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Analytical Modeling of a Communication Channel Based on Subthreshold Stimulation of Neurobiological Networks

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ANALYTICAL MODELING OF A COMMUNICATION CHANNEL BASED ON
SUBTHRESHOLD STIMULATION OF NEUROBIOLOGICAL NETWORKS

by

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The emergence of wearable and implantable machines manufactured artificially or synthesized biologically opens up a new horizon for patient-centered health services such as medical treatment, health monitoring and rehabilitation with minimized costs and maximized popularity when provided remotely via the Internet. In particular, a swarm of machines at the scale of a single cell down to the nano scale can be deployed in the body by non-invasive or minimally invasive operation (e.g., swallowing and injection respectively) to perform various tasks. However, an individual machine is only able to perform basic tasks so it needs to exchange data with the others and outside world through an efficient and reliable communication infrastructure to coordinate and aggregate their functionalities. We introduce in this thesis Neuronal Communication (NC) as a novel paradigm for utilizing the nervous system *in vivo* as a communication medium to transmit artificial data across the body. NC features body-wide communication coverage while it demands zero investment cost on the infrastructure, does not rely on any external energy source, and exposes the body to zero electromagnetic radiation. In addition, unlike many conventional body area networking techniques, NC is able to provide communication among manufactured electronic machines and biologically engineered ones at the same time. We provide a detailed discussion of the theoretical and practical aspects of designing and implementing distinct paradigms of NC. We also discuss NC future perspectives and open

challenges.

ACKNOWLEDGMENTS

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Chapter 1

Introduction

Over the past decade, various techniques have been suggested with respect to communication among the devices implanted on, around or in the body for medical purposed, specially with regards to remotely monitoring the health status of patients especially for those with aging or disability problems. The devices comprise sensors placed on or under the skin to monitor the body's vital signals and communicate the readings to a data sink node. The devices use the air or the body's tissue as a medium to propagate their data carrier signals.

A series of rapid technological advances contribute to a paradigm shift in telemedicine from traditional remote health monitoring to novel remote medical diagnosis and treatment by relying on swarms of very tiny machines to perform complex tasks including drug delivery, cell diagnostic, cell repair, and fighting against cancer and aging, among others. In particular, the technological breakthroughs are promising to manufacture large amounts of inexpensive artificially-made wearable and implantable machines at the scale of a single cell or even smaller down to the nano scale. In addition, modern *synthetic biology* techniques facilitate genetically engineering single cell organisms (e.g., bacteria) to act as a programmed machine to perform pre-designated

tasks [2].

The machines mentioned above may comprise of sensors or actuators (robots) worn on the body (e.g., smart watches), mounted around the body (e.g., clothing with nano fabric or embedded technology), or implanted in colonies deep in the body through noninvasive or minimally invasive processes (e.g., swallowing, injection etc). It is important to note that a single machine of this kind is only able to perform basic tasks, so the deployed machines need a means to communicate across and out of the body to coordinate their functionalities and perform the task cooperatively. Therefore, they must have a means to establish an adequate two-way communication among themselves inside the body as well as the body's exterior to transmit data and control streams.

However, delivering such a high quality communication poses a big hurdle in implementing the mentioned new paradigm and it is yet to be addressed. The problem stems from the fact that the conventional body area communication techniques have not been designed originally to support instantaneous, power-aware and large-scale communication. For this purpose, we introduce the promising idea of *Neuronal Communication (NC)* of utilizing the nervous system as a living communication medium for transmitting artificial data. We elaborate on why and how should a NC paradigm be realized, and what are the promises and the perils of this novel communication paradigm. We will also discuss our vision from the future applications and opportunities that NC brings forth.

1.1   Our Contribution

The primary contributions of this thesis are as the follows:

1. We propose *Neuronal Communication (NC)* as a novel intrabody communicaion paradigm for transceiving artificial data through the nervous system for medical applications.

2. We introduced the idea of using subthreshold stimuli for modulating artificial data.

3. We formulated the response of a neuron to the stimuli through an analytical model comprised of a base part and an extension.

4. We implemented our model in Python and NEURON. We found the results of our analytical model compatible with those of simulation.

5. We provided the future perspective of NC with respect to medical and non-medical applications as well as NC open challenges.

1.2   Thesis Overview

The rest of this thesis is organized as follows. We cover in Chapter 2 the background of our work. In Chapter 3, we mention prior works with respect to popular modalities used in different intrabody communication methods. We provide a detailed discussion of the theoretical and practical aspects of designing and implementing of NC in Chapter 4. In Chapter 5, we introduce an analytical model to explain how artificial data can be modulated through a neurobiological channel by exciting the neuron with subthreshold stimuli applied to its soma. We also present in this chapter the compatibility between the numerical results delivered by our analytical model

and the simulation results obtained from the NEURON software for the same neuron cell. In Chapter 6, we extend the model of the previous chapter by formulating a more natural way of modulating data through distributed data carrier signals applied to arbitrary branches of the dendritic tree. We also show in this chapter that the extended model preserves the properties of the base model. Finally in Chapter 7 we discuss future work that should be done to in designing the protocol stack of NC as well as the open challenges in its safety and sustainability. At the same chapter we conclude this thesis.

Chapter 2

Background

2.1 Motivation

The nervous system delivers a reliable, robust and instantaneous communication across the body. Acquiring the ability to harness and manipulate this excellent communication infrastructure opens up the possibility of enjoying a body-wide and sustainable communication to disseminate artificial data within the body or in-between the body's interior and exterior for medical and non-medical applications. NC aims to feature such a unique body-wide communication with zero infrastructure preparation cost, independency of external energy source, and no body exposure to continuous electromagnetic radiation. In addition, unlike many conventional body area networking techniques, NC is able to provide communication among a heterogeneous set of manufactured electronic machines and biologically engineered ones at the same time.

2.1.1 Medical Applications

The conventional intrabody communication techniques fall short in establishing a high quality communication among—possibly heterogeneous—machines deployed in

swarms in the body, as we will explain in Chapter 3. This problem restricts the deployment of sensors deep in the body, and hence, restricts the access to the important signals of the body (e.g., biochemical changes in the blood or electrical activities within nerves). Moreover, the broadcasting nature of typical intrabody communication poses a big hurdle in the realizing pervasive communication in which it is desired to send control streams onto the body to command actuators (e.g., nanorobots) and get data streams from individual machines within the implemented colonies. NC eliminates both problems by supporting a two-way communication with sensors and actuator machines implanted deep in the body. This is beneficial for several applications in remote patient health monitoring and treatment, rehabilitation and therapy, biofeedback, and assisted living. We discuss a number of them as follows.

2.1.1.1 Medical Internet of Things

NC can disseminate deep body signals that otherwise could not be delivered to the body's surface. Examples of these signals include chemical signals (e.g., glucose, oxygen, hormones, cholesterol, and sodium) as well as electrical signals such as cardiac and respiratory rhythms. These signals can be read by machines that are implanted very deep inside the body where only the nervous system can reach and convey the signals to the outside world. Furthermore, NC features unicast and multicast capabilities (see Section 2.3) that enable us to interact with single or few machines within a colonies of implanted machines to perform micro-operation in the body such as stimulating pancreas to secrete insulin or reading vital signals with high spatial resolution. In this way NC realizes the *Internet of Things (IoT) for health care* [19] and *Internet of Bio-nano things* [2] by featuring a two-way communication mechanism to connect the body's internal organs to the Internet as illustrated in Fig. 2.1. More specifically, the figure illustrates an NC realization scenario of IoT

for health care. In this scenario, some implanted sensors measure the level of a chemical (e.g., glucose) and communicate the data through the nervous system to a smartwatch. The transmitted data can be transduced into small muscular vibration. The smartwatch can decode these physical activities into data and send it to a sink node that is connected to the Internet.
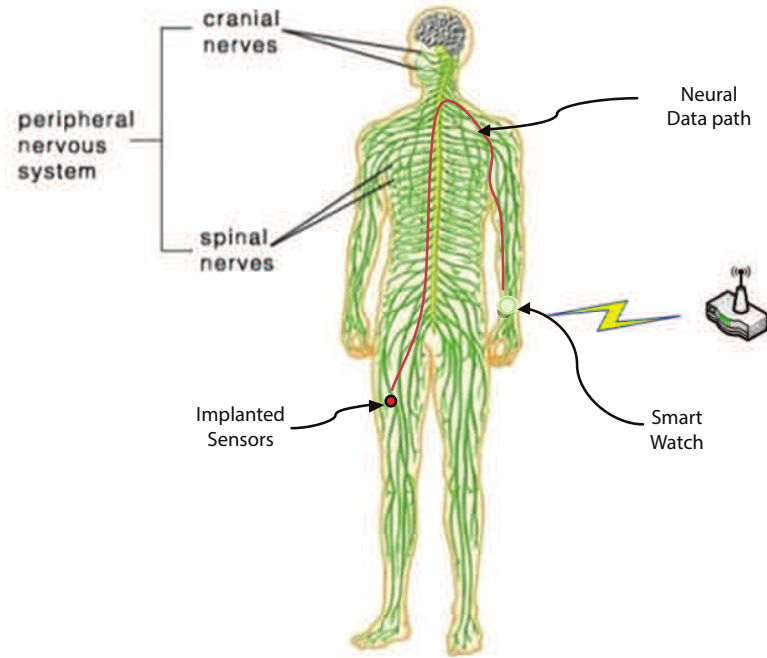
Figure 2.1. A realization of NC for medical Internet of Things.

2.1.1.2 Neuroprosthetics

NC can be utilized in the field of neuroprosthetics where two or more implanted devices communicate with the nervous system and bypass a neural deficit by relaying messages among themselves. The nervous system can adapt and handle signals from implanted devices thanks to its remarkable plasticity feature. As another example, instead of using a pacemaker that applies pulses directly to the heart, a group of machines can monitor the heart rate and provide appropriate feedback to the brain

to normalize its rhythm. A similar scenario is applicable for other body systems such as respiratory, and endocrine glands.

2.1.1.3 Stimulation Therapy

The mechanisms within NC can be utilized for the purpose of stimulation therapy similar to how chiropractic stimulations and craniosacral therapies work. More specifically, it is possible to leverage the mechanisms of NC to apply stimulation through a proper interface on the right neurobiological path to adjust operations of the body organs.

2.1.2 Non-medical Applications

Several non-medical applications are imaginable from approaching the nervous system with a communication engineering perspective. We mention a number of these applications as follows.

2.1.2.1 Novel Biometrics for Security Systems

In Section 2.3.2, we will explain how stimulating the senses can create distinguishable patterns of activity in the brain and we will provide an example in Fig. 2.5. It is imaginable to utilize NC to generate proper stimulations within the nervous system to make distinguishable patterns of activities in functional cortical areas and read them through electrodiagnostic techniques (e.g., EEC, EMG, etc.) The brain's spatiotemporal patterns from different individuals may be used as a biometric for generating distinct security keys.

2.1.2.2 Human Machine Interface and Cybernetics

NC facilitate the interaction between machines and humans by including the elements of stimulation and response. More specifically, NC provides a means to connect the nervous system to the machines or cybernetic agents implanted in or mounted on the body. For instance, input machines can respond to the activities in the nervous system (e.g., muscular micro vibrations) and output machines can stimulate the nervous system to cause desired responses from the nervous system. A proper encoding system can be devised to interpret these activities as meaningful two-way data streams between the human body and machines. As an instance, NC may be used in regulating sympathetic or parasympathetic body reactions for persons in harsh situations (e.g. a battle field).

2.1.2.3 Defensive Applications

NC uses an unconventional communication infrastructure which is almost impossible to eavesdrop or collapse. This is a big advantage for military and defensive applications. In addition, using extra sensing modalities can be utilized through a circuit NC paradigm to increase the performance and efficacy of communications with personnel. As an instance, a haptic (tactile) stimulator may add another cognitive dimension to fighter pilots saturated by visual stimulations.

2.2 The Nervous System

The building blocks of the nervous system are neuron cells or neurons. Fig. 2.2 shows a picture of a real neuron and illustrates the three main organs of a neuron cell. The *soma* is considered to be the main body of the neuron that performs vital activities such as metabolism and protein synthesis. The *dendritic tree* is a hierarchical bran-
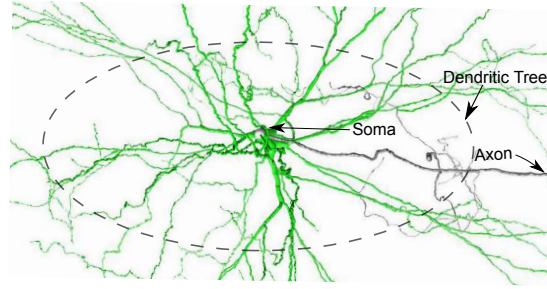
Figure 2.2. Picture of a real neuron.

ching system of projections of the neuronal membrane that preliminarily integrate stimulations toward the soma. Each branch of a dendritic tree is called a *dendrite*. An *axon* is an individual projection of the soma that propagates the generated electrical signals out of the soma. The initial part of the axon is called hillock. It integrates the signals received from the dendritic tree and spikes *Action Potentials (APs)* in case, as explained later in this section.

The neuron membrane is capable of exchanging ions with extracellular fluid through its ion channels. This changes the concentration of ions inside the neuron, and, consequently, causes a change in the cross membrane voltage. An artificial electrical current injected into the neuron can also change the voltage difference accross the two sides of the membrane. In particular, the neuron membrane *depolarizes* when the positive *graded potentials*—caused by the applied stimuli—decrease the membrane's voltage negativity. The graded potentials ripple through the membrane toward the soma and integrate at the junction point of the soma and axon—the axon hillock. If the integrated potentials at the hillock become more positive than a certain voltage threshold, the applied stimuli are considered to be *Suprathreshold*. Otherwise they are *Subthreshold*. Neurons respond to suprathreshold stimuli by spiking uniform APs that can propagate through multiple neurons. Although subthreshold stimuli do not generate APs, they result in *graded potentials* that propagate to the end of the axon.

We rely on this fact to introduce our novel idea of transmitting artificial data across a neurons by applying subthreshold stimuli. We call this concept *Cellular NC Paradigm*, as we explain later in Section 2.3.1.

A large number of neurons connect to each other and build an intricate neuronal network in the body. This sophisticated network is called *nervous system.* It carries out very complex tasks, including, among others, communication among the body's parts and control over their activities. Three distinct parts of the nervous system are illustrated in Fig. 2.3 including the brain, spinal cord and periphery nerve bundles. The nervous system has two division namely, the Central Nervous System (CNS) and the Peripheral Nervous System (PNS). The former consists of the brain and spinal cord, while latter comprises neuronal paths each reaching to distinct body interior and exterior parts. In particular, the PNS comprises the *Autonomous* and *Somatosensory* subdivisions.

Figure 2.3a illustrates a simplified map of the autonomous subdivision in the body with dashed lines. This subdivision is responsible for controlling involuntary activities of many internal organs. The somatosensory subdivision mostly comprises afferent and efferent neural pathways to the limbs and the body's surface, as shown with dash lines in Fig. 2.3b. As it can be seen, a considerable area of the body's exterior is innervated by somatosensory nerves, and hence, is easily accessible for interfacing with outside world through gateway devices (e.g., smartwatches) as we later explain in Section 2.3.2. The PNS innervates the body's organs through neuronal paths from fixed originations to certain destinations. Each path consists of several neurons that are interconnected via electrical junctions or chemical synapses. These separated neuronal paths that exist between two points in the nervous system resemble a hardwired circuit between a sender and a receiver in a communication network and a circuit-switched network. We depend on this feature to propose the *Circuit NC Paradigm*

(a) Autonomous Nerves   (b) Somatosensory Nerves
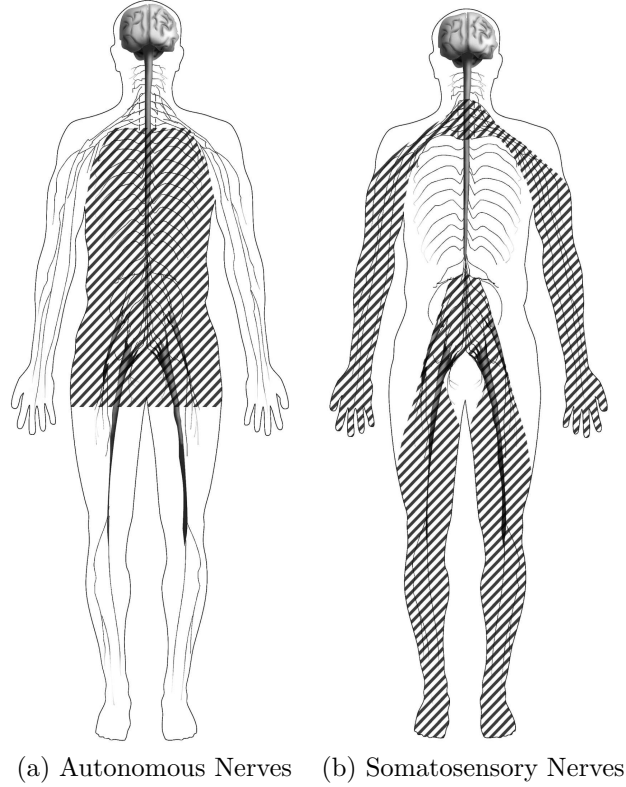
Figure 2.3. The nervous system.

for communicating artificial data through the PNS in Section 2.3.2. In this paradigm, a communication path between source and destination may be formed over a selected neurobiological circuit.

A successful realization of a circuit NC paradigm relies on selecting a proper neuronal path. For instance, it is possible to lessen the brain's irritation that NC artificial activities may cause by using spinal closed-loop circuits like reflex paths, or by using single neurons with long axons. Therefore, in order to design an adequate circuit NC system, it is needed to have a comprehensive knowledge about the numerous neurobiological circuits with various neuron and interconnections types in the nervous system. Although the neurological paths are well investigated in the literature [36], finding the actual paths in the nervous system *in vivo* needs to leverage practical

techniques. Therefore, in rest of this subsection we mention a handful of tracing techniques that can be utilized for this purpose.

2.2.1 Neuronal Circuits

As we will mention later in this subsection, it is important to know what neural tract is used for a specific realization of NC. Fortunately, there are several techniques for tracing neural tract *in vivo*. The majority of these techniques rely on axonal transport of a tracer substance. The direction of transportation can be anterograde from soma to the axon terminals or retrograde if in the opposite direction. The tracer currently being used are *florescent dye* [45], *immunostain* [39] (e.g. immunoperoxidase, immunofluorescence, immunoradioactive, etc) or *genetic tracers* including proteins and viruses (e.g. herpes, pseudo-rabies etc.) The viral tracers can perform transneural tracing by crossing synapses, and can be used to trace neurons from body organs to the brain. A rather dissimilar technique is *Diffusion MRI* [24] in which diffusion of water molecules is used to generate magnetic resonance (MR) images. As we discussed earlier, some of the communication parameters such as propagation delay, attenuation, and signal to noise ratio depend on the underlying tract that is used as the network circuit.

2.2.2 Neuronal Interconnection

The interconnection points between neurons are called *synapses*. Two neurons can be connected to each other through either chemical or electrical synapses. When the electrical signal from a pre-synaptic neuron reaches to a *chemical synapse*, it transduces into neurotransmitter molecules and diffuses toward the post-synaptic neuron where it regenerates an electrical signal. A chemical synapse is basically the environment in

which neurotransmitters diffuse from one neuron to another. Therefore, a chemical synapse forms a molecular communication channel with its characteristics modeled in [35]. However, whether or not a neuron secretes neurotransmitters in response to subthreshold stimuli (see Section. 4.1.1 for definition) depends on the particular neuron type of the species subject to investigation. The other form of neuronal inter-connection is a direct junction between two neurons through which electrical signals transfer from one neuron to another and it is called *electrical synapse*. It is easier to engineer signal communication through electrical junctions as they do not require transduction and propagation of chemical molecules to pass the signal to the next neuron. However, they are less helpful as fewer instances of them are observed.

2.3   The Nervous System For Artificial Data Communication

We mentioned earlier that the nervous system can be used for NC purposes at cellular or circuit levels in which a single cell or neural circuit(s) can be exploited as channels in an NC paradigm, respectively. Accordingly, two biological frameworks for realizing NC are imaginable—i.e., cell framework and circuit framework. In this section we elaborate on these biological frameworks, and compare the properties that the two frameworks deliver to shape two distinguishable NC paradigms—i.e., the cellular NC paradigm and the circuit NC paradigm. In addition, we provide a conceptual model for each framework that illustrates an instance of NC realization through the framework.

(a) A Real Neuron.

(b) Single Neuron Communication Scheme.
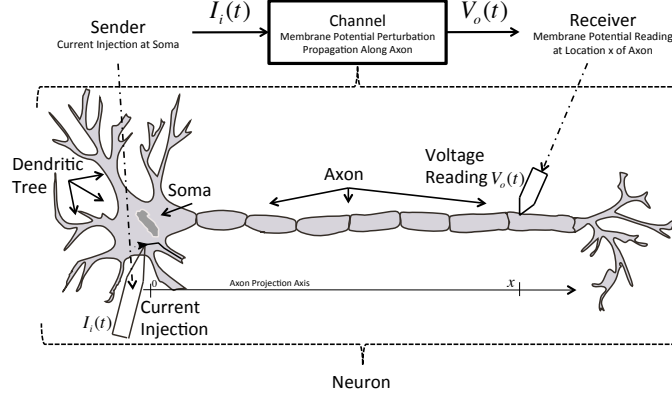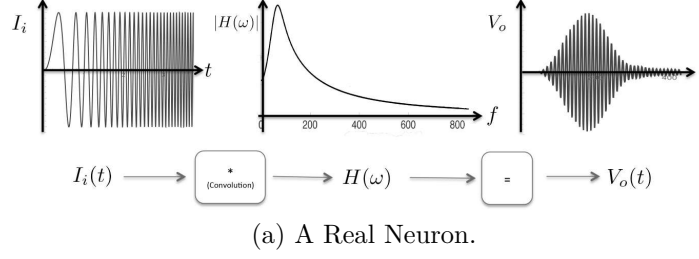
Figure 2.4. Direct interfacing in a cellular NC paradigm.

2.3.1 Cellular NC Paradigm: A Neuron Cell as A Channel

We mentioned in Section 2.2 that applying subthreshold stimuli to a neuron causes its membrane to generate graded potentials and propagate them through the axon. In this subsection we elaborate on the details of a NC paradigm that relies on this mechanism to utilize a neuron cell as a communication channel for transmitting artificial data—cellular NC paradigm. Figure 2.4 illustrates an instance of cellular NC paradigm realization. More specifically, Fig. 2.4a illustrates the case in which an oscillatory subthreshold input signal $I_i(t)$ with varying frequency and fixed amplitude is applied to the neuronal communication channel. The neuronal channel has a frequency-selective transfer function $H(\omega)$ [20] [21] by which the input signal(s) convolute and result in the output signal $V_o(t)$. In this case, an input signal $I_i(t)$ represents the data by frequency modulation (FM). The different frequency compo-

nents attenuate at different rates based on their frequency [20] [21]. This signal is in the form of electrical current and can be applied anywhere on the dendritic tree or the soma. The output signal $V_o(t)$ is in the voltage form and can be picked up at distance x from the soma on the axon $(x \geq 0)$. It is important to remember that in a cellular NC paradigm, the magnitude of an input signal $I_i(t)$ must be kept subthreshold to avoid generating artificial APs. Figure 2.4b illustrates the conceptual model of the paradigm. The input data carrier signal $I_i(t)$ is in the form of electrical current and can be applied anywhere on the dendritic tree or the soma. The output signal $V_o(t)$ is in voltage form and can be picked up on the axon at distance x from the soma $(x \geq 0)$. The single neuron cell used in this way can be thought of featuring a *unicast communication* as there is a one-to-one relation between the source and the destination.

The magnitude of an input signal $I_i(t)$ in a cellular NC paradigm is controlled in such a way that the neuron does not spike APs but yet generates some output i.e., the graded potentials. Therefore, an implementation of cellular NC relies on a *non-spiking regime* of neuronal functionality. This regime has many advantages such as utilizing the sub-band capacity of neurons, adjustability of data transmission range, minimizing interference with normal spiking operation of the nervous system ,and a linear communication channel that preserves original frequency components of the input signal.

2.3.2 Circuit NC Paradigm: A Neuronal Circuit As A Channel

As we mentioned in Section 2.2, the nerve bundles within the nervous system resemble circuits in a circuit-switching network as every organ in the body is innervated by
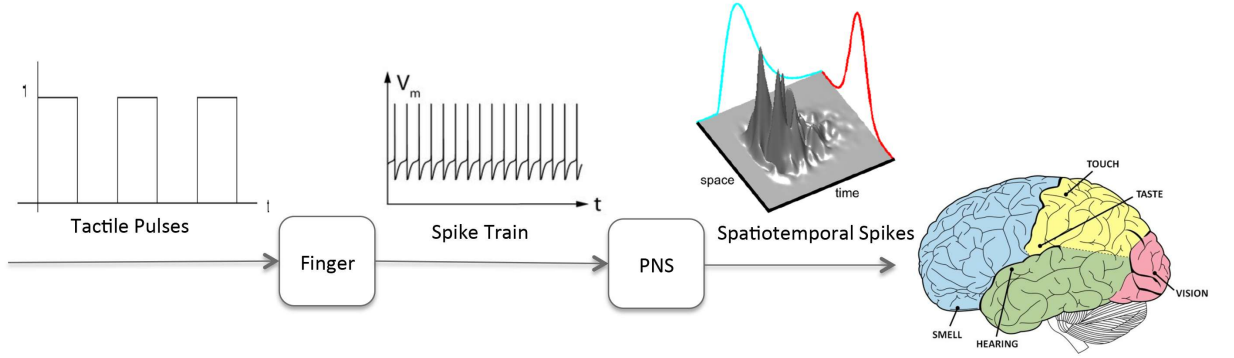
Figure 2.5. An instance of suprathreshold NC.

a distinct neurobiological path within the nervous system. A *circuit NC paradigm* can be realized by utilizing these neurobiological circuits as communication paths between pairs of artificial data senders and receivers. These circuits also provide the rare opportunity of sampling the body's vital signals and fixing internal organs' dysfunctionalities by inducing proper stimulation.

We propose a circuit NC paradigm to be realized by encoding the artificial data through stimuli applied to the senses. As these stimuli generate natural APs, a realization of this paradigm depends on a *spiking regime* of neuronal functionality. Figure 2.5 shows a conceptual model of a circuit NC realization. In this model, a stimulation signal is applied indirectly to the nervous system (e.g., through tactical stimulation) and propagates naturally through the nervous system to the brain. The stimuli make spatiotemporal patterns of activation in the brain as the figure illustrates. These patterns can be read by available technologies (e.g., EEG) and interpreted by a proper decoding system. Table 2.1 lists a summary of the frameworks discussed in this section.

Table 2.1. NC paradigms Summary.

Properties	Paradigms	
	Cell	**Circuit**
Scale	Single Neuron	Neuronal Path
Regime	Non-spiking	Spiking
Interfacing Type	Direct	Natural
Data Modulation	Frequency or Amplitude	Spatiotemporal Patterns in the Brain
Casting Type [*]	U, M, B	M, B

[*] Considered Types: **U**nicast, **M**ulticast, **B**roadcast.

Chapter 3

Related Work

In this chapter, we mention two main branches of classical techniques with respect to intrabody communication, and pinpoint their deficiencies. Most of the literature refer to these techniques collectively as *Body Area Networks (BAN)*. BAN techniques have been around for more than a decade. They comprise sensors placed on or under the skin to monitor the body's vital signals and communicate the readings by electromagnetic (EM) or electric waves to a sink node. The propagation medium for their data carrier signal could be air or the body's tissues. The primary application of BAN is to remotely monitor the health status of patients especially for those with aging or disability problems. We also mention in this chapter the *Molecular Communication (MC)* as a newer intrabody technique, and explained why despite some of its advantages it is still not adequate for establishing an adequate intrabody communication.

3.1   Wireless Body Area Networks (WBAN)

The classical *Wireless Body Area Networks (WBAN)* (e.g., IEEE 802.15.6) [15]) [46] rely on broadcasting short range airborne Electromagnetic (EM) waves with relatively low frequency. For example in Human Body Communication (HBC) applications, WBAN uses 16Hz and 24Hz frequency bands [42]. However, lower frequencies do not work with the small-scale machines deployed as swarms. This is because the thinner machines must have an antenna with a small size due to which the machine has to transceive high frequency EM waves very close to the resonance frequency of the water molecules. But higher EM frequencies increase the wave damping because of excess water molecules resonance. So the machines should emit high power EM waves with two penalties: heating up (and probably deforming) the tissues, and exhausting their scarce energy resources.

In addition, WBAN relies on using license-free radio frequency band such as Industrial, Scientific and Medical (ISM) [42]. This makes WBAN vulnerable to noise and interference from the other networks with the same frequency band such as the so-called WiFi networks (i.e. IEEE 802.11). It also turned out that relying on electromagnetic waves for communicating over the body perimeter brings about concerns with respect to patient safety [12] [25] and security [46] [41].

There are also some other reasons for WBAN inadequacy when it comes to purveying communication to future heterogeneous machines. More specifically, the future machines deployed in the body are not necessarily electrical, and hence, they may not be able to transceive EM waves. Rather, they can be mechanical machines (e.g. DNA origami) or they could be made of biological species synthesized through genetic engineering [2]. With respect to the problems we mentioned above, it would not be possible to provide an adequate communication to the miniature machines using the

conventional WBAN techniques.

3.2 Intra-body Communication (IBC)

Intra-body Communication (IBC) techniques use an alternative way to airborne EM waves. They use the body's surface tissues (e.g., skin and muscles) as a guided propagation media to propagate electric and electromagnetic signals [46] or ultrasound waves [13]. In particular, *Galvanic Coupling* [49] [4] uses the body's surface tissues to transmit electrical current signals among the sensors deployed on the body. However, the characteristics of galvanic coupling communication channels are not deterministic as they depend on physiological variations of individuals (e.g. tissue properties, body geometry) as well as the physical factors of the environment such as humidity. *Ultrasound waves* as a modality for in-body communication is initially suggested in [13] [9] [44] and improved by opto-ultrasonics [43]. These mechanical waves have a good propagation through the body which is composed mostly of water. While side effects of short-time application of ultrasound waves in medical imaging is usually considered as negligible, using these waves for communication purposes in the long run could yield to tissue overheating or deformation, as ultrasonic waves make tissue molecules vibrate at a fast rate.

In addition, both ultrasound and galvanic coupling techniques suffer from several common problems. They present broadcast communication which degrades communication performance and scalability. Both techniques also show big signal attenuation at distal extremities not longer than a hundred centimeters [13] [4]. These techniques are also very energy demanding despite the limited strength of batteries that typically run implanted devices. Therefore, none of the above techniques have the capability of addressing distinct machines on top of its other problems such as excessive power

loss, variant channel properties, and impacts of ambient factors (e.g., temperature and humidity). Furthermore, it is not natural for the body's tissues to conduct such an extra amount of energy stream. Therefore, using IBC techniques over a long period of time may result in deformation of tissues.

3.3 Molecular Communication (MC)

Molecular nano-communication (MC) [35] is a bio-inspired communication paradigm in which the spatiotemporal changes in the concentration of chemical species, and the chemical species themselves, carry information between a transmitter and a receiver. The particles can passively propagate through Brownian motion diffusion (e.g. calcium signaling) or they can be actively transported with the help of flagellated bacteria [14], nanomotors [30], cardiovascular system [8] or nervous system [5]. This is a recent paradigm for establishing communication among intrabody nanomachines in a way compatible to biological communication processes. In 2015 IEEE Communication Society Standard Development Board published IEEE P1906.1 Recommended Best Practice for Nanoscale and Molecular Communication [1]. MC naturally occurs in the body and it is an abstraction of many communication mechanisms in biology, including the main communication systems in the human body—i.e., the endocrine system and the nervous system. The communication engineering community has reasonably recognized the merit of MC for serving broadcast communication in the body. For instance, a linear end-to-end communication channel model for using MC in nanonetworks is introduced in [35]. IEEE has also published a set of recommendations in its P1906.1 [1] document. It may be tempting to think of MC as a biocompatible modality for realizing an intrabody communication through either of the body's natural communication systems. The intrinsic dynamics of each system present a seemingly

insurmountable obstacle to such an achievement. More specifically, the endocrine system is a widespread but slow communication system as it relies on cardiovascular system to propagate molecules. On the other hand, neurotransmitter molecules in the nervous system propagate fast but their propagation distance is through a very narrow synaptic cleft. Therefore, MC would not be the primary means for a fast and extensive intrabody communication.

3.4 Neuronal Communication by Artificial Spiking

Few efforts such as [18] have been made to model the nervous system with a communication perspective. However, they rely on the assumption that neurons linearly transfuse synaptic stimuli to action potentials. This impedes a real world implementation of the communication system based on their model. More specifically, the studies in [6] and [26] focus on how a synaptic connection can be modeled as a communication channel between two neurons. However, the authors did not discuss the communication within a neuron cell. Instead, the study in [18] models a communication with a postsynaptic neuron as a part of the channel. The authors used a linear RC circuit as the equivalent model of an isopotential patch of the neuron's membrane. However, by taking assumption, they overlooked the fact that actual neuron cells have a nonlinear transfer function as it is demonstrated in the gold standard Hodgkin-Huxley (HH) [16] model (see Section 4.1.1 for more details). There exist several concerns that make the practicality of all the mentioned approaches even more unlikely. All the approaches rely on modulating artificial action potentials (APs) as data carrier signals.

First, modulating artificial APs increases the risk of conflict between natural and artificial data flow in the nervous system, and hence, can cause distortions in the body's regulatory systems. For example, the neuroendocrine system may be affected by these artificial APs and secrete inappropriate amount or type of neurotransmitters and hormones. Second, an extra amount of artificially-generated APs can modify the normal synaptic strength within the nervous system. In particular, increasing the activities in synaptic connections over a long period of time may cause the Long-term Potentiation (LTP) and Long-term Depression (LTD) processes to kick off and make abnormal changes in synaptic efficacy which may result in behavioral and cognitive disorders in the person.

Despite the impracticality of the previous efforts, an adequate approach to NC implementation can deliver a fast, reliable and inclusive communication among the devices implanted on/in the body. We will discuss the implementation aspects of NC with novel approaches in more detail in Chapter 4. We finish this section by listing in Table 3.1 a summary of the benefits that a desired NC realization can bring forth compared to the mentioned three conventional intrabody techniques.

Table 3.1. Signal state in time domain.

| Properties | Communication Paradigm | | | |
	NC	WBAN	IBC	MC
Direction	two-way	two-way	one-way	one-way
Deployment Scale	Swarm	A Few Number	A Few Number	Swarm
Casting Type *	U,M,B	M,B	M	M

* Considered Types: **U**nicast, **M**ulticast, **B**roadcast.

Chapter 4

Neuronal Communication (NC) Implementation

In this section, we explain the of utilizing the nervous system as a backbone for artificial data communication by stimuli. For this purpose, we elaborate on how to model the neurons' response to stimuli with different characteristics. Also, we introduce techniques and technologies for direct or indirect interfacing with neurons in a compatible way to the normal operation of the nervous system.

4.1 Modeling Neurons Response to Stimuli

In order to generate data carrier signals by stimulation in a NC system, one must know how the response of the neuronal communication channel varies with the changes in the stimulation signal. More specifically, the neurons respond to variations in amplitude and frequency of the stimulation signal by generating neuronal signals with different characteristics.

4.1.1 Magnitude

As we mentioned in Section 2.3.1, the neurons generate two distinct responses to subthreshold and suprathreshold stimuli. The *quasi-active model* [22] explains how the neurons generate non-spiking graded potential in response to the applied subthreshold stimuli. In [20] and [21], we elaborated on how neurons present a linear transfer function when propagating these graded potentials. This linearity offers a promising opportunity to transfer artificial data in a cellular NC paradigm by modulating the data through subthreshold stimulation. However, this is not the case for suprathreshold stimuli as in this case, the neuronal channel responds nonlinearly as it is demonstrated in the widely accepted *Hodgkin and Huxley (HH) model* of spiking neurons [16]. However, we work around this problem by encoding the data as spatiotemporal patterns of naturally generated action potentials in the nervous system in a circuit NC paradigm as we discussed in Section 2.3.2.

4.1.2 Frequency

The neurons are frequency selective [20] as they respond differently to oscillatory stimuli with different frequencies. This implies that the transfer function (i.e., the electrical impedance) of a neuronal communication channel varies with the frequency of an oscillatory input signal. In particular, the neurons act as band pass filter. The received stimuli in their soma [20] or their dendritic tree [21]. Therefore, the ideal frequency for data carrier signals is the neuron's resonance frequency as it results in the maximum magnitude of the output voltage signal for a same level of input electrical current.

4.2   Stimulating and Interfacing with Neurons

There are two ways imaginable for interfacing between neurons and stimulator devices. The simplest approach is to utilize the natural way that the body uses to generate and propagate signals across the nervous system, i.e., through the five senses. We call this method *Natural Interfacing.* The other way is to stimulate the neurons in an artificial way. This approach is more complicated and involves applying direct stimulation onto the neurons, namely *Direct Interfacing.* In this subsection we introduce workable ideas for realizing each of the interfacing techniques.

4.2.1   Natural Stimulation and Interfacing

We mentioned in Section 2.3.2 that in a circuit NC paradigm the artificial data are communicated through a neurobiological path consisting of multiple neurons. Figure 2.5 illustrates a conceptual model of circuit NC paradigm in which the tactile sense acts as a natural interface to encode mechanical energy to neuronal data carrier signals. Each neurobiological path reaches to distinct body interior and exterior. Therefore, it is very important to choose right neurological path in order to have a proper NC implementation. Furthermore, closed-loop spinal neurological paths (e.g., reflex paths) or long-axons neurons (e.g., from shoulder to arm) avoid the brain engagement in a circuit NC paradigm. The characteristics of neurological paths are well investigated in neurophysiology literature. However, practical techniques are needed to be actually leveraged to find and interface with them *in vivo*. In this subsection, we mention a handful of tracing techniques that can be utilized for this purpose. The majority of these techniques rely on axonal transport of a tracer substance. The direction of transportation can be anterograde from soma to the axon terminals or retrograde for the opposite direction. The tracer currently being used are *florescent*

dye [45] , *immunostain* [39] (e.g. immunoperoxidase, immunofluorescence, immunoradioactive, etc.) or *genetic tracers* including proteins and viruses (e.g. herpes, pseudo-rabies etc.) These viral tracers can perform transneural tracing by crossing synapses and can be used to trace neurons from body organs to the brain. A rather dissimilar technique is *Diffusion MRI* [24] in which diffusion of water molecules is used to generate magnetic resonance (MR) images.

4.2.2 Direct Stimulation and Interfacing

In the rest of this subsection we introduce some practical techniques to directly stimulate and interface with the neurons. These techniques are originally proposed for Central Nervous System (CNS) disease treatment but they actually prove the feasibility of the direct stimulation concept. Therefore, it is also possible to utilize very similar techniques to stimulate peripheral nerves for performing neuronal communication in the Peripheral Nervous System (PNS). A class of older techniques use micro-electrodes to directly inject electrical current into the neurons. These include *Transcranial Direct Current Stimulation (tDCS)*, *Transspinal Direct Current Stimulation (tsDCS)*, *Deep Brain Stimulation (DBS)* and *Spinal Cord Stimulation (SCS)*. Although the above techniques are invasive, they prove the feasibility of the direct stimulation concept. Furthermore, less invasive electrodes are imaginable to be built with future advances in nanotechnology.

Transcranial Direct Current Stimulation (tDCS) [31] is a non-invasive technique that uses two electrodes to modulate neural activities by passing a low strength electrical current through cranial nerves. Transspinal Direct Current Stimulation (tsDCS) [32] is very similar to tDCS but it excites spinal nerves. tsDCS seems to be promising for neuronal communication as there are many spinal nerves close to

the body exterior especially around the neck and shoulders (cervical nerves) as well as waist and hips (lumbar nerves). *Deep Brain Stimulation (DBS)* [34] technique uses two microelectrodes implanted under the scalp along with a neurostimulator to stimulate designated targets in parts of the brain beneath the cortex such as basal ganglia and ventral intermediate nucleus of the thalamus. DBS is usually used on the part of the brain that has many efferent nerves attached to muscles to control voluntary movements. Therefore, the effect of applied stimuli by DBS may be picked up in motor nerves and muscles. *Spinal Cord Stimulation (SCS)* [47] is an older technique based on the idea of applying electrical current stimulation onto the nerves in the spinal cord. However, it requires a surgery for implanting the related devices.

Fortunately, there are also non-invasive techniques that exist. For instance *Transcranial Magnetic Stimulation (TMS)* uses electromagnetic pulses to stimulate neurons. The benefits of this technique justify the hope to develop further non-invasive techniques to stimulate neurons from the body's exterior. This is a non-invasive technique that uses electromagnetic pulses to stimulate neurons. As the name suggests, this technique proposes a means to electromagnetically stimulate cranial neurons. The benefits of this technique justifies the hope to develop further non-invasive techniques to stimulate neurons *in vivo* from the body's exterior.

The above mentioned techniques are primary designed for medical purposes. They actually stimulate a coarse grained level of neuron ensembles. Therefore, they are inadequate for the applications in which finer grained stimulations are desired, e.g., a one-to-one communication between machines. More modern techniques have been recently proposed to perform finer grained levels of stimulation up to individual neurons. For example, [40] suggests to use chemical compositions to make pores on the neuron membrane to conduct depolarizing current and stimulate the neuron. A very known technique of this kind is *optogenetics* [11]. In this technique opsin genes are

engineered in the neurons to synthesize special types of protein that act as light-gated channels through which the ionic current can get into the neuron and depolarize the membrane. The light-gated ion channels can be excited by visible light of a certain wavelength. The light source can be external or be implanted inside the body. Optogenetics delivers a high spatiotemporal resolution thanks to its optical regulation of ionic stimulation. Therefore, it is able to precisely modulate the desired graded potentials in a cellular NC paradigm.

Alternatives to optogenetics may evolve over the time by developing novel *machine-to-neuron* techniques. For example in [33], a nanowire FET transistor is reported to be successfully used to interface electrical signals with a neuron. In particular, it would be possible to manufacture very tiny stimulator devices and getting them into the body by minimally invasive methods such as injection or swallowing. We also envision novel *machine-to-neuron* direct stimulation techniques emerge in the future to stimulate the neurons with a natural approach. This can be accomplished, for example, by releasing neurotransmitter-like ligands through artificial-made devices or genetically-engineered species (e.g., bacteria) produced by synthetic biology techniques. This method does not need to make changes in the neuronal membrane.

Chapter 5

Somato-axonal Communication Channel

In this chapter we elaborate the concept of transmitting artificial data through a neuron cell by modulating the data with applying stimulation signals to the soma. In particular, we explain the details of our analytical model stemmed from the fact that neurons show a deterministic linear (in the frequency domain) transfer function in response to subthreshold stimuli. We will also provide the relevant maths and symbolic formulation of a linear communication channel based on an in vivo neuron cell.

5.1 A Neuron-based Communication System

We proposed earlier in Section 2.3.1 a novel communication paradigm that utilizes a neuron cell (neuron) to transmit artificial data signals between a sender and a receiver using subthreshold stimuli. For the purpose of the following analysis, a neuron can be considered as an electrically excitable structure that propagates electrical stimuli
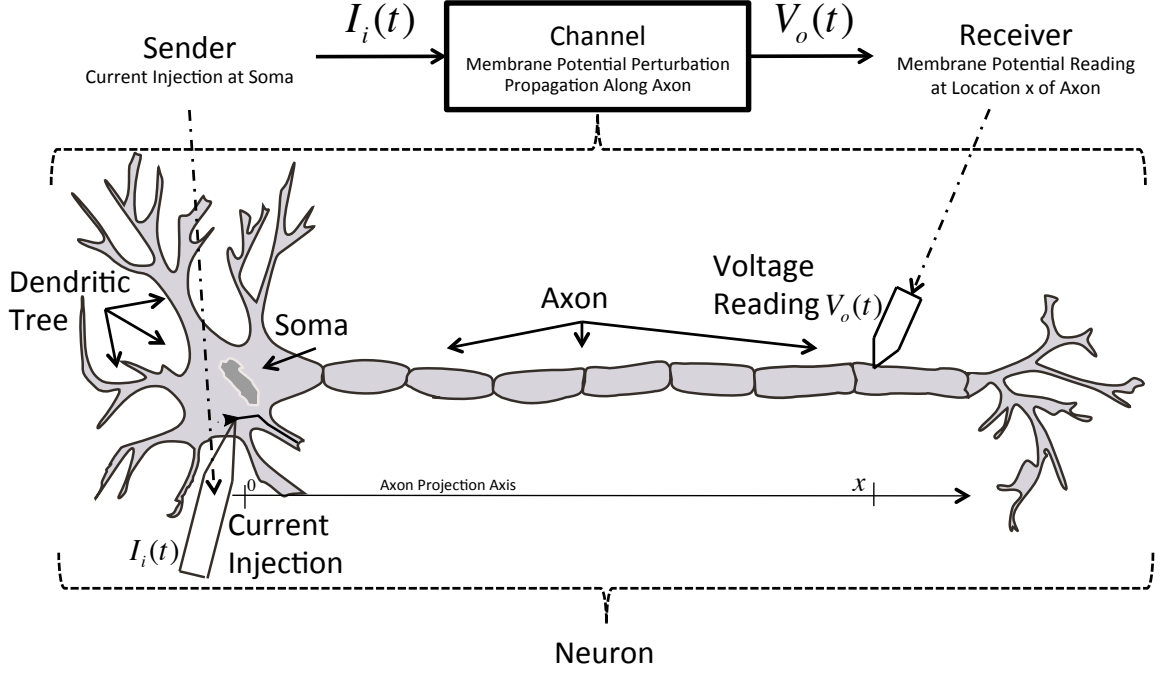
Figure 5.1. The scheme of the proposed neuron-based communication system.

along its length. We assume that when no external perturbation is applied to the neuron, the membrane potential is constant and homogeneous throughout the neuron, and equal to the resting potential E_m, in agreement with widely accepted models from the neurophysiology literature [48]. The communication system proposed in this thesis, as shown in Fig. 5.1, is composed of a *Sender*, which modulates the injection of an electrical current into the soma according to a signal to be transmitted; a *Channel*, which corresponds to the membrane potential perturbation resulting from the current injection, and its propagation along the axon; and a *Receiver*, which recovers the transmitted signal by reading the membrane potential at a location along the axon away from the soma. In particular, we assume that the sender injects the current $I_i(t)$, as function of the time t, into the soma through a technique called somatic current injection [37], where a microelectrode penetrates the membrane at the soma and releases electrical current into the intracellular space. The injected current, and the consequent local perturbation of the membrane potential around the aforementioned

resting potential, are propagated within the neuron in two main directions, namely, within the dendritic tree displaced around the soma, and along the axon. we assume that the receiver is realized through an intracellular electrode through which we read the membrane voltage $V_o(t)$ at a distance x along the axon projection axis from the soma.

Within the aforementioned system, we obtain a communication channel model based on the propagation of the membrane potential perturbation from the current injection to a location x along the axon. As detailed in Sec. 5.2, while the physical processes underlying this model are in general characterized by non-linear behaviors, it is possible to obtain a linear channel model when the proposed communication system meets determinate conditions, i.e., subthreshold stimulation. The obtained channel model is deterministic, since within the scope of this thesis we do not take into account noise arising from natural stochastic perturbations observed in neuronal membrane potential [27]. Nevertheless, we believe that this deterministic channel model is the first necessary step to explore the proposed communication system, and in our future work we plan to incorporate on top of it realistic models of the potential noise sources as well as the impact of interference with natural communication in the nervous system. we also plan to assess the performance of our model by analyzing throughput, packet loss, and average delay.

5.2   Linear Channel Model

We express a linear channel model of a neuron betwwen a sender that injects the current $I_i(t)$, as function of the time t at the soma, and a receiver that reads the membrane potential $V_o(t) = V(x, t)$ at distance x along the axon at time t. This

model is expressed in the frequency ω domain as follows:

$$\tilde{V}_o(\omega) = Z(x,\omega)\tilde{I}_i(\omega)\,,\tag{5.1}$$

where $\tilde{I}_i(\omega)$ and $\tilde{V}_o(\omega)$ are the Fourier transforms of $I_i(t)$ and $V_o(t)$, respectively. The equivalent circuit of the linear channel model is shown in Fig. 5.2, which is valid if the injected current $\tilde{I}_i(\omega)$ satisfies the subthreshold stimulation conditions, expressed in Section. 5.2.1. In this circuit, the dendritic tree is modeled as an impedance $Z_{dendrites}(\omega)$ as function of the frequency ω, whose calculation is expressed in Section. 5.2.4, while the axon is modeled as an infinite transmission line extending from the soma with characteristic impedance $Z_0(\omega)$, expressed in (5.9). According to transmission lines and lumped circuit theory [28], the transimpedance $Z(x,\omega)$ as function of the distance x along the axon and the frequency ω is expressed as follows:

$$Z(x,\omega) = \frac{Z_{soma}(\omega)}{Z_0(\omega)}Z_{axon}(x,\omega)\,,\tag{5.2}$$

where $Z_{axon}(x,\omega)$ is the transimpedance of the axon at distance x from the soma and frequency ω, expressed in Sec. 5.2.3, and $Z_{soma}(\omega)$ is the equivalent impedance at the soma where the sender injects the current $\tilde{I}_i(\omega)$, and it is expressed as the electrical parallel [28] between $Z_{dendrites}(\omega)$ and $Z_0(\omega)$:

$$Z_{soma}(\omega) = \frac{Z_{dendrites}(\omega)Z_0(\omega)}{Z_{dendrites}(\omega) + Z_0(\omega)}\,.\tag{5.3}$$

As detailed in the following, $Z_{dendrites}(\omega)$, $Z_{axon}(x,\omega)$, and $Z_0(\omega)$ are functions of the transmembrane impedance $Z_m(\omega)$ expressed in (5.5).
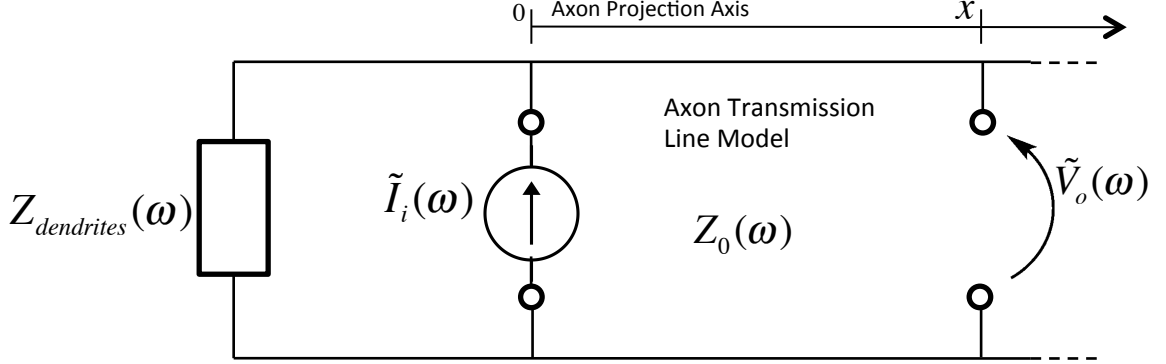
Figure 5.2. Equivalent circuit of the linear channel model.

5.2.1 Subthreshold Stimulation Condition

Upon injection of electrical current, the membrane potential of a neuron varies around the aforementioned resting potential E_m. If the membrane potential of a neuron exceeds a value termed as threshold potential V_{th}, the neuron undergoes a process called action potential stimulation, where the membrane potential raises and falls with a predetermined trajectory as function of the time [36].

The linear channel model expressed in this section is valid only when the membrane potential maintains a value less than V_{th}, named subthreshold condition. This is realized when the current $\tilde{I}_i(\omega)$ injected by the sender in the neuron soma satisfies the subthreshold stimulation condition, expressed as

$$\tilde{I}_i(\omega) : \tilde{V}_o(x,\omega)\,|_{x=0} = Z_{soma}(\omega)\tilde{I}_i(\omega) < V_{th}\,, \tag{5.4}$$

where $x = 0$ denotes the location of the soma along the axon coordinate x. If (6.2) is satisfied (at the soma), then the subthreshold condition is satisfied at any other membrane location, since the equivalent circuit in Fig. 5.2 is composed of passive elements other than the current injection at the soma [28]. V_{th} typically ranges from -60mV to -55mV, depending on the electrophysiological characteristics of the
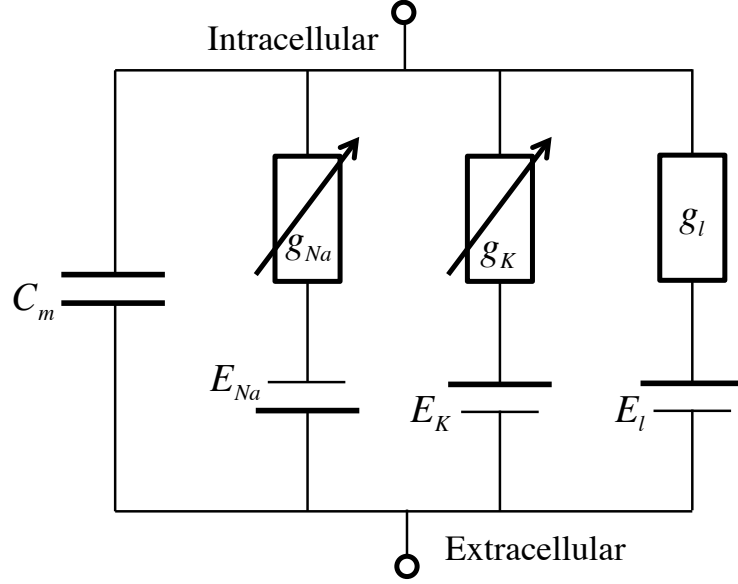
Figure 5.3. Hodgkin-Huxley model of an isopotential membrane patch. neuron [36].

5.2.2 Transmembrane Impedance $Z_m(\omega)$

The transmembrane impedance of a neuron is here defined as the ratio between the membrane potential $\tilde{V}_m(\omega)$ and the transmembrane current $\tilde{I}_m(\omega)$ of an area of neuron membrane where the membrane potential can be approximated as homogeneous, i.e., isopotential membrane patch. In this section, by applying the quasi-active neuron membrane model [22], we express of the transmembrane impedance as follows:

$$Z_m(\omega) = \frac{\tilde{V}_m(\omega)}{\tilde{I}_m(\omega)} = \frac{\alpha_3\omega^3 + \alpha_2\omega^2 + \alpha_1\omega + \alpha_0}{\beta_4\omega^4 + \beta_3\omega^3 + \beta_2\omega^2 + \beta_1\omega + \beta_0}, \tag{5.5}$$

where α_i, $i = 0, 1, 2, 3$, and β_j, $j = 0, 1, 2, 3, 4$ are in (5.6) and (5.7), respectively. In the following, I motivate this result.

The relation between the membrane potential $v_m(t)$ and the transmembrane current $I_m(t)$ of an isopotential membrane patch of a neuron, as functions of the time

t, is generally represented through the widely accepted Hodgkin-Huxley model as an electrical circuit with terminals at each side of the membrane [16], as shown in Fig. 5.3. The capacitance C_m models the lipid bilayer of the membrane patch, and the conductances g_{Na} and g_K model the voltage-gated ion channels, i.e., membrane pores that allow ions to pass through depending on the membrane voltage itself, for the sodium Na^+ and potassium K^+, respectively. The leak conductance g_l models leak channels, i.e., membrane pores that allow ions of various types to pass through independently from the membrane voltage, and the voltage sources E_{Na^+}, E_K, and E_l model the differences in the concentration of different ion species that drive the flow of ions through the membrane channels. The aforementioned resting potential E_m of the neuron is equal to the average of the voltage sources E_{Na^+}, E_K, and E_l weighted by each corresponding conductance. In general, the conductances g_{Na} and g_K are non-linear functions of the membrane voltage $v_m(t)$, which results in a non-linear relation between $v_m(t)$ and the transmembrane current $I_m(t)$.

In the case when the membrane potential $v_m(t)$ satisfies the subthreshold condition at any isopotential membrane patch, corresponding to $v_m(t) < V_{th}$, the aforementioned Hodgkin-Huxley model for the isopotential membrane patch reduces to the quasi-active model detailed in [22]. This model corresponds to the electrical circuit shown in Fig. 5.4, which, in contrast to the Hodgkin-Huxley's, is composed of linear elements. The expressions for the conductances G, g_n, g_h and g'_m, the inductances L_n and L_h, and the capacitance C'_m are provided in [23] as functions of the aforementioned Hodgkin-Huxley parameters. In this thesis, we make the following assumptions: i) at the moment when the sender starts the injection of the current $I_i(t)$ into the soma, the membrane potential at any location of the neuron is equal to the aforementioned resting potential E_m; ii) during the injection of the current $I_i(t)$ into the soma, no other external perturbation is induced on the membrane potential;
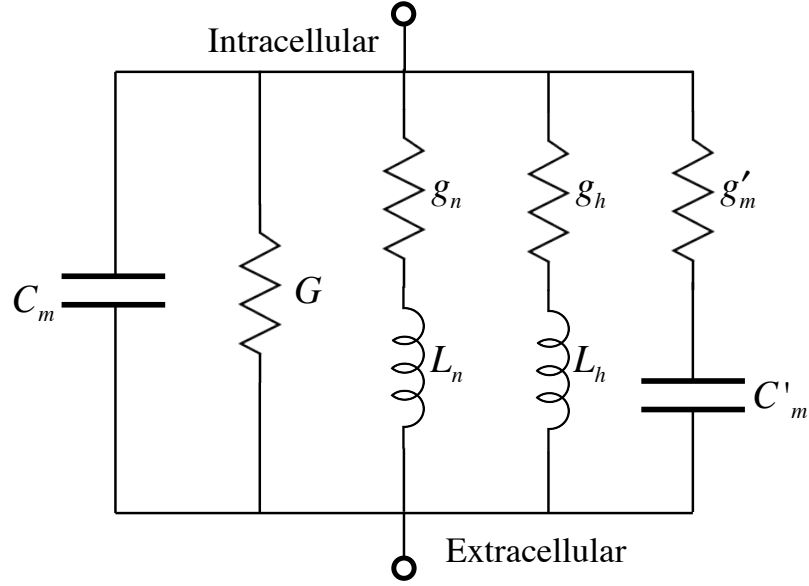
Figure 5.4. Quasi-active model of an isopotential membrane patch in subthreshold condition.

iii) The injection of the current $I_i(t)$ satisfies the subthreshold stimulation condition expressed in (6.2) for its Fourier transform $\tilde{I}_i(\omega)$.

As a consequence, during the transmission of information through the communication system proposed in this thesis, every isopotential membrane patch of the neuron satisfies the aforementioned subthreshold condition, and can be modeled with the linear electrical circuit shown in Fig. 5.4.

According to the quasi-active model, the relation between the Fourier transform $\tilde{V}_m(\omega)$ of the membrane potential $v_m(t)$ and the Fourier transform $\tilde{I}_m(\omega)$ of the transmembrane current $I_m(t)$ of an isopotential membrane patch, the functions of the frequency ω, can be defined as the transmembrane impedance $Z_m(\omega)$ expressed in (5.5), computed at the terminals of the circuit in Fig. 5.4 by applying electrical circuit

analysis [28]. The parameters α_i, $i = 0, 1, 2, 3$ in (5.5) have the following expressions:

$$
\begin{align}
\alpha_0 &= G g_n g_h \tag{5.6} \\
\alpha_1 &= jG \left(L_n g_h + L_h g_n + C'_m g'_m g_h g_n \right) \\
\alpha_2 &= -G \left(L_n L_h + L_n C'_m g'_m g_h + L_h C'_m g'_m g_n \right) \\
\alpha_3 &= -jG L_n L_h C'_m g'_m \,,
\end{align}
$$

while the parameters β_j, $j = 0, 1, 2, 3, 4$ have the following expressions:

$$
\begin{align}
\beta_0 &= g_n G + g_h G + g_h g_n \tag{5.7} \\
\beta_1 &= j \left(g_h g_n G C_m + C'_m g_h g_n G + L_n G + C'_m g'_m g_n G \right. \\
&\quad \left. + L_h G + C'_m g'_m g_h G + L_n g_h + L_h g_n + C'_m g'_m g_h g_n \right) \\
\beta_2 &= - \left(L_n g_h G C_m + L_h g_n G C_m + C'_m g'_m g_h g_n G C_m \right. \\
&\quad + L_n C'_m g_h G + L_h C'_m g_n G + L_n C'_m g'_m G \\
&\quad \left. + L_h C'_m g'_m G + L_n L_h + L_n C'_m g'_m g_h + L_n C'_m g'_m g_n \right) \\
\beta_3 &= -j \left(L_n L_h G C_m + L_n C'_m g'_m g_h G C_m \right. \\
&\quad \left. + L_h C'_m g'_m g_n G C_m + L_n L_h C'_m G + L_n L_h C'_m g'_m \right) \\
\beta_4 &= L_n L_h C'_m g'_m G C_m \,.
\end{align}
$$

5.2.3 Axon Transimpedance $Z_{axon}(x, \omega)$

The axon transimpedance of a neuron is here defined as the ratio between the membrane potential $\tilde{V}(x, \omega)$ at distance x along the axon and the current $\tilde{I}_i(\omega)$ injected by the sender into the soma in the case where we exclude the electrical contribution of the dendritic tree, which corresponds to substituting the impedance of the dendritic
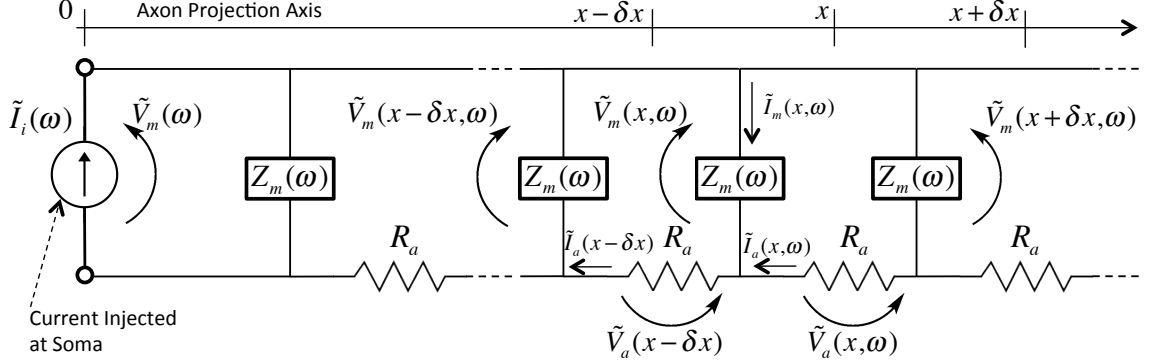
Figure 5.5. Transmission line model of the axon obtained through the Cable Theory. tree in Fig. 5.2 with an open circuit, i.e., $Z_{dendrites}(\omega) \to \infty$. This is expressed as follows:

$$Z_{axon}(x, \omega) = 0.5 Z_0(\omega) e^{-x\sqrt{\frac{4R_a}{Z_m(\omega)d_a}}}, \tag{5.8}$$

where $Z_0(\omega)$ is defined in (5.9), R_a is the membrane axial resistance, which is a parameter determined experimentally, and $Z_m(\omega)$ is the transmembrane impedance (5.5), respectively. In the following, we detail the derivation of (5.8).

The neuron axon is a projection from the soma, and its electrical properties in terms of the aforementioned impedance can be quantified by applying the Cable Theory [38] to the isopotential membrane patch model presented in Sec. 5.2.2. In particular, the neuron axon is modeled through the electrical transmission line shown in Fig. 5.5, where $Z_m(\omega)$ is the transmembrane impedance of an isopotential membrane patch, expressed in (5.5), and R_a is the axial resistance of the axon, defined as the ratio between the membrane potential difference V_a of two adjacent membrane patches, and the ion current flowing in the axon intracellular environment (axoplasm) adjacent to the patches, termed axial current I_a. In agreement with [38], the axial resistance R_a is here considered constant and homogeneous along the axon. According to transmission line theory [48], we define the characteristic impedance $Z_0(\omega)$ of the

axon as

$$Z_0(\omega) = \sqrt{\frac{4 R_a Z_m(\omega)}{\pi^2 d_a^3}}\,, \tag{5.9}$$

Where d_a is the diameter (average) of the axon. In the following derivations, we make the assumption [38] $L \gg \lambda$, where L is the length of the axon, and λ is the membrane's length constant, defined as follows [48]: $\lambda = \sqrt{\frac{\Re\{Z_m\} d_a}{4 R_a}}$, where $\Re\{.\}$ denotes the real part. As a consequence, the electrical transmission line model shown in Fig. 5.5 has infinite extension in the axon projection direction. In addition, the soma is here considered as having negligible size with respect to the axon, and therefore approximated as a point at location 0 along the axon projection axis.

To analytically obtain the axon transimpedance $Z_{axon}(x, \omega)$, with reference to Fig. 5.5, we express the Kirchhoff's current law [28] at a location x along the axon as follows:

$$\tilde{I}_m(x, \omega) = \frac{\tilde{I}_a(x - \delta x, \omega) - \tilde{I}_a(x, \omega)}{\delta x} + \tilde{I}_i(\omega)\delta(x)\,, \tag{5.10}$$

where $\tilde{I}_m(x, \omega)$ and $\tilde{I}_a(x, \omega)$, are the Fourier transforms of the current per unit length flowing through the isopotential membrane patch and the current through the axial resistance R_a, respectively, at location x along the axon projection axis and frequency ω, and $\tilde{I}_i(\omega)$ is the Fourier transform of the current injected by the sender into the soma. δx is an infinitesimal distance along the axon projection axis, while $\delta(.)$ is the Dirac delta operator. Through electrical circuit analysis [28], we obtain the following expressions:

$$\tilde{I}_a(x - \delta x, \omega) = \frac{\pi d_a^2 \tilde{V}_a(x - \delta x, \omega)}{4 R_a} = \frac{\pi d_a^2 (\tilde{V}_m(x - \delta x, \omega) - \tilde{V}_m(x, \omega))}{\delta x 4 R_a}\,,$$

$$\tilde{I}_a(x, \omega) = \frac{\pi d_a^2 \tilde{V}_a(x, \omega)}{4 R_a} = \frac{\pi d_a^2 (\tilde{V}_m(x, \omega) - \tilde{V}_m(x + \delta x, \omega))}{\delta x 4 R_a}\,,$$

$$\tilde{I}_m(x, \omega) = \frac{\pi d_a \tilde{V}_m(x, \omega)}{Z_m(\omega)}\,,$$

where $\tilde{V}_a(x,\omega)$ and $\tilde{V}_m(x,\omega)$ are the voltage at the the axial resistance R_a and the membrane potential, respectively, at location x along the axon projection axis and frequency ω. By substituting (5.11) into (5.10), and taking the limit for $\delta x \to 0$, we obtain the following relation between the membrane potential $\tilde{V}(x,\omega)$ at distance x along the axon and the current $\tilde{I}_i(\omega)$ injected by the sender into the soma:

$$\frac{\pi d_a \tilde{V}_m(x,\omega)}{Z_m(\omega)} = \frac{\pi d_a^2}{4R_a}\frac{\partial^2 \tilde{V}_m(x,\omega)}{\partial x^2} + \tilde{I}_i(\omega)\delta(x)\,, \tag{5.11}$$

which corresponds to a second order linear partial differential equation with the following solution [22]:

$$\tilde{V}_m(x,\omega) = \frac{1}{2}\sqrt{\frac{4R_a Z_m(\omega)}{\pi^2 d_a^3}}\,e^{-x\sqrt{\frac{4R_a}{Z_m(\omega)d_a}}}\tilde{I}_i(\omega)\,, \tag{5.12}$$

where $\tilde{V}_m(x,\omega)$ is the membrane potential at distance x along the axon and $\tilde{I}_i(\omega)$ is the current injected by the sender into the soma as functions of the frequency ω, R_a is the axon axial resistance, and $Z_m(\omega)$ is the transmembrane impedance expressed in (5.5). As a consequence, the axon transimpedance as defined above corresponds to the expression in (5.8).

5.2.4 Dendritic Tree Impedance $Z_{dendrites}(\omega)$

The dendritic tree impedance of a neuron is here defined as the ratio between the membrane potential $\tilde{V}(0,\omega)$ at the soma and the current $\tilde{I}_i(\omega)$ injected by the sender into the soma in the case where we exclude the electrical contribution of the axon, which corresponds to substituting the axon transmission line model in Fig. 5.2 with an open circuit, i.e., $Z_{axon}(x,\omega) \to \infty$. This is computed recursively through a depth-first search with post-order traverse method [10] detailed in Algorithm 2.

Algorithm 1 Recursive calculation of $Z_{dendrites}(\omega)$.

1: **procedure** DendTreeImpedance (*node* dendrite)
2:     **if** dendrite $! = $ NULL **then**
3:         **for** *node* i : dendrite.GetChildren () **do**
4:             DendTreeImpedance (i)
5:             Compute $Z_{dendrites}(\omega) = Z_{d,i}(\omega)$ with (6.4)
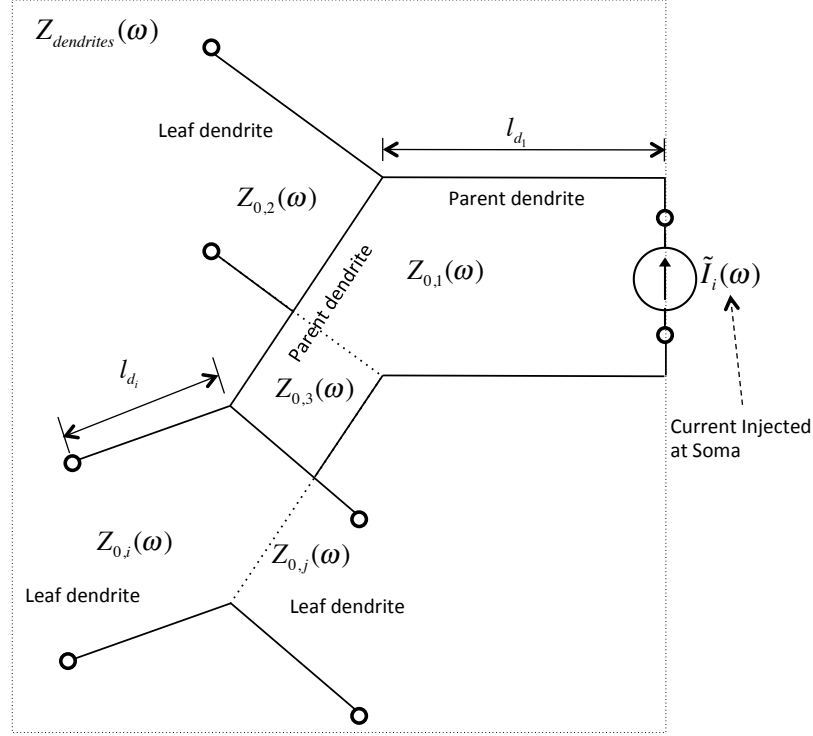
Figure 5.6. Transmission line model of the dendritic tree obtained through the Cable Theory.

From the electrical perspective, the dendritic tree can be modeled through Cable Theory [38] as a branched transmission line, as shown in Fig 5.6, with characteristic impedance $Z_0(\omega)$, expressed in (5.9). In the transmission line model, each branch of the dendritic tree can be either a leaf dendrite, which have an open circuit as end load, or a parent dendrite, whose load is given by the equivalent load of the parallel branching transmission lines, named Children in Algorithm 2.

To analytically obtain the impedance $Z_{d,i}(\omega)$ of a dendrite i, we apply Transmission Line Theory [28] to compute the equivalent impedance of a transmission line

having a characteristic impedance $Z_{0,i}(\omega) = \sqrt{4R_a Z_m(\omega)/(\pi^2 d_i^3)}$, d_i being the dendrite's diameter, a length equal to the physical length of the dendrite l_{d_i}, and a load $Z_{L,i}(\omega)$. This is expressed as

$$
\begin{aligned}
Z_{d,i}(\omega) &= Z_{0,i}(\omega) \\
&\quad \cdot \frac{Z_{L,i}(\omega)\cosh(\gamma(\omega)l_{d_i}) + Z_0(\omega)\sinh(\gamma(\omega)l_{d_i})}{Z_{L,i}(\omega)\sinh(\gamma(\omega)l_{d_i})Z_0(\omega)\cosh(\gamma(\omega)l_{d_i})} \, ,
\end{aligned}
\tag{5.13}
$$

where $\gamma(\omega) = \sqrt{4R_a/(Z_m(\omega)d_i)}$ and R_a is the axial resistance defined in Sec. 5.2.3. If dendrite i is a leaf, the load $Z_{L,i}(\omega) \to \infty$, otherwise, if dendrite i is a parent, $Z_{L,i}(\omega)$ is expressed as the equivalent load of N parallel transmission lines branching from the dendrite i. This is expressed as follows:

$$
Z_{L,i}(\omega) = \frac{\sum_{n=1}^{N} Z_{d,n}(\omega)}{\prod_{n=1}^{N} Z_{d,n}(\omega)} \, ,
\tag{5.14}
$$

where N is the number of dendrites branching out from dendrite i, and $Z_{d,n}(\omega)$ is the impedance of the dendrite n computed at an earlier step in the recursion of Algorithm 2.

5.3   Numerical Results

We present a preliminary comparison of numerical results, obtained by evaluating the analytical expressions of the linear channel model detailed in Sec. 5.2, with results of simulations performed through the NEURON software [7], which is based on the numerical computation of the Hodgkin-Huxley (non-linear) model throughout a neuron with a defined shape, or morphology. we based our results on the biophysical parameters of the giant squid axon, which are considered as standard for neurophysiology model comparison [23]. For these preliminary results, we used a simplified dendritic
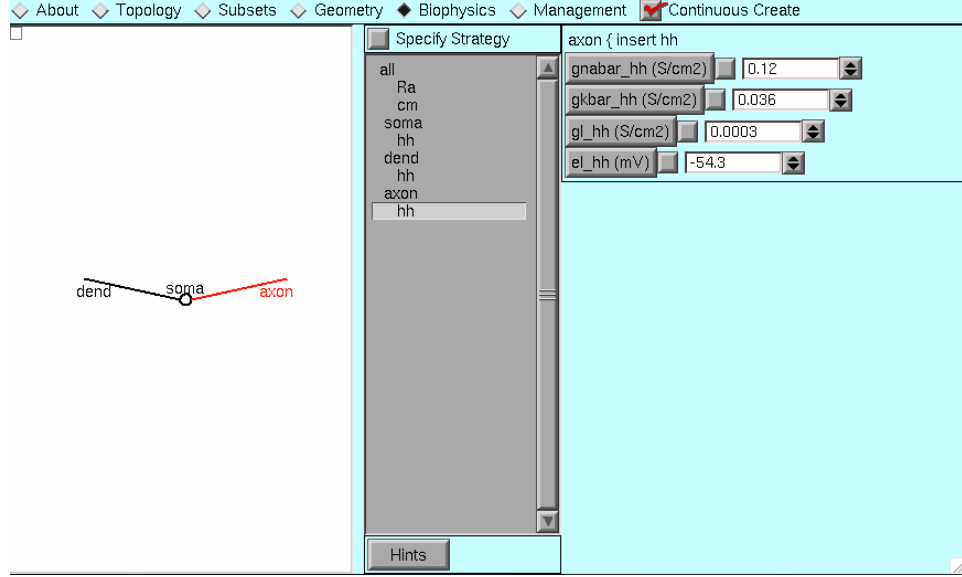
Figure 5.7. NEURON software [7] screenshot showing the neuron morphology used to compute our numerical results.

tree having only one dendrite, as shown in the screenshot of the NEURON software in Fig. 5.7. The parameters are as follows: the lumped elements of the quasi-active model of a membrane patch in Fig. 5.4 are $G = 0.246$ mS/cm^2, $g_n = 0.894$ mS/cm^2, $g_h = 0.072$ mS/cm^2 , $g'_m = 0.432$ mS/cm^2, $L_n = 6.43$ H.cm^2, $L_h = 119$ H.cm^2 , $C_m = 1$ μF/cm^2 and $C'_m = 0.102$ μF/cm^2; the value of the membrane axial resistance is $R_a = 100$ ohm.cm; the length of the axon is $L = 1500$ μm and the length of the single dendrite is $l_{d_1} = 3400$ μm. Additional parameters used in the NEURON software are as follows: dendrites, soma, and axon diameters are equal to 50 μm, 50 μm, and 10 μm, respectively, the number of simulation segments is equal to 70, 5, and 50, respectively, and the length of the soma is equal to 100 μm, which can be considered negligible when compared to the axon and dendrite lengths. The parameter values of the Hodgkin-Huxley model for the giant squid axon [29] used in the NEURON simulations correspond to $\bar{g}_{Na} = 0.12$ S/cm^2, $\bar{g}_K = 0.036$ S/cm^2, $g_l = 0.0003$ S/cm^2, and $E_l = -54.3$ mV.

In Fig. 5.8 and Fig. 5.9 we show the numerical results in terms of magnitude

Figure 5.8. Magnitude of the neuron transimpedance $|Z(x,\omega)|$ for a distance $x = 0.0675$ cm along the axon, and for frequencies ω ranging from 1 Hz to 1000 Hz.

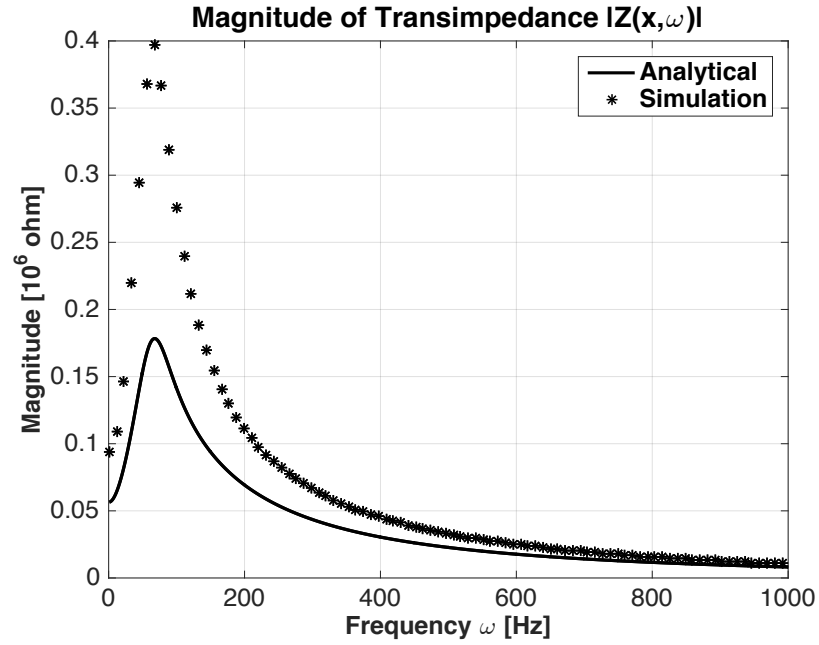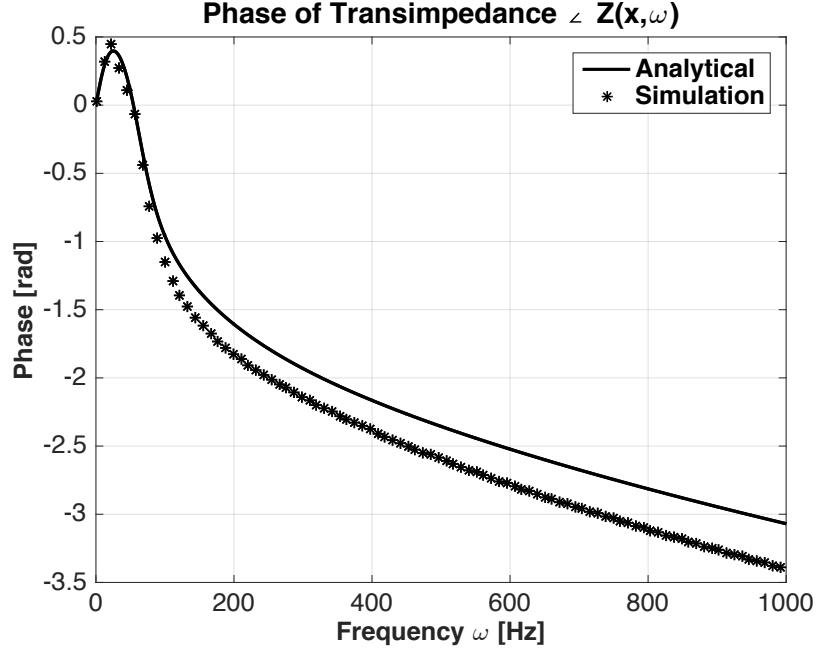Figure 5.9. Phase of the neuron transimpedance $\angle Z(x,\omega)$ (same parameters as in Fig. 5.8).

and phase, respectively, of the neuron transimpedance $Z(x, \omega)$ when the receiver performs the voltage reading at a distance $x = 0.0675$ cm from the soma along the axon projection axis, as shown in Fig. 5.1. The analytical transimpedance values are computed with the linear channel model presented in this thesis by evaluating the formulas in (5.2), (5.3), (5.5), (5.8), and Algorithm 2 for the aforementioned parameters. The simulation-based transimpedance values are computed by running the NEURON software [7] with the following parameters: initial membrane potential equal to the resting potential -65 mV, total simulation time 1000 msec, simulation time step 0.01 msec, and different voltage outputs are computed for sinusoidal injected currents with amplitude 5 nA, which satisfies the subthreshold condition as detailed in the following, and having frequencies from 1 Hz to 1000 Hz.

The preliminary results in Fig. 5.8 and Fig. 5.9 show as similar trend with numerical values of comparable magnitude computed through the linear channel model proposed in this thesis and those computed through numerical simulation with the NEURON software. In particular, we notice that both the two strategies reveal a resonant frequency around 70 Hz, where the curves of the transimpedance magnitude $|Z(x, \omega)|$ show a maximum value. This is in agreement with experimental results, such as in [17]. We think that the main differences observed in the curves at low frequencies might be due to the aforementioned simplified dendritic tree. In the future, we plan to validate our models on neurons with more realistic morphology and geometry

In Fig. 5.10 we show different values of the output voltage $V_o(x, t)$ from NEURON simulations corresponding to sinusoidal injected currents with frequency 50 Hz and varying amplitude ranging from 1 nA to 10 nA. we can observe that for low amplitudes of the injected current the output voltage maintains a sinusoidal shape with the same frequency, therefore confirming a linear behavior in subthreshold stimulation
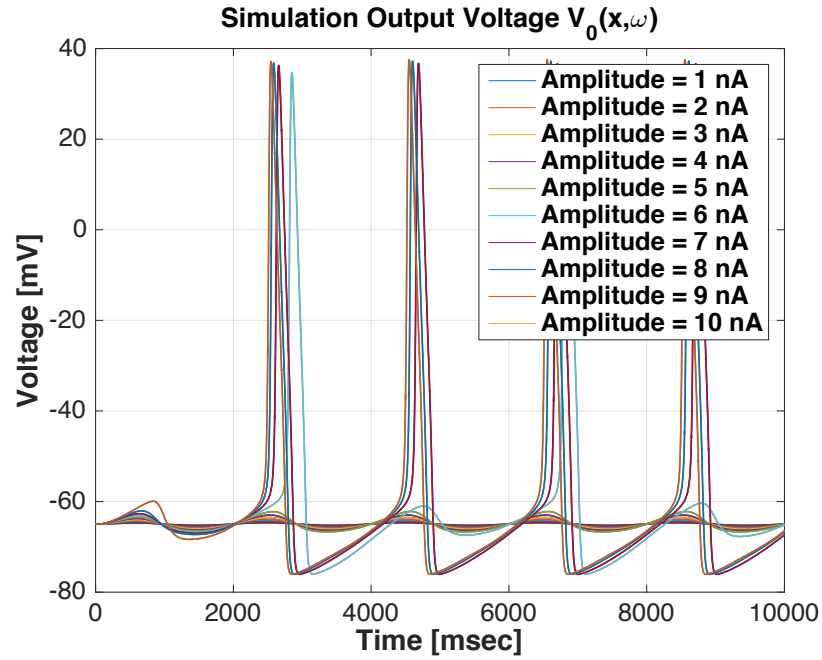
Figure 5.10. Output voltage $V_o(x, t)$ from NEURON simulations upon sinusoidal injected currents with frequency 50 Hz and varying amplitude ranging from 1 nA to 10 nA.

conditions. For high amplitudes, action potential stimulation occurs, and the output voltage shows the emergence of spikes.

Chapter 6

Dendritic Tree Communication Channel

In the previous chapter, we elaborated the case in which a neuron receives stimulation signals to its soma. In this chapter, we consider a more natural circumstance in which the dendritic tree receives stimuli through its branches and integrates them towards the soma. This is a rather complicated analysis as individual neurons have dendritic trees with distinct pattern of branching. We also take into account the morphological and biophysical differences between individual neurons.

6.1 Computational Model of a Dendritic Tree in Subthreshold Regime

In Fig. 6.1 we show a scheme of the computational model detailed in this section. In particular, we consider only the portion of a neuron within the **Nervous System** composed of the **Soma**, which is the main cell's body that contains the nucleus and other organelles, and the dendritic tree, which is an arbitrary hierarchical bran-

ching of **Dendrites**, electrically-conductive projections from the soma [36]. Along the dendrites, special protrusions called dendritic spines allow the connection of the dendritic tree to multiple other neurons, which send electrochemical signals to the dendritic spines through their corresponding extremities, or synapses. Neurons are in general composed also of an axon, a thicker and longer projection from the soma that propagates the electrical excitation along its length and terminates into the synapses. The electrical properties of the dendritic tree, soma, and axon derive from the fact that the neuron is bound by a lipid bylayered membrane that maintains a difference between inner and outer concentrations of ions (electrically-charged molecules), resulting in an electrical potential across the membrane itself. we assume that when no external perturbation is applied to the neuron, the membrane potential is constant and homogeneous throughout the neuron, and equal to the resting potential E_m, in agreement with widely accepted models from the neurophysiology literature [48]. Nevertheless, in this thesis we focus on the propagation of information between the extremities of the dendrites, also called leaves in the rest of the thesis, and the soma. In particular, we abstract the transmission of information through the injection of electrical currents where a microelectrode penetrates the membrane at each leaf and releases electrical current into the intracellular space [37]. The injected current, and the consequent local perturbation of the membrane potential around its resting potential, are propagated through the dendritic tree until reaching the soma. We assume that the reception is realized through an intracellular electrode through which we read the membrane voltage $V_o(t)$ at the soma.

In Chapter 5, we modeled the propagation of information as a linear communication channel between the soma and a remote location of the axon in similar conditions (subthreshold regime), where we considered the complete dendritic tree as an impe-
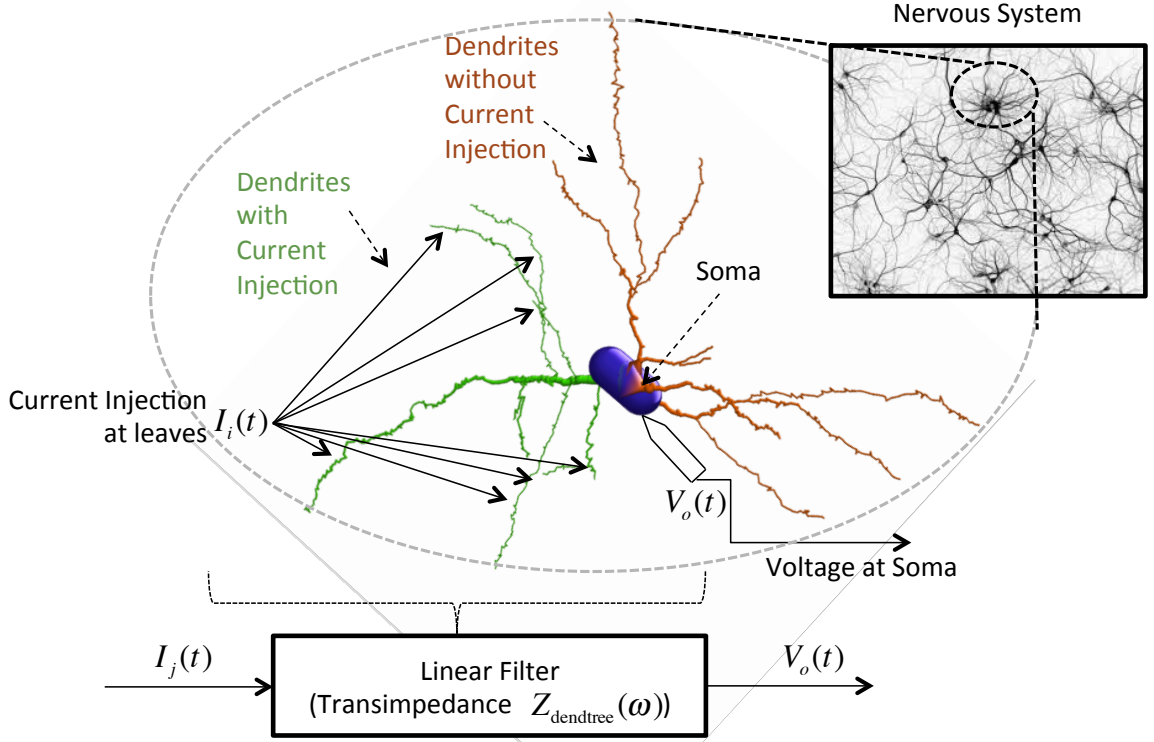
Figure 6.1. Scheme of the proposed computational model of a dendritic tree.[1]

dance load connected to the soma, with no input to any dendrite. In this thesis, we detail the computational model and the development of a tool to model the propagation of information from a subset of leaves of the dendritic tree, *i.e.*, those abstracting the connection from a single presynaptic neuron, to the soma. As shown in Fig. 6.1, we propose a system model where the input is a modulated current $I_{in}(t)$ as function of the time t injected at the aforementioned leaves, and the output is the resulting membrane voltage $V_o(t)$ at the soma. The proposed model is expressed as a linear filter in the frequency ω domain as follows:

$$\tilde{V}_{out}(\omega) = Z_{\mathrm{dendtree}}(\omega)\tilde{I}_{in}(\omega)\,, \tag{6.1}$$

where $\tilde{I}_{in}(\omega)$ and $\tilde{V}_{out}(\omega)$ are the Fourier transforms of $I_{in}(t)$ and $V_{out}(t)$, respectively,

---

[1]The neuron morphology shown in the figure has been generated through [3].

and $Z_{\mathrm{dendtree}}(\omega)$ is the transimpedance of the dendritic subtree, defined here as the portion of the dendritic tree that is connected to a single presynaptic neuron, and it is computed through (2).

6.1.1 The Subthreshold Condition

The linear filter model expressed in (6.1) is valid only when the membrane potential maintains a value less than V_{th} at the soma, named subthreshold condition [36]. This is realized when the current $\tilde{I}_{in}(\omega)$ injected into the dendritic tree satisfies the subthreshold stimulation condition, expressed as

$$\tilde{I}_{in}(\omega) : \tilde{V}_{out}(\omega) < V_{th} , \tag{6.2}$$

V_{th} typically ranges from $-60\mathrm{mV}$ to $-55\mathrm{mV}$, depending on the electrophysiological characteristics of the neuron [36]. Whenever the subthreshold condition is satisfied, the dendritic tree can be modeled as a branched transmission line through Cable Theory [38], as shown in Fig 6.2 and detailed in the following.

6.1.2 The Dendritic Tree Transimpedance $Z_{\mathrm{dendtree}}(\omega)$

The dendritic tree transimpedance $Z_{\mathrm{dendtree}}(\omega)$, defined in (6.1) as the ratio between the voltage $\tilde{V}_{out}(\omega)$ at the soma and the current $\tilde{I}_{in}(\omega)$ injected at the leaves connected to a single presynaptic neuron, is computed through a branched transmission line model, shown in Fig. 6.2. In this model, each dendrite i is modeled by a transmission line with characteristic impedance $Z_{0,i}(\omega) = \sqrt{4R_a Z_m(\omega)/(\pi^2 d_i^3)}$, d_i being the dendrite's diameter, and length equal to the physical length of the dendrite l_{d_i}.

To analytically compute $Z_{\mathrm{dendtree}}(\omega)$, we make the following assumptions:

Figure 6.2. Transmission line model of the dendritic tree used for the computation of the transimpedance $Z_{\mathrm{dendtree}}(\omega)$.

- The current injected at the leaves $\tilde{I}_{in}(\omega)$ and resulting in a voltage $\tilde{V}_{out}(\omega)$ at the soma is equal to the current that would result at the soma $\tilde{I}_{soma}(\omega)$ by applying a voltage $\tilde{V}_{out}(\omega)$ in the condition where the same leaves have zero impedance at their terminals (short circuit).

- The leaves that do not receive current injection in our model are considered as open circuits.

These assumptions are justified by taking into account the linearity and reciprocity of the transmission line abstraction of the dendritic tree, which can be considered

as a two-port electrical network where one port corresponds to the terminals of the soma, and the other port corresponds to the terminals connected to the injected current $\tilde{I}_{in}(\omega)$, in parallel to the terminals of the dendrite subtree leaves, as shown in Fig. 6.2.

As a consequence, we can have the following equivalence:

$$Z_{\text{dendtree}}(\omega) = Z_{\text{soma}}(\omega) , \tag{6.3}$$

where $Z_{\text{soma}}(\omega)$ is the impedance that would be observed at the soma when the dendritic subtree leaves have their terminals in short circuit, and the remaining leaves are open circuits. This can be computed through the computational procedure that we proposed in Chapter 5, which is a recursive algorithm based on a post-order traverse method [10], as detailed in Algorithm 2.

Algorithm 2 Recursive calculation of $Z_{soma}(\omega)$.

1: **procedure** DendTreeSomaImpedance (*node* dendrite)
2:     **if** dendrite ! $=$ NULL **then**
3:         **for** *node* i : dendrite.GetChildren () **do**
4:             DendTreeSomaImpedance (i)
5:             Compute $Z_{soma}(\omega) = Z_{d,i}(\omega)$ with (6.4)

The impedance $Z_{d,i}(\omega)$ at a dendrite i is obtained in Chapter 5 by applying Transmission Line Theory [28] to the transmission line abstraction shown in Fig. 6.2. This is expressed as follows:

$$
\begin{aligned}
Z_{d,i}(\omega) &= Z_{0,i}(\omega) \\
&\quad \cdot \frac{Z_{L,i}(\omega)\cosh(\gamma(\omega)l_{d_i}) + Z_{0,i}(\omega)\sinh(\gamma(\omega)l_{d_i})}{Z_{L,i}(\omega)\sinh(\gamma(\omega)l_{d_i}) + Z_{0,i}(\omega)\cosh(\gamma(\omega)l_{d_i})} ,
\end{aligned}
\tag{6.4}
$$

where $\gamma(\omega) = \sqrt{4R_a/\Re[Z_m(\omega)]d_i}$, R_a is the axial resistance, a parameter determined

experimentally, and $Z_m(\omega)$ is the transmembrane impedance, detailed in Chapter 5. If dendrite i is a leaf subject to current injection, the load $Z_{L,i}(\omega) = 0$, otherwise, if the dendrite i is a leaf without current injection, $Z_{L,i}(\omega) \to \infty$. Finally, if the dendrite i is a parent, $Z_{L,i}(\omega)$ is expressed as the equivalent load of N parallel transmission lines branching from the dendrite i. This is expressed as follows:

$$Z_{L,i}(\omega) = \frac{\sum_{n=1}^{N} Z_{d,n}(\omega)}{\prod_{n=1}^{N} Z_{d,n}(\omega)} \,, \tag{6.5}$$

where N is the number of dendrites branching out from dendrite i, and $Z_{d,n}(\omega)$ is the impedance of the dendrite n computed at an earlier step in the recursion of Algorithm 2.

It is also possible to demonstrate that the computational procedure in Algorithm 2 can be simplified by not accounting for dendritic tree branches connected to leaves that do not receive current injection. In fact, by substituting the open circuit load in the expression in (6.5), the the time on which impedance $Z_{st,i}(\omega)$ of a leaf dendrite i without current injection can be expressed as

$$Z_{st,i}(\omega) = -\mathrm{j}Z_{0,i}(\omega) \cot(\beta l_i) \,, \tag{6.6}$$

where $\beta = 2\pi/\lambda$, λ is the signal wave length, l_i is the length of the leaf dendrite i, and cot the cotangent function. Given that the length of a dendrite is in the order of micrometers [36], and the frequency range that we consider in our model is in the order of kHz, the resulting $Z_{st,i}(\omega)$ will likely assume much higher values than parallel branches connected to short circuit loads at the leaves subject to the current injection, and can be safely removed from the computation in Algorithm 2.

6.2   Computational Tool Implementation

Algorithm 3 Implementation of $Z_{Soma}Calculation$.

1: **procedure** LeavesImpedance (*list* DendriticTree)
2:     *list* LeavesList = Leaf dendrites of DendriticTree
3:     *list* Compute $Z_{LeafDendrite_i}$ with (6.4) by having $Z_L \rightarrow 0$
4: **procedure** ParentsImpedance (*list* LeavesList)
5:     *list* ParentList = All parents if LeavesList nodes
6:     **for** *node* Parent$_i$ in ParentList **do**
7:         **if** Parent$_i$ already computed **then**
8:             Break
9:         **else**
10:             *list* ChildList = Children of Parent$_i$
11:             **for** *node* Child$_j$ in ChildList **do**
12:                 **if** Child$_j$ has any child **then**
13:                     *list* GrandChildrenList = Children of Child$_j$
14:                     RecursiveCount ++
15:                     ParentsImpedance(GrandChildrenList)
16:                     RecursiveCount - -
17:                     $Z_{L,Parent_i}$ = Parallel lump all Child$_j$
18:                 **else**$Z_{L,Parent_i}$ = Parallel lump all Child$_j$
19:             Compute $Z_{ParentDendrite_i}$ with (6.4)
20:     **if** RecursiveCount == 0 **then**
21:         ParentsImpdance(ParentList)

    Algorithm 3 lists the steps we took in our implementation. First of all, we separate out the leaves of the given dendritic tree and set their load impedance to zero. When a parent dendrite is visited, the software identifies all possible children subtrees, calculates their impedances, and lumps them considering they are in parallel. This implementation is compatible with the fact that the impedance of a parent neurite depends on the parallel-lumped impedance of all the children's impedances that are connected to its leaky end, as expressed in (6.4). In the case that the impedance of a child subtree is not yet computed, we have to recursively call (6.4) for this subtree.

6.3   Numerical Results

We present a preliminary comparison of numerical results obtained by running the proposed computational model in Sec. 6.1 through the computational tool detailed in Sec. 6.2, with results of simulations performed through the NEURON software [7]. We based our results on the biophysical parameters of the giant squid axon, which are considered as standard for neurophysiology model comparison [23]. These parameters are detailed in Chapter 5. The dendritic tree morphology corresponds to the pyramidal neuron in the nerocortex of the human brain named 2a pyramidal2aF, and it is extracted from the NeuroMorpho database [3]. The 2a pyramidal2aF was chosen since it does not have axon, and pyramidal neurons are well investigated in neurology.

Fig. 6.3 and Fig. 6.4 show the magnitude and the phase, respectively, of the dendritic tree transimpedance $Z_{\text{dendtree}}(\omega)$. It is important to observe that we have a maximum (resonant frequency) at 67 Hz, and the general trend of both magnitude and phase are in agreement in both the computational tool and NEURON simulation results.
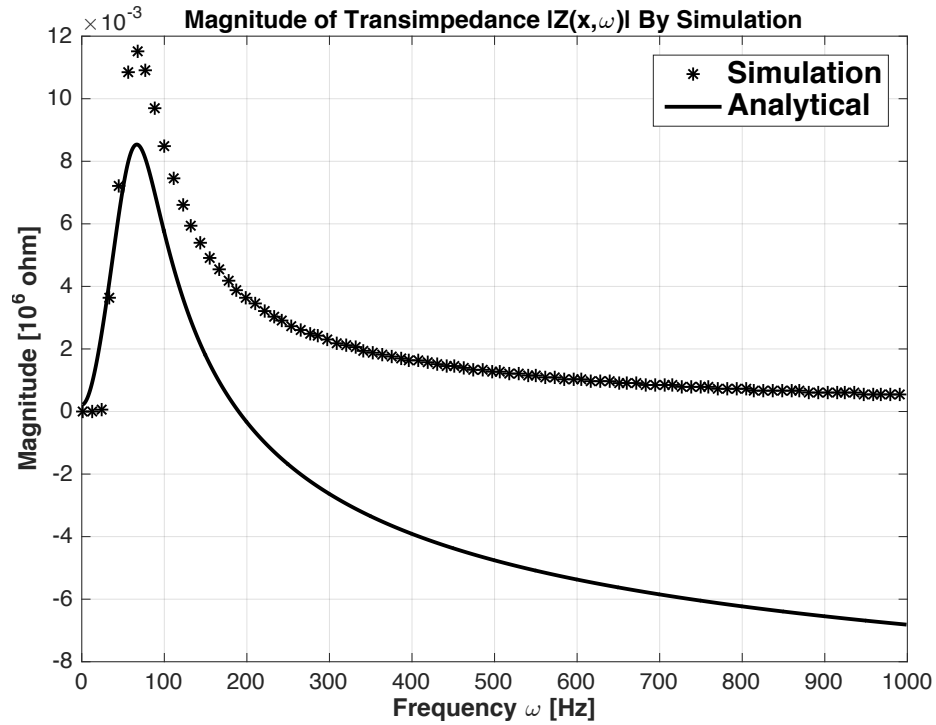
Figure 6.3. Magnitude of the dendritic tree transimpedance $Z_{\mathrm{dendtree}}(\omega)$ for frequencies ω ranging from 1 Hz to 1000 Hz.
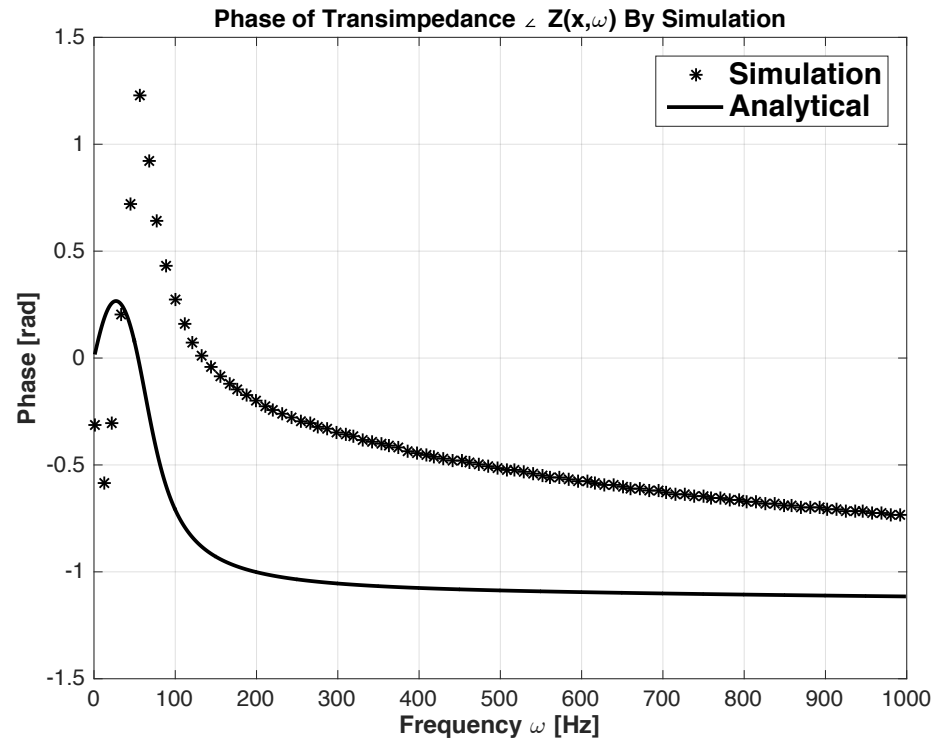

Figure 6.4. Phase of the dendritic tree transimpedance $Z_{\mathrm{dendtree}}(\omega)$ for frequencies ω ranging from 1 Hz to 1000 Hz.

Chapter 7

Future Work and Conclusion

7.1 Open Challenges

Just like any other new paradigm, a real world implementation of NC needs to address several challenges. In this section, we list some the challenges that we believe important.

7.1.1 Physical Layer

7.1.1.1 Noise

Noise is a big challenge in NC just like any other communication system. The interpretation of noise varies with different implementation of NC. More specifically, thermal agitations are the main sources of noise in a cell NC paradigm, as they cause spontaneous fluctuations in the membrane voltage to which subthreshold stimuli are susceptible. As for the circuit NC paradigm, noise manifests as organic spiking inferences caused by natural communication within the nervous system. It is necessary to model each of the noise types to identify important communication channel cha-

racteristics.

7.1.1.2 Communication Channel Memory

Another important challenge in the NC physical layer is caused by the fact that NC relies on neurobiological paths that inherit memory from the neurons and synapses that they are comprised of. Accordingly, the underlying communication channel in NC has memory.

7.1.2 Medium Access Control

For each of NC paradigms a set of proper protocols must be devised to control the access to the shared nervous medium. In particular, we need to design channel access schemes to avoid conflict among multiple data streams flowing through the nervous system with organic and artificial origins. We should also provide a modulation scheme compatible with biological limitations of the nervous system. For example, we need to the neuronal channel resonance frequency in the cellular NC paradigm. For a circuit NC paradigm with tactile stimulation, we want to modulate the data with stimulation patterns less annoying to the person but still causing noticeable spatiotemporal patterns. We also need to provide a practical addressing method to route the data streams to their designated destinations.

7.1.3 Networking Protocols

In general, few efforts have been undertaken in developing standards for newer intra-body communication based on the modalities excluding airborne EM signals. To the best of our knowledge, there is no standard or best practice proposed for designing

network protocols for NC. Therefore, it is necessary to form working groups and task forces on these topics.

7.1.4 Safety

7.1.4.1 Regulatory

As we mentioned earlier in Section 2.1, a NC realization contributes to health care and medical treatment applications. Obviously, this field of applications is highly regulated by authorities. Therefore, realizing NC in practice requires developing a new set of regulatory guidelines and measurements to ensure patient safety and to identify acceptable levels of prospective side effects.

7.1.4.2 Undesired Neuroplasticity

A big increase in synaptic activities due to excessive artificial stimulations may cause the post-synaptic neuron to undergo a neural plasticity process through which it acquires some morphological changes. The changes may manifest through up-regulating the neuron's receptors (i.e. building up more receptors), or by outgrowing new dendrites onto the synapse. These changes yield to Long-term Potentiation (LTP) in which the neuron's sensitivity is increased and hence causes the neurons to be more likely excited by stimuli that would not normally excite the neuron. Therefore, devising safe methods to artificially stimulate neurons are necessary to prevent undesired side effects.

7.1.5 Sustainability

The idea of transmitting artificial data through the nervous system in NC is a very novel concept. Therefore, new investments are needed on developing necessary gui-

delines, proper solutions, and suitable tools and technologies. An investment made on realizing NC has a high pay off after commercialization thanks to the immense market NC has in medical and non-medical applications.

7.2 Conclusion

In this thesis, we introduced the Neuronal Communication (NC) as a novel paradigm for transmitting artificial data through the nervous system. NC addresses inadequacies of so far realized (or proposed) intrabody communication methods that rely on airborne radio signals, body tissue conduits, or molecular communication. We identified the potential of the nervous system to serve as a reliable communication channel free of cost and independent of external energy demands. Such a communication system is motivated by the need of intra-body communication links for the interconnection of the next generation wearable and implantable devices. In particular, we proposed a novel model to account for the subthreshold stimuli propagation from the dendritic tree to the soma, and from there to an arbitrary on the axon. Our model formulates a communication channel model based on a neuron by modulating information through artificial subthreshold stimulation signals.

A system based on the so-called subthreshold electrical stimulation of a neuron does not stimulate neuro-spikes, and can potentially minimize the interference with the normal body functionalities. Moreover, by transmitting information through this type of stimulation, it is possible to express the communication channel with a linear model, which we analytically obtained by stemming from neurophysiology studies. We detailed a computational model and its implementation to obtain the voltage at the axon resulting from a subthreshold current stimulation at the extremities of the dendrites. Our model takes into account any given realistic 3D dendritic tree

with an arbitrary morphology. Numerical results from the model are obtained over a stimulation signal bandwidth of 1KHz, and compared with the results of a simulation through the NEURON software. Numerical results show agreement with simulations made with standard tools.

While this preliminary model does not include stochastic effects that would be unavoidable in the proposed communication system, we plan to extend this work by incorporating the modeling of the major noise sources within the electrochemical processes of neurons. We believe that the results obtained in this preliminary study encourage a new direction of investigation for the realization of sustainable intra-body communication systems.

We believe that our proposed model will contribute to the understanding of the propagation of information in neuron in general, and in particular will go in the direction of enabling the future design of communication systems based on the transmission of information between neuron-interfaced devices, such as those envisioned within the paradigm of the Internet of Bio-Nano Things [2].

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