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Molecular communication: Harnessing biochemical materials to engineer biomimetic communication systems

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ABSTRACT

Molecular communication uses molecules (i.e., biochemical signals) as an information medium and allows biologically and artificially created nano- or microscale entities to communicate over a short distance. It is a new communication paradigm; it is different from the traditional communication paradigm, which uses electromagnetic waves (i.e., electronic and optical signals) as an information medium. Key research challenges in molecular communication include design of system components (i.e., a sender, a molecular propagation system, a receiver, and a molecular communication interface) and mathematical modeling of each system component as well as entire systems. We review all research activities in molecular communication to date, from its origin to recent experimental studies and theoretical approaches for each system component. As a model molecular communication system, we describe an integrated system that combines a molecular communication interface (using a lipid vesicle embedded with channel-forming proteins), a molecular propagation system (using microtubule motility on kinesin molecular motors and DNA hybridization), and a sender/receiver (using giant lipid vesicles embedded with gemini-peptide lipids). We also present potential applications and the future outlook of molecular communication.

1. Introduction

Communication technologies commonly refer to electromagnetic wave-based electronic and optical communications, in a highly networked information-based society where cellular phones and the Internet are essential tools in daily life. The origin of electronic communication goes back to the 1700s; research has aimed to achieve high-speed, high-capacity and long-distance communication. In the near future, such innovation will provide gigabit-class wireless communication. However, the greatest opportunity is to create a new communication paradigm that extends and complements the traditional high-speed communication paradigm, which uses electromagnetic waves (i.e., electronic and optical signals) as an information medium. In this review, we focus on natural communication mechanisms that use molecules (i.e., biochemical signals) as an information medium; molecule-based communication systems are ubiquitously employed in living organisms and have been developed by evolutionary processes for billions of years.

Communication in biological systems is typically achieved by molecules (except for electric signal transduction mechanisms such as nerve systems) and is often found in aqueous environments such as within and between biological cells. For instance, multicellular organisms, including human beings, perform maintenance of homeostasis, growth regulation, kinematic control, memory and learning through inter- and intra-cellular communication using signal-transducing molecules such as hormones [2,79]. If artificially designed and controllable molecule-based communication systems that transmit biochemical information (e.g., status of living organisms) can be developed, which is not feasible using traditional communication, it may be possible to devise a new communication paradigm. In 2005, we named this concept 'molecular communication' [45] and have pioneered the research in this

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field [64,65,43,66,83]. Molecular communication provides molecule-based biomimetic communication mechanisms, and it allows biologically and artificially created nano- or microscale entities (e.g., biological cells and biohybrid devices) to communicate over a short distance. Molecular communication has received increasing attention as an interdisciplinary research area, which spans nanotechnology, biotechnology, and communication engineering [90,61,75,1].

In generic molecular communication, a sender generates molecules, encodes information onto the molecules (called information molecules) and emits the information molecules to the propagation environment. A propagation system transports the emitted information molecules to a receiver. The receiver reacts biochemically according to the received information molecules; this biochemical reaction represents decoding of the information.

Molecular communication is a new and interdisciplinary research area, and as such, it requires research into a number of key areas. The main challenges are: (1) design of a sender that generates molecules, encodes information onto the molecules, and emits 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 resulting in decoding of the information, (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 generic transport of information molecules independent of their biochemical and physical characteristics, and (5) establishment of molecular communication theory and mathematical modeling of system components and entire systems. This review covers all research activities in molecular communication including experimental and theoretical approaches, potential applications and the future outlook.

The review is organized as follows. Section 2 is an overview of generic architecture and research activities in molecular communication. Sections 3–5 explain experimental approaches and achievements that are applicable to the molecular communication interface, the molecular propagation system, and senders/receivers. Section 6 depicts a model molecular communication system that integrates selected compatible key components into a controllable system. Section 7 refers to theoretical approaches in molecular communication. Section 8 briefly describes potential applications to which molecular communication can be applied, and it concludes the review.

2. Overview of molecular communication

2.1. Key features

Molecular communication is a new communication paradigm (Table 1). Unlike traditional communication, which utilizes electromagnetic waves as an information medium, molecular communication utilizes molecules. In addition, unlike in traditional communication where encoded information such as voice, text and video is decoded and regenerated at a receiver, in molecular communication information molecules activate biochemical reactions at a receiver and may recreate phenomena and/or the chemical status, which a sender then transmits. Other features of molecular communication include aqueous environmental communication, low energy consumption communication, and high compatibility with biological systems.

Although the speed/distance of molecular communication is slower/shorter than that of traditional communication, molecular communication may enable transmission of information between biologically and artificially created nano- or microscale entities (e.g., biological cells and biohybrid devices), which is not feasible using traditional communication (e.g., biochemical status of a living organism). Molecular communication has unique features, which do not replace those of traditional communication, but are complementary to them.

2.2. Generic architecture and requirements

Fig. 1 depicts a generic molecular communication architecture that includes the key system components (i.e., senders, molecular communication interfaces, molecular propagation systems, and receivers). A sender generates molecules, encodes information onto the molecules (called information molecules) and emits the information molecules into a propagation environment. The sender may encode information on the type or concentration of molecules. Biochemical molecules, such as proteins, peptides, deoxyribonucleic acids (DNAs) and ions, can be used as information molecules. Possible approaches to creating a sender include genetically modifying eukaryotic cells and artificially constructing biological devices to control the encoding.

It is best to encapsulate the emitted information molecules into a molecular communication interface that acts as a molecular container to hide the biochemical and physical characteristics of the information molecules during propagation. A lipid bilayer vesicle [57,51] is a promising way to encapsulate the information molecules. The encapsulated information molecules are decapsulated at a receiver.

A molecular propagation system passively or actively transports the information molecules (or vesicles that encapsulate information molecules) from a sender to an appropriate receiver through the propagation environment. The propagation environment is an aqueous solution that is typically found within and between cells. Passive transport refers to diffusion-based molecular propagation, while active transport refers to directional molecular propagation with energy consumption. Approaches to constructing molecular propagation systems typically use Brownian motion and biomolecular motors [88,94,97] to passively and actively transport information molecules, respectively.

A receiver selectively receives transported (and decapsulated) information molecules and biochemically reacts to the received information molecules; this biochemical reaction represents decoding of the information. Possible approaches to creating a receiver are to genetically modify eukaryotic cells and to artificially construct biological devices to control the biochemical reaction.

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

Key features	Traditional communication	Molecular communication
Information medium	Electromagnetic waves	Molecules
Signal type	Electronic and optical signals	Biochemical signals
Propagation speed	Light speed (3×10^5 km/s)	Slow speed (*a few* μm/s)
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 information	Biochemical reaction
Energy consumption	High	Extremely low

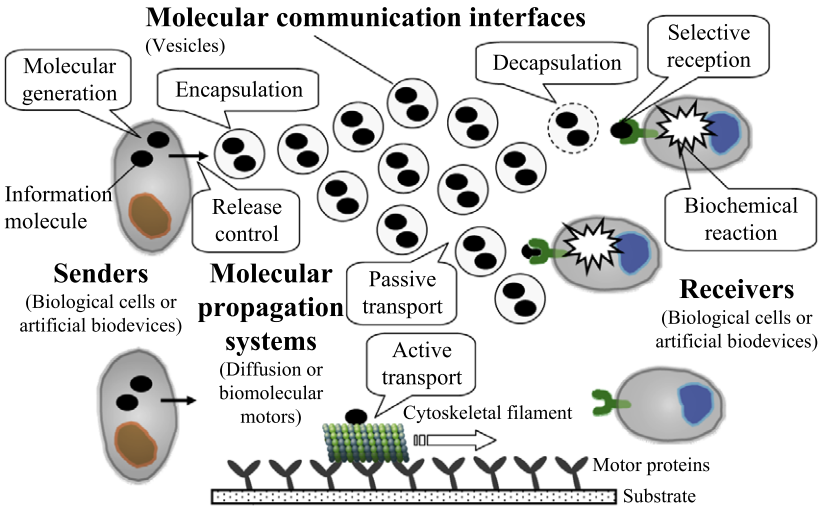

Fig. 1. Generic molecular communication architecture that includes the key system components (i.e., senders, molecular communication interfaces, molecular propagation systems, and receivers).

We define a molecular communication system as a system that meets the following conditions: (1) biological or artificially synthesized molecules are used to construct molecular communication components and systems, (2) each molecular communication process is artificially controllable, and (3) molecules are used as an information medium and biochemical reactions represent decoding of the information.

2.3. Research activities

Molecular communication has received increasing attention in biophysics, biochemistry, information science, and communication engineering. As summarized in Table 2, various workshops and symposia have been organized worldwide in recent years. In 2008, the National Science Foundation (NSF) recognized the importance and impact of molecular communication research [27]. In mid 2008, the Institute of Electrical and Electronics Engineers (IEEE) Emerging Technologies Committee launched a new subcommittee to advance the concept of nano-scale networking and molecular communication [28]. In 2010, Elsevier launched the Nano Communication Networks journal, which focuses entirely on molecular communication research [29].

3. Molecular communication interface

A vesicle-based communication interface provides a mechanism to transport different types of information molecules in diverse propagation environments [67]. A liposome is an artificially created spherical vesicle composed of a phospholipid bilayer membrane surrounding a discrete aqueous compartment (an inner aqueous phase); its diameter can be controlled from tens of nanometers to tens of micrometers [57,51]. The liposomal structure compartmentalizes information molecules from the propagation environment and provides a generic architecture to transport diverse types of information molecules, independent of their biochemical and physical characteristics. The liposomal structure also protects information molecules from denaturation (e.g., molecular deformation and cleavage caused by enzymatic attacks or changes in pH of the outer aqueous phase) in the propagation environment.

Key research issues in implementing the liposome-based communication interface include how liposomes encapsulate information molecules at a sender, and how liposomes decapsulate the information molecules at a receiver. One promising approach is to use a liposome embedded with gap junction proteins [68,69]. A gap junction is an inter-cellular communication channel formed between two neighboring cells; it consists of two docked

Table 2
Major workshops and symposia on molecular communication.

Time	Venue	Event
Mar. 2005	Miami, FL, USA	Panel at IEEE INFOCOM'05 [30]
Oct. 2005	Huntington Beach, CA, USA	Technical session at IEEE CCW'05
Jan. 2006	Tokyo, Japan	International symposium
Nov. 2006	Okinawa, Japan	Symposium at biophysics conference, EABS'06
Dec. 2006	Cavalese, Italy	Panel at BIONETICS'06 [31]
Feb. 2007	Pittsburgh, PA, USA	Technical session at IEEE CCW'07
Sep. 2007	Okazaki, Japan	Domestic workshop
Dec. 2007	Budapest, Hungary	Workshop at BIONETICS'07 [32]
Dec. 2007	Yokohama, Japan	Symposium at biophysics conference [33]
Feb. 2008	Arlington, VA, USA	NSF workshop [27]
Sep. 2008	Kawasaki, Japan	Tutorial at IEICE society conference
Sep. 2008	Boston, MA, USA	Keynote speech at Nano-Net'08 [34]
Nov. 2008	Hyogo, Japan	Workshop at BIONETICS'08 [35]
Aug. 2009	San Francisco, CA, USA	Workshop at IEEE ICCCN'09 [36]
Dec. 2010	Miami, FL, USA	Plenary talk and tutorial at IEEE GLOBECOM'10 [37]

hemichannels (connexons) constructed from self-assembled six gap junction proteins (connexins) [54]. When an open gap junction is formed, molecules whose molecular masses are less than 1.5 kDa can directly propagate through the gap junction channel connecting the two cells according to the molecular concentration gradient. The gap junction hemichannel is closed unless the two hemichannels are docked.

In molecular communication systems using a liposome embedded with gap junction proteins as a molecular communication interface, the sender stores information molecules inside itself and has gap junction hemichannels. When a liposome with gap junction hemichannels physically contacts the sender, gap junction channels are formed between the sender and the liposome, and the information molecules are transferred from the sender to the liposome according to the molecular concentration gradient. When the liposome spontaneously detaches from the sender, the gap junction hemichannels at the sender and at the liposome close and the information molecules are encapsulated in the liposome. A receiver also has gap junction hemichannels, and when the transported liposome physically contacts the receiver a gap junction channel is formed between the liposome and the receiver. Then the information molecules in the liposome are transferred into the receiver according to the molecular concentration gradient; this results in the decapsulation of the information molecules.

The feasibility of designing a communication interface has been investigated by creating connexin (Cx)-embedded liposomes [68,69,52]. Microscopic observations showed that encapsulated calcein (i.e., hydrophilic fluorescent dye used as model information molecules) was transferred from Cx-embedded liposomes to the same kind of Cx-expressing living cells (e.g., from Cx43-embedded liposomes to Cx43-expressing U2OS cells), and that the transferred calcein was decapsulated into the cells [52] (Fig. 2). These results indicate that the Cx-embedded liposomes (i.e., molecular communication interfaces) may encapsulate the information molecules and receive/transfer information molecules from/into a sender/receiver through gap junctions. Interestingly, different types of connexins (e.g., Cx43 and Cx32) cannot form a gap junction channel [54]; thus, calcein was not transferred from the Cx-embedded liposomes to different types of Cx-expressing

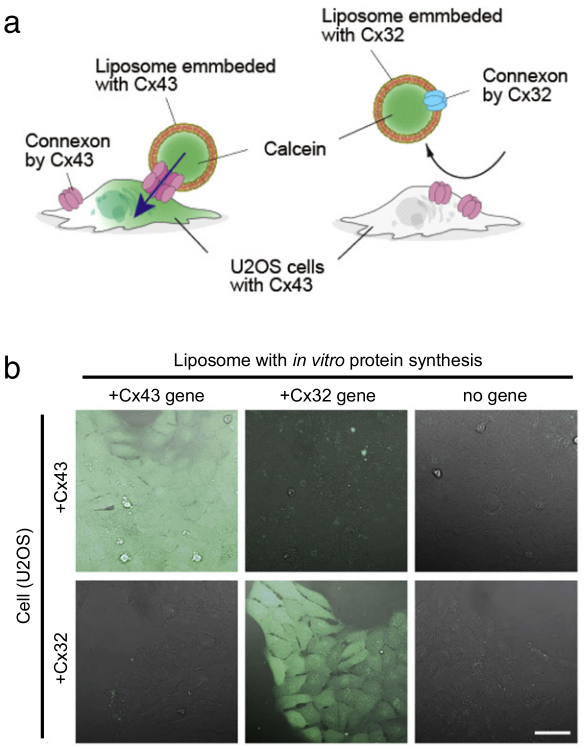

Fig. 2. Example of a molecular communication interface using Cx-embedded liposomes. (a) Schematic illustration of fluorescent dye transfer experiments. (b) Fluorescent dye, calcein, was transferred from Cx-embedded liposomes to the same type of Cx-expressing U2OS cells, and the transferred calcein was decapsulated into the cells. Calcein was not transferred from the Cx-embedded liposomes to different types of Cx-expressing U2OS cells. The scale bar corresponds to 50 μm.
Source: Each panel in (b) is reproduced with permission from [52]; copyright 2009, Elsevier.

living cells [52] (Fig. 2). This selective permeability implies that it will be possible to devise selective encapsulation/decapsulation functionalities.

Other promising approaches to encapsulation and decapsulation functionalities are to use liposome fission and liposome fusion, respectively. In molecular communication systems that use liposome fission and liposome fu-

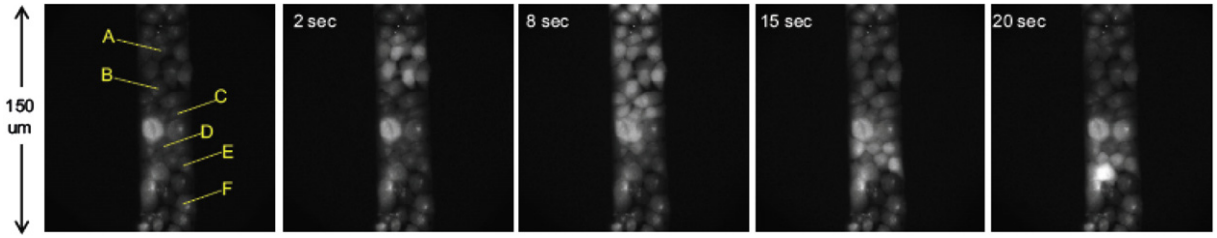

Fig. 3. Example of diffusion-based passive transport in molecular communication using a Cx43-expressing cell-to-cell network. The center of cell A was stimulated and instantly increased its cytosolic Ca^{2+}. Fluorescence images showed that the increase in Ca^{2+} then propagated along the cell line (e.g., cells A, B, C, D, E) at about 5 μm/s and reached the cell that was 10 cells away from the stimulated cell.
Source: Each panel is reproduced with permission from [72]; copyright 2008, IEEE.

sion, the senders and receivers are also liposomes. Small liposomes can be budded and produced from giant sender liposomes by applying chemical triggers for membrane fission such as a surfactant [49] and a multivalent anionic fluorescent dye [101]. Information molecules stored within a giant sender liposome can be encapsulated in a budded, small liposome. Furthermore, the liposome contents can be mixed by liposome fusion; this is triggered by application of an ion [21], a surfactant [58], voltage [93], changes in pH [53], or DNA hybridization [15]. This implies that information molecules can be encapsulated into a small liposome by liposome fission and decapsulated into a receiver liposome by liposome fusion.

4. Molecular propagation system

4.1. Passive transport

The simplest and easiest approach to transporting information molecules (or vesicles that encapsulate information molecules) from a sender to a receiver is to use free diffusion. In biological systems, for instance, neurotransmitters such as acetylcholines diffuse at a synapse (around 100 nm gap between a nerve cell and a target cell); cellular slime molds such as amoebas exhibit chemotaxis by detecting a molecular concentration gradient of cyclic adenosine monophosphates (cAMPs) diffused from hundreds of micrometers away, and pheromones secreted from insects can affect receiver insects, even if they are diffused from over several meters [2,79]. Generally, achievable rates of transmitted information molecules at a receiver are low because of the Brownian motion and the dilution effect in the propagation environment; these observations indicate that diffusion-based passive transport in molecular communication is feasible as long as the receiver sensitivity is high. Possibilities of diffusion-based long-range molecular propagation are discussed in [25].

An alternative diffusion-based passive transport in molecular communication is to use a connexin (Cx)-expressing cell-to-cell network [78,76,72,77,74,73]. In this approach, Cx-expressing cells are connected with each other through gap junction channels formed between adjacent cells, and information molecules propagate through these channels from a sender cell to receiver cells. This means that the Cx-expressing cells act as senders, receivers, and molecular communication interfaces. For instance, in [72], Cx43-expressing cells were micropatterned in the form of a wire, and calcium ion waves (used as model information molecules) were propagated through gap junction channels from cell-to-cell along the cell wire (Fig. 3). The main challenge in this approach is to implement 'switching' and 'filter' mechanisms [76] to control the direction and range of molecular propagation using the selective permeability of the connexins or by dynamically regulating connexin functionalities. This will lead to a controllable propagation system of molecular communication.

4.2. Active transport

Biological systems have directional molecular propagation mechanisms as well as non-directional free diffusion-based molecular propagation mechanisms. Biomolecular motors, such as kinesins, directionally transport cargoes (e.g., subcellular organelles and lipid vesicles) to their designated destinations within a biological cell [88,94,97]. This mechanism is known as 'active transport' and is realized by the enzymatic actions of biomolecular motors, which convert chemical energy, derived from adenosine triphosphate (ATP), into mechanical work. This enables the directional transport of cargoes (i.e., information molecules in molecular communication) along cytoskeletal proteins, such as microtubules (MTs). Biomolecular motors are nano-scale actuators; they have received increasing attention as engineering materials because they also work outside of biological cells when aqueous conditions, such as temperature and pH, are suitable [38,96,89,26].

To construct biomolecular-motor-based molecular propagation systems that enable the transport of specified cargoes (i.e., information molecules or vesicles that encapsulate information molecules) from a sender to a receiver, two types of geometrical arrangement are possible. One is a biomimetic arrangement where kinesins transport cargoes by traveling over immobilized MTs. Cargoes such as nano- or microspheres [71,17,11,103], oil droplets [12] and lipid vesicles [13] have been successfully transported in systems having this arrangement. Considering that the direction of cargo transport is determined by the polarity (i.e., plus- and minus-ends) of immobilized MTs, the main challenge in this arrangement is to align the polarity of MTs into preconfigured network topologies of seamlessly connected MTs with atomic scale accuracy, or into self-organized network topologies of MTs utilizing their dynamic instabilities [59,22].

The other is a synthetic reverse arrangement where MTs transport cargoes by gliding over immobilized kinesins. In this arrangement, cargoes such as nano- or microspheres [7,14,41,40], virus particles [8], proteins [81, 55,23], DNAs [16,91,80] and lipid vesicles [46] have been successfully transported. Considering that the gliding direction of MTs can be controlled by utilizing preconfigured microlithographic tracks [39,47] or by applying electric [95] and magnetic fields [48], the main challenge in this arrangement is to load/unload cargoes onto/from gliding MTs at a sender/receiver in a reversible manner. Tight bindings, such as avidin–biotin or antigen–antibody bindings, that are suitable for permanent bindings may not be suitable for reversible cargo loading/unloading.

On these grounds, a molecular propagation system that selectively loads, transports and unloads cargoes using biomolecular-motor-based motility and DNA hybridization has been proposed [41,42]. In this system, single-stranded DNA (ssDNA) labeled MTs, gliding on kinesin-coated surfaces, act as cargo transporters; ssDNA-labeled cargoes are loaded/unloaded onto/from the gliding MTs. Microscopic observations showed that cargoes (e.g., nano- or microspheres used as model information molecules) were trapped at a micropatterned loading site (at a sender) through DNA hybridization between 10-base ssDNAs immobilized onto a glass substrate and 23-base ssDNAs attached to the cargoes (0 s in Fig. 4) [40]. MTs labeled with 15-base ssDNAs glided on the kinesin-covered surface toward the loading site at an average speed of 0.35 μm/s (0 and 20 s in Fig. 4). A cargo whose ssDNAs were complementary to those on the MT was loaded onto the gliding MT through DNA hybridization (strand exchange) when the MT glided through the loading site (40 s in Fig. 4). The loaded cargo was transported by kinesin-mediated MT motility to micropatterned unloading sites where 23-base ssDNAs were immobilized (50, 60, and 80 s in Fig. 4). When the cargo-loaded MT glided through an unloading site (a receiver), the cargo whose ssDNAs were complementary to those of the unloading site was unloaded from the gliding MT through DNA hybridization (strand exchange) [40]. These mechanisms were also applicable to biochemically fragile cargoes such as lipid vesicles [46]. This confirms that the propagation system is compatible with the vesicle-based molecular communication interface and can deliver vesicles (that encapsulate the information molecule) from a sender to a receiver specified by the DNA base sequences.

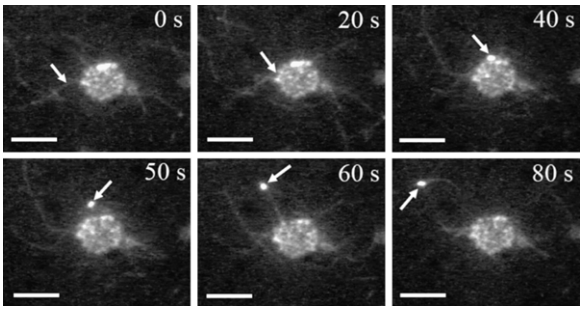

Fig. 4. Example of biomolecular-motor-based active transport in molecular communication using MT motility and DNA hybridization. Each panel shows time-lapsed fluorescence images of cargo loading and transport from a micropatterned loading site. The central circular region in each panel represents a loading site, and small bright dots in each panel represent the cargoes. The white arrows point to the leading head of a gliding MT. One of the cargoes trapped at the micropatterned loading site was loaded onto the gliding MT and transported outside of the loading site. The scale bars correspond to 10 μm.
Source: Each panel is reproduced with permission from [40]; copyright 2009, ACS.

5. Senders and receivers

5.1. Biological-cell-based approaches

The most straightforward approach to creating senders and receivers in molecular communication is to use living cells. In eukaryotic cells, organelles called ribosomes synthesize proteins, which are transported to cell membranes through the vesicle transport between the endoplasmic reticulum (ER) and Golgi apparatus. Then the transported molecules are secreted into the outside of the cell by exocytosis and diffused away [2,79]. The diffused molecules are selectively captured by cell surface receptors. The received molecules are transducted into intra-cellular signals, which induce cell behavior or are taken inside the cell by endocytosis; this results in biochemical reactions such as activation of enzymes and expression of genes [2,79]. This indicates a promising way to use living cells as senders/receivers in molecular communication, because biological cells inherently have most of the required functionalities as senders/receivers in molecular communication. In that case, the greatest research opportunities are how to control these inherent functionalities and how to encode information onto molecules.

For instance, *Escherichia coli* (*E. coli*) bacteria produce inter-cellular messengers such as acyl-homoserine lactones (AHLs) and respond according to the sensed population of surrounding bacteria. It was demonstrated that genetic manipulations for these mechanisms enable artificial control of fluctuation of bacterial populations and bioluminescence [104,9]. A synthetic multicellular system was created in which 'receiver' bacteria (genetically altered prokaryotic cells) to produce fluorescent proteins were programmed to form ring-like patterns of differentiation based on chemical gradients of AHL signals synthesized by 'sender' bacteria. Other patterns, such as ellipses and clovers, were achieved by placing senders in different configurations. Such a synthetic multicellular system is an example of molecular communication that uses bacteria as senders/receivers and free diffusion as a molecular propagation system.

Genetically altered mutant eukaryotic cells could be also used as senders/receivers. In the process of vesicle transport within eukaryotic cells such as yeasts, export molecules are selected and sorted strictly at the ER, and recycled between the ER and Golgi apparatus [87]. If information is encoded on the type of molecules or the concentration of molecules, the genetically altered cells, which change the sorting and secreting molecules in response to the external stimuli such as temperature and light, may act as senders in molecular communication.

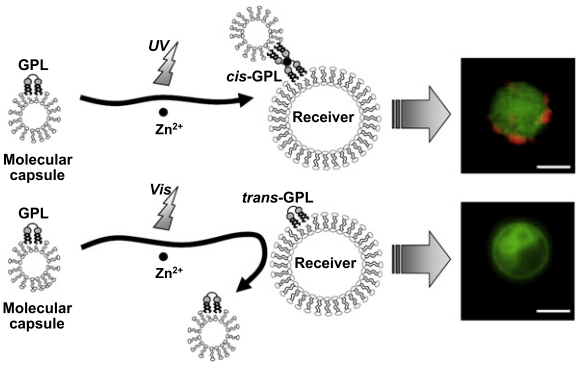

Fig. 5. Photonic control of reception of a small liposome (i.e., a molecular capsule) to a giant receiver liposome using GPLs. Upon UV light irradiation, the GPLs embedded in the molecular capsule and in the receiver drastically changed their conformation through photoisomerization of the azobenzene moiety from the *trans*-form to the corresponding *cis*-form, and enabled assembly of the red fluorescence-labeled molecular capsules and green fluorescence-labeled receiver. The scale bars in the fluorescent images correspond to 10 μm.
Source: This figure is reproduced with permission from [70]; copyright 2009, Taylor & Francis.

5.2. Artificial-cell-based approaches

Another promising approach to creating senders and receivers in molecular communication is to assemble functional molecules that are designed and synthesized artificially. For instance, a synthetic sender/receiver that uses a giant liposome embedded with gemini-peptide lipids (GPLs) has been proposed [84,70]. The GPLs are composed of two amino acid residues, each having a hydrophobic double-tail and a functional spacer unit connected to the polar heads of the lipid. The liposomes embedded with the same type of GPLs in their lipid bilayer membranes assemble in response to specific triggers, such as ions and light [50,85]. Assembled liposomes with GPLs can be dissociated reversibly by applying a complementary trigger (e.g., by applying UV light for liposomal assembly or visible light for liposomal dissociation). The reversible liposomal dissociation and assembly mechanisms may be applied to the selective transmission and reception mechanisms of the information molecules (or small liposomes that encapsulate information molecules) at a sender and receiver (Fig. 5), respectively [84,70]. A small liposome embedded with GPLs acts as a capsule of information molecules (i.e., a molecular capsule) and a giant liposome embedded with GPLs acts as a sender/receiver. A sender/receiver is embedded with distinct GPLs (e.g., a sender has GPL-A and a receiver has GPL-B) and a molecular capsule whose destination is the receiver is embedded with both types of GPLs (i.e., a molecular capsule has GPL-A and GPL-B). When trigger A/B is applied to the sender/receiver and the molecular capsule, a sender/receiver embedded with GPLs that is responsive to the applied trigger transmits/receives the molecular capsule embedded with the same type of GPLs. This selective transmission/reception mechanism, controlled by specific triggers, may lead to creation of not only unicast-type molecular communication, but also multicast- and broadcast-type molecular communication.

As for the biochemical reaction at a receiver, artificial signal transduction systems have been fabricated on a liposomal membrane [70,24,86]. The artificial signal transduction system was inspired by a biological signal transduction system that involves ligand–receptor interaction and G-protein-linked pathways. The system is composed of three molecular components: a GPL as an artificial receptor, an enzyme, and bilayer-forming lipids. Fig. 6 shows that an azobenzene-containing receptor is embedded in the bilayer-forming cationic peptide lipids and an enzyme, lactate dehydrogenase (LDH), is immobilized on the bilayer-forming lipids [70]. In the presence of visible light irradiation as an external stimulus, Cu^{2+} ions bind to the LDH and inhibit LDH activity (corresponding to the off-state). In contrast, in the presence of UV light irradiation, Cu^{2+} ions bind to the receptor and activate LDH activity (corresponding to the on-state); this results in switching of enzymatic activity to the stimulus by molecular recognition of the receptor.

Similar systems can be constructed using GPLs as molecule-responsive receptors [24], instead of the photo-responsive receptors described above. In this case, the molecule-responsive receptor drastically changes the Cu^{2+} ion-binding affinity depending on the presence/absence of 1-hydroxy-2-naphthaldehyde (HNA) molecules as an external stimulus and control of the LDH activity. This indicates that a receiver with GPLs may react biochemically to the received information molecules by applying a specific trigger.

Alternatively, it may be possible to create a ‘white box’-type artificial cell that is composed of only known biological materials and functions in the long run. There are some innovative challenges in the field of synthetic biology; for example, creating artificial organisms that do not exist or could exist in nature and creating standardized biological ‘parts’ to turn artisanal genetic engineering into ‘real’ engineering [10]. By combining these technologies, it may be possible to create, from scratch, an artificial cell acting as a sender/receiver in molecular communication.

6. Model molecular communication system

To construct a realistic molecular communication system, appropriate technologies and approaches described in Sections 3–5 need to be selected and combined. For instance, a molecular communication interface using a liposome embedded with connexins, an active molecular propagation system using MT motility on kinesins and DNA hybridization and a sender/receiver using a giant liposome embedded with GPLs will be compatible with each other and may be integrated into a single system (Fig. 7).

A giant liposome (i.e., a sender) and a small liposome (i.e., a molecular communication interface) have the same types of photo-responsive GPLs and channel-forming connexins in their lipid bilayer membranes, and information molecules are stored in the inner aqueous phase of the sender liposome. When UV light irradiation is applied as an external stimulus, the sender liposome and the small liposome assemble stably, and a gap junction channel is formed between the sender liposome and the small liposome. Next, information molecules are transferred from the sender liposome to the small liposome according to the molecular concentration gradient.

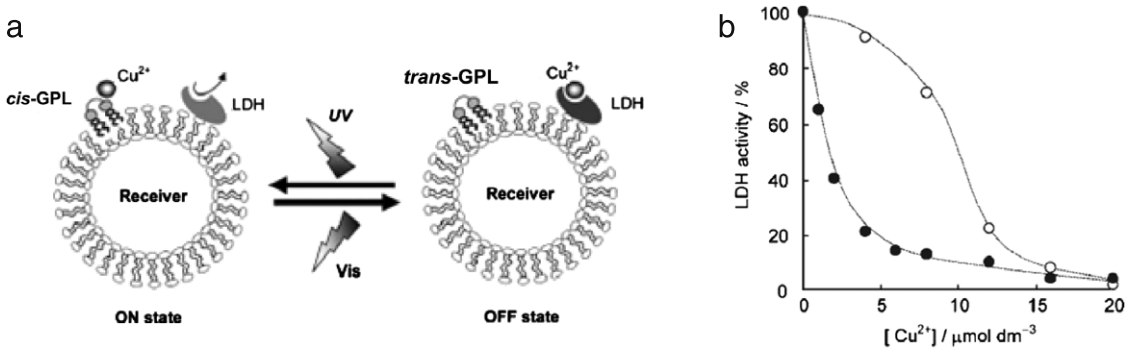

Fig. 6. Photonic control of enzymatic activity at a receiver using GPLs. (a) The photo-responsive GPLs drastically changed the Cu^{2+} ion-binding affinity by the photoisomerization of azobenzene-spacer units. Thus, input of a photonic signal (UV light irradiation) was converted to an amplified chemical signal output at the enzyme by the translocation of Cu^{2+} ions as a mediator between them. (b) Cu^{2+} concentration dependencies of LDH activity at the receiver in the on-state (open circle) or off-state (closed circle).
Source: This figure is reproduced with permission from [70]; copyright 2009, Taylor & Francis.

When visible light irradiation is applied as a trigger of sending, the small liposome dissociates from the sender and information molecules are encapsulated in the inner aqueous phase of the small liposome. The small liposome also has ssDNAs that are complementary to those of an MT, and it is loaded onto the gliding MT through DNA hybridization. The loaded, small liposome is transported by MT motility on kinesins from the sender liposome to a giant receiver liposome, which has ssDNAs complementary to those of the small liposome and channel-forming connexins.

At the receiver liposome, the transported small liposome is unloaded from the gliding MT through DNA hybridization (strand exchange), and connexins in the membranes of the small liposome and the receiver liposome physically and spontaneously come into contact with each other. Then a gap junction channel is formed between the small liposome and the receiver liposome and information molecules are transferred from the small liposome to the receiver liposome according to the molecular concentration gradient. The decapsulated information molecules are captured by GPLs as artificial receptors and then metal ions (as mediators) bind to the information molecule–receptor complex. Consequently, enzymatic activities are switched on, and signal amplification results in the biochemical reaction at the receiver.

This model system can be operated without using external power or control as long as an external stimulus, such as a trigger of sending, is applied to the system. These features will help to create highly miniaturized and scalable systems.

7. Theoretical approaches

Although molecular communication research started with experimental approaches (as described above) to verify the feasibility of molecular communication concept, it is now being extended to theoretical approaches based on information theory. For instance, achievable information rates have been calculated, assuming that distinct information molecules are freely diffused [18,19] or actively transported, using MT motility on kinesins [20]. In another type of active transport where kinesins travel over immobilized MTs to transport information molecules, achievable information rates have been analyzed for unicast and broadcast molecular communication [60,62,63]. Other examples include an information theoretic model of molecular communication based on cellular signaling [56], calculating the maximum capacity for the molecular communication channel between a sender and a receiver [3–6] and mathematical modeling of molecular communication among floating nanomachines that act as senders/receivers in the aqueous environment based on probabilistic timed finite state automata [102]. The design of a protocol stack, address encoding/decoding, link switching and error correction mechanisms for molecular communication networks are discussed in [98–100].

To date, these mathematical models are in the initial phase of research and have many constraints and non-realistic assumptions. However, molecular communication characteristics not seen in traditional electromagnetic wave-based communication have received increasing attention among information scientists, and so the mathematical models will soon become more sophisticated.

8. Conclusions

Molecular communication provides a means to send, transport and receive molecules in a controllable manner; it allows biological and artificially created entities such as cells, sensors and reactors to communicate with each other using molecules. Therefore, molecular communication has significant potential for future applications in a diversity of fields.

Especially, medical and healthcare applications are the most promising ones. For instance, it may be possible to diagnose diseases or stress by directly analyzing biomolecules derived from a drop of sweat or blood using a 'biochip cellular phone'; i.e., a cellular phone equipped with a biochip [44] in which molecular communication components and systems are packaged. Disease marker molecules could be selectively encapsulated and transported from a sender reservoir to their designated receiver sensors where the concentration of each molecule is determined. The results would be transmitted to a medical

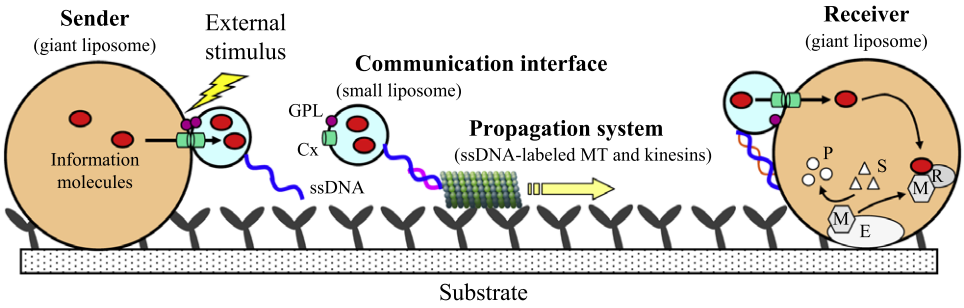

Fig. 7. Model molecular communication system that integrates a molecular communication interface (using a liposome embedded with connexins), a molecular propagation system (using MT motility on kinesins and DNA hybridization) and a sender/receiver (using a giant liposome embedded with GPLs) into a single system. GPL, Cx, ssDNA, MT, R, M, E, S, and P denote a gemini-peptide lipid, a connexin, a single-stranded DNA, a microtubule, a receptor, a mediator, an enzyme, a substrate, and a product, respectively.

specialist via a cellular phone using traditional mobile networks. This system could be used for daily health checkups or preventive medicine that prevents certain diseases before they occur or progress.

Furthermore, considering that molecular communication enables direct communication with living cells, health checkups of targeted cells may be possible. For example, empty molecular capsules could be transported from implantable biochemical sender sensors to targeted receiver cells; typical drug delivery systems transport molecular capsules that encapsulate drugs to targeted cells [92]. The molecules that are produced and secreted from the receiver cells would be captured by or encapsulated in the empty capsules and then returned to the sender sensors to monitor the existence of disease marker molecules or toxins. Molecular communication is related to other research fields such as molecular computing and molecular robotics [82] and it will play an important role in enhancing their potential.

Molecular communication is an emerging interdisciplinary research area; it requires considerable research effort and collaboration among biophysicists, biochemists, and information scientists. We hope more researchers will participate in and contribute to the development of molecular communication.

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