Body Area NanoNetworks with Molecular Communications in Nanomedicine

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ABSTRACT

Recent developments in nano and biotechnology enable promising therapeutic nanomachines (NMs) that operate on inter- or intracellular area of human body. The networks of such therapeutic NMs, body area nanonetworks (BAN[2]s), also empower sophisticated nanomedicine applications. In these applications, therapeutic NMs share information to perform computation and logic operations, and make decisions to treat complex diseases. Hence, one of the most challenging subjects for these sophisticated applications is the realization of BAN[2]s through a nanoscale communication paradigm. In this article, we introduce the concept of a BAN[2] with molecular communication, where messenger molecules are used as communication carrier from a sender to a receiver NM. The current state of the art of molecular communication and BAN[2] in nanomedicine applications is first presented. Then communication theoretical efforts are reviewed, and open research issues are given. The objective of this work is to introduce this novel and interdisciplinary research field and highlight major barriers toward its realization from the viewpoint of communication theory.

INTRODUCTION

Within the last two decades, the outstanding progresses in nano and biotechnology have radically shifted how the human healthcare can be approached. Growing interest in the medical applications of these technologies has recently enabled the emergence of sophisticated nanomedicine applications [1]. Unlike the earlier applications with simple nano-structured materials and devices, these sophisticated applications include therapeutic nanomachines (NMs), such as engineered bacteria and nanorobots. For example, a group of bacteria can be genetically engineered to recognize and destroy tumors in the human body [2]. Besides their great potential, the very tiny size and unknown physics of therapeutic NMs cause crucial unreliability and uncontrollability problems in these applications. For example, artificial cells used for a smart drug delivery application may be easily exposed to an intrinsic and extrinsic biological noise in gene expression. This makes the drug delivery process completely unreliable and uncontrollable [3].

Through a nanoscale communication paradigm, a network of therapeutic NMs, known as a body area nanonetwork (BAN[2]), can be realized to enforce reliability and controllability of complex nanomedicine applications. More important, a BAN[2] can also coordinate nanomedicine tasks among heterogeneous NM[1] populations to reach highly sophisticated behavior and increase the number of design possibilities. For example, a group of non-communicating engineered cells behaves asynchronously and cannot coordinate to perform a predefined task. However, a BAN[2] of communicating synthetic cells can overcome the asynchronous behavior problem and coordinate the cell population for a tissue engineering application [3]. Furthermore, a BAN[2] may be also required in promising nanomedicine applications in order to:

- Coordinate cooperative NM tasks
- Efficiently gather biosensor data
- Correlate the biosensory inputs and make decisions
- Transmit information messages to external entities

A BAN[2] can also augment various other advancements in the emerging molecular computing systems where logic computations are performed via biological entities. Such computations could also enable fine grained detection of diseases and take action through smart drug release [4]. Therefore, a BAN[2] can support the communication of NMs needed for such logic computations.

In the literature, there are four main nanoscale communication paradigms that may provide the interconnection of the therapeutic NMs in a BAN[2]. These are nanomechanical, acoustic, electromagnetic, and molecular communication paradigms [5]. In nanomechanical communication, a message is transmitted by a mechanical contact between transmitter and receiver. Acoustic energy such as pressure variation is used for conveying information in acous-

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[1] Throughout the article, we interchangeably use the terms therapeutic nanomachine and nanomachine to refer to the therapeutic nanomachines that are used in nanomedicine applications.

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tic communication. Electromagnetic communication is enabled by the modulation of electromagnetic waves to transmit information. Furthermore, molecular communication allows NMs to communicate with each other by using molecules as communication carriers. Among these, due to the lack of communication equipment, the nanomechanical and acoustic communication may not be feasible for the realization of the BAN[2]. Although electromagnetic communication equipment (e.g., carbon nanotube radio and antenna) are available, most of these devices are not biocompatible. This may render electromagnetic communication inappropriate for nanomedicine applications. On the other hand, molecular communication is the most promising approach for the realization of BAN[2]s based on the following advantages:

- Molecular communication is biocompatible as it has been already employed in many natural phenomena. For example, in a natural immune system, the white blood cells communicate with each other using molecules to cooperatively sense and eliminate hazardous pathogens. The molecular communication among white blood cells forms the biological immune network, which is an excellent defense mechanism.
- Molecular communication equipmentis currently available as molecular communication systems have already been realized. For example, using nitric oxide signaling elements, an artificial cell-to-cell communication system in mammalian cells has been developed in order to govern a cell population. This system can also serve as a functional tool for complex nanomedicine applications such as gene therapy and artificial gene regulatory networks [7].

Apparently, the BAN[2] with molecular communication has great potential in its operation size and capabilities to enable radically new and promising nanomedicine applications. However, this also brings many crucial communication challenges due to the salient characteristics of molecular communication, outlined as follows:

- Communication carriers are messenger molecules whose propagation speed is extremely low.
- Communication devices and signals are severely prone to thermal noise, molecular noise, drift, and fading.
- Channel characteristics differ significantly from the characteristics of the traditional wireless communication channel.
- Nanoscale materials have high manufacturing defect rates and operational uncertainties.
- The mobility of NMs is governed by the rules of physics in this regime (e.g., the rules of Brownian motion).

In the existing literature, there are also several research efforts toward addressing the unique challenges of molecular communications and nanonetworks. However, to the best of our knowledge, the concept of the BAN[2] in nanomedicine, its associated challenges, and open research problems have not yet been investigated. The aim of this article is to introduce the concept of the BAN[2] and highlight its unique research challenges for an early development stage of efficient and reliable communication and networking techniques.

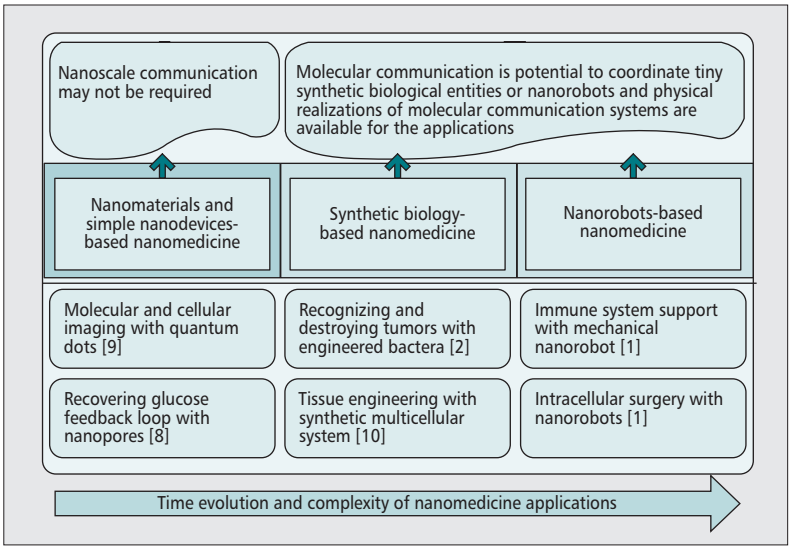

Figure 1. *Three kinds of nanomedicine applications with appropriate nanoscale tools are categorized according to their time evolution and complexities.*

Nanomedicine and Body Area Nanonetworks

In this section, we first introduce a brief overview of nanomedicine. Then we discuss the requirements for a BAN[2] in nanomedicine applications and present the existing BAN[2] proposed or physically realized for a large set of nanomedicine applications.

A Brief Overview of Nanomedicine

Nanomedicine is the process that uses molecular tools and molecular knowledge of the human body to diagnose, treat, and prevent diseases. Nanomedicine is a continuously growing field as nanotechnology and biotechnology develop novel nanoscale tools that can easily be adopted for promising applications. The current and envisioned future nanomedicine applications can be categorized into three main groups according to their chronological evolution stages [1]. The first group includes the first-generation nanomedicine applications with simple and currently available nanoscale tools such as nanopores [8] and quantum dots [9], as shown in Fig. 1. These tools are capable of directly interacting with biological phenomena (e.g., a single cell or a cell organelle). For example, to restore the glucose feedback loop of diabetics, nanopores are used to encapsulate insulinoma cells [8]. The second group involves more remarkable synthetic biology-based tools that are adopted or synthesized from nature, such as engineered bacteria [2] and synthetic cells [10] (Fig. 1). For example, a group of bacteria can be genetically engineered to recognize and destroy tumors in the human body [2]. The third group includes nanomedicine applications with mostly futuristic tools (i.e., bio-hybrid or mechanical nanorobots), which may join the nanomedicine

The nature-made nanonetworks are also indispensable for many vital functionalities. For example, the molecular communication of bacteria in quorum sensing forms a nature-made nanonetwork in which bacteria produce, emit, and receive hormone-like messenger molecules.

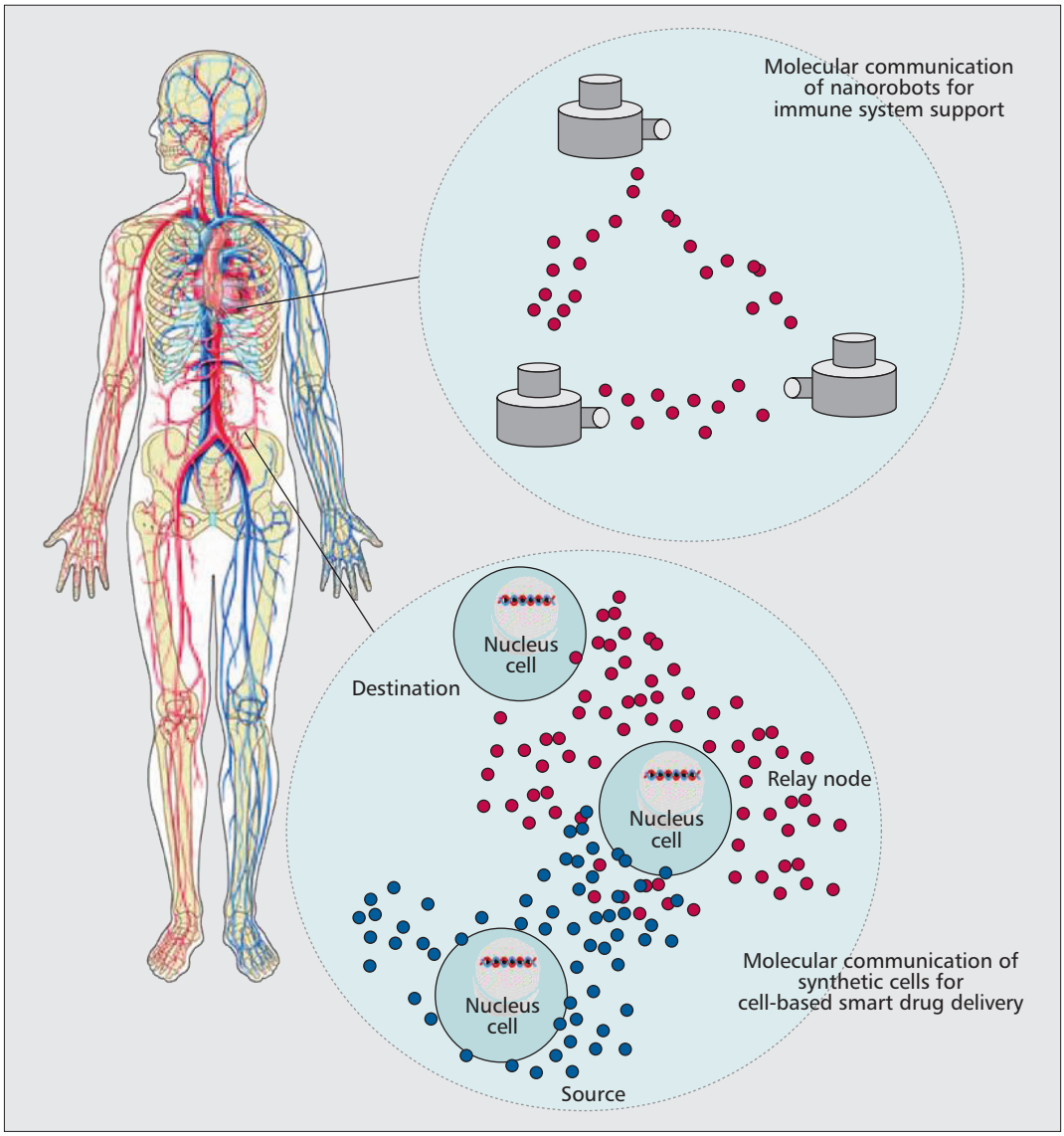

Figure 2. *Two different body area nanonetworks of artificial cells and nanorobots with molecular communication to realize a sophisticated drug delivery and immune system support task.*

equipment set in the longer term. For example, wireless intracellular surgery is expected to be realized via mechanical nanorobots [1].

In Fig. 1, some outstanding nanomedicine applications that employ these three groups of nanomedicine tools are briefed with respect to their time evolution and complexities. As observed in the figure, controllability and reliability of the applications grow into more challenging problems as the applications evolve and become more sophisticated. For example, in a tissue engineering application, an artificial cell population must be governed to reliably form a multicellular system having predefined patterns [10].

Such controllability and reliability issues can be addressed by forming a BAN^2 through molecular communication of therapeutic NMs. A BAN^2 can also coordinate nanomedicine tasks among heterogeneous NM populations to reach highly sophisticated behavior and increase the number of design possibilities. For example, in Fig. 2, artificial cells and nanorobots share molecular information to coordinate and accomplish a sophisticated drug delivery and immune system support task.

In fact, nature-made nanonetworks are indispensable for many vital functions. For example, the molecular communication of bacteria in quorum sensing forms a nature-made nanonetwork in which bacteria produce, emit, and receive hormone-like messenger molecules. This natural process permits bacteria to synchronize all colony activities and change the colony state in response to an external stimulus. Similar to nature, in nanomedicine, BAN^{2}s are required to make the applications more manageable and reliable while providing more sophisticated design possibilities.

Molecular Communications-Enabled Body Area Nanonetworks in Nanomedicine Applications

As shown in Fig. 1, unlike the early nanomedicine applications, synthetic biology- and nanorobots-based applications radically

transform treatment of complex diseases. In these applications, through molecular communication, a BAN^2 of therapeutic NMs can perform computation and logic operations, and make decisions in the treatment of complex diseases. Here, we review some outstanding examples of these BAN^2 proposals.

In synthetic biology, molecular communication systems are designed to control the behavior of synthetic cell populations in both time and space. With broadcasting and receiving messenger molecules, molecular communication can enable robust and predictable population dynamics [3]. For example, in [10], a molecular communication system is proposed to allow genetically engineered cells to form some predefined spatial pattern. The chemical signal acylhomoserine lactone (AHL) is synthesized and emitted by sender cells to the medium, and receiver cells with band-detect gene networks respond to a threshold AHL concentration by forming a ring-like topology. The given molecular communication system is expected to foster promising nanomedicine applications such as tissue engineering, biomaterial fabrication, and biosensing. Furthermore, in [7], a cell-to-cell molecular communication system with nitric-oxide signaling elements is introduced. The given system aims to increase the functionality of synthetic genetic circuits used for coordinating and programming engineered cell populations. It may also serve as a versatile tool in gene therapy applications.

Similarly, nanorobot-based nanomedicine applications also requires BAN^{2}s of nanorobots to provide reliable and controllable operations. The collective efforts of the communicating nanorobots can improve the likelihood of successful operations. Molecular communication clearly helps the nanorobots to easily correlate their sensory observations with their close proximity and an external microsystem designed for a health monitoring task [1].

Communication Theoretical Approaches to BAN^2 for Nanomedicine

In this section, we present the current state-of-the-art channel models and communication theoretical analyses devised for molecular communication systems. We also introduce open research issues, new interests, and developments beyond these models and analyses.

Channel Model and Communication Rate

According to the propagation types of carrier molecules, molecular communication can be mainly categorized into two major groups: those with passive transport and with active transport. In passive transport, information is conveyed from a transmitter NM (TN) to a receiver NM (RN) via free diffusion of carrier molecules, as shown in Fig. 3. The TN emits the molecules to the channel, and the emitted molecules freely diffuse in the medium. Some of these molecules electrochemically interact with the receptors of the RN. Such electrochemical contacts provide the reception of transmitted information. In active transport, molecular information is communicated actively using molecular motors (e.g., kinesin) in molecular rails or microtubules, as shown in Fig. 4.

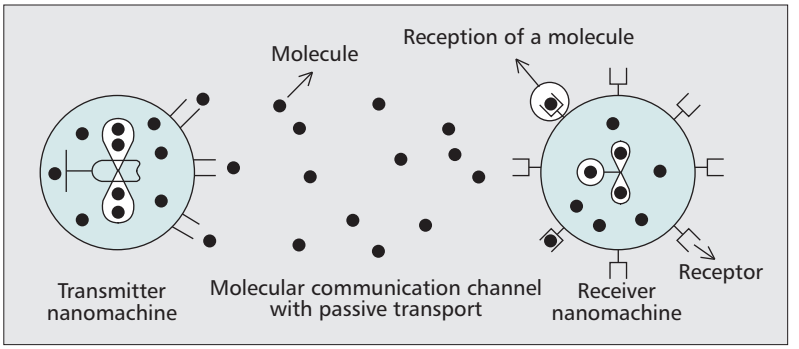

Figure 3. *Molecular communication channel with passive transport of information carrying molecules.*

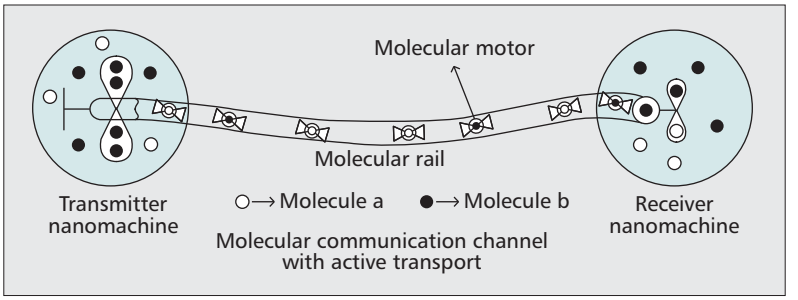

Figure 4. *Molecular communication channel with active transport of information carrying molecules.*

Molecular Communication with Passive Transport — In traditional wireless communication, information messages are encoded via binary bit levels (i.e., bits 0 and 1). These bits also correspond to two different signal levels that are transmitted and received by the transmitter and receiver, respectively. Similarly, a molecular communication channel with passive transport is mostly modeled as a *binary channel* with two bits, 0 and 1 [11]. In the binary channel approach, a single molecule or a number of them are transmitted by a TN at the beginning of the fixed-duration time slots to deliver bit 1. If the molecule or a threshold concentration reach the RN within a slot duration, the RN can correctly receive the bit 1. Otherwise, the RN erroneously receives bit 0. In order to deliver 0, the TN transmits no molecule within a slot duration. However, the molecules emitted in the previous slot intervals may reach the RN later when bit 0 is transmitted. This can clearly result in error in the delivery of 0. In order to mitigate such errors, the binary channel approach is also modified by extending the transmission of a single bit to two slot durations. More specifically, 00, 01, 10, and 11 are transmitted to deliver bits 0 and 1. Hence, the resultant channel is called a *4-input 2-output channel* [12].

In Fig. 5, the communication rates provided by the binary and 4-input 2-output channel approaches are compared for varying values of internode distance between TN and RN. The 4-input 2-output channel approach clearly outperforms the binary channel approach since it mitigates the errors by wisely expanding the

duration of single bit transmission. For the shorter internode distance values (i.e., 0.1–0.5 μm), the 4-input 2-output channel slightly enhances the rate, while it considerably improves the rate for the relatively longer distances. This result reveals that the 4-input 2-output channel may be more appropriate for nanomedicine applications in which NMs are not relatively close to each other. Apart from the binary and 4-input 2-output channel approaches, passive transport is also analytically modeled by incorporating three different phases of molecular communication (i.e., molecular emission, diffusion, and reception) into a single channel model [13].

Molecular Communication with Active Transport — The communication performance of active transport has been characterized mostly by means of an error probability. The molecules, loaded by a TN on molecular motors as shown in Fig. 4, are assumed to degrade and not to reach the RN with error probability p_e. If n distinct molecules are used, each of these n molecules is either successfully received with probability $(1 - p_e)$ or cannot reach the RN with the probability p_e. Hence, such a molecular active transport channel can be modeled as an n-ary *erasure channel*, and the communication rate of this channel can be given as $(1 - p_e) \log n$.

In Fig. 6, the communication rate of the n-ary erasure channel is shown with different p_e values according to varying numbers of distinct molecules (i.e., n) used in the channel.The rate can clearly be increased with n. By comparing the numerical results in Figs. 5 and 6, it can be concluded that active molecular communication may be more proper than passive molecular communication in terms of providing a higher communication rate. However, active molecular communication always necessitates an infrastructure (i.e., molecular rail and motors), while passive molecular communication is not affected by such a restriction. In fact, therapeutic NMs may not require a high communication rate to coordinate and share simple information content in nanomedicine applications. Therefore, active molecular communication may not be preferred if a preset infrastructure is not available.

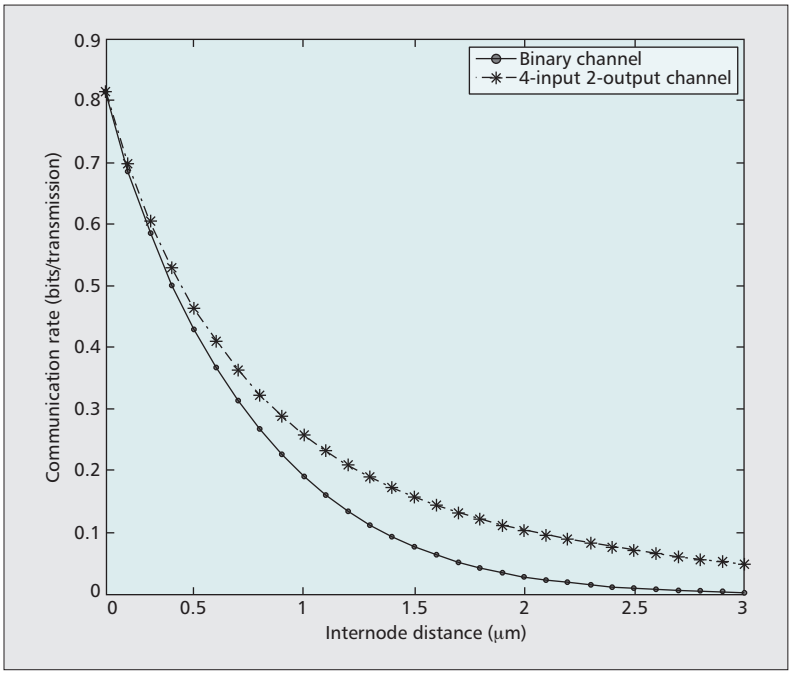

Figure 5. *Communication rate provided by binary channel and 4-input 2-output channel with respect to varying internode distance.*

Channel Noise

The characteristics of communication noise in the molecular communication channel also differ significantly from the traditional wireless communication channel. A theoretical model of molecular noise in diffusion-based molecular communication systems is introduced in [15]. The effect of noise on molecular communication performance is also investigated by considering various molecular transmission, propagation, encoding, and decoding mechanisms [16]. In addition to these efforts, biological noise [3], which is inherently observed in inter/intra cellular processes, must be jointly considered foran exact theoretical model of noise. Furthermore, the probability distribution of the noise process is required to be discovered to find the capacity of the molecular communication channel. In fact, the noise signal is statistically correlated with the channel input as introduced in [14]. Therefore, the channel input and noise should be jointly considered to investigate the information theoretical characteristics of the molecular communication channel. In addition to this, since the emitted molecules continuously diffuse in the medium until they are received, transient and asymptotic behavior of the noise also need to be investigated.

Deployment and Topology

As observed in Fig. 5, the capacity of molecular communication is severely prone to communication distance such that the capacity decreases with the communication distance. Therefore, dense deployment of NMs is imperative for nanomedicine applications to reliably convey messages along the highly delicate paths of a BAN[2]. On the other hand, some nanomedicine applications may require mobile NMs. Unlike the traditional mobility models of ad hoc nodes, in a BAN[2], mobility of NMs is mainly governed by extremely different rules such as Brownian motion. For example, in [6], a communication rate is derived for mobile ad hoc molecular nanonetworks inspired by a natural immune network consisting of mobile and communicating white blood cells. The molecular communication among NMs is assumed to be provided by means of random collisions of mobile NMs. The analytical evaluations of the rate expression manifest that a BAN[2] with mobile NMs can be realized with a sufficiently high end-to-end communication rate. Furthermore, some nanomedicine applications may necessitate a predefined topology of a BAN[2]. For example, a BAN[2] may be deployed on some critical points of the human heart for early detection of a possible heart attack. In such an application, all communication parameters must be regulated with respect to the predefined topology to minimize end-to-end latency so as to report a possible attack before it occurs.

Computation, Logic Operations, and Decision

In complex nanomedicine applications, a BAN[2] of therapeutic NMs performs computation and logic operations, and makes decisions to treat complex diseases. For example, an autonomous biomolecular computer is designed that analyzes the level of messenger RNA and produces a molecule so as to logically control the gene expression processes [4]. However, due to the lack of a central controller, in such applications, all operations must be managed by self-organization of NMs through molecular communication. In these operations, the reliability of molecular communication is crucial in order to efficiently provide computations and logic operations with relatively low error rates. Therefore, reliable and error-tolerant molecular encoding and decoding techniques must be developed for these nanomedicine applications. Furthermore, network information theory may be used to investigate the ultimate computation capability of coordinating NMs in a BAN[2]. Molecular information flow may also be formulated in order to deduce the computation speed. For example, deterministic molecular information flow in nanonetworks is formulated in [14], and this formulation can be used to investigate the computational aspects of a BAN[2].

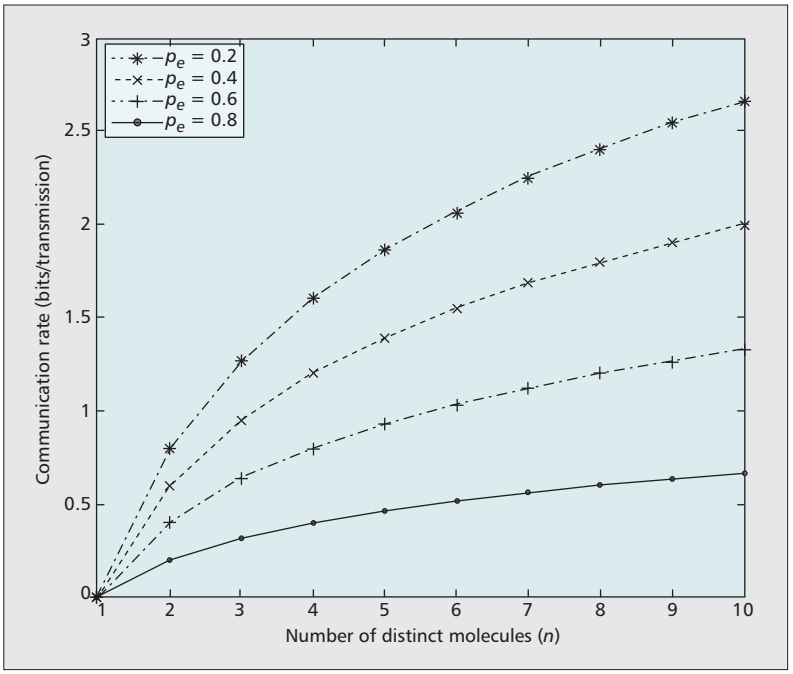

Figure 6. *Communication rate provided by* n*-ary erasure channel with varying channel error probability* p_e *for varying number of distinct molecules used in the channel.*

Medium Access and Routing

In order to achieve communication performance closer to the information theoretical bounds, efficient networking techniques are also required for the realization of a BAN[2]. Due to the very low-end memory and processing capabilities of self-organizing NMs, the developed algorithms entail the minimum level of computational complexity. In [14], the communication performance of a molecular multiple access channel is investigated. The analytical evaluations reveal that different NMs must access the medium using different types of molecules that can be distinguished at the receiver side. This is because communication bandwidth allocated to each NM reduces to almost zero if the same molecule type is used to access the same channel by a set of NMs [14]. Furthermore, the directivity of emitted molecules must be investigated to develop an efficient routing algorithm for the BAN[2]. In fact, a single molecule may diffuse toward all directions according to the rules of Brownian motion. However, a drift velocity may be used to direct a molecule to a specific direction. Therefore, drift velocity and routes may be jointly considered to develop an efficient routing algorithm. Since the propagation speed of molecules is extremely low, routing algorithms must also be delay-tolerant. For example, mobility of NMs may be exploited to tolerate high delay in such a way that transmission strategies of NMs are regulated according to the mobility patterns of NMs. Such a transmission strategy can reduce the delay.

Conclusion

The field of nanomedicine continues to evolve and advance, resulting from extensive research and development efforts in the field of nanotechnology. However, the pace of this development as well as increased opportunities in nanomedicine can be further realized through molecular communication. In this article, we have presented the concept of a BAN[2] that exploits molecular communication for the interconnection of NMs. The article discusses current solutions used in nanomedicine, and the nanomedicine applications are further discussed from the perspective of the BAN[2]. Finally, communication theoretical efforts such as channel capacity, deployment, and topology, as well as networking issues, are reviewed. These issues are further discussed through open research challenges that introduce new interests and development opportunities. Our investigations reveal that the BAN[2] with molecular communication is a necessary and promising tool for future nanomedicine in order to provide controllable, reliable, and efficient applications.

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