Fundamentals of Molecular Information and Communication Science

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***Abstract*—Molecular communication (MC) is the most promising communication paradigm for nanonetwork realization since it is a natural phenomenon observed among living entities with nanoscale components. Since MC significantly differs from classical communication systems, it mandates reinvestigation of information and communication theoretical fundamentals. The closest examples of MC architectures are present inside our own body. Therefore, in this paper, we investigate the existing literature on intra-body nanonetworks and different MC paradigms to establish and introduce *the fundamentals of molecular information and communication science*. We highlight future research directions and open issues that need to be addressed for revealing the fundamental limits of this science. Although the scope of this development encompasses wide range of applications, we particularly emphasize its significance for life sciences by introducing potential diagnosis and treatment techniques for diseases caused by dysfunction of intra-body nanonetworks.**

***Index Terms*—Intra-body nanonetworks, Information science, ICT-based diagnosis and treatment, Molecular communication, Nanonetworks**

I. Introduction

INFORMATION science is an interdisciplinary field that deals with collection, analysis, storage, transmission, and dissemination of information, while the communication theory is a subset of information science that deals with the principles and methods of information transfer between two entities. This fundamental field has shaped the current communication networks over decades.

With the recent advancements in nanotechnology, things are quickly moving from traditional communication architecture to micro and nano scales. Nanotechnology is one of the frontiers of the scientific research in the current age, and it has a huge set of applications in a variety of environments. Some of these include bio-hybrid systems [1], nanoscale sensing [2], intelligent drug delivery [3] and body area networks (BAN) [4]. Although nanotechnology promises a big revolution in the future, the implementation challenges are also huge. Due to their simple architecture, consisting of a small number of molecules along with power and size limitations, nanomachines have scarce processing, memory and networking capabilities. These limitations can be overcome by dense deployment of nanomachines in networked environments, termed as *nanonetworks*.

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Different communication paradigms are suggested for the physical realization of nanonetworks such as nanomechanical, acoustic and electromagnetic. However, the most promising one is molecular communication (MC) [5], where molecules are used to encode, transmit and receive information.

MC systems exist in nature and have evolved over billions of years. These systems can be found all around and within us. Understanding this molecular signaling among living cells from information and communication theoretical (ICT) perspective provides an insight into the ICT-based fundamentals of biological systems as well as inspiration for developing novel nanonetworking techniques.

MC is radically different from traditional communication in various aspects such as the sizes of network entities, information transmission mechanisms, noise sources and fundamental performance limits including transmission delay, achievable data rates, coverage and power. This calls for laying down the foundation of the emerging field of molecular information and communication science. Therefore, the aim of this work is to analyze the existing literature on intra-body nanonetworks and MC techniques to introduce the fundamentals of MC and propose future directions. At the same time, this paper emphasizes on the significance of ICT in life sciences. This enables the development of ICT-based models of disease affected intra-body nanonetworks that can be used to get deeper insight into the disease as well as augment the existing diagnosis and treatment techniques.

Fundamental steps to thoroughly investigate and formalize the science of molecular information and communication are given in Fig.1. In this work, we analyze the literature for existing contributions in each of these steps to propose future directions. Therefore, the rest of the paper is organized as follows. In Section II, we present the state-of-the-art research and open challenges to model intra-body nanonetworks to extract possible MC paradigms. Then, in Section III, we discuss ICT-based characteristics of different MC techniques existing in literature. In Section IV, we propose potential applications of ICT-based bio-inspired nanonetworks in life sciences for diagnosis and treatment of diseases. Finally, we summarize the main aspects of this paper in Section V.

II. Intra-body Nanonetworks

In this section, we review the existing work that proposes ICT-based models of the MC in intra-body nanonetworks such as nervous, cardiovascular and endocrine systems. Moreover,

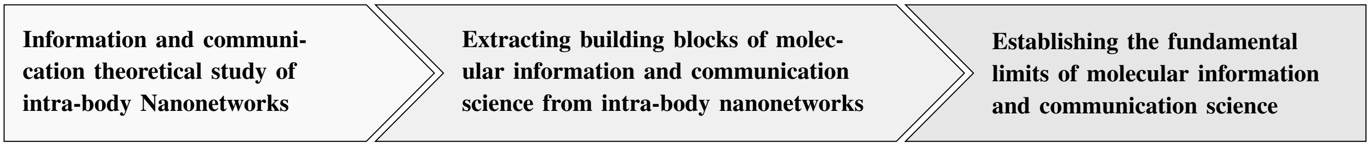


Fig. 1: Framework to formalize the *science of molecular information and communication.*

we highlight some key open issues in the communication-theoretical modeling and analysis of these nanonetworks.

A. Nervous Nanonetwork

Nervous nanonetwork is an ultra large-scale network of neurons gathering and transmitting information between different parts of the body. The communication between neurons takes place through chemical as well as electrical signaling referred to as neuro-spike communication [6].

As depicted in Fig.2(a), a general neural signaling pathway consists of three basic structures; a pre-synaptic neuron, a post-synaptic neuron and a gap between these neurons called synaptic cleft [6]. The information encoded in electrical impulses passes through the axon of a pre-synaptic neuron that conveys this information by releasing neurotransmitters, special types of chemical molecules, into the synaptic cleft. These neurotransmitters then diffuse though the synaptic cleft to be received by the post-synaptic neuron. The physical channel model of this single-input single-output (SISO) neuro-spike communication is given in [6] and the effect of inter-symbol interference on the achievable information rate of the SISO channel is studied in [7]. In reality, there exist multiple synapses between any two neurons, therefore, multiple-input single-output (MISO) communication model is modeled in [8]. Moreover, SISO and MISO synaptic interference channels are investigated in [9].

Although complete neuro-spike communication channel is considered in [6] and [8], there are other studies that analyze the subcomponents of this channel. For instance, a trade-off between information rate and energy efficient transmission is examined within the axonal channel in [11] and a realistic model for vesicle release, which involves the effects of action potential (AP) width variation is proposed in [12]. Moreover, a receiver design in nervous network considering the variability in the anatomy of dendrites is given in [13].

Neuro-spike communication has also been analyzed in the networked environment. An optimization problem for neuronal time division multiple access (TDMA) is formulated in [14], in order to find optimum scheduling. A queueing model for nervous nanonetwork is also proposed in [15], which identifies the delay of network of neurons.

The nervous nanonetwork is an optimum information processing system with respect to energy efficiency rather than the information capacity alone [16]. The information collected from environment by intra-body nanosensor networks is encoded, processed and transmitted by nervous system to corresponding organs. Several studies have been published to estimate these encoding mechanisms, such as, considering the discrete binary and frequency coding, interspike interval codes [17], and rate and interspike interval decoders [18]. On the other hand, in studies such as [19], stimulus response curves are fitted to input-output relationship of neuron with respect to information theoretical parameters. However, more efforts are required to reach the efficiency of neural encoding and decoding mechanism.

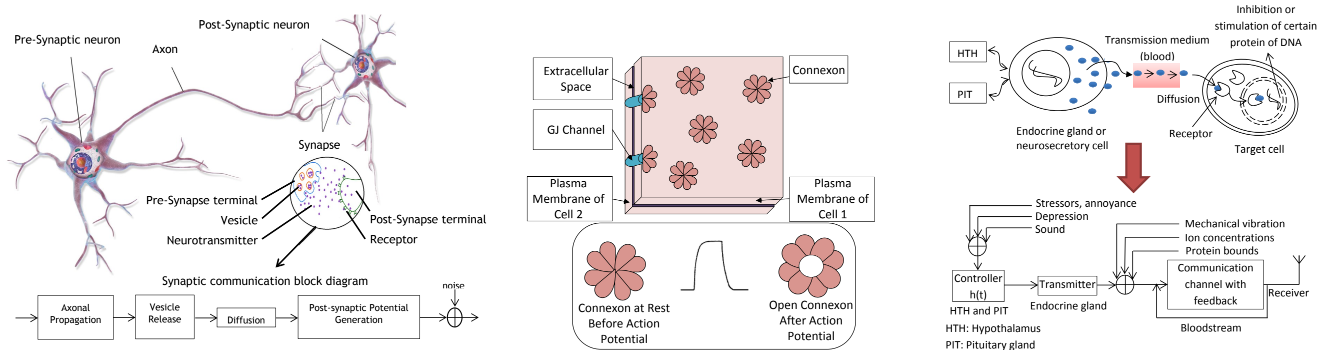
Moreover, information capacity of nervous nanonetwork needs to be quantified in order to implement ICT-based solutions of critical diseases of nervous system. A simple synaptic channel is proposed and analyzed from information theory perspective in [20] to derive the lower bound on capacity. In another work, the correlation among pre-synaptic terminals is suggested to improve information rate [8].

All of the existing models of nervous nanonetwork use over-simplifying assumptions, hence, more comprehensive studies and experiments are needed as listed below.

- ***Realistic models with experimental verification:*** Accurate ICT-based models including effects of AP shape variation, reuptake phenomenon in synapse modeling, and synaptic plasticity are required. Additionally, comprehensive experimental studies are needed to validate the models.
- ***Identifying fundamental characteristics of the model:*** After proposing a complete model, information-theoretical studies are needed to extract and quantify the fundamental characteristics.
- ***Networking paradigms:*** Detailed investigation of networking parameters is required to extract efficient routing algorithms, addressing mechanisms and medium access techniques from nervous nanonetwork.
- ***Energy efficient coding:*** Extracting energy efficient encoding and decoding techniques from these nanonetworks would be a milestone in building the foundations of molecular information and communication science.

B. Cardiovascular Nanonetwork

Two most important types of cells within the heart are the *cardiomyocytes* and the *cardiac pacemaker cells* [21]. Cardiac pacemaker cells are distributed throughout the heart and are responsible to spontaneously generate and propagate APs to cardiomyocytes, which, in turn, create the beating motion of the heart. Cellular bridges form porous gap-junctions (GJs) between the various types of heart cells providing a medium for AP transfer [22]. Two cells connected in the GJ by means of channels called connexons are shown in Fig.2(b). Connexons remain closed in the rest state, however, when an AP arrives, they open and yield an ion diffusion towards the



(a) (b) (c)

Fig. 2: Intra-body molecular communications (a) Neuro-spike communication, (b) GJ communication; the AP causes the connexon channels to open, starting diffusion between the cells, (c) The endocrine nanonetwork [10].

receiver cell, thus causing the AP to be carried forward to the next cell. Generic GJ communication is studied in [23].

GJ channel is modeled from the information theoretical perspective in [24], where a probabilistic physical channel model is provided with a probability mass function for GJ conductance considering the possibility of AP propagation failure. A closed-form expression for channel capacity and correlation between the decrease in capacity and several heart diseases is studied.

More studies are needed to provide foundations for an ICT-based model of cardiovascular molecular nanonetwork. Some open directions are listed bellow.

- ***Experimental verification:*** Assumptions about the independence between calcium release units and membrane potentials require verification by experimental studies that can shed light on the actual capacity of the cardiovascular system, determining the limits of capacity and rate functions for the healthy system.
- ***Large-scale model:*** Physiological studies to find the range and reliability of propagation as well as investigation of networking and routing mechanisms of APs through the heart are needed to consider the contribution of individual cells towards the whole organ.

C. Endocrine Nanonetwork

The endocrine system comprises a set of glands that secrete different hormones through the circulatory system to their recipient cells [25]. Transmission of hormones depends on concentrations of various materials sensed in tissues. The required amount of hormones are then added to the blood stream by the endocrine system to maintain homeostasis in the body [26]. The propagation of hormones depends on blood circulation and Brownian motion within the blood stream [5]. Reception of the hormones is selective because only the target cell can respond to a hormone.

Modeling of entire endocrine system from an ICT perspective is an open research area with huge implications, however, very few studies are present in this field to date. Hormones are considered as modulated molecular information carriers in the model of endocrine nanonetwork in [10]. The suggested framework is shown in Fig.2(c), where various stimuli cause the Hypothalamus to signal the release of hormones to blood. A queueing theory-based insulin mediated GLUT 4 translocation model is present in [27]. Bidirectional communication between neuroendocrine and immune systems is discussed in [28]. In [29], bacteria-to-host communication via hormones is shown. Communication by means of milk borne hormones between the mother and the suckling is proposed in [30].

Further research is needed to explore the modeling of endocrine nanonetwork in the following directions:

- ***ICT-based parameters:*** Key ICT-based parameters such as channel capacity, end-to-end delay, feedback weights, noise sources, synchronization, networking of subsystems are yet to be modeled for endocrine nanonetwork.
- ***Intra and inter-body networks:*** Potential of the endocrine nanonetwork as a connection between separate intra or inter-body networks also needs to be explored.

III. Science of Molecular Information and Communication

MC is radically different from conventional electromagnetic communication, as it uses particles to carry information, thus, imposes a need for reconsidering the communication and information theories and tools with a new perspective. Therefore, in this section, we review various MC approaches present in the literature and introduce a framework to establish the fundamental limits of molecular information and communication science.

A. Molecular Communication Approaches

1) Diffusion-based Molecular Commmunication: Communication inside human body is mostly achieved by diffusion of molecules, for example, calcium signaling among living cells, synaptic communication in neurons, and intra-cellular communication between different cell organelles. A general physical model of diffusion-based MC is depicted in Fig.3(a). It can be categorized into analog and digital communication similar to conventional communication systems [31]. A fundamental

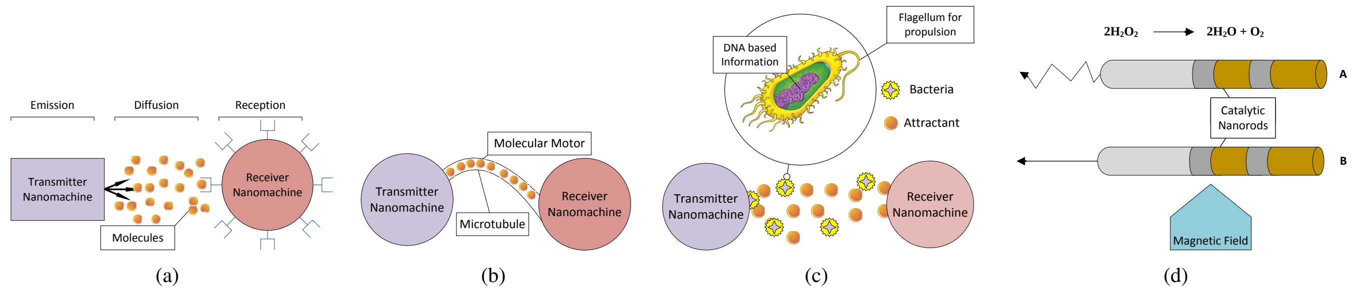


Fig. 3: Molecular communication paradigms. (a) Diffusion-based MC (b) Wired active MC using a microtubule. (c) Bacteria-based wireless MC. (d) Catalytic nanorods in hydrogen peroxide solution without and with applying a magnetic field applied (A) and (B), respectively.

analog communication model is proposed in [32], where information is encoded by continuously emitting molecules with varying concentration. In digital diffusion-based MC, information is encoded into either types of molecules [33], release time of molecules [34] or the intensity of concentration of molecules [35]. Different digital modulation techniques for diffusion-based MC are proposed in [33].

To develop a communication network, it is necessary to develop a physical model and analyze its ICT-based parameters to achieve reliable and efficient communication. We can find various models of diffusion-based MC in the literature. One such model is proposed in [31]. Another model, where particles are released into fluid medium with drift is studied in [34]. Some receiver designs are presented in [36], [37], [38].

One of the most important issues in developing diffusion-based MC is residual molecules from the previous transmission which are considered as noise. Various approaches are suggested to reduce this noise and maximize the rate of information in [39]. Moreover, the information capacity of the channel with residual molecules is studied in [40] by modeling it as *channel with memory*. Other external noise sources and ISI are modeled in [41] and the effect of interference on digital modulation techniques is studied in [42].

Although a significant body of work exists on diffusion-based MC, more research in the following directions is needed.

- ***Shadowing effect:*** Existing models should consider more complex situations such as inter and intracellular environment, where shadowing effect needs to be addressed as it can become dominant due to the presence of obstacles.
- ***Effects of asynchronism:*** More realistic assumptions should be considered about the structure and function of transmitter and receiver and effects of asynchronization between them, as asynchronism causes large delays and reduces the information transmission rate.
- ***Amplification:*** A concept of amplifier nanomachine should also be introduced to cater the problem of attenuation in concentration of molecules due to diffusion.

2) Wired Active Molecular Communication: Wired active MC between a transmitter and a receiver nanomachine is illustrated in Fig.3(b) where information molecules move along preset paths of microtubules to deliver the information from the transmitter to the receiver [43]. The flow of information can be self-propelled by molecular nanomotors as in Fig.3(b) or based on the flow generated by another system such as a blood circulatory system. Based on the assumptions of independence between particles, a simple mathematical model for analyzing information rate is derived in [44]. A Markov channel model with a mathematical formula for calculating transition probability matrix of the model is proposed in [45]. Design and optimization of the shape of a rectangular channel in [46] shows that channel capacity is proportional to the perimeter. A secure wired active channel is proposed in [47], where information molecules are encapsulated inside vesicles while transporting the information. Various approaches for self-organizing microtubule networks such as polymerization/depolymerization and molecular motors are investigated in [48]. Some directions for further studies are mentioned below:

- ***Particle interactions:*** Interactions between various particles traveling together in a microtubule and their effects on the overall model need to be identified.
- ***Channel characteristics:*** Effects of channel characteristics such as its width, shape and length on the model, require further investigation.

3) Wireless Active Molecular Communication:

a) Bacteria-based Wireless Active MC: A typical system of wireless active MC based on bacteria is shown in Fig.3(c). In this type of communication, first, a bacteria that only responds to a set of specific attractants is chosen as a communication vessel. A DNA-based message is then introduced in the cytoplasm of the bacteria and it is released in the environment. The bacteria propels itself towards the receiver using its flagellum in response to the release of attractant particles by the receiver as shown in Fig.3(c) [49]. Communication range, channel capacity, throughput and end-to-end delay analysis is done in [50] shows that bacteria-based communication has huge potential. A physical channel characterization and simulation tool are provided in [51]. Multi-hop communication based on conjugation and the use of antibiotics as message filters is proposed in [52]. Wet lab validations for bacterial conjugation for multi-hop communication are further provided in [53]. The problem of attractant scheduling for multiple transmitter-receiver pairs in close proximity is analyzed in [54]. A simulation tool for bacteria-based communication, BNSim, is introduced in [55].

b) Catalytic Nanomotor Based Wireless Active MC: Catalytic nanomotors are usually platinum or gold nanorod particles that are able to propel themselves and small information containing objects, by catalyzing the free chemical energy present in the environment [49] as shown in Fig.3(d). Without a controlling magnetic field, the nanorods move in arbitrary directions, however, once under the influence of a magnetic field, they can be forced to travel in specific directions. The speed of these particles depends on their dimensions as well as the atmospheric conditions [56]. Physical channel characterization and parameters such as packet delay and loss probability are presented in [57]. Methods for controling catalytic nanomotor direction are presented in [58].

Open directions for future investigation of wireless active MC include the following:

- ***Bacteria-type independent modeling:*** A definitive general model that can apply to a variety of bacteria-based communication scenarios as opposed to existing models for specific scenarios is required.
- ***Medium sharing:*** Scheduling and channel sharing in a multiple bacteria environment needs to be investigated.
- ***Information encoding:*** Developing methods for encoding information into DNA is also an open research direction.
- ***ICT-based parameters:*** Research on source coding techniques, channel capacity as well as networking capabilities of the systems will help improve the current models of wireless active transport.
- ***Biocompatability:*** Further research is required in the biocompatibility of catalytic nanomotors.

4) Physical Contact-based Molecular Communication: Nanocommunication via GJs and synapses are two possible kinds of MC via physical contact. In [59], a collision-based mobile ad hoc molecular nanonetwork (MAMNET) is proposed, which uses neuro-spike communication for transmitting information between two nanomachines. It is shown that the size and speed of nanomachines have a direct relation with the average throughput and a reverse relation with the average message delivery delay. Neurons are used as MC medium in [60]. A microplatform is designed in [61], which is able to pattern the mammalian cells into a predefined network connecting them trough GJs. These preliminary studies are samples of achieving the bio-inspired MC networks.

The open challenges in modeling bio-inspired physical contact-based MC systems coincide with the challenges in modeling of neuro-spike communication and GJ as stated in Section II.

5) FRET-based Molecular Communication: One particular example of molecular devices is the class of fluorophores, e.g., fluorescent proteins, which can be excited by optical and chemical stimuli, and relax to ground-state by releasing photons at visible wavelengths [62]. An excited-state fluorophore non-radiatively transfers its electronic energy state to a nearby ground-state fluorophore, if their optical spectra overlap. This nanoscale phenomenon is defined as the Förster resonance energy transfer (FRET). As proposed in [63], FRET can be exploited as a wireless MC method between functional fluorophores if the information is encoded into their electronic states. It is shown to enable reliable information transfer at exceptionally high rates, on the order of Mbps. A model for FRET-based MAMNET is provided in [64] consisting of sensor and actor fluorophores, which are promising for cancer diagnosis and treatment with single molecule precision.

TABLE I: The categorization of evaluation parameters.

Infrastructure and Physical Characteristics
Biocompatibility, Molecular dynamics, Molecular physics, Complexity, Electrical properties, Type of medium, Type and size of network nodes, Packet type/size, Information sources, Noise sources, Synchronization, Modulation types, Feasibility, Power consumption, Duplexing, Security
Communication Performance Characteristics
Energy per bit, Range, Capacity, Transmission rate, Signal attenuation, Reliability, Error rate, Delay
Networking Functionalities
Routing, Medium sharing, Addressing, Broadcasting, Medium access, Macro-nano interface

Although FRET is extensively studied from communication theoretical perspective, some new directions for further studies are provided below:

- ***Comprehensive analytical models:*** Literature mostly consists of numerical simulation results and lacks comprehensive analytical models that can fully capture the underlying quantum-mechanical processes and provide the fundamental limits such as channel capacity.
- ***Validation:*** Experimental work is currently conducted with ensemble of molecules [65], and thus, the validation of FRET-based communication between a single-pair of fluorophores is still an open issue.

B. Fundamental Limits of Molecular Information Science

Information theory deals with the problems of communication systems related to the following fundamental limits:

- Minimum number of bits necessary to represent an information
- Maximum transmission rate that achieves reliable communication over a noisy channel

These limits are established for conventional communication networks through meticulous research that sprang from the classical paper of Shannon on the theory of communication [66]. Since MC uses particles, i.e., molecules, instead of waves to represent and transmit information, the fundamental limits need to be revisited by taking into account the effects of certain physical and chemical phenomena, which are mostly related to information carrier and transmission medium:

- Size, type, structure, mobility and lifetime of information carriers
- Viscosity, heat capacity, thermal and electrical conductivity of medium

TABLE II: Qualitative and comparative evaluation of different molecular communication paradigms.

	Diffusion-based MC	**Microtubule-based MC**	**Bacteria-based MC**	**Catalytic Nanomotor-based MC**	**Physical Contact-based MC**	**FRET-based MC**
Carrier type	*Molecules*	*Molecules*	*Bacteria*	*Nanorods*	*Molecules*	*Excitons*
Duplexing	*Full-duplex*	*Half-duplex*	*Full-duplex*	*Full-duplex*	*Full-duplex*	*Half-duplex*
Biocompatibility	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*
Broadcasting	*Yes*	*No*	*Yes*	*No*	*No*	*Yes*
Routing	*No*	*No*	*Yes*	*Yes*	*No*	*Yes*
Medium sharing	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*

- Degree of affinity among network entities

Revealing the fundamental limits of MC, with a focus on the unique characteristics of the carriers and medium, would pave the way for the design of reliable and efficient MC systems for particular applications, and give a better understanding of the prevailing MC-based systems of human body. This, in turn, would enable the development of effective diagnosis and treatment techniques, as will be discussed with more detail in Section IV.

In the most general sense, rate, reliability, and energy requirements of any MC system can be defined and represented by the following fundamental limits:

- ***Minimum energy per bit:*** Inspired from the Landauer's principle that determines the theoretical limit of computational energy consumption, finding a minimum energy limit for communication independent of technology has been a long-standing goal of ICT research [67]. Considering the very elementary principles of communication evolved over billions of years in living cells, revealing the minimum possible amount of energy required to transmit one bit of information in MC could open up new horizons for the notion of energy efficient communication. The findings would shed light on the nature's strategies to overcome the energy limitation, which is one of the main challenges of nanonetworks. Energy per bit in MC is likely limited by the distance between sender and receiver, the affinity among network entities as well as the chemical properties of the medium and information carriers. In particular to diffusion-based MC, the limit can be expected to have an intimate relation with *the minimum number of molecules* required for reliable transmission of one bit of information. The same relation exists with *the minimum number of excitons per bit* in the case of FRET-based MC.
- ***Channel capacity:*** Channel capacity, which is the supremum of mutual information between the channel input and output, determines the maximum achievable rate that provides an error-free communication. Being the limit of reliability, the capacity metric incorporates the effects of noise and memory, which may have unusual characteristics in MC. For example, in diffusion-based MC, the discrete nature of information carriers and their Brownian motion impose the counting noise, which is usually termed as molecular or diffusion noise in the literature. Moreover, the long lifetime of carriers in the propagation channel leads to long-range spatial and temporal correlations, which should be accounted for in information theoretical models of MC. Therefore, channel capacity could be an invaluable metric for the efficient analysis of physiological data to diagnose human diseases intimately connected to these correlations. Additionally, revealing the capacity-achieving input distributions could enable the development of novel ICT-based treatment methods based on the effective stimulation of living cells with nanobiomachines through MC. This requires the design of optimum channel coding techniques exploiting the unique characteristics of MC.
- ***Bit error rate:*** Another noise-related metric is the bit error rate (BER), which is set by the relation between transmission rate and channel capacity. Detection errors imposed by the channel and reception noise and the intersymbol interference (ISI) resulting from the channel memory determine the extent of BER. The limit on the detection error is directly related to the number of independent samples that can be acquired in a given observation of the received signal [68]. For diffusion-based MC, this limit is set by the spatio-temporal correlations resulting from diffusion and reception processes. Thus, revealing the correlations in MC would help develop optimum detection schemes that minimize the BER. The designed schemes could be implemented in networks of nanobiomachines deployed for diagnosis and treatment purposes. Also, the errors resulting from ISI could be reduced by exploiting the lifetime characteristics of the information carriers.

C. Performance Evaluation of MC Paradigms

Although focus of this study is mostly on biological applications of the MC architectures described in this section, they also find a wide range of non-biological applications, such as those in military, industrial, and environmental contexts [69].

To select the most suitable architecture for a particular application, biological/non-biological, the MC architectures described here, should be evaluated based on the physical and information theoretical characteristics as categorized in Table I. Based on the review of previous work on different MC paradigms, we conclude that there are many open issues in each of these paradigms that remain to be investigated in order to quantify different ICT-based parameters that will, in turn, enable us to quantitatively evaluate these techniques. However, based on the existing literature, a fundamental qualitative evaluation using some basic physical characteristics and networking parameters of various molecular communication paradigms is given in Table II.

IV. Science of Molecular Information and Communication for Life Sciences

Understanding the fundamentals of molecular nanonetworks finds its major applications in life science, by paving the way for novel and more effective ICT-based diagnosis and treatment techniques for human diseases. This promising approach covers a wide range of research avenues ranging from revealing the correlation between diseases and underlying communication mechanisms to ICT-based abstraction of diagnosis and treatment techniques for improved efficiency. In this section, the potential of applying molecular information and communication science is investigated for various diseases.

A. ICT-based Understanding of Human Diseases

Based on the framework outlined in Fig.4, we propose the following fundamental approaches to develope ICT-based diagnosis and treatment techniques for human diseases:

- ***Revealing the characteristics of disease-affected intra-body nanonetworks*:** Detecting the correlations between diseases and underlying MC mechanisms could reveal unique ICT-based metrics that can be exploited by big data analytics tools to diagnose diseases in a more effective manner. Novel diagnostic tools, built upon nanonetwork simulation frameworks, could seamlessly incorporate ICT-based performance metrics to reduce the redundancy in large and heterogeneous medical data and speed up the identification of communication-related diseases. This unique perspective may also enable the development of new treatment techniques inspired by the existing or upcoming theories and tools in the information science.
- ***Developing biocompatible nanomachines*:** These nanobiomachines can be used to continuously monitor a certain mechanism inside the body, autonomously deliver drug to specific tissues or seamlessly connect to an intra-body nanonetwork and act as a part of that network to fix the detrimental effects of human diseases. Investigating the underlying MC mechanisms can determine optimum strategies for deployment and configuration of these nanobiomachines to effectively diagnose and treat the diseases.

In the following, we discuss certain diseases on which the ICT-based approaches could have unprecedented impact.

1) Nervous System Diseases: Nervous system may face a wide variety of diseases as a result of dysfunction of single neuron or their network. Here, we relate some of the nervous diseases to ICT-based parameters of nervous nanonetworks.

- *Alzheimer's disease*, which degrades the capacity of the brain to encode and retrieve memories, is a result of dysfunction and loss of synaptic communication [70].
- *Multiple sclerosis (MS)*, which decreases the information transmission rate, is resulted from destruction of myelin over axon of neurons [71].
- *Parkinson's disease* results from the death of dopamine producing neurons, which control the release of vesicle, an information carrier, in another set of neurons [72].
- *Amyotrophic lateral sclerosis (ALS)*, *progressive bulbar palsy (PBS)*, and *primary lateral sclerosis (PLS)* are common motor neuron disorders resulting from degeneration or death of the upper and/or the lower motor neurons. These diseases cause communication link failure in nervous nanonetwork, which degrades the ability of the brain to control essential muscle activity such as walking, speaking, swallowing, and breathing [73].

Moreover, the ICT-based models of nervous nanonetworks can be used in building neural implants which can connect to the neural pathway in case of communication failure between brain and a certain body part. For instance, currently researchers are able to control the movements of legs of a completely paralyzed rat, by externally stimulating the spinal cord [74]. In the same scenario, ICT-based understanding of nervous nanonetwork can enable us to receive and encode the signals from motor cortex to stimulate the spinal cord.

Another important application is the detection of the diseases related to blood brain barrier (BBB), which involves one of the most important and complex intra-body molecular communication channels and tightly protects the entry and exit of molecules to and from the central nervous system (CNS) [75]. Dysfunction of the BBB causes critical cellular damages that may lead to different types of neural diseases. Moreover, existence of these BBB prevents the entrance of drugs to the CNS, which makes the treatment of neural diseases difficult. Hence, in addition to providing diagnosis and treatment techniques for the resulted diseases from dysfunction of BBB, understanding the ICT-based fundamentals of these channels may help to develop effective drug delivery mechanisms for the treatment of diseases in CNS.

2) Cardiovascular System Diseases: Cardiac arrhythmia forms one of the most prevalent group of heart conditions that cause irregular heartbeat patterns in patients [22]. The detection of this whole set of disorders is based on standard

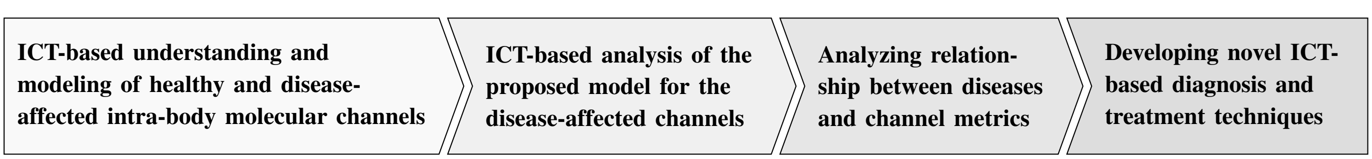


Fig. 4: Framework for developing ICT-based diagnosis and treatment techniques.

electrocardiographic techniques that are manually operated by a practitioner, and thus, prone to human error [76]. Therefore, modeling of these diseases may find ICT-based identification and treatment of these conditions.

3) Endocrine System Diseases: Several studies on biochemical processes of different hormones exist in literature, however, the largest body of literature exists on the insulin signaling within the body making it potentially the first target of an ICT-based study [77], [78]. In a recent work, a novel communication-based method of insulin mediated GLUT 4 translocation based on queueing theory is proposed in [27]. Type 2 diabetes occurs because of insulin resistance in tissue cells making them unable to use sugar effectively and leading to high blood sugar. Understanding the MC failure that reduces the sugar uptake even though the insulin receptors are present on the tissue cells can augment the existing diabetes diagnosis, treatments and management via insulin pumps.

4) Cancer: Not all of the existing intra-body MC systems are in accordance with our health. For instance, the cancer cells that grow out of control and spread to other body parts need to communicate with and receive support from cells named stromal cells [79]. If one can isolate the malignant cells from stromal cells, they would not grow anymore. Hence, understanding the mechanism of this detrimental MC system could provide a unique tool to interrupt the communications and stop the spread of cancer.

Cell-released extracellular vesicles (EVs), carrying a cargo of macromolecules, e.g., plasmid DNA and mRNA, are one of the main components of cell-to-cell communications. Recent findings indicate that these information carriers also play a major role in progression of various types of cancer [80]. Uncovering the molecular mechanisms related to the biogenesis, uptake, and the fate of biomolecules transferred by EVs and revealing the differences between EVs derived from normal and cancer cells and their unique molecular signatures that control the cellular functions could help understand the contribution of this intercellular communication mechanism to tumor progression, thus, provide significant implications for cancer diagnosis and treatment [81]. These information carriers could be utilized as diagnostic and prognostic biomarkers reporting the state of the hallmarks of the cancer. Moreover, they could be exploited as drug carriers for use in targeted cancer therapy.

B. Internet of Bio-Nano Things

Connecting biological entities and nano-devices to the Internet, termed as the Internet of bio-nano things (IoBNT) [82], would open up new horizons of applications. Along with other major applications, IoBNT would play a vital role in healthcare by connecting nanonetworks of bio-sensors and actuators operating inside or near human body, which is called BAN [4], to healthcare provider for remotely monitoring patients' health through the Internet and administering drugs to patients requiring frequent or periodic dosages.

Here we investigate the potential of using MC-based BANs for diagnosis and treatment of various human disorders.

1) Cardiovascular Disease Monitoring: Nanosensors may be used to measure and report critical parameters for cardiovascular diseases such as heart rate and report them to a hub. These readings may then be communicated to actuate automatic drug delivery or request further medical assistance.

2) Artificial Vision and Artificial Hearing: Artificial vision and hearing by means of stimulation of related brain regions with electrical signals is already a reality [83], [84]. Further researches in these directions may contribute towards the development of artificial organs.

3) Hormonal Therapy Management: Hormonal therapies find a variety of applications such as cancer treatment [85] and hormone replacement therapies in sex change [86]. By making use of BANs to provide the precise amounts of hormones required by the body, the treatments can become effective, speedy and the considerable side effects of hormone therapy [87], [88] may be reduced as well.

4) Smart Drug Delivery: Smart drug delivery is the process that aims to deliver medicine to the targeted region in human body saving other areas of the body from its side-effects. Encapsulating drug molecules in active bio-nanomachines that are capable of searching for targets and releasing the drugs only in the targeted location where medication is needed is a promising means of smart drug delivery [3], [89], [90]. These machines can be realized by reengineering living cells [91] or synthetic nano-devices made of nanomaterials such as graphene and carbon nanotube (CNT).

C. Abstraction of Diagnosis and Treatment Techniques

Revisiting the current diagnosis and treatment methodologies from the ICT perspective could create unprecedented opportunities to improve their effectiveness. The literature already includes unique applications of molecular information and communication science, that approach certain treatment techniques as communication problems and provide rigorous optimization frameworks that can account for dynamic constraints. This abstraction could also provide new performance metrics that can be used to compare the efficiency and effectiveness of similar techniques for particular diseases.

1) Particulate Drug Delivery System (PDDS): The goal of a PDDS is to effectively carry drugs, in the form of micro and nano-sized particles, from the injection site to the diseased body parts. Since the injected drugs passively propagate through the bloodstream, healthy parts of the body are prone to be affected negatively. In [92], the authors use MC as an abstraction of PDDS by approaching the drug injection and delivery as the transmission and reception processes in a communication system, and obtain the precise drug delivery rate, which can be readily used to optimize injection rates for the most effective treatment without side effects.

2) Photodynamic Therapy (PDT) of Cancer: PDT is based on localized use of photosensitizing agents that sensitize singlet oxygens upon optical excitation. Singlet oxygens initiate the apoptosis of cancer cells when they are produced in close proximity of these targets. However, PDT suffers from the low-level selectivity, such that healthy cells are also prone to be killed by singlet oxygens. In [93], the authors realize an abstraction of PDT, based on FRET-based sensor/actor nanonetworks, where bioluminescent molecules are considered as sensors reporting the target location, and singlet oxygen synthesizers are taken as actor nodes. Exciton transfer between sensor and actor nodes is elaborated as information transfer to reveal the relationship between reporter/synthesizer concentrations, throughput and coverage of PDT. The obtained tradeoffs could provide optimum deployment strategies that increase the efficiency of the therapy while reducing the side effects.

V. Conclusion

This study introduced an entirely novel perception of molecular communication paradigms to lay down the foundations of science of molecular information and communication. Human body is an epitome of molecular signaling that is being investigated to design and optimize nanonetworks. Therefore, we seized this opportunity to analyze recent literature on intra-body nanonetworks and MC, and present open issues that need to be addressed in order to define and extract the fundamentals of molecular information and communication science. Based on this investigation we proposed a framework to unveil fundamental limits by relating ICT-based characteristics of MC channel to its physical and chemical properties. Finally, we highlighted the potential of molecular information and communication science in life sciences focusing on its applications in developing ICT-based diagnosis and treatment techniques for the diseases caused by malfunction of intra-body nanonetworks.

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