1 Introduction

Historically, communications engineers have dealt with electromagnetic forms of communication: in wireline communication, electric fields move currents down a wire; in wireless communication, electromagnetic waves in the radio-frequency spectrum propagate through free space; in fibre-optic communication, electromagnetic radiation in the visible spectrum passes through glass fibres.

However, this book is concerned with an entirely different form of communication: *molecular communication*, in which messages are carried in patterns of molecules. As we shall see, molecular communication systems come in many varieties. For example, message-bearing molecules may propagate through a liquid medium via simple Brownian motion, or they may be carried by molecular motors; the message may be conveyed in the number and timing of indistinct molecules, or the message may be inscribed directly on the molecule (like DNA); and either the nanoscale properties of individual molecules may be important, or only their macroscale properties (like concentration).

Molecular communication is literally all around us: it is the primary method of communication among microorganisms, including the cells in the human body. In spite of its importance, only in the past decade has molecular communication been studied in the engineering literature. In writing this book, our goal is to introduce molecular communication to the wider community of communications engineers, and collect all the current knowledge in the field into a single reference for the sake of researchers who want to break into this exciting field.

1.1 Molecular Communication: Why, What, and How?

1.1.1 Why Molecular Communication?

Why would engineers want to design a system involving molecular communication? To motivate this question, suppose you are given the following design problem. Your goal is to perform *targeted drug delivery*: to deliver drugs within the human body exactly where they are needed (for example, directly to malignant tumours within the body, as chemotherapy). To accomplish this goal, you have decided to use *thousands of tiny, blood-cell-sized robots* which must cooperate with each other to autonomously navigate through the body, identify tumours, and release their drugs to destroy the

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tumour. To cooperate with each other, the robots must be able to communicate – so how would you design the communication system?

This is a challenging question: as a result of their size, the devices have very small energy reserves, and must glean whatever energy they can from the environment. The devices must also operate in the body without disrupting healthy tissues, or being destroyed themselves by the immune system prior to completing the mission. These features are consistent with the communication challenge faced by microorganisms, and these organisms have solved the problem by exchanging signals composed of molecules – that is, *molecular communication.*

As a result, for engineered systems, molecular communication is a *biologically inspired* solution to the communication problem. This communication could be engineered in two ways: first, an entirely artificial device could be designed to communicate using signalling molecules; and second, the existing molecular communication capabilities of an engineered microorganism (e.g., a bacteria with custom DNA) could be used. Remarkably, both nanoscale robots [1] and artificial bacteria [2] are within the capabilities of contemporary technology. However, nanoscale communication techniques, such as molecular communication, are needed to permit cooperation and unlock the disruptive potential of these systems.

1.1.2 What Uses Molecular Communication?

In Section 1.1.2, an example of tiny robots swimming through the human bloodstream is given. This example leads us to *biological nanomachines*, or *bio-nanomachines*, one of the primary application areas of molecular communication.

For our purposes, bio-nanomachines may be defined as follows:

- *Materials.* A bio-nanomachine is made up of biological materials (e.g., protein, nucleic acid, liposome, biological cell), or a hybrid of biological and non-biological materials.
- *Size.* A bio-nanomachine's size ranges from the size of a macromolecule to the typical size of a biological cell ($\sim$100 μm).[1]
- *Functionality.* A bio-nanomachine's functionality is limited to simple computation (e.g., integrating two types of input signals to produce one output signal), simple sensing (e.g., sensing only one or two types of molecule), and simple actuation (e.g., producing simple mechanical motion).

Figure 1.1 gives an overview of a molecular communication system involving bio-nanomachines [3]. In molecular communication, information is encoded onto (and decoded from) molecules, rather than electrons or electromagnetic waves. First, an information source generates information to encode onto molecules and triggers a group of sender bio-nanomachines to start propagation of information-encoded

[1] The term "nano" sometimes refers to dimensions of 1–100 nm, which is included in this definition; however, biological cells are typically much larger. Recently, the term *mesoscopic* has been used to describe dimensions that span from atomic to microbiological scales. See also [4] for standard definitions of nanonetworking.

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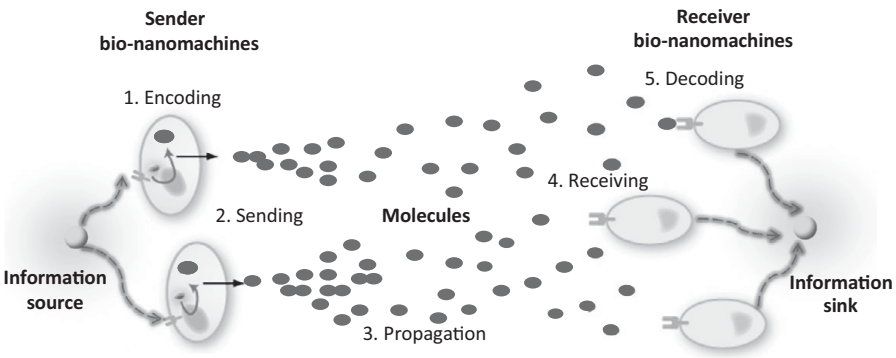

Figure 1.1 An outline of a molecular communication system incorporating bio-nanomachines [3].

molecules. Information-encoded molecules then propagate in the environment, and are detected by a group of receiver bio-nanomachines. Receiver bio-nanomachines may forward incoming molecules to next-hop bio-nanomachines or may pass them to an information sink for decoding information. We discuss this process in greater detail in Chapter 4.

Bio-nanomachines are not the only application for molecular communication – however, they are in many ways the primary motivating application, and the one that informs most of the analysis throughout this book. We give an introduction to applications in Section 1.3, and many detailed examples in later chapters.

1.1.3 How Does It Work? A Quick Introduction

How does molecular communication work? We spend the rest of this book answering this question, but here we give the reader a quick overview, and introduce the basic issues related to designing a molecular communication system.

First, we should be clear with what we mean by "communication." We focus on artificial communication, where a manmade *message* needs to be conveyed from one point to another. A message can be discrete (like a sequence of bits, as in an IP packet), or continuous (like an analog waveform, as in AM radio), but for now, we will assume that the message is discrete. In the simplest form of communication, there are two terminals: a *transmitter*, which sends the message; and a *receiver*, which receives the message. (So far, this is general enough to include any point-to-point communication system, not just molecular communication. This setup can be generalized: in a network setting, there may be many senders and receivers, and a terminal can be both a sender and a receiver for different messages.)

To be able to communicate, the transmitter makes a physical change to its environment, and that change must be measurable at the receiver. Again, this is true of any communication system: for instance, a wireless transmitter induces a changing EM field along an antenna, which can be detected in an antenna at the receiver. However,

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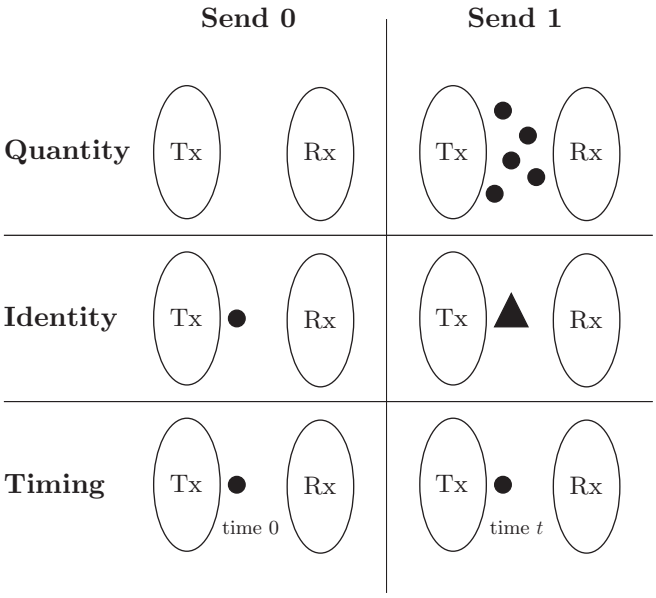

Figure 1.2 Illustration of three simple ways of generating a binary molecular signal.

in molecular communication, the change must be molecular: the transmitter releases molecules into a shared medium, which propagate to (and are detected by) the receiver.

In order to convey distinct messages, each possible message is associated with a molecular *signal*: a unique pattern of molecules for each possible message, which can be distinguished at the receiver. Further, there must be a way for the receiver to *decide* which message was sent, based on the signal that it measures. For instance, say we want to send a message consisting of a single bit, 0 or 1. We can do this in many ways, but here are three possibilities:

- *Signalling with quantity.* Say we have $n > 0$ molecules available at the transmitter. We could send a 0 by releasing zero molecules, or a 1 by releasing n molecules. If the receiver observes 0 molecules, it can conclude that a 0 was sent; if it observes at least one molecule, it can conclude that a 1 was sent.
- *Signalling with identity.* Say we have two types of molecule available at the transmitter, A and B (where the receiver can distinguish A from B). We could send a 0 by releasing molecule A, or a 1 by releasing molecule B. The receiver would decide 0 or 1 if it observed A or B, respectively.
- *Signalling with timing.* Say we have a single molecule available at the transmitter. We could send a 0 by releasing that molecule right now, or we could send a 1 by waiting $t > 0$ seconds before releasing the molecule. The receiver would then decide whether 0 or 1 was sent by measuring the arrival time of the molecule.

This simple example, illustrated in Figure 1.2, encapsulates many of the general techniques that we will describe throughout the book. For example, generalizing a

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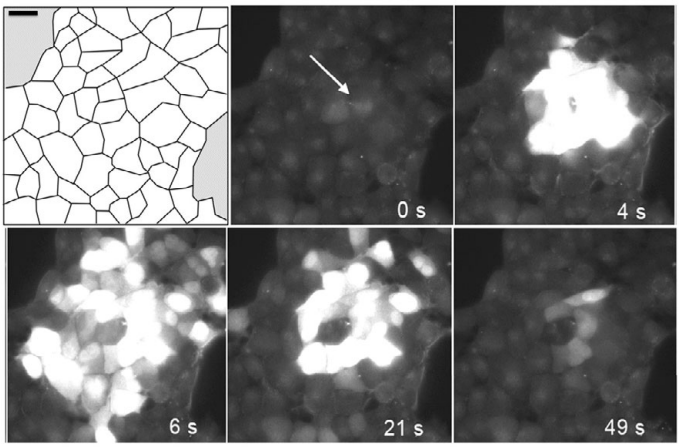

Figure 1.3 Series of images from a lab experiment. A sender cell, upon being stimulated, broadcasts molecular signals, and the receiver cells in the environment respond to the molecular signals [5].

quantity signal, we can manipulate the concentrations of molecules in the medium. We may also wonder how to generate molecular signals; we will see throughout this book that many biological "components" exist to emit and receive message-bearing molecules. As a result, molecular communication systems are often biologically based.

We also see that the propagation of molecules from transmitter to receiver must take place via diffusion: this could be viewed as either discrete Brownian motion, for small numbers of molecules, or continuous diffusion, for large numbers of molecules. Later, we will see that diffusion is a significant source of distortion and constraint on molecular communication systems: for instance, discrete Brownian motion might mean that message-bearing molecules are lost, or that they take an arbitrarily long time to arrive; further, continuous diffusion is a very slow process, which limits the possible rate of information transfer.

Figure 1.3 shows an example of molecular communication in the laboratory. A sender cell is stimulated at time $t = 0$, and encodes a molecular signal, using Inositol trisphosphate (IP_3) and adenosine triphosphate (ATP). Here, information about the stimuli is encoded in the *type* and *number* (i.e., the concentration) of molecules. The sender cell broadcasts the molecular signal into the environment, through external pathways (in the extracellular space) or internal pathways (gap junction channels). The molecular signals diffuse through the two pathways, and receiver cells in the environment detect the molecular signals using receptors. The receiver cells then increase the concentration of intracellular molecules (e.g., calcium), and decode the signals using molecular mechanisms inside the cells. More details of this form of molecular communication, as well as many other forms of molecular communication found in biological systems, are provided in Chapter 3.

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1.2 A History of Molecular Communication

The field of nanotechnology is commonly traced back to the Nobel-laureate physicist Richard Feynman, and his famous 1959 lecture to the American Physical Society, entitled "There's Plenty of Room at the Bottom" (transcribed in [6]). Feynman argued that the laws of physics permit very small devices, far smaller than contemporary technology had managed to produce. Since 1959, Feynman's vision of extreme miniaturization has been realized in many fields, such as integrated circuitry and microscopy. Moreover, new fields of research, such as micro and nanoelectromechanical systems (MEMS and NEMS), were spawned to extend this miniaturization into robotics.

Meanwhile, it has long been recognized that microorganisms, including cells and bacteria, gain information from their environment by gathering chemical messengers sent by their neighbours. A simple example is quorum sensing [7], in which bacteria send molecular messages to one another in order to estimate the local population of their species; the bacteria can take action based on this estimate, such as by forming a colony or by seeking out larger numbers of their species. Further, the means by which cells send messages to one another and control each others' behaviour is a well-studied area of biology known as *cell signalling* (see, e.g., [8]).

The engineering aspects of molecular communication have a research background that stretch back decades. In this section, we give a brief review of this field's history. We begin with a review of the (mostly theoretical) work done by early communications researchers. We then discuss more recent theoretical and implementational work, and conclude with a short review of contemporary research in this field.

1.2.1 Early History and Theoretical Research

Work by early researchers, such as Shannon [9] and Nyquist [10], established information theory and communication theory as mathematical disciplines. The focus was on telegraphic communication, so these theories developed (and remain) largely as subfields of electrical engineering. As abstract models, these techniques can be used in more general studies of communication, such as molecular or biological communication. However, this direction of research has remained on the fringes of information theory until recently, perhaps because Shannon himself discouraged it [11].[2]

Nonetheless, there has long been interest in information theory as a tool for explaining biological behaviour, especially in terms of biomolecular interactions. To the knowledge of the authors, the first discussion on information theory in the context of biomolecular interactions occurred in [12], which analyzed the efficiency of the kidney by recognizing its operation in terms of information processing: the kidney examines molecules and makes decisions on them, either keeping them in

[2] Shannon's point was not that chemistry or biology are inherently inappropriate applications for information theory, it was that the reputation of a rapidly growing field depends on scientific rigour and high-quality work. At the time, such work was found in the electrical applications. The reference [11] is certainly worth re-reading, and its lessons worth remembering, as our field of molecular communication appears poised for rapid growth.

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Figure 1.4 Illustration of Blackwell's "chemical channel." In the first figure, a black ball is introduced to the bag, which already contains a white ball. In the second figure, one of the two balls in the bag is selected at random and removed to form the channel output.

the bloodstream or rejecting them as waste, in an operation reminiscent of Maxwell's demon. The key observation was that gathering molecular information has a minimum energy cost, so information processing explained the kidney's energy consumption. This work was extended by Berger [13], where it was shown that molecular energy efficiency could be explicitly described in terms of rate distortion theory. This result was cited as "visionary" in a book review [14].

Meanwhile, Blackwell [15] described a highly abstract channel model, where successive channel outputs are statistically dependent. This model was called the *chemical channel* by subsequent authors,[3] making it possibly the first molecular communication channel model to appear in the literature. In this model, coloured balls are used to communicate: there are two colours, white and black, and the balls are otherwise identical. At the beginning of the communication session, a bag is filled with a given number of balls of unknown colours. Communication then proceeds as follows: first, the transmitter chooses a colour and drops a new ball of that colour into the bag, then the receiver selects a ball from the bag at random, removes it, and notes its colour; this process is repeated as often as necessary to send a message.

Example 1.1 Consider the chemical channel in Figure 1.4, where the bag initially contains one ball. You can send one bit of information for every three balls by using a *repetition code*: inserting three white balls in a row, or three black balls in a row. The receiver can tell what colour the transmitter has sent by picking the majority of colours out of every group of three: at most one ball will be of the wrong colour. This is not as good as you can do; however, the capacity of the trapdoor channel is an open problem.

If the bag in this example contains many balls, then the random selection is a coarse analog to random diffusion. For instance, say we have molecules instead of balls: the transmitter inserts molecules into the channel, which diffuse randomly into the medium, and are ultimately removed by the receiver. If the molecules are perfectly mixed after each insertion, then we have something like this channel. Berger elaborated on these ideas, showing how they can be used to describe biological molecular communication in his Shannon prize lecture [17].

[3] Early drafts of [16], available on arXiv, credit Thomas Cover with coining the term "chemical channel," though the claim is missing from the published version. The term "trapdoor channel" is also used.

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In its standard form, the trapdoor channel is a poor approximation to diffusion: the assumption of perfect mixing between insertions is not practical. The model can be refined; for example, each ball can have a different probability of being selected. However, it is worth remembering that the trapdoor channel was not originally intended to model diffusion; the diffusion application came later. More recently, researchers have examined *diffusion-mediated* models that explicitly view molecular diffusion as a communication system.

Diffusion can be viewed microscopically, as a process involving individual molecules, or macroscopically, as a process involving continuous concentrations. The latter approach has the advantage of being linear: the (continuous) diffusion equation is a linear partial differential equation, so the considerable body of linear system theory for communication systems can be applied. Early work in this direction emerged from the biological literature: in [18], Detwiler et al. used information theory to present chemical signal transduction in the retina as a communication system (to the authors' knowledge, the first explicit use of information theory in chemical signalling).[4] Building on these results, [21] simulated and analyzed a detailed linear model of a diffusion-mediated cellular transduction system, evaluating its frequency response and its information-theoretic capacity.

1.2.2 First Steps in Theoretical Research

Nearly 20 years have elapsed since the first analytical works on molecular communication. During this time, molecular communication has rapidly developed into a major field of research with practitioners around the world [22]. Here we briefly review the history of progress in theoretical research.

An early area of interest was the information-theoretic analysis of molecular communication. The general information-theoretic model of communication is broad enough to include new methods of information transfer, including molecular communication (and we describe this general model in Chapter 8). For molecular communication, the challenge is to develop information-theoretic equivalents for the various components of the model, such as the transmitter, the receiver, and the channel.

Discrete Brownian motion, modelled as a communication system, focuses on idealized models and the ultimate limits of molecular communication. This is because continuous diffusion is merely the limiting process of discrete Brownian motion, as the number of molecules becomes large. Thus, if we can find the limits of discrete Brownian motion, we have the best that can be done with molecular communication. The first work on discrete diffusion was [23], in which various "ideal" modelling assumptions were made, and the primary source of distortion in the channel was assumed to be the random propagation time of message-bearing molecules from the transmitter to the receiver.

[4] Information theory has been used to analyze neural coding for over 50 years, for example [19, 20], but not explicitly to analyze a chemical communication system.

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It is important to note that discrete diffusion systems require processing that is far beyond contemporary technology: for one thing, these systems require sensing and manipulation of individual molecules; for another, they often assume synchronization between the transmitter and the receiver. However, as research progresses into the ultimate limits of molecular communication, it is natural to consider these systems in terms of information theory.

Theoretical work has been done in other directions as well: continuous diffusion, considering the propagation of concentrations of molecules, is less efficient than discrete diffusion, but feasible to implement in practice, where components exist which can detect and respond to changes in concentration of a given molecular species. The capacity of such systems was considered in [24]. Biomorphic systems, as the focus of implementational work on molecular communication, are natural to analyze with information and communication theory. The previously mentioned work of [21] is an example of this type of analysis; another early work is [25], which analyzed a ligand–receptor system in discrete time.

1.2.3 First Steps in Implementation

The term "molecular communication," meaning an engineered communication system where messages are conveyed in patterns of molecules, was coined in the title of a 2005 paper [26]. That paper, focusing on the possible designs and uses of diffusion-based communication systems, launched a body of research on the implementation of molecular communication. These early works described a variety of biological or chemical components that could be used to assemble practical systems to conduct molecular communication: in other words, this work explores the "hardware" that would form the communication system. In many cases, laboratory experiments have been performed to show the feasibility of molecular communication, or to describe its potential applications.

Initial work identified various subsystems for communication. As one example, the gap junction channels, used by cells to exchange ions, could be used by collections of cells to pass concentrations of ions. If this were done under external control, a message could be passed from one side of the collection to the other [27, 28]. As another example, liposomes (i.e., spherical vesicles which act as "packages" of molecules) can be used to exchange messages: information-bearing molecules can be encapsulated into a liposome, and passed to communication partners. This possibility was explored by [29, 30], and its feasibility was demonstrated in lab experiments in [31].

The practical problem of transporting molecules from a transmitter to a receiver was also explored. Though random diffusion is one solution to this problem, there are alternatives: for example, molecular motors are used in living cells to transport molecules from one place to another. In molecular communication, motors may be used to collect message-bearing molecules (or packages of molecules, e.g. in liposomes) and transport them from the transmitter to the receiver [32]. Experiments validating this approach were presented in [33].

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1.2.4 Organization of Contemporary Research

An initial explosion of interest in molecular communication was thanks in part to a focus on nanoscale communication networks, or *nanonetworks* [34, 35]. Nanonetworks involve collections of very small devices that communicate and cooperate with each other, and in which essential features of the network have nanoscale dimensions. For example, swarms of nanorobots, which may be used in some of the applications described earlier in this chapter, may form a nanonetwork in order to accomplish their task. Molecular communication has been recognized as an enabling technology for nanonetworking [36].

Molecular communication has become increasingly popular among traditional communication engineers. As the background of these researchers is primarily theoretical and simulation-based, there has been a rapid increase in theoretical and simulation-based analysis of molecular communication. Without attempting to be comprehensive, we give several major themes of research:

- Channel modelling and noise analysis are key directions of research. Traditional communication and information theory are based on a set of mathematically precise channel models, such as the additive white Gaussian noise channel. Moreover, within each such channel, there exists a source of distortion, or "noise." However, no widely accepted general channel or noise model exists for molecular communication; depending on the scenario, it is likely that several different channel models are required. For example, in [37], a complete end-to-end model of molecular communication was developed based on continuous diffusion. Theoretical first-arrival-time models have also been proposed, such as the additive inverse Gaussian model for diffusion in the presence of flow [38]. More recent models have arisen from detailed simulations and experimental testbeds [39].
- The information-theoretic capacity of molecular communication, or the maximum rate at which data can be reliably transmitted, is an important open problem. The fully general problem of finding capacity is known to be difficult, but many recent papers have sought either bounds on capacity or the capacity in simplified scenarios, such as: [40] which considered continuous diffusion, simplifying the concentration to a binary variable (taking values of "high" and "low" concentration); and [41], which considered a similar setup with generalized transmission schemes and possible molecular losses. Another direction is described in [42, 43, 44], which examines the symmetries in possible capacity-achieving input strategies, and bounds the general channel capacity. Other results have been obtained for specific channel models, such as [45].
- The development of testbeds has provided researchers with a relatively low-cost way to perform experimental investigations of molecular communication, and this remains an important direction of research. An initial effort in [46] demonstrated that short text messages could be conveyed through the air in bursts of alcohol vapour. A fluidic testbed, similar to the environment found in a blood vessel, was developed in [47]. Sophisticated testbeds demonstrating molecular communication in air ducts [48] and water columns [49] have also been demonstrated.

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- Extensive work has been done on accurate simulation, which is an important tool for system design. This work includes optimization of distance-estimation techniques [50], design of channel shapes for microfluidic molecular communication [51], design of routing schemes in networks [52], and design of signalling techniques [53]. The design and analysis of simulation techniques themselves are an important open problem, and some papers are devoted entirely to that topic (e.g., [54]). Several sophisticated simulation packages have been developed for molecular communication, such as the Actor-based Communication via Reaction-Diffusion (AcCoRD) package [55].
- System-level research has also attracted much recent attention. The problem described at the beginning of this chapter – operation of bio-nanomachines in the human body – was reviewed in [56], and major challenges were identified. Molecular communication for swarm nanorobotics, a related research challenge, was studied in [57, 58]. In response to surging system-level research efforts in molecular communication, and nanonetworking more generally, the IEEE 1906.1 standard has been developed [59], in order to standardize technologies and specifications for nanonetworking. More recently, mobile molecular communication has emerged as a potential enabling technology for a nanonetwork composed of free-floating nanodevices [60].

We will discuss the background of many of these problems in greater detail throughout this book.

1.3 Application Areas

Molecular communication has the potential to advance interdisciplinary and disruptive applications in biological engineering, medical and healthcare, industrial, environmental, and information and communication technology areas [3, 34, 61] (Figure 1.5). In this section, we will briefly go over specific application areas where molecular communication research may advance existing methods and technologies. Some of the selected applications are discussed in more detail in later chapters.

1.3.1 Biological Engineering

Molecular communication may benefit the area of biological engineering to analyze biological materials, engineer biological systems, and interface biological systems with manmade systems. Specific examples of relevant subareas in biological engineering include microelectromechanical systems (MEMS) for analyzing biological samples, tissue engineering for regenerating tissues and organs, and brain machine interfaces (BMI) for interfacing a human brain and electrical devices:

- *Microelectromechanical systems*: MEMS apply microtechnology to develop a small scale system such as a lab-on-a-chip (LOC) [62, 63] or a network-on-chip

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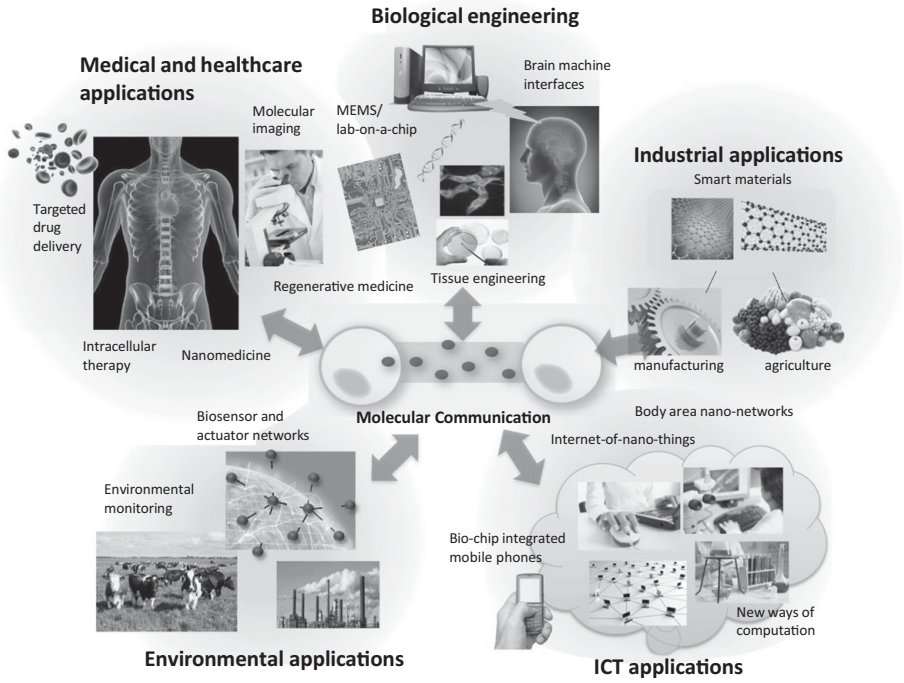

Figure 1.5 Application areas of molecular communication research

(NoC) [64] for on-chip analysis of biological samples (e.g., molecules). A LOC is typically 20 micrometers to a millimeter in size and provides functionalities to manipulate molecules on a single chip, such as moving molecules from one location to the other, mixing one type of molecules with another type of molecules, and separating specific types of molecules from a mixture of molecules. For a LOC, molecular communication may provide nanoscale techniques to manipulate molecules on a chip. For instance, guide and addressing molecules considered in molecular communication (see Chapters 4 and 11) may be used to transport a molecule directionally to a specific location on a chip.

- *Tissue engineering*: Tissue engineering aims at developing a tissue structure from biological cells to restore lost tissues of a patient's body [65]. In tissue engineering, stem cells (e.g., autologous cells) are extracted from a patient's body and cultured in vitro. Engineered extracellular matrices called scaffolds are often used as a template to guide the development and assembly of the cells into a three-dimensional tissue structure. Molecular communication may provide an additional mechanism to produce spatial patterns of molecules and thereby affect the growth and differentiation of the stem cells into specific tissue structures. For instance, bio-nanomachines (e.g., engineered stem cells) may release molecules that propagate in the environment to establish a spatial pattern of molecules, and the bio-nanomachines differentiate based on the established pattern to form a

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structure. The tissue structure is then implanted into the human patient to restore the lost tissues.

- *Brain machine interfaces*: BMI provides a direct channel between the human brain and electrical devices to restore lost functions [66]. In BMI-based motor prostheses, for instance, motor signals generated in the brain are recorded through electrodes implanted in the brain and transmitted to an external device, which interprets the motor signals to control the artificial limb of a patient. Signals generated from an external device may also be transmitted to electrodes implanted in the brain, which in turn stimulate a specific part of the brain to treat a brain disease (e.g., Parkinson's disease). For BMI, molecular communication may provide a molecular or chemical means of interacting with the brain, instead of electrical ways. For such an application, bio-nanomachines may be engineered to implement a molecular communication interface to interact with a human brain as well as a man–machine interface to interact with electronic devices.

1.3.2 Medical and Healthcare Applications

Molecular communication can also be applied to improve the ability of medical or healthcare systems. These systems may be integrated with a group of bio-nanomachines that communicate and cooperate to monitor medical conditions and perform therapy by releasing molecules. Examples of such scenarios are found in molecular imaging for gathering information for diagnosis, and targeted drug delivery and intracellular therapy for performing therapy:

- *Molecular imaging*: Molecular imaging is a technique to monitor cellular function and processes in vitro or in situ, which can be used to gather information for diagnosis. For molecular imaging, a green fluorescent protein (GFP) can be used as a reporter of gene expression, for example. Monitoring and diagnosis can be performed with GFPs by detecting the expression of particular genes in a human body, which indicates a disease or certain medical condition. GFPs can be carried by viruses, introduced in a tissue, and targeted to cancer cells in the tissue. When the tissue is illuminated, the GFP responds to emit florescence and thus the location of cancer cells can be identified. Molecular communication may further improve the ability of molecular imaging, for instance, by providing coordination mechanisms for a group of bio-nanomachines (e.g., viruses carrying GFPs) to gather information about conditions from a larger area in a body, aggregate the information in situ, and transmit the aggregated information (e.g., through fluorescence) to external devices for further diagnosis.
- *Targeted drug delivery*: In targeted drug delivery, therapy on a target site (e.g., diseased cells or tumours) in a human body is performed by encapsulating drug molecules in drug delivery carriers, delivering the carriers to the target site, and releasing the drug molecules from the carriers at the target site. Targeted drug delivery therefore reduces potential side effects of drug molecules on nontargeted sites [67, 68]. Existing research on drug delivery develops drug delivery carriers

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that can be targeted to a specific site in a body (e.g., tumours), where the drug molecules are released in response to specific conditions such as temperature. Molecular communication may provide alternative techniques to improve the accuracy of targeting and efficacy of therapy through the coordination of bio-nanomachines (i.e., drug delivery carriers). For instance, bio-nanomachines that identify a target site may release molecules to recruit other bio-nanomachines in the environment towards the target site, thereby, the concentration of bio-nanomachines at the target site is increased. Also, a group of bio-nanomachines at the target site may communicate to determine the rate of drug release depending on various conditions (e.g., the number of bio-nanomachines at the target site) to achieve a sustained drug release.

- *Intracellular therapy*: Intracellular therapy is similar to drug delivery in delivery of drug molecules to a target site, except that the target site is inside a cell (e.g., an intracellular compartment where pathogens are present) [69]. Intracellular therapy delivers drug molecules to a target site in an intracellular compartment, and it is highly challenging due to the fact that drug delivery carriers need to overcome a number of biological barriers (e.g., cell membranes and various cellular processes such as endocytic events). Molecular communication may allow a group of bio-nanomachines to coordinate to reach a target site for intracellular therapy. For instance, functionally different bio-nanomachines may be introduced to modify the characteristics of a cell (e.g., permeability of the cell membrane) to bypass different types of biological barriers. These functionally different bio-nanomachines may also coordinate to detect multiple conditions to diagnose whether the cell is infected. When a cell is diagnosed as infected, bio-nanomachines carrying drug molecules (e.g., antiviral drugs) may release the drug molecules to combat the pathogens inside the cell.

1.3.3 Industrial Applications

Molecular communication can also be applied in various industries to produce a functional material from molecules. The agricultural industry, for instance, may benefit from food materials containing a number of bio-nanomachines through which the growth process of the food can be controlled. The manufacturing industry may also benefit from smart materials made of bio-nanomachines that have characteristics which are externally controllable or adaptive to changes in the environment. These functional materials may be several orders of magnitude larger than a single bio-nanomachine in size, and thus particular functionalities of such materials may emerge as a result of local interactions among groups of bio-nanomachines. Molecular communication is available for a group of bio-nanomachines to interact in a local environment, since molecular communication is inherently limited to the local environment. To change the functionality of a material, for instance, external stimuli (e.g., chemical, mechanical, electrical) may be applied to a material to initiate molecular communication processes among bio-nanomachines embedded in the

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material. Each bio-nanomachine responds to a change in a local environment, moves to a particular location, and/or transports molecules to a particular location. The movement of bio-nanomachines and molecules in local environments may lead to a change in global structure, and therefore modifies the functionality of the material.

1.3.4 Environmental Applications

Molecular communication can be applied to monitor molecules in an environment that may be contaminated with toxic or radioactive agents. To monitor a large area of an environment, bio-nanomachines may be integrated into large or microscale devices (e.g., motes in wireless sensor networks) and these devices are deployed in the environment to form a large-scale biosensor network [70]. Bio-nanomachines in these devices detect molecules from the environment to provide early warning of contamination in that environment. Molecular communication may be useful to allow a group of bio-nanomachines to process molecules in a cooperative manner. For instance, one type of bio-nanomachines amplifies molecular signals from the environment, another type integrates different molecular signals to identify the location of a toxic source, another type guides the device to the location of the toxic agents, and yet another type degrades toxic molecules into a nontoxic or reusable form.

1.3.5 Information and Communication Technology Applications

Molecular communication may also introduce a breakthrough into information and communication technology through the integration of bio-nanomachines into the currently available silicon-based systems. For instance, a future mobile phone may be integrated with bio-nanomachines capable of molecular communication for on-chip analysis of biochemical signals (e.g., molecules in blood or from sweat) [71]. Such a device itself may be produced from a massive number of communicating bio-nanomachines and can be integrated with a human body. As another example, a dermal display screen is envisioned to be made from a population of 3 billion bio-nanomachines and embedded below the skin surface on a human body [72]. Massively distributed bio-nanomachines capable of molecular communication may also be integrated into the Internet to form the Internet-of-nano-things [73] and body-area nanonetworks [74]. In addition, molecular communication may apply to non-silicon-based computing paradigms, for example, unconventional computation. In unconventional computation, research efforts are made to exploit physical, chemical, or biological materials to develop new computing architectures and to design algorithms for such architectures to solve computationally difficult problems. Unconventional computation has promising features such as extremely high functional complexity and large scale parallelism that cannot be achieved with silicon-based electronic circuits. One promising approach is to use bio-nanomachines and molecular communication as the components for unconventional computation.

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1.4 Rationale and Organization of the Book

As molecular communication is an interdisciplinary field, with elements of electrical engineering, mathematics, chemistry, and biology, it is unlikely that any new researcher in this field would have all the expertise required to quickly make a contribution. Moreover, the needed expertise is found in widely different literature across these disciplines.

Our objective in writing this book is to provide a first reference for new researchers in molecular communication, introducing them to the elements of the field; another objective is to provide enough background and references to allow new researchers to explore the literature further on their own. Our book is directed both towards traditional communications engineers who need a background in the biological principles of molecular communication, and towards chemists and biologists who need exposure to information and communication theory.

The remainder of the book is organized as follows:

- In Chapter 2, we describe biological nanomachines, giving background information about their molecular structure and function.
- In Chapter 3, we describe biological molecular communication, describing how this communication method is used in nature, especially among the biological nanomachines described in Chapter 2.
- In Chapter 4, we describe the molecular communication paradigm, explaining the concept of engineered molecular communication.
- In Chapter 5, we describe a layered architecture model for molecular communication networks, analogous to similar models for conventional communication networks.
- In Chapter 6, we give mathematical models for various types of diffusion-based molecular communication, and describe how to simulate them.
- In Chapter 7, we give mathematical models for biological molecular communication, particularly discussing membrane ion channels and their kinetics.
- In Chapter 8, we build on the mathematical models from Chapters 6 and 7 to describe the information and communication theory of molecular communication.
- In Chapter 9, we consider mobile bio-nanomachines and discuss mobile molecular communication between them.
- In Chapter 10, we discuss experimental approaches to molecular communication, especially low-cost testbeds that have driven recent experimental research.
- In Chapter 11, we discuss the design and engineering of molecular communication components, particularly biochemical building blocks such as proteins, DNA, liposomes, and individual cells.
- In Chapter 12, we discuss the design and engineering of molecular communication systems, focusing on examples of specific applications such as drug delivery, tissue engineering, lab-on-chip systems, and unconventional communication.
- In Chapters 13 and 14, we discuss collective motion of bio-nanomachines through molecular communication: targeted cluster formation in Chapter 13, and large-scale structure formation in Chapter 14.

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- In Chapter 15, we discuss externally controllable molecular communication for interfacing bio-nanomachines with external devices and its application to biological pattern formation.
- In Chapter 16, we discuss standardization in molecular communication, focusing on IEEE standards 1906.1 and 1906.1.1.
- In Chapter 17, we present a brief conclusion.

We have attempted to present the material in such a way as to assume a minimal background in either biology or communication theory, which we hope will give this book broad appeal, although the material may seem like a review to some readers.

References

[1] S. Martel, "Nanorobots for microfactories to operations in the human body and robots propelled by bacteria," *Journal Facta Universitatis Series Mechanics, Automatic Control and Robotics*, vol. 7, pp. 1–10, 2009.

[2] D. G. Gibson et al., "Creation of a bacterial cell controlled by a chemically synthesized genome," *Science*, vol. 329, no. 5987, pp. 52–56, 2010.

[3] T. Nakano, M. Moore, F. Wei, A. V. Vasilakos, and J. W. Shuai, "Molecular communication and networking: Opportunities and challenges," *IEEE Transactions on NanoBioscience*, vol. 11, no. 2, pp. 135–148, 2012.

[4] S. F. Bush, J. L. Paluh, G. Piro, V. Rao, V. Prasad, and A. W. Eckford, "Defining communication at the bottom," *IEEE Transactions on Molecular, Biological, and Multi-Scale Communications*, vol. 1, no. 1, pp. 90–96, 2015.

[5] T. Nakano and J. Shuai, "Repeater design and modeling for molecular communication networks," in *Proceedings of the 2011 IEEE Infocom Workshop on Molecular and Nanoscale Communications,* 2011, pp. 501–506.

[6] R. P. Feynman, "There's plenty of room at the bottom," *Engineering and Science*, vol. 23, no. 5, pp. 22–36, 1960.

[7] M. B. Miller and B. L. Bassler, "Quorum sensing in bacteria," *Annual Review of Microbiology*, vol. 55, pp. 165–199, 2001.

[8] J. Hancock, *Cell Signalling*. Oxford University Press, 2010.

[9] C. E. Shannon, "A mathematical theory of communication," *Bell System Technical Journal*, vol. 27, no. 3, pp. 379–423, 1948.

[10] H. Nyquist, "Certain factors affecting telegraph speed," *Bell System Technical Journal*, vol. 3, pp. 324–346, 1924.

[11] C. E. Shannon, "The bandwagon," *IRE Transactions on Information Theory*, vol. 2, no. 1, p. 3, 1956.

[12] H. A. Johnson and K. D. Knudsen, "Renal efficiency and information theory," *Nature*, vol. 206, pp. 930–931, 1965.

[13] T. Berger, *Rate Distortion Theory: A Mathematical Basis for Data Compression*. Prentice Hall, 1971.

[14] R. M. Gray, "Rate Distortion Theory: A Mathematical Basis for Data Compression (Book Review)," *IEEE Transactions on Information Theory*, vol. 18, no. 1, pp. 217–218, 1972.

[15] D. Blackwell, *Information Theory*, Modern Mathematics for the Engineer: Second Series. McGraw-Hill, 1961, pp. 182–193.

[16] H. Permuter, P. Cuff, B. V. Roy, and T. Weissman, "Capacity of the chemical channel with feedback," *IEEE Transactions on Information Theory*, vol. 54, no. 7, pp. 3150–3165, 2008.

[17] T. Berger, "Living information theory (Shannon lecture)," in *Proceedings of the IEEE International Symposium on Information Theory, Lausanne, Switzerland*, 2002.

[18] P. B. Detwiler, S. Ramanathan, A. Sengupta, and B. I. Shraiman, "Engineering aspects of enzymatic signal transduction: Photoreceptors in the retina," *Biophysical Journal*, vol. 79, pp. 2801–2817, 2000.

[19] H. B. Barlow, "Possible principles underlying the transformation of sensory messages," *Sensory Communication*, pp. 217–234, 1961.

[20] S. B. Laughlin, "A simple coding procedure enhances neurons information capacity," *Zeitschrift für Naturforschung*, vol. 36, pp. 910–912, 1981.

[21] P. J. Thomas, D. J. Spencer, S. K. Hampton, P. Park, and J. P. Zurkus, "The diffusion mediated biochemical signal relay channel," in *Proceedings of the 17th Annual Conference on Neural Information Processing Systems*, 2003.

[22] T. Nakano, "Molecular communication: A 10 year retrospective," *IEEE Transactions on Molecular, Biological, and Multi-Scale Communications*, vol. 3, no. 2, pp. 71–78, 2017.

[23] A. W. Eckford, "Nanoscale communication with Brownian motion," in *Proceedings of the Conference on Information Sciences and Systems*, 2007, pp. 160–165.

[24] A. Einolghozati, M. Sardari, A. Beirami, and F. Fekri, "Capacity of discrete molecular diffusion channels," in *IEEE International Symposium on Information Theory*, 2011.

[25] B. Atakan and O. Akan, "An information theoretical approach for molecular communication," in *Proceedings of the 2nd International Conference on Bio-Inspired Models of Network, Information, and Computing Systems*, 2007, pp. 33–40.

[26] S. Hiyama, Y. Moritani, T. Suda, R. Egashira, A. Enomoto, M. Moore, and T. Nakano, "Molecular communication," in *Proceedings of the 2005 NSTI Nanotechnology Conference*, 2005, pp. 391–394.

[27] T. Nakano, T. Suda, M. Moore, R. Egashira, and K. Arima, "Molecular communication for nanomachines using intercellular calcium signalling," in *IEEE International Conference on Nanotechnology*, 2005, pp. 478–481.

[28] T. Nakano, T. Suda, T. Kojuin, T. Haraguchi, and 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*, 2007, pp. 139–146.

[29] Y. Moritani, S. Hiyama, and T. Suda, "Molecular communication among nanomachines using vesicles," in *Proceedings of the NSTI Nanotechnology Conference*, 2006, vol. 2, pp. 705–708.

[30] Y. Moritani, S.-M. Nomura, S. Hiyama, T. Suda, and K. Akiyoshi, "A communication interface using vesicles embedded with channel forming proteins in molecular communication," in *Proceedings of the 2nd International Conference on Bio-Inspired Models of Network, Information, and Computing Systems*, 2007, pp. 147–149.

[31] M. Kaneda, S.-M. Nomura, S. Ichinose, S. Kondo, K. Nakahama, K. Akiyoshi, and I. Morita, "Direct formation of proteo-liposomes by in vitro synthesis and cellular cytosolic delivery with connexin-expressing liposomes," *Biomaterials*, vol. 30, pp. 3971–3977, 2009.

[32] A. Enomoto, M. Moore, T. Nakano, R. Egashira, T. Suda, A. Kayasuga, H. Kojima, H. Sakibara, and K. Oiwa, "A molecular communication system using a network of

cytoskeletal filaments," in *Proceedings of the 2006 NSTI Nanotechnology Conference*, 2006, pp. 725–728.

[33] S. Hiyama, R. Gojo, T. Shima, S. Takeuchi, and K. Sutoh, "Biomolecular motor-based nano- or microscale particle translocations on DNA microarrays," *Nano Letters*, vol. 9, pp. 2407–2413, 2009.

[34] I. Akyildiz, F. Brunettib, and C. Blázquezc, "Nanonetworks: A new communication paradigm," *Computer Networks*, vol. 52, no. 12, pp. 2260–2279, 2008.

[35] S. F. Bush, *Nanoscale Communication Networks*. Artech House, 2010.

[36] L. Parcerisa and I. F. Akyildiz, "Molecular communication options for long range nanonetworks," *Computer Networks*, vol. 53, no. 16, pp. 2753–2766, 2009.

[37] M. Pierobon and I. F. Akyildiz, "A physical end-to-end model for molecular communication in nanonetworks," *IEEE Journal on Selected Areas in Communications*, vol. 28, no. 4, pp. 602–611, 2010.

[38] K. V. Srinivas, A. W. Eckford, and R. S. Adve, "Molecular communication in fluid media: The additive inverse Gaussian noise channel," *IEEE Transactions on Information Theory*, vol. 58, no. 7, pp. 4678–4692, 2012.

[39] V. Jamali, A. Ahmadzadeh, W. Wicke, A. Noel, and R. Schober, "Channel modeling for diffusive molecular communication – A tutorial review," *Proceedings of the IEEE*, vol. 107, no. 7, pp. 1256–1301, 2019.

[40] A. Einolghozati, M. Sardari, and F. Fekri, "Capacity of diffusion-based molecular communication with ligand receptors," in *IEEE Information Theory Workshop*, 2011.

[41] T. Nakano, Y. Okaie, and J. Q. Liu, "Channel model and capacity analysis of molecular communication with Brownian motion," *IEEE Communications Letters*, vol. 16, no. 6, pp. 797–800, Jun. 2012.

[42] C. Rose and I. S. Mian, "Inscribed matter communication: Part I," *IEEE Transactions on Molecular, Biological, and Multi-Scale Communications*, vol. 2, no. 2, pp. 209–227, 2016.

[43] C. Rose and I. S. Mian, "Inscribed matter communication: Part II," *IEEE Transactions on Molecular, Biological, and Multi-Scale Communications*, vol. 2, no. 2, pp. 228–239, 2016.

[44] C. Rose, I. S. Mian, and M. Ozmen, "Capacity bounds on point-to-point communication using molecules," *Proceedings of the IEEE*, vol. 107, no. 7, pp. 1342–1355, 2019.

[45] H. Li, S. M. Moser, and D. Guo, "Capacity of the memoryless additive inverse Gaussian noise channel," *IEEE Journal on Selected Areas in Communications*, vol. 32, no. 12, pp. 2315–2329, 2014.

[46] N. Farsad, W. Guo, and A. W. Eckford, "Table-top molecular communication: Text messages through chemical signals," *PLOS One*, vol. 8, no. 12, e82935, 2013.

[47] N. Farsad, D. Pan, and A. Goldsmith, "A novel experimental platform for in-vessel multi-chemical molecular communications," in *Proceedings of the IEEE Global Telecommunications Conference (GLOBECOM)*, 2017.

[48] H. Unterweger, J. Kirchner, W. Wicke, A. Ahmadzadeh, D. Ahmed, V. Jamali, C. Alexiou, G. Fischer, and R. Schober, "Experimental molecular communication testbed based on magnetic nanoparticles in duct flow," in *Proceedings of the IEEE 19th International Workshop on Signal Processing Advances in Wireless Communications (SPAWC)*, 2018.

[49] W. Guo, I. Atthanayake, and P. Thomas, "Vertical underwater molecular communications via buoyancy: Gaussian velocity distribution of signal," in *Proceedings of the IEEE International Conference on Communications (ICC)*, 2020.

[50] M. J. Moore, T. Nakano, A. Enomoto, and T. Suda, "Measuring distance with single-spike molecular communication feedback protocols," *IEEE Transactions on Signal Processing*, vol. 60, no. 7, pp. 3576–3587, 2012.

[51] N. Farsad, A. W. Eckford, and S. Hiyama, "Modelling and design of polygon-shaped kinesin substrates for molecular communication," in *Proceedings of the IEEE International Conference on Nanotechnology*, 2012.

[52] P. Lio and S. Balasubramaniam, "Opportunistic routing through conjugation in bacteria communication nanonetwork," *Nano Communication Networks*, vol. 3, no. 1, pp. 36–45, 2012.

[53] M. Kuran, H. Yilmaz, T. Tugcu, and I. F. Akyildiz, "Interference effects on modulation techniques in diffusion based nanonetworks," *Nano Communication Networks*, vol. 3, no. 1, pp. 65–73, 2012.

[54] L. Felicetti, M. Femminella, and G. Reali, "A simulation tool for nanoscale biological networks," *Nano Communication Networks*, vol. 3, no. 1, pp. 2–18, 2012.

[55] A. Noel, K. C. Cheung, R. Schober, D. Makrakis, and A. Hafid, "Simulating with AcCoRD: Actor-based communication via reaction-diffusion," *Nano Communication Networks*, vol. 11, pp. 44–75, 2017.

[56] B. Atakan, O. B. Akan, and S. Balasubramaniam, "Body area nanonetworks with molecular communications in nanomedicine," *IEEE Communications Magazine*, vol. 50, no. 1, pp. 28–34, 2012.

[57] P. Bogdan, G. Wei, and R. Marculescu, "Modeling populations of micro-robots for biological applications," in *Proceedings of the 2nd IEEE Workshop on Molecular and Nanoscale Communication*, 2012.

[58] T. Nakano, "Swarming biological nano machines through molecular communication for targeted drug delivery," in *Proceedings of the 6th International Conference on Soft Computing and Intelligent Systems/13th International Symposium on Advanced Intelligent Systems*, 2012, pp. 2317–2320.

[59] S. F. Bush, J. L. Paluh, G. Piro, V. Rao, V. Prasad, and A. W. Eckford, "Defining communication at the bottom," *IEEE Transactions on Molecular, Biological, and Multi-Scale Communications*, vol. 1, no. 1, pp. 90–96, 2015.

[60] T. Nakano, Y. Okaie, S. Kobayashi, T. Hara, Y. Hiraoka, and T. Haraguchi, "Methods and applications of mobile molecular communication," *Proceedings of the IEEE*, vol. 107, no. 7, pp. 1442–1456, 2019.

[61] M. Moore, A. Enomoto, T. Suda, T. Nakano, and Y. Okaie, *The Handbook of Computer Networks*. John Wiley & Sons, 2007, vol. 3. "Molecular communication: New paradigm for communication among nano-scale biological machines," pp. 1034–1054.

[62] P. Yager, T. Edwards, E. Fu, K. Helton, K. Nelson, M. R. Tam, and B. H. Weigl, "Microfluidic diagnostic technologies for global public health," *Nature*, vol. 442, pp. 412–418, 2006.

[63] P. S. Dittrich and A. Manz, "Lab-on-a-chip: Microfluidics in drug discovery," *Nature Reviews Drug Discovery*, vol. 5, pp. 210–218, 2006.

[64] C. Teuscher, C. Grecu, T. Lu, and R. Weiss, "Challenges and promises of nano and bio communication networks," in *Fifth ACM/IEEE International Symposium on Networks-on-Chip*, 2011, pp. 247–254.

[65] L. G. Griffith and G. Naughton, "Tissue engineering – Current challenges and expanding opportunities," *Science*, vol. 295, no. 5557, pp. 1009–1014, 2002.

[66] J. Clausen, "Man, machine and in between," *Nature*, vol. 457, pp. 1080–1081, 2009.

[67] T. M. Allen and P. R. Cullis, "Drug delivery systems: Entering the mainstream," *Science*, vol. 303, no. 5655, pp. 1818–1822, 2004.
[68] J.-W. Yoo, D. J. Irvine, D. E. Discher, and S. Mitragotri, "Bio-inspired, bioengineered and biomimetic drug delivery carriers," *Nature Reviews Drug Discovery*, vol. 10, pp. 521–535, 2011.
[69] A. Ranjan, N. Pothayee, M. N. Seleem, S. M. Boyle, Ramanathan, Kasimanickam, J. S. Riffle, and N. Sriranganathan, "Nanomedicine for intracellular therapy," *FEMS Microbiology Letters*, vol. 332, pp. 1–9, 2012.
[70] R. Byrne and D. Diamond, "Chemo/bio-sensor networks," *Nature Materials*, vol. 5, pp. 421–424, 2006.
[71] S. Hiyama, Y. Moritani, and T. Suda, "Molecular transport system in molecular communication," *NTT DOCOMO Technical Journal*, vol. 10, no. 3, pp. 49–53, 2008.
[72] R. A. Freitas Jr, *Nanomedicine, Vol. I: Basic Capabilities*. Landes Bioscience, 1999.
[73] I. F. Akyildiz and J. M. Jornet, "The internet of nano-things," *IEEE Wireless Communications*, vol. 17, no. 6, pp. 58–63, 2010.
[74] B. Atakan, O. B. Akan, and S. Balasubramaniam, "Body area nanonetworks with molecular communications in nanomedicine," *IEEE Communications Magazine*, vol. 50, no. 1, pp. 28–34, 2012.