Interfacing of Molecular Communication System With Various Communication Systems Over Internet of Every Nano Things

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***Abstract*—The communication system for health-monitoring applications is a substantial research area considering its practical limitations. One of the potential suggested technologies is the Internet of Every Nano Things (IoENT). Through this work, we demonstrate the different aspects of interfacing of molecular communication (MC) with other nano-communication systems, such as human body communication (HBC), acoustic communication (AC), and tera-Hertz (Thz) communication systems for IoENT. Moreover, we also emphasized eclectic possibilities and various issues related to the applications of IoENT. First, we explored each of the nano-communication systems in detail by showing their mathematical frameworks. Subsequently, we are also concerned about different ways to interface MC with other nano-communication systems, one-by-one. In the end, we also discuss various likely challenges and possible future directions, e.g., availability of devices, mobility of devices and synchronization, etc., in the context of interfacing of diverse technologies.**

***Index Terms*—Acoustic communication (AC), human-body communication (HBC), Internet of Every Nano Things (IoENT), Internet of Nano-Things, molecular communication (MC), tera-hertz communication.**

I. Introduction

IN DECEMBER 1959, a Nobel laureate physicist Richard Feynman emphasized a very well-known statement in his speech entitled "There's Plenty of Room at the Bottom." In his speech, the primary focus was on the field of miniaturization, and emphasized how humans would construct increasingly more miniature and smart machines in the future. Activity surrounding nanotechnology began to slowly increase and the progress got acceleration in the early 2000s. The interconnection between the nano-devices through which it is expected to expand the capabilities of a single nano-device by allowing them to cooperate and share information is called nano-communication networks [1].

The wireless communication (WiCom) systems (6G and beyond) are expected to be more prevalent and subjected to more additional Internet-dependent [2]. This can also be helpful for the wireless medical telemetry systems, which can be composed by several nanoscale devices that will be deployed inside the organisms to provide a more sensitive health monitoring system and treat any detected disease in real-time. Furthermore, the monitoring of oxygen and cholesterol levels, hormonal disorders, and early diagnosis are some examples of possible applications that can take advantage of intrabody nano-sensor networks. The information retrieved by these systems must be accessible outside the body to the external monitoring doctors, nurses, etc. Thus, nano-networks must provide the proper level of connectivity to deliver the sensed information. In addition, a drug delivery system that is composed of nano-nodes could help compensate metabolic diseases such as diabetes. In this scenario, nano-sensors and smart glucose reservoirs can work in a cooperative manner to support regulating mechanisms.

Nanoscale communication is a key enabler paradigm for the several critical health-care and environment applications, e.g., targeted drug delivery (TDD), Internet of Nano Thing (IoNT), early detection of viruses and environment monitoring. Moreover, nanoscale communication can also be applied at the macro-world through implementing nano-sized antennas and devices for certain applications, e.g., designing of an intelligent office using IoNT mechanism [3]. Furthermore, the connectivity among the bio-compatible devices inside the human body also being the potential research area considering health care applications. The network which is formed by the interconnections of several bio-devices to establish the communication among them is specifically described by Internet of Bio Nano Things (IoBNT). The uniquely identifiable primary structural and operational bio-devices that can interect inside the biological enviornment is known as Bio-nano-things. Originating from biological cells and facilitated by artificial biology and nanotechnology, Bio-nano-things are conceptualized to perform specific tasks and functionalities such as sensing, processing, actuation, and interaction with each other. There are several works in the literature that have discussed about IoBNT considering one or two communication paradigms (e.g., [4], [5], and [6]). For instance, authors have introduced the concept of IoBNT through work [4]. In [5], various issues, challenges, components and applications related to IoBNT have also elaborated comprehensively. The aforementioned works have focused on IoBNT considering specific communication setups inside the organism. The IoBNT specifically dealt with the bio-devices in the biological environment for biological applications only. However, there can be possibilities of nano-communication setup for

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nonbiological applications, such as communication in salt-water and in microfludic application where bio-devices not necessarily present.

In these contexts, we can connect the nano-devices that can be either biological or nonbiological. Such a type of network that is formed by interconnecting various nano-devices, is called the Internet of Every Nano Things (IoENT). This IoENT setup is not necessarily a biological application-specific system, indeed it can also be involved in nonbiological nano-communication applications. Using IoENT, one can interface various communication technologies, such as Tera-hertz (Thz) communication, molecular communication (MC), human-body communication (HBC), and acoustic communication (AC), etc. In [6], the IoENT system has widely explored through comprehensive survey. As discussed earlier, recent advancement and expecting continuous progresses in the nano devices pave the way for successful implementation of nano-networks consisting of IoENT. It has been known that molecular transport, electromagnetic, HBC or intrabody communication, Forster resonance energy transfer (FRET), heat transfer, acoustic energy transfer, and nano-mechanical communication can be modified to form a IoENT setup [7].

Out of those aforementioned technologies, one of the promising and emerging nanoscale communication systems is *(MC)*; which has got significant attention considering the above-mentioned application in recent years [8], [9]. In MC, characteristics of specific molecules are used as an information carrier between nano transmitter/transmitters (Tx/NTxs) and nano receiver/receivers (Rx/Rxs). Type of a molecule which used to carry the information is known as information carrying molecules (ICMs). In an MC system, diffusion process of molecules is one of the substantial physical phenomena, which depends on the type of communication channel between Tx and Rx, e.g., 1/2/3-dimensional, bounded/unbounded and active/passive channels [10]. A one of the important design parameters in case of an MC system are diffusion coefficient of messenger molecules (MMs), that depend on the various factors, such as temperature of the medium, viscosity of fluid medium and Stoke's radius of molecules [11].

Few of the examples of natural MC systems are *Synaptic communication* [13], *Bacterial communication* [14], and Pheromone Signaling [15]. Synaptic transmission is an important process in the integrative action of the nervous systems inside the organisms. In this system, synapses by which chemical signals (neurotransmitters) are released from the neuron (called a presynaptic neuron) and diffuse toward other neurons or target cells (also called a post-synaptic neuron) where it generates a signal which excites, inhibits, or modulates cellular activity. On the other hand, Bacteria communicate through a chemical process called Quorum sensing [16], in which they release molecules that serve as messages detected by nearby bacteria. Quorum sensing is a component of bacterial communication that allows bacteria to monitor the surroundings for other bacteria and to vary behavior on a population-wide scale in reaction to modifications in the number and/or species present in a community [17].

The aforementioned types of MC techniques described so far offer a solution for short-range communication among nanomachines. However, there might be cases where nanomachines are too apart from each other and, thus, short-range communication methods are ineffective due to their range limitations. However, there might be circumstances in which nanomachines are placed too apart from each other. Several long-range communication methods are described in [18], e.g., the use of pheromones, pollens, and light transducers for long-range communications among nanomachines. The most prominent of these processes is Pheromone Signaling.

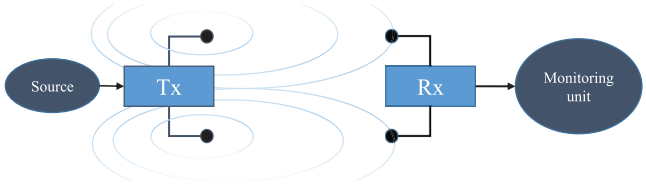

Fig. 1. Block-level diagram of HBC system which uses the human body tissue as the transmission channel and capacitive/galvanic coupling to transmit health informatics [12].

The mathematical models of such types of communication systems help in analyzing and optimizing their performance. For instance, work [19] has proposed the nano-networks of the artificial neural system where nano-machines are linked to neurons to treat neurodegenerative diseases. In these networks, nano-machines are used to replace the damaged segments of the nervous system and they behave exactly like biological entities. In this work, authors have designed the equivalent communication system as a binary channel, and performance optimization methods have also been proposed. Moreover, there is a possibility of introducing additional nodes called neuro-spike relays to increase the range of communication to reduce the probability of neurodegenerative diseases [20]. Moreover, there is plenty of research already going on the communication model of Bacterial transmission (e.g., works [14], [16], [21]). But very limited works have exploited the Pheromone signaling system (e.g., [22]).

On the other hand, *Thz communication* has also been widely explored and one of the rapidly growing technologies in the context of a WiCom systems. Furthermore, it has been studied that despite of environment and molecular losses are dominating factor in Thz systems, it can be used at a nanoscale level for communication between nano scale Tx and Rx [23]. One of the key applications, e.g., in IoNT, the information about the health conditions inside the organisms can be sent to macro-world using bio-compatible interfaces. The major differences between all the above discussed communication technologies are summarized in the Table I.

Apart from MC and Thz communication setups, a paradigm that can be the substantial area of research for in vivo applications is *HBC* [12]; which is shown in Fig. 1. HBC utilizes the human body as a communication medium between devices on and around the body. Electronic data transfer by capacitive and galvanic coupling have been proposed by research and industry as a novel and promising technology for ultralow-power wireless body local area networks. The increased energy-efficiency and enhanced physical security due to signal confinement makes HBC a promising alternative to radio wave-based communication like Bluetooth for IoBNT applications. However,

TABLE I
COMPARISON AMONG ALL THE WICOM TECHNIQUES

Communication Mode	Transmission Medium	Information Carrier	Frequency Range	Speed	Communication Range
Molecular	Blood vessels, Air, Microfluidic	Molecules	None	Very low	Very low
EM based Thz	Intrabody, Air	EM signal	300 GHz to 10 Thz	Very high	Very Low
Free space optical	Underwater, Air,Vacuum	Optical signal	100Thz to 1000 Thz	Very high	High
Acoustic	Air, Intrabody, Underwater	Acoustic	20 Hz to 20,000 Hz	High	Modest
HBC	Intrabody, Air	EM Signal	100KHz to 600 MHz	High	Low

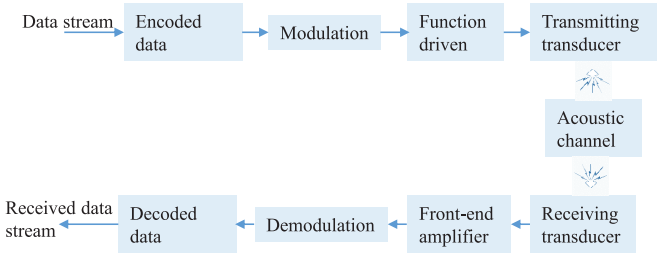

Fig. 2. AC system in which transmission of messages take place between con-specifics via either sound waves through air or through water.

HBC requires tiny amounts of electrical signals to be sent through the body. The safety issues have been explored and discussed widely in the literature of HBC [24].

Another famous technology that can be used to transfer the information in nanoscale networks is AC; in which an acoustic signal is used to carry the information from one end to other [25]. The block level diagram for this system is shown in Fig. 2. In this technology, the sound is produced when a physical object vibrates rapidly, disturbs nearby air molecules (or another surrounding medium), and yields compression waves that travel in all directions away from the source. We perceive these waves as sound when they collide with our eardrums and cause a mechanical disturbance detected by sensory neurons in our inner ear. Both living and nonliving objects produce sound, but only animals use it to communicate.

Among all the WiCom technologies discussed earlier, MC is an indispensable system considering various health and environment related application. Note that an MC system has been widely proposed by the researchers across the world, which will be applied for the sensing at molecular level and the nanoscale intrabody devices interconnections. Furthermore, to communicate with macro-worlds' networks, and with the Internet as well, these systems will require a interfacing or translator device, namely bio-cyber-interface that will convert any molecular signal into electrical [4]. Such application requires the detailed study of interfacing and connection modeling between MC and electromagnetic (EM) wave-based communication systems. At the nanoscale, the Thz communication system is a most suitable EM wave-based technology that can be used for the IoNT application. For instance, by triggering protein vibrational modes using Thz waves, the changes in protein conformation resulting in the activation of a controlled cascade of biochemical and bio-mechanical events [26]. Furthermre, human body absorb energy from EM fields at Thz band, and subsequently release this energy as heat to their immediate surroundings that can also be used to establish the communication between the macro-world devices and in vivo devices [27].

Thus, an MC system can be made a heart of IoENT which can be interfaced with all the other communication systems either separately or in hybrid mode. There are several application oriented challenges for the implementation of such systems in realty. Some works [3], [6], [28] have provided a detailed survey over IoNT. For example, in the year 2010, a work [3] was published. This work discussed the state of the art in electromagnetic communication among nanoscale devices and highlighted the major research challenges in terms of channel modeling, information encoding, and protocols for IoNT. Furthermore, in [28], a comprehensive survey from the architectural level to the encryption level was provided. Furthermore, up to the year 2018, the statuses and future promises of the IoT and IoNT were extensively reviewed and summarized in [6].

Few works have worked on IoBNT, such as [4], [5], [29], and [30]. For example, Akyildiz et al. [4] introduced the concept of IoBNT in which they provided the details of interfacing of IoT and bio-sensors. Also, different aspects of IoBNT such as the bio-cyber interface for IoBNT architecture comprehensively reviewed in [29]. In [5], a review of applications related to IoBNT and new enabling technologies and key challenges was provided. Furthermore, this work was extended in [30], in which authors proposed a maximum likelihood (ML) estimation method for IoBNT application.

Note that all the aforementioned works have focused on either IoT/IoNT or IoBNT in which they mainly consider either biological or nonbiological entities for various health care and environment monitoring applications. In comparison to these works, we focus on the possibilities for interfacing an MC system not only with the Thz communication system but also with the different other types of WiCom systems, e.g., HBC and AC. Such a type of network can be extended to form a IoENT, and mainly in this work, we propose the methodology and challenges to interconnect bio and nonbio nanodevices altogether. Moreover, we also enlist and exploit the various challenges that may arise during the interfacing of MC with other WiCom systems. The key contributions of this article are as follows.

1) We discuss and compare the possible nano-communication technologies, such as MC, Thz communication and HBC communication, and AC.
2) Furthermore, one by one, we explored all the communication technologies in detail in the context of IoENT.

TABLE II
DESCRIPTION OF EXISTING WORKS ON INTERFACING OF MC AND WICOMS

Paper	Description	Type of communication
[70]	A review on internet-of-everything was provided and discussed the interfacing of various WiCom technologies such as acoustic, Thz, and multi-modal communications.	Interfacing of MC with the acoustic and wireless communications
[4]	A review on internet-of-bio-nano-thing was provided and discussed about the bio-cyber interface	Intra-body Thz level
[26], [32]	A stimuli-responsive paradigm which integrates EM and molecular communication by stimulating proteins in the human body was proposed.	Interfacing of MC and Thz
[31]	Summarizes the device level description for the implementation	Not mentioned
[33]	A review on the past and current designs of intra-body nanoscale devices for bio-cyber interface has been provided.	Intra-body Thz level
[71]	Focused on interfacing of MC and Thz communication systems.	Interfacing of MC and Thz
[72]	Thz channel and link budget analysis was exploited for intra-body communication	Intra-body Thz level
[73]	Noise model was elaborated for intra-body communication	Intra-body Thz level
[27]	Photo-thermal modelling was proposed for intra-body communication	Intra-body Thz level
[74]	A modulation and channel access scheme for nanonetworks in the Terahertz Band is developed for nano-scale communication	Intra-body Thz level

3) Furthermore, we address various ways to couple other WiCom systems with MC systems in the context of IoENT.
4) In addition, we enlist various technical challenges for the practical implementation of IoENT in detail.

In the subsequent sections, we explored all the WiCom systems in detail. Sections II and III mainly describe the various aspects of an MC system, such as channel modeling and performance measurement parameters. Section IV-A, is devoted to describing the fundamentals of Thz communication and various issues related to it. The remaining bio-compatible communication systems, e.g., HBC, and AC are elaborated in Section IV-B. Section V focuses on the interfacing of MC with the other WiCom system in the context of IoENT. In Section VI, various research challenges are discussed in the context of the proposed methodology. In the end, this article is concluded in Section VII.

II. DESCRIPTION OF MC AND OTHER COMMUNICATION SYSTEMS

The nanoscale is the obvious territory of molecules, e.g., proteins, DNA, organelles, and the major components of living cells, where nanoscale devices communicate with each other to perform a particular task. These nanoscale devices having sensing, actuating, data storing and computing capabilities are the potential candidates to implement the nanoscale communication setup. As discussed earlier, these types of communication setups are essential to accomplish the various unique applications in the biomedical, industrial, and military fields, such as advanced health monitoring systems, nanosensor networks for biological and chemical attack prevention as well as wireless network on chip systems [31].

In order to implement the nanoscale communication setup considering aforementioned applications, Thz and MC systems are the two largely proposed potential paradigms by various researchers in the existing literature. Several works in the literature have been considered both the paradigms separately for the study and analysis. The question may arise that, to access the best and most effective performance in terms of speed, accuracy, and specificity, is this possible to connect MC with the few other communication technologies? Answer is *yes*. Few of the research work emphasized the interconnectivity between MC and Thz communication systems. Moreover, Thz communication have been shown the compatibility with the nanoscale devices and few works have been discussed the interfacing of MC and Thz systems as well [4], [26], [32], [33]. For example, in [4] and [32], a stimuli-responsive paradigm which integrates EM and MC by stimulating proteins in the human body was proposed. A review on the past and current designs of intrabody nanoscale devices for bio-cyber interface has been provided in [33]. Table II provided the details of existing works on body-centric communication in the context of MC and Thz communication systems. Apart from the interfacing of MC with Thz communication, we may also discuss about the interfacing of MC with the AC and HBC systems. Before discussing interfacing, in the next chapter, we brief all the aforementioned communication systems one-by-one.

III. MOLECULAR COMMUNICATION

An *artificial* MC system basically inspired from the *natural* communication between the cells/bio-molecules inside the organisms that already takes place for the functioning of their body. For instance, cells can produce nucleic acids and proteins, that acts as a molecular signal, and freely diffuse or transport them by Exosomes[1] stimulation of cellular immune responses *in-vivo* [34]. Due to the diversity of natural systems, different natural cellular signalling, such as action potential and quorum sensing processes have been investigated in the recent past years that can inspire the design of these artificial MC systems, and the characteristics of those natural systems also define the requirements for the nano network architecture [35]. Therefore, the nanoscale device known as source nanomachine (SN), that are specific for each system, are built to encode and transmit molecular signal through a communications channel (e.g., fluid media) toward a nanoscale

[1]Exosomes are a class of cell-derived extracellular vesicles of endosomal origin, and are typically 30-150 nm in diameter—the smallest type of extracellular vesicle.

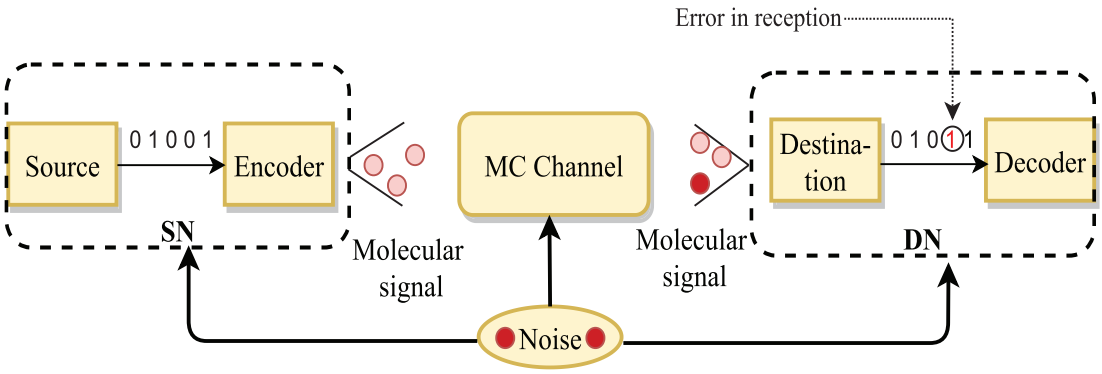

Fig. 3. Simplified MC system in which SN communicates the binary information (01001) to DN through the ICMs. In the figure, ICMs are shown through the "pink" circles, and "red" circles are noise molecules. Here, at the DN, the circled bit shows the error in transmission.

receiver that will retrieve the original molecular information. The nano-devices which capture and retrieve the information are generally called as destination nanomachine (DN) in the MC literature; cf. Fig. 3. To encode a molecular information, scientists can change the structure of the molecule, the gene sequence information or the concentration of information in the propagated molecular signal. At the receiver side, the molecular signal is decoded resulting on the extraction of the original information produced by the nanoscale transmitter [36]. These processes are analogous to the chemical reactions required to produce, propagate and receive molecular signals within a nanonetwork.

An MC system can be designed to work with having single molecule or multiple molecules depending on the requirement of the specific application. For instance, each cell of a bacterial population can be engineered to carry the same molecular information between nanoscale devices. On the other hand, a whole cellular population can be engineered to behave collectively as a logic gate and process molecular signals [37]. Both the techniques are designed to develop a system that can be used for various applications, e.g., disease diagnosis/treatment, health monitoring, drug delivery, tissue engineering or even DNA engineering. The current state-of-art in developing micro-electromechanical systems (MEMSs), nanoparticles, and other nanoscale technologies pave the way for the design of such systems in reality. Furthermore, to monitor remotely and control the nanoscale processes, we need an additional device known as *bio-cyber interface* which is shown in the subsequent section. This nanoscale device can translate the chemical reactions outputs into other molecular or electric signals that can easily be understood by the conventional computer networks and vice versa. Thus, bio-cyber interfaces can be designed for a specific cell stimulation or chemical content sense. Such types of nanonetworks can be deployed inside an organism's body for long-term remote health monitoring, diagnosis, and treatment of diseases. Sensing the chemicals of one particular cell and the possibility of influence on the cell will provide timely prevention and treatment of many disorders, such as cancer, tumors, and neurological disorders like epilepsy, Parkinson's, and Alzheimer's disease. Even such networks can be beneficial to finding the Corona viruses in their early stage.

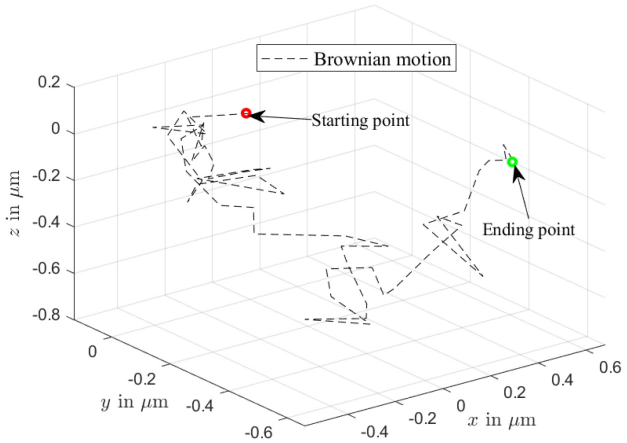

Fig. 4. Demonstration for trajectory of 3-D Brownian motion for a single particle through MATLAB simulation. A circle with "red" color shows the starting point and "green" color circle represents the ending point of the simulation.

The MC system has been widely studied as an independent domain, and numerous studies have already exploited various issues in the contexts of types of the physical channel, different Txs and Rxs, MMs, etc. Furthermore, various issues, such as noise, intersymbol-interference (ISI) and its suppression, detection-estimation, and system performance optimization have been widely explored. Herein, we summarize each issue for the understanding of an MC system.

A. Channel Models in MC Systems

The propagation of a molecule in any medium follows the random Brownian motion. The Brownian motion of molecules-bunch in any medium is defined by the diffusion phenomenon, where each molecule follows the random displacement due to the concentration gradient. In 1-D Brownian motion, a molecule jumps either left or right with spatial-step Δx in time-step Δt. Here, step Δx follows the standard Gaussian distribution [11] as $\Delta x \sim \mathcal{N}(0, 2D_m\Delta t)$, where D_m denotes the diffusion coefficient of molecules. However, in the case of the three-dimensional (3-D) Brownian motion, as shown in Fig. 4, the position (in $x, y,$ and z coordinates) of a tagged

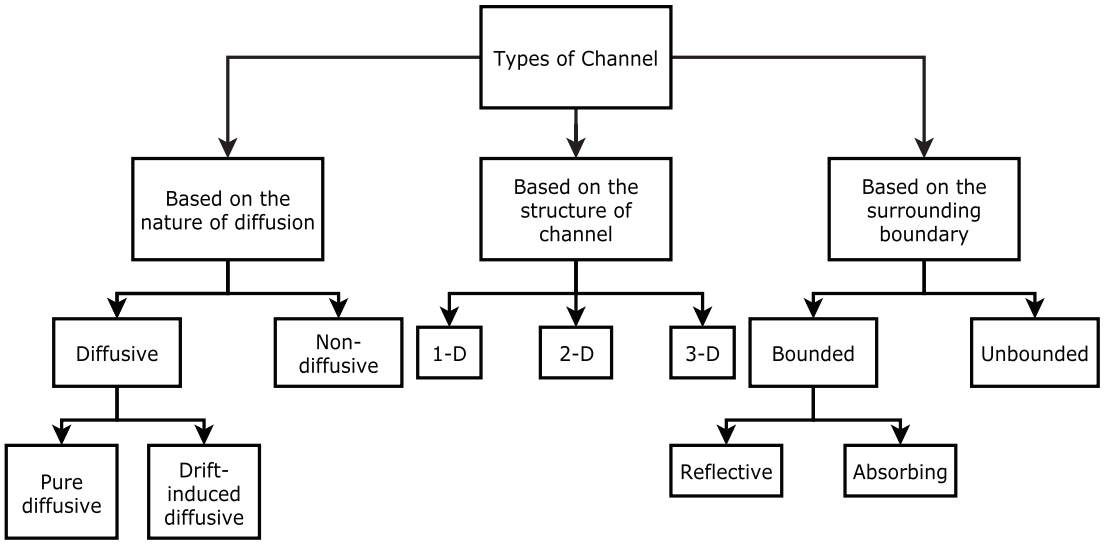

Fig. 5. Classification of MC channels.

molecule at the $(i+1)$th time-step is given as follows:

$$x_{i+1} = x_i + \mathcal{N}(0, 2iD_m\Delta t)$$
$$y_{i+1} = y_i + \mathcal{N}(0, 2iD_m\Delta t)$$
$$z_{i+1} = z_i + \mathcal{N}(0, 2iD_m\Delta t)$$

where $(x_i,\ y_i,\ z_i)$ is an initial position of a tagged molecule. The propagation of MM in an MC channel is mainly governed by presence of drift and diffusion phenomena. The channels can be classified as pure diffusive and drift-induced diffusive channels. In a pure diffusive channel, the flow of molecules is attributed to the Brownian motion from higher to lower concentration regime [36]. While the external drift along with the random diffusion affects the propagation of molecules in the drift-induced diffusive MC channel. Two different analytical approaches have been used so far to study the MC channel. First, the microscopic approach [10], [38], where the analysis focuses on the arrival probability of a single molecule. Second the macroscopic approach in which the concentration of molecules corresponding to the channel impulse response (CIR) is considered to analyze the system [39].

The MC channels can be classified on the basis of: 1) nature of diffusion [40]; 2) structure of channel [41], [42], [43], [44]; and 3) presence of surrounding boundaries. The detailed classification is provided in Fig. 5. In brief, these types of MC channels are described as follows.

1) *Pure Diffusive or Passive:* When the propagation of molecules from Tx to Rx takes place solely due to the diffusion phenomenon, such type of channel is known as pure diffusive channel. In the literature, such a type of channel commonly known as passive channel. This kind of diffusion have limited range and larger propagation time (see [9, Ch. 4.2.3]).
2) *Advective-Diffusive or Active:* in general, the propagation of molecules also speed up by flow of the fluid medium or some biological processes and such type of channel of channel is known as flow-induced diffusive or advective-diffusive channel. Such type of channel is also known as active transport channel. For example bacterial chemotaxis provides the active mechanism of MC. Moreover, *E. coli*, for instance, have several flagella that rotate to produce a biased motion at relatively high speed, for more detail, refer [9, Ch. 4.2.3].
3) *1-D/2-D/3-D:* Based on the dimensions of flow of molecules the channel can be classified as, 1-D, 2-D, and 3-D. Furthermore, 2-D and 3-D channels can be further classified as bounded or unbounded channel. In unbounded channel molecules can move infinitely in any direction, whereas, when channel is surrounded by the closed boundaries or surfaces, such type of channel is known as bounded channel.
4) *Normal-Diffusive/Anomalous-Diffusive:* Based of on the types of diffusion phenomena, the MC channel can be classified as normal-diffusive and anomalous-diffusive channels. In normal diffusion, the displacement of a molecule with diffusion coefficient D_m in one time-step follows the standard Gaussian distribution, with zero mean and mean square displacement (MSD) varies linearly with time, i.e., $< x^2 > \sim 2D_m\Delta t$. When the MSD of a particle varies nonlinearly with time and follows the power law diffusion, i.e., $< x^2 > \sim 2D_m\Delta t^{\alpha}$, such type of motion of a particle known as scaled Brownian motion (SBM) or fractional Brownian motion (fBm). When bunch of molecules follows the SBM or fBm such type of diffusion is known as anomalous diffusion.

The diffusion phenomena can be very fast and efficient for short distances, as commonly found in various natural cellular processes (see [45]). However, for larger distance MC system have to deal with increasingly larger attenuation and propagation time, since the concentration of molecules inversely proportional to the square root of time and distance of travel is proportional to square root of time [10]. The fraction molecules received at the Rx plays a key role for the reliability of communication link. However, the molecules received at the intended Rx in the expected time slot may differ due to the following reasons: 1) molecules emitted from unintended

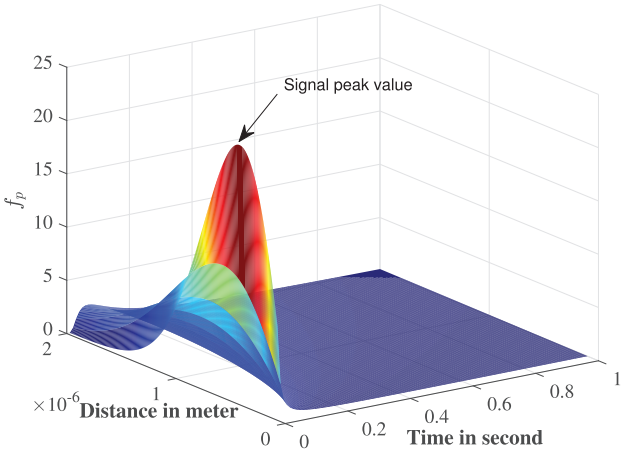

Fig. 6. Variation in first passage time density function with time and distance for 1-D Brownian motion.

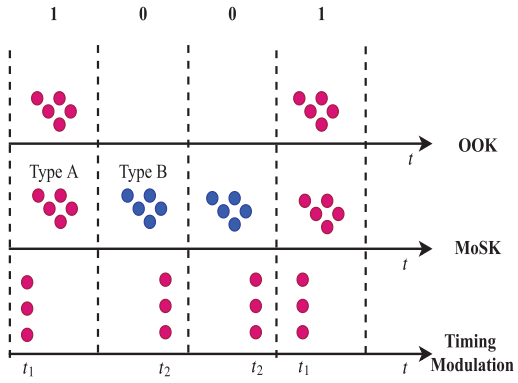

Fig. 7. Pictorial presentation of different types of modulation techniques used in MC.

Tx mixed with MMs known as multiple-source-interference (MSI); 2) molecules emitted form intended Tx may not arrived in the intended time-slot; and 3) molecules emitted from Tx may arrived in later time-slots known as ISI.

The characterization and analytical study of different types of propagation channels are indispensable for the end-to-end performance analysis of an MC system. Different types of channel and Rx leads to the various kind of analytical treatments; for example, the 1-D pure diffusive medium has been defined through Fick's law of diffusion as follows [46]:

$$\frac{\partial c(x,t)}{\partial t} = D_m \frac{\partial^2 c(x,t)}{\partial x^2} \tag{1}$$

where D_m is the diffusion coefficient of molecules, $c(x,t)$ spatial-temporal concentration, and x_o point of release of molecules. The first-passage-time-density (FPTD) of 1-D channel considering perfectly absorbing Rx, using (1) can be obtained as [47]

$$f_p(t) = \frac{d}{\sqrt{4\pi D_m t^3}} \exp\left(\frac{-d^2}{4D_m t}\right) \tag{2}$$

here d is the distance between release and absorbing points in the diffusive channel. However, the FPTD for 1-D drift-induced diffusive channel with velocity of fluid v is defined as [43]

$$f_p(t) = \frac{d}{\sqrt{4\pi D_m t^3}} \exp\left(\frac{-(d-vt)^2}{4D_m t}\right). \tag{3}$$

The variation in FPTD with the time is represented in Fig. 6. It shows the long tail behavior leads to the severe ISI at the Rx, which causes erroneous decisions. Furthermore, for a 3-D diffusive medium with spherical DN is described by the diffusion equation in spherical coordinate system as

$$\frac{\partial c(r,t|r_0)}{\partial t} = D_m \nabla^2 c(r,t|r_0) \tag{4}$$

where $c(r,t|r_0)$ denotes the spherical spatiotemporal probability density function (PDF) of molecules at time t and radial position r in a 3-D spherical coordinate space, given the initial distance r_0 between source and destination. ∇^2 denotes the Laplacian operator. The first hitting rate for the 3-D diffusive channel with perfectly absorbing DN of radius r_r is derived using (4) as [41]

$$f_{\text{hit}}(t) = \frac{r_r}{r_0} \frac{d}{\sqrt{4\pi D_m t^3}} \exp\left(\frac{-d^2}{4D_m t}\right) \tag{5}$$

where $d = r_0 - r_r$ is the distance between SN and surface of the DN.

Furthermore, a spherical Tx can also employs a directional transmission method to communicate with the spherical Rx using ICM. In this case, the diffusion process with a particular direction in a 3-D environment can be described by Fick's second law as [41]

$$c(r,\theta,\phi,t|\mathcal{R}(\phi_1),\phi_1) = D_m \nabla^2 c(r,\theta,\phi,t|\mathcal{R}(\phi_1),\phi_1) \tag{6}$$

where the transmitter employs directions ϕ_1 and ϕ_2 to distinguish between bits 0 and 1. The released molecules in the directions of ϕ_1 and ϕ_2 are uniformly distributed concerning the azimuth angle, i.e., θ, in the interval $\{0,\pi\}$. Also, $\mathcal{R}(\phi_1)$ is the distance between the boundary of the transmitter at ϕ and the center of the receiver and $c(r,\theta,\phi,t|\mathcal{R}(\phi_1),\phi_1)$ is the concentration of molecules at time t and distance r when they are released from a Tx at the initial distance $\mathcal{R}(\phi_1)$ in the direction of $\phi = \phi_1$. The solution of (6) is already obtained in [48].

In the context of IoENT/IoBNT applications, a 1-D MC architecture is not closely co-related practically. However, a 3-D environment with the directional transmission in which Tx releases the ICM in a specific direction can be used to model the IoENT system effectively. Furthermore, such type of 3-D architecture has the advantages of reduction in ISI as well as ILI for multiuser MC systems. Furthermore, with the transmission in two directions, the data rate can be further improved [48].

B. Types of Modulation Schemes in MC System

In MC, specific types of molecules and their characteristics are used to encode and transmit the information from Tx to Rx [10]. There are several types of modulation techniques as shown in Fig. 7, which are extensively used in the MC system [10], [49]. A few of them are classified

as: 1) binary-concentration-shift-keying (BCSK) also named as on-off keying (OOK) [50]; 2) timing modulation [51]; 3) molecular shift keying (MoSK) [52]; and 4) binary direct shift keying (BDSK) [48].

In BCSK, two different concentrations of molecules are transmitted corresponding to the symbols 0 and 1. The OOK is the special case of BCSK, where some fixed number of molecules are used to encode the symbol 1, and zero molecules are used to encode the symbol 0. Note that OOK has been the widely used modulation technique in the existing literature due to its simplicity. The information is encoded based on the time of the release of the molecules from the SN in *timing modulation*, i.e., two different timing instances t_1 and t_2 are used correspond to the symbols 1 and 0, respectively; see Fig. 7, and in *MoSK*, information is encoded based on different types of molecules, i.e., type A molecules are transmitted for symbol 0, and type B molecules are transmitted for symbol 1.

Furthermore, instead of activating one type of molecule in the traditional MoSK modulation, a generalized MoSK (GMoSK) method is proposed in [53]. In this method Tx simultaneously activates several types of molecules, to increase data rate and the potential to further mitigate inter-symbol interference (ISI) beyond MoSK. One more novel method recently proposed in [48] named BDSK in which the Tx uses two different directions to release ICM. This method is extremely use full for the IoNT and IoBNT applications since Tx has to release the molecular information in specific directions.

C. Noise and ISI in MC Systems

In an MC system, MSI also known as noise and ISI are two key issues that need to be addressed for the better performance. The molecules which have the characteristics similar to the information-carrying molecules and are emitted from the other sources act as noise and deteriorate the system performance. The diffusion phenomena can be very fast and efficient for short distances, as commonly found in various natural cellular processes (see [45]). However, for larger distance MC systems have to deal with increasingly larger attenuation and longer propagation time, since the concentration of molecules inversely proportional to the square root of time, and distance of travel is proportional to the square root of time [10].

The fraction of molecules received at the DN plays a key role in the reliability of the communication link. However, the number of molecules received at the intended DN in the expected time slot may differ due to the following reasons: 1) molecules emitted from unintended SN having the same characteristics as MMs can be received at DN known as MSI; 2) molecules emitted form SN may not arrive in the intended time-slot; 3) molecules emitted from SN may arrive in later time-slots known as ISI. For a binary sequence having K number of bits, there are $(K-1)$ ISI components at the DN. The effect of ISI is more severe if CIR of molecules propagation shows the heavy tail behavior; 4) interference caused at the transceiver, due to the molecules emitted by itself, is known as self-interference. Self-interference occurs mainly in an MC systems with cooperative or multiuser environments; and 5) MMs of intended time-slot disruptively absorbed at unintended DN.

D. Performance Measurement

Different types of channels, SNs and DNs, and boundary conditions leads to the different types of analytical models in MC system. One way to analytically model the randomness of the media by using the first passage time model. For the emission point z_o and absorbing point z_a into the channel, the first passage time T is defined as

$$T = \inf\{t : z(t) = z_a\} \tag{7}$$

i.e., the time at which a tagged molecule is absorbed at DN boundary. The probability of a tagged molecule such that it first crosses the receiver boundary is defined as the first passage or first arrival probability $F_p(t)$. And the survival probability $F_s(t)$ is defined as the probability that a tagged molecule has remained at a position $z \leq z_a$ for all times up to t [54]. The stochastic model for the first passage time can be well described using the FPTD function. The FPTD ($f_p(t)$) can also be obtained using the relation between the first survival and arrival probabilities which is defined as $F_p(t) = 1 - F_s(t)$. Therefore, the FPTD can be obtained as

$$f_p(t) = -\frac{\partial F_s(t)}{\partial t}. \tag{8}$$

In the MC literature, several works [42], [43], [55], [56] have used such type of model for different channel conditions. For instance, the FPTD of 1-D diffusive channel can be described using inverse Gaussian distribution [43]. However, Levy's distribution has been used to model the FPTD for 1-D drift-induced channel [56].

For the performance evaluation of the MC system, the expected number of molecules at the DN is an important parameter, which can be obtained using the FPTD model. The arrival probability p of molecules at the DN up to time t, can be evaluated by integrating the FPTD up to the time t as

$$p = \int_0^t f_p(t^*)\, dt^*. \tag{9}$$

Depending upon the modulation technique used for the transmission, a DN may experience the different types of stochasticity. The number of molecules received at the DN and timing of reception of a molecule are two random quantities, which significantly affect the probability of error and MAR performances of an MC system. In case of binary transmission using BCSK from SN to DN, the number of molecules received at the DN is a Binomial distributed random variable, i.e., $N \sim \mathcal{B}(Q, p)$. For the mathematical tractability and under certain conditions[2] the Binomial distribution can be approximated as either Gaussian distribution as $N \sim \mathcal{N}(Qp, Qp(1-p))$ or Poisson distribution as $N \sim \mathcal{P}(Qp)$ [58], [59].

One way to examine the MC system performance is using the probability of error metric. If we consider x and y as the symbols transmitted from the Tx and received at Rx,

[2]For the case of a large number of molecules and respective lower arrival probabilities the Binomial distribution can be closely approximated as Poisson or Gaussian distributions [57].

respectively, then for binary transmission, the expression for probability of error can be obtained as

$$P_e = \Pr(y = 1|x = 0)\Pr(x = 0) + \Pr(y = 0|x = 1)\Pr(x = 1) \tag{10}$$

here $\Pr(x = 0)$ and $\Pr(x = 1)$ are the prior probabilities for symbols 0 and 1, respectively. There are several existing works in the MC literature, such as [55], [60], [61], and [62] and references therein, which approximate the Binomial distribution as the Gaussian distribution and analyze the system in terms of probability of error.

Few works [42], [43], [67] have analyzed the MC system in terms of probability of error considering a timing modulation method. The expression for the probability of error using Gaussian approximation considering MoSK modulation was derived in [64]. Note that in Gaussian approximation, the statistically averaged value of a number of molecules has been used to formulate the expression for probability of error, which leads to a bound. Several existing works, such as [65], [66], and [67] have considered Poisson approximation for the number of molecules received at the DN to formulate the expression of probability of error. The exact closed-form expression for the channel capacity in MC is not available. However, some works have derived the upper and lower bound for the expression of capacity (see [68]). Therefore, the closed-form expression for the capacity/throughput in MC is a challenging task and needs to be explored further. The capacity analysis in the existing literature has been carried out by maximizing the mutual information about the prior probability β as

$$C = \max_{\beta} I(x, y) \quad \text{bits/slot.} \tag{11}$$

Using the above expression, the capacity of the system can be evaluated and analysed for an MC system.

IV. Literature of Other WiCom Systems

A. Thz Communication System

In the existing literature, the Thz communication systems have been exploited extensively on various aspects for 6G, such as designing of Thz antenna, implementation of Thz Tx and Rx, channel models, backhaul connectivity and path-loss models, etc. We summarize the various aspects of Thz communication system that falls in the domain of interfacing of MC and Thz communication systems specifically for health care applications. Next, we discuss the various path-loss models for Thz communication systems.

1) Path Loss Due to Wave Spreading: The attenuation in Thz band is a key factor that affect the performance of the communication system. The total attenuation factor for a given frequency f and wavelength λ in Thz communication is given by

$$L_{\text{total}}(f) = L_{\text{spr}}(f) \cdot L_{\text{abs}}(f) \cdot L_{\text{sca}}(f) \tag{12}$$

here the term $L_{\text{spr}}(f)$ shows the spreading loss factor, $L_{\text{abs}}(f)$ is the molecular absorption loss factor, and $L_{\text{sca}}(f)$ is the scattering loss factor. Furthermore, each of these terms represents the ratio of the output to input powers for a particular intra-body distance. The spreading loss is due to the spreading of EM wave in the space and it can be quantitatively found using the expression

$$L_{\text{spr}}(f) = D_d\left(\frac{\lambda_r}{4\pi d}\right)^2 \tag{13}$$

where D_d is the directivity and effective wavelength $\lambda_g = \lambda/\mu'$, here μ denotes the tissue refractive index and defined in terms of its real part μ' and an imaginary part μ'' as follows:

$$\mu = \mu' + j\mu''. \tag{14}$$

Furthermotr, the directivity D_d is defined as the maximum gain of the nano-antenna and is mathematically define as the ratio of maximum power density $P(\theta, \phi)_{\max}$ and average power density $P(\theta, \phi)_{\text{avg}}$ observed in far field of an antenna and given as

$$D_d = \frac{P(\theta, \phi)_{\max}}{P(\theta, \phi)_{\text{avg}}}. \tag{15}$$

Using the relation provided in [74], one can find the final expression for directivity given as

$$D_d = \frac{4\pi}{\Omega_A} \tag{16}$$

where Ω_A is a solid angle is given as

$$\Omega_A = \int\int_{4\pi} P_n(\theta, \phi) = \int\int_{4\pi} P(\theta, \phi)/P(\theta, \phi)_{\max}. \tag{17}$$

Furthermore, this angle also depends on the specific radiation diagram of the source and antenna being used. For example, for a directional source with a narrow beam of width $\Delta\theta$, Ω_A is given as

$$\Omega_A = \int_{\theta=0}^{2\pi}\int_{\theta=0}^{\Delta\theta} \sin\theta d\theta d\phi = 2\pi(1 - \cos\Delta\theta). \tag{18}$$

2) Path Loss Due to Molecular Absorption: Molecules present in a standard medium are excited by electromagnetic waves at specific frequencies within the Thz band. An excited molecule internally vibrates, in which the atoms show periodic motion, while the molecule as a whole has constant translational and rotational motions. It must be noted that the Thz waves are nonionizing in which they induce vibration, but cannot break molecules. Due to this vibration, part of the energy of the propagating wave is converted into kinetic energy or, from the communication perspective, simply lost. Hence, molecular absorption is calculated by computing the fraction of the incident electromagnetic radiation that is able to pass through the medium at a given frequency. Using the Beer–Lambert law [75], attenuation due to molecular absorption for an EM travelling wave at a distance, d, is given by

$$L_{\text{abs}} = e^{-\mu_{\text{abs}}d} \tag{19}$$

where μ_{abs} denotes the attenuation coefficient, describes the attenuation due to absorption and it depends on the characteristics of medium [76]. Each molecule has a spectrum of absorption that can quickly change even for small wavelength

variations. The disruption of the medium optical uniformity can be expressed in the nonuniformity of the refractive index throughout the medium [77]. Hence, the attenuation coefficient due to the molecular absorption can be calculated using

$$\mu_{\text{abs}} = \frac{4\pi\left(\mu''\right)}{\lambda}. \tag{20}$$

Note that the imaginary term signifies to absorption and it vanishes for nonconducting particles [78]. The efficiency of a particle to absorb radiation can be expressed by the absorption efficiency

$$\eta_{\text{abs}} = \alpha_{\text{abs}}/\alpha_g \tag{21}$$

where α_{abs} is the molecular absorption cross section, and $\alpha_g = \pi r^2$ is the geometric cross section. Alternatively, molecular absorption can be evaluated from the absorption cross section, α_{abs}, and the particle concentration $\rho_v = k/((4/3)\pi r^3)$ with k is the volume fraction of the particle, as

$$\mu_{\text{abs}} = \rho_v \eta_{\text{abs}} \alpha_g. \tag{22}$$

3) Intrabody Path Loss Due to Scattering by Human Tissue: Any organism's body is a collection of many sorts of composites, such as cells, organelles, proteins, and molecules, with distinct geometries and configurations, as well as variable electromagnetic characteristics, when viewed at the nanoscale. Because of the deflection of the beam generated by microscopic nonuniformities in the human body, particle scattering has an impact on the propagation of electromagnetic waves. The size, shape, and refractive index of individual particles, as well as the wavelength of the incident beam, all influence this propagation phenomena [79]. The scattering mechanisms on small spherical objects are described by Rayleigh and Mie theories. Rayleigh scattering occurs when the diameters of the scattering particles are less than the wavelength of the propagating electromagnetic wave. Mie scattering, on the other hand, occurs when the particle sizes are roughly equal to the electromagnetic wave wavelength [80]. There is one more type of scattering known as geometric scattering, which occurs when objects are very large in comparison to wavelength [81]. All the Scatterings have their unique effects. The plane wave impacting on a scattered object located at the origin of a spherical coordinate system (r, θ, ϕ) is used to investigate the effect of scattering. The strength of a scattered wave is defined through intensity (I_{sc}) which is the most essential property. The intensity, I_{sc} is mathematically expressed as

$$I_{sc} = \frac{1}{(kr)^2} I_{in} S(\theta, \phi, \lambda) \tag{23}$$

where $k = 2\pi/\lambda$ is the wave number of the incident radiation, I_{in} is the intensity of incident wave, and $S(\theta, \phi, \lambda)$ is the scattering amplitude function. In general, $S(\theta, \phi)$ depends on the wavelength of the incident beam and on the size, shape, and optical properties of the particle [82]. The scattering function can be expressed in various ways and determined based on the specific application. Scattering functions have been more compactly expressed using basis functions, such as spherical harmonics, wavelets, and Zernike polynomials [83]. Furthermore, the scattering cross section and the scattering efficiency are also key parameters that are needed to characterize the scattering loss and defined in [84]. In brief, analogous to absorption, the scattering efficiency, η_{sc}, represents the ratio of the energy scattered by the particle to the total energy in the incident beam intercepted by the geometric cross section of the particle which is given as

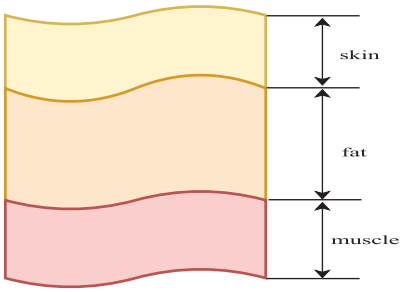

Fig. 8. Simple planar layered model for skin tissues of human body [88].

$$\eta_{sc} = \frac{\alpha_{sc}}{\alpha_g} \tag{24}$$

where α_{sc} is known as a scattering cross section and mainly depends on the size of the particle. Furthermore, the scattering phenomenon can be differently modeled analytically, e.g., when the size of the particle is much smaller than the wavelength, the local electric field produced by the wave is approximately uniform at any instant. This applied electric field induces a dipole in the particle. The induced dipole oscillates because the electric field oscillates, and the dipole, according to classical theory, radiates in all directions. This type of scattering is called *Rayleigh scattering* [85]. The scattering efficiency factor for a small sphere with complex refractive index n absorption is given by [86]

$$\eta_{sc}^{\text{small}} = 2.66\psi \times \text{Re}\left(\frac{n^2-1}{n^2+2}\right)^2 \tag{25}$$

where $\psi = 2\pi r/\lambda_g$ is a dimensionless size parameter of the particle. Now following a similar method as before, we can now obtain the scattering coefficient for small particles as

$$\mu_{sc}^{\text{small}} = \rho_v \eta_{sc}^{\text{small}} \sigma_g. \tag{26}$$

On the other hand, the type of scattering is done by biological cells, i.e., scattering by large particles can be studied using van de Hulst approximation [86]. Now the extinction energy, or total energy removed from the incident beam, is equal to the sum of the energy scattered and absorbed. In [87], the expression for extinction efficiency is given as

$$\eta_{\text{ext}} = 2 - \frac{4}{l}\sin l + \frac{4}{l^2}(1 - \cos l) \tag{27}$$

where $l = 4\psi r(n-1)/\lambda = 2(n-1)\psi$ represents the phase delay of the wave passing through the center of the particle, $\psi = 2\pi r/\lambda_g$ is the dimensionless size parameter of the particle, and $\eta_{sc}^{\text{large}} = \eta_{\text{ext}} - \eta_{\text{abs}}$.

When we talk about the Thz penetration inside the organisms, the scattering from various components can be seen in the an organism's blood. The blood is composed of various components (see Fig. 8). Blood plasma is the liquid component of the blood and is a mixture of mostly water (up to 95 by

volume) and tiny particles of liquefied protein, glucose, minerals, and so forth. It also holds various types of blood cells in suspension, which are considered the larger particles of the blood, namely, platelets (2 microns in diameter), red blood cells (7 microns), and white blood cells (up to 20 microns). We can now obtain the scattering by large particles as

$$\mu_{sc}^{\text{large}} = \rho_v \eta_{sc}^{\text{large}} \sigma_g. \tag{28}$$

One of the most critical parameters that should be examined to evaluate the quality of any communication system is noise After discussing various path-loss models of Thz communication systems, we now enlist the noise-models that is indispensable for the analysis for Body-Centre Thz Propagation.

4) Thermal Noise: The chances of the presence of front-end noise within any communication system are always high, which degrades the performance. Such a type of noise arises mainly due to the thermal agitation of electrons in electronic devices, such as mixtures or detectors and transistors and called as thermal or Johnson–Nyquist noise [89]. Any component in the system that dissipates power generates thermal noise and in an ideal resistor it is approximately white, i.e., the power spectral density (PSD) is nearly constant throughout the frequency spectrum. Random electron motion produces noise voltage, $V(t)$ when a resistor R is at temperature T at the open terminals. With the central limit theorem, $V(t)$ has a Gaussian distribution with a root mean square (rms) voltage of [89]

$$V(t) = \sqrt{4k_b \text{TRB}} \tag{29}$$

where k_b is the Boltzmann constant, and B is the bandwidth of the measuring system.

When a metallic resistance R is at temperature T, random electron motion produces a noise voltage $V(t)$ at the open terminals. Consistent with the central-limit theorem, the PDF of the noise voltage, V_{rms} follows the normal distribution with zero mean as

$$f(x) = \frac{1}{V_{rms}\sqrt{2\pi}} \exp\left(-\frac{x^2}{2V_{rms}^2}\right) \tag{30}$$

where variance of the above PDF is given as

$$\sigma_n^2 = \frac{2(\pi k_b T)^2}{3h} R \ \ \text{V}^2 \tag{31}$$

here h is a Planck constant. Now the mean square spectral density of thermal noise is given as [89]

$$G_v(f) = \frac{2Rh|f|}{e^{\left(\frac{h_f}{k_b T}\right)-1}} \ \text{V}^2/\text{Hz} \tag{32}$$

here f is an operational frequency and other parameters are already defined before. However, the above expression can be approximated for lower frequencies as

$$G_v(f) = 2RkT\left(1 - \frac{h_f}{k_b T}\right) \ \ |f| << \frac{kT}{h}. \tag{33}$$

We can also find the available spectral density using maximum power transfer theorem as

$$G_a(f) = \frac{G_v(f)}{4R}. \tag{34}$$

In this way, the thermal agitation of the charge carriers inside the electronics devices (nano transceivers in our case) is the first source of noise which can find in any in-vivo WiCom system. Note that the Gaussian distribution of the thermal noise is developed based on a model detector containing a considerable number of independent receivers which produce a tiny contribution to the resultant amplitude. The convolution of a large number of elementary distributions approaches a Gaussian distribution even though the elemental distributions themselves may be nonGaussian and all different. In addition, one must remember that the distribution of a thermally excited mode results from a large number of independent statistical forces acting on it at random. The resonant mode model was chosen to easily integrate the quantum effects in the analysis [90].

5) Black-Body Noise: It is well known that the physical body with a temperature above absolute zero radiates some energy. This process is in the ideal case described by the black body radiation or Planck's radiation law. According to Planck's radiation law, the energy released by a black body having temperature T has a spectral density [91]

$$I(f, T) = \frac{2hf^3}{c^2} \frac{1}{e^{\frac{hf}{k_B T}} - 1} \tag{35}$$

where c is the speed of light in the vacuum. From this equation, we can see that more radiation will be there at every wavelength for a higher temperature of a body. Due to the EM radiation of nano-antennas, the human body particles grab part of the EM energy. As a result, the absorbed power will activate the vibration of the particles, which result in heat generation and temperature increase. The intrabody medium could be characterized as a black body since it is associated with a temperature above absolute zero. Even without signal transmission, the intrabody channel always has background noise. Thus, the noise is produced from the black body source with power P in small volume dv as

$$P = I(f, T) A_{\text{eff}} \Omega_A dv \tag{36}$$

where A_{eff} is the effective aperture area defined as $A_{\text{eff}} = (\lambda_g^2/4\pi)$, and Ω_A and λ_g are the solid angle and effective wavelength defined in the earlier section.

6) Langevin Noise: Another type of noise observed at the molecular level due to the internal oscillations results from the cells' random and irregular velocity experienced by the intrabody system. The irregular motion of suspended particles, referred to as the Brownian motion, deals with mesoscopic dynamics, ubiquitous in the micro and nano-world, particularly in the soft and biological matter [92]. For such a scenario, the analysis could be modeled using the Brownian particle equations of motion, referred to as Langevin equations, given by [92]

$$m\frac{dv(t)}{dt} = -\zeta v(t) + \kappa(t) \tag{37}$$

where ζ known as drag constant or friction coefficient and described using Stokes law as $\zeta = 6\pi\eta r$, and $\kappa(t)$ denotes the random force signifies the force due to the rapidly fluctuating part.

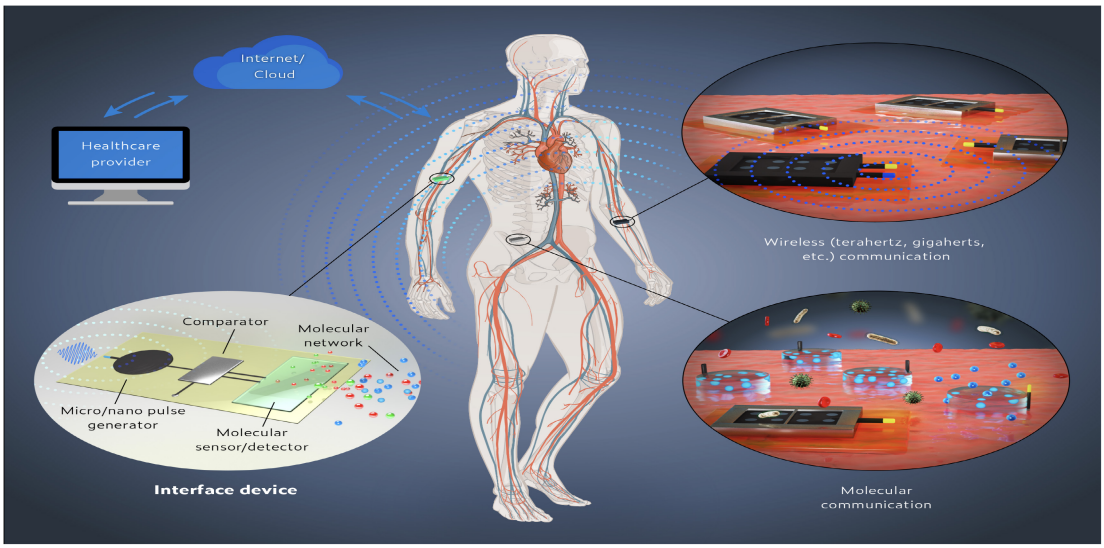

Fig. 9. IoENT: Demonstration of interfacing of MC with the WiCom systems (e.g., Thz, HBC, or AC) for health care application using body implanted bio-interface devices. The interface also responsible to send the health related information to health care provider through the Internet.

The changing velocity of the transmitter nanomachines result in Doppler shifts to the transmitted frequency of light originating from a source moving in relation to the receiver nanomachines. Let $R(f,t)$ be the resultant received signal at frequency f and time t of many plane wave each shifted by the Doppler component appropriate to the particle motion relative to the direction of plane wave. $S(f)$ is the PSD of $R(f,t)/\sqrt{2}$ [72].

Thus, similar to mobile-radio reception, both the in-phase and quadrature components at any given time, t, are independent Gaussian random variables with the following PDF [72]:

$$f(x) = \frac{1}{\sqrt{4\pi\sigma^2}}\exp\left(\frac{x^2}{2\sigma^2}\right) \tag{38}$$

x in this case is the in-phase component of $R(f,t)$ and σ is the RMS value given as

$$\sigma = \sqrt{\int_{-f_m}^{f_m} S(f)\ df}. \tag{39}$$

As the body is composed of many cells, particles, etc., the number of received plane waves and, thus, multipath components is significant. The central limit theorem indicates that the channel response mimics a Gaussian process. Since Doppler shift noise is dependent on signal transmission, this noise element follows a Gaussian distribution [72].

B. Literature of Other In-Vivo Compatible Communication Systems

There are few more systems that show the possibility to be interfaced with the MC system. HBC is a nonradio-frequency approach of wireless BAN, wherein the human body is used as a communication medium in two coupling ways known as: capacitive and galvanic coupling. HBC is a widely explored method in the literature and in full development, given a large number of scientific publishing works depending on different setups and equipment.

When a physical object vibrates rapidly, a sound is produced which disturbs nearby air molecules (or another surrounding medium) and generates compression waves that travel in all directions away from the source [25]. There are various types of AC systems that can be found in the literature as underwater AC, AC in aquatic animals, AC in fish, auditory animal communication, and human speech bird vocalization [93]. Sound serves as a very useful communication modality. The sound waves can be made to vary in frequency, e.g., high pitch or low pitch, amplitude (loudness), and periodicity. Together, these three variables can construct an extremely wide and complex range of signals, for instance an insect's mating call to human speech and vocal music. Since sound waves propagate rapidly via the air about 0.331 km/s, acoustic signals can be quickly started, stopped, or altered to send a time-sensitive message.

V. Interfacing of MC With Other Communication Systems

A. MC and Thz Communication Systems

Our main focus in this article is to discuss various aspects related to transmit the information transmission form inside the body to out of the of the body without harming healthy tissues. It has been known that MC setup is best suitable to be placed inside the organisms due to its biodegradable nature. The information from inside the body can be sent out of the organisms through the interfacing of an MC and a WiCom systems. The concept of MC and Thz communication has been discussed [94]. The fundamental block level diagram is shown in Fig. 9, in which when a sufficient number of MMs reaches molecule detector, a threshold potential difference builds up across the detector. This voltage is sensed by the comparator and its output become 1. The comparator output basically acts as a switch of a nano-pulse generator. When the output of the comparator becomes 1, the generator is switched on and a nano pulse is transmitted through the nano-antenna. The nano-pulse generator can be implanted on a single complementary

metal-oxide-semiconductor (CMOS) chip [95]. In [96], it is shown that the by induced protein interactions, the molecular diffusion process could be assisted in several ways. On the one hand, reactions can proceed more rapidly without an increase in the reactant concentration or metabolic effort. On the other hand, reactions presenting difficult molecular procedures under diffusion may be made feasible by invoking resonances, thereby opening up new metabolic pathways to cellular processes.

B. MC and AC Systems

Acoustic propagation introduces slight pressure variations in the fluid or solid medium, which could satisfy the Helmholtz equation when the time dependence is considered [97]

$$\nabla^2 p(x) + k^2 px = 0 \tag{40}$$

where ∇^2 is the Laplace differential operator and $k = (\omega/c) + i\alpha$ is the complex-valued wave vector with c as the sound speed in the medium and α as the attenuation coefficient of the sound wave in the medium, which is different from medium to medium. By solving (40), the sound pressure can be obtained to describe the sound wave propagation in the medium, where the source of the sound is the motion of the surface in the nano-robot. The behavior of the nano robots is relevant to their physical properties, surrounding medium and the working frequency. The feasibility of *in-vivo* ultrasonic communication is evaluated in [98], where communication effectiveness, power requirements and effects on nearby tissue were examined on the basis of discussion on the principles. And an isolated robot, shown in [7, Sec. 2.5] and an aggregated robot were designed to use in blood vessel, whose size is around 10 μm. Later, the nanoscale opto-ultrasonic communications in biological tissues was discussed in [99], where the generation, propagation model were studied and inline with [98], the hazards and design challenges were investigated.

C. MC and HBC

Power constraints are the key factor when we talk about data transfer to or from the human body through wearable or implantable healthcare monitoring devices. Low power transmission plays a vital role not only in avoiding information leakage or interference with other body-area networks but also in saving power. This is especially true for implantable devices, as the leakage of important information (e.g., pacing speed and pacing threshold setting of pacemaker) to the unintended receiver will lead to life-threatening events. Furthermore, low transmission power is very important as it can also be compatible with the human body. It has been widely studied that an MC system is not only a power-efficient communication system but also a bio-compatible system [100]. Thus, one of the possible proposals is to add the MC systems in between the HBC devices so that they can assist the existing HBC systems that may enable the low power budget transmission system. Moreover, by introducing an MC system in HBC, and thereby limiting the number of electrical devices in the human body the harm-full side effects can also be nullified.

VI. Research Challenges in Interfacing of MC and Other WiCom Systems

A. Devices for Interfacing

To send the in vivo information to the remote server/monitoring unit, as shown in Fig. 9, molecular to WiCom interface nanoscale devices are required. At the perimeter of any molecular-WiCom network, nano-devices/biosensors can be placed to detect and measure molecular signals which then can be forwarded to the bio-cyber interface. These biosensors can detect both physical and the subject of interest (i.e., the environment or cells) and convert it to a signal understood by the bio-cyber interface. Healthcare platforms, such as point-of-care diagnostics, have been built using nanoscale biosensors to enable more rapid detection of diseases [101]. These devices are often comprised of electrochemical biosensors that would detect chemical signals (e.g., biomolecules) and convert them into electrical signals that can be further stored in the platform's memory and produced as the result of the chemical measurement [102]. Besides using electrochemical sensors to detect biomolecules, biosensors can be designed using engineered whole cells at the individual or population level [103]. These whole-cell biosensors provide a simple and cost-efficient solution for detecting and measuring a wide range of analytes, if compared to the electrochemical sensors, including physical and biochemical signals (e.g., temperature and pH, respectively). Whole-cell biosensors are designed using artificial biology. Artificial biology is a formal method for creating artificial systems using biological components. They can be involved to detect and treat cancers, assess the health risks associated with environmental pollution, and discover novel antibiotics.

Graphene can also be utilized in molecular-to-electrical, as well as in electrical-to-molecular transduction [104]. Field effect transistor-based biosensors made of functionalized graphene is promising in the transduction of biomolecular concentrations, e.g., present in the blood, saliva, and tissues [105], [106], into electrical signals. There also exist porous graphene structures, which can be utilized as a membrane in drug reservoirs that can selectively release particular types of molecules through controllable pore sizes [104]. In addition to GRMs, transition metal dichalcogenides (TMDs) are also emerging 2-D layered materials offering great potential for intermodality transduction [107]. A particular member of TMDs is Molybdenum disulfide (MoS2), which has attracted great attention because it is electrically and mechanically robust. In this direction, various applications of MoS2 have been documented including highly susceptible molecular-to-electrical conversion [108] and optical-to-electrical conversion [109], and electro-optic modulators [110]. Black phosphorus (BP), which is another class of 2-D materials with applications in optical detection and modulation, and molecule sensing [111], can be potentially utilized in intermodality transduction.

B. Mobility of Bio-Nanomachines

The devices inside the organisms can change their positions due to the concentration gradient between different points or drift of the channel [112]. A lot of study have been done in

the context of MC setup and different mathematical models have been exploited [42], [113], [114]. When we talk about the interfacing of MC with macro world WiCom devices, it will become more challenging, as the mobile devices inside the organisms searching for the target want to communicate the information through the interface, the mobile devices affects the accuracy of systems performance [115]. To overcome these issues, the possible ways are implementation of localization and positioning algorithms in the MC systems so that the external devices out of the organisms can reliably communicate with internal devices [116]. The localization for mobile devices can be made in two steps, ML estimation can be used and already suggested in [117]. It can be done in two steps; first, the releasing distance is estimated by the observation of the number of received ICM at the RX. And in the second step, the estimated releasing distance is used as an observation to estimate the initial distance by ML estimation [117]. Note that in [117], it has been shown the initial distance can be estimated accurately even though the Tx and Rx are mobile.

C. Inter and Intrabody Synchronization of Devices

The synchronization of devices inside the organisms is a vital factor that affects the performance of the complete communication system. There are various works in the literature that have raised and discussed the synchronization issues in the MC [118], [119], [120], [121], [122]. These works have focused on synchronization among the devices that are implanted inside the body named as interbody synchronization. Despite of several existing work discussed the interbody synchronization, its indispensable to consider the intrabody synchronization for IoBNT applications. The intrabody synchronization is one in which the bio-devices implanted inside the organisms would be synchronized with the other WC devices placed out of the organisms. There are several works that have dealt with the intrabody synchronization issues (e.g., [123] and [124]). In [123], an use of integrated single-lead ECG sensors for the detection of artificial synchronization signals, induced into and propagated throughout the human body. The article [124] proposes a high data rate ultrasonic communication scheme for wireless intrabody networks. This is still challenging and interesting for researchers to find the synchronization methods and various issues associated with it for intrabody communication considering the interfacing of MC with the other communication methods.

D. Energy Constraints

Varying environmental factors and dynamically changing application requirements demand flexibility and adaptation for keeping reliable communication and constant energy harvesting (EH), concurrently. Along with the various energy-efficient methods, such as modulation and detection techniques for effective communication, there is a self-sustainable method known as EH, which can also be embedded during the interfacing of MC with the other WC methods. Recently, the research on EH has widened partially due to the requirement of adequate energy for emerging IoENT applications. The EH methodologies need to be more potent, persistent, and self-sustainable, considering various changing environmental factors for different applications. By reducing the impact of unanticipated and uncontrollable factors, i.e., the uncertainties, the self-sustainable communication networks in the IoENT can be implanted.

Depending on the specific environment and system architecture, various energy sources can be used by the IoENT devices [125]. For example, solar power, flow energy, vibrations, electromagnetic signals, and metabolic sources have been deemed viable for harvesting [126]. There is also the possibility of a hybrid EH technique for the continuous functioning of IoENT devices which has been already proposed in [125] and [126].

The ability to reconfiguration and adaption of tunable devices in varying environmental conditions opens the door for the implementation of such systems in particular. That is, it can provide seamless coverage and uninterrupted operation everywhere. There exist a number of communication technologies, each of which has various advantages and disadvantages for a particular application or an environment (see Table I).

E. Channel Sensing and Spectrum Allocation

For better adaptivity of different devices in IoENT, channel sensing is a substantial phenomenon. For the adaptive and opportunistic selection of the appropriate communication modality along with an industrious tunning of transmission and reception attributes, dynamic channel sensing in multiple modalities is required. The sensing that is capable of tuning the IoENT devices at a greater extent is known as broadband sensing. For example, in an MC system having various types of molecules is required for bio-compatibility. Similarly, for the Thz communication, an extremely wide range of frequencies is required for dynamic tunability [127]. The Thz integrated sensing and communications (ISAC) paradigm envisages a single integrated hardware platform with a common signaling mechanism is already discussed in [128]. Moreover, channel sensing techniques have been widely explored for acoustic communications [129]. For the MC system, the investigation has been begun for channel sensing considering various unstable channel conditions [130], [131].

VII. Conclusion

The nanoscale communication for critical health and environmental monitoring applications is a rapidly growing research area viewing its practical boundaries. One of the conceivable suggested technologies is IoENT. Through this work, we demonstrated the various aspects of interfacing MC with other nano-communication systems, such as HBC, AC, and Thz communication systems in the context of IoENT. Moreover, we have also highlighted eclectic possibilities and various issues related to the applications of IoENT. First, we explored each of the nano-communication systems in detail by showing their mathematical frameworks. Furthermore, in succession, we have enlisted and described different modes to interface MC with other nano-communication systems. In the end, we have also discussed various potential challenges and probable future objectives, e.g., compatibility of

devices, mobility of devices, synchronization aspects, etc., in the context of interfacing of diverse technologies.

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