INVITED PAPER

# Transmitter and Receiver Architectures for Molecular Communications: A Survey on Physical Design With Modulation, Coding, and Detection Techniques

*This article focuses on the design of transmitters and receivers for molecular communication (MC). It also reviews existing literature on transmitter and receiver architectures for realizing MC, including both nanomaterial-based nanomachines and/or biological entities.*

By Murat Kuscu, *Student Member IEEE*, Ergin Dinc, *Member IEEE*, Bilgesu A. Bilgin, *Member IEEE*, Hamideh Ramezani, *Student Member IEEE*, and Ozgur B. Akan, *Fellow IEEE*

**ABSTRACT** | Inspired by nature, molecular communications (MC), i.e., the use of molecules to encode, transmit, and receive information, stands as the most promising communication paradigm to realize the nanonetworks. Even though there has been extensive theoretical research toward nanoscale MC, there are no examples of implemented nanoscale MC networks. The main reason for this lies in the peculiarities of nanoscale physics, challenges in nanoscale fabrication, and highly stochastic nature of the biochemical domain of envisioned nanonetwork applications. This mandates developing novel device architectures and communication methods compatible with MC constraints. To that end, various transmitter and receiver designs for MC have been proposed in the literature together with numerable modulation, coding, and detection techniques. However, these works fall into domains of a very wide spectrum of disciplines, including, but not limited to, information and communication theory, quantum physics, materials science, nanofabrication, physiology, and synthetic biology. Therefore, we believe it is imperative for the progress of the field that an organized exposition of cumulative knowledge on the subject matter can be compiled. Thus, to fill this gap, in this comprehensive survey, we review the existing literature on transmitter and receiver architectures toward realizing MC among nanomaterial-based nanomachines and/or biological entities and provide a complete overview of modulation, coding, and detection techniques employed for MC. Moreover, we identify the most significant shortcomings and challenges in all these research areas and propose potential solutions to overcome some of them.

**KEYWORDS** | Coding; detection; Internet of Bio-Nano Things (IoBNT); modulation; molecular communications (MCs); nanonetworks; receiver; transmitter.

Manuscript received November 5, 2018; revised March 13, 2019; accepted April 30, 2019. Date of publication May 30, 2019; date of current version July 19, 2019. This work was supported in part by the European Research Council (ERC) Projects MINERVA under Grant ERC-2013-CoG #616922 and MINERGRACE under Grant ERC-2017-PoC #780645. *(Corresponding author: Murat Kuscu.)*

**M. Kuscu**, **E. Dinc**, **B. A. Bilgin**, and **H. Ramezani** are with the Electrical Engineering Division, Internet of Everything (IoE) Group, Department of Engineering, University of Cambridge, Cambridge CB3 0FA, U.K. (e-mail: mk959@cam.ac.uk; ed502@cam.ac.uk; bab46@cam.ac.uk; hr404@cam.ac.uk).

**O. B. Akan** is with the Electrical Engineering Division, Internet of Everything (IoE) Group, Department of Engineering, University of Cambridge, Cambridge CB3 0FA, U.K., and also with the Next-generation and Wireless Communications Laboratory (NWCL), Department of Electrical and Electronics Engineering, Koc University, 34450 Istanbul, Turkey (e-mail: oba21@cam.ac.uk).

Digital Object Identifier 10.1109/JPROC.2019.2916081

## I. INTRODUCTION

Molecular communications (MC) is a bioinspired communication method that uses molecules for encoding, transmitting, and receiving information, in the same way by which the living cells communicate [1]. MC is inherently biocompatible, energy-efficient, and robust in physiological conditions. Therefore, it has emerged as the most promising method to realize nanonetworks and Internet of Bio-Nano Things (IoBNT), which defines the artificial networks of nanoscale functional units, such as nanobiosensors and engineered bacteria, integrated with the Internet infrastructure [1], [2]. In that respect, MC is promising for novel applications, especially toward information and communication technology (ICT)-based early diagnosis and treatment of diseases, such as continuous health monitoring, smart drug delivery, artificial organs, and lab-on-a-chip [3], [4] [see Fig. 1(a)]. It bears a significant potential as an alternative to conventional wireless communications, especially in those environments where the latter may fail, such as intrabody medium [5] and confined channels such as pipe networks [6], [7]. However, the discrete nature of information-carrying agents (i.e., molecules), peculiarities arising from the nanophysical and biochemical processes, and computational and energy-based limitations of communicating nanomachines give rise to novel challenges. This necessitates rethinking conventional ICT tools and devising new ones for MC in light of envisioned IoBNT applications.

MC has been extensively studied from various aspects over the last decade. The research efforts are mainly centered around developing information theoretical models of MC channels [8], devising modulation and detection techniques [9], [10], and system theoretical modeling of MC applications [11]. For the physical design of MC transmitter (MC-Tx) and MC receiver (MC-Rx), mainly, two approaches have been envisioned: biological architectures based on engineered bacteria enabled by synthetic biology and nanomaterial-based architectures that are conceptually visualized in Fig. 1(b) [1]. However, none of these approaches could be realized yet, and thus, there is no implementation of any artificial microscale/nanoscale MC system to date. As a result, the overall MC literature mostly relies on assumptions isolating the MC channel from the physical processes regarding the transceiving operations, leading to a plethora of ICT techniques, feasibility, and performance of which could not be validated.

Our objective in this paper is to help close the gap between theory and practice in the MC research by providing a comprehensive account of the recent proposals for the physical design of MC-Tx/Rx and the state-of-the-art theoretical studies covering modulation, coding, and detection techniques. We provide an overview of the opportunities and challenges regarding the implementation of MC-Tx/Rx and corresponding ICT techniques that are to be built on these devices. Throughout this review, we concentrated mostly on the diffusion-based MC, where the transmitted molecules propagate through passive diffusion along concentration gradients. This is the most widely utilized MC configuration in the literature, as the propagation of molecules does not necessitate additional complexity or energy consumption. Moreover, diffusion is the main molecular transport mechanism in many of the widespread natural MC systems, such as synaptic communication, quorum sensing, and $Ca^{2+}$ signaling. However, throughout this review, we also partly cover other MC configurations, such as diffusion-based MC with the additional flow, microfluidic MC, bacteria conjugation-based MC, and molecular-motor powered MC, while discussing the physical design approaches for MC-Tx/Rx.

We first investigate the fundamental requirements for the physical design of microscale/nanoscale MC-Tx and MC-Rx, such as those regarding the energy and molecule consumption, computational complexity, and operating conditions. In light of these requirements, we cover the two design approaches, namely, the nanomaterial-based approach enabled by the newly discovered nanomaterials, e.g., graphene, and the biological approach enabled by the synthetic biology tools. For nanomaterial-based MC-Tx, we investigate architectures based on microfluidics, stimuli-responsive hydrogels, and nanoporous structures, whereas for biological MC-Tx, we particularly focus on transmission schemes based on bacterial-conjugation, virus transmission, genetic circuit-regulated protein transmission, and enzyme-regulated $Ca^{2+}$ transmission. For nanomaterial-based MC-Rx, although we mostly focus on the nanoscale field-effect-transistor biosensor (bioFET)-based designs, we also discuss receiver architectures that are widely utilized in initial macroscale MC experiments. Toward the biological design of MC-Rx, we provide a brief review of synthetic biology tools that are available for sampling and decoding molecular messages.

In this paper, we also provide an overview of the modulation, coding, and detection methods proposed for MC. Modulation techniques in MC fundamentally differ from that in conventional electromagnetic (EM) communications, as the modulated entities, i.e., molecules, are discrete in nature and the developed techniques should be robust against highly time-varying characteristics of the MC channel, as well as the inherently slow nature of the propagation mechanisms. We cover MC modulation techniques that encode information into the concentration, type, ratio, release time, and release order of molecules, as well as the base sequences of nucleotides. We also review the MC channel coding techniques that overcome the extremely noisy and intersymbol interference (ISI)-susceptible nature of MC channels via introducing the redundant bits. Our review covers MC-specific channel coding methods, such as the ISI-free coding scheme employing distinguishable molecule types, as well as the classical coding schemes, such as block and convolution codes adapted to MC. Finally, we review the state-of-the-art MC detection techniques. Detection is, by far, the most studied aspect of MC in the literature. However, in

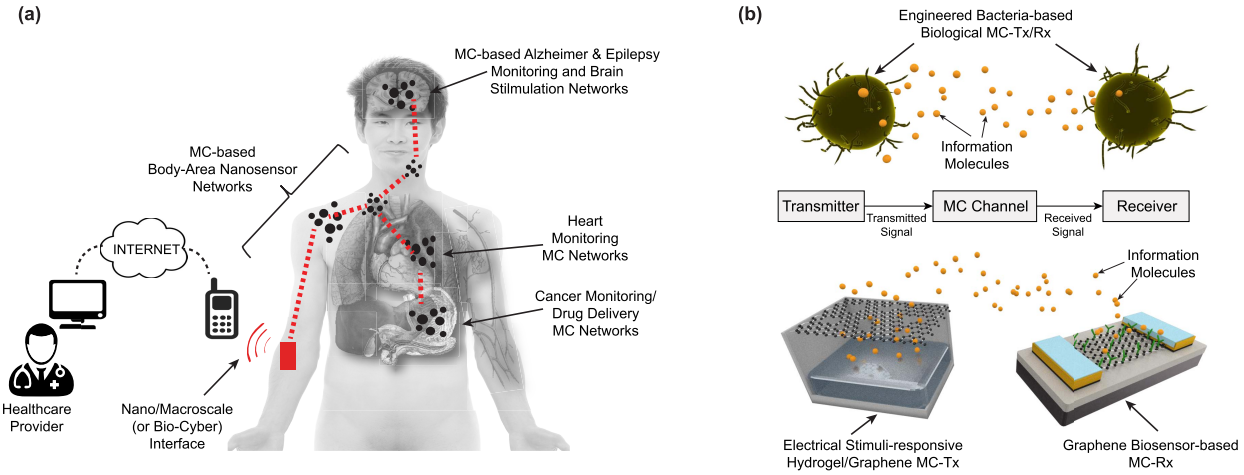


**Fig. 1.** ***(a) Intrabody continuous healthcare application of IoBNT enabled by MC nanonetworks [1]. (b) Components of an MC system with biological- and nanomaterial-based MC-Tx/Rx design approaches, which are reviewed in Sections II and III.***

devising detection methods, the lack of any MC-Rx implementation has led the researchers to make simplifying assumptions about the sampling process, receiver geometry, channel, and reception noise. Therefore, we investigate MC detection methods under two categories: detection with passive/absorbing receivers and detection with reactive receivers. We provide a qualitative comparison of these methods in terms of considered channel and receiver characteristics, complexity, type of required channel state information (CSI), and performance.

In summary, this paper provides: 1) comprehensive design guidelines for the physical implementation of microscale/nanoscale MC-Tx/Rxs using available nanomaterials or biological tools; 2) a comparative review of the state-of-the-art MC modulation, coding, and detection techniques with an evaluation in terms of performance, complexity, and feasibility for the envisioned MC-Tx/Rx architectures; and 3) a detailed account of the design, modeling, and fabrication challenges and future research directions. We believe that this comprehensive review will tremendously help researchers to close the long-standing gap between theory and practice in MC, which has, so far, severely impeded the innovation in this field linked with huge societal and economic impacts.

The remainder of this paper is organized as follows. In Section II, we investigate the design requirements of an MC-Tx and review the physical design options for nanomaterial-based and biological MC-Tx architectures. We focus on the opportunities for the physical design of an MC-Rx in Section III. We provide an overview of the state-of-the-art MC modulation and coding techniques in Section IV. A comprehensive review of the existing MC detection schemes for passive, absorbing, and reactive receivers is presented in Section V. In Section VI, we outline the challenges and future research directions toward the implementation of MC-Tx/Rxs and the development of the corresponding coding, modulation, and detection techniques. Finally, we conclude this paper in Section VII.

## II. MOLECULAR COMMUNICATION TRANSMITTER

MC-Tx encodes information in the physical properties of molecules, such as concentration, type, ratio, order or release time, and releases information molecules (IMs) accordingly. To this aim, information to be transmitted is required to be mapped to a sequence of bits through source and channel coding to represent the information with less number of bits and to introduce additional bits to the information with the purpose of providing error correction, respectively. Then, the modulator unit encodes the information in the property of molecules and controls the release of IMs according to a predetermined modulation scheme. Finally, a power source and an IM generator/container are required to provide energy and IM molecules for MC-Tx. The interconnection of these components in an MC-Tx is illustrated in Fig. 2. In this section, we first discuss the requirements of an MC-Tx and investigate the utilization of different IMs. Then, we review the available approaches in the physical design of MC-Txs, which can be categorized into two main groups: 1) nanomaterial-based artificial MC-Tx and 2) biological MC-Tx based on synthetic biology.

### A. Design Requirements for MC-Tx

*1) Miniaturization:* Many novel applications promised by MC impose size restrictions on their enabling devices, requiring them to be microscale/nanoscale. Despite the avalanching progress in the nanofabrication of bioelectronics devices over the last few decades [12], fabrication of fully functional nanomachines capable of networking

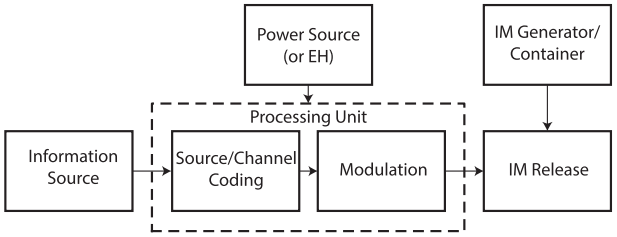


**Fig. 2.** ***Physical architecture of an MC-Tx.***

with each other and their surroundings in order to accomplish the desired task still evades us [13]. Added to the technical difficulties of assembling a working machine at nanoscale is the requirement of powering this machine via an energy harvesting (EH) module, which is imposed by the infeasibility of deploying a battery unit at these dimensions. Moreover, with miniaturization, the surface area-to-volume ratio increases, causing surface charges to become dominant in molecular interactions. This causes the behavior of molecules passing through nanoscale openings to be significantly different than that observed in larger dimensions [14]. Consequently, as the release apertures of many considered molecular transmitter architectures are commonly in nanoscale, peculiarities arising from this phenomenon need to be taken into account in the transmitter design.

*2) Molecule Reservoir:* The size restriction introduces another very important problem for any transmitter architecture, namely, the limited resources of IMs [15]. Typically, a transmitter module would contain reservoirs, where the IMs are stored to be released. However, at dimensions in question, without any replenishment, these reservoirs will inevitably deplete, rendering the nanomachine functionally useless in terms of MC. Moreover, the replenishment rate of transmitter reservoirs has a direct effect on achievable communication rates [16], [17]. Possible theoretically proposed scenarios for reservoir replenishment include local synthesis of IMs, e.g., use of genetically engineered bacteria whose genes are regulated to produce the desired transmitter proteins [18], as well as employment of transmitter harvesting methods [19]. Corresponding technological breakthroughs necessary for the realization of these approaches are emerging with advancements in the relevant fields of genetic engineering [20] and materials engineering [21], [22], respectively.

*3) Biocompatibility:* Most profound applications of nanodevices with MC networking capabilities, such as neural prosthetics, tissue engineering, targeted drug delivery, BMIs, and immune system enhancement, require the implantation of corresponding enabling devices into biological tissue [23]. Combined with the increased toxicity of materials at nanoscale [24], the issue of biocompatibility of these devices stands out as one of the most challenging research issues to be addressed. Moreover, corrosion of implants inside the body is another commonly known issue restricting device durability [25], which has an amplified effect at nanoscale due to the large surface-to-volume ratio. In addition to biochemical toxicity and durability, flexibility of implanted devices is another important aspect of biocompatibility affecting device lifetime. The mechanical mismatch between soft biological tissue and implanted device triggers inflammation, which is followed by the scar tissue formation [26], and, eventually, restricts the implant to carry out its intended task. Accordingly, the last decade has witnessed extensive research on novel biocompatible materials, such as polymers [25], soft organic electronics [27], dendrimers, and hydrogels [28]. It is imperative to note that all issues of biocompatibility mentioned here specifically apply to nanomaterial-based device architectures, and they can be, almost completely, avoided by the choice of biological architecture, e.g., genetically engineered organisms [1]. Host immune response to such organisms is prone to shorten their in-body lifetime as MC nanodevices, which is an observed phenomenon in the case of cells and tissues engineered from biomaterials [29]. On the other hand, in case of successful adaptation to the host immune system, one major concern in utilizing genetically engineered organisms is the possible risk of infection of the host by the introduced organisms. This risk may be minimized by the introduction of suicidal genes to the organisms [30] yet the possibility of random mutations always remains.

*4) Transmission Performance:* Performance of a molecular transmitter should also be evaluated by how much control it has over the transmission of molecules. Important performance metrics include OFF-state leakage, transmission rate precision, resolution, and range, as well as transmission delay. The OFF-state leakage, or unwanted leakage of molecules from the transmitter, from the MC perspective degrades communication significantly by contributing to background channel noise. Moreover, it is unacceptable for some niche applications, such as targeted drug delivery [31], where leakage of drug molecules would cause undesired toxicity to the body. During operation, control over the rate of transmission is essential. For instance, in neural communications' information is encoded, among other fashions, in the number of neurotransmitters released at a chemical synapse, and accordingly, transmitter architectures envisioned to stimulate neurons via the release of neurotransmitters, e.g., glutamate [32], will need to encode information in neurotransmitter concentrations via very precise transmissions. In this respect, transmission rate precision, resolution, and range are all variables that are determinant in the capacity of communication with the recipient neuron. Finally, the transmission delay is, in general, a quantity to be minimized, as it contributes to the degradation in communication rates. Moreover, for instance, in neural communications, where information is also encoded in

the frequency of signals, there is an upper bound on the permissible transmission delay of a transmitter in order to satisfy a given lower bound on maximum frequency transmittable.

## B. Physical Design of MC-Tx

MC uses molecules for information transfer, unlike the traditional communication systems that rely on EM and acoustic waves. Therefore, the physical design of MC-Tx significantly differs from traditional transmitters. The key components of an MC-Tx are illustrated in Fig. 2. The first element in MC-Tx is the information source that represents either a bitwise information generated by a nanomachine or a biological signal from living cells, such as neurons and cardiomyocytes.

The next building block in an MC-Tx is the processing unit, which performs coding, modulation, and control of IM release. This block may not appear in biological systems utilizing MC in a basic way, such as hormonal communication inside a human body, where the information is transferred via a single-molecule type with on–off keying (OOK). For this purpose, MC-Tx processing unit can operate via chemical pathways [6] or through biocompatible microscale processors or via synthetic genetic circuits [33]. In case of biological Tx architectures, processing units performing logic gates and memory functions in the form of synthetic genetic circuits can be embedded into cells.

Inside the processing unit, the first step is to represent analog or digital information with the least number of bits possible through source coding. Then, the channel coding block introduces extra bits to make data transmission more robust against error-prone MC channels. After the coding step, digital information is transformed into an analog molecular signal according to a predetermined modulation scheme. There are various modulation schemes proposed for MC by using molecular concentration, type of molecules, or time of molecule release. The detailed discussion of modulation techniques for MC can be found in Section IV-A. The processing unit controls IM release according to the data being transmitted and the modulation scheme. IM molecules are provided from IM generator/container, which can be realized as either a reservoir containing genetically engineered bacteria to produce IM molecules on demand or a container with a limited supply of IM molecules.

There are two types of molecule release mechanisms: instant release, where a certain number of molecules (in mol) are released to the medium at the same time, and continuous release, where the molecules are released with a constant rate over a certain period of time (mol/s). Instant release can be modeled as an impulse symbol, while continuous release can be considered as a pulse wave. According to application requirements and channel conditions, one of the release mechanisms can be more favorable. Bitwise communications, for example, require rapid fade-out of IMs from the channel, as these molecules will cause ISI for the next symbol; thus, the instant release is more promising. In addition, alarm signals for warning plants and other insects can favor continuous release to increase detection probability and reliability.

The processing unit in MC-Tx may require a power source for performing coding and modulation operations, especially in the nanomaterial-based MC-Txs. Battery-powered devices suffer from limited lifetime and random battery depletions, i.e., unexpected exhaustion of sensor battery due to hardware or software failure, that significantly affect the reliability of systems that rely on MC. Therefore, MC-Tx unit is required to operate as a self-sustaining batteryless device by harvesting the energy from its surrounding. For this purpose, EH from various sources, such as solar, mechanical, and chemical, can be utilized in MC-Tx architectures. Hybrid EH techniques can be employed as well to increase the output power reliability [34]. Concerning the intrabody and body area applications, the human body stands as a vast source of energy [35], which has been exploited to power biomedical devices and implants in many ways, e.g., thermoelectric EH from body heat [36], vibrational EH from heartbeats [37], and biochemical EH from perspiration [38]. Nevertheless, design and implementation of EH methods at microscales/nanoscales for MC still stand as the important open research issues in the literature.

*1) Information-Carrying Molecules:* Reliable and robust MC necessitates chemically stable IMs that can be selectively received. In addition, environmental factors, such as molecular deformation due to enzymes and changes in pH, can have severe effects on IMs [39] and degrade the performance of MC. Next, we provide a discussion on several types of IMs that can be utilized for MC.

*a) Nucleic acids:* Nucleic acids, i.e., deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), are promising candidates as IMs by being biocompatible and chemically stable, especially in in-body applications. In nature, DNA carries information from one generation into another. RNA is utilized as messenger molecules for intercellular communication in plants and animals to catalyze biological reactions, such as localized protein synthesis and neuronal growth [40], [41]. In a similar manner, nucleic acids can be exploited in MC-Tx to carry information. DNA has a double-stranded structure, whereas RNA is single-stranded molecule often folded on to itself, and the existence of hydroxyl groups in RNA makes it less stable to hydrolysis, compared to DNA. Hence, DNA can be expected to outperform RNA as an information-carrying molecule.

Recent advancements in DNA/RNA sequencing and synthesis techniques have enabled DNA-encoded MC [42]–[44]. DNA/RNA strands having different properties, i.e., length [45], dumbbell hairpins [42], [46], short-sequence motifs/labels [43], and orientation [47], can be utilized to encode the bitwise information. For information detection, solid-state-based nanopores [43], [48] and DNA-origami-based nanopores [49] can be utilized to

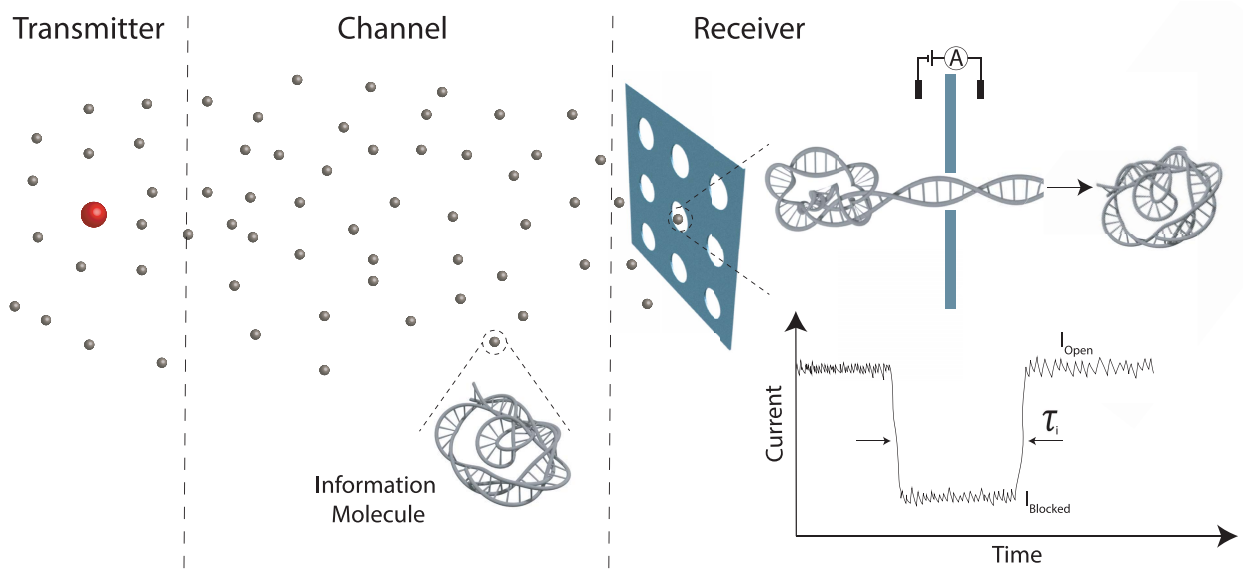


**Fig. 3.** ***System model for DNA-based MCs.***

distinguish the information symbols based on the properties of DNA/RNA strands by examining the ionic current characteristics during translocation, i.e., while DNA/RNA strands pass through the nanopores, as illustrated in Fig. 3. The utilization of nanopores for DNA symbol detection also enables the miniaturization of MC-capable devices toward the realization of IoBNT. According to [42], 3-bit barcode-coded DNA strands with dumbbell hairpins can be detected through nanopores with 94% accuracy. In [47], four different RNA molecules having different orientations are translocated with more than 90% accuracy while passing through transmembrane protein nanopores. Nanopore-based detection can also pave the way for detecting cancer biomarkers from RNA molecules for early detection of cancers, as in [50]. However, this requires high sensitivity and selectivity.

Translocation time of DNA/RNA molecules through nanopores depends on the voltage, concentration, and length of the DNA/RNA symbols, and the translocation of symbols can take from a few milliseconds up to 100-ms time frames [42], [46]. Considering the slow diffusion channel in MC, transmission/detection of DNA-encoded symbols does not introduce a bottleneck, and multiple detections can be performed during each symbol transmission. Therefore, the utilization of DNA/RNA strands is promising for high-capacity communication between nanomachines, as the number of symbols in the modulation scheme can be increased by exploiting multiple properties of DNA/RNA at the same time. Hence, the utilization of DNA as an information-carrying molecule paves the way for high-capacity links between nanomachines by enabling a higher number of molecules that can be selectively received [51].

In addition, information can be encoded into the base sequences of DNAs, which is also known as nucleotide shift keying (NSK). In [52], 35 distinct data files over 200 MB were encoded and stored by using more than 13 million nucleotides. More importantly, this paper proposes a method for reading the stored data in DNA sequences using a random access approach. Owing to the high information density of DNA, application of NSK in DNA-based MC may boost the typically low data rates of MC up to the extent of competing with traditional wireless communication standards. Hence, NSK can enable indoor artificial molecular wireless communications with data rates up to hundereds of megabits per second, and this leads to a novel communication paradigm, molecular information-fidelity (Mi-Fi). In Mi-Fi, multiuser channel access can be achieved through molecular division multiple access (MDMA) capability, i.e., capable of communicating via multiple types of information-carrying molecules, e.g., different DNA strands, at once.

In NSK, information-carrying DNA and RNA strands can be placed into bacteria and viruses. In [53], bacteria-based nanonetworks, where bacteria are utilized as a carrier of IMs, have been proposed and analytically analyzed. In [54], a digital movie is encoded into DNA sequences, and these strands are placed into bacteria. However, DNA/RNA reading/writing speed and cost at the moment limit the utilization of NSK in a practical system. Theoretical and experimental investigations of DNA-/RNA-encoded MC stand as a significant open research issue in the MC literature.

*b) Elemental ions:* Elemental ion concentrations, e.g., $Na^+$, $K^+$, and $Ca^{2+}$, dictate many processes in biological systems. For instance, in a neuron at steady state, more $Na^+$ and $K^+$ ions are maintained via active transmembrane ion channels in extracellular and intracellular media, respectively, and an action potential is instigated by a surge of $Na^+$ ions into the cell upon the activation of

transmembrane receptors by neurotransmitters from other neurons. On the other hand, $Ca^{2+}$ ions are utilized in many complex signaling mechanisms in biology, including neuronal transmission in an excitatory synapse, exocytosis, cellular motility, apoptosis, and transcription [55]. This renders elemental ions one of the viable ways to communicate with living organisms for a diverse range of possible applications, such as neural interfacing, disease monitoring, diagnosis, and treatment. Correspondingly, many transmitter device [56] and nanonetwork architectures [57] based on the elemental ion signaling have been proposed in the literature.

*c) Neurotransmitters:* Neural interfacing is one of the hottest contemporary research topics with applications, including neural prosthetics, spinal cord injury treatment, and brain–machine interfaces. In this respect, stimulation of neurons using their own language, i.e., neurotransmitters, stands out as the best practice. Various transmitter architectures for the most common neurotransmitters, e.g., glutamate, $\gamma$-aminobutyric acid (GABA), aspartate, and acetylcholine, have been reported in the literature [32], [58], [59].

*d) Proteins:* Proteins comprise the basic building blocks of all mechanisms in life. They are synthesized by cells from amino acids utilizing information encoded inside DNA and regulate nearly all processes within the cell, including the protein synthesis process itself so that they form a self-regulatory network. Proteins are commonly used as IMs by biological systems both in intracellular pathways, e.g., enzymes within vesicles between the endoplasmic reticulum and the Golgi apparatus [60], and intercellular pathways, e.g., hormones within exosomes, vesicles secreted from a multitude of cell types via exocytosis [61]. Artificial transmission of proteins has been long considered within the context of applications, such as protein therapy [62]. From MC point of view, use of proteins as IMs by genetically engineered bacteria is regarded as one of the possible biological MC architectures, where engineered genetic circuits have been proposed to implement various logic gates and operations necessary for networking [63].

*e) Other molecules:* Many other types of molecules have been used or considered as IMs in the literature. These include synthetic pharmaceuticals [64], therapeutic nanoparticles [65], as well as organic hydrofluorocarbons [66] and isomers [67].

*2) Nanomaterial-Based MC-Tx Architectures:* In the literature, MC-Tx is generally assumed to be an ideal point source capable of perfectly transmitting molecular messages encoded in the number, type, or release time of molecules to the channel instantly or continuously, neglecting the stochasticity in the molecule generation process and the effect of the Tx geometry and channel feedback. Despite various studies investigating MC, the physical implementation of MC-Tx stands as an important open research issue, especially in microscale/nanoscale. However, there exist some works on the macroscale demonstration of MC. Farsad *et al.* [68] implemented a macroscale MC system with an electronically controlled spray as MC-Tx, which is capable of releasing alcohol, and alcohol metal-oxide sensor as MC-Rx. According to this experiment, the macroscale MC setup achieves 0.2 b/s with 2-m communication range. Since there is almost no microscale/nanoscale implementation of MC-Tx, we investigate and propose MC-Tx architectures by exploiting recent advancements in nanotechnology, novel materials, and microfluidics.

As discussed in Section II-A, design of MC-Tx in microscale/nanoscale is an extremely challenging task, including various requirements, such as biocompability, miniaturization, and lifetime of the device. For reducing the dimensions of MC-Tx architectures to microscales, microfluidics and microfluidic droplet technologies are promising. Inside droplets, IMs can be transmitted in a precisely controlled manner, such that even logic gates can be implemented with microfluidic chips, as demonstrated in [69]. Feasibility of utilizing droplets for communication purposes has been suggested in [70]. In addition, microfluidic chips can be fabricated by using polydimethylsiloxane (PDMS) that is a biocompatible polymer [71]. Farsad *et al.* [72] theoretically compared the achievable data rates of passive transport, i.e., diffusive channel, and active transport, i.e., flow-assisted channel via external pressure or molecular motors, in a microfluidic environment. According to this study, active transport improves achievable data rates, owing to faster movement of IMs from Tx to Rx compared to passive transport. A new modulation scheme based on the distance between droplets has been introduced in [73] by exploiting hydrodynamic microfluidic effects.

Although it is not originally proposed as MC-Tx, microfluidic neural interfaces with chemical stimulation capabilities, i.e., devices that release neurotransmitters, such as glutamate or GABA to stimulate or inhibit neural signals [74]–[76], operates same as MC-Tx. Therefore, the studies on neural interfaces with chemical stimulation capabilities can be considered as the baseline for designing microscale/nanoscale MC-Tx. However, leakage of IM molecules, while there is no signal transmission, stands as a significant challenge for microfluidic-based MC-Txs. It is not possible to eliminate the problem, but there are some possible solutions to reduce or control the amount of leakage. Hydrophobic nanopores can be utilized, as shown in Fig. 4(a), such that the liquid inside the container can be separated from the medium when there is no pressure inside the MC-Tx. This solution has two drawbacks. Since there is a need for external pressure source, it is hard to design a practical stand-alone MC-Tx with this setup. Second, this solution does not completely eliminate the IM leakage; hence, Jones and Stelzle [77] suggest the utilization of porous membranes and electrical control of fluids to further improve MC-Tx against IM leakage.

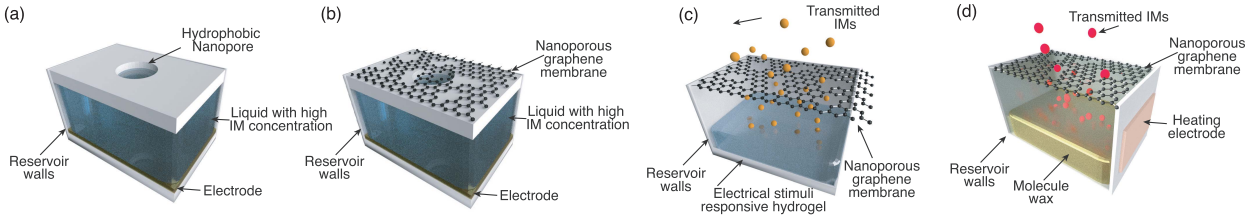


**Fig. 4.** ***MC-Tx architectures. (a) Microfluidic-based MC-Tx with hydrophobic nanopore. (b) Microfluidic-based MC-Tx with hydrophobic nanopore and nanoporous graphene membrane. (c) MC-Tx with thin film hydrogels with nanoporous graphene membrane. (d) MC-Tx with molecule wax and nanoporous graphene membrane.***

Nanoporous graphene membranes can provide molecule selectivity [78] by adjusting the pore size depending on the size of IM. In addition, graphene is also proven to be biocompatible, as demonstrated in [79]. If the pore size of the graphene membrane can be adjusted in a way that IMs can barely pass through, negatively charging the graphene membrane can decrease the pore size with the additional electrons, such that some level of control can be introduced to reduce the IM leakage. In addition, an electrode plate placed at the bottom of the container can be utilized to pull and push charged IMs, as illustrated in Fig. 4(b). This way, an electric field ($E$-field) can be generated in the liquid containing charged IMs, and the direction of $E$-field can be utilized to ease or harden the release of charged IMs. Thanks to their biocompatibility and controlled IM release mechanism, microfluidic-based MC-Txs enhanced with nanoporous membranes pave the way for several in-body applications, e.g., enabling communication between nanomachines flowing through the human body, interfacing with cells, and implementing artificial synapses, toward realizing IoBNT.

MC-Tx can be also realized with electrical stimuli-responsive thin film hydrogels by performing $E$-field-modulated release and uptake of IMs [80], as shown in Fig. 4(c). Hydrogels, widely utilized in smart drug delivery, are biocompatible polymers that can host molecules and reversibly swell/deswell in a water solution upon the application of the stimuli, resulting in release/uptake of molecules. This architecture can be further improved via porous graphene controlling its microenvironment. The $E$-field stimuli can be generated by two electrodes placed at the opposite walls of the reservoir. Refilling the IM reservoirs is another significant challenge in the MC-Tx design, which can be solved with the replenishable drug delivery methods, e.g., oligodeoxynucleotides (ODN) modification [81], click chemistry [82], and refill lines [83]. In this way, the utilization of hydrogels further enhances in-body MC applications by extending the device lifetimes via molecule uptake mechanisms.

Up to this point, we consider the design of MC-Tx only in the liquid medium. For airborne MC, we propose an MC-Tx architecture consisting of a molecular reservoir sealed by a porous graphene membrane, accommodating a wax layer containing IMs, as shown in Fig. 4(d). The rest of the reservoir is filled with water, in which the IMs dissolve. Upon the application of heat via $E$-field through conducting walls of the reservoir, the module sweats IM-rich water through membrane pores, and IMs become airborne upon evaporation and provide a continuous release of IMs. For this reason, this MC-Tx architecture is promising for applications, where the continuous release of molecules is favorable in order to increase the detection probability and reliability, such as sending molecular warning signals to plants and insects.

*3) Biological MC-Tx Architectures:* An alternative approach to nanomaterial-based architectures for MC, which, in most cases, are inspired by their biological counterparts, resides in rewiring the already established molecular machinery of the biological realm to engineer biological nanomachines that network via MC to accomplish specific tasks. At the cost of increased complexity, this approach has various advantages over nanomaterial-based designs, including inherent biocompatibility and already integrated production, transport, and transmission modules for a wealthy selection of IMs and architectures.

*a) Bacterial conjugation-based transmission:* Bacterial conjugation is one of the lateral gene transfer processes between two bacteria. More specifically, some plasmids inside bacteria, mostly circular small double-stranded DNA molecules physically distinct from the main bacterial DNA, can replicate and transfer itself into a new bacteria [84]. These plasmids encode the conjugative "sex" pilus that, upon receiving a right molecular stimulus from a neighboring bacteria, is translated. The produced pilus extends out of the donor cell, attaches to the recipient cell, and, then, retracts to get the two cells in contact with their intracellular media joined through the pilus hole. Single-strand DNA (ssDNA) of the plasmid is then transferred from the donor cell to the recipient cell. Utilizing bacterial conjugation as a means of information transmission for MC necessitates at least partial control over bacteria behavior, which is achieved by means of genetically engineering the bacteria.

At the core of all genetical engineering schemes lies the concept of gene regulation via a process known as

RNA interference (RNAi), which provided us the means of manipulating gene expressions in targeted cells or bacteria, paving the way for genetically engineered bacteria-based MC architectures [85]. RNAi is observed to serve as a mediator of interkingdom MC [86]. In particular, it is shown that short hairpin RNA (shRNA) expressing bacteria elicit RNAi in mammals [87], rendering bacteria-mediated RNAi-based diagnosis and therapeutics a promising prospect [88]. In this respect, recently, McKay *et al.* [89] proposed a platform of genetically engineered bacteria as vehicles for localized delivery of therapeutics toward applications for Crohn's disease. From MC perspective, genetically engineered bacteria have been envisioned to be utilized in various ways with different transmitter architectures. In the following, we collate various novel research directions in biological transmitter architectures for MC enabled by the recent advancements in genetic engineering.

It is important to note that conjugative pili are typically few microns in length, which, from the MC point of view, dramatically decreases the transmission radius. Accordingly, [53] has proposed engineered bacteria with flagella, e.g., *E. coli* as the carriers of information, i.e., sequenced DNA strands, which establishes a communication link between two nanomachine nodes that can interface and exchange DNA strands with the bacteria. The sequenced DNA message resides within a plasmid. The behavior of the bacteria is controlled via chemotaxis by the release of attractants from the nodes and regulated by encoded active regions on the plasmid. To avoid interference with behavior regulation, the message section of the plasmid is inactivated, i.e., it is not expressed, which can be achieved by avoiding consensus promoter sequences within the message. Consensus promoters are necessary for the RNA polymerase to attach to the DNA and start transcription. The message section of the plasmid also contains the destination address, which renders message relaying across nodes possible. The authors develop a simulator for the flagellated bacteria propagation, which they combine with analytical models for biological processes involved to obtain the end-to-end delay and capacity of the proposed MC channel for model networking tasks. In [90], utilization of flagellated bacteria for the medium-range ($\mu$m–mm) MC networks is suggested, where the authors present a physical channel characterization of the setup together with a simulator based on it. Sugrañes and Akyildiz [91] extend the model in [53] by accounting for mutations in the bacteria population and also considering the asynchronous mode of operation of the nodes. Balasubramaniam *et al.* [92] also considered a similar setup utilizing bacterial conjugation but employ opportunistic routing, where opportunistic conjugation between bacteria is allowed in contrast to strict bacteria-node conjugation assumed in [53]. However, it requires node labeling of bacteria and additional attractant release by bacteria to facilitate the bacteria–bacteria contact for opportunistic routing. The authors extend this work with [93] by additionally assuming the nanomachine nodes as capable of releasing antibiotics that kill bacteria with useless or no content to decrease the noise levels by avoiding overpopulation. Moreover, they allow a multiple number of plasmids per bacterium, which, contrary to their previous work and [53], allows simultaneous communication between multiple source and destination nodes over the same network.

An important factor that restricts reliable successful delivery in conjugation-based bacterial networks is incomplete DNA transfer due to the fragile nature of the process, the effect of which is pronounced over multiple transfers. To mitigate losses due to this effect, which always results in a loss of information from the tail part of DNA, [94] devises a forward–reverse coding (FRC) scheme, where messages are encoded in both directions and sent simultaneously over the same channel via dedicated sets of bacteria, to equally distribute losses to both ends of DNA. The performance of FRC is later compared with a cyclic shift coding (CSC) scheme, in which a DNA message is partitioned into $N$ smaller blocks and is cyclically shifted to create $N$ versions of the same content starting with corresponding blocks, and similar to FRC transmitted simultaneously via dedicated bacteria populations [95]. Expectedly, CSC provided higher link probability than FRC, which outperformed straight encoding.

The MC-Tx module of the architecture based on the bacterial conjugation outlined earlier, indeed, is composed of several submodules, i.e., the transmitter module of the nanomachine node, the bacteria itself via chemotaxis, and the pilus-based sexual conjugation module, which is a reflection of the trademark high complexity involved with biological architectures. In return, the reward is the achievement of unprecedented data rates via MC, owing to the high information density of DNA.

*b) Virus-based transmission:* Viruses have initially been studied as infectious agents and tools for investigating cell biology; however, their use as templates for transferring genetic materials to cells has provided us the means of genetically engineering bacteria [96] and unlocked a novel treatment technique in medicine, e.g., gene therapy [97]. A virus is a biomolecular complex that carries DNA (or RNA), which is packed inside a protein shell, called capsid, that is enveloped by a lipid layer. The capsid has (at least) an entrance to its interior, through which the nucleic payload is packed via a ring ATPase motor protein [98]. Located near the entrance are functional groups that facilitate docking on a cell by acting as ligands to receptors on it. Once docked, the nucleic content is injected into the cell, which triggers the cell's production line to produce more of virus' constituent parts and DNA. These self-organize into fully structured viruses, which finally burst out of the host cell to target new ones.

From MC perspective, viral vectors are considered to be one of the possible solutions in transmitting DNA between nanonetworking agents. The concept is similar to a bacterial conjugation-based transmission, as both encode information into transmitted DNA, but, in contrast, viral vectors

are immotile and their propagation is dictated by passive diffusion. However, they are comparatively smaller than bacteria so that more of them can be deployed in a given channel, and they diffuse faster. Moreover, the ligand–receptor docking mechanism, which serves as a header for receptor-/cell-specific long-range targeting, enables the possibility of the design of very complex and large-scale networking schemes with applications in gene therapy [4]. Furthermore, considering the high information density of DNA, virus-based MC stands out as one of the MC protocols viable to support high data rates. Yet, models of MC networks utilizing viral vectors are still very few. In particular, [63] proposes the utilization of engineered cells as platforms for devices and sensors to interface to nanonetworks. These engineered cells are assumed to be capable of virus production and excretion to facilitate desired networking, where a modular approach is presented for modeling of the genetic circuitry involved in the modulation of viral expression based on incoming extracellular signaling. Based on the model developed in [63], [99], and [100] investigate viral MC networking between nanomachines that communicate with each other in a diffusive medium via DNA messages transmitted within viruses, where the former analyses the reliability of a multipath topology and the latter derives reliability and delay in multihop relay networks.

*c) Genetic circuit-regulated protein transmission:* So far, we have investigated biological transmitter architectures, where the message to be conveyed has been encoded in sequences of nucleotides, e.g., DNA or RNA. Yet, the most abundant form of intercellular MC interaction in nature occurs via proteins, whose expression levels are determined by the genetic circuitry and metabolic state within the cells. Typically, proteins that are produced within a cell via transcriptional processes are either excreted out via specialized transmembrane protein channels or packed into vesicles and transported to the extracellular medium via exocytosis. As a result of exocytosis, either the vesicle is transported out wholly, e.g., an exosome [101], or it fuses with the cell membrane and only the contents are spewed out. Proteins on the membranes of exosomes provide addressing via ligand–receptor interactions with membrane proteins of the recipient cell. Upon a match, the membranes of exosome and the recipient cell merge, and the exosome contents enter the recipient cell. This establishes a one-to-one MC link between two cells. In case the contents are merely spewed out to the external medium, they diffuse around contributing to the overall concentrations within the extracellular medium. This corresponds to local message broadcast, and it has been long observed that populations of bacteria regulate their behavior according to the resulting local molecule concentrations resulting from these broadcast messages, referred to as the phenomenon of quorum sensing.

This mode of communication, even though lacking the information density of nucleotide chains, therefore supporting lower data rates, is commonly employed, by nature, as MC schemes. They are considerably more energy efficient compared to DNA transmission schemes, which justifies their use, by nature, as signaling agents for comparatively simple nanonetworking tasks. In this respect, in the context of MC among bacterial networks, quorum sensing has been proposed as a means to achieve synchronization among the nodes of the network [102], as well as a tool for power amplification of MC signals, increasing the range of transmitted signals [103]. Instead of utilizing quorum sensing to improve MC, Martins *et al.* [104] proposed quorum jamming to suppress the intrinsic quorum networking of a bacterial network with the aim of preventing them to form biofilms. This idea has possible applications in fighting infectious diseases caused by antibiotic-resistant bacteria, where the jamming signals can be delivered to the infectious population via the use of genetically engineered bacteria. In contrast to these works that consider quorum sensing, [105] considers exosome secretion as a possible means for the realization of nanonetworks composed of a large number of bionanomachines. Unluturk *et al.* [18] presented a detailed model of engineered genetic circuitry based on mass action laws that regulate gene expressions, which, in turn, dictate transmitter protein production. This paper stands as a basis for the future engineered genetic circuitry-based protein transmission modeling.

*d) Enzyme regulated $Ca^{2+}$ circuits:* $Ca^{2+}$ ions are utilized in many complex signaling mechanisms in biology, including neuronal transmission in an excitatory synapse, exocytosis, cellular motility, apoptosis, and transcription [55]. Moreover, they play a major role in intracellular and intercellular signal transduction pathways, where the information is encoded into local $Ca^{2+}$ concentration waves under the control of enzymatic processes. Intracellular organelles, including mitochondria and endoplasmic reticulum, accumulate excess $Ca^{2+}$ ions and serve as $Ca^{2+}$ storages. Certain cellular events, such as an extracellular signal generated by a toxin, trigger enzymatic processes that release bound $Ca^{2+}$ from organelles, effectively increasing local cytosolic $Ca^{2+}$ concentrations [106]. These local concentrations can propagate like waves within cells and can be injected to adjacent cells through transmembrane protein gap junction channels, called connexins [107].

Establishing controlled MC using this inherent signaling mechanism was first suggested by [108], where the authors consider communicating information between two nanomachines over a densely packed array of cells that are interconnected via connexins. The authors simulate MC within this channel to analyze the system parameter-dependent behavior of intercellular signal propagation and its failure. They also report on experiments relating to so-called cell wires, where an array of gap junction transfected cells are confined in a wire configuration and signals along the wire are propagated via $Ca^{2+}$ ions. The communication was characterized as limited range and slow speed. Later, $Ca^{2+}$ relay signaling over one-cell-thick

cell wires was investigated in [63] and [109] via dedicated simulations, where the former explored amplitude and frequency modulation characteristics and the latter aimed at understanding the communication capacity of the channel under stochastic effects. Simulations to determine the effects of tissue deformation on $Ca^{2+}$ propagation and the capacity of MC between two nanomachines embedded within 2-D cell wires with a thickness of multiple cells were carried out in [110]. As a part of their study, the authors propose various transmission protocols and compare their performance in terms of achieved rates. In a later study [111], the authors employ $Ca^{2+}$ signaling nanomachines embedded within the deformable cell arrays to infer deformation status of the array as a model for tissue deformation detection. This is achieved by estimating the distance between nanomachines from observed information metrics coupled with strategic placements of nanomachines. Motivated by tissue health inference via embedded nanomachines, Barros *et al.* [112] identified three categories of cells that employ $Ca^{2+}$ signaling, namely, excitable, nonexcitable, and hybrid, which, respectively, model muscle cells, epithelium cells, and astrocytes, and model the $Ca^{2+}$ communication behavior within channels that comprised of these cells. We refer the reader to [113] for a more detailed discussion of existing literature, theoretical models, experiments, applications, and future directions in this field of MC.

*e) Other biological architectures:* In addition to the biological transmission architectures described earlier, molecular motors' sliding on cytoskeletal protein structures, e.g., microtubules, and carrying cargo, i.e., vesicles, between cells is another option that has been considered by the MC community. In particular, Moore *et al.* [114] and Enomoto *et al.* [115] describe a high-level architecture design for MC over such channels. The comparison of active, i.e., molecular motors on microtubules, and passive, i.e., diffusion, vesicle exchanges among cells shows that active transport is a better option for intercellular MC in case of a low number of available vesicles and passive transport can support higher rates when large numbers of vesicles are available [116]. Two design options to form a microtubule nanonetwork in a self-organizing manner, i.e., via a polymerization/depolymerization process and molecular motor-assisted organization, are proposed in [117]. A complementary approach to molecular motor-based microtubular MC is presented in [118], where an on-chip MC test bed design based on kinesin molecular motors is presented. In this approach, instead of molecular motors gliding over microtubules as carriers of molecules, microtubules are the carriers of molecules, e.g., ssDNA, gliding over a kinesin covered substrate.

Other transmitter approaches that involve the use of biological entities are biological-nanomaterial hybrid approaches. A promising approach is to utilize IM production mechanisms of bacteria in nanomaterial-based transmitter architectures. In this direction, Sankaran *et al.* [119] report on an optogenetically controlled living hydrogel, that is, a permeable hydrogel matrix embedded with bacteria from an endotoxin-free *E. coli* strain, which releases IMs, i.e., antimicrobial and antitumoral drug deoxyviolacein, in a light-regulated manner. The hydrogel matrix is permeable to deoxyviolacein; however, it spatially restricts the movement of the bacteria. This hybrid approach proposes a solution to the reservoir problem of nanomaterial-based architectures. Moreover, to cover a variety of IMs simultaneously, this approach can be built upon by utilizing many engineered bacteria and controlling their states via external stimulus to control their molecular output [120].

## III. MOLECULAR COMMUNICATION RECEIVER

The MC-Rx recognizes the arrival of target molecules to its vicinity and detects the information encoded in a physical property of these molecules, such as concentration, type, or release time. To this aim, it requires a molecular receiver antenna that consists of a biorecognition unit followed by a transducer unit. The biorecognition unit, i.e., the interface with the molecular channel, holds a molecular recognition event that is specifically selective to the information-carrying molecules, e.g., it selectively reacts to these target molecules. Then, the transducer unit generates a processable signal, e.g., electrical or biochemical signal, based on this molecular reaction. Finally, a processing unit is needed to detect the transmitted information based on the output of the molecular antenna. The interconnection of these components in an MC-Rx is illustrated in Fig. 5 [121]. Since this structure is fundamentally different from EM communication receivers, it is necessary to thoroughly investigate the receiver architecture specification. To this aim, in this section, we first discuss the requirements of a receiver to be operable in an MC application and the communication theoretical performance metrics that must be taken into consideration while designing the receiver. Then, we review the available approaches in the physical design of MC-Rxs, which can be categorized into two main groups: 1) biological receivers based on synthetic gene circuits of engineered bacteria and 2) nanomaterial-based artificial MC-Rx structures.

### A. Design Requirements for MC-Rx

While designing the MC-Rx, its integrability to a mobile nanomachine with limited computational, memory, and energy resources, which requires to operate independently in an MC setup, must be taken into consideration. This dictates the following requirements for the functionality and physical design of the receiver [121].

1) *In Situ Operation:* In-device processing of the molecular message must be one of the specifications of the receiver since it cannot rely on any postprocessing of the transduced signals by an external macroscale device or a human controller.
2) *Label-Free Detection:* Detection of information-carrying molecules, i.e., IMs, must be done based

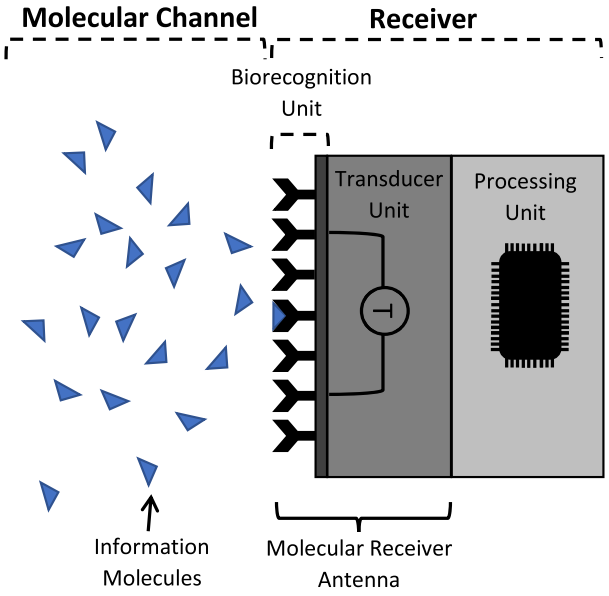


**Fig. 5.** ***Components of an MC-Rx.***

on their intrinsic characteristics, i.e., no additional molecular labeling procedure or preparation stage is required.

3) *Continuous Operation:* MC-Rx requires to observe the molecular channel continuously to detect the signal encoded into concentration, type/ratio/order, or release time of molecules. Thus, the functionality of the molecular antenna and the processing unit should not be interrupted. Since receptors are needed in the biorecognition unit for sensing target molecules, it is important to have reusable receptors, i.e., they must return to their initial state after signal detection to be ready for the next channel use.
4) *Energy Efficiency:* Due to the limitations of nanomachines, the energy usage of the MC-Rx must be optimized. In addition, as discussed in Section II-A, batteries may not be the feasible solutions for the long-term activity of nanomachines, e.g., as an implanted device. Thus, the receiver may need to be designed with EH units to be energy self-reliance.
5) *Biocompatibility and Biodurability:* One of the most important MC application areas is the life science, e.g., it promises diagnosis and treatment techniques for diseases caused by dysfunction of intrabody nanonetworks, such as neurodegenerative diseases [3]. These *in vivo* applications dictate further requirements for the device. First, it must not have any toxic effects on the living system. Moreover, the device needs to be flexible, not to cause any injury to the living cells due to mechanical mismatches. Furthermore, there must not be any physiological reactions between the device and the environment, and it must not cause immunological rejection. On the other hand, the physiological environment should not degrade the performance of the device with time.
6) *Miniaturization:* Finally, to be integrated into a nanomachine, the MC-Rx must be built on microscale/nanoscale components.

## B. Communication Theoretical Performance Metrics

The general performance metrics defined for EM communications, e.g., signal-to-noise ratio (SNR), bit error rate (BER), and mutual information, can also be used for MC. However, new performance metrics are needed to fully evaluate the functionality of an MC-Rx since molecules are used as IMs in MC. The most important performance metrics are summarized as follows.

1) *Limit of Detection (LoD):* LoD is a well-known performance metric in the biosensing literature [122]. It shows the minimum molecular concentration in the vicinity of the biosensor needed for distinguishing between the existence and the absence of target molecules. Since the input signal in MC-Rxs is a physical property of information carriers, LoD corresponds to the sensitivity metric used for evaluating the performance of the EM communication receivers, which indicates the minimum input signal power needed to generate a specified SNR at the output of the device.
2) *Selectivity:* This metric is defined based on the relative affinity of the biorecognition unit to the IMs and interferer molecules [123]. Note that interferer molecules can be non-IMs in the medium or other types of IMs in case of the MC system with multiple IMs, such as molecule shift keying (MoSK). High selectivity, i.e., very lower probability of interferer–receptor binding compared to target molecule–receptor binding, is needed to uniquely detect the IMs in the vicinity of the MC-Rx.
3) *Operation Range:* The biorecognition unit does not provide an infinite range of molecular concentration detection, as it has finite receptor density. The response of the device can be divided into two regions: the linear operation and the saturation region [124]. The range of molecular concentration in the vicinity of the MC-Rx that does not lead to the saturation of receptors is called the linear operation region. In this region, the output of molecular antenna provides better information about changes in the molecular concentration. Thus, when the information is encoded into the concentration of molecules, the receiver must work in the linear operation region. However, for other encoding mechanisms, e.g., MoSK, the receiver can work in both regions.

4) *Molecular Sensitivity:* In addition to the aforementioned sensitivity metric that is mapped to LoD for MC-Rxs, a molecular sensitivity can also be defined for an MC-Rx. This metric indicates the smallest difference in the concentration of molecules that can be detected by an MC-Rx [123]. It is of the utmost importance when the information is encoded in the molecular concentration. The metric can be defined as the ratio of changes in the output of the molecular receiver antenna to the changes in the molecular concentration in the vicinity of the MC-Rx when the device performs in the linear operation region.
5) *Temporal Resolution:* This metric is defined to evaluate the speed of the molecular concentration sampling by the receiver. Since the electrical processes are much faster than molecular processes, it is expected that the diffusion and the binding kinetics limit the temporal resolution. Thus, the biorecognition unit should be realized in a transport-limited manner to detect all the messages carried by molecules into the vicinity of the MC-Rx, i.e., the binding kinetics should not be a limiting factor on the sampling rate [121].

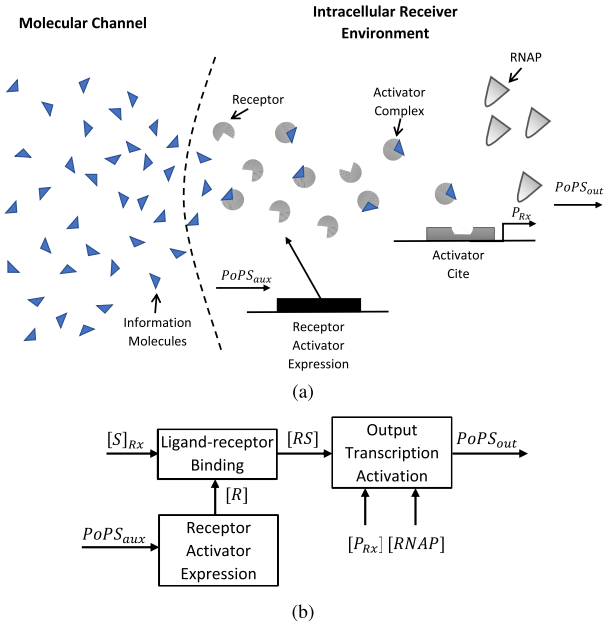


**Fig. 6.** ***Biological circuitry of an MC-Rx [127].***

## C. Physical Design of MC Receiver

Most of the existing studies on the performance of MC ignore the physical design of the receiver and assume that the receiver can perfectly count the number of molecules that: 1) enter a reception space with transparent boundaries; 2) hit a 3-D sphere that absorbs molecules; or 3) bind to receptors located on its surface [6]. However, the processes involved in the molecular-to-electrical transduction affect the performance of the receiver. Thus, the comprehensive communication theoretical modeling of these processes is required. Available approaches in the physical design of MC-Rxs can be categorized into two main groups as follows.

*1) Biological MC-Rx Architectures:* Synthetic biology, the engineering of biological networks inside living cells by modifying the natural gene circuits or creating new synthetic ones, has seen remarkable advancements in the last decade. As a result, it becomes possible to device engineered cells, e.g., bacteria, for use as biological machines, e.g., sensors and actuators, for various applications. Synthetic biology also stands as a promising means of devising nanoscale biotransceivers for IoBNT applications, by implementing transmission and reception functionalities within living cells [18]. Due to their nature, the biological MC-Rxs are promising for *in vivo* applications, such as monitoring the condition of a living organism, e.g., human or animal, regenerating biological tissues and organs, localized cancer treatment, immune system support, and interfacing artificial devices with nervous systems.

Synthetic biology is already mature enough to allow performing complex digital computations, e.g., with networks of genetic NAND and NOR gates, as well as analog computations, such as logarithmically linear addition, ratiometric, and power-law computations, in synthetic cells [125]. Synthetic gene networks integrating computation and memory is also proven feasible [126]. More importantly, the technology enables implementing bionanomachines capable of observing individual receptors, as naturally done by living cells. Thus, it stands as a suitable domain for practically implementing more information-efficient MC detectors based on the binding state history of individual receptors, as discussed in Section V.

In DNAs, gene expression is the process that produces a functional gene product, such as a protein. The rate of this expression can be controlled by the binding of another protein to the regulatory sequence of the gene. In biological circuits, activation and repression mechanisms that regulate the gene expressions are used to connect DNA genes together, i.e., the gene expression of a DNA generates a protein that can then bind to the regulatory sequence of the next DNA to control its expression [128]. In [129], polymerases per second (PoPS) is defined as the unit of input and output of a biological cell, i.e., the circuit processes a PoPS signal as input and generates another PoPS signal at its output using the aforementioned connections among DNAs. The literature in applying synthetic biology tools to design bacteria-based MC-Rxs is scarce. An MC biotransceiver architecture integrating molecular sensing, transmitting, receiving, and processing functions through genetic circuits is introduced in [18]. However, the analysis is based on the assumption of linearity and time invariance of the gene translation networks and does not provide any insight into the associated noise sources. The necessary biological elements for an MC-Rx are shown

in Fig. 6 [127]. The process of receiving information is initiated by the receptor activation expression, which gets a PoPS auxiliary signal as its input and generates receptor proteins, denoted by $R$, at its output. The incoming signal molecules from the molecular channel, i.e., $S_{\mathrm{Rx}}$, then bind to these receptors in the ligand–receptor binding unit and form activator complexes, called RS. Finally, the concentration of RS initiates the output transcription activation, in which RNA polymerase proteins, RNAP, bind to the promoter sequence, $P_{\mathrm{Rx}}$, and produce the PoPS output signal, $\mathrm{PoPS}_{\mathrm{Out}}$. Assuming that the intracellular receiver environment is chemically homogeneous, the transfer function of the aforementioned biological circuit is derived in [127] to provide a system-theoretic model for the MC-Rx. Genetic circuits are shown to provide higher efficiency for analog computations compared to digital computations [130]. Thus, analog computing functionalities of genetic circuits are utilized in [131] to derive an analog parity-check decoder circuit.

The major challenge in using genetic circuits for implementing MC-Rx arises from the fact that the information transmission in biological cells is through molecules and biochemical reactions. This results in nonlinear input–output behaviors with system-evolution-dependent stochastic effects that are needed to be comprehensively studied to evaluate the performance of the device. In [132]–[134], initiative studies on mathematical modeling of cellular signaling are provided. However, it is shown in [135] that the characterization of the communication performance of these systems is not analytically tractable. In addition, a computational approach is proposed to characterize the information exchange in a biocircuit-based receiver using the experimental data published in [136]. The results in [135] reveal that the rate of information transfer through biocircuit-based systems is extremely limited by the existing noises in these systems. Thus, comprehensive studies are needed to characterize these noises and derive methods to mitigate them. In addition, existing studies have only focused on the single transmitter–receiver systems; thus, the connection among biological elements for MC with multiple receiver cells remains as an open issue.

*2) Nanomaterial-Based Artificial MC-Rx Architectures:* MC-Rxs with artificial structures can be used in both *in vivo* applications, for which biocompatibility of the device and biostability of its response must be investigated, and *in vitro* applications. Apart from biomedical applications, such as health monitoring and drug delivery that can also be achieved using biological MC-Rxs, artificial MC-Rxs can also be used for applications, such as environmental monitoring to detect paste, pollution, toxic or radioactive agents, food and water quality control, and safe conversion of undesired materials [15]. Similar to biosensors, MC-Rxs are also designed to detect the concentration of an analyte in a solution. Thus, existing literature on MC-Rx design is focused on analyzing the suitability and performance of available biosensing options for receiving the information in the MC paradigm [68], [121], [137]–[139]. In this direction, researchers must consider the fundamental differences between a biosensor and an MC-Rx, arising from their different application areas, as stated in the following.

1) Biosensors are designed to perform typically in the equilibrium condition. However, MC-Rxs must continuously observe the environment and detect the information encoded into a physical property related to the molecules, such as concentration, type/ratio/order, or arrival time.
2) Biosensors are mostly designed for laboratory applications with macroscale readout devices and human observers to compensate for the lack of an integrated processor, which is not applicable for an MC-Rx.

Thus, while the biosensing literature provides insights for MC-Rx design, ICT requirements of the device and its performance in an MC paradigm must be considered to reach appropriate solutions.

Among existing biosensing options, the electrical biosensors are mainly under the focus of the MC-Rx design [121]. The remaining options, i.e., optical and mechanical sensings [140], [141], need macroscale excitation and detection units, making them inappropriate for an MC-Rx that requires *in situ* operation. Biocatalytic- [142] and affinity-based [143] sensors are two types of electrical biosensors with different molecular recognition methods. Biocatalytic recognition is based on two steps. First, an enzyme, immobilized on the device, binds with the target molecule, producing an electroactive specie, such as hydrogen ion. The arrival of this specie near the working electrode of the transducer is then being sensed, as it modulates one of the electrical characteristics of the device. Glucose and glutamate sensors are examples of the biocatalytic electrical sensors [142], [144]. Alternatively, binding of receptor–ligand pairs on the recognition layer of the sensor is the foundation of affinity-based sensing [143].

Affinity-based sensing, which is feasible for a wider range of target molecules, such as receptor proteins and aptamer/DNAs [143], [145], provides a less complicated sensing scheme, compared to the biocatalytic-based sensing. For example, in the biocatalytic-based sensing, the impact of the additional products of the reaction between the target molecule and enzyme on the performance of the device and the application environment must be analyzed thoroughly. Hence, affinity-based recognition is more appropriate for the design of a general MC system. However, this recognition method is not possible for nonelectroactive information-carrying molecules, such as glutamate and acetylcholine, which are highly important neurotransmitters in the mammalian central nervous system [146]. Thus, it is essential to study the design of biocatalytic-based electrical biosensors as MC-Rx when these types of information carriers are dictated by the application, e.g., communicating with neurons.

Recent advances in nanotechnology led to the design of bioFETs, providing both affinity- and biocatalytic-based

**Table 1** Design Options, Performance, and Applications of bioFETs

| Transducer channel | Bioreceptor | Limit of detection | Application | Ref. |
|---|---|---|---|---|
| SWCNT | Acetylcholine(Ach) receptor | 100 pM | ACh detection | [149] |
| SWCNT | Receptor protein (antibody) | 1 ng/ml | Prostate cancer detection | [150] |
| SWCNT | Anti Carcinoembryonic antigen (CEA) | $\sim$ 55 pM | CEA detection | [151] |
| SiNW | Receptor protein (antibody) | $\sim$2 fM | Prostate cancer detection | [152] |
| SiNW | Estrogen receptors | 10 fM | dsDNA detection | [153] |
| ZnO NW | Anti-Immunoglobulin G(IgG) antibodies | $\sim$0.3 nM | IgG antibodies sensing | [154] |
| Graphene | Glucose oxidase (enzyme) | 0.1 mM | Glucose sensor | [144] |
| Graphene | Glutamic dehydrogenase(enzyme) | 5 $\mu$M | Glutamate sensor | [144] |
| Graphene | Pyrene-linked peptide nucleic acid (pPNA) | 2 pM | DNA sensor | [155] |
| Graphene | Single-stranded probe DNA | 10 pM | DNA sensor | [148] |
| Graphene | Immunoglobulin E (IgE) aptamers | 0.3 nM | IgE protein detection | [156] |
| $MoS_2$ | Glucose oxidase (enzyme) | 300 nM | Glucose sensor | [147] |

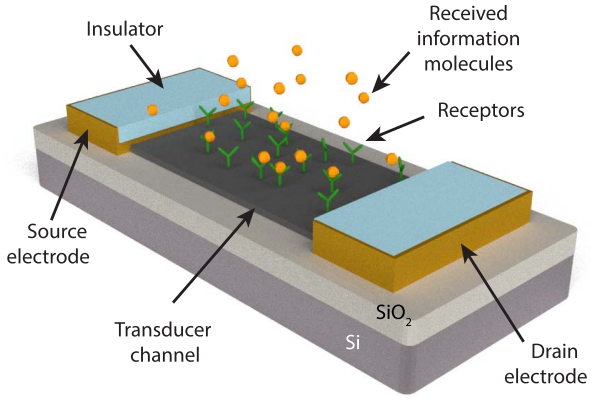


**Fig. 7.** ***Conceptual design of a bioFET-based MC-Rx.***

electrical sensings with use of nanowires (NWs), nanotubes, organic polymers, and graphene as the transducer unit [144], [147]–[149]. Detection of target molecules by bioFETs is based on the modulation of transducer conductivity as a result of either affinity- or biocatalytic-based sensings. Simple operation principles together with the extensive literature on FETs have been established through many years, electrical controllability of the main device parameters, high-level integrability, and plethora of optimization options for varying applications make FET-based biosensing technology also a quite promising approach for electrical MC-Rx. Moreover, these sensors promise label-free, continuous, and *in situ* operation in nanoscale dimensions. Thus, the design of an MC-Rx based on the principles of affinity-based bioFETs is the main approach considered in the literature [121], [137], which will be overviewed in the rest of this section.

*a) Nanoscale bioFET-based MC-Rx architectures:* As shown in Fig. 7, a bioFET consists of source and drain electrodes and a transducer channel, which is functionalized by ligand receptors in affinity-based sensors [145]. In this type of sensors, the binding of target molecules or analytes to the ligand receptors leads to accumulation or depletion of the carriers on the semiconductor channel. This modulates the transducer conductivity, which, in turn, alters the flow of current between source and drain. Thus, by fixing the source-to-drain potential, the current flow becomes a function of the analyte density and the number of analyte charges. Since the ligand receptors are being selected according to the target molecule, i.e., ligands, bioFETs do not require any complicated postprocessing, such as labeling of molecules. Moreover, the measurement of source–drain current does not need any macroscale readout unit. Thus, bioFETs can be used for direct, label-free, continuous, and *in situ* sensing of the molecules in an environment as a stand-alone device.

One of the significant advantages of bioFETs over other electrical sensors is their wide range of design parameters. A list of FET-based biosensors and their applications in sensing different type of molecules is provided in Table 1. In the following, we further describe these vast design options.

*Type of Bioreceptors:* First important design parameter arises from the type of receptors used in the biorecognition unit. Type of receptors causes the selectivity of receiver for a certain type of molecules that will be used as an information carrier in the MC paradigm. Among possible receptor types for affinity-based bioFETs, natural receptor proteins and aptamer/DNAs are appropriate ones for an MC-Rx since their binding to the target molecule is reversible and their size is small enough to be used in a nanomachine [143], [145]. As an example, the FET transducer channel is functionalized with natural receptors, e.g., neuroreceptors, to detect taste in bioelectronic tongues [157] and odorant in olfactory biosensors [158]. An advantage of these type of receptors is their biocompatibility that makes them suitable for *in vivo* applications. In addition, use of aptamers, i.e., artificial single-stranded DNAs and RNAs, in the recognition unit of bioFETs provides detectors for a wide range of targets, such as small molecules, proteins, ions, aminoacids, and other oligonucleotides [148], [156], [159]. Since an immense number of aptamer-ligand combinations with different affinities exist, it provides a

powerful design option to control the selectivity of the MC-Rx. The appropriate aptamer for a target ligand can be found using the SELEX process, i.e., searching a large library of DNAs and RNAs to determine a convenient nucleic acid sequence [160].

*Material Used for Transducer Channel:* One of the most important bioFET design parameters is the material used as the transducer channel between source and drain electrodes, which determines the receiver geometry and affects the electrical noise characteristics of the device. NWs [152], single-walled carbon nanotubes (SWCNTs), graphene [161], molybdenum disulfide ($MoS_2$) [147], and organic materials, such as conducting polymers [162], are some examples of nanomaterials suitable for use in a bioFET channel. In the first generation of bioFETs, 1-D materials, such as SWCNT and NW, were used as the channel in a bulk form. However, using in the form of a single material or aligned arrays outperformed the bulk channels in terms of sensitivity and reduced noise [163]. Among possible NW materials, such as $SnO_2$, ZnO, and $In_2O_3$ [164], silicon NW (SiNW) bioFETs have shown high sensitivity, high integration density, high-speed sampling, and low power consumption [165]–[167]. However, their reliable and cost-effective fabrication is still an important open challenge [148], [168]. Comprehensive reviews exist on the performance of SiNW bioFETs, their functionality in biomedical applications, such as disease diagnostics, their top–down and bottom–up fabrication paradigms, and integration within complementary metal–oxide–semiconductor (CMOS) technology [163], [169], [170]. It is concluded that SiNW bioFETs must be designed according to the requirements arose by applications since defining an ideal characteristic for these devices is difficult. In addition, both theoretical and experimental studies are needed to find the impact of structure parameters on their functionality. Moreover, fine balancing of important structural factors, such as number of NWs and their doping concentration and length, in SiNW bioFETs design and fabrication remains a challenge, which affects the sensitivity, reliability, and stability of the device. SWCNT-based bioFETs offer higher detection sensitivity due to their electrical characteristic; however, these devices also face fabrication challenges, such that their defect-free fabrication is the most challenging among all candidates [171]. Note that the existence of defects can adversely affect the performance of SWCNT bioFETs in an MC-Rx. Moreover, for *in vivo* applications, the biocompatibility of CNTs and biodurability of functionalized SWCNTs are still under doubt [172]–[174]. While both NWs and CNTs have 1-D structure, use of 2-D materials as the transducer channel leads to higher sensitivity; since a planar structure provides higher spatial coverage, more bioreceptors can be functionalized to its surface and all of its surface atoms can closely interact with the bond molecules. Thus, graphene, with its extraordinary electrical, mechanical, and chemical characteristics, is a promising alternative for the transducer channel of bioFETs [168], [175].

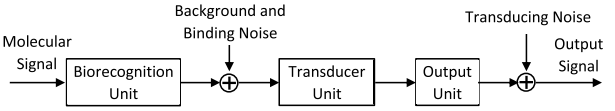


**Fig. 8.** ***Block diagram of a bioFET-based MC-Rx.***

The intrinsic flexibility of graphene provides a higher chance of integration into devices with nonplanar surfaces, which can be more suitable for the design of nanomachines in an MC application, such as communicating with neurons [161]. There is currently a tremendous amount of interest in building different configurations of graphene bioFETs, e.g., back-gated [176] or solution-gated [175]. Moreover, researches has shown its superior sensing performance for various analytes, e.g., antigens [177], DNA [178], bacteria [179], odorant compounds [175], and glucose [180].

General block diagram of a bioFET-based MC-Rx is shown in Fig. 8. The biorecognition unit is the interface between the communication channel and the receiver, thus, it models sensing of the concentration of ligands. The random motion of ligands near the surface of the receiver, which is governed by the Brownian motion, leads to fluctuations in the number of bound receptors. This fluctuation can be modeled as a binding noise, which depends on the transmitted signal and can adversely affect the detection of the ligands concentration [181]. The communication theoretical models of binding noise are presented in [182] and [183]. Background noise, also called biological interference [121], is resulted from the binding of molecules different from targeted ligands that might exist in the communication channel and show a similar affinity for the receptors [181]. Note that this is different from ISI and cochannel interference studied in [184] and [185]. Stochastic binding of ligands to the receptors modulated the conductance of the FET channel, which is modeled by the transducer unit in Fig. 8. These conductance changes are then reflected into the current flowing between the source and drain electrodes of FET by the output unit. The surface potential of the FET channel—thus, its source-to-drain current—can be affected by undesirable ionic adsorptions in application with ionic solutions [121]. Hence, a reference electrode can be used in the solution to stabilize the surface potential [123]. Finally, the transducing noise shown in Fig. 8 covers the impact of the noise added to the received signal during transducing operation, including thermal noise, caused by thermal fluctuations of charge carriers on the bound ligands, and $1/f$ (flicker) noise, resulted from traps and defects in the FET channel [186]. Flicker noise can be the dominant noise source in low frequencies, as it increases with decreasing the frequency [121]. Detailed information on the impact of the aforementioned noise processes on the performance of bioFETs can be found in [186] and [187]. Moreover, experimental studies are provided in [188] on

the noise resulted from the ion dynamic processes related to ligand–receptor binding events of a liquid-gated SiNW array FET by measuring the noise spectra of the device before and after binding of target molecules.

While the existing biosensing literature can provide insight for the MC-Rx design, there is a need for investigation of design options according to the communication theoretical requirements of an MC-Rx. Few studies have focused on evaluating the performance of bioFETs in an MC paradigm. A SiNW bioFET-based MC-Rx is modeled in [121] based on the equilibrium assumption for the receptor–ligand reaction at the receiver surface. The study provides a circuit model for the transducer unit of the receiver. This paper is further extended in [137], where the spatial and temporal correlation effects resulting from the finite-rate transport of ligands to the stochastic ligand–receptor binding process are considered to derive the receiver model and its noise statistics. In [189], an MC-Rx consisting of an aerosol sampler, a SiNW bioFET functionalized with antibodies, and a detection stage is designed for virus detection. The performance of the receiver is studied by considering the system in steady state. While the receiver model in [189] takes into account the flicker noise and the thermal noise, it neglects the interference noise by assuming that the MC-Rx performs in a perfectly sanitized room. Moreover, the models used in all of these studies assume the ligand–receptor binding process in the thermal equilibrium, and they do not capture well the correlations resulting from the time-varying ligand concentration occurring in the case of MCs. More importantly, these studies only cover SiNW bioFET receivers and do not provide much insight into the performance of other nanomaterials as the transducer channel, such as graphene that promises to provide higher detection sensitivity due to its 2-D structure.

Thus, the literature misses stochastic models for nanomaterial-based MC nanoreceiver architectures that are needed to study the performance of the receiver in MC scenarios, i.e., when the device is exposed to time-varying concentration signals of different types and amplitudes. These models must capture the impacts of receiver geometry, its operation voltage characteristics, and all fundamental processes involved in sensing of molecular concentration, such as molecular transport, ligand–receptor binding kinetics, and molecular-to-electrical transduction by changes in the conductance of the channel. To provide such a model for graphene-based bioFETs, the major factors that influence the graphene properties must be taken into account. The number of layers is the most dominant factor since electronic band structure, which has a direct impact on the electrical properties of the device, is more complex for graphene with more number of layers [190]. Next important parameter is the substrate used in the graphene-based bioFET, especially when the number of layers is less than three [190], [191]. The carrier mobility in the graphene sheet is reported to be reduced by more than an order of magnitude on the $SiO_2$ substrate due to charged impurities in the substrate and remote interfacial phonon scattering [192]. On the other hand, it is shown that the impacts of the substrate can be reduced in the suspended single-layer graphene sheet, resulting in higher carrier mobility [193]. Moreover, as a result of graphene's large surface area, the impact of impurities on its performance can be substantial [191]. The atomic type, amounts, and functional groups on the edges of graphene, which are hard to measure and control, are also among the properties that can result in trial-to-trial variations in the performance of the fabricated device [194]–[196]. In addition, inherent rippling in graphene sheet, defects, and size of the sheet also affect the properties of the device [191], [197]–[199].

*b) Other MC-Rx architectures:* Few studies exist on the practical MC systems, taking into account the physical design of the receiver. In [68], the isopropyl alcohol (rubbing alcohol) is used as the information carrier, and commercially available metal-oxide semiconductor alcohol sensors are used as MC-Rx. This paper provides a test bed for MC with macroscale dimensions, which is later on utilized in [200] to estimate its combined channel and receiver model. This test bed is extended to a molecular multiple-input–multiple-output (MIMO) system in [201] to improve the achievable data rate. In [138], the information is encoded in the pH level of the transmitted fluid, and a pH probe sensor is used as the MC-Rx. Since the use of acids and bases for information transmission can adversely affect the other processes in the application environment, such as in the body, magnetic nanoparticles (MNs) are used as information-carrying molecules in microfluidic channels in [139]. In this study, a bulky susceptometer is used to detect the concentration of MNs and decode the transmitted messages. In addition, the performance of MN-based MC, where an external magnetic field is employed to attract the MNs to a passive receiver, is analyzed in [202].

However, the focus of the aforementioned studies is using macroscale and commercially available sensors as the receiver. Thus, these studies do not contribute to the design of a nanoscale MC-Rx. As discussed in Section II-B1, recent advancements in DNA/RNA sequencing and synthesis techniques have enabled DNA/RNA-encoded MC [42], [43]. For information transmission, communication symbols can be realized with DNA/RNA strands having different properties, i.e., length [45], dumbbell hairpins [42], [46], and short-sequence motifs/labels [43]. For information detection, solid-state nanopores [43] and DNA-origami-based nanopores [49] can be utilized to distinguish the information symbols, i.e., the properties of DNA/RNA strands by examining the current characteristics while DNA/RNA strands passing through the nanopores. As presented in Fig. 3, MC-Rx contains receptor nanopores, through which these negatively charged DNA strands pass, owing to the applied potential, and as they do, they obstruct ionic currents that normally flowthrough. The duration of the current obstruction is proportional to the length of the DNA strand that passes through, which is

**Table 2** Comparison Matrix for MC Modulation Schemes

| Description | Encoding Mechanism | ISI Reduction | # of Molecule Type | # of Symbols |
|---|---|---|---|---|
| On-off keying (OOK) [203] | Concentration | No | 1 | 2 |
| Concentration shift keying (CSK) [66] | Concentration | No | 1 ($b$ Concentration levels) | $2^b$ |
| Pulse amplitude modulation (PAM) [204] | Concentration | No | 1 ($b$ Concentration levels) | $2^b$ |
| Molecule shift keying (MoSK) [9] | Molecule type | Moderate | $k$ | $k$ |
| Depleted MoSK (D-MoSK) [205] | Molecule type | No | $k$ | $2^k$ |
| Isomer-based ratio shift keying (IRSK) [67] | Molecule ratio | Moderate | $k$ | $k$ |
| Release time shift keying (RTSK) [206]–[208] | Release timing | No | 1 ($b$ Timing intervals) | $2^b$ |
| Molecular array-based communication (MARCO) [209] | Molecule order | High | $k$ | $2^k$ |

utilized for selective sensing. The use of nanopores for DNA/RNA symbol detection also enables the miniaturization of MC capable devices toward the realization of IoBNT. According to [42], 3-bit barcode-coded DNA strands with dumbbell hairpins can be detected through nanopores with 94% accuracy. In [47], four different RNA molecules having different orientations are translocated with more than 90% accuracy while passing through the transmembrane protein nanopores. The time of the translocation event depends on the voltage, concentration, and length of the DNA symbols, and the translocation of symbols can take up to a few milliseconds up to 100-ms time frames [42], [46]. Considering the slow diffusion channel in MC, transmission/detection of DNA/RNA-encoded symbols does not introduce a bottleneck, and multiple detections can be performed during each symbol transmission.

## IV. MODULATION AND CODING TECHNIQUES FOR MC

### A. Modulation Techniques for MC

In MC, several modulation schemes have been proposed to encode information into concentration, molecule type, and molecule release time, as shown in Table 2. The first and simplest modulation method that was proposed for MC is OOK, in which a certain number of molecules are released for the high logic and no molecule is released to represent the low logic [203]. In a similar manner, by using a single molecule, concentration shift keying (CSK) that is analogous to amplitude shift keying (ASK) in traditional wireless channels is introduced in order to increase the number of symbols in the modulation scheme by encoding information into concentration levels [66]. In [204], a similar modulation scheme based on the concentration levels is proposed and named pulse-amplitude modulation (PAM), which uses pulses of continuous IM release instead of instantaneous release as in CSK. The number of concentration levels that can be exploited significantly depends on the molecule type and the channel characteristics, as ISI at MC-Rx can be a limiting factor.

Hitherto, we have discussed modulation techniques that use a single type of molecules. However, information can be encoded by using multiple molecules, such that each molecule represents different symbols, and $k$ information symbols can be represented with $2^k$ different types of molecules in MoSK [9], that is, 1-bit MoSK requires two molecules to encode bit-0 with molecule A and bit-1 with molecule B. The modulation of each molecule in MoSK is based on other modulation techniques, such as OOK. MoSK can achieve higher capacity, but the main limiting factor for this modulation type is the number of molecules that can be selectively received. Kabir *et al.* [205] further improved MoSK by representing the low logic with no molecule release and enabling simultaneous release of different type of molecules, such that $2^k$ symbols can be represented with $k$ molecules, which is named depleted MoSK (D-MoSK), that is, 1-bit D-MoSK is equivalent to OOK. 2-bit D-MoSK requires only two molecules, and four distinct symbols can be encoded with these molecules (molecule A and molecule B), such as N (00), A (01), B (10), and AB (11), where $N$ represents no molecule release. Furthermore, Kim and Chae [67] propose the utilization of isomers, i.e., the molecules having the same atoms in a different orientation, and a new modulation scheme, named isomer-based ratio shift keying (IRSK), in which information is encoded into the ratio of isomers, i.e., molecule ratio keying.

The release time of molecules can be also used to encode information. Garralda *et al.* [204] proposed pulse position modulation, in which the signaling period is divided into two blocks, such that a pulse in the first block means high logic and a pulse in the second block means low logic. More complex modulation schemes based on release timing, i.e., release time shift keying (RTSK), where information is encoded into the time interval between molecule release, have been investigated in [206] and [207]. The channel characteristics in case of RTSK is significantly different than other modulation schemes, as additive noise is distributed with the inverse Gaussian distribution in the presence of flow in the channel [207] and the Levy distribution without any flow [206].

In MC, ISI is an important performance-degrading factor during detection due to the random motion of particles in the diffusive channels. The effects of ISI can be compensated by considering ISI-robust modulation schemes. In [210], an adaptive modulation technique exploiting the memory of the channel is utilized to encode information into the emission rate of IMs, and this approach makes the channel more robust against ISI by adaptive control of the number of released molecules. In addition, the order of

**Table 3** Comparison Matrix for MC Channel Codes

| Code | Mod. | Transmission/ # of Mol. | Channel Model Prop./Dim./B.N. | Detection | Reception | C.D. | # of Mol. Types | Coding Rate ($\frac{k}{n}$) | E.C. |
|---|---|---|---|---|---|---|---|---|---|
| ISI-free code [216], [217] | MoSK | Reg./Single | Diff.+Drift/1d/No | Abs. | Imm. | No | 2 | $\frac{2}{4}, \frac{2}{5}, \frac{4}{7}, \frac{3}{8}, \frac{3}{11}, \frac{4}{23}, \frac{5}{47}$ | No |
| MoCo-based code [218] | OOK | Reg./Single | Diff.+Drift/1d/Yes | Abs. | Add.Thr.=1 | Yes | 1 | $2/4$ | No |
| Hamming codes [219], [220] | OOK | Reg./Many | Diff./3d/No | Non-Abs. | Add.Thr. | No | 1 | $\frac{2^m-m-1}{2^m-1}$, $m=3,4,5$ | Yes |
| SOCC [221] | OOK | Reg./Many | Diff./3d/No | Non-Abs. | Add.Thr. | No | 1 | $k/(k+1)$, $k=1,2$ | Yes |
| SOCC [222] | OOK | Reg./Many | Diff./3d/No | Abs. | Add.Thr. | No | 1 | $k/(k+1)$, $k=1,2$ | Yes |
| EG-LDPC [223] | OOK | Reg./Many | Diff./3d/No | Abs. | Add.Thr. | No | 1 | $\frac{4^s-3^s}{4^s-1}$, $s=2,3,4$ | Yes |
| Convolutional code [224] | PAM | Reg./Many | Diff./3d/No | Abs. | Add.Thr. | No | 1 | $1/2$ | No |
| SPC code [131] | OOK | Reg./Many | Diff./3d/Yes | Reactive | LLR | No | 2 | $2/3$ | No |

Abbreviations — Abs.: Absorbing – Add.Thr.: Additive with threshold – B.N.: Background Noise – C.D.: Channel Dependent – Diff.: Diffusion – Dim.: Dimension – E.C.: Energy Considered – Imm.: Immediate – Mod.: Modulation – Mol.: Molecule – Non-Abs.: Non-absorbing – Prop.: Propagation – Reg.: Regular

molecules can be also used for information encoding as in molecular array-based communication (MARCO) [209]. In this approach, different types of molecules are released consecutively to transmit symbols, and by assuming perfect molecular selectivity at the transmitter, the effects of ISI can be reduced.

The modulation schemes based on the concentration, molecule type/ratio/order, and molecule release time offer a limited number of symbols. Therefore, MC suffers from low data rates by considering limited number of symbols and slow diffusive propagation. To tackle this problem, a large amount of information can be encoded into the base sequences of DNAs, i.e., NSK. For this purpose, information can be encoded directly using nucleotides with an error coding algorithm, such as Reed–Solomon (RS) block codes [211], or an alphabet can be generated out of DNA sequences (1–150 bp/letter) to encode information. The latter approach can yield higher performance in terms of BER, considering the complexity and the size of MC-Tx and MC-Rx architectures. Although identification of base pairs with nanopores can be performed with relatively low costs and high speeds [212], [213], there is yet no practical system to write DNA sequences with a microscale device. Therefore, future technological advancements toward low-cost and practical synthesis/sequencing of DNA are imperative for MC communications with high data rates, e.g., on the order of megabits per second.

## B. Coding Techniques for MC

Encoding of information before transmission is classically done for two reasons: source coding is done for statistically efficient representation of data form a discrete input source and channel coding is done to control errors that occur due to channel noise via introducing redundant bits. Source coding practices are independent of channel characteristics, and as a result, they do not differ for MC with respect to traditional communications from an ICT point of view. For this reason, we do not cover source coding in this review. On the other hand, MC channels are typically diffusive, a process which has slow and omnidirectional propagation. As a consequence, IMs quickly accumulate in the channel after a series of transmissions, rendering MC extremely noisy and susceptible to ISI. Moreover, as coding has a computational burden on both transmitter and receiver ends, and energy is a scarce resource at nanoscale, energy efficiency of employed channel codes is also a crucially important aspect. This calls for utilization of lower complexity block codes, such as simple parity codes or cyclic codes, e.g., the Hamming codes [214], instead of the state-of-the-art high complexity codes with high computational burden, such as the Turbo codes [215]. On the other hand, the noisy nature of MC channels and overpronounced effects of ISI renders channel codes developed for conventional EM communications ill-adjusted for MC, calling for the invention of novel coding techniques specifically tailored for MC. Table 3 enlists the channel coding practices so far employed in the MC literature. In the following, we summarize these works and highlight their contributions.

The first MC specific code in the literature is aimed at mitigating the effects of ISI in MC, as it is the main source of high BERs. Shih *et al.* [216] introduced the ISI-free coding scheme under the MoSK modulation, where two distinguishable molecules encode for bit-0 and bit-1, respectively. The receiver is absorbing, i.e., detects everything that hits, and it immediately receives bit-0 or bit-1 upon detection depending on the type of detected molecule. The authors work with the example of a $(4,2,1)$ ISI-free code, where an $(n,k,l)$ ISI-free code is an $(n,k)$ block code, i.e., maps $k$-bit information into $n$-bit codewords, and is error-free, provided that there are no more than level-$l$ crossovers. Here, crossover is the phenomenon of late detection of a molecule belonging to previously transmitted symbols, and a level-$l$ crossover means that the detected molecule was transmitted one symbol ago. The ISI-free code is a fixed code, in which it is invariant with respect to the change in channel parameters. The (4,2,1) code implemented in [216] is based on the idea of finding a codebook with codewords, whose level-1 permutation sets, i.e., possible detection sequences under maximum level-1 crossover assumption, are disjoint. However, level-1 permutation sets of codewords depend on values of neighboring bits at the boundary of contiguous codewords, where if they are same, crossovers between contiguous codewords do not contribute new elements to the level-1 permutation set, making finding codewords with disjoint permutation sets easier. To achieve this,

(a)

| Information bits | Starting with 0 | Level-1 permutation | Starting with 1 | Level-1 permutation |
|---|---|---|---|---|
| 00 | 0000 | 0000 | 1111 | 1111 |
| 01 | 0001 | 0001, 0010 | 1000 | 0100, 1000 |
| 10 | 0011 | 0101, 0011 | 1100 | 1100, 1010 |
| 11 | 0111 | 0111, 1011 | 1110 | 1101, 1110 |

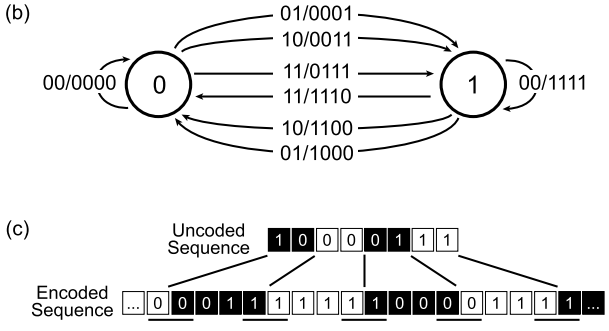


**Fig. 9.** *(a) Employed codewords for two states, e.g., starting with 0 or 1, together with their level-1 permutations. (b) State transition diagram. (c) Encoding example for the ISI-free (4,2,1) code. Note the same bits at the boundaries of contiguous words [216].*

the authors devise a two-state encoder architecture, whose codeword assignments and state diagram are illustrated in Fig. 9 together with an example encoding. Note that contiguous codewords always have the same neighboring bits. The receiver decodes the information bits from the codeword received by adding the number of 1's modulo $n = 4$ and converting the result to binary, which is a fairly simple decoding rule, therefore favorable for MC. The authors also compare the ISI-free (4,2,1) code with convolutional and repetition codes and verify the comparable BER performance with much less computational burden. In their work [217], the authors extend the ISI-free $(n, k, l)$ codes to account for higher level crossovers, namely, for levels $l = 2,3,4,5$. Furthermore, they introduce the ISI-free $(n, k, l, s)$ codes, in which the codewords have at least $l$ final and $s$ initial identical bits, instead of the symmetric at least $l$ identical bits at both ends of ISI-free $(n, k, l)$ codes, and show that they significantly outperform the $(n, k, l)$ codes under similar computational burdens. In essence, the motivation for $(n, k, l, s)$ codes comes from the asymmetry of intercodeword error probabilities arising from crossover at the start and at the end of a codeword. More specifically, if one compares the probability of a given molecule having level-$l$ crossover forward, that is, arriving later than the $l$ molecules released after it, to the probability of having level-$l$ crossover backward, that is, arriving earlier than the preceding $l$ molecules, one finds latter to fall far more rapidly with increasing $l$. Thus, to reduce the computational burden, $s$ is typically chosen lower than $l$, signifying the low probability of backward crossover errors. Finally, the authors demonstrate that ISI-free $(n, k, l, s)$ codes can deliver better BERs than convolutional codes with less computational resources. As its weaknesses, the work considers a very simple 1-D diffusive channel model with positive drift velocity, which lacks many phenomena that the diffusive MC enjoys in three dimensions. In particular, transmitted IMs are doomed to hit the receiver, which is very different from the 3-D case, where there is always the probability that no molecules will reach the receiver. The extent of this simplification reveals itself in the assumption that the transmitter releases a single molecule per symbol, which, owing to the drift in the channel and the absorbing nature of receiver, is always detected.

MC-adapted version of the classical Hamming codes was introduced in [218], where the traditional Hamming distance metric on the codeword space, given by the number of bit differences between two binary codewords, is replaced by the so-called molecular coding distance function (MoCo). In its essence, MoCo is defined in terms of the negative logarithms of probabilities $Pr(\{x \rightarrow y\})$ of receiving codeword $y$ when $x$ was transmitted, and the code aims at generating a codebook with maximal minimum pairwise MoCo distance between constituent codewords. MoCo distance is not a metric, as it is not symmetric, and the triangular inequality is not verified by the authors. This paper, too, considers a 1-D diffusive channel with drift and an absorbing receiver; however, in contrast to [216] and [217], it uses synchronized time-slotted OOK modulation scheme with only a single type of IM, and the receiver is additive with a threshold equal to 1, i.e., it counts the number of hits in a period and claims high logic reception with a single hit. In the case of (4,2) block codes, the authors demonstrate that the code generated using MoCo performs superior to the Hamming code by carrying out an error rate analysis for both codes. However, as shortcomings, MoCo depends on detection probabilities that are sensitive to variations in channel properties and are, in general, unknown to Tx and Rx. Moreover, even if adaptive techniques may be envisioned, calculation of the MoCo-based codebook (at Tx) and the decoding region partition (at Rx) requires significant computational resources at Tx and Rx, respectively, and overhead communication would have to be considered for the synchronized code updating.

Leeson and Higgins [219] propose the classical Hamming codes to introduce error correction in MC, where they consider a 3-D diffusive channel with time-slotted OOK modulation scheme in a channel with finite memory. The receiver is modeled as a nonabsorbing sphere that immediately detects molecules that arrive at it, and reception is decided upon the additive count of arriving molecules during the transmission period. The Hamming codes are error-correcting block codes with coding ratio $k/n = (2^m - 1)/(2^m - m - 1)$, where $m$ is the number of parity check bits, and [219] considers the Hamming codes for $m = 3,4,5$. Their results show that the Hamming codes can deliver coding gains up to $\approx 1.7$ dB at a transmission distance of 1 $\mu$m and for low BERs. Here, the coding gain is defined as the gain the code introduces in a required number of

IMs per transmission to achieve a given BER. At high BERs, i.e., low quantities of transmitted IMs, extra ISI introduced by parity bits overweighs error correction, and uncoded transmission performs better. The authors also incorporate an energy model for transmission, where energy is taken to be proportional to the number of transmitted IMs. They show that the energy required to transmit the extra parity bits causes the coded transmission to be energy inefficient at small communication distances; however, coding becomes more efficient at larger distances. Later on, over the same channel model, a Hamming minimum energy code (MEC) scheme was proposed in [220]. In a trade-off of having larger codeword lengths against generating codewords with lower average weights by using more 0-bits, the authors trade between the rate and the energy efficiency of communication. In subsequent works [221], [222], again, over the same channel except with an absorbing receiver in [222], self-orthogonal convolutional codes (SOCCs) are proposed, and their performances against Hamming MECs and uncoded transmissions are investigated with respect to both BER and energy efficiency. Both works conclude that in nanoscale, MC SOCCs have higher coding gains, i.e., they are more energy efficient, compared to the uncoded transmission and to the Hamming MECs for the low BER ($10^{-5}$–$10^{-9}$) region. Moreover, SOCCs are also reported to have shorter critical distances than the Hamming MECs, where the critical distance is defined as the distance, at which extra energy requirements of employing coding are compensated by the coding gain. Lu *et al*. [222] additionally explore the energy budget of nano-to-macro and macro-to-nanomachine MCs and arrive at the conclusion that in MC involving macromachines, the critical distance of the codes decreases. Yet, in another work [223], the Hamming codes are evaluated against cyclic 2-D Euclidean geometry low-density parity-check (EG-LDPC) and cyclic Reed–Muller codes by considering the same channel model, as in [222]. Again, the comparison of codes is carried out for different MC scenarios involving nanomachines and macromachines, and it reveals, in the case of nano-to-nanomachine MC, that in the BER region $10^{-3}$–$10^{-6}$, the Hamming codes with $m = 4$ are superior, and at lower BER regions, LDPC codes with $s = 2$ exhibit the lowest energy cost. Here, $s \geq 2$ is the density parameter in LDPC codes, where coding density increases to 1 monotonically as $s \to \infty$. Moreover, in macro-to-nano and nano-to-macro MCs, the results indicate that LDPC codes with $s = 2$ and $s = 3$ are the best options, respectively.

The performance of convolutional coding techniques in diffusive MC systems has been investigated by utilizing PAM with $M = 1, 2, 4$ pulse amplitude levels for varying key factors, such as transmission rate and communication range (0.8 $\mu$m–1 mm) [224]. The findings indicate that while convolutional coding with high transmission rate and $M = 1$, i.e., OOK modulation, does outperform the uncoded transmission in short- and medium-range communications, no coding does better than convolutional codes in the long-range MC. Furthermore, an increase in the number of pulse amplitude levels causes deterioration in achieved BERs, which is attributed to increased ISI, implying that OOK modulation is better suited to MC than PAM.

All the aforementioned works apply various channel coding techniques for error correction in MC; however, they do not provide any details into mechanisms of implementation of these codes from the device architecture perspective. Marcone *et al.* [225] devised a molecular single parity check (SPC) encoder with OOK modulation for an MC design based on genetically engineered bacteria that are assumed to network with each other via signaling molecules, e.g., N-acyl homoserine lactones (AHLs). The implementation of joint encoder–modulator module is achieved via the design of genetic circuits that regulate gene expression levels, and the transmission materializes from ensuing biomolecule concentrations dictated by biochemical reactions. Developed SPC encoder, which appends to 2-bit information a parity check bit via biological XOR gate based on designed genetic circuits, provides an error detection mechanism, however with no correction. Still, the introduced design serves as a basis for genetic circuit-based designs of more complex block codes with error correction capabilities. In this paper, there is no evaluation of the proposed coding scheme, as this paper considers only the transmitter side of MC. A year later, Marcone *et al.* [131] extended their work in [225] by introducing the biological analog decoder circuit, which computes *a posteriori* log-likelihood ratio (LLR) of transmitted bits from observed transmitter concentrations. LLR is defined as the gain of the probability of detection over nondetection in decibel. This enabled them to analyze the whole end-to-end MC over a diffusive channel. Via simulations, they manage to verify the intended operation of designed modulated SPC encoder and the analog decoder and observe network performance close to an electrical network operating in high noise.

## V. DETECTION TECHNIQUES FOR MC

Detection is one of the fundamental aspects of communications having a tremendous impact over the overall communication performance. The detection of MC signals is particularly interesting due to the peculiarities of the MC channel and communicating nanomachines, which impose severe constraints on the design of detection methods. For example, the limited energy budget and computational capabilities of nanomachines due to their physical design restrict the complexity of the methods. The memory of the diffusion channel causes severe ISI and leads to time-varying channel characteristics with very short coherence time. The stochastic nature of the Brownian motion and sampling of discrete message carriers bring about different types of noise, e.g., counting noise and receptor binding noise. The physiological conditions, in which most of the nanonetwork applications are envisioned to operate, imply the abundance of molecules with similar characteristics

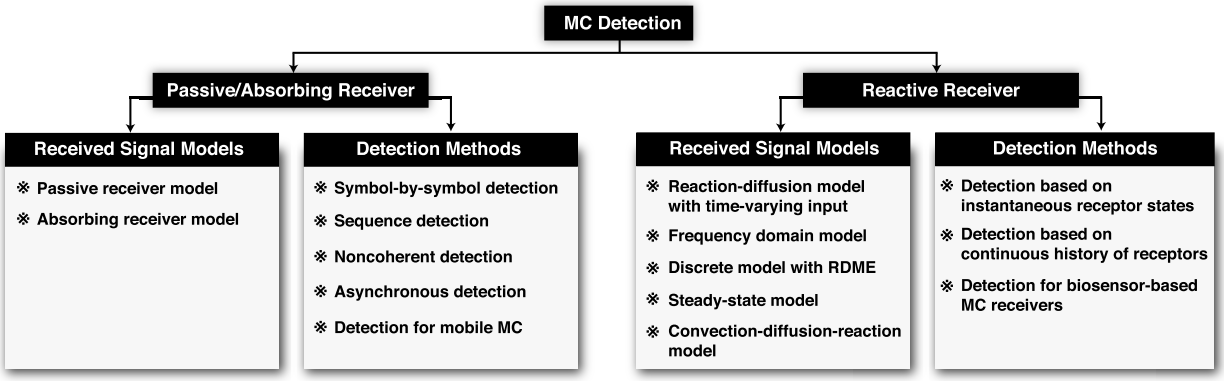


**Fig. 10.** ***Fundamental aspects of MC detection investigated in this paper.***

that can lead to strong molecular interference. These challenges have been addressed in MC to different extents. In this section, we provide an overview of the state-of-the-art MC detection approaches, along with a discussion on their performances and weaknesses.

We classify the existing approaches according to the considered channel and received signal models, which reflects the envisioned device architectures that impose different constraints or allow different simplifications over the problem. Accordingly, we divide the detection methods into two main categories: MC detection with passive and absorbing receivers and MC detection with reactive receivers, as shown in Fig. 10.

## A. MC Detection With Passive and Absorbing Receivers

The nonlinearities and complexity of the MC system often lead researchers to use simplifying assumptions to develop detection methods and analyze their performances. To this end, the intricate relationship between molecular propagation and sampling processes is often neglected.

Passive receiver (PA) concept is the most widely used simplifying assumption in the MC literature, as it takes the physical sampling process out of the equation, such that researchers can focus only on the transport of molecular messages to the receiver location. Accordingly, the passive receiver is often assumed to be a spherical entity, whose membrane is transparent to all kind of molecules, and it is a perfect observer of the number of molecules within its spherical reception space, as shown in Fig. 11 [226]. In the passive receiver approximation, the receiver has no impact on the propagation of molecules in the channel. Passive receivers can also be considered, as if they include ligand receptors that are homogeneously distributed within the reception space with very high concentration and infinitely high rate of binding with ligands, such that every single molecule in the reception space is effectively bound to a receptor at the time of sampling.

Another modeling approach, i.e., absorbing receiver (AB) concept [227], considers receiver as a hypothetical entity, often spherical, which absorbs and degrades every single molecule that hits its surface, as demonstrated in Fig. 11. This approach improves the assumption of passive receiver one step further toward a more realistic scenario, including a physical interaction between the receiver and the channel. In contrast to the passive receiver, the absorbing receiver can be considered to have receptors located over the surface. For a perfect absorbing receiver, this means a very high concentration of receptors with infinitely high absorption rate, such that every molecule that hits the surface is bound and consumed instantly.

Physical correspondence of both models is highly questionable. Nevertheless, they are widely utilized in the literature, as they provide upper performance limits. However, ignoring the receptor–ligand reactions, which often leads to further intricacies, e.g., receptor saturation, stands as a major drawback of these approaches.

*1) Received Signal Models:* When constructing the received signal models for the diffusion-based MC, the transmitter (Tx) geometry is usually neglected, assuming that the Tx is a point source that does not occupy any space. This assumption is deemed valid when the distance between Tx and Rx is considerably larger than the physical sizes of the devices. Throughout this section, we will mostly focus on the OOK modulation, where the Tx performs an impulsive release of a number of molecules to transmit bit-1 and does not send any molecule to transmit bit-0. This is the most widely used modulation scheme in MC detection studies, as it simplifies the problem while capturing the properties of the MC channel. However, we will also briefly review the detection schemes corresponding to other modulation methods, e.g., timing-based modulation and MoSK, throughout this section.

Molecular propagation in the channel is usually assumed to be only through free diffusion or through the combination of diffusion and uniform flow (or drift). In both cases, the channel geometry is often neglected and assumed to

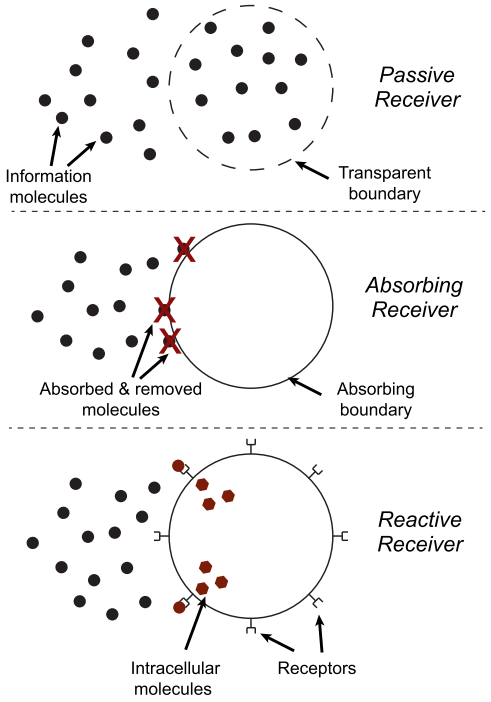


**Fig. 11.** ***Hypothetical MC-Rx models used for developing detection methods.***

be unbounded, and molecules are assumed to propagate independently of each other. In some studies addressing passive receivers, researchers consider the existence of enzymes in the channel, which reduces the impact of the ISI by degrading the residual messenger molecules through the first-order reaction [228]. For a 3-D free-diffusion channel with uniform flow in the presence of degrading enzymes, the number of molecules observed in the spherical reception space of a passive receiver follows nonstationary Poisson process [10], [229], that is

$$N_{\mathrm{RX|PA}}(t) \sim \mathrm{Poisson}\left(\lambda_{\mathrm{RX}}(t)\right) \tag{1}$$

where the time-varying mean of this process $\lambda_{\mathrm{RX}}(t)$ can be given by

$$\lambda_{\mathrm{RX}}(t) = \lambda_{\mathrm{noise}} + Q \sum_{j=1}^{\lfloor \frac{t}{T_s}+1 \rfloor} s[i] P_{\mathrm{obs}}(t-(j-i)T_s). \tag{2}$$

The mean depends on the number of transmitted molecules $Q$ to represent bit-1, the symbols transmitted in the current symbol interval as well as in the previous symbol intervals, i.e., $s[i]$, and the length of a symbol interval $T_s$. Most MC studies include an additive stationary noise in their models, representing the interfering molecules available in the channel as a result of an independent process in the application environment. These molecules are assumed to be of the same kind with the messenger molecules, and their number is represented by a Poisson process and captured by $\lambda_{\mathrm{noise}}$. Channel response is integrated into the model through the function $P_{\mathrm{obs}}(t)$, which is the probability of a molecule transmitted at time $t = 0$ to be within the sampling space at time $t$. When Tx–Rx distance is considerably large, ligands are typically assumed to be uniformly distributed within the reception space. As a result, the channel response can be written as

$$P_{\mathrm{obs}}(t) = \frac{V_{\mathrm{RX}}}{(4\pi D t)^{3/2}} \exp\left(-kC_E t - \frac{|\vec{r}_{\mathrm{eff}}|^2}{4Dt}\right) \tag{3}$$

where $V_{\mathrm{RX}} = (4/3)\pi d_{\mathrm{RX}}^3$ is the volume of the spherical receiver with radius $d_{\mathrm{RX}}$, $D$ is the diffusion coefficient, $C_E$ is the uniform concentration of the degrading enzymes in the channel, $k$ is the rate of enzymatic reaction, and $\vec{r}_{\mathrm{eff}}$ is the effective Tx–Rx distance vector, which captures the effect of uniform flow [229]. Assuming that Tx and Rx are located at $\vec{r}_{\mathrm{TX}} = (0,0,0)$ and $\vec{r}_{\mathrm{RX}} = (x_0,0,0)$, respectively, and the flow velocity is given by $v_x, v_y, v_z$ in 3-D Cartesian coordinates, the magnitude of the effective distance vector can be written as follows:

$$|\vec{r}_{\mathrm{eff}}| = \sqrt{(x_0 - v_x t)^2 + (v_y)^+ (v_z)^2}. \tag{4}$$

For an absorbing receiver, the received signal is usually taken as the number of molecules absorbed by the Rx within a time interval [227]. For a diffusion channel without flow, the probability density for a molecule emitted at $t = 0$ to be absorbed by a perfectly absorbing receiver of radius $r_r$ and located at a distance $r$ from the Tx at time $t$ is given by

$$f_{\mathrm{hit}}(t) = \frac{r_r}{r} \frac{1}{\sqrt{4\pi D t}} \frac{r - r_r}{t} \exp\left(-\frac{(r-r_r)^2}{4Dt}\right) \tag{5}$$

and the cumulative distribution function (CDF) is given by

$$F_{\mathrm{hit}}(t) = \int_0^t f_{\mathrm{hit}}(t')dt' = \frac{r_r}{r} \operatorname{erfc}\left[\frac{r-r_r}{\sqrt{4Dt}}\right] \tag{6}$$

where erfc is the complementary error function [227]. The CDF can be used to calculate the probability of a molecule transmitted at time $t = 0$ to be absorbed within the $k$th signaling interval, that is

$$P_k = F_{\mathrm{hit}}(kT_s) - F_{\mathrm{hit}}([k-1]T_s). \tag{7}$$

When considering multiple independent molecules emitted at the same time, the number of molecules absorbed at the $k$th interval becomes the Bernoulli random variable with the success probability of $P_k$. Assuming that the success probability is low enough, the Gaussian approximation of

**Table 4** Comparison Matrix for MC Detectors With Passive and Absorbing Receivers

| Description | Channel Characteristics | Modulation & Transmit Waveform | Detector Type | Rx Type | Measurement Method | CSI Req. | Complex. | Perf. |
|---|---|---|---|---|---|---|---|---|
| One-shot fixed-threshold detector [230] | Diffusion | CSK/OOK-Impulse | SbS | PA | Sampling | Ins. CSI | Low | Sub. |
| Weighted sum detector [231] | Diff./Flow/En./EI | CSK/OOK-Impulse | SbS | PA | Sampling | Ins. CSI | Low | Opt. |
| Weighted sum detector [229], [232] | Diff./Flow/En./EI | CSK/OOK-Impulse | SbS | PA | Sampling | Ins. CSI | Low | Sub. |
| Adaptive-threshold detector [233] | Diff./EI | CSK/OOK-Impulse | SbS | PA | Sampling | No CSI | Moderate | Sub. |
| Adaptive-threshold detector [234]–[236] | Diffusion | CSK/OOK-Impulse | SbS | AB | Energy | No CSI | Low | Sub. |
| Linear equalizer (MMSE) [10] | Diffusion | CSK/OOK-Pulse | Seq. | PA | Sampling | Ins. CSI | Very High | Sub. |
| Nonlinear equalizer (DFE) [10] | Diffusion | CSK/OOK-Pulse | Seq. | PA | Sampling | Ins. CSI | Very High | Sub. |
| ML sequence detector with Viterbi [10] | Diffusion | CSK/OOK-Pulse | Seq. | PA | Sampling | Ins. CSI | Very High | Opt. |
| ML sequence detector with Viterbi [232] | Diff./Flow/En./EI | CSK/OOK-Impulse | Seq. | PA | Sampling | Ins. CSI | Very High | Opt. |
| ML sequence detector with Viterbi [237] | Diffusion | MoSK-Impulse | Seq. | PA | Sampling | Ins. CSI | Very High | Opt. |
| Near ML sequence det. with RS Viterbi [230] | Diffusion | CSK/OOK-Impulse | Seq. | PA | Sampling | Ins. CSI | High | Sub. |
| Strength-based ML detector [238] | Diffusion | CSK/ASK-Impulse | SbS | PA | Energy | Ins. CSI | High | Opt. |
| Sampling-based ML detector [239] | Diffusion | CSK/ASK-Impulse | SbS | PA | Sampling | Ins. CSI | High | Opt. |
| Derivative-based detector [240] | Diffusion | CSK/OOK-Impulse | SbS | AB | Energy | Ins. CSI | Moderate | Sub. |
| Noncoherent detector [241] | Diffusion | CSK/B-CSK-Pulse | SbS | PA | Sampling | No CSI | Low | Sub. |
| Local convexity-based noncoherent det. [242] | Diffusion | CSK/OOK-Pulse | SbS | PA | Sampling | No CSI | Moderate | Sub. |
| Noncoherent ML threshold-based det. [243] | Diff./EI | CSK/OOK-Impulse | SbS | PA&AB | Sampling | Stat. CSI | Low | Opt. |
| Noncoherent ML sequence detector [243] | Diff./EI | CSK/OOK-Impulse | Seq. | PA&AB | Sampling | Stat. CSI | High | Opt. |
| Noncoherent decision-feedback detector [243] | Diff./EI | CSK/OOK-Impulse | Seq. | PA&AB | Sampling | Stat. CSI | Very High | Sub. |
| Noncoherent blind detector [243] | Diff./EI | CSK/OOK-Impulse | SbS | PA&AB | Sampling | No CSI | Low | Sub. |
| ML sequence detector with CC codes [244] | Diff./EI | CSK/ASK-Impulse | Seq. | PA | Sampling | No CSI | Very High | Opt. |
| Asynchronous fixed-threshold detector [245] | Diffusion | CSK/OOK-Impulse | SbS | PA | Sampling | Ins. CSI | Moderate | Sub. |
| Asynchronous adaptive-th. det. with DF [245] | Diffusion | CSK/OOK-Impulse | SbS | PA | Sampling | Ins. CSI | High | Sub. |
| Adaptive-threshold detector (Mobile MC) [246] | Diff./TV | CSK/OOK-Impulse | SbS | PA | Sampling | Ins. CSI | Very High | Sub. |
| Single-sample th. det. (Mobile MC) [247] | Diff./Flow/TV | CSK/OOK-Impulse | SbS | PA | Sampling | Out. CSI | High | Sub. |
| ML sequence detector (Timing Channel) [248] | Diffusion | Release time-Impulse | Seq. | AB | Arrival time | Ins. CSI | Very High | Opt. |
| Sequence detector with modified Viterbi [248] | Diffusion | Release time-Impulse | Seq. | AB | Arrival time | Ins. CSI | High | Sub. |
| Symbol by symbol timing detector [248] | Diffusion | Release time-Impulse | SbS | AB | Arrival time | No CSI | Low | Sub. |
| ML detector with FA & LA times [208], [249] | Diffusion | Release time-Impulse | SbS | AB | Arrival time | Ins. CSI | Moderate | Opt. |

Abbreviations — Diff.: Diffusion – En.: Enzyme – EI: External Interference – TV: Time-varying – SbS: Symbol-by-symbol detector – Seq.: Sequential detector – PA: Passive receiver – AB: Absorbing receiver – Ins. CSI: Instantaneous CSI – Stat. CSI: Statistical CSI – Out. CSI: Outdated CSI – Sub.: Sub-optimal – Opt. Optimal – Complex.: Complexity – Perf.: Performance – DF: Decision-Feedback – FA: First Arrival – LA: Last Arrival – CC codes: Constant Composition codes – RS: Reduced-State

the Bernoulli random process can be used to write

$$N_{\mathrm{RX|AB}}[i] \sim \mathcal{N}\left(\mu[i], \sigma^2[i]\right) \tag{8}$$

where its signal-dependent mean and variance can be written as a function of current and previously transmitted bits $s[i]$, that is

$$\mu[i] = Q \sum_{i}^{k} P_k s[i-k+1] \tag{9}$$

$$\sigma^2[i] = \sigma^2_{\mathrm{noise}} + Q \sum_{i}^{k} P_k(1-P_k) s[i-k+1]. \tag{10}$$

Note that as in the case of passive receiver, the received signal model includes the contribution of a stationary noise through its variance $\sigma^2_{\mathrm{noise}}$. Unfortunately, in the literature, there is no analytical model for absorbing receivers in diffusion-based MC channels with uniform flow and degrading enzymes.

*2) Detection Methods:* Detection methods for MC, in general, can be divided into two main categories depending on the method of concentration measurement: sampling- and energy-based detections. Passive receivers are usually assumed to perform sampling-based detection, which is based on sampling the instantaneous number of molecules inside the reception space at a specific sampling time [239]. Absorbing receivers, on the other hand, are typically assumed to utilize energy-based detection, which uses the total number of molecules absorbed by the receiver during a prespecified time interval, that is usually the symbol interval [238]. In some studies, passive receivers are also considered to perform energy-based detection through taking multiple independent samples of a number of molecules inside the reception space at different time instants during a single-symbol interval and passing them through a linear filter that outputs their weighted sum as the energy of the received molecular signal [229], [232].

As in conventional wireless communications, detection can be done on symbol-by-symbol (SbS) or sequential basis. The SbS detection tends to be more practical in terms of complexity, whereas the sequence detectors require the receiver to have a memory to store the previously decoded symbols. Due to the MC channel memory causing a considerable amount of ISI for high data rate communication, the sequence detectors are more frequently studied in the literature.

Next, we review the existing MC detection techniques developed for passive and absorbing receivers by categorizing them into different areas depending on their most salient characteristics. A comparison matrix for these methods can also be seen in Table 4.

*a) Symbol-by-symbol detection:* SbS MC detectors in the literature are usually proposed for very low-rate communication scenarios, where the ISI can be neglected,

asymptotically included into the received signal model with a stationary mean and variance, or approximated by the weighted sum of ISI contributions of a few previously transmitted symbols. In [230], a one-shot detector is proposed based on the asymptotic approximation of the ISI, assuming that the sum of decreasing ISI contributions of the previously transmitted symbols can be represented by a Gaussian distribution through central limit theorem (CLT) based on Lindeberg's condition. A fixed-threshold detector is proposed, maximizing the mutual information between transmitted and decoded symbols. Similarly, in [229] and [232], a matched filter in the form of a weighted sum detector is proposed using a different asymptotic ISI approximation, as, though, it results from a continuously emitting source leading to a stationary Poisson distribution of interference molecules inside the reception space. In this scheme, a passive receiver performs energy-based detection taking multiple samples at equally spaced sampling times during a single-symbol transmission, and the weights of the samples are adjusted according to the number of molecules expected at the corresponding sampling times. This matched filter is proven to be optimal in the sense that it maximizes SNR at the receiver. However, the optimal threshold of this detector does not lend itself to a closed-form expression, and thus, it should be numerically obtained through resource-intensive search algorithms. Similarly, in [231], considering also the external sources of interference, another linear matched filter is designed, maximizing the expected signal-to-interference-plus-noise ratio (SINR) for SbS detection, and shown to outperform previous schemes, especially when the ISI is severe. There are also adaptive-threshold-based SbS detection methods relying on receivers with a memory of varying length, taking into account only the ISI contribution of a finite number of previously transmitted symbols [233]–[236], [238], [239]. In these schemes, the adaptive threshold is updated for each symbol interval using the ISI estimation based on the previously decoded symbols. SbS detection is also considered in [243] and [245], which will be discussed in the following in the context of noncoherent and asynchronous detection.

*b) Sequence detection and ISI mitigation:* Optimal sequence detection methods based on maximum *a posteriori* (MAP) and maximum likelihood (ML) criteria are proposed in [10] for MC with passive receivers. Even though the complexity of the sequence detectors is reduced by applying the Viterbi algorithm, it still grows exponentially with increasing channel memory length. To reduce the complexity further, a suboptimal linear equalizer based on the minimum mean-square error (MMSE) criterion is proposed. To improve the performance of the suboptimal detection, a nonlinear equalizer, i.e., decision-feedback equalizer (DFE), is also proposed in the same study. DFE is shown to outperform linear equalizers with significantly less complexity than optimal ML and MAP sequence detection methods. Similarly, a near-optimal ML sequence detector employing the Viterbi algorithm is proposed in [230]. Another optimal ML sequence detector is proposed in [232] for MC with uniform flow and enzymes that degrade IMs.

In addition to the sequence detection methods and equalizers, there are other approaches proposed to overcome the effects of the ISI on detection. For example, Akdeniz *et al.* [250] proposed to shift the sampling time by increasing the reception delay to reduce the effect of ISI. In [240], a derivative-based signal detection method is proposed to enable high data rate transmission. The method is based on detecting the incoming messages relying on the derivative of the channel impulse response (CIR).

*c) Noncoherent detection:* Most of the MC detection methods require the knowledge of the instantaneous CSI in terms of CIR. However, CIR in MC, especially in physiologically relevant conditions, tends to change frequently, rendering the detection methods relying on the exact CIR knowledge useless. Estimating the instantaneous CIR is difficult and requires high computational power. To overcome this problem, researchers propose low-complexity noncoherent detection techniques. For example, Damrath and Hoeher [236] develop a simple detection method for absorbing receivers, which does not require channel knowledge. In this scheme, the receiver performs a threshold-based detection by comparing the number of absorbed molecules in the current interval to that of the previous symbol interval. The adaptive threshold is updated in every step of detection with the number of molecules absorbed. However, this method performs poorly when a sequence of consecutive bit-1s arrives. Similarly, in [241], the difference of the accumulated concentration between two adjacent time intervals is exploited for noncoherent detection. In [242], the local convexity of the diffusion-based channel response is exploited to detect MC signals in a noncoherent manner. A convexity metric is defined as the test statistics, and the corresponding threshold is derived. There are also methods requiring only the statistical CSI rather than the instantaneous CSI [243]. In addition, constant-composition codes are proposed to enable ML detection without statistical or instantaneous CSI and shown to outperform uncoded transmission with optimal coherent and noncoherent detection when the ISI is neglected [244].

*d) Asynchronous detection:* The synchronization between the communicating devices is another major challenge. However, in the previously discussed studies, synchronization is assumed to be perfect. To overcome this limitation, an asynchronous peak detection method is developed in [245] for the demodulation of MC signals. Two variants have been proposed. The first method is based on measuring the largest observation within a sampling interval. This SbS detection method is of moderate complexity and nonadaptive, comparing the maximum observation to a fixed threshold. The second method is adaptive and equipped with decision feedback to remove the ISI contribution. In this scheme, the receiver

takes multiple samples per bit and adjusts the threshold for each observation based on the expected ISI.

*e) Detection for mobile MC:* Majority of MC studies assume that the positions of Tx and Rx are static during communication. The mobility problem of MC devices has just recently started to attract researchers' attention. For example, MC between a static transmitter and a mobile receiver is considered in [246], where the authors propose to reconstruct the CIR in each symbol interval using the time-varying transmitter–receiver distance estimated based on the peak value of the sampled concentration. Two adaptive schemes, i.e., concentration-based adaptive threshold-detection and peak-time-based adaptive detection, are developed based on the reconstructed CIR. In [247], different mobility cases, including mobile TX and RX, mobile TX and fixed RX, and mobile RX and fixed TX, are considered to develop a stochastic channel model for diffusive mobile MC systems. The authors derive analytical expressions for the mean, pdf, and autocorrelation function (ACF) of the time-varying CIR through an approximation of the CIR with a log-normal distribution. Based on this approximation, a simple model for outdated CSI is derived, and the detection performance of a single-sample threshold detector relying on the outdated CSI is evaluated.

*f) Other detection techniques:* MC detection problem is also addressed for MoSK modulation. In [237], an optimal ML sequence detector employing the Viterbi algorithm is proposed, assuming that a passive receiver can independently observe MC signals carried by different types of molecules. This assumption greatly simplifies the problem and enables the application of detection methods developed for CSK-modulated MC signals for MoSK signals as well.

Diffusion-based molecular timing (DBMT) channels are also addressed from detection theoretical perspective. DBMT channels without flow are accompanied by a Levy distributed additive noise having a heavy algebraic tail in contrast to the exponential tail of the inverse Gaussian distribution, which DBMT channel with flow follows [249]. In [248], an optimal ML detector is derived for DBMT channels without flow; however, the complexity of the detector is shown to have exponential computational complexity. Therefore, they propose suboptimal yet practical SbS and sequence detectors based on the random time of arrivals of the simultaneously released IMs and show that the performance of the sequence detector is close to the one of the computationally expensive optimal ML detectors.

In DBMT channels without flow, linear filtering at the receiver results in a dispersion larger or equal to the dispersion of the original, i.e., unfiltered, sample, rendering the performance of releasing multiple particles worse than releasing a single particle. Based on this finding, Murin *et al.* [249] developed a low-complexity detector, which is based on the first arrival (FA) time of the simultaneously released particles by the TX. The method is based on the observation that the probability density of the FA gets concentrated around the transmission time when the number of released molecules $M$ increases. Neglecting ISI, it is shown in the same paper that the proposed FA-based detector performs very close to the optimal ML detectors for small values of $M$. However, the ML detection still performs significantly better than the FA for high values of $M$. The detection based on the order statistics has been extended in the same authors' later work [208], where they consider also the detection based on the last arrival (LA) time. Defining a system diversity gain as the asymptotic exponential decrease rate of error probability with the increased number of released particles, they showed that the diversity gain of the LA detector approaches to that of computationally expensive ML detector.

## B. MC Detection With Reactive Receivers

This type of receiver samples the molecular concentration of incoming messages through a set of reactions it performs via specialized receptor proteins or enzymes, as shown in Fig. 11. The reactive receiver approach is more realistic in the sense that natural cells, e.g., bacteria and neurons, sense MC signals through their receptors on the cell membrane, and many types of artificial biosensors, e.g., bioFETs, are functionalized with biological receptors for higher selectivity. Since synthetic biology, focusing on using and extending natural cell functionalities, and artificial biosensing are the two phenomena that are considered for the practical implementation of MC-Rxs, studying MC detection with reactive receivers has more physical correspondence.

Diffusion-based MC systems with reactive receivers, in most cases, can be considered as reaction–diffusion (RD) systems with finite reaction rates. Although RD systems, which are typically highly nonlinear, have been studied in the literature for a long time, they do not usually lend themselves to analytical solutions, especially when the spatiotemporal dynamics and correlations are not negligible. To be able to devise detection methods and evaluate their performance in the MC framework, researchers have come up with different modeling approaches, which will be reviewed in the following. For the sake of brevity, we focus our review on detection with receivers equipped with ligand receptors, which have only one binding site.

The ligand–receptor binding reaction for a single receptor exposed to time-varying ligand concentration $c_L(t)$ can be schematically demonstrated as follows:

$$\mathrm{U} \underset{k_-}{\overset{c_L(t)k_+}{\rightleftharpoons}} \mathrm{B} \tag{11}$$

where $k_+$ and $k_-$ are the ligand–receptor binding and unbinding rates, respectively, and $U$ and $B$ denote the unbound and bound states of the receptor, respectively. When there are $N_R$ receptors, assuming that all of them

are exposed to the same concentration of ligands, reaction rate equation (RRE) for the number of bound receptors can be written as follows [183]:

$$\frac{dn_B(t)}{dt} = k_+ c_L(t)\left(N_R - n_B(t)\right) - k_- n_B(t). \tag{12}$$

As is clear, while the binding reaction is second order depending on the concentrations of both ligands and available receptors, unbinding reaction is first order and only depends on the number of bound receptors.

Most of the time, the bandwidth of MC signals can be assumed to be low enough to drive the binding reaction to near equilibrium and allow applying quasi-steady-state assumption for the overall system. In this case, time-varying concentration $c_L(t)$ can be treated constant, i.e., $c_L(t) = c_L$, and $dn_B(t)/dt = 0$, which results in the following expression for the mean number of bound receptors:

$$\mathrm{E}[n_B] = \frac{c_L}{c_L + K_D} N_R \tag{13}$$

where $K_D = k_-/k_+$ is the dissociation constant, which is a measure of affinity between the specific type of ligand and receptor. Even at equilibrium, the receptors randomly fluctuate between the bound and unbound states. The number of bound receptors $n_B$ at equilibrium is a Binomial random variable with success probability $p_B = c_L/(c_L + K_D)$, and its variance can be given accordingly by

$$\mathrm{Var}[n_B] = p_B(1 - p_B)N_R. \tag{14}$$

More insight can be gained by examining the continuous history of binding and unbinding events over receptors. The likelihood of observing a series of $n$ binding–unbinding events at equilibrium can be given by

$$\mathrm{p}(\{\tau^B, \tau^U\}_n) = \frac{1}{Z} e^{-\sum_{j=1}^{n} \tau_j^U \left(\sum_{i=1}^{M} k_i^+ c_i\right)} \prod_{j=1}^{n} \sum_{i=1}^{M} k_i^+ c_i k_i^- e^{-k_i^- \tau_j^B} \tag{15}$$

where $Z$ is the normalization factor, $\tau_j^U$ and $\tau_j^B$ are the $j$th unbound and bound time intervals, respectively, $c_i$, $k_i^+$, and $k_i^-$ are the concentration, binding rate, and unbinding rate of the $i$th type of ligand, respectively, and $M$ is the number of ligand types present in the channel [251], [252]. Note that the likelihood is equally valid for the cases of single receptor and multiple receptors, as long as the collected $n$ samples of unbound and bound time intervals are independent. These observable characteristics of the ligand–receptor binding reactions have been exploited to infer the incoming messages to different extents, as will be reviewed in the following.

*1) Received Signal Models:* The nonlinearities arising from the interaction of time-varying MC signals with receptors have led to different approaches for modeling MC systems with reactive receivers compromising on different aspects to develop detection techniques and make the performance analyses tractable. A brief review of these modeling approaches is provided as follows.

*a) Reaction–diffusion models with time-varying input:* One of the first attempts to model the ligand–receptor binding reactions from an MC theoretical perspective is provided in [183], where the authors develop a noise model for the fluctuations in the number of bound receptors of a receiver exposed to time-varying ligand concentrations as MC signals. The model is based on the assumption of a spherical receiver, in which ligand receptors and information-carrying ligands are homogeneously distributed. For an analytically tractable analysis, the concentration of incoming ligands is assumed to be constant between two sampling times, i.e., during a sampling interval, and the ligand–receptor binding reaction is assumed to be at equilibrium at the beginning of each sampling interval. In light of these assumptions, the authors obtained the time-varying variance and the mean of the number of bound receptors, which are valid only for the corresponding sampling interval. A more general approach without the equilibrium assumption to obtain the mean number of bound receptors with time-varying input signals, i.e., ligand concentration, is contributed by [253] and [254] through solving the system of differential equations governing the overall diffusion–reaction MC system. The authors of both studies consider a spherical receiver with ligand receptors on its surface and a point transmitter, which can be anywhere on a virtual sphere centered at the same point as the receiver but larger than that to obtain a spherical symmetry to simplify the overall problem. As a result, the transmitter location cannot be exactly specified in the problem. Deng *et al.* [254] considered that the spherical receiver is capable of binding ligands at any point on its surface, which is exactly equal to the assumption of an infinite number of receptors. On the other hand, [253] considers a finite number of receptors uniformly distributed on the receiver surface and addresses this challenge through boundary homogenization. However, boundary homogenization for a finite number of receptors does not take into account the negative feedback of the bound receptors on the second-order binding reaction [see (12)], and thus, the developed analytical model is not able to capture the indirect effects of a finite number of receptors, e.g., receptor saturation. This is clear from their analysis, such that the discrepancy between the analytical model and the particle-based simulation results is getting larger with increasing ligand concentration.

*b) Frequency-domain model:* Another modeling approach is provided in [255], where the authors, assuming that the probability of a receptor to be in the bound state is very low, take the number of available,

i.e., unbound, receptors equal to the total number of receptors at all time points. The complete first-order characteristics of the resulting RRE enables them to carry out a frequency-domain analysis, through which they show that the ligand–receptor binding reaction manifests low-pass filter characteristics. However, this approximate model is relevant only when the probability of receptor–ligand binding is very low.

*c) Discrete model based on reaction–diffusion master equation:* To capture the stochasticity of the RD MC, another approach is introduced in [256], where the authors develop a voxel-based model based on the RD master equation (RDME), with the diffusion and reactions at the receiver modeled as the Markov processes. The 3-D MC system is discretized and divided into equal-size cubic voxels, in each of which molecules are assumed to be uniformly distributed, and allowed to move only to the neighboring voxels. In the voxel accommodating the Tx, the molecules are generated according to a modulation scheme, and the Rx voxel hosts the receptor molecules, where the ligands diffusing into the Rx voxel can react based on a law of mass action. The jump of a ligand from one voxel to another is governed by a diffusion rate parameter, which is a function of the voxel size and the ligand diffusion coefficient. The number of ligands and bound receptors are stored in a system state vector, which is progressed with a given state transition rate vector storing the reaction, diffusion, and molecule generation rates. In the continuum limit, the model is able to provide closed-form analytical expressions for the mean and the variance of the number of bound receptors for small-scale systems. However, for larger systems, with a high number of voxels, the efficiency of the model is highly questionable.

*d) Steady-state model:* In addition to the above-mentioned approaches considering time-varying signals, some researchers prefer using the assumption of steady-state ligand–receptor binding reaction with stationary input signals at the time of sampling, based on fact that the bandwidth of incoming MC signals is typically low because the diffusion channel shows low-pass filter characteristics and the reaction rates are generally higher than the diffusion rate of molecules. This assumption enables the separation of the overall system into two: a deterministic microscale diffusion channel and the stochastic ligand–receptor binding reaction at the interface between the receiver and the channel. Accordingly, at the sampling time, the ligand concentration around the receptors assumes different constant values corresponding to different symbols. The only fluctuations are resulting from the binding reaction, where the random number of bound receptors follows the Binomial distribution, whose mean and variance are given in (13) and (14), respectively. The steady-state assumption is applied in [257], where the authors derive RD channel capacity for different settings.

*e) Convection–diffusion–reaction system model:* Microfluidic MC systems with reactive receivers are studied by a few researchers. Kuscu and Akan [137] developed a 1-D analytical model, assuming that the propagation occurs through convection and diffusion, and a reactive receiver, which is assumed to be a SiNW bioFET receiver with ligand receptors on its surface, is placed at the bottom of the channel. The interplay among convection, diffusion, and reaction is taken into account by defining a transport-modified reaction rate, tailored for the hemicylindrical surface of the SiNW bioFET receiver. However, the authors assume steady-state conditions for the reaction, to be able to derive a closed-form expression for the noise statistics. The molecular-to-electrical transduction properties of the bioFET are reflected to the output current of the receiver through modeling the capacitive effects arising from the liquid–semiconductor interface and the $1/f$ noise resulting from the defects of the SiNW transducer channel. Kuscu and Akan [258] considered a 2-D convectional RD system that does not lend itself to closed-form analytical expressions for the received signal. The authors develop a heuristic model using a two-compartmental modeling approach, which divides the channel into compartments, in each of which either transport or reaction occurs, and derive an analytical expression for the time course of the number of bound receptors over a planar receiver surface placed at the bottom of the channel. The model well captures the nonlinearities, such as Taylor–Aris dispersion in the channel, depletion region above the receiver surface, and saturation effects resulting from a finite number of receptors, as validated through finite element simulations of the system in COMSOL. However, the model assumes that the channel and the receiver are empty at the beginning of the transmission and, therefore, does not allow an ISI analysis.

*2) Detection Methods:* The literature on detection methods for MC with reactive receivers is relatively scarce, and the reason can be attributed partly to the lack of analytical models that can capture the nonlinear ligand–receptor binding reaction kinetics and resulting noise and ISI. Nevertheless, the existing methods can be divided into three categories depending on the type of assumptions made and considered receiver architectures.

*a) Detection based on instantaneous receptor states:* The first detection approach is based on sampling the instantaneous number of bound receptors at a prespecified time, as shown in Fig. 12, and comparing it to a threshold. Deng *et al.* [254] studied a threshold-based detection for OOK-modulated ligand concentrations using the difference between the number of bound molecules at the start and the end of a bit interval. In [255], converting the ligand–receptor binding reaction to a completely first-order reaction with the assumption that all of the receptors are always available for binding, the authors manage to transform the problem into the frequency domain. For the modulation, they consider MoSK with different receptors corresponding to different ligands; therefore, the problem basically reduces to a detection problem of the

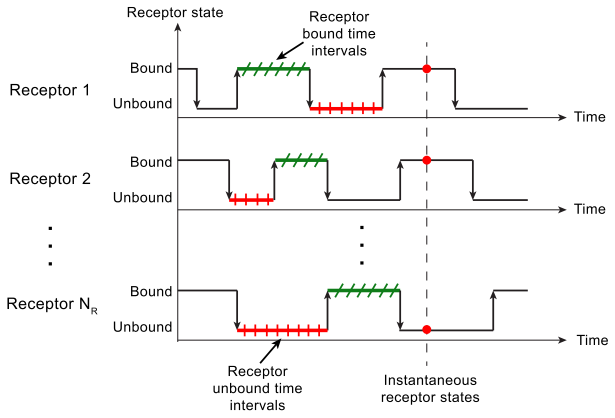


**Fig. 12.** ***Different methods for sampling receptor states in reactive MC-Rxs.***

concentration-encoded signals for each ligand–receptor pair. To reduce the amount of noise, they propose to apply a whitening filter to the sensed signal in the form of a number of bound receptors and then utilize the same detection technique they proposed in [237]. An energy-based detection scheme is proposed in [259], where the test statistics is the total number of binding events that occur within a symbol duration. They propose a variable threshold-detection scheme with varying memory length. The article also takes into account the ISI; however, the model assumes that all the receptors are always available for binding and completely neglects the unbinding of ligands from the receptors, making the reaction irreversible. Kuscu and Akan [252] study the saturation problem in MC-Rxs with ligand receptors. As a part of their analysis, they investigated the performance of an adaptive threshold ML detection using the instantaneous number of bound receptors. The effect of the receiver memory that stores the previously decoded bits is also investigated, and their analysis reveals that the performance of MC detection based on a number of bound receptors severely decreases when the receptors get saturated, which occurs when they are exposed to a high concentration of ligands as a result of strong ISI. This is because near saturation, it becomes harder for the receiver to discriminate between two levels of a number of bound receptors corresponding to different bits.

*b) Detection based on a continuous history of receptor states:* The second detection approach is based on exploiting the continuous history of binding and unbinding events occurring at receptors or the independent samples of time intervals that the receptors stay bound and unbound, as demonstrated in Fig. 12. As we see in the likelihood function in (15), the unbound time intervals are informative of the total ligand concentration, whereas the bound time intervals are informative of the type of bound molecules. This is exploited in [252], where the authors tackle the saturation problem in reactive receivers. For a receiver with ligand receptors and a memory storing a finite number of previously decoded bits, they propose to exploit the amount of time the individual receptors stay unbound. Taking the ligand concentration stationary around the sampling time, and assuming steady-state conditions for the ligand–receptor binding reaction, they developed an ML detection scheme for OOK concentration-encoded signals, which outperforms the detection based on a number of bound receptors in the saturation case. A simple intracellular reaction network to perform the transduction of unbound time intervals into the concentration of a certain type of molecules inside the cell is also designed. In a similar manner, in [260] and [261], using a voxel-based MC system model introduced in [256], and by neglecting the ISI, the authors developed an optimal MAP demodulator scheme based on the continuous history of receptor binding events. Different from [252], the authors assume the time-varying input signal. The resulting demodulator is an analog filter that requires the biochemical implementation of mathematical operations, such as logarithm, multiplication, and integration. The demodulator also needs to count the number of binding events. In [260], they provide an extension of the demodulator for the ISI case by incorporating decision feedback and show the performance improvement with increasing receiver memory.

One of the challenges of reactive receivers is their selectivity toward the messenger molecules, which is not perfect in practice. It is highly probable, especially in physiologically relevant environments, that there are similar ligands in the channel, which can also bind the same receptors, even though their unbinding rate is higher than that of the correct, i.e., messenger, ligands. This causes a molecular interference, which impedes the detection performance of the receiver, especially when the concentration of interferer molecules is not known to the receiver. Muzio *et al.* [262] evaluated the performance of the one-shot ML detection schemes based on the number of bound receptors and unbound time intervals in the presence of interference from a similar ligand available in the environment, number of which in the reception space follows the Poisson distribution, with a known mean. They proposed a new ML detection scheme based on estimating the ratio of messenger ligands to the inferring ligands using the bound time intervals sampled from each receptor. It is shown that the proposed method substantially outperforms the others, especially when the concentration of interferer molecules is very high. Note that the above-mentioned detection techniques are built on MC models that neglect the receiver geometry by treating it as a transparent receiver, inside which ligands and receptors are homogeneously distributed, and they require the receiver to store an internal model, i.e., CIR, of the RD channel.

*c) Detection for biosensor-based MC receivers:* The third set of detection methods deals with the biosensor-based receivers, where the binding events are transduced into electrical signals. In bioFET-based receivers, the concentration of bound charge-carrying ligands is converted into

electrical signals that are contaminated with additional noise. It is not possible to observe individual receptors states; therefore, the detection based on a continuous history of binding events is not applicable to these receivers. Accounting for the $1/f$ noise and binding fluctuations at steady-state conditions, Kuscu and Akan [137] developed an optimal ML detection scheme for CSK in the absence of ISI. Approximating the binding and $1/f$ noise with a Gaussian distribution, they reduced the overall problem to a fixed-threshold-detection problem and provided closed-form analytical expressions for the optimal thresholds and corresponding symbol error rates. The performance evaluation reveals that the $1/f$ noise, which is resulting from the defects of the semiconductor FET channel, surpasses the binding noise resulting from the fluctuations of the receptor states, especially at low frequencies, and severely degrades the detection performance.

## VI. CHALLENGES AND FUTURE RESEARCH DIRECTIONS

After providing a comprehensive survey of existing studies on different aspects of MC, in this section, we discuss the most important challenges toward the realization of microscale/nanoscale MC setups and evaluation of their ICT-based performance. In this direction, we highlight both the required theoretical studies and the experimental investigations to validate the theoretical models. The physical architecture of MC-Tx/Rx is one of the least studied topics in the MC literature; however, it significantly affects the accuracy of theoretical studies. Thus, we provide an in-depth discussion on the required investigations of the MC Tx/Rx architecture. The second shortcoming of the MC literature is the use of nonrealistic assumptions in the existing MC-Tx/Rx and channel models, which has led to imprecise performance estimations not applicable to real scenarios. Hence, we explain the requirements of realistic modeling, such as taking into account the impact of the stochastic molecule generation process, Tx/Rx geometry, and stochastic noise dynamics. We also describe open research problems in the developed modulation, coding, and detection techniques for MC and emphasize important factors that must be considered in future investigations.

### A. Challenges for Physical Design and Implementation of MC-Tx

Theoretical modeling of MC-Tx in the literature generally relies on unrealistic simplifying assumptions due to the lack of experimental studies on microscale/nanoscale implementation of MC-Tx. Therefore, MC-Tx is often assumed as an ideal point source capable of perfectly transmitting molecular messages, which completely neglects important factors in the IM release process, such as the stochasticity in the molecule generation process, the effect of Tx geometry, and the channel feedback. As modeling microscale/nanoscale MC-Tx without any experimental data seems not possible, the requirement for empirical transmitter models is the most pressing challenge for MC, as end-to-end channel models are required to consider the effects of both MC-Tx and MC-Rx. Based on the empirical channel models, the communication theoretical investigation of MC, i.e., analysis of capacity, modulation, coding, and detection, needs to be revisited, as communication parameters show a strong dependence on the channel model. Other challenges regarding the practical implementation of a microscale/nanoscale MC-Tx are listed as follows.

1) *Energy:* Microscale/nanoscale MC-Tx and MC-Rx are required to work as stand-alone devices with their own energy sources. Since battery-powered devices have limited lifetime, EH techniques are promising to develop energy neutral devices, such that all operations of the device can be powered via harvested energy from various sources, such as solar, mechanical, and chemical. To design such systems, one needs to first calculate the harvestable energy budget of an MC-Tx and an MC-Rx, i.e., the amount of energy harvestable from the surrounding based on application scenarios and medium. Then, both transmitter and receiver operations, e.g., modulation, coding, and detection, are required to be developed, accordingly not to exceed the available energy budget. Considering miniaturized MC-Tx and MC-Rx, the harvestable energy can be quite limited so that complex algorithms may not be feasible in a realistic MC scenario.
2) *Data Rate:* MC is mostly promising in applications without high data rate requirements, as MC suffers from slow propagation channels. This problem can be tackled by encoding a large amount of data in DNA/RNA strands, which is named NSK, as discussed in Section IV-A. This way, the amount of transmitted information can be increased up to hundereds of megabytes per IM, such that MC can achieve data rates on the order of megabits per second. Although sequencing of DNA/RNA strands can be performed via stand-alone devices utilizing nanopores, there is yet any practical low-cost system to write DNA sequences with a microscale/nanoscale device.
3) *Molecule Leakage:* In the case of nanomaterial-based MC-Txs, there are two significant design challenges: molecule leakage and molecule reservoir/generation. Molecule leakage, while transmitting low logic or no information, is unavoidable for practical MC-Tx designs. The leaking molecules increase ISI in the channel and also contribute to an additional problem in molecule reservoir/generation by lowering the molecule budget of MC-Tx. In order to tackle this problem, we have proposed some solutions based on the molecule wax as an IM container and hybrid MC-Tx designs, where genetically engineered bacteria can be utilized to replenish IM sources. However, these solutions have not been

implemented, and the feasibility of such systems as MC-Tx still stands as an important open research issue.

4) *Biological Complexity:* In the case of biological MC-Tx architectures, the main difficulty in design stems from the complexity of involved biological elements. Understanding of molecular basis underlying cellular mechanisms, i.e., cellular biology, and development of techniques to manipulate them, i.e., synthetic biology, are essential to unlock the reliable use of engineered biological entities for MC. Moreover, as, in many applications, data propagated in nanonetworks eventually need to be connected to electronic devices, any biological network architecture must be interfaced with an electronic architecture. Thus, the development of MC architectures within this space requires an extremely high interdisciplinary engagement between the fields of ICT, biology, and synthetic biology, as well as materials science and nanofabrication. Another issue, which, again, is caused by the inherent complexity of biological organisms, is the fact that genetically engineered cells are not the best survivors, and complications in their engineered metabolisms cause the accelerated death of the cell.

### B. Challenges for Physical Design and Implementation of MC-Rx

Despite existing theoretical studies on the performance of MC and few macroscale experimental setups, the literature lacks comprehensive investigation of the physical design of microscale/nanoscale MC-Rx structures. This leads to critical open challenges needed to be tackled for the realization of the MC promising applications.

1) *Ligand–Receptor Selection:* As mentioned in Section III-C, both genetic circuit-based and artificial architectures use ligand–receptor reactions to sense the concentration of target molecule by the MC antenna. This calls for the careful selection of appropriate ligand–receptor pairs for the MC paradigm. In this regards, the binding and dissociation, i.e., unbinding, rates of these reactions are among the important parameters that must be taken into consideration. The binding rate controls sensitivity, selectivity, and the response time of the device. While high dissociation rates reduce the reusability of the device, very low values are also not desired, as they decrease the sensitivity of the receiver. The existing interferer molecules in the application environment and their affinities with the receptors are the next important design parameter that must be studied to minimize the background noise.
2) *Realistic ICT-Based Modeling of Artificial Structures:* For artificial biosensor-based MC-Rxs, the literature is lacking analytical models that can capture transient dynamics, as the available models developed from the sensor application perspective are mostly based on the equilibrium assumption. However, in MC applications, since the concentration signals are time-varying, equilibrium models may not be realistic. Therefore, devising MC detection methods for artificial receivers requires developing more complex models that can also capture the stochastic noise dynamics without steady-state assumption for different types of biosensors based on nanomaterials, e.g., graphene bioFET. The models should also include the effects of operating voltages for bioFETs, receiver geometry, and gate configuration, and channel ionic concentration determining the strength of the Debye screening. The models should be validated through wet-lab experiments, and microfluidic platforms stand as a promising option for implementing test beds for MC systems with artificial MC-Rxs.
3) *Biological Circuits Complexity:* In the case of implementing MC-Rxs with genetic circuits, the information transmission is through molecules and biochemical reactions, which results in nonlinear input–output behaviors with system-evolution-dependent stochastic effects. This makes the analytically studying the performance metrics difficult if not impossible. Moreover, the existing noise in genetic circuits must be comprehensively studied, and methods to mitigate this noise must be derived, as it significantly reduces the achievable mutual information of the MC [135].
4) *Bio–Cyber Interface:* While MC expands the functionality of nanomachines by connecting them to each other and making nanonetworks [263], the connection of these nanonetworks to the cybernetworks, i.e., making IoBNT, further extends the applications of these nanomachines [1]. Continuous health monitoring and bacterial sensor–actor networks inside the human body are two promising examples of these applications. To this aim, implementation of microscale/nanoscale bio–cyber interfaces is required. The bio–cyber interface needs to decode the molecular messages, process it, and send the decoded information to a macroscale network node through a wireless link. In bioFET-based MC-Rxs, owing to the molecular-to-electrical transducer unit, the electrical signal generated by the receiver can be sent to the cybernetworks through EM wireless communications. However, the connection of biological MC-Rxs to the cybernetworks remains as an open issue.

Finally, it is worthwhile to mention that the physical architecture of the device is mainly dictated by the application requirements. As an example, biological MC-Rxs are only promising and feasible for *in vivo* applications. On the other hand, utilizing artificial structures for *in vivo* applications necessitate a comprehensive investigation of

the receiver biocompatibility. Moreover, the physiological conditions imply solutions with high ionic concentrations, an abundance of interferers and contaminants, and the existence of disruptive flows and fluctuating temperature, which may degrade the receiver's performance in several aspects. First, high ionic concentration creates a strong screening effect, reducing the Debye length, thus impedes the sensitivity of the receiver [187]. Moreover, contaminants and disruptive flows may alter the binding kinetics, impede the stability of the receptors, and, even, separate them from the dielectric layer. These call for the comprehensive investigation of these factors, their impact on the performance of the device, and methods to control their effects. To control the screening problem, using highly charged ligands and very small size receptors, such as aptamers, are theoretically efficient. However, the frequency-domain technique promises for much more realistic solutions. Zheng *et al.* [264] revealed that frequency-domain detection outperforms the conventional time-domain technique in terms of sensitivity in highly ionic solutions. An alternative solution to overcome the Debye screening limitations in detection is proposed in [265], where it is shown that applying a high-frequency alternating current between the source and the drain electrodes, instead of a dc current, weakens the double-layer capacitance generated by the solution ions. They show that the effective charges of the ligands become inversely dependent on the Debye length instead of the exponential dependence. As a result, the screening effect on the bound ligands is significantly reduced, and the FET-based biosensing becomes feasible even for physiological conditions. Similar approaches are taken by others to overcome the Debye screening with radio frequency operation of graphene bioFETs, which are summarized in [266].

### C. Challenges for Developing MC Modulation Techniques

There are various modulation schemes that are proposed for MC by utilizing concentration, molecule type/order/ratio, and release timing. However, these studies mostly utilize simplified channel models based on MC-Tx, which is an ideal point source, and MC-Rx, which is capable of perfectly detecting multiple molecules selectively. Therefore, the performance of the proposed schemes under realistic conditions is still unknown, and this can be tackled by implementing the proposed schemes in an experimental MC setup. In addition, some of the modulation schemes require synchronization, which is hard to achieve considering the error-prone diffusive channel and low-complexity MC devices at microscale/nanoscale. Furthermore, energy efficiency is another important challenge for MC-Tx designs as being powered via limited energy harvested from the medium. Therefore, energy-efficient and low-complexity modulation schemes for MC without strict synchronization requirements still stand as a significant research problem.

### D. Challenges for Developing MC Channel Coding Techniques

Even though there is some literature on MC channel coding techniques, the field is still very new and open for research. Some of the most pressing directions are highlighted in the following.

1) *Adaptive Coding:* The propagation time through MC channel and detection probabilities at the receiver are affected by various environmental parameters, such as temperature, diffusion speed, channel contents, reaction rates, and distance between nodes, which calls for adaptive channel coding techniques for error compensation [267]. In this respect, none of the coding schemes investigated even considers to probe the channel for its characteristics in order to adapt itself.
2) *Irregular Signaling:* All of the coding schemes discussed have been evaluated under the regular time-slotted transmission assumption, which, in any realistic MC scenario, will never be the case. For instance, fluctuations in the intersymbol duration caused by irregular transmission would have a significant effect on suffered ISI, the primary source of BER in MC, and, therefore, needs to be considered by channel codes.
3) *Simplicity of Models:* More channel codes for MC need to be invented. The only works that do so are [216]–[218], and they have very simple transmission and channel models, i.e., in all works, the transmitter releases only a single molecule per transmission period, and the channel is 1-D.

### E. Challenges for Developing MC Detection Techniques

As reviewed in Section V, the MC detection problem has been widely addressed from several aspects for different channel and receiver configurations. However, the proposed solutions are still far from being feasible for envisioned MC devices. The main reason behind this discrepancy between the theoretical solutions and the real practice, which is also revealed by the preliminary experimental airborne MC studies performed with macroscale off-the-shelf components [68], [268], is that there is no microscale/nanoscale MC test bed that can be used as a validation framework to optimize the devised methods. In parallel to this general problem regarding MC technologies, major challenges for MC detection can be further detailed as follows.

1) *Synchronization:* The majority of the proposed detection techniques assume a perfect synchronization between the transmitter and the receiver. In fact, synchronization is essential for the proper operation of the proposed solutions. There are many studies proposing different synchronization methods, e.g., using quorum sensing to globally synchronize the actions of nanomachines in a nanonetwork [269],

blind synchronization and clock synchronization based on the ML estimation of the channel delay [270], [271], and peak observation-time- and threshold-trigger-based symbol synchronization schemes employing a different type of molecule for the purpose of synchronization [272]. However, these methods are either too complex for the limited capabilities for the nanomachines or they rely on stable CSI, which is not the case for time-varying MC channels. Moreover, the effect of these nonideal synchronization techniques on the performance of the proposed detection methods has not been revealed. Another potential solution to the synchronization problem could be to develop asynchronous detection techniques that obviate the need for synchronization. As reviewed in Section V-A, there are a few promising solutions for asynchronous MC detection, e.g., peak-detection and threshold-based detection methods [245]. However, they are mostly built on simplifying assumptions for receiver and channel geometry and properties, which may result in unexpected performance in real applications.

2) *Physical Properties of the Receiver:* Although there is a little physical correspondence for passive and absorbing receivers, many of the detection schemes are built on these assumptions, as they enable a mathematically tractable analysis. As reviewed in Section V-B, although they consider the effect of receptor reactions, the initial studies on reactive receivers also follow similar assumptions on the device architecture and the geometry to simplify the analyses. However, for practical systems, the physical properties of the realistic receiver architectures and their impact on the molecular propagation in the MC channel should be taken into consideration to the most possible extent. Finite element simulations on microfluidic MC channel with bioFET receivers and macroscale MC experiments with alcohol sensors clearly reveal the effect of the coupling between the MC-Rx and the channel [258], [268]. The coupling is highly nonlinear, and in most of the cases, it is not analytically tractable; therefore, beyond the available analytical tools, researchers may need to focus on stochastic simulations and experiments to validate the performance of the proposed detection techniques in realistic scenarios.

3) *Physical Properties of the Channel:* Most of the MC detection studies assume free diffusion, or diffusion plus uniform flow, for molecular propagation in an unbounded 3-D environment. However, in practice, MC channel will be bounded with varying boundary conditions and can include nonuniform and disruptive flows, obstacles, temperature fluctuations, charged molecules affecting the diffusion coefficient, and particles leading to channel crowding. Some of these aspects have recently started to be addressed through channel modeling studies, e.g., subdiffusive MC channel due to molecular crowding [273] and diffusion-based MC in multilayered biological media [274]. However, these simplified models are not able to provide enough insight into the detection problem in realistic channels. The highly time-varying properties of the MC channel have also been addressed by researchers through channel estimation techniques [275], [276] and noncoherent detection techniques [241]–[243], which are reviewed in Section V-A. These studies are built on simplifying the assumptions on channel and receiver architecture.

4) *Reactive Receivers:* Although reactive receiver concept provides a more realistic approach to the detection problem, the research in this direction is still at its infancy, and the developed received signal models are not complex enough to reflect many intricacies. For example, most of the previous studies assume independent receptors being exposed to the same ligand concentration; however, this is not always the case, as the binding of one receptor can affect the binding of neighboring ones [277], and receptors can form cooperative clusters to control sensitivity by exploiting spatial heterogeneity [278], [279]. The interplay between diffusion and reaction is also often neglected in these studies by assuming that the timescales of both processes are separated sufficiently. However, in most practical cases, reaction and diffusion rates are close to each other, and reactions are correlated with the transport process, which depends on the channel properties [182], [280]. These problems are crucial to analyze the spatiotemporal correlations among the receptors and the coupling between the diffusion channel and the reactive receiver. Moreover, except for a few recent studies [131], [281], [282], the design of intracellular reaction networks to implement the proposed detectors is usually neglected. The additional noise and delay stemming from these reaction networks should be taken into account while evaluating the performance of the overall detection. Furthermore, a proper analysis of the tradeoff among energy, detection accuracy, and detection speed is required to develop an optimization framework for the detector design in reactive receivers.

5) *Receiver Saturation:* Another challenge associated with reactive receivers is the saturation of receptors in the case of strong ISI or external interference, which can severely limit the receiver dynamic range and hamper the ability of the receiver to discriminate different signal levels. The saturation problem has been recently addressed in [252] through the steady-state assumption for the ligand–receptor binding reactions; however, in general, it is neglected to assume an infinite number of receptors on the receiver. The problem can also be alleviated by adaptive threshold-detection techniques and

adaptive transmission schemes as in detection with passive/absorbing receivers.

6) *Receiver Selectivity:* Receiver selectivity is also a major issue for MC detection, and it has just started to be addressed from the MC perspective. The physiologically relevant environments usually include many similar types of molecules, and the receptor–ligand coupling is not typically ideal, such that many different types of ligands present in the channel can bind the same receptors as the messenger ligands, causing molecular interference. Even if there are different types of receptor molecules for each ligand type in an MC system with MoSK, the crosstalk between receptors is unavoidable because of the nonideal coupling between receptor and ligands. Therefore, there is a need for selective detection methods exploiting the properties of ligand–receptor binding reaction. The amount of time a receptor stays bound is informative of the ligand unbinding rate, which is directly linked with the affinity between the particular types of ligand–receptor pairs. The bound time intervals are exploited in [262] to detect the MC messages based on the ML estimation of the ratio of correct ligands to the interferers. However, this technique requires the receiver to know the type and the probability distribution of the interferer molecules, and it is developed only for one type of interferer. To implement selective detection methods in engineered bacteria-based MC devices, the kinetic proofreading and adaptive sorting techniques implemented by reaction networks of the T cells in the immune system can be exploited [251], [283]. In addition, MC spectrum sensing methods can be developed based on the information inferred from the receptor bound time intervals to apply cognitive radio techniques in crowded MC nanonetworks, where many nanomachines communicate using the same type of molecules [284].

## VII. CONCLUSION

MC has attracted significant research attention over the last decade. Although ICT aspects of MC, i.e., information theoretical models of MC channels and modulation and detection techniques for MC and system theoretical modeling of MC applications, are well-studied, these research efforts mostly rely on the unrealistic assumptions, isolating the MC channel from the physical processes regarding transmitting and receiving operations. The reason being that although there are some proposals for MC-Tx/Rx based on synthetic biology and nanomaterials, there is no implementation of any artificial microscale/nanoscale MC system to date. As a result, the feasibility and performance of ICT techniques proposed for MC could not be validated.

In this paper, we provide a comprehensive survey on the recent proposals for the physical design of MC-Tx/Rx and the state of the art in the theoretical MC research, covering modulation, coding, and detection techniques. We first investigate the fundamental requirements for the physical design of microscale/nanoscale MC-Tx/Rx in terms of energy and molecule consumption and operating conditions. In light of these requirements, the state-of-the-art design approaches as well as novel MC-Tx/Rx architectures, i.e., artificial Tx/Rx designs enabled by the nanomaterials, e.g., graphene, and biological Tx/Rx designs enabled by synthetic biology, are covered. In addition, we highlight the opportunities and the challenges regarding the implementation of Tx/Rx and corresponding ICT techniques that are to be built on these devices.

The guidelines on the physical design of MC-Tx/Rxs provided in this paper will help researchers to design experimental MC setups and develop realistic channel models, considering the transceiving processes. In this way, the long-standing discrepancy between theory and practice in MC can be overcome toward unleashing the huge societal and economic impact of MC by paving the way for ICT-based early diagnosis and treatment of diseases, such as IoBNT-based continuous health monitoring, smart drug delivery, artificial organs, and lab-on-a-chip. ■

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## ABOUT THE AUTHORS

**Murat Kuscu** (Student Member, IEEE) received the B.Sc. degree in electrical and electronics engineering from Middle East Technical University, Ankara, Turkey, in 2011, and the M.Sc. and Ph.D. degrees from the Electrical and Electronics Engineering Department, Koc University, Istanbul, Turkey, in 2013 and 2017, respectively.

He is currently a Research Assistant with the Internet of Everything (IoE) Group, Department of Engineering, University of Cambridge, Cambridge, U.K. His current research interests include nanoscale and molecular communications, and the Internet of Everything.

**Ergin Dinc** (Member, IEEE) received the B.Sc. degree in electrical and electronics engineering from Boğaziçi University, Istanbul, Turkey, in 2012, and the Ph.D. degree in electrical and electronics engineering from Koc University, Istanbul, in 2016.

From 2016 to 2017, he was a Postdoctoral Researcher with the KTH Royal Institute of Technology, Stockholm, Sweden. He is currently a Postdoctoral Research Associate with the Electrical Engineering Division, University of Cambridge, Cambridge, U.K. He conducts theoretical and experimental research on molecular communication, neural communication, and cyber–physical systems.

**Bilgesu A. Bilgin** (Member, IEEE) received the B.S. degree in electrical and electronics engineering from Middle East Technical University, Ankara, Turkey, in 2008, and the M.Sc. and Ph.D. degrees in mathematics from Koc University, Istanbul, Turkey, in 2011 and 2015, respectively.

From 2015 to 2017, he was a Postdoctoral Fellow with the Next-generation and Wireless Communications Laboratory, Koc University. He is currently a Postdoctoral Research Associate with the Engineering Department, University of Cambridge, Cambridge, U.K. His current research interests include molecular communication, intrabody nanonetworks, partial differential equations, and dynamical systems.

**Hamideh Ramezani** (Student Member, IEEE) received the B.S. degree in electrical engineering, major in communication, from the University of Tehran, Tehran, Iran, in 2011, the M.S. degree in electrical engineering, major in communication systems, from the Sharif University of Technology, Tehran, in 2013, and the Ph.D. degree in electrical and electronics engineering from Koc University, Istanbul, Turkey, in 2018. She is currently working toward the Ph.D. degree at the Internet of Everything (IoE) Group, Department of Engineering, University of Cambridge, Cambridge, U.K.

She is a Research Assistant with the Internet of Everything (IoE) Group, Department of Engineering, University of Cambridge. Her current research interests include biosensing, nanoscale neural and molecular communications, and the Internet of Everything.

**Ozgur B. Akan** (Fellow, IEEE) received the Ph.D. degree from the Broadband and Wireless Networking Laboratory, School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA, USA, in 2004.

He is currently the Head of the Electrical Engineering Division, Internet of Everything (IoE) Group, Department of Engineering, University of Cambridge, Cambridge, U.K., and the Director of the Next-Generation and Wireless Communications Laboratory, Department of Electrical and Electronics Engineering, Koc University, Istanbul, Turkey. His current research interests include wireless, nano, molecular, and neural communications, and the Internet of Everything.

Dr. Akan is a Series Editor of the *IEEE Communications Magazine*, an Inaugural Associate Editor of the IEEE NETWORKING LETTERS, and an Associate Editor of the *IET Communications* and the *Nano Communication Networks* journal.