

Molecular communication nanonetworks inside human body

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ABSTRACT

To realize molecular nanonetworks, the foundations of molecular information theory should be established through identification of the existing molecular communication mechanisms, and architectures and networking techniques for nanomachines should be developed, which demand novel engineering efforts. Luckily, these engineering skills and technology have been prepared for us by the natural evolution in the last several billions of years. Indeed, the human body is a massive nanoscale molecular communications network as it is composed of billions of interacting nanomachines, i.e., cells. Intra-body biological systems are closely linked to each other and communicate primarily through molecular transactions. Thus, vital activities inside the human body are regulated by everlasting communication performance and operations of intra-body molecular nanonetworks. However, natural intra-body molecular nanonetworks are yet to be explored with the elegant tools of information and communication theories. In this paper, first, the elementary models for significant intra-body molecular communication channels, i.e., nanoscale neuro-spike communication channel, action potential-based cardiomyocyte molecular communication channel, and hormonal molecular communication channel, are introduced. Next, molecular nanonetworks belonging to multi-terminal extensions of channel models, i.e., nervous, cardiovascular molecular, and endocrine nanonetworks are discussed. Furthermore, heterogeneous communication network of intra-body molecular nanonetworks together with five senses, i.e., nanosensory networks, is explored from the perspectives of communication and network theories. Moreover, open research challenges, such as extension of molecular channel models to multi-terminal cases, and developing a communication theory perspective to understand the physiology and to capture potential communication failures of intra-body biological systems, are provided. Our objectives are to learn from the elegant molecular communication mechanisms inside us for engineering practical communication techniques for emerging nanonetworks, as well as to pave the way for the advancement of revolutionary diagnosis and treatment techniques inspired from information and communication technologies, which is promising for future nanomedicine and bio-inspired molecular communication applications.

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1. Introduction

Recently, enormous improvements in the field of nanotechnology have enabled the realization of powerful and functional man-made tiny devices inspired from the behavior of atomic and molecular structures. *Nanomachines*,

composed of nanoscale components, are independently operating full-featured devices capable of tasks ranging from computing and data storing to sensing and actuation, i.e., they not only function as computers, but also establish connections with the world to detect a physical quantity, as living organisms. In [2], the similarities between nanomachines and living cells are expressed, and the need for communication between nano-machines is highlighted.

Some applications of nanonetworks, among others, are: a number of nanomachines communicating for effective

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drug delivery [92]; multiple nanosensors deployed on human body to monitor glucose, sodium, and cholesterol [27,56] to detect the presence of different infectious agents [91]; a set of molecular and nanoscale computing devices, i.e., nanocomputers [85], jointly executing an application-specific task. However, realization of these applications mandates addressing the unique challenges posed by the physical characteristics of nanomachines, e.g., dimensions of nanomachines, scarce memory and processing capabilities, and their operating environment on the nanoscale communications.

Several communication paradigms are considered for use in nanonetworks, but the most promising is *molecular communications*, where molecules are used to encode, transmit and receive information [9]. One of the main reasons is that molecular communication of nanoscale entities is an existing natural phenomena, and offers a field of study for developing solutions through modeling nanonetworks. Another reason is that nanonetworks can be built upon such naturally occurring phenomena with appropriate tools, thus ensuring feasible engineering solutions.

To realize molecular nanonetworks, the foundations of molecular information theory should be established through identification of the existing molecular communication mechanisms, and architectures and networking techniques for nanomachines should be developed, which demand novel engineering efforts. Fortunately, these engineering skills and technology have been prepared within us by the natural evolution in the last several billions of years.

Indeed, the *human body is a large-scale heterogeneous communication network of nanonetworks* as it is composed of billions of interacting nanomachines, i.e., cells, whose functionalities primarily depend on nanoscale molecular communications. Hence, *the vital conditions of the human body directly depend on the performance, reliability, and continuous functioning of intra-body molecular nanonetworks*. Human biological systems are connected to each other and communicate primarily through molecular transactions. For example, nervous system is an ultra-large scale communication network of nerve cells, i.e., neurons, which communicates the external stimulus to brain and enables communication between different systems by conveying information with molecular impulse signal known as *spike*. The heart is a nanonetwork of muscle cells, i.e., cardiomyocytes, communicating via cardiac electrical impulses, i.e., *action potentials*, over molecular communication channels through the gap-junctions for continuous circulation of blood. Endocrine system, a network of glands, provides the communication among cells through specific *molecular information carriers*, i.e., hormones, and regulates concentrations of molecules inside the body.

Biological systems communicate to fulfill the needs of human body, to ensure its continuity and detect the problems to meet the solution mechanisms to heal the body. The network of intra-body molecular nanonetworks operates to preserve the equilibrium state, i.e., homeostasis, inside the human body. Any communication failure and impairment that are beyond the recovery capabilities of this network leads to diseases; e.g., impairment of communication skill of neurons results in *multiple sclerosis (MS)*

disease, excessive generation and transmission of action potentials yields *tachycardia*, i.e., excessive heart rhythm, and insufficient amount of insulin secretion and transmission, or irresponsive cells to endocrine molecular information (insulin) leads to *diabetes*.

Although medicine has developed treatment strategies depending on the severity of the diseases and immensely gained ground, it is not yet sufficient to discover the underlying reasons for many crucial health problems. One of the significant directions for completely understanding the nature of the diseases and the complete picture of biological systems' interaction, and healing terminal illnesses is to investigate the issues dealt with medicine community with the perspective of communication theory thoroughly supported with medical background. This brings two major fields together to propose fast and unified solutions to diseases from both medicine and communication theory perspectives.

Sustaining effective communication capabilities in the intra-body molecular nanonetworks is detrimental for the functional and metabolic efficiency of human body. Furthermore, understanding potential disorders caused by communication failures paves the way for the possible development of a new generation of ICT-inspired treatment techniques. In addition, identification of the existing intra-body molecular communication mechanisms, establishment of the information theoretical foundations of these channels, will be a significant step towards the development of real implementable architectures and communication techniques for emerging applications of nanonetworks. *Therefore, introducing the basics of potential models for the molecular communication channels, identifying the intra-body molecular nanonetworks, understanding its communication, network, and information theoretical capabilities and shortcomings, and ultimately contributing to the development of ICT-inspired solutions for certain diseases and bio-inspired solutions for nanonetworks are the main objectives of this article.*

Thus, in this paper, we investigate the molecular information transduction gateways for: (1) *nanoscale neuro-spike communication channel*, (2) *action potential-based cardiomyocyte molecular communication channel*, (3) *hormonal molecular communication channel*, which are the main molecular communication paradigms of nervous, cardiovascular, and endocrine nanonetworks, and capture potential communication failures in each of these nanonetworks leading to diseases in order to pave the way for the design of ICT-inspired diagnosis and treatment techniques. What these systems have in common is the underlying basic principle of molecular communication. It comprises molecule or signal generation, transduction and reception processes that are the basic constituents of a classical communication system.

From molecule transduction among the organelles of a single cell to the feedback compensation pathways or channels between biological systems, each vital activity inside the human body involves in the course of molecular communication. In addition to the vastly explored field of neural networks, which is an excellent artifact of communications within the human body, some other communication processes, such as cellular signaling pathways [59],

protein interaction networks [93], gene regulatory networks [41], and DNA processing approaches [31], have been identified and studied mostly from the perspectives of medical and computational biology. Cellular signaling concept has been studied in [6], where rate distortion theory is utilized for analyzing performance-cost tradeoffs in cellular decision making. In [59], to understand the signaling mechanism of the molecular communication medium, an information theoretical model is proposed.

The calcium signaling concept and the design of a molecular communication system based on intercellular calcium signaling networks are described in [2,69], respectively. The work in [69] also describes possible functionalities, e.g., signal switching and aggregation, that may be achieved in such networks. There is also some current work focusing on communication with biological molecular motors [2,64], intra-cellular aqueous nanobubbles [66], and artificial cells [84]. Several kind of protein interfaces are listed according to their functionalities, receptor–ligand interactions, e.g., activation or blocking due to therapeutic drugs, and methods for detecting protein interactions are suggested in [18]. In [55], several novel nonviral delivery systems for gene therapy application are reviewed. In [95], an artificial cell-to-cell communication system for mammalian cells using nitric oxide signaling is developed as a building block for complex artificial gene regulatory networks.

Although there is a limited amount of work on nanoscale and molecular communications, the intra-body molecular nanonetworks have not been investigated from the information and communication theoretical point of view. The current literature mostly contains very preliminary results on modeling and analysis of general molecular communication channels based on a set of simplifying assumptions [2]. In [75], a physical channel for molecular communication is modeled by a linear time-invariant (LTI) system, and the channel transfer function is derived. Clearly, molecular mobility and diffusion dynamics are not linear, and may well exhibit time-varying characteristics. The noise in molecular communication channel is modeled in [65]. A molecular communication channel as a binary symmetric channel is modeled and its mutual information and capacity is analyzed in [8, 10]. Similarly, the single, multiple access, broadcast, and relay channel capacities are investigated in [11,12]. The common fundamental drawback in these studies is that they simply present idealized results based on simplifying models, e.g., LTI channel model in [75], Gaussian channel noise in [11,12]. The actual information theoretical analysis of molecular nanonetworks of biological nanomachines is still an unknown.

Our research starts with the fundamental pursuit of bringing groundbreaking molecular communication solutions out by observing and understanding the intra-body biological processes we inherently have. One principle objective of this article is to point out the essentials in developing solution strategies for intra-body failures and potential problems. The other goal is to pave the way for the *development of ICT-inspired revolutionary diagnosis and treatment techniques*. These objectives can be realized through identification of elementary models for molecular

communication mechanisms inside the human body. With this motivation, we identify the blocks for molecular communication channels, reveal the pathways for specifying and analyzing the molecular nanonetworks, and discuss the possible outcomes of analyses for intra-body molecular networks. Furthermore, we investigate the fundamental relations between health problems and various communication channel failures and networking problems, and illustrate the underlying link, message delivery problems or deficiencies due to inefficient communication mechanisms within and among nervous, cardiovascular and endocrine nanonetworks resulted from the breakdowns in physiological operations or malfunctioning of tissues.

The remainder of this article is organized as follows. First, in Section 2, a general framework for intra-body molecular communication channels are introduced, and nanoscale neuro-spike communication channel, action potential-based cardiomyocyte molecular communication channel and hormonal molecular communication channel are investigated. Next, in Section 3, molecular nanonetworks for nervous, cardiovascular and endocrine systems inside the human body are introduced. Furthermore, in Section 4, communication pathways among the tremendous network of these nanonetworks are given. Moreover, in Section 5, future research issues and communication theoretic challenges are outlined together with the understanding of underlying pathology of intra-body systems from communication theory perspective to leverage the contribution of medicine and pave the way for future nanomedicine applications. Finally, the article is concluded in Section 6.

2. Intra-body molecular communication channels

Intra-body biological systems operate in conjunction with each other to realize complex vital activities. Apart from the coexistence of these systems, basically each is composed of a communicating mass of molecular cellular structures to aggregate for implementing certain biological tasks. What they have in common is the principle communication mechanism for implementing certain tasks, which might be through *molecular information transfer* by way of molecular ion channels, or simply *action potential transduction* to signal the target cells. Although the stimulation mechanisms behind the communication might differ even in distinct substructures, the building principles of molecular communication for biological systems can be realized within a general framework of intra-body molecular communication channels.

2.1. A general framework for molecular communication channels

In general, a molecular *nanonetwork* is simply composed of *nanomachines* or *nanonodes*. A general molecular nanonetwork with two nanomachines or nanonodes is composed of three main functional blocks comprising the molecular communication system, namely, (i) the transmitter, (ii) the channel, and (iii) the receiver, accounting for the emission, propagation and reception processes, respectively, as illustrated in Fig. 1.

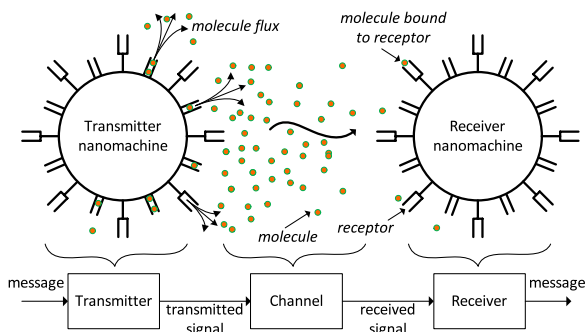


Fig. 1. General molecular communication system with two nodes.

The transmitter generates a signal, i.e., transmitted signal, which encodes the information message to be exchanged. The molecule emission process provides an output signal by the emission of molecules in the space according to a given input and used molecular information encoding mechanism, e.g., molecular concentration and molecule type in action potential-based molecular communication channel, amplitude and rate of electrochemical impulses (spikes) in neuro-spike communication channel. The propagation process provides the transport of the modulated signal by means of a molecule diffusion process, which is defined as the movement of molecules in a fluid from an area of higher concentration to an area of lower concentration. In some cases, e.g., hormonal molecular communication in endocrine nanonetworks, the propagation process is governed by both diffusion and drift due to external active mobility, e.g., bloodstream carrying hormone molecules. The receiver collects the incoming information from the received signal and recovers the transmitted message. A typical reception mechanism observed among living cells is based on ligand-receptor binding process [13], in which, arriving molecules at the receiver nanomachine collide and bind to the unbound receptor of the receiver.

In fact, molecular nanonetworks are directly inspired by communication networks among living entities already present in nature. We will first explore the basic foundations for molecular information gateways of single-input single-output molecular nanoscale communication channels, i.e., (a) nanoscale neuro-spike communication channel, (b) action potential-based cardiomyocyte molecular communication channel, and (c) hormonal molecular communication channel. All these three specific molecular communication channels are captured by the model in Fig. 1, whose functional blocks vary and will be specialized in the following subsections.

We study the constituents for three specific intra-body molecular channels in terms of their respective functionalities in molecular communication. Therefore, we combine the principles of human physiology and physical laws governing the molecular and signal transduction pathways and mechanisms with the perspectives of communication and network theories.

Considering the complete set of the physiological processes inside the human body, from the tiniest functioning molecular unit to largest scale systems cooperating for sustainment of homeostasis, it is unfeasible to study

whole communication processes within cellular, organic, systemic structures inside the human body, to which the efforts in medical science have been devoted for centuries. Hence, we mainly concentrate on the fundamental communication principles of three main intra-body molecular nanoscale communication channels, i.e., (a) *nanoscale neuro-spike communication channel*, (b) *action potential-based cardiomyocyte molecular communication channel*, and (c) *hormonal molecular communication channel*.

2.2. Nanoscale neuro-spike communication channel

Nervous nanonetwork, composed of ganglions, i.e., mass of nerve cell bodies as the network nodes, is responsible for gathering information from different parts of the body, and processing it and generating the required response for the body. It is a distributed network overall the body and it extends up to extremities [72].

Neurons, electrically excitable *nerve cells* capable of storing, processing and transmitting information through *chemical* and *electrical signaling mechanisms*, are considered as *nanotransceivers* of the *nervous nanonetwork*. They receive signals from other neurons or sensory cells, which changes the *membrane electrical polarization*. Electrical potential is spread along the cell body and combined at the base of axon, causing the generation of *action potentials*, which are then transmitted through the axon and arrive to its branches, where the neuron makes an interface with other neurons through *synapses*, i.e., the conductive links between postsynaptic and presynaptic cells [72], where cell-to-cell signals are produced [40]. Action potentials, i.e., *spikes* or *impulses*, are used to carry information from one neuron to the other. Hence, we call the communication among neurons as *neuro-spike communication* [15].

In the literature, there are some studies concentrating on neuro-spike communication. In [39], molecular neuro-spike communication is introduced. Then, its channel capacity and error probability are analytically investigated. In [16], nanoscale neuro-spike communication characteristics through developing a realistic physical channel model between two terminals is investigated. The neuro-spike communication channel is analyzed based on the probability of error in spike detection at the output, and the channel delay is characterized. In [17], synaptic Gaussian interference channel is investigated. Furthermore, the *achievable rate region* for the channel is characterized in terms of power or firing rate.

Performance of neuro-spike communication depends on the physical features of neurons, which affect the action potential transmission characteristics through neurons. Although areas of the axon covered with a *myelin sheath* cannot regenerate *action potentials*, they can rapidly conduct an electrical field to the next node of *Ranvier*, where the *action potential* is regenerated and transmitted further along the axon [72]. Another way to increase conduction velocity is to increase the diameter of an axon, through which axons with *myelin sheaths* can transmit action potentials extremely fast [72].

There are mainly two different types of synapses, *electrical* and *chemical synapses* [82]. *Electrical synapse* is a *mechanical* and *electrically conductive link* that is

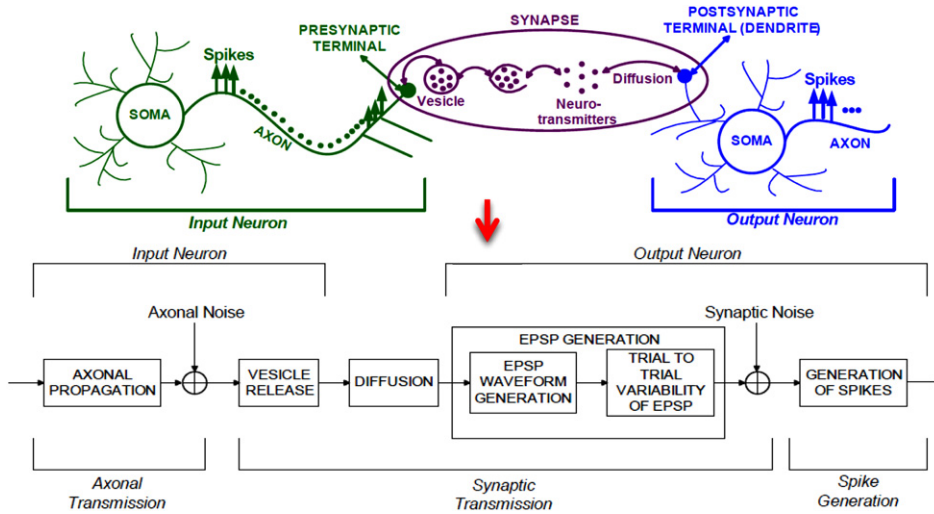


Fig. 2. Realistic channel model for nanoscale neuro-spike communication.

formed in a narrow gap between two neurons, i.e., the *presynaptic* and *postsynaptic* neurons. Despite causing amplitude loss in signal transmitted, it conducts nerve impulses faster compared to *chemical synapse*. Mostly, the electrical impulses can be transmitted in either direction [82]. Different from electrical synapses, chemical synapses are specialized links through which signals are transmitted from neurons to other neurons and non-neuronal cells. Chemical synapses allow neurons to form communication paths within the *CNN*, enable the nervous nanonetwork to communicate with and control other networks within the body, and they are crucial to the biological computations that underlie perception and thought. An arriving spike yields an influx of calcium ions through voltage-dependent calcium ion channels. Calcium ions then bind to the proteins found within the membranes of the synaptic vesicles. The vesicles then release their contents, *neurotransmitters*, i.e., *information molecules*, to the synaptic cleft [61]. The release of a *neurotransmitter* is triggered by the arrival of a nerve impulse, i.e., action potential, and occurs through an unusually *rapid process of cellular secretion*. Therefore, we consider *neuro-spike communication channel* as series of electrical and molecular channels and model it accordingly.

The neuro-spike communication between single presynaptic neuron and single postsynaptic neuron includes the *axonal*, *synaptic* and *spike generation phases* [15]. Synaptic transmission is composed of vesicle release, diffusion, and generation and trial-to-trial variability of *excitatory postsynaptic potential (EPSP)*, i.e., the excitation due to the vesicle release. There are two major sources of noise in neuro-spike communication, axonal and synaptic noises. Hence, the overall model of single-input single-output neuro-spike communication channel for *action potential generation and propagation phases* between two neurons is illustrated in Fig. 2.

2.3. Action potential-based cardiomyocyte molecular communication channel

The heart, as both serving as the source, i.e., *transmitter*, and the destination, i.e., *receiver*, for the *cardiovascular*

network, can be modeled as a *transceiver* of the communication system of the overall body. It has an inherent signal generating and transmission mechanism, which is of great importance, and needs to be given a special attention to understand the characteristics of transmission of blood to every single cell, i.e., *destination* inside human body.

Various mathematical and circuit models for cardiac action potentials and ion channels are developed in the literature. The Hodgkin–Huxley model is a electrical circuit model of cardiomyocyte surface membrane describing how action potentials in neurons are initiated and propagated [42]. In [90], a safety factor for conduction was formulated and computed for reduced membrane excitability and reduced gap junction coupling conditions. A multicellular ventricular fiber model is used to determine mechanisms of conduction failure during acute ischemia in [89]. In [83], it is shown that fibroblasts establish successful conduction between sheets of cardiomyocytes over long distances, explaining electrical synchronization of heart transplants. Furthermore, computer simulations show the feasibility of conduction in the absence of gap junctional coupling in [83]. Despite the current effort is on the physiological operational principles and physical channel models, to the best of our knowledge, there is no work focusing on the information theoretical foundations and principles of communication between cardiomyocytes and within the overall cardiovascular system.

The gap junction coupling is important for the organization of the heart tissue as a mass of electrically connected communicating cells through specialized membrane proteins. A generic model for molecular communication through gap junction channels is implemented in [68]. Furthermore, there exists some preliminary research on molecular channel of heart muscle cells, i.e., *cardiomyocytes*. The role of gap junctions in the cardiac electrical impulse, i.e., *cardiac action potential*, propagation is investigated in [83]. Changes in gap junction channels for various cardiovascular diseases are investigated in [44]. A review of the features of cardiac electrical function and discussion of underlying ionic bases are provided in [87]. A model for

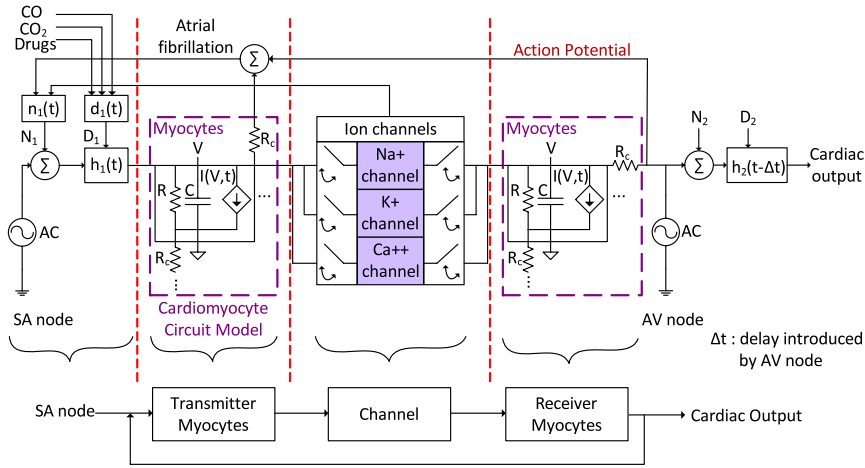


Fig. 3. Cardiomyocyte molecular communication channel.

the electrical activity of the heart is presented and a solution approach for electrical potential distribution based on the bidomain model is suggested [58]. In [45], authors conduct numerical simulations of electrically coupled cells to understand how an action potential is initiated in the atrial cells. Although electrical activity and ionic properties of heart are studied in different works, none of them concentrates on the mechanism of cardiomyocytes from molecular communication perspective.

We consider and model heart as a *molecular nanonet-work of cardiomyocytes*. Cardiomyocytes communicate through the transmission of the cardiac action potential, which we consider as the main information carrier. Cardiac cells, different from the muscle cells, are very convenient for the transmission of the *cardiac action potential*, which is crucial for the *electrical conduction system of the heart* [50]. *Cardiac muscle cells* have a contraction rate determined by the *sinoatrial (SA) node* known as *pacemaker*. *SA node* generates electrical impulses, i.e., *action potentials*, similar to neuro-spikes produced by nerve cells, i.e., neurons. Hence, we model the *SA node* as the primary transmitter in this molecular communication. Since the *cardiac muscle cells* are *electrically coupled*, impulses from *SA node* spread rapidly through the walls of the atria, causing both atria to contract together.

There is another specialized cardiac muscle tissue, *atrioventricular (AV) node*, located in the wall between the right atrium and the right ventricle. *AV node* causes a *delay* before the electrical impulses are broadcast to the walls of the ventricle, ensuring that atria empty completely before ventricles contract.

At the same time, specialized muscle fibers called *purkinje fibers* conduct the electrical signals, i.e., the *action potential signals* throughout the ventricular walls. This entire cycle, a single heartbeat, is a result of *successful molecular communication of action potential* over the nanonetwork of cardiomyocytes and lasts about 0.8 s [38,19].

The channel we outlined in Fig. 3 is, in fact, molecular ion channel. In the conduction system of heart, molecular ion channels play a crucial role. They create the pathways from extracellular medium to intracellular medium, or vice versa, for certain ions, and contribute the contraction

process of the *cardiac muscle cells* according to the concentration levels of potassium (K^+), sodium (Na^+), calcium (Ca^{++}) ions, which determine the existence and direction of ion flows generating *action potential signals*. Hence, ion channels enable the creation and propagation of *action potentials* [50]. As a result of *action potential generation*, i.e., inflow of Ca^{++} ions to cardiac muscle cells, the intracellular concentration of calcium increases, and calcium ions bind to the protein troponin, a protein that is found on the actin filament, causing the *cardiomyocytes* to start to contract [29].

Heart can be described by a circuit model, similar to Hodgkin–Huxley model [42], in which K^+ , Na^+ and Ca^+ channels are considered as molecular current sources. In our circuit model for a single cardiomyocyte, there is a parallel capacitance (C_i) to the voltage-dependent current source due to charge difference of intra and extra media, as the voltage difference determines whether the specific ion channels will be open or closed, i.e., whether or not there is current inflowing. The current is the sum of bidirectional K^+ , Na^+ and Ca^+ ion currents, $I_i = I_K + I_{Na} + I_{Ca}$. The circuit model is incorporated into the cardiomyocyte molecular communication channel model of the heart in Fig. 3.

There is a potential difference between the intracellular and extracellular media of *cardiac muscle cells* (V_i). Due to the potential difference, K^+ , Na^+ and Ca^+ molecules are diffused through these channels in the opposite direction of voltage gradient. Therefore, the voltage gradient is the determining factor for the molecule currents.

To construct the overall communication model of heart, the ion channels, their diffusion process through the cardiac muscle cells, *action potential* generation and transmission through the cardiac cells and the autonomic structure of cardiac muscle cells should be combined carefully. Although in [45], the propagation of *action potentials* is modeled using circular symmetry approximation, it is so hard to construct the overall communication models for human heart and cardiovascular system. The pacemaking cells in *SA node* is controlled by *autonomic nervous system*. Therefore, when stimulated by *sympathetic* and *parasympathetic nervous systems*, the *action potentials* are enhanced and degraded, respectively. The capacity of blood flow through

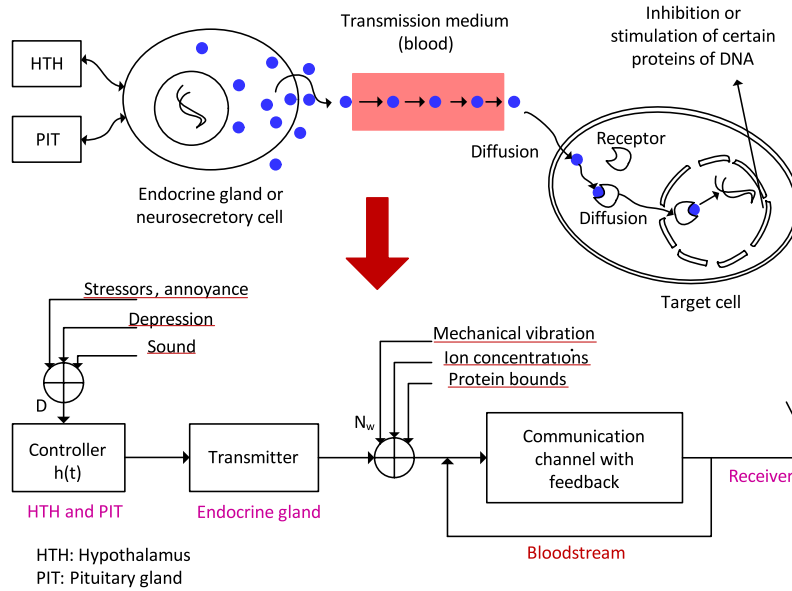


Fig. 4. Hormonal molecular communication channel.

coroners also controls the ion diffusion into/off the cardiac cells, which reshapes the *action potential* and its duration, hence the pumping rate of ventricles. In addition to the contribution of ion channels to *action potential generation*, other factors, such as O_2 molecule and nutrients, also affect the *action potential generation process*, as energy, i.e., ATP, should be provided for muscular contraction.

The *action potential* generated by the *SA node* passes down the cardiac conduction system, and arrives before the other cells have had a chance to generate their own spontaneous *action potential*. This is the electrical conduction system of the heart (normal conduction of electrical activity within the heart). If the *SA node* does not function, a group of cells further down the heart will become the heart's pacemaker, which is known as an ectopic pacemaker. These cells form the *atrioventricular (AV) node*, which is an area between the left atria and the right ventricles, within the atrial septum.

While constructing the overall information theoretical and communication model for heart, we consider the effects of *noise* on *SA* (N_1) and *AV nodes* (N_2), and *external disturbance factors* on *SA* (D_1) and *AV nodes* (D_2). Opening and closing of ion channels, atrial fibrillation, which is some sort of heart rhythm disorder caused by the inability of ventricles to pump efficiently when the *action potential* cannot be transmitted from atria to ventricles due to irregular and rapid rhythm of the heart's atrial chambers, and the cardiac output itself are the main sources for noise generation in heart. Furthermore, some drugs, CO_2 and CO are the main disturbance factors for the heart. Intrinsic noise and disturbance filters used by *SA* and *AV nodes*, i.e., $n_1(t)$ and $h_1(t)$, and $h_2(t)$, respectively, are incorporated into the communication model for heart. Overall communication model for heart is illustrated in Fig. 3 with the fundamental blocks of the molecular communication system.

2.4. Hormonal molecular communication channel

Endocrine system, which is a nanonetwork of glands, provides communication among cells, senses the molecule concentration changes in tissues and secretes hormones for the regulation of body. It has a crucial role in *homeostasis*, i.e., *regulation of internal environment and maintaining a stable, constant condition*. Hence, it acts like a *molecular sensor and actor network*, to maintain the homeostasis. In our model, we consider hormones as *modulated molecular endocrine network information carriers*.

Endocrine glands are controlled by the *nervous nanonetwork*. When the cell receptors are signaled, glands secrete certain hormones, i.e., *chemical messengers*, directly to blood vessels since endocrine glands are ductless. The secreted hormone targets a specific tissue and instructs the tissue to produce a particular substance [47].

Hormones have different biochemistries. They can be divided into two groups according to the ability to diffuse through the cell membrane of the receiver, i.e., target cell. *Lipid-soluble hormones*, e.g., steroids, are carried by the cardiovascular nanonetwork as in Fig. 4 and can diffuse through the membrane and directly deliver the message, i.e., stimulate or inhibit certain regions of DNA. On the other hand, *lipid-insoluble hormones* cannot penetrate through the cell membrane by themselves and need extra messengers to translate the message to the cytoplasm of the target cell. Due to its outweighing number [74], we consider *lipid-soluble hormones* in our channel model. *Lipid-soluble hormones* can diffuse through the cell membrane and target the receptors in the cytoplasm. The cytoplasmic receptors diffuse into the nucleus to act on DNA by stimulating certain regions. Therefore, *lipid-soluble hormone* activity is long durational. Steroids and thyroid hormones are main *lipid-soluble hormones* having direct effect on DNA [74].

Successful delivery rate of hormones within the human body network directly depends on at what concentration they are transmitted (secreted) to the blood (affected by the nervous nanonetwork), at what concentration they are being circulated within the blood stream (controlled by cardiovascular nanonetwork), and the rate of removal of the hormone from the blood plasma, i.e., *metabolic clearance rate* [40].

The propagation of the hormones is due to the combination of the blood circulation rate that stimulates a net hormone movement on top of their free diffusion, i.e., *diffusion with drift*. Molecules diffuse with drift when the *Brownian motion* is coupled with a drifting contribution to the molecule velocity. At the same time, the *clearance rate* depends the concentration of hormone in the plasma, and its rate of disappearance from the plasma per unit time.

Reception process of the channel is selective due to the incompatible chemical structure of hormones to any other receptor type except for the target cells' receptors. In fact, once these molecular information carriers (hormones) are broadcast (secreted) into the communication medium (blood), only one type of nanoreceiver, i.e., cells of the target receiver tissue, responds. Furthermore, *endocrine nanonetwork* have different response times to the stimuli, and concentration of the molecular hormone substances is incredibly small. Moreover, target cells may be promoted or inhibited depending on the stimulation type. Hence, the reception process should be modeled considering its highly time-sensitive and input-dependent nature.

Diffusion in cytoplasm is the fourth step for the successful diffusion of the molecular endocrine information towards the ultimate nanoreceivers, i.e., receptors inside the cell, e.g., DNA, and binding to it. The capacity of diffusion-based molecular communication channels with ligand–receptor binding have been information theoretically modeled and analyzed [8,10–12].

The endocrine cell responds to changes in the concentration of a substance in the extracellular fluid, and provides homeostatic regulation of concentration of substances inside it through *negative feedback mechanism*. After a hormone is released, its further release is suppressed by its products and activity of the target cells. *Feedback regulation of hormones* can occur at all levels, including in the synthesis and processing of hormones and releasing stored hormones [40]. Consider hormone secretion as a *negative feedback regulatory system*. Note that the endocrine cell acts as a *sensor*. For example, any increase in blood glucose level triggers pancreas secretory glands to increase the hormonal information, i.e., insulin, emission rate into transmission channel, i.e., bloodstream, for further transduction of hormonal molecular information to target cells, i.e., receptors. After signaled, targets of the molecular information start glucose uptake and utilization. Hence, the glucose level of the blood is decreased by molecular feedback regulation between the transmission channel and hormonal molecular information source [32].

Overall *hormonal molecular communication channel* is constructed by considering endocrine glands as *transmitter* and the target cells are the *receiver* as in Fig. 4. The bloodstream is the communication channel between the *transmitter* and the *receiver*. Channel is a *feedback channel*,

which regulates the overall system using the *negative feedback* given by the target cell concentration. Furthermore, the system is under the control, $h(t)$, of nervous network nodes, i.e., *hypothalamus* and *pituitary gland*, regulating the hormonal activities inside the body. On the other hand, the channel is susceptible to some *disturbance factors* (D), such as stressors, annoyance, antipsychotic agents, depression, fat gain and sound [94,63]. In addition to that, the *transmitter side* is exposed to noise (N_w) due to the extracellular ion concentrations and mechanical vibrations during secretion, and protein bounds during hormone transmission through the *feedback channel*, i.e., *bloodstream* [80].

3. Intra-body molecular nanonetworks

We explore the basic communication interactions among the main functional subunits of multi-terminal molecular structures inside the human. In fact, we mainly concentrate on intra-body molecular nanonetworks, i.e., nervous, cardiovascular, endocrine nanonetworks.

3.1. Nervous nanonetwork

The *nervous nanonetwork* is intrinsically a large-scale network of nanotransceivers, i.e., neurons, spanning the overall body. It is divided into two main subnetworks, namely *central nervous network* (CNN) and *peripheral nervous network* (PNN). CNN integrates the sensory input information and provides the motor output to the effector cells, i.e., muscle cells, gland cells [47,72]. It is the main processor of the body. PNN is grouped into two parts, which are *somatic nervous subnetwork* (SoNS) and *autonomic nervous subnetwork* (ANS). SoNS collects information from the receptors of five-senses and heads through sensory neurons to convey to CNN. ANS transports the motor outputs generated by CNN to muscles and glands through motor neurons. The main function of the PNN is to connect the CNN to the systems. ANS carries information from CNN through motor neurons to smooth muscles, cardiac muscles and glands [72]. Hence, we consider PNN as the gateway network for CNN to reach the rest of the Internet in human body.

ANS is composed of two subnetworks, i.e., *sympathetic nervous subnetwork* (SNS) and *parasympathetic nervous subnetwork* (PSNS). SNS controls most of the internal organs, neural and hormonal stress, i.e., *flight-or-fight responses*.

Hence, SNS directly communicates with the *cardiovascular* and *endocrine networks*. PSNS is responsible for regulation of internal organs and glands, which occurs unconsciously. Its action is basically complementary to that of the SNS. PSNS is the *energy conservation and restoration center* of the body unlike the *flight-or-fight response* of SNS [72]. Naturally, rather than functioning in opposition to each other, sympathetic and parasympathetic divisions complement each others operation. The sympathetic division typically functions in actions requiring quick responses. The parasympathetic division functions with actions that do not require immediate reaction.

Finally, the brain, built by complex synaptic connections of interacting neurons in CNN, is also a nervous

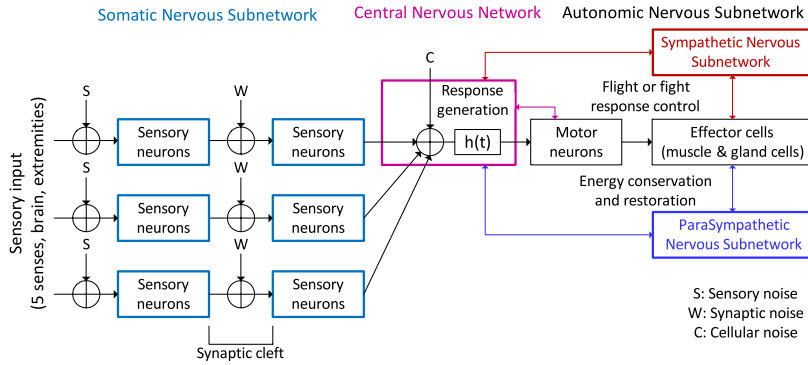


Fig. 5. Communication architecture for overall nervous network.

communication network itself as the main processor and memory for the information coming from all other networks inside the human body and controlling their activity. It acts like a *large-scale ultrafast network switch* among the other networks inside us, and by collecting the sensory inputs for further processing in *CNN*, and delivering motor outputs through the spinal cord, it achieves the communication with the rest of the *internal Internet*.

Hence, the complete architecture for the nervous nanonetwork can be established using the connections and communication relations among its subnetworks, i.e., *SoNS*, *CNN* and *ANS*. Furthermore, *nervous nanonetwork* is susceptible to various major noise sources, which are *sensory* and *cellular noises* apart from *axonal* and *synaptic noises* described in the model for *nanoscale neuro-spike communication channel*. *Sensory noise* (S) is noise in sensory signals and sensory receptors. It limits the amount of information that is available to other areas of the *CNN*. *Cellular noise* (C) is an underestimated contributor to neuronal variability. The stochastic nature of neuronal mechanisms becomes critical in the many small structures of the *CNN*. Finally, *synaptic noise* (W) results from the noisy biochemical processes that underlie synaptic transmission. Adding up these noise sources can account for the observed postsynaptic-response variability. Incorporating the noise sources into the network model, *communication architecture for overall nervous network* is established, as depicted in Fig. 5. Despite excluded in *nervous network model*, there is another noise type, due to the random opening and closing of ion channels, which is I_w . It is the electrical noise in neurons, especially channel noise from voltage-gated ion channels, limits neuronal reliability and cell size, producing millisecond variability in action-potential initiation and propagation [30].

3.2. Cardiovascular molecular nanonetwork

Cardiovascular system, a broad network reaching to every single cell inside the body, is basically a large-scale molecular communication network. It transports amino acids, electrolytes, gases, hormones, and blood cells from or to the cells. Hence, we consider *cardiovascular system*, i.e., the system of blood, heart and blood vessels, as a huge dynamical communication network distributed over the body, i.e., *cardiovascular molecular nanonetwork*.

Understanding the multi-molecule transmission scheme helps determine the transmission characteristics of *systemic blood circulation*. Plasma communicates with interstitial fluid, a solution surrounding the cells, through pores and inter-cellular clefts to provide the cells with nutrients and helps waste removal [46]. This molecular communication process is guided by hydrostatic and osmotic pressures of plasma and interstitial fluid, determining the rate and direction of the transmission for each granule of molecular information.

To construct the overall communication model of heart as a nanonetwork of cardiomyocytes, we need to carefully investigate not only individual communication channels, but also the interactions with other specific nodes in the *cardiovascular* and *nervous nanonetworks*. For example, the pacemaking cells in *SA node* are controlled by *ANS*. Thus, when stimulated by *SNS* and *PSNS*, action potentials are enhanced and degraded, respectively. The capacity of blood flow through coroners also controls the molecular communication channels among cardiomyocytes by varying the ion diffusion, and hence, the action potential and its duration, which, in turn, affects the pumping rate of ventricles.

3.3. Endocrine nanonetwork

Endocrine system, which is a network of glands, provides the communication among cells, senses the molecule concentration changes in the tissues and initiates the hormonal secretion process for the regulation of the molecular stability inside body. Hence, it acts like a *sensor and actor network*, to maintain the homeostasis.

In analyzing the overall communication model of *endocrine nanonetwork*, a network model with the source nodes, where hormone is generated, and the end-to-end path composed of links, through which the hormones are transmitted to destinations, should be defined. The *endocrine nanonetwork nodes* should be modeled as broadcast stations providing unidirectional transmission of hormone molecules from glands to target destinations in a broadcast medium, and bloodstream as the communication link of hormonal molecular communication, which will finally pave the way for analyzing the *information generation and delivery capacity of the overall endocrine nanonetwork* with network information theory.

4. Network of intra-body molecular nanonetworks

To understand the molecular communication among different intra-body nanonetworks, we need to consider the relation between *nervous*, *cardiovascular* and *endocrine nanonetworks*, and intra-body molecular nanosensor networks.

Five senses, i.e., audition (hearing), vision (sight), tactition (touch), olfaction (smell) and gustation (taste), along with the nervous nanonetwork and brain construct a large-scale nanosensor network within human body. The external stimuli signal, e.g., acoustic, visual, pressure signal, detected by these sensors are converted into neuro-spike signals by sensory neurons, which act as signal converters, and carried by the nervous nanonetwork to the brain. Depending on the nature of the external stimuli, e.g., a loud scream, a frightening scene, pressure sense, communication paths emanate from nervous nanonetwork and extend to special nodes of endocrine and cardiovascular nanonetworks.

4.1. Communication among nervous, cardiovascular molecular, and endocrine nanonetworks

In the communication between sympathetic nervous subnetwork and cardiovascular molecular nanonetwork, the vasomotor center, a special portion of medulla in nervous nanonetwork, has a substantial role. It transmits excitatory impulses through the sympathetic nerve fibers to the heart when there is need to increase heart rate and contractility, such as muscle exercise and under other types of stress. Conversely, it sends signals to the vagus nerves, which, in turn, transmit parasympathetic impulses to the heart to decrease the rate and contractility and hence, heart pumping when needed. The neurons of the *sensory area* receive sensory nerve signals from the *cardiovascular molecular nanonetwork*. Output signals emanating from the sensory area, then help control activities of both the *vasoconstrictor* and *vasodilator areas* of the *vasomotor center*, thus providing “reflex” control of many *cardiovascular functions* [40]. *Hypothalamus* and many parts of the *cerebral cortex* can also excite or inhibit the *vasomotor center* [40]. Thus, widespread basal areas of the brain can have profound effects on *cardiovascular nanonetwork functions*.

Nervous nanonetwork causes rapid increases or decreases in the amount of *action potential traffic flow* in *cardiomyocyte nanonetwork*, which is detected by way of receptors. Activation of receptors stimulate related hormonal molecular information emission, causing vasodilation or vasoconstriction, i.e., changes in the blood pressure. The best known of the nervous network arterial pressure control mechanisms is the baroreceptor reflex, which is based on special neurons, baroreceptors [46]. They reside mainly in the aorta and function as a molecular nanonetwork by sensing the drastic changes in blood pressure and communicating this information to the brain.

Hormonal changes and molecular concentrations inside the body are detected by endocrine and nervous nanonetworks, and these nanonetworks complement each other in order to maintain *homeostasis*. Chemically, both

nervous and endocrine nanonetworks utilize hormonal molecular information in signaling and communication, but in different ways. As an example, norepinephrine functions as a neurotransmitter and as an adrenal hormone in the *nervous* and *endocrine nanonetworks*, respectively [47]. Endocrine nanonetwork nodes, i.e., glands, are responsible for hormonal molecular emission process. The hormonal molecular information is directly secreted, i.e., transmitted, into cardiovascular nanonetwork. Nervous nanonetwork nodes, i.e., neurons, collect the molecular information from cardiovascular nanonetwork by sympathetic and parasympathetic fiber connections, and transmit the information to *CNN* regions. The hypothalamus controls the communication between the nervous and the endocrine nanonetworks, and regulates the hormonal emission process by signaling the endocrine nodes [47]. When it signals, the specific endocrine node, i.e., pituitary gland, releases hormones that control many of the *endocrine system's functions*.

4.2. Communication between nanosensor networks and nervous nanonetwork

4.2.1. Audio molecular nanosensor network

The nerve impulses travel from the left and right ears to both sides of the brain stem and up to the portion of the cerebral cortex dedicated to sound, which is in the temporal lobe [40]. Human localize sound within the *CNN*, by comparing arrival-time differences and loudness, i.e., signal powers, in brain circuits that are connected to both ears, which is commonly referred to as *Echo Positioning (EPS)* [46]. The *outer ear* helps get sound and imposes low-pass filtering to the sound signal and transmitting it to the middle ear. The *middle ear* includes the ear bones, i.e., ossicles [40]. Besides their role in the transmission of sound, these bones help protect the ear from damage by constricting and limiting sound transmission when sound is too loud [86]. Therefore, the middle ear should be modeled as an adaptive communication channel, in which the bones attenuate the carrier when sound level is too high. The *inner ear* has a crucial role in hearing by the cochlea. After sound strikes the ear drum, the movement is transferred to the ear bones, which press it into one of its fluid-filled ducts through the oval window of cochlea. Therefore, inner ear should be analyzed considering and modeling it as an *acoustic-to-molecular nanoscale communication gateway*. The fluid inside this duct is moved, flowing against the receptor cells, and stimulating the nerve cells, which then send information through the auditory nerve to the center of the *nervous nanonetwork*, i.e., the brain [40].

Different methods are developed for identification and modeling of the *audio molecular nanosensor network*. For example, in [57], benefiting from artificial neural networks, authors investigate an extended ear type system for multiple inputs and outputs. Measurement of *auditory evoked potential responses* for the extended system enables the characterization of auditory disorders. Furthermore, in [22], authors develop a computer processing method to evaluate audition using analytical technology of speech signal.

4.2.2. Visual nanosensor network

Our *visual nanonetwork* perceives the objects by *distinguishing their energy levels*. Here, the important issue about how to detect and store the information arises. Information, i.e. photons coming from source, enters the eye through an opening in the center of iris, i.e., pupil. Eye has the ability to focus on the information using its inherent adjustable lens. After gathering the information, the lens output is transmitted to the retina, the inner part of the eye containing visual receptors, i.e., rods and cones. Basically, the information is detected in the *visual nanonetwork* by rods and cones responding to faint and bright light information, respectively. When light stroke the receptors, the strength of the stimulus specified by the number of photons and their frequency determines the amount of depolarization of a receptor cell. In the visual nanosensor network, retinal, a light-sensitive form of vitamin A, is an essential signaling molecule in the rods and cones. In the presence of light, the chemical structure of retinal molecule is altered for nerve impulse, i.e., action potential, generation [20]. The amplitude of the receptor's response determines the number of *action potential generating neurons* extending from the retina through the visual nerves for further processing in the *CNN* [46,40]. Which neurons have responded to the stimuli and how much they respond give a way to interpret how efficiently the cells are processing the information coming from light. Moreover, the timing of the responses gives an idea about the sustainability of the information during processing. Information storage in the *visual nanonetwork* is managed by the variability of the responses of the neurons.

Visual nanosensors have applications in optical industry, optical communications and pattern recognition. Appropriate design of nanosensors for optically selective, sensitive sensing systems is needed for naked-eye detection of pollutants for environmental cleanup of toxic heavy-metal ions [28]. In [96], authors present an automatic speech recognition (ASR) technique integrating audio–visual sensory information, which makes ASR more robust against speaker's distance, interference and environmental noises.

4.2.3. Somatosensory network

The somatosensory receptors are distributed over the skin, muscles, internal organs and the *cardiovascular nanonetwork*. The body can react many different stimuli, such as temperature, pressure, texture and chemical properties of the objects, through specialized receptors. After the stimulus is detected by sensory cells, nerve endings are depolarized and then an *action potential* is initiated, which is then transmitted to *CNN* for further processing. This *action potential* usually travels towards the spinal cord [33].

Somatosensory networks have clinical and neurological applications. *Somatosensory evoked potential (SEP)* is widely used for detecting the abnormal nerve conduction in various diseases [34]. Authors in [7] propose a new signal processing method in order to predict externally applied forces to human hands by deriving a relationship between the surface electromyographic (SEMG) signals, i.e., the electrical potential generated by muscle

cells when activated, and experimentally known forces. Furthermore, in [53], the relation between the objects weight and the motor outputs during the grasping motion is investigated [54].

4.2.4. Olfactory nanosensor network

The receptor neurons in the nose are particularly interesting because they are the only direct recipient of stimuli among the nanosensory networks. When the molecules of odorant are detected by the receptors, an *action potential* in the receptor neuron is generated by the activation of ion channels, causing Ca^{++} inflow into the cells. Olfactory sensory neurons project axons within the olfactory nerve to the brain. These axons pass to the olfactory bulb, which, in turn, projects *olfactory information* to the olfactory cortex and other areas. Odor information is stored in long-term memory and has strong connections to emotional memory, possibly due to the *olfactory nanonetwork's* close anatomical ties to the limbic system and hippocampus, areas of the brain that have long been known to be involved in emotion and placing memory, respectively [81]. Different from other nanosensor networks, olfaction, i.e., smell, is an adaptive sense. Olfactory adaptation, which is the normal inability to distinguish a particular odor after exposed to the specific odorant, is the adaptation mechanism of the neurons to protect themselves from being overloaded. Therefore, if the particular odor information does not change, the system ignores that information until a different information, i.e., odorant, is sensed and system starts to respond to this new information [26], i.e., olfactory nanosensory network responds primarily to changes in stimulation.

Nanosensor systems for the rapid detection of specific odorants have applications in biotechnology, medicine, and food safety. In [49], authors explore the real time detection of odorant molecules with single atomic resolution and high sensitivity using a 'bioelectronic nose' inspired from human olfactory receptor. In [43], authors introduce a gas discrimination system that integrates a cross-reactive array of chemiresistive nanosensors to accurately and efficiently identify the gas (odor) to which the system is exposed.

4.2.5. Gustatory molecular nanosensor network

Taste is detected through the taste receptors, i.e., the ion channels and G-protein coupled receptors, which are capable of detecting bitterness, sweetness, saltiness, sourness and umami [14]. Tongue has taste pores top of the taste receptors, where the food is dissolved to contact with the receptors and ion channels. After detection, the taste information is simply sent to the brain via nerves.

Gustatory molecular nanosensors have applications in many fields ranging from medicine and food industry to military defense and national safety. In [51], authors describe the development of the biosensor intelligent system with software on electronic tongue and electronic nose for rapid analysis of gaseous, liquid and heterogeneous matters.

Nanosensor networks, in brief, build our connection with external sensible stimuli, e.g., sound, light, temperature, pressure, texture, smell, taste and so on. The response of these networks are directly communicated through *nervous nanonetwork* for further processing in special lobes of brain. Besides, *nanosensory networks* prepare the body responses, i.e., actions and reactions, to various stimuli through elaborated communication relations among molecular nanonetworks. In fact, even a simple special case, e.g., intra-body audio molecular nanosensor network, is a very complex process in terms of communication and information theory perspectives. It involves audition sense, nervous, cardiovascular and endocrine nanonetworks. External acoustic wave initiates a series of communication processes in the network. First, it is transduced into neuro-spike communication signal. Next, the molecular communication within the endocrine nanonetwork as a response to this stimulus amplifies the traffic load in the cardiovascular molecular nanonetwork. Therefore, investigation of the communication principles, end-to-end rate and delay characteristics, flow control, bottlenecks and potential communication failures, even for a *nanosensory network to single stimulus* from the perspectives of communication, information, and network theories needs lots of effort and devotion.

Akyildiz et al. describe nanosensor technology and electromagnetic communication among nanosensors [3]. The state of the art in nanosensor technology is surveyed. Furthermore, some applications of wireless nanosensor networks are highlighted to emphasize the need for communication among nanosensor devices. A new network architecture for the interconnection of nanosensor devices with existing communication networks is provided. The communication challenges in terms of terahertz channel modeling, information encoding and protocols for nanosensor networks are highlighted, defining a roadmap for the development of this new networking paradigm.

5. Future research avenues

The biological systems provide the cooperation of human body as a whole even in abnormal conditions. However, in some diseases, biological systems cannot overcome the problems related to peripheral factors or originating from body itself. In this paper, we focus on the unsolved or partially diagnosed problems of human health, related to the improper or inadequate operation of *cardiovascular, endocrine, nervous nanonetworks* and *nanosensory networks*.

Medicine has been mainly concentrating on the recruitments of the physiologically indispensable organ systems in human body. As a matter of fact, urgent treatment of cardiac and brain diseases are crucial as these organs are strategically much more important for survival and they have control mechanisms over the other vital organ systems in human body. Thus, crucial effort is attached on cardiovascular surgery, neurosurgery, endocrinology and metabolic diseases, etc. Major advances in medicine has enabled the treatment many illnesses, such as diabetes, heart failure, cardiac arrhythmias, renal failure, and many cancer types [70]. However, especially for

some nervous system related illnesses, such as multiple sclerosis (MS), epilepsy, meningitis, medicine has been inadequate, as main reasons for these illnesses have been still not understood [21]. Moreover, for the remaining physiological illnesses, the remedies that medicine provided can be strengthened by understanding the underlying causes for illnesses by investigation of molecular communication principles and relations among biological systems. In this paper, we aim to open the way for extracting the communication relations and channels for molecular nanonetworks, and analyzing the problems in molecular and signal transmission paths that cause burdens to harmonic operation of molecular communication of nanonetworks independently, or as a whole.

To realize the communication links and failures among intra-body nanonetworks, we need to concentrate on the foundations of communication structures and tasks inside the biological systems from the perspectives of molecular communications and network theory. Open research issues, hence, include the modeling and analyses for *molecular communication channels, intra-body molecular nanonetworks*, and finally, *investigation of operational principles and diseases arisen from improper processing of molecular nanonetworks inside the body from the perspective of communication and networking theories*.

5.1. Molecular communication channels

Molecular communications has been widely investigated in the literature, most particularly from the perspectives of propagation media, diffusion and the noise sources employed in the diffusion process. In [73], several bio-inspired techniques are discussed according to whether a fixed physical link is required for signal propagation or not, i.e., either wired or wireless communication. Pheromones, spores, pollen and light transduction are discussed. In the second group, neuron-based communication techniques and capillaries flow circuit are explored. In [4], nano-electromagnetic communication and molecular communication are envisioned, and propagation models are discussed. In [76], a new physical end-to-end communication model for molecular communication is introduced, and numerical results are provided. In [77], authors provide a mathematical study of the noise at the reception of the molecular information in a diffusion-based molecular communication system when the ligand-binding reception is employed. The reception noise is modeled by following the ligand–receptor kinetics and the stochastic chemical kinetics. In [35], diffusion-based molecular communication is studied through N3Sim, a physical simulation framework for molecular communication. In [60], the diffusion-based molecular communication, whose physical channel is governed by Ficks laws of diffusion, is focused on. In [78], the noise sources in diffusion-based molecular communication are analyzed using signal processing, statistics and communication engineering instruments. Important diffusion-based noise sources, i.e., the particle sampling and counting noise, are investigated.

Although there exists preliminary research on diffusion-based molecular communication commonly for generic

frameworks, the main molecular communication directions for biological systems and specifically, communication pathways inside the human body are not explored yet. Hence, future research issues include the communication models and extensive performance analyses for intra-body molecular communication channels. More specifically:

5.1.1. Nanoscale neuro-spike communication channel

- Based on the neuro-spike communication channel model in [16], the neuro-spike synaptic multiple-access, relay, and broadcast channels should be defined, derived, and analyzed from communication theoretical perspective.
- Fundamental communication parameters and metrics, such as interference, channel access, and collision probability over multi-neuron connections, should be investigated.
- Network information theoretical analysis of the realistic multi-terminal neuronal communication channels should also be performed to find the corresponding achievable rate regions. Furthermore, the results in [17], can be extended to multi-output case for achieving automatic gain control.

5.1.2. Action potential-based cardiomyocyte molecular communication channel

- The information theoretical foundations of molecular communication between two cardiomyocytes should be investigated. The reception of an action potential by the receiver cardiomyocyte should be modeled by molecular detection and counting process under the light of detection and estimation theory.
- Based on the *cardiomyocyte molecular communication channel model* given in Section 2.3, the investigation of the realistic multi-terminal channel models for multiple-access, broadcast, and relay channels and analysis of their information theoretical capacities to find the required molecular communication rates for sustainability of heart functions should be implemented.
- The statistical properties of all noise and disturbance sources should be mathematically investigated and modeled through stochastic modeling of the potential sources for *interference* and *fading* of the communication signal in the channel. The *information capacity of cardiomyocyte molecular communication channel* should be derived.

5.1.3. Hormonal molecular communication channel

- Ligand–receptor binding models could be benefited to mathematically model and analyze the molecular diffusive communication channel, in which hormones propagate and bind to the receptors [18,8,10–13].
- The noise sources of the communication system should be defined and mathematically modeled, and the rate and delay performance of hormonal molecular communication channel should be analyzed.

5.2. Intra-body molecular nanonetworks

Realization of molecular nanonetworks stem from the development of nanomachines. In [5], the state-of-the-art in nanomachines are explained for a better understanding of the nanonetwork scenarios. Furthermore, nanonet-

works and components are described and compared with traditional communication networks. In [36], molecular transmission between nano-scale devices over medium distances, is studied, and a molecular network architecture is proposed to realize the communication between nanomachines that can be deployed over different distances. In addition, flagellated bacteria and catalytic nanomotor techniques are proposed to cover the medium-range. Both techniques are based on the transport of DNA encoded information between emitters and receivers by means of a physical carrier. In [79], a mathematical expression for the capacity of diffusion-based molecular communication nanonetworks is provided. In [52], *Concentration Shift Keying* and *Molecule Shift Keying* modulations are proposed for coding and decoding information in nanonetworks. In [24], a bacteria-based nanonetwork for communication between nanoscale devices is described. The communication is achieved by switching of DNA molecules by chemotaxis. Furthermore, an analytical model is developed to assess the communication range, capacity, end-to-end delay and throughput by considering the available information about the biological mechanisms used. In [1], authors propose *Quorum Sensing*, a mechanism used by bacteria to sense their own population and coordinate their actions, through the emission and sensing of molecules called autoinducers, as a novel way to achieve synchronization between nodes of a nanonetwork. Molecular nanonetworks have been explored with different perspectives. Many studies concentrate on developing new modulation scenarios and molecular sensing mechanisms without considering intra-body molecular pathways. However, understanding of molecular channel foundations inside human body will contribute to extension of *single-input single-output (SISO)* channel models to *multi-input multi-output (MIMO)* cases, i.e., intra-body molecular nanonetworks: *nervous, cardiovascular, endocrine nanonetworks*, and then, the overall network of multi-terminal molecular communication nanonetworks will be concentrated on.

5.2.1. Nervous nanonetwork

Extension of the results in the modeling and analysis of neuro-spike communication channels to the study of the overall nervous nanonetwork composed of ultra-large scale and heterogeneous connections of various types of neurons should be implemented as illustrated in Fig. 5. Therefore, this architecture should correspond to combination of multiple-access, relay and broadcast channels. The network information theoretical analysis of the entire nervous network should be performed to reveal its network information capacity.

5.2.2. Cardiovascular molecular nanonetwork

To construct the overall communication model of heart as a nanonetwork of cardiomyocytes, not only individual communication channels, but also the interactions with other specific nodes in the *cardiovascular* and *nervous nanonetworks* should be carefully investigated. Hence, all these factors should be incorporated into the model of *cardiovascular nanonetwork*, and the overall model should be analyzed using information, communication and network theoretical tools.

5.2.3. Endocrine nanonetwork

Overall communication model of *endocrine nanonetwork* with the source nodes, where hormone is generated, and the end-to-end path composed of links, through which the hormones are transmitted to destinations, should be defined. The *endocrine nanonetwork nodes* as broadcast stations providing unidirectional transmission of hormone molecules from glands to target destinations in a broadcast medium should be considered and mathematically modeled. The *information generation and delivery capacity of the overall endocrine nanonetwork* should be analyzed.

5.2.4. Multi-terminal molecular communication inside us

- The noise, potential communication failures, and the information capacity should be analyzed in order to reveal the fundamental limits for intra-body molecular channels.
- The principle communication relations among the nervous, cardiovascular and endocrine nanonetworks should be investigated. Basically, nanosensor networks, which collect the information through various receptors, are the communication links between the intra-body networks and the outside world. The output signals of nanosensory networks are transduced into neuro-spike communication channels. Nervous network, is then stimulated and hormonal molecular information, depending on the type of the stimulation, is secreted into the bloodstream. To understand the communication between the nervous and endocrine nanonetworks, a detailed communication theoretical analysis on the neuro-secretion process should be performed. Finally, the traffic load in the cardiovascular molecular nanonetwork is altered, which is to be sensed by nervous nanonetwork. Thus, the overall network of intra-body nanonetworks communicate through feedback regulation mechanisms, and each response emanating from a nanonetwork is transported to another nanonetwork for the generation of required response. Thus, intra-body multi-terminal molecular communication nanonetworks should be analyzed from the perspectives of communication, information, and network theories, by proper understanding of the physiology, and mathematical modeling of these interactions, investigating the theoretical limitations, and identifying the potential communication failures.
- To the best of our knowledge, there is no unified network simulator for intra-body molecular nanonetworks although there are some web-based neural network simulators implemented by modeling of motor neurons [23], and a cardiovascular simulator to complement research with the medical experimental data [67], and a diffusion-based molecular communication simulator, NanoNS, developed based on the commonly used network simulator (NS-2) [37]. A molecular nanonetworks simulator should be developed to evaluate the theoretical results, capture potential communication failures in each of these nanonetworks leading to diseases, and pave the way for the design of ICT-inspired diagnosis and treatment techniques.

5.3. Physiology and underlying pathology of intra-body systems from communication theory perspective

Biological operation principles and most particularly, diseases of intra-body systems should be investigated from the perspectives of communication and network theories.

5.3.1. Nervous nanonetwork

- Multiple sclerosis (MS), the illness resulted from destruction of myelin, affects the ability of nerve cells in the brain and spinal cord to communicate with each other [48]. In MS, the human immune system attacks and damages the myelin. When myelin is lost, the axons can no longer effectively conduct signals. Therefore, analyzing the symptoms of MS could enable us to discover the role of myelin in nervous system.
- Epilepsy, a demyelinating disease, is the damage of myelin sheath of neurons. One of the reasons for epilepsy is neuroleptics [62]. Hence, understanding the role of neuroleptics on myelin tissue loss helps nanomedicine improve treatment opportunities, such as enhancing the effectiveness of communications between neurons by enabling the myelin sheath to be more resistant to this type of drugs.
- Meningitis, which is the inflammation of the meninges covering the brain and spinal cord, can lead to serious long-term consequences, such as deafness, epilepsy, hydrocephalus and cognitive deficits [71]. Symptoms of meningitis, such as the decrease of sodium amount in blood and dehydration, can give a path to analyze the reasons behind signal transmission failures and molecular communication ion channel nonfunctionalities.
- Destruction of occipital lobe causes cortical blindness. Hence, communication relations of occipital lobe with visual nanosensor network, and role of this brain portion especially in visual perception should be investigated, and thus, the main causes for visual deficits could be analyzed.
- Damage of temporal lobe can result in fear to display normal fear and anxieties. Therefore, operation of temporal lobe in controlling this kind of actions should be analyzed and alternative treatment methods for enabling effective communication inside nervous nanonetwork should be developed, suppressing such damages caused by deterioration of signaling pathways.

5.3.2. Cardiovascular nanonetwork

- Reasons for sudden cessation of normal cardiac rhythm, i.e., cardiac arrest, tachycardia, i.e., extremely rapid heart beat, and asystole, i.e., losing the ability of contraction, could be analyzed from the perspectives of communication and information theories by studying the cardiac action potential waveform texture.
- Cardiac tamponade, which is the condition that the tissue surrounding the heart fills with excess fluid or blood [88], blocking the proper heartbeat rate, could also be studied to find the relation between the permeability of this tissue and the extracellular fluid molecules, which will help extract the characteristics of heart tissue.

- The partial pressure of oxygen in blood, and its effect on suppressing other molecules in vessels could also be analyzed to investigate the effect of oxygen amount in *pressure regulation mechanism of cardiovascular nanonetwork*.
- Cardiovascular transmission problems due to overactivity of daily living, such as varsity, due to long periods of standing on feet and over walking should be analyzed, and ICT solutions for regulation of the blood circulation should be proposed.
- High blood pressure, i.e., hypertension, should be studied to understand the reaction of body to external stimuli. Studying the molecular communication principles and signaling interactions among nervous, cardiovascular and endocrine nanonetworks provides a mathematical model for the response of body to environment, and hence, treatment of hypertension could be succeeded through joint contribution of medicine and ICT fields.

5.3.3. Endocrine nanonetwork

- The role of *endocrine nanonetwork* in regulating the amounts of blood molecules, i.e., the fundamentals of communication between endocrine and cardiovascular nanonetworks should be understood. Especially for glucose and lipid molecules, in order to understand the role of liver in adjusting blood cholesterol level and model insulin and glucagon secretion processes, hormonal signaling mechanisms and models should be investigated and molecular emission, propagation and reception processes should be incorporated into them.
- Circadian rhythm, which is important in adjusting the body to environmental alterations, such as seasonal changes, variation in the amount of light during the day and night, and temperature variations, should be investigated and solutions for how the human body establishes the communication with outside world through nanosensory networks should be quested.
- Neurotransmitters should be analyzed to understand the relation between *endocrine* and *nervous nanonetworks*, and to provide the reasons behind *spike transmission capability of neurons*.

5.3.4. Nanosensor networks

- The communication theoretical behavior of inner ear should be analyzed considering and modeling it as an acoustic-to-molecular nanoscale communication gateway.
- The human eye is a complex nanosensor collecting light, i.e., *photonic molecular information*, and conveying through the network of light sensors, i.e., rods and cones, where they convert the light input to neural signals to be finally transmitted to brain. However, the human eye is disturbed by the nerves and blood vessels in front of the visual sensors, which leads to imperfections in vision. Therefore, visual sensing mechanism should be analyzed by incorporating the effect of visual nerves and vessels on the ability to see, and a communication model for human eye can be developed to pave the way for future diagnosis and enhanced treatment opportunities.

- Tactition is an important sense to be studied in detail. The conditions under which the human cannot sense and respond to various stimuli should be investigated and communication models to overcome inability to sense pain, chemical stimuli and pressure could be developed.
- Neural adaptation mechanisms underlying olfactory fatigue should be investigated to understand how the human body responds to over stimuli.
- Common gustation disorders, such as ageusia and dysgeusia (which may be resulted from chemotherapy) [25] that prevent the detection of taste, could be studied and solution approaches could be developed.

6. Conclusion

Molecular communication has been a promising field for nanoscale communication applications, and state-of-the-art technology enables the production of *nanomachines*, i.e., simple nano devices capable of a wide range of tasks, especially for ICT and nanomedicine applications.

Human body itself has never been predicated on a resource for ICT field although it houses different kinds of communication channels, and nanonetworks of sensory, signaling and molecular pathways. Besides, the overall internal network, that we term as human internal Internet in this article, supports the integrity of all biological systems by various controlling mechanisms through communication of molecules and signals, as information carriers.

In brief, investigation of the fundamental intra-body communication paths, and their role in providing the integrity of all biological systems through nanonetwork relations broadens the contributions and promotes the development of ICT field. Thus, with this background, ICT is anticipated to give substantial contributions for the development of nanoscale molecular communication networks inspired from human's biological network, and to pave the way for developing ICT inspired curing strategies for intra-body diseases.

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