is a common knowledge that the dendrites of a pyramidal neuron contain many separate branches, which means that each branch of a dendrite acts like a little nonlinear output device, summing and outputting a local spike if that branch get enough

inputs at roughly the same time. We use our brain and our neurons and we make our neurons doing non linear computations in order to understand our brain and understand the way neurons compute signals. In other words, I am thinking how I can have the ability to think. It means the brain can do many computations beyond treating each neuron as a machine for summing up inputs and spitting out a spike. Yet, that is the basis for all the units that make up an artificial neural network. It suggests that deep learning and its artificial intelligence brethren have but glimpsed the computational power of an actual brain. But if we think the brain is a computer, because it is like a neural network, then now we must admit that individual neurons are computers too. All 17 billion of them in your cortex; perhaps all 86 billion in your brain. And so it means your cortex is not a neural network. Your cortex is a neural network of neural networks. Of course, neurons receive many more than two inputs, and have many more than two branches: so the range of logical functions they could compute is astronomical. What if the input here was not a simple Poisson spike train? What if our cell had a different biophysical morphology? Would all these logical operations be validated again? A neuron's dendritic nonlinearity that is optimal for integrating synaptic inputs depends on the statistics of its presynaptic activity causal patterns to generate Boolean gates. Knowing, though, that the dendrites of a neocortical neuron can compute logical gating in one extend, like the results in this thesis work, is of vital importance for artificial intelligence and machine learning algorithms in the context of human cognition, something that could change the way we -with our brain- think about the brain.

# 5
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# 6
# Terms of use

NEURON simulation environment (version 7.5) for modelling approaches, and Python scripting language for data analysis. All simulations were performed in the High Performace Computing Cluster of Poirazi lab.

No reproducibility of the figures depicted.