

Chapter 2

Molecular Communication Technology as a Biological ICT

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Abstract This chapter 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 coded 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 chapter describes key concepts, architecture, potential applications of molecular communication as well as existing research on engineering molecular communication components and systems.

Keywords Molecular communication · Nano-networks · Nanomachines

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2.1 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 [34], and any biochemical molecules, complexes, circuits that act as processing units [10] while examples of synthetic biological nanomachines are artificial molecular machines [33] and genetically engineered biological cells that are programmed to produce intended functions [13, 17, 21, 54].

Molecular communication is a new paradigm for communication between nanomachines over a short (nanoscale or microscale) range [27]. In molecular communication, information 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 [38]. 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 drug delivery 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, 30, 38, 45].

Research on molecular communication has started when the initial idea of molecular communication was presented in 2005 [27]. 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., [18, 26, 37, 40]). Research on theoretical foundations of molecular communication is also underway. The importance of information theory for small scale communication systems is addressed and research efforts are currently being made for addressing information theory for various classes of molecular communication (e.g., [2, 15, 16, 31, 32, 36]).

This article is organized in the following manner. [Section 2.2](#) gives an overview of various forms of molecular communication in biological systems. [Section 2.3](#) describes a generic architecture of molecular communication where senders and receivers communicate using molecules through key communication processes. [Section 2.4](#) describes existing research on engineering molecular communication components and systems, and [Sect. 2.5](#) concludes this article.

Column 1: Molecular Communication

A New Information and Communication Paradigm

Molecular communication is a new information and communication paradigm based on mechanisms and materials from biological systems. In molecular communication, information is represented with biochemical molecules, called *information molecules*, such as protein and DNA molecules. Information molecules are transmitted by the sender of communication, propagated in the environment, and received by the recipient of communication, which in turn decodes the information (i.e., reacts to the information molecules). Molecular communication provides a biocompatible solution as it adopts mechanisms and materials from biological systems, and its applications to medical and environmental domains are highly anticipated.

Comparison with Telecommunication

Molecular communication displays distinctive features that are not found in the current method of telecommunication based on electrical or optical signals. In telecommunication, electromagnetic waves propagate in space, or electrons/optical signals propagate via communication cables/links, by which digital information (texts, audio, and movies) is transmitted at a high speed and over a long distance. In molecular communication, on the other hand, information molecules (chemical signals) propagate in an aqueous environment. The speed and range of propagation are extremely limited compared to those of telecommunication, yet molecular communication potentially transmits information that cannot be transmitted using the current telecommunication technology. For instance, a macromolecule such as a protein exhibits an extremely complex structure which represents some biological function (e.g., catalysis of some chemical reactions). Molecular

Table 2.1 Telecommunication and molecular communication

	Telecommunication	Molecular communication
Information carrier	Electromagnetic waves, electrical/optical signals	Chemical signals
Media	Space, cables	Aqueous
Speed	Speed of light (3×10^8 m/s)	Extremely slow (nm \sim μ m/s)
Range	Long distance (\sim km)	Short distance (nm \sim m)
Information	Texts, audio, videos	Chemical reactions, states
Other features	Reliable, high energy consumption	Unreliable, biocompatible energy efficient

communication therefore enables transmission of functional information, allowing the recipient of communication to undergo biochemical reactions.

Also, current telecommunication is designed to transmit information accurately and reliably by consuming electrical power. On the other hand, molecular communication becomes fundamentally stochastic and unreliable due to the noise effects in the molecular environment. However, molecular communication presents unique features such as biocompatibility and energy efficiency that may be explored to enable new Information Communication Technology applications. Table 2.1 summarizes the features of molecular communication and telecommunication.

Column 2: Potentials of Molecular Communication

A Communication Paradigm for Bio-nanomachines

In the current telecommunication paradigm, silicon based devices communicate via electrical or optical signals. The recent engineering technology makes it possible to miniaturize as well as mass produce such communication devices. In the area of sensor networks, tiny sensing devices, called motes, are distributed to form a communication network. In molecular communication, even smaller devices, called bio-nanomachines or simply nanomachines, communicate. Nanomachines are nano-to-micro meter scale devices capable of computing, sensing, actuating, and such nanomachines can be synthesized using naturally existing biological machines and mechanisms by using bio-engineering technology.

Applications of Molecular Communication

Molecular communication is expected to impact a variety of technological domains. First, molecular communication provides a direct method for interfacing with biological systems, and thus applications to health and environmental domains are anticipated. As an example, consider a body network system where implant bionanomachines monitor health conditions. The body sensor networks technology mainly embeds silicon devices in the

body, while in the molecular communication paradigm, silicon devices may be replaced with biocompatible nanomachines, allowing them to directly communicate with cells, organs and tissues in the body. Also, continuing research on molecular communication may develop drug delivery systems where the delivery of molecules is controllable, environmentally friendly communication systems that may degrade and are integrated with the environment, and brain machine interfaces through which biochemical molecules directly interact with the brain and brain tissues.

In addition, molecular communication is expected to create a new unconventional computing paradigm. The area of molecular computing has demonstrated that basic computing and memory units can be made from biological materials and mechanisms. Molecular communication may provide a means to interconnect these basic units to form a large-scale massively parallel computing circuit. It may be possible in the future to have a computer that does not require electrical power and that does not produce heat. Further, unique features found in biological systems such as stochastic behavior, self-replication (cell division), self-organization (morphogenesis), and energy efficiency, may be explored to create a radically new computing paradigm.

2.2 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.

2.2.1 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) [14].
- (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) *Reaction-diffusion 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.

2.2.2 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. 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 [44, 47, 51]. 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, 50]. The receiver bacterium may also release pheromones that form a chemical gradient that guides a sender

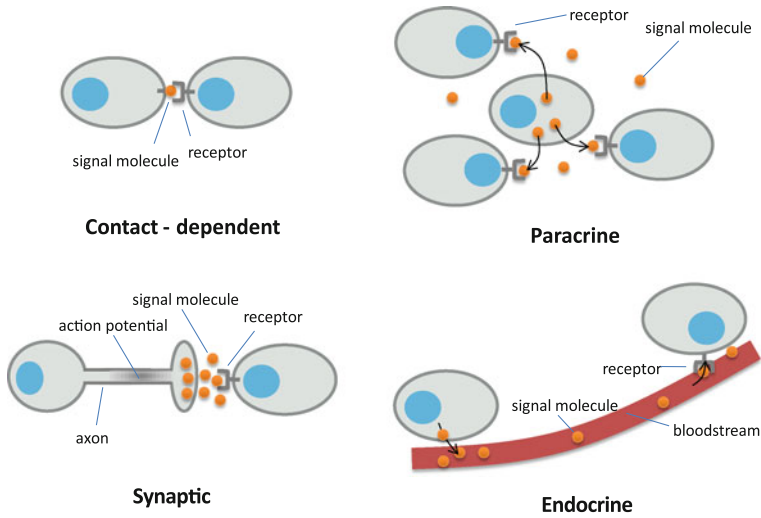


Fig. 2.1 Molecular communication in biological systems

bacterium toward a receiver bacterium (i.e., the closer to the receiver, the higher the chemical concentration).

Column 3: Communication in Our Body

Cell Communication

In molecular communication, communicating entities communicate information by sending, propagating and receiving information molecules. This is a common and ubiquitous method by which biological cells in our body communicate. Molecular communication provides a method for our cells to coordinate and maintain bodily functions and conditions necessary to sustain our life. In addition to those cells constituting a multi-cellular organism, unicellular organisms such as bacterial cells also communicate with each other by exchanging chemical signals in order to coordinate activities among a group of cells.

Examples of Cell Communication

In cell biology, cell communication mechanisms are often divided into four major types as shown in Fig. 2.1 in this column, out of which the first two types are for nearby cells to communicate (i.e., short distance communication) and the last two are for distant cells to communicate (i.e., longer distance communication.)

The first type is called contact-dependent by which signal molecules propagate from one cell to the other when the two cells physically contact. In this case, signal molecules expressed on the surface of one cell binds to the cell surface receptors on the other cell. The second type of cell communication is called paracrine, in which sender cells secrete signal molecules such as protein and peptide molecules to the extracellular space, which bind to the receptors of nearby receiver cells. The third type is synaptic, and this is how neurons propagate signals. In this type of communication, one end of a neuron, upon stimulation, generates an electrical gradient called the action potential. The action potential propagates over the axon toward the other end of the neuron, where this action potential produce chemical signals (neurotransmitters) that diffuse in the synapse to stimulate the next neuron (post-synaptic neuron). Synaptic communication provides a fast (e.g., 100 m/s) and long distance communication (a few meters). There exists another long distance communication mechanism, called endocrine—the fourth type. In this type, hormonal signals are transported or broadcast via a bloodstream to distant target cells or organs in our body.

Column 4: Intracellular Material Transport

Passive and Active Modes of Cell Communication

Modes (or mechanisms) of cell communication can be classified into passive or active modes based on how signal molecules propagate. The passive mode of cell communication relies on the random walk or free diffusion of signal molecules. Thus, it is difficult to propagate signal molecules over a long distance as well as to move large signal molecules in a high viscosity environment such as the cellular cytosol. The active mode provides a solution by consuming chemical energy, and one instance that enables the active mode of cell communication is a family of molecular motors, such as myosin and dynein (Fig. 2.2).

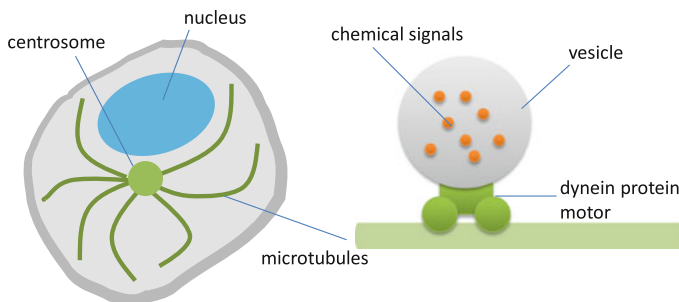


Fig. 2.2 Active mode of communication by molecular motors

Molecular Motors Transport Materials inside the Biological Cell

Molecular motors directionally walk along the protein rails by consuming chemical energy obtained from ATP (Adenosine Triphosphate) hydrolysis. Molecular motors are attached to a vesicle or cargo containing a set of signal molecules and actively move toward the destination. Molecular motors are in this sense vehicles running on the highway of protein rails within the cell. The active mode of cell communication propagates signal molecules directionally to a target location, providing a more reliable communication method than the passive mode. With the current bionanotechnology, motor proteins can be purified from the cell and the active transport mechanism can be reconstructed in vitro. Recent research successfully demonstrated the application of molecular motors to an in vitro molecule delivery system where molecules can be loaded to molecular motors, transported, and unloaded at the destination [1], which is directly applicable to the development and advancement of Lab-on-a-chip or μ -TAS (Micro-Total Analysis Systems).

1. S. Hiyama, R. Gojo, T. Shima, S. Takeuchi, K. Sutoh, "Biomolecular-Motor-Based Nano- or Microscale Particle Translocations on DNA Microarrays," *Nano Lett*, **9**(6):2407–2413 (2009)

2.3 Molecular Communication Architecture

As described in Sect. 2.2, 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

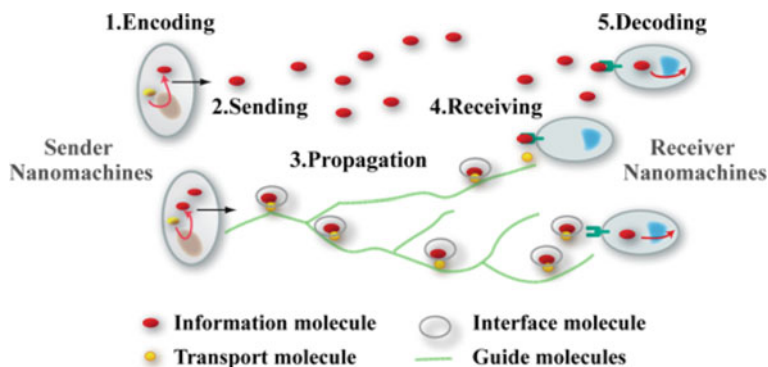


Fig. 2.3 Generic representation of molecular communication

engineer artificial biological systems. In this section, we attempt to describe an abstract architecture for molecular communication.

2.3.1 Generic Representation of Molecular Communication

Figure 2.3 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 [48], 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 [49]. 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 [37].

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).

2.3.2 Molecular Communication Processes

The components in molecular communication perform the following general phases of communication (Fig. 2.1): encoding of information into an information molecule by the sender nanomachine, sending of the information molecule into the environment, propagation of the information molecule through the environment, receiving of the information molecule by the receiver nanomachine, and decoding of the information molecule into a chemical reaction at the receiver nanomachine.

2.3.2.1 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 [46]. 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.

2.3.2.2 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.

2.3.2.3 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 environment. 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 [37]. The vesicle prevents the information molecules from chemically reacting with other molecules outside the vesicle.

2.3.2.4 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).

2.3.3 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.

2.3.3.1 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.

2.3.3.2 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 interference 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.

2.3.3.3 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.

2.3.3.4 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.

2.3.3.5 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% energy efficiency [28, 55]. 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.

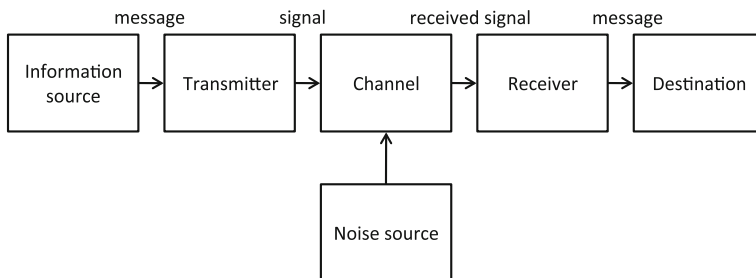


Fig. 2.4 Shannon's communication model

Column 5: Communication Model

Shannon's Communication Model

Claude Shannon, the founder of information theory, published "A Mathematical Theory of Communication" in 1948. As shown in Fig. 2.4 in this column, the model consists of information source, transmitter, channel containing the noise source, receiver and destination. This model assumes that the information source produces a message which is converted by the transmitter to the signal in the form that can propagate over the channel. During propagation, the signal may be altered or lost being affected by the noise. The signal is received by the receiver and a message is reconstructed from the received signal at the destination.

Molecular Communication Model

Molecular communication may be understood based on the Shannon's communication model described above where the goal is to deliver a message produced by the information source to the destination. In the first phase of communication, a message (or information) needs to be coded using signal molecules. One approach for coding is to represent information based on the number of molecules. For example, 10 molecules may be used to represent 10. Another approach is to represent information based on types of molecules. In this case, different molecules are used to convey different information, assuming that the receiver has receptors to receive the molecules. Some other approaches include modifying a molecular structure to represent information, or modulating a concentration change pattern similar to FM (Frequency Modulation) in radio communication.

In the second phase of communication, information carrying molecules propagate in the molecular communication environment, i.e., a communication channel. An approach to propagate molecules is passive propagation. In this case, signal molecules randomly walk in the environment to reach the receiver. Another approach is active propagation. In this case, chemical

energy is consumed to propagate signal molecules directionally or against the concentration gradient. The noise in the molecular communication environment is thermal noise or other molecules that chemically react with the information molecules.

The last phase of communication is to reconstruct (or decode) information from received signals at the receiver. Decoding in molecular communication indicates that the receiver reacts to received molecules. Decoding may for instance lead to chemical reactions, conformational changes, and energy conversion at the destination. At the cellular scale, decoding may lead to growth, differentiation, migration or death of biological cells.

Column 6: How Many Bits of Information can be Transmitted via Molecular Communication?

Information Carrying Molecules

Molecular communication is very slow and only applicable to a small range of the environment (e.g., μm range), although molecular communication may be able to deliver a large amount of information. Consider using a protein molecule to encode information. Assume that the protein molecule can take two structurally and functionally different states: phosphorylated and unphosphorylated states, then this protein can store one bit of information. If the protein molecule can take multiple stable states, say N states, then the amount of information that can be stored is $\log_2 N$. Let's scale up to the size of a cell and consider the amount of information that can be stored therein. It is known that an *E. Coli* bacterium has chromosome containing a 4.6 million basepair in a $2 \mu\text{m}^2$ cross-sectional area [1]. Since a DNA base is either one of the four: cytosine (C), guanine (G), adenine (A), thymine (T), the number of possible states N is $4^{4,600,000}$, and the information amount ($\log_2 N$) is 9.2 M bits. As a comparison, a memory density achieved with the silicon technology is expected to be 24.5 Gbits/cm² in 2014. This means that only 490 bits are stored in a $2 \mu\text{m}^2$ area. This indicates that molecular communication may provide a method for transferring a large amount of information.

Functional Molecule

A unique feature of molecular communication is that information carries (i.e., information molecules) have a physical property (e.g., a chemical state or structure) that represents some function. An enzyme, for instance, is a protein family that acts as a catalyst of a specific chemical reaction. A set of the DNA molecules, genetic information of a bacterial cell from the previous example, carries functions that allow the cell to perform massively parallel information processing by detecting, processing and synthesizing a number of molecules in the environment. Coming back to the advancement of silicon

technology, an expected transistor density around 2014 reaches 664 M/cm^2 . Assume that a simple logic requires four transistors, then only three logic units can be realized in a $2 \mu\text{m}^2$ area, whereas the bacterial cell performs complex information processing. Molecular communication transmits functional information carries—there is a potential as a breakthrough information technology.

1. M.L. Simpson, G.S. Saylorb, J.T. Flemingb, B. Applegate, “Wholecell biocomputing,” *Trends in Biotechnology*, vol 19, issue 8, pp. 317–323 (2001)

2.4 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.

2.4.1 *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.

2.4.1.1 Synthetic Biological Cells

The area of synthetic biology has demonstrated that new communication capabilities can be added to biological cells through genetic engineering [6, 12, 53, 54]. 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 [54], 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 [13], 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 [21], 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 [17], 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.

2.4.1.2 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 [19, 29]. 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 [19], chemical components for a minimal cell that is capable of replication are proposed. In [29], 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, 43].

Column 7: Engineering Nanomachines I

Synthetic Biology: Programming Biological Cells

Biological nanomachines (nanomachines in short) are small scale molecular machines with computing, sensing, and actuating functions. An approach to synthesizing nanomachines is to program a naturally existing cell via genetic engineering to perform an intended function. In the area of Synthetic Biology, a biological cell was genetically modified to induce a programmed behavior that is not found in the native version of the cell.

Genetically Engineered Biological Cells

Representative work in Synthetic Biology includes engineering of an inverter, bi-stable switch (called the toggle switch) and oscillator, each implemented in a bacteria cell.

In the development of the inverter [1], a DNA sequence is inserted into a bacterium to output an mRNA sequence only in the absence of an input mRNA (i.e., a NOT gate) (Fig. 2.5). In the absence of an input mRNA, an RNA polymerase recognizes the promoter region of the DNA sequence to perform transcription, producing an output mRNA. When an input mRNA coding a repressor is present as an input, the expressed repressor binds to the promoter region, blocking the binding of the RNA polymerase to the promoter region, thereby no output mRNA is produced. In addition to the inverter, other basic units (NOR and NAND) as well as more complex circuits have been demonstrated.

In the development of the toggle switch, a DNA sequence inserted in a bacterium contains two genes A and B that repress each other's expression

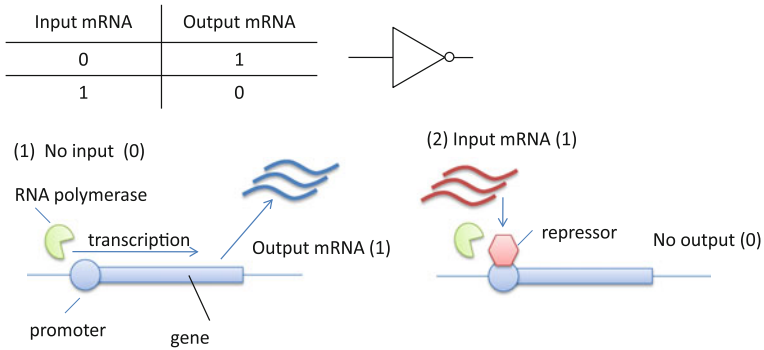


Fig. 2.5 Inverter design

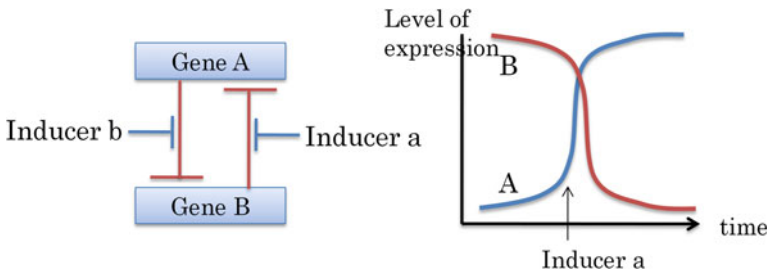


Fig. 2.6 Toggle switch design

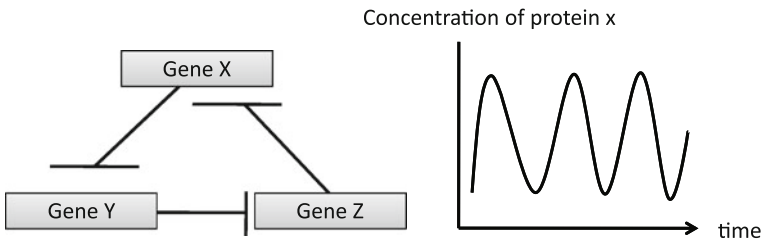


Fig. 2.7 Oscillator design

(Fig. 2.6, left). Since the expression of one gene represses that of the other, this system can take one of the two stable states (i.e., either of the protein product reaches a high concentration), representing one bit memory. The bit-state in this system can be externally altered by adding an inducer that forces the expression of gene A or B (Fig. 2.6, right).

In the development of the oscillator, a DNA sequence inserted in a bacterium causes three protein products to oscillate the concentrations over time. The DNA sequence here contains three genes X, Y, Z respectively coding proteins x , y , z that repress each other as shown in Fig. 2.7, left.

When X is expressed, protein product x represses the expression of Y, which then promotes expression of Z. As a result of Z expressed, X is then repressed. In this manner, the protein product x (and also other two) oscillates in the concentration as shown in Fig. 2.7, right.

The functional modules being developed in synthetic biology will be useful for developing a molecular communication system. The MIT (Massachusetts Institute of Technology)'s BioBricks project [2] aims at establishing a standard library for engineering and programming biological cells. It is expected in Synthetic Biology that one can program a biological cell in a manner we currently develop a software program using an API (application Programming Interface).

1. R. Weiss, S. Basu, S. Hooshangi, A. Kalmbach, D. Karig, R. Mehreja, I. Netravali, "Genetic circuit building blocks for cellular computation, communications, and signal processing," Nat. Comput. vol 2, pp. 47–84 (2003). The BioBricks Foundation, <http://bbf.openwetware.org/>

Column 8: Engineering Nanomachines II

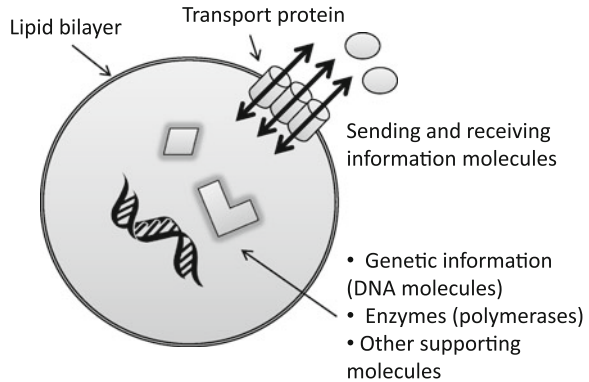
Engineering a Cell from Scratch

Another approach to engineering nanomachines is to chemically synthesize a cell from scratch using biological materials. Briefly, a cell-like container called liposome can be made from a lipid bi-layer that assembles into a spherical form, and chemical compounds necessary for genetic transcription and translation (e.g., genetic materials and regulatory proteins) can be embedded. The cell-like container provides a local environment where specific chemical reactions can occur. The cell-like container separates the inside from the outer environment, preventing the inside compounds from reacting with other molecules in the environment. Although the lipid bi-layer is highly compatible with our body and its use for medical applications is highly anticipated, the structure is not so durable in our body. Polymerosomes, emerging synthetic materials that exhibit increased stability, are thus considered an alternative to encapsulate chemical compounds to create an artificial cell [1].

Molecular Communication Using Artificial Cells

It is possible to implement a communication interface by adding a transport protein on the surface of an artificial cell (Fig. 2.8). A transport protein is a transmembrane protein that allows specific molecules to cross the membrane. When embedded on the surface of an artificial cell, it allows the artificial cell to uptake molecules in the environment and to release inside molecules to the outside. This is indeed nanomachine capable of receiving and sending molecules. Surprisingly, in the area of

Fig. 2.8 Design of an artificial cell



artificial cells, a self-replicating artificial cell is under consideration and development [2].

1. M. Doktycz, M. Simpson, Nano-enabled synthetic biology, *Mol. Syst. Biol.* 3:125 (2007)

2. A.C. Forster, G.M. Church, “Towards synthesis of a minimal cell,” *Mol. Syst. Biol.* 2:45 (2006)

2.5 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 Sect. 2.2, passive transport propagates information molecules freely in the environment while active transport propagates information molecules directionally using motors.

2.5.1 Engineered Passive Transport Mechanisms

2.5.1.1 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 [22, 53]. 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.

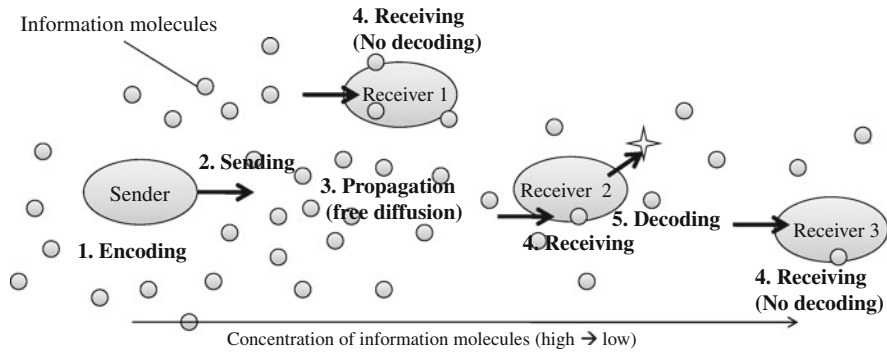


Fig. 2.9 An example communication sequence based on free-diffusion based molecular communication

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. 2.9, 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. 2.9. 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 and 3) do not produce any reactions (receiving only and no decoding).

2.5.1.2 Gap Junction Mediated Reaction–Diffusion Based Molecular Communication

Another type of engineered passive transport is to use reaction–diffusion 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.

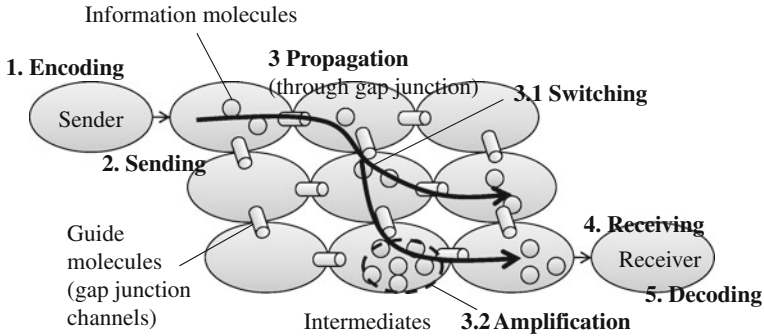


Fig. 2.10 An example communication sequence based on gap junction mediated reaction-diffusion based molecular communication

In [42], 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 reaction-diffusion 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 [41].

An example communication sequence based on this type of molecular communication is illustrated in Fig. 2.10. 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 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).

2.5.2 Engineered Active Transport Mechanisms

2.5.2.1 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 [35, 49]. 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) [11, 18]. 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 [24, 26]. The direction 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 [25].

An example communication sequence based on the first example is illustrated in Fig. 2.11. 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

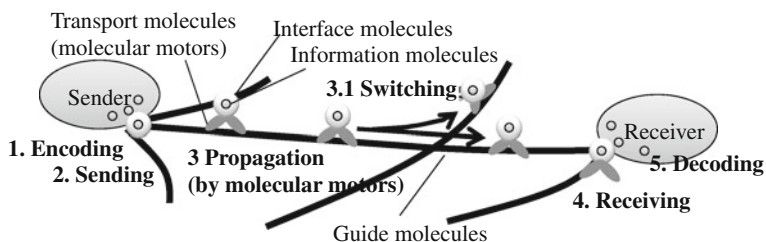


Fig. 2.11 An example communication sequence based on molecular motor-based molecular communication

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.

2.5.2.2 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 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 [39]. 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 molecular communication is found in bacterial cells, *E. faecalis* that perform conjugative plasmid transfer [52]. 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

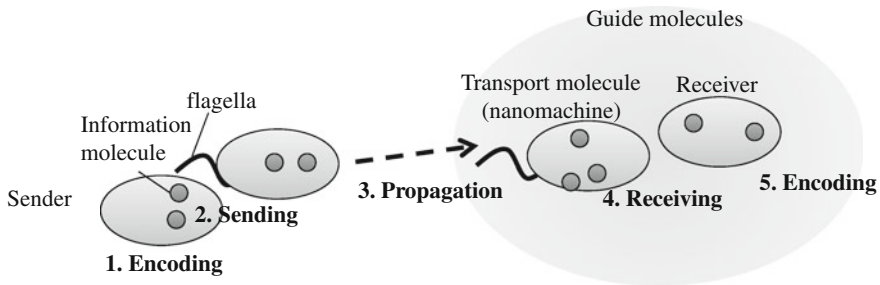


Fig. 2.12 An example communication sequence based on bacterial motor-based molecular communication

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. 2.12. In this type of molecular communication, the sender and receivers contain information molecules therein (e.g., DNA or RNA molecules within cells), and the transport molecule (or the transport nanomachine) is used to transport information molecules between them. First, the sender transports information molecules to the transport nanomachine via bacterial conjugation. The receiver of communication emits guide molecules (e.g. pheromones) in the environment to attract the transport molecule (or the transport nanomachine). The transport molecule propels closer to the receiver, indicating the propagation process. Once the transport molecule and receivers are physically touched (aggregated), the information molecule is transported to the receiver which shows some response (receiving and decoding).

2.6 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.

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 [37].

One example of a generic and abstract communication interface is found in drug delivery [30]. 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.

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 [26]. 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.

Column 9: Pattern Formation

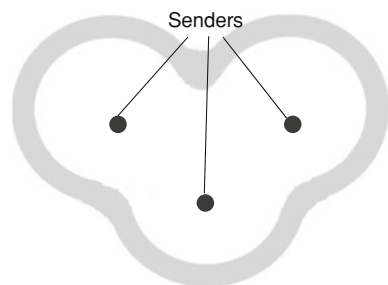
Morphogenesis and Molecular Communication

Molecular communication plays a key role in morphogenesis—the developmental processes of a biological organism. During the early stage of embryo development, a group of cells communicate through chemical signals referred to as morphogens. Morphogens are secreted by a cell to form a morphogen gradient in the environment. The concentration of the morphogen is the highest around the secreting cell and it becomes lower as the distance from the cell becomes longer. The cells in the environment respond to the morphogen concentration; they grow and differentiate to form a complex multi-cellular structure such as tissues and organs.

Artificial Morphogenesis

It is possible to control the biological structure to be formed by using information molecules that code morphological information. Such a study may be called artificial morphogenesis. As an example, consider a case where the three sender cells that secrete some signal molecules are placed as in Fig. 2.13. Assume that the receiver cells called band-detectors that detect and react to a specific concentration range of the signal molecules, are uniformly distributed in the environment. When the three sender cells synthesize and secrete about the same amount of signal molecules, the receiver cells on the edge of the heart-like shape (Fig. 2.13) will respond. If these receiver cells differentiate into different cell types, the heart-like structure emerges. Artificial morphogenesis is one of the promising application areas of molecular communication. It has a potential to advance and contribute to the development of artificial organs and regenerative medicine.

Fig. 2.13 An example of pattern formation



Column 10: A Molecular Communication System

Cellular Internet

We are currently developing a molecular communication system based on biological cells and cell–cell communication channels called gap junction channels—a micro-scale internet made of biological cells. We have applied bionanotechnology to create a cell wire, a line of connected cells that propagates chemical signals [1]. We have also successfully identified conditions under which chemical signals are amplified to propagate over a long distance [2]. Our ongoing efforts are toward developing a programmable molecular communication system that can control cellular behavior such as the growth, death, and differentiation of biological cells.

Dynamic Switching With Gap Junction Channels

Gap junction channels can have a different selectivity and permeability in response to various factors. Such dynamic properties can be exploited to implement networking functions such as switching. Figure 2.14a illustrates a possible design of switching cells. It is assumed in the figure that:

- Cell A expresses Cx_1 and Cx_2 ; Cell X expresses Cx_1 ; Cell Y expresses Cx_2 , where Cx_n denotes a specific protein that constitutes gap junction channels.
- The same types of Cx can form a channel, but different types of Cx cannot.
- Signal molecules are more permeable to gap junction channels with Cx_1 than those with Cx_2 .

If cells are structured as shown in Fig. 2.14a, gap junction channels are formed between Cell A and Cell X with Cx_1 and between Cell A and Cell Y with Cx_2 ; and signal molecules incoming to Cell A propagate preferentially to Cell X. The same cellular structure can then perform dynamic switching as shown in Fig. 2.14b. In this figure, an external signal is applied to decrease the permeability of gap junction channels made of Cx_1 , allowing more signals to propagate toward gap junction channels made of Cx_2 (i.e.,

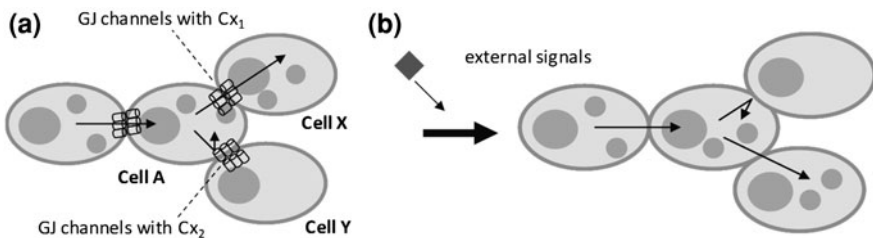


Fig. 2.14 Dynamic switching

toward Cell Y). Such switching may be possible with an external signal that can activate a specific kinase inside cells, which in turn phosphorylate a specific type of a gap junction constituting protein (i.e., Cx_1 in this case) that leads to the decreased permeability of the channels.

1. T. Nakano, T. Koujin, T. Suda, Y. Hiraoka, T. Haraguchi, "A Locally Induced Increase in Intracellular Ca^{2+} Propagates Cell-to-cell in the Presence of Plasma Membrane ATPase Inhibitors in Non-excitable Cells," *FEBS Lett.* vol 583, issue 22, pp. 3593-3599 (2009)

2. T. Nakano, Y.H. Hsu, W.C. Tang, T. Suda, D. Lin, T. Koujin, T. Haraguchi, Y. Hiraoka, "Microplatform for Intercellular Communication," in *Proc. Third Annual IEEE International Conference on Nano/Micro Engineered and Molecular Systems*, pp. 476-479 (2008)

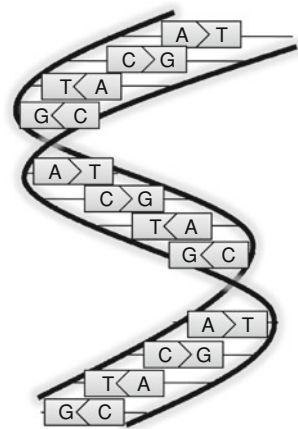
Column 11: DNA Molecules Walk

DNA (Deoxyribonucleic acid)

It is very well known that DNA carries and stores genetic information of biological systems. The double helix structure of DNA discovered by James D. Watson is also well known. Chemically, basic units of a DNA strand, namely DNA basis, are adenine (abbreviated A), guanine (G), cytosine (C), and thymine (T), where A and T, as well as G and C, are structurally complementary and can base pair via a hydrogen bond (Fig. 2.15).

DNA molecules have been considered new materials in the area of engineering. For example, in DNA computing and DNA nanotechnology areas, DNA molecules are used to solve computational problems or to create a nanoscale structure based on the self-assembling properties. In addition, recent research and development in the areas demonstrated that

Fig. 2.15 DNA double helix structure



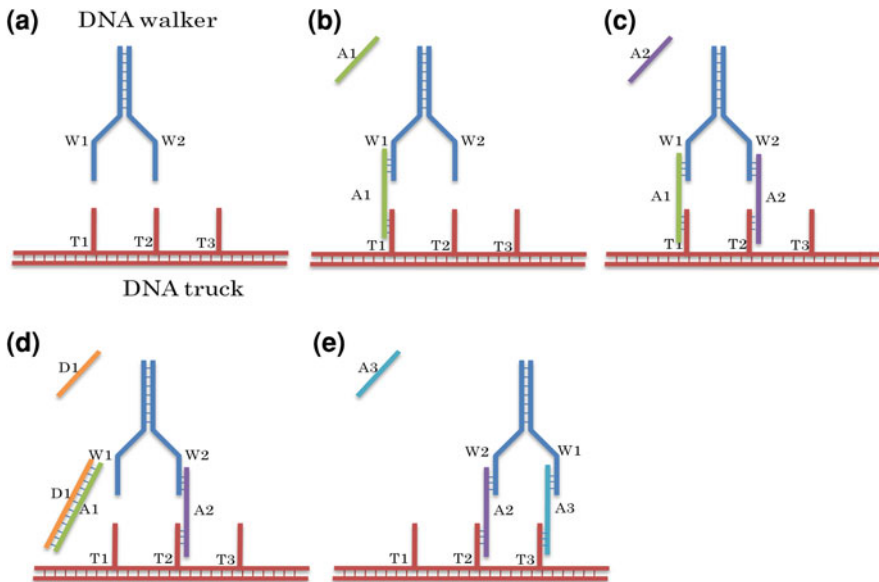


Fig. 2.16 DNA walker

specific structures of DNA molecules called DNA walkers or DNA spiders can “walk” in the nanoscale environment. Further, in this chapter, we discussed that an addressing mechanism can be implemented using DNA molecules.

DNA Walker

Figure 2.16 illustrates that a DNA walker progresses along the DNA track from the left to right. As shown in (a), the DNA walker has two legs, W1 and W2, and the DNA track has three branches, T1, T2, and T3. Each of the two legs and three branches is a single-stranded DNA sequence containing specific DNA basis.

First, a single strand DNA sequence A1, partially complementary to both W1 and T1, is introduced in the environment, then A1 forms a bridge to bind W1 to T1 (b). Second, a single strand DNA sequence A2, partially complementary to both W2 and T2, is introduced, then A2 forms a bridge to bind W2 to T2 (c). Third, a single strand DNA sequence D1, perfectly complementary to A1 is introduced, then D1 detaches W1 from T1, freeing leg W1 from the DNA track (d). Last, a single strand DNA sequence A3, partially complementary to W1 and T3 is introduced, then A3 forms a bridge to bind W1 to T3 (e). The DNA walker in this manner can walk in the nanoscale environment.

1. P. Yin, H. Yan, X.G. Daniell, A.J. Turberfield, J.H. Reif, A unidirectional DNA walker that moves autonomously along a track. *Communications of Angewandte Chemie International Edition* 43:4903–11 (2004)

Column 12: Recent Activities and Future Challenges

Recent Activities

The idea of using biological molecules in communication technology, namely molecular communication, has first appeared in 2005 and a line of research since then has started to address various issues on molecular communication. Molecular communication represents an interdisciplinary research area that spans over information technology, biology and nanotechnology, and as such information scientists, biologists and nanotechnologies commonly form a collaborative research group. Currently, research efforts are being made at National Institute of Information and Communications Technology (Japan), NTT DoCoMo (Japan), Tokyo University (Japan), Tokyo Medical and Dental University (Japan), Nara Institute of Science and Technology (Japan), University of California, Irvine (USA), Georgia Institute of Technology (USA), York University (Canada), Waterford Institute of Technology (Ireland), Middle East Institute of Technology (Turkey), and many others.

The first international symposium on molecular communication technology was held in Tokyo 2006 supported by National Institute of Information and Communications Technology, Japan. A workshop on molecular communication was held in Washington, DC 2008 financially supported by NSF (National Science Foundation, USA). In addition, technical sessions and panel discussions were held at various international conferences including IEEE INFOCOM 2005 (International Conference on Computer Communications), BIONETICS 2006 (Bio Inspired models of Network, Information and Computing Systems), and IEEE CCW 2007 (Computer Communications Workshop). Currently, BIONETICS [1] and Nano-Net [2] are the two major conferences that gather molecular communication researchers.

Future Challenges

Experimental efforts are so far focused on addressing typical physical layer issues of computer communications in addition to addressing issues related to designing and engineering system components. Theoretical efforts are also underway to investigate information representation using molecules and analyze the information transfer capacity in nano-to-micro scale environments. To further advance the area, the research on molecular communication will face the following challenges.

The first challenge is to identify, design, and engineer (or fabricate) building blocks necessary to provide a full molecular communication functionality. It is necessary to identify applicable biological materials and mechanisms, design system components using biological materials and mechanisms, apply bio-nanotechnology or biologically inspired methods (e.g., self-organization) to fabricate system components, and quantify the capacity and characteristics (e.g., durability in a biological environment).

As the second challenge, independent components engineered need to be integrated into a working communication system that robustly and stably functions. General research challenges include investigating a robust design architecture that allows communication components to self-organize and function under the influence of noise, and developing protocols, mechanisms and architectures that allow interfacing and networking among components.

The last challenge is to develop innovative applications of molecular communication systems. As mentioned, molecular communication systems are highly anticipated in medical domains. For instance, nanomachines capable of molecular communication may be implanted in a human body to interact with cells, tissues and organs for the purpose of human health monitoring. There are many other domains that molecular communication or networking of nanomachines may impact. To facilitate the design and development of applications, it is necessary to develop standard libraries, tools and frameworks.

1. BIONETICS (International Conference on Bio-Inspired Models of Network, Information, and Computing Systems) <http://www.bionetics.org/>
2. Nano-net (International ICST Conference on Nano-Networks) <http://www.nanonets.org/>

2.7 Summary

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 impact various technological domains including health (e.g., nanomedicine [20] and tissue engineering [8, 23]), environment (e.g., environmental monitoring), IT (e.g., unconventional computing [1] and body sensor networks [55]), and military (e.g., biochemical sensors).

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