POINT OF VIEW

Moving Forward With Molecular Communication: From Theory to Human Health Applications

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I. MOLECULAR COMMUNICATION THEORY AND HUMAN HEALTH

The birth of wireless communication systems nearly 1 century ago has transformed and redefined the way humans communicate and interact. This transformation, which has opened boundaries between societies and eliminated cultural barriers, has evolved from the original paradigm of wireless electromagnetic communication systems. This paradigm has experienced numerous evolutionary developments that have not only brought along seamless connectivity for human interactions but also communication between machines and devices.

While the aforementioned communication systems are man-made artifacts, the research community has more recently turned its attention to other communication strategies that have spontaneously evolved in nature. These are at the basis of the information flow among and within biological cells, the fundamental units of life, and their organization into more complex organisms. At the basis of these strategies, information is encoded into molecules and exchanged through chemical

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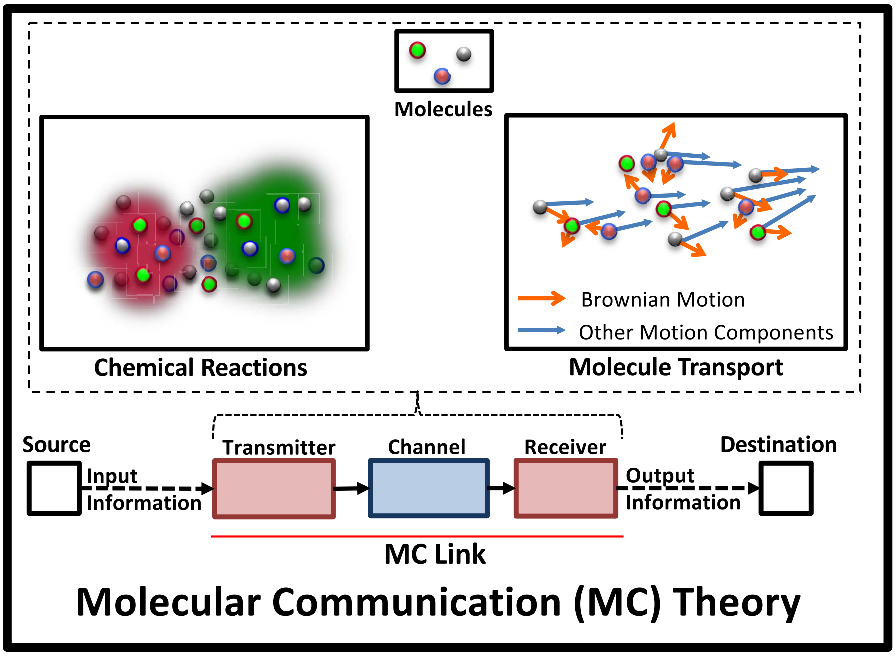

Fig. 1. *Functional elements of the MC theory.*

reactions and molecule transport processes. This has been abstracted by communication engineers into the molecular communication (MC) paradigm [1], which is the basis of the MC theory as a discipline.

As schematically shown in Fig. 1, the foundational elements of the MC theory are the molecules, which are the smallest identifiable units of information about the chemical composition and properties of a substance, the chemical reactions, which manipulate the composition and structure of single or a few molecules reacting together, and the molecule transport processes, which propagate the molecules in the space. The latter is, in general, resulting from unavoidable thermally driven random Brownian forces and may include other components, e.g., flow and/or active transport, such as transport in the blood stream or motion of the cells themselves. MC theory analyzes the propagation of information between a source and a destination, where this information might be, in general, relayed by one or more MC links composed of a transmitter, channel, and receiver, based on the aforementioned foundational elements.

In the past decade of MC theory research, initial studies on the physical characteristics of communication channels based on various molecule transport processes have resulted in numerous models consisting of the processes of diffusion, molecular motors, gap junctions, and chemotaxis [2]. Some of these models have been expanded to address problems related to the expression of their maximum theoretical communication capacity, and the design of suitable modulation and coding techniques, and networking protocols to utilize and optimize the transfer of information propagated by molecules through multiple interconnected links.

Despite the aforementioned advancements made in the theoretical studies, the definition of technologies to support practical and useful applications of MC theory, while essential to motivate further growth of this field in the research community, is still very limited. In this point-of-view paper, we present a novel perspective of MC theory in light of current and future studies for its application to human health.

Information and communication technologies applied to human health are currently concerned with the acquisition, storage, analysis, modeling, and exchange of patient health information by means of *in silico* computing platforms and the Internet. MC theory holds the potential to enable the sensing and control of this information as it propagates *in vivo* through the biochemistry underpinning the patient's body, its cells, and their molecular content. For example, cancer development and progression are believed to arise from abnormalities in the propagation of molecular information underlying cell differentiation and proliferation, among others [9]. Innovative solutions to these problems may come from decades of knowledge on information processing and communication in electrical systems and their translation into biochemical systems operated by the MC theory. If this direction is pursued, the MC theory will be a key technology for addressing two of the 21st-century grand challenges for engineering, i.e., engineering better medicines and advancing health informatics, as defined by the National Academy of Engineering [10].

We identify two main directions for applying MC theory to human health, namely, those of the natural or synthetically engineered systems, as further illustrated in Fig. 2. In the natural system direction, the MC theory is applied to model information flows at the: 1) body

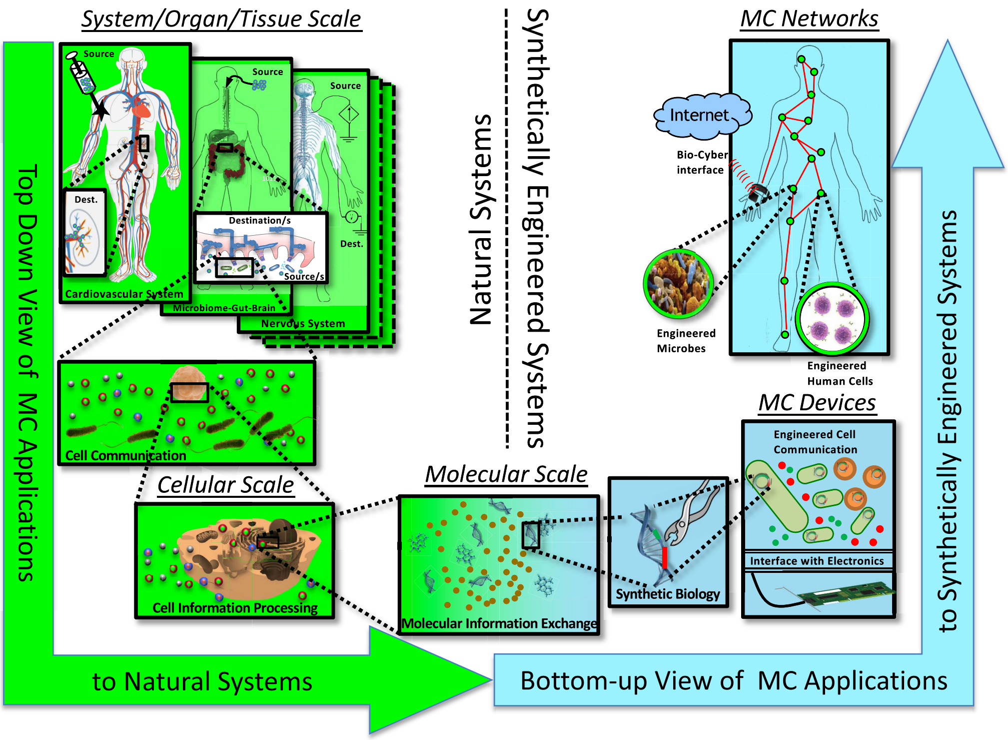

Fig. 2. *MC theory application to human health in the natural and synthetically engineered systems directions.*

system scale, where organs and tissues are interconnected to perform a specific function; 2) cellular scale, where cells coordinate with each other and process information; and 3) molecular scale, where information is encoded into substances and exchanged through chemical reactions and molecule transport. In the synthetically engineered system direction, the MC theory is applied to engineer the following: 1) MC components, by utilizing genetic programming tools from synthetic biology and technologies to interface with classical electronics; 2) MC devices, which are engineered biological systems, from microbes to human cells, capable of preprogrammed MC behaviors; and 3) MC networks, where engineered biological systems interconnect to each other to pervasively monitor and control human health parameters and interface to the broader Internet [2].

As a support to the aforementioned application directions, and contrary to most of the current literature, further research in the MC theory should be coupled with experimental validation in controlled environments, especially for technologies that will be subject to future clinical trials. In particular, *in vitro* wet-lab experimental platforms should be envisioned as part of the development of human health applications of the MC theory.

In the rest of this paper, we support our vision of MC theory applications to human health with current and future research paths, as well as list some of the existing experimental platforms to date. Finally, we conclude by discussing the next challenges and future opportunities in this growing multidisciplinary field of research.

II. APPLICATION TO NATURAL SYSTEMS

A. System/Organ/Tissue Scale

The human body is composed of multiple systems, where tissues and organs coordinate to execute specific physiological functions. The MC theory is applied to model and characterize the flow of information in these systems for various applications, ranging from the optimization of the propagation and delivery of drug molecules within the body to the exploitation of intrabody communication channels for body-area network infrastructures.

1) Cardiovascular System: MC theory has been applied to model the propagation of nanoscale and microscale drug molecules, with the long-term goals of optimizing the drug delivery rate at the target tissue while minimizing the toxic spread of the drug in healthy tissues [3]. This model is based on an MC abstraction where the source of information is the drug to be injected in the system and the destination is the target tissue, interconnected by MC links. These links are based on drug molecule diffusion and fluid flow through the network of blood vessels, where the blood velocity is analytically obtained by taking into account the heartbeat, the physical properties of the blood, and the elasticity of the vessel walls. An accurate expression of the delivery rate of drug molecules at the target tissue, as well as in other regions of the body, is obtained as a function of the drug injection rate and location, which can be subsequently optimized for the aforementioned goals.

2) Nervous System: The propagation of information-carrying electrochemical stimuli through neurons and their interconnections has been modeled, characterized, and experimented as a communication system in the MC literature [4]. In particular, communication theoretical parameters such as the frequency response of a passive quasi-linear propagation of stimuli through a single neuron and the error rate and delay of the propagation of a nonlinear active spike through multiple subsequent neurons have been obtained [4], [5]. Estimations of the amount of information that can be carried by spikes through neuron interconnections, i.e., synapses, have been obtained in [6]. In this direction, the possibility of interfacing with classical electronics will enable the utilization of the nervous system and its underlying MC links to interconnect wearable and implantable devices via intrabody communication for future theranostics [5]. A further direction for the MC theory is the study of the correlation between impairments in transmitting information through these links and nervous system disorders.

3) Microbiome–Gut–Brain: MC theory is applied to model usable communication channels on top of the biological processes underlying the microbiome–gut–brain axis (MGBA), composed of the gut microbial community, the gut tissues, the enteric nervous system, and their intercommunications. A recently funded National Science Foundation (NSF) project is expanding over the aforementioned nervous system studies to explore the utilization of the MGBA as a heterogeneous communication network infrastructure. The aim is to realize minimally invasive, heterogeneous, and externally accessible electrical/MCs between electrical and biological devices. In these communications, the source/s modulate natural communication parameters, such as neural electrical activity (enteric and autonomic), mechanical muscular activity, concentration of chemical compounds (e.g., hormones, metabolites, and neurotransmitters), and gut microbial community composition, at specific locations of the MGBA or through ingestion, and the destination/s sense the same or other affected parameters at other MGBA locations, e.g., muscular system [7].

B. Cellular Scale

Cells are the basic functional and structural units of life, and they interact and coordinate while making up the tissues and organs that compose the aforementioned systems. MC theory is utilized to model and characterize their mutual information exchange, as well as their information uptake and release from/into the environment, for applications ranging from cancer detection and classification to the sensing and control of the gut microbial community.

1) Cell Communication: Cells exchange information between each other through different types of molecules, e.g., signaling molecules or hormones, and interactions, e.g., diffusion or contact. While MC theory applications to model and characterize natural cell communication are limited in terms of abstract models that focus on specific processes, we envision that the current research in pharmacology, as well as radiology, can contribute toward an integrated detailed model that links internal signaling pathways and their effect on the intercellular communication. This may include detailed structures of the cells, intracellular pathway systems, and the integration of all these to determine how it has an impact on signaling diffusion between cells. Mapping out the relationship between the intracellular to intercellular signaling has the potential of creating communication centric tools to support the biopharmaceutical and biotechnology industries.

2) Cell Information Processing: Cells have the natural ability to adapt to changing environmental circumstances to maximize their chances to grow, reproduce, and/or maintain the homeostasis of the multicellular body, by processing information coming from the external environment and accordingly regulating their behavior through genetic programs. MC theory is employed to quantify this ability by estimating the flow of this information from the external environment to the cell behavior adaptation, with the goal of developing a novel metric to compare and classify different cells, possibly involved in diseases. This estimation has been studied for a *Escherichia coli* (*E. coli*) bacterium and for other two human gut bacteria species [8]. Consequently, the flow of information about the chemical composition of the human gut environment can be modeled by a series of MC links, where the sender is the gut environment and the destination is the consequent adaptation of the cell metabolism, defined as the complex network of chemical reactions that underlie the conversion of chemical compounds to energy, cellular building blocks, and waste. A similar MC link abstraction is applied to quantify the disruption in this information flow as a consequence of mutations in the cell genetic code, leading to cancer [9]. In particular, information on the concentration of a growth hormone in the cell environment, which modulates cell growth and proliferation, is normally propagated to the cell nucleus through intracellular MC links based on chained interactions of proteins. In the presence of mutations, these propagation links are disrupted by noise, leading to uncontrolled growth of the cell.

C. Molecular Scale

Molecular structure, chemical reactions, and transport processes are at the basis of the aforementioned information propagation at all scales of the human body, and their modeling and characterization in different MC links are at the foundation of MC theory and all its applications to human health as described in this paper.

Molecular Information Exchange: One of the fundamental transport processes considered in the MC theory is free diffusion, which is the bulk effect of the unavoidable Brownian motion forces on molecules, and it is most commonly mathematically modeled through Fick's second law [11], [12]. Numerous studies have focused on characterizing the communication channel based on the molecule transport process, including the interactions from molecule-to-molecule collisions [11]. This covers free diffusion, as well as diffusion in bounded environments, such as calcium ions through the gap junction of cells or neurotransmitters through the synaptic clefts of neurons [6]. Besides free diffusion, the more complex advection–diffusion molecule transport has also been considered, where flows assist the propagation of the molecules, as in the aforementioned cardiovascular system [3]. Understanding the process of information encoding into molecule composition and structure as well as how this affects the chemical reactions and transport processes can provide new insights into how diseases emerge, such as the molecular basis of cancer initiation and progression [9]. This can be due to changes in the protein folding process resulting in new structures that can affect the molecular transport as well as the carried information, leading to deviations from the optimal capacity and, ultimately, affecting the healthy behavior of cells.

III. APPLICATION TO SYNTHETICALLY ENGINEERED SYSTEMS

A. Molecular Scale

Several different properties of the chemical substances can be, in principle, utilized to engineer information encoding and exchange in an MC system. Molecular composition and structure, concentration, density, pressure, or temperature do not depend on the amount of substance, such as molecule number, total mass, occupied volume, enthalpy, or entropy. On the one hand, some of these properties can be modulated *in vitro* and then delivered from the external environment to an intrabody natural MC system, such as the chemical composition of antigens to stimulate immune system antibodies. On the other hand, synthetic biology is making possible to tap into the molecular sensing, processing, and actuation capabilities of cells to realize fully integrated *in vivo* MC systems.

Synthetic Biology: This interdisciplinary field of engineering provides a viable path to the practical realization of MC-capable systems through the programming of cells' genetic code. In particular, biological circuit engineering, built through the modification of genetic regulatory networks embedded in biological cells, is realized by modifying or reassembling predefined parts of deoxyribonucleic acid (DNA) into functional genes, linked together into cause-effect networks by mutual activation and repression mechanisms that regulate their expression into proteins.

B. MC Components

Despite some first results detailed in the following section, the field of MC theory currently lacks an in-depth design, analysis, and characterization, both computational and experimental, of the biochemical processes and the synthetic biology components that may be utilized to engineer MC systems, in a similar way as components such as amplifiers, encoders, filters, and antennas are being designed for electrical communication systems.

1) Engineered Cell Communication: The engineering of cell communications based on the aforementioned programming of DNA biological circuits is one of the latest frontiers in synthetic biology, where MC links can be engineered by programming cells to function as transmitters and/or receivers of information-bearing molecules. Attempts have been made in the design of engineered cell communications through modeling and characterizing the minimal subset of genetic circuit elements, which is necessary to realize a basic MC link, as well as defining general guidelines to optimize these systems [13], [14].

2) Interfaces With Electronics: The monitoring, data acquisition/analysis, and control of engineered MC systems for human health come necessarily from technologies to interface the MC realm to classical electronics. To this end, in contrast to the widespread use of fluorescent markers in synthetic biology, an ongoing research is directed toward harnessing biochemical processes where the propagation of electrons is coupled with the elements at the basis of MC theory. In particular, redox (reduction–oxidation) processes are chemical reactions where electrons are transferred between molecules, one that loses electrons (oxidized) and another that gains electrons (reduced). In [15], a redox-based proof-of-concept device is demonstrated to enable fast and reliable information exchange between electrical and biological (molecular) domains.

C. MC Devices

1) Engineered Microbes: Bacteria, as single-cell organisms, utilize MC to enable the population to survive and evolve through environmental changes. They are used extensively by synthetic biologists due to the ease of programming new functionalities through the manipulation and insertion of the genetic code. In the area of theoretical MC, a number of approaches that tie synthetic biology to MC between the cells have resulted in various types of application. A very good example is the use of MC between engineered bacteria that respond and switch between chemoattractants and repellants, resulting in social cooperation for target localization [16]. Localization established through motile bacteria can allow the disease to be targeted at a single cell level, which can prevent further spreading. Besides analytical and simulation works, wet-lab experiments have also been developed to demonstrate elements of engineered MC systems, where an oscillator was created from a circuit of two genes that can switch between positive and negative feedbacks, and this can be used for controlled timing of drug release within the body [17].

2) Engineered Human Cells: While engineering of microbes has provided key insights and platforms for synthetic biology, developments have also been made toward engineering human cells. The engineering of human cells is performed through genome editing, enabling gene insertion and correction, as well as chromosomal rearrangements. Human pluripotent cells, which can be programmed into any cell type in the human body, are candidate cells that are used extensively for engineering human cells. The engineering of these cells can be established through gene knockouts, which allows certain gene functions to be turned off [18]. Numerous applications have resulted from engineering human pluripotent cells, such as programming them to become tissue cells as well as generating of immune T-cells. While the development of MC systems from human pluripotent cells has not been researched, it can certainly provide new tools for human cell engineering. In particular, the development process of stem cells involves numerous communications during differentiation. Therefore, corrective actions at the genetic level for optimal communication capacity between the cells can provide new approaches for avoiding diseases during differentiation, growth, and proliferation.

D. MC Networks

While engineering the cells can lead to controlled MC to perform special functions, a key is the ability to network between the individual engineered systems, and ultimately, networking to the cyber-world via the Internet. A vision toward this goal has been proposed with the concept of the Internet of Bio-Nano things [2]. This includes artificial cells that are designed to act as gateways for translating between different molecule types, and a biocyber interface for translating molecular signals to electrical signals that will communicate to an external device. Synthetic biology has enabled cells to produce various types of engineered molecules, where a number of approaches can be used to develop the artificial cell gateways that can translate molecules between different MC systems, and this can be built from the metabolic engineering of cellular pathways to allow cells to produce various types of chemical enzymes.

IV. EXISTING EXPERIMENTAL PLATFORMS

In this section, we will discuss some of the wet-lab experimental platforms that have been developed to date to support MC theory research. Experience gained through these platforms could serve to develop future *in vitro* prototypes and *in vivo* implementations of the MC theory applications to human health.

A. Bacterial Quorum Sensing Microfluidic Platform

One of the first MC-funded projects that comprised both theoretical as well as experimental research was the NSF molecular nanocommunication networks (MoNaCo) project [19]. The vision and objective of the project were to develop theoretical communication and networking theory that can be proved through an experimental platform for a synthetically engineered MC system. The MC model for the project was based on bacterial quorum sensing (QS) and is illustrated in Fig. 3(a). The platform utilizes a microfluidic device that controls the flow of N-Acyl homoserine lactones (AHL) signaling molecules between two compartments, each containing a population of *E. coli* bacteria. The *E. coli* bacteria are synthetically engineered to encode components of QS from the bacterium *Vibrio fischeri* (*V. fischeri*). As illustrated in Fig. 3(a), the bacteria within the transmitter compartment upon excitation will release molecules that flow along the microchannel toward another population of bacteria representing the receiver. At the receiver, the *E. coli* bacteria are engineered with DNA from the *V. fischeri*, which enables them to fluoresce once the autoinducer molecules arrive with a certain concentration. This fluorescing of the bacteria indicates a successful communication process through the microchannel.

The platform can be used to understand how communication between different species can affect a community of bacteria. In particular, a controlled microbial environment can be placed in the compartments, where the analysis can be conducted on the molecular transport of varying signaling molecules passed through the microfluidic channels to determine the impact on the microbial community composition and structure. Instability in the gut microbial communities is known to result in different types of gastrointestinal diseases.

B. *In Vivo* Nervous System Information Transfer

An MC experimental platform for natural systems has also been developed to measure the information transfer through the nervous system of an earthworm, and the platform is illustrated in Fig. 3(b) [4]. Earthworms contain a single nerve cord that runs through the entire body, connecting the mouth all the way to the tail, which makes them very attractive for understanding the signal spike propagation behavior. The experiment involves stimulating the nervous system using electrodes that are inserted into the skin and against the nerves, where the earthworm is held through an insulating foam rubber. The spikes are generated through both dc and ac currents, where multiple electrical pulses with different amplitudes, frequencies, and waveforms can be transmitted. The receiving signal is analyzed through a digital oscilloscope, which is also used for data acquisition. The experimental platform can provide the ability to analyze

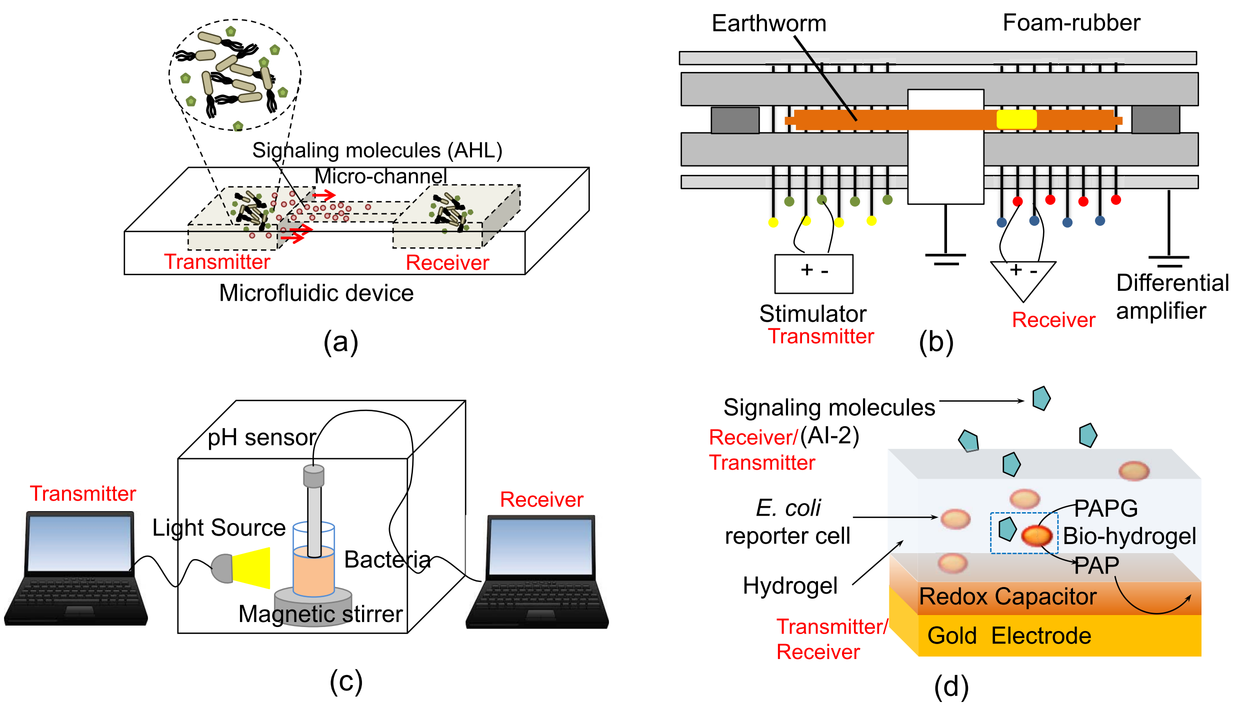

Fig. 3. ***Example experimental platforms for MC. (a) Cellular communication using microfluidic platform. (b) System level for in vivo nervous system information transfer. (c) Optical-to-chemical modulator for biological interfaces. (d) Hydrogel-based chemo–electro signal transduction device.***

communication performance when peripheral nerve damage occurs, and possibly design communication-based strategies to restore functions that are lost due to neurological diseases.

C. Biological Optical-to-Chemical Modulator

A platform for interfacing between the electrical and biological domains has been developed using the bacteria biological modulator [20]. The platform, which is illustrated in Fig. 3(c), uses synthetically engineered bacteria to create a biological modulator that acts as an interface between two computers transmitting data [20]. The transmitting computer converts digital bits into light signals that are projected on the engineered bacteria, which converts it to photon production that is diffused into the medium. The diffused proton changes the pH of the medium, and this is detected through a sensor. A benefit of this particular conversion process is the speed, which is very different from the current MC systems that can take from minutes to hours. This platform lays the groundwork for future implantable devices that can interface wirelessly with external devices and control their behavior.

D. Hydrogel-Based Chemo-Electro Signal Transduction Device

A further interface between the electrical and molecular domains is being studied through a redox-based experimental platform [15], as illustrated in Fig. 3(d), with reference to the MC research direction introduced in Section III-B2. This wet-lab interface device prototype is composed of a dual-film coating where the outer film is a hydrogel entrapping genetically engineered *E. coli* cells, and the inner film is a redox capacitor that amplifies the detection of redox-active molecules at the gold electrode. These cells are engineered as reporters, which respond to the presence of a certain molecule (signaling molecule AI-2) by converting the redox-inactive substrate 4-Aminophenyl β-D-galactopyranoside (PAPG) molecules into redox-active p-aminophenol (PAP). Research has begun investigating this technology to create a novel generation of bioelectronic components that will serve as the basis of the intelligent drugs, capable of biochemical and electrical computation and actuation.

While a number of different experimental platforms have been developed to validate and demonstrate the theory of MC, there are still numerous opportunities still available with existing technologies that have been developed in the field of biotechnology. A good example is the organ-on-a-chip that allows cell culture of an organ to be grown on a microfluidic device, simulating the internal physiological activities. This has also been extended toward human-on-a-chip, where multiple organs-on-a-chip can be networked together to simulate the MC between organs.

V. CHALLENGES AND OPPORTUNITIES

The application of MC theory to human health in the aforementioned directions will face the following main challenges: 1) incomplete biological knowledge; 2) individuality and variations; 3) mutations and evolution; 4) safety and security; and 5) ethical concerns.

Our current knowledge of biological processes is far from being complete, especially when related to complex diseases such as cancer, the function and control of the milieu of natural genetic programs in our cells, or the basis of information propagation and processing in our nervous system. Consequently, while the MC theory has to rely on possibly inaccurate and ever-evolving models from the literature, there is also an opportunity to contribute to scientific discovery by generating novel hypotheses, e.g., by comparison with communication strategies adopted in electrical systems.

The information contained in the cells' genetic code, as well as the way this information is utilized (expressed) by an organism, varies between individuals, as well as between cells within a single body. While this challenges MC theory applications by introducing noise sources, a great opportunity stands in exploiting engineering techniques for the development of reliable (or adaptive) communication systems to overcome (or address) the need for personalized healthcare solutions.

The cells' genetic code is inevitably subject to random changes, or mutations, and the survival of a cell with a permanent mutation over another nonmutated cell of the same type may result in the evolution of the behavior of that type of cells, and the tissue, organ, or systems they may be part of. This process adds a very novel dimension to the aforementioned characterization and engineering of communications through the MC theory, where not only the channels but also the behaviors of the transmitters and receivers themselves are subject to noise and changes, possibly disrupting or enhancing these communications.

Since the applications of MC theory to human health promise to tap into the propagation of health information in the human body, the safety of the developed systems should be a primary concern. While biocompatibility should be investigated through appropriate animal testing and clinical trials as for any other medical device, the possibility to interact with the body information processes from the external environment through the aforementioned interfaces adds another dimension to safety in the direction of a molecular-layer cybersecurity. For these same reasons, ethical concerns should also be addressed, and necessary guidelines and policies are developed as a result. While this is not in the scope of this point-of-view paper, we recognize the importance of an upfront debate toward an ethical regulation of this research, as well as the future resulting technologies. ■

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REFERENCES

[1] I. F. Akyildiz, J. M. Jornet, and M. Pierobon, "Nanonetworks: A new frontier in communications," *Commun. ACM*, vol. 54, no. 11, pp. 84–89, Nov. 2011.

[2] I. F. Akyildiz, M. Pierobon, S. Balasubramaniam, and Y. Koucheryavy, "The Internet of bio-nano things," *IEEE Commun. Mag.*, vol. 53, no. 3, pp. 32–40, Mar. 2015.

[3] Y. Chahibi, M. Pierobon, S. O. Song, and I. F. Akyildiz, "A molecular communication system model for particulate drug delivery systems," *IEEE Trans. Biomed. Eng.*, vol. 60, no. 12, pp. 3468–3483, Dec. 2013.

[4] N. A. Abbasi, D. Lafci, and O. B. Akan, "Controlled information transfer through an *in vivo* nervous system," *Sci. Rep.*, vol. 8, no. 1, Feb. 2018, Art. no. 2298.

[5] A. Khodaei and M. Pierobon, "An intra-body linear channel model based on neuronal subthreshold stimulation," in *Proc. IEEE Int. Conf. Commun. (ICC)*, Kuala Lumpur, Malaysia, May 2016, pp. 1–7.

[6] M. Veletić, P. A. Floor, Z. Babić, and I. Balasingham, "Peer-to-peer communication in neuronal nano-network," *IEEE Trans. Commun.*, vol. 64, no. 3, pp. 1153–1166, Mar. 2016.

[7] I. F. Akyildiz *et al.*, "Microbiome-gut-brain axis as a biomolecular communication network for the Internet of bio-nano things," Tech Rep., Feb. 2019.

[8] M. Pierobon, Z. Sakkaff, J. L. Catlett, and N. R. Buan, "Mutual information upper bound of molecular communication based on cell metabolism," in *Proc. IEEE 17th Int. Workshop Signal Process. Adv. Wireless Commun. (SPAWC)*, Edinburgh, U.K., Jul. 2016, pp. 1–6.

[9] Z. Sakkaff, A. Immaneni, and M. Pierobon, "Applying molecular communication theory to estimate information loss in cell signal transduction: An approach based on cancer transcriptomics," in *Proc. 5th ACM Int. Conf. Nanosc. Comput. Commun.*, Reykavik, Iceland, Sep. 2018, pp. 1–16.

[10] S. Olson, *Grand Challenges for Engineering: Imperatives, Prospects, and Priorities: Summary of a Forum*. Washington, DC, USA: Nat. Academies Press, 2016.

[11] M. Pierobon and I. F. Akyildiz, "A physical end-to-end model for molecular communication in nanonetworks," *IEEE J. Sel. Areas Commun.*, vol. 28, no. 4, pp. 602–611, May 2010.

[12] V. Jamali, A. Ahmadzadeh, C. Jardin, C. Sticht, and R. Schober, "Channel estimation for diffusive molecular communications," *IEEE Trans. Commun.*, vol. 64, no. 10, pp. 4238–4252, Oct. 2016.

[13] A. Marcone, M. Pierobon, and M. Magarini, "Parity-check coding based on genetic circuits for engineered molecular communication between biological cells," *IEEE Trans. Commun.*, vol. 66, no. 12, pp. 6221–6236, Dec. 2018.

[14] C. Harper, M. Pierobon, and M. Magarini, "Estimating information exchange performance of engineered cell-to-cell molecular communications: A computational approach," in *Proc. IEEE Int. Conf. Comput. Commun. (INFOCOM)*, Honolulu, HI, USA, Apr. 2018, pp. 729–737.

[15] Y. Liu *et al.*, "Using a redox modality to connect synthetic biology to electronics: Hydrogel-based chemo-electro signal transduction for molecular communication," *Adv. Healthcare Mater.*, vol. 6, no. 1, Jan. 2017, Art. no. 1600908.

[16] Y. Okaie *et al.*, "Cooperative target tracking by a mobile bionanosensor network," *IEEE Trans. Nanobiosci.*, vol. 13, no. 3, pp. 267–277, Sep. 2014.

[17] T. Danino, O. Mondragón-Palomino, L. Tsimring, and J. Hasty, "A synchronized quorum of genetic clocks," *Nature*, vol. 463, no. 7279, pp. 326–330, Jan. 2010.

[18] Y. Chen *et al.*, "Engineering human stem cell lines with inducible gene knockout using CRISPR/Cas9," *Cell Stem Cell*, vol. 17, no. 2, pp. 233–244, Aug. 2015.

[19] I. F. Akyildiz, F. Fekri, R. Sivakumar, C. R. Forest, and B. K. Hammer, "Monaco: Fundamentals of molecular nano-communication networks," *IEEE Wireless Commun.*, vol. 19, no. 5, pp. 12–18, Oct. 2012.

[20] L. Grebenstein *et al.*, "Biological optical-to-chemical signal conversion interface: A small-scale modulator for molecular communications," in *Proc. ACM/IEEE Int. Conf. Nanosc. Comput. Commun. (NanoCom)*, Reykjavik, Iceland, Sep. 2018, pp. 1–29.