An Information Theory of Neuro-transmission in Multiple-access Synaptic Channels

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Abstract—Information theory provides maximum possible information transfer over communication channels, including neural channels recently emerged as remarkable for disruptive nano-networking applications. Information theory was successfully applied to quantify the ability of biological sensory neurons to transfer the information from dynamic stimuli. However, a little of information theory has been subjected to quantify the reliability of neuro-transmission between synaptically coupled neurons. Neuro-transmission, regarded as molecular synaptic communication, relays information between neurons and significantly affects the overall brain processing performance. In this study, we use concepts from information theory to provide the framework based on closed-form expressions that quantify the information rate allowing assessment of neuro-transmission when the parameters are provided for any type of neurons. Considering Poissonian statistics and the rate coding model of neural communication, we show how the information transferred between cortical neurons depend on the molecular, physiological and morphological diversity of cells, the firing rate, and the synaptic wiring. With synaptic redundancy, we infer the ability of an isolated post-synaptic neuron to reliably convey information encoded in the spike train from a pre-synaptic neuron. Estimating information rate between neurons primarily serves in the evaluation of the overall performance of biological neural nano-networks and the development of artificial nano-networks.

Index Terms—Channel Capacity, Intra-Body Communications, Neural Nano-Network, Poisson Channel, Synaptic Transmission.

I. INTRODUCTION

Recent advances in microelectromechanical systems (MEMS)/nanoelectromechanical systems (NEMS) and systems biology enable the design of micro/nano-scale devices. This unfolds a new frontier for interdisciplinary signaling techniques, including neural communication potentially used as a paradigm for inter-connecting artificial neural-like micro/nano-scale devices [1], [2], [3]. Micro/nano-scale devices interconnected among themselves and biological neurons create neural-like nano-networks which offer radically new concepts of fine-grained diagnosis and treatment of neural disorders.

Two types of neural signaling mechanisms – action potential transmission and neuro-transmission – are the basis for the remarkable ability of the brain to sense, process, and act upon the environment [4]. Action potentials or spikes (Fig. 1) play a central role in neuron-to-neuron communication by encoding information and propagating electrochemical signals along neurons towards axonal boutons. Neuro-transmission, however, refers to molecular signaling of spike-modulated particles called neuro-transmitters in chemical synapses. A chemical synapse1 links two neurons; in particular, the axonal terminal of a pre-synaptic (transmitting) neuron with the dendrite of a post-synaptic (receiving) neuron. Since multiple axonal terminals typically arise from a single neuron, multiple synapses connect each neuron with adjacent neurons (Fig. 1).

Despite various studies of neuro-transmission in neuro-biological– and computational neuroscience over the last decades summarized in the review paper by Averbeck et al. [5], some basic aspects of signal transduction still remain insufficiently characterized, in particular those pertaining to information processing. Shannon’s information theory has been recently used to quantify the amount of information exchanged among neurons. This mathematical theory of communication classifies information as a measurable quantity: “A basic idea in information theory is that information can be treated like a physical quantity, such as mass or energy” [6]. When applied to neural connections, information theory defines upper limits – the channel capacity – on precisely how much information can be communicated between components of a neural system given any degree of noise contamination.

Information theory initially offered the possibility of comparing quantitatively the function of different neurons and sensory systems. Several studies [7], [8], [9], [10], [11] quantified the ability of sensory neurons to encode dynamic stimuli. These studies are complemented by few studies on neuro-transmission [12], [13], [14], [15] that quantified the ability of post-synaptic neurons to reconstruct the message from pre-synaptic neurons. The work of Manwani and Koch [12] can be seen as the first step in modeling and quantifying the effects of neuro-transmission on information processing. Manwani and Koch derived theoretical lower bounds on the information capacity (few bits per second) of a simple model of the bipartite synapse2. They adopted 1) signal estimation paradigm – which assumes the information encoded in the mean spiking rate/intensity of the pre-synaptic neuron, with the objective to estimate the continuous input signal from the post-synaptic response, and 2) signal detection paradigm – which observes the binary input, with the objective to detect the presence or absence of a pre-synaptic spike from the

1 In the central nervous system, chemical synapses are more common than electrical synapses that connect neurons by gap junctions capable of passing spikes directly, without transduction to neuro-transmitters.
2 The bipartite synapse refers to the functional integration and physical proximility of the pre-synaptic terminal and post-synaptic terminal.
post-synaptic response. Other very relevant papers include work by Akan and co-workers [13], [14], [16], [17], [18], [19] who provided a comprehensive mathematical model of multiple synapses including the stochastic behavior of the input and dynamic nature of the vesicle\(^3\) release process. They derived the achievable rate region for a single bipartite synaptic channel (few hundreds of bits per second) and the channel with 5 synapses (few thousands of bits per second).

The system models and mathematical approaches used in the initial studies of information theory in neuro-transmission are important, yet having limitations in preserving the physiological plausibility. This led to enormous discrepancies between the estimates. In particular, the available studies neglected direct modeling of spontaneous neuro-transmission independent of stimulus-evoked release which is a key regulator of post-synaptic efficacy [20]. Maham and co-workers considered spontaneous action potentials which, from the communications engineering point of view, lead to evoked erroneous vesicle releases [15], [21]. Spontaneous vesicle releases are, conversely, not evoked by action potentials nor spontaneous action potentials. Thereby, spontaneous vesicle releases and evoked erroneous vesicle releases do not refer to the same phenomenon. Note, however, that Maham and co-workers indirectly considered the effect of spontaneous neuro-transmission by referring to the variable quantal amplitude in post-synaptic response to vesicle releases [22], [23]. In addition, the available studies never exposed the dependence in post-synaptic response to vesicle releases [22], [23]. In this study, we use the signal estimation paradigm assuming the rate neural coding at the pre-synaptic neuron [7] to quantify information rates between a pair of synaptically integrated cortical neurons, overcoming the identified limitations in modeling. The rate neural coding is a scheme that assumes all information about the stimulus is contained in the spiking rate of the neuron. Alternative schemes – temporal neural coding, population neural coding and sparse neural coding – are not considered in this study. Our method is different from the other available approaches as the mathematical objective is to estimate the continuous input signal transmitted over a Poisson communication channel from the post-synaptic response. Although the Poissonian nature of synaptic channels was indicated every time the spiking sequence obeyed Poisson statistics, we applied the Poisson channel results to the capacity analysis of a single neural synapse for the first time in our previous work [24]. We now upgrade our previous model by analyzing multiple synapses that link two cells and operate jointly forming the so-called multiple-access synaptic channel shown in Fig. 1. Our aim is to provide the theoretical framework based on closed-form analytical expressions that can be used to evaluate the information capacity between two neurons. The generality of the framework allows assessment of neuro-transmission between any types of neurons when synapses\(^4\). Astrocytes cannot produce spikes and were not initially suspected of playing an important and active role in neuro-transmission. However, astrocytes account for over 70% of all cells in the central nervous system, and are now known to appreciably support neuronal functions through the effect on pre-synaptic calcium concentrations.

In this study, we use the signal estimation paradigm assuming the rate neural coding at the pre-synaptic neuron [7] to quantify information rates between a pair of synaptically integrated cortical neurons, overcoming the identified limitations in modeling. The rate neural coding is a scheme that assumes all information about the stimulus is contained in the spiking rate of the neuron. Alternative schemes – temporal neural coding, population neural coding and sparse neural coding – are not considered in this study. Our method is different from the other available approaches as the mathematical objective is to estimate the continuous input signal transmitted over a Poisson communication channel from the post-synaptic response. Although the Poissonian nature of synaptic channels was indicated every time the spiking sequence obeyed Poisson statistics, we applied the Poisson channel results to the capacity analysis of a single neural synapse for the first time in our previous work [24]. We now upgrade our previous model by analyzing multiple synapses that link two cells and operate jointly forming the so-called multiple-access synaptic channel shown in Fig. 1. Our aim is to provide the theoretical framework based on closed-form analytical expressions that can be used to evaluate the information capacity between two neurons. The generality of the framework allows assessment of neuro-transmission between any types of neurons when synapses\(^4\). Astrocytes cannot produce spikes and were not initially suspected of playing an important and active role in neuro-transmission. However, astrocytes account for over 70% of all cells in the central nervous system, and are now known to appreciably support neuronal functions through the effect on pre-synaptic calcium concentrations.

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the type-specific parameters can be obtained from theoretical or empirical data. In the framework, we account for spontaneous neuro-transmission, expose the dynamics of neuro-transmission to the intracellular calcium concentration, and analyze both bipartite and tripartite synapses. We select the set of theoretical parameters to demonstrate the applicability of the analysis and find that the achievable rates of information transferred between a pre-synaptic neuron and a post-synaptic neuron attain a few tens of bits per second under synaptic redundancy.

The contribution of this study is threefold:

1) The findings and results on neuro-transmission in multiple-access synaptic channels provide an advancement to what we previously reported on neuro-transmission in single-synaptic channels proved to follow Poissonian nature [24]. This shall be of primary importance in understanding the performance of the neural communication as a suitable paradigm for artificial neural-like micro/nano-scale devices.

2) The mathematical method presented in this paper overcome theoretical difficulties to directly apply results from Poissonian channels to multiple-access synaptic channels. From the application point of view, the mathematical method can serve as a core module of the future cognitive brain-machine interfaces and neural prostheses [25], [26], central to monitoring aberrant information transfer over synapses and diagnosing synaptopathies (any dysfunction in synapse structure and physiology that can result in major defects in communication performance between neurons). A potential increase in information transfer between cells above the reference capacity values indicates neuro-developmental disorders (e.g., epilepsy, characterized by increased glutamatergic synaptic transmission) or neuro-degenerative disorders (e.g., Huntington disease, characterized by increased glutamatergic synaptic transmission and deficit of glutamate clearance by the glial cells).

3) The study serves as an additional progressive step in a bottom-up approach of quantifying the information processing power of the brain. In this context, the bottom-up approach initially implies computation of information rates at the basic level of individual synapses and then extends to computations of information rates at the level of multiple synapses, multiple neurons, and, ultimately, the brain. This is a long-standing problem not only in neuroscience but in the wide scientific community.

The remainder of this paper is organized as follows. Section II defines a system model used for capacity computation. Section III presents the fundamental steps taken in the derivation of the core analytical closed-form equations for the computation of the theoretical upper bounds on the capacity of a multiple-synaptic channel. Section IV presents the numerical results. Ultimately, Section V provides concluding remarks including the limitations of the model and study.

II. SYSTEM MODEL

A. System model for single-synaptic Poisson channel

The following briefly reviews the fundamental system model developed for a single-synaptic channel in [24]. In the study of neural information transfer limits, we used a non-homogeneous Poisson impulse process [9, Chapter 3], [10], [11] to describe random placement of spikes. A Poisson process is a mathematical object that consists of points, here spikes, randomly located on a mathematical space. We characterized the process by the firing rate \( \lambda_1 \) proportional only to the stimulus (a rationale is given in [24]). The rate of a Poisson process denotes the average density of the points in the space. We defined the transmitting spiking sequence \( v(t) \) as a non-homogeneous Poisson impulse process

\[
v(t) = \sum_{n=1}^{N_1(t)} \delta(t - t_n),
\]

where \( \delta \) is the Dirac delta function, \( t_n \) is the spike generation time, and \( \{N_1(t) : 0 \leq t \leq T \} \) is a non-homogeneous Poisson process with rate \( \lambda_1(t) \) [9], and

\[
E[N_1(t)] = \int_0^t \lambda_1(u)du.
\]

The operator \( \mathbb{E}[\cdot] \) denotes mathematical expectation.

Signal transduction (from spikes to neurotransmitters) starts upon arrival of individual spikes at axonal boutons/pre-synaptic terminals. The intracellular calcium concentration within a pre-synaptic terminal, driven differently in bipartite and tripartite synapses, modulates the vesicle/neuro-transmitter release. The higher the intracellular calcium concentration, the higher the vesicle release probability \( P_R \). The experimental data from electrophysiological, molecular and imaging studies demonstrated that synaptic terminals set their vesicle release dynamically following beta distribution [27]. This distribution addresses a number of complex physiological mechanisms including the vesicle depletion process.

Owing to the property of splitting non-homogeneous Poisson processes [28], we defined the emitted neuro-transmitter sequence \( x(t) \) injected into the synaptic cleft/channel by the pre-synaptic terminal as a non-homogeneous Poisson process

\[
x(t) = \sum_{n=1}^{N_2(t)} q_n \delta(t - t_n),
\]

where \( q_n \) is the number of injected neuro-transmitters at the time \( t_n \), \( \{N_2(t) : 0 \leq t \leq T \} \) is a non-homogeneous Poisson process [9], and

\[
\mathbb{E}[N_2(t)] = \int_0^t P_R \lambda_1(u)du.
\]

The physiological processes that lead to both evoked and spontaneous releases (e.g., opening of voltage-controlled calcium channels, \( Ca^{2+} \) build-up, soluble N-ethylmaleimide-sensitive factor activating protein receptor (SNARE) complex,
and vesicle docking) are the same. This makes both of them equivalent from the modeling point of view. Hence, we used a non-homogeneous Poisson impulse process to describe random placement of spontaneous vesicle releases. More specifically, we defined the spontaneously emitted (noisy) neuro-transmitter sequence $s(t)$ injected into the synaptic cleft/channel by the pre-synaptic terminal as a non-homogeneous Poisson process

$$s(t) = \sum_{n=1}^{N(t)} q_n \delta(t - t_n),$$  \hspace{1cm} (5)

where $q_n$ is the number of spontaneously injected neuro-transmitters at the time $t_n$. \{ $N(t) : 0 \leq t \leq T$ \} is a non-homogeneous Poisson process with rate $\lambda_0$, normally significantly lower than $\lambda_1$, and

$$\mathbb{E}[N_0(t)] = \int_0^t \lambda_0(u) du. \hspace{1cm} (6)$$

In the molecular synaptic channel, the neuro-transmitter propagation probability $P_P$ addresses the neuro-transmitter diffusion towards the post-synaptic terminal. The diffusion is random and caused by the stochastic nature of the Brownian motion in a fluid medium of synaptic cleft. Based on the existing study in molecular communications, we employ the model where single neuro-transmitter delivery (not binding) is described with the neuro-transmitter propagation probability that follows a Bernoulli distribution [29]. The successful delivery occurs with the probability $P_P$ and failure occurs with the probability $1 - P_P$.

At the receiving post-synaptic neuron, the neuro-transmitter binding probability $P_B$ addresses the ligand-binding mechanism. The ligand-binding mechanism is associated with the binding and unbinding reaction of receptors (e.g., $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor – AMPAR, and N-methyl-D-aspartate – NMDAR) and ligand molecules. In the mechanism, the AMPAR and NMDAR remain in their state, bound or unbound, or change their state by undergoing two possible chemical reactions (the particle binding reaction, if the receptors were unbound to neuro-transmitters, or the particle release reaction, if the receptors were bound to neuro-transmitters) [30], [31]. For the purpose of mathematical validity [24], we modeled the neuro-transmitter binding probability to follow a Bernoulli distribution. The successful binding occurs with the probability $P_B$ and failure occurs with the probability $1 - P_B$.

B. System model for multiple-access synaptic Poisson channel

Due to mathematical simplicity, we assume that all pre-synaptic terminals within a transmitting neuron follow the same dynamics of the spontaneous- and spike-controlled vesicle release. Therefore, $s(t)^{(i)} = s(t)$ and $x(t)^{(i)} = x(t)$, $\forall i \in \{1, \ldots, N\}$, where $N$ is the number of synapses which connect two neurons, as shown in Fig. 2.

Let $S^{(i)}$ be a Poisson-type point process representing the noisy effect of spontaneous vesicle release from the $i$th pre-synaptic terminal. $S^{(i)}$ is then directed by the rate

$$\lambda_0^{(i)}(t) = P_P^{(i)} P_B^{(i)} \lambda_0(t) \hspace{1cm} (7)$$
due to the property of splitting non-homogeneous Poisson processes.

Let $X^{(i)}$ be a Poisson-type point process representing the effect of information signal released from the $i$th pre-synaptic terminal. $X^{(i)}$ is then directed by the spiking-dependent rate

$$\lambda_1^{(i)}(t, \lambda_1) = P_R P_P^{(i)} P_B^{(i)} \lambda_1(t) \hspace{1cm} (8)$$
due to the property of splitting non-homogeneous Poisson processes. In (7) and (8), $P_P^{(i)}$ is the neuro-transmitter propagation probability between the $i$th pre-synaptic terminal and the $i$th post-synaptic terminal, and $P_B^{(i)}$ is the neuro-transmitter binding probability at the $i$th post-synaptic terminal.

For directly opposed pre- and post-synaptic terminals, we model the single synaptic Poisson channel as an additive noise channel as

$$Y^{(i)} = S^{(i)} + X^{(i)}, \hspace{1cm} (9)$$

where $Y^{(i)}$ is the post-synaptic graded potential that arises from the dendritic response to bound neuro-transmitters to the $i$th post-synaptic terminal. We consider excitatory synapses; the graded excitatory potentials are referred to as the Excitatory Post-Synaptic Potentials (EPSPs). $S^{(i)}$ and $X^{(i)}$ in (9) have to be uncorrelated to ensure the mathematical tractability in the following. The uncorrelatedness is valid under the assumption that the noise and signal sources are independent and thus uncorrelated, and the ligand-binding mechanism is either ideal or the neuro-transmitter binding probability $P_B$ follows a Bernoulli distribution. A detailed rationale is given in [24, Section IV-D]. Under these assumptions, the output $Y^{(i)}$ given in (9) is a Poisson-type point process directed by the rate

$$\lambda_2^{(i)}(t) = \lambda_0^{(i)}(t) + \lambda_1^{(i)}(t) \hspace{1cm} (10)$$

where $\lambda_0^{(i)}$ and $\lambda_1^{(i)}$ are the synaptic Poisson channel coefficient between the $i$th pre-synaptic terminal and the $i$th post-synaptic terminal, as shown in Fig. 2.

The post-synaptic neuron integrates multiple received EPSPs increasing the chance of accurately receiving the transmitted spike. If a sufficient number of EPSPs is synchronously integrated/received, the membrane of the post-synaptic neuron depolarizes reaching the spike threshold (Fig. 1). If the spike threshold is reached, the neuron generates a spike. Accordingly, we consider the multiple-access synaptic channel, also referred to as the symmetric Multiple-Input-Multiple-Output (MIMO) synaptic Poisson channel where symmetry stems from the same number of transmitters and receivers, as an additive noise channel with the output point process

$$Y = \bigcup_{i=1}^{N} Y^{(i)} \bigg| \text{thresholding} = \bigcup_{i=1}^{N} \left( S^{(i)} + X^{(i)} \bigg| \text{thresholding} \right), \hspace{1cm} (11)$$

where $Y$ represents the post-synaptic membrane potential, i.e., the received spike train.

Note that $Y^{(i)}$ in (11) are dependent. Chen and Xia [32], however, proved that the sum of dependent point processes still
converges to a Poisson point process. This result allows us to consider \( Y \) as the non-homogeneous Poisson point process, as ‘thresholding’ applied in (11) leads to the effect of thinning or splitting the non-homogeneous Poisson process. Again, the known property of non-homogeneous Poisson processes is that splitting leads to another non-homogeneous Poisson process.

Let \( \lambda_2(t) \) denote the rate of \( Y \). Two factors complicate the calculation of \( \lambda_2 \):

1) \( Y^{(i)} \)s, or more specifically \( X^{(i)} \)s, in (11) are dependent point processes initiated by the same point process at the transmitting neuron (emitted spike train \( v(t) \)); consequently, their rates \( \lambda_2^{(i)} \)s cannot be summed directly determining the rate of the resultant process;
2) \( Y^{(i)} \)s represent EPSPs quantified in millivolts and induced by activities of corresponding pre-synaptic terminals; it is enough that \( M \) EPSPs occur simultaneously at a single patch of the membrane of the post-synaptic terminal to depolarize the membrane from the resting potential and reconstruct the spike sent by the transmitting neuron. Reconstructed spikes are considered as points whose average density defines \( \lambda_2 \).

Since dependency of \( Y^{(i)} \)s and non-linearity in spike reconstruction impede us of defining \( \lambda_2 \) by summing rates \( \lambda_2^{(i)} \) of processes \( Y^{(i)} \)s from (10) and applying ‘thresholding’, we aim to determine \( \lambda_0 \) and \( \lambda_1 \) as the rates of the processes \( \bigcup_j \mathcal{S}^{(i)} \big|_{\text{thresholding}} \) and \( \bigcup_j \mathcal{X}^{(i)} \big|_{\text{thresholding}} \), respectively. We do it in the following section.

### III. Capacity of Multiple-Access Synaptic Poisson Channel

We analyze the information processing limits subject to the rate amplitude constraint

\[
\lambda_2^{(i)} \in [\lambda_0^{(i)} + \lambda_1^{(i)}, \Lambda], \tag{12}
\]

where \( \Lambda \) is the maximum spiking rate at the input, and an average energy constraint

\[
\mathbb{E} \left[ \int_0^T \lambda_2^{(i)}(t)dt \right] \leq (\Lambda_0 + \lambda_0^{(i)})T, \tag{13}
\]
where $\Lambda_0$ is an arbitrary spiking rate, $0 \leq \Lambda_0 \leq \Lambda$, and $T$ is the total transmission time [24].

The capacity computation for the multiple-access synaptic Poisson channel now stems from the capacity formula derived for the single-access Poisson channel, derived in [24]. Namely, both channels have Poisson-type point processes as inputs (the emitted spike train $v(t)$) and outputs. The outputs of a single-access channel and a multiple-access synaptic channel are the Poisson-type point processes that denote EPSP sequences and received spike trains, respectively. The corresponding rates are the key parameters used for the capacity computation for both channels. The analytical formulation of the rate of a received spike train is missing at the moment. Hence, the mathematical problem of capacity computation for the multiple-access synaptic Poisson channel relates to the mathematical problem of computation of the rate $\lambda_2$ of the output Poisson-type point process $Y$ that denotes a received spike train, or, equivalently, $\lambda_0$ and $\lambda'_1$ as the rates of the processes $\bigcup_i S^{(i)}$ and $\bigcup_i X^{(i)}$, respectively, since $\lambda_2(t) = \lambda_0(t) + \lambda'_1(t, t_1)$.

To compute $\lambda'_1$ as the rate of $\bigcup_i X^{(i)}$ representing the information signal, we first count synchronous graded potentials/EPSPs $n^{\text{sync}}$ evoked by the spiking sequence at the membrane of the post-synaptic terminals at the receiving neuron (Fig. 3(a), lower plot). We then relate the resulting potential to the spike threshold. If the threshold is reached, the emitted spike is successfully received contributing to the rate $\lambda'_1$.

The EPSPs are regarded as synchronous as falling in time bins equal to the refractory period (Fig. 3(b)). The refractory period is defined as the time period after spike generation during which a neuron is incapable of or inhibited from repeating a spike. After counting synchronous EPSPs (Fig. 3(c)), we resort to the corresponding density histogram to estimate their distribution (Fig. 3(d)). The minimum number of synchronous EPSPs is zero, obtained when none of the synapses responds; the maximum number of synchronous EPSPs in $N$, obtained when all synapses respond. From Fig. 3(d), we infer that the truncated normal distribution for $0 < n^{\text{sync}} < N$ given by

$$f_1(n^{\text{sync}}; \mu_1, \sigma_1) = \frac{f_N(n^{\text{sync}}; \mu_1, \sigma_1)}{F_N(N|\mu_1, \sigma_1) - F_N(0|\mu_1, \sigma_1)}, \tag{14}$$

and 0 otherwise, adequately describes the density histogram. In (14), $f_N$ is the standard normal distribution and $F_N$ is its cumulative distribution function

$$F_N(x|\mu, \sigma) = \frac{1}{2} \left(1 + \text{erf} \left( \frac{x - \mu}{\sigma \sqrt{2}} \right) \right). \tag{15}$$

The mean $\mu_1$ and variance $\sigma^2_1$ intuitively follow from the system model as

$$\mu_1 = \mathbb{E} \left[ P_{R \theta}^{(i,i)} \right] N \approx \mathbb{E} \left[ P_R \right] \mathbb{E} \left[ P_R \right] \mathbb{E} \left[ P_{R \theta} \right] N, \tag{16}$$

$$\sigma^2_1 \propto \mu_1, \tag{17}$$

where $\sigma^2_1$ is the variances of the truncated normal distribution that is derived from a normally distributed random variable by bounding the random variable from below and above.

respectively, where $\propto$ in (17) denotes proportionality. In our scenario, we set $\sigma^2_1 = \mu_1$.

Since the receiving neuron reconstructs the erroneous spike when the number of synchronous erroneous EPSPs reaches the threshold $(n^{\text{sync}} \geq \text{threshold})$, we now define the rate $\lambda'_0$ of the process $\bigcup_i X^{(i)}$ owing to the property of splitting the non-homogeneous Poisson processes as

$$\lambda'_0(t) = \left(1 - F_1(\text{threshold} | \mu_1, \sigma_1)\right) \lambda_1(t), \tag{18}$$

where $1 - F_1(\text{threshold} | \mu_1, \sigma_1)$ defines the down-scaling factor as a surface under the probability density function (\leq 1), $F_1$ is the cumulative distribution function of $f_1$ given as

$$F_1(n^{\text{sync}}; \mu_1, \sigma_1) = \frac{F_N(n^{\text{sync}}; \mu_1, \sigma_1) - F_N(0|\mu_1, \sigma_1)}{F_N(N|\mu_1, \sigma_1) - F_N(0|\mu_1, \sigma_1)}. \tag{19}$$

For highly reliable synapses, $F_1(\text{threshold} | \mu_1, \sigma_1) \approx 0$, implying $\lambda'_0(t) \approx \lambda_1(t)$, as should be.

Similarly, to compute $\lambda_0$ as the rate of $\bigcup_i S^{(i)}$ representing the noise from the spontaneous release, we count synchronous potentials/EPSPs $n^{\text{sync}}$ evoked by the spontaneous vesicle release (erroneous EPSPs) at the membrane of the post-synaptic terminals of the receiving neuron in time bins equal to the refractory period. If the threshold is reached, the erroneous spike is received contributing to the rate $\lambda_0$. After counting synchronous erroneous EPSPs, we resort to the corresponding density histogram to estimate their distribution. The minimum number of synchronous erroneous EPSPs is zero, obtained when none of the synapses erroneously responds; the maximum number of erroneous synchronous EPSPs in $N$, obtained when all synapses erroneously respond. From Fig. 3(d), we infer that the truncated normal distribution $f_0(n^{\text{sync}}; \mu_0, \sigma_0)$, defined as in (14), adequately describes the density histogram. As evidence, we use “visual comparison” between the truncated normal distribution and non-parametric Epanechnikov kernels that are optimal in a mean square error sense (also refer to Fig. 5(a)–Fig. 5(c)). The mean $\mu_0$ and variance $\sigma^2_0$ intuitively follow from the system model as

$$\mu_0 = \lambda_0 \tau N, \tag{20}$$

$$\sigma^2_0 \propto \mu_0, \tag{21}$$

respectively, where $\tau$ is the refractory period given in seconds. In our scenario, we set $\sigma^2_0 = \mu_0$.

Since the receiving neuron reconstructs the erroneous spike when the number of synchronous erroneous EPSPs reaches the threshold $(n^{\text{sync}} \geq \text{threshold})$, we now define the rate $\lambda'_0$ of the process $\bigcup_i S^{(i)}$ owing to the property of splitting the non-homogeneous Poisson processes as

$$\lambda'_0(t) = \left(1 - F_0(\text{threshold} | \mu_0, \sigma_0)\right) \lambda_0(t), \tag{22}$$

where $F_0$ is the cumulative distribution function of $f_0$, defined as in (14). For highly reliable synapses, $F_0(\text{threshold} | \mu_0, \sigma_0) \approx 1$, implying $\lambda'_0(t) \approx 0$, as should be.
Ultimately, the rate of the output process $Y$ is given as

$$
\lambda_2(t) = \lambda_0(t) + \lambda_1^s(t, \lambda_1) = (1 - F_0(\text{threshold} | \mu_0, \sigma_0)) \lambda_0(t) + (1 - F_1(\text{threshold} | \mu_1, \sigma_1)) \lambda_1^s(t). \tag{23}
$$

In our previous work [24], we defined the upper bound on information capacity for the $i$th bipartite single-synaptic Poisson channel, where the spontaneous vesicle release is constant, as [24]:

$$
\mathcal{C}_{\text{bipartite}}^{(i)} = \max_{0 \leq \eta \leq 1} \mathbb{E} \left[ \eta \phi(P_{R\alpha^{(i,i)}} \Lambda) - \phi(\eta P_{R\alpha^{(i,i)}} \Lambda) \right], \tag{24}
$$

where the expectation is taken over the distribution of the random variable $P_{R\alpha^{(i,i)}}$, $\eta$ is the probability of the channel input taking the value $\Lambda$, $\zeta$ is the ratio of average-to-peak power, $0 \leq \zeta \leq 1$, and

$$
\phi(x) = \ln \left( \alpha^{(i,i)} \lambda_0(x) + x \right) - \ln \left( \alpha^{(i,i)} \lambda_0 + x \right), \tag{25}
$$

We now define the upper bound on information capacity between two neurons for the bipartite multiple-access Poisson synaptic channel with constant spontaneous vesicle release $\lambda_0$. Replacing the rate of the output $P_{R\alpha^{(i,i)}} \Lambda$ in (24) with the rate $(1 - F_1(\text{threshold} | \mu_1, \sigma_1)) \Lambda$, and the rate of the noise $\alpha^{(i,i)} \lambda_0$ in (24) with the rate $(1 - F_0(\text{threshold} | \mu_0, \sigma_0)) \lambda_0$, we obtain (26) where the expectation is taken over the distribution of the random variable $P_{R\alpha^{(i,i)}}$, $\eta$ is the probability of the channel input taking the value $\Lambda$, $\zeta$ is the ratio of average-to-peak power, $0 \leq \zeta \leq 1$, and
\( C_{\text{bipartite}} = \max_{0 \leq \eta \leq \xi} \mathbb{E} [\eta \phi ((1 - F_1(\text{threshold} | \mu_1, \sigma_1)) \Lambda) - \phi (\eta (1 - F_1(\text{threshold} | \mu_1, \sigma_1)) \Lambda)] \) \( \text{(26)} \)

\[ \phi(x) = \ln \left( (1 - F_0(\text{threshold} | \mu_0, \sigma_0)) \lambda_0 + x \right)^{(1-F_0(\text{threshold} | \mu_0, \sigma_0))\lambda_0 + x} \]

\( \ln (1 - F_0(\text{threshold} | \mu_0, \sigma_0)) \lambda_0 (1 - F_0(\text{threshold} | \mu_0, \sigma_0)) \lambda_0 \)

(27)

\( \phi(x) \) is given in (27).

In our previous work [24], we also defined the upper bound on information capacity for the \( i \)-th tripartite single-synaptic Poisson channel, where the spontaneous vesicle release is time-varying owing to additional contribution to the intracellular calcium concentration within the \( i \)-th pre-synaptic terminal due to the astrocytic feedback, as [24]

\[ C_{\text{bipartite}}^{(i)} = \frac{1}{T} \int_0^T \mathcal{C}_{\text{bipartite}}^{(i)}(\lambda, \Lambda, \eta)dt , \]

(28)

where \( C_{\text{bipartite}}^{(i)} \) is given in (24).

We now define the upper bound on information capacity between two neurons for the tripartite multiple-access Poisson synaptic channel with time-varying spontaneous vesicle release \( \lambda_0(t) \). Replacing the \( C_{\text{bipartite}}^{(i)} \) in (28) with \( C_{\text{bipartite}} \) given in (26), we obtain

\[ C_{\text{triptite}} = \frac{1}{T} \int_0^T C_{\text{bipartite}}(\lambda, \Lambda, \eta)dt . \]

(29)

The core equations given in (26) and (29) are derived under the assumption that the post-synaptic terminals have perfect Channel State Information (CSI) while the pre-synaptic terminals have no CSI. The assumption of CSI is pivotal for the mathematical tractability of the method. The optimal solution to the problem imposed in this study would be to derive the upper bound on information rate when neither the pre- and post-synaptic terminals have the CSI. Nonetheless, the unknown closed-form bound without CSI at present impedes us from finding more exact capacity bounds for multiple-access synapses. In addition, we prefer having known CSI at the post-synaptic sides over having perfect CSI at both the pre- and post-synaptic sides; the former is more likely to be the tightest upper bound.

The core equations given in (26) and (29) largely resemble equations derived by Chakraborty and Narayan in the analysis of optical channels with fading [33] and Frey in the analysis of optical channels with random noise rate [34], respectively. This resemblance stems from the assumption to describe both synaptic- and optical channels as Poisson channels.

### IV. Numerical Results

We developed the simulation framework in MATLAB 2017a (MathWorks) according to the system model given in Section II and the parameter set given in Table I. In the framework, we characterize the emitted spike train by a firing rate proportional to the stimulus. Accordingly, Fig. 4(a)–Fig. 4(c) (top-row plots) reproduce the samples/realizations of spike trains by firing rates proportional to the constant stimulus. Similarly, Fig. 4(d)–Fig. 4(f) (top-row plots) reproduce the realizations of spike trains by firing rates proportional to a sine wave.

Let us first focus on the transmission of these spike trains over the multiple-synaptic channel with \( N = 100 \) bipartite synapses [35]. This means 100 transmitting pre-synaptic terminals and 100 receiving post-synaptic terminals. Note that the number of synapses linking each neuron to adjacent neurons reaches thousands, additionally complicating matters in real neural circuits. In the framework, we assumed an instantaneous stimulus-evoked neuro-transmitter release from pre-synaptic terminals synchronous with spikes. Without any loss of generality, we simulate synapses where neuro-transmitters do not spill-over due to the random Brownian motion, pull back into the pre-synaptic neuron through re-uptake, or metabolize by enzymes due to unbinding to available receptors. In other terms, we set the neuro-transmitter propagation- and binding probabilities to unity (\( P_H = P_B = 1 \)), implying even tighter upper bounds for realistic synapses from the ones that follow.

Fig. 4(a)–Fig. 4(c) (middle-row plots) and Fig. 4(d)–Fig. 4(f) (middle-row plots) visualize the corresponding EPSP raster-plots\(^7\) (with EPSP timings), given the dynamics of neuro-transmitter release from pre-synaptic terminals follows the beta probability density functions in Fig. 4(g)–Fig. 4(i).

\(^7\)A raster-plot is a graphic representation of occurrences/events in a temporal relation, here used to represent the activity of a group of post-synaptic terminals.
The EPSP in raster-plots indicate responses of post-synaptic terminals. Its density is intuitively proportional to the spiking rate, the spontaneous neuro-transmission rate, and the vesicle release probability. EPSPs travel just a short distance along the membrane at post-synaptic terminals and diminish as they spread, eventually disappearing. Since they have an additive effect, we consider only synchronous EPSPs as relevant for the reconstruction of emitted spikes. EPSPs considered as synchronous can be mutually delayed in reality, but must fall in same time bins (here equal to the refractory period). In
addition, we consider a mean value of EPSPs since evoked potentials do not come in just one size but rather in a range of slightly different sizes, or gradations. EPSPs are quantified in millivolts. Multiple synchronous EPSPs result in greater membrane depolarization from the resting potential ($\approx -90$ mV) to the threshold ($\approx -70$ mV). We set the mean EPSP value to 0.67 mV implying that approximately 30 synchronous EPSPs are enough to occur at a single patch of the membrane of the post-synaptic terminal to reconstruct the spike [36]. Given the EPSP raster-plots, we count the synchronous EPSPs from spikes and spontaneous release independently, as explained in Section III, and reconstruct the spikes at the receiving neuron. Fig. 4(a)–Fig. 4(c) (bottom-row plots) and Fig. 4(d)–Fig. 4(f) (bottom-row plots) show the received spike trains corresponding to the analyzed scenarios.

Let us now focus on the information processing limits of the considered pair of neurons. We use the closed-form mathematical equation (26) to examine the upper bounds on information rate that can be transferred reliably over the multiple-synaptic channel. Eq. (26), however, uses truncated normal distributions which estimate the probability histograms of synchronous EPSPs from spikes and spontaneous release. Fig. 5(a)–Fig. 5(c) show the density histograms and estimated truncated normal probability density functions corresponding to the raster-plots from Fig. 4(a)–Fig. 4(c) (middle-row plots). As a reference, we fit the obtained density histograms by Epanechnikov kernels. These kernels are non-parametric representations of the probability density function. They are optimal in a mean square error sense. Fig. 5(d)–Fig. 5(f) show the computed upper bounds on information rate using truncated normal distributions (solid lines), and numerically computed upper bounds on information rate using Epanechnikov kernels (dashed lines), evaluated as functions of the peak spiking rate $\Lambda$. We observe that the information rate first increases exponentially and then saturates for high peak spiking rates (approximately 20 spikes per second). For the analyzed scenario, we also observe the low level of discrepancy between the analytical and numerical results. This success implies the initial validity of our mathematical method.

Beside emitted spiking rates, the upper bounds on information rate depend on the molecular cell properties that drive dynamics of stimulus-evoked and spontaneous neurotransmission. Fig. 6(a)–Fig. 6(c) show the more detailed dependence of the capacity upper bound on the stimulus-evoked dynamics directed by beta probability density functions shaped by parameters $\alpha$ and $\beta$. From the result, we infer that the capacity increases with the first-order moment of the distribution of the vesicle release. The first-order moment of beta distribution increases with $\alpha$ and decreases with $\beta$. In other terms, when emitted spikes do not reliably trigger a neuro-transmitter release, then the capacity severely suffers.

Finally, Fig. 7(a)–Fig. 7(c) show the dependence of the capacity upper bound on the number of synapses $N$. From what we observe, the multiple-access synaptic system, in the neural system also referred to as the symmetric MIMO system, obviously profits in terms of information transfer with increased synaptic redundancy. In terms of the communications engineering terminology, we infer that neurons successfully adopt a form of diversity technique to send the same information via multiple pre-synaptic terminals across independent synaptic channels, compensating for channel imperfections. Sending multiple copies of the same signal across independent channels, and having a different amount of distortion suffered by each copy, neurons clearly increase the chances of accurately receiving the transmitted information. Ultimately, the upper bounds on information rate depend on the electrophysiological properties that affect the amplitudes of graded potentials at the membrane of the post-synaptic neuron. Fig. 7(d)–Fig. 7(f) show the dependence of the capacity upper bound on the mean EPSP voltage varied from 0.5 mV to 2 mV [36]. The inverted U-shaped capacity isolines indicate that the capacity first increases with an increase in the mean EPSP voltage, but then decreases: if the mean EPSP is too small, then more synchronously received EPSPs are required at the membrane of the receiving neuron to trigger post-synaptic spikes, decreasing chances of reconstructing information spikes; conversely, if the mean EPSP is too big, then less synchronously received EPSPs are required at the membrane of the receiving neuron to trigger post-synaptic spikes, increasing chances of reconstructing erroneous spikes.

From the presented results, we infer that unreliable multi-access synaptic Poisson channels transfer information rates up to few bits per second. More reliable multi-access synaptic Poisson channels transfer information rates up to a few tens of bits per second. According to Shannon’s channel coding theorem [6], at transmission rates below the computed values, arbitrarily high reliability of neuro-transmission is achievable using specific neural coding and decoding schemes. At transmission rates above the computed values, arbitrarily high reliability is impossible, no matter how sophisticated the transmitter and receiver are. In other terms, the capacity is characterized by the maximum number of spike trains that neurons can select and transmit over synapses, such that the receiving neurons, based on the received trains, can detect/determine without error.

Although the presented estimates are significantly less than what has been reported previously, it is not instructive to directly compare the presented values with the values from the literature as the underlying system models are very different.

V. CONCLUDING REMARKS

In the present paper, we proposed an extended mathematical framework for computation of the upper bounds on information capacity over multiple-access synaptic channels. The proposed framework builds on the mathematical framework for computation of the upper bounds on information capacity over a single synaptic channel already presented in [24]. Employing the set of theoretical parameters, we computed the upper bounds on information capacity over multiple-access synaptic channels that link two isolated cortical neurons to reach a few tens of bits per second. These estimates, even loose stemming from the reliable transmission of neuro-transmitters through the channel and binding to receiving receptors set in the simulation framework, are significantly less than what has been reported in the available literature. Nonetheless,
Fig. 5. (a)-(c) The density histograms corresponding to Fig. 4(a)–Fig. 4(c) (middle-row plots), respectively, and estimated truncated normal probability density functions of synchronous EPSPs compared to Epanechnikov kernels; the mean EPSP voltage is set to 0.67 mV. (d)-(f) Upper bounds on information rate as functions of the peak spiking rate computed from equation (26) using truncated normal distributions and Epanechnikov kernels from Fig. 5(a)–Fig. 5(c), respectively.

Fig. 6. Effects of the vesicle/neuro-transmitter release probability density function directed by parameters $\alpha$ and $\beta$ on the upper bound on information rate: The peak spiking rate is 50 spike/s, the refractory period is 10 ms, the mean EPSP voltage is 0.67 mV, the average rate of the spontaneous release is 5 vesicle/s, and the synaptic size (number of synapses) is: (a) 50, (b) 100, and (c) 200.

unreliable neuro-transmitters propagation and binding are adequately addressed in the system model. The developed framework possesses generality that allows assessment of neurotransmission between any types of cortical neurons based on theoretical- and experimental data sets.

In terms of limitations, we underline that the considered synaptic setup deviates from the realistic synaptic setup. In ordinary cortical circuits, synapses normally span from the transmitting neuron to multiple receiving neurons, not only one as considered here. In other terms, we developed the multiple-access synaptic model for a single-input-single-output neural model. This model deviates from the multiple-access synaptic model for a single-input-multiple-output neural model. In addition, the considered setup does not address the effect of residual neuro-transmitters in synaptic cleft that eventually bind to the post-synaptic terminals affecting graded potentials that originate from both evoked and spontaneous vesicle releases. Inclusion of the effect of the residual neuro-transmitters would impose significant modification of the derived analytical results. In the context of the presented study, this remains an open issue. Finally, specific synapses in ordinary cortical circuits have very special properties, e.g., feed-forward and recurrent synapses, that deviate from regular synapses considered here. These deviations would make the estimations of a number of bits transmitted per seconds unreliable. However, for the practical application in nano-networking, the model
can be considered as adequate as we expect miniature artificial devices to interconnect with one adjacent entity at first.

Ultimately, we point out that our ongoing project is to back-up the numerical- and simulation results with experimental data. The experimental data providing a set of signaling-related parameters required for the closed-form equations derived here is missing in the available literature. Hence, we were not able to provide such comparisons in this paper and additionally verify the theory.

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