Part Ⅱ Recent Research and Development in Molecular Communication Technology

Molecular Communication: Biological Communications Technology

NAKANO Tadashi, Michael Moore, ENOMOTO Akihiro, and SUDA Tatsuya

This article provides a comprehensive overview of state-of-the art research on molecular communication—a molecule-based communication paradigm for biological machines. Unlike current telecommunications based on electric or optical signals, molecular communication exploits biological molecules as information carriers. In molecular communication, senders of communication encode information onto molecules and transmit to the environment. The information coded molecules then propagate in the environment to reach receivers of communication, which capture and biochemically react to the molecules (i.e., decode the information from the information carrying molecules). Since biological molecules are compatible with biological systems, molecular communication is expected to impact medical domains such as human health monitoring where implant biological machines interact with biological cells through molecular communication. This article describes key concepts, architecture, potential applications of molecular communication as well as existing research on engineering molecular communication components and systems.

Keywords
Molecular communication, Biological communications, Communication engineering

1 Introduction

Biological nanomachines (or "nanomachines", for short) are nanoscale to microscale devices that either exist in the biological world or are artificially created from biological materials and that perform simple functions such as sensing, logic, and actuation. Example nanomachines from the biological world include biological cells[4], molecular motors that produce mechanical work using chemical energy[46], and any biochemical molecules, complexes, circuits that act as processing units[10] while examples of synthetic biological nanomachines are artificial molecular machines[35] and genetically engineered biological cells that are programmed to produce intended functions[15][19][23][56].

Molecular communication is a new paradigm for communication between nanomachines over a short (nanoscale or microscale) range[28]. In molecular communication, infor-

mation is encoded to and decoded from molecules, rather than electrons or electromagnetic waves. Using electrons or electromagnetic waves for communication is particularly limited at the nanoscale and microscale range because of power constraints and physical limitations in the size and nature of communication components (i.e., biological nanomachines). Because nanomachines are too small and simple to communicate using electrons or electromagnetic waves, molecular communication provides a novel mechanism for nanomachines to communicate by propagating molecules that represent information.

A promising area that molecular communication contributes to is medical domains[36]. Imagine that a biological system (e.g., the human body) is composed of a large number of cells (i.e., nanomachines), that each cell performs simple and specific operations such as uptake, processing, and release of molecules, and that cells interact to perform various functions of the body (e.g., distributing molecules for metabolism and replication of cells). Molecular communication provides mechanisms to transport molecules between cells, and thus, it may help perform targeted delivery of drugs by providing mechanisms to transport drugs (information-encoded molecules) between drug repositories embedded in a human body (sender nanomachines) and specific cells in a human body (receiver nanomachines). Molecular communication also provides mechanisms for nanomachines to communicate, and thus, it may help drug repositories (sender nanomachines) to coordinate and control the amount and timing of drug release. Targeting delivery of drugs to specific cells in a human body and creating molecular communication for such applications involve understanding how molecules are transported within a biological system, how molecules are addressed to specific locations within a biological system (i.e., molecule-addressing mechanisms in a biological system), or even adding receptor molecules to a biological system to produce an addressing mechanism[5][32][40][47].

Research on molecular communication has started since the initial idea of molecular communication was presented in 2005[29]. Existing research on artificially creating molecular communication is based on understanding the design of molecular communication in biological systems and on modifying the functionality of existing molecular communication in biological systems (e.g., [20][28][39][42]). Research on theoretical foundations of molecular communication is also underway. The importance of information theory for small scale communication systems is addressed in[2], and research efforts are currently being made for addressing information theory for various classes of molecular communication (e.g., [17][18][33][34][38].)

This article is organized in the following manner. Section **2** gives an overview of various forms of molecular communication in biological systems. Section **3** describes a generic architecture of molecular communication where senders and receivers communicate using molecules through key communication processes. Section **4** describes existing research on engineering molecular communication components and systems, and Section **5** concludes this article.

2 Molecular communication in biological systems

Molecule-based communication or molecular communication is a common and ubiquitous method by which biological nanomachines communicate. Various modes and mechanisms of molecular communication are found within and between cells. In the following, modes and mechanisms of molecular communication are categorized based on how signal molecules are propagated, namely, whether signal molecules simply diffuse in the environment or they directionally propagate by consuming chemical energy. The former type of communication is called passive transport-based molecular communication, and the latter type active transport-based molecular communication.

2.1 Passive transport-based molecular communication

Passive transport provides a simple method of propagating signal molecules within a cell and between cells. In passive transport, signal molecules randomly diffuse in all available directions, making it particularly suited to environments that are highly dynamic and unpredictable. Passive transport is also suited to situations in which infrastructure for communications is not feasible. Passive transport, however, requires a large number of signal molecules to reach a distant destination, and owing to the random movement of molecules, the time to reach a destination increases with the square of the distance. Passive transport is also not suitable to propagate large signal molecules in a crowded environment such as the interior of cells.

In the following, we describe three examples of passive transport-based molecular communication from biological systems, including (a) free diffusion-based molecular communication, (b) gap junction mediated diffusion-based molecular communication, and (c) reaction-diffusion-based molecular communication.

(a) **Free diffusion-based molecular communication:** In this mode of molecular communication, cells release signal molecules (e.g., proteins and peptides) into the extracellular environment, and neighboring cells capture the signal molecules with protein receptors, resulting in the activation of a chemical reaction (e.g., increased metabolism or transcription of cellular proteins). An example of free diffusion-based molecular communication is quorum sensing, a communication mechanism for bacterial cells. In quorum sensing, bacterial cells release an autoinducer, acyl homoserine lactone (AHL) into the environment, and detect the concentration of AHL in the environment, to estimate the number of nearby bacteria. When the AHL concentration is sufficiently high in the environment, the bacteria interpret this as a large number of bacteria in the environment, and thus, the bacteria start transcribing DNA to perform group functions (e.g., enough bacteria to generate an infection, form a biofilm, or generate luminescence)[16].

(b) **Gap junction mediated diffusion-based molecular communication:** Diffusion of signal molecules can be guided through cell-cell communication channels called gap junction channels[4]. Gap junction channels are physical channels formed between two adjacent cells, connecting the cytoplasm of the two cells. Gap-junction channels allow only connected cells to communicate, enabling coordinated actions among adjacent cells, such as synchronized heart-beating by cardiomyocytes.

(c) **Diffusion-reaction-based molecular communication:** Diffusion of signal molecules can involve biochemical reactions to achieve a different mode of communication that allows propagation of impulses. As a result of the quick increase and decrease of signal molecules in their concentrations, the signal molecules appear as an impulse that propagates in the environment. For instance, some glial cells produce impulses of calcium ions (Ca^{2+}) for intercellular communication. The endoplasmic reticulum (ER) in a cell gathers and stores calcium ions, and when a cell is stimulated (e.g., by a physical stimulus), it releases the stored calcium ions from the ER and the calcium diffuses to adjacent cells through cell-cell junction channels. The diffused calcium in turn stimulates the adjacent cells, causing a chain reaction of calcium stimulation. Shortly after being stimulated and releasing calcium, a cell pumps calcium within the cell back into the ER and suppresses further stimulation, thus creating a short impulse of calcium through the cell. Because the communication propagates in a short impulse of calcium concentration, cells can communicate at a higher frequency. Neurons similarly produce ion impulses (called action potentials) that propagate over the length of the neuron.

2.2 Active Transport-Based Molecular Communication

Active transport provides a communication mechanism to directionally transport signal molecules to specific locations. Active transport can propagate signal molecules over longer distances (up to meters in length) as compared with diffusion-based passive transport. Large signal molecules and vesicles diffuse poorly in passive transport because of their size; on the other hand, active transport consumes chemical energy and generates sufficient force to directionally transport large signal molecules[11]. Active transport provides a communication mechanism with a high degree of reliability even when the number of signal molecules to transport is small. Because the transport of signal molecules is directional, the probability of signal molecules reaching the destination is higher than when using passive transport, and thus active transport requires fewer signal molecules to perform communication. However, active transport often requires communication infrastructure to produce and maintain the transport, guide, and interface molecules (e.g., molecular motors, microtubules filaments, and vesicles). Active transport of molecules also requires a regular supply of energy to overcome the chemical interactions between signal molecules and molecules in the environment.

In the following, we describe two examples of active transport-based molecular communication from biological systems, including (a) molecular motor-based molecular communication and (b) bacterial motor-based molecular communication.

(a) **Molecular motor-based molecular communication:** This type of molecular communication is found within a cell where molecular motors are used to transport signal molecules. A molecular motor is a protein or a protein complex that converts chemical energy (e.g., ATP hydrolysis) into mechanical work at the molecular scale. Inside a cell, molecular motors transport signal molecules or large vesicles (e.g., liposomes, cell organelles) that contain signal molecules[46][49][53]. Molecular motors consume chemical energy (e.g., ATP) to transport signal molecules or the vesicles along the preestablished guide molecules (e.g., along a star-shaped topology that the guide molecules form inside a cell).

(b) **Bacterial motor-based molecular communication:** Bacteria move directionally based on chemical concentrations in the environment. Bacteria also exchange DNA through the process of conjugation. In this process, two types of bacteria, a sender bacterium with an F-plasmid (i.e., a genetic sequence that enhances the transfer of genetic information) and a receiver bacterium without F-plasmid, transfer a DNA chromosome through a pilus (i.e., a projection from the sender bacterium to the receiver bacterium forming a bridge for transmitting DNA). Transfer of DNA between bacteria may allow the receiver bacterium to acquire DNA that produces some useful cellular functionality (e.g., protein production, antibiotic resistance). Therefore, bacteria essentially transport DNA to other bacteria in the environment[9][52]. The receiver bacterium may also release pheromones that form a chemical gradient that guides a sender bacterium toward a receiver bacterium (i.e. the closer to the receiver, the higher the chemical concentration).

3 Molecular communication architecture

As described in Section **2**, there exist varieties of modes and mechanisms of molecular communication in biological systems. One may ask whether it is possible to generalize necessary components and processes for molecular communication. Establishing a generalized architecture for molecular communication may help understand design principles of biological systems as well as help engineer artificial biological systems. In this section, we attempt to describe an abstract architecture

for molecular communication.

3.1 Generic representation of molecular communication

Figure 1 depicts a generic molecular communication architecture. It consists of components functioning as information molecules (i.e., signal molecules such as proteins or ions) that represent the information to be transmitted[50], sender nanomachines that release the information molecules (e.g., cells, cellular organelles, protein machinery), receiver nanomachines that detect information molecules, and the environment in which the information molecules propagate from the sender nanomachine to the receiver nanomachine[51]. It may also include transport molecules (e.g., molecular motors) that transport information molecules, guide molecules (e.g. microtubule or actin filaments) that direct the movement of transport molecules, and interface molecules (e.g., vesicles) that allow any type of information molecule to be transported by a transport molecule[39].

Components of molecular communication are made up of molecules, and must be designed with the thought in mind that molecular communication occurs in an aqueous or air environment, which generates a significant amount of noise. The noise in the environment comes from a number of factors. For instance, the environment contains energy and forces that constantly interact with the various molecular communication components. Such energy and forces include thermal energy, electrical fields, magnetic fields, and electromagnetic waves (e.g., light energy that is absorbed by molecules). The environment also contains molecules and nanomachines that do not participate in molecular communication, and these generate noise. Such molecules and nanomachines include solvent molecules (e.g., water molecules), solute molecules (e.g., energy molecules necessary to support the nanomachines), and other nanomachines (e.g., nanomachines to maintain chemical concentrations in the environment or act as structural components). The noise in the environment determines the degree of randomness in molecular communication (e.g., randomness in the movement of information molecules and randomness in the timing of, rate of, and energy for chemical reactions).

3.2 Molecular communication processes

The components in molecular communication perform the following general phases of communication (Fig. 1): encoding of information into an information molecule by the sender nanomachine, sending of the information molecule into the environment, propaga-

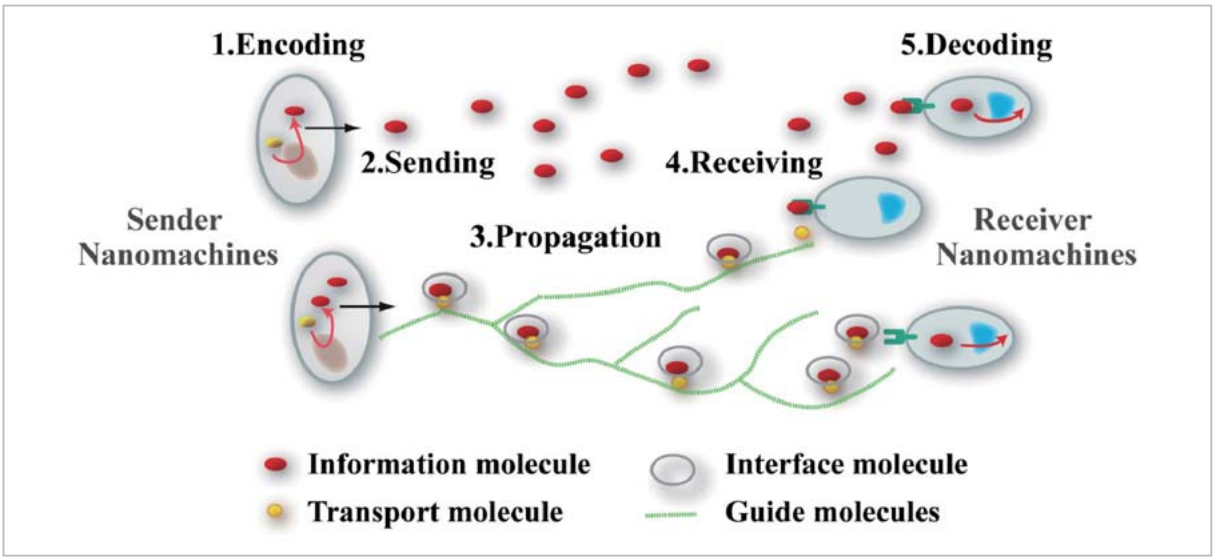


Fig. 1 Generic representation of molecular communication

tion of the information molecule through the environment, receiving of the information molecule by the receiver nanomachine, and decoding of the information molecule into a chemical reaction at the receiver nanomachine.

• Encoding

Encoding is the phase during which a sender nanomachine translates information into information molecules that the receiver nanomachine can detect. Information may be encoded onto the type of information molecules used. Information may also be encoded in various characteristics of information molecules such as the three-dimensional structure of the information molecule, in the specific molecules that compose the information molecules, or in the concentration of information molecules (the number of information molecules per unit volume of solvent molecules).

The amount of information that a sender encodes onto a single information molecule is limited by the molecular structure of a receiver nanomachine. A receiver nanomachine is capable of only a limited number of configurations; thus, when a receiver nanomachine receives an information molecule, the receiver nanomachine receives only the amount of information corresponding to the number of configurations possible in the receiver nanomachine[48]. If a receiver nanomachine achieves only two configurations, the receiver nanomachine only understands one bit of information at a time.

A sender nanomachine may transmit information about which a receiver nanomachine does not have information. For instance, in biological systems, certain types of cells communicate through exchanging DNA molecules. An arbitrary DNA sequence is decoded at a receiving cell into proteins that introduce new functionality into a receiver cell. If a sender nanomachine in molecular communication can transmit arbitrary information molecules, it is possible to send new functionality to the receiver nanomachine.

• Sending

Sending is the phase during which a sender nanomachine releases information molecules into the environment. A sender nanomachine may release information molecules by either unbinding the information molecules from the sender nanomachine (e.g., by budding vesicles from a biological cell if a sender nanomachine is a biological cell with endoplasmic reticulum), or by opening a gate that allows the information molecule to diffuse away (e.g., by opening a gap junction channel in the cell membrane of a sender nanomachine). A sender nanomachine may also catalyze a chemical reaction that produces transport molecules elsewhere.

Because of its size, a sender nanomachine contains a limited amount of energy and information molecules. This results in a limited communication capability that the single sender nanomachine alone can generate. Thus, the sender nanomachine of molecular communication generally relies on the environment for supplying (chemical) energy and information molecules. In addition, multiple sender nanomachines may release the same information molecules, resulting in a stronger signal in the environment.

• Propagation

The sender and receiver nanomachines are at different locations in the environment, and propagation is the phase during which the information molecule moves from the sender nanomachine through the environment to the receiver nanomachine. The information molecule may diffuse passively through the environment without using chemical energy or may bind to a transport molecule (e.g., a molecular motor that generates motion[7]) and actively propagate through the environment using energy.

In passive transport, information molecules randomly move according to forces in the environment. Large information molecules or high-viscosity environments result in slower diffusion through the environment. In active transport, a transport molecule carries information molecules through the environment, and it consumes chemical energy to reduce the randomness in its movement in the environ-

ment. By providing more control over the movement of information molecules, active transport may decrease the time necessary for information molecules to reach the receiver nanomachine and also increase the probability of information molecules successfully reaching the receiver nanomachine.

During propagation, an interface molecule may also be necessary to protect information molecules from noise in the environment. For instance, information molecules may be contained in a vesicle-based interface molecule and propagate through the environment[39]. The vesicle prevents the information molecules from chemically reacting with other molecules outside the vesicle.

• Receiving / Decoding

Receiving is the phase during which the receiver nanomachine captures information molecules being propagated in the environment. Decoding is the phase during which the receiver nanomachine, upon capturing information molecules, decodes the received molecules into a chemical reaction. One option for capturing information molecules is to use receptors that are capable of binding to a specific type of information molecule. Another option for capturing them is to use channels (e.g., gap-junction channels) that allow them to flow into a receiver nanomachine without using receptors. Chemical reactions for decoding at the receiver nanomachine may include producing new molecules, performing a simple task, or producing another signal (e.g., sending other information molecules).

3.3. Characteristics of Molecular Communication

A variety of communication characteristics result from using biological nanomachines as senders and receivers, using molecules as an information carrier, and from the propagation of information molecules through an aqueous environment. First, the environment noise causes the propagation of information molecules to be fundamentally stochastic and to have a relatively large communication delay. Second, information is encoded onto molecules and the amount of information that a receiver nanomachine can receive is limited by the number of possible configurations in the receiver nanomachine. Third, the biological molecules and materials used to create components for molecular communication cause communication to exhibit characteristics of biocompatibility and energy efficiency. Each of the unique characteristics of molecular communication is described below.

• Stochastic communication

The stochastic behavior of molecular communication arises from environmental factors such as unpredictable movement of molecules in the environment, as well as from communication component factors such as nanomachines stochastically reacting to information molecules and nanomachines and information molecules degrading over time. Environmental factors and communication component factors inherently affect the design of molecular communication. For instance, in order to be robust to the environmental noise, the sender nanomachines increase the signal-to-noise ratio by releasing a large number of information molecules, and receiver nanomachines chemically react to information molecules only when a relatively large number of information molecules are present in the environment. Sending a large number of information molecules is highly redundant, so that degradation of a few information molecules during propagation does not impact communication. In addition, non–information molecules (noise-causing molecules) in the environment may not trigger chemical reaction at a receiver nanomachine as long as the noise from those molecules is significantly less than the signal from a large number of information molecules.

• Large communication delay

Molecules in the environment that do not participate in molecular communication cause information molecules to propagate slowly through the environment. In both passive and active transport, the speed of propagation is bounded at a relatively lower speed (i.e., micrometers per second in an aqueous environment) because of the large amount of inter-

ference with the molecules in the environment. In addition, because of the possibly large delay in the environment, information molecules may remain in the environment for a period of time and arrive at a receiver nanomachine after a widely varying amount of time (e.g., hours after release at the sender nanomachine).

The delay in an information molecule propagating from a sender to a receiver nanomachine determines various communication characteristics of molecular communication. If the information molecules stay in the environment for an extended length of time (e.g., DNA molecules can be chemically stable for months), a sender nanomachine must delay a new communication until the information molecules used in an old communication degrade in the environment to prevent the old communication from interfering with the new communication. Thus, the frequency at which a sender nanomachine sends information molecules is determined by the length of time information molecules stay in the environment before degrading.

• Molecule based coding

In molecular communication, information is encoded in various characteristics of information molecules such as the type of information molecules used, three-dimensional structure, chemical structure (e.g., protein), sequence information (e.g., DNA), or concentration (e.g., calcium concentration) of information molecules[48]. A physical substance (i.e., the information molecule) propagates from a sender nanomachine to a receiver nanomachine, and the receiver nanomachine chemically reacts to incoming information molecules. Because information is encoded onto molecules in molecular communication, the amount of information that a sender encodes onto a single information molecule (or the amount of information that a receiver nanomachine receives) is limited by the number of possible configurations in the receiver nanomachine.

• Biocompatibility

Sender and receiver nanomachines in molecular communication communicate through sending, receiving, and decoding (chemically reacting to) information molecules. Since molecular communication uses the same communication mechanisms as biological systems, nanomachines in molecular communication can directly communicate with various natural components in a biological system using encoding and decoding methods available to the biological system. Biocompatibility of molecular communication may enable applications such as inserting nanomachines into a biological system for medical applications that require biologically friendly nanomachines.

• Energy efficiency

Through the fine-tuning of natural evolution, molecular communication in biological systems has achieved a high degree of energy efficiency. For example, under some conditions, myosin (a type of a molecular motor) converts chemical energy (i.e., ATP) to mechanical work with 90 percent energy efficiency[30][57]. Chemical energy may be possibly supplied by the environment in which nanomachines operate. For example, molecular communication systems deployed in a human body may harvest energy (e.g., glucose) from the human body, requiring no external energy sources.

4. Engineered molecular communication

Advanced bio-nanotechnology and improved understanding in cell and molecular biology have made it possible to design and engineer molecular communication systems. A common approach for designing and engineering molecular communication systems is to extend or modify existing biological systems. Accordingly, many molecular communication systems are engineered by exploiting biological systems. This section overviews the state-of-the-art research in engineering of molecular communication components and systems. A collection of molecular communication research including that in related areas is categorized below into (1) engineering of

sender and receiver nanomachines, (2) engineering of transport mechanisms for propagating information molecules, and (3) engineering of communication mechanisms that are necessary to build larger-scale integrated molecular communication systems.

4.1 Engineering of sender and receiver nanomachines

Sender and receiver nanomachines need communication functionality such as that to synthesize, store and release information molecules for sender nanomachines, and to capture and react to specific information molecules for receiver nanomachines. There are two basic classes of approaches for developing nanomachines: they are modifying existing biological cells, or producing simplified cell-like structures using biological materials that achieve communication functionality.

4.1.1 Synthetic biological cells

The area of synthetic biology has demonstrated that new communication capabilities can be added to biological cells through genetic engineering[6][14][55][56]. In[6], sender nanomachines are engineered to synthesize and release information molecules (AHL molecules) using specific metabolic pathways. Receiver nanomachines are also engineered to respond to the information molecules by synthesizing specific reporter proteins in a concentration dependent manner (if the concentration of the information molecule falls in a certain concentration range.) The information molecules that sender nanomachines release are membrane permeable and freely diffuse from senders to receivers; therefore, they communicate through free-diffusion-based molecular communication.

Synthetic biology has also demonstrated that many other capabilities can be introduced into biological cells through genetic engineering. Demonstrated functionality in the area includes the following:

- **Logic functions:** In[56], computational building blocks were engineered based on DNA transcription and translation processes. An example of building blocks is a biochemical inverter, where the input mRNA generates a repressor protein that prevents DNA transcription processes, producing no output mRNA. In the absence of the input mRNA, DNA transcription processes proceed to generate an output mRNA. Other building blocks were designed. Similarly, in[15], signal transduction pathways in eukaryotic cells were modified by synthetic signaling proteins to demonstrate gating behaviors such as AND or OR gates.
- **Toggle switches:** In[23], a one bit memory was implemented with two genes inserted into a bacterium. Its bistability is achieved by the two genes under the control of promoters that are mutually repressed by the product of the other gene. Two inducers are also introduced to suppress the product of one of the two genes, which are used to switch from one state to the other.
- **Oscillators:** In[19], a bacterium has inserted DNA sequences that cause the bacterium to oscillate the concentration of three protein products (TetR, cI, LacI) over time. The DNA sequences to be inserted into the bacterium were selected, so that TetR blocked the promoter sequence of cI, cI blocked the promoter sequence of LacI, and LacI blocked the promoter sequence of TetR. Thus, at time t, TetR is active; cI is blocked; and LacI starts being produced. At time t_1, LacI becomes active; TetR is blocked; and cI starts being produced.

These functions can be used to increase the complexity of senders and receivers of molecular communication. For example, logic functions can be used at receiver nanomachines to produce programmed responses based on received information molecules; Toggle switches (i.e., 1 bit memories) can be used to retain a communication-related memory inside cells (e.g,. a communication status of whether sending or waiting); oscillators (i.e., clocks) can be used at sender nanomachines to control the timing of release. However, it is noted that introducing multiple functions faces a technical difficulty of a possible interference with existing functions (e.g., at

the protein level), and it is not technically easy.

4.1.2 Artificial cells

The other approach to engineering sender and receiver nanomachines is to create simplified cell-like structures using biological materials (e.g., through embedding of proteins in a vesicle). Simplification of biological systems (e.g., cells) may lead to components that are easier to engineer.

One example of the approach of simplification is to start with a lipid bilayer and then add functionality as necessary[21][31]. The lipid bilayer is similar to the membrane that encloses a cell. The lipid bilayer forms into a vesicle (a spherical lipid bilayer), and functional proteins (e.g., a receptor) are either embedded into the vesicle or are captured inside the vesicle. In[21], chemical components for a minimal cell that is capable of replication are proposed. In[31], an active receptor and enzyme are successfully embedded into a lipid bilayer, producing sender and receiver functionalities. By restricting the number of functionalities that are embedded in the vesicle, it is not necessary to consider the various complex processes (e.g., other metabolic pathways in the cell and processes to maintain the structure of the cell) occurring in a natural biological nanomachine. For instance, it is possible to select chemicals to cause the vesicles to form tubular projections to connect the vesicles without concern for the various other chemical processes[3][45].

4.2 Engineering of transport mechanisms

Research in engineering molecular communication includes developing transport mechanisms for propagating information molecules. This section describes engineering of passive transport mechanisms and active transport mechanisms. As described in Section **2**, passive transport propagates information molecules freely in the environment while active transport propagates information molecules directionally using motors.

4.2.1 Engineered passive transport mechanisms

4.2.1.1 Free-diffusion based molecular communication

One type of engineered passive transport is to use free diffusion based molecular communication, where communication is inherently a broadcast or random walk of information molecules. In free diffusion–based passive transport, a receiver may have receptors that are specific and that respond only when a certain type of information molecule is present in a high enough concentration[24][55]. Thus, the sender may select the receiver nanomachine by sending the information molecules that cause a response at the receptors of the desired receiver nanomachine. The sender may also set the concentration of information molecules (by adjusting the number of information molecules to transmit) so that only nearby receivers with the specific receptor are capable of responding, and distant receivers do not respond. For instance, an engineered bacterium produces VAI (Vibrio fischeri autoinducer) information molecules, and the VAI information molecules diffuse through the environment and bind to VAI-specific receptors (i.e., a specific DNA sequence that binds VAI) in a receiver bacterium that produces a response (e.g., GFP expression).

An example communication sequence based on this type of molecular communication is illustrated in Fig. 2, where the sender of communication specifies receivers of communication in a concentration-dependent manner. The sender synthesizes and transmits information molecules in the environment (encoding and sending). The information molecules transmitted into the environment create a concentration gradient with its highest concentration value around the sender as shown in Fig. 2. The receivers implement a band detector[6]; i.e., they produce a reaction if its concentration falls in a specific concentration range. Therefore, those receivers that are within the concentration range (receiver 2) respond (receiving and decoding), but those that are outside the concentration range (receivers 1

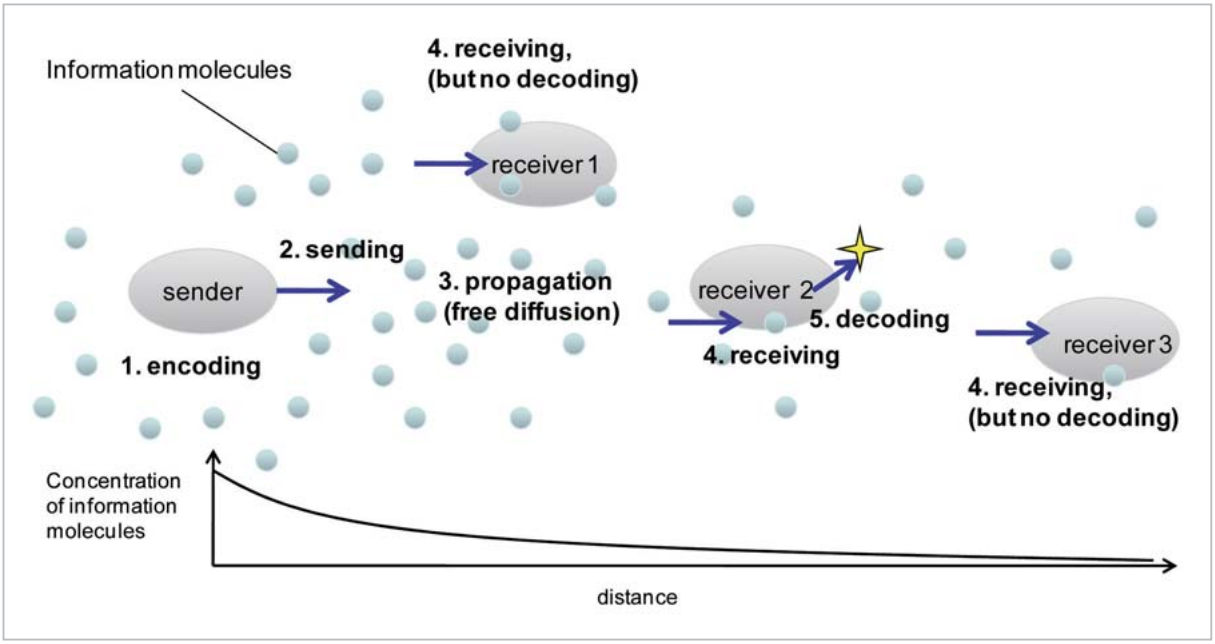


Fig.2 *An example communication sequence based on free-diffusion based molecular communication*

and 3) do not produce any reactions (receiving only and no decoding).

4.2.1.2 Gap junction mediated diffusion-reaction based molecular communication

Another type of engineered passive transport is to use diffusion-reaction-based molecular communication, where information molecules react in the environment to increase and decrease their concentrations while diffusing. This form of transport can cause a wave-like impulse of information molecules that propagate through the environment.

In[44], cell wires have been demonstrated to propagate calcium waves over a line of patterned cells. Diffusion of calcium waves are mediated by diffusion of calcium signals through gap junction channels, and therefore, this is gap junction mediated diffusion-reaction-based molecular communication. Inside a cell, a calcium store (e.g., ER) has calcium release channels. The calcium release channels release calcium signals from the calcium store when calcium signals activate the calcium channels. Released calcium signals diffuse inside a cell and activate nearby calcium channels, which, in turn, release calcium signals from their calcium stores. The concentration of calcium inside a cell increases through this positive feedback. When the concentration of calcium becomes high, the cell uses various calcium pumps to remove calcium signals from the cell. This acts as a negative feedback. The positive and negative feedback produce a propagating impulse wave of calcium signals inside a cell. In addition, if multiple cells are coupled through cell-cell channels called gap-junction channels, Ca^{2+} increase of one cell can propagate to the other cell, allowing a longer distance molecular communication between nanomachines. Since gap junction channels can have different selectivity and permeability, this property can be used to implement filters and switching mechanisms to control the direction and range of propagation[43].

An example communication sequence based on this type of molecular communication is illustrated in Fig. 3. The sender synthesizes some stimulating molecules that can initiate cell-cell signaling at intermediate cells (encoding). The sender then emits the stimulating molecules (sending), which trigger cell-cell signaling at intermediate cells. Upon receiving the stimulating molecules, intermediate cells generate diffusive molecules and

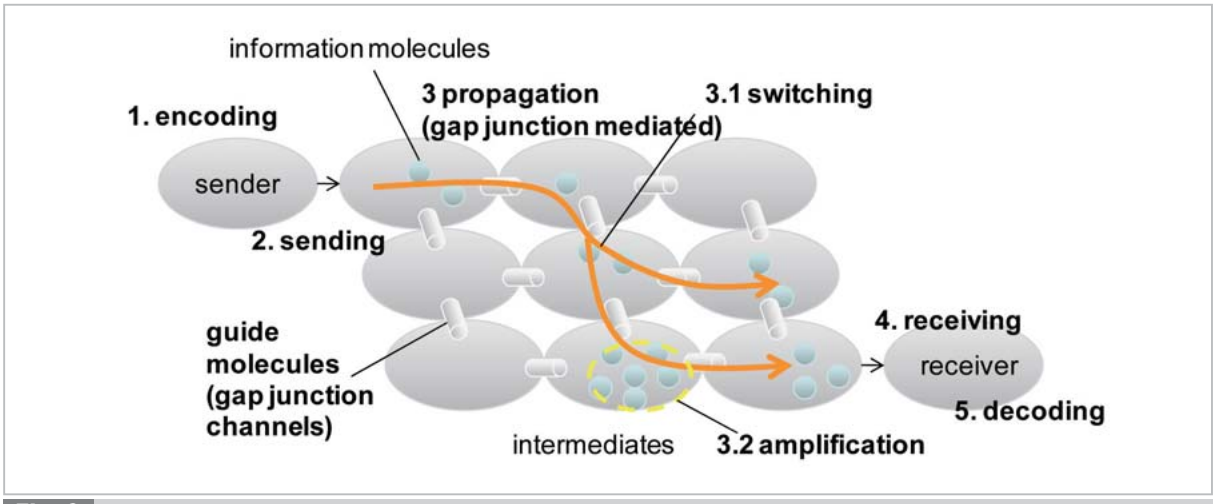


Fig.3 *An example communication sequence based on gap junction mediated diffusion-reaction based molecular communication*

propagate them through gap junction channels intercellularly (propagation). During propagation, diffusive molecules may be directed toward target receivers (switching) or amplified for longer distance propagation (amplification). The receiver reacts to nearby intermediate cells that receive the diffusive molecules and initiates biochemical processes (receiving and decoding).

4.2.2 Engineered active transport mechanisms

4.2.2.1 Molecular motor-based molecular communication

One type of engineered active transport is to use molecular motors to transport information molecules or interface molecules containing information molecules. Biological systems include a variety of molecular motors (e.g., kinesin, myosin, cilia, flagella, etc.). Existing research on engineering active transport, however, focuses on only a few types of molecular motors (i.e., kinesin, dynein). Two examples of active transport using molecular motors introduced here are molecular motors walking on filaments and filaments propagating on a patterned surface coated with molecular motors.

In the first example, engineered active transport uses molecular motors, guide molecules (e.g., microtubule filaments) that self-organize into a network, and molecular motors (e.g., dynein, kinesin) that actively transport information molecules along the guide molecules[37][51]. This first example uses components and processes similar to the active transport mechanisms in biological systems. In biological systems, a network of guide molecules (e.g., actin or microtubule filaments) is created within a cell in a self-organizing manner through dynamic instability of guide molecules, and molecular motors (such as dynein and kinesin) transport information molecules to specific locations within the cell by walking along a network of guide molecules. Engineering of the self-organization of the filaments can produce simple patterns of filaments (e.g., a star-shaped pattern or a random mesh pattern)[12][20]. Through designing self-organization processes of creating filament patterns and through selectively transporting on the designed filament pattern, molecular motors may be guided to desired locations (e.g., desired receiver nanomachine or a desired set of receiver nanomachines).

In the second example of engineered active transport using molecular motors, the arrangement of microtubules and motors is inverted. A surface of a glass is coated with the molecular motor (e.g., kinesin), and the motors push the filaments along the surface. In this arrangement, transport molecules (i.e., the filament) load information molecules at a sender nanomachine and unload the information molecules at a receiver[26][28]. The direc-

tion of filament movement is guided by adding walls (e.g., deposited proteins) onto the glass surface through lithographic techniques. Various patterns may be generated that gather filaments toward a receiver nanomachine. For instance, an arrow-shaped wall pattern acts a directional rectifier to ensure that filaments propagate in a single direction (e.g., only clockwise) by rectifying filaments that are propagating opposite the arrowhead direction[27].

An example communication sequence based on the first example is illustrated in Fig. 4. The sender encodes information using information molecules, and injects into interface molecules (e.g., vesicles). The sender then emits the interface molecules to molecular motors (e.g., through a budding mechanism). The interface molecules are then attached to and loaded on molecular motors. The interface molecules are propagated by molecular motors that move along guide molecules (e.g., rail molecules). During propagation, molecular motors may switch guide molecules to reach destination receivers. When molecular motors approach to the receiver, interface molecules containing information molecules are fused into the receiver. This allows receivers to receive information molecules and invoke reactions in response to information molecules.

4.2.2.2 *Bacterial motor-based molecular communication*

In another type of engineered active transport, a transport molecule itself is a nanomachine using molecular motors to move itself toward a receiver nanomachine along chemical gradients in the environment. This example uses components and processes similar to self-propulsion of single-cell organisms (e.g., a bacterium) through an aqueous solution. In biological systems, a bacterium (i.e., a transport nanomachine) uses cilia or flagella (molecular motors that generate propeller-like forces) to move itself along chemical gradients toward favorable conditions (e.g., food source, light) and away from unfavorable conditions (e.g., harmful chemicals, light). With the engineered transport nanomachine with molecular motors, the receiver may generate guide molecules (similar to a gradient of a food source or pheromone in the environment in the bacterium example) to indicate where the receiver is and to influence the direction in which the transport nanomachine moves through the environment. The transport nanomachine does not require preestablished filament networks, since guide molecules emitted by a receiver randomly diffuse to form the chemical gradient around the receiver. For instance, the pseudopodia of a cell (projections from a cell) can form complex shapes such as a structure that links the entrance and exit of a maze[41]. The pseudopodia form the structure by growing toward a chemical gradient of food originating from both the entrance and the exit of the maze. Active transport using pseudopodia is robust, since the pseudopodia adapt match to the shape of the maze. Another example of this type of molec-

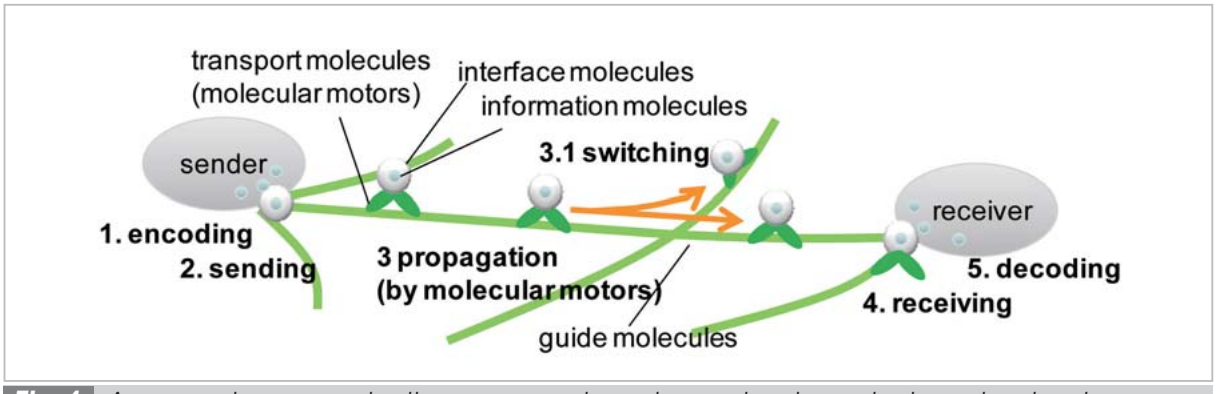


Fig.4 *An example communication sequence based on molecular motor-based molecular communication*

ular communication is found in bacterial cells, *E. faecalis* that perform conjugative plasmid transfer[54]. Female *E. faecalis* secretes pheromones to the environment, and male *E. faecalis* respond to the pheromones in the environment. Once male *E. faecalis* receive the pheromones, they activate gene transcriptions to express cell surface adhesion proteins, allowing male and female *E. faecalis* to aggregate, so that the plasmid is transferred from male to female *E. faecalis*.

An example communication sequence based on this type of molecular communication is illustrated in Fig. 5. In this type of molecular communication, the sender and receivers contain information molecules in them (e.g., DNA or RNA molecules within cells). The sender of communication emits guide molecules (e.g. pheromones) to attract receivers. The receivers of communication propel to move closer to the sender, representing the propagation process. Once the sender and receivers are physically touched (aggregated), the sender and receiver exchange information molecules (encoding, sending, receiving, decoding).

4.3 Engineering of communication mechanisms

Existing research in molecular communication focuses on building components for molecular communication as overviewed in this section. Such components, however, must work together to produce useful molecular communication. Existing research in creating integrated molecular communication systems includes developing a generic interface for interacting with a biological system and creating an addressing mechanism to enhance communications, each of which is briefly reviewed in this subsection.

4.3.1 Communication interfaces

A communication interface provides a generic abstraction for communication that is reused by a variety of communication mechanisms. In molecular communication, a generic and abstract communication interface allows sender and receiver nanomachines to transport a variety of molecules using the same communication mechanism. Creating a generic and abstract communication interface is important in a molecular communication network, since, with such a communication interface, a communication component is designed without requiring details of other communication components[39].

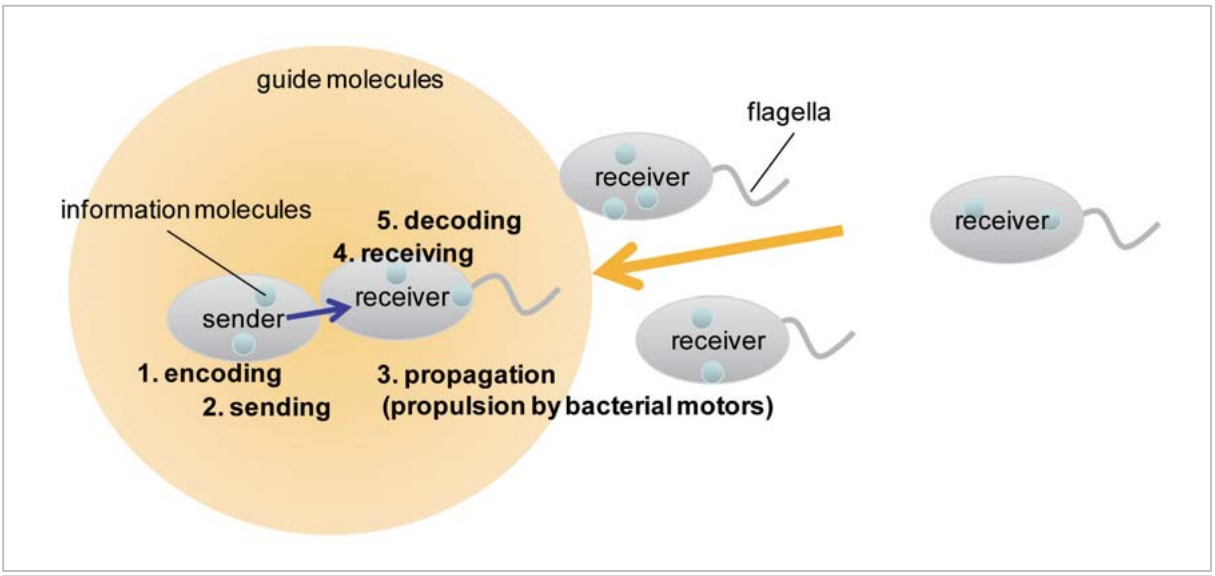


Fig.5 *An example communication sequence based on bacterial motor-based molecular communication*

One example of a generic and abstract communication interface is found in drug delivery[32]. In drug delivery, varieties of drugs are encapsulated in nanoscale capsules and target some location in the human body. Targeting molecules embedded in the nanoscale capsule bind to a specific receptor embedded in the target location inside the human body. The location of the receptor molecule in the human body thus determines the eventual location of the nanoscale capsules. With this interface, drug targeting mechanisms do not rely on characteristics of the drug (i.e., the information molecule) being transported. Nanoscale capsules act as a generic and abstract communication interface. The interface molecules allow any type of information molecule to concentrate at the correct location, which reduces the amount of drug necessary for results, and thus reduces side effects from drugs reaching undesired locations. The nanoscale capsule also protects information molecules from environmental noise and prevents the information molecules from chemically reacting with molecules outside the interface during the propagation.

4.3.2 Addressing mechanisms

One important feature in communication is the ability to send information to a specific receiver. In molecular communication, an addressing mechanism allows a sender nanomachine to specify the receiver nanomachine. With a generic addressing mechanism, the sender nanomachine would have a generic abstraction for specifying receiver nanomachines. In diffusion-based communication in biological systems, a receiver nanomachine is addressed according to which information molecule is being used. On the other hand, a molecular communication system using a generic addressing mechanism is more flexible and imposes fewer constraints on which information molecules are used in molecular communication.

One approach for a generic addressing mechanism is using DNA sequences[28]. In the addressing mechanism investigated, the information molecule includes a single-stranded DNA with a sequence that specifies the address of a receiver nanomachine. The receiver nanomachine has an address DNA that is complementary to and thus binds to the single-stranded DNA on the information molecule. Using DNA sequences in addressing provides a method for generating a large number of addresses, since DNA sequences may be arbitrarily produced (with existing technology, DNA up to 10,000 base pairs in length) and binding of DNA sequence is understood (as evidenced by construction of various shapes from designed DNA sequences). Adding an addressing mechanism to molecular communication would allow the creation of more complex molecular communication networks.

5 Conclusions

Molecular communication integrates techniques from biology to interact with biological systems, from nanotechnology to enable nanoscale and microscale interactions, and from computer science to integrate into larger-scale information and communication processing systems. Although research in molecular communication is in its infancy and has only reproduced functionality already available in biological systems, continuing research in molecular communication will lead to integrated molecular communication systems in which various components of molecular communication work together to provide full communication functionality. Molecular communication has significant potential, since it interacts directly with biological systems at nanoscales and microscales, and it may potentially impacts various technological domains including health (e.g., nanomedicine[22] and tissue engineering[8][25]), environment (e.g., environmental monitoring), IT (e.g., unconventional computing[1] and body sensor networks[57]), and military (e.g., biochemical sensors).

References

1 Adamatzky, Al, B. D. L. Costello, and T. Asai, "Reaction-diffusion computers", Elsevier, 2005.

2 Atakan, B. and Ozgur B. Akan, "An information theoretical approach for molecular communication", in Proc. 2nd International Conference on Bio-Inspired Models of Network, Information, and Computing Systems, Dec. 2007.

3 Akiyoshi, K., A. Itaya, S. M. Nomura, N. Ono, and K. Yoshikawa. 2003. Induction of neuron-like tubes and liposome networks by cooperative effect of gangliosides and phospholipids. Federation of European Biochemical Societies Letters 534(1–3):33–8.

4 Alberts, B., A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter. 2002. Molecular biology of the cell. New York:Garland Science.

5 Allen, T. M., and P. R. Cullis. 2004. Drug delivery systems: Entering the mainstream. Science 303:1818–22.

6 Basu, S., Y. Gerchman, C. Collins, F. Arnold, and R. Weiss, "A synthetic multicellular system for programmed pattern formation", Nature. April 21 2005. Vol. 434, 1130-1134.

7 Barron, J. T., L. Gu, and J. E. Parrillo. 1998. Malate-aspartate shuttle, cytoplasmic NADH redox potential, and energetics in vascular smooth muscle. Journal of Molecular Cell Cardiology 30:1571–9.

8 Burg, K. J. L. and T. Boland, "Minimally invasive tissue engineering composites and cell printing", IEEE Engineering in medicine and biology magazine, 2003.

9 Berg, J. M., J. L. Tymoczko, and L. Stryer. 2002. Biochemisty. 5th ed. New York: Freeman.

10 Bray, D., "Protein molecules as computational elements in living cells", Nature, Vol. 376, 27 Jul. 1995.

11 Bullock, T. H., M. V. L. Bennett, D. Johnston, R. Josephson, E. Marder, and R. D. Fields. 2005. The neuron doctrine: Redux. Science 310:791–3.

12 Chakravarty, A., L. Howard, and D. A. Compton. 2004. A mechanistic model for the organization of microtubule asters by motor and non-motor proteins in a mammalian mitotic extract. Molecular Biology of the Cell 15:2116–32.

13 Check, E. 2006. Synthetic biologists try to calm fears. Nature 441:388–9.

14 Dennis, T., J. Lee, T. Ozdere, T. J. Lee, and L. You, "Engineering gene circuits: foundations and applications", Nanotechnology in Biology and Medicine Methods, Devices and Applications, Ed. T. Vo-Dinh. CRC Press, Chapter 21, 2007.

15 Dueber, J. E., E. A. Mirsky, and W. A. Lim, "Engineering synthetic signaling proteins with ultrasensitive input/output control", Nature Biotechnology 25, 660-662, 2007.

16 de Kievit, T. R., and B. H. Iglewski. 2000. Bacterial quorum sensing in pathogenic relationships. Infection and Immunity 68(9):4839–49.

17 Eckford, A., "Nanoscale communication with Brownian motion", in Proc. 41st Annual Conference on Information Sciences and Systems, 2007.

18 Eckford, A., "Achievable information rates for molecular communication with distinct molecules", in proc. Workshop on Computing and Communications from Biological Systems: Theory and Applications, 2007.

19 Elowitz, M. B. and S. Leibler. "A synthetic oscillatory network of transcriptional regulators". Nature. 2000 Jan. 20;403(6767):335-8.

20 Enomoto. A., M. Moore, T. Nakano, R. Egashira, T. Suda, A. Kayasuga, H. Kojima, H. Sakakibara, and K. Oiwa. 2006. A molecular communication system using a network of cytoskeletal filaments. In Technical Proceedings of the 2006 NSTI Nanotechnology Conference and Trade Show 1:725–8.

21 Forster, A. C. and G. M. Church, “Towards synthesis of a minimal cell”, Molecular Systems Biology 2006.
22 Freitas Jr., R.A., Nanomedicine, vol. I: Basic Capabilities, Landes Bioscience, 1999.
23 Gardner, T. S., C. R. Cantor, and J. J. Collins, “Construction of a genetic toggle switch in Escherichia coli,” Nature. 2000 Jan 20;403(6767):339-42.
24 Gerchman, Y., and R. Weiss. 2004. Teaching bacteria a new language. Proceedings of the National Academy of Sciences 101(8):2221–2.
25 Griffith, L. G., and G. Naughton, “Tissue engineering- current challenges and expanding opportunities”, Science, Vol. 295, pp. 1009-1014, 2002.
26 Hess, H., C. M. Matzke, R. K. Doot, J. Clemmens, G. D. Bachand, B. C. Bunker, and V. Vogel. 2003. Molecular shuttles operating undercover: A new photolithographic approach for the fabrication of structured surfaces supporting directed motility. Nano Letters 3(12):1651–5.
27 Hiratsuka, Y., T. Tada, K. Oiwa, T. Kanayama, and T. Q. P. Uyeda. 2001. Controlling the direction of kinesin-driven microtubule movements along microlithographic tracks. Biophysical Journal 81:1555–61.
28 Hiyama, S., Y. Isogawa, T. Suda, Y. Moritani, and K. Suto. 2005. A design of an autonomous molecule loading/transporting/unloading system using DNA hybridization and biomolecular linear motors in molecular communication. Grenoble, France: European Nano Systems.
29 Hiyama, S., Y. Moritani, T. Suda, R. Egashira, A. Enomoto, M. Moore and T. Nakano, “Molecular Communication”, in Proc. of the 2005 NSTI Nanotechnology Conference, poster presentation, U.S.A., May 2005.
30 Howard, J. 2001. Mechanics of motor proteins and the cytoskeleton. Sunderland, MA: Sinauer.
31 Kikuchi , J. , A. Ikeda , and M. Hashizume . 2004 . Biomimetic materials. Encyclopedia of Biomaterials and Biomedical Engineering . New York : Marcel Dekker
32 Langer, R. 2001. Perspectives: Drug delivery—drugs on target. Science 293:58–9.
33 Liu, J. Q. and H. Sawai, “A new channel coding algorithm based on photo-proteins and GTPases”, 1st International Conference on Bio-Inspired Models of Network, Information, and Computing Systems, Dec. 2006.
34 Liu, J. Q. and T. Nakano, “An information theoretic model of molecular communication based on cellular signalng”, in proc. Workshop on Computing and Communications from Biological Systems: Theory and Applications, 2007.
35 Mavroidis, C., A. Dubey, and M. L. Yarmush, “Molecular machines”, Annu. Rev. Biomed. Eng. 2004. 6:363-95.
36 Montemagno, C. D. 2001. Nanomachines: A roadmap for realizing the vision. Biomedical Journal of Nanoparticle Research 3(1):1–3.
37 Moore. M, A. Enomoto, T. Nakano, R. Egashira, ,T. Suda, A. Kayasuga, H. Kojima, H. Sakakibara, and K. Oiwa. 2006. A design of a molecular communication system for nanomachines using molecular motors. In Proceedings of the Fourth Annual IEEE Conference on Pervasive Computing and Communications Workshops. Washington, DC: IEEE Computer Society.
38 Moore, M., A. Enomoto, T. Nakano, A. Kayasuga, H. Kojima, H. Sakakibara, K. Oiwa, and T. Suda, “Molecular-motor Based Communication on a Microtubule Topology”, 2nd International Workshop on Natural Computing, Dec. 2007.
39 Moritani, Y., S. Hiyama, and T. Suda. 2006. Molecular communication among nanomachines using vesicles. In NSTI Nanotechnology Conference and Trade Show. Cambridge, MA: NSTI.

40 Moritani, Y., S. Hiyama, and T. Suda. 2006. Molecular communication for health care applications. In Proceedings of the Fourth Annual IEEE International Conference on Pervasive Computing and Communications Workshops. Washington, DC: IEEE Computer Society.
41 Nakagaki, T., H. Yamada, and Á. Tóth. 2000. Maze-solving by an amoeboid organism. Nature 407:470.
42 Nakano, T., T. Suda, M. Moore, R. Egashira, A. Enomoto, and K. Arima. 2005. Molecular communication for nanomachines using intercellular calcium signaling. In Proceedings of the 5th IEEE Conference on Nanotechnology, Nagoya, Japan, July 11–15, 2005.
43 Nakano, T., T. Suda, T. Koujin, T. Haraguchi, Y. Hiraoka, "Molecular Communication through Gap Junction Channels: System Design, Experiments and Modeling", in Proceedings of the 2nd International Conference on Bio-Inspired Models of Network, Information, and Computing Systems (BIONETICS 2007), Dec. 2007.
44 Nakano, T., Y. H. Hsu, W. C. Tang, T. Suda, D. Lin, T. Koujin, T. Haraguchi, and Y. Hiraoka, "Microplatform for Intercellular Communication", in Proceedings of the Third Annual IEEE International Conference on Nano/Micro Engineered and Molecular Systems, Jan. 2008.
45 Nomura, S., Y. Mizutani, K. Kurita, A. Watanabe, K. Akiyoshi. 2005. Changes in the morphology of cell-size liposomes in the presence of cholesterol: formation of neuron-like tubes and liposome networks. Biochim Biophys Acta 1669(2):164–9.
46 Oiwa, K., and H. Sakakibara. 2005. Recent progress in dynein structure and mechanism. Current Opinion in Cell Biology 17:98–103.
47 Peppas, N. A., and Y. Huang. 2004. Nanoscale technology of mucoadhesive interactions. Advanced Drug Delivery Reviews 56:1675–87.
48 Schneider, T. D. 1991. Theory of molecular machines. I, Channel capacity of molecular machines. Journal of Theoretical Biology 148:83–123.
49 Shima, T., T. Kon, K. Imamula, R. Ohkura, and K. Sutoh. 2006. Two modes of microtubule sliding driven by cytoplasmic dynein. Proceedings of the National Academy of Sciences 103(47):17736–40.
50 Smith, J. M. 2000. The concept of information in biology. Philosophy of Science 67(2):177–94.
51 Suda, T., M. Moore, T. Nakano, R. Egashira, and A. Enomoto. 2005. Exploratory research on molecular communication between nanomachines. In 2005 Genetic and Evolutionary Computation Conference, Late-breaking Papers. New York:ACM press.
52 Tamarin, R. H. 1999. Principles of genetics. New York: WCB/McGraw-Hill.
53 Toba, S., and K. Oiwa. 2006. Swing or embrace? New aspects of motility inspired by dynein structure in situ. BIOforum Europe. 10:14–6.
54 Wakabayashi, K. and M. Yamamura, "A realization of information gate by using enterococcus faecalis pheromone system", DNA7, LNCS 2340, pp. 269-278, 2002.
55 Weiss, R., and T. F. Knight. 2000. Engineered communications for microbial robotics. DNA computing. In 6th International Meeting on DNA Based Computers, DNA 2000. New York: Springer Lecture Notes in Computer Science, 2054.
56 Weiss, R., S. Basu, S. Hooshangi, A. Kalmbach, D. Karig, R. Mehreja, and I. Netravali, "Genetic circuit building blocks for cellular computation, communications, and signal processing", Natural Computing. 2003. Vol. 2, 47-84.
57 Yasuda, R., H. Noji, K. Kinosita, and M. Yoshida. 1998. F1-ATPase Is a highly efficient molecular motor that rotates with discrete 120 steps. Cell 93:1117–24.
58 Yang, G.-Z. (ed.), Body sensor networks, Springer, 2006.

59 You, L., R. S. Cox III, R. Weiss, and F. H. Arnold. 2004. Programmed population control by cell-cell communication and regulated killing. Nature 428:868–71.

***NAKANO Tadashi**, Ph.D.*

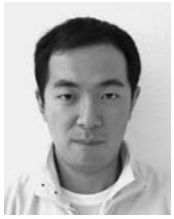
Assistant Adjunct Professor, Department of Computer Science, University of California, Irvine

Internet Technology, Molecular Communication

Michael J. Moore

Department of Computer Science, University of California, Irvine

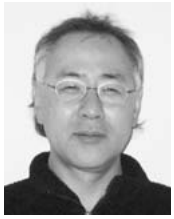
Computer Systems and Networking, Design and Development of Communication Systems using Biological Molecules



ENOMOTO Akihiro

Department of Computer Science, University of California, Irvine

Computer Systems and Networking, Design and Development of Communication Systems using Biological Molecules



***SUDA Tatsuya**, Ph.D.*

Professor, Department of Computer Science, University of California, Irvine

Distributed Systems, Sensor Networks, Molecular Communication