A Biochemically-Engineered Molecular Communication System
(Invited Paper)

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Abstract. Molecular communication uses molecules (i.e., chemical signals) as an information carrier and allows biologically- and artificially-created nano- or cell-scale entities to communicate over a short distance. It is a new communication paradigm and is different from the traditional communication paradigm that uses electromagnetic waves (i.e., electronic and optical signals) as an information carrier. Key research challenges in molecular communication include design of a sender, design of a molecular propagation system, design of a receiver, design of a molecular communication interface, and mathematical modeling of molecular communication components and systems. This paper focuses on system design and experimental results of molecular communication and briefly refers to recent activities in molecular communication.

Keywords: Nanotechnology, Bioengineering, Biochemical communication system, Functional soft materials.

1 Introduction

Molecular communication [1]-[2] is inspired by the biological communication mechanisms (e.g., cell-cell communication using hormones) [3] and artificially creates a biochemically-engineered communication system in which communication processes are controllable. Molecular communication uses molecules (i.e., chemical signals) as an information carrier and allows biologically- and artificially-created nano- or cell-scale entities (e.g., cells and biohybrid devices) to communicate over a short distance. It is a new communication paradigm and is different from the traditional communication paradigm that uses electromagnetic waves (i.e., electronic and optical signals) as an information carrier.

In molecular communication, a sender encodes information onto molecules (called information molecules) and emits the information molecules to the propagation environment. A propagation system transports the emitted information molecules to a

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receiver. The receiver, upon receiving the transported information molecules, reacts biochemically to the received information molecules (this biochemical reaction represents decoding of the information).

Molecular communication is a new and interdisciplinary research area that spans the nanotechnology, biotechnology, and communication technology, and as such, it requires research into a number of key areas. Key research challenges in molecular communication include 1) design of a sender that generates molecules, encodes information onto the generated molecules, and emits the information encoded molecules (information molecules), 2) design of a molecular propagation system that transports the emitted information molecules from a sender to a receiver, 3) design of a receiver that receives the transported information molecules and biochemically reacts to the received information molecules, 4) design of a molecular communication interface between a sender and a molecular propagation system and also between the propagation system and a receiver to allow a generic transport of information molecules independent of their biochemical/physical characteristics, 5) mathematical modeling of molecular communication components and systems. This paper focuses on system design and experimental results of molecular communication.

The rest of this paper is organized in the following manner. Section 2 presents key features and basic communication processes in molecular communication. Section 3 explains detailed system design and initial experimental results of key components in a molecular communication system. Section 4 briefly describes selected recent activities in molecular communication and concludes the paper.

2 Key Features and Basic Communication Processes

Molecular communication is a new communication paradigm and is different from the traditional communication paradigm (Table 1). Unlike the traditional communication that utilizes electromagnetic waves as an information carrier, molecular communication utilizes molecules as an information carrier. In addition, unlike in the traditional communication where encoded information such as voice, text, and video is decoded and regenerated at a receiver, in molecular communication, information molecules cause some biochemical reactions at a receiver and recreate phenomena and/or chemical status that a sender transmits. Other features of molecular communication include aqueous environmental communication, stochastic nature of communication, low energy-consumption communication, and being highly compatible with biological systems.

Although the communication speed/distance of molecular communication is slower/shorter than that of the traditional communication, molecular communication may carry information that is not feasible to carry with the traditional communication (such as biochemical status of a living organism) between the entities that the traditional communication does not apply (such as biological entities). Molecular communication has unique features that are not seen in the traditional communication and is not competitive but complementary to the traditional communication.

Figure 1 depicts an overview of a molecular communication system that includes senders, molecular communication interfaces, molecular propagation systems, and receivers.

Table 1. Comparisons of key features between the traditional communication and molecular communication

Key features	Traditional communication	Molecular communication
Information carrier	Electromagnetic waves	Molecules
Signal type	Electronic and optical signals	Chemical signals
Propagation speed	Light speed (3×10^5 *km/sec*)	Slow speed (*a few μm/sec*)
Propagation distance	Long (ranging from *m* to *km*)	Short (ranging from *nm* to *m*)
Propagation environment	Airborne and cable medium	Aqueous medium
Encoded information	Voice, text, and video	Phenomena and chemical status
Behavior of receivers	Decoding of digital info	Biochemical reaction
Communication model	Deterministic communication	Stochastic communication
Energy consumption	High	Extremely low

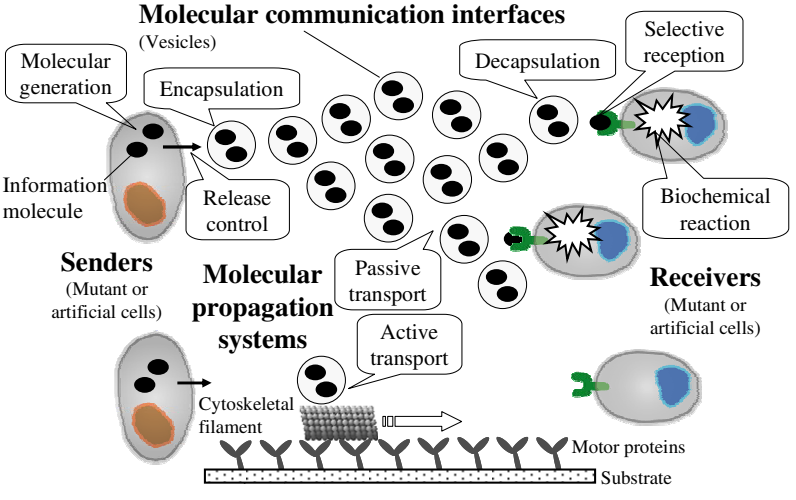

Fig. 1. An overview of a molecular communication system

A sender generates molecules, encodes information onto the generated molecules, and emits the information encoded molecules (information molecules) into a propagation environment. The sender may encode information on the type of the information molecules used or the concentration of the information molecules used. Possible approaches to create a sender include genetically modifying eukaryotic cells and artificially constructing biological devices that are capable of performing the encoding.

A molecular communication interface acts as a molecular container that encapsulates information molecules to hide the characteristics of the information molecules during the propagation from the sender to a receiver to allow a generic transport of information molecules independent of their biochemical/physical characteristics. Using a lipid bilayer vesicle [4] is a promising approach to encapsulate the information molecules. Encapsulated information molecules are decapsulated at a receiver.

A molecular propagation system passively or actively transports information molecules (or vesicles that encapsulate information molecules) from a sender to an appropriate

receiver through the propagation environment. The propagation environment is aqueous solution that is typically found within and between cells. Using biological motor systems (motor proteins and cytoskeletal filaments) [5] are a promising approach to actively and directionally transport information molecules.

A receiver selectively receives transported and decapsulated information molecules, and biochemically reacts to the received information molecules. Possible approaches to create a receiver are to genetically modify eukaryotic cells and to artificially construct biological devices as to control the biochemical reaction.

3 Detailed System Design and Initial Experimental Results

This section describes detailed system design and initial experimental results of key components in a molecular communication system, and shows that our system design is feasible.

3.1 Molecular Communication Interface

A vesicle-based communication interface provides a mechanism to transport different types of information molecules in diverse propagation environments [6]. This is because the vesicle structure (i.e., a lipid bilayer membrane) provides a generic architecture that compartmentalizes and transports diverse types of information molecules independent of their biochemical/physical characteristics. The vesicle structure also protects information molecules from denaturation (e.g., molecular deformation caused by changes in temperature or pH) in the propagation environment. Key research issues in implementing the vesicle-based communication interface include how vesicles encapsulate information molecules at a sender and how vesicles decapsulate the information molecules at a receiver.

The authors of this paper have proposed a molecular communication interface that uses a vesicle embedded with gap junction proteins (Fig. 2) [7]. A gap junction is an inter-cellular communication channel formed between neighboring two cells, and it consists of two docked hemichannels (connexons) constructed from self-assembled six gap junction proteins (connexins) [8]. When a gap junction is open, molecules whose molecular masses are less than 1.5 kDa can directly propagate through the gap junction channel connecting two cells according to the molecular concentration gradient. A gap junction hemichannel is closed unless two hemichannels are docked.

In the molecular communication interface that the authors of this paper proposed, a sender stores information molecules inside itself and has gap junction hemichannels. When a vesicle with gap junction hemichannels physically contacts the sender, gap junction channels are formed between the sender and the vesicle, and the information molecules are transferred from the sender to the vesicle according to the molecular concentration gradient. When the vesicle detaches from the sender spontaneously, the gap junction hemichannels at the sender and at the vesicle close, and the information molecules transferred from the sender to the vesicle are encapsulated in the vesicle. Encapsulation of information molecules in a vesicle allows a molecular propagation system to transport the information molecules from the sender to a receiver independent of their biochemical/physical characteristics. A receiver also has gap junction

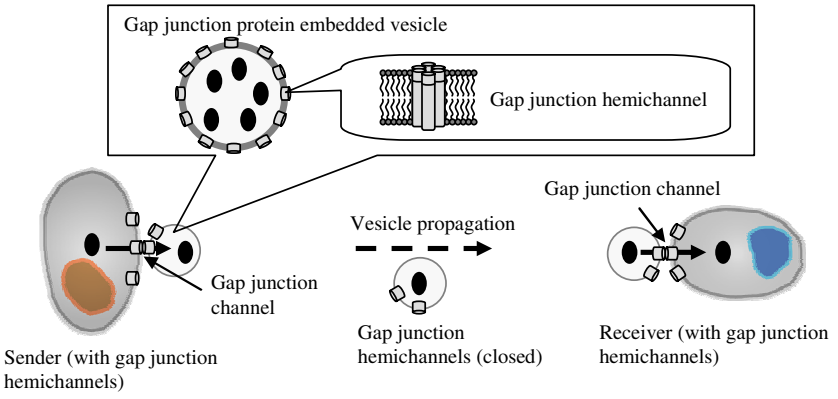

Fig. 2. A schematic diagram of a molecular communication interface using a vesicle embedded with gap junction proteins

hemichannels, and when the transported vesicle physically contacts the receiver, a gap junction channel is formed between the vesicle and the receiver, and the information molecules in the vesicle are transferred into the receiver according to the molecular concentration gradient.

In order to investigate the feasibility of the designed communication interface, the authors of this paper created connexin-43 (one of the gap junction proteins) embedded vesicles [7]. Microscopic observations confirmed that calceins (hydrophilic dyes used as model information molecules) were transferred between connexin-43 embedded vesicles and the transferred calceins were encapsulated into the vesicles [9]. This result indicates that the created connexin-43 embedded vesicle (a molecular communication interface) may encapsulate information molecules and receive/ transfer information molecules from/into a sender/receiver through gap junctions.

3.2 Molecular Propagation System

In eukaryotic cells, biological motors (e.g., kinesins) load/unload particular types of cargoes (e.g., vesicles) without external stimuli and transport them along cytoskeletal filaments (e.g., microtubules (MTs)) using the energy of adenosine triphosphate (ATP) hydrolysis [5]. Because of these biological capabilities of autonomous loading/unloading and transporting of specified cargoes, there is considerable interest in incorporating kinesins and MTs into artificially-created transporters and actuators in nano- or cell-scale systems and applications [10].

The authors of this paper have proposed a molecular propagation system that uses the reverse geometry of MT motility on kinesins and DNA hybridization/strand exchange [11]. The proposed propagation system uses DNA hybridization/strand exchange to achieve autonomous loading/unloading of specified cargoes (e.g., vesicles encapsulating information molecules) at a sender/receiver and MT motility to transport the loaded cargoes from a sender to a receiver (Fig. 3).

In order to use the DNA hybridization/strand exchange, each gliding MT, cargo, and unloading site is labeled with different single-stranded DNAs (ssDNAs). Note

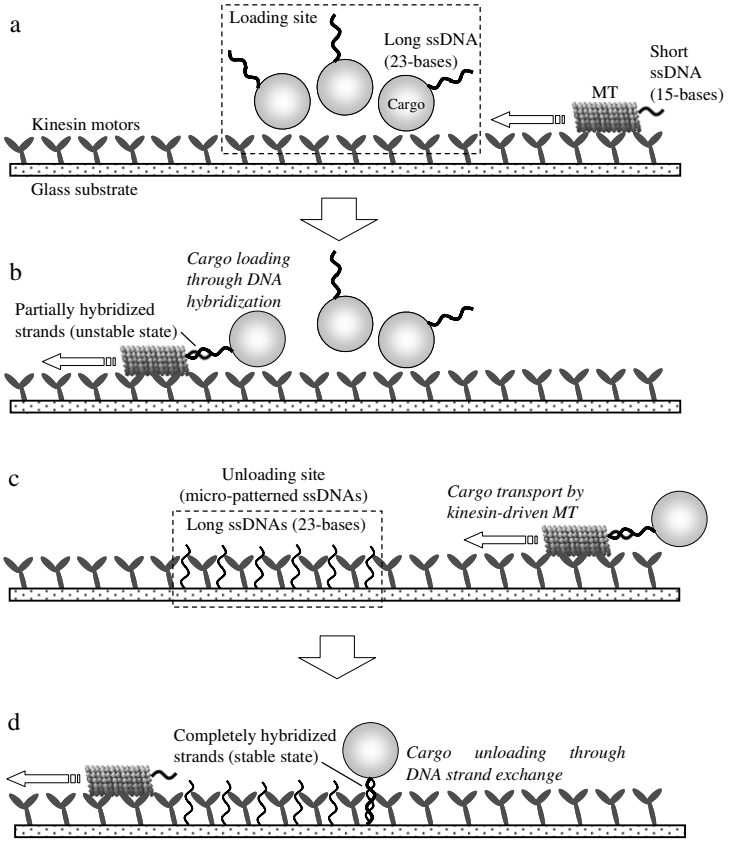

Fig. 3. A schematic diagram of a molecular propagation system using the reverse geometry of MT motility on kinesins and DNA hybridization/strand exchange

that the length of an ssDNA attached to an MT is designed to be shorter than that of the cargo, and the length of an ssDNA attached to a cargo is designed to be as long as that of the unloading site. Cargoes are pooled at a given loading site (a given sender) (Fig. 3a) and the ssDNA for the cargo is designed to be either complementary or non-complementary to that of the MT. When an MT labeled with an ssDNA passes through a given loading site, a cargo labeled with an ssDNA complementary to that of the MT is selectively loaded onto the gliding MT through DNA hybridization without external stimuli (Fig. 3b), while cargoes labeled with a non-complementary ssDNA remain at the loading site. The cargo loaded onto the MT (i.e., an MT-cargo complex) is transported by MT motility on kinesins toward a given unloading site (a given receiver) (Fig. 3c). To achieve autonomous unloading at a given unloading site, the ssDNA attached to each unloading site is designed to be either complementary or non-complementary to that attached to the cargo. When the MT-cargo complex passes through an unloading site, the cargo labeled with an ssDNA complementary to that attached to the unloading site is selectively unloaded from the gliding MT through DNA strand exchange without external stimuli (Fig. 3d).

In order to investigate the feasibility of the designed propagation system, the authors labeled MTs with ssDNAs using a chemical linkage that cross-links thiolated ssDNAs and amino groups of MTs, while maintaining smooth gliding of labeled MTs on kinesins [12]. Microscopic observations confirmed that 23-bases ssDNA labeled cargo-microbeads (used as model vesicles in which information molecules were encapsulated) were selectively loaded onto gliding MTs labeled with complementary 15-bases ssDNAs [12]. Microscopic observation also confirmed that loaded cargoes were selectively unloaded from the gliding MTs at a micro-patterned unloading site where complementary 23-bases ssDNAs were immobilized [13]. These results indicate that gliding MTs may load/unload cargo-vesicles at a sender/receiver through the DNA hybridization/strand exchange.

3.3 Receiver

A receiver selectively receives transported and decapsulated information molecules, and biochemically reacts to the received information molecules. Researchers at NAIST (Nara Institute of Science and Technology) worked with the authors of this paper and have proposed a receiver that uses a giant liposome embedded with gemini-peptide lipids [14]-[15]. A liposome is an artificially created vesicle that has the lipid bilayer membrane structure similar to vesicles and cells. The gemini-peptide lipids are composed of two amino acid residues, each having a hydrophobic double-tail and a functional spacer unit connecting to the polar heads of the lipid. The liposomes embedded with the same type of gemini-peptide lipids in their lipid bilayer membranes assemble in response to an external stimulus (e.g., light, ions, and temperature) [16]-[17]. This allows a selective reception of information molecules at a receiver (Fig. 4).

The gemini-peptide lipids are used as a molecular tag. A small liposome embedded with a molecular tag acts as a container of information molecules (a molecular container) and a giant liposome embedded with a molecular tag act as a receiver. A receiver is embedded with a specific molecular tag and a molecular container whose destination is the receiver is also embedded with the same type of molecular tag. When an external stimulus is applied to the receivers and the molecular containers, a receiver embedded with a molecular tag that is responsive to the applied external stimulus receives molecular containers embedded with the same type of molecular tag. This selective reception mechanism controlled by external stimuli may lead to creation of not only unicast-type but also multicast- and broadcast-type molecular communication.

In order to investigate the feasibility of the designed receiver, researchers at NAIST created molecular containers (liposomes with a diameter approximately 100 nm) and receivers (liposomes with a diameter larger than 2 μm) both containing zinc-ion responsive molecular tags in their lipid bilayer membranes. When zinc ions were added to the aqueous environment where both the molecular containers and receivers exist, the selective binding of the molecular containers to the receivers was observed [14]. The researchers at NAIST also created molecular containers and receivers both containing photo-responsive molecular tags in their lipid bilayer membranes to control reception of molecular containers to a receiver [15]. The photo-responsive molecular tag embedded in the receiver also acted as an artificial receptor, and interacted with an enzyme (signal amplifier) embedded in the receiver through metal ions when

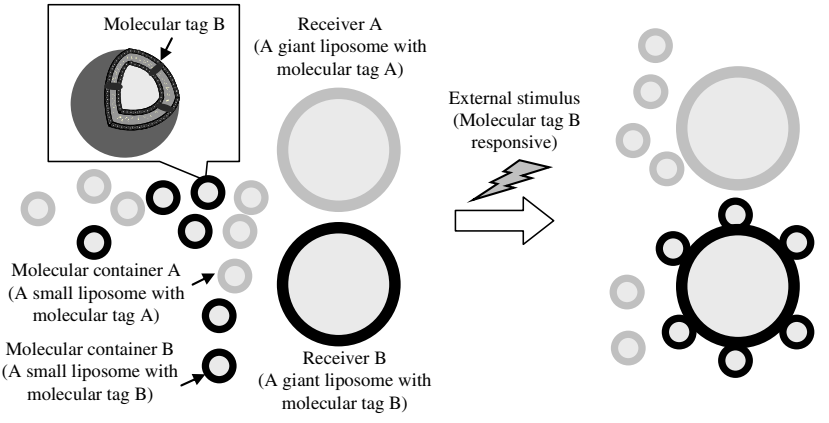

Fig. 4. A schematic diagram of receivers using giant liposomes with gemini-peptide lipids

a photonic signal was applied; achieving the signal amplification at the receiver by applying a photonic signal [15]. These results indicate that a receiver may selectively receive tagged molecular containers (encapsulating information molecules) and may biochemically react to the received information molecules by applying an external stimulus.

3.4 Integrated Molecular Communication System

The above sections have described system components in molecular communication (i.e., a molecular communication interface using a vesicle embedded with gap junction proteins, a propagation system using the MT motility on kinesins and DNA hybridization/strand exchange, and a receiver using a giant liposome embedded with gemini-peptide lipids). Described system components are compatible with each other and will be integrated into a single system (Fig. 5). Note that assembled liposomes

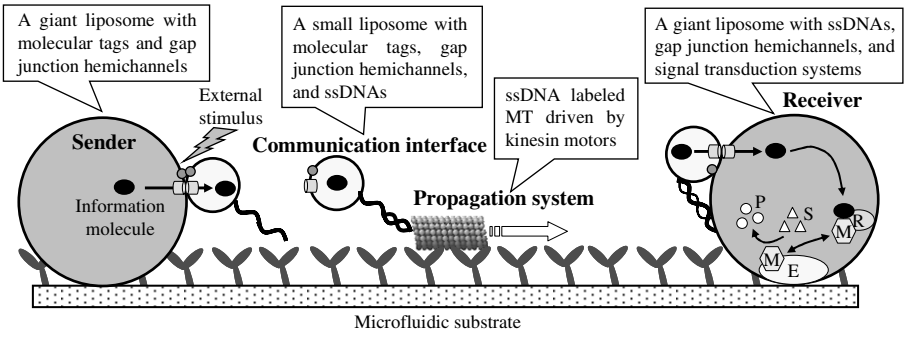

Fig. 5. A schematic diagram of an integrated molecular communication system. R, M, E, S, and P represent a receptor, a mediator, an enzyme, substrates, and products, respectively.

with molecular tags (gemini-peptide lipids) can be dissociated reversibly by applying a complementary external stimulus (e.g., applying UV-light for liposome assembly and applying visible light for liposome dissociation), and the selective reception mechanism may be applied to the selective transmission mechanism of molecular containers (small liposomes) at a sender.

4 Conclusions

This paper described basic concepts and key system components of molecular communication. This paper also discussed in detail system design of a communication interface that uses a vesicle embedded with gap junction proteins, a propagation system that uses MT motility on kinesins and DNA hybridization/strand exchange, and a receiver that uses a giant liposome with gemini-peptide lipids. The feasibility of the designed system components was confirmed through the biochemical experiments.

Molecular communication is an emerging interdisciplinary research area and is receiving increasing attention in the areas of biophysics, biochemistry, information science, and communication engineering [18]-[21]. The authors of this paper hope that a number of researchers participate in and contribute to the development of molecular communication.

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