Neuronal Communication: Presynaptic Terminals as Transmitter Array

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ABSTRACT

In this paper, a communication engineering model is proposed for capturing the actual behavior of biological neurons by accounting for the specific and unique processing performed by the presynaptic terminals. Specifically, experimental evidences show that: *i*) the release sites from a single axon can have variable release probabilities, even when the axon contacts the same postsynaptic neuron; *ii*) this variability in the release probability implies a compartmentalization at the level of the presynaptic terminals of the neuronal processing; *iii*) the specificity of the presynaptic terminal processing is driven by and reflects the complex biophysical mechanisms activated at the axon terminals by the spikes fired by the neuron in response to a stimulus. Stemming from these experimental evidences, we propose to model the presynaptic terminals as an array of transmitters, where each transmitter models the specific processing made by a presynaptic terminal. We conduct the analysis through a stochastic approach, since the synaptic transmission is inherently stochastic. In particular, we first analytically characterize the stochastic filtering of the spike train performed by each presynaptic terminal. Then, we characterize the propagation of the presynaptic-filtered signal through the synaptic cleft, and we derive the signaling delay as a function of the distance between the pre- and the postsynaptic neurons. Finally, the conducted theoretical analysis is validate through numerical simulation.

Keywords

Neuro-spike communications, neurons, intrabody nanonetworks

1. INTRODUCTION

Recent developments in nanotechnology and communication engineering are enabling the realization of a new generation of nanoscale devices implantable inside the human body [1, 2]. When interconnected in a network, referred to as *Intrabody nanonetwork*, these miniaturized devices or nanomachines are able to perform complex tasks, by overcoming their individual limitations.

Very recently, intrabody nanonetworks have been proposed for monitoring the human nervous system [3, 4] by exploiting the dimensional similarity of the nanomachines with the nervous biological structures. The aim is to develop radically new medical diagnosis and treatment techniques. However, several questions and challenges arise to design a fully functional intrabody nanonetwork deployed inside the nervous system. Certainly, the first step is to understand the physiological mechanisms underlying the neuronal activities with an engineering perspective for mapping such mechanisms into communication engineering system models [5, 6].

The communication models available in literature consider the synapses (illustrated in Fig. 1), i.e., the junctions through which the neurons signal to each other, acting solely as stochastic conveyers of information. However, this model is too simplistic. In fact, biological synapses act as unique dynamic signaling units, whose effects on the transmitted signal from one neuron to another can vary enormously depending on the activity history at either or both side of the synapse [7].

Specifically, numerous experimental evidences show that this property, referred to as *synapse-specific signaling*, is a universal property and potentially unique for each synaptic connection made by a single axon [7, 8, 9]. In fact, it is determined by the unique interaction between the pre- and the postsynaptic neurons. More in detail, the synapse-specific signaling is driven by and reflects the complex biophysi-

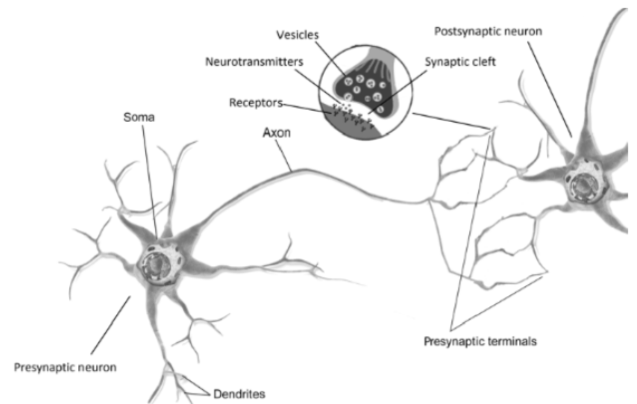

Figure 1: Biophysical communication between a presynaptic and a postsynaptic neuron.

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cal mechanisms activated at the presynaptic terminals by the electrical signals, known as action potentials (APs) or spikes, fired by the neuron in response to a stimulus. So, when an AP reaches different presynaptic terminals, the synapse-specific signaling determines different patterns of neurotransmitter release. As a consequence, a presynaptic neuron simultaneously transmits several different signals to a targeted postsynaptic neuron.
Stemming from these experimental evidences, it is clear that an effective neuron communication model should take into account for the synaptic signaling dynamics. Hence, in this paper, a communication engineering model is designed for capturing the actual behavior of biological neurons, by accounting for the specific neural processing performed by the presynaptic terminals. To the best of our knowledge, this is the first work that address this key issue.
Specifically, we propose to model the presynaptic terminals of a neuron as an array of transmitters, where each transmitter models the local processing performed by the corresponding presynaptic terminal. We conduct the analysis through a stochastic approach, since the biological synaptic transmission is inherently stochastic. More in detail, we first analytically characterize the stochastic filtering of the spike train performed by a presynaptic terminal. Then, we characterize the propagation of the presynaptic-filtered signal within the synaptic cleft, and we derive the signaling delay as a function of the distance between the presynaptic transmitter and the postsynaptic receiver. Finally, the theoretical analysis is validated through numerical simulation. Our theoretical analysis, in agreement with experimental evidences [7, 8, 9], shows that the neuronal information is encoded in the neurotransmitter release patterns of the presynaptic terminals.
The rest of the paper is organized as follows. In Section 2, we design the communication engineering model to take into account for the complex local processing performed by the presynaptic terminals. In Section 3, we validate the theoretical analysis. Finally, Section 4 concludes the paper.

2. PRESYNAPTIC TERMINALS: SYSTEM-THEORETICAL MODEL

The mechanisms underlying the neurotransmitter release have yet to be fully identified. However, the wealth and complexity of the protein-protein and protein-lipid interactions have been shown to control the release of neurotransmitters [9, 10]. Specifically, experimental evidences have shown that the overall probability that a given release site, i.e., a specialized region of the plasma membrane at which specific proteins involved in the release process are localized, would release transmitters in response to a given AP is an extremely complex phenomenon that can be modulated by many factors and it can vary enormously at the different terminals of an axon under the same conditions [9, 10]. Thus, release sites from a single axon can have different release probabilities, even when the axon contacts the same postsynaptic neuron. However, the experiments also shown that the release probability is very similar for synapses that share the same dendritic branch, indicating so that the release probability is branch-specific. Specifically, the release probability is not randomly distributed among the presynaptic terminals, but it is rather segregated at the level of individual dendrites, since it reflects the non-uniformity of the dendritic activities [10].

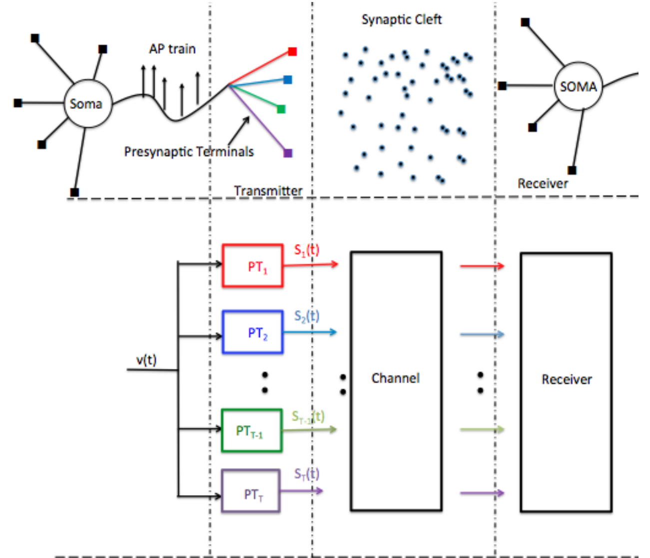

Figure 2: Transmitter Model for the Presynaptic Terminals.

By accounting for these evidences, in the following the term *presynaptic terminal* denotes a subset of the axon terminals characterized by homogeneous release probability since they share the same dendritic branch.
As previously described, each presynaptic terminal filters independently and in a distinguishing manner the incoming AP sequence. This phenomenon, along with the variation observed in the release probability in the different presynaptic terminals, lead us to propose the systems-theoretic communication model shown in Fig. 2. According to this model, the set of the presynaptic terminals are modeled as an array of transmitters, where each transmitter models the stochastic processing specific of a particular presynaptic terminal.
The number of the presynaptic terminals depends on the neuron characteristics [9, 10], and, without loss of generality, we denote with $\mathcal{T} \triangleq \{1, 2, \dots, T\}$ the set of distinct presynaptic terminals, whose cardinality is $|\mathcal{T}| = T$.
In the following, we first characterize the input-output relationship of each presynaptic terminal. Then, we characterize the propagation of the presynaptic-filtered signal, by determining the signaling delay.

2.1 Presynaptic Terminal Filtering

The AP train $v(t)$ traveling on the axon of the presynaptic neuron is modeled as a non-homogeneous Poisson impulse process, since this model has been shown to be able to effectively describe the neuron trial-to-trial variability [11]. Specifically, $v(t)$ is equal to:

$$v(t) = \sum_{j=1}^{N(t)} \delta(t - t_j). \quad (1)$$

In (1), t_j is the arbitrary spike arrival time, and $N(t)$ is a non-homogeneous Poisson process whose rate $\lambda(t)$ is a function of the time, hence $E[N(t)] = \int_0^t \lambda(u) du$.
Neurotransmitters are released in the form of packets, quanta.

A quantum corresponds to the content of a synaptic vesicle [12] that instantaneously appears in the synaptic cleft. The idealization of the vesicle discharge into the cleft as a point source situated on the presynaptic membrane is reasonable, since the pore radius though which neurotransmitters are released is negligibly small in comparison with the radius of the synaptic cleft [13]. Since a presynaptic terminal denotes a subset of the axon terminals characterized by homogeneous release probability, a release of neurotransmitters from a presynaptic terminal could correspond to the releases of more than one vesicle. In the following, we denote with Q_i the overall neurotransmitter quantum discharged by the i-th presynaptic terminal, that accounts for the quanta possibly released by the axon terminals constituting the considered presynaptic terminal.

DEFINITION 1. *R_i denotes the subset of the spike arrival times $\{t_j\}_{j=1}^{N(t)}$ that produce an overall neurotransmitter quantum release at the i-th presynaptic terminal.*

Stemming from this definition and with reference to the arbitrary k-th AP of the incoming train, the signal $s_i(t)$ at the output of the i-th presynaptic terminal is given by:

$$s_i(t) = Q_i \delta(t - t_k) \mathbf{1}_{R_i}(t_k), \tag{2}$$

where $\mathbf{1}_{R_i}(\cdot)$ is the indicator function of R_i, defined as:

$$\mathbf{1}_{R_i}(t_k) = \begin{cases} 1, & \text{if } t_k \in R_i \\ 0, & \text{if } t_k \notin R_i. \end{cases} \tag{3}$$

By accounting for (2) and (1), it results that the response of the i-th presynaptic terminal to the spike train $v(t)$ is:

$$s_i^v(t) = Q_i \sum_{k=1}^{N(t)} \delta(t - t_k) \mathbf{1}_{R_i}(t_k) = Q_i \sum_{j=1}^{N_i(t)} \delta(t - t_j), \tag{4}$$

where $N_i(t)$ is the stochastic process representing the number of releases until time t due to the incoming stimulating train $v(t)$[1]. By denoting with P_{rel_i} the release probability of the i-th presynaptic terminal, the rate of the releases can be calculated as[2]:

$$\lambda_i(t) = P_{\mathrm{rel}_i} \lambda(t). \tag{5}$$

Hence the expected value of $N_i(t)$ is given by:

$$\begin{aligned} E[N_i(t)] &= \int_0^t \lambda_i(u) du = P_{\mathrm{rel}_i} \int_0^t \lambda(u) du = \\ &= P_{\mathrm{rel}_i} E[N(t)]. \end{aligned} \tag{6}$$

REMARK 1. *From* (4) *and* (5)*, it results that the presynaptic terminals modulate the incoming spike train through their release probabilities, according to the experimental evidences [9, 10, 7, 8].*

[1]In (4) we supposed that the overall neurotransmitter quantum does not change with the AP time instants of the incoming train. More in general, Q_i could be a function of such time instants since the axon terminals involved in the release could vary with the AP time instants. However, the generalization to such a case is immediate to obtain, and the rest of the analysis continues to hold.

[2]The release is assumed to occur only when a spike invades the presynaptic terminal, i.e., the spontaneous release probability is assumed to be zero [14].

2.2 Transmission of the Presynaptic Signals

When an overall quantum of neurotransmitters is released, it propagates throughout the synaptic cleft. The propagation of this pulse can be analytically modeled by solving the Fick's laws of the diffusion for a two-dimensional disc [13, 12]. Hence, by accounting for (2), if at $t_j \in R_i$ a quantum Q_i is released from the i-th presynaptic terminal, the concentration at the m-th postsynaptic dendrite located at a distance r_{im} from the i-th presynaptic terminal as a function of time t is given by [13, 12]:

$$c_{i,m}(t, r_{im}) = \frac{Q_i}{4\pi a D(t - t_j)} e^{-\frac{r_{im}^2}{4D(t-t_j)}}, \tag{7}$$

where D is the diffusion coefficient of the synaptic cleft, and a denotes the height of the disc. By exploiting (4), it results that the released spike train of the i-th presynaptic terminal creates a variation in the neurotransmitter concentration at the distance r_{im} from the i-th presynaptic terminal given by the following pulse train:

$$\overline{c}_{i,m}(t, r_{im}) = \sum_{j=1}^{N_i(t)} \frac{Q_i}{4\pi a D(t - t_j)} e^{-\frac{r_{im}^2}{4D(t-t_j)}}. \tag{8}$$

REMARK 2. *The rate of the concentration pulse train generated by the i-th presynaptic terminal coincides with the rate of the released spike, i.e., $\lambda_i(t) = P_{rel_i}\lambda(t)$. This implies that the information carried on the postsynaptic neuron is dictated by the dynamic processing of the presynaptic terminal, in agreement with the experimental evidences. In other words, the neuronal information is encoded in the release patterns of the presynaptic terminals, that in turns are driven by and reflects the complex biophysical mechanisms of protein-protein and protein-lipid interactions between the presynaptic and postsynaptic neurons [7, 8, 9].*

To derive the delay with which a neurotransmitter concentration pulse arrives at the m-th postsynaptic dendrite located at a distance r_{im} from the i-th presynaptic terminal, we compute the time instant at which $c_{i,m}(t, r_{im})$ reaches its global maximum [15]. In fact, $c_{i,m}(t, r_{im})$ has only one local maximum, which is also its global maximum. We can therefore compute the position of this maximum by taking the time derivative of the pulse equation and finding the time instant at which it is equal to zero:

$$\frac{dc_{i,m}(t, r_{im})}{dt} = \frac{d}{dt} \frac{Q_i e^{-\frac{r_{im}^2}{4D(t-t_j)}}}{4\pi a D(t - t_j)} = 0. \tag{9}$$

From (9), by isolating the variable t we can obtain the time at which the pulse has its maximum. This time can be interpreted as the time t_{im} the concentration pulse spends to reach the postsynaptic membrane located at a distance r_{im} from the i-th presynaptic terminal if the neurotransmitter quantum was released at t_j, i.e., t_{im} can be interpreted as the delay:

$$t_{im} = t_j + \frac{r_{im}^2}{4D}. \tag{10}$$

Since the i-th presynaptic terminal generates the pulse train $\overline{c}_{i,m}(t, r_{im})$ and since the temporal distance between two successive releases is $\frac{1}{\lambda_i(t)}$, at the distance r_{im}, the maximum

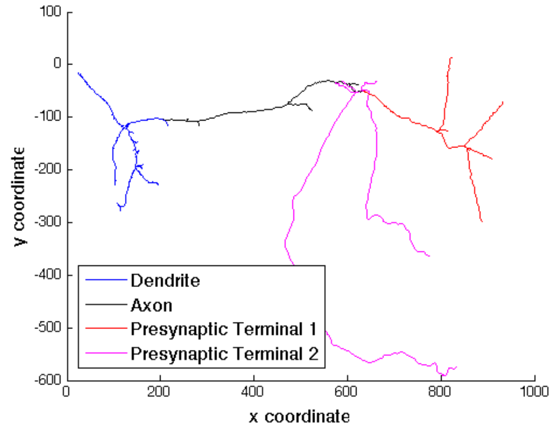

Figure 3: NMO-07522 Neuron morphology with two presynaptic terminals.

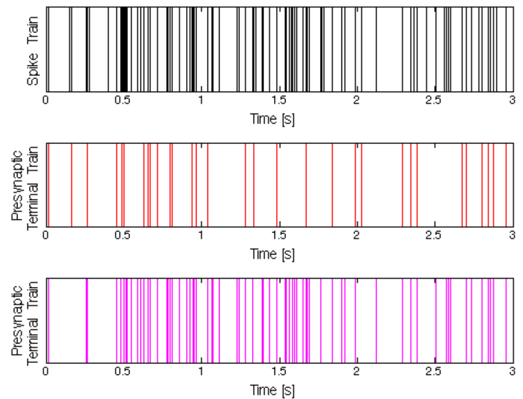

Figure 4: Presynaptic Terminal Responses vs time: i) incoming AP train (1st plot); ii) response of the first presynaptic terminal (2nd plot) with $P_{\mathrm{rel}_1} = 0.3$; iii) response of the second presynaptic terminal (3rd plot) with $P_{\mathrm{rel}_2} = 0.7$.

of the concentration pulse is assumed every T_i seconds with T_i given by:

$$T_i \triangleq \frac{1}{\lambda_i(t)} = \frac{1}{P_{\mathrm{rel}_i}\lambda(t)}. \tag{11}$$

3. VALIDATION OF THE THEORETICAL RESULTS

In this section, we validate the theoretical results through simulations. Specifically, we use the realistic experimentally reconstructed mouse neuron morphology "NMO-07522" [16] released by NeuroMorpho.org archive. The neuron morphology is shown in Fig. 3. The considered neuron exhibits two different presynaptic terminals, since, as described in Section 2, it is possible to individuate two different homogeneous release zones contacting two different dendritic branches. The release probabilities of the two presynaptic terminals are set equal to 0.3 and 0.7 according to the data reported in [7].

In Fig. 4, we report the responses of the two presynaptic terminals when they are stimulated by a non-homogeneous Poisson AP train with a sinusoidal rate whose average values is 32Hz. We note that the first presynaptic terminal, characterized by a lower release probability, generates a signal $s_1^v(t)$ whose rate is lower than the one of $s_2^v(t)$, generated by the second presynaptic terminal, characterized by a larger release probability. These results are in agreement with the theoretical analysis, and they confirm that the presynaptic terminals modulate the incoming spike train through their release probabilities.

In Fig. 5, we report the concentration pulse train generated at a distance of $r_{1m} = 20$nm by the signal emitted from the first presynaptic terminal as function of the time. We adopt the same simulation setting described in [12], i.e., $Q_1 = 4700$ molecules, $a = 20$nm and $D = 7.6 \cdot 10^8 nm^2/s$. We first note that the results confirm the theoretical analysis, i.e., the rate of the concentration pulse train generated by the first presynaptic terminal coincides with the rate of the released spike, i.e., $\lambda_1(t) = P_{\mathrm{rel}_1}\lambda(t)$. This implies that the neuronal information is encoded in the release patterns of the presynaptic terminals. Furthermore, we observe that the the maximum of the concentration pulse is achieved every $T_1 = \frac{1}{P_{\mathrm{rel}_1}\lambda(t)}$, as predicted analytically.

In Fig. 6, we report the concentration pulse train generated at a distance of $r_{2m} = 20$nm by the signal emitted by the second presynaptic terminal as function of the time. We adopt the same simulation setting described above, and all the previous consideration continue to hold. Furthermore, since the processing performed by the second presynaptic terminal is different from the one performed by the first presynaptic terminal, the concentration pulse train is different.

4. CONCLUSIONS

In this paper, we proposed a transmitter model for capturing the actual behavior of biological neurons. Specifically, we have modeled the presynaptic terminals as an array of transmitters, with each transmitter characterizing the stochastic filtering performed by a presynaptic terminal. Then, we have analytically characterized the propagation of the presynaptic-filtered signal, and we derived the signaling delay as a function of the distance between the pre- and the postsynaptic neurons. The conducted theoretical analysis, in agreement with the experimental evidences, shows that the neuronal information is encoded in the release patterns of the presynaptic terminals. These patterns, in turns, are driven by and reflects the complex biophysical mechanisms of protein-protein and protein-lipid interactions between the presynaptic and postsynaptic neurons.

5. ACKNOWLEDGMENT

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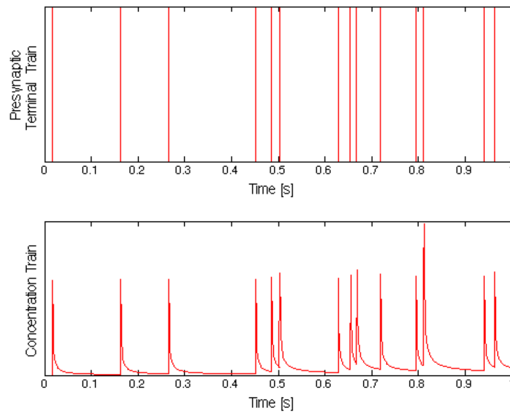

Figure 5: Concentration Pulse Train due to the first Presynaptic Terminal.

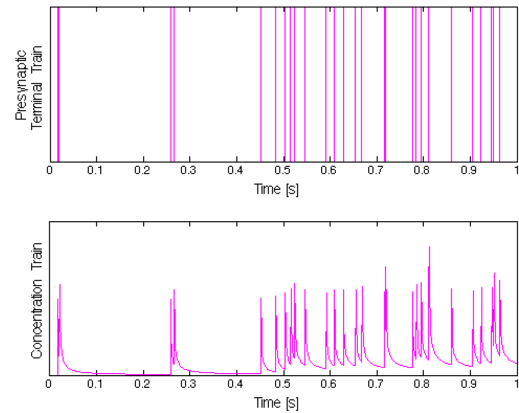

Figure 6: Concentration Pulse Train due to the second Presynaptic Terminal.

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