Chapter 2

Literature Survey

2.1 Introduction

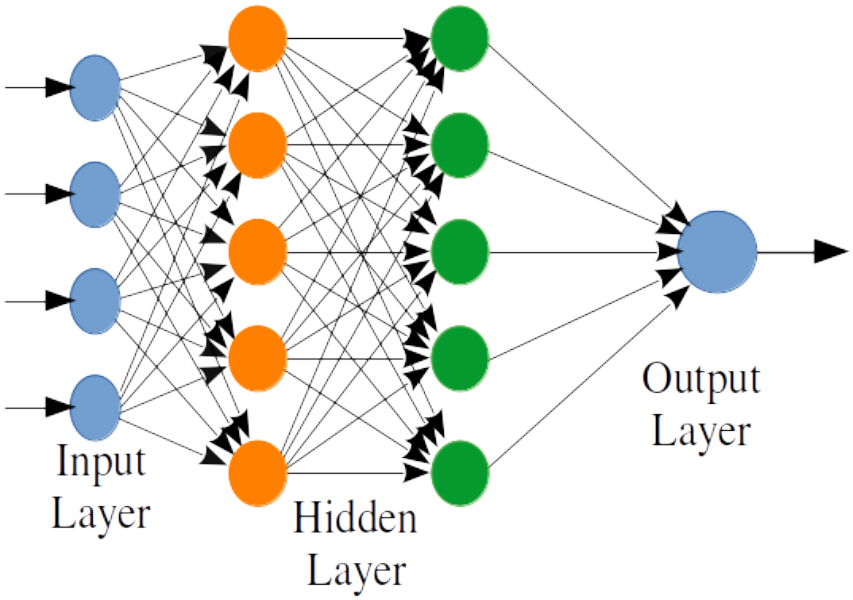

Figure 2-1: A simple artificial neural network representation.

Biological neural nets are one of the complex networks that are yet to be explored in detail. A simplified translation of biological neural nets is the artificial neural network with its ability to adapt to input-output mapping [35, 36]. Majority of the dedicated biological neural nets in general and artificial neuronal networks in particular are mostly represented with the cell body being connected with weighted inputs as shown in Fig.2-1 and linear summation of the inputs triggers an activation function at the cell body. At the core of such neural networks are the basic computational units which are either called as a biological

neuron in case of a biological network or a perceptron in case of an artificial neural network. Some of such neural network are 'Non-leaky and integrate-and-fire model' [12], 'Hodgkin and Huxley(HH) model' [37–40], 'leaky integrate-and-fire model' [10, 41], 'exponential integrate-and-fire model' [42, 43] that simulate the neuron behavior as a linear or quasi-linear integration of inputs and fails to accommodate local neuronal dynamics of a real arborized neuron. The problem with such kind of network is over-simplification of the basic computational unit. However, recent findings proposes these basic computational units to be much more complex [7, 44, 45] than a simple linear integrator. In order to understand the computational capability of a single neuron, one has to have a clear knowledge about the neuron morphology, their electronic structure as well as the localized dynamics. Apart from the physiological properties, one needs to understand the dynamic range of computational capabilities due to connectivity with other neurons. Along with the physiological properties and dynamic computation capability of neuron, the reticulated modification of neuron morphology contributes to the enhanced plasticity range of neurons. Considering the morphological complexity due to dendritic arborization alone, these computational units are capable of complex function formation. One such model is the Rall's equivalent cylinder model, that attempts to link neuron morphology to the learning [46–49] that results in Rall's equivalent cylinder. But one of the major drawbacks of Rall's cylinder is its inability to accommodate non-linearity due to localized AIC. In order to have an idea about the complexity of a real neuron morphology let's take a look into the different neuron morphologies taken from https://neuromorpho.org/ in Fig.2-2.

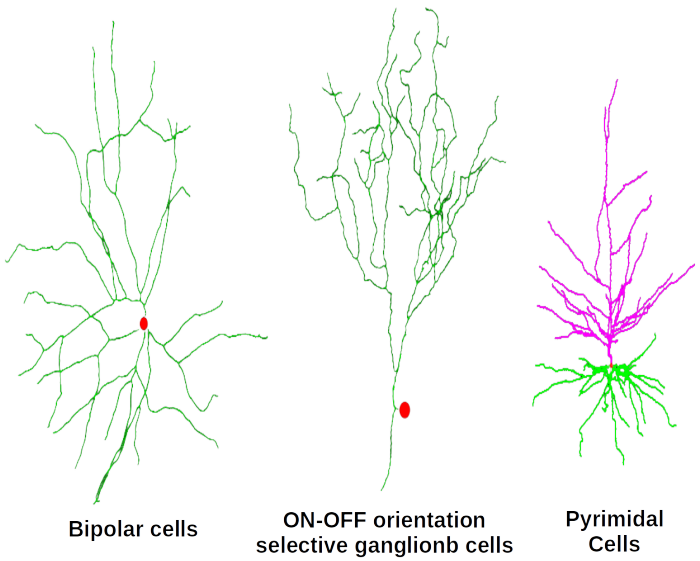

Figure 2-2: Actual neurons with dendritic arborization collected from https://neuromorpho.org/

Looking into the morphologies of different neurons in Fig.2-2, extracted from different layers of neuronal networks give us an indication of the computational complexity of individual neuron [15, 44]. A number of literature pointed out toward dendritic structural plasticity [50–52] in neurons. If we consider the dendritic arborization of the neurons in Fig.2-2, combination of inputs to distal dendrites alone will behave as a complex memory unit facilitating multiple functions corresponding to unique combination of inputs [51, 52]. On the other hand, if connectivity facilitated by dendritic spines are considered for individual dendrite, the computational capability of a single neuron becomes even more robust [52–54]. However, the question persists is the homogeneity and heterogeneity of neurons' morphology and electrophysiology [55–57] within a layer and their respective structure-function relationships. Recent findings pointed out the significance of type-specific function formation in neurons aligned to specific cytoarchitectonic landmarks [58–61], facilitating short-term memory whereas local protein synthesis ensures the long-term memory confined to a distinct layer. Thus a detailed understanding of the link between neuron morphology and type-specific function relation is gaining significant attention and is the key toward understanding circuit level computations performed by unique neuron morphology.

2.2 Morphological Significance

In the late 1950s and early 1960s, many extracellular electric field interpretations, including those of Andersen [62] and Rall [48], suggested the presence of active propagation of action potentials (AP) in dendrites. However, in a seminal study by Kandel and Spencer [63], they discovered small spike-like structures called fast prepotentials while recording extracellular potential and hypothesized that those were AP generated in distal dendrites. Later in the 1970s, improved microelectrodes-based extracellular data acquisition became possible, revealing AP in cerebellar Purkinje cells, hippocampal and cortical pyramidal cells [64–66]. Because of the availability of new imaging techniques, such as voltage-sensitive dyes, high-speed fluorescent imaging [67–69], and glutamate uncaging [70], similar findings have been widely reported. Measurements such as array tomography, optical sectioning microscopy, and volume electron microscopy, on the other hand, have been used to study and understand the functional roles of different dendrite structures, as well as visualization of neuronal morphologies [71–73]. Later, due to the active nature of dendrites, these structures are assumed and hypothesized to be far more complex than a simple integrator of incoming synaptic signals [74–76]. Much has

been studied and confirmed about the distribution of localized AICs in dendrites as well as voltage-gated ion channels using the techniques mentioned above. However, the role of such diverse distribution of localized AICs within similar types of neurons has not yet been quantified, and it is assumed to alter the firing properties of neurons depending on the type of functioning network with which one neuron is associated [77]. Dendritic Na^+ ions appear to be expressed in the majority of neurons and are mostly associated with AP back-propagation, local AP initiation, and synaptic signal amplification, whereas K^+ channels actively contribute to Long Term Potentiation (LTP) [78]. However, the degree of signaling varies from neuron to neuron depending on dendrites' local geometry, such as diameter, branching patterns, and the presence of other voltage-gated ion channels in the dendrites [79–82]. The structure-function relationship concerning channel density and local geometry is generally poorly understood, but these properties are thought to be critical in defining the functional role of active dendrites [83]. Dendritic ion channels have also been reported as an important aspect in terms of Long Term Potentiation (LTP)/ Long Term Depression (LTD) as being capable of AP back-propagation [84, 85] and local spike generation [86–88], giving dendrites the ability to be interpreted within the framework of meta-plasticity [89].

Despite the fact that the behavior and properties of these tiny units (dendrites) have been recorded and reported in the literature, little is known about their signal processing capabilities. Wilfrid Rall [46, 48, 49, 90] performed major works on the characterization and behavior of a passive dendritic fiber, which resulted in Rall's 3/2 rule and Rall's equivalent cylinder. Although Rall's postulates support some of the properties of a limited class of neurons, they might not be sufficient to discuss the role of non-linearities in dendrites. Apart from Rall's postulates, the majority of the framework is based on the dendrites' passive nature, so consideration of the effect of localized AICs to characterize dendritic local responses is required to realize the structure-function relationship. Advancements in technologies also shed ample light on the remodeling of dendrites to maximize neuronal surface area to accommodate more synaptic contacts to enhance the type-specific functionality of neurons [91, 92]. A type-specific function is not dependent on promoting dendritic spine growth alone, rather is also described as a function of dendritic arbor growth and retraction [51, 84, 93]. Deterministic dendritic growth for function-specific computation and stochastic growth mediating enhanced computational functionality has also been reported [92, 94, 95]. Coupled with type-specific morphogenesis, localized AICs in dendritic arbor promote non-linear computation either in sensory or motor neurons [84, 96–98]. Thus the literature gives us a vivid picture of the importance of neuronal morphology in

complex computations and structure-function relationship that needs further investigation to understand their role from systems neuroscience perspective. Thus a detailed investigation of morphogenesis, type-specific morphological change and localized non-linear dynamics in dendritic arbor has been conducted and discussed in detail in the following sections.

2.2.1 Morphogenesis and Type-Specificity of Neuron Morphology

Morphogenesis is the basic way by which the neurons achieve type-specificity. Previous research on morphogenesis and structural plasticity concluded that "Once development was ended, the fonts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult center the nerve paths are something fixed and immutable, nothing may be regenerated" [99]. However, recent research paints a very different picture [100, 101] and supports the hypothesis of a permanently plastic brain. Novel experience, learning new skills and altered afferent input as a function of environmental changes are now acknowledged as modulators of brain function and neuroanatomic circuitry. The type-specific function of the neurons are derived by the precise organizations of inputs and the outputs. Similar type-specific neurons make input connections to precise layers and projects onto similar layers [102]. Each cortical region is connected to only a subset of other regions, and the axonal and dendritic arbors of individual neurons arborize in precise, layer-specific patterns within any particular region with highly precise functional connectivity [103, 104]. Afferent axons can target specific neurons while avoiding others, resulting in input vectors which are often consistent for neurons of the same type but differ between cell types [55–57, 102]. In fact, a spatial deviation of neuron morphology from their targeted location has been reported as cause and effects of neurological disorder. These effects due to displacement or significant restructuring of dendritic arbor has been consistently reported in a number of studies [100, 105, 106] suggesting a central role of neuron morphology in type-specific function formation and computation. Morphogenesis can be seen mostly during early learning stage when new skills are being learned of when exposed to an unknown environment [91, 107, 108] that facilitates the type-specific cell birth and development to achieve a targeted function [109–111]. Thus the type-specific morphology of a neuron is achieved by the localized population functionality, their connectivity with the associated layers, regulatory proteins inducing dendritic arborization and gene encoding to activate type-specific physiological properties.

2.2.2 Morphology and Structure-Function Relationship

Type-specificity of a neuron is determined during the birth of a new neuron and its associated region. After the birth of a neuron in a particular region, population responses and respective gene expression triggers primary dendritic arbor to achieve type-specificity [91, 92, 100]. Failing to reach type-specificity and homeostasis leads to death of the neuron, whereas, reaching type-specificity, the neuron develops secondary dendrites to maximize its connectivity with neighboring neurons via synaptic connections that helps enhance the neuron function and complex protein activation for stabilization [112–114]. Numerous literature confirms distinct neuronal morphologies performing distinct function [115–117] and a probable relationship between structures and functions. Each type-specific cell are unique and analogous in morphology and electrophysiology [117–119] and multiple studies have been conducted on visual cortex to classify and understand homogeneity and heterogeneity in type-specific neurons. Previous studies confirms sub-class of cells with similar morphological and physiological homogeneity but dissimilar in terms of their projections and input connections [102]. Multiple in-vivo experimentation and high resolution imaging with advanced staining techniques have confirmed unique cell types performing similar tasks inherit morphological similarity in terms of dendritic stratification and electrophysiology [117, 120, 121].

Detailed in-vivo investigation of vertebrate retinal projection alone has classified as many as 20 retinorecepiant sites where more than 50 RGC types relay sensory inputs from the retina[121, 122]. Specific sensory RGC types are connected to precise locations in the retina to extract information and finally project onto the different stratus. Similar RGC sub-types are connected with very precise mossaic patterns, positioning to avoiding interaction with similar RGC types, extracting information and projecting via a stratified axon. Axons in some regions are extensively stratified, relay the same information to multiple regions to interpret in multiple ways. Thus type-specific neurons with identical electrophysiology, performing similar functions establish a clear understanding of neuron morphology and its probable role in type-specific computations. Added to the complex morphology, distinct electrophysiology and local non-linearity enhances the compute capability of the neuron [97].

2.2.3 Localized Active Ion Channels and Non-linearity

Apart from deterministic type-specific neuron morphology and stochastic synaptic connectivity with neighboring neurons, electrophysiology of type-specific cells are homogeneous [117–119]. Uniqueness of type-specific morphology [100, 101], coupled with connectome specificity [123–125] and distinct electrophysiology [118, 119, 123] shapes the local function of a neuron. Electrophysiological properties of a neuron such as active and passive membrane dynamics [96, 126, 127] have been demonstrated to play a significant role in the establishment of complex computational function formation. Dendritic spikes were first discovered in a study by Kandel and Spencer [63], prior to which dendrites are considered as passive in nature and called these spike-like structures fast pre-potentials. These pre-potentials attract the attention of the greater neuroscience community to investigate its basis [128–130]. With the advancement of technology, availability of sophisticated imaging techniques and staining methods in current years, existence of AICs at precise locations of dendritic arbor has been substantiated [131–134] which are capable of generating active AP in dendritic arbor. Several literature confirms differential distribution of AICs [135–137] whereas others corroborate existence of voltage gated and Ca^{2+} activated Na^{+} and K^{+} ion channels at localized regions of dendritic arbor and axons [131, 138, 139]. Some of the studies associated with motor neuron associate these localized ion channels to better motor control and strength [84, 132, 140]. Non-linearity due to AICs in localized regions of dendrites are suspected to be link to enhanced performance capability. In fact in-vivo and in-silico experimentation [84, 140] successfully links active integration to better muscle force control. Similar in-silico models and in-vivo experimentation have been conducted to understand the role of AICs at precise locations and active integration of dendritic signals in computational efficacy [32, 97, 141, 142]. Findings from studies [143] imply that active dendritic processes are predominantly essential for the onset of the non-linearly mixed network representation in mouse L5 pyramidal neurons, which is recommended for a specific aspect of sensorimotor behavior. Active dendritic integration serves to reinforce fundamental microcircuit computation, the generation of mixed selectivity, and high-dimensional network representations that are easily modified by experience in pyramidal neurons. This type of general computation could enable cortical areas to actively learn representations that are easy to decode and provide accurate transformations for use in adaptive behaviors. As a result, active dendritic processing in pyramidal neuron-based microcircuits underpins a fundamental computation that enables representation learning in cortical areas. Similar investigation considering binary neuron-based model integrates sub-linear and supra-linear neuron function

capable of performing linear operations but fails to compute non-linear operations [32]. The non-linear operation is considered as one of the key components for OS [32, 144]. The extent of computational capability using non-linear neuron is well explored with model integration [32, 145, 146] and in-vivo experiments [144, 147]. The non-linear model is able to evaluate linear as well as nonlinear functions [32] projecting the computational capability and significance of non-linearity in neurons compared to its linear counterparts.

2.3 Summary

The full potential of a neuron has remained unaddressed given the scarcity of advanced tools and instrumentation techniques over time, and a bottom-up approach that focuses on circuit level inference in shaping complex neuronal systems has remained unexplained. Individual neurons shaping network level interpretation from the bottom up will allow for better understanding of network dynamics as a function of individual neurons, better diagnosis of neurodegenerative conditions, and formulation and construction of superior prosthetic devices. Available studies investigate morphogenesis and adeptly links it to neuron type specificity. Dendrite arbor growth, extension, and retraction of daughter dendritic branches to achieve type-specificity have all been investigated and substantiated in research findings. It has already been reported that neuron morphology for type-specific cells, input connectivity layers, and projection layers are all significantly related. However, the precise connectivity patterns of neurons with their inputs have remained unexplored and serve as the foundation for understanding the complex computations performed by neurons. Mathematical models combined with likely connectivity patterns and neuronal morphologies can aid in understanding the structure-function relationship in type-specific function formations. Studies confirm dedicated electrophysiology of type-specific neurons in addition to morphogenesis and neuron morphological factors.Regionalized non-linearity in neurons is considered to have a significant role in improved functional and cognitive abilities. Localized non-linear dynamics in an arborized neuron itself behaves as *"network within a neuron"*. Thus, understanding neuron morphology in conjunction with localized non-linearity will improve our understanding of a biological neuron's true compute capability.