Molecular Communication and Networking: Opportunities and Challenges

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***Abstract*—The ability of engineered biological nanomachines to communicate with biological systems at the molecular level is anticipated to enable future applications such as monitoring the condition of a human body, regenerating biological tissues and organs, and interfacing artificial devices with neural systems. From the viewpoint of communication theory and engineering, molecular communication is proposed as a new paradigm for engineered biological nanomachines to communicate with the natural biological nanomachines which form a biological system. Distinct from the current telecommunication paradigm, molecular communication uses molecules as the carriers of information; sender biological nanomachines encode information on molecules and release the molecules in the environment, the molecules then propagate in the environment to receiver biological nanomachines, and the receiver biological nanomachines biochemically react with the molecules to decode information. Current molecular communication research is limited to small-scale networks of several biological nanomachines. Key challenges to bridge the gap between current research and practical applications include developing robust and scalable techniques to create a functional network from a large number of biological nanomachines. Developing networking mechanisms and communication protocols is anticipated to introduce new avenues into integrating engineered and natural biological nanomachines into a single networked system. In this paper, we present the state-of-the-art in the area of molecular communication by discussing its architecture, features, applications, design, engineering, and physical modeling. We then discuss challenges and opportunities in developing networking mechanisms and communication protocols to create a network from a large number of bio-nanomachines for future applications.**

***Index Terms*—Biological nanomachines, communication architecture and protocols, molecular communication, nanonetworks.**

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I. Introduction

ADVANCES IN biological science and nanotechnology make it possible to engineer, from biological materials and mechanisms, small-scale functional devices that are capable of interacting with biological molecules and cells in nano to micrometer scale environments. Examples of such biological devices, hereafter referred to as *bio-nanomachines*[1] include purified protein molecules [1], genetically engineered cells [2], artificial protocells, and bio-silicon hybrid devices [3].

Given the unique characteristics of bio-nanomachines, such as their small-scale, bio-compatibility, and energy efficiency, it is envisioned that bio-nanomachines can interface with existing biological systems to enable a set of new functions in health (e.g., nanomedicine and tissue engineering), environmental (e.g., quality control), Information and Communication Technology (ICT) (e.g., implantable bio-sensor and actuator networks), and military applications (e.g., biochemical sensing). The potential of interfacing bio-nanomachines has led to the emerging interdisciplinary research area of *molecular communication* or *nanonetworks* [4]–[6].

Looking back in history, the area of molecular communication was pioneered by Suda and colleagues in 2005 with the aim of establishing communication networks that were compatible with the design of bio-nanomachines [7]–[9]. The initial efforts have been made to design various molecular communication systems and investigate the feasibility in laboratory settings (e.g., [10]–[16]). The initial efforts have also been made to theoretically quantify the characteristics of molecular communication (e.g., [17]–[21]). These initial efforts are however limited to small-scale networks of several biological nanomachines. The key challenge to advance the area of molecular communication to the second stage is to create a network system from a large number of biological nanomachines that is robust to environments encountered in applications. Developing robust and scalable networking mechanisms and communication protocols is anticipated to introduce new avenues into integrating engineered and natural biological nanomachines into a single networked system.

In this paper, we first provide a comprehensive overview of the area of molecular communication by reviewing the architecture, features, applications, design, engineering, and physical models. We then discuss challenges and opportunities in developing networking mechanisms, communication protocols, and standardization for molecular communication. The main contributions of this paper, in comparison to other survey and review papers (such as [4]–[6], [22]), include the following:

[1]Nanomachines are roughly defined as small-scale machines in this paper; no distinction is made between microscale and nanoscale.

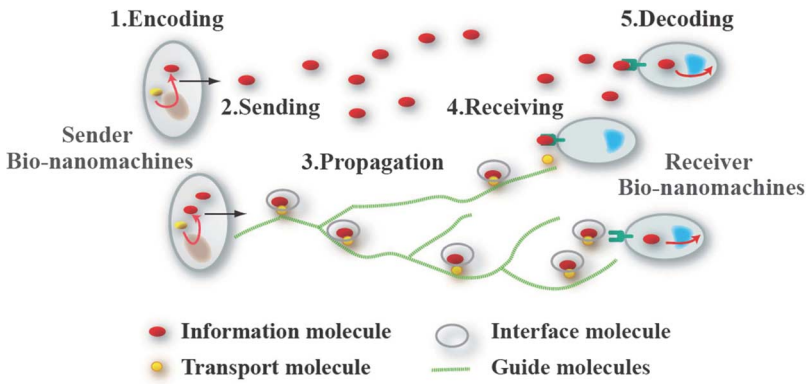

Fig. 1. Molecular communication architecture [4].

- *Overview of molecular communication and its related areas*: One facet of this paper is to provide a brief overview of the area of molecular communication. The architecture and potential application areas of molecular communication are briefly discussed, and engineering efforts in molecular communication and its relevant areas are highlighted.
- *Description of a methodology to examine basic properties of molecular communication*: A simple model of random walk is used to describe the process of molecular communication. The model describes key properties such as the average latency that may represent the quality of molecular communication. The model considers three classes of molecular communication characterized as random walk, random walk with drift, and random walk with reaction.
- *Discussion of current research issues*. Various issues in developing networking mechanisms and communication protocols are discussed based on an approach that provides a layer-by-layer perspective of computer communication. Each issue provides potential challenges and opportunities for future research in molecular communication.

The remainder of this paper is organized as follows. In Section II, we describe the generic architecture, basic components, and typical phases of molecular communication. General features and anticipated applications of molecular communication are also discussed. Section III summarizes the biological materials and methods that can be used to engineer molecular communication systems. Section IV uses a simple physical model to examine various properties that may affect the quality of molecular communication. Section V discusses current research issues and recent activities leading towards advanced molecular communication and networking. Finally, a short summary of the main aspects of this paper is given in Section VI.

II. Molecular Communication Paradigm

A starting requirement in molecular communication research is to generalize communication processes to develop an abstract communication architecture. Specific examples of molecular communication appear in natural bio-nanomachines which communicate with each other or which transport materials within a cell. We generalize the examples of communication between bio-nanomachines, from the perspective of communication engineering, to identify the key components and processes necessary for the molecular communication architecture. In this section, we provide an overview of the molecular communication paradigm by describing an abstract architecture. We also discuss general characteristics of molecular communication systems and potential application areas where this paradigm may advance the existing methods and technologies.

A. Molecular Communication Architecture

Fig. 1 shows an architectural design for molecular communication [4], [5], [9]. It consists of components functioning as information molecules that represent the information to be transmitted, sender bio-nanomachines that release the information molecules, receiver bio-nanomachines that detect information molecules, and the environment in which the information molecules propagate from the sender bio-nanomachine to the receiver bio-nanomachine. The system may also include transport molecules to move information molecules, guide molecules to direct the movement of transport molecules, interface molecules that allow a transport molecule to selectively transport information molecules, and addressing molecules (not shown) that are attached to information molecules or interface molecules to specify the receiver bio-nanomachine.

Fig. 1 also shows the general phases of communication: encoding of information into an information molecule by the sender bio-nanomachine, sending of the information molecule into the environment, propagation of the information molecule through the environment, receiving of the information molecule by the receiver bio-nanomachine, and decoding of the information molecule into a chemical reaction at the receiver bio-nanomachine.

The basic components involved in each phase of molecular communication are described in more details as follows:

- *Encoding* is the phase during which a sender bio-nanomachine translates information into information molecules that the receiver bio-nanomachine can detect. Information may be encoded in various forms within the information molecules, such as in the three-dimensional structure of the information molecule (e.g. a specific type of molecule), in the specific molecules that compose the information molecules (e.g. DNA is formed by the specific sequence of nucleotides), or in the concentration of information molecules (i.e. the number of information molecules per unit volume of solvent molecules) modulated over time

(e.g. a neuron can produce spikes of neurotransmitter at a particular frequency).

- *Sending* is the phase by which a sender bio-nanomachine releases information molecules into the environment. A sender bio-nanomachine may release information molecules by either unbinding information molecules from the sender bio-nanomachine (e.g., by budding vesicles from a biological cell if a sender bio-nanomachine is a biological cell), or by opening a molecular gate that allows the information molecules to diffuse away (e.g., by opening a gap junction channel in the cell membrane of a sender bio-nanomachine). A sender bio-nanomachine may also catalyze a chemical reaction that produces information molecules elsewhere.
- *Propagation* is the phase during which information molecules move from the sender bio-nanomachine through the environment to the receiver bio-nanomachine. An information molecule may diffuse passively through the environment without using chemical energy, or may bind to a transport molecule (e.g., a molecular motor that generates motion) to actively propagate through the environment by breaking down ATP to form energy. During propagation, an interface molecule may also be necessary to protect information molecules from noise in the environment. For instance, an information molecule may be contained in a vesicle-based interface molecule and propagate through the environment. The vesicle prevents the information molecule from chemically reacting with other molecules outside the vesicle.
- *Receiving* is the phase during which the receiver bio-nanomachine captures information molecules propagating in the environment. One option for a receiver bio-nanomachine to capture information molecules is to have a surface structure permeable to the information molecules. For instance, a biological cell has a plasma-membrane permeable to some signal molecules and the receptors within the cell directly bind to the information molecules propagating in the environment. Another option is to use surface receptors that are capable of binding with a specific type of information molecule and inducing reactions within the receiver bio-nanomachine. Yet another option is to use surface channels (e.g., chemically gated-channels) that allow information molecules to flow into a receiver bio-nanomachine.
- *Decoding* is the phase during which the receiver bio-nanomachine, upon capturing information molecules, decodes the received molecules into a chemical reaction. Chemical reactions for decoding at the receiver bio-nanomachine may include the production of new molecules, the performing of a simple task, or the production of another signal (e.g., sending other information molecules).

B. Expected Characteristics

Table I compares some aspects of molecular communication with telecommunication in terms of devices, signal types, signal propagation speed, range, and medium [5], [6], [9]. Overall, a variety of characteristics of molecular communication arise from using biological mechanisms and components for communication in an aqueous environment. These include:

- *Encoding and decoding with chemical signals*: Molecular communication propagates chemical signals from a sender bio-nanomachine to a receiver bio-nanomachine, upon which the receiver bio-nanomachine chemically reacts with the incoming chemical signals. Here information can be encoded within the physical properties or characteristics of information molecules, such as the type of information molecules used, their three-dimensional structure (e.g., protein), sequence information (e.g., DNA), or concentration (e.g., calcium concentration). A high density of information may be encoded into a molecular structure [23]. In addition, functional information may be encoded. For example, a DNA sequence can be used to encode a functional protein. When transmitted, a receiver bio-nanomachine may acquire new functionality (e.g., resistance to toxic molecules) as a result of gene expression.
- *Slow speed, limited range, large jitter, and high loss rate*: The speed and range of molecular communication are extremely slow and short, and vary depending on the biological materials, mechanisms used, and the environment. The fastest and longest-range communication is achieved through neural signaling which propagates electrochemical signals (i.e., action potentials) at 100 m/s over several meters; on the other hand, the free diffusion of molecules via Brownian motion is limited to the micrometer range. In addition, molecular communication experiences large signal jitter and a high loss rate because the movement of molecules is often unpredictable and the molecules arrive at a receiver bio-nanomachine after a widely varying period of time. Moreover, the molecules may degrade in the environment and not even arrive at a receiver bio-nanomachine.
- *Biocompatibility*: Sender and receiver bio-nanomachines communicate by sending, receiving, and chemically reacting with information molecules. Since molecular communication uses the same communication mechanisms as biological systems, bio-nanomachines in molecular communication may be able to directly communicate with natural components in a biological system by using encoding and decoding methods available to the biological system. The biocompatibility of molecular communication may enable applications such as the implanting of bio-nanomachines into a biological system for medical applications that require biologically friendly bio-nanomachines.
- *Energy efficiency, low heat dissipation, and chemically operated*: Molecular communication uses mechanisms and materials from biological systems, and is therefore expected to be energy efficient and achieve low heat dissipation. Myosin molecular motors, for example, convert chemical energy (i.e., ATP) to mechanical work with nearly 100 percent efficiency [24]. The chemical energy necessary for molecular communication is expected to be supplied by the environment in which bio-nanomachines are deployed. For instance, bio-nanomachines implanted in the human body may harvest energy (e.g., glucose)

TABLE I
TELECOMMUNICATION AND MOLECULAR COMMUNICATION [5], [6], [9]

Communication	Telecommunication	Molecular Communication
Devices	Electronic devices	Bio-nanomachines
Signal types	Optical/electrical	Chemical
Propagation speed	Speed of light	Extremely slow
Propagation range	m - km	nm - μm
Media	Air/cables	Aqueous

from the environment, and as such require no external energy sources.

C. Applications Envisioned

Functional applications of molecular communication use bio-nanomachines to sense molecules, transport molecules, and modify molecules. Applications are being considered in biomedical, environmental, and manufacturing areas [5], [25]. Here we briefly discuss how molecular communication may apply to the three areas:

1) Biomedical Applications:

- *Lab-on-a-chip*: In lab-on-a-chip applications, the chemical analysis of biological samples is performed on a chip with dimensions in the mm to cm range. Analysis of biological samples is required for medical applications to diagnose disease or for general scientific studies of biological samples. Molecular communication provides techniques to transport specific molecules to specific locations of a chip. In one possible implementation, each transport molecule (e.g., a microtubule filament which glides along a surface of molecular motors) has an interface molecule to selectively transport a specific type of molecule of the sample and an addressing molecule (e.g., a single-stranded DNA sequence which binds to a complimentary sequence) for where on the chip to transport the molecule [26]. Molecular communication may have implementation advantages since it uses molecular level mechanisms for directly manipulating the molecules in the sample and does not require translation of information to/from electrical signals. In addition, molecular communication may allow lab-on-a-chip applications to scale further down since molecular communication components can be at the nanometer scale.
- *Health monitoring*: Monitoring performed within an organism (i.e. human, animal, or plant) enables identification of specific molecules in the body [25], [27]–[30]. The existence of specific molecules may serve as a bio-marker for a disease or a certain medical condition. More detailed information such as the spatial distribution of molecules can be used to provide information for further diagnosis. For such applications, bio-nanomachines are implanted in the body, and molecular communication provides potential methods for gathering information about the molecules of the body, aggregating the information, and transmitting it to external devices.
- *Drug delivery*: Drug delivery systems facilitate the administration and distribution of drugs within an organism. Implanted bio-nanomachines can use molecular signals within the organism, or molecular signals released by other bio-nanomachines, to pinpoint target locations for drug delivery and thereby reduce the potential for side-effects at non-target locations [31]–[33]. Existing techniques include the use of capsules that release drugs in response to specific conditions such as temperature. Molecular communication may provide alternative techniques to control the release of drugs such as cooperative drug release by a group of bio-nanomachines.
- *Regenerative medicine*: Bio-nanomachines made of living cells can divide and grow to form a functional structure (e.g., tissues and organs). Such bio-nanomachines can be applied to aspects of regenerative medicine. As in developmental biology, the formation of a functional structure would progress based on molecular communication among bio-nanomachines. Molecular communication provides techniques to control patterns of communication and thereby affect the growth and differentiation of the bio-nanomachines into specific structures.

2) Environmental Applications:

- *Environment monitoring*: The environment may be exposed to toxic or radioactive agents. Information about these molecules could help to identify problems and to provide a map for cleaning up the environment in response to illegal contamination or an accidental spill [34]. Bio-nanomachines can be integrated into large or microscale environments to map out the locations of molecules within that environment. Molecular communication provides techniques for the bio-nanomachines to process molecular information from the environment and communicate this information to other bio-nanomachines.
- *Waste/pollution control*: The monitoring of molecules in the environment may provide information that is only of low-level resolution. Bio-nanomachines could be deployed to monitor molecules in the environment and thus identify more precisely the location of a toxic source. For example, bio-nanomachines can identify and use specific types of molecules to tag waste in the environment [5]. They can also move to the source of the toxin or can also amplify molecular signals [35] that in turn guide other bio-nanomachines or larger-scale devices to the location of the molecular signal to degrade the material into a non-toxic or reusable form.

3) Manufacturing Applications:

- *Pattern and structure formation*: Molecular communication can be used to control the transport of molecules, and can be modified to produce novel patterns of molecules [36]. A system can be programmed to form a specific pattern of molecules by having each location in the system correspond to an address and then transporting bio-nanomachines or specific types of molecules to each address. After the molecules or bio-nanomachines are transported to each address, chemical processes can be activated to complete the structure. It may also be possible to augment a biological system with molecular addresses and transport molecules by the augmented addresses. If patterning processes can be programmed in sequences of molecules, then it may be possible to produce a large

TABLE II
DESIGN AND ENGINEERING OF MOLECULAR COMMUNICATION COMPONENTS

Components	Examples Categorized by Materials
Bio-nanomachines	Modified cells [37], [38], [39], Artificial cells [3], [40], [41]
Information molecules	Synthetic particles [42]
Guide and transport molecules	Gap junction channels [16], [43], [44], Molecular motors and filaments [12], [15] [45], [46], Bacteria [47], [48], neurons [49]
Interface molecules	Liposomes [13], [50]
Addressing molecules	DNA molecules [10]

variety of shapes and structures while using the same manufacturing machinery.

III. DESIGN AND ENGINEERING OF COMPONENTS FOR MOLECULAR COMMUNICATION

The molecular communication systems described in the previous section are designed and engineered from biological mechanisms and materials. In this section, we review recent research results concerning the design and engineering of components for molecular communication. A summary of this section is provided in Table II with a list of research results from biology, chemistry, and nanotechnology for engineering components that are applicable to developing molecular communication systems.

A. Sender and Receiver Bio-Nanomachines

Sender and receiver bio-nanomachines require chemical functionality for effective communication: sender bio-nanomachines must be able to synthesize, store, and release information molecules, while receiver bio-nanomachines need to capture and react to specific information molecules. Two basic approaches for engineering bio-nanomachines with functionality for communication are the modification of existing biological cells or the production of simplified cell-like structures using biological materials [22].

- *Modified biological cells*: The first approach for engineering bio-nanomachines has been used and demonstrated in synthetic biology [37]–[39], wherein a sending function is implemented by modifying a metabolic pathway of a biological cell which then synthesizes and releases specific signal molecules. A receiving and processing function is also implemented by genetic engineering to allow a cell to capture signal molecules and produce intended chemical reactions. Synthetic biology has also demonstrated that many other functions can be introduced into biological cells, such as logic gates, toggle switches, and oscillators. These functions can be used to increase the complexity of sending and receiving processes. Examples of functions which can be embedded in bio-nanomachines for molecular communication include: logic gates to produce programmed responses based on received signal molecules, toggle switches (i.e., 1 bit memories) to retain a communication-related memory such as whether a bio-nanomachine is in a state of sending or waiting, and oscillators (i.e., clocks) to control the timing of release.
- *Artificial cells*: Another approach to engineering sender and receiver bio-nanomachines is to create simplified cell-like structures using biological materials (e.g., by embedding proteins in a vesicle). One example is to start with a lipid bilayer and then add functionality as necessary. The lipid bilayer, which is similar to the membrane that encloses a cell, forms into a vesicle (a spherical lipid bilayer) in which functional proteins (e.g., a receptor) are either embedded or captured [3]. In [40], [41], sender and receiver bio-nanomachines capable of transmission and reception were synthesized from vesicles embedded with photo-responsive molecular switches. Experimental results showed that these devices can be photo-controlled to transmit or react to chemical signals, and thus demonstrated the potential of this approach for creating bio-nanomachines.

B. Information Molecules

Information molecules carry information and propagate from a sender bio-nanomachine to a receiver bio-nanomachine in the environment. The size and structure of the information molecules may affect how the information molecules propagate in the environment. Information molecules need to be chemically stable and robust against environmental noise and interference from other molecules. In addition, certain information molecules degrade over time in the environment and thus require a sender bio-nanomachine to transmit a large number of information molecules.

Examples of information molecules from biological systems include endocrine hormones, local mediators such as cytokines, neurotransmitters (e.g., dopamine, histamine), intracellular messengers (e.g., Ca^{2+} and cyclic AMP), and DNA/RNA molecules. Information molecules can also be synthesized for specific purposes as demonstrated in drug delivery by, for example, using nanoparticles to target particular tissue types [42].

C. Guide and Transport Molecules

Guide and transport molecules provide reliable mechanisms for propagating information molecules. A required functionality for these molecules is to direct the propagation of information molecules toward target locations (i.e., receiver bio-nanomachines). Guide and transport molecules can be viewed as bio-nanomachines specialized for transporting molecules.

Numerous examples in biological systems can be used to design and engineer guide and transport molecules for molecular communication. For instance, gap junction channels can be used as engineered guide molecules [16], [43], [44]. These channels mediate the propagation of signal molecules between cells through intercellular communication pathways. Engineered molecular communication systems could use gap junction channels to mediate the diffusion of information molecules in the communication pathways, and thus receiver bio-nanomachines can be targeted by selecting where gap junction channels appear. In addition, gap junction channels with different selectivity and permeability properties can be

exploited to implement additional functions such as filtering and switching [51].

Molecular motors can be used to transport information molecules over protein filaments (i.e., guide molecules). In [45], microtubules (i.e., guide molecules) self-organize into a network and motor proteins (i.e., transport molecules) actively transport information molecules along the guide molecules. The specific patterns of microtubule filaments can be designed to form a pathway for molecular motors to walk to target locations of the network [15], [52]. It is also possible to have an inverted design where a surface is coated with motor proteins that push the filaments along the surface. In this inverted arrangement, transport molecules (i.e., the filament) load information molecules at a sender bio-nanomachine, propagate directionally via the motor proteins, and unload the information molecules at a receiver [12], [46].

Self-propelling organisms (e.g., bacteria) can also be used as transport molecules [47], [48]. Bacteria, for example, can be induced to move toward a receiver bio-nanomachine along a concentration gradient of attractant molecules in the environment. The attractant molecules function as guide molecules, since the receiver bio-nanomachine generates the attractant molecules to indicate where the receiver bio-nanomachine is and to influence the direction in which the transport molecules (bacteria) move through the environment.

A network of neurons can also be used as guide molecules that propagate information molecules between bio-nanomachines [49]. A sender bio-nanomachine may transmit neurotransmitters (e.g., acetylcholine) or ions (e.g., calcium ions) to cause an action potential in a neuron. The action potential may propagate one neuron to the other in the network toward a receiver bio-nanomachine. A receiver bio-nanomachine may chemically react to the action potential of a nearby neuron to decode information from the action potential.

D. Interface Molecules

Interface molecules allow bio-nanomachines to transport a variety of information molecules using the same communication mechanism [13]. The interface molecules allow any type of information molecule to be delivered to and concentrated at a target location. The interface molecules may also protect information molecules from environmental noise and prevent the information molecules from chemically reacting with other molecules in the environment outside the vesicle.

An example of a generic and abstract communication interface found in drug delivery is a nanoscale capsule which encapsulates drugs and targets a specific location in the body [50]. The capsule circulates via the blood stream and binds to specific receptors at the target location where drugs are released. This approach reduces the unwanted side-effects of drug reactions at non-target locations.

E. Addressing Molecules

Addressing molecules allow a sender bio-nanomachine to specify the receiver bio-nanomachine according to a generic addressing mechanism. A molecular communication system with generic addressing is more flexible since it imposes fewer constraints on which information molecules are used.

One example of a generic addressing mechanism is using DNA sequences to represent addresses [10]. In this example, an information molecule is attached to a single-stranded DNA with a sequence that specifies the address of a receiver bio-nanomachine. The receiver bio-nanomachine has the single-stranded DNA that is complementary to and thus binds to the single-stranded DNA on the information molecule. Using DNA sequences in addressing provides a large addressing space, since arbitrary DNA sequences can be made with existing technology and chemical properties of DNA sequences are well understood.

IV. Theoretical Modeling of Molecular Communication

Theoretical models serve as a fundamental tool that can be used to quantify, compare, and improve the quality of molecular communication such as average latency (i.e., average propagation delay), jitter (i.e., variation in latency), and loss rate (i.e., the probability that a molecule transmitted by a sender bio-nanomachine is not received by the intended receiver bio-nanomachine.) Theoretical models can also be used to design new mechanisms and protocols for molecular communication. The area of biophysics has developed a number of theoretical models (e.g., quantum, molecular, cellular, and organ level dynamics models) and computational methods that can be used to advance the area of molecular communication. This section, based upon a simple model of a random walk, considers three different classes of molecular communication: pure random walk, random walk with drift, and random walk with reaction by amplifiers; and discusses the quality of molecular communication in terms of average latency, jitter, and loss rate.

A. Pure Random Walk

The first class of molecular communication we consider relies only on random walk (i.e., no directional drift of information molecules and no chemical reaction of information molecules during propagation). Random walk is the most fundamental mechanism that molecular communication relies on to propagate a molecule. Random walk does not require any additional mechanism to propagate a molecule. Many examples of this class of molecular communication are found in biology. One example is intracellular metabolites propagating between cells. Another example is DNA binding molecules (e.g., repressors) propagating over a DNA segment to search for a binding site [53].

For simplicity, let us start with a one-way molecular communication in a semi-infinite interval $(-\infty, d]$ with a sender bio-nanomachine at $x = 0$ and a receiver bio-nanomachine at $x = d(> 0)$. The sender bio-nanomachine encodes information onto an information molecule and releases it at time $t = 0$; the molecule then randomly walks in the environment; and upon arrival of the molecule, the receiver bio-nanomachine decodes the information from the molecule.

The latency in this class of molecular communication can be defined as the time that the molecule first hits the receiver bio-

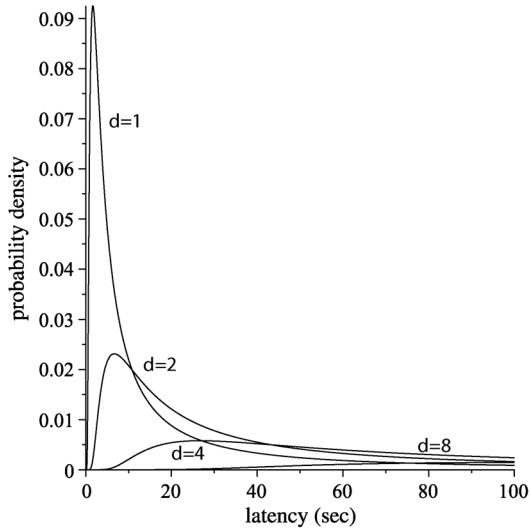

Fig. 2. The probability density function of the latency in a semi-infinite interval $(-\infty, d]$ for various sender and receiver bio-nanomachine distances $d = \{1, 2, 4, 8\}$ $(\mu\mathrm{m})$. $D = 0.1$ $(\mu\mathrm{m}^2/\mathrm{s})$.

nanomachine, known as First Passage Time (FPT) [54], and its probability density function is given by

$$f(t) = \begin{cases} 0 & (t = 0) \\ \frac{d}{\sqrt{4\pi D t^3}} \exp\left(-\frac{d^2}{4Dt}\right) & (t > 0) \end{cases} \quad (1)$$

where D is the diffusion coefficient of the molecule.

Fig. 2 shows the probability density function of the latency for various distances d between sender and receiver bio-nanomachines. Fig. 2 demonstrates that the latency is greatly affected by the distance d. The average latency for a receiver bio-nanomachine at any location is infinity (i.e., $\int_0^\infty t f(t) dt = \infty$), which indicates that a receiver bio-nanomachine is expected to wait for an infinitely long amount of time to receive the molecule [17]. The jitter is also infinity. The loss rate can be obtained from $1 - \int_0^T f(t)dt$, assuming that the receiver bio-nanomachine waits for the time duration T.

The quality of molecular communication differs significantly when the environment is bounded. Fig. 3 shows the probability mass function $p(t)$ of the latency (t) obtained from numerical simulation in a finite interval $[0, d]$ for various d where $x = 0$ is reflecting. The average latency in this case is finite and is equal to $d^2/2D$ [53]. The jitter can be calculated as $\sum_{i=0}^{\infty}(i\Delta - (d^2/2D))^2 p(i\Delta)$, where Δ is the simulation time step length. The loss rate is given as $1 - \sum_{i=0}^{T} p(i\Delta)$ under the same assumption that a receiver bio-nanomachine waits for the time duration T.

B. Random Walk With Drift

The second class of molecular communication we consider is random walk with drift. Information molecules may undergo a directional drift which continuously propagates molecules in the direction of the drift [55], [56]. An example of this class of molecular communication is found in our body. Cells in the body secrete hormonal substances which circulate with the flow of the blood stream and propagate to distant target cells distributed throughout the body. This class of molecular communication also represents the active mode of molecular communication by which motor proteins carry and directionally propagate molecules from a sender bio-nanomachine to a receiver bio-nanomachine [57], [58].

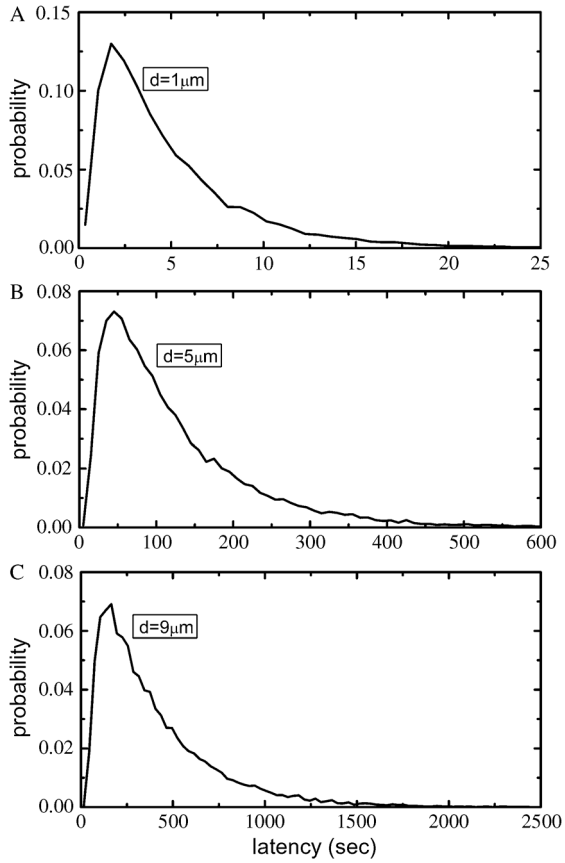

Fig. 3. The probability mass function of the latency in a finite interval $[0, d]$ for various $d = \{1, 5, 9\}$ $(\mu\mathrm{m})$. $D = 0.1$ $(\mu\mathrm{m}^2/\mathrm{s})$.

When a molecule propagates in a fluid medium modeled as a semi-finite interval $(-\infty, d]$, the probability density function of the latency is given by replacing d^2 in (1) with $(d - vt)^2$, where $v(\geq 0)$ is the velocity of the fluid medium. Fig. 4 shows the probability density function of the latency for various $v > 0$ and demonstrates that the fluid medium becomes an effective medium to propagate molecules over long distances. For the fluid velocity $v > 0$, the average latency is d/v and the expected latency decreases in proportion to the inverse of v. The jitter is $Dd/2v^3$ and diminishes quickly as v increases. The loss rate can be obtained using (1) where d^2 is replaced with $(d - vt)^2$ in a manner similar to the semi-finite interval case in subsection A.

C. Random Walk With Reaction by Amplifiers

The third class of molecular communication we consider is random walk with chemical reactions by amplifiers. Amplifiers in the environment can increase the reliability of molecular propagation by increasing the number of propagating information molecules. Amplifiers are located in the environment and react with molecules that propagate in the environment. As a result, amplifiers produce a copy of the molecule which propagates in the environment. This class of molecular communication may be enabled by exploiting protein molecules such as those responsible for amplifying calcium ions, adeno-

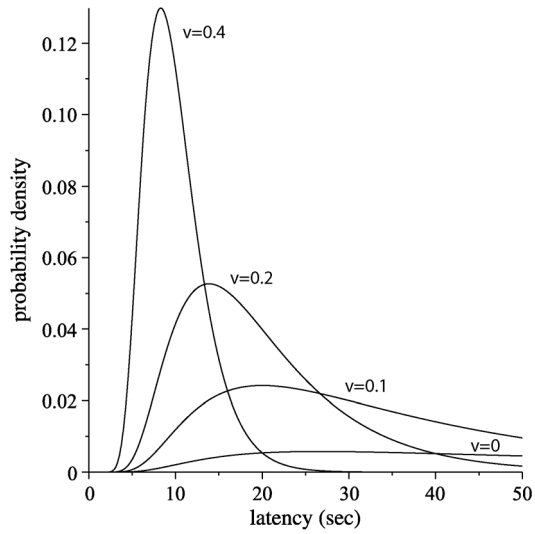

Fig. 4. The probability density function of the latency in a fluid medium for various fluid velocity $v = \{0, 0.1, 0.2, 0.4\}$ $(\mu\mathrm{m/s})$. $D = 0.1$ $(\mu\mathrm{m}^2/\mathrm{s})$ and $d = 4$ $(\mu\mathrm{m})$.

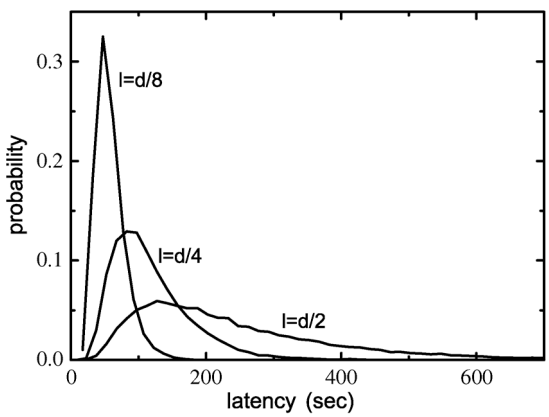

Fig. 5. The probability mass function of the latency for various inter-repeater distances $l = \{d/2, d/4, d/8\}$ at $N = 2$. $d = 10$ $(\mu\mathrm{m})$ and $D = 0.1$ $(\mu\mathrm{m}^2/\mathrm{s})$.

sine triphosphate (ATP), and cyclic adenosine monophosphate (cAMP) [59].

To see the impact of amplifiers on the quality of molecular communication, consider a finite interval $[0, d]$ with a sender bio-nanomachine at $x = 0$ and a receiver bio-nanomachine at $x = d$. ($x = 0$ is reflecting.) Repeaters are placed uniformly over the interval where the inter-repeater distance is l. Each repeater is activated when a molecule first arrives at the repeater, and once activated, it releases N molecules. (The activation is only one time for each repeater.)

The probability mass functions $p(t)$ of the latency (t) obtained from numerical simulation for various l and N are given in Figs. 5 and 6, respectively. Fig. 5 shows that the latency decreases as a larger number of amplifiers are placed. Fig. 6 shows that the latency also decreases as a larger number of molecules are released by an amplifier. The average latency is $\sum_{i=0}^{\infty} i\Delta p(i\Delta)$, and the jitter and loss rate can be obtained from $p(t)$ in a manner similar to the finite interval case in subsection A.

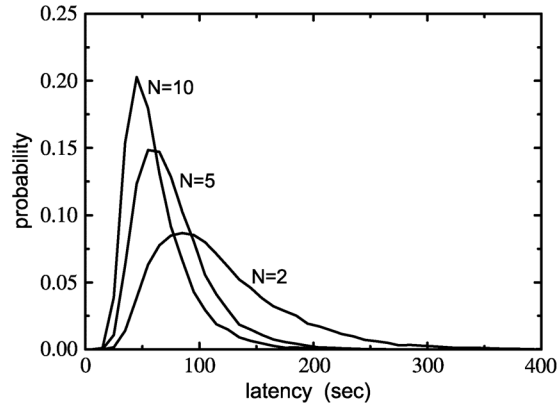

Fig. 6. The probability mass function of the latency for various numbers of molecules that a repeater releases $N = \{2, 5, 10\}$ at $l = d/4$. $d = 10$ $(\mu\mathrm{m})$ and $D = 0.1$ $(\mu\mathrm{m}^2/\mathrm{s})$.

V. Research Issues and Challenges

Recent research in molecular communication remains limited to the design and analysis of small-scale networks of several bio-nanomachines with simplistic assumptions about bio-nanomachines and the environment. A key challenge to advance the area of molecular communication to the next stage is to develop robust and scalable techniques to create large-scale networks which function in the environment of practical applications. In this section, we discuss from a computer networks perspective the research issues and challenges that need to be addressed to achieve robust and large-scale molecular communication networks. We begin with a discussion of the physical layer responsible for transmitting molecules over physical media. We then progress to the link layer for reliable molecule transmission within a single network, and finally to the network layer for molecule transmission among multiple networks. Other issues related to higher layers, standardization, and design tools will also be briefly mentioned in this section.

A. Physical Layer Issues

Signal Propagation: One issue in the physical layer concerns the propagation of signals in various media and environments. Wireless communication has developed theory and computational methods to predict and characterize how electromagnetic waves propagate in various media and environments. For molecular communication, it is also necessary to develop or identify theory and computational methods, which provide the basis for designing molecular communication. The typical models used in the current research in molecular communication are in part described in Section IV. A more complete list of models includes random walk models [17], [18], [21], [60], random walk with drift models [55]–[58], diffusion-based models [61]–[66], diffusion-reaction based models [67], and active transport models [21]. These models are relatively simple and need to be extended to increase their applicability, for instance, by considering more complex geometry (e.g., intracellular environment, the human body), structures of molecules, and interactions among molecules.

Signal Modulation: Another issue in the physical layer concerns the modulation and demodulation of signals. In computer networks, physical properties such as voltage or current are

varied to transmit information. In molecular communication, a receiver bio-nanomachine can distinguish different types of molecules (e.g., calcium is a type of molecule or a specific sequence of DNA is a type of molecule), thus each type of molecule represents a different signal [18], [68], [69]. Similar to computer networks, physical properties of molecules of the same type can be modulated to represent information. For instance, bio-nanomachines can be designed to react based on the number or concentration of the molecule. In this case, information can be represented by modulating the amplitude, frequency, phase, or other aspects of the concentration or the number of the molecule [17], [20], [21], [26], [56], [57], [58], [67], [70]–[72]. Efforts until now have introduced unrealistic assumptions such as a sender bio-nanomachine precisely transmitting a molecule, a receiver bio-nanomachine precisely interpreting a molecule, or complete synchronization between sender and receiver bio-nanomachines. These assumptions will need to be relaxed in future work in order to increase the feasibility of the modulation schemes and their compatibility with the design of bio-nanomachines.

Signal Amplification: Another commonly observed issue in the physical layer is the attenuation and distortion of signals [70], [71]. Molecular communication relies on the propagation of molecules in an aqueous environment for which the signal level (e.g., the concentration of information molecules) decreases with distance from the sender bio-nanomachine. To overcome this problem, repeater bio-nanomachines that amplify information molecules can be placed between sender and receiver bio-nanomachines. For example, a sender bio-nanomachine releases calcium ions, the calcium ions diffuse, and intermediate repeater bio-nanomachines amplify the signal level to reach the receiver bio-nanomachine [44], [73]. Currently, there are only a limited number of studies on signal amplification and various issues remain to be solved, including the design and implementation of repeaters not only for calcium but also for other types of signal modulation.

Channel Capacity: Another subject to be addressed is to identify the capacity of a communication channel. In computer networks, information theory is applied to measure channel capacity. Information theory similarly can be applied in molecular communication to model the effect of noise sources, such as the randomness in the propagation of molecules, on the channel capacity. In the literature, molecular communication channels have been investigated using various propagation models and modulation schemes [17], [18], [21], [55]–[58], [61]–[64], [67], [74]. Unfulfilled needs in this area include measuring the channel capacity using physically realistic models, comparison of various communication channels in terms of capacity, and designing molecular communication channels to increase the capacity.

Hardware Devices and Interfaces: The physical layer must also consider the design of hardware devices and interfaces between the devices. Hardware devices for propagating molecules for molecular communication were described in Sections II and III, which include protein motors, cell-cell channels, and self-propelling organisms. Biological systems use a greater variety of media and mechanisms for communication, which could be explored for possible use in molecular communication Molecular communication may also require hardware devices (e.g., bio-nanomachines) to interface between molecular communication networks which use different propagation mechanisms. In addition, some applications require hardware devices to interface with optical or electrical systems (e.g., wireless sensor networks) that operate outside the molecular communication environment [75]–[77]. In synthetic biology, biobrick developers have defined common interfaces and libraries according to inputs, outputs, and tolerances of bio-components [78]. Anticipated work in this area involves further development, testing, and interfacing of hardware devices for molecular communication. Reliable techniques to modify the functionality of hardware devices are also required.

B. Link Layer Issues

Error Handling: One important issue in the link layer is concerned with error handling to improve the reliability of transmission. In computer networks, various channel coding schemes are used to detect or correct bit errors that may occur during data transmission. Molecular communication may also face similar issues related to errors during molecule transmission. Information molecules may degrade in the environment or arrive with a large amount of jitter (i.e. dispersed arrival times and in a different order from original transmission), which may lead to unintended receiver reactions (i.e., errors). One technique to avoid errors in molecular communication is to use redundant molecules. For instance, a sender bio-nanomachine often transmits a large number of molecules and the receiver bio-nanomachine reacts only when it detects a threshold number of such molecules. A larger number of molecules increases the signal to noise ratio and reduces the impact of noise or fluctuation [21]. The sender bio-nanomachine can determine the number of molecules required according to communication parameters such as distance to the receiver bio-nanomachine and noise levels in the environment. Another technique to avoid errors is to optimize the rate of transmission from a sender bio-nanomachine such that the error rate at the receiver bio-nanomachine is minimized [20]. Similar techniques can also be applied to maximize the probability of in-sequence molecule delivery [69]. One technique to detect errors is for information molecules to include redundant information (e.g., an additional DNA sequence in an information carrying DNA molecule) that allows forward error correction at the receiver bio-nanomachine [79]. Current research is still limited and challenges remain to design and compare biologically implementable error handling schemes.

Addressing: Yet another issue in the link layer is to implement addresses by which a sender can specify the receiver. In biological systems, the receiver bio-nanomachine is often specified by the type of molecule used by the sender bio-nanomachine. Another possible generic addressing scheme described earlier uses DNA molecule tags to implement addressing molecules for molecular communication. In another scheme, called the beacon coordinate system [80], the receiver location is described by distances to several beacons and a mobile carrier, capable of distance measurement (e.g. a bacterium), transports information to the location described by the distances. Current research on addressing receiver bio-nanoma-

chines has suggested several techniques for identifying receiver bio-nanomachines by type of molecule or by location; however, many unresolved issues remain. From existing techniques, it is unclear how many addresses are required for a single network, what the precision of addresses is, and how receiver bio-nanomachines can be dynamically addressed.

Synchronization: Synchronization of the clocks of multiple devices allows the devices to perform some function at the same time or to avoid collisions through time-slotted communication. In biological systems, some examples of synchronization include heart cells contracting together at the same time, quorum sensing by bacteria to decide when to form a film, or sequential cell differentiation during developmental growth. Similarly, in molecular communication, bio-nanomachines may also need to synchronize their activities to achieve application functionality [81]. For instance, a group of bio-nanomachines may use synchronization to determine when to releases molecules in a cooperative manner [82]. Synchronization in molecular communication is challenging due to large propagation delays and jitter. Further development of synchronization is required for functionality such as synchronization with unknown distances between the sender and receiver bio-nanomachines, with various numbers of sender and receiver bio-nanomachines, and with non-diffusion techniques for molecular communication.

Media Access Control: The link layer must also provide media access control which makes shared media (i.e., broadcast media) available for multiple sender and receiver bio-nanomachines. Without media access control, the simultaneous transmission of information molecules can elicit a response from an unintended receiver bio-nanomachine. In biological systems, interference is often avoided by using a different type of molecule for each receiver bio-nanomachine, similar to using a different channel in a wireless network to avoid interference. This requires a large number of different types of molecules that do not interfere with each other. In the case where interference does occur, media access control involving techniques such as switching, channel reservation, or multiplexing is required. At the present time, however, no such approaches exist. An issue to be addressed in this area is therefore to design techniques that can handle multiple bio-nanomachines in shared media and to identify the feasibility of implementing these techniques into bio-nanomachines.

Flow Control: Another developmental aspect of the link layer is concerned with buffer overflow at the receiver bio-nanomachine. In computer networks, flow control is implemented for a sender to adjust the rate of frame transmission, so that the receiver is able to process incoming frames. Molecular communication may face a similar issue. If a sender bio-nanomachine transmits molecules at a higher rate than the receiver bio-nanomachine can process, some molecules may remain in the environment and be degraded [83]. A receiver bio-nanomachine may require different time periods to process information molecules since decoding the information may be rapid (e.g., a fast chemical reaction) or extremely slow (e.g., cell growth on the order of hours). Therefore, molecular communication may require the use of a flow control technique to improve the efficiency of transmission and correctness in processing of molecules. At present, no flow control techniques for molecular communication have been developed.

Distance Measurement: Distance information may be useful for tuning the distribution of bio-nanomachines (e.g., for sensor applications [60]) or optimizing molecular communication (e.g., the transmission rate). In electronic radio networks, a pair of transceivers which communicate by radio waves can use time-of-flight and signal attenuation of the radio waves to measure distance between the transceivers [84]. In molecular communication, similar techniques may apply since the expected time for a molecule to propagate increases with distance (i.e., a characteristic similar to time-of-flight) and the concentration of molecules decreases with distance (i.e., a characteristic similar to signal attenuation). Several protocols have been designed for a bio-nanomachine to measure distance to another bio-nanomachine using the diffusion of molecules [85]–[87]. Although existing work in molecular communication has identified signal characteristics which may be used for measuring distance; it remains unclear how sender and receiver bio-nanomachines can convert signal characteristics representing distance into useful chemical changes for an application. For example, it has yet to be demonstrated how the knowledge about distance from a distance measurement protocol can be integrated with a transmission scheme to produce the anticipated increase in channel capacity of a transmission scheme.

C. Network Layer Issues

Routing: The main issue to overcome in the network layer is that of routing. Routing concepts from computer networks can be applied to increase the scale and complexity of molecular communication networks. Without routing, the range of molecular communication is limited to the distance over which molecules can reliably propagate. At longer distances, molecules are dispersed and unlikely to arrive at the receiver bio-nanomachine within a reasonable amount of time, or are too low in concentration to be detected by the receiver bio-nanomachine. Similar to computer networks, routing in molecular communication may involve router bio-nanomachines located on the path to the receiver bio-nanomachine. In current research designs, molecular communication is limited to static routing tables which do not adapt to dynamic locations or network conditions. For instance in [47], a sender bio-nanomachine transmits information using a bacterium with addressing molecules (e.g., type X and Y molecules) to indicate the desired receiver bio-nanomachines. In this system, router bio-nanomachines receive the bacterium and apply statically defined chemical processes to retransmit information using a bacterium which follows chemical gradients to the next router bio-nanomachine on the path to the receiver bio-nanomachine. A similar mechanism is explored to create a routing system based on bacteria in [88]. An issue requiring attention is how to produce a dynamic routing system that can adapt to dynamic conditions such as bio-nanomachines dynamically moving in the environment.

In-Network Processing: Similar to sensor networks, molecular communication networks may contain a large number of

bio-nanomachines that are located close by and therefore sense similar information. In molecular communication networks, techniques to process and combine information (i.e. in-network processing) are likely to improve the scalability and performance of molecular communication networks. In biology, a large number of receptors are distributed over an organism (e.g., a slime mold) to sense the environment and collectively determine if the environment is favorable. In molecular communication, [89] describes a technique for a large number of distributed bio-nanomachines to agree on the average value of sensed concentrations. The current techniques for molecular communication are limited and further development is expected to design signal processing techniques based on operations in biological systems or sensor networks to improve the scalability and performance of molecular communication networks.

Other Network Layer Issues: Many other network layer issues will need to be addressed in molecular communication, such as congestion control and topology management. However, since existing research on lower layer issues is limited, only a small amount of research on other network layer issues has been performed. Other issues will become more apparent in the future as larger networks are established.

D. Higher Layer, Cross-Layer and Multi-Scale Issues

Higher layer issues and mechanisms in computer networks may apply to molecular communication for reliable end-to-end molecule transmission (i.e., the transport layer) and for application development (i.e., application layer), although no research on this subject has been performed yet. Some possible goals for higher layers include integrating the Internet to include access to bio-nanomachines [90] or generalized techniques to integrate multiple layers of communication protocols. This could introduce issues requiring techniques for micro- to macroscale interaction such as how to address and interact with specific bio-nanomachines and how to securely control access to bio-nanomachines. In developing applications, all issues discussed thus far need to be solved within biological constraints and with application goals and requirements taken into consideration.

E. Standardization

The standardization of communication protocols in computer networks is important for integrating a number of devices into a large-scale network. For molecular communication networks, standardization may be especially critical since terminology, devices, and techniques originate from diverse disciplines including biology, engineering, and information science. As a starting point, the IEEE P1906.1 Standards Working Group for Nanonetworking was established in 2011 for standardizing molecular communication protocols [91]. The initial efforts are being made to provide a definition of molecular communication, a conceptual model for molecular communication, and common terminology for molecular communication. Further efforts are expected to define standard protocols and to provide design guidelines to integrate a large number of bio-nanomachines into a single functional network.

F. Modeling and Simulation Tools

Modeling and simulation tools are necessary to evaluate various designs for molecular communication networks. In biophysics, simulation techniques have been developed to model physical processes in biological systems such as intercellular and intracellular signaling. Researchers in molecular communication are especially interested in communication and networking aspects of biological systems and how to re-engineer them to produce new functionality for practical applications. NanoNS has been built based on a computer network simulator to model molecular communication through diffusion processes [92]. N3Sim is another physical simulation framework for diffusion-based molecular communication [93]. A molecular motor simulator has also been developed to compare communication characteristics of several molecular communication designs [21]. A general purpose simulator for nanoscale networks is also under development with a set of common libraries [94]. However, there are currently no comprehensive tools for evaluating molecular communication networks. A key challenge is therefore to integrate the large number of tools into a single package and to make it possible to consistently compare and evaluate various designs for molecular communication networks.

VI. Conclusion

In this paper, we have provided a comprehensive overview of the emerging and interdisciplinary area of molecular communication. We first presented the architectural design and biological engineering of components for molecular communication. The quality of molecular communication was then examined using a simple biophysical model of random walk. Lastly, we presented from a computer communication perspective a number of unresolved research issues that need to be addressed within the various layers of molecular communication in order to create a functional network from a large number of bio-nanomachines.

Molecular communication integrates techniques from biology for interacting with biological systems, from nanotechnology for enabling nano- to microscale interactions, and from computer science for designing scalable and robust networks. Molecular communication has high potential capacity for impact, since biological systems pervade many environments and applications, but the current techniques available for molecular communication are limited. The area of molecular communication is in its infancy and numerous challenges and opportunities exist to advance this area as discussed in this paper.

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