Chapter 1
Communication Engineering Meets Medical Science: *The Advanced Targeted Nanomedical Solution*

1.1 Introduction

With the rise in global population, the increase in the number of medically challenging diseases and the low number (as well as uneven distribution) of medical personnel, there is the need for a new approach to global healthcare delivery. In particular, the lack of clear-cut, permanent cures for cancer, Alzheimer's disease, human immunodeficiency virus (HIV), diabetes, cardiovascular diseases (such as severe coronary artery disease) and Ebola, as well as the projected increase in the proportion of the population at risk of some of these diseases [1, 2] means that everyone has something to worry about.

In his paper titled 'There's plenty of room at the bottom: An invitation to enter a new field of physics' [3], published in 1959, the physicist and Nobel prize winner Richard P Feynman stated that there would one day be nanotechnologies with associated possibilities. Recent advances in nanotechnology have triggered the exploration of advanced concepts in the field of medicine to address the abovementioned health challenges. This exploration gave birth to a highly specific medical intervention termed *nanomedicine* [4]. Fundamentally, nanomedicine focuses on the diagnosis, therapy, monitoring and control of diseases at the cellular levels of systems, with a high degree of specificity. This shift in thinking from contemporary medicine towards nanomedicine is motivated by the fact that diseases manifest from miniscule activities in the cells of living organisms such as humans. Typically, disorders in the activities of a cell or a group of cells result in uncoordinated communication among many other cells in the body. This is consequential to the pathological manifestation of subjective evidences such as headache, fatigue, fever and so on—*symptoms of diseases*. Hence, the fundamental concept of nanomedicine is that it is insightful and seemingly effective in tackling health challenges at the cellular level [5]. In nanomedicine, nanoparticles (usually 30–300 nm in diameter [6]) are designed and developed to deliver drug molecules to the disease cells (with minimal adverse effects to healthy cells), conduct highly precise in vivo disease diagnosis/analysis on specific cells and identify/mark disease agents in the body for elimination. It has

U. Chude-Okonkwo et al., *Advanced Targeted Nanomedicine*, Nanomedicine and Nanotoxicology, https://doi.org/10.1007/978-3-030-11003-1_1

found application in many disease therapies, such as in the treatment of cancer [7, 8], Alzheimer's disease [9], HIV [8], diabetes [10] and cardiovascular diseases [11].

Over the course of treatment for many of these diseases, it has been found that different individuals may respond differently when subjected to the same treatment. And even for the same individual with a particular ailment, physiological conditions often change with time, as is observable in cancer therapy [12]. For instances, intrinsic anticancer drug resistance appearing prior to chemotherapy, as well as acquired resistance due to drug treatment, remain the dominant impediments to curative cancer therapy [13]. The same applies to the treatment of Alzheimer's disease, where the vast heterogeneity in the disease aetiology involves very complex and divergent pathways [14]. Hence, there is the need for a personalised nanomedical approach to disease intervention that is based on the stratification of in-depth individual demographic and historical information. This personal nanomedicine is also termed *targeted nanomedicine*.

An important factor that must be noted at this point is the relationship between information exchange and diseases. Cells in our bodies are constantly sending and receiving signals, and many pathological conditions arise due to the breakdown in signalling/communication between or among cells. This is evident from diseases such cancer [15], Alzheimer's disease [16], multiple sclerosis [17], diabetes [18], stroke [19], etc. Hence, diseases and their treatments can be addressed using conventional communication paradigms, approaches, tools and devices. The targeted nanomedicine approach that relies heavily on the principle of information exchange/communication is termed *advanced targeted nanomedicine* (ATN). The rudimentary framework for ATN is molecular communication (MC) engineering. MC is a communication paradigm that uses biochemical signals to achieve information exchange among naturally and artificially created bio-nanosystems over short distances [20–24].

This chapter presents the role of communication principles, ideas and systems in understanding and treating diseases. The discussion is extended to concepts such as molecular communication, nanomedicine and ATN.

1.2 Communication Engineering and Medicine

From the standpoint of evolution theory, the idea that man evolved from molecules through single-cell and multicell organisms offers us a way of connecting communication principles to medical interventions. In the illustration presented in Fig. 1.1, molecules are the centre of the wheel of evolution. At that fundamental level, interactions (communications) exist between the molecules in the forms of covalent and non-covalent bonding. At the single-cell level, where viruses and bacteria reside, communications between these organisms are basically achieved by the interchange of signalling molecules such as in quorum sensing [25] and pheromonal signalling [26]. The last level is the multicellular level of evolution, where man exists. At this level, communications among organisms of the same species are achieved using their

Fig. 1.1 An illustration of molecules-to-human evolution

naturally equipped facilities such as auditory systems, olfactory systems, visual systems, chemoreceptor systems and mechanoreceptor systems. In the case of man and some animals, communication is achieved through a syntactically organised system of signals, such as voice sounds, intonations or pitch, gestures or written symbols that communicate thoughts or feelings.

1.2.1 Diseases as Breakdown in Communication

Communication at the various level of the evolution wheel is crucial to the continuous and harmonious existence of each species, especially at the single-cell level and beyond. These organisms communicate in a network format among themselves to spread knowledge, establishing/improve relationships so as to achieve cohesive organisation, attain greater productivity, search for food and mates and avoid dangers. Figure 1.2 illustrates the different levels of communication networks associated with humans and other multicellular animals. Here, the *social communication network* involves person-to-person interactions, which enable humans to spread knowledge, establish relationships, build cohesive organisation, increase productivity and ultimately ensure survival. For a human to be able to establish a social communication network, it is required that the network of body organs (brain, liver, heart, lung, kidney, etc.) must be established and working. In this sense, the entropy required to work, walk, talk, see, think, live, etc., must be properly 'exchanged/communicated' among the organs. These organs are primarily made up of cells, which themselves communicate over the *cellular network*. Different organs have different cells that work collaboratively to achieve the primary task of the particular organ. And each

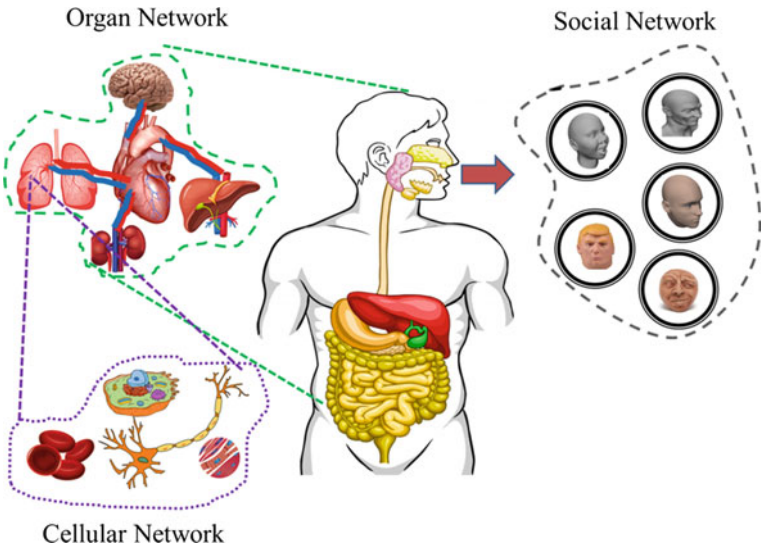

Fig. 1.2 Illustration of the different levels of communication networks associated with humans (and other multicellular animals)

organ works collaboratively with the other organs to keep the host alive in order to communicate with other humans to build a more progressive and resilient society.

Typically, any breakdown in the communication among the organs renders the host organism ineffective and may lead to the death of the host. Implicitly, the breakdown in communications at the cellular level affects the effectiveness of the host organs to perform their primary tasks, which invariably affect communication in the entire organ network and the human at large. The breakdown in communication results in diseases that usually manifest as observable symptoms. For instance, defects in pancreatic cells make them unable to produce enough insulin to signal to the muscle, fat and liver cells the presence of glucose in the blood, resulting in the Type I diabetes with its attendant symptoms [27]. In Type II diabetes, while the pancreatic cells are properly functioning, the muscle, fat and liver cells do not respond appropriately to the insulin signalling [27]. Cell growth and death are strictly controlled by signalling, and when there is a breakdown in the ability of a cell to respond appropriately to growth or death signalling, cancer results [15]. Indeed, a large number of diseases are caused by defective communication within the cellular network.

1.2.2 *Communication Principles: A Tool for the Analysis of Pathological Conditions*

As a breakdown in communication causes diseases, it follows that treatment can be based purely on re-establishing normal communication at the points of breakdown. This is the primary objective of medical therapeutic approaches to the treatment of pathological conditions. Consider a communication network abstracted to represent a typical electronic communication network as shown in Fig. 1.3a. The network consists of nodes/vertices connected by edges, which are communication links. In an electronic communication network, these nodes can be mobile phones, computers, sensors and other communication devices. Typically, in electronic communication networks, the nodes and the edges are continually and inevitably at risk of being damaged, thereby disrupting essential services. The damage to network components might be due to environmental factors, ageing, or technical failure. To re-establish essential services in a damaged network, the affected components must be repaired or reconfigured. The service normalisation approach will include identifying the faulty nodes and edges, repairing them, replacing them and reconfiguring the network (rewiring and re-routing). Various algorithms such as special rings [28], mesh restoration [29], the p-cycle technique [30], distributed checkpointing and recovery protocol [31] and graph theory [32] have been proposed for the recovery and restoration of electronic communication networks.

In the same vein, Fig. 1.3b considers the nodes to be cells, tissues and the organs in the human body and the edges to be blood vessels, lymphatic vessels, nerve fibres and the extracellular space. And just like in electronic communication networks, the cellular and organ networks are continually and inevitably at risk of being damaged, thereby disrupting the harmonious working of the body system, resulting in diseases. The damage to the network components (basically, cells) might be due to

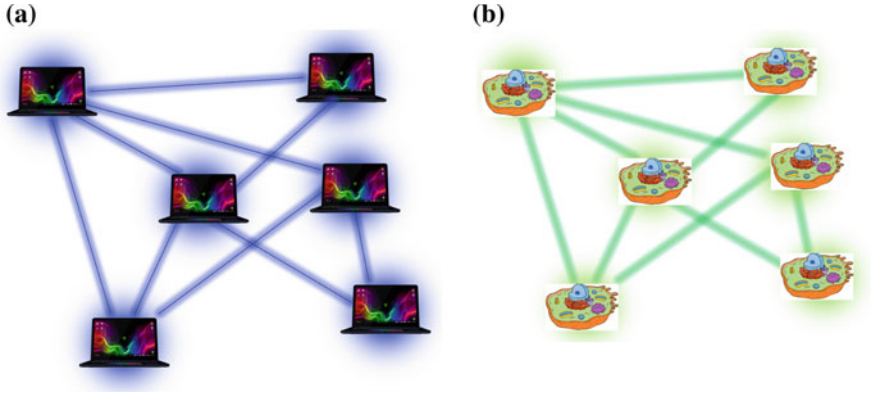

Fig. 1.3 Simplified communication network abstracted to represent, **a** a typical electronic communication network and **b** a communication network of biological nanosystems

environmental factors (pathogens, extreme weather conditions, etc.), ageing or physical injury (accidents). To re-establish effective communication across the damaged links in the network, the affected cells must be repaired or reconfigured. This is the primary objective of medical therapy. The communication normalisation approach will include identifying the faulty nodes and edges (disease diagnosis), repairing the nodes/edges by using medications that target disease cells (cell repair), removing the effected nodes/edges (surgery) and reconfiguring the network (replacement surgery, tissue engineering, implants and prosthesis). Therefore, we can borrow the tools and principles of electronic communication to analyse and address many health challenges.

Naturally, the cellular network in living organism has the capability to execute self-reconfiguration to address network restoration. The self-recovery capability is due to the fact that the network is intrinsically equipped with memory capability to keep track of the developmental stages of the network components. This enables it to use information in its memory to repair, remodel and reproduce network components, or isolate/remove components and reconfigure network links. However, this process of recovery usually takes a long time, and in most cases, many years—*evolution*. In contemporary medical practice, it is desired that the process of network recovery is achieved within a very short period (seconds, minutes and hours).

On this basis, the first stage in contemporary medical methods for re-establishing effective communication at the damaged links is to identify the faulty nodes and edges. This stage is termed diagnosis and is usually carried out in vitro, which includes taking blood, urine and tissue samples and running lab-based tests. Based on the results of diagnosis, medications are administered with different modalities such as ingestion and injection. Sometimes, outright physical removal/repair/replacement of the defective cells from the network may be necessary, necessitating the use of surgical operations, which are done using macro tools such as forceps, scalpels, retractors, haemostats, chisels, drills, curettes, etc.

However, the real-time capability of in vivo diagnosis compared to in vitro diagnosis [33, 34], the uncertainty of oral ingestion [35], the drug wastage and increase in nonspecific toxicity in normal cells of drug delivery by injection [36] and invasiveness of the contemporary surgical approach make the existing medical approach to disease treatment challenging. To address these challenges, a paradigm shift from the vastly explored macro-medicine to nanomedicine has become a focal point in recent times. Nanomedicine [4] is geared towards improving the efficiency of medical and healthcare systems using nanoscale concepts, devices, tools, technologies and techniques. For instance, in traditional drug delivery methods [37] such as intravascular injection and oral ingestion, the drug particles are eventually distributed throughout the cardiovascular system from where only a small percentage of the administered drug particles reach the targeted (pathological) cells and perform therapeutic actions. Hence, the traditional drug delivery systems result in drug wastage and increase in nonspecific toxicity in normal cells. Severity in the issue of toxicity is evident from chemotherapy for cancer treatment, where side effects include alopecia, compromised immunity, fatigue, haemophilia, loss of appetite, painful urination, nausea and vomiting, nail toxicity and anaemia [38].

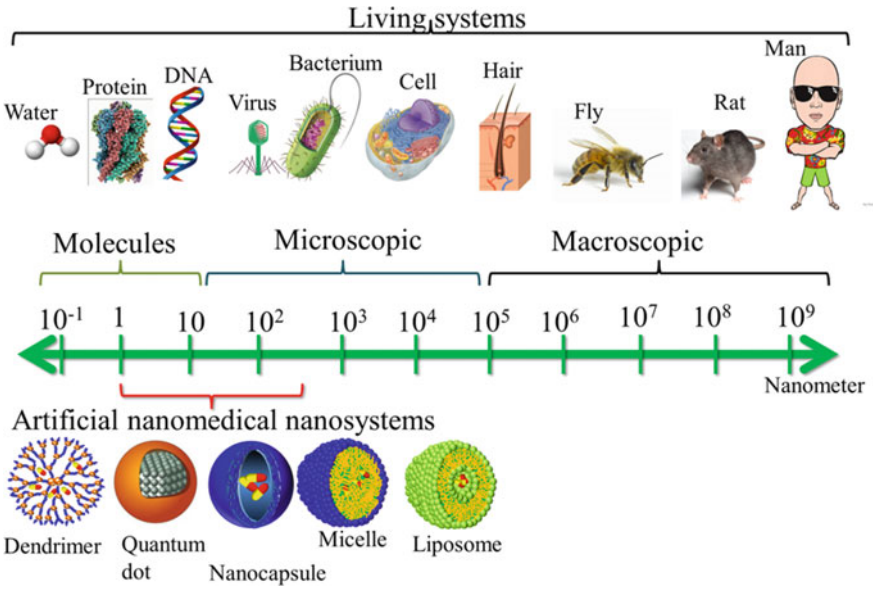

Fig. 1.4 Comparative exposition of some objects from macro- to nanoscales

Using a nanomedical approach, in vivo diagnosis can be conducted, which provides real-time diagnostic capability. Also, drug localisation to targeted cells is achieved in nanomedicine by encapsulating, entrapping or encapsidating drug and therapeutic molecules/particles or agents in nanosystems of nanoscale sizes (see Fig. 1.4). These drug-carrying nanosystems are mainly conveyed to the targeted cells in a controlled manner through the cardiovascular system, which ordinarily carries nutrients to all cells in the body. In the case of cancer treatment, the targeting process is often aided by the enhanced permeability and retention (EPR) effect, which is the property by which nanosystems of certain sizes tend to accumulate in tumour tissue much more than they do in normal tissues. Also, instead of invasive surgery, nanorobots can be introduced to the targeted disease cell to perform precise cellular surgery (nanosurgery) with no or minimal inversion.

1.3 Molecular Communication Engineering

While the progress in nanomedicine over the years is commendable, the translation of expectations and promises of efficacious results is still challenged by the complexity and heterogeneity of disease sites and routes to the site, among other factors [5, 39]. These challenges translate to poor pharmacokinetics and inappropriate biodistribution of the nanomedical nanosystems at the targeted cells after being introduced into the body. To address these challenges, the obvious approach is to

have a way of monitoring and coordinating the delivery and activities of sets of nanosystems from the point of introduction into the body, through the course of their activities in the body, and until they are eliminated from the body. By adopting such a strategy, we can develop nanomedical systems that are composed of nanosystems capable of concurrently providing in vivo therapeutic and monitoring functionalities. We can also incorporate in vivo diagnostic functionality into such nanosystems.

However, contemporary nanomedical approaches and nanosystems are not capable of combining these functions. The most that can be achieved at present is the use of nanosystems with multifunctional capability, which is being considered under the subject of *theranostics* [40, 41]. The term theranostics was coined to define ongoing efforts to develop more specific, individualised therapies for various diseases, and to combine diagnostic and therapeutic capabilities into a single nanosystem [40]. The generalised structure of a theranostics nanosystem incorporates multifunctional capabilities such as magnetic particles [42], folate ligands for targeting [43], pH sensors [44], contrast agents [45], X-ray agents [46] and ultrasonic agents [47].

Nevertheless, the tiny size of nanosystems limits how much functionality can be incorporated into a single nanosystem. And this invariably limits the range of functions it can carry out. Compared to conventional computing/communications systems, the very tiny size of nanoparticles limits their computational capabilities, which ordinarily enables them to function as secure, standalone multitaskable systems. Moreover, as can be deduced from our discussion so far, the system design and operation of the contemporary nanomedical therapeutic systems are such that the nanosystems are pre-equipped with capabilities that enable them to execute predefined tasks, independent of each other. Hence, to make the system more efficient, a game changer will obviously be to have various sets of nanosystems, each with different capabilities and functionalities, working cooperatively to achieve effective nanomedical solutions. In other words, the nanosystems have to communicate with each other and with the targeted cells. This idea puts nanomedicine capability into an entirely new and challenging perspective. The challenges include those associated with the design and development of nanoparticles that can cooperatively communicate with one another to address health problems. This brings us to the concept of molecular communication (MC) engineering, which is a communication paradigm that uses biochemical signals to achieve information exchange among naturally and artificially created bio-nanosystems within the body. The collaborative communication capability can offer us the ability to control and even change the course of an entire nanomedical therapeutic process. Figure 1.5 provides an illustrative comparison between a theranostic approach and an MC-based nanomedical approach to disease treatment. In the theranostic approach, nanosystems with multiple functionalities but no communication capability are deployed, while in the MC-based nanomedical approach, nanosystems with single/multiple functionalities including communication capability are deployed.

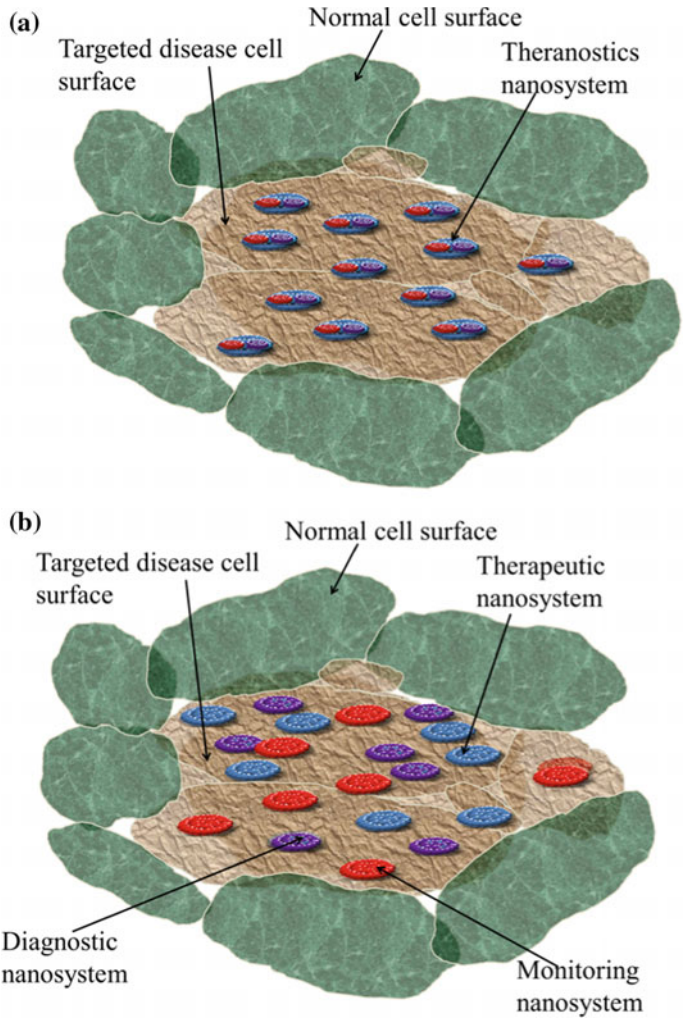

Fig. 1.5 Illustration of the difference between **a** theranostic approach and **b** MC-based nanomedical approach for disease treatments

1.3.1 Basics of Molecular Communication Engineering

A communication system inspired by biological systems such as cells, MC has been proposed as a new communication paradigm that uses biochemical signals to transfer information from one nanosystem to another over a short distance. MC is realised through the transmission and reception of biochemical information encoded in the concentration and type of molecules. However, instead of using the electromagnetic wave as the information carrier (depicted in Fig. 1.6), information is conveyed by

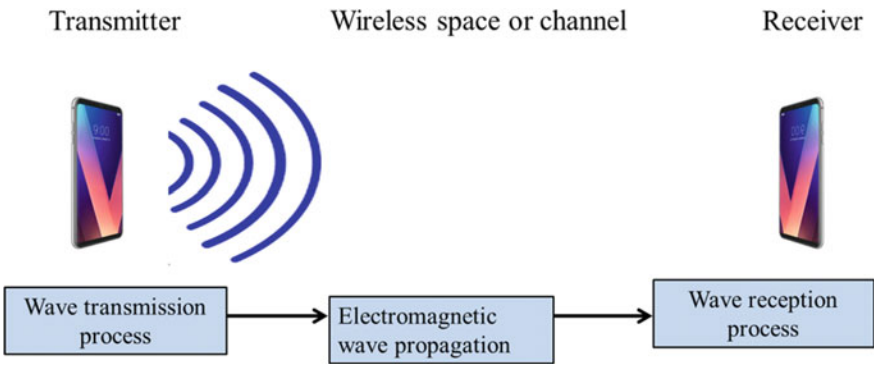

Fig. 1.6 Illustrative block diagram of electronic communication system

molecules, and a combination of molecules and electric pulses in the case of nervous signalling, as shown in Fig. 1.7. The same general principle of communication that applied to electronic communication can be extended to MC, albeit with some variations.

Since the pioneering work of Suda et al. [20], there has been an increase in the number of research expositions and articles in MC. Some interesting introductory/review/survey articles on recent works on MC and its applications can be found in [5, 21, 48–51]. However, not much attention has been given to research in experimentation and the actual system design/engineering/fabrication of components. This trend is understandable since MC is still a budding multidisciplinary research area.

1.3.2 Molecular Communication Engineering: A Nanomedical Tool

MC research and applications can primarily be categorised into *abstraction tool* and *solution tool* as shown in Fig. 1.8.

As an abstraction tool, MC can aid in gaining deep understanding, better representation, optimum design, proper characterisation, accurate analysis and evaluation of nanoscale systems and networks. For instance, the MC concept is used in [52] and [53] to abstract drug transportation through the cardiovascular system and extracellular spaces (ECS), respectively. In [54], the various noise effects that cause uncertainty in the cardiovascular system are analysed, modelled and evaluated from the MC-based information theory perspective.

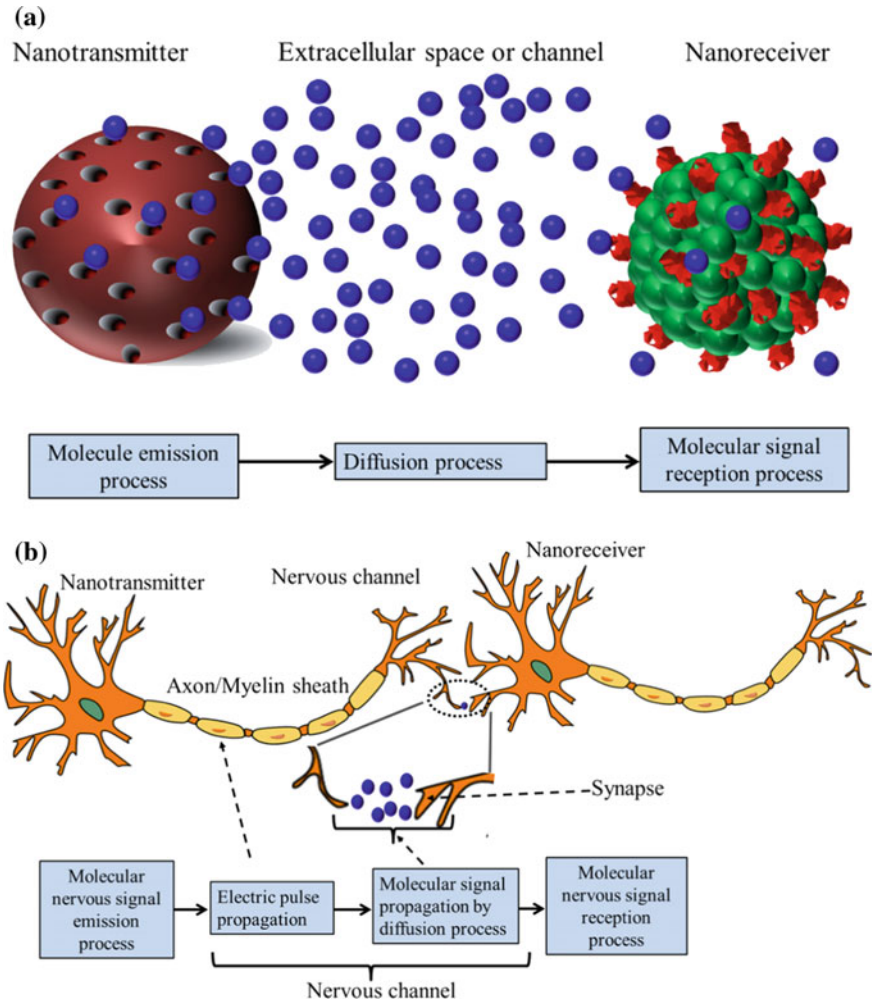

Fig. 1.7 Illustrative block diagram of biological systems communication system representing, **a** cell-to-cell communication and **b** nervous systems communication

As a solution tool, the MC paradigm can be employed to provide novel ideas, techniques, methods, technology and devices to address contemporary challenges in many application areas. In respect of nanomedical applications, MC has been considered as a platform for overcoming contemporary challenges in targeting and efficient administration of drugs at the desired locations. For example, a molecular communication-based TDD solution for the delivery of therapeutic drugs to multiple disease sites that may or may not express trigger stimuli is presented in [55]. In [24], an MC model applied to targeted drug delivery, where inactive drug particles are transmitted and received/processed by means of enzyme catalysis to minimise

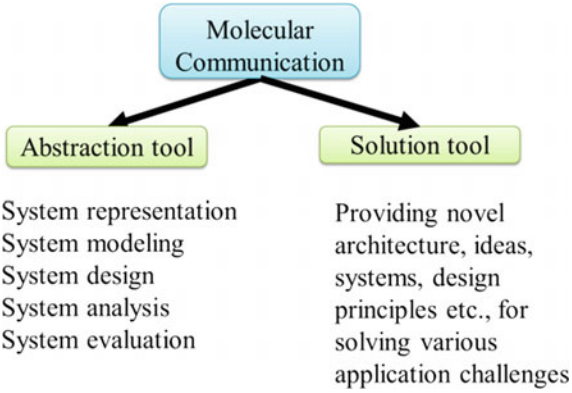

Fig. 1.8 Illustrative categorisation of molecular communication

toxicity, is presented. Furthermore, an MC-based structure is proposed in [56] for combating cardiovascular diseases.

1.4 Advanced Targeted Nanomedicine

Irrespective of the tremendous progress so far, the preclinical studies and clinical trials of targeted nanomedicine remain detached, particularly due to poor understanding of the pathological factors, which arises from the dynamics of the disease conditions and properties. The dynamism stems from the fact that over the course of treatment for many diseases, it has been found that different individuals may respond differently when subjected to the same treatment [57]. Moreover, even for the same individual with a particular ailment, physiological conditions often change with time, as is observable in cancer therapy [12, 13]. Hence, there is the need for a personalised nanomedical approach to disease intervention that is based on the individual patient's stratified ex vivo and in vivo medical information.

The desire for targeted nanomedicine, the need for combined in vivo diagnostic, therapeutic and monitoring in nanomedical systems and the ultimate aspiration to control an entire nanomedical process present an entirely new challenge in nanomedical science. The challenges include obtaining and stratifying the patient's information, using real-time information to control nanomedical processes. The solution to these challenges can be built upon the principles of communications to acquire, process and use patients' real-time medical information to make decisions on treatment course and modalities, as well as control the nanomedical process. Here, we define this solution under the platform of *advanced targeted nanomedicine*, whose framework is illustrated in Fig. 1.9.

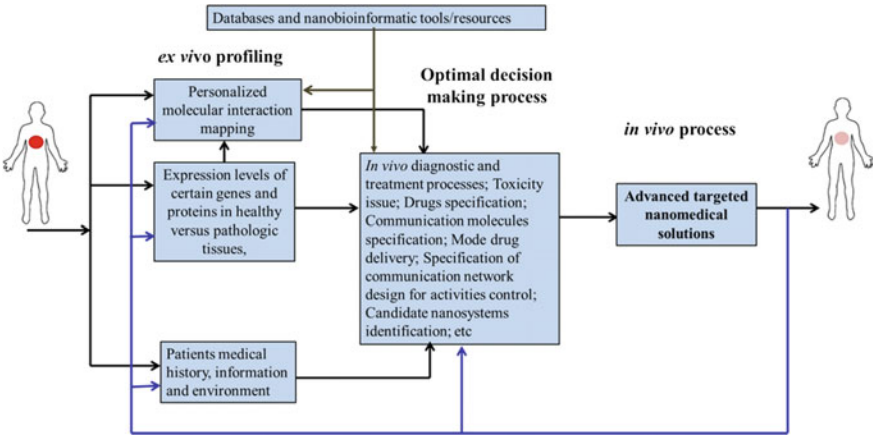

Fig. 1.9 Illustrative framework of advanced targeted nanomedicine solution

1.4.1 Ex Vivo Profiling

Firstly, ex vivo biomarker profiling is conducted, in which the expression levels of certain genes and proteins in healthy versus pathologic tissues of a patient are acquired and quantified. This serves to predict how well a given patient might respond to a given therapeutic intervention, and to quantify any side effects. Genotyping patients, for instance, has been shown to be highly useful in assuring optimal efficacy and minimal toxicity [58]. Second, by using the information from gene and protein profiling and bio-nanoinformatic resources/tools, the comprehensive knowledge of how the nanomaterials interact with the patient's biological system is obtained. This exercise helps in quantifying the toxicity of the advanced targeted nanomedicine process [59]. The integration of the individual's medical history and physiological factors, such as age, race, sex, living environment, nutrition, genetic background, drug metabolism and health condition into the personalised therapeutic decisions is also crucial.

1.4.2 Optimal Decision-Making Process

Based on the information from gene and protein profiling, molecular interaction mapping, medical/physiological conditions, and existing nanobioinformatic databases, optimal decisions can be made regarding the modalities for in vivo diagnosis, therapy and process monitoring. The information can also help in deciding on the appropriate choice of drug molecules, as well as the molecules for communication among nanosystems. The information from the ex vivo profiling will also be utilised to define the choice of nanomaterials in the design of nanosystems for the nanomedical pro-

cess. Further, we can utilise the ex vivo information in the design and development of the communication components/architecture and networks and for the delivery of the ATN solutions. The typical ATN communication network may include an in vivo sub-nanonetwork comprised of interconnected nanosystems that diagnose diseases, deliver therapeutic molecules to targets and monitor the progress of the ATN process. Typical nanonetwork nanosystems include nanotransmitters, nanoreceivers, nanosensors, molecular switches, nanoattenuators and nanorelays. The communication between nanosystems at the nanonetwork level is often achieved by means of molecular signalling and/or electric signalling.

The ATN may also include a body area network [60] of sensors that can help obtain real-time readings of some biosignals, which can be used to further optimise the decision-making process and change the course of therapy as desired. Examples of biosignal readings include electroencephalograph, blood pressure and electrocardiograph. For instance, the effect of in vivo nanosystems distribution on blood pressure and heart rate has to be taken into consideration while deploying nanoparticles/systems for nanomedical applications. Larger forms of communication networks such as the local area network (LAN), metropolitan area network (MAN) and the Internet can also be integrated as feedback paths to the ex vivo profiling and optimal decision-making processes systems, and for remote processing, monitoring and control.

1.4.3 In Vivo Process

The in vivo process involves the practical deployment of the ATN solutions or systems, as illustrated in Fig. 1.10. Deployments include sets of nanosystems that communicate by means of MC to form a nanonetwork. The nanonetwork of optimally chosen nanosystems (nanotransmitter, nanosensors, nanoreceivers, etc.) is usually introduced into the targeted site through the cardiovascular network, and is charged with the task of in vivo diagnosis, therapy and monitoring of the ATN process. The EEG, ECG, blood pressure and heart rate sensors continuously measure the respective changes in biosignal readings and transmit the values to the ex vivo and decision-making information processing systems for improved modification of the ATN process. Nanosensor readings and other important information from the nanonetwork are also fed to the ex vivo and decision-making systems (by physical interaction or through the local area network via the nanonetwork-to-body area network interface) for improved modification of the ATN process. The associated communication network solutions involve heterogeneity that is indicative of the diverseness of the types of signalling in the entire network, which may include molecular signalling, electric signalling, magnetic signalling and electromagnetic wave signalling.

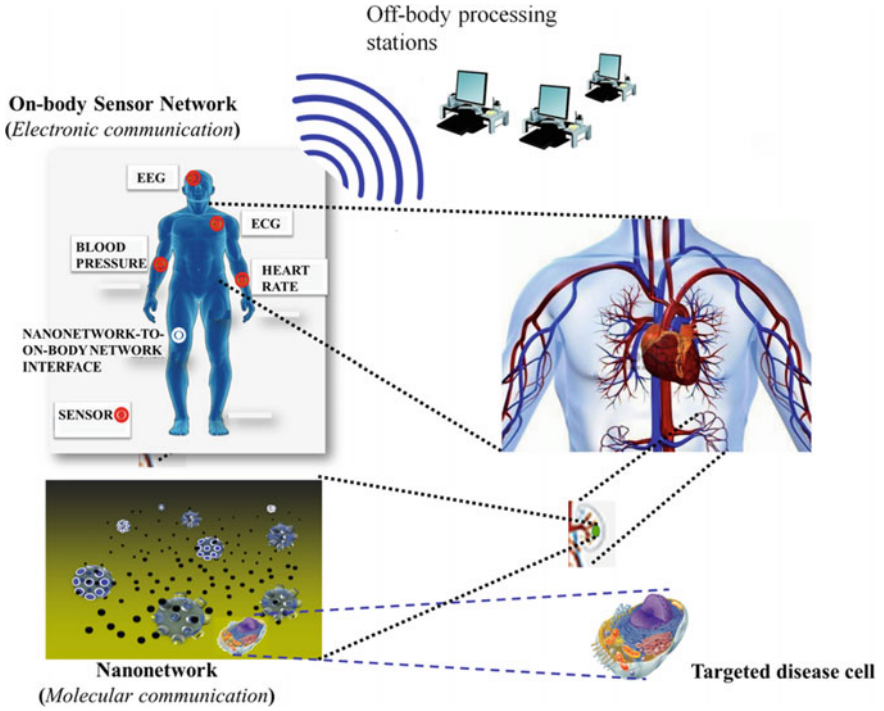

Fig. 1.10 Illustration of typical ATN solution

References

1. Jemal A, Ward EM et al (2017) Annual report to the nation on the status of cancer, 1975–2014, featuring survival. J Nat Cancer Inst 109
2. Association AS (2018) Alzheimer's disease facts and figures. Alzheimer's Dement 14:367–429
3. Feynman RP (1959) There's plenty of room at the bottom. Miniaturization, 282–296
4. Wagner V, Dullaart A, Bock AK, Zweck A (2006) The emerging nanomedicine landscape. Nat Biotechnol 24:1211–1217
5. Chude-Okonkwo UA, Malekian R, Maharaj BT, Vasilakos AV (2017) Molecular communication and nanonetwork for targeted drug delivery: a survey. IEEE Commun Surv Tutor 19(4):3046–3096
6. Debbage P (2009) Targeted drugs and nanomedicine: present and future. Current Pharm Des 15:153–172
7. Duncan R (2006) Polymer conjugates as anticancer nanomedicines. Nat Rev Cancer 6:688–701
8. Muthu MS, Singh S (2009) Targeted nanomedicines: effective treatment modalities for cancer. AIDS and brain disorders. Futur Med 4(1):105–118
9. Gregori M, Masserini M, Mancini S (2015) Nanomedicine for the treatment of Alzheimer's disease. Nanomedicine 10:1203–1218
10. Krol S, Ellis-Behnke R, Marchetti P (2012) Nanomedicine for treatment of diabetes in an aging population: state-of-the-art and future developments. Nanomed Nanotechnol Biol Med 8:S69–S76

11. Godin B, Sakamoto JH, Serda RE, Grattoni A, Bouamrani A, Ferrari M (2010) Emerging applications of nanomedicine for the diagnosis and treatment of cardiovascular diseases. Trends Pharmacol Sci 31:199–205
12. Bozic I, Allen B, Nowak MA (2012) Dynamics of targeted cancer therapy. Tr Mol Med 18:311–316
13. Bar-Zeev M, Livney YD, Assaraf YG (2017) Targeted nanomedicine for cancer therapeutics: towards precision medicine overcoming drug resistance. Drug Res Updat 31:15–30
14. Peng X, Xing P, Li X, Qian Y, Song F, Bai Z, Han G, Lei H (2016) Towards personalized intervention for Alzheimer's disease. Gen Proteomics Bioinf 14:289–297
15. Bazigou E, Rallis C (2007) Cell signaling and cancer. Genome Biol 8:1–3
16. Ho GJ, Drego R, Hakimian E, Masliah E (2005) Mechanisms of cell signaling and inflammation in Alzheimer's disease. Curr Drug Targets-Inflam Allerg 4:247–256
17. Heink S, Yogev N, Garbers C, Herwerth M, Aly L, Gasperi C et al (2017) Trans-presentation of IL-6 by dendritic cells is required for the priming of pathogenic T H 17 cells. Nat Immunol 18:74–85
18. Seino S, Shibasaki T, Minami K (2010) Pancreatic β-cell signaling: toward better understanding of diabetes and its treatment. Proc Jpn Acad, Series B 86:563–577
19. Guo S, Lo EH (2009) Dysfunctional cell-cell signaling in the neurovascular unit as a paradigm for central nervous system disease. Stroke 40:S4–S7
20. Suda T, Moore M, Nakano T, Egashira R, Enomoto A, Hiyama S, Moritani Y (2005) Exploratory research on molecular communication between nanomachines. Gen Evolut Comput Conf (GECCO) Late Break Papers 25:29–34
21. Akyildiz IF, Brunetti F, Blázquez C (2008) Nanonetworks: a new communication paradigm. Comput Netw 52:2260–2279
22. Nakano T, Eckford AW, Haraguchi T (2013) Molecular communication. Cambridge University Press
23. Nakano T, Suda T, Okaie Y, Moore MJ, Vasilakos AV (2014) Molecular communication among biological nanomachines: a layered architecture and research issues. IEEE Trans Nanobio 13:169–197
24. Chude-Okonkwo UA (2014) Diffusion-controlled enzyme-catalyzed molecular communication system for targeted drug delivery. IEEE Global Commun Conf, pp 2826–2831
25. Miller MB, Bassler BL (2001) Quorum sensing in bacteria. Ann Rev Microbiol 55:165–199
26. Swaney WT, Keverne EB (2009) The evolution of pheromonal communication. Behav Brain Res 200:239–247
27. Atkinson MA, Eisenbarth GS, Michels AW (2014) Type 1 diabetes. The Lancet 383:69–82
28. Grover WD (2004) Mesh-based survivable networks: options and strategies for optical, MPLS, SONET, and ATM networking. Prentice Hall, Upper Saddle River, NJ
29. Avci SN, Hu X, Ayanoglu E (2011) Recovery from link failures in networks with arbitrary topology via diversity coding. IEEE Global Telecommun Conf (GLOBECOM 2011), pp 1–6
30. Vasseur JP, Pickavet M, Demeester P (2004) Network recovery: protection and restoration of optical, SONET-SDH, IP, and MPLS. Elsevier
31. Neogy S (2015) Checkpointing with minimal recover in Adhocnet based TMR. Int J UbiComp 6(4):28–44
32. Habibi D, Phung QV (2012) Graph theory for survivability design in communication networks. In Zhang Y (ed) New frontiers in graph theory. InTech
33. Pelaz B, Alexiou C, Alvarez-Puebla RA, Alves F, Andrews AM, Ashraf S et al (2017) Diverse applications of nanomedicine. ACS Nano 11(13):2313–2381
34. Sadovoy A, Teh C (2015) Encapsulated biosensors for advanced tissue diagnostics. In: Meglinsky I (ed) Biophotonics for medical applications, pp 321–330
35. Clewell HJ, Gearhart JM, Gentry PR, Covington TR, Van Landingham CB, Crump KS, Shipp AM (1999) Evaluation of the uncertainty in an oral reference dose for methylmercury due to interindividual variability in pharmacokinetics. Risk Anal 19:547–558
36. Bae YH, Park K (2011) Targeted drug delivery to tumors: myths, reality and possibility. Journal of Controlled Release 153:198

37. Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, Bannerjee SK (2012) Drug delivery systems: an updated review. Int J Pharm Investig 2:2–11
38. Understanding chemotherapy: A guide for patients and families (2014) Atlanta, GA: American Cancer Society
39. Shi J, Kantoff PW, Wooster R, Farokhzad OC (2017) Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer 17:20–37
40. Xie J, Lee S, Chen X (2010) Nanoparticle-based theranostic agents. Adv Drug Deliv Rev 62:1064–1079
41. Lim EK, Kim T, Paik S, Haam S, Huh YM, Lee K (2014) Nanomaterials for theranostics: recent advances and future challenges. Chem Rev 115:327–394
42. Issa B, Obaidat IM, Albiss BA, Haik Y (2013) Magnetic nanoparticles: surface effects and properties related to biomedicine applications. Int J Mol Sci 14:21266–21305
43. Ghaghada KB, Saul J, Natarajan JV, Bellamkonda RV, Annapragada AV (2005) Folate targeting of drug carriers: a mathematical model. J Controll Release 104:113–128
44. Chen X, Cheng X, Gooding JJ (2012) Multifunctional modified silver nanoparticles as ion and pH sensors in aqueous solution. Analyst 137:2338–2343
45. Jin Y, Jia C, Huang SW, O'Donnell M, Gao X (2010) Multifunctional nanoparticles as coupled contrast agents. Nat Commun 1:41–48
46. Rhyner MN, Smith AM, Gao X, Mao H, Yang L, Nie S (2006) Quantum dots and multifunctional nanoparticles: new contrast agents for tumor imaging. Nanomedicine 1:209–217
47. Rapoport N, Gao Z, Kennedy A (2007) Multifunctional nanoparticles for combining ultrasonic tumor imaging and targeted chemotherapy. J Nat Cancer Inst 99:1095–1106
48. Balasubramaniam S, Ben-Yehuda S, Pautot S, Jesorka A, Koucheryavy Y (2013) A review of experimental opportunities for molecular communication. Nano Commun Netw 4:43–52
49. Nakano T, Moore MJ, Wei F, Vasilakos AV, Shuai J (2012) Molecular communication and networking: opportunities and challenges. IEEE Trans Nanobio 11:135–148
50. Farsad N, Yilmaz HB, Eckford A, Chae CB, Guo W (2014) A comprehensive survey of recent advancements in molecular communication. IEEE Commun Surv Tutor 18(3):1887–1919
51. Abbasi QH, Yang K, Chopra N, Jornet JM, Abuali NA, Qaraqe KA, Alomainy A (2016) Nano-Communication for biomedical applications: a review on the state-of-the-art from physical layers to novel networking concepts. IEEE Access 4:3920–3935
52. Chahibi Y, Pierobon M, Song SO, Akyildiz IF (2013) A molecular communication system model for particulate drug delivery systems. IEEE Trans Biomed Eng 60:3468–3483
53. Wei G, Marculescu R (2014) Miniature devices in the wild: modeling molecular communication in complex extracellular spaces. IEEE J Sel Areas Commun 32:2344–2353
54. Chahibi Y, Akyildiz IF (2014) Molecular communication noise and capacity analysis for particulate drug delivery systems. IEEE Trans Commun 62:3891–3903
55. Okonkwo UA, Malekian R, Maharaj BT (2016) Molecular communication model for targeted drug delivery in multiple disease sites with diversely expressed enzymes. IEEE Trans Nanobio 15(3):230–245
56. Chahibi Y, Balasingham I (2015) An intra-body molecular communication networks framework for continuous health monitoring and diagnosis. In: 37th annual international conference of the IEEE engineering in medicine and biology society (EMBC), pp 4077–4080
57. Reitz C (2016) Toward precision medicine in Alzheimer's disease. Annals of Transl Med 4(6):107–113
58. Lammers T, Rizzo LY, Storm G, Kiessling F (2012) Personalized nanomedicine. Clin Cancer Res 18:4889–4894
59. Zhang XQ, Xu X, Bertrand N, Pridgen E, Swami A, Farokhzad OC (2012) Interactions of nanomaterials and biological systems: Implications to personalized nanomedicine. Adv Drug Deliv Rev 64:1363–1384
60. Atakan B, Akan OB, Balasubramaniam S (2012) Body area nanonetworks with molecular communications in nanomedicine. IEEE Commun Mag 50:28–34