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Nanomachine-to-Neuron Communication Interfaces for Neuronal Stimulation at Nanoscale

Fabio Mesiti and Ilangko Balasingham, Senior Member, IEEE

Abstract—The recent advancements in nanotechnology have been instrumental in initiating research and development of intelligent nanomachines, in a variety of different application domains including healthcare. The stimulation of the cerebral cortex to assist the treatment of brain diseases have been investigated with growing interest in the past, where nanotechnology offers a dramatic breakthrough. In this paper, we discuss the feasibility of a nanomachine-to-neuron interface to design a nanoscale stimulator device called synaptic nanomachine (SnM), compatible with the neuronal communication paradigm. An equivalent neuron-nanomachine model (EqNN) is proposed to describe the behavior of neurons excited by a network of SnMs. Sample populations of neurons are simulated under different stimulation scenarios. The assessment of the existing correlation between SnM stimulus and response, as well as between neurons and clusters of neurons, has been performed using statistical methods. The obtained results reveal that a controlled nanoscale stimulation induces apparently an oscillatory behavior in the neuronal activity and localized synchronization between neurons. Both effects are expected to have the basis of important cognitive and behavioral functions such as learning and brain plasticity.

Index Terms—Nanomachines, neurons, neuronal stimulation, nanomachine-neuron interface, synchronization.

I. INTRODUCTION

A long time has passed from the first conceptual vision of a nanoscale technology capable to interact with the invisible elements of matter, and the Feynman’s prediction “There’s a plenty of room at the bottom” in 1959 is not anymore an abstract thought. Carbon nanotubes, nanowires or nanoparticles are nanoscale objects which offer novel solutions in energy production, pollution control, and plant monitoring. Nanomedicine and nanoscale drug delivery mechanisms, designed ad-hoc for a specific patient and disease, are expected to become feasible in ten to fifteen years, promising more effective therapies. In recent years, engineering applications of nanotechnology have also been investigated with increasing interest for the design of bio-inspired intelligent nanodevices or nanomachines connected in a network [1] for passive sensing or active tasks operating in a biological environment. Synthetic molecular motors [2] and molecular diffusion [3], have been recently proposed for communication between nanomachines, along with innovative nanonetworking protocols [4]. Energy harvesting (piezoelectric nanogenerators, vibrations transduction [5]) and chemical techniques (ATP synthesis and enzymatic bio-fuel cells [6]) are viable methods to store energy at nanoscale. A wireless nanotransmitter prototype, powered by nanogenerators, has been recently unveiled in [7] where the transmitted signal is detected by an external radio device, confirming that efficient nanodevices are nearly feasible.

According to the advances in nanotechnology and nanocommunications, a design strategy for intelligent nanodevices interfaced with the neuronal tissue is proposed in this paper. Neuron cells are organized in complex anatomical and functional networks [8], where neuronal links can turn inefficient because of a neurodegenerative disease. Invasive and non-invasive stimulations of the cerebral cortex have been considered in the past, with increasing interest, for the treatment of mental disorder and depression, with promising benefits also in Parkinson and Alzheimer [9], [10], [11]. However, a nanoscale device is expected to achieve a more advanced and precise neuronal stimulation at cellular level. A first characterization of neuron-to-nanomachine communications has been recently illustrated [12], indicating the recent and increasing interest on this research issue.

In our paper, we first define a conceptual neuronal nanomachine acting at cellular level, with the main aim of employing nanodevices to assist or restore not working neurons. Then, possible solutions for a machine-to-neuron interface are presented along with a theoretical scheme, supported by computer simulations to investigate the impact of a nanomachine-based stimulation in typical neuronal networks. The paper outline is as follows. In Section II, the cortex anatomy is described, while Section III shows the feasibility of machine-to-neuron interfaces. In Section IV the equivalent neuron-nanomachine scheme is illustrated, whereas in Section V a base-scenario for the proposed simulations is pointed out. Section VI describes the statistical methods used to explain the results reported in Section VII. Section VIII draws the final considerations.

II. ANATOMY OF THE NEURONAL SYSTEMS

The neuronal system of humans and animals is a complex structure where connected groups of neuron cells cooperate to regulate the functions of the organism. Impressive amounts of electrochemical inputs signals, coming from the peripheral parts of the body, are collected, decoded and processed by the cerebral cortex with high accuracy. Before presenting the proposed nanomachine-to-neuron interface, in what follows we describe important concepts from neuroscience to capture the biological aspects of neurons.
A. Single Neuron

The neuron cell is the smallest processing unit of the cortex and can be compared to an electronic transceiver which integrates and processes several inputs, to produce an output signal [12],[13]. The typical anatomical structure is depicted in Fig. 1 where the core and the terminals are shown. The output neuronal response is described by a time-varying membrane potential, typically around -65 mV, characterized by short peaks called Action Potentials (APs) or spikes, regarded as binary source of information ('1' = spike, '0' = no spike). The dynamics of the spike trains can be described by mathematical models with different level of complexity (Integrate & Fire (IF) and Hodgkin-Huxley (HH) are the most popular [14]). The main communication channel for the propagation of APs is the axon, which connects the neuronal terminals of different cells in a junction called synapse, which can be electrical (gap junction), when the membranes of two neurons are in physical contact, or chemical, when the input signals cause a release of neurotransmitters which bind to receptors on the receiving neuron. The resulting end-to-end communication is based on: 1) a transmitting presynaptic neuron; 2) the communication axonal channel; 3) the synaptic junction with the receiving postsynaptic neuron.

B. Population of Neurons

The cortex is organized in anatomical and functional clusters of neurons [8] with highly specialized tasks (segregation), which cooperate for high level functions (integration). Then, the overall network response is determined by populations of neurons and their connectivity map. Resorting to graph theory, neurons (nodes) are linked by axonal strains (edges) with variable synaptic strengths (weights) giving rise to topologies ranging from random networks, when the number of edges per node is randomly distributed, to small-world networks, when neurons aggregated in a cluster are strongly connected each other (high clustering, CL) but less frequently with cells of different clusters (short path-length, PL). An important observation is that a small-world topology well describes the brain structure [8] and recent experiments observed a loss of cluster-to-cluster connectivity (increased path-length) in brains affected by Alzheimer’s disease [15].

III. NEURON-NANOMACHINE COMMUNICATION

The neuron size ranges from 4 to 100 μm (1 μm = 10^-6 m) which appears extremely small but from the molecular point of view, “there is a plenty of room” to place nanoscale devices for stimulation tasks. Two main classes of techniques have been conducted in the past for brain stimulation [11]:

- Invasive: an electric current is directly injected in the neuronal tissue with electrodes;
- Non-invasive: electromagnetic or magnetic fields (EMF/MF) excite the cellular structure.

A third class is suggested and discussed in this paper, based on the deployment of autonomous or coordinated nanomachines in the neuronal tissue, to directly apply or indirectly induce a stimulus on the cerebral cortex. The neuron is a biological computational unit with presynaptic input terminals, processing unit and postsynaptic output terminals [13]. Following this scheme, a well suited location to place a nanomachine-to-neuron interface is the input side, where signals from other cells are received. From now on, we call this conceptual device synaptic nanomachine, identified with the symbol \( SnM \), to emphasize the bio-inspired similarities with the synaptic junction.

The output of each neuron depends on the cellular membrane, a bi-layered structure where the concentration of ions \((K^+, Na^+, Ca^{2+}, Cl^-)\) outside and inside the cell is balanced by dynamic ion channels [14], [16]. The mobility of ions through open channels generates inwards and outwards currents which affects the total membrane potential. To put it simple, the activation of the channels is delegated to the synaptic junctions, where each presynaptic signal is converted in a proportional variation of potential in the postsynaptic membrane, called postsynaptic potential (PSP). When positive, the membrane is depolarized and an Excitatory PSP (EPSP) occurs. On the contrary, a negative variation hyperpolarizes the membrane and the PSP is Inhibitory (IPSP). To facilitate the reading, a list of symbols most used in this paper is provided in Tab. I. When the summation of all EPSPs and IPSPs amplifies the potential above a physiologic threshold, a postsynaptic spike is generated. The task of SnMs is the activation of postsynaptic ion channels in the target cells, evoking multiple PSPs which properly drive the output potential. We summarize our reasoning as follows:

1) One or more SnMs connected to target neurons;
2) Each SnM emulates a synaptic junction, opening postsynaptic channels;
3) The flow of ions through the channels generates multiple EPSPs (IPSPs);
4) The firing activity of the target neuron is enhanced (inhibited).

In the literature, diverse efforts to interface the neuron’s body with synthetic nanoscale materials have been reported. In [17] the authors describe the successful attempt to interface nanowire (NW) FET transistors (SiNW-neurons) with soma, dendrites and axon, allowing high precision measurement and stimulation with an array of 50 NW connections per neuron. The synthesis of ion channels and pores, assembled artificially by chemical composition have been reported in [18], whereas
synthetic nanoscale actuators (nanotoggles, nanokeys and nanotweezers) to manipulate ion channels are proposed in [19]. Hence, the advances in the molecular manipulation of the matter can allow the fabrication of bio-inspired SnM interfaces. Upon these considerations and the available nanotechnology, we identify a set of possible SnM interface implementations, as elaborated further in what follows.

A. Gap Junction Interface

With gap junctions, two cellular membranes in direct contact are separated by only 3 nm and for each side, clusters of connexines (Cx36) proteins [20], combine to form a channel with diameter 1-2 nm, the connexone, allowing bidirectional flows of ions (currents) between cells. Synthetic connexines assembled in-situ by SnMs could allow the opening of additional ion channels on the membrane, enhancing the neuronal activity. In Fig. 2, a sample scenario with multiple SnMs attached to the target neuron is depicted. This method is motivated and supported by neuroscientific studies [21], [22] reporting the important role of gap junctions in oscillatory behaviors and synchronization phenomena between neurons.

B. Molecular Interface

In chemical synapses, each presynaptic impulse enables the release of transmitter molecules which diffuse across the synaptic connection and bind to receptors on the postsynaptic neuron, activating the opening of ion channels. The molecules propagation can be modeled with three processes [3]: 1) emission, where the particles concentration is regulated by driving input signals; 2) diffusion through the biological environment; 3) reception. According to this paradigm, the release process can be enhanced using a set of SnMs to synthesize suitable neurotransmitters, which diffuse in the target synaptic connections and enable the opening of ion channels.

C. Direct Current

An alternative method is the direct current injection on the target membrane with nanostimulators, emulating the biology of the presynaptic input signals and to enhance the firing activity. However, nanoscale devices are expected to rely on a very limited amount of energy, insufficient to generate APs with high amplitude (around 30-100 mV [14]). On the other hand, the injection of multiple low-amplitude PSP contributions (20-50 times smaller than AP), can be a more realistic technique for feasible implementations of low-energy nanostimulators.

IV. Equivalent NEURON-NANOMACHINE SCHEME

To analyze the relationships between the SnM and the neuronal response, we provide a conceptual scheme which describes the PSP contributions generated by the machines on the target neuron, independently from the implementation method. To this purpose, a generalized model to capture the temporal behavior of the neuron membrane potential, as a function of the past activity, and the input pattern, is the Spike Response Model (SRM) [23]. In the simplified version, SRM0 [23], the dependence on the past is neglected and the response only depends on the last input. The general SRM0 expression of the potential \( u_i(t) \) for \( N_s \) presynaptic inputs is:

\[
\begin{align*}
  u_i(t) &= \eta(t - \hat{t}_i) + h_i(t) \\
  h_i(t) &= \sum_{j=1}^{N_s} \omega_{ij} \sum_k c_0(t - t_j^{(k)}) + \\
  &+ \int_0^\infty \kappa_0(s) I_e(t-s) ds
\end{align*}
\]  

(1)

where the index \( j \) refers to presynaptic inputs and \( i \) is the postsynaptic (target) neuron, connected by a link of weight \( \omega_{ij} \). The temporal instants \( t_j^{(k)} \) are the \( k \)-th spiking times of the \( j \)-th presynaptic neuron, whereas the response kernels \( \eta, c_0 \) and \( \kappa_0 \) describe the different contributions to the output signal. The kernel \( \eta \) defines the shape of the postsynaptic AP emitted in \( t = \hat{t}_i \), \( c_0 \) describes the PSP evoked by one presynaptic spike and \( \kappa_0 \) is the linear response of the cellular membrane to an input pulse of current \( I_e(t) \). The term \( h_i(t) \) in Eq. (1) stands for the total postsynaptic potential, that comprises all the input contributions. When \( h_i(t) \) exceeds a dynamic spiking threshold \( \vartheta(t) \), determined by the physiological parameters of the cell and the past activity [14], the target neuron \( i \) emits an AP in \( t = \hat{t}_i \). Then, a simplified postsynaptic spiking condition for invariant threshold \( \vartheta \) can be written as:

\[
\text{if } h_i(t) \geq \vartheta \text{ then } u_i(t|\hat{t}_i) = \eta(t - \hat{t}_i)
\]  

(2)

The main advantage is that a generalized description can be mapped to the biophysical model (for example IF or HH) of any specific target neuron. If we associate each individual PSP contribution \( \omega_{ij}c_0(t-t_j) \) of Eq. (1) to one single SnM, activated in \( t = \hat{t}_i \), we obtain the Equivalent Neuron-Nanomachine scheme (EqNN), depicted in Fig. 3, which describes the input/output function between nanomachine inputs and output signal of the neuron, according to Eq. (1). In the EqNN scheme, the set of SnMs is represented with equivalent presynaptic neurons \( j = 1, \ldots, N_s \) assumed
isolated, independent each other and driven by an input current \( I_s(t) \) which models the activation of the nanomachines. As for biological neurons, the number of spikes per unit of time, emitted by the equivalent neurons (the firing rate), is proportional to the amplitude of the input current \([14]\). The higher the current, the higher the activation frequency of the nanomachines, which can be regarded as the intensity of the stimulation.

The purpose of the EqNN scheme is to provide a practical representation of the SnMs, which can also be easily implemented in simulations or in-vivo tests, to assess a stimulation scenario. In addition, the EqNN scheme can be helpful in the system analysis and optimization. For example, resorting to Eqs. (1) and (2), we can determine the minimum number of active SnMs to trigger a spike in the target cell:

\[
N_s \geq \frac{\theta - \epsilon}{\omega_s \cdot \max \epsilon_0(s)},
\]

where \( k = 1 \) (one spike per presynaptic node) and \( \omega_{ij} = \omega_s \) for all \( j \) in Eq. (1). To evaluate only the contribution of PSPs in reaching the threshold, we neglected the external input current, i.e., \( I_e \to 0 \), such that the contribution of \( \epsilon_0 \) is marginal and can be associated to a single term \( \epsilon \to 0 \). Since we are interested in the firing threshold, we used the peak value of \( \epsilon_0(s) \) which adds up to the summation of \( N_s \) contributions, under the hypothesis of synchronized input (i.e., each SnM activates in the same time instant). We notice that, from Eq. (3), the minimum number of PSPs to evoke a postsynaptic AP is inversely proportional to the synaptic weights and the PSP amplitude. The synchronization between nanodevices is not trivial and high levels of desynchronization in the activation can dramatically delay the generation of spikes in the target neuron. Suitable machine-to-machine communication protocols, as envisioned in [4], or remote synchronization control are possible methods to mitigate such inefficiencies, whose analysis is out of the scope of this paper.

The activation frequency of SnMs also plays an important role in the design of the stimulation scenario. Recalling the EqNN scheme, when a constant \( I_s \) is applied, the equivalent neurons generate equidistant spikes at constant rate \( R_s \), \([14]\). On the other hand, a time varying \( I_s(t) \) can modulate the firing rate as needed. The EqNN scheme allows us to model the behavior of SnMs with different activation frequencies \( R_s(t) \), adding a level of flexibility in the design. We formalize this property by defining a general functional association between \( R_s(t) \) and the input current:

\[
\begin{align*}
R_s(t) &= f_0(R_s, N_s, \omega_s, P) \\
I_s(t) &= I_p \cdot f_d(t)
\end{align*}
\]

where \( I_p \) is the input current (peak value) and \( f_d(t) \) is an arbitrary driving function (adimensional, causal, real valued) which shapes the current. The activation function \( f_0(\cdot) \) describes the effective \( R_s(t) \) of nanomachines by means of the firing rate of the equivalent neurons and the stimulation setup \((N_s, \omega_s)\). Importantly, the behavior of the target neuron to the stimuli strongly depends on the physiological parameters of the cell, generally identified with \( P \). In other words, the strength of the stimuli proportionally increases the potential of the target neuron and the APs are generated with a rate in agreement with the threshold in Eq. (2). In this respect, the frequency \( R_s(t) \) can be derived with experimental tests on the specific cell, however it can be not deterministic due to the variability of the neuronal response, as explained later. At least in theory, in our scheme it is possible to design any driving function \( f_d(t) \), e.g., sinusoidal, impulsive, chirp. On the other hand, the biological mechanisms of target neurons limit the reaction to fast stimulation changes, in agreement with the refractory period after each AP (the minimum interval between consecutive spikes).

**A. Stochastic Behavior of Neurons**

In-vivo recordings of the neuronal response are not deterministic and arbitrary input, applied with repetition to the membrane, leads to a response with a certain degree of variability. This apparently unpredictable behavior of neurons has been challenging the neuroscientists for years and a reasonable explanation is the presence of background noise components, caused by adjacent active neurons, similarly to wireless communication systems. Fluctuations of the synaptic strengths \( \omega_{ij} \), the variable number of ion channels activated by the synaptic junctions, thermal noise and network failures, are the most common constituents of irregularity in the neuronal response \([14],[24],[5]\) mainly internal to the system. To keep the reasoning as simple as possible, we introduce in the target neuron, a diffusion input noise component, as proposed in existing works, \([25],[26]\), which fits the fluctuations of the membrane potential of the target cell due to the background activity of adjacent neurons in the population. Recalling the EqNN scheme of Fig. 3, the input noise is identified with the current:

\[
I_n(t) = \mu_n + \sigma_n \cdot n(t)
\]

where \( n(t) \) is Gaussian distributed with zero mean and unit variance. The parameters \( \mu_n \) and \( \sigma_n \), \([25]\) are used to fit the noise to specific properties of the population (population size and synaptic weights). Hence, the total (noisy) postsynaptic potential \( h^{(n)}_t \) can be derived from Eq. (1) as follows:

\[
h^{(n)}_t(t) = \epsilon_0(t) + \\
+ \int_0^\infty \epsilon_0(s)(I_e(t-s) + I_n(t-s))ds \\
\simeq h(t) + I_n(t)
\]
where \( \varepsilon^{EN}(t) = \sum_{j=1}^{N_E} \omega_j \sum_k c_0(t - t_j^{(k)}) \). From the literature, we can identify two types of noise input: sub-threshold, which generates a potential always below the firing threshold, and super-threshold, where the above-threshold potential induces the firing. As far as we assume that noise has only sub-threshold components, the term \( I_n(t) \) can be taken out of the integral and considered as an independent, additive random input. Consequently, the minimum number of nanomachines derived in Eq. (3) can be computed according to Eq. (6):

\[
N_s \geq \frac{\theta - \varepsilon - \varepsilon_n}{\omega_s \cdot \max_s c_0(s)},
\]

where \( \varepsilon_n = E \{ I_n(t) \} = \mu_n \) accounts for the average deviation due to the noise. The input noise can also have an impact on the nanomachine activation frequency of Eq. (4) because of the random components present in biological neurons. This can be explained resorting to the threshold condition of Eq. (2) applied on the total (noisy) PSP in Eq. (6): if \( h_1(t) + I_n(t) \geq \theta \), then an AP is emitted. The AP emission is also dependent on \( I_n \). A positive \( I_n \) moves the potential towards the threshold, increasing the spiking rate. On the contrary, the spiking rate for negative amplitude of noise \( I_n \) is reduced proportionally. Upon this consideration, we add a correction term \( c_n(\varepsilon_n) \) on the activity frequency \( R_a(t) \) defined in Eq. (4) for ideal neurons:

\[
P_a^{(n)}(t) = f_a(R_s, N_s, \omega_s, P) + c_n(\varepsilon_n)
\]

where \( c_n(\varepsilon_n) \) depends on the mean value of the input noise, found with experiments.

## V. SnM Base-Scenario

The scope of our paper is to show the impact of SnMs on sample populations of neurons. However, the biology of neurons is various, with highly specialized types of cells which exhibit different dynamics [26]. In this section, we define a general biological base-scenario, inspired by existing works reported in [27], [25] and [26] to verify the proposed SnM stimulation setup. Computer simulations are based on the EqNN scheme implemented with mathematical software. The overall scenario is defined as follows:

1) The neuron: each cell is described with the Izhikevic's model [26], which is well suited for low-complexity simulations of large networks. The general expression of the membrane potential for most of the thalamic neurons, is determined by two differential equations:

\[
\begin{align*}
\dot{v}(t) &= 0.04v(t)^2 + 5v(t) + 140 - u(t) + I(t) \\
\dot{u}(t) &= a[bv(t) - u(t)]
\end{align*}
\]

The spike generation is regulated by a reset condition on the threshold \( \theta \): if \( v(t^*) \geq \theta \), then \( v(t^*) = c \) and \( u(t^*) = u(t^*) + d \). The parameters \( a, b, c, d \) define the neuron type, \( t[mV] \) is the time, \( v(t)[mV] \) the potential and \( u(t)[mV] \) a recovery variable to describe the dynamics, whereas \( I(t)[mA] \) is the total input current. Excitatory neurons are well fitted by the Regular spiking (RS) model with parameters \( (a, b, c, d) = (0.02, 0.2, -65, 2) \), whereas the Fast Spiking (FS) model, \( (a, b, c, d) = (0.1, 0.2, -65, 8) \), is more suited for inhibitory neurons.

2) Classes of neurons: we define the following classes \( \chi \), identified by a letter: excitatory \( (\chi = E, \text{RS}) \) and inhibitory \( (\chi = I, \text{FS}) \) neurons, SnM equivalent neurons \( (\chi = S, \text{RS}) \) and target neurons \( (\chi = T, \text{RS}) \) [26].

3) The network: typical populations of \( N \) cells have a balanced contribution of \( N_E \) excitatory and \( N_I \) inhibitory neurons, in the ratio \( \gamma_E = N_E/N_I = 4/1 \) [25]. We define the coefficient \( \alpha_E = 1/(1 + \gamma_E) \), such that \( N_E = \alpha_E N \) and \( N_I = (1 - \alpha_E)N \).

4) The SnM stimulation: \( N_s \) SnMs attached to a subset of excitatory target neurons in the number of \( N_T = \alpha_T N_E \), with \( \alpha_T \) between 0 and 1. Typical value can be \( \alpha_T = 0.3 \).

5) Synaptic strenghts: the links from presynaptic to postsynaptic neurons \( (A \to B) \) are weighted by the terms \( w_{A \to B} \) depending on the cell type. We use the following setup, derived from [27]: \( w_{EE} = 0.5 \), \( w_{EI} = -3w_{EE} \), \( w_{IE} = 2w_{EE} \), \( w_{IE} = -3w_{EE} \).

6) Topology: fully connected network (fixed synaptic strength), random network (connectivity probability \( p_C \)).

7) Background noise: according to Eq.(5), we define \( \mu_{nE} = \mu_{nI} = 0 \) and \( \sigma_{nE} = 5 \), \( \sigma_{nI} = 3 \) in order to ensure a stronger level of noise for excitatory neurons.

## VI. Single Neuron and Population Response

The characterization of both individual and population response is of great importance to assess the impact of the proposed nanomachine simulation. To this end, we present a collection of analytical and statistical methods to compare the responses of different simulation scenarios.

### A. Neuron Spiking Process

A common assumption in neuroscience is to consider the neuronal spike trains as a time variant point process [28], characterized by the probability of observing one event in a temporal interval. A regular point process is defined as [29]:

\[
P\{1 \text{ event in } [t, t+\Delta) | N_t, s_k \} = \lambda(t|N_t, s_k)\Delta
\]

where \( \lambda(t|N_t, s_k) \) is the intensity function of the process, depending on time \( t \), number of events \( N_t \) occurred to \( t \) and sequence of Event Times \( s_k = [s_1, s_2, \ldots, s_N] \). Alternatively, the sequence of Inter Spike Intervals (ISI) describes the distribution of the interevent times (the ISIs) \( t_k = s_k - s_{k-1} \) with \( k = [2, \cdots, N] \) and intensity function \( \mu(t|N_t, t_k) \). In both cases, \( \lambda(\cdot) \) and \( \mu(\cdot) \) completely describe the process. The dependence on the past history represents the memory of the process, whereas the time dependence characterizes a possible non-stationary response (inhomogeneous process).

Special hypothesis are often adopted to simplify the analysis: 1) no memory: \( \lambda(t, N_t, s_k) = \lambda(t) \); 2) the process only depends on the last event in \( t = s^* \), then \( \lambda(t, N_t, s_k) = \lambda(t|t - s^*) \); 3) the process is stationary (homogeneous): \( \lambda(t, N_t, s_k) = \lambda(N_t, s_k) \). In a memoryless process, ISIs are i.i.d. (independent identically distributed) and we have a renewal process. Moreover, an exponential ISI distribution leads to a Poisson process, often used to fit with good approximation the typical single neuron response. In this case, the
probability density function (pdf) \( p_r(t) \) of a random variable \( \tau \) representing the ISIs, can be written as:

\[
p_r(t) = h(t) \cdot \exp \left\{ - \int_0^t h(\gamma) d\gamma \right\}
\]

(11)

with

\[
h(t) = \frac{p_r(t)}{S(t)} = \frac{p_r(t)}{\int_t^\infty p_r(\theta) d\theta}
\]

(12)

\( S(t) \) refers to the survival function of the process, that is the probability of zero events in \([t, t+\Delta]\), whereas \( h(t) \) is the hazard function which represents the spiking rate of the neuron conditioned on the survival until \( t \).

The spiking process of stimulated neurons is expected to follow more complex arbitrary and stimulus-conditioned distributions and a-priori descriptions are difficult. Data-fitting advanced techniques to exploit the actual distribution, according to a given goodness-of-fit, have been proposed in the past [30]. However, a simple and reliable method which answers our needs is the computation of ISI histograms to estimate Eqs. (11)-(12), as proposed in [29] for the analysis of single neuron responses. In the histogram computation, the time length \( T \) of the experiment is discretized into \( B \) time bins of length \( \delta \), such that \( T = B\delta \):

\[
\text{Hist}(k) = \frac{1}{B\delta} \sum_{i=0}^{B-1} \Theta_k(\tau_i)
\]

(13)

where the indicator function \( \Theta_k(\tau_i) \) accounts for the ISI \( \tau_i \) relying within the \( k \)-th bin:

\[
\Theta_k(\tau_i) = \begin{cases} 
1, & k\delta \leq \tau_i < (k+1)\delta \\
0, & \text{otherwise}
\end{cases}
\]

(14)

The estimator in Eq. (13) is non-biased, i.e., \( E\{\text{Hist}(k)\} = p_r(k\delta) \) and shows an increasing estimation error for decreasing density. From Eq. (13), the estimator of the corresponding hazard function is straightforward:

\[
\text{Haz}(k) = \frac{\text{Hist}(k)}{\sum_{i=k}^{B-1} \text{Hist}(i) \cdot \delta}
\]

(15)

where numerator and denominator refer to \( p_r(t) \) and \( S(t) \), respectively. Under external stimulation, a useful estimation is the peristimulus time histogram (PSTH) [28],[29] where the firing rate and timing are aligned in correspondence of the stimulus to exploit any meaningful stimulus-response correlation. Since the correlation is measured with an alternative stimulus to exploit any meaningful stimulus-response correlation, we consider the standard histogram formulation.

Then, we need to relate the estimated distribution of the experimental spiking process with the parameters set of the stimulation and population scenario, characterized by \( S = \{N, \alpha_E, \omega_{EE}, P\ | N_a, \alpha_T, I_0 \cdot f_0(t), \omega_S\} \) according to the notation of Section V. The distribution of interevent times \( \tau_i \) and the intensity function \( \mu(\cdot) \) are an intuitive choice to describe the response as a function of \( S \). Furthermore, the hazard function estimation in Eq. (12) can show the existing relationship between the spiking rate of target neurons and the stimulation setup, whereas the ISI distribution in Eq. (11) can unveil hidden deviations of the neuronal process under stimulation conditions. As note aside, the statistical analysis of the resulting point process is a powerful tool for the information processing of the neuronal network to exploit a possible stimulus-response mapping, as discussed in [31]. In this respect, the characterization of the mutual information between neurons can be a compelling research argument for future investigations of nanoscale stimulations.

B. Stimulus-Response Correlation

To further characterize the neuronal response, we also investigate the neuron-to-neuron and stimulus-to-neuron correlations by means of a cross correlation assessment (CCA) as described in [25] and [27], where the authors reported the appearance of fast oscillations in a populations of balanced excitatory-inhibitory neurons with irregular firing rate. To motivate our reasoning, it is interesting to notice that cross correlation (CC) and synchronization patterns are often observed in the brain and the consequent oscillations of the neuronal response, ranging from 1 to 70-100 Hz, are considered one of the most effective responsible for the generation of the local field potential measured with electroencephalograph (EEG) recordings. In this respect, a recent review paper [32], pointed out the origin of the field potential.

Let us describe the CCA. First, the individual neuronal activity is recorded with a binary spike indicator function \( S_i(t) = \{0, 1\} \) (1 = neuron \( i \) fires in \( t \)). Then, the total activity of a group of homogeneous neurons is:

\[
n(\chi; t) = \sum_{i \in \chi} S_i(t)
\]

(16)

where \( \chi \) indicates a specific class of neurons as defined in Section V. From Eq. (16), we derive the CC between two generic classes of neurons \( \chi_A \) and \( \chi_B \) with \( N_A \) and \( N_B \) elements respectively:

\[
CC(\chi_A, \chi_B; t_L) = \frac{1}{N_A N_B (T - t_L)} \times \sum_{i=1}^{T-t_L} n(\chi_A; t) n(\chi_B; t + t_L)
\]

(17)

where \( t_L \) is the time-lag between the two sequences \( n(\chi_A; t) \) and \( n(\chi_B; t) \). Then, CCA measures the similarity of two spike sequences as a function of the time shift \( t_L \) between them. For the sake of simplifying the notation, from now on we omit the time-lag \( t_L \) when referring to the CC in Eq. (17).

We are mainly interested in the internal CC(\( E, I \)) between excitatory (\( \chi_A = E \)) and inhibitory (\( \chi_B = I \)) neurons of the population, as well as the external CC(\( S, E/I \)) between the SnM stimulus modeled with equivalent neurons (\( \chi_A = S \)) and the E/I networks (\( \chi_B = E/I \)). On one hand, the external correlations \( CC(S,E) \) and \( CC(S,I) \) provide an insight of the existing input/output similarities between stimulus and response of E/I neurons. On the other hand, \( CC(E,I) \) can also show an existing development of meaningful oscillatory behaviors between biological neurons in the same population, under stimulation conditions.

VII. Evaluation of the Results

In what follows, we discuss a set of computer simulations to verify selected stimulation conditions, based on the
proposed EqNN scheme. For a better comprehension, results are organized in categories to emphasize different peculiar aspects of the obtained responses and to assess the impact of two operational layers: 1) the SnM stimulation setup; 2) the simulated population of biological neurons. Each configuration is based on the base-scenario defined in Section V, whereas 200 repeated trials of 1500 ms have been conducted to achieve a sufficient amount of data for statistical reliability.

A. Emerging of Periodic Correlation

In the first scenario, we compare the spontaneous response of a fully connected population with the response obtained with SnMs at constant activation rate (the number of active periods per seconds). The network parameters are $N = 125$ with ratio $\alpha_E = 0.8$, and $\omega_{EE} = 1$. $N_T = 30$ target neurons are stimulated by $N_S = 10$ excitatory SnMs modeled as equivalent neurons with $f_d(t) = 10$, $I_p = 1 mA$ to induce the constant activation frequency $R_a \simeq 21 Hz$ (refer to Section IV). As first analysis, the population raster plot is depicted in Fig. 4, which traces the spiking activity for each neuron. Recalling that each SnM activation evokes one PSP on the target membrane potentials and that the network is fully connected, it is evident the tendency of the population to follow the activity of the target neurons, which exhibit enhanced activity.

This behavior is more clear observing the distribution of the experimental stochastic process (Eq. (13)-(15)), depicted in Fig. 5 for spontaneous and stimulation conditions. The top subplot shows the spiking event distribution, with an increased activity in correspondence of the stimulation, whereas the ISI histogram (middle subplot) shows a typical distribution which resembles a neuronal Poisson process. Before $t = 50$ ms, the spiking probability is zero because of the absolute refractory period. Then, firings are slightly more frequent (relative refractory period). After a peak, the spiking probability decreases exponentially as expected. The hazard function in the last subplot, shows that after the refractory periods, the mean value tends to stabilize to a constant value, corresponding to the average interevent time exhibited by an exponential ISI distribution with estimated intensity $\lambda(t) \simeq 0.165$ s (memory is neglected), depicted for comparison. Interestingly, we can notice from the topmost subplot that the average spike rate is $\lambda(t) \simeq 1/\mu(t) \simeq 6.06$ spike/s. Moreover, we can also notice slight peaks in the ISI distribution (middle plot) in correspondence of multiples of $1/R_a = 1/21 Hz \simeq 50$ ms, indicating an increased neuronal activity.

The CCA depicted in Fig. 6 as a function of the time lag, also offers some interesting cues. In the first subplot, the $CC(S, E)$ correlation shows an enhanced synchronous activity of $E$ cells when SnMs are active, in correspondence of the activation period $1/R_a \simeq 50$ ms. For comparison, we analyze separately target, $T$, and free, $E_F$, neurons (without SnM
Basically, the intensity of the input stimuli depends on the proposed scenarios and the analysis of its properties.

C. Equivalent Neuron-machine

The intensity of the SnMs begins to activate the ion channels on the target neuron, whose intensity is regulated by the driving function \( f_d(t) \), which evokes synchronization phenomena in clusters of neurons as indicated with ellipses. The effect of enhanced excitatory activity leads to the activation frequency of the SnMs, as noticed in the topmost network, a weaker driving function is adequate to enhance the quasi-periodic behavior. As note aside, in this large sparse network, a weaker driving function is adequate to enhance the oscillations and synchronization patterns, also partially visible in the rasterplot of Fig. 4.

B. Network Structure

In the second scenario, we investigate the role of the number of SnMs in contact with the target neuron. The synaptic strength is fixed by \( \omega_S = 1 \) whereas \( N_s \) varies between 1 and 50, according to [18] where a feasible mesh of 50 nanowires attached to a single cell has been tested. Similarly to the first scenario, we identify a flat area for \( N_s \leq 10 \), where the target neuron is prevented from spiking. We also notice in passing that such limit corresponds to the number of SnMs used in our stimulation setup. In conclusion, we deduce that given an adequate number of SnMs, the stimulation setup at nanoscale enables the firing of the target neuron, whose intensity is regulated by the driving function \( f_d(t) \). The analysis of Fig. 8 has been derived for a selected neuron configuration and can be applied to any specific target neuron, in order to determine the optimal stimulation setup. As practical consideration, the EqNN scheme is analyzed for generic RS excitatory neurons with low background noise (quasi-ideal conditions). However, in realistic environment and large populations, the sub-threshold dynamics is maintained high by adjacent neuronal activity, increasing the target membrane potential towards the firing threshold, as explained in Section IV. Consequently, the minimum requirements to induce the AP firing, are relaxed.

VIII. Final Considerations and Conclusions

The results obtained under stimulation conditions, revealed peculiar characteristics of the population response, such as low frequency oscillation and synchronization between neurons and clusters of neurons. The neuroscientific literature [14],
[22] and [21] demonstrated that such phenomena have a fundamental role in learning, plasticity and cognitive functions. Therefore, highly interdisciplinary studies including nanoscale engineering and neuroscience, could identify optimal stimulation strategies to achieve a specific behavior of the neuronal response. Several issues of great interest will be considered in future works:

- The frequency domain analysis of the stimulated neuronal response, by means of the power spectrum density, to exploit the frequency components of the signal representing the membrane potential, when an external input is applied to the cell;
- In a wider perspective, the future availability of reliable nanomachines/nanosensors (SnM’s) with communication capabilities and coordinated by nanocommunication protocols, can allow the design of closed loop stimulations. The information retrieved from nanosensors is processed by a central unit, which dynamically optimizes the SnM stimulation, according to the response;
- More detailed statistical analyses of a wider range of neuron types for alternative network topologies, such as the small-world structure, could exploit further elements of correlation between stimulus and response;
- Since synapses and neuronal connections adapt to environmental changes, the spike time dependent plasticity (STPD) can be taken into account to verify the long-term potentiation/depression in the neuronal response, fundamental for learning and brain development.

However, the general analyses here proposed are intended to define the very first steps of a novel approach, where the emerging nanotechnology can be applied to in-situ monitoring tasks and treatment of brain diseases. One advantage of our analysis is the general formulation for different neuronal networks and types of cells. Moreover, according to the continuous advancements of nanotechnology in finding new materials as well as solutions for the suspected incompatibility with biological systems and the human body, the proposed strategies can provide a valuable support for the design of feasible and enhanced neuronal nanoscale interfaces.

REFERENCES

Fabio Mesiti received his M.Sc. degree in telecommunication engineering in 2005, and the Ph.D. in electronics and communications engineering in 2009 from Politecnico di Torino (Italy), where he worked as a Post-doc researcher from 2010 to 2011. Since 2011, he has been an ERCIM fellow and Post-doc researcher at the Norwegian University of Science and Technology (NTNU) in Trondheim (Norway). His research interests mainly include cross-layer modeling in wireless networks, optimization and performance analysis of wireless communications systems, and channel coding for quantum communication and quantum key distribution (QKD) systems. He is involved in the theoretical modeling of the biological effects induced by radio frequency exposure on cerebral tissue, applications for the treatment of neurodegenerative diseases, neuronal information theory, statistical analysis of the neuronal activity at the cellular level under external stimulation, and the design of novel stimulation techniques and devices at nanoscale. He also serves as a member of the technical program committee of international IEEE conferences.

Ilangko Balasingham received M.Sc. and Ph.D. degrees from the Department of Telecommunications, the Norwegian University of Science and Technology (NTNU), Trondheim, Norway, in 1993 and 1998, respectively, both in signal processing. He completed his master’s degree thesis at the Department of Electrical and Computer Engineering, the University of California Santa Barbara, USA. From 1998 to 2002, he worked as a Research Scientist developing image and video streaming solutions for mobile handheld devices at Fast Search & Transfer ASA, Oslo, Norway, which is now part of Microsoft Inc. Since 2002, he has been with the Intervention Centre, Oslo University Hospital, Oslo, Norway, as a Sr. Research Scientist, where he heads the Wireless Sensor Network Research Group. He was appointed as a Professor in Signal Processing in Medical Applications at NTNU in 2006. His research interests include super robust short range communications for both in-body and on-body sensors, body area sensor networks, microwave short range sensing of vital signs, short range localization and tracking mobile sensors, and nano-neural communication networks. He has authored or co-authored 142 papers and has been active in organizing special sessions and workshops on wireless medical technologies at the major conferences and symposia. He was the General Chair of the 2012 Body Area Networks (BODYNETS) conference and is a Senior IEEE member.