Synaptic Communication Engineering for Future Cognitive Brain-machine Interfaces

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***Abstract*—Disease-affected nervous systems exhibit anatomical or physiological impairments that degrade processing, transfer, storage, and retrieval of neural information leading to physical or intellectual disabilities. Brain implants may potentially promote clinical means for detecting and treating neurological symptoms by establishing direct communication between the nervous and artificial systems. Current technology can modify neural function at the supracellular level as in Parkinson's disease, epilepsy, and depression. However, recent advances in nanotechnology, nanomaterials, and molecular communications have the potential to enable brain implants to preserve the neural function at the subcellular level which could increase effectiveness, decrease energy consumption, and make the leadless devices chargeable from outside the body or by utilizing the body's own energy sources. In this study, we focus on understanding the principles of elemental processes in synapses to enable diagnosis and treatment of brain diseases with pathological conditions using biomimetic synaptically interactive brain-machine interfaces. First, we provide an overview of the synaptic communication system, followed by an outline of brain diseases that promote dysfunction in the synaptic communication system. We then discuss technologies for brain implants and propose future directions for the design and fabrication of cognitive brain-machine interfaces. The overarching goal of this paper is to summarize the status of engineering research at the interface between technology and the nervous system and direct the ongoing research towards the point where synaptically interactive brain-machine interfaces can be embedded in the nervous system.**

***Index Terms*—Brain-machine Interface (BMI); Molecular Communications; Nervous System; Synaptic Communication; Synaptopathy**

I. Introduction

The human nervous system is an advanced large-scale biological information processing network that controls other intra-body systems and muscle cells by gathering, processing, and evaluating information about the internal state of the body and the external environment. The nervous network contains billions of neurons that generate and transmit electrical and molecular signals [1]–[3]. Apart from neurons, the nervous network contains trillions of glia that provide the neurons with mechanical and metabolic support [4]–[6].

Pathological processes in the nervous system frequently affect communication performance [7], [8]. Impaired communication performance further leads to sensory malfunctions, motor malfunctions, or cognitive malfunctions. In line with these complications, three classes of brain implants, called *brain-machine interfaces* (BMIs) or *neural implants*, are designed for providing clinical means for detection and treatment.

- Sensory BMIs deliver physical stimuli (e.g., sound, sight, touch, pain, and warmth) to the sensory organs for the correction of auditory, occipital, and somatosensory malfunctions. Examples of sensory BMIs are cochlear and retinal implants, that translate external auditory and visual content into sensory firings that could be perceived by patients suffering from deafness and blindness, respectively [9].
- Motor BMIs deliver brain signals to the organs or muscles that have lost functional mobility due to traumatic injury or stroke, or translate brain signals into control commands for an artificial device of interest, e.g., interfaces with computers or robotic arms [10].
- Cognitive BMIs represent devices that restore communication among damaged or disparate areas in the nervous system [11]. The success of cognitive BMIs strongly depends on understanding the principles of neural signal processing, wiring, and communication that we put in focus in this paper.

The fundamental communication units in the nervous system are *synapses* [12]. Synapses permit neurons to transmit signals to other neurons or targeted cells. Trillions of synapses anatomically and functionally integrate neurons and areas in the nervous system.

In this special issue on molecular communications and networking, we focus on understanding the very specific principles of *neurotransmission* in the human brain referred in engineering community as *(molecular) synaptic communication*. Thorough understanding of synaptic communication will enable early detection and control in pathological brain conditions through the incorporation of biomimetic features into the design of future cognitive BMIs. We explain the synaptic configuration by examining the communication- and information-theoretical synapse models recently developed, and propose future interdisciplinary efforts in neurophysiology and engineering to establish and fabricate artificial systems that alter, regulate, and/or mimic the synaptic pathways. Synaptically interactive BMIs realized by advances in nanotechnology, nanomaterials, and molecular communications, will outperform current technologies by providing fine-grained control of neural circuits. This will ensure accuracy of therapeutic effects and may minimize side effects.

The rest of the paper is organized as follows. In Section II,

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we present the state-of-the-art research and open challenges in modeling each segment of the complex (molecular) synaptic communication system by explaining the synaptic communication system through the molecular communication paradigm where the pre-synaptic terminal within the pre-synaptic communication sub-system is abstracted as a *molecular transmitter* and the post-synaptic terminal within the post-synaptic communication sub-system is abstracted as a *molecular receiver*. In Section III, we present several neurodevelopmental and neurodegenerative conditions with the objective to understand and associate their relationship with impairments either in the pre-synaptic sub-system, the synaptic channel, or the post-synaptic sub-system. Understanding synaptic impairments through communication-theoretical modeling is the ground towards fine-grained control of the nervous system. In Section IV, we present the state-of-the-art and future disruptive solutions for diagnosis and treatment of neural impairments that stem from interdisciplinary efforts with the momentous role of molecular communication engineering. In Section V, we outline the complete framework for the development of sovereign biomimetic nano-devices as brain implants focusing on open research questions in terms of theoretical modeling and verification, and nano-device fabrication and testing. Ultimately, we conclude the paper in Section VI.

II. Characterization of Synaptic Communication System

The human nervous system is divided into two sections: the Central Nervous System (CNS) and the Peripheral Nervous System (PNS) [1]. The CNS is further divided into the *brain*, which is associated with processing, integrating, and coordinating the information received from sensory organs, and the *spinal cord*, which is associated with the transmission of information signals from the brain to the body. The PNS is further divided into the *somatic nervous system*, which is associated with skeletal muscles and voluntary control of body movements, and the *autonomic nervous system*, which is associated with the functions of internal organs and glands.

Neurons are the fundamental functional units of the nervous system. Depending on the type, neurons process specific neural information: the *sensory neurons* compose the PNS and bring signals from the outer parts of the body (muscles, skin, glands) into the CNS; the *motor neurons* compose the CNS and bring signals out of the CNS to the outer parts of the body; the *inter-neurons* receive information from other neurons (either sensory neurons or inter-neurons) and transmit information to other neurons (either motor neurons or inter-neurons).

An organized flow of information between neurons occurs in electrical and chemical synapses [13]. When connected by *electrical synapses*, neurons communicate electrical signals directly over specialized inter-cellular connections called gap junctions that connect cytoplasms of two cells. Electrical synapses are unidirectional but can be bidirectional. They are fast and found in neural systems that require the coordinated activity of a neural population, e.g., neurons in the reticular nucleus of the thalamus are connected by electrical synapses to inhibit ventrobasal thalamic relay neurons [14]. This inhibition

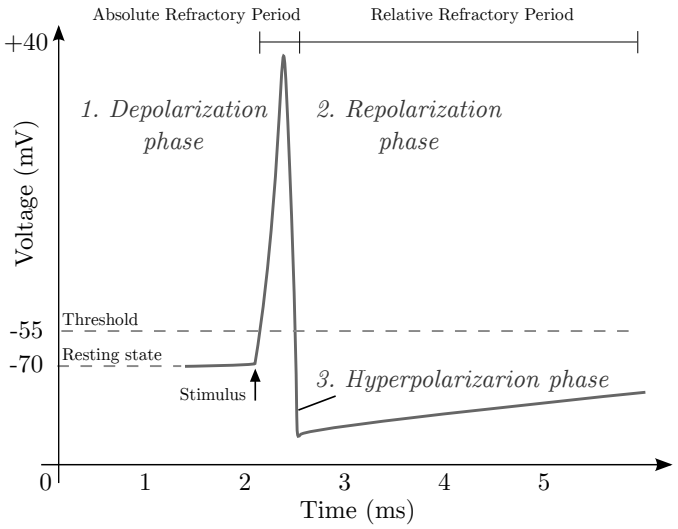


Fig. 1. A difference in potentials between the interior of a neuron and the surrounding extracellular medium forms the action potential. Three processes create the stereotyped trajectory of action potentials: the depolarization, the repolarization, and the hyperpolarization. 1. The *depolarization* makes the neuron's membrane potential less negative either due to the positively charged ions (sodium Na^+, calcium Ca^{2+}, and potassium K^+) flowing in, or the negatively charged ions (chloride Cl^-) flowing out. 2. The *repolarization* follows after depolarization of neuron's membrane potential to define the drop in membrane potential triggered by the regulation of ion channels in the membrane; 3. The *hyperpolarization* makes the neuron's membrane potential more negative, either because of the positively charged ions flowing out, or the negatively charged ions flowing in. Refractory periods additionally control the timing between consecutive action potentials: the absolute refractory period is the interval during which a new action potential is impossible regardless of the intensity of stimulation, whereas the relative refractory period is the interval during which a new action potential is inhibited but not impossible.

is thought to shape the receptive field of ventrobasal neurons that process peripheral sensory information and relay to the cortex. Electrical synapses are also found in olfactory bulb and hippocampus. When connected by *chemical synapses*, neurons transduce electrical signals and communicate molecular messengers over the synaptic cleft. Chemical synapses are unidirectional. Unlike electrical synapses, which are a distinctive minority in higher vertebrates [1], chemical synapses are found in most of the neuron junctions.

Electrical and chemical synapses have fundamentally different underlying mechanisms. In this paper, we focus on molecular communication aspects expressed in chemical synapses found throughout the nervous system between both excitatory and inhibitory neurons. To ease the analysis, we divide the (molecular) synaptic communication system into the *pre-synaptic communication sub-system*, the *synaptic channel*, and the *post-synaptic communication sub-system*.

A. Pre-synaptic Communication Sub-system

Pre-synaptic neurons encode information in stereotyped impulses called action potentials or spikes (refer to Fig. 1 for details) [15]. Action potentials propagate toward other cells through axons, known as unidirectional electrochemical transmission lines extending from the neuron body/soma (Fig. 2).

Two types of axons exist: unmyelinated and myelinated [3]. Myelin is a sheath formed by surrounding glia that provides

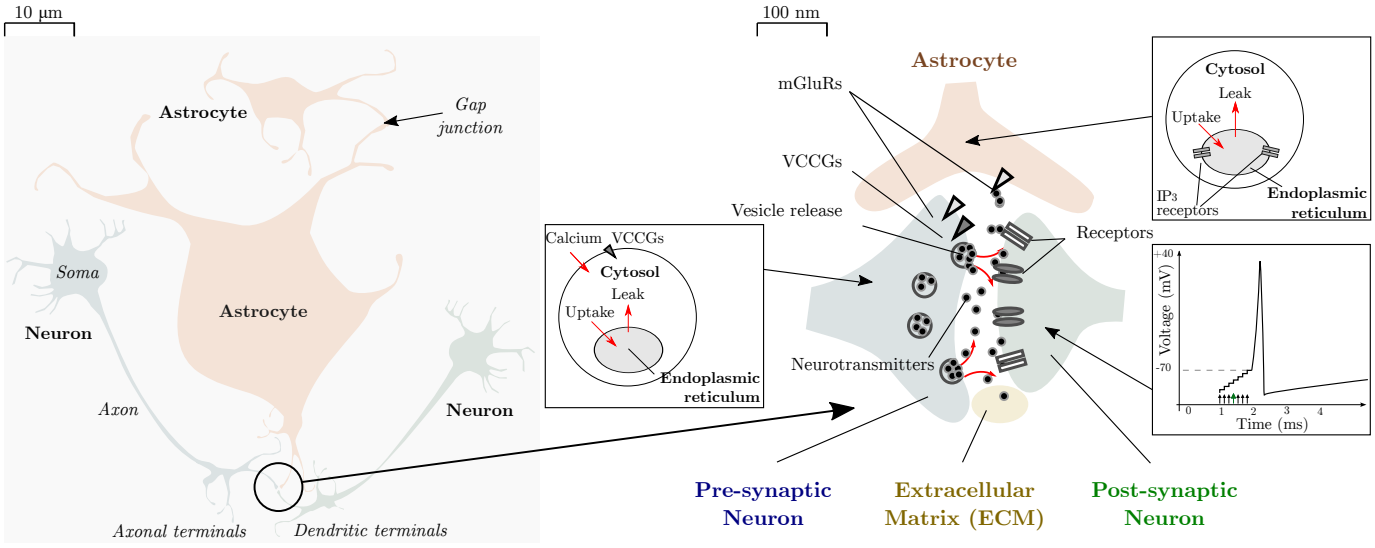


Fig. 2. The neuro-astrocyte network (left) and four units that contribute to synaptic signaling — the pre-synaptic terminal, post-synaptic terminal, astrocyte, and the extracellular matrix (ECM) — forming the concept of the **tetrapartite synapse** (right). A pre-synaptic action potential train results in the opening of voltage-controlled calcium gates (VCCGs) and the release of vesicular glutamate from the pre-synaptic neuron into the synaptic cleft. Glutamate diffuses through the cleft and activates NMDARs and AMPARs located on the post-synaptic neuron and mGluRs located on the astrocytic membrane. Activation of astrocytic mGluRs evokes IP_3. Internal calcium is released from stores enabling the release of astrocytic glutamate in the cleft. Astrocytic glutamate binds to pre-synaptic mGluRs and post-synaptic NMDARs and AMPARs. The surrounding extracellular matrix modulates functions of pre- and post-synaptic receptors and ion channels, and diffuse molecular signals as products of its activity-dependent proteolytic cleavage.

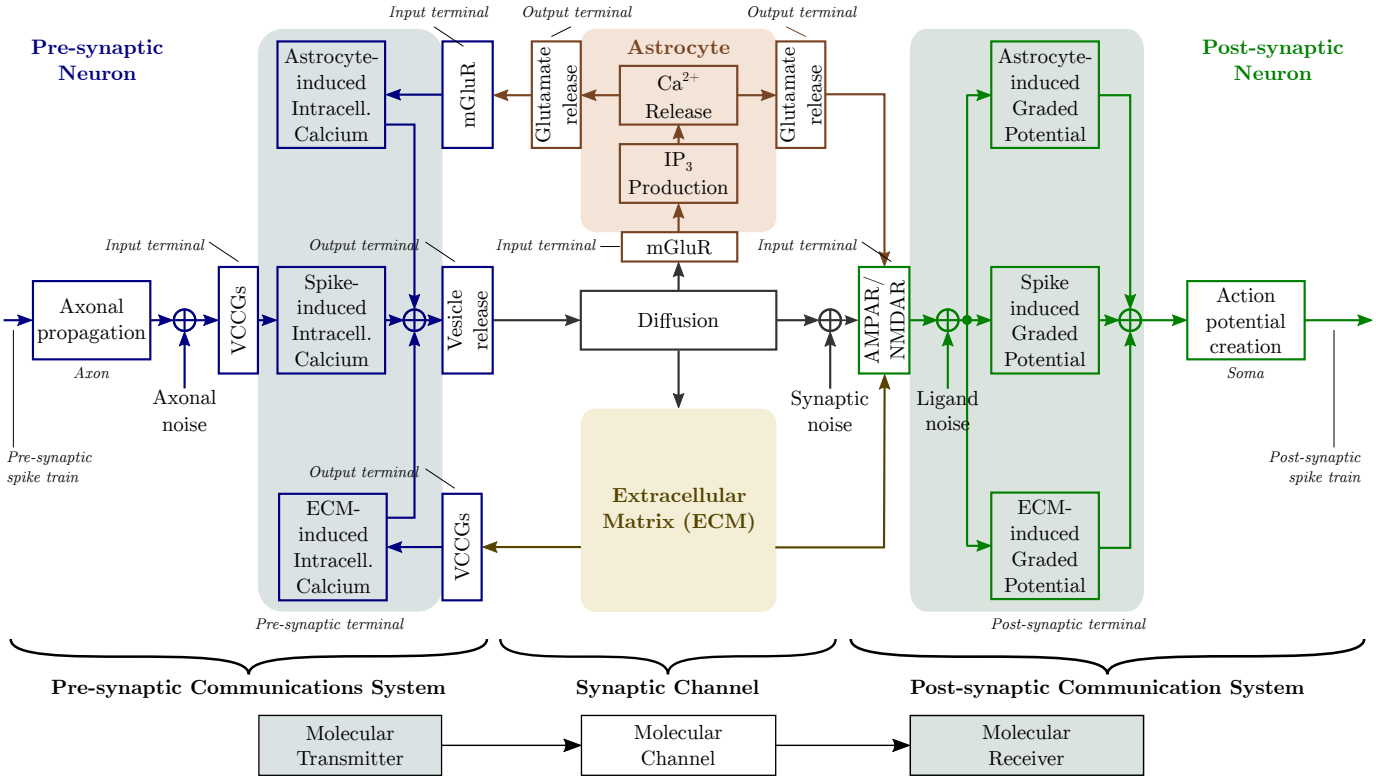


Fig. 3. The comprehensive schematic representation of the processes along the communication pathways in the tetrapartite synapse. In the pre-synaptic side, three additive calcium contributions are identified — one due to firing activity and the opening of voltage-gated calcium channels, one due to astrocytic activity and the opening of mGluRs, and one due to the ECM activity and the opening of voltage-gated calcium channels. In the post-synaptic side, three additive graded potential contributions are identified — one due to firing activity at the pre-synaptic side, one due to the astrocytic activity and the opening of extra-synaptic AMPARs and NMDARs, and one due to the ECM activity and the opening of AMPARs and NMDARs. The figure also provides the basic block diagram of a molecular communication system color-coded for easier mapping with compartments of the tetrapartite synapse.

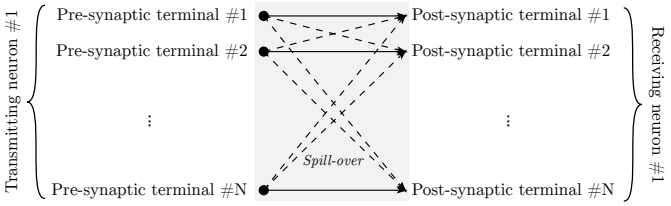
a layer of insulation and prevents a reduction of the electrical signal from an action potential. In unmyelinated axons, the action potential provokes another action potential in the membrane immediately adjacent and moves continuously down the

axon like a wave. In myelinated axons, the action potential propagates due to the periodic gaps in the myelin sheath where the axon is reduced in diameter. The gaps allow ions to enter and exit the cell. The current from an action potential at one gap provokes another action potential at the next gap. In neurons with myelinated axons, action potentials travel much faster than action potentials in equivalent neurons that lack myelin sheaths [2], [3].

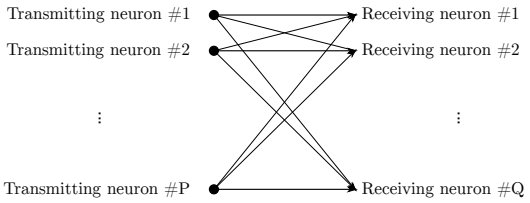
Using the cable theory-based models, researchers extensively investigated the geometrical and electrical properties and the functionality of unmyelinated and myelinated axons (see [16], [17] and references therein). However, they only considered the unique amplitude and shape of action potentials during axonal propagation. Using communication-theoretical models, researchers incorporated the variations in the amplitude and width of action potentials and demonstrated the impact of action potential variation on neuronal calcium signaling, neurotransmitter release process, and the overall synaptic performance [18], [19]. The existing models do not include analysis of delay in action potential propagation due to differences in axonal conduction velocity and conduction distance, and dynamic refractoriness. The refractoriness imposes the time period called the *refractory period* during which a neuron is incapable of or inhibited from repeating an action potential due to the inactivation property of voltage-gated sodium channels and the lag of potassium channels in closing (Fig. 1).

Action potentials are not memoryless. In analyses, however, action potentials are subject to statistical treatment where point processes are used to approximate spike trains. In point processes, the elapsed times between action potentials exhibit the properties of random variables with a minimum separation time due to the refractoriness. These times are regarded as being taken from an underlying probability distribution (with a minimum value that is greater than zero) that does not vary with time of observation, making the stochastic point processes stationary. Renewal processes belong to an important class of stationary point processes applied in the analysis of synaptic communication. The Poisson process is the most commonly encountered simple renewal process in the communication-theoretical modeling of synaptic communication. It denotes a mathematical object that consists of points, here action potentials, randomly located in a mathematical space. The number of action potentials in a region of finite size is a random variable with a Poisson distribution. The rate of this Poisson process denotes the average density of the action potentials in the space (refer to [20] for a detailed analysis of Poisson processes used in computational neuroscience). Alternatives to the Poisson process are the Erlang-, the Weibull-, the Gamma-, the Log-Normal-, and the Inverse Gaussian process, as well as more detailed mathematical models with serial correlations in periods between consecutive action potentials, such as the hidden Markov- and the doubly-stochastic process [21]. The latter models are more realistic and account for the history of action potentials and action potential adaptation.

The arrival of action potentials at the axonal bouton/terminal, known as the *pre-synaptic terminal* that is abstracted as a *molecular transmitter* in Fig. 3, leads to *signal*



(a) Synaptic MIMO configurations at the cell level; synaptic MIMO is symmetric in a neuron-to-neuron communication channel formed by one transmitting neuron and one receiving neuron since each transmitting pre-synaptic terminal links to only one directly opposed receiving post-synaptic terminal.



(b) Neuronal MIMO configurations at the tissue level; neuronal MIMO is asymmetric since each transmitting neuron links through its pre-synaptic terminals to an arbitrary number of receiving neurons.

Fig. 4. MIMO configurations in the nervous system.

transduction. Signal transduction starts with the opening of voltage-controlled calcium gates in the membrane and a resulting influx of calcium ions into the cellular cytosol (see Fig. 2) [12]. The calcium influx increases the internal calcium ion concentration within each terminal. An increase in internal calcium ion concentration initiates the chemical mechanisms leading to the release of synaptic vesicles in the synaptic channel. The vesicles contain molecular messengers called neurotransmitters. Linked biological mechanisms — the calcium influx, the calcium production and uptake, and the vesicle release and replenishment — describe the internal dynamics of the isolated pre-synaptic terminals (refer to Fig. 3). We characterized these mechanisms as input-output systems considering the driving chemical and ionic processes as signals [22]. A common model for vesicle/neurotransmitter release and replenishment includes a pool-based model where vesicles are grouped into two distinct pools, a pool of readily releasable vesicles and a pool containing the vesicles farther from the pre-synaptic site [23]. The process of releasing vesicles denotes the end of signal transduction as molecules continue to transport messages in the remaining communication pathway between neurons.

One of the fundamental features of pre-synaptic neurons is their natural diversity scheme. They send the same information encoded in action potentials via multiple pre-synaptic terminals/molecular transmitters across different synaptic/molecular channels to compensate for individual channel imperfections. When compared with diversity schemes used in the conventional wireless communication systems, the diversity scheme of pre-synaptic neurons resembles *space diversity scheme* where the signal is transmitted over several different propagation paths using multiple transmitter antennas (transmit diversity). When sending multiple copies of the signal, the

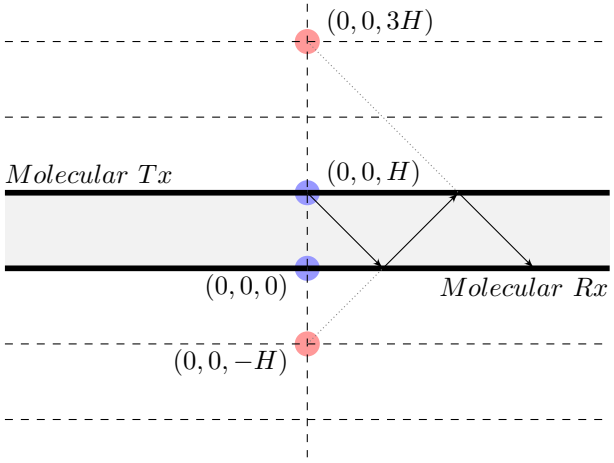


Fig. 5. Diffusion of neurotransmitters in synaptic cleft; modified from [34].

pre-synaptic terminals associated with the same neuron act as a dynamic array of molecular transmitters [24]. Their synapses form the multiple-access synaptic system which we refer to as the molecular multiple-input-multiple-output (MIMO) system (Fig. 4). The molecular MIMO system profits in terms of information transfer with increased synaptic redundancy [25]–[27].

B. Synaptic Channel

Cell adhesion molecules accumulate at pre- and post-synaptic sites to align pre- and post-synaptic terminals, control synapse formation, and regulate dendritic spine morphology and synaptic receptor function [28]. When released from the pre-synaptic terminal, neurotransmitters follow the rules of diffusion-based molecular communications to propagate through the synaptic cleft towards a homogenization. The diffusion is random and caused by the stochastic nature of the Brownian motion.

Extensive physical communication models of general diffusion-based molecular communications are available in the literature [29]–[33]. These models are, however, not suitable for the synaptic channel due to unique system boundaries and reaction complexity in the synaptic cleft. One of the most adequate synaptic channel models that exists in the literature [34] encompasses the effects of the geometrical structure of synapse and re-uptake phenomenon. In the model, the synaptic cleft is considered as a rectangular box with finite height ($H \approx 20$ nm [35]) and top and bottom planes corresponding to the pre- and post-synaptic membranes, respectively, both extending to infinity as shown in Fig. 5. The diffusion channel with pre-synaptic re-uptake is derived from the channel with no-flux boundary conditions, where the resulting neurotransmitter concentration in the cleft is given as the solution of Fick's equation as a function of the number of neurotransmitters in one vesicle, the effective diffusion coefficient (e.g., the effective glutamate diffusion coefficient is measured as $D \approx 0.3\ \mu\text{m}^2/\text{ms}$ [36]), the reflections from the membranes, and the re-uptake probability (see [34, eq. (6)].

However, the existing channel models are unable to account for the *synaptic interference* and the *cleft shadowing effects* that, respectively, refer to

- the escape/spill-over of released neurotransmitters in the synaptic channel that activate receptors located outside the synaptic cleft and generate cross-talk with nearby synapses [37], [38], and
- the interaction of released neurotransmitters with the surrounding astrocytes and the extracellular matrix [39].

Accordingly, this opens the door for further research endeavors on synapse-specific communication models that do not consider synapses as isolated communication channels with only directly opposing post-synaptic terminals that can detect neurotransmitters.

Astrocytes fill the spaces between neurons and modulate synaptic activity [40]. They inter-connect through gap junctions forming an astrocytic network where the intracellular signaling is performed with calcium signaling (Fig. 2). The consequence of the increased calcium concentration in the astrocytic cytosol is the release of neurotransmitters/gliotransmitters from the astrocyte. Glutamate is one of the most important and abundant excitatory neuro- and gliotransmitters in the brain, which bind to several types of glutamate-sensitive receptors: *ligand-activated ion channels* or *ionotropic receptors*, that open directly in response to glutamate binding (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor – AMPAR, and N-methyl-D-aspartate – NMDAR), and *metabotropic receptors*, where glutamate binding triggers a signaling pathway to indirectly open or close channels (metabotropic glutamate receptors – mGluRs).

When the astrocyte cell is in the vicinity of the *bipartite synapse*, that includes only the pre- and post-synaptic unit, the concept of a *tripartite synapse* is introduced to underline the presence of the astrocytic terminal in the vicinity of two neurons [41]. The mechanisms behind tripartite synapse are complex and take into account compartments and physiological processes not involved in bipartite synapses: the mGluRs from the astrocytic membrane, the production of secondary messenger inositol 1,4,5-triphosphate (IP_3) which triggers intracellular release of calcium ions from internal stores, and the release of gliotransmitter molecules that further diffuse in the synaptic cleft and eventually bind to neuronal receptors providing astrocytic feedback (refer to Fig. 3 for details). In the co-authored papers [42], [43], we proposed communications models of tripartite linear and time-invariant synapses including the astrocytic feedback and modulation of activities of both the pre- and post-synaptic terminals.

The extracellular matrix (ECM) is a molecular network composed of secretions from neurons and astrocytes. ECM molecules (e.g., tenascin-C, laminin, fibronectin, retinoschisin and hyaluronan) modulate activities of pre- and post-synaptic receptors and ion channels and increase the number of interaction pathways in a synapse [39], [44]. The ECM responds to synaptic activity either by creating the shadowing effect or by transmitting its activity-dependent molecules as additional messengers. These observations suggest that the ECM is a fourth essential element of a synapse, then termed as a *tetrapartite synapse* [45]. Logically though, it might be instructive

to revise the nomenclature and refer to the system of the pre-synaptic terminal, the ECM, and the post-synaptic terminal as the tripartite synapse, since the ECM is not an optional component, unlike astrocytes, but a mandatory component of the synaptic system. Ultimately, we introduce the schematic representation of the tetrapartite in Fig. 2, but emphasize that communication-theoretical models of the tetrapartite synapse are an open issue.

C. Post-synaptic Communication Sub-system

Post-synaptic neurons modulate the output signal in a form of graded potentials according to the rate of a neurotransmitter concentration present at the *post-synaptic terminal* that is abstracted as a *molecular receiver* in Fig. 3. The reading of the concentration is achieved by means of the ligand-receptor binding process. In the process, 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 neurotransmitters, or the particle release reaction if the receptors were bound to neurotransmitters) [46], [47]. Apart from AMPAR and NMDAR, the post-synaptic neuron reads the neurotransmitter/glutamate concentration by means of mGluRs.

The neurotransmitter concentration is subject to an unwanted perturbation modeled with the ligand noise. In the literature, the general ligand-receptor binding process applicable to the synaptic system is modeled through the *ligand-receptor kinetics* and the *stochastic chemical kinetics* [48]. The ligand-receptor kinetics stems from the classical chemical kinetics and incorporates all the mathematical relations necessary to simulate the random effects in the ligand-receptor kinetics. The stochastic chemical kinetics studies how the populations of the chemical species evolve in a system using chemical master equations. The reversible second-order chemical reaction and the reversible first-order chemical reaction are considered as the chemical master equations in [48]. The former chemical master equation is the most complete formulation but does not provide a closed-form solution. The latter chemical master equation is simpler and provides a closed-form solution to the problem of the stochastic modeling of the ligand-receptor kinetics as a function of the neurotransmitter concentration at the post-synaptic side and neurotransmitter binding and release rates. The solution states that the first time derivative of the probability of having n_b bound receptors among the N_R receptors at the post-synaptic membrane, $\mathrm{d}P_{n_b}/\mathrm{d}t$, depends on the following three terms: the probability P_{n_b-1} of having n_b-1 bound chemical receptors and having a binding reaction, the probability P_{n_b+1} of having n_b+1 bound chemical receptors and having a release reaction, and the negative of the probability P_{n_b} of having either a release reaction or a binding reaction (see [48, eq. (25)].

If the neurotransmitters are excitatory, a mixture of positively charged ions flows through the membrane (excitatory post-synaptic current). The influx and a decrease in the efflux of positively charged ions define the amplitude of the excitatory post-synaptic potential (Fig. 6, left) that are fundamental in creating signals for information processing within the brain.

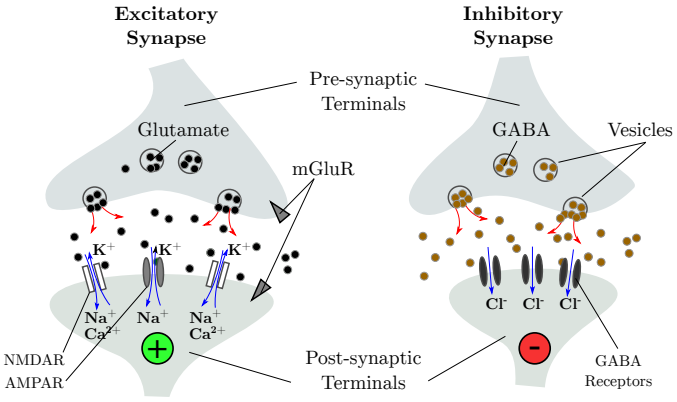


Fig. 6. The excitatory (glutamatergic) and inhibitory (gamma-aminobutyric acid – GABAergic) synapses providing depolarization and repolarization of the neural membrane, respectively. The co-existence of both types of synapses in essential for normal information processing in the brain.

The existing molecular communication models generally consider excitatory synaptic systems. Conversely, if the neurotransmitters are inhibitory, a mixture of negatively charged ions flows through the membrane (inhibitory post-synaptic current). The influx of negative ions defines the amplitude of the inhibitory post-synaptic potential (Fig. 6, right) that are fundamental in suppressing unwanted signals for information processing within the brain. When an increased excitation of the brain occurs, such as is seen in epilepsy (refer to Section III-A), the brain needs inhibitory synapses to tone down and regulate the activity of other cells [49]. Excitatory- and inhibitory post-synaptic potentials have an additive effect [2]. Larger excitatory graded potentials result in greater membrane depolarization which increases the likelihood that the post-synaptic cell reaches the threshold and fires an action potential. Larger inhibitory graded potentials result in greater membrane repolarization which decreases the likelihood that the post-synaptic cell reaches the threshold and fires an action potential.

Given the overall (excitatory or inhibitory) voltage and/or current applied to the cell, computational neuron models are used to mediate the analysis of synaptic communication and clarify the core principles that underlie action potential creation and information processing. We classify computational models according to their complexity as:

- phenomenological firing models representing the dynamics of neurons, and
- conductance-based models representing detailed electrophysiology of neurons.

The most famous **phenomenological firing models** are *Integrate-and-Fire*-based models [50], [51], e.g., Leaky-, Non-Linear-, Quadratic-, Exponential Integrate-and-Fire models, and Spike Response Model, which describe temporal changes in the membrane potential with differential equations augmented by the rule that neuron fires an action potential whenever the membrane potential reaches the threshold value. Integrate-and-Fire models are computationally simple and favorable in computer simulations. Nonetheless, they do not reproduce the neural firing with a high degree of accuracy.

The most famous **conductance-based models** are *Hodgkin-*

TABLE I
TABULAR SUMMARY OF THE COMPUTATIONAL NEURON MODELS

Single-Compartment Models		Multi-Compartment Models
Physiological Firing Models	**Conductance-Based Models**	
Integrate-and-Fire model	Hodgkin-Huxley model	Traub model
Leaky Integrate-and-Fire model	FitzHugh-Nagumo model	Pinsky-Rinzel model
Non-Linear Integrate-and-Fire model	Moris-Lecar model	Li-Rinzel model
Spike Response model	Wang-Buzsaki model	
Izhikevich model		

Huxley-based models. The Hodgkin-Huxley model incorporates a set of non-linear differential equations (see [52]) that can accurately reproduce electrophysiological data. Nonetheless, due to its computational complexity, the model is usually difficult to analyze and implement. This led researchers to propose computationally simpler models as FitzHugh-Nagumo model [53], [54], Morris-Lecar model [55], Wang-Buzsaki model [56], and Hindmarsh-Rose model [57].

A compromise between computationally efficient Integrate-and-Fire models and biologically plausible Hodgkin-Huxley model is a simple firing model proposed by Izhikevich [58]. The Izhikevich model is a type of Hodgkin-Huxley model based on bifurcation theory and normal form reduction to a two-dimensional system of ordinary differential equations. The Izhikevich model is both accurate and favorable in computer implementations. Although the model reproduces spiking, bursting, mixed-mode, post-inhibitory, and continuous spiking patterns with frequency adaptation, as well as spike threshold variability, bistability of resting and spiking states, and subthreshold oscillations and resonance [58], it can only depolarize neurons embedded into a network by the synaptic depolarization received by the simulated connections. Under these conditions, there is no upper bound on the maximum firing rate [59].

In addition, we classify the computational models according to the level of compartmentalization as:

- single-compartment models, and
- multi-compartment models given for the quantities representing compartments with uniform and non-uniform geometrical and electrical properties, respectively.

Integrate-and-Fire- and Hodgkin-Huxley-based models are **single-compartment models** which do not involve the dendrites and/or the axon of a neuron that both are at most locally uniform and require a discretization of the spatial variable to treat the differential equations. Conversely, **multi-compartment models** are the result of a discretization. Among others, the Pinsky-Rinzel model [5], [60] is a known 2-compartment reduction of the complex 19-compartment Traub model [61]. The Pinsky-Rinzel model is able to accurately characterize the somatic and dendritic membrane potentials. Another model is the Li-Rinzel model [5], [6], [62] able to describe experimental observations on synaptic behavior where glia are connected to the synapse. We provide a tabular summary of the available computational neuron models in Table I.

III. TOWARDS THE CHARACTERIZATION OF DISORDERED SYNAPTIC COMMUNICATION SYSTEM

Any dysfunction in synapse structure and physiology can result in major defects in communication performance between neurons. Communication problems in the brain may cause brain dysfunction. We use the term **synaptopathy** [63] for brain disorders that have arisen either from dysfunction in the pre-synaptic communication sub-system, the synaptic channel, or the post-synaptic communication sub-system.

Understanding synaptopathies through communication-theoretical models is the first step towards the characterization of the disordered synaptic communication system. Analyzing malfunctioning synapses through disease-specific synapse models opens the door for further research on synapse-specific communication models. This would provide valuable insights into the underlying impairments by setting together different synaptic compartments/units and observing their effects on the whole synaptic system. Disease-specific models would also aid in the development of innovative BMIs and optimize their actions to preserve the function of impaired compartments. In this section, we focus on initial understanding of several *neurodevelopmental conditions* that result in impairments of the growth and development of the brain and *neurodegenerative conditions* that result in progressive loss of structure or death of neurons. Moreover, we identify their relationship with the "synaptic hardware and logic".

A. Neurodevelopmental System Disorders

Autism spectrum disorders (ASD) are complex sets of behaviorally defined disorders characterized by social interaction and communication impairments, and repetitive and restricted behaviors. Glutamate deficits are involved in ASD at the post-synaptic side implicating both the ionotropic (AMPAR and NMDAR) and metabotropic receptors (mGluRs). Several studies observed down-regulation in AMPAR, and up-regulation in NDMA and mGlurR1 and mGluR5 in ASD [64]. There are no pharmaceutical interventions approved for ASD that address glutamate deficits.

Epilepsy comprises a group of neurological disorders characterized by epileptic seizures defined as uncontrolled and excessive electrical activity of central neurons. Alterations in neuronal and glial morphology (specifically in reduced dendritic branching and AMPAR and NMDAR) and the ECM associate with the development of epilepsy. Current evidence supports a hypothesis that an altered balance of excitatory and inhibitory synapses facilitates epilepsy [63]. In particular,

excitatory glutamatergic synaptic transmission is increased, whereas inhibitory gamma-aminobutyric acid (GABAergic) synaptic transmission is decreased [65]. Potential treatments of epilepsy counteract excitatory-inhibitory imbalance.

Down syndrome is a behaviorally defined disorder characterized by deficits in learning and memory, language, and executive functions, resulting from the presence of an extra copy of chromosome 21 [63]. GABAergic transmission is involved in Down syndrome [66]. Through a high release probability, extensive GABA supports an over-inhibition of synapses and mediates the excitatory-inhibitory imbalance [67]. Potential treatments of Down syndrome decrease GABAergic synaptic transmission and the excitation-inhibition imbalance.

Hyperekplexia is a motor disorder in humans characterized by neonatal hypertonia and an exaggerated startle reflex to tactile, auditory, or other stimuli. Dysfunctions in an inhibitory neurotransmitter glycine and the corresponding glycine receptors (GlyRs) at the post-synaptic side in the spinal cord, brainstem, and retina are involved in hyperekplexia [68]. Potential treatments of hyperekplexia enhance GABAergic or glycinergic transmission [63].

B. Neurodegenerative System Disorders

Alzheimer disease (AD) is a disorder that causes dementia and cognitive disabilities in the elderly. AD is characterized by the accumulation of amyloid-β-peptides, and/or altered activity of the catalytic subunits that produce amyloid-β peptides called presenilins [69]. Amyloid-β-peptides exacerbate calcium regulation and glutamate release at the pre-synaptic side, and trigger aberrant activation of NMDARs at the post-synaptic side. Pre-synaptic disruption of presenilins in *Cornu Ammonis* field 3 (CA3) and post-synaptic disruption of presenilins in *Cornu Ammonis* field 1 (CA1) neurons in hippocampus impair the intracellular calcium release from internal stores [70]. Decreased presenilin function also impairs synaptic communication through impaired NMDAR function. Although synapses do not appear to be the starting point for the AD, knowing that several upstream pathogenic mechanisms act to promote dysfunction in synaptic communication indicate that strategies aimed at preventing synapse failure might provide effective therapeutic benefit for cognitive decline in AD [63].

Parkinson disease (PD) is a disorder that causes loss of motor function, rigidity, postural instability, and tremor. PD is characterized by massive degeneration of dopaminergic neurons. Dopamine functions as both an inhibitory and excitatory neurotransmitter depending on the receptors that it binds to. Accumulating evidence demonstrates that α-synuclein, a protein particularly enriched in the pre-synaptic terminals, acts as a negative regulator keeping balanced the amount of dopamine neurotransmission in the pre-synaptic terminal [71]. An increased evoked dopamine release decreases levels of α-synuclein; a decreased evoked dopamine release is characterized by increased levels of α-synuclein. In addition to dopamine neurotransmission, PD is associated with altered excitatory glutamatergic synaptic activity through altered NMDAR at the post-synaptic terminal. A deeper understanding of dysfunctional synaptic communication triggered in both sporadic and familial forms of PD might offer new possibilities for treating PD.

TABLE II
TABULAR SUMMARY OF SYNAPTOPATHIES AFFECTING SYNAPTIC COMMUNICATION COMPARTMENTS

	Pre-synaptic sub-system	Synaptic channel	Post-synaptic system
Alzheimer disease	✗		✗
Parkinson disease	✗		✗
Huntington disease	✗	✗	
Schizophrenia			✗
Autism			✗
Epilepsy	✗	✗	✗
Down syndrome	✗		
Hyperekplexia	✗		✗

Huntington disease (HD) is a disorder causing uncontrolled movements, emotional problems, and loss of cognitive ability. HD is characterized by widespread neuronal death at the late stage of the disease. Changes in synaptic communication associated with an increased release of glutamate and deficit of glutamate clearance by the glia are key events in HD pathogenesis [72]. An increased release of glutamate links with a reduction in pre-synaptically located mGluR2 that leads to decreased feedback control.

Schizophrenia is a brain disorder that alters perception, emotion, and judgment causing hallucinations, delusions, and loss of cognitive ability. Unlike other neurodegenerative diseases, schizophrenia lacks agreeable pathological hallmarks, which makes it one of the least understood psychiatric disorders. Schizophrenia is, however, believed to result from problems in synaptic communication at glutamatergic, GABAergic, and dopaminergic synapses characterized through altered receptors at the post-synaptic side [73].

We provide a tabular summary of synaptopathies and the affected synaptic communication compartments in Table II.

IV. ENGINEERING SOLUTIONS FOR BRAIN IMPLANTS

In this section, we explore potential solutions for brain pathologies that stem from synergistic and interdisciplinary efforts where experts of the physical sciences, biological sciences, systems biology, and clinicians work in concert.

A. State-of-the-Art

Oral medication, ablative neurosurgical procedures, and neuromodulation techniques are used today to treat synaptopathies. Different techniques interface and intervene with the nervous system with the goal of excitation, inhibition, modification, or regulation of aberrant neural activity. Relative to oral medication and ablative neurosurgical procedures, neuromodulation has the advantage of higher spatiotemporal precision. Neuromodulation involves implantable devices that apply *electromagnetic*, *chemical*, or *optical* modulating variables.

- Electromagnetic agents change the extracellular potential of cells and naturally affect cellular activity. The

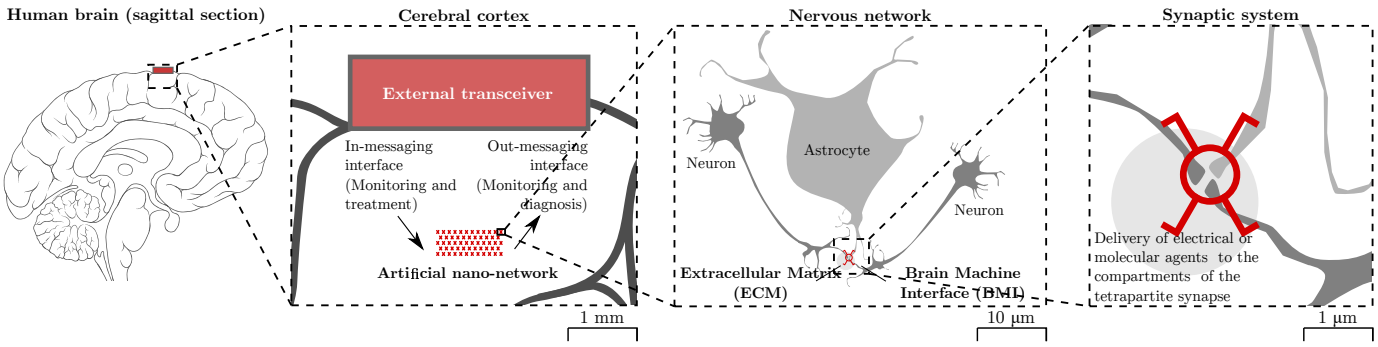


Fig. 7. Future miniaturization and insertion of BMI units in the cerebral cortex. The BMI architecture includes an external transceiver that controls the synaptically interactive nano-devices in the cortex (e.g., via radio-frequency-, optical-, or ultrasonic waves) and provides the energy. The synaptically interactive nano-devices report states of targeted synapses to the external transceiver (e.g., via exosomes). At the synaptic level, they perform excitation, inhibition, modification or regulation of the pre-synaptic terminal, astrocyte, ECM, and post-synaptic terminal delivering electrical and molecular agents.

most common clinical electromagnetic neuromodulation technologies currently used are *deep brain stimulation* (DBS), *intracranial cortical stimulation*, *transcranial direct current stimulation* (tDSC), and *transcranial magnetic stimulation* (TMS) (see [74] and references therein). An emerging noninvasive neuromodulation technology is magnetogenetics. This technology combines magnetic agents and genetics targeting the iron-binding protein ferritin to the neuronal membrane. A magnetic field is then used either to exert a magnetic force on ferritin or to heat the iron-containing complexes, resulting in neuronal activation [75].

- Unlike electromagnetic agents, potentially more effective chemical agents scarcely enter into the CNS due to the existence of the blood-brain barrier formed by capillary endothelial cells. Chemical neuromodulation techniques use either implantable devices, focused ultrasound, lipophilic vesicles, or nanoparticle formulations to overcome the blood-brain barrier and ensure delivery of adequate chemical concentrations to targeted neural compartments (see [76] and references therein). The state-of-the-art solutions for brain pathologies involve the application of nanoparticles synthesized from various materials (e.g., polymers, lipids, and viruses) [77]–[79]. By using either passive or active targeting strategies, nanoparticles can increase the intracellular concentration of drugs in neurons via receptor-mediated endocytosis while preventing toxicity to other cells. Molecular communication paradigm has been recently proposed to model the particulate drug delivery systems as communication systems [80]–[84], and allow the optimization by appropriately designing the nanoparticles to maximize their ability to deliver therapeutic effect in a timely and efficient way. The optimization also refers to the mode of administration and dosage optimization by determining the nanoparticle injection rate in terms of nanoparticle concentration, the timing of the dosage, and the location of injection. However, to optimize brain drug delivery systems, the existing molecular communication models need to be revised and modified to include the stringent blood-brain barrier as the essential bottleneck component of the communication channel if nanoparticles are applied intravenously.
- A neuromodulation technique, called optogenetic neuromodulation, combines optics and genetics. The key reagents in optogenetic neuromodulation are light-sensitive proteins (channelrhodopsin and halorhodopsin) that express light-sensitive ion channels. Optogenetic neuromodulation has better precision compared to electromagnetic and chemical neuromodulation [85], [86].

Central to advancing neuromodulation and developing novel brain implants is increasing the accuracy by which neuromodulation generates therapeutic effects, and reducing untoward side effects. A promising strategy is to minimize the size of electronic devices to micro- and nano-scale enabling them to perform targeted sensing and actuation tasks.

Berger and his team proposed a miniature *hippocampal cognitive neural prosthesis* to address damage to the hippocampus and surrounding regions of the temporal lobe resulting in a permanent loss of the ability to form long-term memories [11]. The basic idea in his research is to replace damaged tissue (CA3-CA1 path) with an artificial system that mimics the functions of the original neural circuitry. The hippocampal cognitive neural prosthesis consists of a low-noise amplifier, an analog-to-digital converter, an action potential sorter, a programmable hippocampal neural network integrated circuit, and a charge-metering stimulus amplifier. A programmable hippocampal neural network integrated circuit is a core module of the prosthesis that converts short-term memory into long-term memory. This conversion, that is the fundamental step during the learning process, is based on a mathematical model of processes by which the hippocampal CA3 and CA1 regions encode memory items via spatiotemporal neural encoding of short-term memory [87]. The programmable hippocampal neural network integrated circuit has been recently fabricated in 40 nm technology with a core area of 0.122 mm^2 and test power of 84.4 μW [88].

Maharbiz and his team proposed an ultra-miniature wireless system built from low-power CMOS circuitry coupled with ultrasonic power delivery and backscatter communication [89]. The system enables massive neural recordings from the brain utilizing thousands of 10–100 μm scale sensor nodes, called

neural dust, and a *sub-cranial interrogator*. The neural dust senses and reports local extracellular electrophysiological data. The sub-cranial interrogator provides power and communication links to the neural dust. Muller and her team [90] have recently upgraded the neural dust without sacrificing the micro-scale size by proposing the stimulation in a system called *StimDust*. The StimDust senses peripheral nerves and treats disease in a patient-specific approach. The StimDust is 6.5 mm^3, 10 mg wireless peripheral nerve stimulator tested *in-vivo* at the sciatic nerve of an anesthetized rodent.

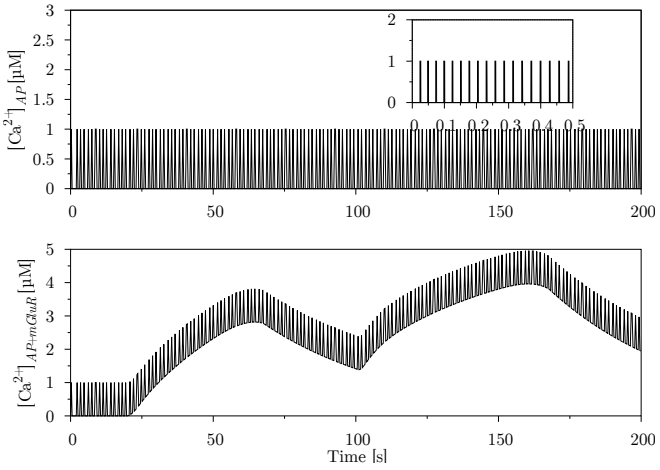
Balasubramaniam and his team proposed the hybrid wireless optogenetic neural dust, called *Wi-Opt Neural Dust*, that integrates the wireless optogenetic component to the neural dust to provide nerve stimulation [91], [92]. The Wi-Opt Neural Dust has a built-in miniature LED able to stimulate the genetically engineered cells and harvest energy from ultrasonic vibrations. Unlike the StimDust, the Wi-Opt Neural Dust is still in its conceptual phase.

B. Future Cognitive Brain-machine Interfaces

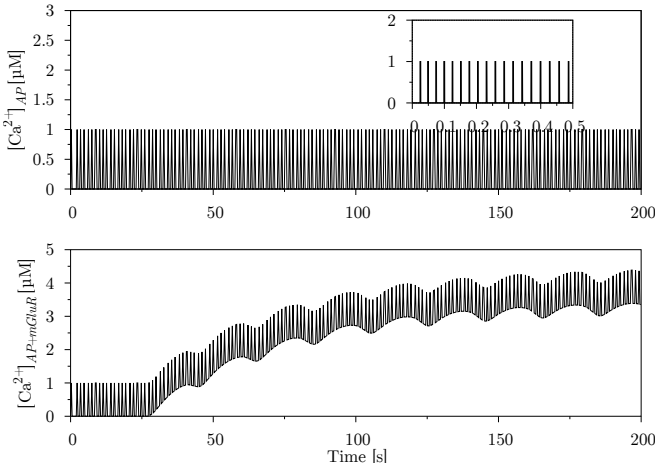
New ideas and concepts in neuroscience started with the development of nanomaterials, nanotechnology, and molecular communications. Nanomaterials enable superior neural stimulation techniques involving opto-electric, opto-thermal, magneto-electric, magneto-thermal and acousto-electric transduction mechanisms (refer to [93] for a review). However, an emerging approach in nanotechnology is constructing sovereign *biomimetic electronic nano-devices*. In clinical neurology, the biomimetic nano-device is anticipated either to interact with biological neurons to perform excitation, inhibition, modification or regulation of biological activity, or to replace dysfunctional or dead neurons (e.g., in Huntington disease affected brains) (Fig. 7). The synaptically inter-connected neural-like nano-devices able to collaboratively execute complex neural tasks in a distributed manner lead to the concept of *neural artificial nano-networks* [94], [95].

A promising strategy in the design of biomimetic nano-devices is to apply a *bio-hybrid approach* [96]. The bio-hybrid approach hinges on the use of existing biological cells as models for the development due to the dimensional similarities. Biological cells operate as fully functional miniature devices evolutionary engineered to signal or communicate messages from a cellular perspective and keep organisms alive.

Several theoretical studies of "physical layer" in synaptic communication have been developed in this decade to understand how single neurons integrate, process and communicate electrochemical and molecular signals [22], [24], [97]–[99], and interact with the surrounding glia [42], [43]. Important models have evolved within the EU project MINERVA: *Communication Theoretical Foundations of Nervous System Towards Bio-Inspired Nanonetworks and ICT-Inspired Neuro-Treatment* (FP7-IDEAS-ERC #616922) [25], [34], [100], [101]. MINERVA has significantly contributed to bridging the gap between life sciences and communication engineering. Jointly, the models apply engineering abstractions and tools to characterize the neuro-anatomical and physiological properties by communications systems and communication-theoretical



(a) Scenario with constant astrocytic activation with a square wave sustained for 60 seconds and repeated at $t = 120$ seconds. Upper plot: the intracellular calcium concentration due to action potentials; every time an action potential reaches the pre-synaptic terminal, a rapid increase of calcium level is observed in the terminal (values are normalized to the maximum). The inset is a zoomed-in portion of the main plot. Lower plot: the intracellular calcium concentration due to action potentials and glutamate from the astrocyte; in correspondence of astrocytic glutamate release, further calcium ions flow into the terminal, increasing the calcium level.



(b) Scenario with astrocytic activation with a square wave with duty cycle equal to 33% active for 10 seconds (the inactive phase is 20 seconds).

Fig. 8. Astrocyte-mediated excitation of vesicle release through controllable intracellular calcium concentration at the pre-synaptic terminal (*in-silico* study) [42].

measures (e.g., signal attenuation, signal delay, range, reliability, signal-to-noise ratio, and energy consumption), and contribute to:

- understanding the impact of an artificial stimulation applied to neurons or even glia (see Fig. 8) in order to induce a certain response to the targeted neurons,
- identifying the role and significance of specific compartments either within the pre-synaptic sub-system, synaptic channel, or post-synaptic sub-system in the communication process, and
- providing further tools for the design and implementation of biomimetic devices mimicking the behavior of neurons and glia at the micro- and nano-scale.

Although detailed disease-specific communication models po-

tentially crucial in remedying synapse dysfunctions are missing, the existing models are complemented with studies on information processing and quantification. They provide information-theoretical measures (e.g., transmission rate, capacity, and error rate) essential in identifying aberrance in neural encoding and decoding. Several studies addressed through Shannon's information theory quantified the ability of sensory neurons to encode dynamic stimuli [19], [25], [102]–[107], and the ability of post-synaptic neurons to receive the message from pre-synaptic neurons [26], [108]–[110]. These studies are central to monitoring information transfer over synapses and diagnosing synaptopathies reviewed in Section III, as well as ways prospective nano-devices synaptically inter-connect and interface to biological neurons. Thus, a core module of the future BMIs will be based on the mathematical models defined in these studies.

The design of an interface between prospective nano-devices and neurons is challenging and requires devoted studies and experiments. Apart from optical fibers [111], individual neurons have been interfaced with hybrid structures consisting of arrays of nano-wire field-effect transistors intended for detection, excitation, and inhibition of neural signal propagation [112]. The nano-wire field-effect transistors are supposed to provide electrical stimuli to create a detectable action potential in the targeted cell (see [112, Fig. 1 and Fig. 2]). Conceptual alternatives are sensors able to emit an agent invoking trans-membrane calcium chemical signaling which leverages the vesicle release and induces signaling between cells [113], and nano-devices, called *Synaptic Nano-Machines* which interact with the targeted neuron establishing additional connexon channels and allowing the flow of ions and currents [114], [115].

Unlike approaches of diagnosis and treatment of brain pathologies with bio-nano-device interfaces that affect molecular communications in neural synapses, a novel trans-disciplinary approach analyzed in the recently granted EU project GLADIATOR: *Next-generation Theranostics of Brain Pathologies with Autonomous Externally Controllable Nanonetworks: a Trans-disciplinary Approach with Bio-nanodevice Interfaces* (EU-H2020-FET-Open #828837) is mediated by molecular communications. The approach bridges synthetic biology, cellular biosciences, nanobiotechnology, biomedical engineering, and communication and information technology to provide an autonomous BMI-platform for the management of malignant brain tumours. The conceptual platform is an architecture of cell-based and electronic components also applicable for the management of synaptic brain disorders. Cell-based components consist of organoids of engineered *neural stem cells* which synthesize and release *exosomes* acting as natural bionanodevices. Exosomes — cell-derived extracellular vesicles — propagate by means of controllable molecular communications to interfere with the underlying disease pathways and provide a breakthrough therapeutic intervention. Exosomes-mediated communication between pre- and post-synaptic neurons participates in the maintenance of neural homeostasis and in the modulation of synaptic plasticity [116]. A hybrid bio-electronic interface consists of coupled external and implantable electronic components. External miniature wearable components provide communication, ultrasound power transfer, and radiofrequency stimulation for the potentiation of reprogramming neural stem cells and exosomes. Implantable biological and electronic components provide the exosome reporting.

V. Open Research Questions

Focusing on communication-theoretical modeling, we outline the framework in Fig. 9 for completing the development of novel nanotechnology-based diagnosis and treatment techniques.

A. Theoretical Development and Verification

Despite various communication-theoretical studies of synaptic communication over the last decade, some basic aspects remain insufficiently characterized or uncharacterized, in particular those pertaining to the interaction of neurons with glia (astrocytes, oligodendrocytes, ependymal cells, and microglia) and the ECM:

- Open directions for future investigation on glial feedback include analysis of essential brain processes such as *plasticity*, *learning*, and *memory*. Activity-dependent synaptic plasticity is believed to underlie learning and memory, and the development of neural circuits [3]. Synaptic plasticity refers to the ability of synapses to strengthen or weaken over time based on correlations of pre- and post-synaptic firing. The synaptic dynamics implies time-variance which then require more rigorous mathematical analysis where glutamate-dependent receptors located on the post-synaptic terminal have a leading role.
- Open directions for future investigation on the ECM-impact on synaptic communication include creation of pioneering communication models that will embrace the modulation of ion channels and receptors, in particular, the voltage-controlled calcium gates at the pre- and post-synaptic terminal, and the AMPAR and NMDAR at the post-synaptic terminal, as we indicate in Fig. 3.
- Open directions for future investigation of the nervous system include the analysis of "data-link and network layers" that will include the population of neurons and reveal medium-access and biological routing techniques.

The aforementioned areas remain challenging tasks whose addressing completes the first phase in the modeling of functional healthy synapses (Fig. 9). The next phase is to establish communication models for each specific synaptopathy from Section III and, optimally, individualize for each specific patient to augment the effect of diagnosis and treatment. Disease- and patient-specific models will provide valuable insights into disease mechanisms and optimization of agent release from BMIs (Fig. 10). The main challenge in designing such models is experimental parameterization. For a parameter to be validated, it needs to be reproducible and clinically comparable reflecting a physiologically sound process.

Central to verification of theoretical communication models is correlating them with *in-vitro* and *in-vivo* physiological and pathological behaviors of individual neurons and synapses. This requires adequate experimental recordings of

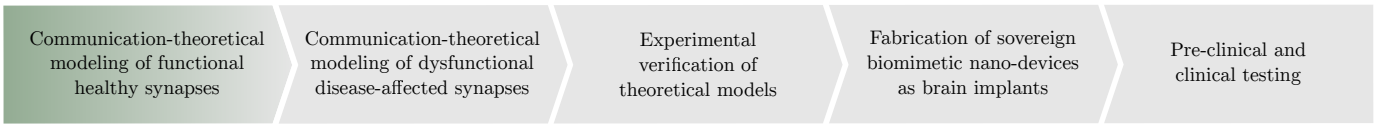


Fig. 9. Framework for developing nanotechnology-based diagnosis and treatment techniques for synaptopathies. Gray color indicates open research problems.

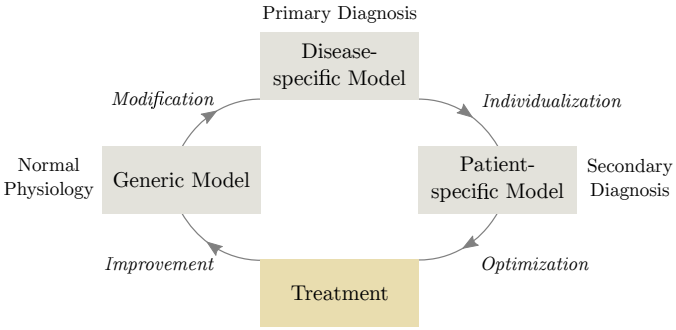


Fig. 10. Optimization of medical treatment through disease-specific- and patient-specific models.

the electrical activities of individual neurons and synapses with high spatiotemporal resolution and electrical sensitivity. Electrophysiology is the branch of neuroscience that explores the electrical activity of neurons: action potentials, graded potentials, and the functions of ion channels. The three main categories of electrophysiology techniques are defined depending on the recording electrode placements in the neural specimen: *extracellular recordings* (the electrode is placed outside the targeted neuron), *intracellular recordings* (the electrode is inserted into the targeted neuron), and *patch clamp techniques* (the electrode — a glass micropipette — is placed to make tight contact with a tiny area, or patch, of neuronal membrane) [117]. An alternative to these three categories is optical imaging based on voltage- and calcium-sensitive dyes [118].

Many approaches have been taken toward the goal of exploring neural activity at individual synapses [119]. Some of the techniques include: the patch-clamp or loose patch of synaptic boutons, restricting perfusion to selectively enable release, local stimulation of release with high potassium or sucrose, local stimulation of release by electrical means, activation with toxin, optical activation, minimal stimulation of axon bundles to evoke release from a single site, amperometric measurements of single vesicle release, imaging calcium transients, imaging vesicle activity, and ultrasensitive graphene optoelectronic probes [120].

B. Nano-device Fabrication and Testing

The ability to scale the electronic devices to the size of a typical neuron is challenging. Applying nanotechnology and nanomaterials may give us the ability to produce miniature cognitive BMIs with improved electrical and mechanical properties [121]. Nanotechnology has already drastically improved fabrication methods of neural electrodes (nanoelectrodes, nanoelectrode arrays, and nanoelectrode ensembles) demonstrating greater bio-integration properties, enhanced prolonged electrical properties, and an improved signal specificity. Promising nanomaterials for fabrication of future BMIs include carbon-based materials (graphene and carbon nanotubes), conducting polymers, hydrogels, and hybrid materials that ensure long-term stability, sufficient mechanical strength and toughness, and low thermal noise. Among these materials, graphene-based materials provide a versatile platform that might address the following technological challenges in neural interface design [122]:

- Electrical stimulation that allows the creation of signals at individual neurons: Porous graphene oxide electrodes have been reported to stimulate neurons with charge injection values between 1 and 3 mC cm^{-2} and devoid damage or adverse reaction [123], [124]. Structured or 3D films of graphene-based materials and composite films including graphene are also reported to show great potential.
- Recording capabilities that allow detection of signals at individual neurons: Graphene offers a unique advantage by enabling fabrication of sensors based on a field-effect transistor configuration, that reduce the sensitivity to external noise due to their intrinsic signal amplification and allow a high level of integration density [125].
- Excellent biocompatibility, biodegradability, and mechanical compliance of the neural tissue: Good biocompatibility and biodegradability features of graphene that help to minimize foreign-body reaction have been reported in the literature [126], [127].

Finally, another emerging challenge is the ability to communicate and power cognitive BMIs avoiding the side effects that can occur to the brain [92].

The ultimate phase in the framework outlined in Fig. 9 is confined to pre-clinical testing in cells, organoid structures (organ-on-a-chip), and animals, before human studies and clinical testing. Apart from technical challenges, this phase raises ethical, social, and legal challenges with regards to personhood, stigma, autonomy, privacy, research ethics, safety, responsibility, and justice [128].

VI. Conclusion

Research related to future nanotechnology-based brain devices and clinical applications is an emerging field that brings together specialties in the fields of medicine, biology, materials science, biomedical engineering, communications engineering, and computer science. Developing novel brain implants thus requires effective collaboration between basic scientists, engineers, and clinicians. Recent theoretical advances made in the field of molecular communications and understanding the elemental communications principles of functional brain synapses are essential for brain machine interfaces (BMIs) that can

alter, regulate, and mimic synaptic pathways. While important progress has been made in bionanotechnology towards the realization of synaptically interactive BMIs, numerous open research questions must be solved before clinical applications are realistic. With increased scientific activity, we anticipate fabrication, testing, and, ultimately, implementation of synaptically interactive BMIs to clinical use in the coming decade.

ACKNOWLEDGEMENT

The authors would like to thank Dr. Jacob Bergsland for constructive comments and discussions. This work was supported in part by the EU under grants #675353 (EU-H2020:MSCA:ITN WiBEC – *Wireless In-body Environment Communications*) and #828837 (EU-H2020-FET-Open GLADIATOR – *Next-generation Theranostics of Brain Pathologies with Autonomous Externally Controllable Nanonetworks: a Trans-disciplinary Approach with Bionanodevice Interfaces*), and the Research Council of Norway under grant #270957 (RCN:WINNOW – *Wireless In-body Sensor and Actuator Networks*).

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