Communication Theory Aspects of Synaptic Transmission

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Abstract—Biological structures are typically based on molecular communication systems which use a myriad of molecule types to encode messages. Among the cells found in living organisms, interconnected neurons communicate by means of neurotransmitters, particles that serve as physical carriers of information. Owing to information propagation among the nanoscale components, neuronal communication is recently identified as a potential candidate for nano-networking. This paper elaborates on the concept of molecular synaptic transmission between neurons, aiming to give an insight into the performance of physical end-to-end model according to the cell physiology. The synaptic transmission is investigated from several aspects: the transmitter (pre-synaptic terminal), the channel (synaptic cleft), and the receiver (post-synaptic terminal), with a goal to characterize the propagation of the spiking rate function between neurons. Moreover, some ideas on how to incorporate the impact of astrocytic processes to the neuronal communication are presented.

I. INTRODUCTION

Classic electromagnetic communication between futuristic nano-scale electronic devices is hardly feasible unless based on graphene components and carbon nano-tube antennas operating in a terahertz band. Nonetheless, since several biological structures found in living organisms can be considered as nano-machines, a bio-inspired approach [1] of identifying similar architectures can be useful to learn and understand the principles governing their operations and interactions. The most fascinating, complex, and advanced intra-body nano-network is the neuronal nano-network that effectively coordinates and influences the activity of all parts of the body by means of molecular communication between its nodes.

Molecular communication is a promising concept for nano-networking. The molecules are typically emitted following the specific physiological mechanisms. Then, they propagate through a spontaneous diffusion in a (fluidic) medium, and eventually bind to receptors located at the receiver side. Neurons, in particular, generate spike trains of Action Potentials (AP’s), i.e., electrochemical peaks in the cellular membrane potential, in response to chemical inputs collected by dendrites (which serve as an interface to other neurons). The AP’s are propagated to the pre-synaptic terminal down through the nerve fiber called axon (which serves as a communication channel connecting the soma to the pre-synaptic terminal). Then the information propagates to the next interconnected neuron via synapses consisting of the pre-synaptic terminal, and the post-synaptic terminal, separated by the cleft, an extracellular space where molecules diffuse between terminals.

There are some existing work that closely looks at the issue of synaptic transmission from the communication theory perspective [2]–[5]. The multiple-access neuro-spike communication is investigated in [2] focusing on the rate region of synaptic communication channel and its dependence on dynamics of neuronal spiking, vesicle release process, and vesicle pool features. Same authors extended their work [3] computing the ergodic capacity of the synaptic multiple-input multiple-output communication channel, and investigating its performance using the statistical properties of neuronal communication. The pioneering work on synaptic interference channels is also presented in [4], [5]. Unlike the existing literature, this paper examines a diffusion-based molecular communication confined to the synaptic transmission of neurotransmitters between two interconnected neurons, aiming to develop a mathematical framework defining the frequency response of the overall system. In particular, we focus on the bio-hybrid approach [1] capturing the crucial mechanism of calcium signaling and physiological processes to represent the system as a cascade of modules (equivalent circuits) whose frequency responses are of interest. The neuronal anatomy and its communication equivalent representation are shown in Fig. 1. We investigate the components marked in bold. In reality, however, there are various biological processes as well as other adjacent cells that influence the neuronal anatomy.
communication. In the last part of this paper, we present some ideas on how to incorporate the influence of a type of glia cells (non-neuronal cells which actively support the neuronal communication) named astrocytes into our communication equivalent model.

The end-to-end model of the synaptic communication expounded in this paper can be applied in a futuristic perspective to correctly design nano-devices that might serve many purposes. The model also provides a description of the front-end interfaces for devices supporting or replacing damaged or dysfunctional parts of the brain (biomimetic devices and prostheses).

II. SYNAPTIC TRANSMISSION: BIOLOGICAL BACKGROUND

1) Pre-synaptic terminal: When the AP reaches the pre-synaptic terminal, it leads to the opening of Voltage Controlled Calcium Gates (VCCG’s) and a resulting influx of calcium ions, Ca$^{2+}$, into the cellular cytosol. This increases the internal calcium ion concentration $[\text{Ca}^{2+}]_{\text{pre}}$. Then the excess calcium will be absorbed by internal buffers (such as the endoplasmic reticula), with a certain time constant $\tau_{\text{Ca}}$. An increase in $[\text{Ca}^{2+}]_{\text{pre}}$ initiates the chemical mechanisms leading to the release of neurotransmitters, which are molecules that diffuse from one neuron to the other through the synaptic cleft. Neurotransmitters are stored in synaptic vesicles located in the pre-synaptic terminal. The vesicles are transported to the synaptic terminal and attached to the pre-synaptic membrane at release sites.

The probability for neurotransmitter release, $P_{\text{rel}}$, increases when a high frequency spike train or a burst of spikes reaches the pre-synaptic terminal, since $[\text{Ca}^{2+}]_{\text{pre}}$ builds up when many spikes are fired over a short time interval. The relation between $P_{\text{rel}}$ and $[\text{Ca}^{2+}]_{\text{pre}}$ is complicated, and for this reason, no exact mathematical formula has been found at present. One effect that complicates matters is that the effective concentration around vesicle release sites depends on the distance $d$ to the VCCG’s [6]. $[\text{Ca}^{2+}]_{\text{pre}}$ needs to reach levels of about 100 $\mu$M in the vicinity of a vesicle release site for neurotransmitters to be released. If $\text{Ca}^{2+}$ enters at about $d \approx 10$ nm from the vesicle release site, a release of neurotransmitters usually follows, since then $[\text{Ca}^{2+}]_{\text{pre}} > 100$ $\mu$M. If $d$ is larger than about 100 – 200 nm, intracellular buffers will bind most of the calcium before $[\text{Ca}^{2+}]_{\text{pre}}$ gets close to 100 $\mu$M. $P_{\text{rel}}$ is a product of two terms $P_{\text{rel}} = P(\text{Ca}^{2+}) \times P(\text{Ves})$ [7], where $P(\text{Ca}^{2+})$ reflects the $\text{Ca}^{2+}$ binding process (to internal buffers) and $P(\text{Ves})$ reflects the vesicle release process.

2) Post-synaptic terminal: The neurotransmitters that reach the post-synaptic terminal lock onto receptors embedded in the membrane, which then opens and lets a mixture of Na$^+$, K$^+$, and $\text{Ca}^{2+}$ flow through. It affects the amplitude of the Excitatory Post-Synaptic Potential (EPSP) in the receiving neuron. There exists a myriad of neurotransmitter molecules and post-synaptic receptors activated by neurotransmitters, making synaptic communication difficult to be fully comprehended. To simplify the discussion, we only mention the neurotransmitter glutamate and two receptors, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate) and NMDA (N-methyl-D-aspartate).

AMPA is a fast ion-conducting receptor mainly permeable to Na$^+$ and K$^+$. The current through the AMPA receptors is typically given by

$$I_{\text{AMPA}}(t) = G_{\text{AMPA}}(t) \times P_{\text{AMPA}}(t) \times (V_{\text{EPSP}} - E_x),$$

where $G_{\text{AMPA}}$ is a modifiable conductance factor, $P_{\text{AMPA}}(t)$ is the open receptor probability, $V_{\text{EPSP}}$ is the post-synaptic potential, and $E_x$ is the reversal potential of the relevant ion. The rise-time in $P_{\text{AMPA}}$ is almost instantaneous compared to the decay time, $\tau_{\text{AMPA}}$, and so

$$P_{\text{AMPA}}(t) \approx P_{\text{max}} e^{-t/\tau_{\text{AMPA}}}.$$  

NMDA is mainly permeable to Na$^+$, K$^+$ and Ca$^{2+}$ and is significantly slower than AMPA. The NMDA receptors require that both pre- and post-synaptic neurons fire subsequently in order to become fully conductive. This is the main difference between AMPA and NMDA. NMDA activity determines how the conductance of AMPA gates is modified/changed (this process is summarized in [8]). They are therefore essential for long term changes in the synaptic strength (plasticity), which is crucial for memory and learning.

Since plasticity (dynamic wiring of neurons) is not focused here, we analyze the simplified scenario where the conductance of the post-synaptic terminal is mainly determined by AMPA receptors. However, NMDA receptors are essential for communication between astrocytes and neurons as discussed in Section V. The analysis of plasticity is to be pursued in future work.

III. SYNAPTIC TRANSMISSION: THE END-TO-END MODELING

The neuronal signaling is stochastic since spiking times are variable from trial-to-trial even when the same stimulus is applied [8]. To get around this complication, the concept of averaged neuronal behavior is used to transform information about a single input variable, i.e., the stimulus, into a single continuous output variable, i.e. the trial-averaged spiking rate. Hence, we consider the averaged neuronal behavior aiming to define a mathematical framework of synaptic transmission in terms of the frequency response defined for the modules that compose the system. To this end, we inspect the synaptic transmission of neurotransmitters as diffusion-based particle communication.

We assume that the information encoded in a spiking sequence modulates the particle (neurotransmitter) concentration at the transmitter side, i.e., the pre-synaptic terminal. Neurotransmitters then propagate through the synaptic cleft, which contains homogeneous fluidic medium, following the law of diffusion process. At the receiver side, i.e., the post-synaptic terminal, neurotransmitters from the cleft bind to the NMDA and AMPA receptors, and evoke the EPSP. Thereby, the analysis of synaptic transmission is distributed into three modules, namely, the transmitter, the channel,
the receiver. Owing to neurotransmitter propagation through the channel and neurotransmitter reception both being subject to general particle diffusive-based molecular communication paradigm, we adopt pioneering results from [9] to define an overall physical end-to-end model of synaptic transmission.

A. Pre-synaptic Terminal

In the model of synaptic transmission, emission is performed by the pre-synaptic terminal. The pre-synaptic terminal, however, functions as the transceiver module composed of two sub-modules. In this work, we name them as Calcium Gateway (CaG) and Molecular Transmitter (MTx), respectively, as shown in Fig. 2. The CaG sub-module first receives Ca$^{2+}$ (refer to Section II-1) and then enables the succeeding block within the pre-synaptic terminal, i.e., the MTx sub-module, to perform its task of emitting neurotransmitters. Calcium signaling is, thereby, substantial in adequate functioning of the neuronal system.

The spiking sequence is an input to the CaG sub-module, denoted with A in Fig. 2. Its output is the magnitude of calcium ion concentration at the pre-synaptic terminal, [Ca$^{2+}$]$^{\text{pre}}$, which is a result of ionic inward current through VCCG's during a spike. We presume that the sub-module A can be considered as a Linear Time-Invariant (LTI) block with its impulse response $h_A(t)$ depending on the calcium influx as well as the internal buffer uptake. Given the trial-averaged spiking sequence $s(t)$ as input, the average output concentration is given by the convolution [10]:

$$[\text{Ca}^{2+}]_{\text{pre}} = \kappa_1 \int_{-\infty}^{t} h_A(\tau) s(t - \tau) d\tau,$$

where factor $\kappa_1$ converts the convolution result to moles. The neuronal response generates a contribution to [Ca$^{2+}$]$^{\text{pre}}$ proportional to the number of spikes over a given time interval. Since we can replace the trial-averaged neural response function $s(t)$ with the time-dependent spiking rate $r_{\text{spike}}(t)$ within any well-behaved integral [10], we can write

$$\int h_A(\tau) s(t - \tau) d\tau = \int h_A(\tau) r_{\text{spike}}(t - \tau) d\tau,$$

and, equivalently,

$$A(f)S(f) = A(f)R(f),$$

where $A(f)$ is the frequency response of the sub-module A, and $S(f)$ and $R(f)$ are the Fourier transforms of $s(t)$ and $r_{\text{spike}}(t)$, respectively. Hereinafter, the time-dependent spiking rate $r_{\text{spike}}(t)$ is considered as an input to the end-to-end model of synaptic transmission. Owing to limited page resources, we only present the basic concepts applied and the final results of mathematical derivations. Detailed insights are given in [11].

To determine $h_A(t)$ and the corresponding frequency response, two concepts are explored: 1) the dynamics of calcium ion concentration [12], and 2) electrical circuit analysis, where the CaG sub-module is identified with a parallel RC circuit. Namely, in active status (active spiking), there is an elevation in calcium ion concentration due to the influx of Ca$^{2+}$ from the extracellular environment – a process corresponding to the capacitor charging phase. In idle state (spiking silence), there is a depression in calcium ion concentration due to the Ca$^{2+}$ binding performed by intracellular buffers – a process corresponding to the capacitor discharging phase. Hence, we relate the capacitor voltage to concentration and derive the frequency response of analyzed module as

$$A(f) = (1 + j2\pi f R_C C_{\text{Ca}})^{-1}. $$

The resistor and capacitor values are computed as $R_C = \xi \tau_{\text{Ca}} / \nu$ and $C_{\text{Ca}} = \nu / \xi$, respectively, where $\tau_{\text{Ca}}$ is the time constant of Ca-buffer uptake, and $\xi$ and $\nu$ are factors that emerge in derivation and are used to convert from [mole] to [volt] and [mole/second] to [coulombs/second], respectively.

The task of the succeeding MTx block is to modulate the neurotransmitter concentration according to the intracellular concentration level at the preceding block. Given the [Ca$^{2+}$]$^{\text{pre}}$ as an input to the MTx, further modeling, including the neurotransmitter emission, the neurotransmitter propagation through the channel, and the neurotransmitter reception largely resemble the modeling of general molecular communication systems [9]. Depending on [Ca$^{2+}$]$^{\text{pre}}$ as an input to the MTx sub-module, denoted with B in Fig. 2, the neurotransmitters are either released or not from the vesicles. On average,
the output of the MTx sub-module is characterized by the neurotransmitter release rate $r_{\text{pre}}$. Signal $r_{\text{pre}}$ is defined as the time derivative of the neurotransmitter concentration in the proximity of the pre-synaptic terminal, whose level is variable due to the dynamics of neurotransmitters leaving the pre-synaptic terminal. We consider the MTx sub-module as an LTI block and identify with the particle emitter module within the general molecular communication channel [9]. The frequency response of the MTx sub-module is derived as

$$B(f) = (1 + j2\pi f/D)^{-1}, \quad (7)$$

where $D$ is the neurotransmitter diffusion coefficient considered as a constant value for the fluidic medium inside the synaptic cleft.

B. Synaptic Cleft

When the MTx releases the neurotransmitters, they propagate through the synaptic cleft which serves as molecular communication channel. The input of the channel, considered as an LTI system and denoted with $C$ in Fig. 2, is the neurotransmitter release rate $r_{\text{pre}}$. The neurotransmitter concentration at the receiver side (post-synaptic terminal), denoted as $c_{\text{post}}$, is considered as the channel output. Particles follow the rules of the diffusion process to propagate through the channel towards a homogenization, and reach the post-synaptic terminal. The Green’s function $g_d(x,t)$, stemming from the particle concentration distribution flux study, is used to describe the impulse response of the system (see details in [9] and [13]). The vector $x$ contains the three-dimensional space Cartesian coordinates. Hence, the frequency response of the channel module is

$$C(f) = \int_{-\infty}^{\infty} g_d(x_{\text{post}}, t)e^{-j2\pi ft}dt, \quad (8)$$

where $x_{\text{post}}$ contains the Cartesian coordinates of the post-synaptic terminal. Eq. (8) is numerically computed.

C. Post-synaptic Terminal

The post-synaptic terminal acting as the receiver module (considered as an LTI system), senses the neurotransmitter concentration $c_{\text{post}}$ by means of the AMPA and NMDA receptors, which are equally exposed to the $c_{\text{post}}$. As an input to the receiver at the $x_{\text{post}}$, denoted with $D$ in Fig. 2, the neurotransmitter concentration modulates the output referred to as the EPSP, $V_{\text{EPSP}}$. The EPSP is proportional to the ratio of the number of bound chemical receptors (with rate constant $k_b$) over the total number of the receptors $N_R$. As stated in Section II-2, we focus on AMPA receptors and consequently $N_R = N_{\text{AMPA}}$. Owing to proper interpretation of the reception process described with a series RC circuit [9], we derive the following frequency response of the post-synaptic terminal:

$$D(f) = j2\pi f N_R \times (1 + j2\pi f N_R/k_b)^{-1}. \quad (9)$$

IV. Numerical Results

Bode plots confined to the CaG sub-module (module A), the neurotransmitter emission performed by the MTx sub-
module (module B), the neurotransmitter propagation through the channel (module C), and the neurotransmitter reception (module D) are computed for a diffusion coefficient of neurotransmitters (glutamate) $D = 0.3 \ \mu m^2/ms$ [14], synaptic cleft width 20 nm [15], the number of receptors $N_R = 100$, and rate constant $k_b = 10^8 \ \text{M}^{-1}\text{s}^{-1}$ [9]. Results are displayed in Figs. 3, 4, 5 and 6.

The magnitude of module A (Fig. 3) shows non-linear behavior as a function of the angular frequency and monotonically decreases as the frequency increases. From the plot, we observe that module A has an attenuation of 0 dB for the frequencies below the corner frequency ($10^4$ rad/s) which corresponds to a unity pass band gain. High frequency components in $r_{spike}(t)$ above the corner frequency are attenuated by $-20 \ \text{dB}$ per decade. This means that rapid changes in spiking rate do not propagate well to the other neuron, and are hardly detectable. Conversely, slow changes in spiking rate function are detectable at the output. For input frequencies below the corner, the phase angle is close to zero. At corner, the phase angle is $-45$ degrees and then asymptotically approaches $-90$ as the angular frequency increases. The inference about the magnitude and phase angle of modules B and C (Figs. 4 and 6) is similar since they also act as low-pass filters (with significantly lower corner frequencies). Module D, however, acts as a high-pass filter (Fig. 6).

V. EXTENSION TO TRIPARTITE SYNAPSE

In this section we discuss how to extend the proposed model of synaptic transmission including the effects of astrocytes, initially thought to be supporting cells to the neurons, not actively involved in the communication process. However, discoveries made over the last decades have shown that astrocytes play active role in neuronal communications (see [16], [17] for a review).

Astrocytes are a type of glia cells connected in network, located in the extra-neuronal space. Some astrocytes have terminals that are enwrapped around synapses. These synapse-astrocyte entities are named tripartite synapses. In the tripartite system, the neuronal activity affects the astrocytic behavior which, in turn, affects the neuronal behavior. Glutamate released from the pre-synaptic neuron can lock onto metabotropic glutamate receptors (mGluR) on the astrocyte membrane, which further triggers the production of inositol 1,4,5-trisphosphate (IP$_3$). IP$_3$ enables the release of calcium in the astrocytic cytosol [16]. This process is plotted in Fig. 7 using the theoretical models derived in [18]. As the neuronal spiking rate increases, more glutamate is released into the synaptic cleft, which leads to an elevation of IP$_3$ (the dotted line). When the increase in cytosol calcium concentration reaches a certain level, the astrocyte releases glutamate into the extracellular space. These glutamate molecules affect both pre- and post-synaptic terminals in the neighboring neurons.

A. Effect of astrocytic activity on pre-synaptic terminal

A mathematical model of this scenario is derived in [20]. An expression relating the glutamate released from the pre-synaptic terminal, the astrocytic IP$_3$ concentration [IP$_3$]$_{astro}$, and astrocytic calcium concentration [Ca$^{2+}$]$_{astro}$ are derived. On the astrocytic side, glutamate release occurs when [Ca$^{2+}$]$_{astro}$ > [Ca$^{2+}$]$_{astro,\text{threshold}}$. The glutamate molecules are detected by mGluR receptors located on the pre-synaptic terminal. This leads to release of Ca$^{2+}$ inside the pre-synaptic terminal from internal storage facilities (like endoplasmic reticulum), in a similar way as for astrocytes. The result is an elevation of calcium concentration in the pre-synaptic terminal, [Ca$^{2+}$]$_{pre}$ (mGluR). This concentration is added to the one resulting from the spiking activity of the relevant neuron, [Ca$^{2+}$]$_{pre}$ (AP), but has significantly slower dynamics (a time scale of seconds compared to milliseconds for AP induced calcium elevation). The total cytosolic concentration in the pre-synaptic terminal of a tripartite synapse is therefore

$$[\text{Ca}^{2+}]_{\text{pre}} = [\text{Ca}^{2+}]_{\text{pre}}^{(\text{mGluR})} + [\text{Ca}^{2+}]_{\text{pre}}^{(\text{AP})}. \quad (10)$$

Since astrocytes are connected by gap junctions, enhanced levels of calcium in one astrocyte can propagate to other astrocytes (a calcium wave) [19]. This can further affect remote neurons.
From this relation it is clear that the astrocytic activity results in increased pre-synaptic activity that might contribute to enhance the strength of the synapse at the post-synaptic side for a given firing rate. The effect of astrocytes on the pre-synaptic terminal should be included in block A in Fig. 2.

### B. Effect of astrocytic activity on post-synaptic terminal

Glutamate released from astrocytes locks onto NMDA receptors (as well as other slow receptors on the post-synaptic membrane) [21]. This leads to a slow inward current \( I_{\text{astro}} \) on the adjacent neuron through glutamate binding to NMDA receptors. Higher firing rates are observed when compared with rest conditions \( I_{\text{astro}} = 0 \).

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### VI. CONCLUSION

This paper proposes a model of the synaptic transmission based on the fundamentals of communication theory, which can analyze interconnections between neurons through frequency response functions. A future extension of the proposed communication model should take into account the astrocytic effects on the tripartite synapse, both in terms of communication between astrocyte and pre/post synaptic neurons. However, it is important to note that other messengers (molecules) travel between neurons and astrocytes that may both inhibit and exhibit the neuronal behavior. To get the complete picture, we will also have to include the effect of these messengers as well.

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**REFERENCES**


