Biochemical Mechanisms of Dendritic Nonlinearities and their Application into Computational Models

Matthew Babik

Abstract

While dendritic spines make up only a small portion of the entire neuronal system, multiple intracellular mechanisms are localized to these points to trigger unique signaling pathways. Biochemical interactions of membrane channels, intracellular protein cascades, and spine morphologies all give rise to nonlinear mechanisms of signal transduction. Large branch summation events, in which multiple incoming signals are integrated towards the soma, are mediated by these mechanisms. Information on this topic is utilized within computational studies to create accurate pyramidal neural networks. However, the methods to incorporate these nonlinear mechanisms into programs can be thoroughly debated. The purpose of this paper is to discuss the advantages and disadvantages of current approaches that incorporate nonlinear signal transduction into neuronal models.

Introduction

Dendritic nonlinearities are a signaling method implemented by neurons in the prefrontal cortex (PFC) to increase the computational power of a single neuron. This type of signaling has been associated with learning-related mechanisms and higher-level cognitive functions, such as emotions (Poirazi et al., 2014). Dendrites utilizing nonlinearities tend to propagate incoming signals through vast integrative networks known as dendritic branches. The nonlinearities themselves occur directly at the spines of the dendrite which process the incoming signal and generate dendritic spikes alongside nearby spines (Spruston, 2013). The tendency for a signal to propagate towards the soma occurs by spiking, which has the ability to elicit action potentials based on its strength (Spruston, 2013). Dendritic spikes are caused by the summation of incoming signals from multiple dendritic spines. These signals can be increased or decreased by subcellular memorization mechanisms that take into account previous depolarizations (Poirazi et al., 2014). A variety of biochemical mechanisms mediate these signaling interactions and can occur locally or communally along a particular dendritic branch. Nonlinear mechanisms that are isolated to particular spines tend to occur through interactions with Na+, K+, Ca2+ cation channels (Poirazi et al., 2014). Spatiotemporal relationships between spines regulate signals and the manner in which they are processed communally. These spatial relationships utilize N-methyl D-aspartate (NMDA) receptors and their intracellular effects to regulate synaptic connections (Poirazi et al., 2014). The cyclic adenosine monophosphate response element-binding protein (CREB) transcription factor also acts relative to local signals received by a synapse. This transcription factor helps to produce proteins that induce long-term potentiation at the spine that was depolarized. The coupling of all these biochemical reactions creates the pattern of nonlinearities experienced by the neuronal network.

Biochemical Mechanisms of Dendritic Nonlinearities

Cation Channels

Ion channels on the dendritic spines of PFC neurons exhibit unique biophysical properties and can be controlled by intracellular processes. Certain mRNA are trafficked by chaperone proteins into localized dendritic locations as a consequence of synaptic activity in the area (Bramham & Wells, 2007).

Dendritic spines contain the intracellular machinery to translate these messages, thus modifications are highly regulated and able to be localized to the environment near the postsynaptic area (Bramham & Wells, 2007). These mRNA typically contain information to produce new ion channels in a dynamic system that may lead to the overexpression or underexpression of a particular channel protein.

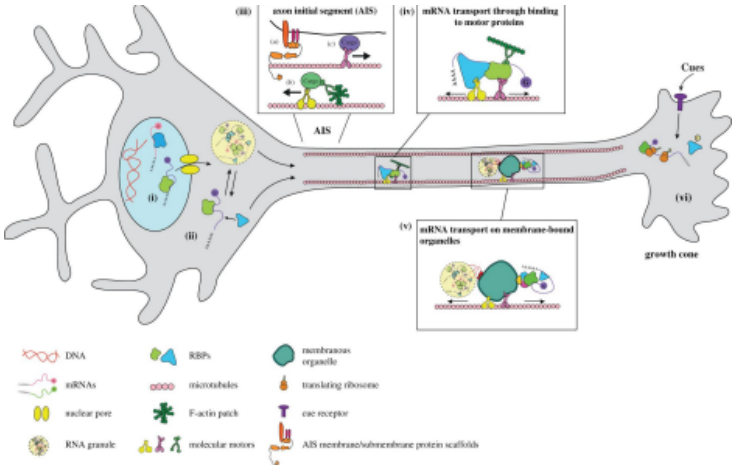

Figure 1. The localization and simulation of mRNA translation within a dendritic spine. (Benita et al., 2020)

If the activity of an ion channel is increased within these locations, the neuron will actively modify the dendrite in response to synaptic activity (Bramham & Wells, 2007). Depolarizations of particular channels are also important to maintain the integrity of the spines. The localized production of the Arg protein expands the actin cytoskeleton, which underlies the morphology of the dendritic spine (Bramham & Wells, 2007; Lo et al., 2020). This protein is transcribed locally in a spine after a depolarization event by Ca2+ions via NMDA receptor channels where it can then exert its effects (Bramham & Wells, 2007). All dendritic spines start from the actin cytoskeleton pushing on the cellular membrane to produce a small bubble. This bubble will begin to localize intracellular machinery and eventually produce a working

dendritic spine. This unique production of the Arg protein acts to maintain the stability of the spine through its interactions with the cytoskeleton and thus also maintains the synaptic connection (Bramham & Wells, 2007; Lo et al., 2020).

Post-translational modifications of ion channels elicit unique activity-dependent responses that allow for nonlinear signal propagation. These changes depend on the type of protein and the mechanism it acts with intracellularly (Shah et al., 2010). Local depolarization and plasticity of the synapse cause changes in the phosphatases and kinases present within the postsynaptic area (Shah et al., 2010). The involvement of cascade proteins creates mechanisms of biochemical backpropagation that tend to act on the ion channels. This type of backpropagation governs the activity of a particular synapse (Shah et al., 2010). For example, in CA1 dendrites, activation of protein kinases A, C, mitogen-activated protein kinase (MAPK), and extracellular signal-regulated kinase (ERK) modify A-type K+ion channels. Modification of these channels can elicit enhanced AP propagation (Hoffman & Johnston, 1998; Shah et al., 2010). A well-studied post-translational modification involves the attachment of the protein calmodulin to the Ca2+ mediated potassium channel “KCa2.2” (Shah et al., 2010). Calmodulin acts as an intermediate to attach Ca2+ and activate the channel, allowing the affinity of the protein to be regulated in order to vary the activity of K+influx (Allen et al., 2007; Xia, 1998). The phosphorylated state of KCa2.2-bound calmodulin is controlled by localized phosphatase (phosphatase 2A) and kinase CK2 (Allen et al., 2007; Shah et al., 2010). Phosphorylation of calmodulin decreases the activity of the channel due to a lower affinity of Ca2+for calmodulin (Allen et al., 2007; Shah et al., 2010; Xia, 1998). Likewise, the removal of this phosphate will increase the affinity for Ca2+. This process leads to bidirectional activation of the channel. In all, the mechanisms presented have the ability to create unique depolarizations and allow for the retention of information relative to the inputs received.

In addition, distributions of ion channels in spines also play a role in nonlinear processing (Remy et al., 2009). The inactivation of Na+ channels strongly regulates spike generation within CA1 pyramidal neurons (Remy et al., 2009; Poirazi et al., 2014). Inactivation of these channels leads to increased dendritic excitability globally in the cell (Remy et al., 2009). This feature thus aids in inducing synaptic plasticity relative to the surrounding neurons. Local distributions of voltage-gated ion channels and their properties tend to be altered after long-term potentiation (LTP) induced excitatory stimulation (Poirazi et al., 2014). These LTP stimulations decrease the peak depolarization required to elicit a dendritic spike. This change leads to a slow but permanent increase in the ability of a dendritic branch to influence the voltage of the soma (Poirazi et al., 2014; Losonczy et al., 2008). This effect is well understood and is known as branch strength potentiation (Poirazi et al., 2014). Overall, this

phenomenon shows that if plasticity is induced on a spine, it will propagate to the surrounding dendrites via A-type currents (A-type currents occur via Ca2+ mediated K+ channels) (Poirazi, 2014) Ionic conductances, particularly those with Ca2+, Na+, and NMDA, have been shown to elicit back and forward propagation of dendritic spikes (Poizari, 2014).

Spatiotemporal Associations of Dendrites

The morphological diversity of dendritic trees is capable of affecting signal conduction towards the soma. Dendritic trees act as large summation devices that will properly conduct a signal once a certain threshold has been reached. This is opposed to linear dendritic signaling which acts through simple transmission pathways (Poirazi et al., 2014). These mechanisms are developed through different voltage-dependent conductance factors, particularly via voltage-dependent ion channels (Losonczy et al., 2008). Although these factors are associated with a biophysical view of dendrites, the biochemical interplay inside the cell allows for nonlinearities to occur. The most notable biochemical system that creates these dendritic properties involves the activation of NMDA spikes. NMDA reception is tied to mechanisms of back and forward propagation of dendritic spikes (Losonczy & Magee, 2006). These methods of propagation assist in signal summation events and strengthen synaptic connections as a form of LTP induction (Remy & Spruston, 2007). However, this type of LTP induction is only performed by Parvalbumin-expressing (PV+) GABAergic interneurons (Remy & Spruston, 2007; Cornford et al., 2019).

NMDA reception can cause dendritic regenerative events known as NMDA spikes. 1 These spikes have much higher amplitude and duration than spikes generated by Na+, A-type K+, or Ca2+ mediated potassium channels (Poirazi et al., 2014). However, these spikes still have a lower amplitude than Ca2+ channel spikes2(Poirazi et al., 2014). NMDA spikes are highly localized, being almost purely confined to the dendritic branch of the overall system (Iacobucci, & Popescu, 2019). As the spike acts both forwards and backwards on the system, it is capable of affecting all the spines of a branch (Iacobucci & Popescu, 2019). This effect is described as spatial coupling and has been investigated as a mechanism for intracellular detection of spines that form a synaptic connection (Iacobucci & Popescu, 2019).

In addition to stimulation of the dendritic branch, receptor activation by NMDA can affect the processing of signals purely within dendritic spines (Iacobucci & Popescu, 2019). Spatial coupling influences the overall activity of all NMDA receptors in a spine after a particular NMDA receptor has allowed Ca2+ions to pass through (Iacobucci & Popescu, 2019). This mechanism acts biochemically through interactions with calmodulin, calcium ions, and the local NMDA receptors within the dendritic spine (Iacobucci & Popescu, 2019; Shah 2010). This form of mediation is inhibitory towards NMDA reception and serves as a method to autoinhibit the movement of Ca2+ across the membrane and prevent oversaturation of the ion (Iacobucci & Popescu, 2019).

CREB transcription factor

CREB is a multipurpose transcription factor that enables nonlinear mechanisms in dendritic spines. This protein acts to stabilize long-term memory (particularly in amygdala-related fear memorization engrams) and alters cellular machinery based on this stabilization (Poirazi et al., 2014;

Poirazi et al., 2019; Zhou, 2009). CREB enables the initiation of multiple cascade events which produce plasticity-related proteins when intracellular conditions permit such connections (Zhou, 2009; Poirazi, 2014). In particular, this transcription factor produces proteins involved in the MAPK and mTOR pathways (Zhou, 2009). Both of these cascades are involved in maintaining synaptic integrity after LTP induction. These plasticity-related proteins will eventually cause higher-level functional changes in the physiology of the amygdala by recruiting neuronal cells for the formation of fear engrams. As CREB changes neuronal conformation, it also acts on particular spines to dictate temporal and spatial synaptic cluster formation (Poirazi, 2014; Poirazi, 2019; Zhou, 2009).

The formation of synaptic clusters by CREB mechanisms also leads to the induction of the effects of NMDA spikes within a particular space of the dendritic tree, further propagating methods of nonlinear integration. Additionally, NMDA Ca 2+ channels are shown to influence the spatial dynamics of synaptic clusters during development (Kastellakis & Poirazi, 2019).

The biochemical mechanisms elicited by the CREB protein allow for compartmentalized dendritic spine generation (Poirazi, 2014; Kastellakis & Poirazi, 2019). Specifically, portions of dendritic branches utilize cluster formation as a method of localized spike induction to a particular section of the neuron (Kastellakis & Poirazi, 2019). In this interaction, the MAPK signaling pathway involves the protein Ras GTPase, which is known to increase spine volume after induction of the cascade (Kastellakis & Poirazi, 2019; Kastellakis, 2015). The number of spines is increased by inducing actin molecules from the cytoskeleton in the dendritic branch to push the membrane upward and form a localized pocket (Kastellakis & Poirazi, 2019; Kastellakis, 2015).

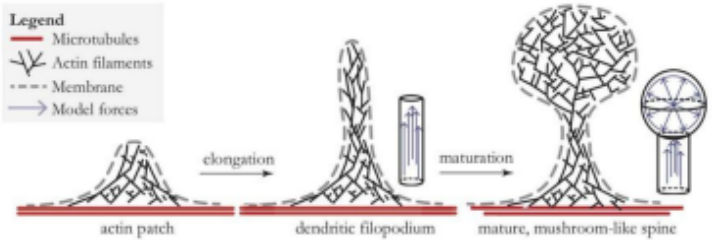

Figure 2. The creation of dendritic spines from actin filaments. (Miermans et al., 2017

An increase in spine volume is integral to synaptic cluster formation, although multiple processes are acting to produce this output (Kastellakis, 2015; Poirazi, 2014).

Modeling dendritic nonlinearities

While mathematical modeling of nonlinear networks has been capable of creating simulations that can process information similar to neurons, networks utilizing functions that integrate known biochemical mechanisms are missing. Higher-order statistical operations, while capable of creating unique integrations (structures beyond simple Hebbian networks), still exhibit faults relative to the biochemical to biophysical interplay (Cox & Adams, 2009; Stöckel & Eliasmith, 2021). Models that give further attention to nonlinear biochemical mechanisms tend to be modeled within single neuron simulations (Poirazi et al., 2003).

These simulations can better account for the large degree of spinal interactions within the “tree-like” networks seen within in vivo cell lines (Stöckel & Eliasmith, 2021; Poirazi & Papoutsi, 2020). Single neuron programs are more capable of modeling spatial and temporal interactions due to the greater ability to model spike firing. The summation of spike inputs is thus able to be based on the biochemical mechanisms mediating spine relationships (Poirazi & Papoutsi, 2020). Due to this complexity on the single-cell level, a wide variety of methods have been proposed for creating multicellular models.

In particular, the transformation functions utilized on the input vectors across neurons in these networks have used non-orthogonal basis functions (multiple correlated independent variables) (Stöckel & Eliasmith, 2021). Networks that use these basis functions linearly combine them to create a processing unit so that the movement of signals is nonlinear (Stöckel & Eliasmith, 2021). Overall, this type of transformation is an attempt to roughly model spikes created by incoming signals and their intracellular properties.

Current models also utilize varying degrees of pre-population versus post-population signal integration (Stöckel & Eliasmith, 2021; Poirazi & Papoutsi, 2020). This variation models biochemical mechanisms utilized for spike integration. Dendritic spines formed by NMDA stimulation produce synaptic clusters capable of being modeled by this population data (Poirazi & Papoutsi, 2020). As this form of integration is commonly utilized within nonlinear neural networks, these models take advantage of dendritic spike summation in order to produce

a possible output (Stöckel & Eliasmith, 2021). This enables nonlinear functions to utilize the connections of the pre-population along with those of the post-population, a property that is mediated by the biochemical mechanisms discussed (Stöckel & Eliasmith, 2021). Overall, this approach of modeling utilizes operations of synaptic filtering to produce nonlinear relationships between somatic input currents and the neural response.

A common challenge within computational neuroscience is building accurate models of the pyramidal tract that can properly integrate excitatory and inhibitory interactions into one signal. A recent method developed to navigate this issue is to separate the two pathways and afterward combine the resulting values using least squares regression optimization to find the updated weights during backpropagation (Stöckel & Eliasmith, 2021). Previous methods utilized inhibitory interneurons that mediate the incoming excitatory signal before progressing. In the new program, the inhibition function is integrated alongside the other nonlinear connections established (Stöckel & Eliasmith, 2021; Drix et al., 2020). The current method not only saves computational space but also prevents loss of signal integrity (Stöckel & Eliasmith, 2021).

Conclusion

Based on current models of dendritic nonlinearities, the ability of current computational models to accurately represent pyramidal neurons shows benefits as well as issues. While these models are capable of gaining insight into higher-order functioning based on the work of biophysical studies since the 1990s, accurate modeling of inhibition is still a problem.

Current neural engineering frameworks integrate inhibition functions with non-orthogonal functions in order to maintain the integrity of the signal. However, this only roughly approximates many of the mechanisms present within the postsynaptic cell. Multiple variables exist on the biochemical level to create the observed patterns of dendritic nonlinearities. These biochemical processes exhibit temporal and spatial relationships relative to the induction of their intracellular mechanisms. These factors lead to variations and randomness that may not be fully accounted for in the final calculation of weights within neuronal models. Due to insufficient information surrounding the biochemical mechanisms that underlie dendritic nonlinearities, it may be a better approach to utilize biophysical models for larger neuronal systems. Strictly adhering to current biochemical knowledge may create limits on the ability of these simulations to portray higher-order functioning.

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