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Microbiome-Gut-Brain Axis as a Biomolecular Communication Network for the Internet of Bio-NanoThings

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ABSTRACT This article presents fundamental challenges in the development of a self-sustainable and biocompatible network infrastructure to interconnect the next-generation electrical and biological wearable and implantable devices, i.e., the Internet of Bio-NanoThings. The direct contact of IoBNT devices with the human body, where the cells naturally communicate and organize into networks, suggests the possibility to exploit these biological communications for the device-to-device interconnection. The aim of this work is to investigate minimally invasive, heterogeneous, and externally accessible electrical/molecular communication channels to transmit information between these devices through the Microbiome-Gut-Brain Axis (MGBA), composed of the gut microbial community, the gut tissues, the enteric nervous system. A framework to develop a network infrastructure on top of the biological processes underlying the MGBA, and the intercommunications among its components is proposed. To implement this framework, the following challenges need to be tackled. First, physical channel models should be developed to quantitatively characterize electrical and molecular communications through the MGBA. Second, novel technological solutions in information modulation, coding and routing should be developed. Third, to support these efforts with experimental data, a first-of-a-kind implantable MGBA network probe device composed of a hub connected to an ensemble of electrical and molecular stimulation and sensing modules should be designed and engineered, together with an innovative gut-on-a-chip in-vitro model system. The discussion in this paper establishes the basis for a completely novel transdisciplinary networking domain at the core of the next-generation biomedical systems for pervasive, perpetual, and remote healthcare.

INDEX TERMS Molecular communication, nanonetworks, Internet of Bio-NanoThings, intra-body networks, biomedical implants, biosensors.

I. INTRODUCTION

Over the last decade, the transformative concepts of information processing and propagation in the molecular domain have dramatically reshaped the frontiers of communication and networking research, with biomedicine as a natural application field [1].

As a result, nanotechnology and biotechnology-enabled wearable and implantable devices with ever increasing biocompatibility and operational autonomy are being developed. These devices promise to pervasively, perpetually, and precisely sense, process, control, and exchange body health parameters in real time, and allow remote interrogation, which we classify under the paradigm of the Internet of Bio-NanoThings (IoBNT) [2]. This paradigm will enable accurate sensing and control of complex biological dynamics

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in the human body, and eventually be the basis of the next-generation biomedical solutions for unsolved clinical problems.

The IoBNT is envisioned to be a heterogeneous network of electronic and biological devices, deployed inside and outside of the body as shown in Fig. 1, communicating through different means, ranging from electromagnetic waves and coupling, electrical and mechanical stimulation, to Molecular Communication (MC) [1]. Electronic devices comprise implantable and wearable electronic devices such as brain implants, pacemakers, and smart watches, whereas biological devices comprise manipulated natural cell and tissues or man-made synthetic ones such as engineered immune system cells, engineered gut microbes, and artificial cornea.

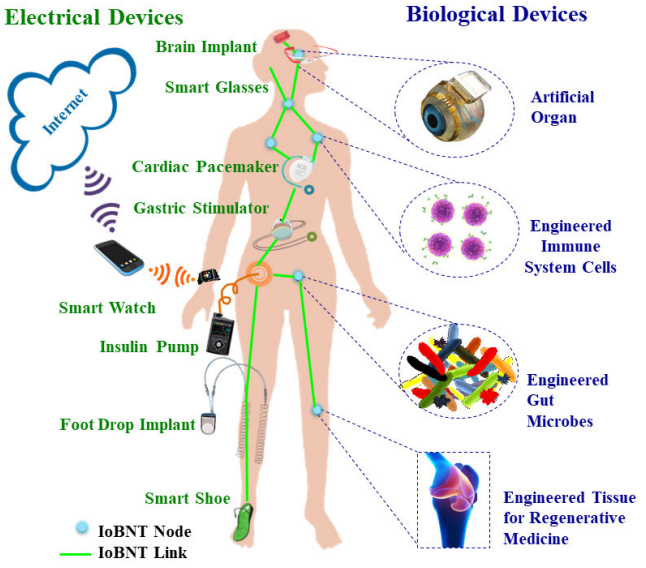

FIGURE 1. The Internet of Bio-NanoThings paradigm.

Developing the IoBNT communication network infrastructure requires the following main prerequisites: (i) integrating accurate and predictable models of communication and networking parameters, (ii) minimizing the interference with natural body functions in order to prevent any psychological or physical discomfort, (iii) interconnecting heterogeneous devices (electrical and molecular), (iv) accessibility from outside the body in a minimally invasive fashion.

These requirements greatly reduce the practicality of classical telecommunications solutions, especially for realizing intra-body IoBNT links [2]. The direct contact of the IoBNT devices with the human body, where cells and multicellular organs naturally communicate and interconnect into networks, suggests the possibility to exploit these biological communications for the interconnection of these devices. Therefore, in this paper we detail a conceptual framework for the realization of a network infrastructure where **artificial communications between wearable/implantable devices are realized by exploiting natural biological communications systems in the human body**.

The focus of the conceptual framework introduced in this paper will be the **Microbiome-Gut-Brain Axis (MGBA)**, where electrical signals propagating through the nervous system are converted to molecular signals that influence the gut microbial communities, and *vice versa*. The information propagates by means of natural communication links and interfaces, which are present in the nervous system, the endocrine system, and the immune system [3]. The holistic nature of the MBGA encompasses electrical and molecular communication domains and interfaces between them. The accessibility of MBGA from the external environment through the alimentary canal, and the presence of microbial cells, which are genetically programmable as biological devices, make this system particularly interesting to explore in light of the IoBNT paradigm. A direct connection with the MGBA will also provide a large amount of data about the health of the central and autonomous nervous system, as well as the gut.

This article discusses the **utilization of the MGBA as an IoBNT communication network infrastructure** to transmit and receive information generated by and/or directed to electronic and biological devices, as shown in Fig. 2, where this infrastructure is also envisioned to communicate with the external environment through dedicated molecular (alimentary canal) and electrical (wireless data transfer through skin) interfaces.

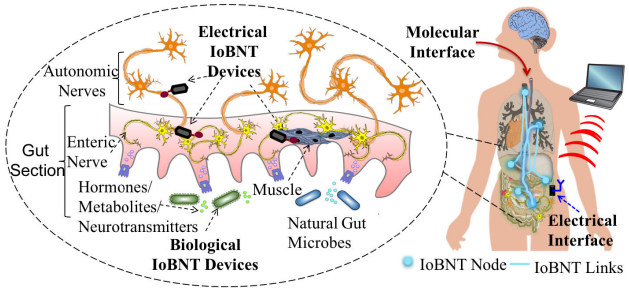

FIGURE 2. Microbiome-Gut-Brain-Axis IoBNT communication network infrastructure.

To this end, we present a methodology that comprises both analytical and experimental efforts. The analytical effort builds on top of neuroscience and bioinformatics to abstract and model with reliable mathematical expressions the propagation of device-sourced information through biological tissues utilized as communication channels, which include the modeling of i) electrical communications between devices connected through nerves in the gut muscle, enteric, and autonomic systems; ii) molecular communications involving biological devices and natural gut microbes through interactions with hormones, metabolites and neurotransmitters, and iii) the heterogeneous electrical and molecular communications interface between the gut and the central nervous system. The experimental effort is based on the design of a unique integrated network probe device composed of a hub connected to an ensemble of electrical and molecular stimu-

lation and sensing interfaces. This probe device is intended to be first utilized in an *in vitro* environment, which is composed of an innovative gut-on-a-chip system able to co-culture cells that compose the MGBA. Then, an implantable version of the probe, which explores wireless power and data transfer technology to establish connectivity with the external environment, is to be utilized into laboratory rats to collect *in vivo* data on the MGBA communications. On top of these models and experiments, as part of our methodology we introduce design elements, opportunities, and challenges to realize the aforementioned IoBNT network infrastructure.

This paper is organized as follows. In Sec. II, we detail how analytical models of communication channels for device-to-device communications can be derived from models of biochemical processes underlying the MGBA. In Sec. III, we describe a methodology to design devices to derive empirical data to complement the analytical channel models in *in vivo* and *in vitro* settings. In Sec. IV, based on the MGBA-based channel models, we describe the main element of a network infrastructure of IoBNT applications, as well as the main features of a simulation environment to aid the design of such networks. Finally, in Sec. V, we draw our conclusions.

II. ANALYTICAL METHODOLOGY

The MGBA refers to the bidirectional communication network between the brain and the gastrointestinal tract, which in general includes the Central Nervous System (CNS), the Autonomic Nervous System (ANS), the Enteric Nervous System (ENS), the gastrointestinal tract, and its microbiome [3]. According to recent studies [4]–[6], through the MGBA, the gut microbiota influences brain functions, behavior, stress and pain modulation systems, and brain neurotransmitter systems, whereas the brain controls gut motility, gut wall permeability and microbial composition. On the one hand, the electrical stimulation sent from the CNS goes through the autonomic nerves reaching the enteric nerves, enteric muscles, and further the cells in the intestinal walls, surrounded by the gut mucosa. The incoming electrical signals are transduced to molecular signals by these cells and then released to the gut lumen (internal space of the gut) in the form of secretion of acids and mucus, and immune system products. These molecular signals affect the communication among gut microbes and alters their community composition [7]. On the other hand, the changes in the gut microbial community interactions, composition, or secretion of compounds such as hormones, metabolites and neurotransmitters, at the gut mucosa are detected by the cells in the intestinal walls as molecular signals, which are transduced to electrical signals by these cells and propagate back to the CNS through the ENS and ANS [6].

Along with the fundamental expertise accumulated on molecular communication and nanonetworks [8], in recent years the ability to successfully apply fundamental communication engineering abstractions, concepts, and modeling strategies to characterize biological systems has been demonstrated. Examples can be found in the study of drug propagation in the cardiovascular system [9], information flow through engineered bacteria [10] and gut microbes [11], and communications via peripheral nerves [12].

In this paper, by stemming from some of the aforementioned examples, we describe the ambitious challenge of modeling the complete, complex, and heterogeneous MGBA communications. In this direction, it is essential to define physical channel models of *electrical communications* through nerves and muscles; *molecular communications* involving gut microbes and their interactions with hormones, metabolites and neurotransmitters; and the *transduction between electrical and molecular communications* through the MGBA. Within each of the aforementioned modeling efforts, the MGBA-based channels need to be characterized in terms of

(i) admissible input-output value and frequency ranges within biocompatible boundaries,
(ii) delay between a stimulation onset and the sensing of its consequences after propagation through the channels,
(iii) noise and variability of the input-output response,
(iv) cross-talk with natural communications and with other simultaneous stimulations.

A. PHYSICAL CHANNEL MODELS OF COMMUNICATIONS THROUGH ENTERIC AND AUTONOMIC NERVES, AND MUSCLE ACTIVITY

The modeling of electrical communication channels through the MGBA stems from neuroscience literature [13], where the processes underlying electrical signal propagation through neurons are described. Different options for electrical stimulation and electrical activity sensing should be considered for transmitting information signals between devices through the ENS. These signals should be minimally interfering with the natural gut functions, but at the same time exploiting any possible stimulation pattern to maximize the information capacity between a stimulation and a sensing location.

Previous efforts on modeling the information transmission through neurons by communication theory focus on the propagation of signals carrying natural information but lack the methodology describing how artificial information can be transmitted without interfering with the natural information flow. In particular, in [14], the authors develop a physical channel model of the neuro-spike propagation between two interconnected neurons investigating the probability of error and delay. In [15], a specific part of the neuron, the synapse, is investigated to characterize the propagation of the spiking rate function between neurons. In [16], multiple synaptic paths directed to a single postsynaptic terminal is modeled and the information rate per spike is derived. This work has been extended to compute the ergodic capacity of the synaptic Multiple-Input Multiple-Output (MIMO) communication channel [17]. Another approach models neuron-to-neuron communication by a frequency response dividing it into intra-neuronal and inter-neuronal blocks [18].

To tackle the problem of transmitting information signals between devices interfaced with neurons, we briefly review the system proposed in [12], [19]. In particular, this system utilizes the so-called **subthreshold electrical stimulation**, which potentially allows the propagation of artificial information from one end of the neuron to the other end minimally interfering with the natural neuro-spike communications occurring at the same neuron.

As shown in Fig. 3, we consider the **Sender**, which modulates the injection of electrical current $I_i(t)$ into the soma according to the signal to be transmitted. The **Channel** corresponds to the membrane potential perturbation resulting from the current injection, and its propagation along the axon. The **Receiver** recovers the transmitted signal by reading the membrane potential $V_o(t)$ at a distance x from the soma along the axon. This system can be described with a linear channel model by leveraging the quasi-active model of the neuron's membrane from neurophysiology literature [20]. This linear model of electrical signalling through a single neuron is valid only when the membrane potential maintains a value less than V_{th}, named subthreshold condition, which typically ranges from -60 mV to -55 mV, where there is no stimulation of a neuro-spike, or Action Potential (AP) [13]. This threshold defines the admissible input-output values of this communication system. An analytical model of the transimpedance (V_o/I_i) of a single neuron is derived as function of the input frequency components. By studying this model for the propagation of electrical signals through a neuron, the frequency range, the attenuation, and the delay can be extracted as parameters that will be the constraints for the design of modulation and coding techniques and medium access control protocols, described in Sec. IV-A.

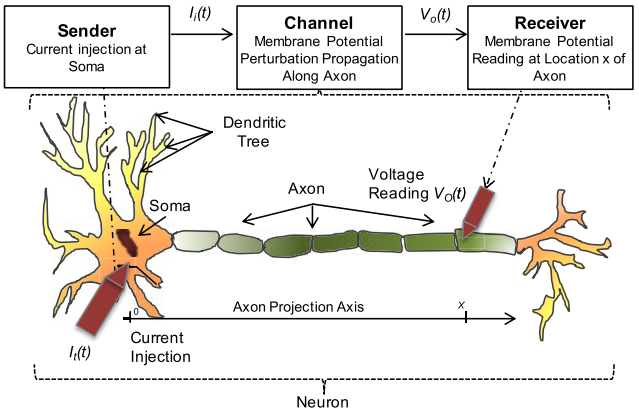

FIGURE 3. Scheme of a single-neuron-based communication system [12].

To obtain channel models of electrical communications in the MGBA over its neurons, the aforementioned studies should be complemented by existing mathematical and computational models from enteric neurobiology [21]. These computational models represent the natural communication processes in enteric nerves, their interconnections with the autonomic nerves, and the impact of these communications on muscle dynamics. Models describing the chemistry, the morphology, and the connectivity of the ENS neurons can be found in the literature [21]. In addition, the result of electrical signals in the ENS such as muscle contractions and mucosal secretion are observable and measurable [22]. These two properties make the ENS stand out in terms of possibility to obtain quite accurate models compared to other parts of the nervous system [23]. For this aim, biophysics-based mathematical models of individual neurons, *e.g.*, Intrinsic Sensory Neurons (ISN), should be considered. ISNs are the building blocks of ENS since they connect every neuron type in the ENS and make recurrent connections with themselves [24].

To capture the peculiarities of the enteric neurons, the aforementioned channel models should be revisited by considering cross-talk interactions with natural AP-based communications through leaky-integrate-and-fire models [25] coupled with the After-Hyperpolarizing (AH) potential characteristic of enteric neurons, which represents the decrease of the membrane potential below the resting potential following the peak of the AP [23]. Furthermore, the synaptic models should be refined for different types of enteric neurons adopting either slow [26] or fast [27] Excitatory PostSynaptic Potential (EPSP) at the receiving neuron. The observable output of the ENS, *i.e.*, the mechanical contraction of smooth muscles stimulated by electrical signals, can be modeled based on the conductance model [28] of muscle fibers.

On top of these models describing single neurons and connection of neurons, the topology of neuron interconnections is built either randomly into anatomically relevant mesh structures [28] or following the topology extracted by experiments. In addition, models of the interconnection with the autonomic nerves, and the correlated myoelectrical activity of the smooth muscle should be incorporated, as described in [21]. Noise should be also considered by integrating stochastic models, such as [29], [30]. Another noise source is the person-to-person variability in the ENS mesh structure, which should be taken into account to increase the reliability of the communication channels in the IoBNT infrastructure.

B. PHYSICAL CHANNEL MODELS OF COMMUNICATIONS THROUGH THE GUT MICROBIAL COMMUNITY

As part of the conceptual framework detailed in this paper, communication channels in the gut are based on the paradigm of MC [1], where the transmission, propagation, and reception of information is realized through molecules and chemical reactions. In particular, in our framework the communications through the gut are based on the release and sensing of molecules and/or the manipulation of the microbial community composition in the mucosa and lumen. The release of molecules can be realized through ingestion, injection, or by engineered microbes, and sensing can be realized through excretion samples, biological sensors, or engineered microbes as well. As in Sec. II-A, this information transmission should be minimally interfering with the natural gut functions, and at the same time maximize the information capacity of these channels.

To evaluate the feasibility of such channels, the theoretical information transmission performance in terms of mutual information has been estimated in [10] for an *E. coli* bacterium, and in [11] for other two gut bacteria species. This estimation is based on the bacteria metabolism, defined as the complex network of chemical reactions that underlie the conversion of chemical compounds to energy, cellular building blocks, and waste. The transmitted information is encoded into the release rate, concentration, molecule type or release times of chemical compounds in the proximity of the bacterial cells, where the chemical compounds participate in metabolic chemical reactions within the bacterial cells as shown in Fig. 4. These chemical reactions are chained into pathways, where input chemical compounds are broken down generating energy, and at the same time biomass, *i.e.*, cellular components, are built up consuming energy. The transmitted information is modulated at the microbes into changes in the cell's behavior such as the growth (biomass) rate, and rates of uptake/secretion of chemical compounds to/from the environment in response to the released chemical compounds. These changes then reflect into the gut microbial community behavior and composition. The transmitted information can then be received by another device by means of the aforementioned sensing techniques, or transduced by the MBGA into nervous system activity, as described in Sec. II-C.

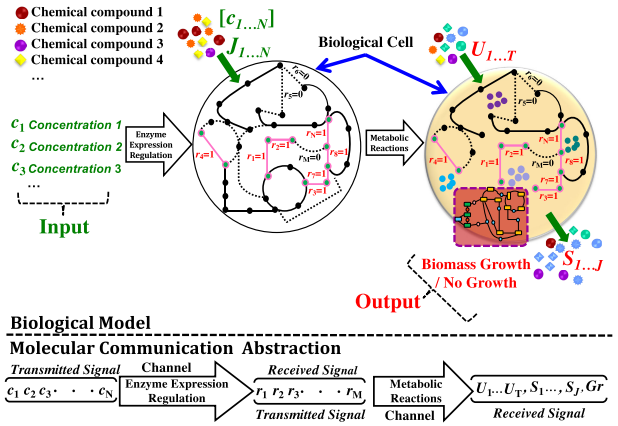

FIGURE 4. Scheme of a molecular communication channel based on microbial metabolism [11].

To model the aforementioned communication system at a single microbe cell, in [11] the cell metabolism is abstracted as a series of two channels, *i.e.*, the Enzyme Expression Regulation Channel and the Metabolic Reaction Channel, as shown in Fig. 4. Advances in DNA sequencing and metagenomics studies provide a wealth of data on the gut microbes, their metabolism, and their interactions, including their organization into interdependent consortia [31], such as the gut microbial community. The methodology proposed to obtain these channel models stems from bioinformatics techniques for metabolic network modeling and simulation applied to these data, *i.e.* **GEnome-scale Modeling (GEM)** and **Flux Balance Analysis (FBA)** [32]. The results obtained in [11] in terms of mutual information of these channels demonstrate the potential of utilizing species within the gut microbial community to propagate information. In particular, it is observed that the encoding of information into different compounds results into different values of mutual information, which opens the road for optimizing these communication channels with a proper design of information encoding schemes based on molecule release.

To generalize the aforementioned channel models to cover multiple microbe cells and possibly the entire microbial community, a potential approach is to combine multi-community metabolic simulation techniques [33], [34], and ecological models of microbial community dynamics and stability [35] with the theory of diffusion-based and advection-based molecular communication, *e.g.*, as utilized in [9] to model the propagation of information in the cardiovascular system. For the former, mixed-bag FBA and multi-species FBA consider a joint metabolic model of multiple species in steady state, possibly interacting [33], while dynamic FBA (dFBA) [36] focuses on the temporal dynamics of a metabolic model for a single input chemical compound at a time. In contrast, an approach based on ecological mathematical models [35] can include the effects of variable perturbations to the community evolution, such as when microbes are added to the community, or flushed away. A diffusion-based molecular communication channel model, able to represent the diffusion of the molecules between microbes within the mucosa and along the lumen can be derived from the mathematical expression of the molecular diffusion through mucus, *e.g.*, in [37]. By combining these diverse models, similar communication channel metrics as mentioned in Sec. II-A can be derived. In addition, the cross-talk with natural processes should also be evaluated in terms of how much a particular stimulation pattern could result in an unhealthy perturbation of the microbial community dynamics.

C. COMMUNICATIONS FROM/TO NERVOUS SYSTEM TO/FROM GUT MICROBIOME

The MBGA is characterized by an intercommunication of the aforementioned electrical and molecular channels detailed in Sec. II-A and II-B, respectively. We intend to harness this feature to develop a communication gateway between devices interfaced to different systems, *i.e.*, from gut (mucosa, lumen) to the nervous system (ENS, muscles) and *vice versa*. To model this intercommunication, we propose to consider the following main mechanisms:

(i) the modulation of gut microbial community composition alters the chemistry in the gut with consequent modulation of the ENS activity;
(ii) the modulation of the microbial metabolism results in a modulation of secrete metabolites, such as Short-Chain Fatty Acids (SCFA), that have neuroactive properties, or in neurotransmitter themselves, which again modulate the ENS activity;
(iii) the release of signaling molecules (that are small molecules different from the metabolites) by neurons alters the microbial community interactions

(iv) the muscular activity, *e.g.*, a contraction, can mechanically displace the gut microbiota and even change its composition.

As a consequence, the ENS activity model and the microbial metabolic models should be combined with models of the release of signaling molecules and electrical/molecular signal transduction mechanisms, respectively. Furthermore, a biomechanical model such as in [38] and its connection to the ENS model, in particular the myoelectrical activity of the smooth muscle and the aforementioned ecological models, is required to account for the muscular activity. All these modeling efforts should be tuned and validated by in-vitro and in-vivo experiments, projected in Sec. III. In addition, the propagation of molecules across the intestinal wall and tissues can be modeled according to diffusion and convection equations [39]. Unlike previous literature on diffusion-based MC models [8], [10], analogous to free-space channel model in wireless communication, the transport in interstitial space, where molecules should navigate around the cells, diffuse inside and outside of cells is analogous to channel models with reflection and refraction in crowded environments.

III. EXPERIMENTAL METHODOLOGY

The analytical methodology proposed in Sec. II is based on physiological models of the MGBA and its components. These models are in part sourced by existing literature, where available, and in part complemented and tested with the results of the experimental methodology described in this section. In this direction, a **complete gut-on-a-chip (GOAC)** model [40] able to grow samples of the gut tissues, their innervation, and the gut microbial community, with stimulation and sensing interfaces for *in vitro* experiments will be developed for testing electrical and molecular (II-B) channels individually, and their interconnection as described in respectively Sec. II-A, II-B, and II-C, respectively. Subsequently, *in vivo* experiments will be conducted on rats using the **Integrated Network Probe Device (INPD)** described in Sec. III-A, capable of spanning all possible stimulation and sensing modalities of interest for the development and the validation of the MGBA communication channels, towards the realization of the intrabody IoBNT communication network infrastructure described in Sec. IV.

A. DEVICES FOR EXPERIMENTAL VALIDATION OF MGBA CHANNEL MODELS

To support the experimental methodology, interfaces to sense/actuate signals on different MGBA parameters, as well as hub devices that integrate these signals, are envisioned to be utilized both for *in vitro* and as an INPD for *in vivo* experiments, as described in Sec. III-B and Sec. III-C, respectively. This device will record and control signals to/from all the components constituting the MGBA communications such as electrical signals through ANS, ENS, the gut muscular tissue, and molecular signals such as the concentration of molecules (hormones, metabolites, neurotransmitters), as well as the microbial community composition. To this end, we envision a design with multiple **electrical and molecular interfaces** to electrical and molecular stimulators and sensors, *i.e.*, **Bio-NanoThings (BNT)**, and one or more **Hubs** that connect these interfaces to the outside of the body through a wireless power and data transfer link compatible with the Enercage-HC2 system presented in Sec. III-C, as illustrated in Fig. 5. These interfaces will implement the transmitters and receivers introduced in Sec. II. After the testing stage, these interfaces and their connected circuits can be separated from the aforementioned hubs and be the bases to design standalone wearable and implantable IoBNT devices capable of communicating via intrabody MGBA channels.

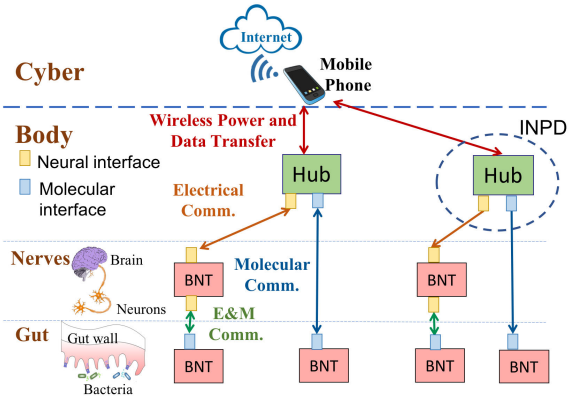

FIGURE 5. Scheme of the design of the integrated network probe device proposed for the experimental methodology described in this paper.

B. IN VITRO EXPERIMENTAL PLATFORM BASED ON ORGAN-ON-A-CHIP DEVICE

The *in vitro* GOAC environment is expected to mimic actual gut functions in a more controllable, low noise environment as a first step towards *in vivo* experiments, allowing us to refine the channel models developed using the methodology described in Sec. II, and subsequently the accuracy of the simulator described in Sec. IV-C. Organ-on-a-chip (OOAC) microfluidic devices aim to create minimal functional units of tissue or organs by reconstituting key structural and physical features. Researchers have fabricated chips to model several tissues and organs, including liver [41], hearth [42], kidney [43], lung [44], intestine [45], and muscle [46], among others. For example, a human GOAC microfluidic device has been developed to study interactions between on-chip cultured human intestinal epithelial cells and the gut microbiome in a setting that mimics the human intestinal microenvironment [47]. In such systems, selected *in vivo* human gut components can be incorporated to create an *in vitro* gut-on-a-chip system. The microfluidic nature of OOAC systems can be exploited to establish a well-defined and controllable microenvironment for the envisioned GOAC capable of monitoring and controlling pH, temperature, delivery of nutrients/oxygen/drugs, and removal of waste. Physiological peristaltic motions, *i.e.*, the natural muscular contractions, can also be mimicked at the chip level through integration of vacuum side chambers to study the mechanical activity.

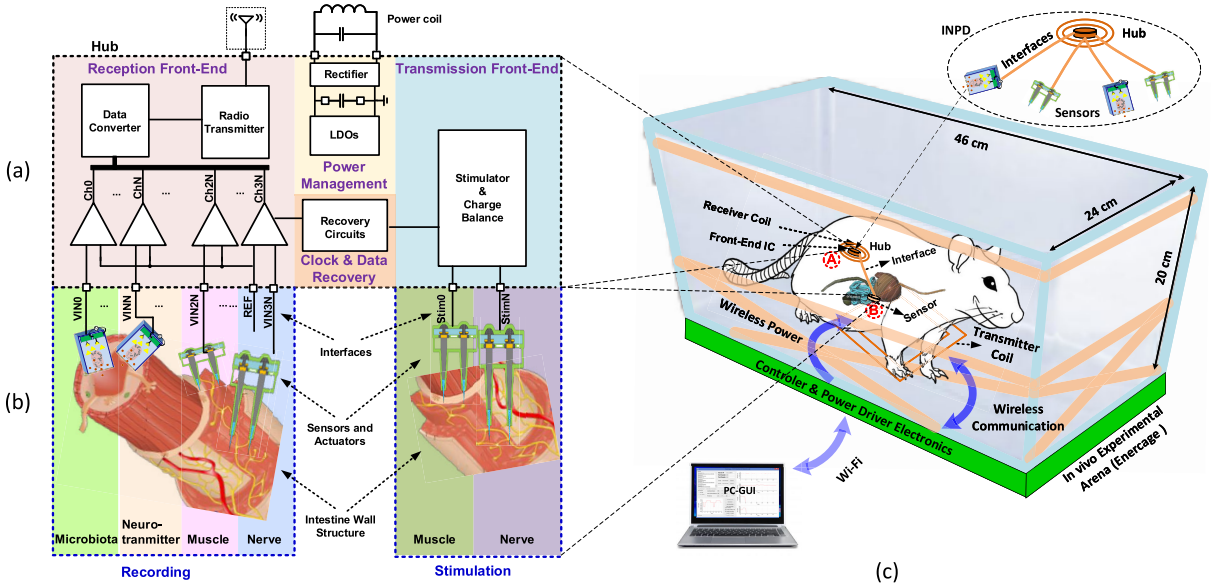

FIGURE 6. Schematic of a) the hub and b) the biological interfaces of the integrated network probe device, and c) *in-vivo* experimental arena.

Due to its controllability, GOAC provides a perfect experimental testbed to study the MGBA communication channels where the individual communication links can be isolated and tested. Also, this platform limits noise and variability among the individuals compared to an *in vivo* setting, which helps in the definition of general models. Moreover, this *in vitro* platform will be also utilized to test the devices and interfaces designed considering the criteria described in Sec. III-A to assure accurate operations and biocompatibility before conducting *in vivo* experiments. In this controlled environment by tuning system parameters to extremes, limits of operation without damaging tissues and altering the microbial balance will be examined.

While GOAC systems can achieve control over specific individual aspects of the tissue environment, existing examples are still relatively simple compared to the actual gut ecosystem. To create a GOAC more reflective of the physiological function under test is a challenge that needs to be addressed. Other challenges include culturing human intestinal cells, living microbiota and enteric nerves in the same chip while maintaining cell viability.

C. IN VIVO EXPERIMENTAL PLATFORM

Following the *in vitro* experiments, refined channel models for communications over the MGBA and tested devices capable of interfacing with the MGBA will be integrated to be tested further in an *in vivo* experimental platform. In order to capture other unexpected properties of the actual body environment and dynamically measure communication parameters, *in vivo* experiments should be on animal models. In preclinical studies, researchers prefer to use small animal models such as rodents because of lower cost, rapid growth, ease of maintenance, and similarity of their biological and behavioral characteristics to those of humans. Here, we describe our methodology based on rat models, which are very suitable to observe the overall effects on a living subject in its natural environment.

A wireless experimental arena, called **EnerCage-HC2**, will host the rats to provide more natural conditions for long time continuous experiments than conventional methods which limit their mobility by tethered wires [48]–[50]. Any device implanted in the rat will be connected to the cage using magnetic induction links for wireless power and data transfer. The EnerCage-HC2 system, presented in [51], is built around a standard homecage using a new 4-coil inductive link which powers wirelessly and communicates with a stimulating headstage [52]. Wireless power, in the EnerCage system, is delivered in the near-field domain at 13.56 MHz, a Federal Communications Commission (FCC) approved operating frequency for Industrial, Scientific, and Medical (ISM) applications.

For *in vivo* experiments, a novel device implanted in the rat's body as shown in Fig. 6 is needed to stimulate and record electrical and molecular signals exchanged over the MGBA to test the aforementioned MGBA channels. The details of design for this implantable device which will be directly in contact with MGBA components such as nerves and gut microbes via its interfaces, as described in Sec. III-A. This device will also be connected to the EnerCage-HC2 to relay commands from outside the body to the device and the information collected from the body to the outside during the tests. Using this device, the limits of operation to interfere with the natural body functions and to alter cells or tissues will be tested in order to define electrical and molecular signals' limits for biocompatibility. While passing electrical signals through neurons or molecular signals through tissues, the time, frequency and location that is not used by the natural functions will be identified similar to cognitive radio networks where secondary users use spectrum left vacant by the primary users. Furthermore, long term experiments should

be conducted to observe and minimize the effects of electrical signals stimulating neurons on the degradation of neural fibers or the effects of molecular signals stimulating bacteria on the composition and livelihood of the gut microbiome.

D. INTEGRATED NETWORK PROBE DEVICE HUB

A compact novel hub should be serving as the main part of the INPD that operates wirelessly in conjunction with the existing smart *in vivo* experimental arena, Enercage-HC2, described in Sec. III-C. The integrated hub should include electronic circuits to drive electrical and molecular interfaces, and process them to be transmitted to outside the body. The electrical interfaces are electrodes that record and stimulate smooth muscle activity from gut serosa muscle membranes, *i.e.,* membrane found on the outer wall of the organs of the abdominal cavity, record local neural activity from enteric, vagus nerve, *i.e., nerve running through brain to abdomen controlling hearts, lungs, and digestive track*, and autonomic nervous systems, and the molecular interfaces are the biosensors to detect microbial activity and concentrations of molecules, such as neurotransmitters, hormones, and metabolites in the gut mucosa. A rendered view of the wireless hub system, including its interfaces with the target biological environment of the MGBA, is depicted in Fig. 6-a and b. Moreover, the location of the hub in the rat body under the skin, and its utilization in the EnerCage experimental arena, are illustrated in Fig. 6-c.

Even though an ultrasound-powered, mote-sized Implantable Medical Device (IMD) has been recently proposed to record neural activity from the peripheral nervous system [53], to the best of our knowledge, the researchers do not demonstrate the functionality of that system on a freely behaving animal. *Moreover, electronics for joint stimulation and recording of enteric nerves, muscles, and microbial activity have not yet been considered or demonstrated.* Hence, a novel design is required for the implantable hub adopting a System-on-a-Chip approach (SoC) for ultimate miniaturization. The SoC should utilize ultra-low power and ultra-low noise Application-Specific Integrated Circuit (ASIC) design techniques to deal with multiple stringent constraints imposed on the interface modules and wireless powering and communication in a wireless smart arena. These constraints include the following:

- non-uniform and non-linear responses from the biosensors and electrodes,
- strong rejection of artifacts coming from the stimulator on the recording side,
- reliable power transfer in every location of the smart experiment arena with record-setting RF-to-DC power conversion efficiency,
- sub-threshold operation of the analog front-end for ultra-low power operation,
- minimum silicon footprint for cost reduction and ease of implantation with minimal damage,
- input-referred noise well below that of the transducer.

In addition, bio-compatibility should be kept in mind when designing and fabricating the hub. For example, in an effort to minimize the heat generated in the wireless power delivery and management blocks to prevent possible tissue damage, and satisfy the regulatory requirements, such as electromagnetic power specific absorption rate (SAR), the wireless power transmission link should operate at relatively low frequencies with minimal absorption in the tissue, minimum power consumption, and minimum area to be implantable. This is a challenge but not a major concern, since the operating frequency in molecular sensing systems is within Hz range [54], while in neural recording system is within tens of kHz range [55], hence wireless transmission link can be used sparsely to generate less heat. Finally, *considering the difficulties in placement and attachment in a moving environment, such as the gut,* the hub will be assembled on a compact and flexible substrate, which can be surgically implanted under the skin or in the abdominal area (point A in Fig.6-c), close to where molecular and electrical sensors/actuators should be implanted (point B in Fig.6-c).

Recording channels should employ ultra-low-noise amplifiers, followed by ultra-low-power data converters to prepare data packets for transmission via EnerCage to a computer outside of the cage. The same computer should be programmed to initiate modulation of the nerves and muscle systems based on closed-loop algorithms that analyze the incoming data or animal behavior. The SoC should also include data/clock recovery and efficient stimulation circuits to convey outside-sourced information to the nervous and muscular systems. A power management unit will convert wireless RF power to multiple DC supplies required by other circuit blocks in the hub. The main blocks of the implantable hub presented in Fig.s 6-a and -b are the transmission front-end, the reception front-end, data recovery, and the power management unit, detailed in the following.

1) TRANSMISSION FRONT-END

While molecular signals can be stimulated externally by the ingestion of a pill or injection of a substance which does not require specific circuitry at the implantable hub, here we focus on the hub requirements for the electrical stimulation of the nerve cells through the neural interfaces detailed in Sec. III-E. Conventional nerve stimulation studies mostly focus on Deep Brain Stimulation (DBS), which has been widely accepted as an effective therapy method for the partial cure of Parkinson's disease, tremor, and dystonia [56], [57]. In the electrical stimulation methods, Voltage-Controlled Stimulation (VCS), Current-Controlled Stimulation (CCS), and Switched-Capacitor Stimulation (SCS) are the most common topologies. VCS enables power-efficient stimulation; however, variations in the electrode position and accordingly in the electrode impedance [58] over time complicates limiting and balancing the stimulation charge [59], [60]. Whereas CCS provides precise charge control and safe operation, it has low power efficiency due to the dropout voltage across its current sources [61], [62]. SCS, designed in [63], takes

advantage of both the high efficiency of VCS and the safety of CCS using capacitor banks to transfer quantized amount of charge to the tissue. We have presented the first integrated wireless SCS SoC with inductive capacitor charging and charge-based stimulation capabilities, which can improve both stimulator efficiency and stimulus efficacy in DBS in [64]. The amount and the shape of the stimulus current for different stimulation scenarios for muscle and nerve manipulation can be adjusted via a current steering Digital to Analog Converter (DAC), which can be controlled by the user through the wireless link of the EnerCage.

2) RECEPTION FRONT-END

A multimodal-sensing module that captures signals from the enteric nerve system, the gut microbial activity, and muscular movements to realize signal reception from both electrical and molecular channels should be developed. For nerve and muscle activity sensing, it is required to detect ultra-low voltage levels on the order of micro volts [48], [65], which should be considered in conjunction with the ultra-low energy consumption requirements of an IMD imposed by wireless powering [66]. For detecting molecules and microbial activity via biosensors, the reception circuit will require current detection components with wide range sensing capability and high linearity performance [67]. For this, it is key to identify the low-end sensitivity, *i.e.*, the minimum detectable signal for the system. The design of low-current detection instrumentation pertaining amperometric bio-sensors is widely explored in [68].

Another important challenge to realize the reception front-end is the adaptation of the electronic system to biological systems in terms of accommodating very different time scales. In fact, the dynamics of a biomolecular event, such as a change in the gut microbial composition, may happen in a longer time frame than electrical events at the nervous systems, *i.e.*, minutes or even hours compared to milliseconds. Therefore, the electronic system should be designed to accommodate a very long integration time with respect to more classical electrical systems [69].

To digitize the sensed analog signal, following the reception front-end, a new hybrid ADC architecture should be developed, which combines ultra-low power, high resolution, and small footprint specifications. Following the ADC, digitized electrical and biochemical signals should be compressed, packetized, and wirelessly transmitted from inside the host body to the Internet via EnerCage and a computer.

3) POWER MANAGEMENT UNIT

Since the integrated hub is considered to be small and arbitrarily placed, electromagnetically-coupled Wireless Power Transmission (WPT) links pose a challenge, as demonstrated in [70], [71]. The Power Management Unit (PMU) may overcome this challenge by including an active voltage-multiplying rectifier, a duty-cycled wireless charging system, and a power-control loop. This unique PMU should operate in a way that each IMD, regardless of its orientation inside the host body, utilizes the lowest amount of power trickling into the entire array of implants, while ensuring correct bio-signal acquisition, pre-processing, ADC, and back telemetry operations.

E. NEURAL AND MOLECULAR GUT INTERFACES FOR THE INTEGRATED NETWORK PROBE DEVICE

In this section, we investigate possible solutions for neural and molecular interfaces connected to the implantable hub (wirelessly or wired depending on the location of the interest area) in order to stimulate and sense electrical and molecular signals at different locations of the MGBA. The stimulated and sensed data should be processed to obtain the parameters of the underlying physical channels discussed in Sec. II.

1) ELECTRICAL AND MECHANICAL ACTIVITY SENSORS AND STIMULATORS

Recording and stimulation of the central nervous system (*i.e.*, brain and spinal cord) is heavily studied and various types of microelectrodes capable of capturing and influencing the electrical activity of CNS such as the Utah Microelectrode Array [72] and the Michigan Probe [73] are been introduced. At the same time, the recording and stimulation of the ENS capable of interfacing with enteric neurons and gut muscles have not been fully explored to date. The motility of the gut, and the complex intestinal wall structure pose challenges for stable placement and efficient operation of electrodes to be implanted for this purpose. To design and develop electrodes specifically tailored for enteric neuron interfacing, the membrane potentials and conductance of enteric neurons, which are different than previously studied systems, should be taken into account [74]. Besides, the aspect ratios should be adjusted to suit the target areas varying with respect to the gut layer of interest. The particular geometry of the electrodes and their coating should be also tailored to minimize tissue damage and provide bio-compatibility.

2) MOLECULAR (HORMONES, NEUROTRANSMITTERS, METABOLITES) SENSORS AND STIMULATORS

As mentioned above,the gut microbiota and the ENS interface through neural and hormonal signals between immune cells, enteric neurons, smooth muscle cells, interstitial cells, and the gut microbiome. Furthermore, gut microbes can influence the ENS by producing hormones which act as local neurotransmitters (*e.g.*, GABA (gamma-aminobutyric acid), serotonin, melatonin, histamine, acetylcholine), by Short-Chain Fatty Acids (SCFAs) (*e.g.*, butyric acid, propionic acid and acetic acid), and by generating catecholamines in the lumen of the gut [3], [75]. Therefore, the effect of gut microbes on the MGBA can be studied by the manipulation of gut microbial community composition through the modulation of neurotransmitters, food, antibiotics, and probiotics.

The first step for designing molecular sensors and stimulators is to utilize the *in vitro* GOAC described in Sec. III-B as a development platform, where the microfluidic environment

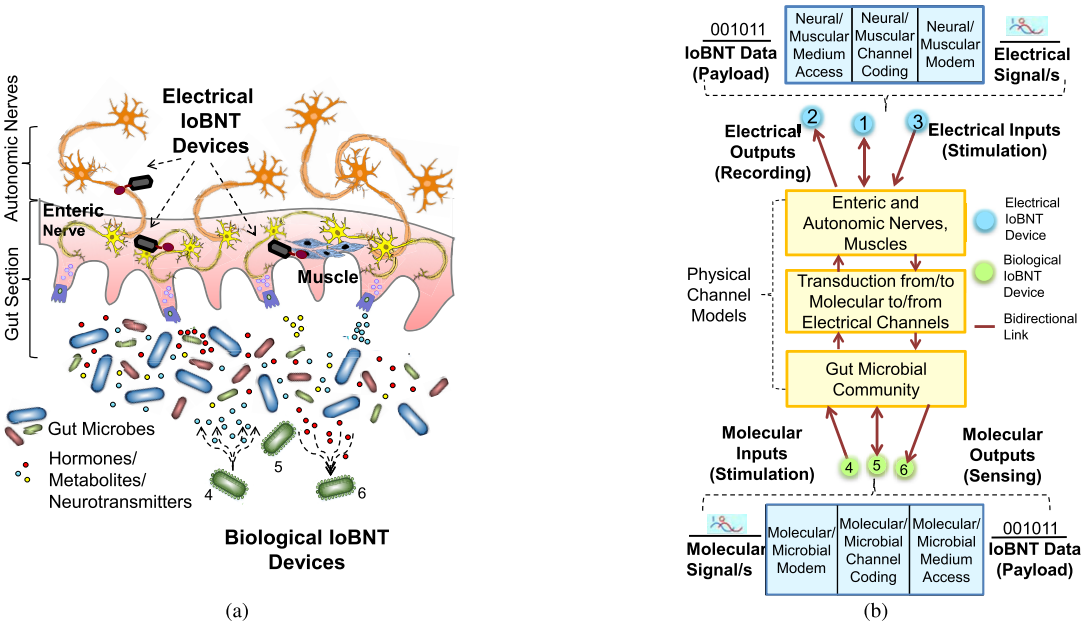

FIGURE 7. (a) The communication processes involved in MGBA stimulation and sensing. (b) The corresponding proposed physical channel models and IoBNT network infrastructure components.

allows to simulate the effect of the release of molecular signals to manipulate the microbial community composition in real time. While the optically transparent nature of the GOAC device will allow optical measurements and imaging, platinum surface electrodes integrated on the system can be used for electrochemical detection of molecules [76], [77] such as hormones, neurotransmitters, and metabolites in real time. Over multiple rounds of stimulation, the amount and kinetics of the interaction of molecules of interest with the microbial community can be analyzed in real time. To realize sensors able to test electrical to molecular channels, neurons will be stimulated using the electrodes within a range of frequencies and amplitudes, and the corresponding molecular sensors will be tuned to observe the corresponsing changes in the lumen by electrochemical sensors in terms of concentration of hormones, neurotransmitters, and other relevant molecules.

In addition to the aforementioned interfaces, necessary to generate and transmit signals through the MGBA, supplementary capability of measuring additional pertinent information from the gut environment should also be included in the implanted electronics, with sensors to evaluate the correlation between the MGBA communications channels and other physiological parameters, such as stress-strain, pH, temperature, heartbeat rate, and blood pressure.

IV. INTERNET OF BIO-NANOTHINGS COMMUNICATION NETWORK INFRASTRUCTURE

To interconnect IoBNT devices through the MGBA channels investigated analytically and experimentally with the methodologies described in Sec. II and Sec. III, respectively, a network infrastructure needs to be defined regulating access to resources for all biological and electrical devices as shown in Fig. 7-a. Resources in this context can be considered as the limited number and variability of molecules in the environment, the energy consumed by the devices for transmission and reception, and the transmission time and location clear of natural communications in the body. The components of this infrastructure constitute channel coding, medium access, and modulation/demodulation (modem) modules, tailored to the transmission of information via electrical or molecular stimulation, the propagation of information along MGBA, and the reception of information via electrical or molecular sensors, as shown in Fig. 7-b.

By jointly investigating neural/muscular and molecular/microbial medium access, channel coding and modulation in a cross-layer fashion, we aim to increase the data rate as high as possible to approach the theoretical channel capacity over MGBA channels determined by the models described in Sec. II. The design of the infrastructure including these modules should generate electrical or molecular signal waveforms within the admissible input-output value and frequency ranges while minimizing delay and noise, and minimizing disruption to the natural communications in the MGBA necessary to maintain its homeostasis (healthy state). Furthermore, the wired structures of neuronal communication and the wireless structure of bacterial communication should be exploited to develop a reliable addressing through the MGBA. By taking into account the peculiarities of the MGBA, in the following we will discuss the cross-layer design of electrical and molecular infrastructure components.

A. ELECTRICAL INFRASTRUCTURE COMPONENTS

The electrical infrastructure components are responsible for stimulating and sensing the electrical activity for electrical communications through channels based on enteric and autonomic nerves, where the underlying biological processes

of electrical signal propagation will be leveraged to design novel modulation, channel coding, and medium access solutions for IoBNT. Considering the subthreshold communication described as in Sec. II-A over a single neuron as illustrated in Fig. 3, the sender should limit the current injected to the soma such that it does not create a membrane potential exceeding the threshold which in turn creates a ''spike'' to carry the information to the next neuron over the synapse [19].

If an amplitude modulation scheme is considered for this communication link, the modulator component of the sender should select current levels representing symbols within the subthreshold potential range [78] with the modulation depth limited by the subthreshold noise [30]. To avoid crossing the threshold, *i.e.*, interfering with natural communications, the medium access component should avoid the simultaneous transmission from multiple sources, whose input currents when summed up might create a membrane potential larger than the threshold. Besides, the channel coding component should increase the frequency of symbols corresponding to lower membrane potentials so that even when multiple signals are summed up, there is less chance of crossing the threshold. All these three modules should be jointly designed to accommodate more users with higher data rates while still keeping cross-talk to natural communications below the limit.

Furthermore, the synaptic transmission, which is the release of molecules called neurotransmitters by a pre-synaptic to a post-synaptic neuron capturing these neurotransmitters, brings a new dimension to the waveform design. Since in ENS, neurons operate with more than one type of neurotransmitter [79], the type of neurotransmitter can be used either to add one more dimension to the amplitude-frequency domain of modulation, or to assign different neurotransmitters to different users allowing simultaneous transmission over the same channel.

B. MOLECULAR INFRASTRUCTURE COMPONENTS

The molecular infrastructure components are responsible for stimulating and sensing molecular activity to realize molecular communications through the gut mucosa and lumen, as described in Sec. II-B, where the intestinal wall, gut microbial communities, and food intake contribute to the molecular composition of the gastrointestinal tract. The microbes' behavior in terms of uptake and consumption of chemical compounds, and their growth rate will be leveraged to design novel modulation, channel coding, and medium access solutions for IoBNT. Joint design of these three components is necessary due to the requirement of minimal disruption to natural communication occurring in the gut.

Keeping disruption to natural communications over MGBA at minimum for molecular signals translates into avoiding dysbiosis, *i.e.*, the disruption of microbial balance in the gut, which might cause severe diseases such as Crohn's disease or colorectal cancer [80]. Considering the microbial community structure described in Sec. II-B, and illustrated in Fig. 4, the excess or lack of a chemical compound can interfere with the metabolic reactions, and in turn disrupt the growth balance of the community. To avoid a break in this balance, information should not be encoded on the properties of a molecular signal composed of probiotics promoting the reproduction of only one microbial species in the medium. If a concentration based modulation scheme is adopted where molecular signals are represented by chemical compound concentrations, the modulator should adjust the concentration levels such that any change in these will still transmit the information but not disrupt the community structure [34]. The medium access module should also contribute to keeping this balance by regulating the simultaneous access to the chemical compounds while trying to give enough resources to all the transmitters for a timely and successful information delivery. Medium access control techniques tailored for molecular communication such as amplitude division multiple access and molecular code division multiple access schemes can be adapted to the MGBA environment to satisfy the aforementioned requirements.

C. BIOMOLECULAR INTRABODY NETWORK SIMULATOR

A new simulator for heterogeneous intrabody communication networks should be developed as part of the framework to aid the design of MGBA-based IoBNT networks. This simulator will incorporate the physical channel models described in Sec. II and aid in the estimation of the performance of these channels as well as the aforementioned network infrastructure components in terms of attenuation, delay, noise, capacity, cross-talk and interference.

Even though several open-source network simulators exist today, such as ns-3 [81], these cannot be directly used for biomolecular intrabody communication because: (i) these simulators are built on top of well-defined propagation models for electromagnetic or acoustic communication, where instead we would require computational models describing the underlying biological processes; (ii) these simulators are developed with the classic network protocol stack in mind, where instead the limited capability of IoBNT devices will requite to design the infrastructure in a cross-layer fashion as discussed in Sec. IV.

The main challenges of a biomolecular intrabody network simulator are discussed below:

- *Computational models:* Considering the complex and massively interacting gut-microbiome structure, creating a complete model for simulating the gut, capable of accounting for all the microbial species and all the different tissues throughout the nine meters of the gastrointestinal tract, poses a great challenge. Existing models, focusing either on a specific tissue or specific interaction in the gut, should be integrated to built a spatio-temporal multiscale representation of the gut ranging from nanoseconds to years and from molecules to systems. A challenge to achieve this goal stands in incorporating the complete physical structure of the gut and its potential changes to the models. Another

challenge arises from the need of immense computational power and vast amounts of storage to run these computational models, which can be addressed by high performance computing.

- *Flexibility to design modulation, channel coding, and medium access schemes:* Considering the biochemical nature of signaling, a distinction between different communication stack layers is not as straightforward as in classical networking [1]. The simulator should provide flexibility to design modulation, channel coding, and medium access, as well as allowing cross-layer design for both electrical and molecular channels.
- *Performance evaluation:* To provide insightful results, the simulator is required to compute not only communication parameters such as delay and achievable rate, but also other parameters representing biocompatibility constraints and the constraints on the proposed devices such as measuring cross-talk with natural communications and metabolic burden on genetically engineered bacteria. The simulator should also be able to obtain results in multiple spatio-temporal scales as mentioned above.

V. CONCLUSION

This article presents fundamental challenges in the development of a self-sustainable and bio-compatible network infrastructure to interconnect the next-generation electrical and biological wearable and implantable devices, *i.e.*, Internet of Bio-NanoThings. Microbiome-Gut-Brain Axis is investigated as a possible infrastructure to build this network of Bio-NanoThings inside the human body. The challenges and the requirements to realize the proposed infrastructure are addressed and the analytical and experimental methodologies are given as a roadmap for future studies. This novel communication concept using MGBA as an intrabody communication infrastructure will provide transformative bio-inspired communication systems and network architectures, with future impact on applications for health-care (*e.g.*, systems for advanced and perpetual tele-health monitoring and control).

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